

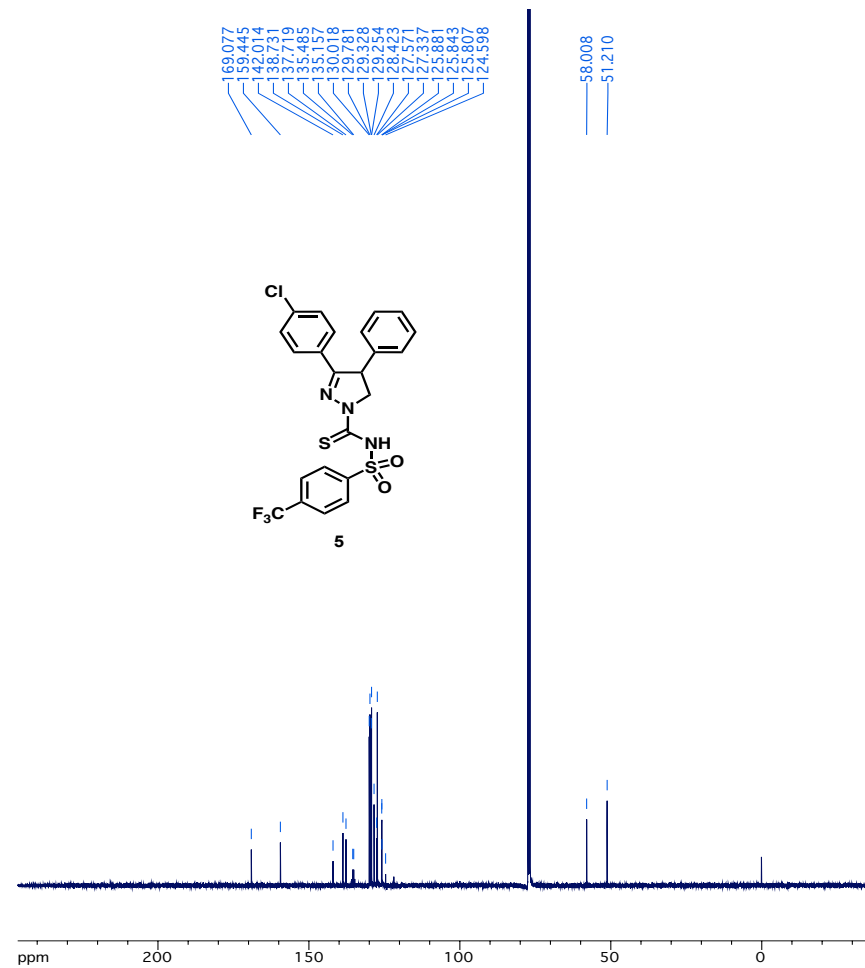
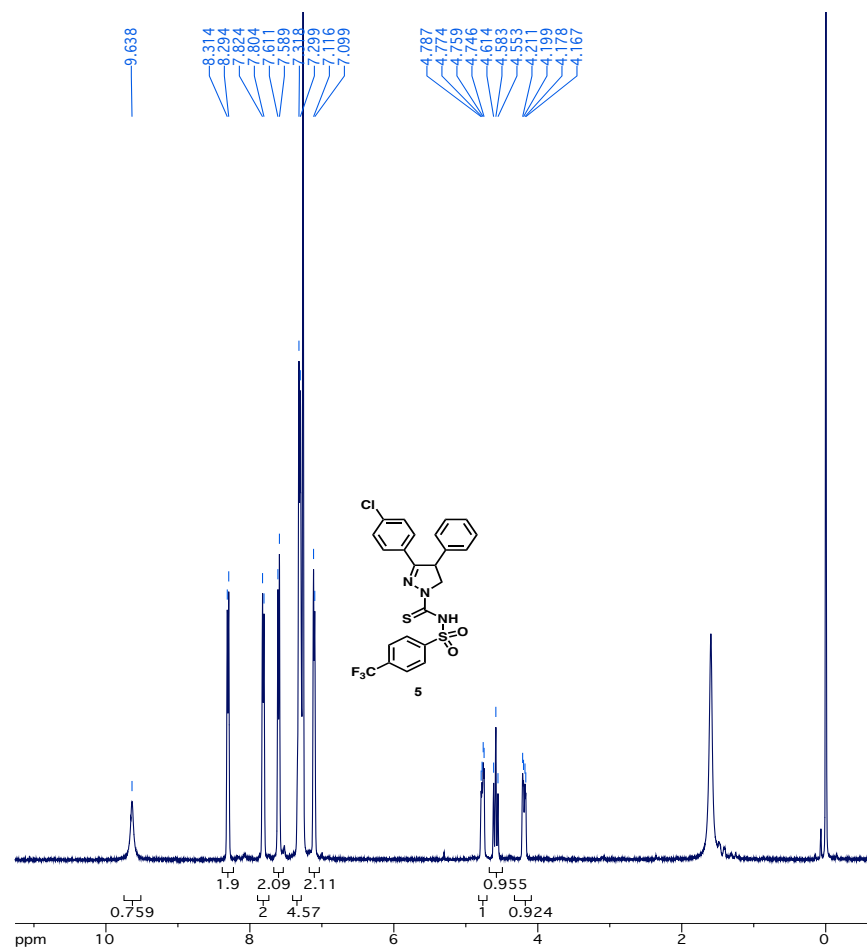
**A Novel Approach for the Synthesis of Peripherally Acting Dual Target Inhibitor
of Cannabinoid-1 (CB1 Receptor) and Inducible Nitric Oxide Synthase (iNOS) (S-
MRI-1867/Zevaquenabant)**

Malliga R. Iyer

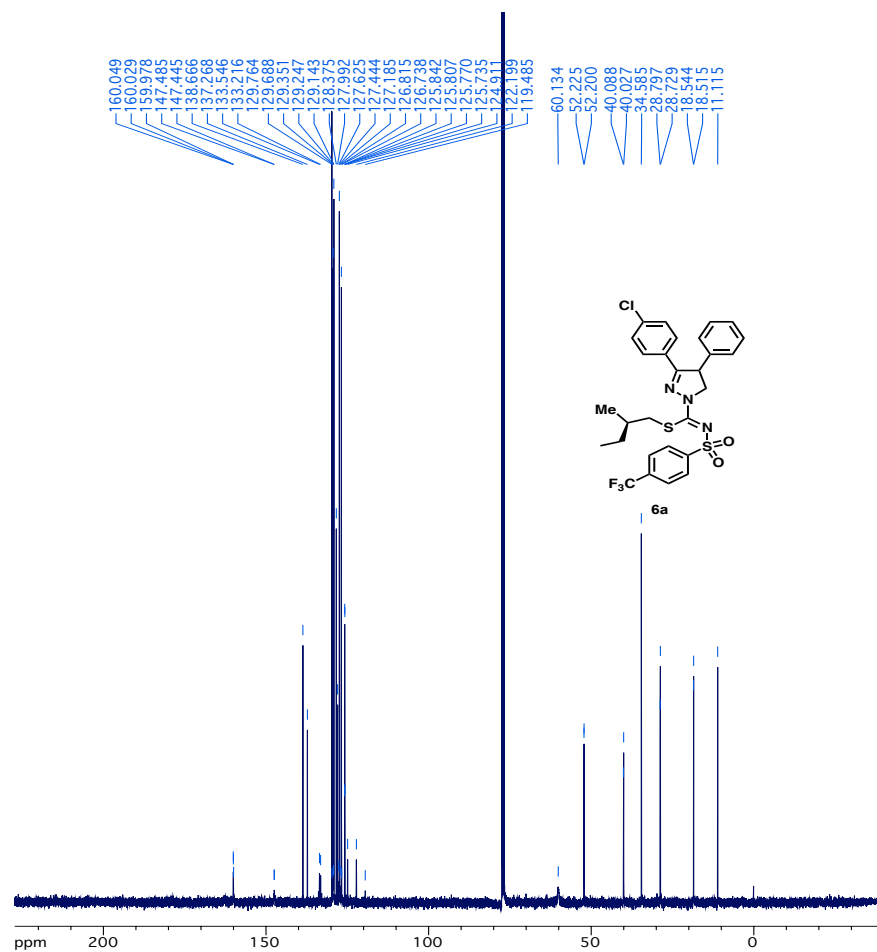
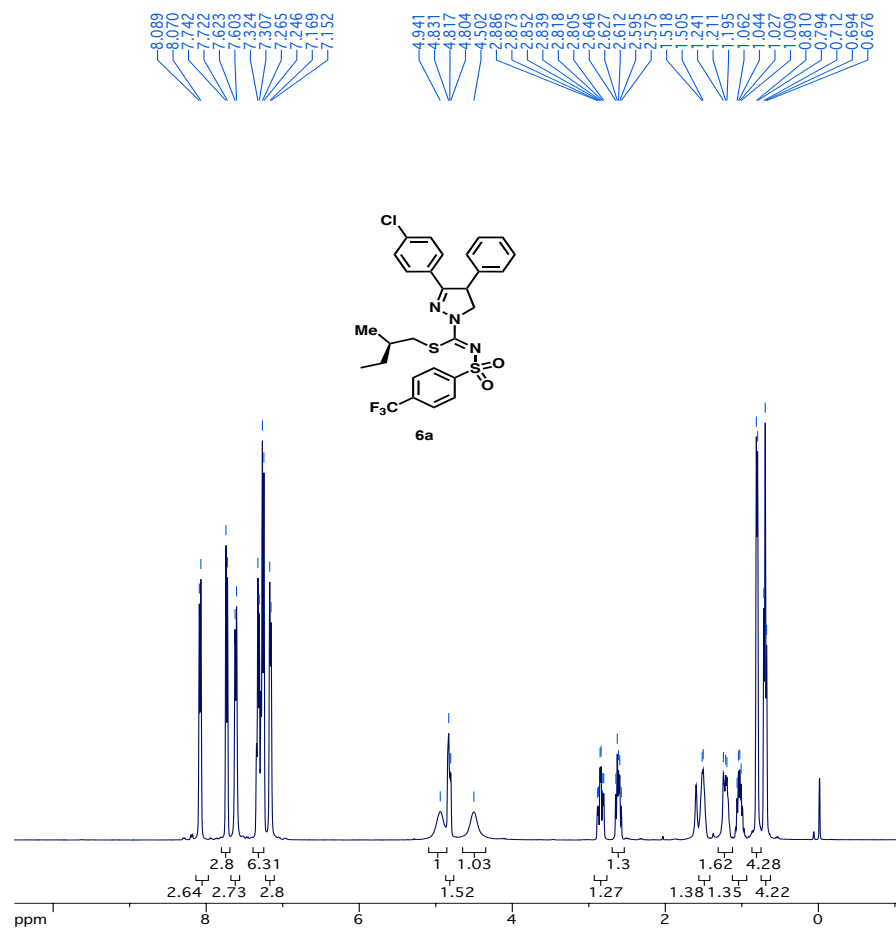
Section on Medicinal Chemistry, National Institute on Alcohol Abuse and
Alcoholism, National Institutes of Health, 5625 Fishers Lane, Rockville, MD 20852, USA.

Supporting Data:

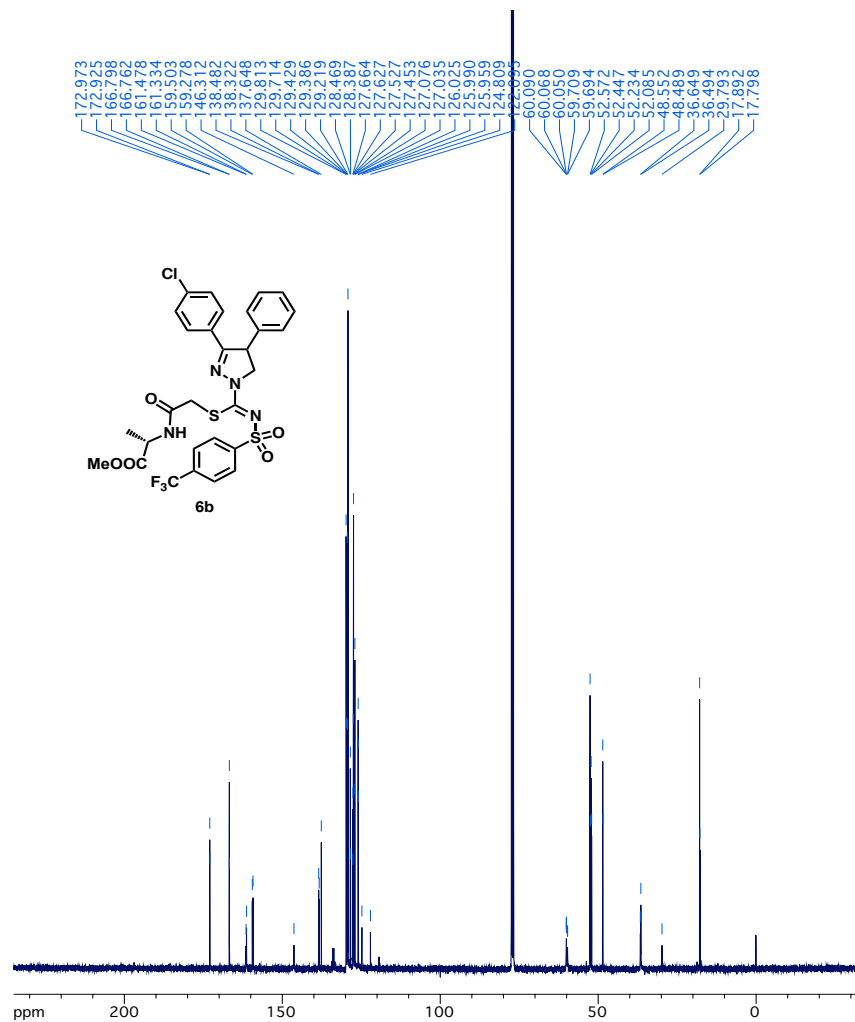
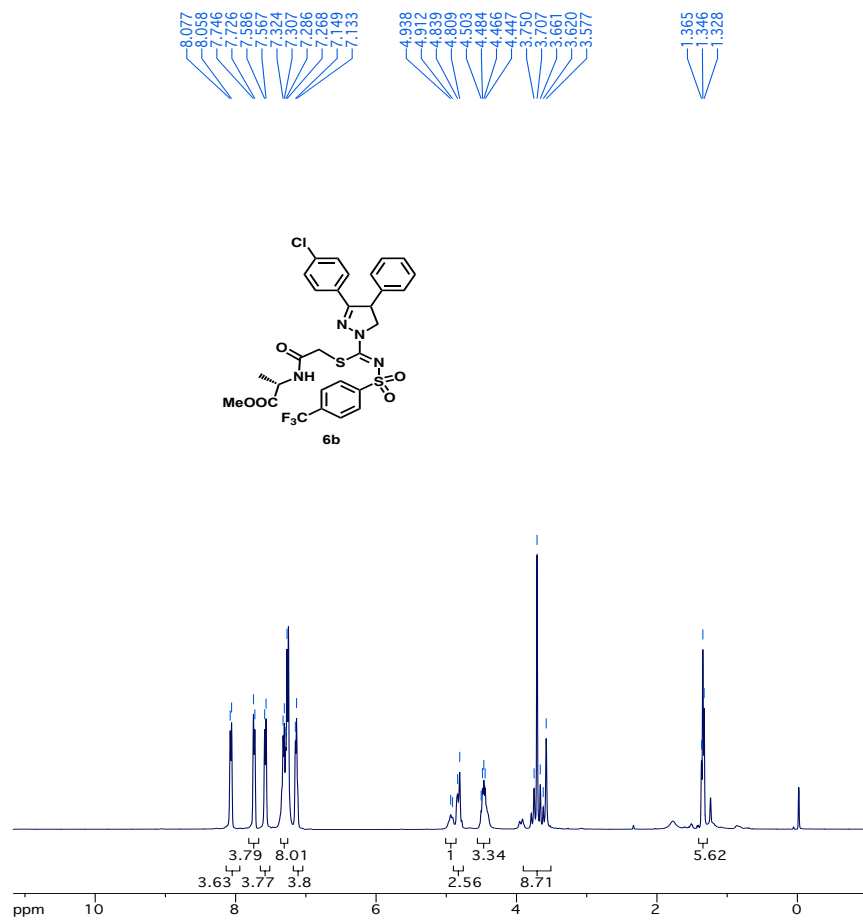
¹H-NMR and ¹³C-NMR of Compound **5**



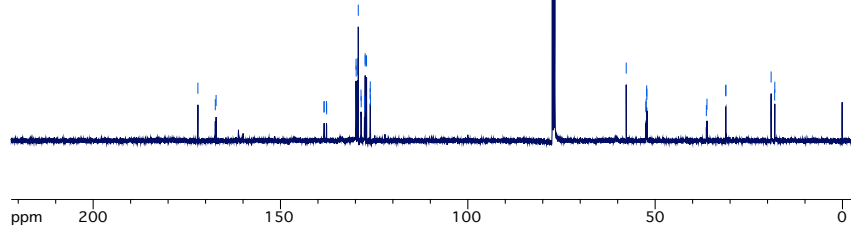
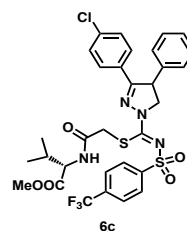
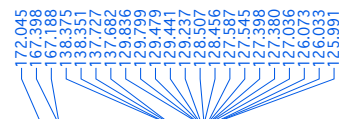
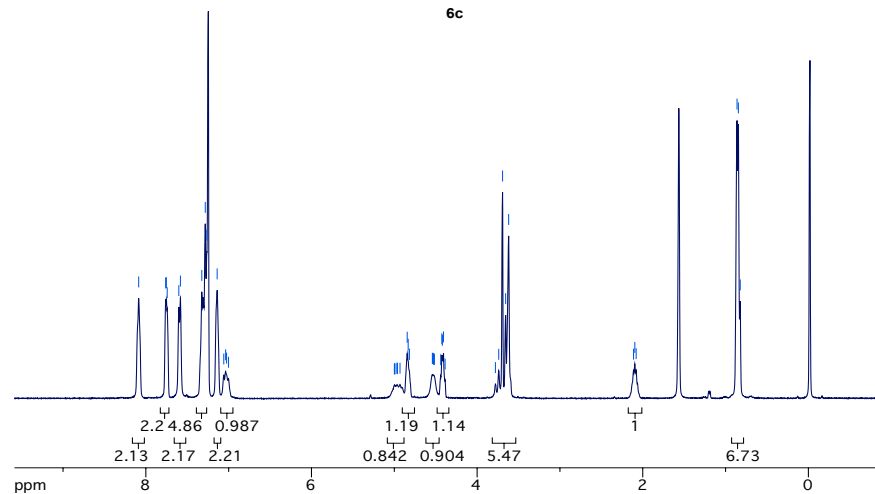
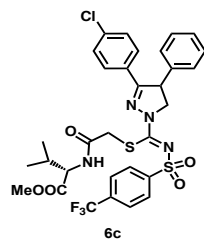
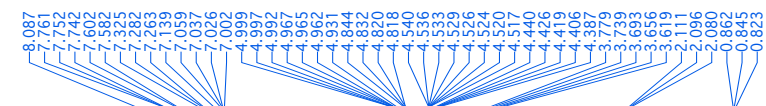
¹H-NMR and ¹³C-NMR of Compound 6a



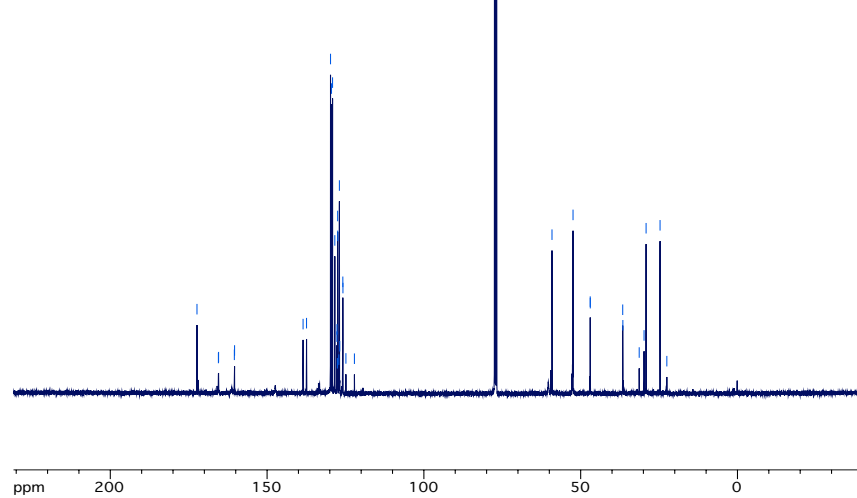
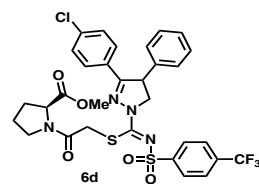
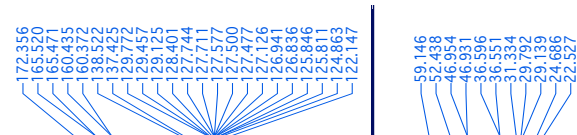
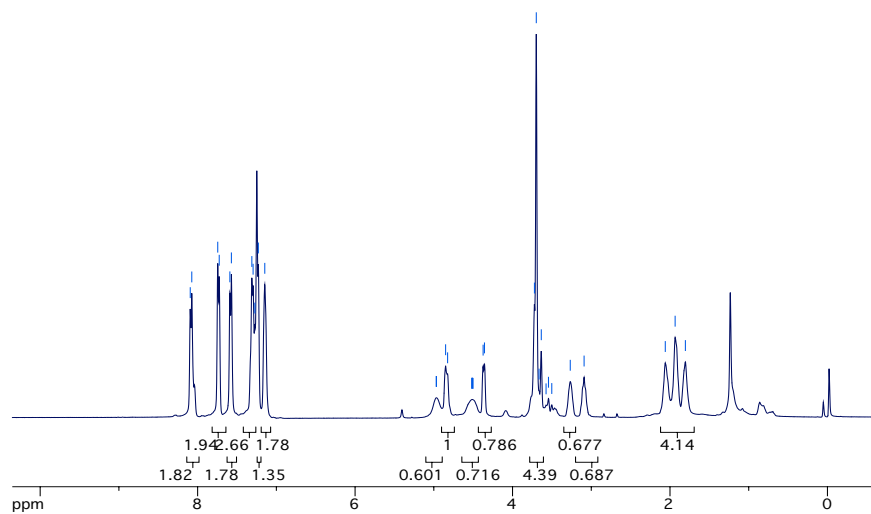
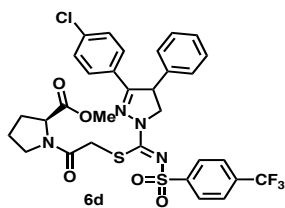
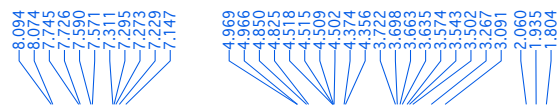
¹H-NMR and ¹³C-NMR of Compound **6b**



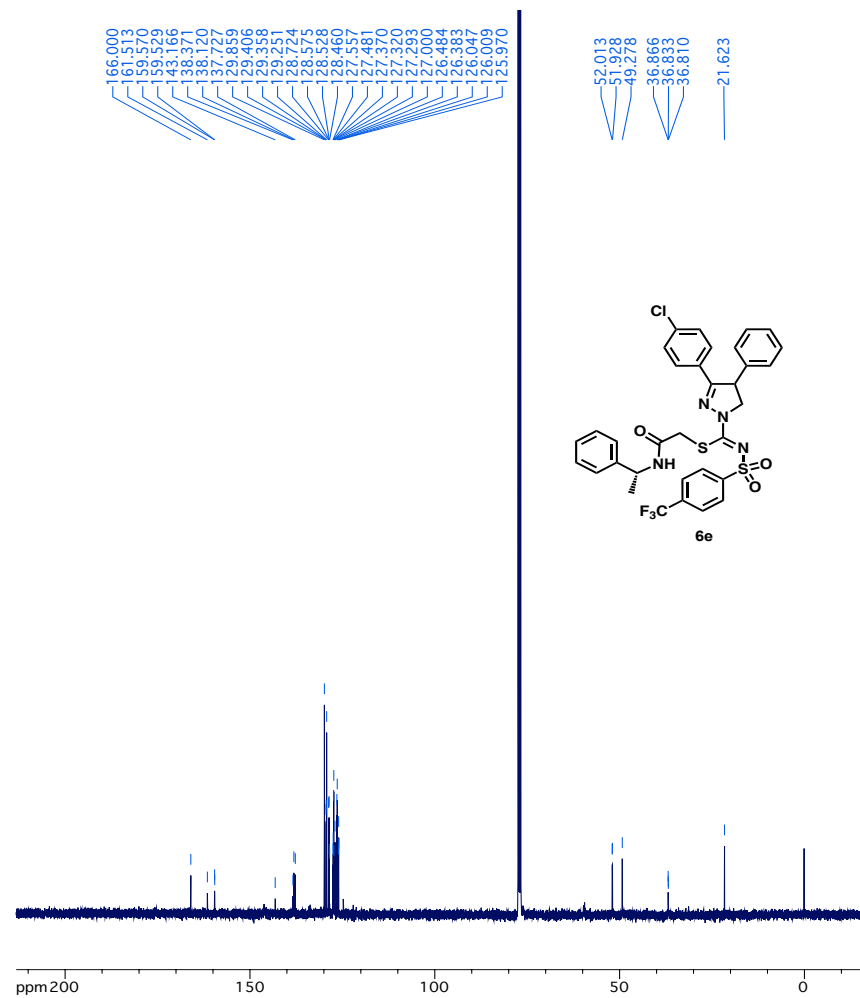
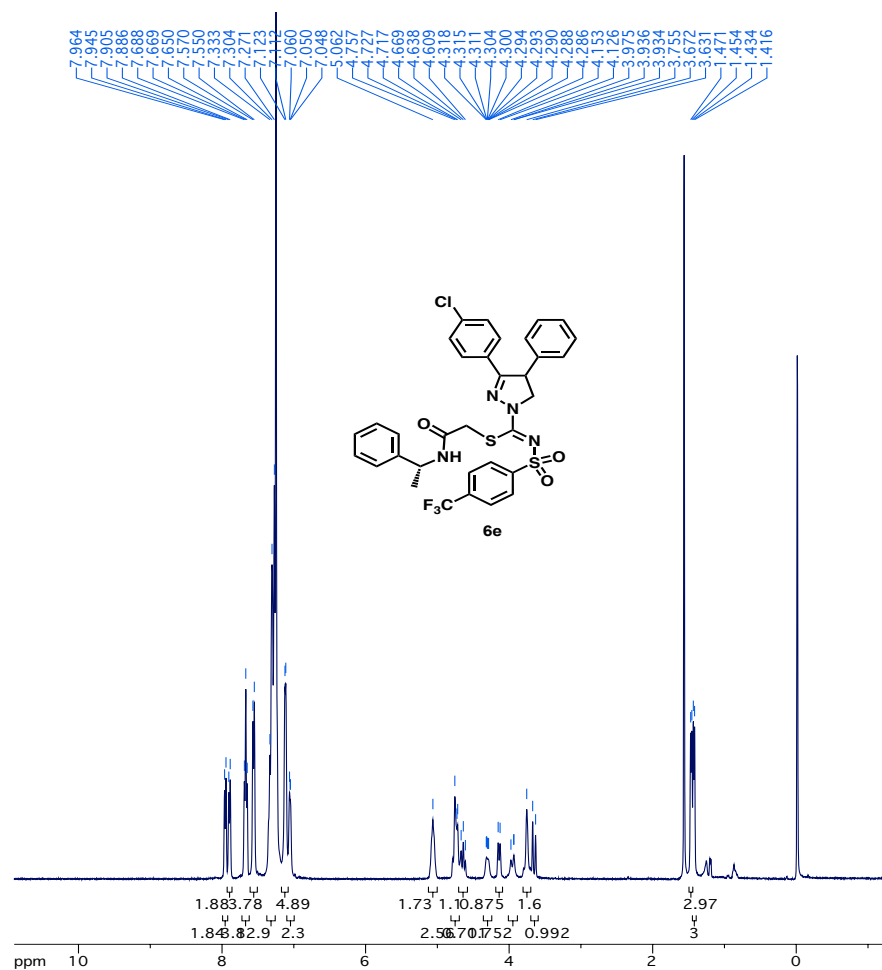
¹H-NMR and ¹³C-NMR of Compound **6c**



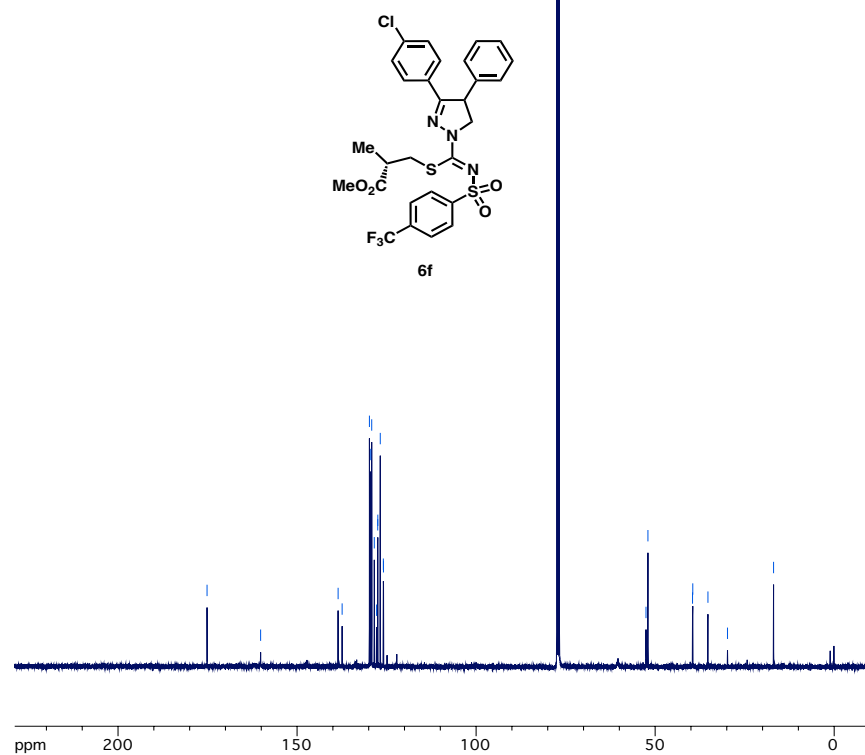
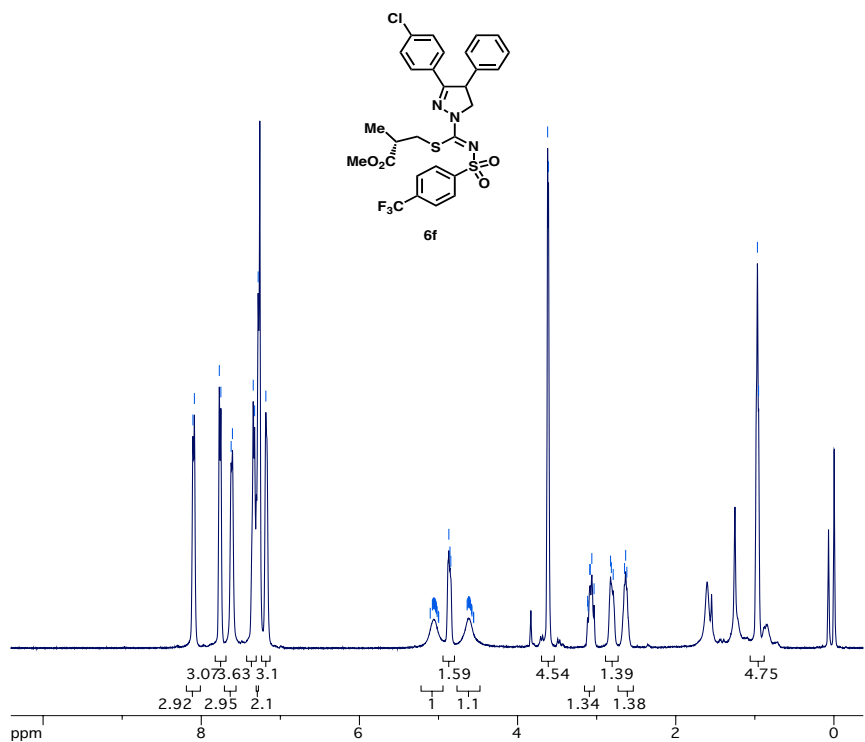
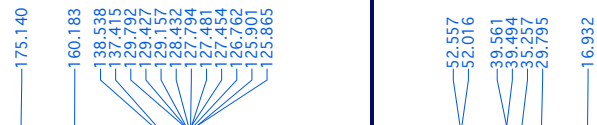
¹H-NMR and ¹³C-NMR of Compound **6d**



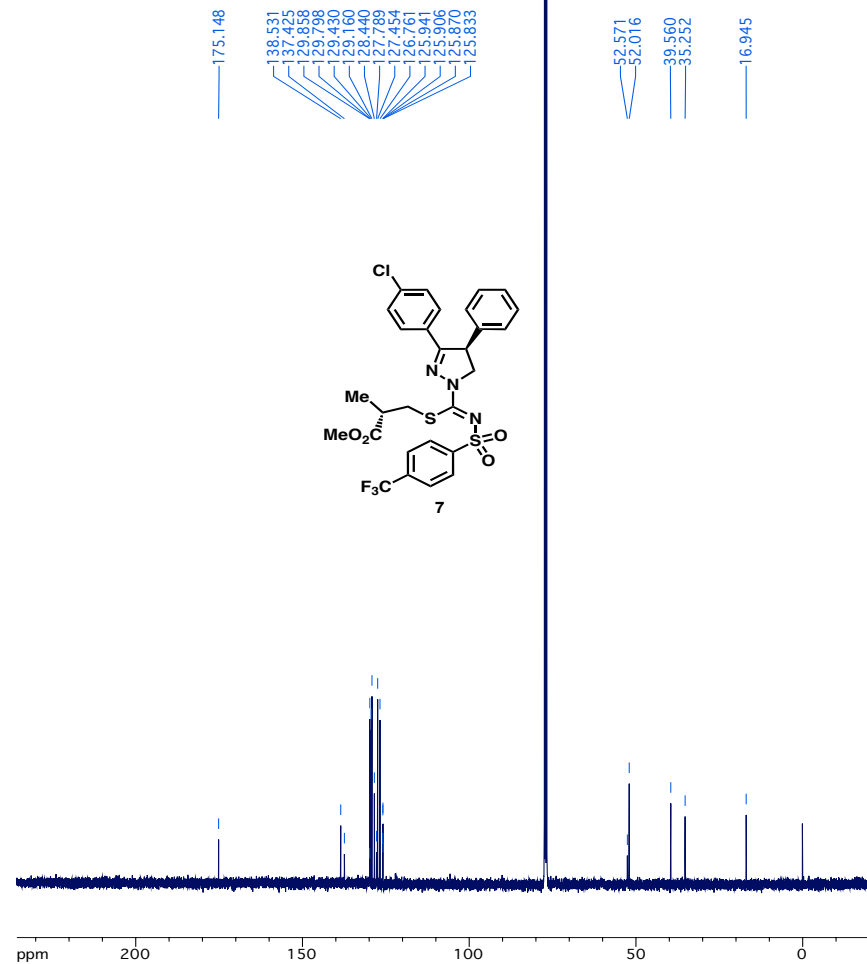
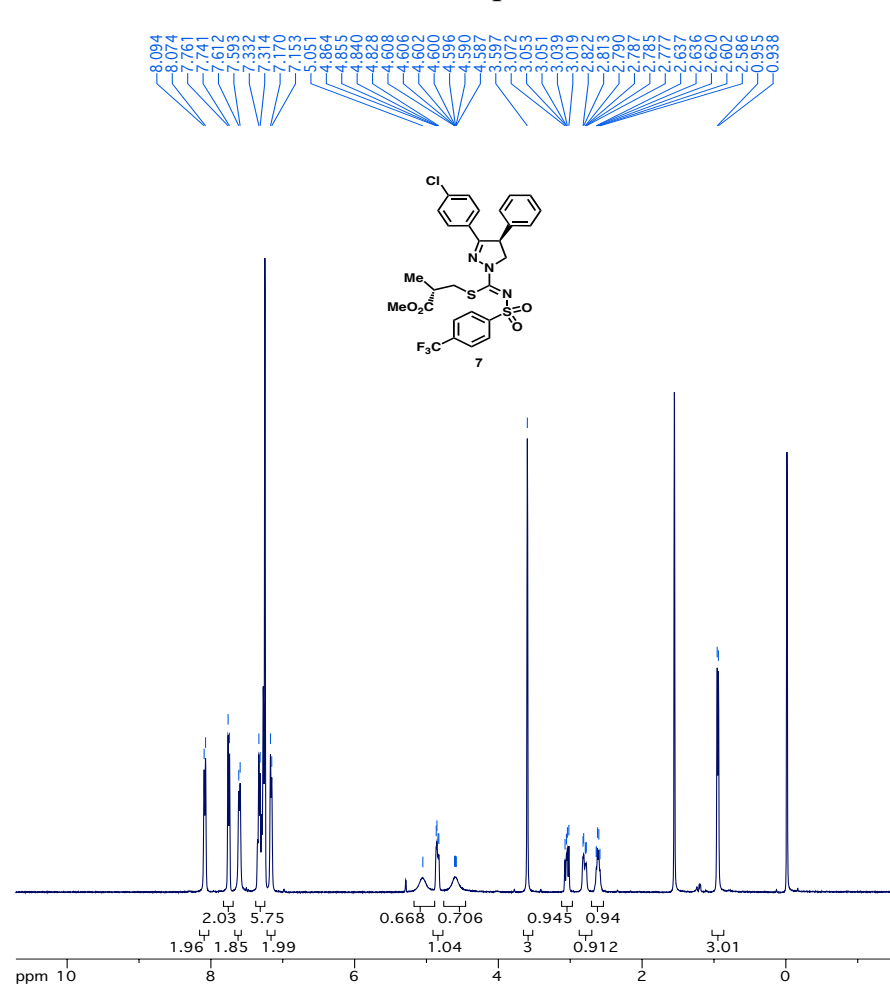
¹H-NMR and ¹³C-NMR of Compound 6e



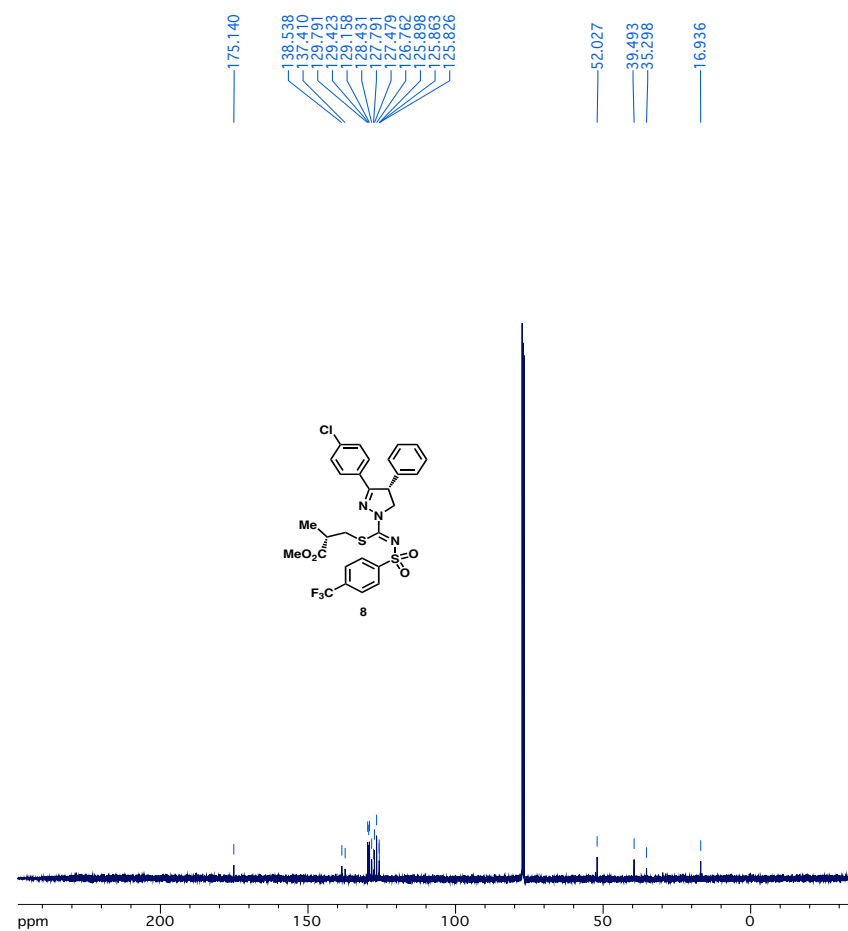
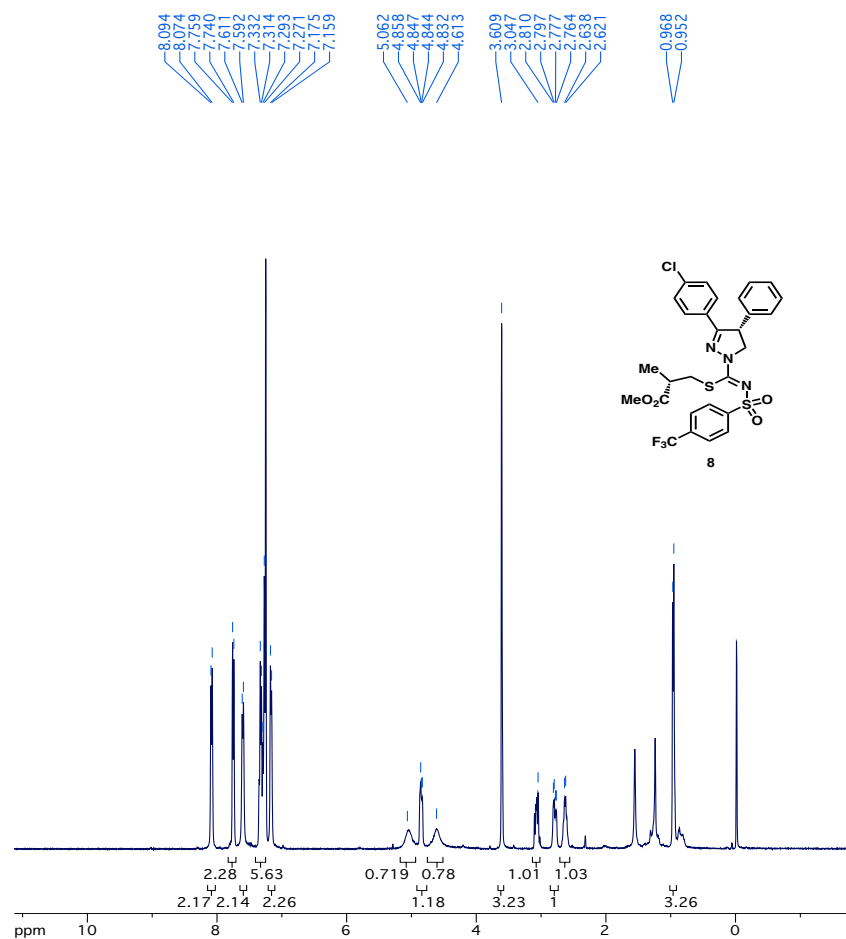
¹H-NMR and ¹³C-NMR of Compound 6f



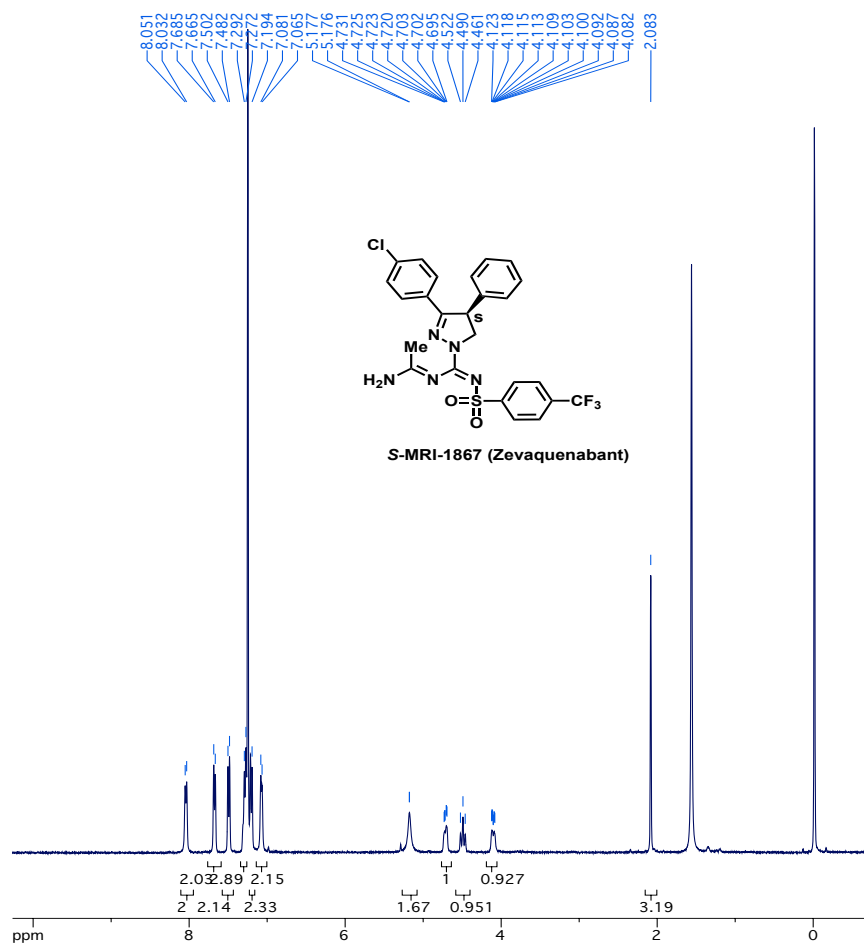
¹H-NMR and ¹³C-NMR of Compound 7



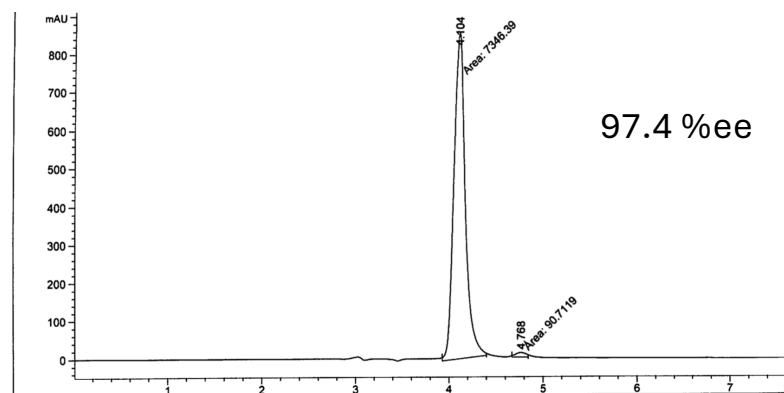
¹H-NMR and ¹³C-NMR of Compound 8



¹H-NMR for *S*-MRI-1867



Chiral HPLC data for *S*-MRI-1867



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Area Percent Report
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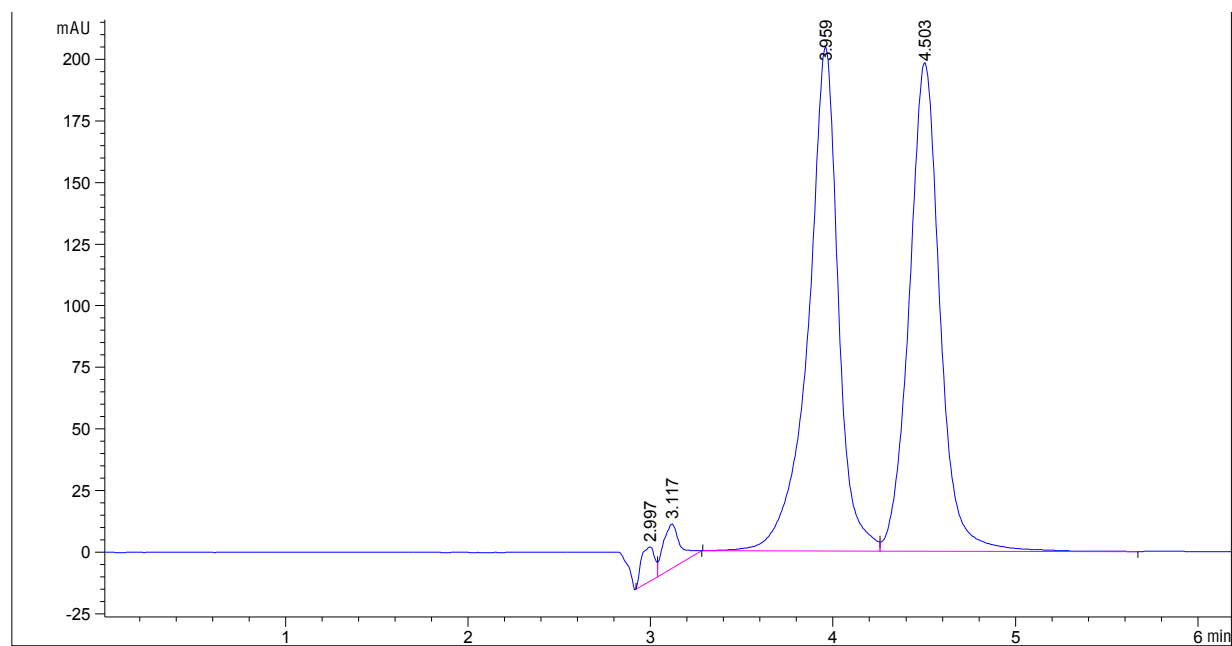
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.104	MM	0.1406	7346.39307	870.90625	98.7803
2	4.768	MM	0.1283	90.71194	11.78431	1.2197
Totals :				7437.10500	882.69056	

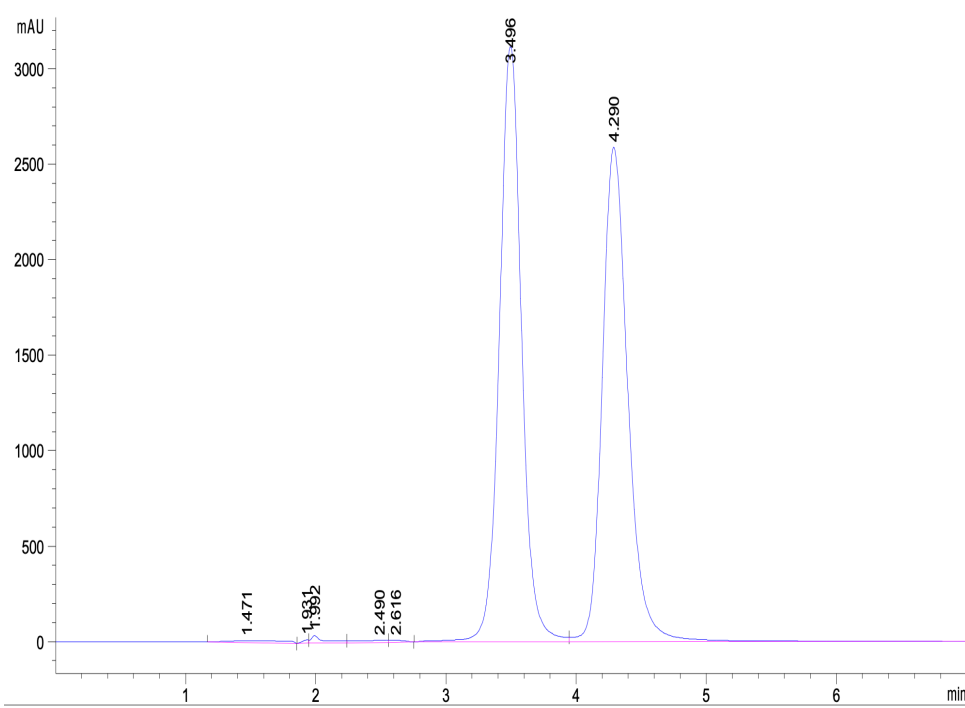
Conditions: (*R,R*)-Whelk-O1 chiral column (250 mm x 4.6 mm/5μm): 100% EtOH 1.0 mL/min (254 nm)

Chiral HPLC data for *S*-MRI-1867

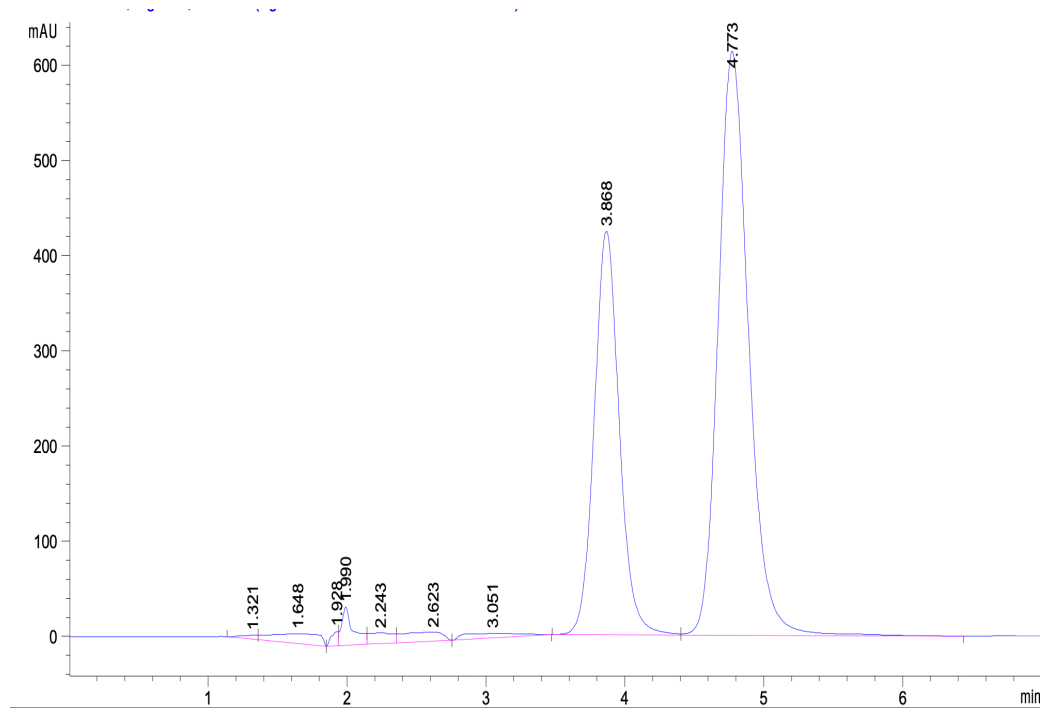


Conditions: (*R,R*)-Whelk-O1 chiral column (250 mm x 4.6 mm/5 μ m): 100% EtOH 1.0 mL/min (254 nm)

Chiral HPLC data for diastereomeric **6a** and **6b**



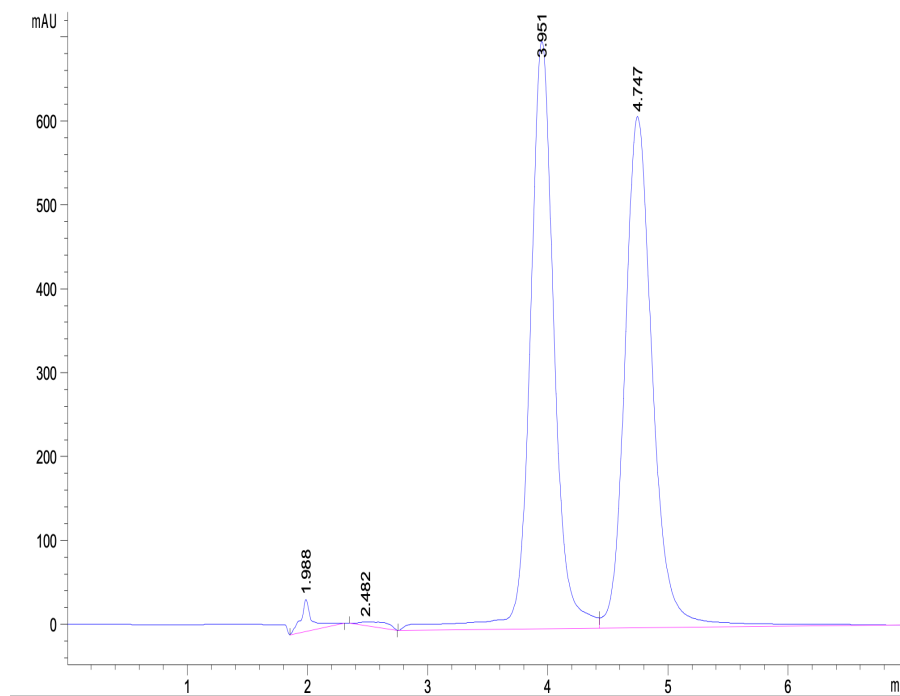
6a



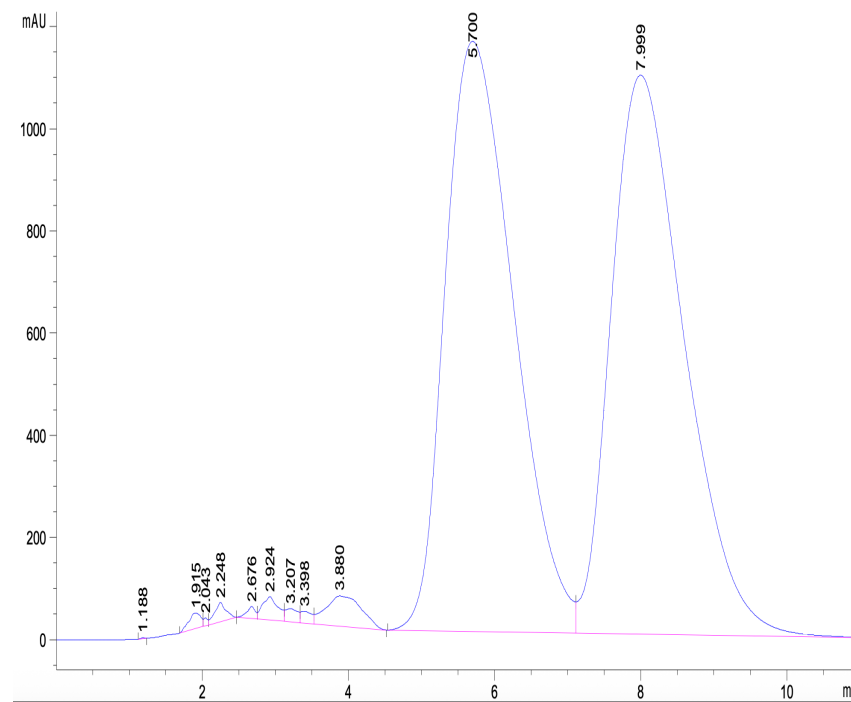
6b

Conditions: (*R,R*)-Whelk-O1 chiral column (250 mm x 4.6 mm/5 μ m): 100% EtOH 1.5 mL/min (254 nm)

Chiral HPLC data for diastereomeric **6c** and **6d**



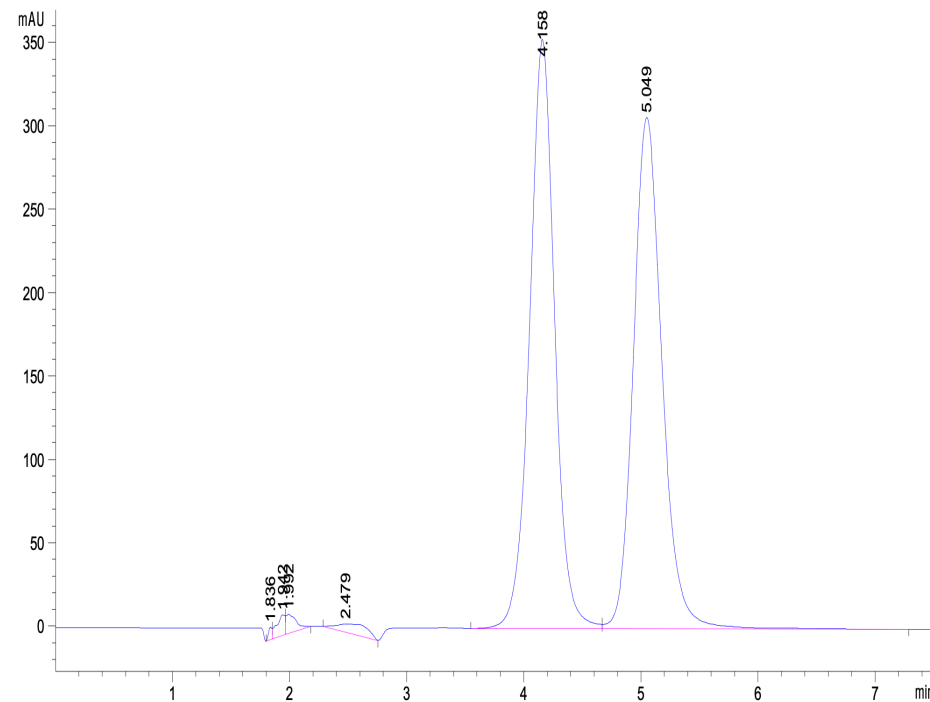
6c



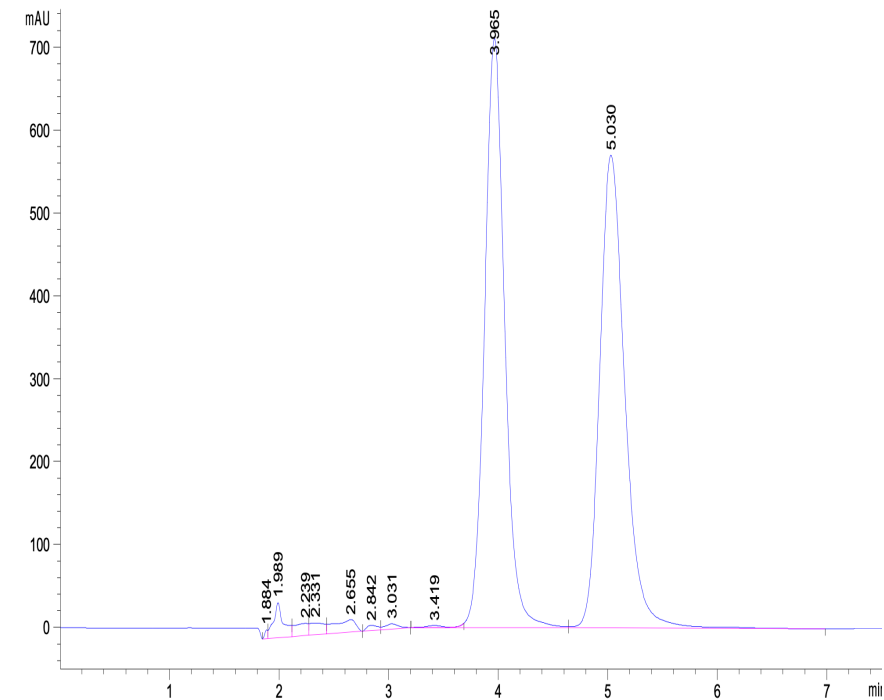
6d

Conditions: (*R,R*)-Whelk-O1 chiral column (250 mm x 4.6 mm/5 μ m): 100% EtOH 1.5 mL/min (254 nm)

Chiral HPLC data for diastereomeric **6e** and **6f**



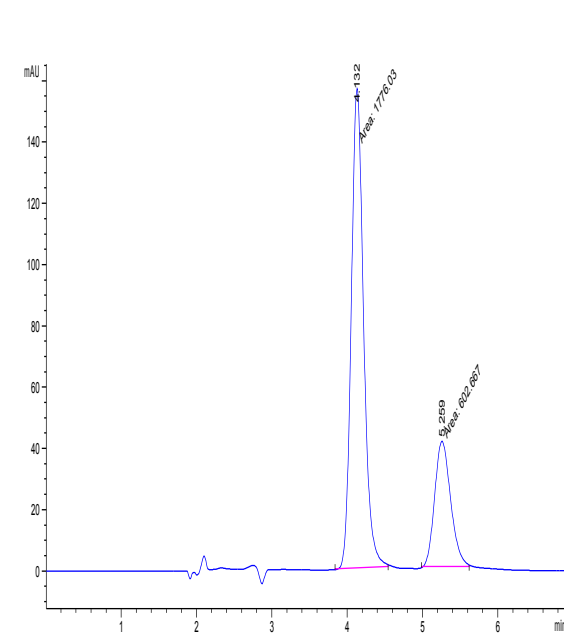
6e



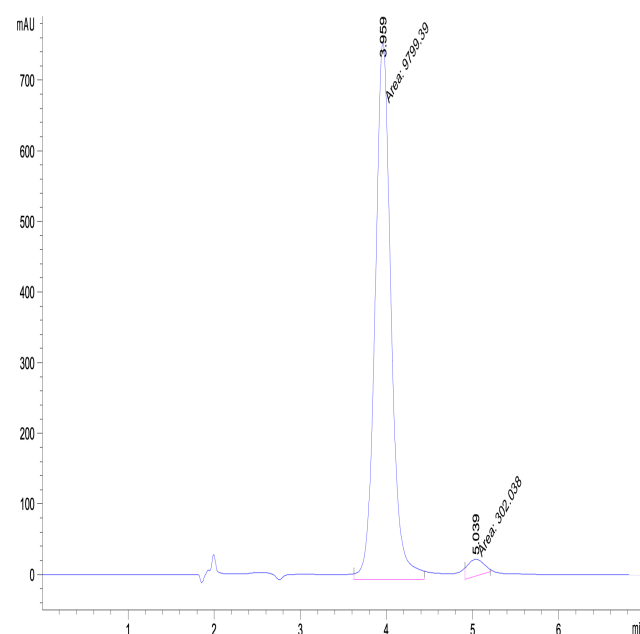
6f

Conditions: (*R,R*)-Whelk-O1 chiral column (250 mm x 4.6 mm/5 μ m): 100% EtOH 1.5 mL/min (254 nm)

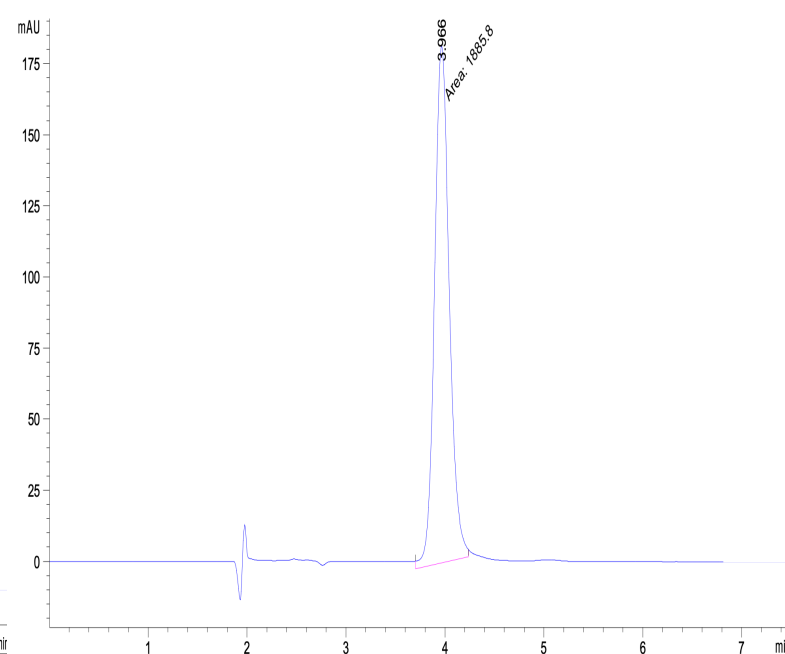
Chiral HPLC data for diastereomeric **7 (S, S)**



75:25 ratio S, S + S, R diastereomers



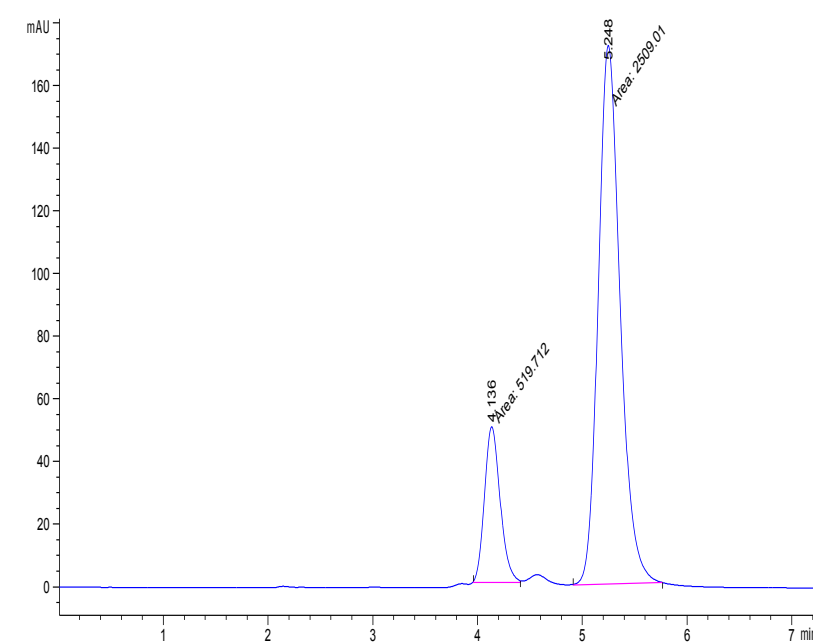
97:3 ratio S, S + S, R diastereomers



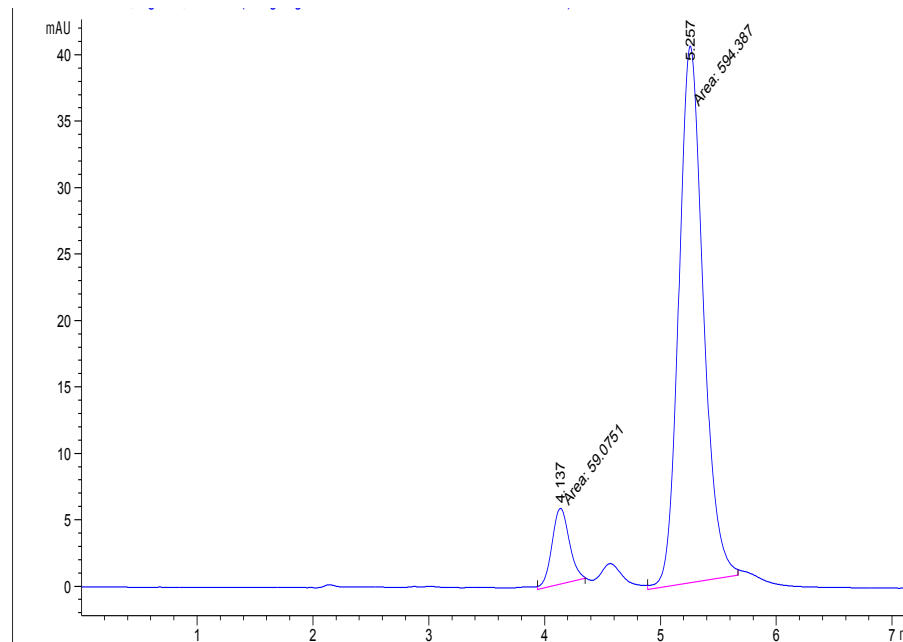
>99.9% S, S diastereomer

Conditions: (*R,R*)-Whelk-O1 chiral column (250 mm x 4.6 mm/5 μ m): 100% EtOH 1.5 mL/min (254 nm)

Chiral HPLC data for diastereomeric **8** (**S**, **R**)



17:83 ratio **S**, **S** + **S**, **R** diastereomers



9:91 ratio **S**, **S** + **S**, **R** diastereomers

Conditions: (*R,R*)-Whelk-O1 chiral column (250 mm x 4.6 mm/5 μ m): 100% EtOH 1.5 mL/min (254 nm)