Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting information

Diastereoselective Synthesis and Profiling of Bicyclic Imidazolidinone Derivatives Bearing a Difluoromethylated Catechol Unit as Potent Phosphodiesterase 4 Inhibitors

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1. Methods

Synthesis of target compounds

All reactions were performed in oven-dried (150°C) glassware. Catalytic hydrogenations were carried out in a steel autoclave with external stirring and heating. Column chromatography was performed using Kieselgel 40-60μm 60A silica gel. 1D and 2D NMR spectra were recorded at room temperature in $CDCl_3$. The chemical shifts (^1H, ^{13}C) are given ppm (δ) in relative to the solvent signal. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Peaks in IR-spectra data are reported in cm^{-1} with the following relative intensities: s (strong), m (medium), w (weak), br (broad), sh (shoulder). Concentrations *c* in optical rotation angles are given in g/100 mL. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Analytical thin-layer chromatography was performed on silica gel plates with QF-254. Visualization was accomplished with UV light or the solution of anisaldehyde/H_2SO_4 in ethanol. Elemental analysis was performed by the Analytical Laboratory of the Institute of Organic Chemistry. HRMS were measured on electrospray ionization (ESI) instrument with a time-of-flight (TOF) detector. GC-MS was performed on a Chromatec 5000 with Agilent DB-1MS column 122-0132. EI mass spectra were recorded on a Finnigan MAT Incos 50 spectrometer (70 eV). Chiral HPLC analysis was performed on a Shimadzu LC-20 Prominence with a UV-VIS photodiode array detector.

Glacial acetic acid was recrystallized two times. CH_2Cl_2 (technical grade), MeCN (technical grade), DMF, Et_3N, and Me_3SiBr were redistilled from CaH_2, acetone was distilled from Na_2SO_4. Hexane, methyl tert-butyl ether (MTBE), EtOAc and methanol were technical grade and distilled without drying agents. (−)-(1*R*,2*S*)-2-phenylcyclohexanol (99% ee), ethyl vinyl ether, $SnCl_4$, NaN_3, NaI, $NaBH_3CN$, NH_4OAc, nitroethane, isovanillin, (bromomethyl)cyclopropane, DBU, DIBAL-H, methanesulfonyl chloride, DMSO, triphosgene, Lawesson's reagent, methyl iodide, NaH (in mineral oil), Raney nickel (50% slurry in water), $Zn(OTf)_2$, $Cr(NO_3)_3 \bullet 9H_2O$, $TMSCF_2Br$, BrF_2CCO_2Et were purchased from commercial sources and used as received.

Docking

Docking was performed using AutoDock Vina software (X-Score function)[1] with using standard parameters with the degree of exhaustiveness set to 16. For the docking of predesigned structures (Figures 3, 4 in the manuscript and on pp. 82-84 in Supporting information) PDE4B structure 1XMU[2] (catalytic domain of human phosphodiesterase 4B in complex with Roflumilast) was used. Protein structure was prepared according to classical AutoDock scenario: ligand and water molecules were removed, atoms of Zn^{2+} and Mg^{2+} were remained in the protein structure, polar hydrogens, Gasteiger-Huckel charges and studied ligands were added to protein (*pdbqt* input files of ligands to be prepared using AutoDock Tools 1.5.6). The obtained protein model was verified by successful redocking of Roflumilast.

3D structures of ligands were generated using ChemBio3D Ultra 13.0 (MM2 force field for geometry optimization). Gasteiger charges and all the active torsions were added to the structures of ligands using AutoDock Tools 1.5.6 software.

AutoGrid implemented in AutoDock Tools 1.5.6 was used for defining the active site. The dimensions of the grid were set to 40 Å × 40 Å × 40 Å points with grid spacing 0.375 Å. The grid was centered on the co-crystallised ligand present in the complex. These dimensions and position of the grid box were defined

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[1] O. Trott and A. J. Olson, *J. Comput. Chem.*, 2010, **31**, 455.

[2] G. L. Card, B. P. England, Y. Suzuki, D. Fong, B. Powell, B. Lee, C. Luu, M. Tabrizizad, S. Gillette, P. N. Ibrahim, D. R. Artis, G. Bollag, M. V. Milburn, S.-H. Kim, J. Schlessinger and K. Y. J. Zhang, *Structure* **2004**, *12*, 2233-2247.

so as to include the entire binding site of the enzyme and provide space for the translational and rotational of the ligand.

Top scored poses according to predicted free energy of binding were selected for further comparison and analysis of protein-ligand interactions. Docking results were compared by the total score values.

Visualization of interactions of molecules with PDE4 was done using Pymol v. 2.1.1.

DFT calculations

Quantum-chemical calculations were performed with the Gaussian 16 Rev A.03 program[3]. For calculations of thermodynamics DFT MN15L/Def2TZVP level of theory was used. In the development of the theoretical models of all compounds geometrical parameters from various experimental X-Rays taken from The Cambridge Structural Database (CCDC) and Protein Data Bank (RCSB) were used as starting points. All calculations were performed in water (SMD model), the approach of Martin and co-workers was followed[4]. Cartesian coordinates are given in angstroms, absolute energies for all substances are given in hartrees. Analysis of vibrational frequencies was performed for all optimized structures. All compounds were characterized by only real vibrational frequencies. Wavefunction stability, using *stable* keyword, was also checked for all calculations.
Geometry optimization of all generated structures was performed using following keywords[5]:
 # opt freq MN15L/Def2TZVP/Fit scrf=(smd,solvent=water) guess=Always ***pressure=1357*** *nosymm SCF=YQC*

Biology

1. *In vitro* enzymatic assay for recombinant human PDE4B1

Materials: Apremilast is purchased from Cayman Chemicals (Ann Arbor, MI, Item Number 18502), PDE Assay Buffer (BPS Catalog number 60393), PDE Binding Agent (BPS Catalog number 60390), PDE Binding Agent Diluent (cAMP) (BPS Catalog number 60391), PDE-4B1 (BPS Catalog number 60041), substrate (100 nM FAM-cAMP).

Assay conditions: The serial dilution of the compounds was first performed in 100% DMSO with the highest concentration at 0.3mM. Each intermediate compound dilution (in 100% DMSO) will then get directly diluted 10x fold into assay buffer for 10% DMSO and 5µl of the dilution was added to a 50µl reaction so that the final concentration of DMSO is 1% in all of reactions. The enzymatic reactions were conducted at room temperature for 60 minutes in a 50µl mixture containing PDE assay buffer, 100nM FAM-cAMP, a PDE4B1 enzyme and the test compound. After the enzymatic reaction, 100 µl of a binding solution (1:100 dilution of the binding agent with the binding agent diluent) was added to each

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[3] Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.

[4] R. L. Martin, P. J. Hay, L.R. Pratt**,** *J. Phys. Chem. A*, **1998**, *102* (20), pp 3565–3573.

[5] For detailed description of all keywords, basis sets and functionals please refer to Gaussian 16 manual or http://www.gaussian.com/keywords.

reaction and the reaction was performed at room temperature for 60 minutes. Fluorescence intensity was measured at an excitation of 485 nm and an emission of 528 nm using a Tecan Infinite M1000 microplate reader.

Data analysis: PDE activity assays were performed in duplicate at each concentration. Fluorescence intensity is converted to fluorescence polarization using the Tecan Magellan6 software. The fluorescence polarization data were analyzed using the computer software, Graphpad Prism. The fluorescence polarization (FP_t) in absence of the compound in each data set was defined as 100% activity. In the absence of PDE and the compound, the value of fluorescent polarization (FP_b) in each data set was defined as 0% activity. The percent activity in the presence of the compound was calculated according to the following equation: % activity = $(FP-FP_b)/(FP_t-FP_b)\times 100\%$, where FP= the fluorescence polarization in the presence of the compound. The values of % activity versus a series of compound concentrations were then plotted using non-linear regression analysis of Sigmoidal dose-response curve generated with the equation $Y=B+(T-B)/1+10^{((LogEC50-X)\times Hill\ Slope)}$, where Y=percent activity, B=minimum percent activity, T=maximum percent activity, X= logarithm of compound and Hill Slope=slope factor or Hill coefficient. The IC_{50} value was determined by the concentration causing a half-maximal percent activity.

2. *In vitro* selectivity enzymatic assay for a series of PDE4 isotypes

Materials: Apremilast is purchased from Cayman Chemicals (Ann Arbor, MI, Item Number 18502), PDE Assay Buffer (BPS Catalog number 60393), PDE Binding Agent (BPS Catalog number 60390), PDE Binding Agent Diluent (cAMP) (BPS Catalog number 60391).

Enzymes and Substrates:

Assay	Catalog #	Enzyme Lot #	Enzyme Used (ng) / Reaction	Substrate
PDE4A1A	60040	160926-G	0.1	100 nM FAM-cAMP
PDE4A4B	60039	110411	0.06	100 nM FAM-cAMP
PDE4A10	60038	110428-GC	0.128	100 nM FAM-cAMP
PDE4B2	60042	121218-G1	0.025	100 nM FAM-cAMP
PDE4C1	60044	90812	0.24	100 nM FAM-cAMP
PDE4D2	60048	130102-GC	0.03	100 nM FAM-cAMP
PDE4D3	60046	121011	0.025	100 nM FAM-cAMP
PDE4D7	60047	101101	0.045	100 nM FAM-cAMP

Assay conditions: 0.1μM dilutions of the test compounds were prepared in assay buffer (10% DMSO concentration) and 5μl of the dilution was added to a 50μl reaction so that the final concentration of DMSO is 1% in all of reactions. The enzymatic reactions were conducted at room temperature for 60 minutes in a 50μl mixture containing PDE assay buffer, 100nM FAM-cAMP, a PDE enzyme and the test compound. After the enzymatic reaction, 100 μl of a binding solution (1:100 dilution of the binding agent with the binding agent diluent) was added to each reaction and the reaction was performed at room temperature for 60 minutes. Fluorescence intensity was measured at an excitation of 485 nm and an emission of 528 nm using a Tecan Infinite M1000 microplate reader.

Data analysis: PDE activity assays were performed in duplicate at each concentration. Fluorescence intensity is converted to fluorescence polarization using the Tecan Magellan6 software. The fluorescence polarization data were analyzed using the computer software, Graphpad Prism. The fluorescence polarization (FP_t) in absence of the compound in each data set was defined as 100% activity. In the absence of PDE and the compound, the value of fluorescent polarization (FP_b) in each data set was defined as 0% activity. The percent activity in the presence of the compound was calculated according to the following equation: % activity = $(FP-FP_b)/(FP_t-FP_b)\times100\%$, where FP= the fluorescence polarization in the presence of the compound.

3. PDE4B Cell Signaling Pathway Assay

Materials: HEK293 cell line (ATCC # CRL-1573), MEM/EBSS medium (Hyclone # SH30024.01), Fetal Bovine Serum (ThermoFisher # 26140-079), Non-essential amino acids (Hyclone #SH30238.01), Na-pyruvate (Hyclone #SH30239.01), Penn-strep (Hyclone # SV30010), Lipofectamine™ 2000 (Invitrogen # 11668027), Opti-MEM I Reduced Serum Medium (Invitrogen #31985-062), PDE4B DNA (Origene # RC211956), Forskolin (BPS Bioscience # 27067), ONE-Step luciferase assay system (BPS Bioscience # 60690)

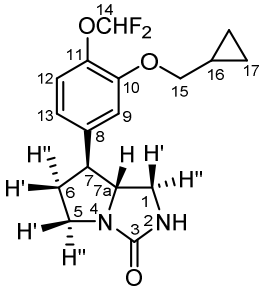
Cell Culture: HEK293 cells were cultured in MEM/EBSS medium with 10% Fetal bovine serum, 1% Penn-strep, 1% Non-essential amino acid, 1 mM Na-pyruvate.

Assay conditions: HEK293 cells were seeded at 30,000 cells per well into 96-well microplate in 100 µl of growth medium. Cells were incubated at 37°C and 5% CO_2 overnight. The following day, using Lipofectamine 2000, the cells were transiently transfected with a PDEB expression vector and a CRE luciferase reporter. Cells were incubated at 37°C and 5% CO_2 for 6 hours. The cells were then treated with test compounds in 50 ul of fresh growth medium for ~24 hours. Following treatment, Forskolin was added in 5 ul of growth medium to stimulated wells to a final concentration of 10 uM. Cells were placed at 37°C and 5% CO_2 for an additional 5-6 hours. The next day, cells were lysed and a luciferase assay was performed using ONE-Step luciferase assay system: add 100 µl of One-Step Luciferase reagent per well and rock at room temperature for ~30 minutes. Luminescence was measured using a luminometer (BioTek Synergy™ 2 microplate reader).

Data analysis: Cell based assays were performed in triplicate at each concentration. To obtain the normalized luciferase activity of CRE reporter, subtract background luminescence then from the CRE reporter. The normalized luciferase activity data was analyzed using the Graphpad Prism. In the absence of the compound, the normalized luciferase activity (L_t) in each data set was defined as 1. The fold induction in the presence of each compound was calculated according to the following equation: fold induction = L/L_t, where L= the normalized luciferase activity in the presence of the compound, L_t= the normalized luciferase activity in the absence of the compound. The values of % luminescence versus a series of compound concentrations were then plotted using non-linear regression analysis of Sigmoidal dose-response curve generated with the equation $Y=B+(T-B)/1+10^{((LogEC50-X)\times Hill\ Slope)}$, where Y=percent luminescence, B=minimum percent luminescence, T=maximum percent luminescence, X= logarithm of compound and Hill Slope=slope factor or Hill coefficient. The EC_{50} value was determined by the concentration causing a half-maximal percent activity.

2. Synthetic procedures and characterization data

7-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)hexahydro-3H-pyrrolo[1,2-c]imidazol-3-one (1a)



Rel-(7*S*,7a*R*)-**1a** (*rac*-**1a**)

To a solution of azide **12a** (0.162 g, 0.407 mmol) in methanol (6 ml) in a vial equipped with a magnetic stirrer was added Boc_2O (0.089 g, 0.407 mmol). Then a suspension of Raney® nickel (ca. 100 mg, washed with methanol) in methanol (2 ml) was added. The vial was placed to a steel autoclave which was flushed and filled with H_2 to a pressure of 20 bar. The mixture was stirred at r.t. for 2 h, then the autoclave was heated to 60°C and the mixture was stirred at this temperature for 6 h. Then the autoclave was cooled to r.t., slowly evacuated and the catalyst was removed. The solvent was then evaporated under vacuum. The residue was dissolved in DMSO (5 ml) and the resulting solution was gently refluxed for 30 min in argon atmosphere. Then the solvent was evaporated under vacuum (ca. 100°C, 10 Torr) and the residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:1 → EtOAc/MeOH = 1:0 → 10:1) to yield 0.075 g (55%) of pyrroloimidazolidinone *rac*-**1a**. Yellow solid, m.p. = 127–129°C. R_f = 0.71 (EtOAc/MeOH = 3:1).

(−)-(7S,7aR)-**1a**

To a solution of azide **12c** (0.011 g, 0.021 mmol) in methanol (2 ml) in a vial equipped with a magnetic stirrer was added Boc_2O (0.005 g, 0.021 mmol). Then a suspension of Raney® nickel (ca. 10 mg, washed with methanol) in methanol (0.5 ml) was added. The test tube was placed to a steel autoclave which was flushed and filled with H_2 to a pressure of 10 bar. The mixture was stirred at r.t. for 2 h. Then the autoclave was slowly evacuated and the catalyst was removed. The solvent was then evaporated under vacuum. The residue was dissolved in DMSO (1 ml) and the resulting solution was gently refluxed for 30 min in argon atmosphere. Then the solvent was evaporated under vacuum (ca. 100°C, 10 Torr) and the residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:1 → EtOAc/MeOH = 1:0 → 10:1) to yield 0.003 g (42%) of pyrroloimidazolidinone (−)-(7S,7aR)-**1a**. Yellow oil.

^{1}H NMR (300 MHz, COSY, HSQC, NOESY, $CDCl_3$) δ 7.10 (d, J = 7.8 Hz, 1H, 12-CH), 6.78 (s, 1H, 9-CH), 6.77 (d, J = 7.8 Hz, 1H, 13-CH), 6.59 (t, J = 75.6 Hz, 1H, 14-CHF_2), 6.01 (s, br, 1H, 2-NH), 3.85 (d, J = 6.9 Hz, 2H, 15-CH_2), 3.78 – 3.61 (m, 2H, 5-CH' and 7a-CH), 3.52 (dd, J = 10.2, 8.0 Hz, 1H, 1-CH), 3.33 (ddd, J = 10.2, 9.7, 2.7 Hz, 1H, 5-CH''), 3.29 (dd, J = 10.8, 10.2 Hz 1H, 1-CH), 2.76 (ddd, J = 11.1, 10.6, 8.0 Hz, 1H, 7-CH), 2.37 (dddd, J = 12.6, 8.1, 8.0, 2.7 Hz, 1H, 6-CH''), 2.04 (dddd, J = 12.6, 11.1, 9.7, 9.1 Hz, 1H, 6-CH'), 1.34 – 1.13 (m, 1H, 16-CH), 0.63 (m, 2H, 17-CH_2), 0.34 (m, 2H, 17-CH_2).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$) δ 165.96 (3-C), 150.84 (10-C), 139.52 (t, J = 4.2 Hz, 11-C), 138.27 (8-C), 123.11 (12-C), 120.04 (13-C), 116.27 (t, J = 259.5 Hz, 14-C), 113.97 (9-C), 74.11 (15-C), 66.15 (7a-C), 48.76 (7-C), 45.26 (5-C), 41.37 (1-C), 34.59 (6-C), 10.25 (16-C), 3.26 (17-C).

Characteristic 2D-NOESY correlations: 7a-CH/9-CH, 7a-CH/13-CH, 7-CH/6-CH''.

^{19}F NMR (188 MHz, $CDCl_3$) δ -81.42 (d, J = 75.4 Hz).

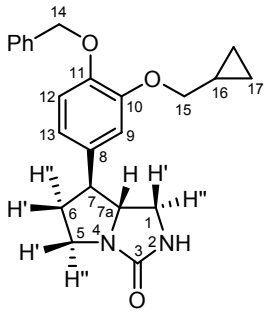
HRMS (ESI): m/z calcd. for $[C_{17}H_{21}F_2N_2O_3]^+$ 339.1515, found 339.1511 $[M+H]^+$.

For (−)-(7S,7aR)-**1a**:

Optical rotation: $[\alpha]^{20}_D = -22°$ ($CHCl_3$, C = 0.3 g/100ml).

Chiral HPLC: e.e. 96% (RT: 20.2 min; Column: CHIRALPAK IA-3; Solvent: Hexane/i-PrOH = 90:10; Temperature: 40°C; Flow rate: 1 ml/min; Injection volume: 5 μL).

***Rel*-(7*S*,7a*R*)-7-(4-(benzyloxy)-3-(cyclopropylmethoxy)phenyl)hexahydro-3H-pyrrolo[1,2-c]imidazol-3-one (1b)**



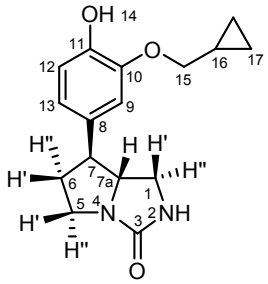
To a solution of azide **12b** (0.142 g, 0.324 mmol) in methanol (2 ml) in a vial equipped with a magnetic stirrer were added Boc_2O (0.0704 g, 0.324 mmol) and triethylamine (0.090 ml, 0.648 mmol). Then a suspension of Raney® nickel (ca. 30 mg, washed with methanol) in methanol (1 ml) was added. The vial was placed to a steel autoclave which was flushed and filled with H_2 to a pressure of 50 bar. The mixture was stirred at r.t. for 1 h, then the autoclave was heated to 50°C and the mixture was stirred at this temperature for 3 h. The autoclave was cooled to r.t., then evacuated and Raney® nickel (ca. 30 mg) was added. The autoclave was filled with H_2 (50 bar) and the mixture was stirred for 1 h at 50°C. Then the autoclave was cooled to r.t., slowly evacuated and the catalyst was removed. The solvent was then evaporated under vacuum. The residue was dissolved in recrystallized DMSO (1 ml). The resulting solution was degassed under vacuum for 15 min and then gently refluxed for 50 min in argon atmosphere. Then the solvent was evaporated under vacuum (ca. 100°C, 10 Torr) and the residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:1 → 0:1) to yield 0.053 g (43%) of pyrroloimidazolidinone **1b**. Brown solid, m.p. = 103–105°C (recrystallized from Hexanes/MTBE = 1:1). R_f = 0.78 (EtOAc/MeOH = 3:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.28 (m, 5H, Ph), 6.87 (d, J = 8.2 Hz, 1H, 12-CH), 6.78 (d, J = 2.1 Hz, 1H, 9-CH), 6.71 (dd, J = 8.2, 2.1 Hz, 1H, 13-CH), 5.13 (s, 2H, 14-CH_2), 5.07 (s, 1H, 2-NH), 3.88 (d, J = 6.8 Hz, 2H, 15-CH_2), 3.76 – 3.64 (m, 2H, 5-CH'' and 7a-CH), 3.52 (dd, J = 9.9, 8.7 Hz, 1H, 1-CH), 3.36 (ddd, J = 9.8, 9.2, 2.6 Hz, 1H, 5-CH'), 3.30 (dd, J = 11.1, 9.9 Hz, 1H, 1-CH), 2.80 – 2.65 (m, 1H, 7-CH), 2.37 (dddd, J = 12.6, 8.1, 8.1, 2.6 Hz, 1H, 6-CH), 2.05 (dddd, J = 12.6, 12.5, 9.2, 9.2 Hz, 1H, 6-CH), 1.39 – 1.22 (m, 1H, 16-CH), 0.63 (m, 2H, 17-CH_2), 0.36 (m, 2H, 17-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.63 (3-C), 149.75 (10-C), 148.35 (11-C), 137.56 (i-Ph), 132.79 (8-C), 128.60 (m-Ph), 127.90 (13-C), 127.36 (o-Ph), 120.35 (p-Ph), 115.73 (12-C), 114.66 (9-C), 74.65 (15-C), 71.64 (14-C), 66.16 (7a-C), 48.69 (7-C), 45.35 (5-C), 41.40 (1-C), 34.64 (6-C), 10.64 (16-C), 3.43 (17-C).

HRMS (ESI): m/z calcd. for $[C_{23}H_{27}N_2O_3]^+$ 379.2016, found 379.2025 $[M+H]^+$.

***Rel*-(7*S*,7a*R*)-7-(3-(cyclopropylmethoxy)-4-hydroxyphenyl)hexahydro-3H-pyrrolo[1,2-c]imidazol-3-one (1c)**



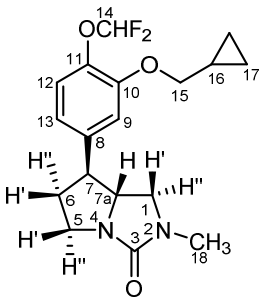
To a solution of benzyl ether **1b** (0.071 g, 0.188 mmol) in methanol (2 ml) in a vial was added Pd/C (0.035 g, 10 wt%). The vial was placed to a steel autoclave which was flushed and filled with H_2 to a pressure of 45 bar. The autoclave was heated to 60°C and the mixture was stirred at this temperature for 3 h, then the autoclave was cooled to r.t., slowly evacuated and the catalyst was removed by centrifugation. The resulting solution was evaporated and dried under vacuum to yield 0.051 g (94%) of phenol **1c**. White solid, m.p. = 152–153°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, J = 8.5 Hz, 1H, 12-CH), 6.71 (d, J = 8.5 Hz, 1H, 13-CH), 6.67 (s, 1H, 9-CH), 5.77 (s, br, 1H, 2-NH), 5.13 (s, 1H, 14-OH), 3.87 (d, J = 7.1 Hz, 2H, 15-CH_2), 3.79 – 3.62 (m, 2H, 5-CH' and 7a-CH), 3.52 (dd, J = 10.0, 8.9 Hz, 1H, 1-CH), 3.41 – 3.28 (m, 1H, 5-CH''), 3.30 (dd, J = 11.1, 10.0 Hz, 1H, 1-CH), 2.72 (m, 1H, 7-CH), 2.36 (m, 1H, 6-CH''), 2.03 (m, 1H, 6-CH'), 1.34 – 1.19 (m, 1H, 16-CH), 0.67 (m, 2H, 17-CH_2), 0.36 (m, 2H, 17-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.71 (3-C), 146.31 and 145.30 (10-C and 11-C), 131.06 (8-C), 120.45 (12-C), 114.79 (13-C), 111.50 (9-C), 74.29 (15-C), 66.21 (7a-C), 48.84 (7-C), 45.33 (5-C), 41.38 (1-C), 34.73 (6-C), 10.46 (16-C), 3.45 (17-C).

HRMS (ESI): m/z calcd. for $[C_{16}H_{20}N_2O_3Na]^+$ 311.1366, found 311.1358 $[M+Na]^+$.

***Rel*-(7*S*,7a*R*)-7-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-2-methylhexahydro-3H-pyrrolo[1,2-c]imidazol-3-one (1d)**



A solution of pyrroloimidazolidinone *rac*-**1a** (0.014 g, 0.044 mmol) in dry THF in Schlenk flask under argon atmosphere was cooled to 0°C. NaH (60% suspension in oil, 0.0075 g, 0.178 mmol) was added and the reaction mixture was stirred for 40 min. Then CH_3I (5.5 µl, 0.089 mmol) was added, the reaction mixture was stirred for 2 h allowing to warm to r.t. Methanol (5 ml) was added and the solvent was evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: EtOAc/MeOH = 1:0 → 10:1) to yield 0.0137 g (88%) of methylated amide **1d**. Yellow oil. R_f = 0.69 (EtOAc/MeOH = 3:1).

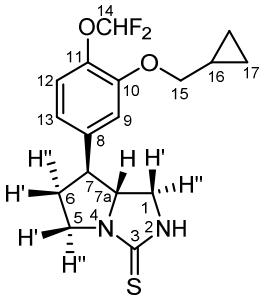
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 7.6 Hz, 1H, 12-CH), 6.79 (s, 1H, 9-CH), 6.78 (d, J = 7.6 Hz, 1H, 13-CH), 6.60 (t, J = 75.6 Hz, 1H, 14-CHF_2), 3.87 (d, J = 6.9 Hz, 2H, 15-CH_2), 3.72 (ddd, J = 11.6, 8.5, 7.9 Hz, 1H, 7a-CH), 3.62 (ddd, J = 9.6, 7.9, 1.8 Hz, 1H, 5-CH’’), 3.41 (dd, J = 9.7, 7.9 Hz, 1H, 1-CH), 3.40 – 3.32 (m, 1H, 5-CH’), 3.22 (dd, J = 9.7, 1.8 Hz, 1H, 1-CH), 2.84 (s, 3H, 18-CH_3), 2.74 – 2.62 (m, 1H, 7-CH), 2.36 (dddd, J = 12.8, 12.8, 7.9, 2.1 Hz, 1H, 6-CH’’), 2.03 (m, 1H, 6-CH’), 1.36 – 1.20 (m, 1H, 16-CH), 0.66 (m, 2H, 17-CH_2), 0.36 (m, 2H, 17-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.95 (3-C), 150.96 (10-C), 139.61 (t, J = 3.1 Hz, 11-C), 138.52 (8-C), 123.22 (12-C), 120.25 (13-C), 116.30 (t, J = 260.0 Hz, 14-C), 113.97 (9-C), 74.24 (15-C), 63.27 (7a-C), 49.28 (7-C), 48.28 (5-C), 46.05 (1-C), 34.72 (6-C), 31.00 (18-C), 10.34 (16-C), 3.35 (17-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.44 (d, J = 75.5 Hz).

HRMS (ESI): m/z calcd. for $[C_{18}H_{23}F_2N_2O_3]^+$ 353.1671, found 353.1668 $[M+H]^+$.

***Rel*-(7S,7aR)-7-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)hexahydro-3H-pyrrolo[1,2-c]imidazole-3-thione (1e)**



To a stirred solution of pyrroloimidazolidinone *rac*-**1a** (0.0335 mg, 0.099 mmol) in toluene (2 ml) Lawesson's reagent (0.0515 g, 0.129 mmol) was added. The reaction mixture was stirred at 100°C for 1.5 h under argon atmosphere, then cooled to r.t. and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:0 → 5:1 → 3:1) to yield 0.014 g (40%) of thione **1e**. White solid, m.p. = 109.7–111.3°C. R_f = 0.86 (EtOAc).

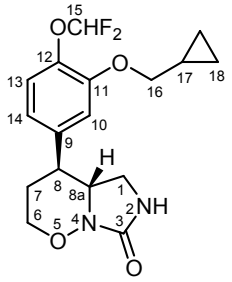
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 7.7 Hz, 1H, 12-CH), 6.78 (s, 1H, 9-CH), 6.76 (d, J = 7.7 Hz, 1H, 13-CH), 6.60 (t, J = 75.5 Hz, 1H, 14-CHF_2), 6.50 (s, 1H, 2-NH), 4.08 (m, 2H, 5-CH'' and 7a-CH), 3.86 (d, J = 6.9 Hz, 2H, 15-CH_2), 3.70 (dd, J = 10.0, 9.7 Hz, 1H, 1-CH), 3.58 (ddd, J = 12.1, 9.6, 2.7 Hz, 1H, 5-CH'), 3.47 (dd, J = 10.0, 4.1 Hz, 1H, 1-CH), 2.84 (ddd, J = 11.8, 10.9, 7.8 Hz, 1H, 7-CH), 2.48 (dddd, J = 12.7, 8.0, 7.8, 2.7 Hz, 1H, 6-CH''), 2.15 (dddd, J = 12.7, 11.8, 9.6, 9.3 Hz, 1H, 6-CH'), 1.38 – 1.17 (m, 1H, 16-CH), 0.70 – 0.61 (m, 2H, 17-CH_2), 0.35 (m, 2H, 17-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.12 (3-C), 151.04 (10-C), 139.76 (t, J = 2.9 Hz, 11-C), 137.32 (8-C), 123.32 (12-C), 119.96 (13-C), 116.22 (t, J = 260.0 Hz, 14-C), 113.84 (9-C), 74.22 (15-C), 69.33 (7a-C), 49.02 (7-C), 47.52 (5-C), 45.87 (1-C), 34.56 (6-C), 10.28 (16-C), 3.33 (17-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.47 (d, J = 75.5 Hz).

HRMS (ESI): m/z calcd. for $[C_{17}H_{21}F_2N_2O_2S]^+$ 355.1286, found 355.1276 $[M+H]^+$.

***Rel*-(4*S*,4a*R*)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)hexahydro-7H-imidazo[1,5-b][1,2]oxazin-7-one (2a)**



To a solution of azide **22a** (0.061 g, 0.172 mmol, 6.5 : 1 mixture of isomers) in methanol (1.5 ml) in a Schlenk flask equipped with a magnetic stirrer was added a solution of Boc_2O (0.0375 g, 0.172 mmol) in methanol (0.5 ml). Then a suspension of Raney® nickel (ca. 100 mg, washed with methanol) in methanol (1 ml) was added. The flask was connected to a balloon filled with H_2 (1 bar). The mixture was stirred at r.t. for 10 min, then the balloon was disconnected and the catalyst was removed and washed with hot methanol (5 × 3 ml). The solvent was then evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 5:1 → 1:1) to yield 0.045 g (61%) of Boc-protected aminooxazine which was immediately used in the next step.

The Boc-protected aminooxazine (0.045 g, 0.105 mmol) was dissolved in CH_2Cl_2 (1 ml) and the solution was cooled to 0°C. Trifluoroacetic acid (0.5 ml) was added and the mixture was stirred at 0°C for 1 h, then it was evaporated and dried under vacuum. The residue was dissolved in CH_2Cl_2 (0.5 ml) and the resulting solution was cooled to 0°C. A solution of triphosgene (0.018 mg, 0.06 mmol) in CH_2Cl_2 (0.5 ml) and triethylamine (0.090 ml, 0.624 mmol) were added, and the reaction mixture was stirred at 0°C under argon for 1 h. The solution was evaporated under vacuum and the residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:1 → 0:1) to yield 0.014 g (23%) of **2a**. Colorless oil. R_f = 0.62 (EtOAc/MeOH = 3:1).

^{1}H NMR (300 MHz, COSY, HSQC, NOESY, $CDCl_3$) δ 7.13 (d, J = 7.8 Hz, 1H, 13-CH), 6.80 (s, 1H, 10-CH), 6.79 (d, J = 7.8 Hz, 1H, 14-CH), 6.61 (t, J = 75.5 Hz, 1H, 15-CHF_2), 5.47 (s, 1H, 2-NH), 4.09 (ddd, J = 10.7, 4.8, 2.3 Hz, 1H, 6-CH''eq), 4.02 (ddd, J = 12.0, 10.7, 2.1 Hz, 1H, 6-CH'ax), 3.87 (d, J = 6.9 Hz, 2H, 16-CH_2), 3.86 – 3.81 (m, 1H, 8a-CH), 3.29 (dd, J = 9.0, 6.7 Hz, 1H, 1-CH), 3.02 (ddd, J = 9.0, 2.5 Hz, 1H, 1-CH), 2.87 (ddd, J = 12.3, 10.5, 4.1 Hz, 1H, 8-CH_{ax}), 2.14 (dddd, J = 13.8, 12.3, 12.0, 4.8 Hz, 1H, 7-CH'ax), 1.90 (dddd, J = 13.8, 4.1, 2.3, 2.1 Hz, 1H, 7-CH''eq), 1.36 – 1.20 (m, 1H, 17-CH), 0.70 – 0.61 (m, 2H, 18-CH_2), 0.40 – 0.33 (m, 2H, 18-CH_2).

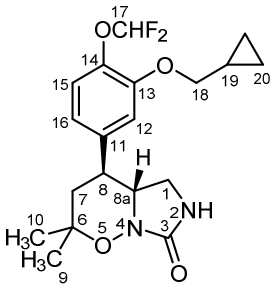
^{13}C NMR (75 MHz, HSQC, $CDCl_3$) δ 160.22 (3-C), 151.04 (11-C), 139.85 (9-C), 139.14 (12-C), 123.32 (13-C), 120.38 (14-C), 116.22 (t, J = 260.0 Hz, 15-C), 114.13 (10-C), 74.24 (16-C), 69.73 (6-C), 60.30 (8a-C), 41.79 (8-C), 40.60 (1-C), 31.38 (7-C), 10.30 (17-C), 3.34 (18-C).

Characteristic 2D-NOESY correlations: 8a-CH/10-CH, 8a-CH/14-CH, 8-CH/7-CH''eq.

^{19}F NMR (282 MHz, $CDCl_3$) δ -81.69 (d, J = 75.5 Hz).

HRMS (ESI): m/z calcd. for $[C_{17}H_{21}F_2N_2O_4]^+$ 355.1464, found 355.1459 $[M+H]^+$.

***Rel*-(4*S*,4a*R*)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-2,2-dimethylhexahydro-7H-imidazo[1,5-b][1,2]oxazin-7-one (2b)**



To a solution of azide **22b** (0.152 g, 0.398 mmol) in methanol (2 ml) in a vial equipped with a magnetic stirrer was added a suspension of Raney® nickel (ca. 100 mg, washed with methanol) in methanol (0.5 ml). The vial was placed to a steel autoclave which was flushed and filled with H_2 to a pressure of 10 bar. The mixture was stirred at r.t. for 1 h, then the autoclave was evacuated and Raney® nickel (ca. 50 mg) was added. The autoclave was filled with H_2 (10 bar) and the mixture was stirred for 40 min. Then the autoclave was slowly evacuated and the catalyst was removed. The solvent was then evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (2.8 ml) and the resulting solution was cooled to 0°C. A solution of triphosgene (0.059 mg, 0.199 mmol) in CH_2Cl_2 (1 ml) and triethylamine (0.170 ml, 1.20 mmol) were added, and the reaction mixture was stirred at r.t. under argon for 2 h. 10% aqueous solution of HCl (10 ml) was added, and the reaction mixture was poured into a mixture of CH_2Cl_2 (50 ml) and water (50 ml). The aqueous layer was back-extracted with CH_2Cl_2 (2 × 30 ml). The combined organic layers were washed with water (2 × 50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:1 → 0:1) to yield 0.078 g (51%) of **2b**. White solid, m.p. = 163–165°C. R_f = 0.71 (EtOAc/MeOH = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 8.7 Hz, 1H, 15-CH), 6.78 (dd, J = 8.7, 2.0 Hz, 1H, 16-CH), 6.77 (d, J = 2.0 Hz, 1H, 12-CH), 6.61 (t, J = 75.5 Hz, 1H, 17-CHF_2), 4.62 (s, 1H, 2-NH), 3.88 (d, J = 6.9 Hz, 2H, 18-CH_2), 3.67 (ddd, J = 10.9, 7.3, 6.2 Hz, 1H, 8a-CH), 3.30 (dd, J = 9.3, 7.3 Hz, 1H, 1-CH), 3.06 (dd, J = 9.3, 6.2 Hz, 1H, 1-CH), 3.03 (dd, J = 10.9, 6.2 Hz, 1H, 8-CH), 1.86 – 1.80 (m, 2H, 7-CH_2), 1.48 (s, 3H, 9-CH_3 or 10-CH_3), 1.38 (s, 3H, 9-CH_3 or 10-CH_3), 1.31 – 1.23 (m, 1H, 19-CH), 0.69 – 0.63 (m, 2H, 20-CH_2), 0.41 – 0.32 (m, 2H, 20-CH_2).

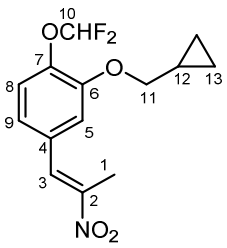
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.13 (3-C), 151.09 (13-C), 139.88 (11-C), 138.90 (14-C), 123.34 (15-C), 120.18 (16-C), 116.25 (t, J = 260.0 Hz, 17-C), 113.93 (12-C), 79.81 (6-C), 74.30 (18-C), 60.32 (8a-C), 42.98 (7-C), 41.25 (1-C), 40.96 (8-C), 28.51 and 23.00 (9-C and 10-C), 10.34 (19-C), 3.36 (20-C).

Characteristic trans-diaxial J constant: J = 10.9 Hz (8-CH/8a-CH)

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.48 (d, J = 75.7 Hz).

HRMS (ESI): m/z calcd. for $[C_{19}H_{25}F_2N_2O_4]^+$ 383.1777, found 383.1775 $[M+H]^+$.

2-(cyclopropylmethoxy)-1-(difluoromethoxy)-4-(2-nitroprop-1-en-1-yl)benzene (4a)



To a solution of 3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzaldehyde **6a** (0.811 g, 3.35 mmol) in nitroethane (6.7 ml) ammonium acetate (0.258 g, 3.35 mmol) and AcOH (3 ml) were added. The reaction mixture was intensively stirred at 90°C under argon atmosphere for 9 h and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:0 → 20:1) to yield 0.542 g (54%) of nitroalkene **4a**. Yellow oil. R_f = 0.58 (Hexane/EtOAc = 3:1).

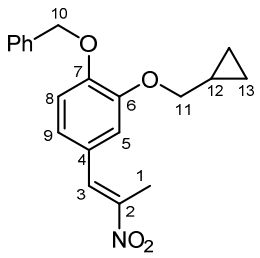
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H, 3-CH), 7.20 (d, J = 7.9 Hz, 1H, 8-CH), 7.00 (d, J = 7.9 Hz, 1H, 9-CH), 6.99 (s, 1H, 5-CH), 6.68 (t, J = 75.1 Hz, 1H, 10-CHF_2), 3.89 (d, J = 6.9 Hz, 2H, 11-CH_2), 2.42 (s, 3H, 2-CH_3), 1.38 – 1.18 (m, 1H, 12-CH), 0.65 (m, 2H, 13-CH_2), 0.36 (m, 2H, 13-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.66 (7-C), 148.01 (2-C), 141.54 (6-C), 132.60 (3-C), 130.85 (4-C), 122.90 (8-C), 122.67 (9-C), 116.07 (5-C), 115.98 (t, J = 260.5 Hz, 10-C), 74.17 (11-C), 14.00 (1-C), 10.11 (12-C), 3.25 (13-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.59 (d, J = 74.9 Hz).

HRMS (ESI): m/z calcd. for $[C_{14}H_{16}F_2NO_4]^+$ 300.1042, found 300.1048 $[M+H]^+$.

1-(benzyloxy)-2-(cyclopropylmethoxy)-4-(2-nitroprop-1-en-1-yl)benzene (4b)



To a solution of 4-(benzyloxy)-3-(cyclopropylmethoxy)benzaldehyde **6b** (0.416 g, 1.47 mmol) in nitroethane (2.5 ml) ammonium acetate (0.120 g, 1.48 mmol) and AcOH (1.3 ml) were added. The reaction mixture was intensively stirred at 90°C under argon atmosphere for 10 h and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:0 → 10:1) to yield 0.387 g (77%) of nitroalkene **4b**. Yellow solid, m.p. = 74–75°C (recrystallized from ethanol). R_f = 0.58 (Hexane/EtOAc = 3:1).

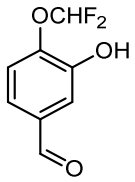
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H, 3-CH), 7.51 – 7.29 (m, 5H, Ph), 7.37 (d, J = 8.2 Hz, 1H, 8-CH), 7.01 (s, 1H, 5-CH), 6.95 (d, J = 8.2 Hz, 1H, 9-CH), 5.22 (s, 2H, 10-CH_2), 3.91 (d, J = 6.9 Hz, 2H, 11-CH_2), 2.46 (s, 3H, 2-CH_3), 1.41 – 1.21 (m, 1H, 12-CH), 0.65 (m, 2H, 13-CH_2), 0.37 (m, 2H, 13-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.80, 149.34 and 146.09 (2-C, 6-C and 7-C), 136.81 (i-Ph), 133.87 (3-C), 128.72 (m-Ph), 128.12 (9-C), 127.24 (o-Ph), 125.63 (4-C), 124.41 (p-Ph), 116.83 (8-C), 114.62 (5-C), 74.59 (11-C), 71.15 (10-C), 14.30 (1-C), 10.48 (12-C), 3.47 (13-C).

HRMS (ESI): m/z calcd. for $[C_{20}H_{21}NO_4]^+$ 340.1543, found 340.1544 $[M+H]^+$.

Elemental analysis: calcd. C, 70.78; H, 6.24; N, 4.13; found C, 71.01; H, 6.23; N, 4.16.

4-(difluoromethoxy)-3-hydroxybenzaldehyde (5a)



Preparation procedure from ethyl 2-bromo-2,2-difluoroacetate

To a stirred solution of 3,4-dihydroxybenzaldehyde **3** (5.0 g, 36.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (4.78 ml, 36.2 mmol) in DMF (50 ml) and water (1 ml) mixture was added NaOH (2.9 g, 72.4 mmol). The reaction mixture was intensively stirred at 70°C for 2 h and then the resulting solution was poured into a mixture of EtOAc (50 ml) and 10% solution of HCl (50 ml). The aqueous layer was back-extracted with EtOAc (2 × 30 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 10:1 → 5:1) to yield 3.43 g (50%) of 4-(difluoromethoxy)-3-hydroxybenzaldehyde **5a**. White solid. R_f = 0.24 (Hexane/EtOAc = 3:1).

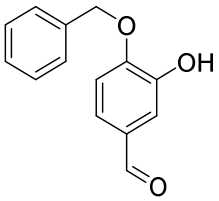
Preparation procedure from potassium 2-bromo-2,2-difluoroacetate

To a stirred solution of 3,4-dihydroxybenzaldehyde **3** (0.500 g, 3.62 mmol) and potassium 2-bromo-2,2-difluoroacetate (0.772 g, 3.62 mmol) in DMF (5 ml) and water (0.1 ml) mixture was added NaOH (0.145 g, 3.62 mmol). The reaction mixture was intensively stirred at 70°C for 2 h and then the resulting solution was poured into a mixture of Et_2O (20 ml) and 10% solution of HCl (20 ml). The aqueous layer was back-extracted with Et_2O (20 ml). The combined organic layers were washed with water (20 ml) and brine (20 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 10:1 → 5:1) to yield 0.360 g (53%) of 4-(difluoromethoxy)-3-hydroxybenzaldehyde **5a**. White solid. R_f = 0.24 (Hexane/EtOAc = 3:1).

^{1}H NMR spectrum is concordant with the one reported in literature.[6]

[6] S. J. Williams, S. C. Zammit, A. J. Cox, D. M. Shackleford, J. Morizzi, Y. Zhang, A. K. Powell, R. E. Gilbert, H. Krum and D. J. Kelly, *Bioorganic & Medicinal Chemistry Letters*, **2013**, *23*, 6868-6873.

4-(benzyloxy)-3-hydroxybenzaldehyde (5b)

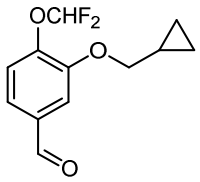


To a stirred solution of 3,4-dihydroxybenzaldehyde **3** (4.6 g, 33.3 mmol) in DMF (40 ml) were added K_2CO_3 (4.14 g, 30.0 mmol), KI (0.112 g, 0.675 mmol) and benzyl bromide (4.4 ml, 37.1 mmol). The reaction mixture was stirred at 60°C for 11.5 h under argon atmosphere. Then the resulting solution was poured into a mixture of EtOAc (150 ml) and water (150 ml). The aqueous layer was back-extracted with EtOAc (100 ml). The combined organic layers were washed with water (2 × 100 ml) and brine (100 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: EtOAc/Hexane = 40% → 50% → 70%) to yield 5.15 g (68%) of 4-(benzyloxy)-3-hydroxybenzaldehyde **6b**. For analytical purposes the product was recrystallized from hexane/CH_2Cl_2 = 1:1 mixture (4 ml). White solid. R_f = 0.43 (EtOAc/Hexane = 40%).

^{1}H NMR spectrum is concordant with the one reported in literature.[7]

[7] J. Jian, J. Fan, H. Yang, P. Lan, M. Li, P. Liu, H. Gao and P. Sun, *Journal of Natural Products*, **2018**, 81, 371-377.

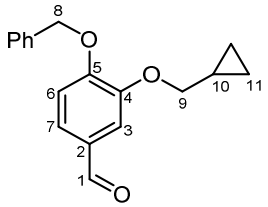
3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzaldehyde (6a)



To a stirred solution of 4-(difluoromethoxy)-3-hydroxybenzaldehyde **5a** (1.225 g, 6.52 mmol) in dry THF (18 ml) in Schlenk flask under argon atmosphere was added K_2CO_3 (1.785 g, 12.9 mmol) and the reaction mixture was cooled to 0°C. (Bromomethyl)cyclopropane (1.4 ml, 14.4 mmol) was added and the reaction mixture was gently refluxed under argon atmosphere for 5.5 h. Then (bromomethyl)cyclopropane (0.7 ml, 7.2 mmol) was added, the reaction mixture was refluxed for 5.5 h and then cooled to r.t. 2M solution of NaOH (70 ml) was added to the mixture and the resulting solution was poured to CH_2Cl_2 (70 ml). The aqueous layer was back-extracted with CH_2Cl_2 (3 × 35 ml). The combined organic layers were washed with brine (100 ml), dried over Na_2SO_4 and evaporated under vacuum to yield 1.413 g (90%) of **6a**. White solid. R_f = 0.63 (Hexane/EtOAc = 1:1).

^{1}H NMR spectrum is concordant with the one reported in literature.[8]

4-(benzyloxy)-3-(cyclopropylmethoxy)benzaldehyde (6b)



To a stirred solution of 4-(benzyloxy)-3-hydroxybenzaldehyde **5b** (5 g, 21.91 mmol) in DMF (40 ml) were added K_2CO_3 (6.06 g, 43.81 mmol) and (bromomethyl)cyclopropane (4.25 ml, 43.81 mmol). The reaction mixture was stirred at 90°C for 2.5 h under argon atmosphere and then cooled to r.t. MTBE (100 ml) was added and the resulting mixture was poured into a saturated solution of $NaHCO_3$ (100 ml). The organic layer were washed with water (100 ml) and brine (100 ml), dried over Na_2SO_4 and evaporated under vacuum to yield 6.126 g (99%) of 4-(benzyloxy)-3-(cyclopropylmethoxy)benzaldehyde **6b**. White solid, m.p. = 48.5–50.0°C. R_f = 0.60 (Hexane/EtOAc = 1:1).

^{1}H NMR (300 MHz, CDCl3) δ 9.82 (s, 1H, 1-CHO), 7.38 (s, 1H, 3-CH), 7.53 – 7.20 (m, 5H, Ph), 7.37 (d, J = 7.8 Hz, 1H, 6-CH), 6.99 (d, J = 7.8 Hz, 1H, 7-CH), 5.26 (s, 2H, 8-CH_2), 3.94 (d, J = 6.9 Hz, 2H, 9-CH_2), 1.43 – 1.24 (m, 1H, 10-CH), 0.65 (m, 2H, 11-CH_2), 0.38 (m, 2H, 11-CH_2).

^{13}C NMR (75 MHz, CDCl3) δ 190.99 (1-C), 154.24 and 149.76 (4-C and 5-C), 136.49 (i-Ph), 130.52 (2-C), 128.73 (m-Ph), 128.14 (7-C), 127.12 (o-Ph), 126.51 (p-Ph), 113.38 (6-C), 111.98 (3-C), 74.10 (9-C), 71.01 (8-C), 10.31 (10-C), 3.46 (11-C).

HRMS (ESI): m/z calcd. for $[C_{18}H_{19}O_3]^+$ 283.1329, found 283.1319 $[M+H]^+$.

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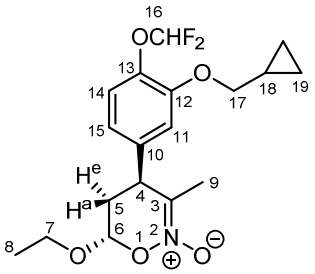
[8] Y. Lin, P. Huang, S. Liu, L. Sima, L. Chen and D. Wang, *Research on Chemical Intermediates*, **2013**, *39*, 2107-2113.

4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-6-ethoxy-3-methyl-5,6-dihydro-4H-1,2-oxazine 2-oxide (7a)



A solution of nitroalkene **4a** (0.574 g, 1.92 mmol) in dry CH_2Cl_2 (12 ml) with CaH_2 (ca. 0.05 g) was cooled to −94°C (acetone/liquid nitrogen) in a Schlenk flask under argon atmosphere. $SnCl_4$ (0.247 ml, 2.11 mmol) was added with intensive stirring. In 10 min a solution of ethyl vinyl ether (0.734 ml, 7.68 mmol) in dry CH_2Cl_2 (8 ml) was added dropwise. The reaction mixture was intensively stirred at −94°C for 20 min, then the resulting yellow-colored solution was poured into a mixture of EtOAc (200 ml) and saturated aqueous solution of K_2CO_3 (200 ml). The aqueous layer was back-extracted with EtOAc (2 × 100 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 10:1 → 5:1 → 1:1) to yield 0.299 g (42%) of nitronate. The fraction with initial nitroalkene was collected and recycled nitroalkene was subjected to the same procedure two more times to yield 0.168 g of nitronate **7a**. Overall yield of nitronate **7a** (after 3 cycles): 0.467 g (66%). White solid, m.p. = 114–116°C (recrystallized from Hexanes/Et_2O = 1:1). R_f = 0.20 (Hexane/EtOAc = 1:1).

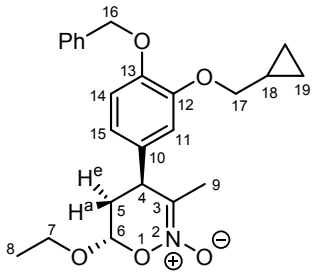
^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.12 (d, J = 8.2 Hz, 1H, 14-CH), 6.75 (d, J = 8.2 Hz, 1H, 15-CH), 6.71 (s, 1H, 11-CH), 6.61 (t, J = 75.4 Hz, 1H, 16-CHF_2), 5.36 (s, 1H, 6-CH), 4.05 (dq, J = 14.5, 7.0 Hz, 1H, 7-CH_2), 3.85 – 3.83 (m, 1H, 4-CH), 3.83 (d, J = 6.5 Hz, 2H, 17-CH_2), 3.71 (dq, J = 14.5, 7.0 Hz, 1H, 7-CH_2), 2.25 (dd, J = 13.3, 7.7 Hz, 1H, 5-CH_{eq}), 2.07 (t, J = 13.3 Hz, 1H, 5-CH_{ax}), 1.86 (s, 3H, 9-CH_3), 1.26 (t, J = 7.0 Hz, 3H, 8-CH_3), 1.26 (m, 1H, 18-CH), 0.64 (m, 2H, 19-CH_2), 0.35 (m, 2H, 19-CH_2).

^{13}C NMR (50 MHz, HSQC, $CDCl_3$) δ 151.31 (12-C), 139.83 (13-C), 138.89 (10-C), 123.40 (15-C), 122.84 (3-C), 120.81 (14-C), 116.16 (t, J = 260.5 Hz, 16-C), 113.56 (11-C), 101.02 (6-C), 74.17 (17-C), 65.18 (7-C), 40.59 (4-C), 34.49 (5-C), 17.67 (9-C), 15.13 (8-C), 10.18 (18-C), 3.31 (19-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -81.73 (d, J = 75.6 Hz).

HRMS (ESI): m/z calcd. for $[C_{18}H_{24}F_2NO_5]^+$ 372.1617, found 372.1629 $[M+H]^+$.

4-(4-(benzyloxy)-3-(cyclopropylmethoxy)phenyl)-6-ethoxy-3-methyl-5,6-dihydro-4H-1,2-oxazine 2-oxide (7b)



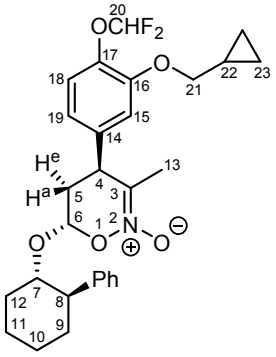
A solution of nitroalkene **4b** (0.350 g, 1.03 mmol) in dry CH_2Cl_2 (7 ml) with CaH_2 (0.05 g) was cooled to −94°C (acetone/liquid nitrogen) in a Schlenk flask under argon atmosphere. $SnCl_4$ (0.135 ml, 1.13 mmol) was added with intensive stirring. In 10 min a solution of ethyl vinyl ether (0.400 ml, 4.18 mmol) in dry CH_2Cl_2 (4 ml) was added dropwise. The reaction mixture was intensively stirred at −80°C for 50 min, then the resulting yellow-colored solution was poured into a mixture of EtOAc (50 ml) and saturated aqueous solution of K_2CO_3 (50 ml). The aqueous layer was back-extracted with EtOAc (2 × 30 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 10:1 → 5:1 → 1:1) to yield 0.382 g (93%) of nitronate **7b**. White solid, m.p. = 78–82°C (recrystallized from Hexanes/Et_2O = 1:1). R_f = 0.32 (Hexane/EtOAc = 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.27 (m, 5H, Ph), 6.85 (d, J = 7.6 Hz, 1H, 14-CH), 6.68 (s, 1H, 11-CH), 6.67 (d, J = 7.6 Hz, 1H, 15-CH), 5.34 (dd, br, J = 2.6, 1.7 Hz, 1H, 6-CH_{eq}), 5.12 (s, 2H, 16-CH_2), 4.04 (dq, J = 14.3, 7.1 Hz, 1H, 7-CH), 3.84 (d, J = 6.6 Hz, 2H, 17-CH_2), 3.81 – 3.63 (m, 2H, 4-CH and 7-CH), 2.22 (ddd, J = 13.8, 7.6, 1.7 Hz, 1H, 5-CH_{eq}), 2.08 (ddd, J = 13.8, 11.0, 2.6 Hz, 1H, 5-CH_{ax}), 1.84 (s, 3H, 9-CH_3), 1.26 (t, J = 7.1 Hz, 3H, 8-CH_3), 1.37 – 1.16 (m, 1H, 18-CH), 0.62 (m, 2H, 19-CH_2), 0.34 (m, 2H, 19-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.91 and 148.39 (12-C and 13-C), 137.25 (i-Ph), 133.23 (10-C), 128.45 (m-Ph), 127.78 (15-C), 127.21 (o-Ph), 123.52 (3-C), 120.80 (p-Ph), 115.49 (14-C), 113.97 (11-C), 100.97 (6-C), 74.30 (17-C), 71.39 (16-C), 64.95 (7-C), 40.18 (4-C), 34.30 (5-C), 17.48 (9-C), 15.03 (8-C), 10.36 (18-C), 3.27 (19-C).

HRMS (ESI): m/z calcd. for $[C_{24}H_{30}NO_5]^+$ 412.2118, found 412.2114 $[M+H]^+$.

(4S,6S)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-3-methyl-6-(((1S,2S)-2-phenylcyclohexyl)oxy)-5,6-dihydro-4H-1,2-oxazine 2-oxide (7c)



A mixture of nitroalkene **4a** (0.530 g, 1.77 mmol), (+)-(1R,2S)-*trans*-phenylcyclohexanol vinyl ether **8** (0.451 g, 2.22 mmol) and CaH_2 (ca. 0.1 g) in dry CH_2Cl_2 (40 ml) was cooled to −94°C (acetone/liquid nitrogen) in a Schlenk flask under argon atmosphere. $SnCl_4$ (0.210 ml, 1.77 mmol) was added with intensive stirring. The reaction mixture was intensively stirred at −94°C for 1 h, then the resulting dark red solution was poured into a mixture of EtOAc (200 ml) and saturated aqueous solution of K_2CO_3 (200 ml). The aqueous layer was back-extracted with EtOAc (2 × 100 ml). The combined organic layers were washed with saturated aqueous solution of K_2CO_3 (100 ml), water (100 ml) and brine (100 ml), dried over Na_2SO_4, filtered through Celite® and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 10:1 → 5:1 → 1:1) to yield 0.138 g (16%) of nitronate. The fraction with initial nitroalkene was collected and the recycled nitroalkene was subjected to the same procedure three more times to yield 0.168 g of nitronate **7a**. Overall yield of nitronate **7c** (after 4 cycles): 0.379 g (24%). Colorless oil. R_f = 0.38 (Hexane/EtOAc = 1:1).

^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.38 – 7.08 (m, 5H, Ph), 7.03 (d, J = 8.1 Hz, 1H, 18-CH), 6.57 (s, 1H, 15-CH), 6.56 (d, J = 8.1 Hz, 1H, 19-CH), 6.55 (t, J = 75.5 Hz, 1H, 20-CHF_2), 5.53 (s, 1H, 6-CH), 4.15 (ddd, J = 11.2, 11.2, 3.8 Hz, 1H, 7-CH_{ax}), 3.77 (d, J = 6.8 Hz, 2H, 21-CH_2), 3.15 (dd, J = 11.4, 7.5 Hz, 1H, 4-CH), 2.58 (ddd, J = 11.2, 11.2, 2.7 Hz, 1H, 8-CH_{ax}), 2.34 (dd, J = 11.6, 2.3 Hz, 1H, 12-CH), 2.05 – 1.92 (m, 2H, 5-CH_2), 1.92 – 1.84 (m, 3H, 9-CH_2 and 11-CH), 1.82 – 1.71 (m, 1H, 10-CH), 1.65 – 1.47 (m, 1H, 11-CH), 1.48 – 1.36 (m, 1H, 10-CH), 1.27 (s, 3H, 13-CH_3), 1.33 – 1.15 (m, 2H, 12-CH and 22-CH), 0.62 (m, 2H, 23-CH_2), 0.32 (m, 2H, 23-CH_2).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$) δ 151.08 (16-C), 144.23 (i-Ph), 139.52 (17-C), 138.78 (14-C), 128.31 and 127.60 (o-Ph and m-Ph), 126.14 (p-Ph), 123.12 (19-C), 122.31 (3-C), 120.84 (18-C), 116.12 (t, J = 259.9 Hz, 20-C), 113.47 (15-C), 95.01 (6-C), 76.27 (7-C), 74.07 (21-C), 50.98 (8-C), 39.84 (4-C), 34.14 (11-C), 33.99 (5-C), 30.12 (12-C), 26.10 (10-C), 24.51 (9-C), 17.22 (13-C), 10.12 (22-C), 3.22 (23-C).

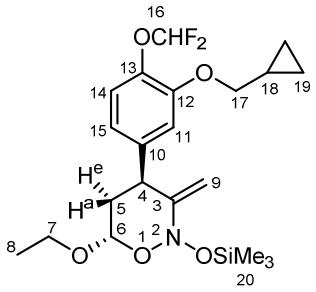
^{19}F NMR (282 MHz, $CDCl_3$) δ -82.50 (d, J = 75.4 Hz).

HRMS (ESI): m/z calcd. for $[C_{28}H_{34}F_2NO_5]^+$ 502.2400, found 502.2398 $[M+H]^+$.

Optical rotation: $[\alpha]^{20}_D$ = +206° ($CHCl_3$, C = 1 g/100 ml).

HPLC: e.e. = 96% (RT: 9.6 min; Column: CHIRALPAK IA-3; Solvent: Hexane/i-PrOH = 95:5; Temperature: 40°C; Flow rate: 1 ml/min).

4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-6-ethoxy-3-methylene-2-((trimethylsilyl)oxy)-1,2-oxazinane (9a)



To a solution of nitronate **7a** (0.106 g, 0.286 mmol) in dry CH_2Cl_2 (1.5 ml) in Schlenk flask triethylamine (0.060 ml, 0.429 mmol) was added with intensive stirring under argon atmosphere. The reaction mixture was cooled to −50°C and Me_3SiBr (0.053 ml, 0.400 mmol) was added. The mixture was intensively stirred for 30 min at −50°C and then kept for 20 h at −20°C without stirring. The resulting solution was poured into a mixture of hexane (100 ml) and 0.25M aqueous solution of $NaHSO_4$ (100 ml). The aqueous layer was back-extracted with hexane (2 × 30 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum to yield 0.125 g (99%) of enamine silyl ether **9a**. Colorless oil. The product was used on the next step without additional purification.

^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.08 (d, J = 7.6 Hz, 1H, 14-CH), 6.90 (d, J = 1.4 Hz, 1H, 11-CH), 6.86 (dd, J = 7.6, 1.4 Hz, 1H, 15-CH), 6.59 (t, J = 75.6 Hz, 1H, 16-CHF_2), 5.04 (dd, J = 5.4, 4.5 Hz, 1H, 6-CH), 4.96 (s, 1H, 9-CH), 4.10 (s, 1H, 9-CH), 4.04 – 3.88 (m, 2H, 4-CH and 7-CH), 3.84 (d, J = 6.9 Hz, 2H, 17-CH_2), 3.54 (dq, J = 14.5, 7.0 Hz, 1H, 7-CH), 2.20 (ddd, J = 13.2, 9.1, 4.5 Hz, 1H, 5-CH_{eq}), 2.08 (dt, J = 13.2, 5.4 Hz, 1H, 5-CH_{ax}), 1.23 (t, J = 7.0 Hz, 3H, 8-CH_3), 1.31 – 1.12 (m, 1H, 18-CH), 0.61 (m, 2H, 19-CH_2), 0.32 (m, 2H, 19-CH_2), 0.24 (s, 9H, 20-Si$(CH_3)_4$).

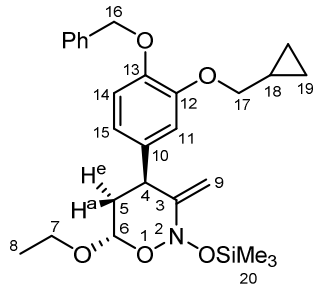
^{13}C NMR (75 MHz, HSQC, $CDCl_3$) δ 158.0 (br, 3-C), 150.40 (12-C), 139.79 and 139.41 (10-C and 13-C), 122.53 (15-C), 121.22 (14-C), 116.39 (t, J = 259.2 Hz, 16-C), 115.20 (11-C), 99.27 (6-C), 97.94 (9-C), 74.02 (17-C), 64.15 (7-C), 40.86 (4-C), 36.48 (5-C), 15.04 (8-C), 10.25 (18-C), 3.18 (19-C), -0.78 (20-C).

^{19}F NMR (188 MHz, $CDCl_3$) δ -81.32 (d, J = 75.7 Hz).

^{29}Si NMR (40 MHz, $CDCl_3$) δ 26.55 (s).

HRMS (ESI): m/z calcd. for $[C_{21}H_{32}F_2NO_5Si]^+$ 444.2012, found 444.2005 $[M+H]^+$.

4-(4-(benzyloxy)-3-(cyclopropylmethoxy)phenyl)-6-ethoxy-3-methylene-2-((trimethylsilyl)oxy)-1,2-oxazinane (9b)



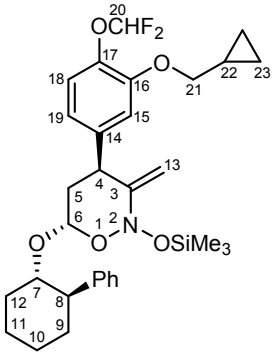
To a solution of nitronate **7b** (3.00 g, 0.286 mmol) in dry CH_2Cl_2 (28 ml) in Schlenk flask triethylamine (1.52 ml, 10.9 mmol) was added with intensive stirring under argon atmosphere. The reaction mixture was cooled to −50°C and Me_3SiBr (1.35 ml, 10.21 mmol) was added. The mixture was intensively stirred for 80 min at −50°C and then kept for 20 h at −20°C without stirring. The resulting solution was poured into a mixture of hexane (200 ml) and 0.25M aqueous solution of $NaHSO_4$ (200 ml). The aqueous layer was back-extracted with hexane (2 × 100 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried over Na_2SO_4 and evaporated under vacuum to yield 0.125 g (99%) of enamine silyl ether **9b**. Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.29 (m, 5H, Ph), 6.88 (s, 1H, 11-CH), 6.87 (d, J = 8.2 Hz, 1H, 14-CH), 6.79 (d, J = 8.2 Hz, 1H, 15-CH), 5.14 (s, 2H, 16-CH_2), 5.07 (t, J = 4.7 Hz, 1H, 6-CH_{eq}), 4.93 (s, br, 1H, 9-CH), 4.07 (s, br, 1H, 9-CH), 4.03 – 3.89 (m, 2H, 4-CH and 7-CH), 3.87 (d, J = 6.9 Hz, 2H, 17-CH_2), 3.57 (dq, J = 9.4, 7.0 Hz, 1H, 7-CH), 2.22 (ddd, J = 13.4, 9.6, 4.6 Hz, 1H, 5-CH_{eq}), 2.07 (dt, J = 13.4, 5.5 Hz, 1H, 5-CH_{ax}), 1.36 – 1.20 (m, 1H, 18-CH), 1.25 (t, J = 7.0 Hz, 3H, 8-CH_3), 0.61 (m, 2H, 19-CH_2), 0.34 (m, 2H, 19-CH_2), 0.25 (s, J = 3.2 Hz, 9H, 20-Si$(CH_3)_3$).

^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 149.44 and 148.08 (12-C and 13-C), 137.73 and 136.55 (i-Ph and 10-C), 128.55 (m-Ph), 127.83 (15-C), 127.43 (o-Ph), 121.41 (p-Ph), 115.98 (14-C), 115.51 (11-C), 99.41 (6-C), 83.31 (9-C), 74.52 (17-C), 71.71 (16-C), 64.22 (7-C), 40.65 (4-C), 36.75 (5-C), 15.15 (8-C), 10.65 (18-C), 3.36 (19-C), -0.65 (20-C) (9-CH_2 not observed).

HRMS (ESI): m/z calcd. for $[C_{27}H_{39}NO_5Si]$ 484.2514, found 484.2511 $[M+H]^+$.

(4S,6S)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-3-methylene-6-(((1S,2R)-2-phenylcyclohexyl)oxy)-2-((trimethylsilyl)oxy)-1,2-oxazinane (9c)



To a stirred solution of nitronate **7c** (0.362 g, 0.724 mmol) in dry CH_2Cl_2 (1.2 ml) in Schlenk flask triethylamine (0.120 ml, 0.870 mmol) was added under argon atmosphere. The reaction mixture was cooled to −78°C and Me_3SiBr (0.105 ml, 0.796 mmol) was added. The mixture was intensively stirred for 30 min at −78°C and then kept for 45 h at this temperature without stirring. The resulting solution was poured into a mixture of hexane (100 ml) and 0.25M aqueous solution of $NaHSO_4$ (100 ml). The aqueous layer was back-extracted with hexane (2 × 50 ml). The combined organic layers were washed with water (2 × 50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum to yield 0.409 g (99%) of enamine silyl ether **9c**. Yellow oil. The product was used on the next step without additional purification.

^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.39 – 7.14 (m, 5H, Ph), 7.07 (d, J = 7.6 Hz, 1H, 18-CH), 6.70 (s, 1H, 15-CH), 6.69 (d, J = 7.6 Hz, 1H, 19-CH), 6.60 (t, J = 75.7 Hz, 1H, 20-CHF_2), 5.38 (t, br, J = 4.4 Hz, 1H, 6-CH_{eq}), 4.77 (s, br, 1H, 13-CH), 4.06 (ddd, J = 10.6, 10.6, 3.5 Hz, 1H, 7-CH_{ax}), 3.86 (s, br, 1H, 13-CH), 3.82 (d, J = 7.0 Hz, 2H, 21-CH_2), 3.51 (s, br, 1H, 4-CH), 2.62 (ddd, J = 10.6, 10.6, 3.2 Hz, 1H, 8-CH_{ax}), 2.35 (d, J = 10.0 Hz, 1H, 12-CH), 2.06 (ddd, J = 10.5, 10.5, 2.5 Hz, 1H, 5-CH_{ax}), 2.00 – 1.67 (m, 5H, 5-CH_{eq}, 9-CH_2, 10-CH and 11-CH), 1.67 – 1.17 (m, 4H, 10-CH, 11-CH, 12-CH, 22-CH), 0.64 (m, 2H, 23-CH_2), 0.35 (m, 2H, 23-CH_2), 0.28 (s, 9H, 24-$Si(CH_3)_3$).

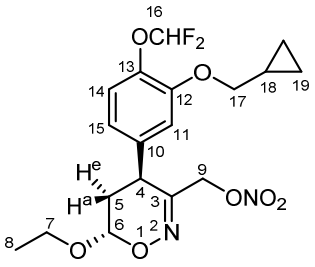
^{13}C NMR (75 MHz, HSQC, $CDCl_3$) δ 158.0 (br, 13-C), 150.35 (16-C), 144.33, 139.59 and 139.24 (i-Ph, 14-C and 17-C), 128.15 and 128.00 (o-Ph and m-Ph), 125.93 (p-Ph), 122.55 (19-C), 121.33 (18-C), 116.41 (t, J = 259.1 Hz, 20-C), 115.32 (15-C), 97.63 (13-C), 93.88 (6-C), 76.26 (7-C), 74.03 (21-C), 50.38 (8-C), 40.44 (4-C), 36.86 (11-C), 34.55 (5-C), 30.70 (12-C), 26.25 (10-C), 24.88 (9-C), 10.30 (22-C), 3.29 (23-C), -0.41 (24-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.32 (d, J = 75.7 Hz).

^{29}Si NMR (40 MHz, $CDCl_3$) δ 26.07 (s).

HRMS (ESI): m/z calcd. for $[C_{31}H_{42}F_2NO_5Si]$ 574.2795, found 574.2791 $[M+H]^+$.

4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-6-ethoxy-5,6-dihydro-4H-1,2-oxazin-3-yl)methyl nitrate (10a)



To a stirred solution of enamine silyl ether **9a** (0.469 g, 1.06 mmol) in CH_2Cl_2 (2 ml) was added a solution of chromium (III) nitrate nonahydrate (0.849 g, 2.12 mmol) in THF (10 ml). The reaction mixture was intensively stirred at r.t. for 2 h, then poured into a mixture of EtOAc (50 ml) and 0.25M aqueous solution of $NaHSO_4$ (50 ml). The aqueous layer was back-extracted with EtOAc (3 × 30 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:0 → 20:1 → 10:1 → 5:1 → 3:1) to yield 0.193 g (44 %) of nitrate **10a**. White solid, m.p. = 62–64°C. R_f = 0.66 (Hexane/EtOAc = 1:1).

^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.14 (d, J = 7.7 Hz, 1H, 14-CH), 6.79 (s, 1H, 11-CH), 6.78 (d, J = 7.7 Hz, 1H, 15-CH), 6.61 (t, J = 75.4 Hz, 1H, 16-CHF_2), 5.19 (t, J = 1.7 Hz, 1H, 6-CH_{eq}), 4.83 (d, J = 13.0 Hz, 1H, 9-CH), 4.73 (d, J = 13.0 Hz, 1H, 9-CH), 4.16 – 3.74 (m, 1H, 7-CH), 3.85 (d, J = 7.1 Hz, 2H, 17-CH), 3.76 – 3.47 (m, 2H, 4-CH and 7-CH), 2.29 (ddd, J = 13.0, 7.9, 1.7 Hz, 1H, 5-CH_{eq}), 2.08 (ddd, J = 13.0, 13.0, 1.2 Hz, 1H, 5-CH_{ax}), 1.26 – 1.24 (m, 1H, 18-CH), 1.23 (t, J = 7.1 Hz, 3H, 8-CH_3), 0.65 (m, 2H, 19-CH_2), 0.36 (m, 2H, 19-CH_2).

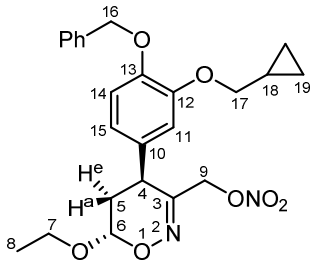
^{13}C NMR (75 MHz, HSQC, $CDCl_3$) δ 153.76 (3-C), 151.43 (12-C), 137.13 (10-C), 123.61 (15-C), 120.93 (14-C), 116.24 (t, J = 260.2 Hz, 16-C), 114.65 (11-C), 96.10 (6-C), 74.29 (17-C), 71.52 (9-C), 64.20 (7-C), 34.89 (4-C), 32.57 (5-C), 15.05 (8-C), 10.25 (18-C), 3.30 (19-C) (13-C not observed).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.52 (d, J = 75.3 Hz).

FT-IR (KBr, cm^{-1}, characteristic O-NO_2 bands): 1632, 1286, 847, 758.

HRMS (ESI): m/z calcd. for $[C_{18}H_{23}F_2N_2O_7]^+$ 417.1468, found 417.1461 $[M+H]^+$.

(4-(4-(benzyloxy)-3-(cyclopropylmethoxy)phenyl)-6-ethoxy-5,6-dihydro-4H-1,2-oxazin-3-yl)methyl nitrate (10b)



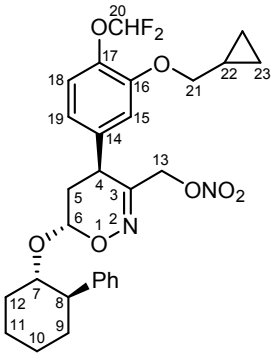
The crude enamine silyl ether **9b** was dissolved in CH_2Cl_2 (14 ml) was added a solution of chromium (III) nitrate nonahydrate (5.63 g, 14.06 mmol) in THF (28 ml). The reaction mixture was intensively stirred at r.t. for 2.5 h, then poured into a mixture of EtOAc (100 ml) and 0.25M aqueous solution of $NaHSO_4$ (100 ml). The aqueous layer was back-extracted with EtOAc (2 × 100 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 5:1) to yield 1.72 g (53 %) of nitrate **10b**. Yellow oil. R_f = 0.74 (Hexane/EtOAc = 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.27 (m, 5H, Ph), 6.88 (d, J = 9.3 Hz, 1H, 15-CH), 6.73 (s, 1H, 11-CH), 6.71 (d, J = 9.3 Hz, 1H, 14-CH), 5.19 (s, 1H, 6-CH_{eq}), 5.14 (s, 2H, 16-CH_2), 4.79 (d, J = 13.0 Hz, 1H, 9-CH), 4.72 (d, J = 13.0 Hz, 1H, 9-CH), 3.96 – 3.81 (m, 1H, 7-CH), 3.86 (d, J = 6.8 Hz, 2H, 17-CH_2), 3.70 – 3.54 (m, 2H, 4-CH and 7-CH), 2.27 (ddd, J = 13.1, 7.7, 2.2 Hz, 1H, 5-CH_{eq}), 2.09 (td, J = 13.1, 1.5 Hz, 1H, 5-CH_{ax}), 1.37 – 1.27 (m, 1H, 18-CH), 1.23 (t, J = 7.0 Hz, 3H, 8-CH_3), 0.64 (m, 2H, 19-CH_2), 0.36 (m, 2H, 19-CH_2).

^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 154.35 (3-C), 150.14 and 148.68 (12-C and 13-C), 137.31 and 131.42 (i-Ph and 10-C), 128.61 (m-Ph), 127.96 (15-C), 127.37 (o-Ph), 121.09 (p-Ph), 115.94 (14-C), 114.55 (11-C), 96.24 (6-C), 74.42 (17-C), 71.55 (9-C and 16-C), 64.12 (7-C), 34.49 (4-C), 32.37 (5-C), 15.10 (8-C), 10.49 (18-C), 3.42 (19-C).

HRMS (ESI): m/z calcd. for $[C_{24}H_{29}N_2O_7]^+$ 457.1969, found 457.1962 $[M+H]^+$.

((4S,6S)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-6-(((1S,2R)-2-phenylcyclohexyl)oxy)-5,6-dihydro-4H-1,2-oxazin-3-yl)methyl nitrate (10c)



To a stirred solution of enamine silyl ether **9c** (0.409 g, 0.715 mmol) in CH_2Cl_2 (1.5 ml) was added a solution of chromium (III) nitrate nonahydrate (0.573 g, 1.430 mmol) in THF (7 ml). The reaction mixture was intensively stirred at r.t. for 2 h, then poured into a mixture of EtOAc (80 ml) and 0.25M aqueous solution of $NaHSO_4$ (80 ml). The aqueous layer was back-extracted with EtOAc (2 × 50 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 20:1 → 10:1 → 5:1) to yield 0.168 g (43 %) of nitrate **10c**. Yellow oil. R_f = 0.73 (Hexane/EtOAc = 1:1). Mixture of diastereomers (ratio 4,6-*trans*/4,6-*cis* = 4.5 : 1).

Major isomer (4,6-*trans*):

^{1}H NMR (300 MHz, COSY, $CDCl_3$) δ 7.41 – 7.11 (m, 5H, Ph), 7.08 (d, J = 6.5 Hz, 1H, 18-CH), 6.60 (s, 1H, 15-CH), 6.60 (d, J = 6.5 Hz, 1H, 19-CH), 6.59 (t, J = 75.4 Hz, 1H, 20-CHF_2), 5.39 (s, 1H, 6-CH_{eq}), 4.33 (d, J = 13.3 Hz, 1H, 13-CH), 4.20 (d, J = 13.3 Hz, 1H, 13-CH), 3.96 (ddd, J = 11.2, 11.2, 3.9 Hz, 1H, 7-CH_{ax}), 3.81 (d, J = 6.9 Hz, 2H, 21-CH_2), 2.94 (dd, J = 12.5, 7.3 Hz, 1H, 4-CH_{ax}), 2.58 (ddd, J = 11.2, 11.2, 3.3 Hz, 1H, 8-CH_{ax}), 2.42 (ddd, J = 26.5, 13.1, 2.9 Hz, 1H, 12-CH), 2.21 – 1.71 (m, 6H, 5-CH_2, 9-CH_2, 10-CH and 11-CH), 1.67 – 1.19 (m, 4H, 10-CH, 11-CH, 12-CH and 22-CH), 0.66 (m, 2H, 23-CH_2), 0.36 (m, 2H, 23-CH_2).

^{13}C NMR (50 MHz, $CDCl_3$) δ 152.42 (3-C), 151.04 (16-C), 144.55 (i-Ph), 139.86 (t, J = 3.7 Hz, 17-C) 136.71 (14-C), 128.16 and 127.98 (o-Ph and m-Ph), 125.97 (p-Ph), 123.24 (19-C), 121.02 (18-C), 116.16 (t, J = 260.0 Hz, 20-C), 114.00 (15-C), 90.90 (6-C), 76.45 (7-C), 74.01 (21-C), 70.64 (13-C), 50.93 (8-C), 34.54 (4-C), 34.08 (11-C), 34.02 (5-C), 30.56 (12-C), 26.15 (10-C), 24.69 (9-C), 10.13 (22-C), 3.29 (23-C).

^{14}N NMR (22 MHz, $CDCl_3$) δ -45.55.

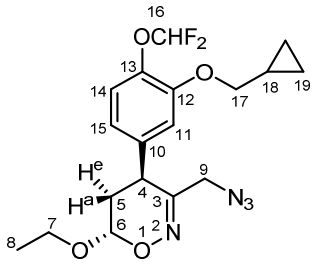
^{19}F NMR (188 MHz, $CDCl_3$) δ -81.49 (d, J = 75.4 Hz).

HRMS (ESI): m/z calcd. for $[C_{28}H_{33}F_2N_2O_7]^+$ 547.2250, found 547.2245 $[M+H]^+$.

Minor isomer (4,6-*cis*):

^{1}H NMR (300 MHz, characteristic signals, COSY, $CDCl_3$) δ 6.64 (t, J = 75.4 Hz, 1H, 20-CHF_2), 4.86 (d, J = 13.0 Hz, 1H, 13-CH), 4.71 (d, J = 13.0 Hz, 1H, 13-CH), 3.87 (d, J = 7.0 Hz, 2H, 21-CH_2), 3.25 (dd, J = 9.1, 6.1 Hz, 1H, 4-CH).

3-(azidomethyl)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-6-ethoxy-5,6-dihydro-4H-1,2-oxazine (11a)



To a stirred solution of nitrate **10a** (0.193 g, 0.465 mmol) in DMF (5 ml) was added sodium azide (151 mg, 2.33 mmol). The mixture was intensively stirred at 60°C for 5 h, then poured into a mixture of Et_2O (50 ml) and water (50 ml). The aqueous layer was back-extracted with Et_2O (2 × 30 ml). The combined organic layers were washed with brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 20:1 → 10:1 → 5:1) to yield 0.178 g (97%) of azide **11a**. Yellow oil. R_f = 0.69 (Hexane/EtOAc = 1:1).

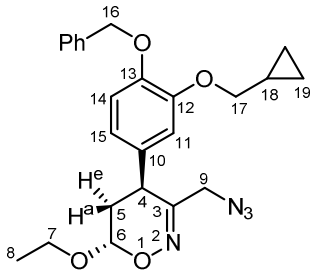
^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.14 (d, J = 7.4 Hz, 1H, 14-CH), 6.77 (d, J = 7.4 Hz, 1H, 15-CH), 6.77 (s, 1H, 11-CH), 6.61 (t, J = 75.4 Hz, 1H, 16-CHF_2), 5.18 (dd, J = 2.5, 1.9 Hz, 1H, 6-CH_{eq}), 3.93 – 3.85 (m, 1H, 7-CH), 3.84 (d, J = 6.6 Hz, 2H, 17-CH_2), 3.83 (d, J = 13.6 Hz, 1H, 9-CH), 3.74 (dd, J = 12.1, 7.8 Hz, 1H, 4-CH), 3.64 (dq, J = 14.1, 7.0 Hz, 1H, 7-CH), 3.44 (d, J = 13.6 Hz, 1H, 9-CH), 2.30 (ddd, J = 13.4, 7.8, 1.9 Hz, 1H, 5-CH_{eq}), 2.10 (ddd, J = 13.4, 12.1, 2.5 Hz, 1H, 5-CH_{ax}), 1.39 – 1.06 (m, 1H, 18-CH), 1.24 (t, J = 7.0 Hz, 3H, 8-CH_3), 0.64 (m, 2H, 19-CH_2), 0.35 (m, 2H, 19-CH_2).

^{13}C NMR (50 MHz, HSQC, $CDCl_3$) δ 156.62 (3-C), 151.23 (12-C), 137.72 and 136.80 (10-C and 13-C), 123.54 (15-C), 120.88 (14-C), 116.23 (t, J = 255.6 Hz, 16-C), 114.26 (11-C), 95.86 (6-C), 74.09 (17-C), 64.06 (7-C), 52.61 (9-C), 34.69 (4-C), 32.79 (5-C), 15.08 (8-C), 10.18 (18-C), 3.32 (19-C).

^{19}F NMR (188 MHz, $CDCl_3$) δ -81.50 (d, J = 75.3 Hz).

HRMS (ESI): m/z calcd. for $[C_{18}H_{23}F_2N_4O_4]^+$ 397.1682, found 397.1673 $[M+H]^+$.

3-(azidomethyl)-4-(4-(benzyloxy)-3-(cyclopropylmethoxy)phenyl)-6-ethoxy-5,6-dihydro-4H-1,2-oxazine (11b)



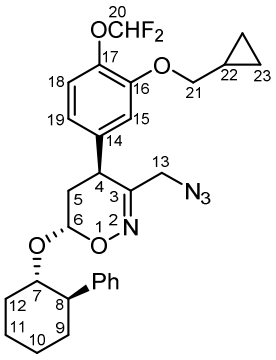
To a stirred solution of nitrate **10b** (1.69 g, 3.70 mmol) in DMF (40 ml) was added sodium azide (1.20 g, 18.51 mmol). The mixture was intensively stirred at 60°C for 6 h, then poured into a mixture of MTBE (200 ml) and water (200 ml). The aqueous layer was back-extracted with MTBE (2 × 100 ml). The combined organic layers were washed with brine (200 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 5:1) to yield 1.538 g (95%) of azide **11b**. Yellow oil. R_f = 0.69 (Hexane/EtOAc = 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.27 (m, 5H, Ph), 6.88 (d, J = 8.4 Hz, 1H, 15-CH), 6.73 (s, 1H, 11-CH), 6.71 (d, J = 8.4 Hz, 1H, 14-CH), 5.17 (t, J = 2.0 Hz, 1H, 6-CH_{eq}), 5.14 (s, 2H, 16-CH_2), 3.97 – 3.80 (m, 1H, 7-CH), 3.86 (d, J = 6.8 Hz, 2H, 17-CH_2), 3.80 (d, J = 13.4 Hz, 1H, 9-CH), 3.74 – 3.56 (m, 2H, 4-CH and 7-CH), 3.45 (d, J = 13.4 Hz, 1H, 9-CH), 2.29 (ddd, J = 13.5, 7.8, 2.1 Hz, 1H, 5-CH_{eq}), 2.11 (td, J = 13.5, 2.6 Hz, 1H, 5-CH_{ax}), 1.37 – 1.17 (m, 1H, 18-CH), 1.25 (t, J = 7.1 Hz, 3H, 8-CH_3), 0.63 (m, 2H, 19-CH_2), 0.35 (m, 2H, 19-CH_2).

^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 157.22 (3-C), 150.06 and 148.59 (12-C and 13-C), 137.42 and 132.21 (i-Ph and 10-C), 128.59 (m-Ph), 127.92 (15-C), 127.37 (o-Ph), 121.19 (p-Ph), 115.94 (14-C), 114.72 (11-C), 96.05 (6-C), 74.41 (17-C), 71.59 (16-C), 63.98 (9-C), 52.61 (7-C), 34.51 (4-C), 32.84 (5-C), 15.10 (8-C), 10.52 (18-C), 3.39 (19-C).

HRMS (ESI): m/z calcd. for $[C_{24}H_{29}N_4O_4]^+$ 437.2183, found 437.2178 $[M+H]^+$.

(4S,6S)-3-(azidomethyl)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-6-(((1S,2R)-2-phenylcyclohexyl)oxy)-5,6-dihydro-4H-1,2-oxazine (11c)



To a stirred solution of nitrate **10c** (0.103 g, 0.189 mmol, 4.5 : 1 mixture of isomers) in DMF (3 ml) was added sodium azide (0.061 g, 0.945 mmol). The solution was intensively stirred at 60°C for 5.5 h, then poured into a mixture of Et_2O (75 ml) and water (75 ml). The aqueous layer was back-extracted with Et_2O (3 × 30 ml). The combined organic layers were washed with brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 10:1 → 5:1) to yield 0.090 g (91%) of azide **11c**. Colorless oil. R_f = 0.71 (Hexane/EtOAc = 1:1).

^{1}H NMR (300 MHz, COSY, $CDCl_3$) δ 7.40 – 7.11 (m, 5H, Ph), 7.07 (d, J = 8.5 Hz, 1H, 18-CH), 6.58 (t, J = 75.5 Hz, 1H, 20-CHF_2), 6.57 (d, J = 8.5 Hz, 1H, 19-CH), 6.56 (s, 1H, 15-CH), 5.39 (s, 1H, 6-CH), 3.93 (td, J = 10.5, 4.0 Hz, 1H, 7-CH_{ax}), 3.81 (d, J = 6.9 Hz, 2H, 21-CH), 3.23 (d, J = 14.7 Hz, 1H, 13-CH), 3.14 (d, J = 14.7 Hz, 1H, 13-CH), 2.87 (dd, J = 12.3, 7.4 Hz, 1H, 4-CH_{ax}), 2.58 (td, J = 12.5, 3.4 Hz, 1H, 8-CH_{ax}), 2.46 – 2.32 (m, 1H, 12-CH), 2.08 – 1.72 (m, 6H, 5-CH_2, 9-CH_2, 10-CH and 11-CH), 1.67 – 1.17 (m, 4H, 10-CH, 11-CH, 12-CH and 22-CH), 0.65 (m, 2H, 23-CH_2), 0.35 (m, 2H, 23-CH_2).

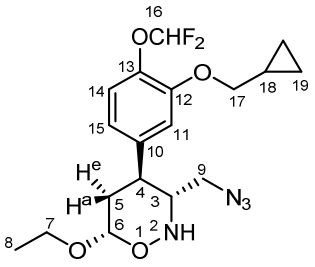
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.21 (3-C), 151.03 (16-C), 144.68 (i-Ph), 139.83 (t, J = 3.3 Hz, 17-C), 137.39 (14-C), 128.17 and 128.05 (o-Ph and m-Ph), 125.94 (p-Ph), 123.21 (19-C), 121.19 (18-C), 116.21 (t, J = 259.0 Hz, 20-C), 114.19 (15-C), 90.62 (6-C), 76.34 (7-C), 74.08 (21-C), 51.61 (13-C), 50.93 (8-C), 34.63 (4-C), 33.96 (11-C), 32.36 (5-C), 30.55 (12-C), 26.22 (10-C), 24.72 (9-C), 10.21 (22-C), 3.31 (23-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.46 (d, J = 75.2 Hz).

FT-IR (KBr, cm^{-1}, characteristic CH_2-N_3 bands): 2103 (asymmetric), 1272 (symmetric).

HRMS (ESI): m/z calcd. for $[C_{28}H_{33}F_2N_4O_4]^+$ 527.2464, found 527.2463 $[M+H]^+$.

3-(azidomethyl)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-6-ethoxy-1,2-oxazinane (12a)



To a stirred solution of azide **11a** (0.170 g, 0.429 mmol) in AcOH (6.25 ml) was added $NaBH_3CN$ (0.244 g, 3.86 mmol). The reaction mixture was intensively stirred at r.t. for 2 h, then poured into a mixture of EtOAc (50 ml) and saturated aqueous solution of K_2CO_3 (50 ml). The aqueous layer was back-extracted with EtOAc (2 × 20 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 10:1 → 5:1 → 3:1) to yield 0.162 g (95%) of azide **12a**. Colorless oil. R_f = 0.53 (Hexane/EtOAc = 1:1).

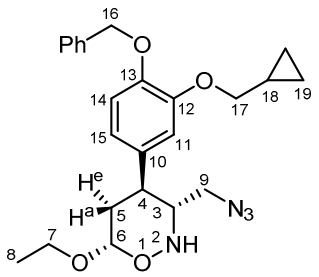
^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.11 (d, J = 8.1 Hz, 1H, 14-CH), 6.78 (s, 1H, 11-CH), 6.75 (d, J = 8.1 Hz, 1H, 15-CH), 6.60 (t, J = 75.6 Hz, 1H, 16-CHF_2), 5.65 (s, 1H, 2-NH), 4.87 (s, 1H, 6-CH_{eq}), 3.85 (d, J = 6.9 Hz, 2H, 17-CH_2), 3.94 – 3.77 (m, 1H, 7-CH), 3.57 (dq, J = 14.3, 7.1 Hz, 1H, 7-CH), 3.37 – 3.22 (m, 2H, 3-CH and 9-CH), 3.13 (dd, J = 12.5, 4.5 Hz, 1H, 9-CH), 3.08 (ddd, J = 10.8, 10.8, 5.6 Hz, 1H, 4-CH_{ax}), 2.11 – 1.94 (m, 2H, 5-CH_2), 1.40 – 1.21 (m, 1H, 18-CH), 1.30 (t, J = 7.1 Hz, 3H, 8-CH_3), 0.64 (m, 2H, 19-CH_2), 0.34 (m, 2H, 19-CH_2).

^{13}C NMR (50 MHz, HSQC, $CDCl_3$) δ 151.02 (12-C), 140.27 (10-C), 123.30 (15-C), 119.87 (14-C), 116.25 (t, J = 259.9 Hz, 16-C), 114.27 (11-C), 97.87 (6-C), 74.16 (17-C), 63.83 (7-C), 61.37 (3-C), 51.15 (9-C), 37.92 (4-C), 36.51 (5-C), 15.28 (8-C), 10.30 (18-C), 3.26 (19-C) (13-C not observed).

^{19}F NMR (188 MHz, $CDCl_3$) δ -81.38 (d, J = 75.7 Hz).

HRMS (ESI): m/z calcd. for $[C_{18}H_{25}F_2N_4O_4]^+$ 399.1838, found 399.1836 $[M+H]^+$.

3-(azidomethyl)-4-(4-(benzyloxy)-3-(cyclopropylmethoxy)phenyl)-6-ethoxy-1,2-oxazinane (12b)



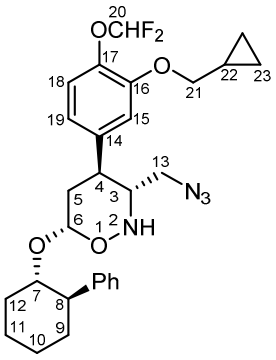
To a stirred solution of azide **11b** (1.493 g, 3.42 mmol) in AcOH (50 ml) was added $NaBH_3CN$ (1.94 g, 30.9 mmol). The reaction mixture was intensively stirred at r.t. for 3.5 h, then diluted with saturated aqueous solution of K_2CO_3 (100 ml) and EtOAc (50 ml). The solution was poured into a mixture of EtOAc (150 ml) and saturated aqueous solution of K_2CO_3 (200 ml). The aqueous layer was back-extracted with EtOAc (2 × 75 ml). The combined organic layers were washed with brine (200 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 3:1 → 1:1) to yield 1.33 g (89%) of azide **12b**. Colorless oil. R_f = 0.60 (Hexane/EtOAc = 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.27 (m, 5H, Ph), 6.87 (d, J = 8.2 Hz, 1H, 14-CH), 6.76 (d, J = 2.2 Hz, 1H, 11-CH), 6.69 (dd, J = 8.2, 2.2 Hz, 1H, 15-CH), 5.63 (s, 1H, 2-NH), 5.13 (s, 2H, 16-CH_2), 4.87 (d, J = 2.9 Hz, 1H, 6-CH_{eq}), 3.87 (d, J = 6.9 Hz, 2H, 17-CH_2), 3.85 – 3.77 (m, 1H, 7-CH), 3.57 (dq, J = 10.0, 7.1 Hz, 1H, 7-CH), 3.31 (dd, J = 12.4, 2.2 Hz, 1H, 9-CH), 3.27 – 3.19 (m, J = 6.4 Hz, 1H, 3-CH), 3.13 (dd, J = 12.4, 4.6 Hz, 1H, 9-CH), 3.01 (td, J = 11.3, 5.5 Hz, 1H, 4-CH_{ax}), 2.11 – 1.94 (m, 2H, 5-CH_2), 1.38 – 1.24 (m, 1H, 18-CH), 1.30 (t, J = 7.1 Hz, 3H, 8-CH_3), 0.63 (m, 2H, 19-CH_2), 0.35 (m, 2H, 19-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.79 and 148.17 (12-C and 13-C), 137.74 (i-Ph), 134.89 (10-C), 128.58 (m-Ph), 127.89 (15-C), 127.40 (o-Ph), 120.01 (p-Ph), 115.96 (14-C), 114.57 (11-C), 98.09 (6-C), 74.44 (17-C), 71.69 (16-C), 63.78 (9-C), 61.61 (3-C), 51.18 (7-C), 37.62 (4-C), 36.54 (5-C), 15.33 (8-C), 10.60 (18-C), 3.39 (19-C).

HRMS (ESI): m/z calcd. for $[C_{24}H_{31}N_4O_4]^+$ 439.2340, found 439.2333 $[M+H]^+$.

(4S,6S)-3-(azidomethyl)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-6-(((1S,2R)-2-phenylcyclohexyl)oxy)-1,2-oxazinane (12c)



To a stirred solution of azide **11c** (0.025 g, 0.048 mmol) in AcOH (0.7 ml) $NaBH_3CN$ (0.027 g, 0.428 mmol) was added. The reaction mixture was intensively stirred at r.t. for 1 h, then poured into a mixture of EtOAc (10 ml) and saturated aqueous solution of K_2CO_3 (10 ml). The aqueous layer was back-extracted with EtOAc (2 × 5 ml). The combined organic layers were washed with water (15 ml) and brine (15 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 10:1 → 5:1 → 3:1) to yield 0.017 g (67%) of azide **12c**. Colorless oil. R_f = 0.62 (Hexane/EtOAc = 1:1).

^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.49 – 7.22 (m, 5H, Ph), 7.05 (d, J = 7.7 Hz, 1H, 18-CH), 6.63 (s, 1H, 15-CH), 6.62 (d, J = 7.7 Hz, 1H, 19-CH), 6.57 (t, J = 75.7 Hz, 1H, 20-CHF_2), 4.96 (s, 1H, 6-CH), 4.10 (d, J = 12.1 Hz, 1H, 2-NH), 3.83 (d, J = 6.8 Hz, 2H, 21-CH_2), 3.80 – 3.71 (m, 1H, 7-CH), 3.00 (dddd, J = 11.8, 5.0, 1.6 Hz, 1H, 3-CH_{ax}), 2.77 (dd, J = 12.9, 1.6 Hz, 1H, 13-CH), 2.66 (ddd, J = 10.6, 10.6, 2.5 Hz, 1H, 8-CH), 2.45 (dd, J = 12.9, 5.0 Hz, 1H, 13-CH), 2.44 (ddd, J = 11.8, 11.8, 3.1 Hz, 1H, 4-CH_{ax}), 2.25 – 2.14 (m, 1H, 12-CH), 2.01 – 1.74 (m, 6H, 5-CH_2, 9-CH_2, 10-CH, 11-CH), 1.73 – 1.54 (m, 1H, 11-CH), 1.46 – 1.19 (m, 3H, 10-CH, 12-CH, 22-CH), 0.64 (m, 2H, 23-CH_2), 0.35 (m, 2H, 23-CH_2).

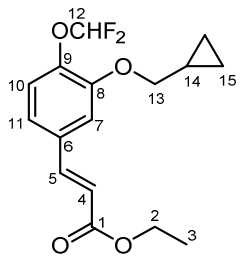
^{13}C NMR (75 MHz, HSQC, $CDCl_3$) δ 150.85 (16-C), 144.63 (i-Ph), 140.31 (14-C), 139.44 (t, J = 3.0 Hz, 17-C), 128.92 and 128.13 (o-Ph and m-Ph), 126.85 (p-Ph), 123.10 (19-C), 119.99 (18-C), 118.04 (t, J = 259.7 Hz, 20-C), 113.63 (15-C), 93.32 (6-C), 77.82 (7-C), 74.09 (21-C), 61.15 (3-C), 51.01 (8-C), 50.34 (13-C), 37.75 (4-C), 36.77 (11-C), 33.58 (5-C), 31.39 (12-C), 26.11 (10-C), 24.84 (9-C), 10.28 (22-C), 3.28 (23-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.37 (d, J = 75.1 Hz).

HRMS (ESI): m/z calcd. for $[C_{28}H_{35}F_2N_4O_4]^+$ 529.2621, found 529.2624 $[M+H]^+$.

Optical rotation: $[\alpha]^{20}_D$ = +206° ($CHCl_3$, C = 0.3 g/100 ml).

ethyl (E)-3-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)acrylate (14a)



To a stirred solution of aldehyde **6a** (0.518 g, 2.14 mmol) in CH_2Cl_2 (5 ml) was added ethyl (triphenylphosphoranylidene)acetate (0.785 g, 2.24 mmol) under argon atmosphere. The reaction mixture was intensively stirred at r.t. for 6 h and then evaporated under vacuum. A mixture of hexane/Et_2O = 9:1 (50 ml) was added to the residue, and the white precipitate was filtered out. The resulting solution was evaporated under vacuum and subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 4:1) to yield 0.648 g (97%) of ester **14a**. For analytical purposes the product was recrystallized from pentane. White solid, m.p. = 48.5–50.5°C (recrystallized from pentane). R_f = 0.73 (Hexane/EtOAc = 1:1).

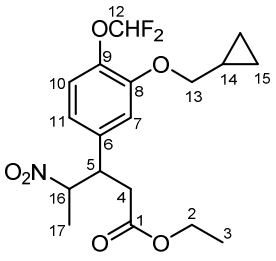
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 16.0 Hz, 1H, 5-CH), 7.11 (d, J = 7.9 Hz, 1H, 10-CH), 7.05 (s, 1H, 7-CH), 7.04 (d, J = 7.9 Hz, 1H, 11-CH), 6.64 (t, J = 75.3 Hz, 1H, 12-CHF_2), 6.32 (d, J = 16.0 Hz, 1H, 4-CH), 4.22 (q, J = 7.0 Hz, 2H, 2-CH_2), 3.86 (d, J = 6.9 Hz, 2H, 13-CH_2), 1.30 (t, J = 7.0 Hz, 3H, 3-CH_3), 1.35 – 1.18 (m, 1H, 14-CH), 0.62 (m, 2H, 15-CH_2), 0.33 (m, 2H, 15-CH_2).

^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 166.65 (1-C), 150.65 (8-C), 143.44 (5-C), 141.89 (9-C), 132.98 (6-C), 122.58 (10-C), 121.40 (4-C), 118.63 (11-C), 116.04 (t, J = 260.2 Hz, 12-C) 113.21 (7-C), 73.94 (13-C), 60.55 (2-C), 14.26 (3-C), 10.08 (14-C), 3.19 (15-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.53 (d, J = 75.2 Hz).

GC-MS (EI): m/z 312 (M^+).

ethyl 3-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-nitropentanoate (15a)



To a stirred solution of ester **14a** (0.648 g, 2.07 mmol) in nitroethane (1.5 ml) was added DBU (0.310 ml, 2.07 mmol). The reaction mixture was stirred for 30 h, then 2M aqueous solution of HCl (15 ml) was added. The mixture was poured into a mixture of MTBE (30 ml) and water (30 ml). The aqueous layer was back-extracted with MTBE (2 × 15 ml). The combined organic layers were washed with brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 9:1 → 6:1) to yield 0.729 g (91%) of nitro compound **15a** as two isomers mixture. Isomers were separated for analytical purposes (isomer A: 0.293 g, isomer B: 0.280 g, mixed fraction: 0.156 g).

Isomer A: Colorless oil. R_f = 0.45 (Hexane/EtOAc = 3:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J = 8.2 Hz, 1H, 10-CH), 6.76 (s, 1H, 7-CH), 6.72 (d, J = 8.2 Hz, 1H, 11-CH), 6.56 (t, J = 75.5 Hz, 1H, 12-CHF_2), 4.73 (dq, J = 9.2, 6.6 Hz, 1H, 16-CH), 3.91 (q, J = 7.1, 2H, 2-CH_2), 3.81 (d, J = 6.9 Hz, 2H, 13-CH_2), 3.59 (ddd, J = 9.7, 9.2, 5.0 Hz, 1H, 5-CH), 2.68 (dd, J = 15.8, 9.7 Hz, 1H, 4-CH), 2.58 (dd, J = 15.8, 5.0 Hz, 1H, 4-CH), 1.28 (d, J = 6.6 Hz, 3H, 17-CH_3), 1.24 – 1.12 (m, 1H, 14-CH), 1.02 (t, J = 7.1, 3H, 3-CH_3), 0.56 (m, 2H, 15-CH_2), 0.28 (m, 2H, 15-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.21 (1-C), 150.53 (8-C), 139.87 (9-C), 136.19 (6-C), 122.65 (10-C), 120.51 (11-C), 116.13 (t, J = 259.3 Hz, 12-C), 114.60 (7-C), 86.62 (16-C), 73.80 (13-C), 60.59 (2-C), 45.94 (5-C), 37.39 (4-C), 17.39 (17-C), 13.79 (3-C), 9.95 (14-C), 2.97 (15-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -87.79 (d, J = 75.3 Hz).

Isomer B: Colorless oil. R_f = 0.41 (Hexane/EtOAc = 3:1).

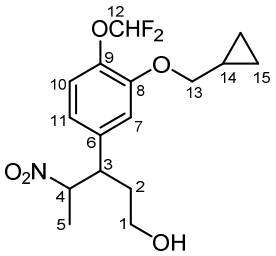
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.9 Hz, 1H, 10-CH), 6.74 (s, 1H, 7-CH), 6.72 (d, J = 8.9 Hz, 1H, 11-CH), 6.56 (t, J = 75.5 Hz, 1H, 12-CHF_2), 4.84 (dq, J = 8.4, 6.7 Hz, 1H, 16-CH), 4.00 (q, J = 7.2, 2H, 2-CH_2), 3.80 (d, J = 6.9 Hz, 2H, 13-CH_2), 3.63 (ddd, J = 9.1, 8.4, 6.0 Hz, 1H, 5-CH), 2.78 (dd, J = 16.0, 6.0 Hz, 1H, 4-CH), 2.66 (dd, J = 16.0, 9.1 Hz, 1H, 4-CH), 1.52 (d, J = 6.7 Hz, 3H, 17-CH_3), 1.27 – 1.15 (m, 1H, 14-CH), 1.08 (t, J = 7.2 Hz, 3H, 3-CH_3), 0.58 (m, 2H, 15-CH_2), 0.30 (m, 2H, 15-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.74 (1-C), 150.38 (8-C), 139.93 (9-C), 136.61 (6-C), 122.50 (10-C), 120.41 (11-C), 116.23 (t, J = 259.1 Hz, 12-C), 114.59 (7-C), 86.55 (16-C), 73.91 (13-C), 60.91 (2-C), 45.62 (5-C), 36.31 (4-C), 16.93 (17-C), 13.93 (3-C), 10.04 (14-C), 3.09 (15-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.34 (d, J = 75.3 Hz).

MS (EI): m/z 387 (M^+).

3-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-nitropentan-1-ol (16a)



A solution of nitro ester **15a** (0.280 g, 0.722 mmol) in dry CH_2Cl_2 (12 ml) in Schlenk flask under argon atmosphere was cooled to −78°C and the 1.2M solution of DIBAL-H in toluene (2.4 ml) was added with intensive stirring. The reaction mixture was stirred for 5 min at −78°C and then 16 h allowing to warm to r.t. The reaction mixture was again cooled to −78°C and the 1.2M solution of DIBAL-H in toluene (1.2 ml) was added, then the mixture was allowed to warm to r.t. and stirred for 8.5 h. The 1M aqueous solution of HCl (10 ml) was added and the resulting solution was poured into a mixture of CH_2Cl_2 (50 ml) and water (50 ml). The aqueous layer was back-extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 7:1 → 5:1 → 3:1 → 1:1) to yield 0.139 g (56%) of alcohol **16a**.

Isomer A (obtained from isomer A of ester **15a**): colorless oil. R_f = 0.45 (Hexane/EtOAc = 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 7.5 Hz, 1H, 10-CH), 6.75 (s, 1H, 7-CH), 6.73 (d, J = 7.5 Hz, 1H, 11-CH), 6.62 (t, J = 75.4 Hz, 1H, 12-CHF_2), 4.78 – 4.62 (m, 1H, 4-CH), 3.86 (d, J = 6.9 Hz, 2H, 13-CH_2), 3.51 (dd, J = 10.6, 5.3 Hz, 1H, 3-CH), 3.40 – 3.25 (m, 2H, 1-CH_2), 1.86 (dd, J = 13.6, 6.5 Hz, 1H, 2-CH), 1.32 (d, J = 6.6 Hz, 3H, 5-CH_3), 1.30 – 1.23 (m, 1H, 14-CH), 0.96 (dd, J = 13.6, 6.7 Hz, 1H, 2-CH), 0.65 (m, 2H, 15-CH_2), 0.35 (m, 2H, 15-CH_2) (OH not observed).

^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 150.99 (8-C), 139.36 (9-C), 136.85 (6-C), 123.22 (10-C), 120.80 (11-C), 114.80 (7-C), 87.96 (4-C), 74.21 (13-C), 59.84 (1-C), 46.73 (3-C), 35.33 (2-C), 18.04 (5-C), 10.23 (14-C), 3.30 (15-C) (C-12 not observed).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.44 (d, J = 75.5 Hz).

Isomer B (obtained from isomer B of ester **15a**): colorless oil. R_f = 0.24 (Hexane/EtOAc = 1:1).

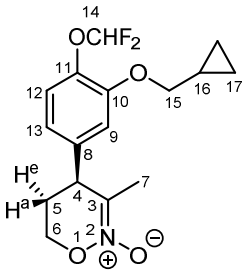
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 7.6 Hz, 1H, 10-CH), 6.74 (d, J = 7.6 Hz, 1H, 11-CH), 6.74 (d, J = 1.7 Hz, 1H, 7-CH), 6.59 (t, J = 75.4 Hz, 1H, 12-CHF_2), 4.78 (dq, J = 12.0, 6.6 Hz, 1H, 4-CH), 3.84 (d, J = 6.8 Hz, 2H, 13-CH_2), 3.57 (ddd, J = 12.0, 6.1, 4.9 Hz, 1H, 3-CH), 3.35 (m, 2H, 1-CH_2), 2.10 – 1.95 (m, 1H, 2-CH), 1.81 (ddd, J = 14.0, 11.1, 4.9 Hz, 1H, 2-CH), 1.61 (d, J = 6.6 Hz, 3H, 5-CH_3), 1.29 – 1.15 (m, 1H, 14-CH), 0.63 (m, 2H, 15-CH_2), 0.34 (m, 2H, 15-CH_2) (OH not observed).

^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 150.70 (8-C), 141.88 (9-C), 137.19 (6-C), 122.87 (10-C), 120.69 (11-C), 116.33 (t, J = 255.9 Hz, 12-C), 114.95 (7-C), 87.98 (4-C), 74.22 (13-C), 59.91 (1-C), 46.52 (3-C), 33.67 (2-C), 17.58 (5-C), 10.24 (14-C), 3.30 (15-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.27 (d, J = 75.7 Hz).

MS (EI): m/z 345 (M^+).

4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-3-methyl-5,6-dihydro-4H-1,2-oxazine 2-oxide (18a)



A solution of nitro alcohol **16a** (0.244 g, 0.707 mmol) in dry CH_2Cl_2 (2.2 ml) in Schlenk flask under argon atmosphere was cooled to 0°C. Triethylamine (0.160 ml, 1.13 mmol) and methanesulfonyl chloride (0.070 ml, 0.905 mmol) were added. The reaction mixture was intensively stirred at 0°C for 15 min and then kept without stirring at this temperature for 5.5 h. The solution was diluted with water (10 ml) and poured into CH_2Cl_2 (30 ml). The aqueous layer was back-extracted with CH_2Cl_2 (2 × 30 ml). The combined organic layers were washed saturated solution of NH_4Cl (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum.

The 1M solution of NaI in acetone (1.2 ml) was added and the mixture was kept at r.t. for 64 h. The solution was diluted with EtOAc (10 ml) and poured into a mixture of EtOAc (30 ml) and water (30 ml). The aqueous layer was back-extracted with EtOAc (3 × 30 ml). The combined organic layers were washed with water (50 ml) and brine (2 × 40 ml) and brine (40 ml), dried over Na_2SO_4 and evaporated under vacuum to give crude iodide **17a**.

The crude product was dissolved in dry CH_2Cl_2 (2.3 ml) and DBU (0.085 ml, 0.571 mmol) was added. The reaction mixture was stirred at r.t. for 3.5 h, then diluted with EtOAc (40 ml) and poured into a 0.25M solution of $NaHSO_4$ (40 ml). The aqueous layer was back-extracted with EtOAc (2 × 20 ml). The combined organic layers were washed with brine (40 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:1 → 0:1) to yield 0.146 g (63%) of nitronate **18a**. Colorless oil. R_f = 0.05 (Hexane/EtOAc = 1:1).

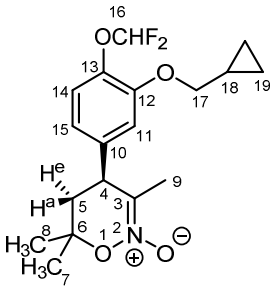
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.3 Hz, 1H, 12-CH), 6.73 (d, J = 8.3 Hz, 1H, 13-CH), 6.70 (s, 1H, 9-CH), 6.60 (t, J = 75.4 Hz, 1H, 14-CHF_2), 4.41 (m, 2H, 6-CH_2), 3.83 (d, J = 7.0 Hz, 2H, 15-CH_2), 3.80 – 3.60 (m, 1H, 4-CH), 2.36 (dt, J = 13.5, 6.3 Hz, 1H, 5-CH_{eq}), 2.01 (ddd, J = 13.5, 11.9, 7.7 Hz, 1H, 5-CH_{ax}), 1.89 (s, 3H, 7-CH_3), 1.43 – 1.07 (m, 1H, 16-CH), 0.64 (m, 2H, 17-CH_2), 0.34 (m, 2H, 17-CH_2).

^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 150.95 (10-C), 139.54 (8-C), 123.36 (12-C), 122.24 (3-C), 120.64 (13-C), 115.85 (t, J = 255.5 Hz, 14-C), 113.64 (9-C), 74.24 (15-C), 69.27 (6-C), 43.65 (4-C), 30.38 (5-C), 18.23 (7-C), 10.20 (16-C), 3.28 (17-C) (11-C not observed).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.51 (d, J = 75.4 Hz).

HRMS (ESI): m/z calcd. for $[C_{16}H_{19}F_2NO_4]^+$ 328.1355, found 328.1350 $[M+H]^+$.

4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-3,6,6-trimethyl-5,6-dihydro-4H-1,2-oxazine 2-oxide (18b)



A solution of nitroalkene **4a** (0.628 g, 2.10 mmol) in dry CH_2Cl_2 (18 ml) with CaH_2 (ca. 0.05 g) was cooled to −78°C (acetone/dry ice) in a Schlenk flask under argon atmosphere. $SnCl_4$ (0.270 ml, 2.31 mmol) was added with intensive stirring. In 5 min a solution of 2-methylpropene (excess, ca. 1 g) in dry CH_2Cl_2 (13 ml) was added dropwise. The reaction mixture was intensively stirred at −78°C for 1 h, then the resulting orange-colored solution was poured into a mixture of EtOAc (70 ml) and saturated aqueous solution of K_2CO_3 (70 ml). The aqueous layer was back-extracted with EtOAc (2 × 50 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:1 → 0:1) to yield 0.584 g (78%) of nitronate **18b**. For analytical purposes the product was recrystallized from hexane/Et_2O = 1:1 mixture. White solid, m.p. = 104–108°C (recrystallized from hexane/Et_2O = 1:1). R_f = 0.12 (Hexane/EtOAc = 1:1).

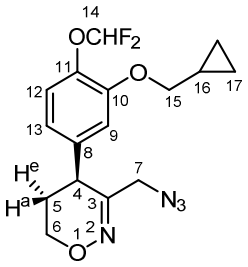
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 8.1 Hz, 1H, 14-CH), 6.74 (d, J = 8.1 Hz, 1H, 15-CH), 6.69 (s, 1H, 11-CH), 6.62 (t, J = 75.4 Hz, 1H, 16-CHF_2), 3.84 (d, J = 6.8 Hz, 2H, 17-CH_2), 3.66 (dd, J = 10.4, 8.0 Hz, 1H, 4-CH_{ax}), 2.11 (dd, J = 13.9, 8.0 Hz, 1H, 5-CH_{eq}), 1.97 – 1.84 (m, 1H, 5-CH_{ax}), 1.88 (s, 3H, 9-CH_3), 1.45 (s, 3H, 7-CH_3 or 8-CH_3), 1.42 (s, 3H, 7-CH_3 or 8-CH_3), 1.33 – 1.18 (m, 1H, 18-CH), 0.66 (m, 2H, 19-CH_2), 0.36 (m, 2H, 19-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.36 (12-C), 139.92 (13-C), 139.06 (10-C), 123.37 (14-C), 121.45 (3-C), 120.77 (15-C), 116.19 (t, J = 260.0 Hz, 16-C), 113.57 (11-C), 81.39 (6-C), 74.26 (17-C), 43.22 (5-C), 41.76 (4-C), 27.89 and 22.21 (7-C and 8-C), 17.35 (9-C), 10.22 (18-C), 3.31 (19-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.53 (d, J = 75.4 Hz).

HRMS (ESI): m/z calcd. for $[C_{18}H_{24}F_2NO_4]^+$ 356.1668, found 356.1658 $[M+H]^+$.

3-(azidomethyl)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-5,6-dihydro-4H-1,2-oxazine (21a)



To a stirred solution of nitronate **18a** (0.146 g, 0.446 mmol) in dry CH_2Cl_2 (0.9 ml) in Schlenk flask was added triethylamine (0.095 ml, 0.699 mmol) under argon atmosphere. The reaction mixture was cooled to −78°C and Me_3SiBr (0.082 ml, 0.624 mmol) was added. The mixture was intensively stirred for 30 min at −78°C and then kept for 28 h at −20°C without stirring. The mixture was allowed to warm to 0°C (ice water bath), and the solution of $CoBr_2$ (0.195 g, 0.891 mmol) in THF (2 ml) was added. The reaction mixture was stirred for 45 min at 0°C, then 72 h at r.t., then the resulting solution was poured into a mixture of EtOAc (40 ml) and 0.25M aqueous solution of $NaHSO_4$ (40 ml). The aqueous layer was back-extracted with EtOAc (2 × 30 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum to give bromide **20a**.

The crude product was dissolved in DMF (6 ml) and sodium azide (0.145 g, 2.23 mmol) was added. The mixture was intensively stirred at 60°C for 4.5 h and then poured into a mixture of MTBE (40 ml) and water (40 ml). The aqueous layer was back-extracted with MTBE (2 × 30 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 10:1 → 5:1) to yield 0.119 g (76%) of azide **21a**. Colorless oil. R_f = 0.56 (Hexane/EtOAc = 1:1).

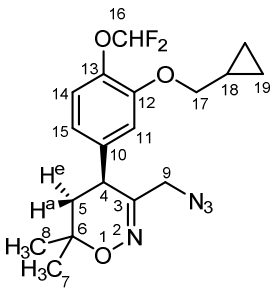
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 7.7 Hz, 1H, 12-CH), 6.74 (s, 1H, 9-CH), 6.73 (d, J = 7.7 Hz, 1H, 13-CH), 6.60 (t, J = 75.4 Hz, 1H, 14-CHF_2), 4.06 (t, J = 5.1 Hz, 2H, 6-CH_2), 3.88 (d, J = 14.6 Hz, 1H, 7-CH), 3.84 (d, J = 7.2 Hz, 2H, 15-CH_2), 3.62 (d, J = 14.6 Hz, 1H, 7-CH), 3.55 (dd, J = 10.2, 6.1 Hz, 1H, 4-CH_{ax}), 2.30 (dd, J = 13.2, 6.1 Hz, 1H, 5-CH_{eq}), 1.98 (ddd, J = 13.2, 10.2, 5.1 Hz, 1H, 5-CH_{ax}), 1.35 – 1.14 (m, 1H, 16-CH), 0.63 (m, 2H, 17-CH_2), 0.34 (m, 2H, 17-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.22 (3-C), 151.11 (10-C), 139.77 and 138.68 (8-C and 11-C), 123.28 (12-C), 120.77 (13-C), 116.14 (t, J = 260.1 Hz, 14-C), 114.18 (9-C), 74.06 (15-C), 64.02 (6-C), 52.99 (7-C), 36.77 (4-C), 28.36 (5-C), 10.13 (16-C), 3.22 (17-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.47 (d, J = 75.4 Hz).

HRMS (ESI): m/z calcd. for $[C_{16}H_{20}F_2N_4O_3]^+$ 353.1420, found 353.1414 $[M+H]^+$.

3-(azidomethyl)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-6,6-dimethyl-5,6-dihydro-4H-1,2-oxazine (21b)



To a stirred solution of nitronate **18b** (0.552 g, 1.56 mmol) in dry CH_2Cl_2 in Schlenk flask (9 ml) was added triethylamine (0.324 ml, 2.33 mmol) under argon atmosphere. The reaction mixture was cooled to −78°C and Me_3SiBr (0.290 ml, 2.18 mmol) was added. The mixture was intensively stirred for 1 h at −78°C and then kept for 48 h at −20°C without stirring. The mixture was allowed to warm to 0°C (ice water bath), and the solution of $CoBr_2$ (0.688 g, 3.14 mmol) in dry THF (6 ml) was added. The reaction mixture was stirred for 30 min at 0°C and 5 h at r.t., then the resulting solution was poured into a mixture of EtOAc (50 ml) and 0.25M aqueous solution of $NaHSO_4$ (50 ml). The aqueous layer was back-extracted with EtOAc (2 × 25 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum to give bromide **20b**.

The crude product was dissolved in DMF (20 ml) and sodium azide (0.505 g, 7.78 mmol) was added. The mixture was intensively stirred at 60°C for 5.5 h and then poured into a mixture of MTBE (70 ml) and water (70 ml). The aqueous layer was back-extracted with MTBE (3 × 30 ml). The combined organic layers were washed with water (60 ml) and brine (60 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 1:0 → 10:1 → 5:1) to yield 0.488 g (83%) of azide **21b**. Yellow oil. R_f = 0.76 (Hexane/EtOAc = 1:1).

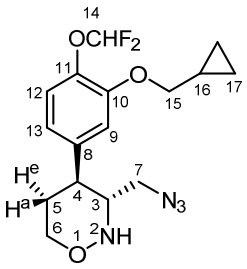
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 8.0 Hz, 1H, 14-CH), 6.76 (d, J = 8.0 Hz, 1H, 15-CH), 6.74 (s, 1H, 11-CH), 6.62 (t, J = 75.4 Hz, 1H, 16-CHF_2), 3.89 (d, J = 14.5 Hz, 1H, 9-CH), 3.85 (d, J = 6.6 Hz, 2H, 17-CH_2), 3.55 (dd, J = 12.0, 7.7 Hz, 1H, 4-CH_{ax}), 3.52 (d, J = 14.5 Hz, 1H, 9-CH), 2.11 (dd, J = 13.6, 7.7 Hz, 1H, 5-CH_{eq}), 1.90 (dd, J = 13.6, 12.0 Hz, 1H, 5-CH_{ax}), 1.39 (s, 3H, 7-CH_3 or 8-CH_3), 1.31 (s, 3H, 7-CH_3 or 8-CH_3), 1.29 – 1.19 (m, 1H, 18-CH), 0.65 (m, 2H, 19-CH_2), 0.36 (m, 2H, 19-CH_2).

^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 154.13 (3-C), 151.31 (12-C), 139.62 and 137.97 (10-C and 13-C), 123.53 (14-C), 119.98 (15-C), 117.89 (t, J = 260.0 Hz, 16-C), 114.15 (11-C), 75.25 (6-C), 74.20 (17-C), 52.85 (9-C), 40.15 (5-C), 37.67 (4-C), 28.46 and 22.54 (7-C and 8-C), 10.24 (18-C), 3.33 (19-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.49 (d, J = 75.4 Hz).

HRMS (ESI): m/z calcd. for $[C_{18}H_{22}F_2N_4O_3]^+$ 381.1733, found 381.1729 $[M+H]^+$.

3-(azidomethyl)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-1,2-oxazinane (22a)



To a stirred solution of azide **21a** (0.109 g, 0.309 mmol) in AcOH (2.7 ml) $NaBH_3CN$ (0.175 g, 2.78 mmol) was added. The reaction mixture was intensively stirred at r.t. for 1 h, then saturated aqueous solution of Na_2CO_3 (10 ml) was added into the flask. The mixture was poured into a mixture of EtOAc (30 ml) and saturated aqueous solution of Na_2CO_3 (30 ml). The aqueous layer was back-extracted with EtOAc (2 × 20 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 10:1 → 5:1 → 1:1) to yield 0.098 g (89%) of azide **22a** as a mixture of diastereomers (ratio 3,4-*trans*/3,4-*cis* = 6.5 : 1). Colorless oil. R_f = 0.43 (Hexane/EtOAc = 1:1).

Major isomer:

^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.12 (d, J = 8.9 Hz, 1H, 12-CH), 6.79 (d, J = 2.4 Hz, 1H, 9-CH), 6.77 (dd, J = 8.9, 2.4 Hz, 1H, 13-CH), 6.61 (t, J = 75.6 Hz, 1H, 14-CHF_2), 5.49 (s, br, 1H, 2-NH), 4.12 (m, 1H, 6-CH_{ax}), 3.87 (d, J = 6.9 Hz, 2H, 15-CH_2), 3.83 (ddd, J = 11.8, 2.9, 2.6 Hz, 1H, 6-CH_{eq}), 3.35 – 3.25 (m, 1H, 3-CH), 3.30 (dd, J = 13.0, 6.9 Hz, 1H, 7-CH), 3.10 (dd, J = 13.0, 8.0 Hz, 1H, 7-CH), 2.67 (ddd, J = 11.8, 10.1, 4.5 Hz, 1H, 4-CH_{ax}), 2.02 – 1.89 (m, 1H, 5-CH_{ax}), 1.84 (dddd, J = 13.5, 4.5, 2.6, 2.2 Hz, 1H, 5-CH_{eq}), 1.34 – 1.20 (m, 1H, 16-CH), 0.65 (m, 2H, 17-CH_2), 0.36 (m, 2H, 17-CH_2).

^{13}C NMR (75 MHz, HSQC, $CDCl_3$) δ 150.95 (10-C), 140.22 and 139.57 (8-C and 11-C), 123.24 (12-C), 120.19 (13-C), 116.31 (t, J = 259.7 Hz, 14-C), 113.89 (9-C), 74.11 (15-C), 70.85 (6-C), 61.92 (3-C), 51.50 (7-C), 44.23 (4-C), 33.53 (5-C), 10.28 (16-C), 3.29 (17-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -81.59 (d, J = 75.6 Hz).

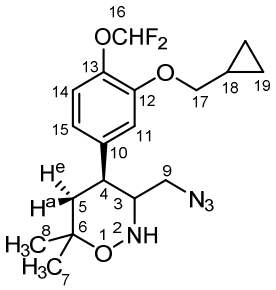
HRMS (ESI): m/z calcd for $[C_{16}H_{21}F_2N_4O_3]^+$ 355.1576, found 355.1571 $[M+H]^+$.

Minor isomer:

^{1}H NMR (300 MHz, COSY, HSQC, characteristic signals, $CDCl_3$) δ 4.23 – 4.19 (m, 1H, 6-CH), 3.95 (dd, J = 11.3, 2.7 Hz, 1H, 6-CH), 3.36 (m, 1H, 4-CH), 2.95 (dd, J = 12.1, 3.4 Hz, 1H, 7-CH), 2.15 – 2.12 (m, 1H, 5-CH), 1.76 – 1.71 (m, 1H, 5-CH).

^{13}C NMR (75 MHz, HSQC, characteristic signals, $CDCl_3$) δ 69.93 (6-C), 60.92 (3-C), 47.89 (7-C), 41.35 (4-C), 26.01 (5-C).

3-(azidomethyl)-4-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-6,6-dimethyl-1,2-oxazinane (22b)



To a stirred solution of azide **21b** (0.293 g, 0.771 mmol) in AcOH (2.5 ml) $NaBH_3CN$ (0.435 g, 6.94 mmol) was added. The reaction mixture was intensively stirred at r.t. for 4 h and then saturated aqueous solution of Na_2CO_3 (excess) was added into the flask. The mixture was poured into a mixture of EtOAc (60 ml) and saturated aqueous solution of Na_2CO_3 (60 ml). The aqueous layer was back-extracted with EtOAc (2 × 40 ml). The combined organic layers were washed with water (70 ml) and brine (70 ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 10:1 → 5:1 → 3:1) to yield 0.180 g (61%) of azide **22b**. Colorless oil. R_f = 0.39 (Hexane/EtOAc = 3:1).

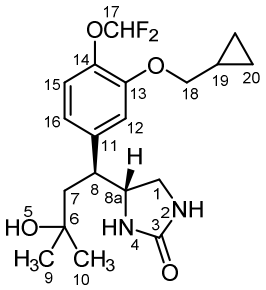
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 7.7 Hz, 1H, 14-CH), 6.77 (s, 1H, 11-CH), 6.76 (d, J = 7.7 Hz, 1H, 15-CH), 6.61 (t, J = 75.6 Hz, 1H, 16-CHF_2), 5.33 (s, br, 1H, 2-NH), 3.87 (d, J = 6.9 Hz, 2H, 17-CH_2), 3.32 (d, J = 10.8 Hz, 1H, 9-CH), 3.21 – 3.06 (m, 1H, 3-CH), 3.13 (d, J = 10.8 Hz, 1H, 9-CH), 2.83 (td, J = 10.1, 7.4 Hz, 1H, 4-CH_{ax}), 1.78 – 1.68 (m, 2H, 5-CH_2), 1.40 (s, 3H, 7-CH_3 or 8-CH_3), 1.33 – 1.20 (m, 1H, 18-CH), 1.24 (s, 3H, 7-CH_3 or 8-CH_3), 0.65 (m, 2H, 19-CH_2), 0.36 (m, 2H, 19-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.51 (12-C), 140.44 and 139.45 (10-C and 13-C), 123.22 (14-C), 120.21 (15-C), 115.36 (t, J = 256.9 Hz, 16-C), 113.92 (11-C), 74.84 (6-C), 74.12 (17-C), 61.51 (3-C), 51.38 (9-C), 43.85 (5-C), 40.93 (4-C), 29.29 and 22.07 (7-C and 8-C), 10.31 (18-C), 3.31 (19-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.39 (d, J = 75.6 Hz).

HRMS (ESI): m/z calcd. for $[C_{18}H_{24}F_2N_4O_3]^+$ 383.1889, found 383.1877 $[M+H]^+$.

***Rel-(R)-4-((S)*-(1-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-3-hydroxy-3-methylbutyl)imidazolidin-2-one (24b)**



To a solution of **2b** (0.078 g, 0.204 mmol) in methanol (2 ml) in a vial equipped with a magnetic stirrer was added a suspension of Raney® nickel (ca. 50 mg, washed with methanol) in methanol (1 ml). The vial was placed to a steel autoclave which was flushed and filled with H_2 to a pressure of 40 bar. The mixture was stirred at 70°C for 5.5 h. Then the autoclave was cooled to r.t. and slowly evacuated, and then the catalyst was removed. The solvent was evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: EtOAc/MeOH = 1:0 → 10:1 → 3:1) to yield 0.068 g (87%) of alcohol **3b**. Colorless oil. R_f = 0.55 (EtOAc/MeOH = 3:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H, NH), 7.08 (d, J = 8.4 Hz, 1H, 15-CH), 6.75 (s, 1H, 12-CH), 6.71 (d, J = 8.4 Hz, 1H, 16-CH), 6.59 (t, J = 75.5 Hz, 1H, 17-CHF_2), 4.86 (s, 1H, NH), 3.85 (d, J = 6.7 Hz, 2H, 18-CH_2), 3.10 (dd, J = 8.9, 8.6 Hz, 1H, 1-CH), 3.00 (t, J = 8.6, 8.2 Hz, 1H, 1-CH), 2.96 – 2.82 (m, 2H, 8-CH and 8a-CH), 1.99 (dd, J = 14.7, 4.3 Hz, 1H, 7-CH), 1.87 (dd, J = 14.7, 7.1 Hz, 1H, 7-CH), 1.32 – 1.22 (m, 1H, 19-CH), 1.25 (br, 1H, OH), 1.19 (s, 3H, 9-CH_3 or 10-CH_3), 1.10 (s, 3H, 9-CH_3 or 10-CH_3), 0.64 (m, 2H, 20-CH_2), 0.35 (m, 2H, 20-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.38 (3-C), 150.78 (13-C), 141.81 (14-C), 139.37 (t, J = 2.9 Hz, 11-C), 123.05 (15-C), 120.65 (16-C), 116.32 (t, J = 259.6 Hz, 17-C), 114.54 (12-C), 74.17 (18-C), 70.64 (6-C), 58.87 (8a-C), 47.81 (7-C), 47.02 (1-C), 45.61 (8-C), 31.90 and 28.36 (9-C and 10-C), 10.29 (19-C), 3.30 (20-C).

^{19}F NMR (282 MHz, $CDCl_3$) δ -82.36 (d, J = 75.5 Hz).

HRMS (ESI): m/z calcd. for $[C_{19}H_{26}F_2N_2O_4]^+$ 385.1933, found 385.1925 $[M+H]^+$.

3. Biological studies: primary data

In vitro enzymatic assay for recombinant human PDE4B1

Compounds

Compound I.D.	Stock Concentration	Dissolving Solvent	Test Range (μM)	Intermediate Dilution
rac-**1a**	10mM	DMSO	0.0003 - 3	10 % DMSO in PDE Assay Buffer
(7S,7aR)-**1a**	10mM	DMSO	0.001 - 10	10 % DMSO in PDE Assay Buffer
rac-**1b**	10mM	DMSO	0.001 - 10	10 % DMSO in PDE Assay Buffer
rac-**1c**	10mM	DMSO	0.001 - 10	10 % DMSO in PDE Assay Buffer
rac-**1d**	10mM	DMSO	0.0003 - 3	10 % DMSO in PDE Assay Buffer
rac-**1e**	10mM	DMSO	0.0003 - 3	10 % DMSO in PDE Assay Buffer
rac-**2a**	10mM	DMSO	0.001 - 10	10 % DMSO in PDE Assay Buffer
rac-**2b**	10mM	DMSO	0.0003 - 3	10 % DMSO in PDE Assay Buffer
rac-**24b**	10mM	DMSO	0.0003 - 3	10 % DMSO in PDE Assay Buffer
Apremilast*	10mM	DMSO	0.001 - 10 for PDE4B1	10 % DMSO in PDE Assay Buffer

*Reference compound.

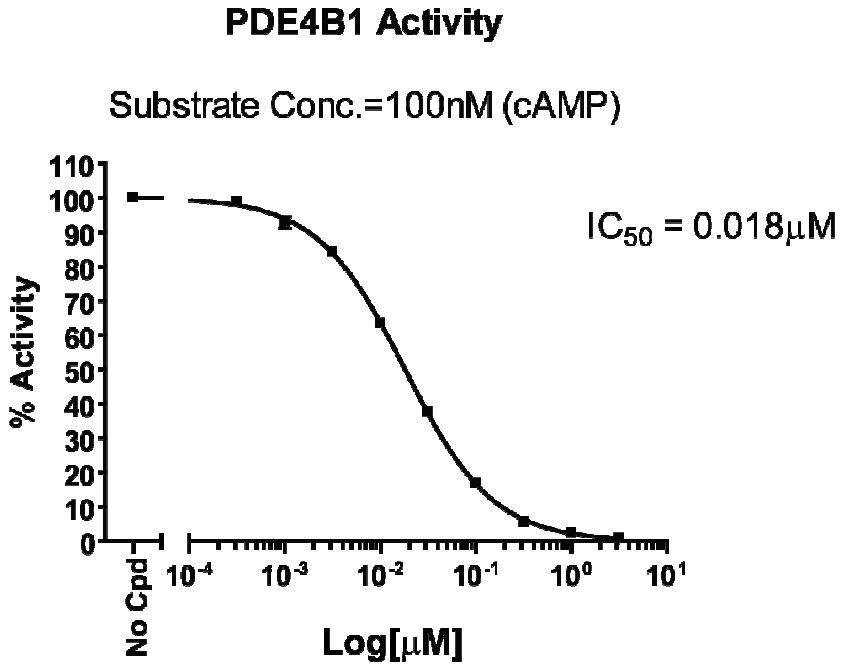
Enzymes and Substrates

Assay	BPS Catalog	Enzyme Lot #	Enzyme Used (ng) / Reaction	Substrate
PDE-4B1	60041	90520	0.05	100 nM FAM-cAMP

Data for the effect of each compound on PDE4B1 activity is presented below. The IC_{50} of all compounds against PDEs are summarized in Table 1 in the manuscript.

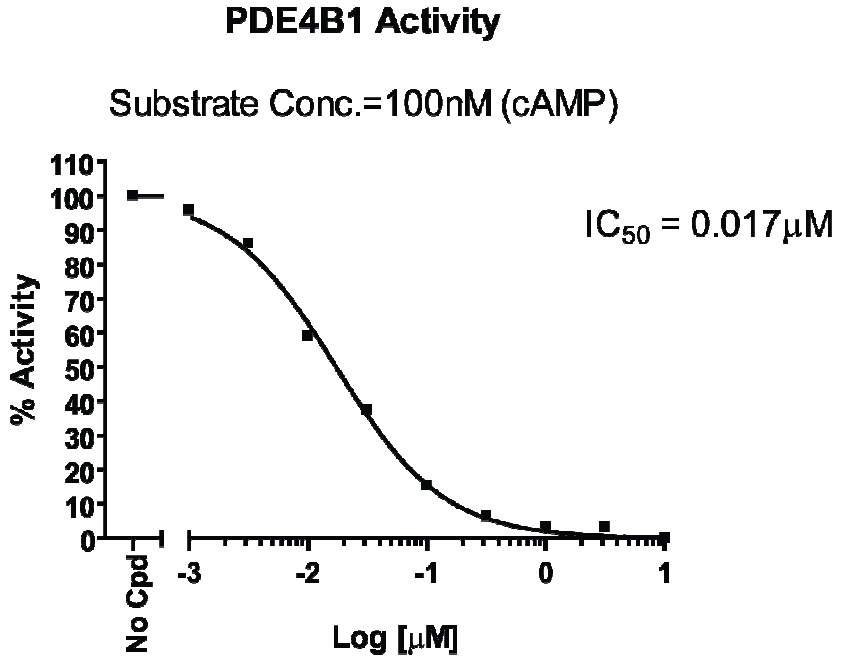
Data for the Effect of *rac*-**1a** on PDE4B1 Activity

rac-**1a** [μM]	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	161	165	99	101
0.0003	159	163	97	100
0.001	150	155	91	94
0.003	141	140	84	84
0.01	109	112	62	64
0.03	74	74	37	38
0.1	44	45	16	17
0.3	28	30	5	6
1	23	24	2	3
3	22	22	1	1
Background	21	21	0	0



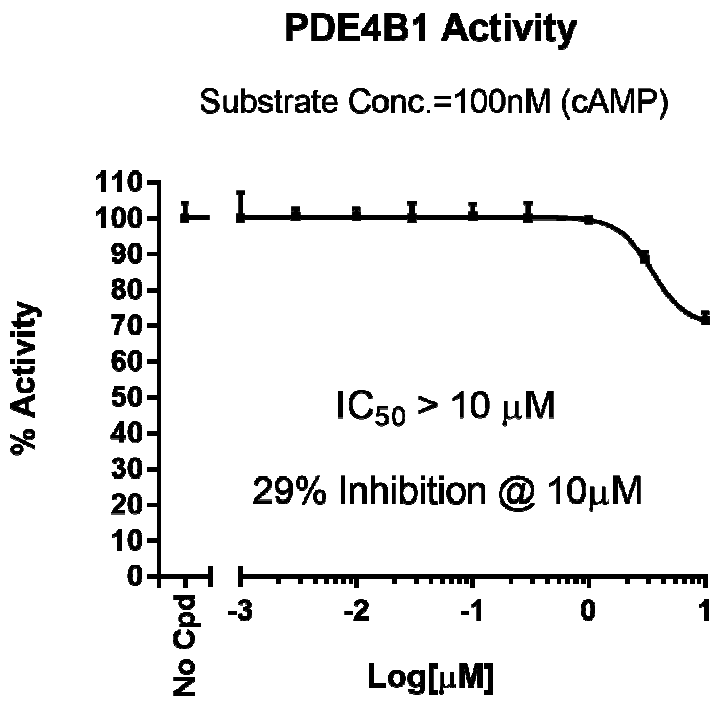
Data for the Effect of (−)-(7S,7aR)-**1a** on PDE4B1 Activity

(−)-(7S,7aR)-**1a** [μM]	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	155	153	101	99
0.001	149	148	97	95
0.003	136	135	87	86
0.01	100	99	60	58
0.03	72	70	38	37
0.1	41	42	15	16
0.3	31	28	7	5
1	26	25	4	3
3	25	26	3	4
10	22	21	1	-1
Background	21	21		



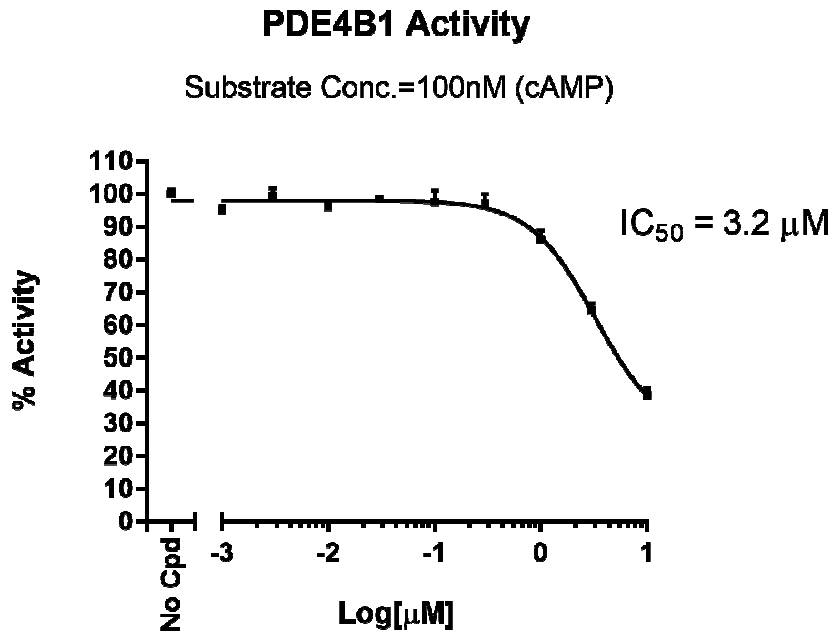
Data for the Effect of *rac*-**1b** on PDE4B1 Activity

rac-**1b** [μM]	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat 1	Repeat 2	Repeat 1	Repeat 2
No Compound	129	123	103	97
0.001	121	131	95	105
0.003	128	125	102	99
0.01	125	128	99	102
0.03	123	130	97	103
0.1	124	129	98	103
0.3	130	123	103	97
1	125	127	99	100
3	113	116	87	90
10	98	95	73	70
Background	22	21		



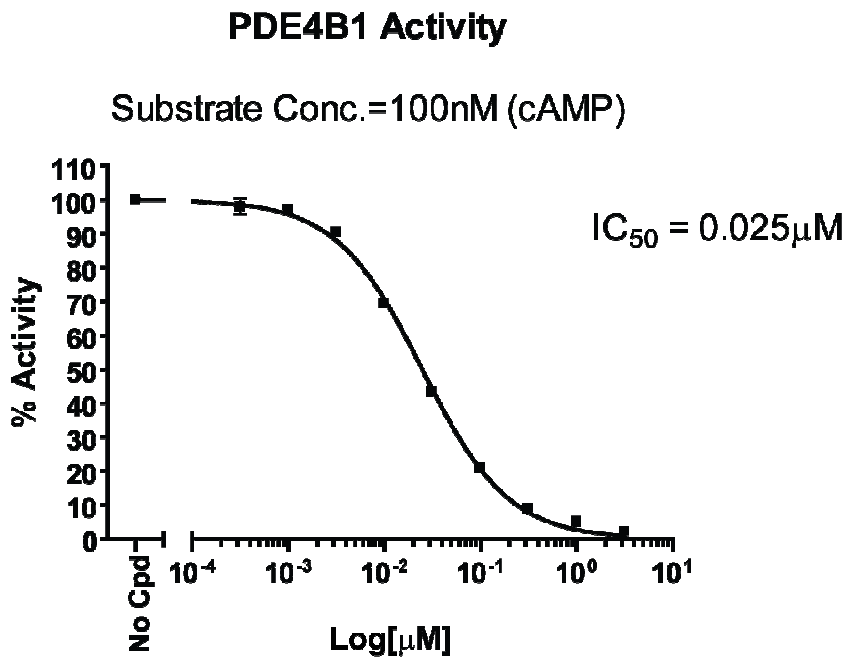
Data for the Effect of *rac*-**1c** on PDE4B1 Activity

rac-**1c** [μM]	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat 1	Repeat 2	Repeat 1	Repeat 2
No Compound	129	127	101	99
0.001	124	122	96	94
0.003	127	129	98	101
0.01	123	125	95	97
0.03	127	126	99	98
0.1	128	123	100	95
0.3	128	123	99	95
1	116	111	88	84
3	89	92	63	66
10	64	61	40	37
Background	21	23		



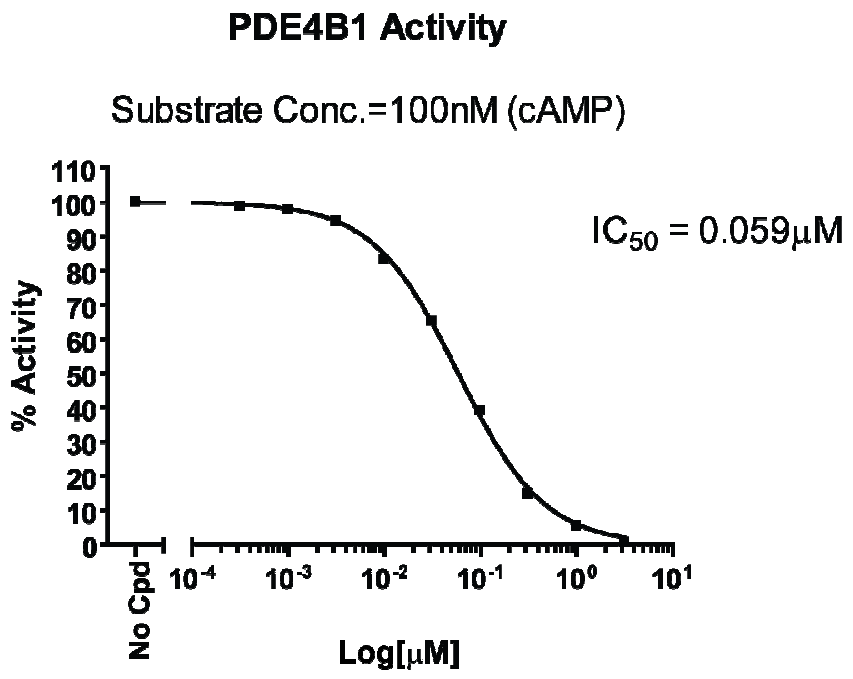
Data for the Effect of *rac*-**1d** on PDE4B1 Activity

rac-**1d** [μM]	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	166	165	100	100
0.0003	166	159	100	96
0.001	161	161	97	97
0.003	151	152	90	91
0.01	120	123	69	70
0.03	84	83	44	43
0.1	50	53	20	22
0.3	33	35	8	9
1	28	29	5	5
3	25	24	2	2
Background	22	21	0	0



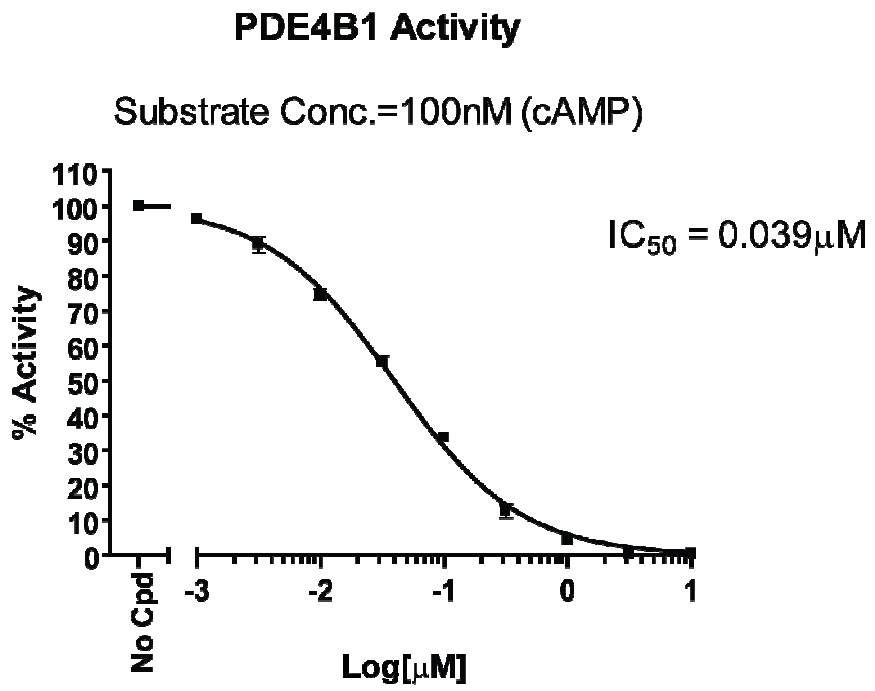
Data for the Effect of *rac*-**1e** on PDE4B1 Activity

rac-**1e** [μM]	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	163	162	100	100
0.0003	163	159	100	97
0.001	158	160	97	98
0.003	156	153	95	94
0.01	139	138	84	83
0.03	114	113	65	65
0.1	78	75	40	38
0.3	44	41	16	14
1	29	29	6	5
3	22	23	0	1
Background	21	22	0	0



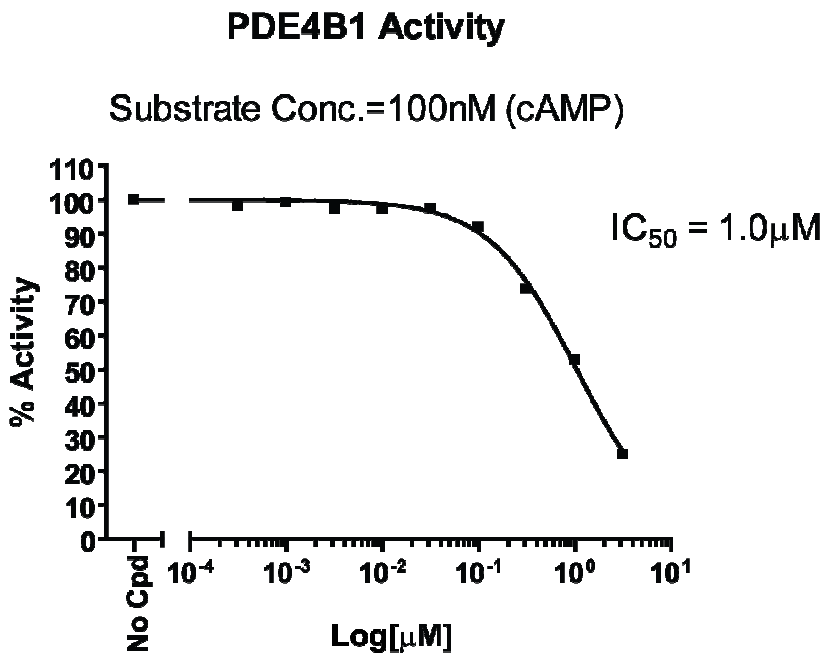
Data for the Effect of *rac*-**2a** on PDE4B1 Activity

rac-**2a** [μM]	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	162	157	102	98
0.001	156	152	97	95
0.003	147	141	91	86
0.01	122	127	73	76
0.03	100	96	57	54
0.1	67	69	33	34
0.3	36	42	11	15
1	28	27	5	4
3	21	22	0	1
10	22	23	0	1
Background	21	22		



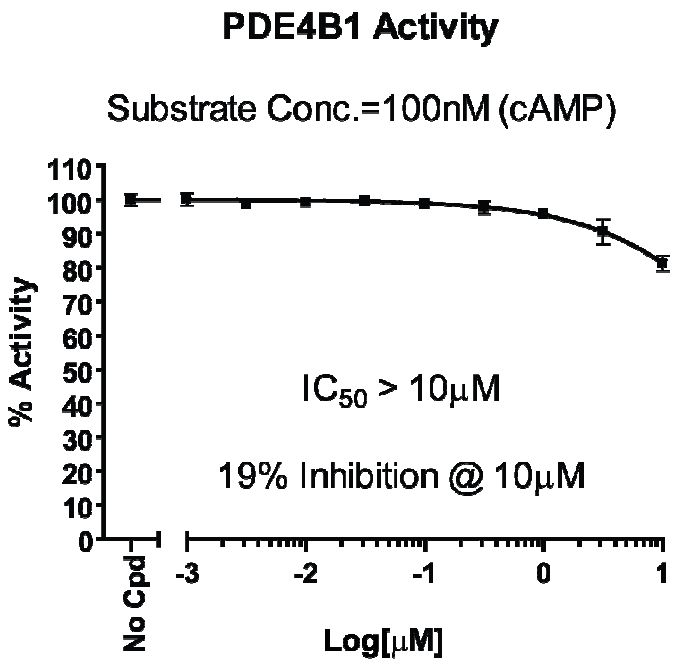
Data for the Effect of *rac*-**2b** on PDE4B1 Activity

rac-**2b** [μM]	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	165	168	99	101
0.0003	165	163	99	98
0.001	164	167	98	100
0.003	163	163	97	97
0.01	163	161	98	96
0.03	162	163	97	98
0.1	154	155	92	92
0.3	126	130	72	75
1	98	98	53	53
3	56	59	24	26
Background	21	23	-1	1



Data for the Effect of *rac*-**3b** on PDE4B1 Activity

rac-**3b** [μM]	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	156	152	102	98
0.001	157	152	102	98
0.003	151	154	98	100
0.01	154	151	100	98
0.03	154	153	100	99
0.1	152	153	98	99
0.3	148	153	96	100
1	150	147	97	95
3	146	137	94	87
10	132	126	83	79
Background	20	21		



In vitro selectivity enzymatic assay for a series of PDE4 isotypes

Compounds

Compound I.D.	Stock Concentration	Dissolving Solvent	Test Range (μM)	Intermediate Dilution
(7S,7aR)-**1a**	10mM	DMSO	0.1	10 % DMSO in PDE Assay Buffer
rac-**1d**	10mM	DMSO	0.1	10 % DMSO in PDE Assay Buffer
rac-**1e**	10mM	DMSO	0.1	10 % DMSO in PDE Assay Buffer
rac-**2a**	10mM	DMSO	0.1	10 % DMSO in PDE Assay Buffer
Apremilast*	10mM	DMSO	10	10 % DMSO in PDE Assay Buffer

*Reference compound.

Enzymes and Substrates

Assay	Catalog #	Enzyme Lot #	Enzyme Used (ng) / Reaction	Substrate
PDE4A1A	60040	160926-G	0.1	100 nM FAM-cAMP
PDE4A4B	60039	110411	0.06	100 nM FAM-cAMP
PDE4A10	60038	110428-GC	0.128	100 nM FAM-cAMP
PDE4B2	60042	121218-G1	0.025	100 nM FAM-cAMP
PDE4C1	60044	90812	0.24	100 nM FAM-cAMP
PDE4D2	60048	130102-GC	0.03	100 nM FAM-cAMP
PDE4D3	60046	121011	0.025	100 nM FAM-cAMP
PDE4D7	60047	101101	0.045	100 nM FAM-cAMP

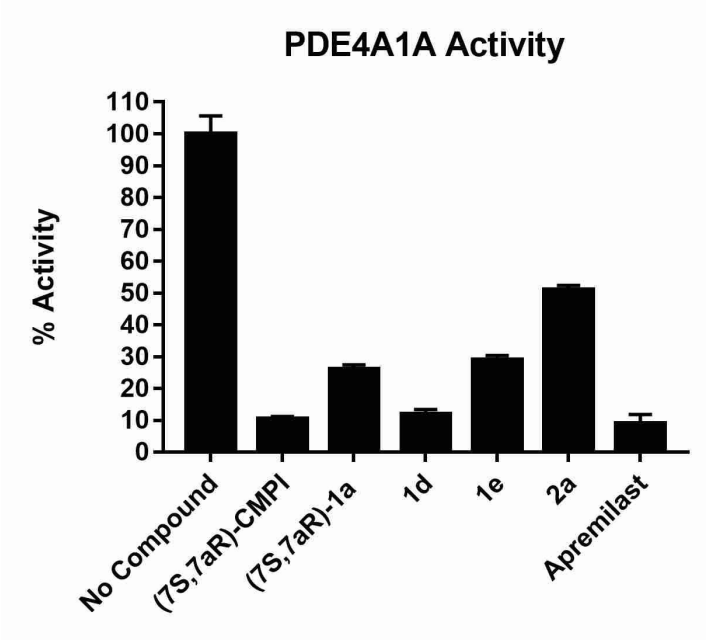
The values of percentage activity were plotted on a bar graph below.

PDE4A1A

Data for the Effect of the Compounds on PDE4A1A Activity

Compounds	PDE4A1A Activity [Fluorescent Polarization (mp)]		% Activity	
	Repeat 1	Repeat 2	Repeat 1	Repeat 2
No Compound	107	101	104	96
(7S,7aR)-**CMPI**, 0.1μM	29	30	10	11
rac-**1e**, 0.1μM	46	44	30	28
rac-**1d**, 0.1μM	30	32	11	13
Apremilast, 0.001μM	89	90	82	83
Apremilast, 0.01μM	58	61	45	48
Apremilast, 0.1μM	27	30	7	11
Blank	20	22		

Compound 0.1μM	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	162	163	100	100
rac-**2a**	94	92	52	50
(7S,7aR)-**1a**	59	56	27	25
Apremilast, 10μM	23	22	2	1
Background	20	21		

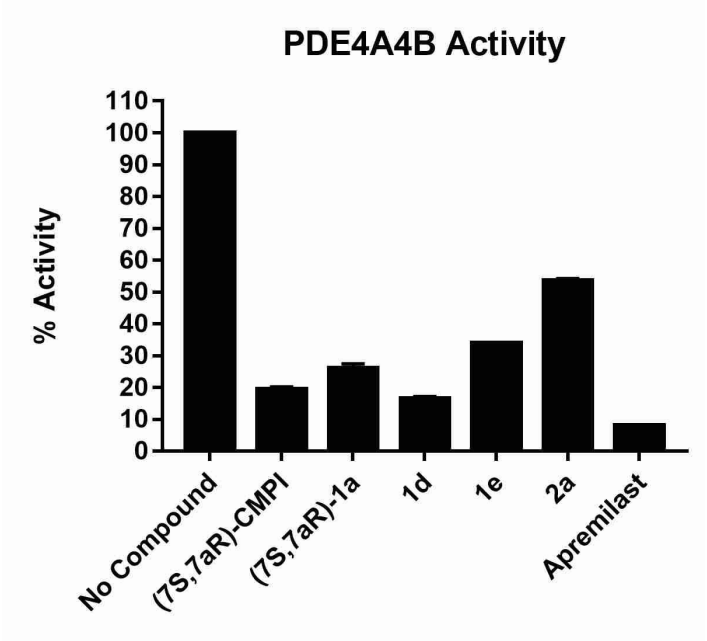


PDE4A4B

Data for the Effect of the Compounds on PDE4A4B Activity

Compounds	PDE4A4B Activity [Fluorescent Polarization (mp)]		% Activity	
	Repeat 1	Repeat 2	Repeat 1	Repeat 2
No Compound	150	151	100	100
(7S,7aR)-**CMPI**, 0.1μM	46	46	20	19
rac-**1e**, 0.1μM	65	65	34	34
rac-**1d**, 0.1μM	43	42	17	16
Apremilast, 0.001μM	129	138	84	90
Apremilast, 0.01μM	80	84	46	49
Apremilast, 0.1μM	31	32	8	8
Blank	20	21		

Compound 0.1μM	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	164	170	98	102
rac-**2a**	99	97	54	53
(7S,7aR)-**1a**	58	60	25	27
Apremilast, 10μM	22	23	1	2
Background	20	21		

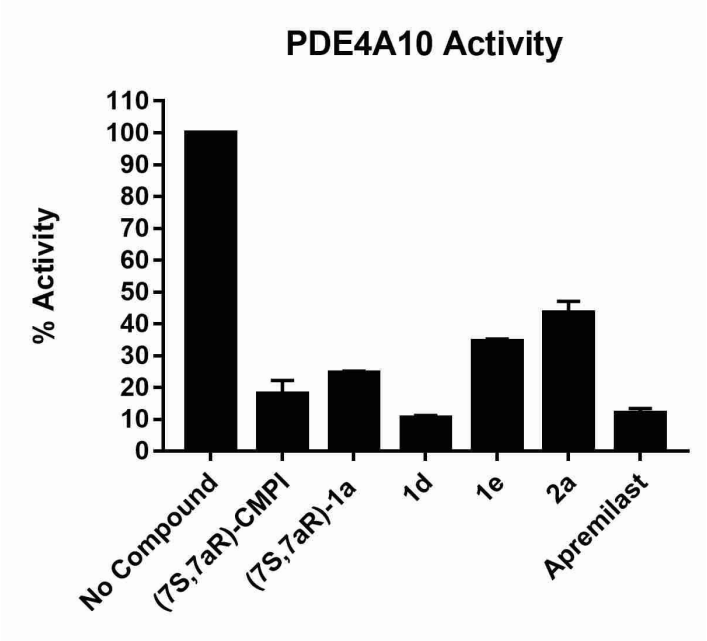


PDE4A10

Data for the Effect of the Compounds on PDE4A10 Activity

Compounds	PDE4A10 Activity [Fluorescent Polarization (mp)]		% Activity	
	Repeat 1	Repeat 2	Repeat 1	Repeat 2
No Compound	136	138	100	100
(7S,7aR)-CMPI, 0.1μM	46	40	21	15
rac-**1e**, 0.1μM	62	63	34	35
rac-**1d**, 0.1μM	35	34	11	10
Apremilast, 0.001μM	124	124	88	89
Apremilast, 0.01μM	75	71	46	42
Apremilast, 0.1μM	38	36	13	11
Blank	22	23		

Compound 0.1μM	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	106	100	103	97
rac-**2a**	58	54	46	41
(7S,7aR)-**1a**	41	40	25	24
Apremilast, 10μM	22	23	2	3
Background	20	21		

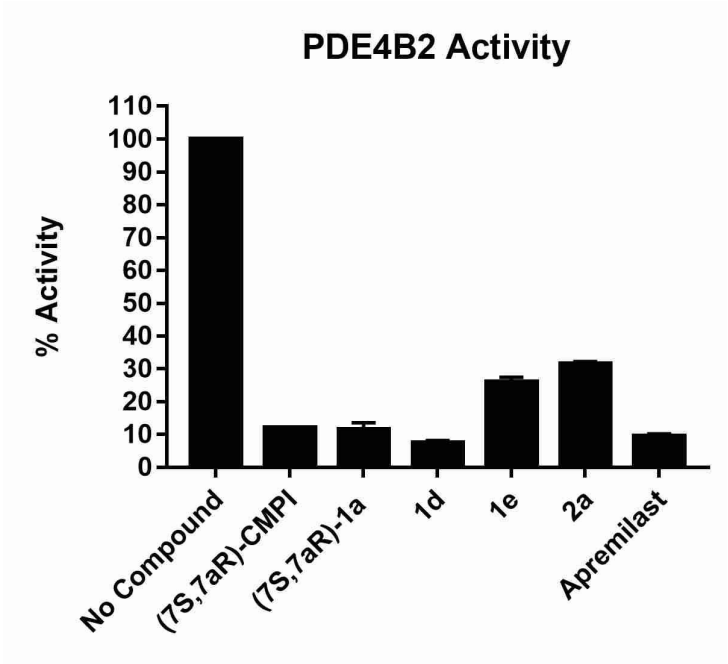


PDE4B2

Data for the Effect of the Compounds on PDE4B2 Activity

Compounds	PDE4B2 Activity [Fluorescent Polarization (mp)]		% Activity	
	Repeat 1	Repeat 2	Repeat 1	Repeat 2
No Compound	138	138	100	100
(7S,7aR)-**CMPI**, 0.1μM	37	36	12	12
rac-**1e**, 0.1μM	54	51	27	25
rac-**1d**, 0.1μM	30	32	7	8
Apremilast, 0.001μM	122	119	86	84
Apremilast, 0.01μM	78	78	48	48
Apremilast, 0.1μM	33	34	9	10
Blank	22	23		

Compound 0.1μM	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	113	109	102	98
rac-**2a**	48	50	31	32
(7S,7aR)-**1a**	29	32	10	13
Apremilast, 10μM	22	20	2	0
Background	20	21		

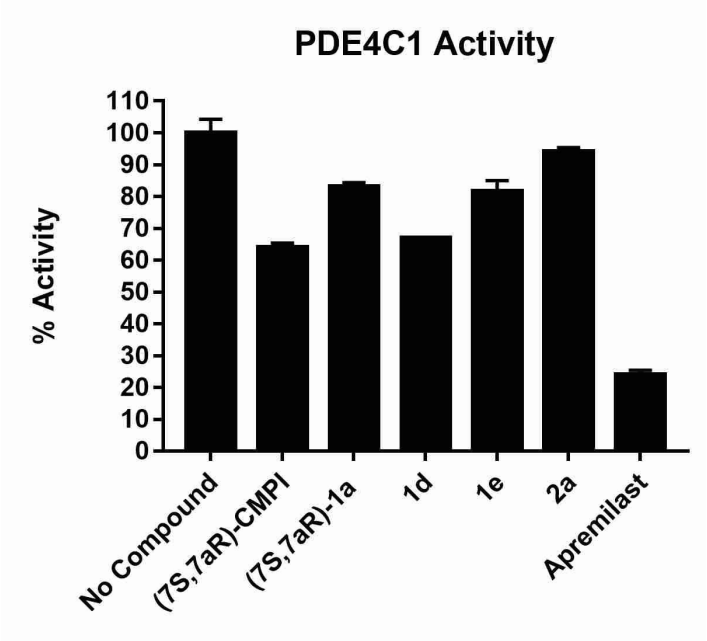


PDE4C1

Data for the Effect of the Compounds on PDE4C1 Activity

Compounds	PDE4C1 Activity [Fluorescent Polarization (mp)]		% Activity	
	Repeat 1	Repeat 2	Repeat 1	Repeat 2
No Compound	146	139	103	97
(7S,7aR)-**CMPI**, 0.1μM	98	100	63	65
rac-**1e**, 0.1μM	122	117	84	79
rac-**1d**, 0.1μM	102	102	67	67
Apremilast, 0.001μM	136	133	95	92
Apremilast, 0.01μM	100	104	65	68
Apremilast, 0.1μM	49	51	23	25
Blank	19	21		

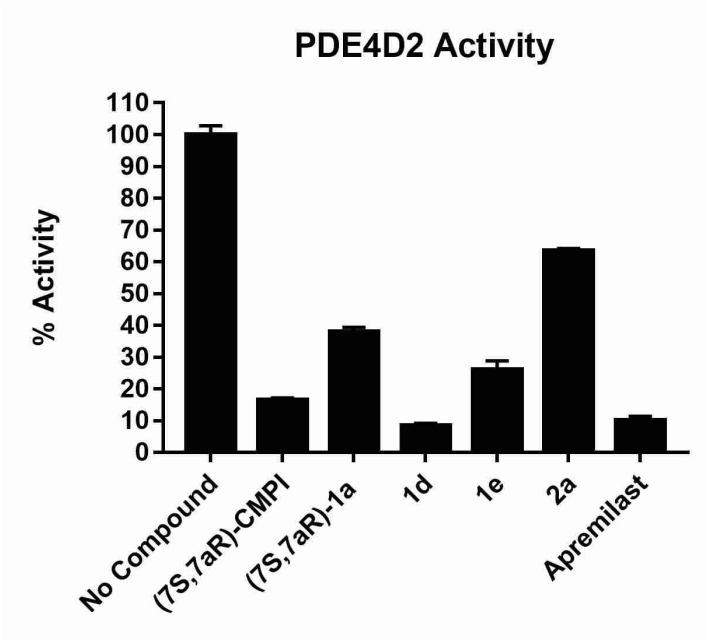
Compound 0.1μM	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	164	165	100	100
rac-**2a**	157	155	95	93
(7S,7aR)-**1a**	141	138	84	82
Apremilast, 10μM	24	21	3	1
Background	20	21		



PDE4D2

Compounds	PDE4D2 Activity [Fluorescent Polarization (mp)]		% Activity	
	Repeat 1	Repeat 2	Repeat 1	Repeat 2
No Compound	103	105	98	102
(7S,7aR)-**CMPI**, 0.1μM	35	36	16	17
rac-**1e**, 0.1μM	45	42	28	24
rac-**1d**, 0.1μM	28	30	8	9
Apremilast, 0.001μM	91	93	84	87
Apremilast, 0.01μM	59	59	45	46
Apremilast, 0.1μM	31	30	11	9
Blank	22	22		

Compound 0.1μM	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	160	157	101	99
rac-**2a**	108	107	64	63
(7S,7aR)-**1a**	74	72	39	37
Apremilast, 10μM	24	22	3	1
Background	20	21		

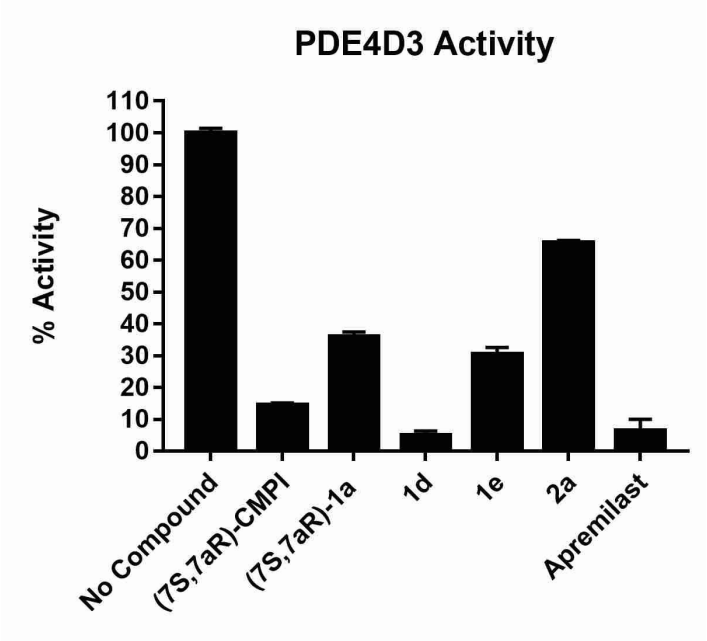


PDE4D3

Data for the Effect of the Compounds on PDE4D3 Activity

Compounds	PDE4D3 Activity [Fluorescent Polarization (mp)]		% Activity	
	Repeat 1	Repeat 2	Repeat 1	Repeat 2
No Compound	126	124	101	99
(7S,7aR)-**CMPI**, 0.1μM	37	35	15	14
rac-**1e**, 0.1μM	51	55	29	32
rac-**1d**, 0.1μM	25	27	4	6
Apremilast, 0.001μM	112	116	88	91
Apremilast, 0.01μM	70	67	47	44
Apremilast, 0.1μM	30	26	9	4
Blank	21	22		

Compound 0.1μM	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	159	158	100	100
rac-**2a**	111	112	65	66
(7S,7aR)-**1a**	71	69	37	35
Apremilast, 10μM	21	23	1	2
Background	20	21		

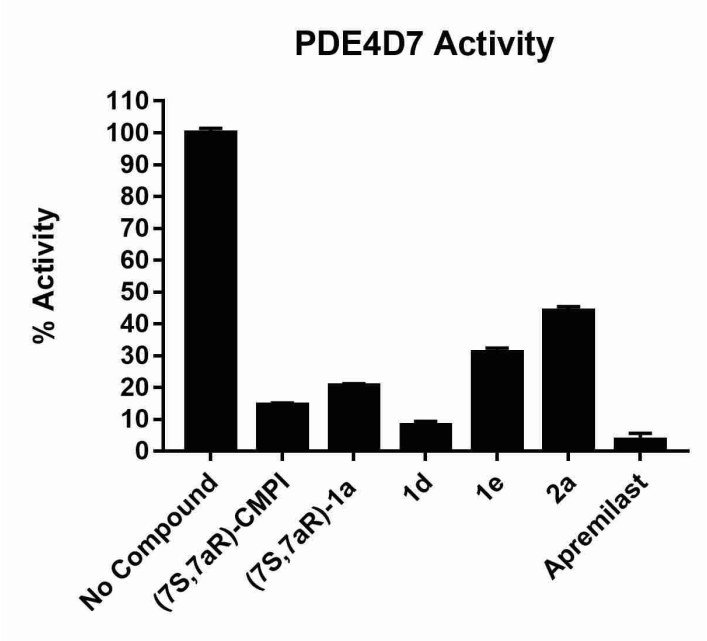


PDE4D7

Data for the Effect of the Compounds on PDE4D7 Activity

Compounds	PDE4D7 Activity [Fluorescent Polarization (mp)]		% Activity	
	Repeat 1	Repeat 2	Repeat 1	Repeat 2
No Compound	103	102	101	99
(7S,7aR)-**CMPI**, 0.1μM	32	33	14	15
rac-**1e**, 0.1μM	45	47	30	32
rac-**1d**, 0.1μM	29	26	9	7
Apremilast, 0.001μM	88	89	82	83
Apremilast, 0.01μM	56	55	43	42
Apremilast, 0.1μM	25	23	5	2
Blank	21	21		

Compound 0.1μM	PDE Activity [(Fluorescent Polarization (mp)]		% Activity	
	Repeat1	Repeat2	Repeat1	Repeat2
No Compound	140	139	101	99
2a	71	75	43	45
(7S,7aR)-**1a**	45	44	21	20
Apremilast, 10μM	22	22	1	1
Background	20	21		



PDE4B Cell Signaling Pathway Assay

Compounds

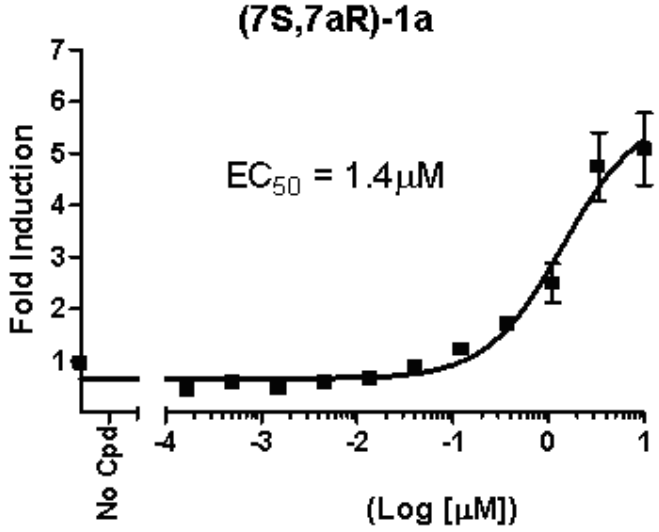
Compound I.D.	Dissolving Solvent	Stock Concentration	Test Range (uM)	Intermediate Dilution
(7S,7aR)-**1a**	DMSO	10 mM	10-0.0002	0.1% DMSO in assay medium
rac-**2a**	DMSO	10 mM	10-0.0002	0.1% DMSO in assay medium
Apremilast	DMSO	10 mM	10-0.0002	0.1% DMSO in assay medium

Apremilast, an inhibitor for the PDE4 signaling pathway, was used as a positive control.

Data for the effect of each compound on PDE4B activity is presented below.

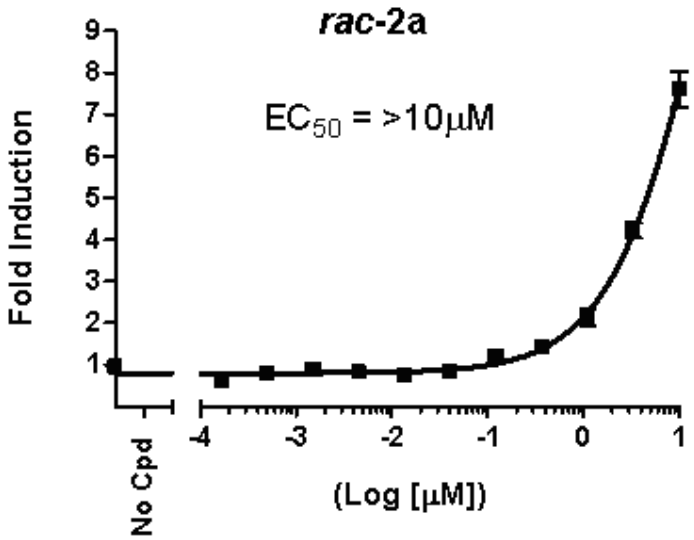
Raw Data for the Effect of (7S,7aR)-**1a** on PDE4B activity

(7S,7aR)-**1a** (uM)	Luminescence intensity			Fold Induction		
	Repeat1	Repeat2	Repeat3	Repeat1	Repeat2	Repeat3
No Cpd	2262	2782	3447	0.8	0.9	1.2
0.0002	1199	1622	1334	0.4	0.5	0.4
0.0005	1693	1662	1998	0.6	0.5	0.7
0.002	1035	1627	1552	0.3	0.5	0.5
0.005	1562	1992	1754	0.5	0.7	0.6
0.013	1513	2408	2084	0.5	0.8	0.7
0.04	1959	3254	2544	0.6	1.1	0.9
0.12	2987	3617	4095	1.0	1.2	1.4
0.4	4465	5193	5279	1.5	1.8	1.8
1.1	5064	8562	7884	1.7	3.0	2.7
3.3	9818	15846	14956	3.4	5.6	5.2
10	13511	18308	11673	4.7	6.4	4.1
Background	98	167	120			



Raw Data for the Effect of *rac*-2a on PDE4B activity

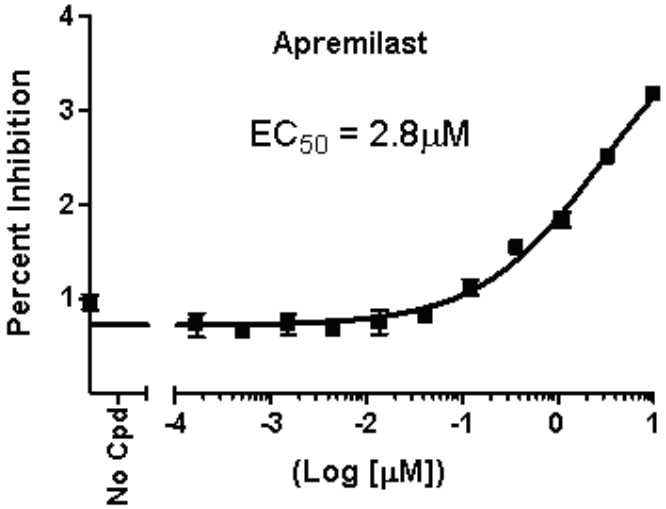
rac-**2a** (uM)	Luminescence intensity			Fold Induction		
	Repeat1	Repeat2	Repeat3	Repeat1	Repeat2	Repeat3
No Cpd	2575	1919	2184	1.1	0.8	0.9
0.0002	1643	1214	1636	0.7	0.5	0.7
0.0005	1723	2085	1860	0.7	0.9	0.8
0.002	1856	1896	2451	0.8	0.8	1.0
0.005	1885	1624	2291	0.8	0.7	1.0
0.013	1885	1643	1674	0.8	0.7	0.7
0.04	1703	1717	2504	0.7	0.7	1.1
0.12	2642	2794	2924	1.1	1.2	1.3
0.4	3779	2779	3383	1.6	1.2	1.5
1.1	5711	4684	4211	2.5	2.0	1.8
3.3	9901	8709	9890	4.4	3.9	4.4
10	18938	16405	15746	8.5	7.3	7.0
Background	98	167	120			



Raw Data for the Effect of Apremilast on PDE4B activity

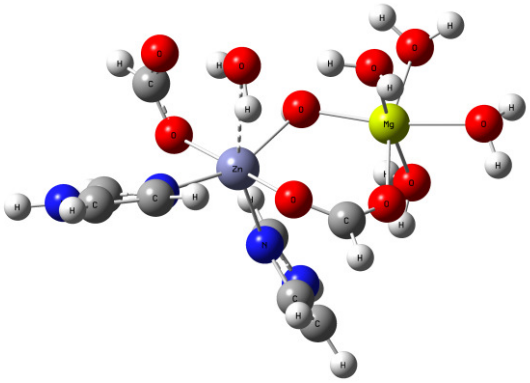
Apremilast (uM)	Luminescence intensity			Fold Induction		
	Repeat1	Repeat2	Repeat3	Repeat1	Repeat2	Repeat3
No Cpd	1700	2115	2286	0.8	1.0	1.1
0.0002	1338	1172	2039	0.6	0.6	1.0
0.0005	1364	1253	1440	0.6	0.6	0.7
0.002	1325	1276	1996	0.6	0.6	0.9
0.005	1334	1691	1164	0.6	0.8	0.6
0.013	1696	1077	1966	0.8	0.5	0.9
0.04	1699	1540	1895	0.8	0.7	0.9
0.12	2047	2583	2497	1.0	1.2	1.2
0.4	3233	3061	3451	1.5	1.5	1.6
1.1	3520	4120	3984	1.7	2.0	1.9
3.3	5346	5206	*9264**	2.5	2.5	
10	6698	6646	*11983**	3.2	3.2	
Background	131	44	92			

** Data points were excluded from the analysis*



4. Quantum-chemical calculations

Complex [CX-1]$^{+}$



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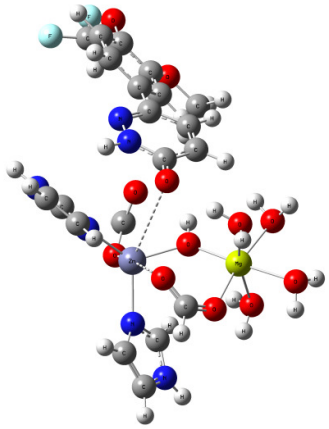
H	1.36768500	-0.01513700	2.47508400
H	1.32643700	-0.64253500	-0.76434300
H	-1.10968000	-2.25282100	3.28998900
H	-1.94568300	1.26415300	1.72104800
O	-3.09263700	-4.27688800	1.61476800
O	0.97754900	-2.29755700	1.25947000
C	0.94301200	-3.55704900	1.33660100
O	-1.85817800	-1.95538800	-0.24902800
H	1.85566800	-4.05090100	1.75796100
O	-1.91483200	0.73261100	0.91037400
O	-1.71379900	-1.87037500	2.63426700
O	-0.00200800	-4.30906100	0.99140700
O	-2.76756800	-3.59589200	-2.57988400
H	-4.74622100	-3.61868400	-3.01519900
H	-3.40608800	-4.10561500	0.70353200
N	0.31527200	-3.16441400	-2.16019600
C	0.11487200	-2.23239900	-3.08536600
C	1.68721500	-3.25598100	-1.99724200
N	-1.58489100	-5.95420600	-0.94660000
C	-1.41971100	-6.91616000	0.03975400
C	-2.15664900	-6.57684300	-1.97324900
C	-3.97064000	-3.75231100	-2.21338900
H	1.40303900	-1.02603200	-4.24601800
N	-2.35033800	-7.88152000	-1.69244800
H	-1.94692800	-9.10518100	0.04146200
O	-4.37464700	-4.03738900	-1.06217300
H	-2.76356500	-8.56532300	-2.32182900
C	-1.89148900	-8.12069700	-0.41349100
H	-0.97529000	-6.67353400	1.00146800
H	-2.43291000	-6.12341500	-2.92225600
H	-0.85365300	-1.89474600	-3.45104900
H	3.35532400	-2.15490400	-3.03974600
C	2.30949700	-2.37850100	-2.84993400
H	2.12967100	-3.95375200	-1.28810300

N	1.29176000	-1.74450900	-3.53444000
Mg	-0.62043200	-0.98390700	1.00810500
Zn	-1.32864400	-3.81506700	-0.86662500
H	0.33553700	1.11708400	2.43618500
H	-2.82972800	0.43698500	0.78115600
H	0.11641000	0.10729100	-1.33212700
H	-1.97425000	-1.49515300	-1.09416200
H	-2.24513700	-2.63108400	2.32013900
H	-2.18679000	-4.60050000	1.47761500

DFT MN15L, solvent water, smd model		
Sum of electronic and zero-point Energies=	-3267.484408	$E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-3267.448982	$E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-3267.448038	$E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-3267.543325	$E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.335499	

Complex [CX-2]$^{+}$

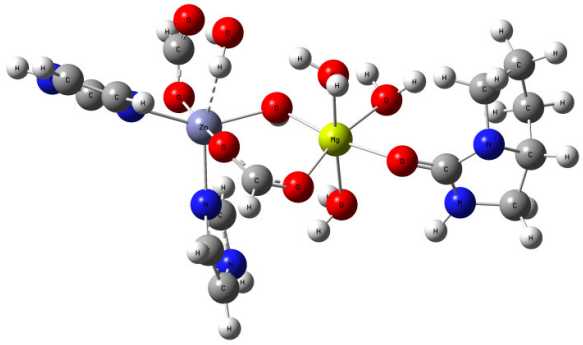


O	0.46296500	0.42553200	0.02775400
O	2.39390000	-0.40284800	2.06197500
H	3.00268700	-0.40707300	1.30618300
H	0.96530800	0.16077500	-0.76063900
H	1.70756500	-3.07067800	2.86376900
H	0.06805100	0.04463700	3.75345000
O	1.53034500	-2.36428100	0.05954900
C	1.45752600	-3.62558100	-0.09818300
O	-1.35675400	-1.87052800	0.95249100
H	2.25769100	-4.07039000	-0.74793600
O	-0.34523100	0.15896900	2.88251000
O	0.86934500	-2.61925700	3.05414300
O	0.60373800	-4.39499700	0.38785400
O	-3.78911600	-2.10250000	-1.06960700
H	-5.36586700	-0.96809800	-0.50019200
N	-0.94365200	-2.82692300	-2.17943600
C	-0.73063000	-1.55068300	-2.48185600
C	0.00135800	-3.55393000	-2.88268400
N	-2.90248200	-5.04340100	0.06673200
C	-2.33532600	-6.25226500	0.43792000
C	-4.22052900	-5.22115600	0.09904800
C	-4.56130700	-1.67108300	-0.15530900
H	0.64072600	-0.56114600	-3.74724700
N	-4.51577300	-6.48412900	0.46593100
H	-3.31451700	-8.20215200	0.99458100
O	-4.51101300	-1.95282800	1.06114000
H	-5.45369900	-6.86766400	0.55815900
C	-3.33166100	-7.16052600	0.68823400
H	-1.25732600	-6.37951400	0.50109600
H	-4.97434200	-4.47364300	-0.14007700
H	-1.30819100	-0.70650900	-2.10556400
H	1.60872400	-2.86141000	-4.30018000
C	0.77941900	-2.69811100	-3.61817100
H	0.06332300	-4.63685500	-2.79741900
N	0.29432600	-1.43217200	-3.35149000
Mg	0.48061200	-1.23824000	1.45000500
Zn	-2.04157900	-3.19175200	-0.37300500
H	2.29983400	0.53756000	2.28208000
H	-1.28347800	-0.03678500	3.04107500
H	-0.44144500	0.54119700	-0.30534000
H	-2.14370900	-1.53806300	1.40571300
H	0.20422500	-3.34153200	3.06554400

O	-1.23933200	-4.58287500	3.14561700
C	-2.31159400	-4.01255000	3.44075700
N	-3.50805600	-4.68247300	3.29927700
C	-2.45552200	-2.67452300	3.96782400
N	-4.75252200	-4.22645600	3.51118200
H	-3.46306400	-5.64456800	2.94911900
C	-3.70246900	-2.17919300	4.21541300
H	-1.54383500	-2.10098000	4.16018700
C	-4.86160500	-2.98731400	3.95282900
H	-3.83003700	-1.17634000	4.63315700
C	-6.23887500	-2.46570300	4.14579600
C	-7.28671200	-3.32363700	4.51678400
C	-6.48498200	-1.09378300	3.93166700
C	-8.57824900	-2.81044800	4.67511900
H	-7.08860300	-4.38308200	4.69481800
C	-7.77693100	-0.57672100	4.09225900
H	-5.66913400	-0.44331400	3.60922700
C	-8.81396100	-1.45571400	4.47089300
H	-9.41553800	-3.44866000	4.97267800
O	-8.13587600	0.71931700	3.90772800
O	-10.09104800	-0.92921700	4.68902400
C	-7.10170500	1.62930700	3.53004200
C	-10.81734100	-0.77399200	3.52478700
H	-6.65680000	1.34025900	2.56102300
H	-6.31230000	1.66881200	4.30173900
H	-7.58554200	2.61092500	3.44013000
F	-11.88531500	-0.03302000	3.84813100
F	-11.28594400	-1.98145400	3.11776300
H	-10.24997400	-0.31137200	2.69663900

DFT MN15L, solvent water, smd model		
Sum of electronic and zero-point Energies=	-4188.620483	$E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-4188.569889	$E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-4188.568945	$E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-4188.700166	$E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.522772	

Complex [CX-3]$^{+}$

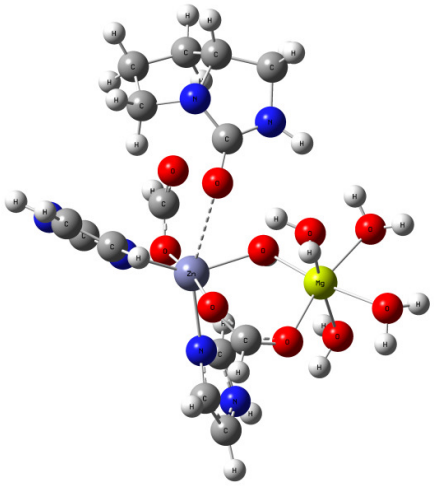


O	0.20352100	-0.02014600	-0.51362700
H	0.97205900	-0.55780700	-0.77254700
H	-1.34877000	-2.30739500	3.34600400
H	-2.68673700	0.88729000	1.74755700
O	-3.00653400	-4.62339200	1.52987600
O	0.79081400	-2.28766200	1.22444000
C	0.87471300	-3.54701800	1.26662900
O	-2.02073200	-2.14370200	-0.26039800
H	1.85178300	-3.96104500	1.62733400
O	-2.38305100	0.51064700	0.90501300
O	-1.94562700	-2.04273200	2.62845000
O	-0.01244000	-4.37568200	0.94717600
O	-2.83933600	-3.75789600	-2.68628800
H	-4.82054900	-3.91199800	-3.07605000
H	-3.34637600	-4.47036100	0.62598100
N	0.26128300	-3.16786500	-2.20712500
C	0.03333800	-2.22967800	-3.12028000
C	1.63213800	-3.19241000	-2.01276800
N	-1.51839600	-6.07484500	-1.06742300
C	-1.25173100	-7.03289800	-0.09938100
C	-2.07197200	-6.72783200	-2.08494200
C	-4.02007600	-4.00340900	-2.29314900
H	1.28347700	-0.93662900	-4.22680900
N	-2.16064100	-8.04647400	-1.81537200
H	-1.61454200	-9.25449900	-0.10917900
O	-4.37573000	-4.33292800	-1.13892400
H	-2.54309000	-8.75228400	-2.43972000
C	-1.64656400	-8.26417600	-0.55370800
H	-0.79894400	-6.76973600	0.85265000
H	-2.40845600	-6.28716400	-3.02046100
H	-0.94365500	-1.93659600	-3.50223400
H	3.26289400	-1.98521000	-2.99300700
C	2.22608700	-2.26654000	-2.83321500
H	2.09465100	-3.88136000	-1.30815800
N	1.19267600	-1.67155800	-3.52931600
Mg	-0.89115200	-1.07422400	1.02707800

Zn	-1.37142800	-3.91246600	-1.00975200
H	-3.18793700	0.14391500	0.50519500
H	-0.32756200	0.03677800	-1.32534800
H	-2.20621900	-1.65354600	-1.07636500
H	-2.35848300	-2.87623600	2.32412600
H	-2.05515200	-4.76600400	1.38441000
O	0.00815900	0.12060900	2.52388900
C	0.03477100	1.35805000	2.69104000
N	-0.39217100	1.99497300	3.84364200
N	0.49002800	2.26793300	1.80134800
C	-0.52633300	3.43707600	3.50952500
C	-1.66288200	1.51768300	4.44788100
C	0.47790400	3.61480600	2.36300300
H	1.07881700	1.97662400	1.02564200
C	-2.00950400	3.54981600	3.14208100
H	-0.28291700	4.06312400	4.38329900
C	-2.67179600	2.67258900	4.21648300
H	-1.96391000	0.57948600	3.95000000
H	-1.52236200	1.30183300	5.51820500
H	0.14059600	4.36024100	1.62564400
H	1.47665900	3.90313300	2.73615200
H	-2.15395900	3.11457400	2.13322200
H	-2.37715400	4.58723700	3.13364700
H	-3.66072000	2.29334300	3.91529400
H	-2.79884400	3.25462300	5.14526800

DFT MN15L, solvent water, smd model		
Sum of electronic and zero-point Energies=	-3610.162714	$E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-3610.121165	$E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-3610.120221	$E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-3610.230046	$E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.475390	

Complex [CX-4]$^{+}$

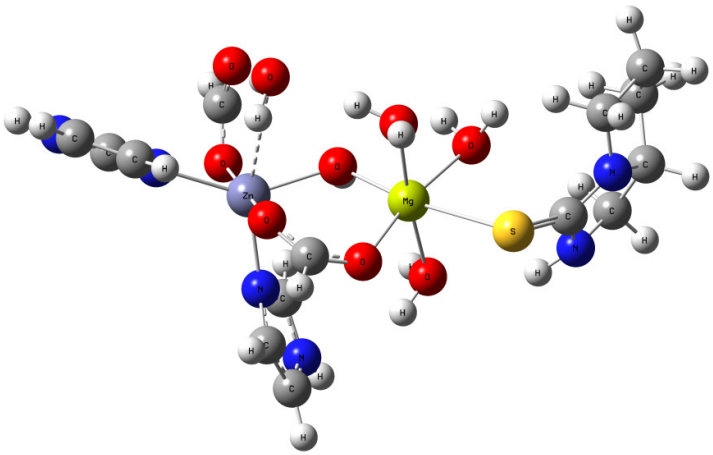


O	0.16911400	0.12966300	-0.55767900
O	1.00147000	0.15359500	2.32810400
H	1.89068200	0.15507700	1.94041400
H	0.91204500	-0.29219900	-1.02415300
H	0.21655000	-2.50235100	3.32433100
H	-1.62471600	0.89257900	2.47330300
O	1.44888600	-2.14586200	0.78055400
C	1.58519000	-3.40515800	0.79696300
O	-1.74153600	-2.16387400	0.19551200
H	2.64253000	-3.77886800	0.81569100
O	-1.84738000	0.31731000	1.72478300
O	-0.63493000	-2.20712500	2.96474900
O	0.67168000	-4.26108400	0.79337100
O	-2.93318200	-3.78166800	-2.22497800
H	-4.94553200	-3.77557500	-2.45500900
N	0.06366300	-3.10621000	-2.25716000
C	-0.41776700	-2.12886600	-3.01868100
C	1.43521200	-3.09310100	-2.44613000
N	-1.49337100	-6.03632300	-0.48803600
C	-1.01966200	-6.87335400	0.51248100
C	-2.37891800	-6.75235200	-1.17659300
C	-4.09611700	-3.90012000	-1.72983400
H	0.45965700	-0.73383800	-4.34062400
N	-2.47808700	-7.99932000	-0.67379700
H	-1.53112800	-9.01386800	0.98335800
O	-4.37972200	-4.14093500	-0.53587100
H	-3.07990200	-8.73499200	-1.03587200
C	-1.62474600	-8.09822200	0.40692800
H	-0.28936500	-6.53157700	1.23992800
H	-2.94407200	-6.41243400	-2.04144000
H	-1.46542600	-1.84608200	-3.10523000
H	2.71902500	-1.78295200	-3.75592800
C	1.76964700	-2.10492500	-3.33780200
H	2.08709400	-3.80167900	-1.93829200
N	0.57573200	-1.50909900	-3.69253200
Mg	-0.31429400	-1.10936700	1.15586500
Zn	-1.30287500	-3.93664900	-0.68833900
H	0.75059000	1.08978600	2.35862600

H	-2.62261300	-0.18301900	2.02876100
H	-0.55018200	0.11912200	-1.21063600
H	-2.10531300	-1.66075200	-0.54963800
H	-1.10685400	-3.03773300	2.73312300
O	-2.28451000	-4.42132300	2.30239600
C	-3.40787500	-4.20616800	2.78560700
N	-4.30886400	-5.19982200	3.14217200
N	-3.94546600	-2.98041900	3.05179600
C	-5.60462600	-4.54739100	3.45259600
C	-4.52456500	-6.28906300	2.15219000
C	-5.18817700	-3.11264200	3.81031100
H	-3.31624100	-2.18758700	3.17853400
C	-6.40308300	-4.72792200	2.15897700
H	-6.10008400	-5.05547700	4.29678500
C	-6.01026500	-6.15271000	1.73501900
H	-3.83617400	-6.13795100	1.30367900
H	-4.30717700	-7.27408400	2.59675000
H	-5.93950100	-2.37180800	3.49342600
H	-5.01026800	-3.00127000	4.89471700
H	-6.05119300	-3.98474700	1.42100500
H	-7.48720400	-4.59943600	2.30213500
H	-6.14278000	-6.33471600	0.65626200
H	-6.62596500	-6.88670900	2.28325700

DFT MN15L, solvent water, smd model		
Sum of electronic and zero-point Energies=	-3610.163951	$E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-3610.122519	$E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-3610.121575	$E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-3610.229437	$E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.474904	

Complex [CX-5]$^{+}$

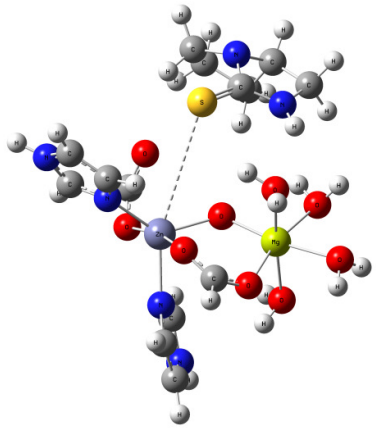


O	0.59136200	-0.14229500	-0.32619800
H	1.34929300	-0.67425900	-0.62654400
H	-1.05173000	-2.59816400	3.43080300
H	-2.32080100	0.55330600	2.06410200
O	-2.94359600	-4.55005000	1.47832000
O	1.06280300	-2.62111400	1.25955500
C	1.02448700	-3.88172300	1.19309600
O	-1.71679300	-2.16469100	-0.17677200
H	1.93267100	-4.42037900	1.56586500
O	-1.91469000	0.39993800	1.19382000
O	-1.59774400	-2.22399100	2.72200200
O	0.08429700	-4.59099500	0.75505100
O	-2.62014800	-3.53417600	-2.69103200
H	-4.59073400	-3.37436600	-3.12584700
H	-3.24398700	-4.24196900	0.60040700
N	0.42771200	-3.20766300	-2.22234300
C	0.23566200	-2.19405500	-3.06050500
C	1.79817400	-3.30663700	-2.04796900
N	-1.71404000	-6.07562500	-1.17783800
C	-1.48309900	-7.09567400	-0.26571400
C	-2.40267900	-6.62443700	-2.17296200
C	-3.83418500	-3.61273000	-2.33002200
H	1.53220400	-0.88010100	-4.08519400
N	-2.61298400	-7.93734700	-1.94202700
H	-2.07877400	-9.26624400	-0.32422200
O	-4.26541200	-3.92614100	-1.19798300
H	-3.10776800	-8.57428300	-2.56162500
C	-2.03722900	-8.25995100	-0.73054300
H	-0.93787400	-6.91922300	0.65796400
H	-2.75229100	-6.11537700	-3.06810900
H	-0.72893300	-1.82859700	-3.40844500
H	3.47409400	-2.10564800	-2.95822700
C	2.42703200	-2.35101800	-2.80607300
H	2.23621100	-4.06495800	-1.40142800
N	1.41555400	-1.66052600	-3.44313100
Mg	-0.50519400	-1.26557400	1.14605400
Zn	-1.21725600	-3.94794600	-1.03669000
H	-2.65909300	0.10867800	0.64118900
H	0.04355000	-0.04250300	-1.12330700

H	-1.87058400	-1.61971600	-0.96411500
H	-2.09870700	-2.98637900	2.36266600
H	-2.03877700	-4.85773500	1.29845300
C	0.24199800	1.64935700	2.86399100
N	-0.51226700	2.36089000	3.72379000
N	0.48932600	2.38800500	1.75137600
C	-1.04956000	3.58033600	3.06597700
C	-1.46901800	1.78418800	4.68799800
C	-0.51327100	3.46225000	1.62459400
H	0.79289400	1.87025100	0.92633700
C	-2.55295100	3.44774000	3.31709400
H	-0.65081200	4.47730900	3.57462600
C	-2.57337600	2.85369100	4.73588000
H	-1.84624400	0.81910400	4.29493900
H	-0.99582300	1.59620400	5.66466100
H	-1.31010800	3.16520800	0.91660800
H	-0.05117200	4.39458900	1.27093200
H	-2.97524400	2.72557800	2.59120400
H	-3.09436800	4.40157400	3.22939600
H	-3.54504300	2.42645000	5.02378700
H	-2.30592200	3.63603400	5.46812100
S	0.83289700	0.08655500	3.14583500

DFT MN15L, solvent water, smd model		
Sum of electronic and zero-point Energies=	-3933.104508	$E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-3933.062596	$E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-3933.061652	$E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-3933.173148	$E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.473184	

Complex [CX-6]$^{+}$

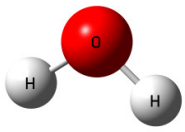


O	-0.63322200	-0.05931400	-0.35871500
O	0.26113500	-0.05641100	2.51654700
H	1.18200100	0.09666600	2.25252600
H	0.14362600	-0.27976500	-0.90225400
H	0.50214700	-2.94409600	3.18789700
H	-2.52773600	-0.53649000	2.95831700
O	1.25678100	-2.02966300	0.65587900
C	1.71783900	-3.19736100	0.50564300
O	-1.80729400	-2.86848900	0.27848000
H	2.83468600	-3.28681600	0.49816100
O	-2.48014200	-0.60090200	1.99044400
O	-0.43426300	-2.86015500	2.94614800
O	1.05898400	-4.25556200	0.36255700
O	-2.65198800	-4.42468800	-2.35873300
H	-4.62318800	-4.82053400	-2.59294300
N	0.00555400	-3.03487500	-2.37561100
C	-0.73821500	-2.15221200	-3.03528800
C	1.32216300	-2.69545400	-2.64011800
N	-0.81911200	-6.38414100	-0.70410300
C	-0.18166500	-7.12021500	0.28407700
C	-1.51142800	-7.25883400	-1.42730800
C	-3.76407300	-4.78328600	-1.86736100
H	-0.29629400	-0.51617400	-4.29418000
N	-1.33696400	-8.50921600	-0.95474200
H	-0.20916800	-9.33318900	0.69485200
O	-3.99816600	-5.09682000	-0.67876800
H	-1.75406600	-9.35034200	-1.34637600
C	-0.49501000	-8.44591400	0.13775500
H	0.44439800	-6.64218400	1.03267700
H	-2.12846200	-7.02857500	-2.29270800
H	-1.82555100	-2.11245400	-3.03935400
H	2.17831800	-1.05100700	-3.92006400
C	1.35888000	-1.60590300	-3.47261200
H	2.15155300	-3.26567100	-2.22624700
N	0.03876500	-1.28116800	-3.71375000
Mg	-0.67769800	-1.52870500	1.25140100
Zn	-0.94401600	-4.28295500	-0.87096500
H	-0.16171700	0.81182600	2.42430200
H	-3.23646600	-1.16485400	1.75395400
H	-1.38352300	-0.19701100	-0.96021400

H	-2.58802500	-2.57231800	-0.21176400
H	-0.72026400	-3.77611700	2.75029600
C	-3.58051700	-4.60580300	3.38670400
N	-4.93914800	-4.85346200	3.41540100
N	-3.36055000	-3.33816900	3.78187900
C	-5.62490100	-3.52853900	3.43432200
C	-5.56851000	-5.68704200	2.35889400
C	-4.58813400	-2.61445100	4.08739200
H	-2.42604100	-2.97539400	3.94827100
C	-5.92425700	-3.32222000	1.94761900
H	-6.56082800	-3.58935400	4.01412800
C	-6.48390900	-4.70581700	1.58460800
H	-4.77781200	-6.11593100	1.72502600
H	-6.13660600	-6.51397300	2.81304400
H	-4.58034000	-1.60083700	3.65281400
H	-4.74075500	-2.53329400	5.17878700
H	-4.96266100	-3.13092900	1.41840600
H	-6.61945100	-2.49249700	1.74802300
H	-6.48854700	-4.91796300	0.50543200
H	-7.52145400	-4.78189900	1.95501200
S	-2.37846300	-5.70942300	2.96380500

DFT MN15L, solvent water, smd model		
Sum of electronic and zero-point Energies=	-3933.113535	$E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-3933.071348	$E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-3933.070404	$E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-3933.180677	$E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.471709	

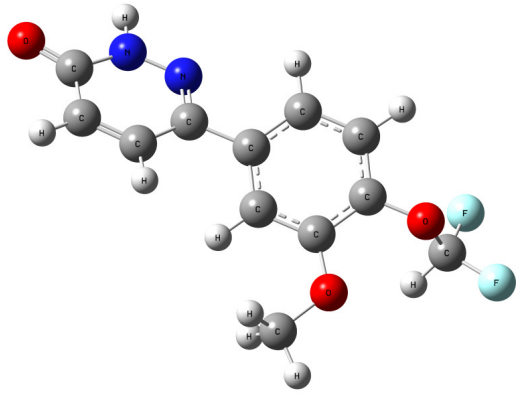
H_2O



O	-2.94274200	-4.54929400	1.47338700
H	-3.24179900	-4.24387400	0.60525500
H	-2.04181900	-4.85658600	1.29853800

DFT MN15L, solvent water, smd model		
Sum of electronic and zero-point Energies=	-76.367044	$E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-76.364209	$E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-76.363265	$E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-76.378555	$E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.021399	

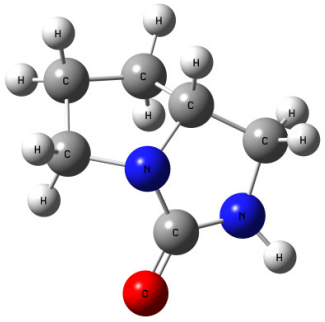
Zardaverine



F	0.02728000	11.81373100	10.09223100
O	3.69855600	6.23068000	0.56384700
O	-0.19068000	10.93410500	8.11519600
F	1.36001200	12.49365300	8.52677800
C	3.15168400	6.69853100	1.57875300
N	3.26970200	8.04597400	1.87103200
C	1.17461300	10.17209700	4.77110700
C	0.64028700	10.88556400	5.84815400
C	2.35678800	5.97273800	2.54410300
O	0.42708200	8.35626300	8.45381400
C	1.47175300	8.80622900	4.91617200
C	1.22865900	8.15681600	6.14423000
N	2.76412900	8.72582500	2.90855500
C	1.82214300	6.62988200	3.61358100
C	0.69278500	8.86946800	7.22525300
C	2.04522800	8.04005000	3.77884200
C	0.39918000	10.23864900	7.05466200
C	0.73185800	11.40054300	9.03047700
C	0.70727600	6.96994100	8.65277200
H	1.48518800	7.10243900	6.26118900
H	1.49162100	10.65365500	9.32511300
H	1.19941500	6.09443600	4.33577500
H	2.19912800	4.90480000	2.37482800
H	1.78316100	6.76111100	8.51541000
H	1.34646800	10.66951000	3.81425000
H	3.82326900	8.61355700	1.22414800
H	0.11792000	6.34583700	7.95759000
H	0.38965900	11.94712800	5.76293700
H	0.41497300	6.75215500	9.68862800

DFT MN15L, solvent water, smd model		
Sum of electronic and zero-point Energies=	-997.484386	$E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-997.468369	$E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-997.467425	$E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-997.522766	$E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.212569	

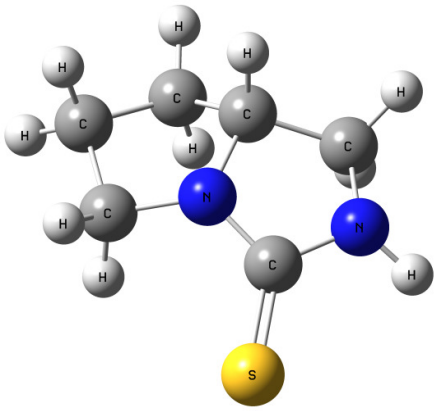
Ligand 1a'



O	0.06201400	0.11560300	2.54142300
C	0.05695400	1.34270500	2.69825100
N	-0.40046100	2.00000700	3.83896300
N	0.48252300	2.26588500	1.78386800
C	-0.54612300	3.43528000	3.48957400
C	-1.68075500	1.51127900	4.41588400
C	0.46609600	3.61026800	2.35197800
H	1.18186400	1.98597600	1.10075000
C	-2.03237800	3.53929200	3.13385300
H	-0.31017500	4.07427200	4.35739000
C	-2.66069100	2.69718000	4.25357000
H	-2.00516600	0.62034600	3.85291800
H	-1.55193900	1.22017100	5.47031300
H	0.13822500	4.36116500	1.61516500
H	1.45895800	3.90153700	2.74006100
H	-2.19597400	3.06332100	2.14710700
H	-2.40283200	4.57541000	3.09763400
H	-3.68365100	2.35658800	4.03267500
H	-2.69210700	3.29146900	5.18388900

DFT MN15L, solvent water, smd model		
Sum of electronic and zero-point Energies=	-419.034296	$E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-419.026960	$E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-419.026016	$E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-419.059290	$E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.163911	

Ligand 1e'



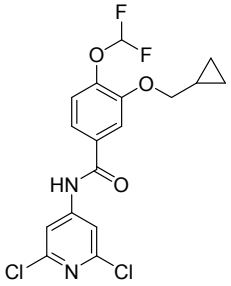
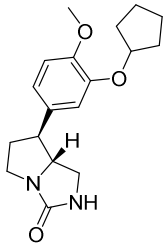
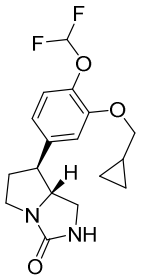
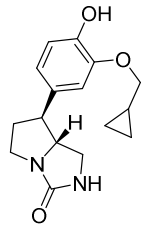
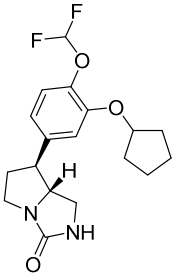
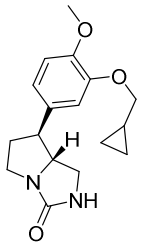
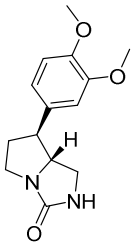
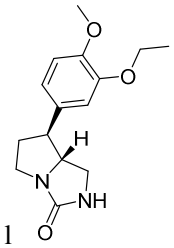
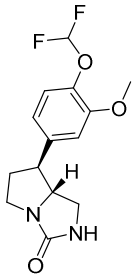
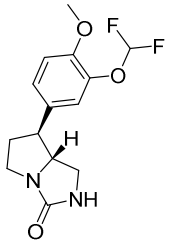
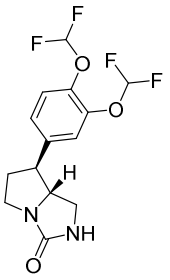
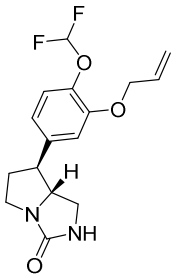
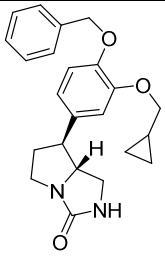
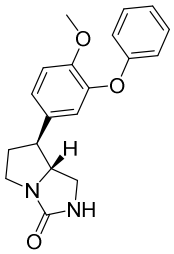
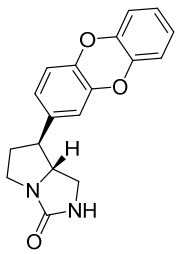
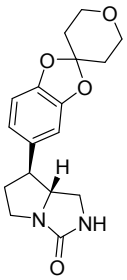
C	0.26426800	1.64414100	2.87507900
N	-0.52542700	2.35061600	3.71757400
N	0.52995800	2.42173400	1.77701300
C	-1.05049300	3.57245100	3.06123600
C	-1.48849500	1.77161600	4.66663300
C	-0.53189000	3.43276000	1.61898100
H	0.87239000	1.92568500	0.95661500
C	-2.55320000	3.47149300	3.32952400
H	-0.62796400	4.46813600	3.55576200
C	-2.57073800	2.86185000	4.74230600
H	-1.88610400	0.82551400	4.25323000
H	-1.01898100	1.55246400	5.63933200
H	-1.32675300	3.06592900	0.94078000
H	-0.13009000	4.37469900	1.21951400
H	-2.99930000	2.76522200	2.60355200
H	-3.07567900	4.43735800	3.25823800
H	-3.54863300	2.45291800	5.03667400
H	-2.27860800	3.62997900	5.48058500
S	0.85767600	0.10074800	3.14451700

DFT MN15L, solvent water, smd model		
Sum of electronic and zero-point Energies=	-741.984631	$E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-741.976734	$E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-741.975789	$E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-742.011017	$E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.161445	

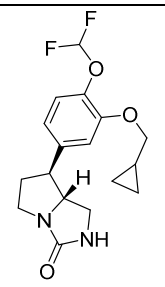
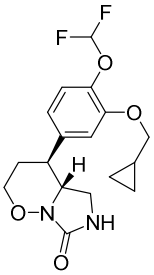
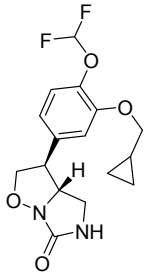
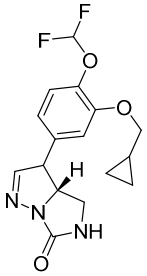
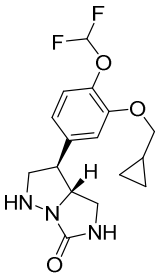
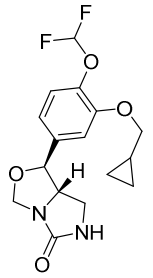
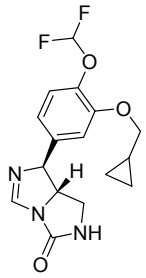
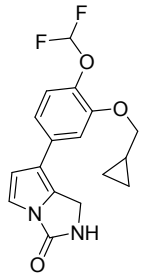
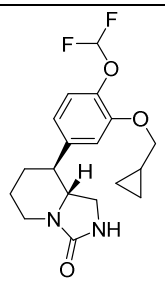
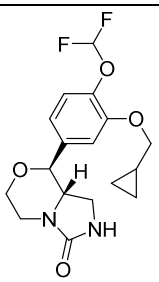
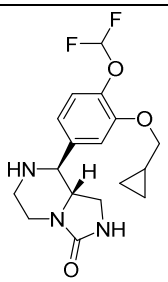
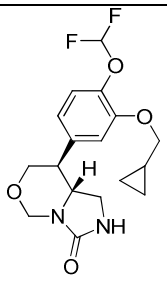
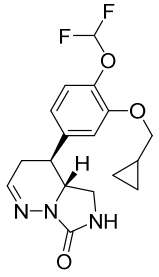
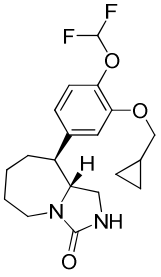
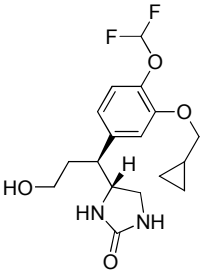
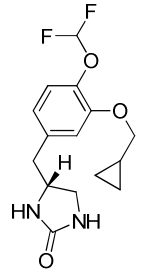
5. Molecular docking

Structures used in docking and binding energies of ligand in a top scored pose are shown below:

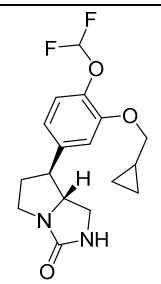
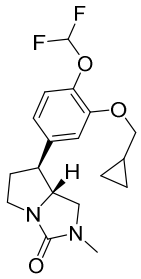
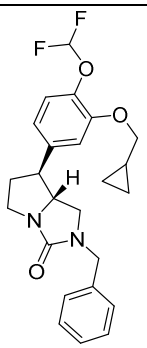
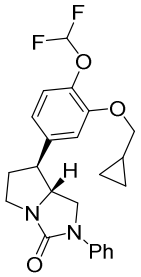
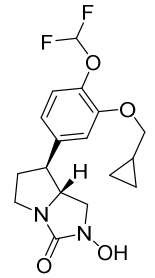
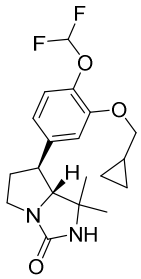
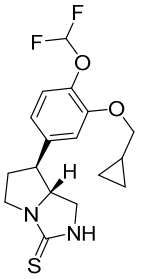
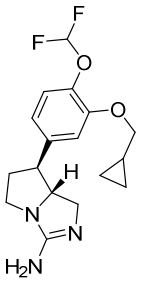
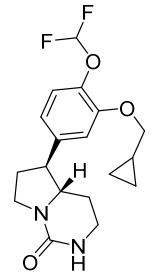
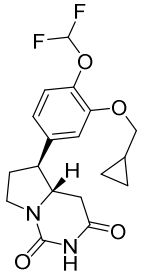
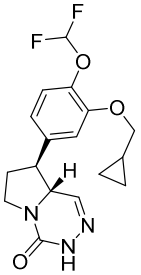
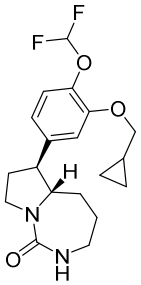
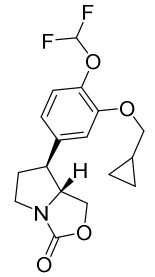
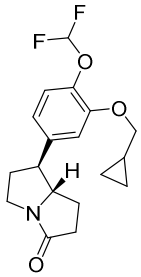
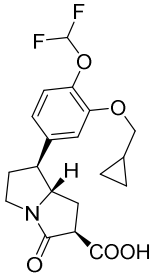
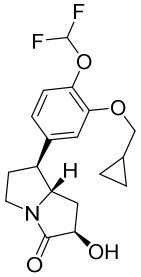
Variation of catechol ring C:

			
Roflumilast	**CMPI**	(7*S*,7a*R*)-**1a**	**1c**
-9.5 kcal/mol	-9.7 kcal/mol	-10.7 kcal/mol	-8.9 kcal/mol
			
-10.1 kcal/mol	-9.3 kcal/mol	-8.7 kcal/mol	-8.8 kcal/mol
			
-9.4 kcal/mol	-9.0 kcal/mol	-9.7 kcal/mol	-9.5 kcal/mol
			
1b			
-9.7 kcal/mol	-10.4 kcal/mol	-9.8 kcal/mol	-9.6 kcal/mo

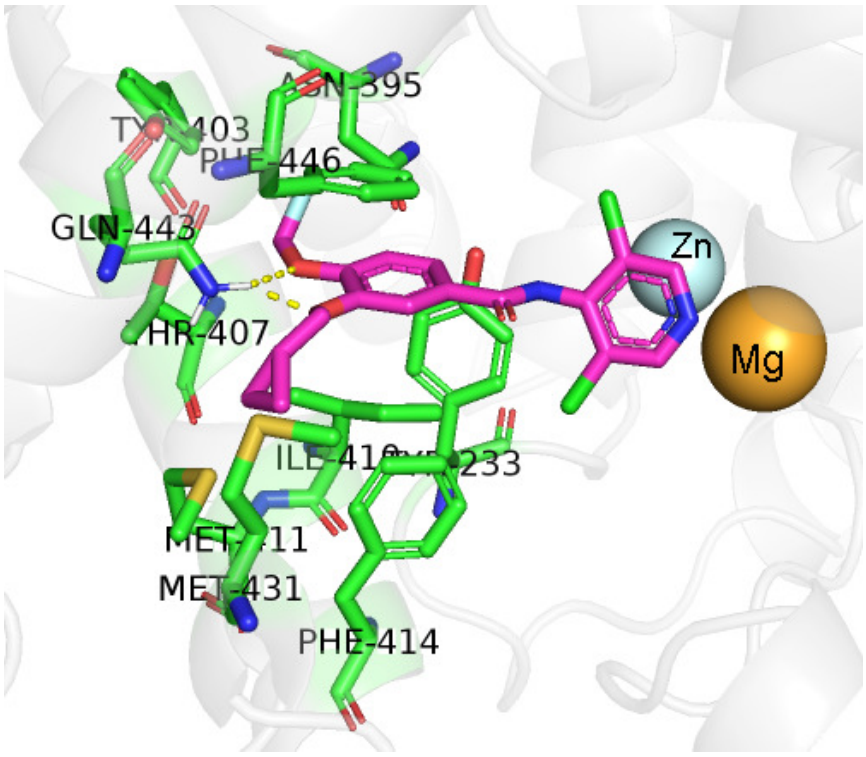
Variation of ring B:

			
(7*S*,7a*R*)-**1a**	**2a**		
-10.7 kcal/mol	-10.1 kcal/mol	-9.6 kcal/mol	-9.9 kcal/mol
			
-9.4 kcal/mol	-9.7 kcal/mol	-9.6 kcal/mol	-9.1 kcal/mol
			
-9.5 kcal/mol	-9.8 kcal/mol	-9.4 kcal/mol	-9.5 kcal/mol
			
-10.0 kcal/mol	-8.4 kcal/mol	-9.0 kcal/mol	-9.2 kcal/mol

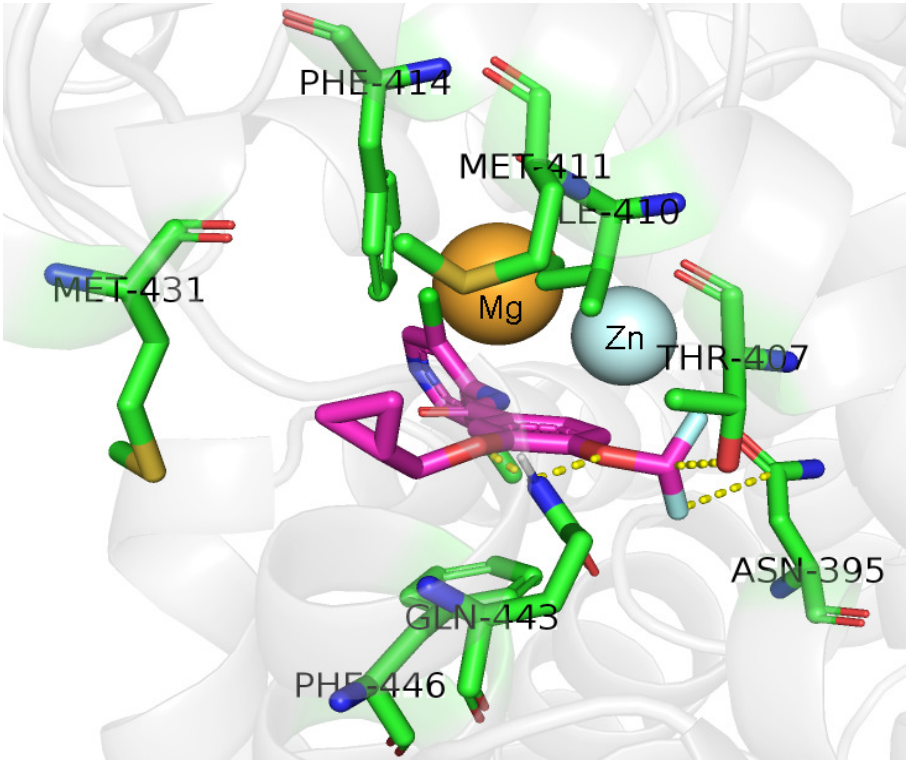
Variations in ring A:

 (7*S*,7a*R*)-**1a** -10.7 kcal/mol	 **1d** -9.7 kcal/mol	 -9.9 kcal/mol	 -10.9 kcal/mol
 -10.2 kcal/mol	 -9.6 kcal/mol	 **1e** -9.9 kcal/mol	 -9.6 kcal/mol
 -9.9 kcal/mol	 -9.3 kcal/mol	 -10.2 kcal/mol	 -9.3 kcal/mol
 -9.7 kcal/mol	 -9.8 kcal/mol	 -9.6 kcal/mol	 -9.6 kcal/mol

Binding modes of Roflumilast (crystal structure 1XMU)

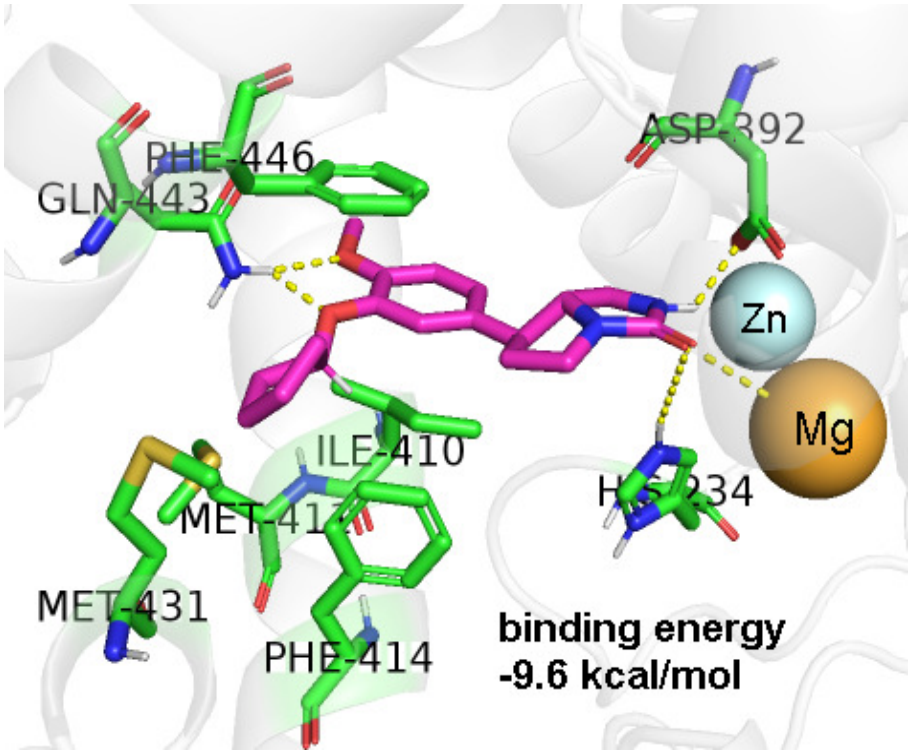


Residues in Q pocket of PDE4B interacting with Roflumilast.

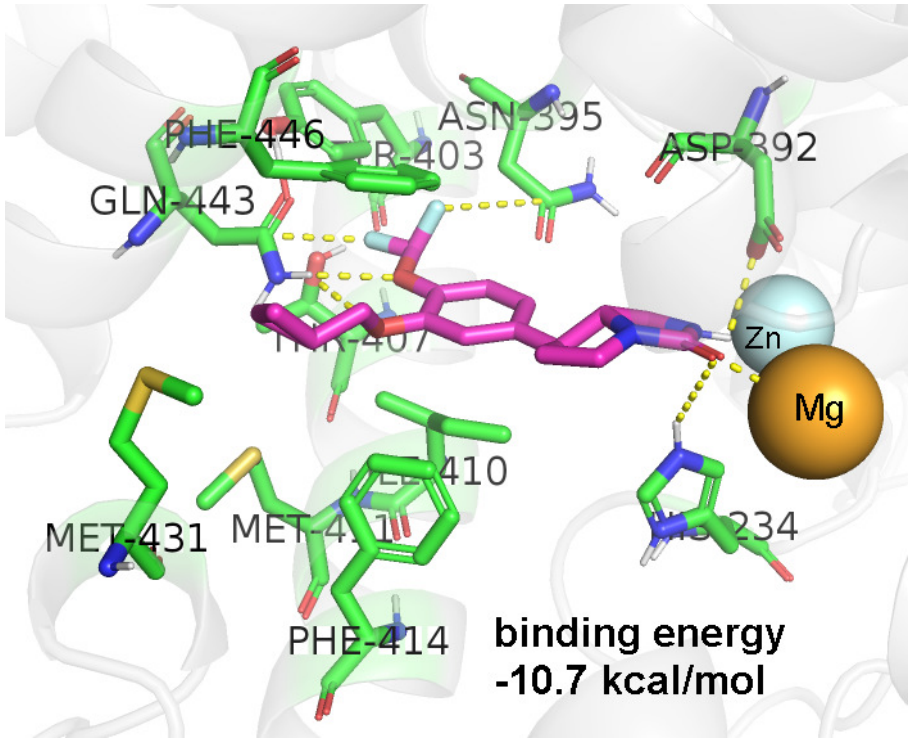


Close view on the difluoromethyl group making hydrogen bond with THR407 and multipolar interaction with TRP332.

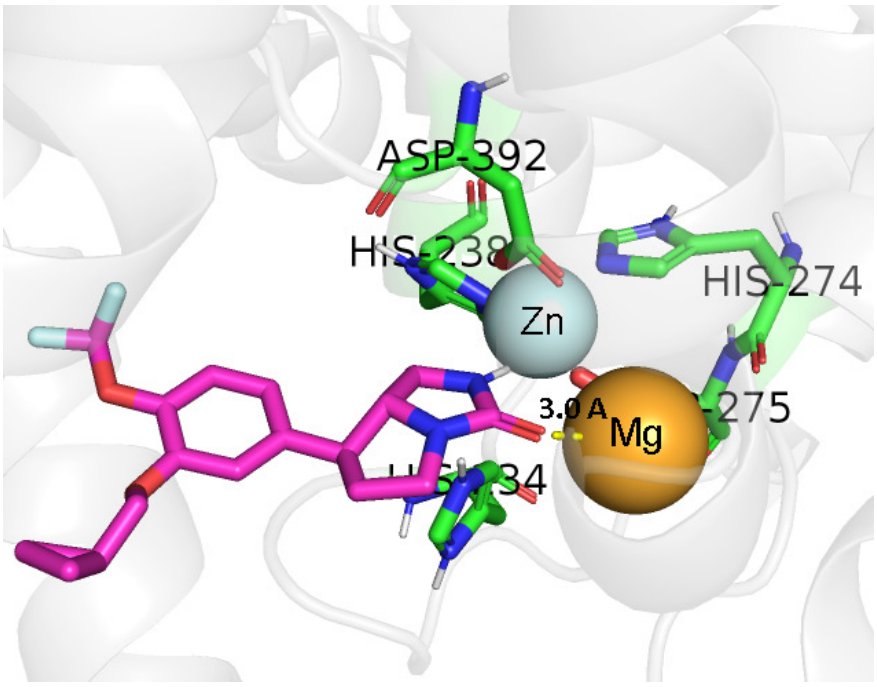
Molecular docking of CMPI and compound 1a into the catalytic site of PDE4B



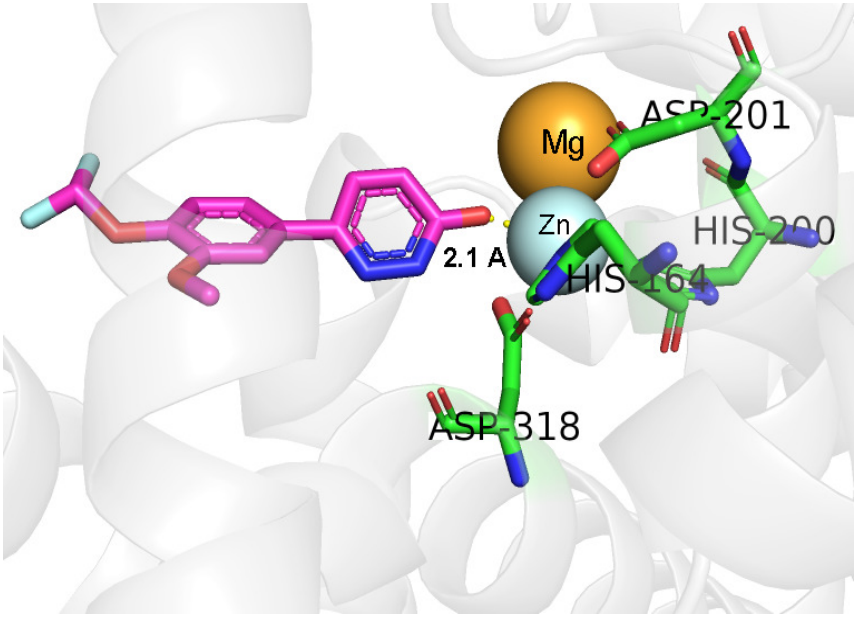
Residues in Q and M pockets of PDE4B interacting with **CMPI** and the resulting binding energy.



Residues in Q and M pockets of PDE4B interacting with **1a** and the resulting binding energy.

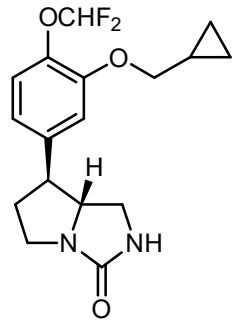


Docking of **1a** into the catalytic site of PDE4B (close view on the interactions in M pocket).



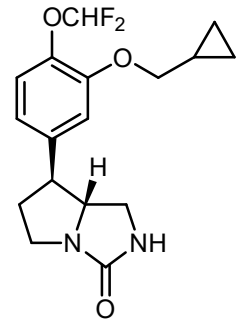
Interaction of Zardaverine with the Zn^{2+} ion in M pocket of PDE4D (crystal structure 1XOR).

^{1}H NMR (300 MHz, $CDCl_3$)



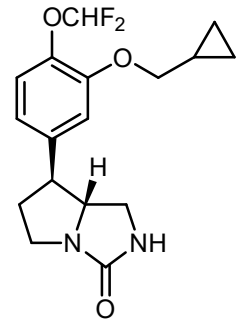
1a

^{13}C NMR (75 MHz, $CDCl_3$)



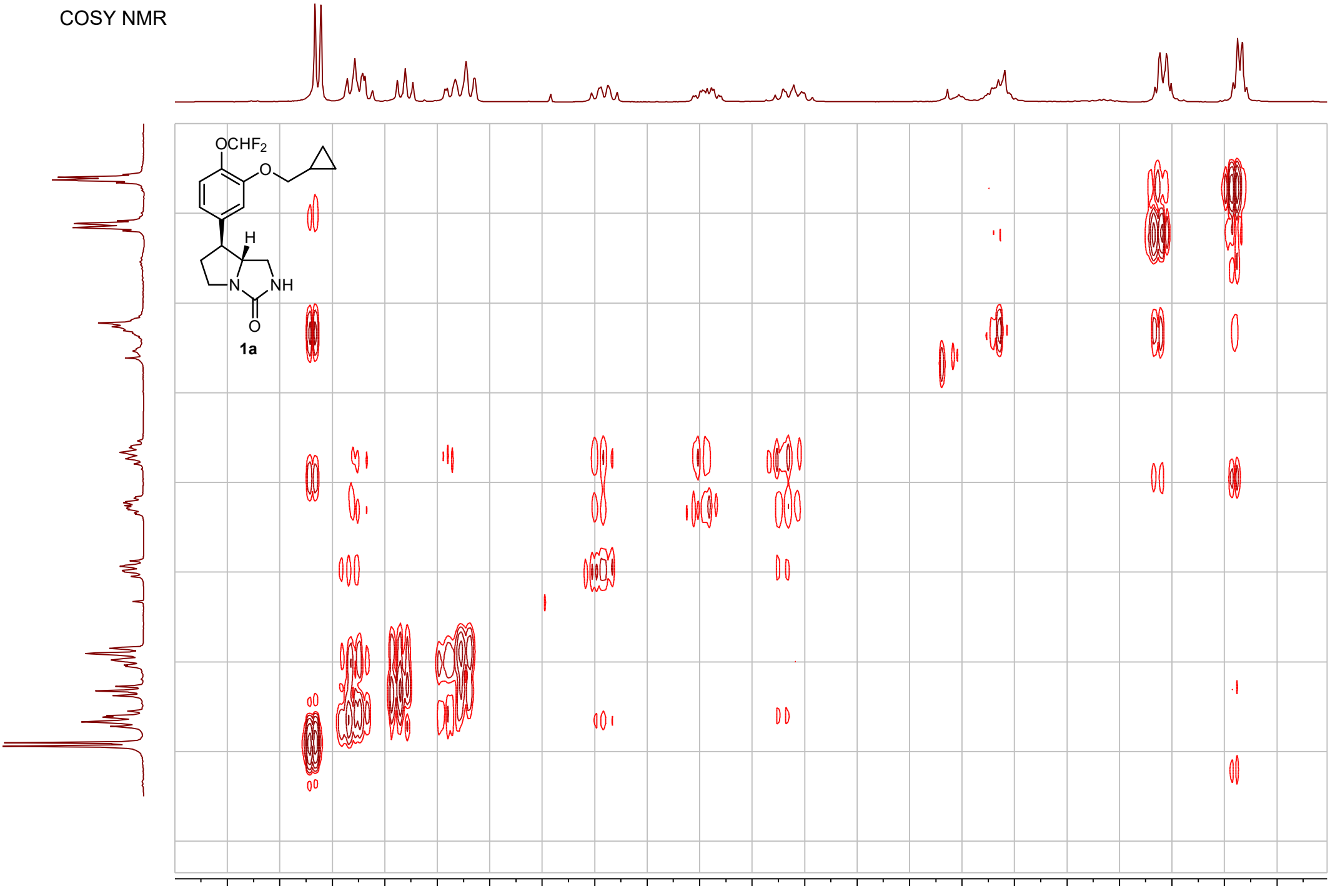
1a

^{19}F NMR (188 MHz, $CDCl_3$)

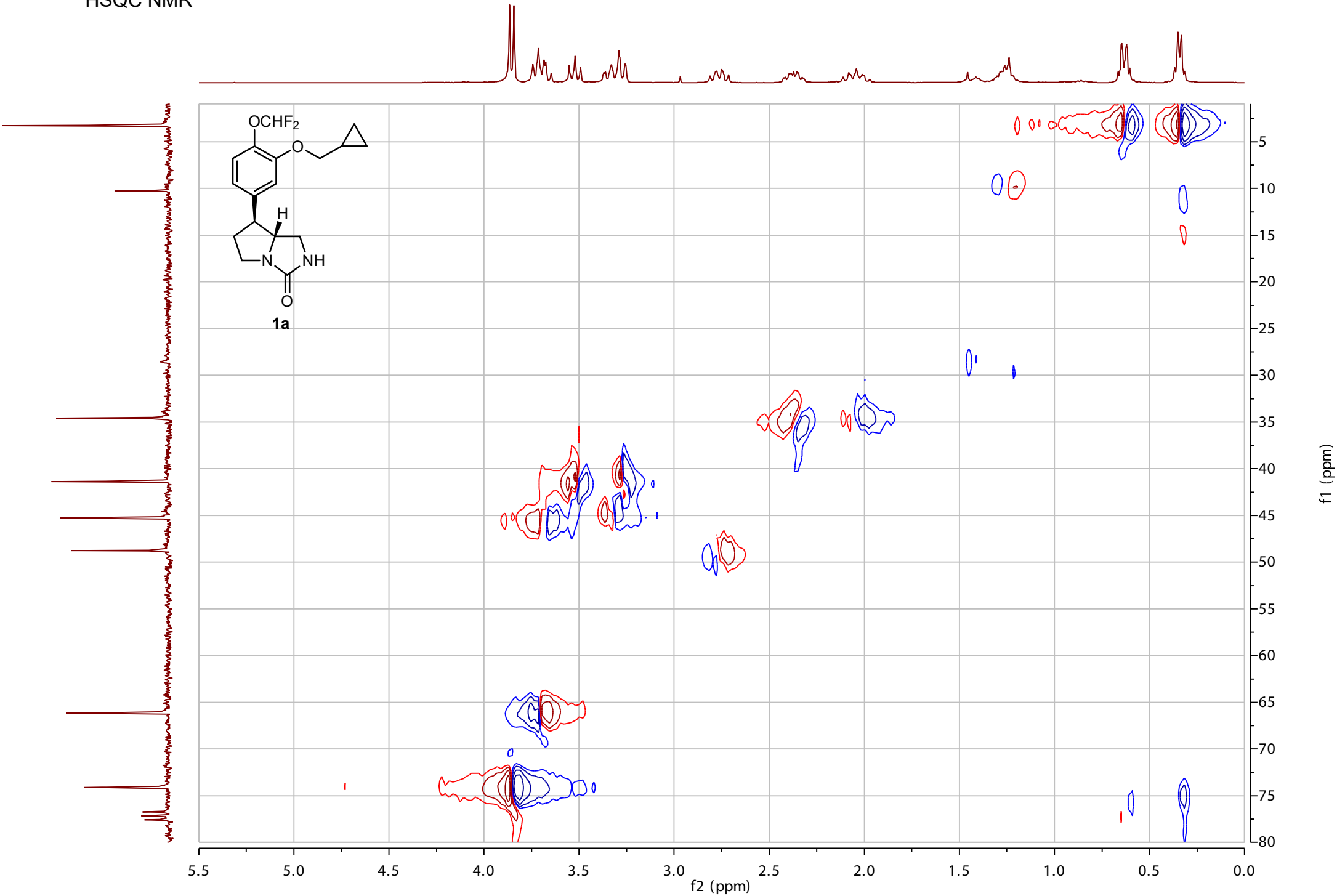


1a

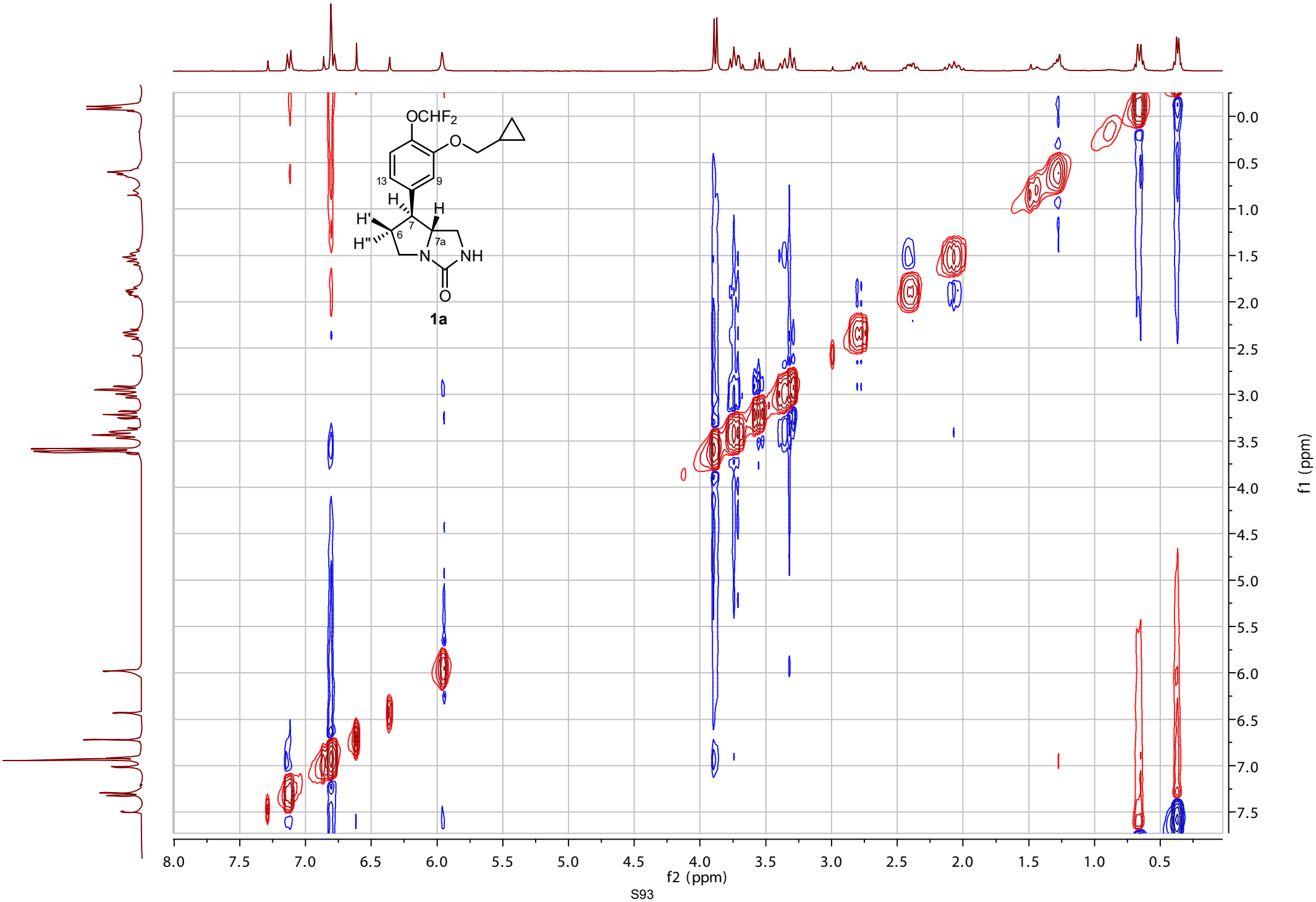
COSY NMR


OCHF2
O
H
N
NH
O
1a
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
f2 (ppm)

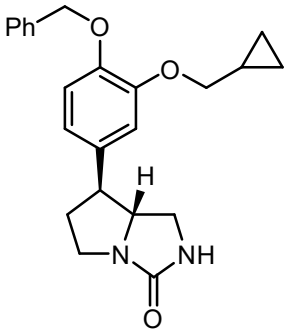
HSQC NMR


OCHF2
O
H
N
NH
O
1a
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
f1 (ppm)
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80

NOESY NMR

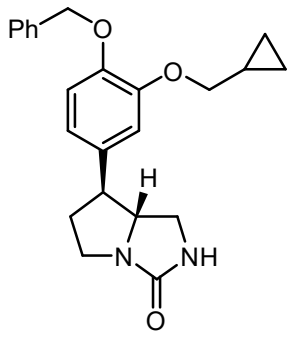

OCHF2
O
13
9
H
H
H'
H"
6
7
7a
N
NH
O
1a
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

^{1}H NMR (300 MHz, $CDCl_3$)



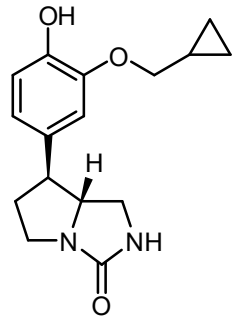
1b

^{13}C NMR (75 MHz, $CDCl_3$)



1b

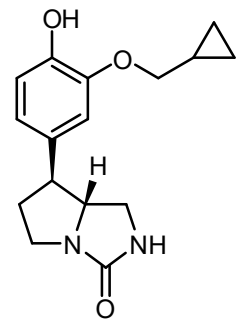
^{1}H NMR (300 MHz, $CDCl_3$)



1c

S96

^{13}C NMR (75 MHz, $CDCl_3$)

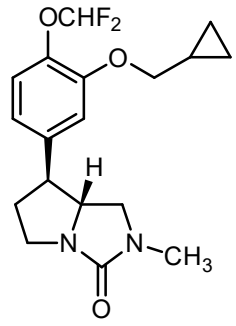


1c

165.71
146.31
145.30
131.06
120.45
114.79
111.50
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
74.29
66.21
48.84
45.33
41.38
34.73
10.46
3.45

f1 (ppm)

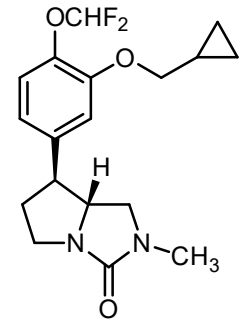
^{1}H NMR (300 MHz, $CDCl_3$)



1d

S98

^{13}C NMR (75 MHz, $CDCl_3$)



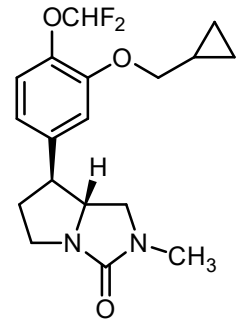
1d

163.95
150.96
139.65
139.61
139.57
138.52
123.22
123.22
120.25
119.74
116.30
113.97
112.85
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
74.24
63.27
49.28
48.28
46.05
34.72
31.00
10.34
3.35

f1 (ppm)

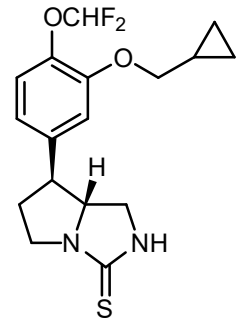
S99

^{19}F NMR (282 MHz, $CDCl_3$)



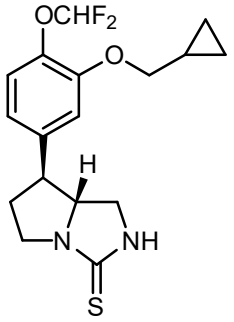
1d

^{1}H NMR (300 MHz, $CDCl_3$)



1e

^{13}C NMR (75 MHz, $CDCl_3$)



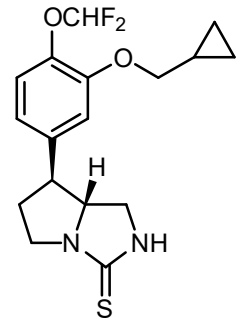
1e

187.12
151.04
139.76
137.32
123.32
119.96
119.66
116.22
113.84
112.77
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
74.22
69.33
49.02
47.52
45.87
34.56
10.28
3.33

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

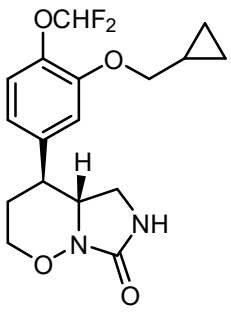
f1 (ppm)

^{19}F NMR (282 MHz, $CDCl_3$)



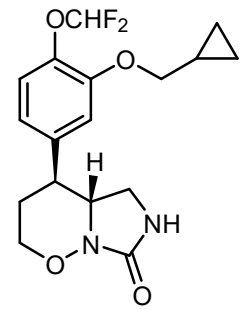
1e

^{1}H NMR (300 MHz, $CDCl_3$)



2a

^{13}C NMR (75 MHz, $CDCl_3$)

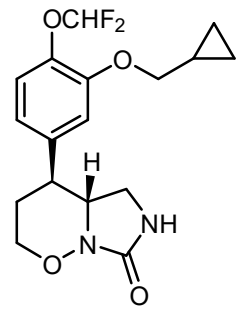


2a

160.22
151.04
139.85
139.14
123.32
120.38
119.66
116.22
114.13
112.77
77.59 CDCl3
77.16 CDCl3
76.74 CDCl3
74.24
69.73
60.30
41.79
40.60
31.38
10.30
3.34

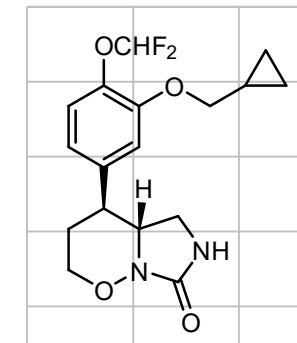
f1 (ppm)

^{19}F NMR (282 MHz, $CDCl_3$)



2a

COSY NMR

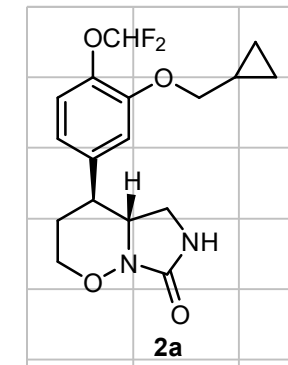


2a

f2 (ppm)

f1 (ppm)

HSQC NMR

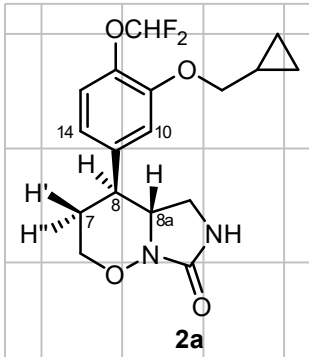


2a

f2 (ppm)

f1 (ppm)

NOESY NMR

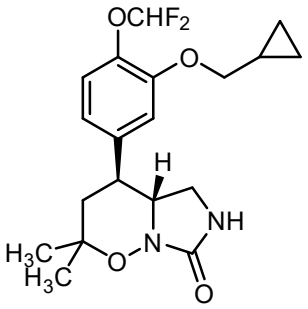


2a

f2 (ppm)

f1 (ppm)

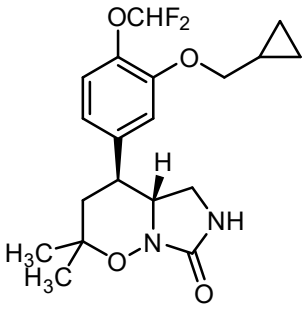
^{1}H NMR (400 MHz, $CDCl_3$)



2b

S110

^{13}C NMR (101 MHz, $CDCl_3$)



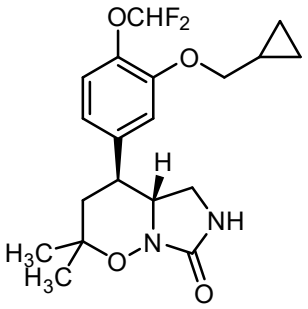
2b

160.13
151.09
139.88
138.90
123.34
120.18
118.83
116.25
113.93
113.66
79.81
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
74.30
60.32
42.98
41.25
40.96
28.51
23.00
10.34
3.36

f1 (ppm)

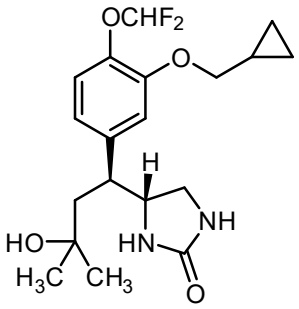
S111

^{19}F NMR (282 MHz, $CDCl_3$)



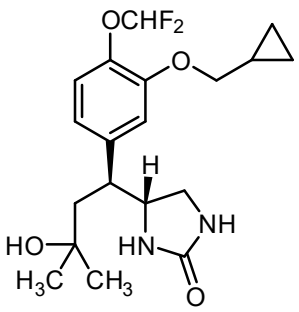
2b

^{1}H NMR (300 MHz, $CDCl_3$)



24b

^{13}C NMR (75 MHz, $CDCl_3$)



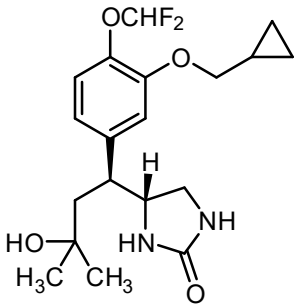
24b

164.38
150.78
141.81
139.41
139.37
139.34
123.05
120.65
119.76
116.32
114.54
112.88
77.58
77.36
77.16
76.74
74.17
70.64
58.87
47.81
47.02
45.61
31.90
28.36
10.29
3.30

f1 (ppm)

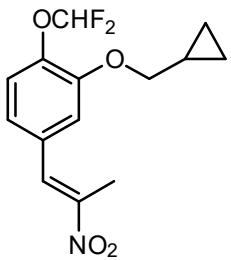
S114

^{19}F NMR (282 MHz, $CDCl_3$)



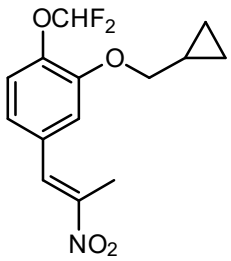
24b

^{1}H NMR (300 MHz, $CDCl_3$)



4a

^{13}C NMR (75 MHz, $CDCl_3$)



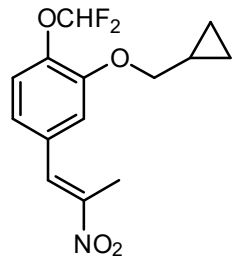
4a

150.66
141.54
132.60
130.85
122.90
122.67
119.43
116.07
115.99
112.52
77.16
74.17
14.00
10.11
3.25

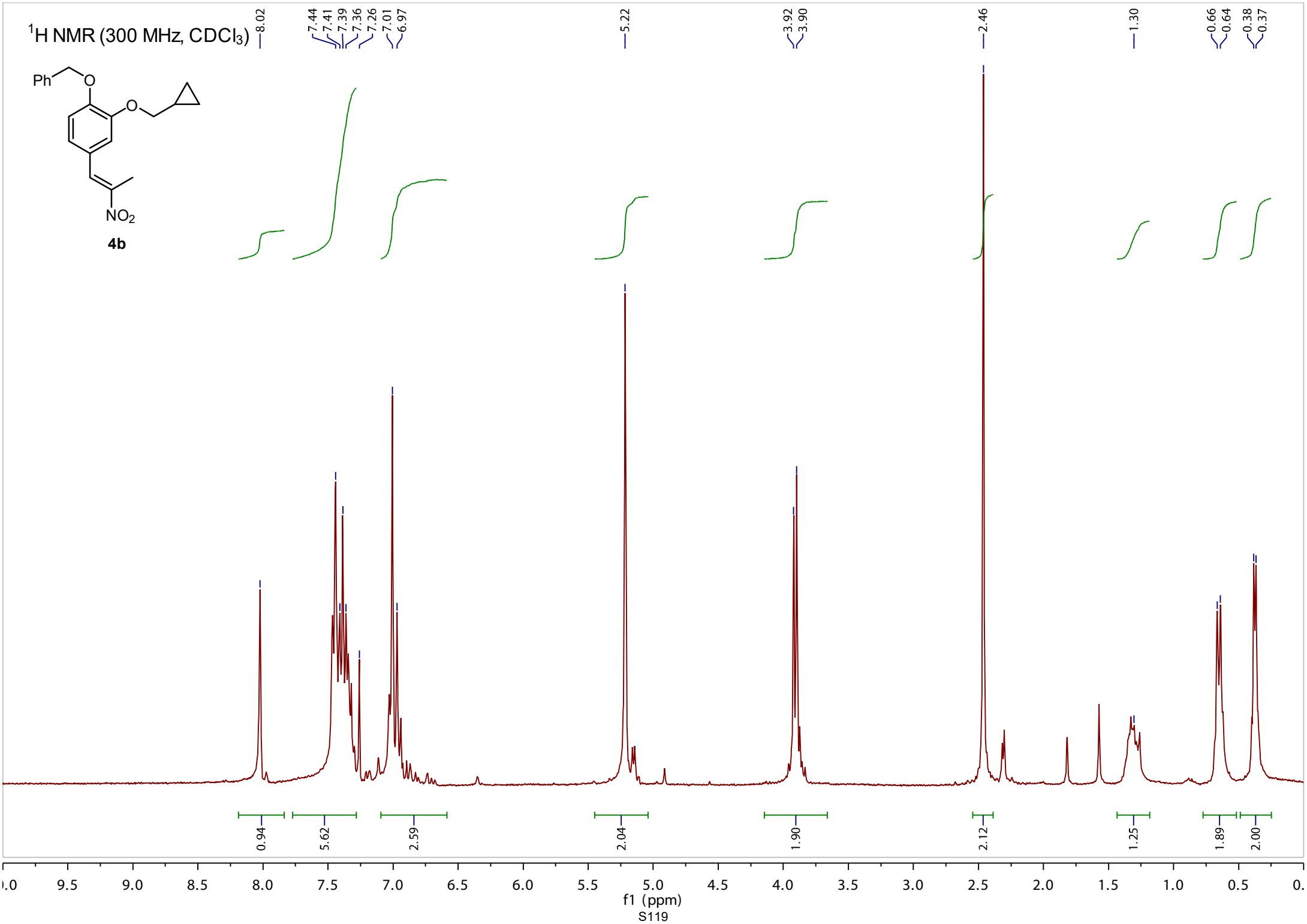
f1 (ppm)

S117

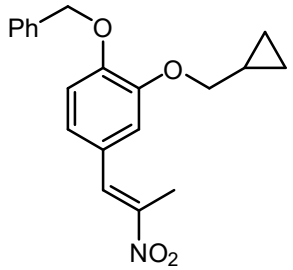
^{19}F NMR (282 MHz, $CDCl_3$)



4a


^{1}H NMR (300 MHz, $CDCl_3$)
8.02
7.44
7.41
7.39
7.36
7.26
7.01
6.97
5.22
3.92
3.90
2.46
1.30
0.66
0.64
0.38
0.37
Ph
O
O
NO_2
4b
0.94
5.62
2.59
2.04
1.90
2.12
1.25
1.89
2.00
f1 (ppm)

^{13}C NMR (75 MHz, $CDCl_3$)

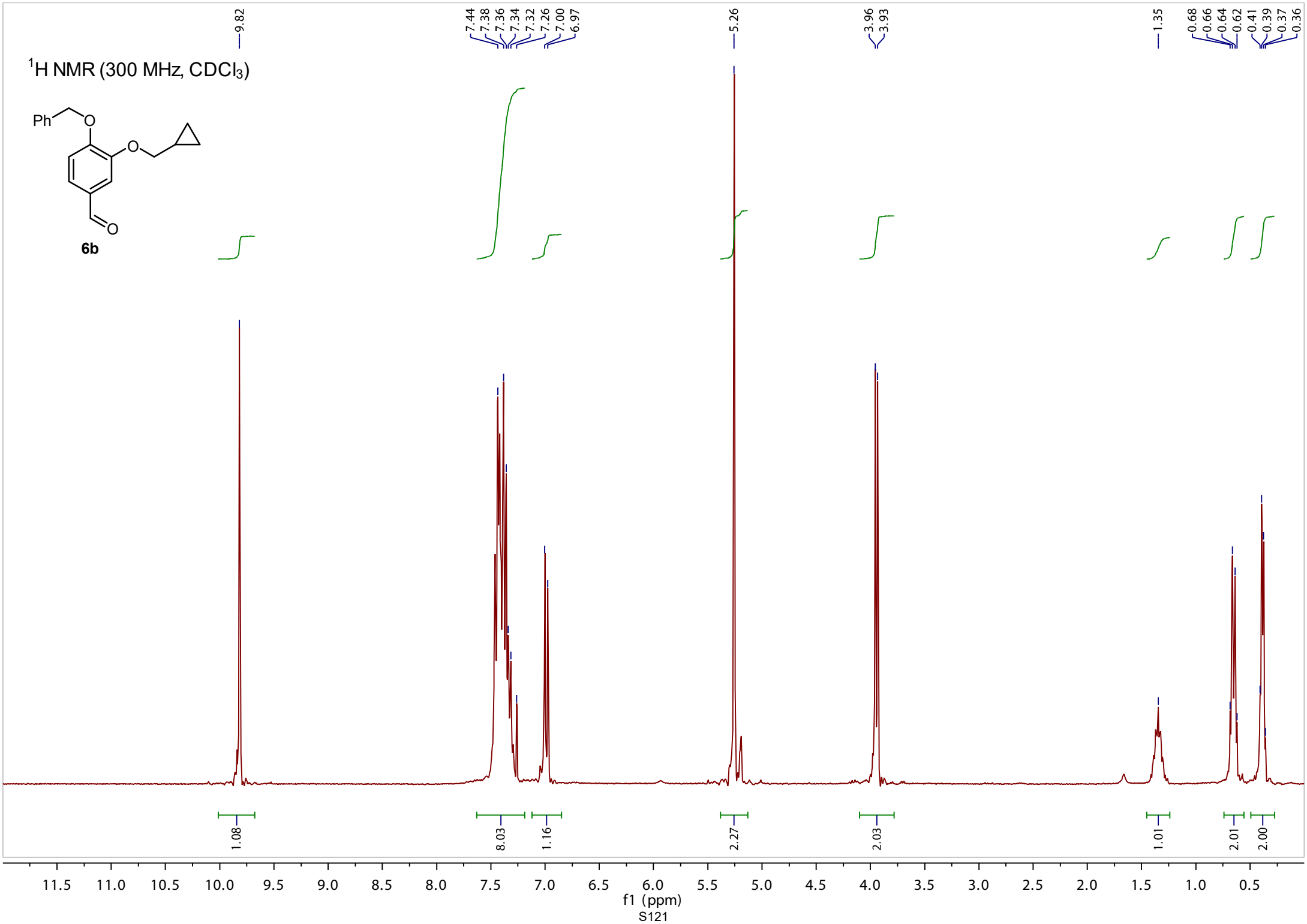


4b

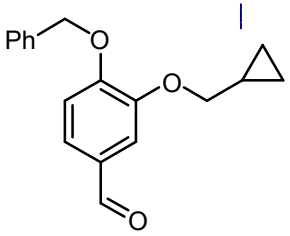
150.80
149.34
146.09
136.81
133.87
128.72
128.12
127.24
125.63
124.41
116.83
114.62
77.16 CDCl3
74.59
71.15
14.30
10.48
3.47

f1 (ppm)

S120


9.82
7.44
7.38
7.36
7.34
7.32
7.26
7.00
6.97
5.26
3.96
3.93
1.35
0.68
0.66
0.64
0.62
0.41
0.39
0.37
0.36
1H NMR (300 MHz, CDCl3)
Ph
O
O
O
6b
1.08
8.03
1.16
2.27
2.03
1.01
2.01
2.00
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
S121

^{13}C NMR (75 MHz, $CDCl_3$)



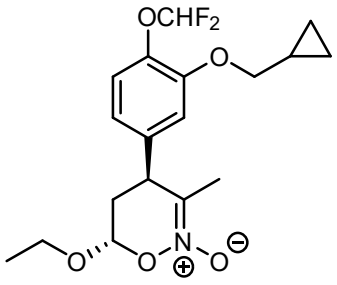
6b

190.99
154.24
149.76
136.49
130.52
128.73
128.14
127.12
126.51
113.38
111.98
77.16 CDCl3
74.10
71.01
10.31
3.46

f1 (ppm)

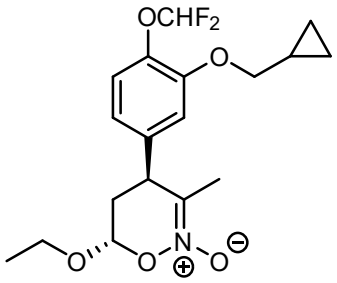
S122

^{1}H NMR (300 MHz, $CDCl_3$)



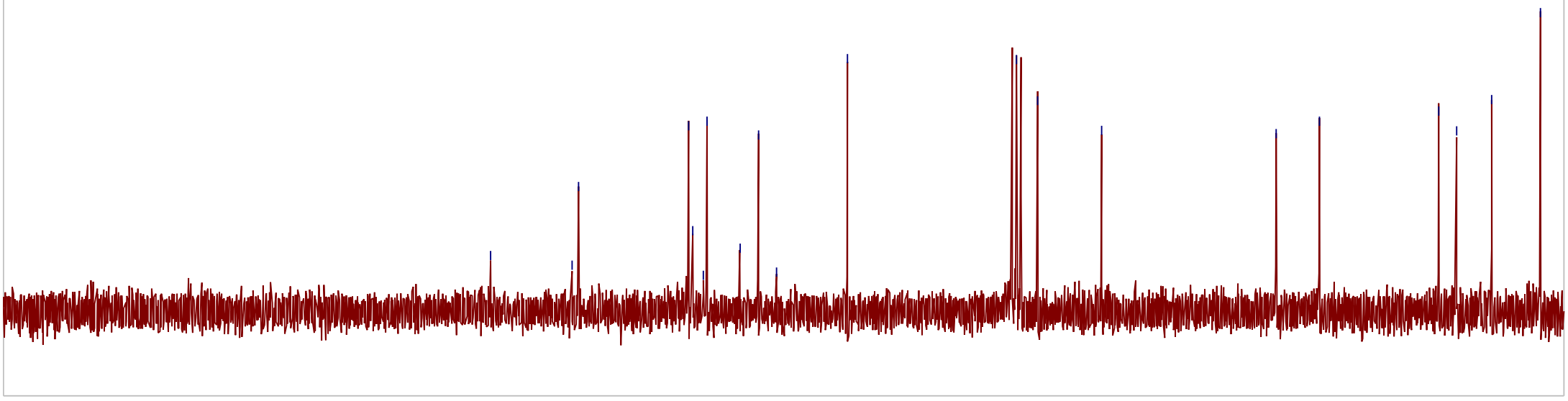
7a

^{13}C NMR (50 MHz, $CDCl_3$)



7a

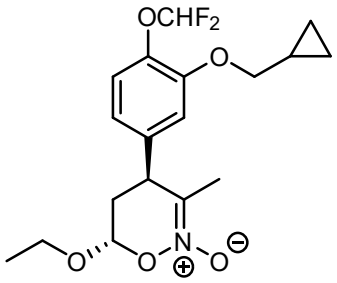
151.31
139.83
138.89
123.40
122.84
121.34
120.81
116.16
113.56
110.99
101.02
77.16
74.17
65.18
40.59
34.49
17.67
15.13
10.18
3.31



220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

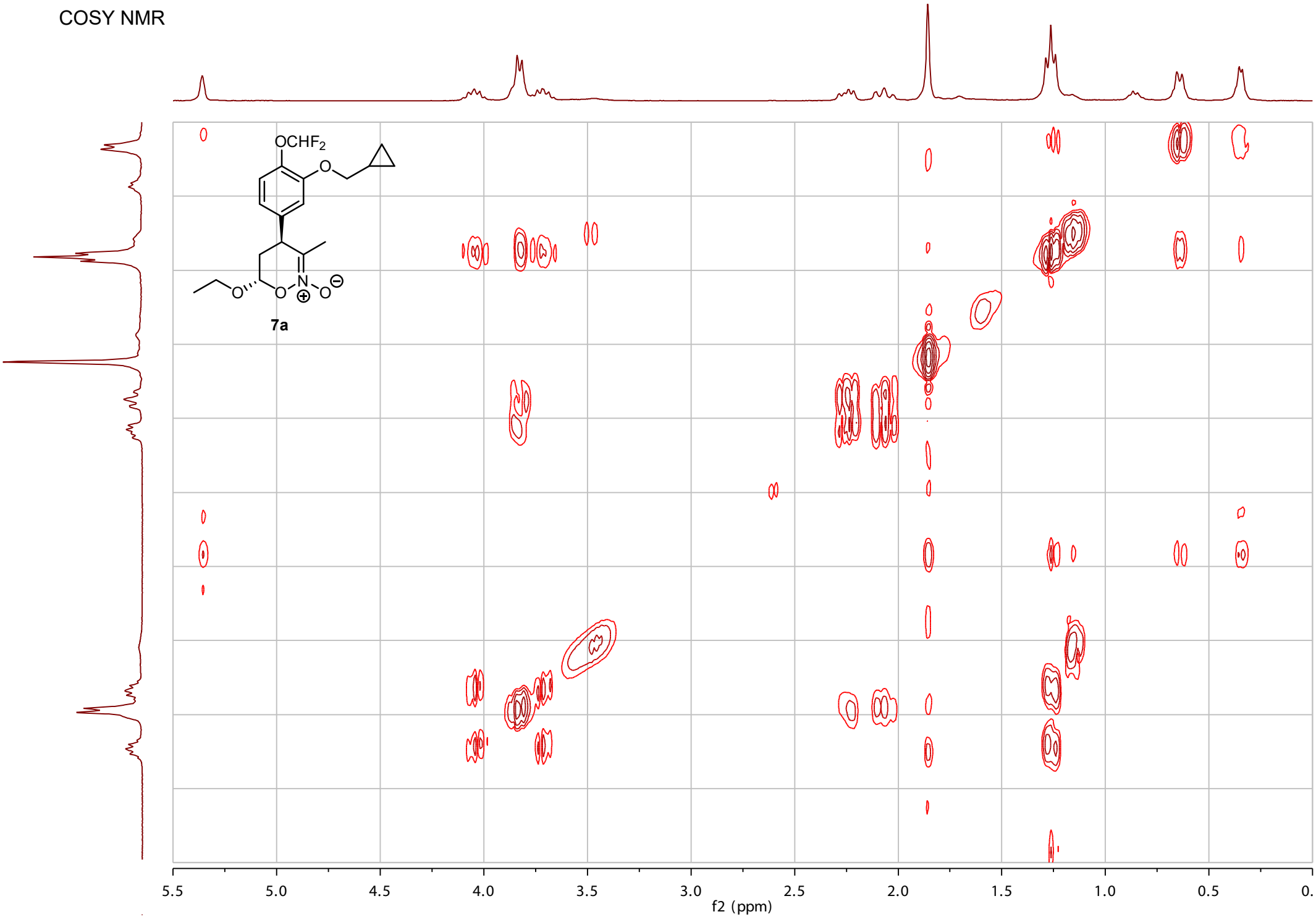
f1 (ppm)

^{19}F NMR (282 MHz, $CDCl_3$)

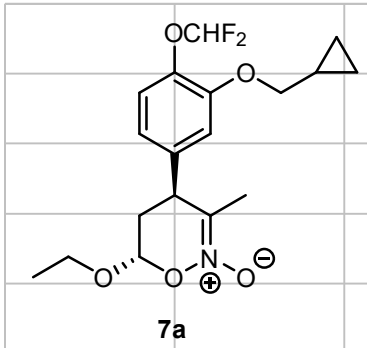


7a

COSY NMR



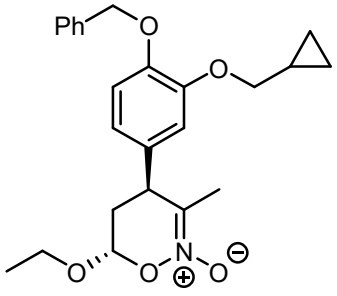
HSQC NMR


OCHF2
O
O
N
O
O

7a

5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
f1 (ppm)

^{1}H NMR (300 MHz, $CDCl_3$)



7b

7.45 7.43 7.36 7.26 6.87 6.84 6.68 5.34 5.12 4.07 4.04 4.02 3.85 3.82 3.76 3.73 3.71 2.26 2.23 2.21 2.19 2.07 1.84 1.28 1.26 1.24 0.63 0.60 0.35 0.34

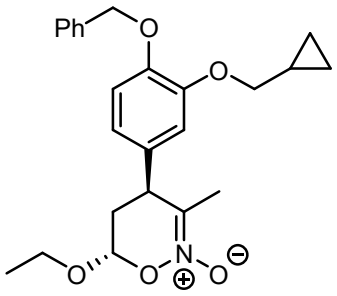
CH_2Cl_2

5.27 1.04 1.93 2.98 2.00 1.02 3.95 1.99 3.34 4.03 1.98 2.00

f1 (ppm)

S128

^{13}C NMR (75 MHz, $CDCl_3$)



7b

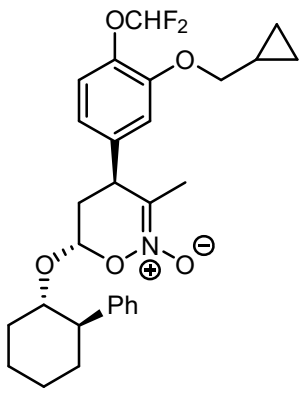
149.91
148.39
137.25
133.23
128.45
127.78
127.21
120.80
115.49
113.97
100.97
77.50 CDCl3
77.07 CDCl3
76.65 CDCl3
74.30
71.39
64.95
40.18
34.30
17.48
15.03
10.36
3.27

CH_2Cl_2

f1 (ppm)

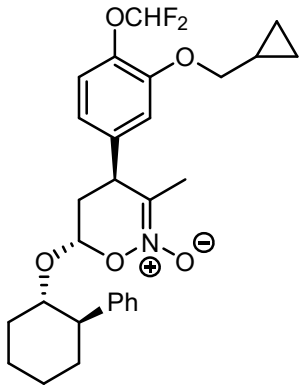
S129

^{1}H NMR (300 MHz, $CDCl_3$)



7c

^{13}C NMR (75 MHz, $CDCl_3$)



7c

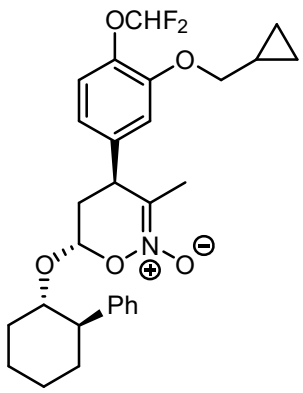
151.08
150.51
144.24
138.78
128.31
127.61
126.14
123.12
122.31
120.84
119.56
116.12
113.48
112.68
95.02
77.16
76.28
74.08
50.99
39.84
34.14
33.99
30.13
26.10
24.51
17.23
10.12
3.22

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

f1 (ppm)

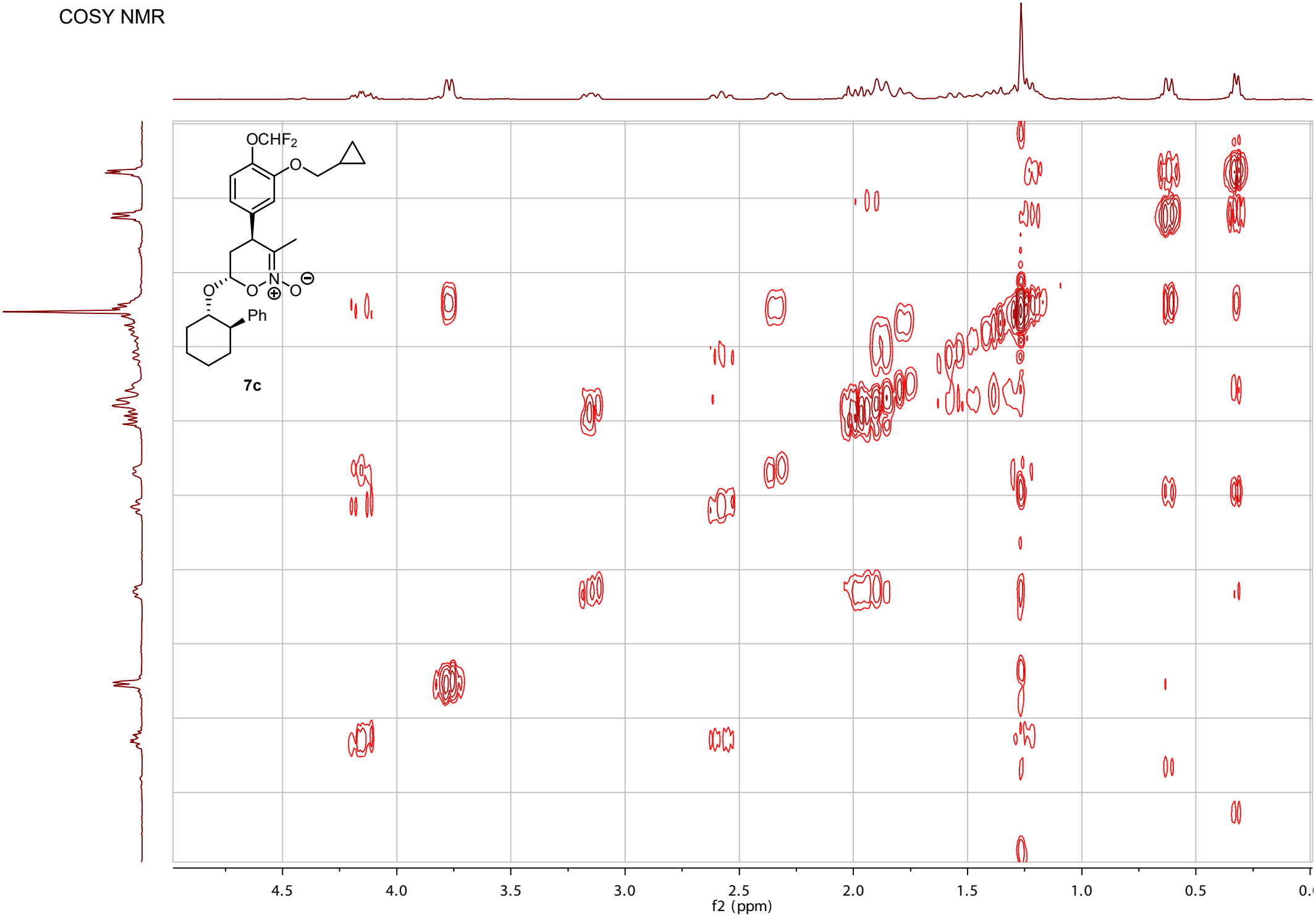
S131

^{19}F NMR (282 MHz, $CDCl_3$)

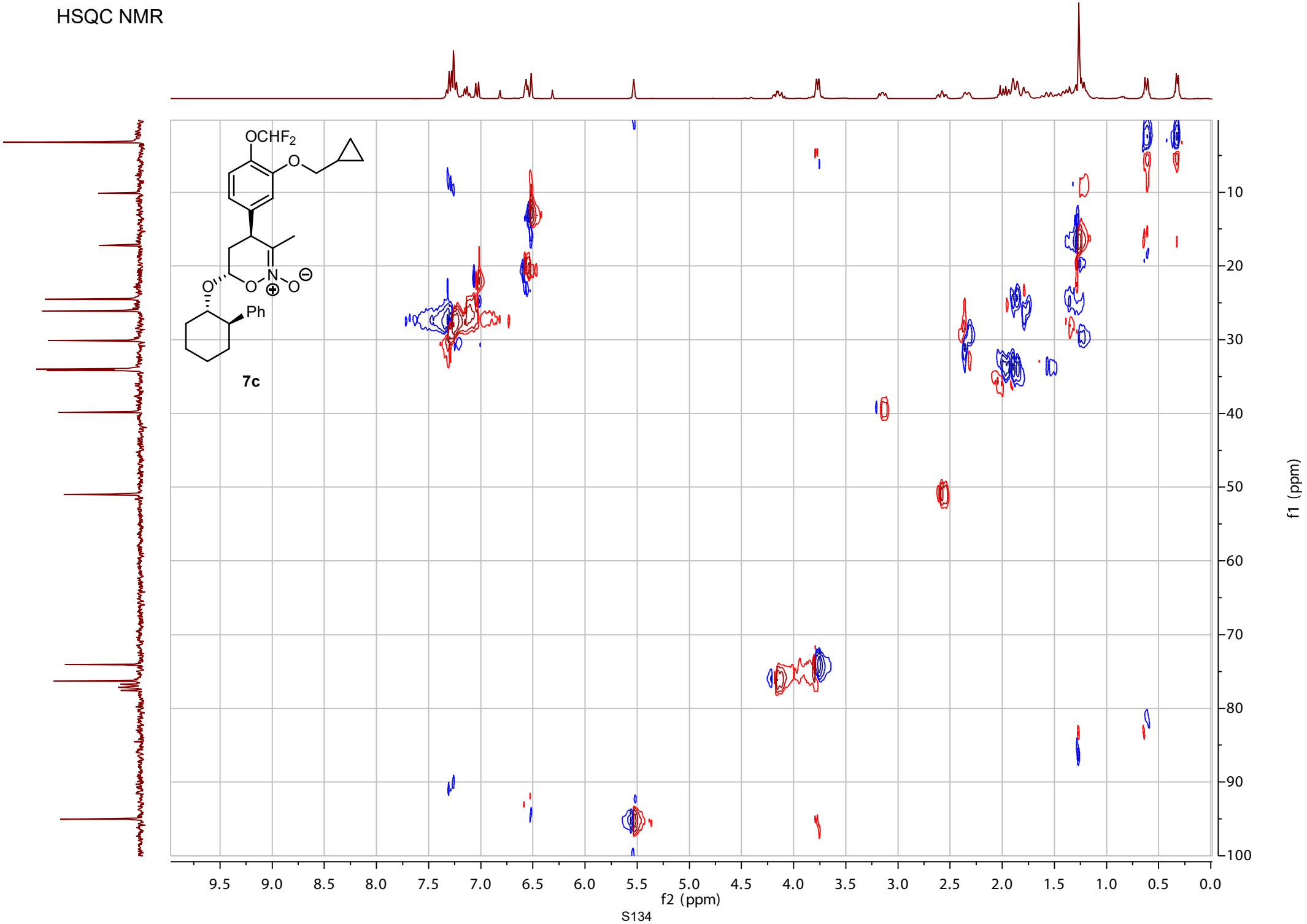


7c

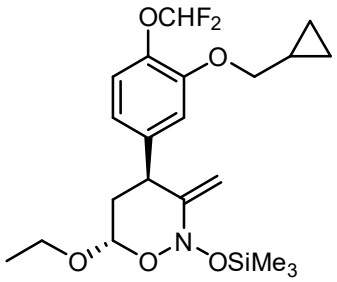
COSY NMR



HSQC NMR


OCHF2
O
O
N
O
O
Ph
7c
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
f1 (ppm)

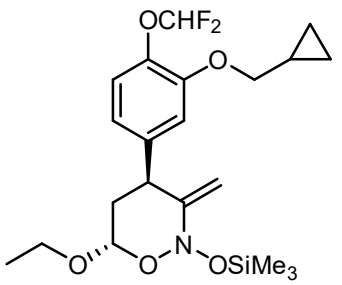
^{1}H NMR (300 MHz, $CDCl_3$)



9a

S135

^{13}C NMR (75 MHz, $CDCl_3$)

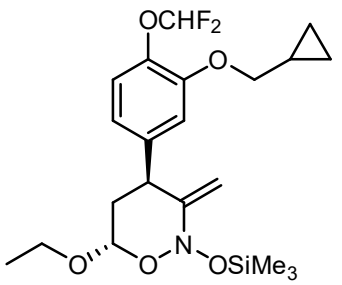


9a

150.40
139.79
139.41
122.53
121.22
119.82
116.39
115.20
112.95
99.27
97.94
74.02
64.15
40.86
36.48
15.04
10.25
7.29
3.18
-0.78

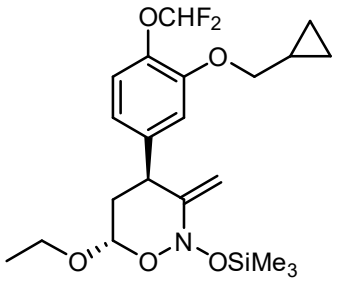
f1 (ppm)

^{19}F NMR (188 MHz, $CDCl_3$)



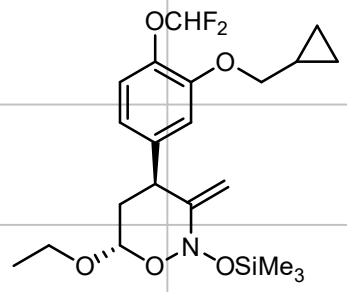
9a

^{29}Si NMR (40 MHz, $CDCl_3$)



9a

COSY NMR

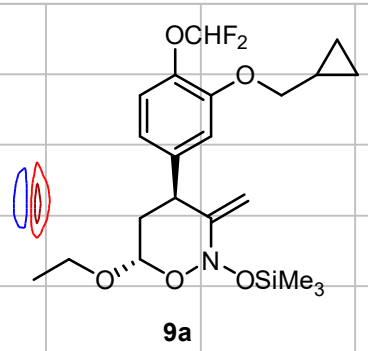


9a

5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.

f2 (ppm)

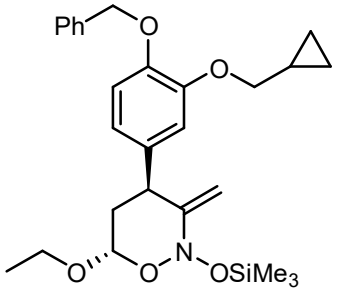
HSQC NMR


OCHF2
O
O
N
O
OSiMe3

9a

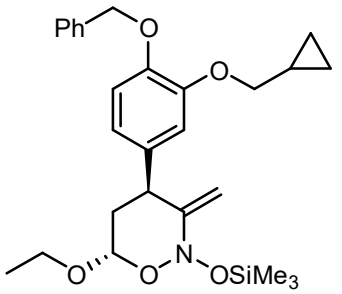
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
-5
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
f1 (ppm)

^{1}H NMR (300 MHz, $CDCl_3$)



9b

^{13}C NMR (75 MHz, $CDCl_3$)



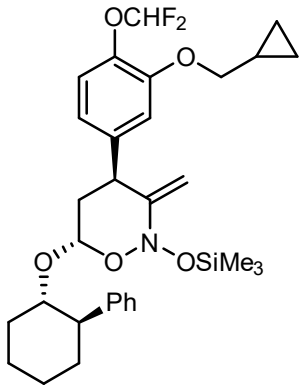
9b

149.40
148.10
137.74
128.55
127.83
127.43
121.41
115.98
115.51
99.41
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
74.52
71.71
64.22
40.65
36.75
15.15
10.65
3.36
-0.65

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

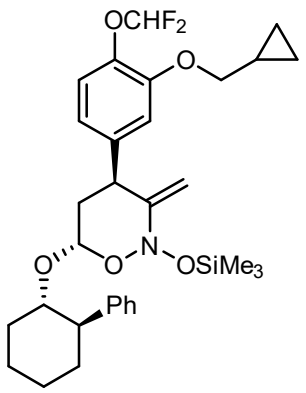
f1 (ppm)

^{1}H NMR (300 MHz, $CDCl_3$)



9c

^{13}C NMR (75 MHz, $CDCl_3$)



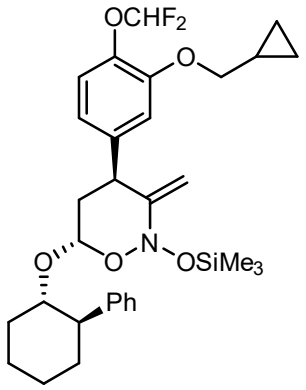
9c

150.35
144.33
139.59
128.15
128.00
125.93
122.55
121.33
119.85
116.42
115.32
112.98
97.63
93.88
77.16
76.26
74.03
50.38
40.44
36.86
34.55
30.70
26.25
24.88
10.30
3.29
-0.41

f1 (ppm)

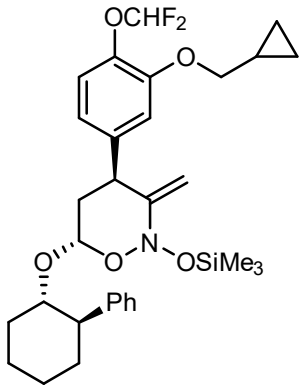
S144

^{19}F NMR (282 MHz, $CDCl_3$)



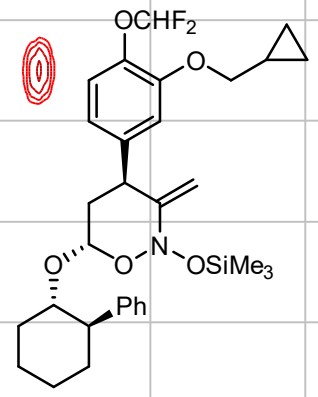
9c

^{29}Si NMR (40 MHz, $CDCl_3$)



9c

COSY NMR

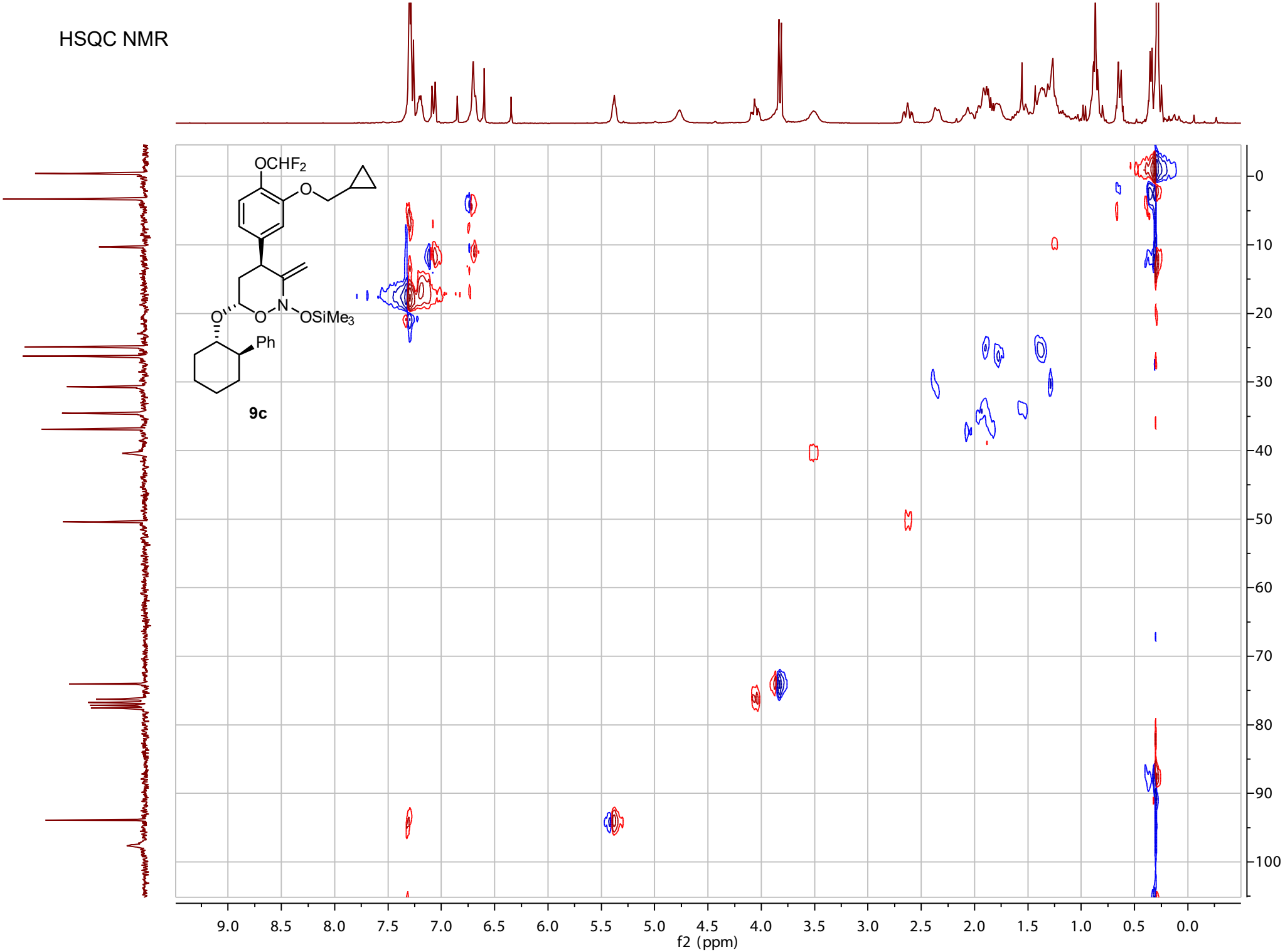


9c

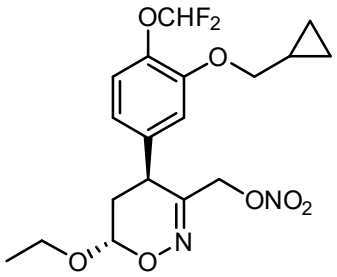
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

f2 (ppm)

HSQC NMR

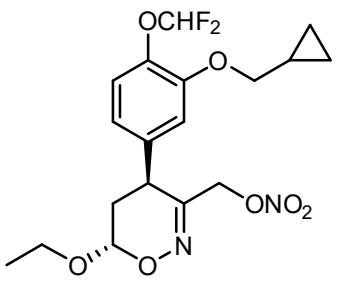


^{1}H NMR (300 MHz, $CDCl_3$)



10a

^{13}C NMR (75 MHz, $CDCl_3$)



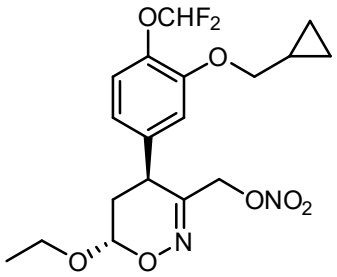
10a

153.76
151.43
137.13
123.61
120.93
119.69
116.24
114.65
112.79
96.10
74.29
71.52
64.20
34.89
32.57
15.05
10.25
3.30

f1 (ppm)

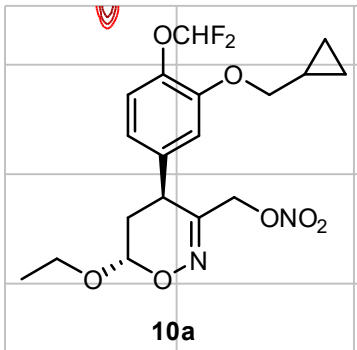
S150

^{19}F NMR (282 MHz, $CDCl_3$)



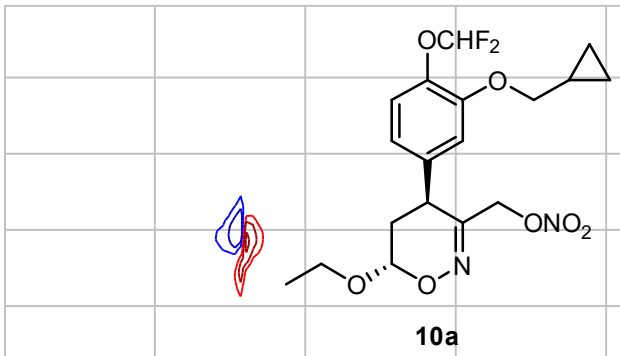
10a

COSY NMR



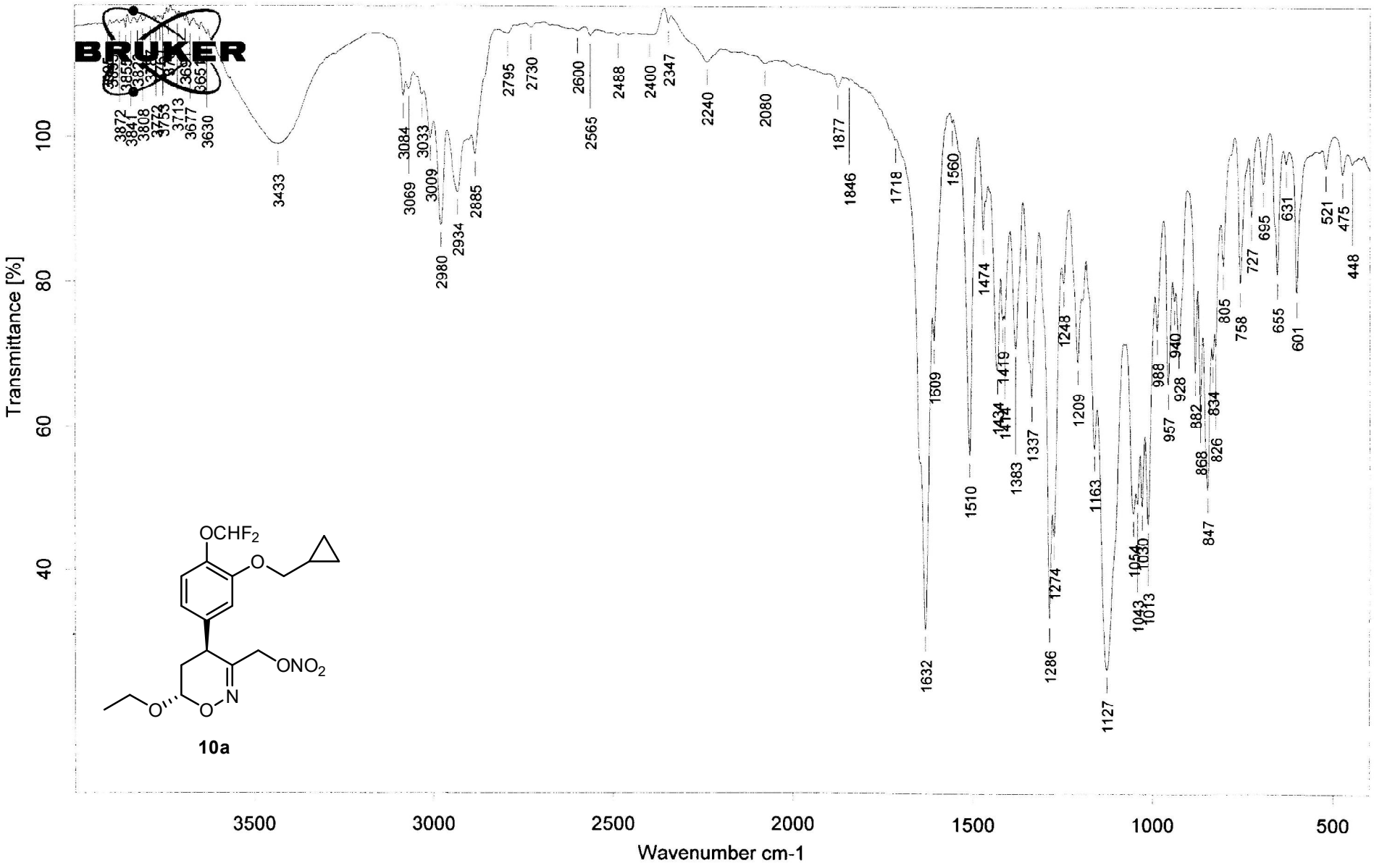
10a

HSQC NMR


OCHF2
O
ONO2
N
O
O

10a

5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
f1 (ppm)



10a

D:\EDL\VAD-166.1 ДОРОХОВ. VAD-166 , прессовка с KBr,1/200..	02.11.2015

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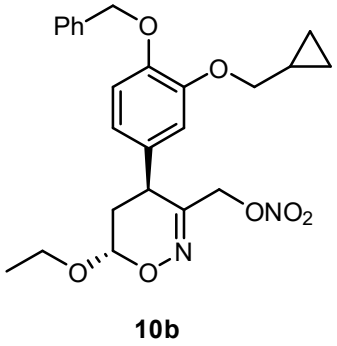
^{1}H NMR (300 MHz, $CDCl_3$)



10b

7.46 7.44 7.40 7.37 7.35 7.33 7.31 7.26 7.11 6.89 6.86 6.73 6.69

5.19 5.14 4.81 4.77 4.74 4.70

3.90 3.87 3.84 3.68 3.66 3.64 3.61 3.58

2.31 2.26 2.24 2.13 2.09 2.05

1.31 1.25 1.23 1.21

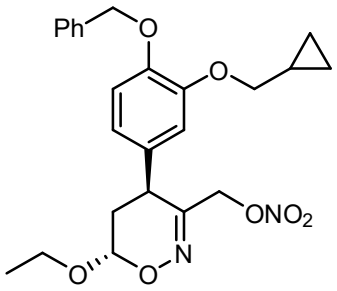
0.65 0.62 0.37 0.35

4.92 1.07 1.90 2.93 1.81 2.87 1.95 1.82 3.87 1.94 2.00

f1 (ppm)

S155

^{13}C NMR (75 MHz, $CDCl_3$)

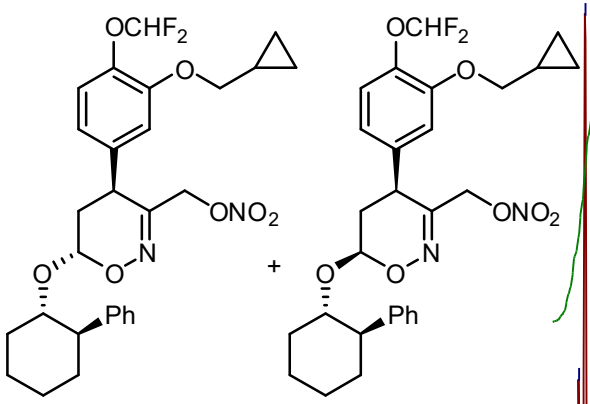


10b

154.35
150.14
148.68
137.31
131.42
128.61
127.96
127.37
121.09
115.94
114.55
96.24
77.59 CDCl3
77.16 CDCl3
76.74 CDCl3
74.42
71.55
64.12
34.49
32.37
15.10
10.49
3.42

f1 (ppm)

^{1}H NMR (300 MHz, $CDCl_3$)



10c

+

10c'
(minor 4,6-*cis* isomer)

d.r. 4.5 : 1

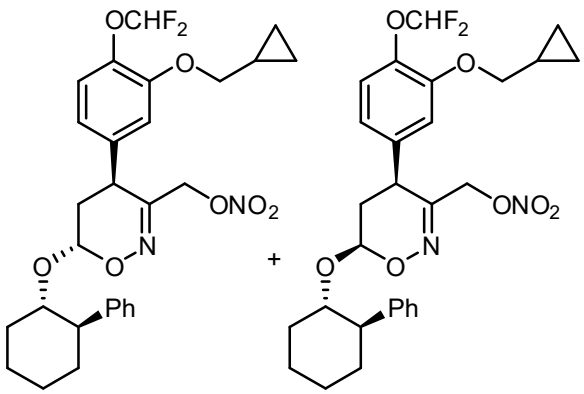
7.35 7.31 7.29 7.26 7.24 7.20 7.17 7.09 7.06 6.84 6.60 6.60 6.59 6.34 5.39 4.36 4.31 4.22 4.17 3.95 3.83 3.80 2.95 2.93 2.61 2.58 2.54 2.44 2.40 2.35 1.94 1.89 1.56 1.41 1.27 0.67 0.64 0.37 0.35

9.65 1.14 3.82 1.05 1.23 1.02 1.07 2.21 0.71 1.00 1.10 2.01 9.01 10.59 2.77 2.80

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.

f1 (ppm)

^{13}C NMR (50 MHz, $CDCl_3$)



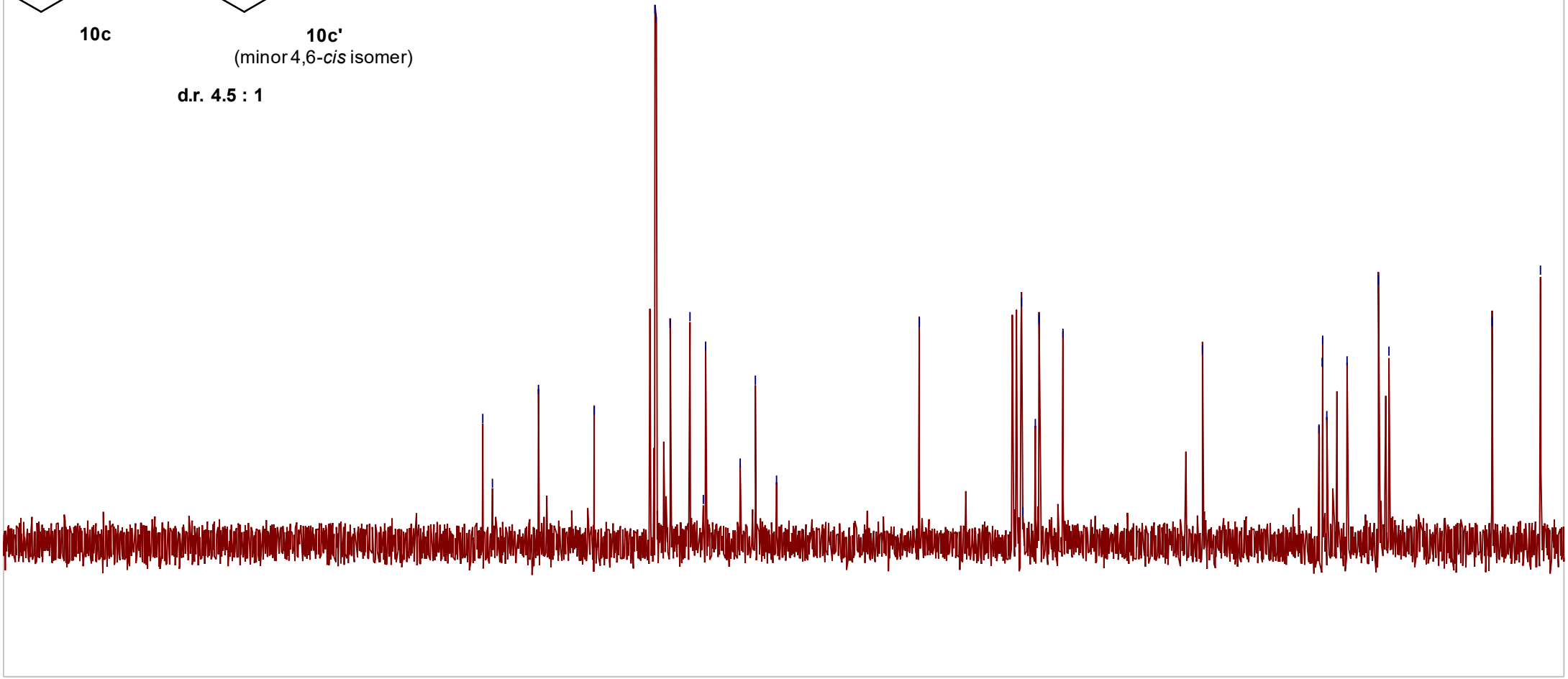
10c

+

10c'
(minor 4,6-*cis* isomer)

d.r. 4.5 : 1

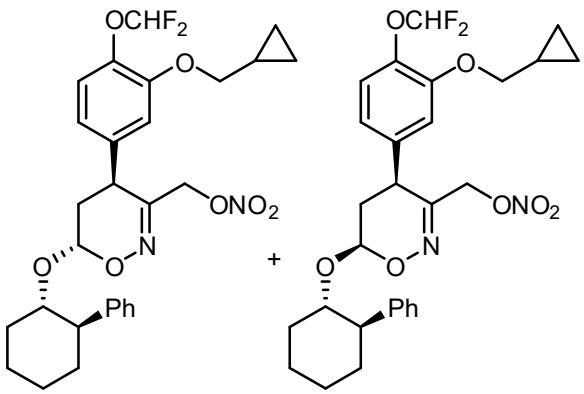
152.42
151.04
144.55
136.71
128.16
127.98
125.97
123.24
121.33
121.02
116.15
114.00
110.99
90.90
76.45
76.29
74.50
74.01
70.64
50.93
34.54
34.08
34.02
33.40
30.56
26.15
24.69
10.13
3.29



220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

^{14}N NMR (22 MHz, $CDCl_3$)



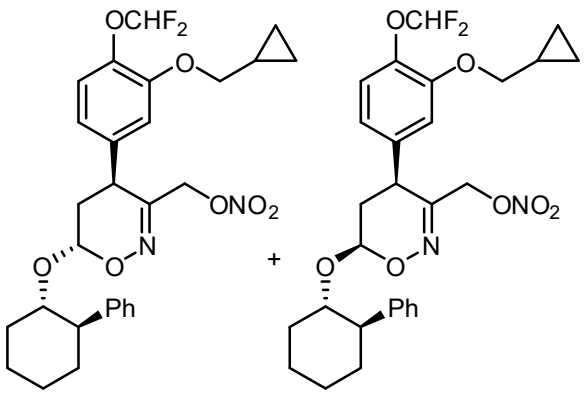
10c

+

10c'
(minor 4,6-*cis* isomer)

d.r. 4.5 : 1

^{19}F NMR (188 MHz, $CDCl_3$)



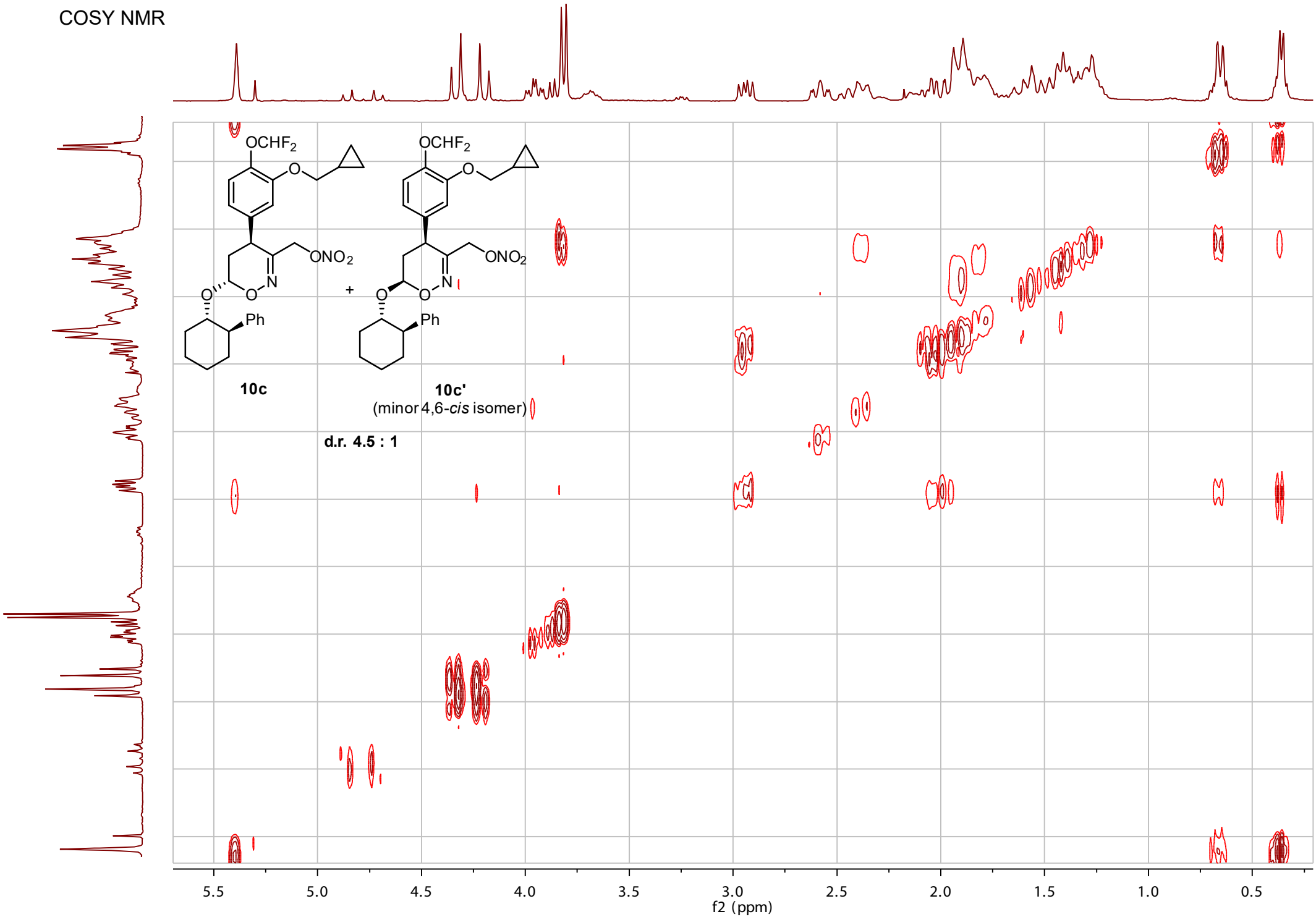
10c

+

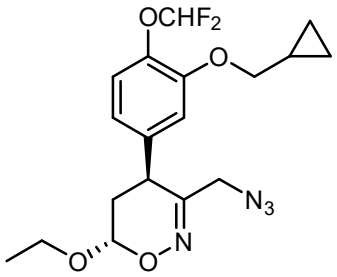
10c'
(minor 4,6-*cis* isomer)

d.r. 4.5 : 1

COSY NMR


OCHF2
O
ONO2
N
O
O
Ph
+
OCHF2
O
ONO2
N
O
O
Ph
10c
10c'
(minor 4,6-cis isomer)
d.r. 4.5 : 1
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

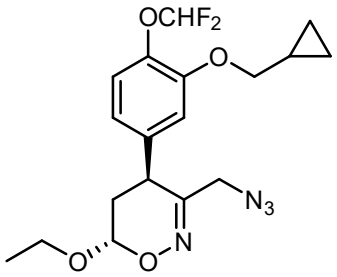
^{1}H NMR (300 MHz, $CDCl_3$)



11a

S162

^{13}C NMR (50 MHz, $CDCl_3$)



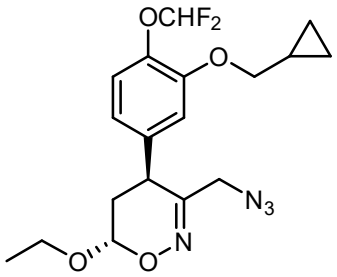
11a

156.62
151.23
137.72
136.80
123.54
120.88
119.94
116.17
114.26
112.14
95.86
77.16
74.09
64.06
52.61
34.69
32.79
15.08
10.18
3.32

f1 (ppm)

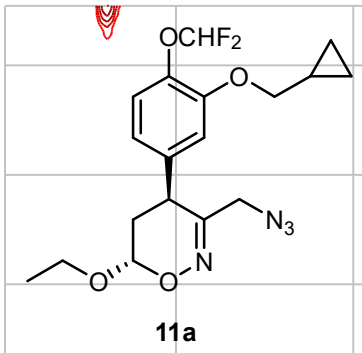
S163

^{19}F NMR (188 MHz, $CDCl_3$)



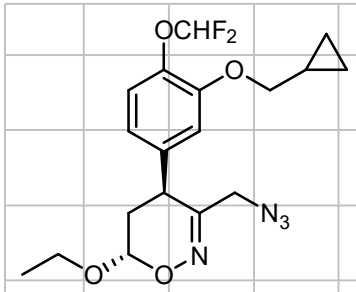
11a

COSY NMR



11a

HSQC NMR

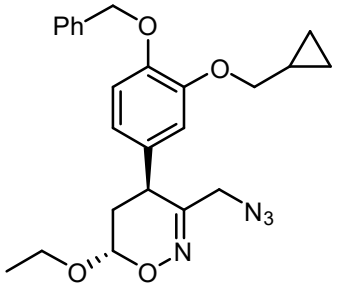


11a

f2 (ppm)

f1 (ppm)

^{1}H NMR (300 MHz, $CDCl_3$)



11b

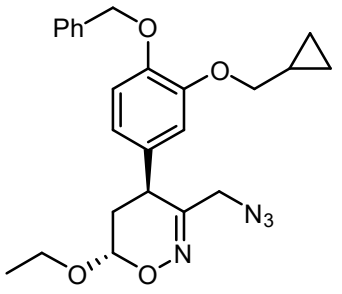
7.46 7.44 7.37 7.34 7.26 6.90 6.87 6.73 6.70 5.17 5.14 3.89 3.87 3.85 3.82 3.78 3.69 3.64 3.47 3.43 2.33 2.30 2.28 2.25 2.11 1.27 1.25 1.23 0.64 0.61 0.36 0.35

5.38 1.18 1.94 3.12 4.14 2.16 0.96 2.00 4.40 2.03 2.04

f1 (ppm)

S167

^{13}C NMR (75 MHz, $CDCl_3$)



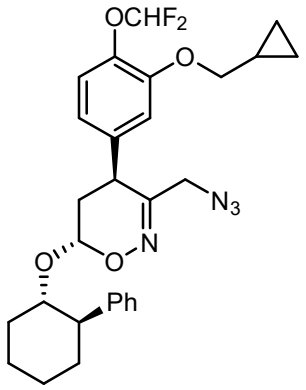
11b

157.22
150.09
148.59
137.41
132.21
128.59
127.92
127.37
121.19
115.94
114.72
96.05
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
74.41
71.59
63.98
52.61
34.51
32.84
15.10
10.52
3.39

f1 (ppm)

S168

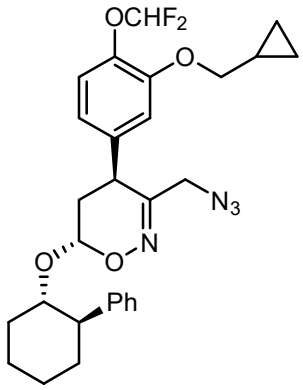
^{1}H NMR (300 MHz, $CDCl_3$)



11c

S169

^{13}C NMR (75 MHz, $CDCl_3$)

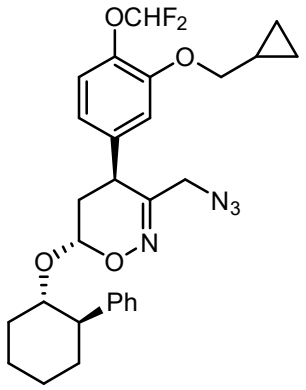


11c

155.21
151.03
144.68
137.39
128.17
128.05
125.94
123.21
121.59
121.19
119.65
116.20
114.19
112.76
90.62
77.16
76.34
74.08
51.61
50.93
34.63
33.96
32.36
30.55
26.22
24.72
10.21
3.31

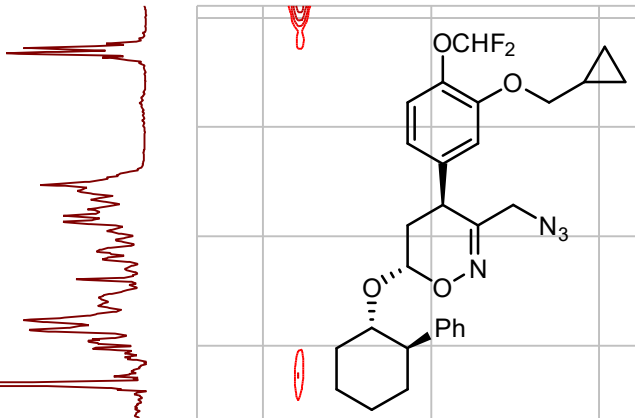
f1 (ppm)

^{19}F NMR (282 MHz, $CDCl_3$)



11c

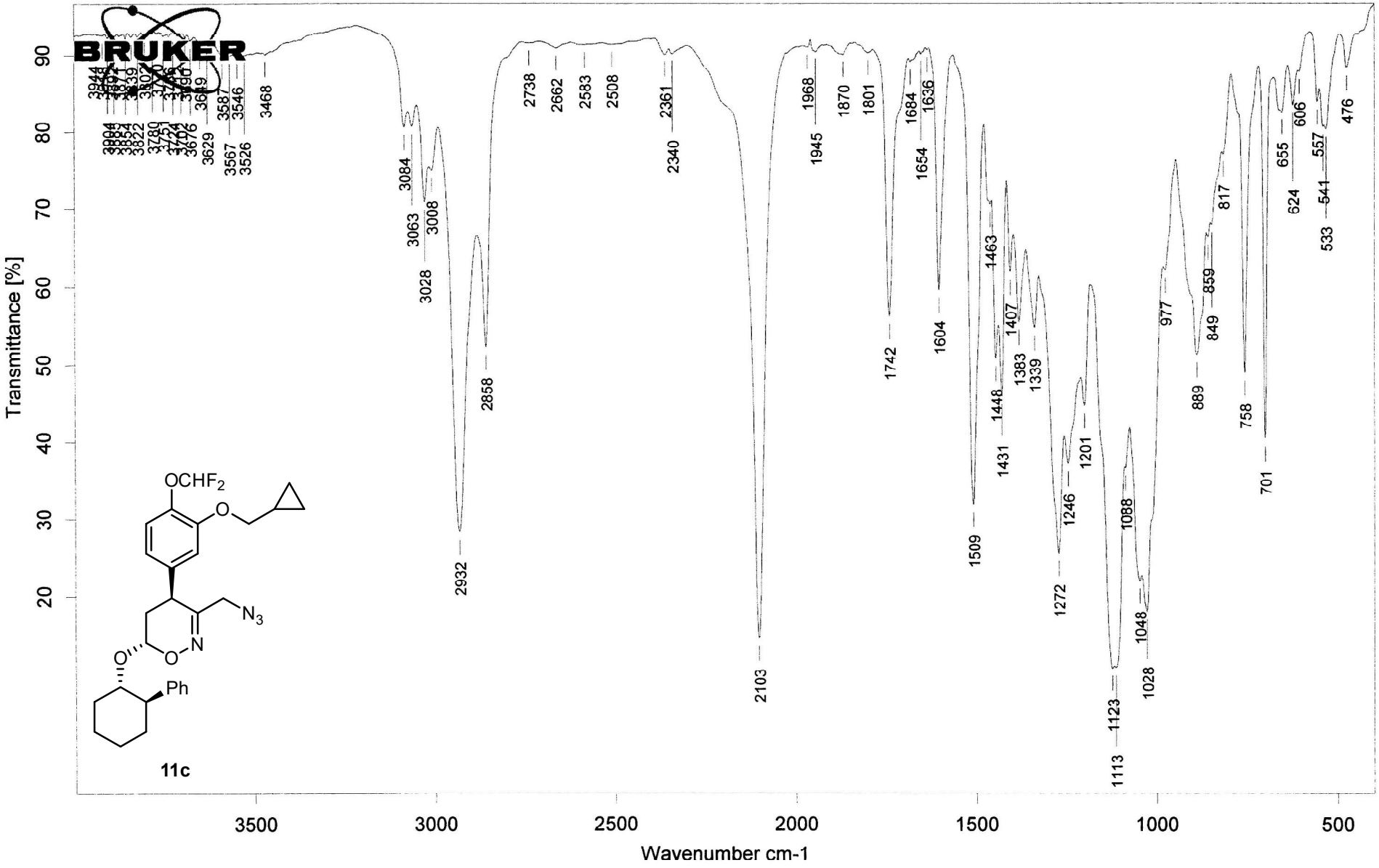
COSY NMR



11c

5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

f2 (ppm)



D:\EDL\VAD179.0	ДОРОХОВ.	VAD179,	тонкий слой пл. KBr		23.12.2015

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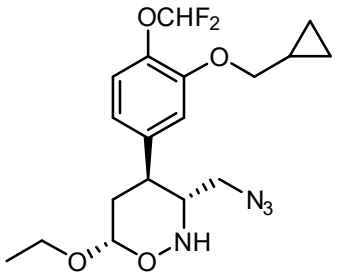
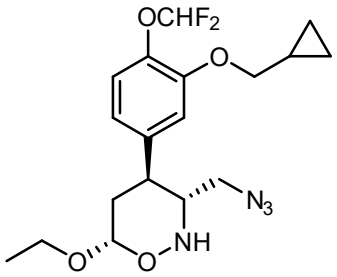
^{1}H NMR (300 MHz, $CDCl_3$)



12a

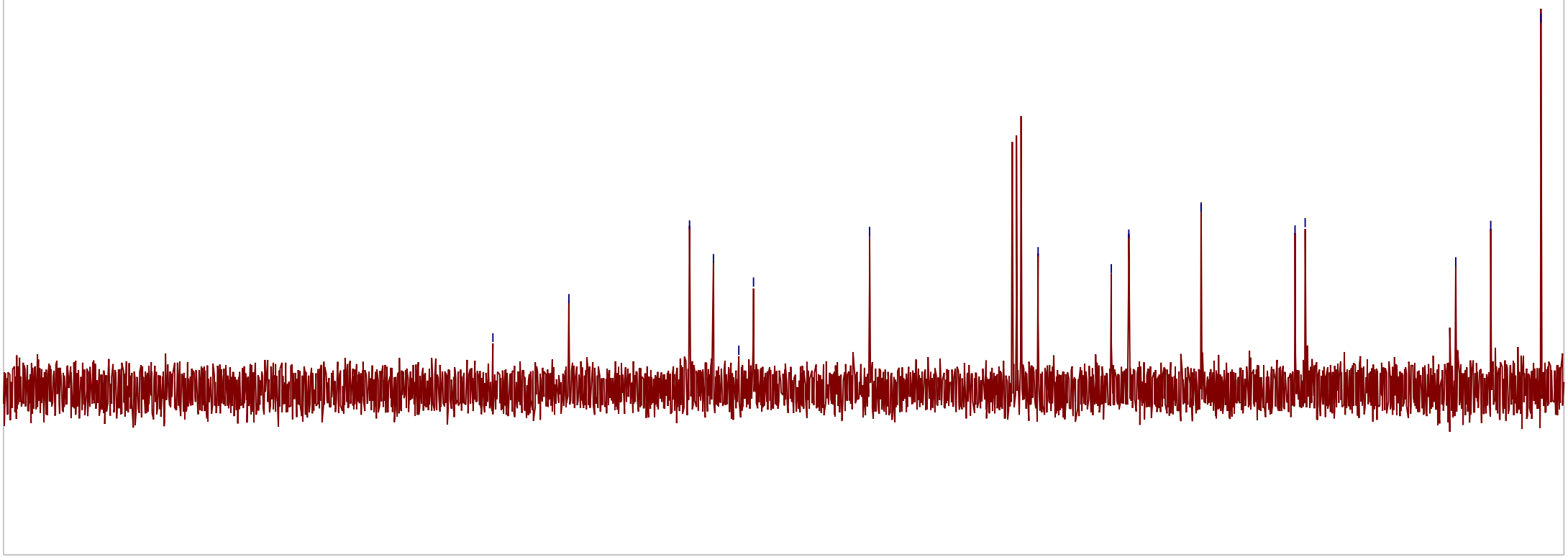
S174

^{13}C NMR (50 MHz, $CDCl_3$)



12a

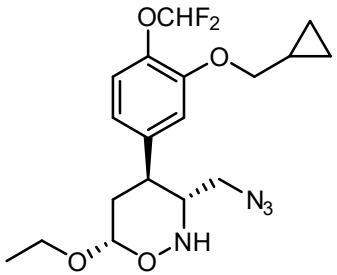
151.02
140.27
123.30
119.87
116.33
114.27
97.87
74.16
63.83
61.37
51.15
37.92
36.51
15.28
10.30
3.26



210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

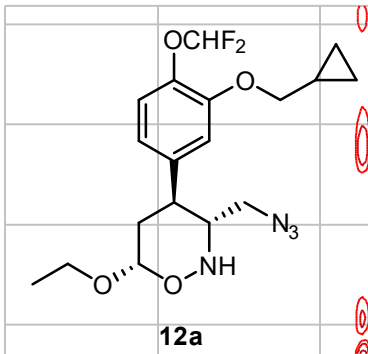
f1 (ppm)

^{19}F NMR (188 MHz, $CDCl_3$)



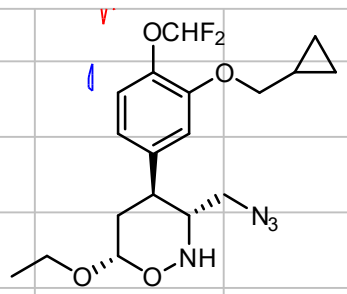
12a

COSY NMR



12a

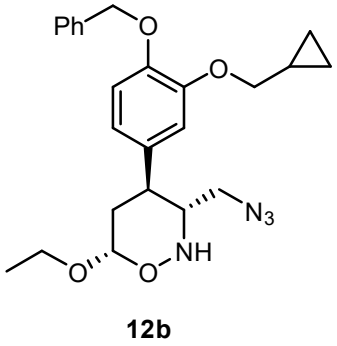
HSQC NMR


OCHF2
O
N3
NH
O
O

12a

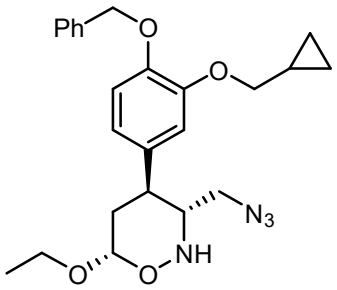
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
f1 (ppm)
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80

^{1}H NMR (300 MHz, $CDCl_3$)



12b

^{13}C NMR (75 MHz, $CDCl_3$)



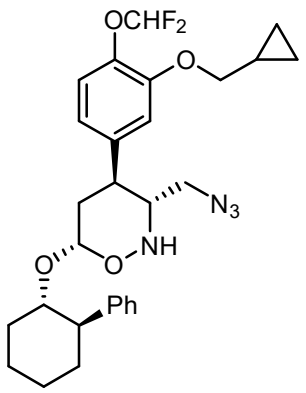
12b

149.80
148.20
137.62
134.89
128.58
127.89
127.40
120.01
115.96
114.57
98.09
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
74.44
71.69
63.78
61.61
51.18
37.62
36.54
15.33
10.60
3.39

f1 (ppm)

S180

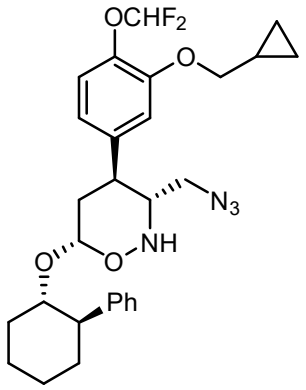
^{1}H NMR (300 MHz, $CDCl_3$)



12c

S181

^{13}C NMR (75 MHz, $CDCl_3$)

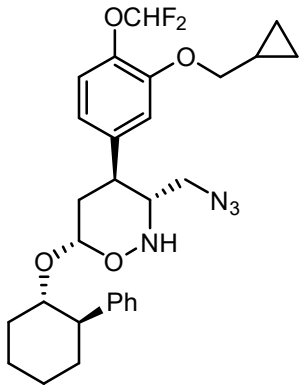


12c

150.85
144.63
140.30
139.46
128.92
128.13
126.85
123.10
119.98
119.74
116.30
113.61
112.86
93.31
77.81
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
74.08
61.15
51.01
50.34
37.75
36.76
33.58
31.38
26.11
24.84
10.27
3.28

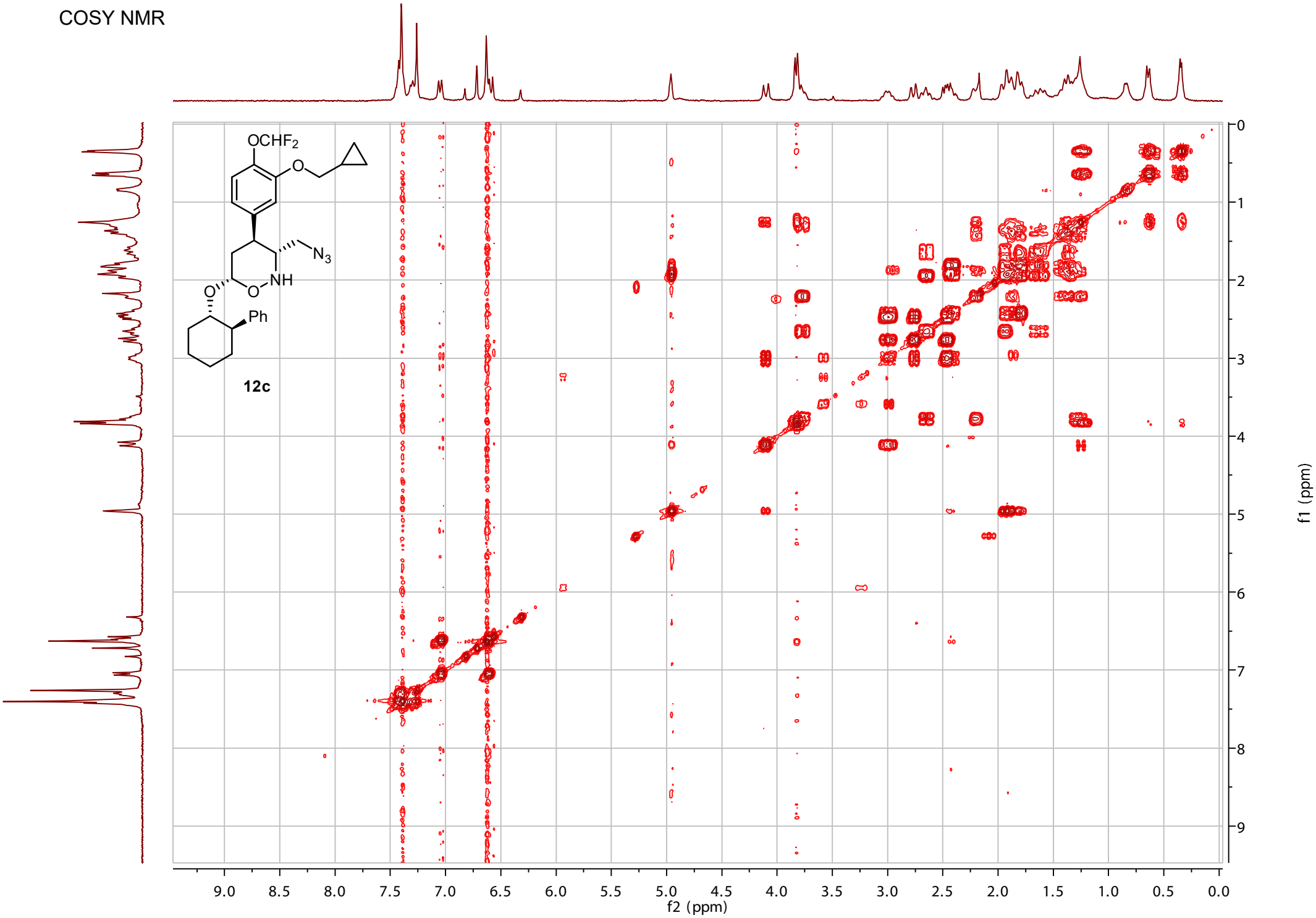
f1 (ppm)

^{19}F NMR (282 MHz, $CDCl_3$)

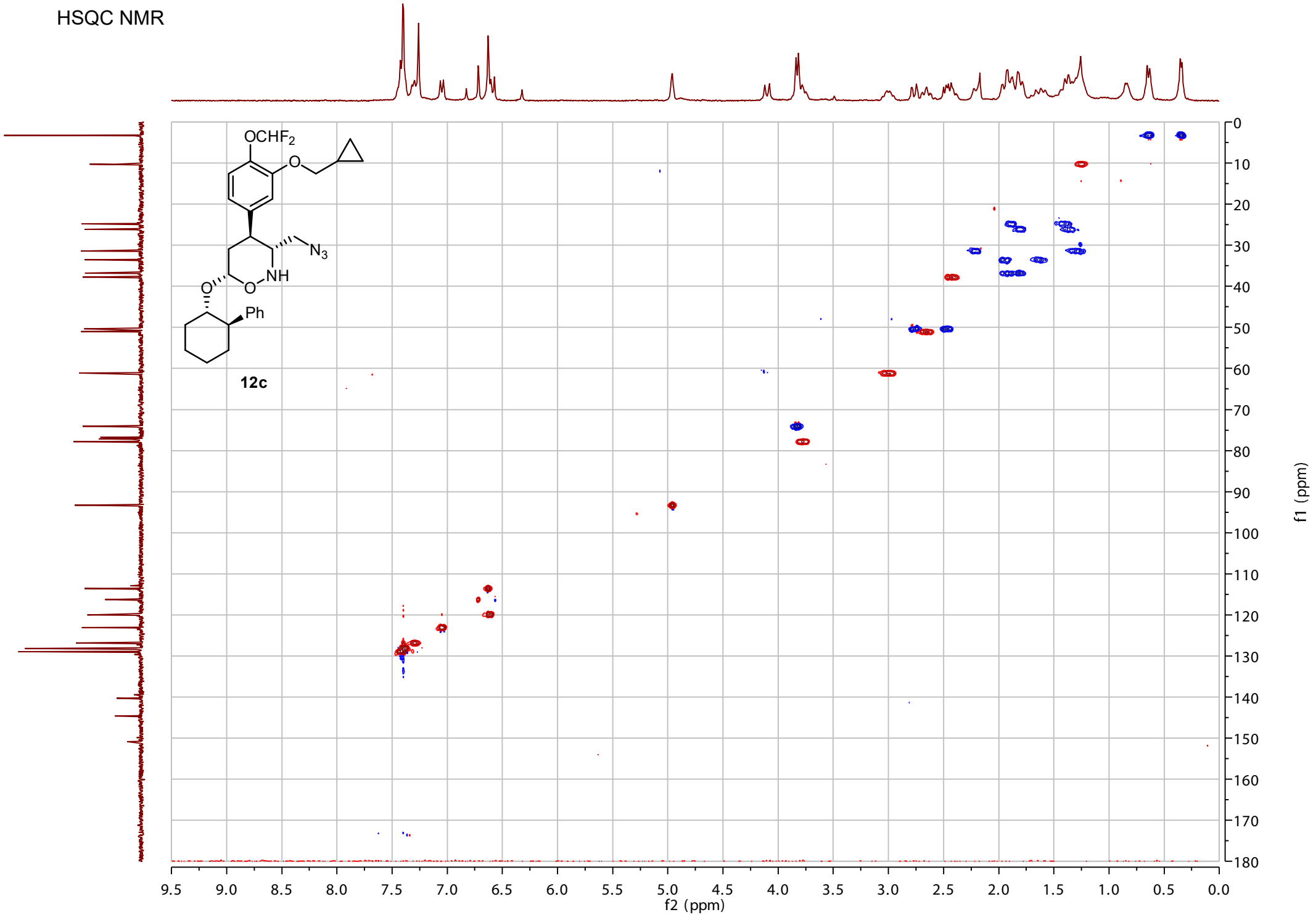


12c

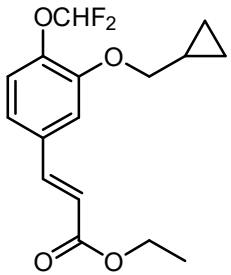
COSY NMR


OCHF2
O
N3
NH
O
O
Ph
12c
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0
1
2
3
4
5
6
7
8
9
f1 (ppm)

HSQC NMR


OCHF2
O
N3
NH
O
O
Ph
12c
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
f1 (ppm)

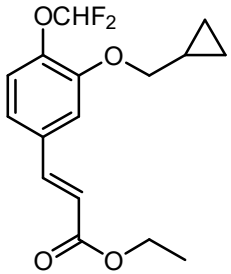
^{1}H NMR (300 MHz, $CDCl_3$)



14a

S186

^{13}C NMR (75 MHz, $CDCl_3$)



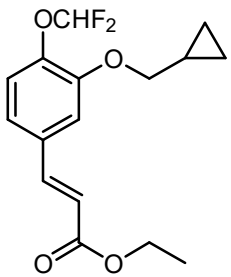
14a

166.65 150.65 143.44 143.44 141.89 132.98 122.58 122.58 121.40 121.40 119.49 118.63 118.63 116.05 113.21 113.21 112.60 77.16 73.94 60.55 14.26 14.26 10.08 10.08 3.19

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

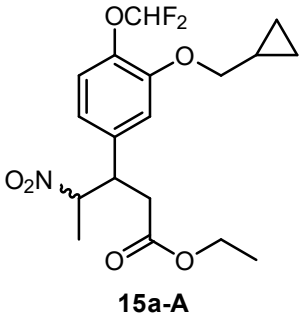
f1 (ppm)

^{19}F NMR (282 MHz, $CDCl_3$)



14a

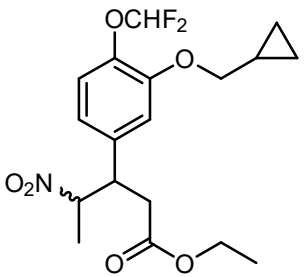
^{1}H NMR (300 MHz, $CDCl_3$)



15a-A

S189

^{13}C NMR (75 MHz, $CDCl_3$)



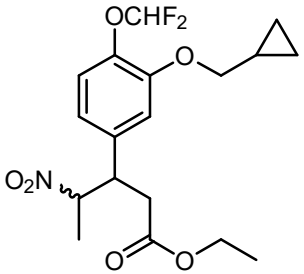
15a-A

170.21
150.53
139.87
136.19
122.65
120.51
119.56
116.13
114.60
112.69
86.62
77.16 CDCl3
73.80
60.59
45.94
37.39
17.39
13.79
9.95
2.97

f1 (ppm)

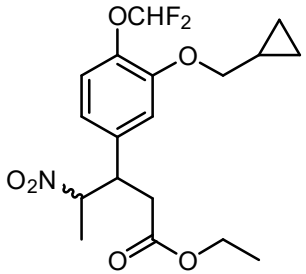
S190

^{19}F NMR (282 MHz, $CDCl_3$)



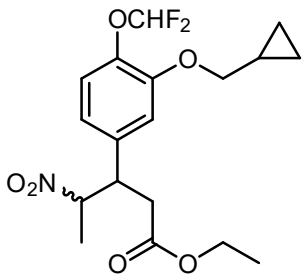
15a-A

^{1}H NMR (300 MHz, $CDCl_3$)



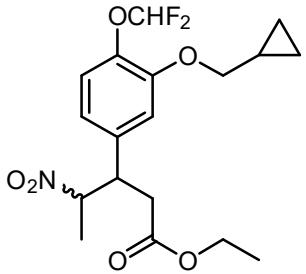
15a-B

^{13}C NMR (75 MHz, $CDCl_3$)



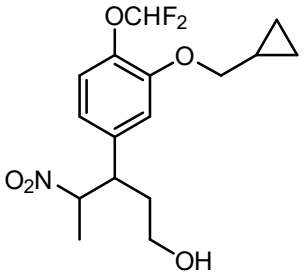
15a-B

^{19}F NMR (282 MHz, $CDCl_3$)



15a-B

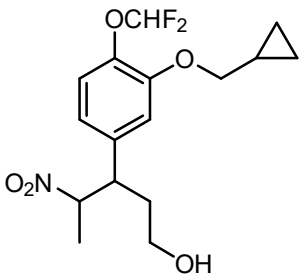
^{1}H NMR (300 MHz, $CDCl_3$)



16a-A

S195

^{13}C NMR (75 MHz, $CDCl_3$)

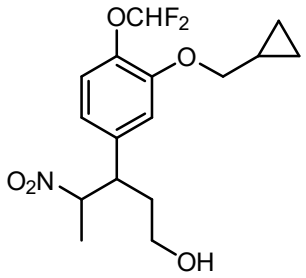


16a-A

150.99
139.36
136.85
123.22
120.80
114.80
87.96
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
74.21
59.84
46.73
35.33
18.04
10.23
3.30

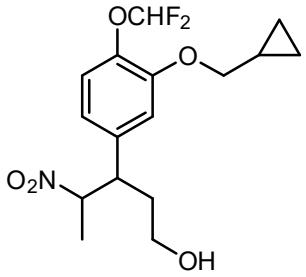
f1 (ppm)

^{19}F NMR (282 MHz, $CDCl_3$)



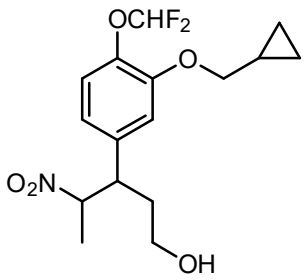
16a-A

^{1}H NMR (300 MHz, $CDCl_3$)



16a-B

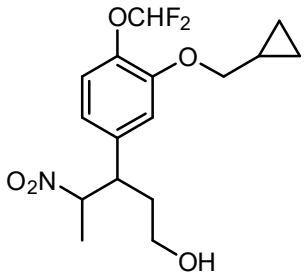
^{13}C NMR (75 MHz, $CDCl_3$)



16a-B

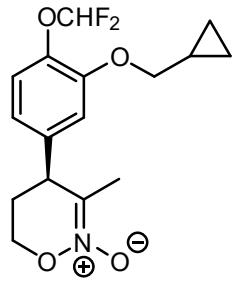
S199

^{19}F NMR (282 MHz, $CDCl_3$)



16a-B

^{1}H NMR (300 MHz, $CDCl_3$)



18a

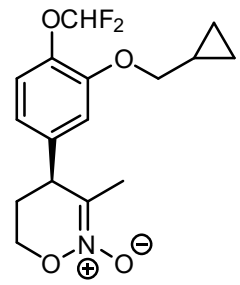
7.26 7.14 7.11 6.86 6.75 6.72 6.70 6.60 6.35 4.42 4.41 3.85 3.82 3.73 3.71 2.33 2.02 1.98 1.89 1.83 1.25 0.65 0.62 0.35 0.34

4.55 2.35 3.56 1.35 5.42 1.20 1.94 2.00

f1 (ppm)

S201

^{13}C NMR (75 MHz, $CDCl_3$)

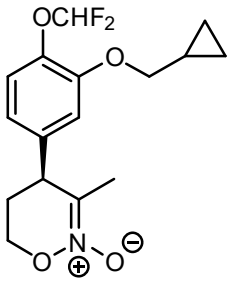


18a

150.95
139.54
123.36
120.64
119.21
115.89
113.64
112.44
77.16
74.24
69.27
43.65
30.38
18.23
10.20
3.28

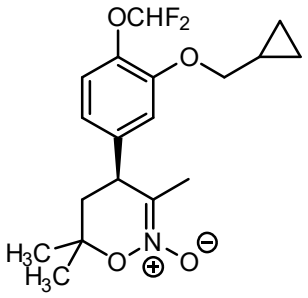
f1 (ppm)

^{19}F NMR (282 MHz, $CDCl_3$)



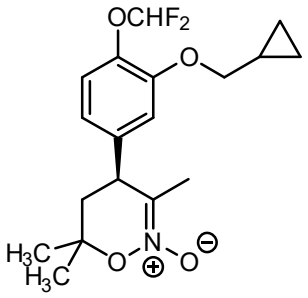
18a

^{1}H NMR (300 MHz, $CDCl_3$)



18b

^{13}C NMR (75 MHz, $CDCl_3$)

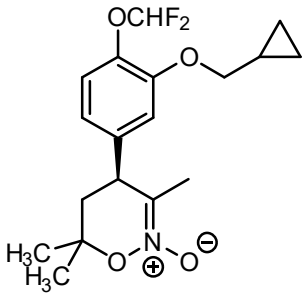


18b

151.36
139.92
139.06
123.37
121.45
120.77
119.64
116.19
113.57
112.75
81.39
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
74.26
43.22
41.76
27.89
22.21
17.35
10.22
3.31

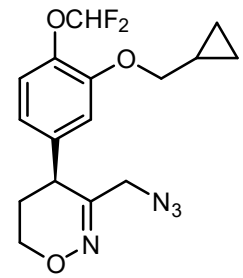
f1 (ppm)

^{19}F NMR (282 MHz, $CDCl_3$)



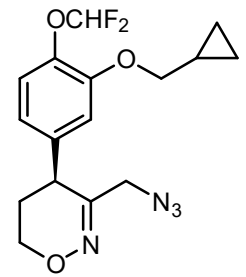
18b

^{1}H NMR (300 MHz, $CDCl_3$)



21a

^{13}C NMR (75 MHz, $CDCl_3$)

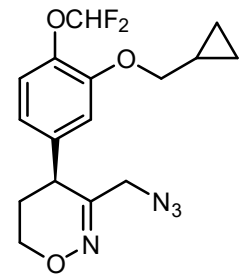


21a

154.22
151.11
139.77
138.68
123.28
120.77
119.58
116.14
114.18
112.69
77.58 CDCl3
77.16 CDCl3
76.73 CDCl3
74.06
64.02
52.99
36.77
28.36
10.13
3.22

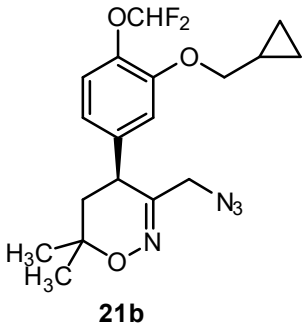
f1 (ppm)

^{19}F NMR (282 MHz, $CDCl_3$)



21a

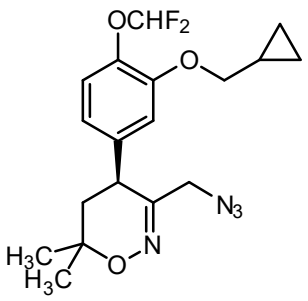
^{1}H NMR (300 MHz, $CDCl_3$)



21b

S210

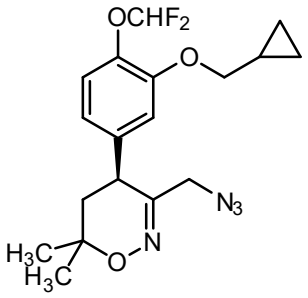
^{13}C NMR (75 MHz, $CDCl_3$)



21b

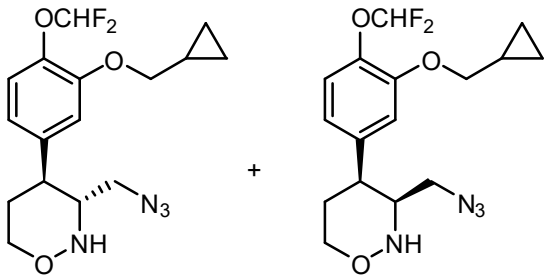
154.13
151.31
139.62
137.97
123.53
121.35
121.00
119.98
117.84
114.46
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
75.25
74.20
52.85
40.15
37.67
28.46
22.54
10.24
3.33

^{19}F NMR (282 MHz, $CDCl_3$)



21b

^{1}H NMR (300 MHz, $CDCl_3$)



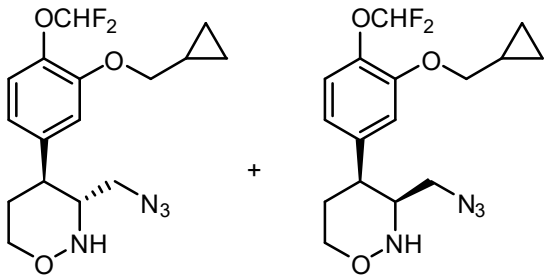
22a

+

22a'
(minor 3,4-*cis* isomer)

d.r. 6.5 : 1

^{13}C NMR (75 MHz, $CDCl_3$)



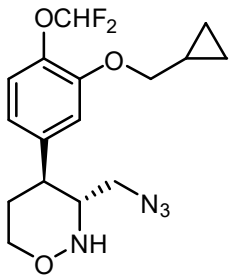
22a

+

22a'
(minor 3,4-*cis* isomer)

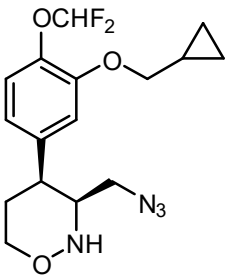
d.r. 6.5 : 1

^{19}F NMR (282 MHz, $CDCl_3$)



22a

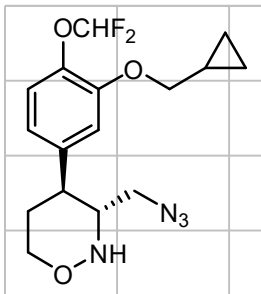
+



22a'
(minor 3,4-*cis* isomer)

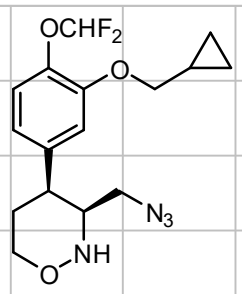
d.r. 6.5 : 1

COSY NMR



22a

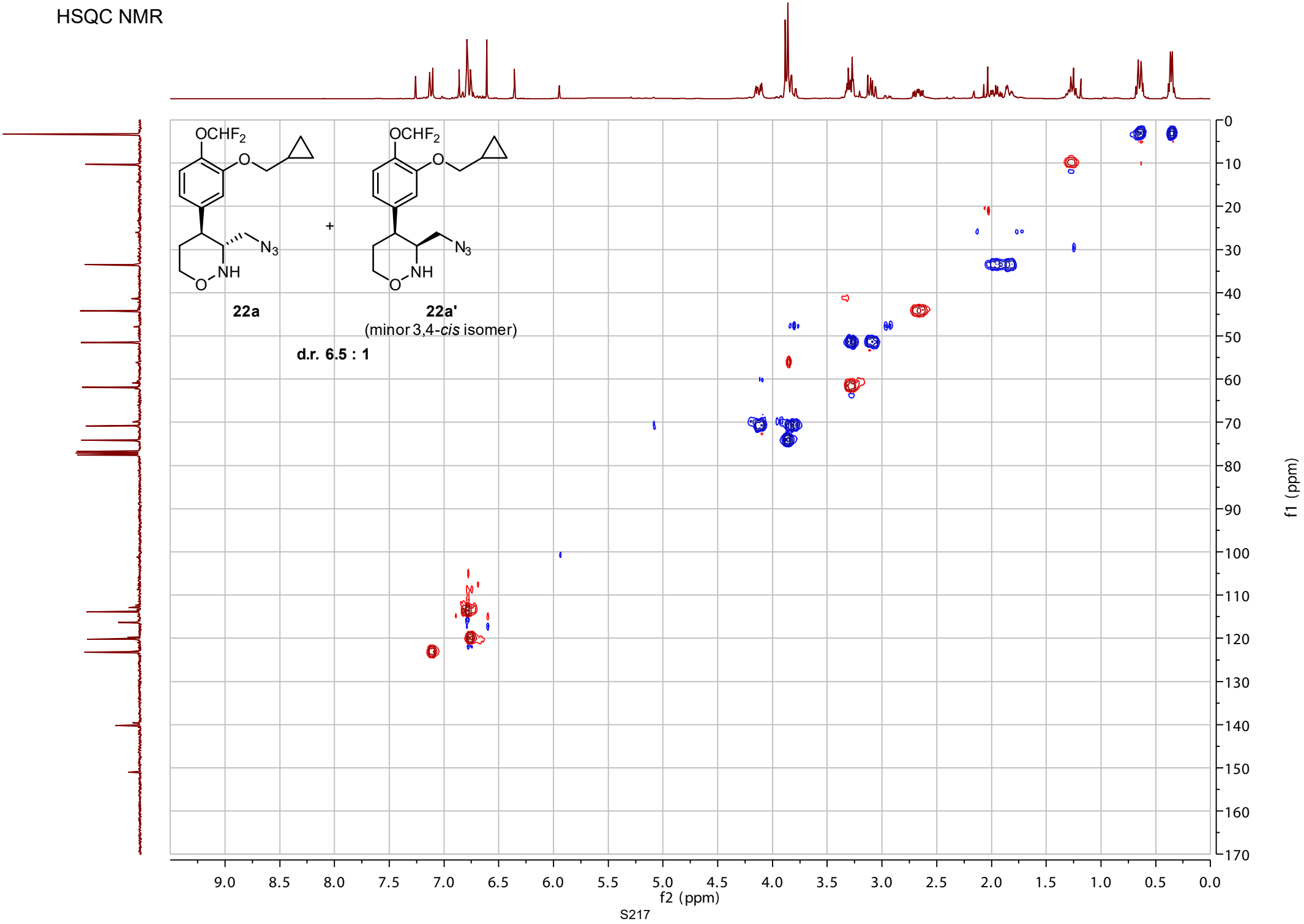
+



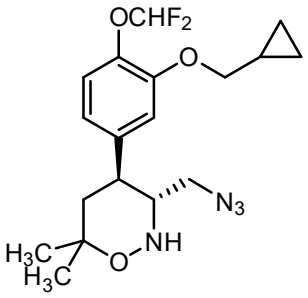
22a'
(minor 3,4-*cis* isomer)

d.r. 6.5 : 1

HSQC NMR


OCHF2
O
N3
NH
O
22a
+
OCHF2
O
N3
NH
O
22a'
(minor 3,4-cis isomer)
d.r. 6.5 : 1
f2 (ppm)
f1 (ppm)

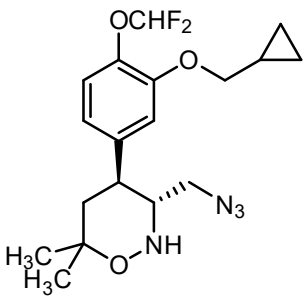
^{1}H NMR (300 MHz, $CDCl_3$)



22b

S218

^{13}C NMR (75 MHz, $CDCl_3$)

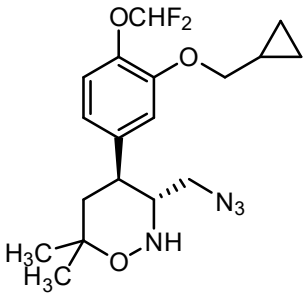


22b

149.51
140.44
139.45
123.22
120.21
117.06
113.92
113.66
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
74.84
74.12
61.51
51.38
43.85
40.93
29.29
22.07
10.31
3.31

f1 (ppm)

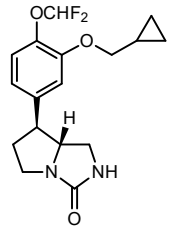
^{19}F NMR (282 MHz, $CDCl_3$)



22b

SHIMADZU LabSolutions

Analysis Report

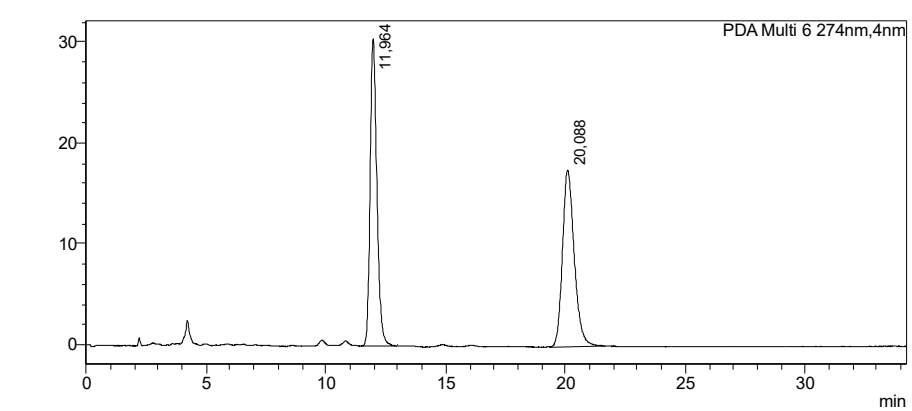


rac-**1a**

<Sample Information>

Sample Name	: VAD157_rac		
Sample ID	: VAD157_rac		
Data Filename	: VAD159.lcd		
Method Filename	: multiwave.lcm		
Batch Filename	:		
Vial #	: 1-100	Sample Type	: Unknown
Injection Volume	: 3 uL		
Date Acquired	: 20.02.2016 15:19:39	Acquired by	: PZ
Date Processed	: 29.10.2010 17:13:31	Processed by	: PZ

<Chromatogram>



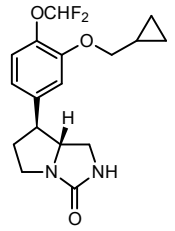
<Peak Table>

PDA Ch6 274nm

Peak#	Ret. Time	Area	Height	Area%
1	11,964	596933	30452	49,928
2	20,088	598644	17514	50,072
Total		1195576	47966	100,000

SHIMADZU LabSolutions

Analysis Report

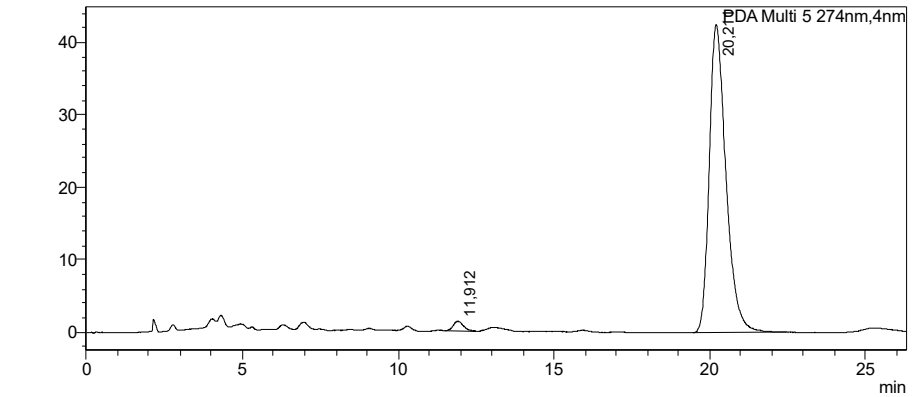


(-)-(7S,7aR)-**1a**

<Sample Information>

Sample Name	: VAD183_chir		
Sample ID	: VAD183_chir		
Data Filename	: VAD160.lcd		
Method Filename	: multiwave.lcm		
Batch Filename	:		
Vial #	: 1-101	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 20.02.2016 16:40:00	Acquired by	: PZ
Date Processed	: 29.10.2010 17:17:58	Processed by	: PZ

<Chromatogram>



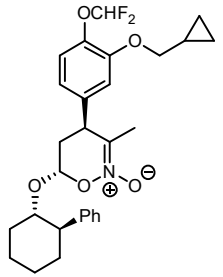
<Peak Table>

PDA Ch5 274nm

Peak#	Ret. Time	Area	Height	Area%
1	11,912	29655	1321	1,839
2	20,211	1582470	42511	98,161
Total		1612125	43831	100,000

SHIMADZU LabSolutions

Analysis Report

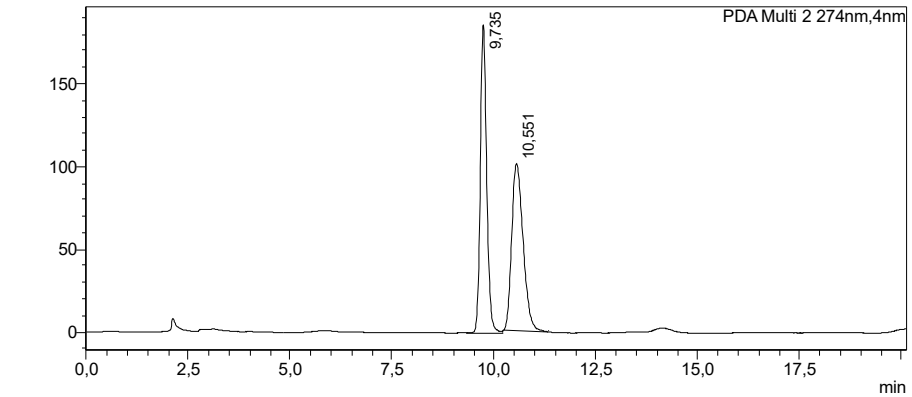


rac-**7c**

<Sample Information>

Sample Name	: VAD108_5		
Sample ID	: VAD108_5		
Data Filename	: VAD108_5_mod.lcd		
Method Filename	: 231014.lcm		
Batch Filename	:		
Vial #	: 1-16	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 10.04.2015 16:52:40	Acquired by	: PZ
Date Processed	: 29.10.2010 17:01:16	Processed by	: PZ

<Chromatogram>



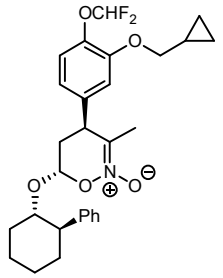
<Peak Table>

PDA Ch2 274nm

Peak#	Ret. Time	Area	Height	Area%
1	9,735	2034034	186760	50,758
2	10,551	1973297	101385	49,242
Total		4007332	288145	100,000

SHIMADZU LabSolutions

Analysis Report

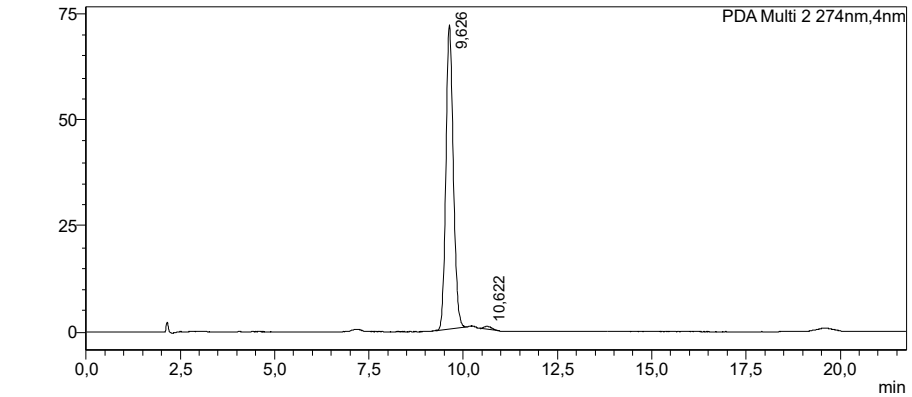


(+)-(4S,6S,7S,8R)-**7c**

<Sample Information>

Sample Name	: VAD_169_1		
Sample ID	: VAD_169_1		
Data Filename	: VAD169_1_mod.lcd		
Method Filename	: 231014.lcm		
Batch Filename	:		
Vial #	: 1-20	Sample Type	: Unknown
Injection Volume	: 5 uL		
Date Acquired	: 24.11.2015 19:12:54	Acquired by	: PZ
Date Processed	: 29.10.2010 17:37:56	Processed by	: PZ

<Chromatogram>



<Peak Table>

PDA Ch2 274nm

Peak#	Ret. Time	Area	Height	Area%
1	9,626	983095	71810	99,008
2	10,622	9850	676	0,992
Total		992945	72486	100,000