

Supplementary Materials

Design and Synthesis of D₃R Bitopic Ligands with Flexible Secondary Binding Fragments: Radioligand Binding and Computational Chemistry Studies

Gui-Long Tian¹, Chia-Ju Hsieh¹, Michelle Taylor², Ji Youn Lee¹, Robert R. Luedtke² and Robert H. Mach¹

¹ Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

² Department of Pharmacology and Neuroscience, University of North Texas Health Science Center-Fort Worth, Texas, TX 76107, USA

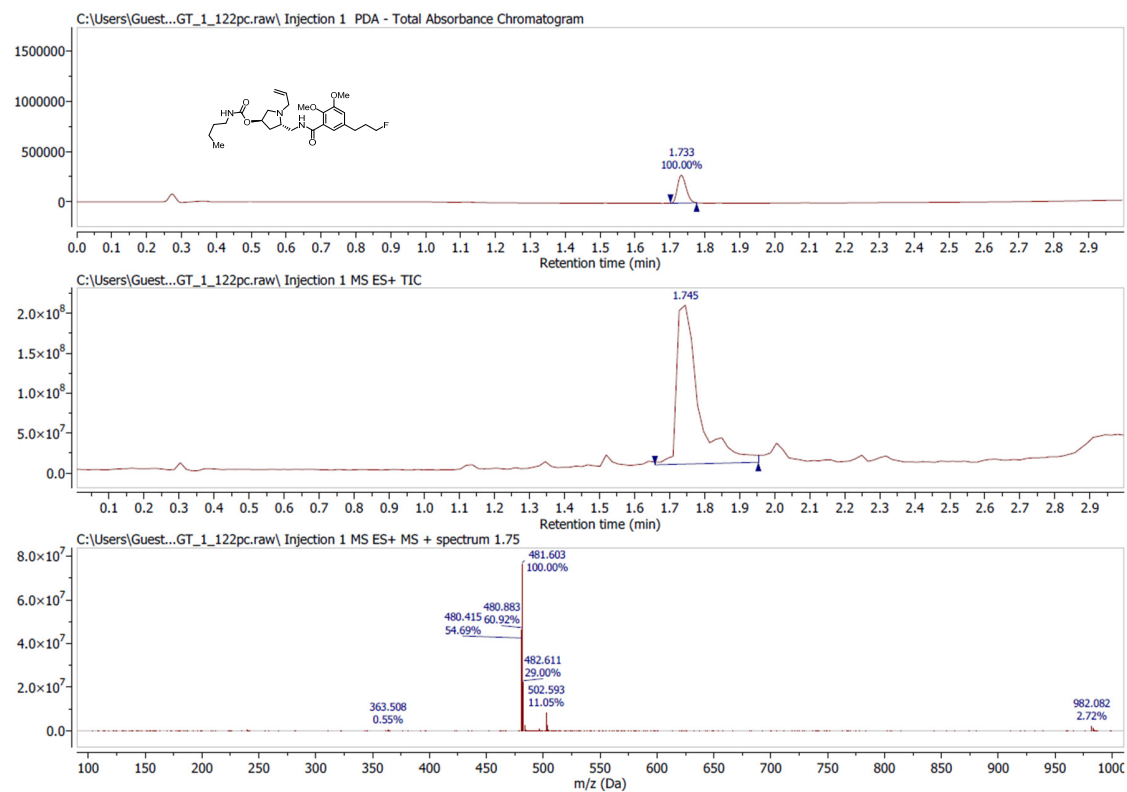
* Correspondence: rmach@pennmedicine.upenn.edu

Compounds purity and graphs.

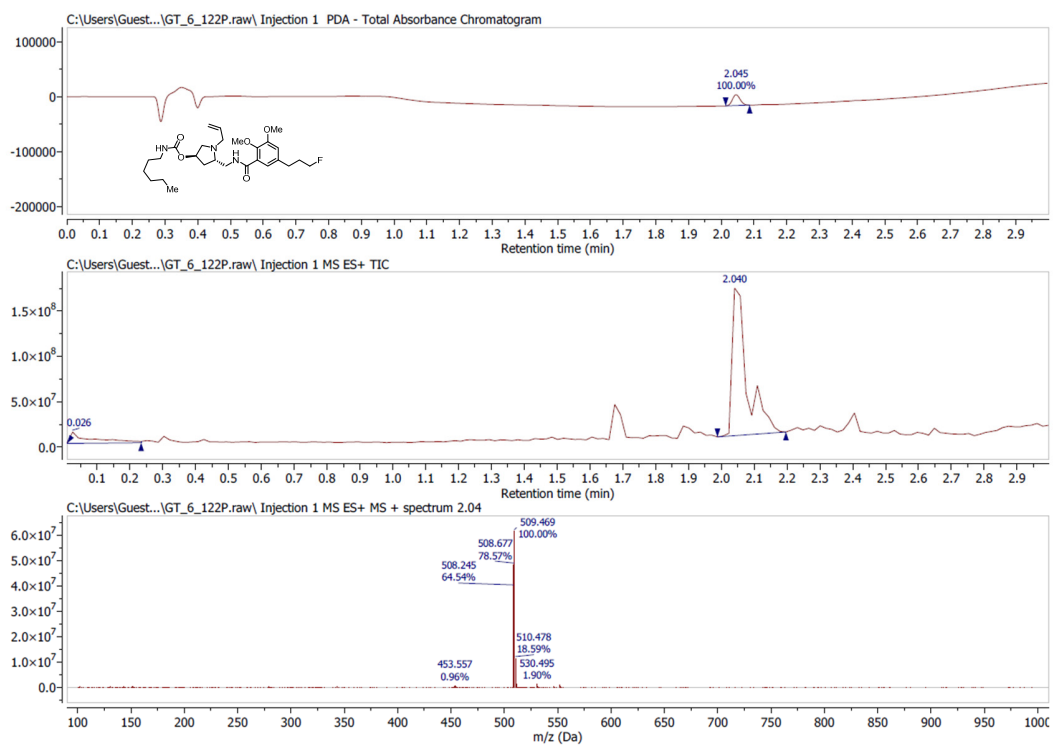
Compounds	Structure	Purity
(R, S)-trans-2a		99.99
(R, S)-trans-2b		99.99
(R, S)-trans-2c		95.19
(R, S)-trans-2d		99.99
(R, S)-trans-2e		98.55
(R, S)-trans-2f		97.72
(R, S)-trans-2g		95.34
(R, S)-trans-2h		97.02
(R, S)-trans-2i		97.70
(R, S)-trans-2j		99.99
(S, R)-trans-2d		96.48
(S, S)-cis-2d		96.06
(R, R)-cis-2d		99.99

(S, R)-trans-2i		97.68
(S, S)-cis-2i		96.06
(R, R)-cis-2i		99.99

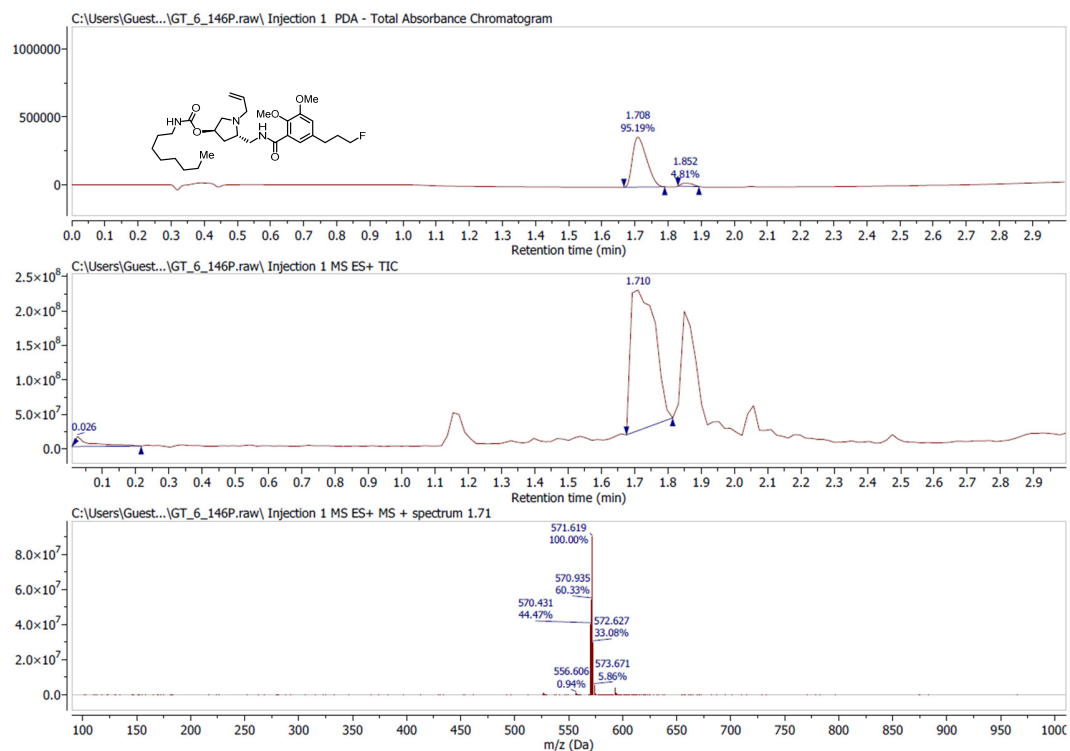
(R, S)-trans-2a GT-1-122



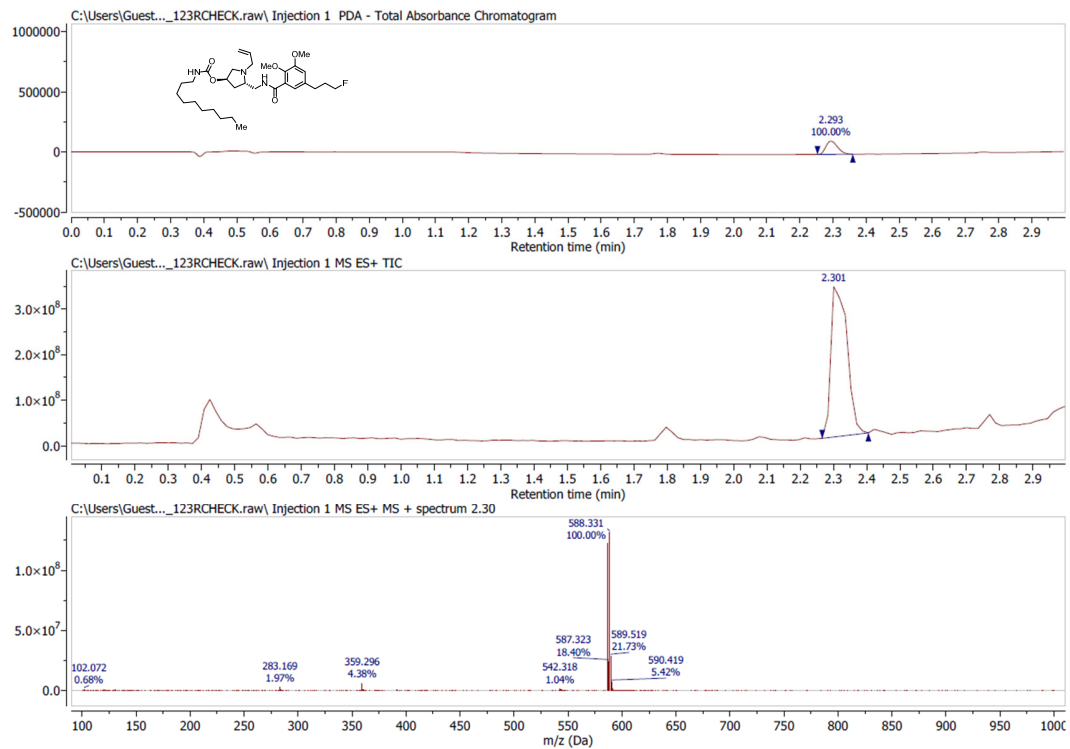
(R, S)-trans-2b GT-6-122



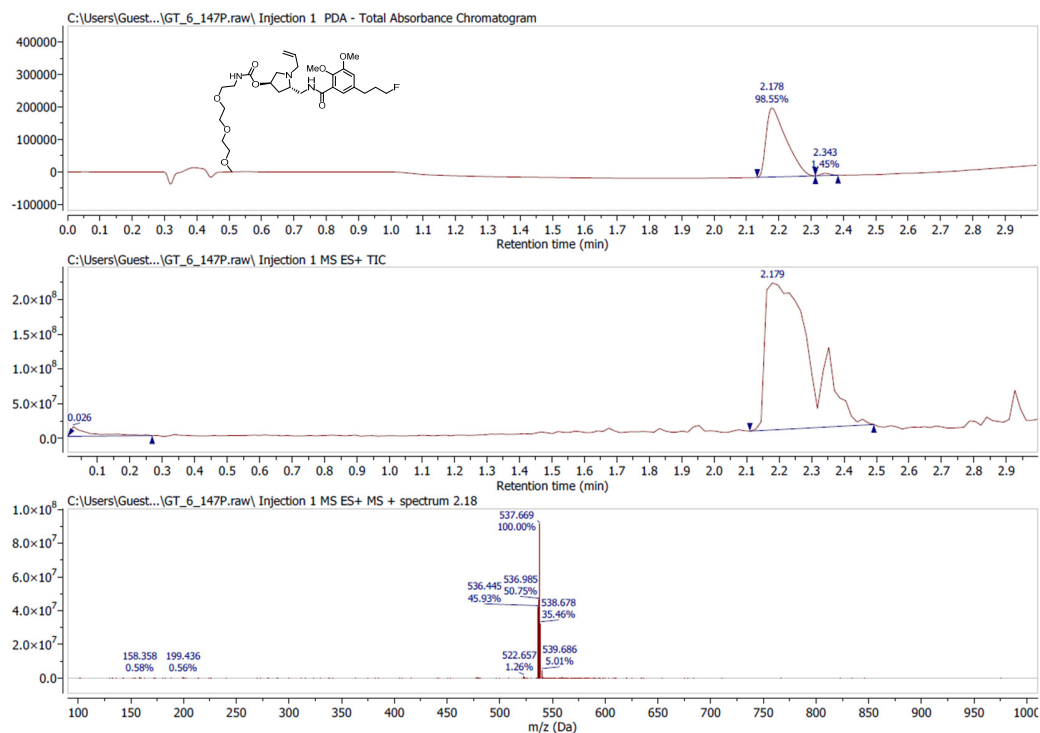
(R, S)-trans-2c GT-6-146



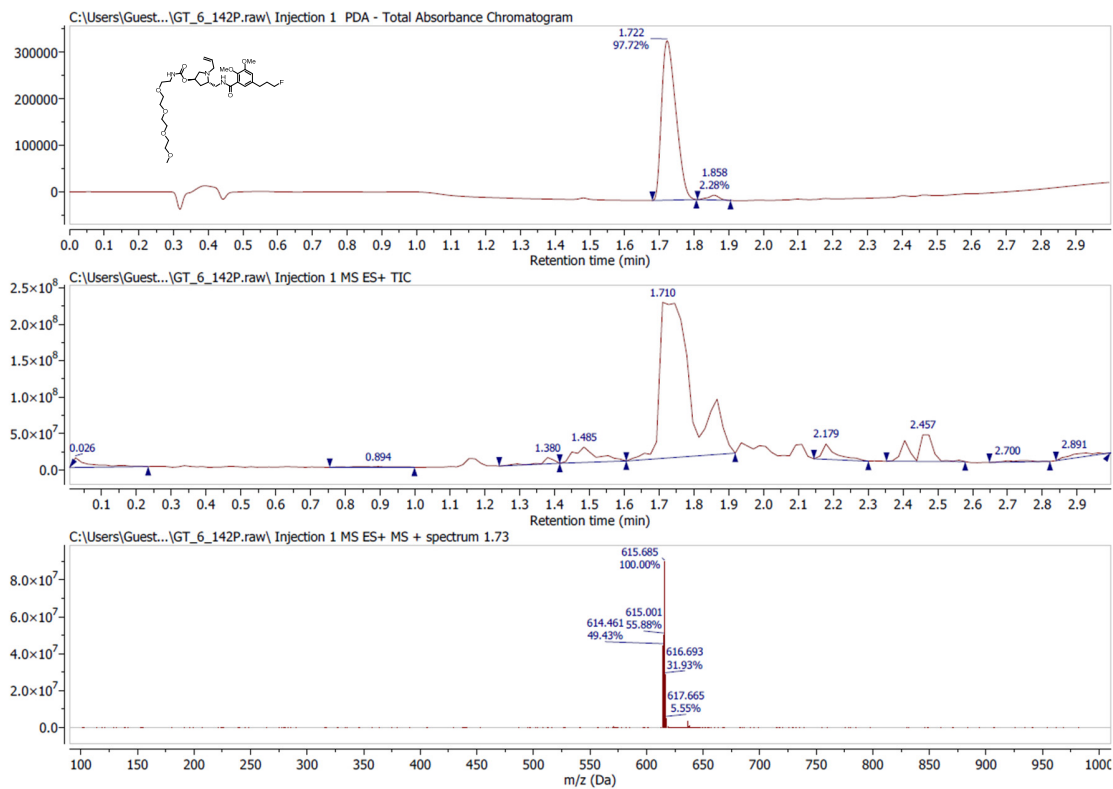
(R, S)-trans-2d GT-6-123



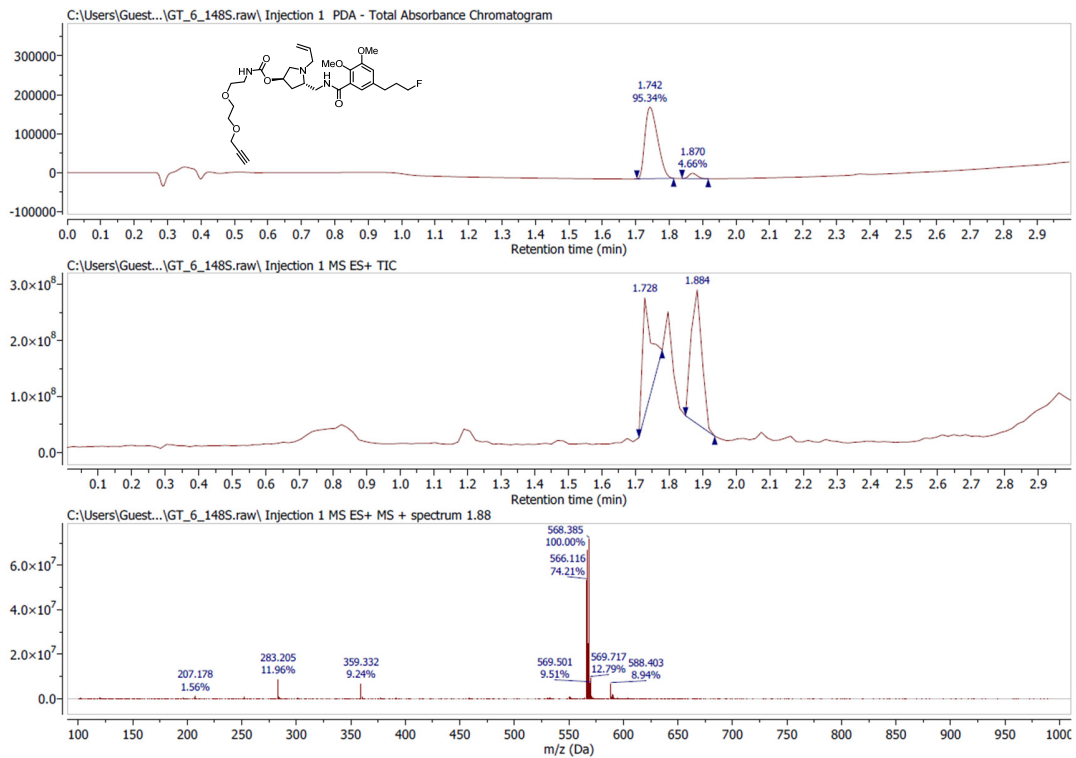
(R, S)-trans-2e GT-6-147



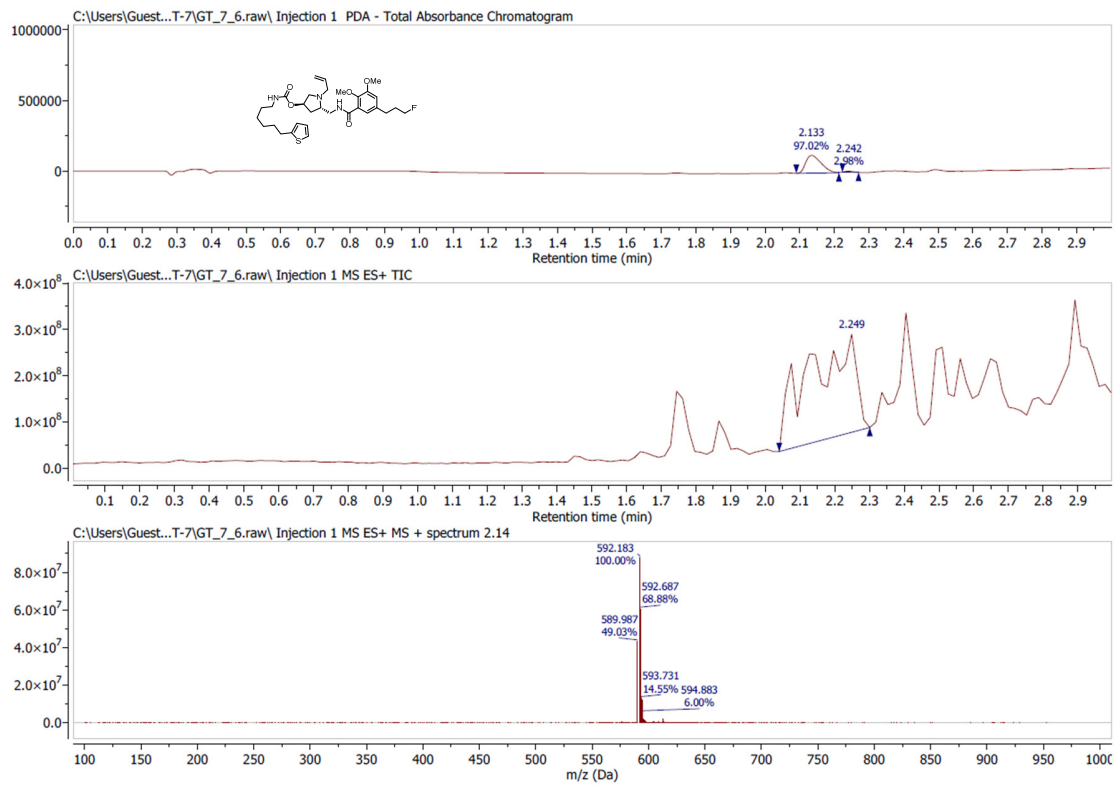
(R, S)-trans-2f GT-6-142



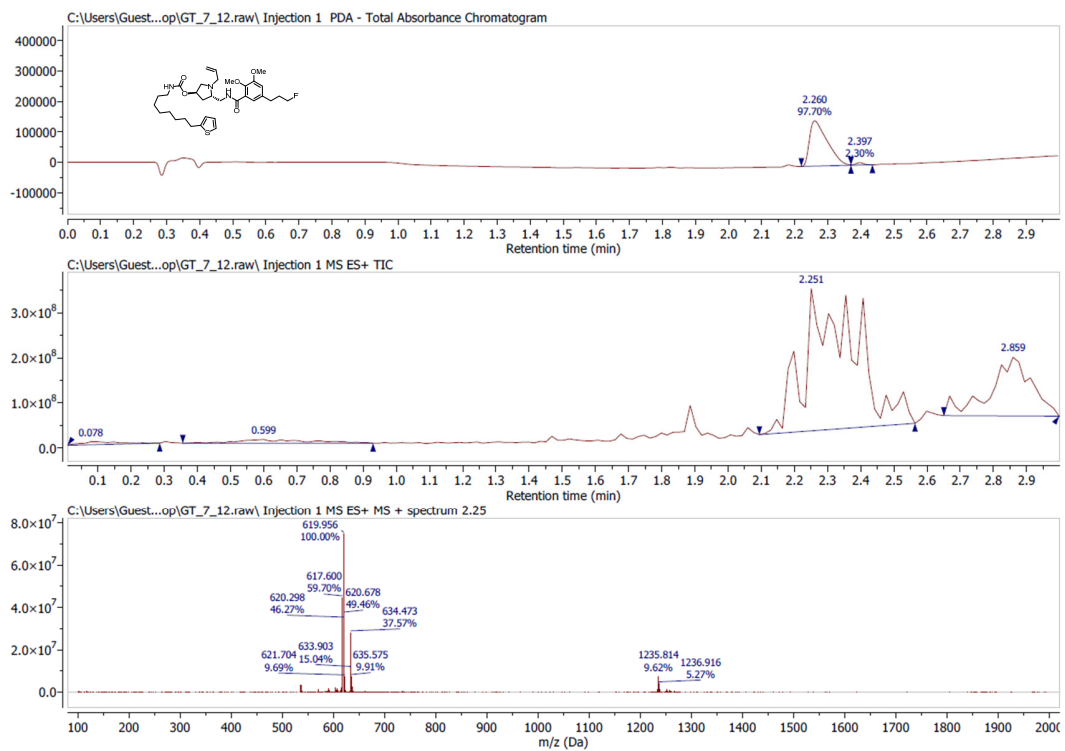
(R, S)-trans-2g GT-6-148



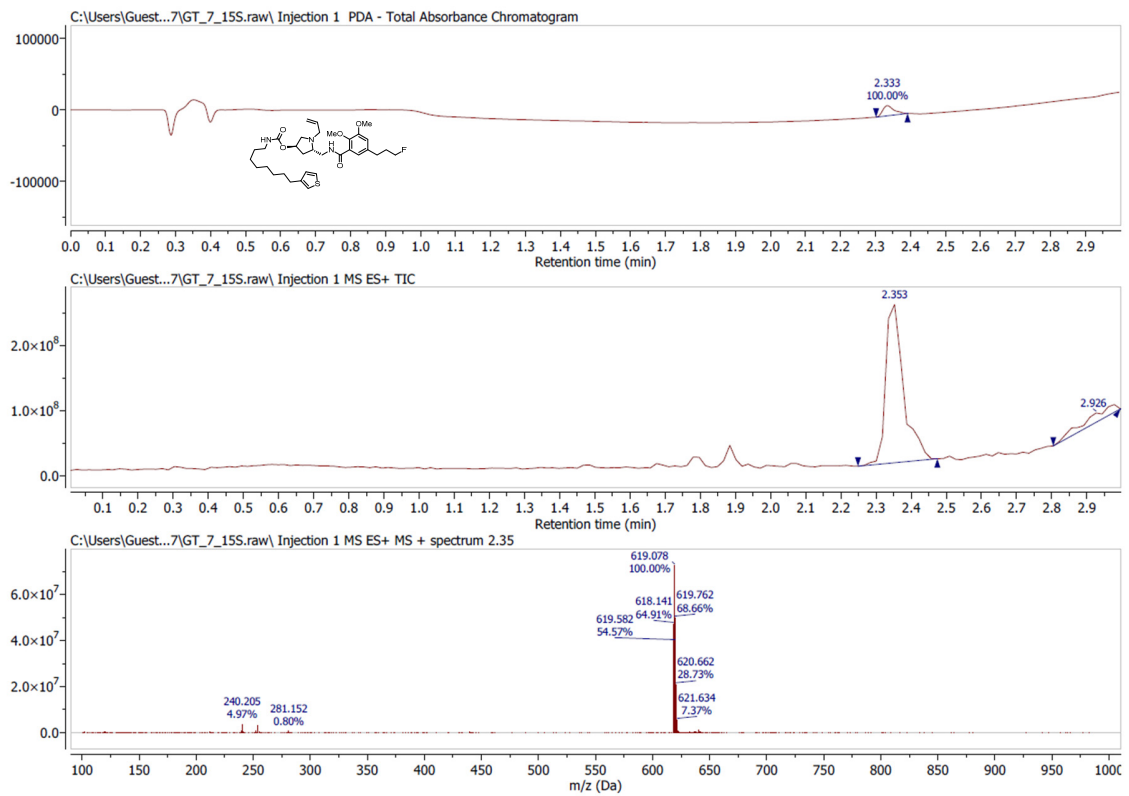
(R, S)-trans-2h GT-7-6



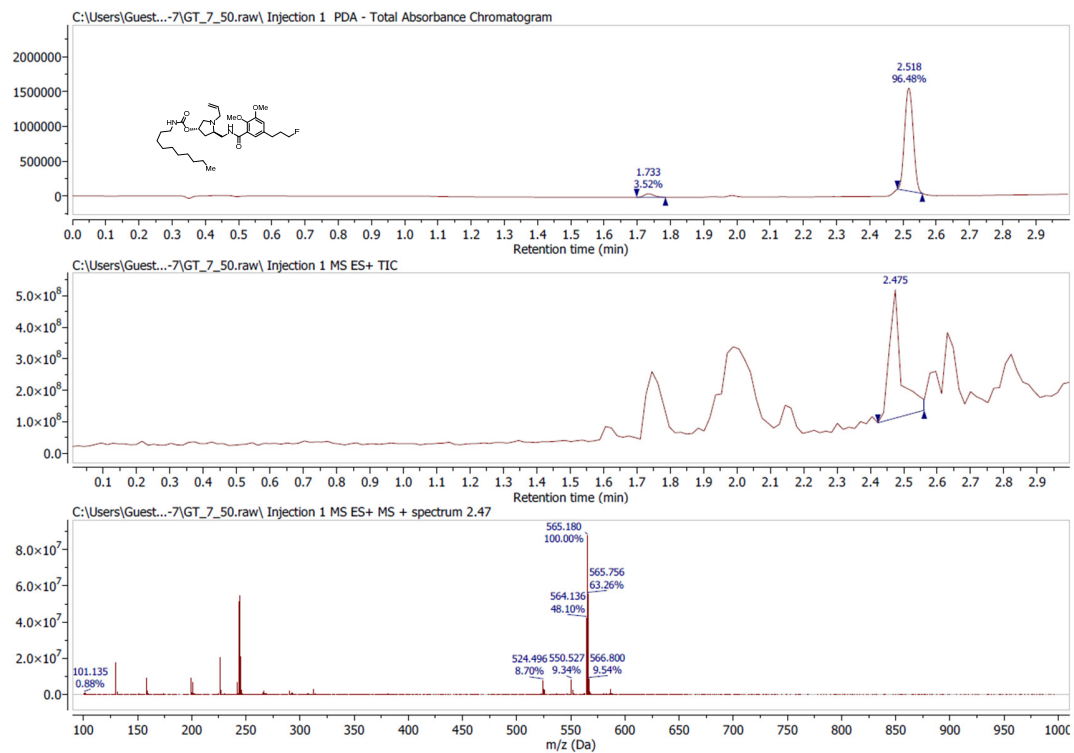
(R, S)-trans-2i GT-7-12



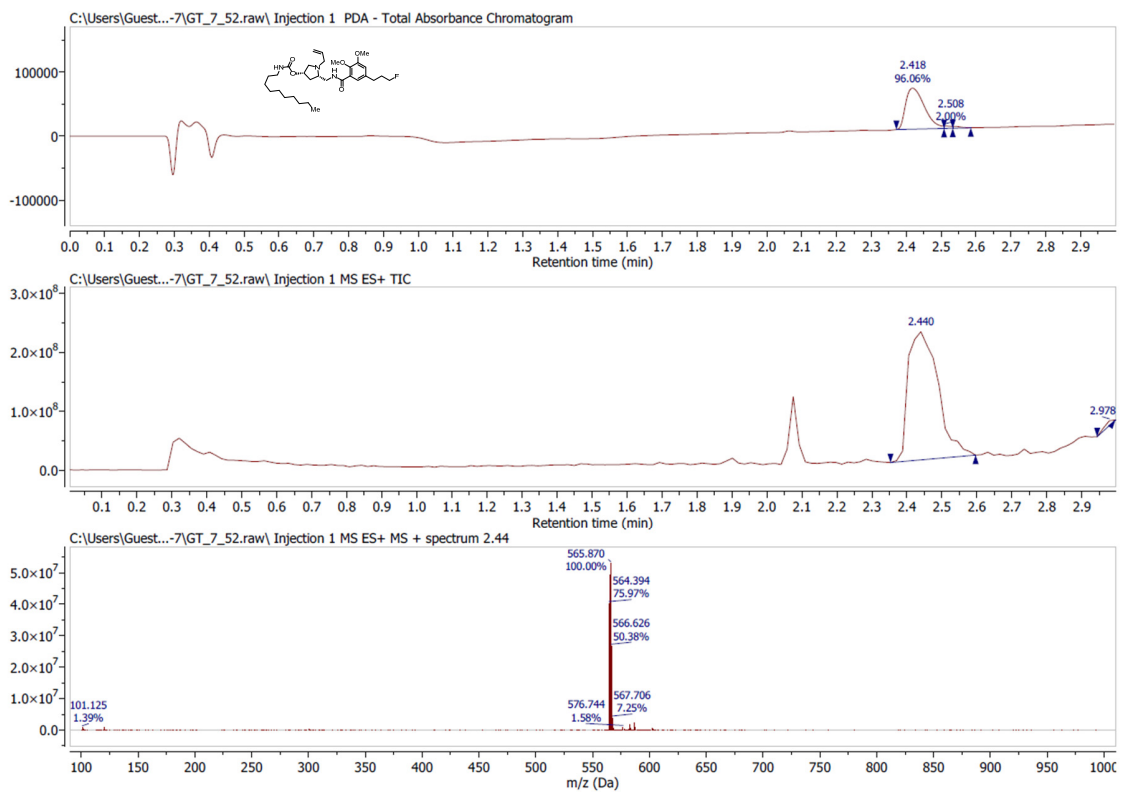
(R, S)-trans-2j GT-7-15



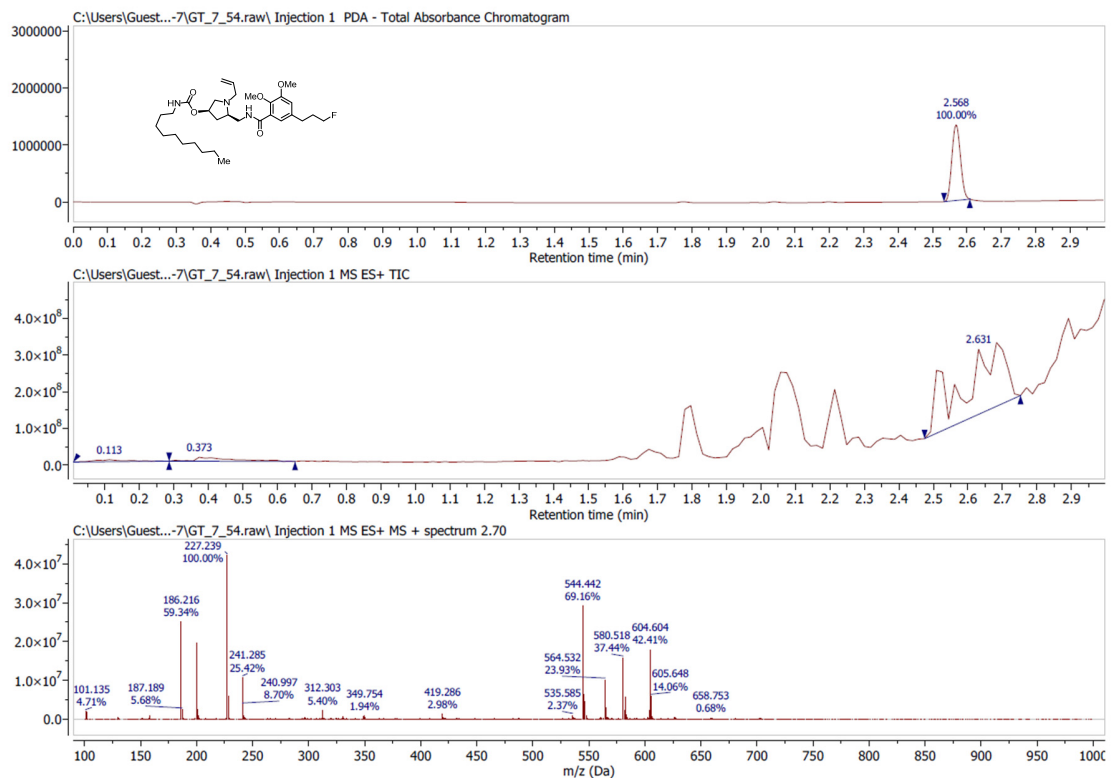
(S, R)-trans-2d GT-7-50



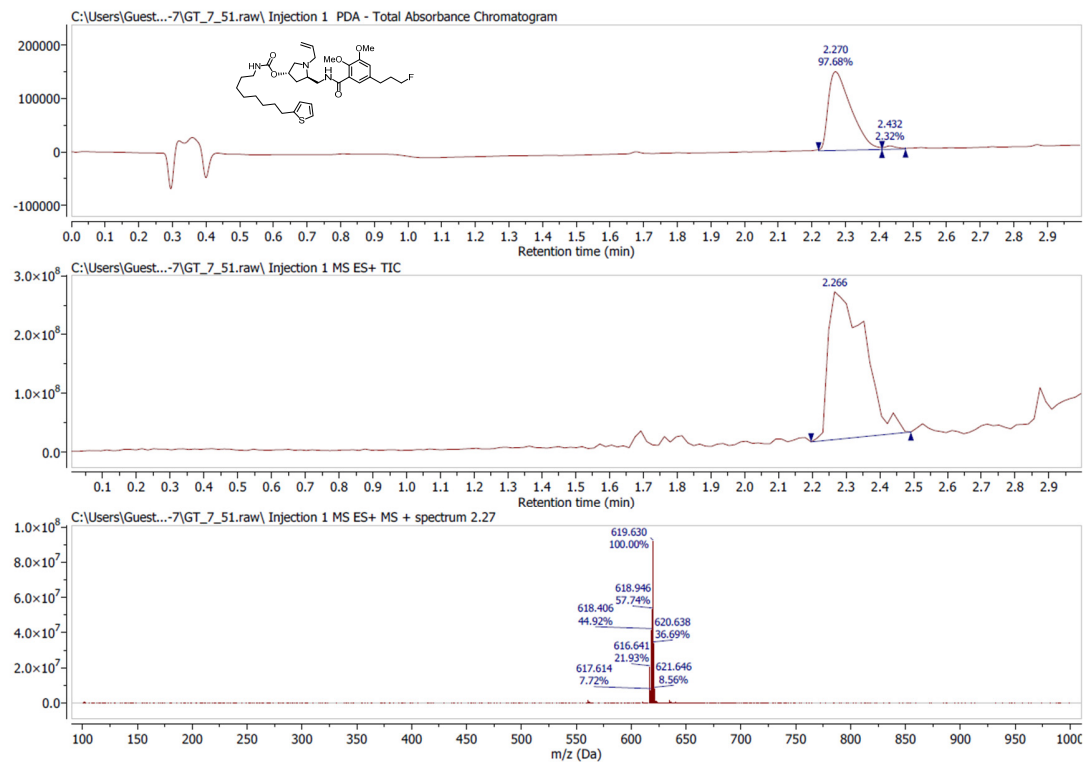
(S, S)-cis-2d GT-7-52



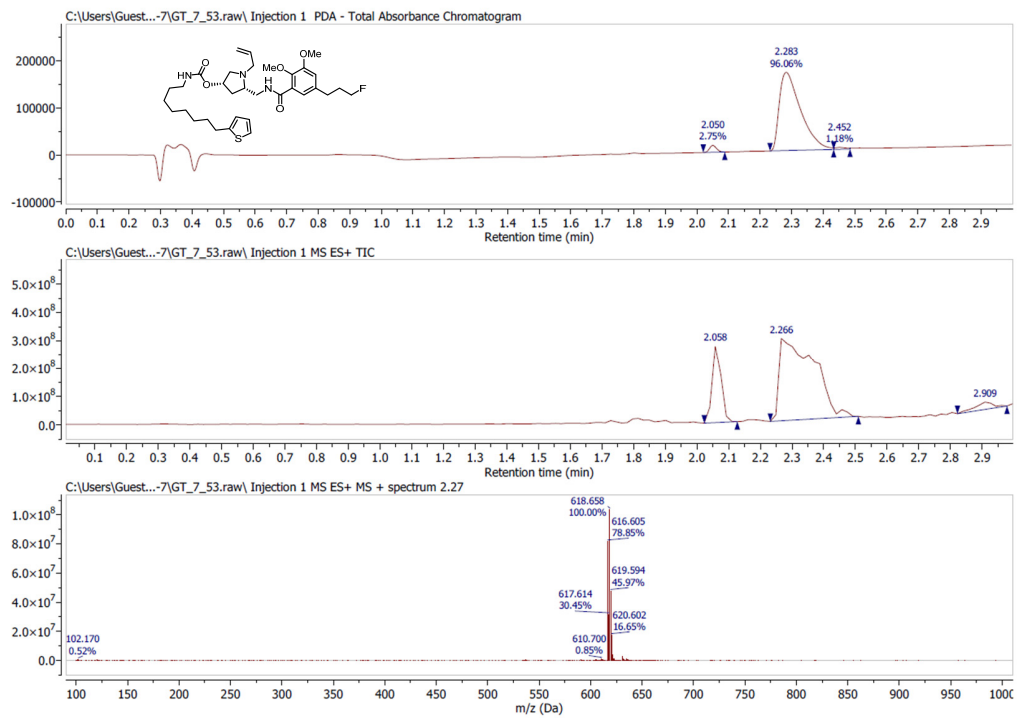
(R, R)-cis-2d GT-7-54



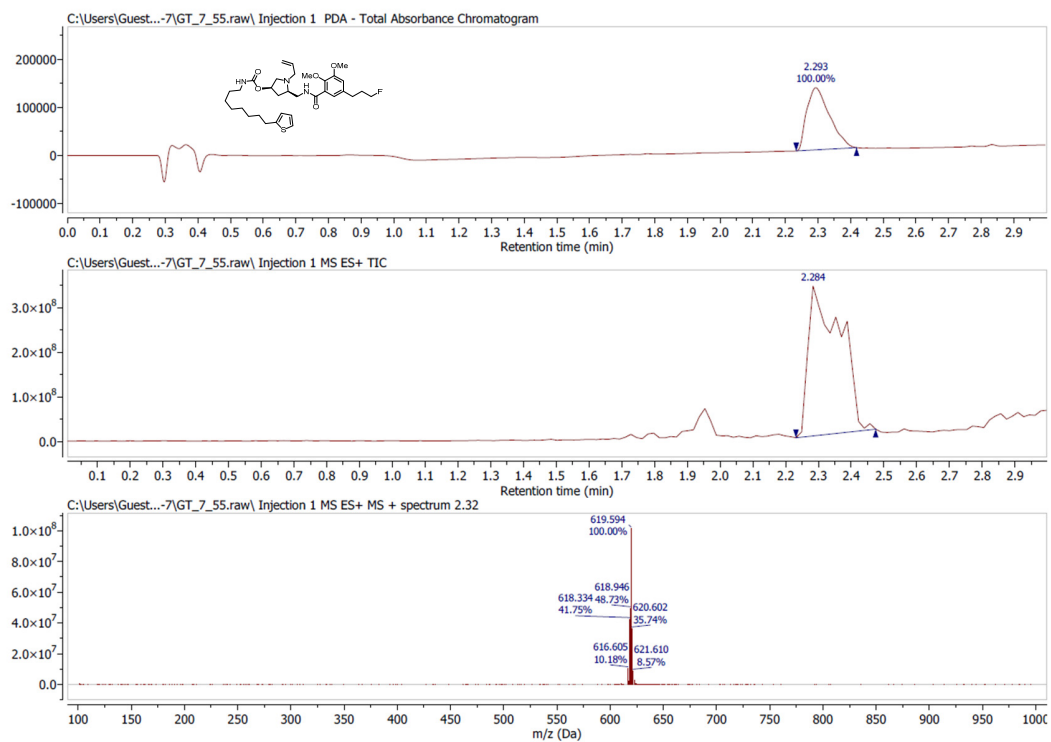
(S, R)-trans-2i GT-7-51



(S, S)-cis-2i GT-7-53

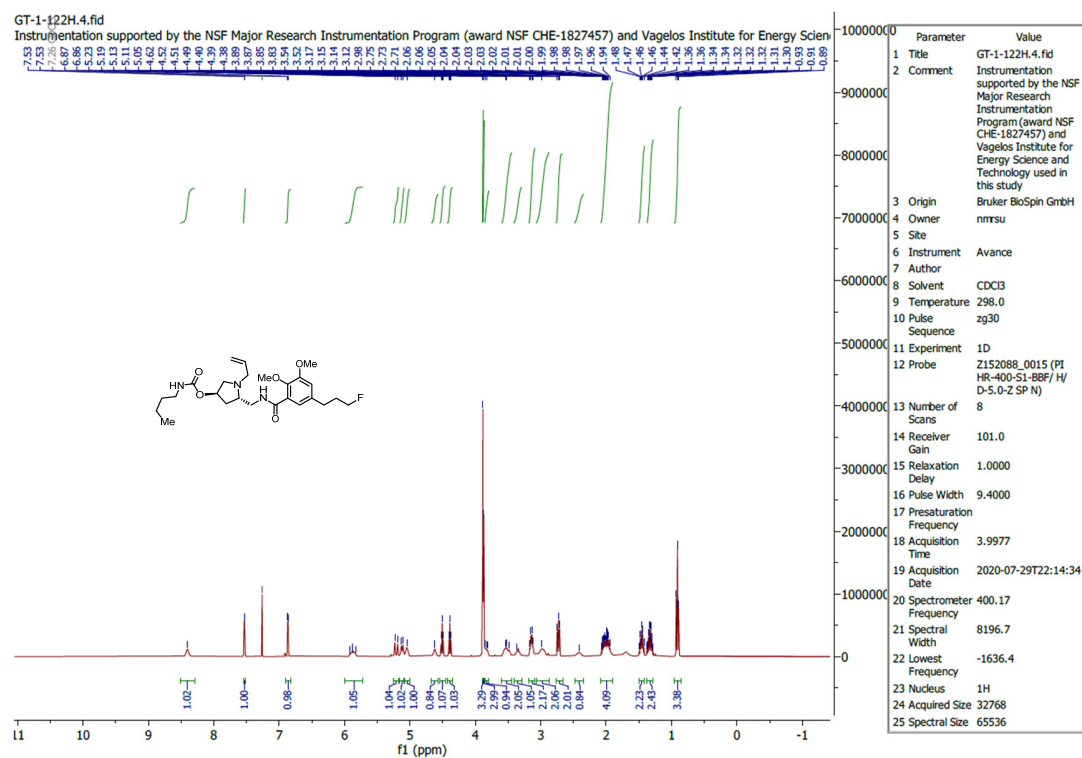


(R, R)-cis-2i GT-7-55



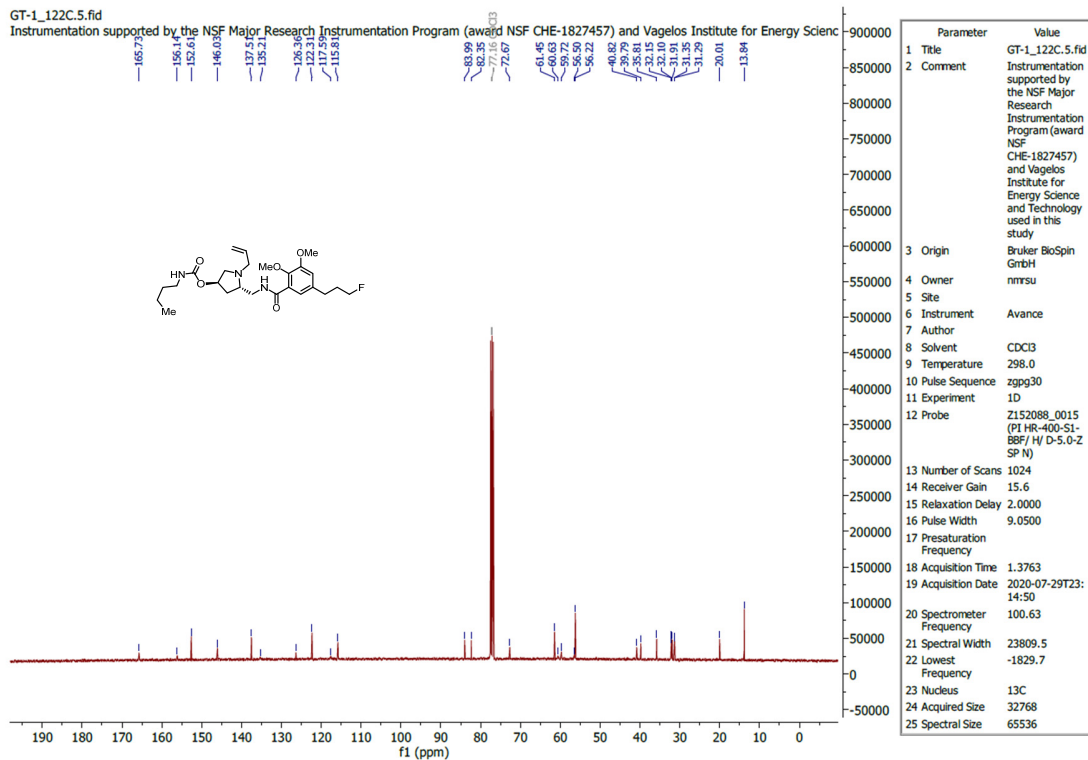
^1H and ^{13}C NMR Spectrum

(3*R*,5*S*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl butylcarbamate ((*R,S*)-*trans*-**2a**). *GT-1-122*

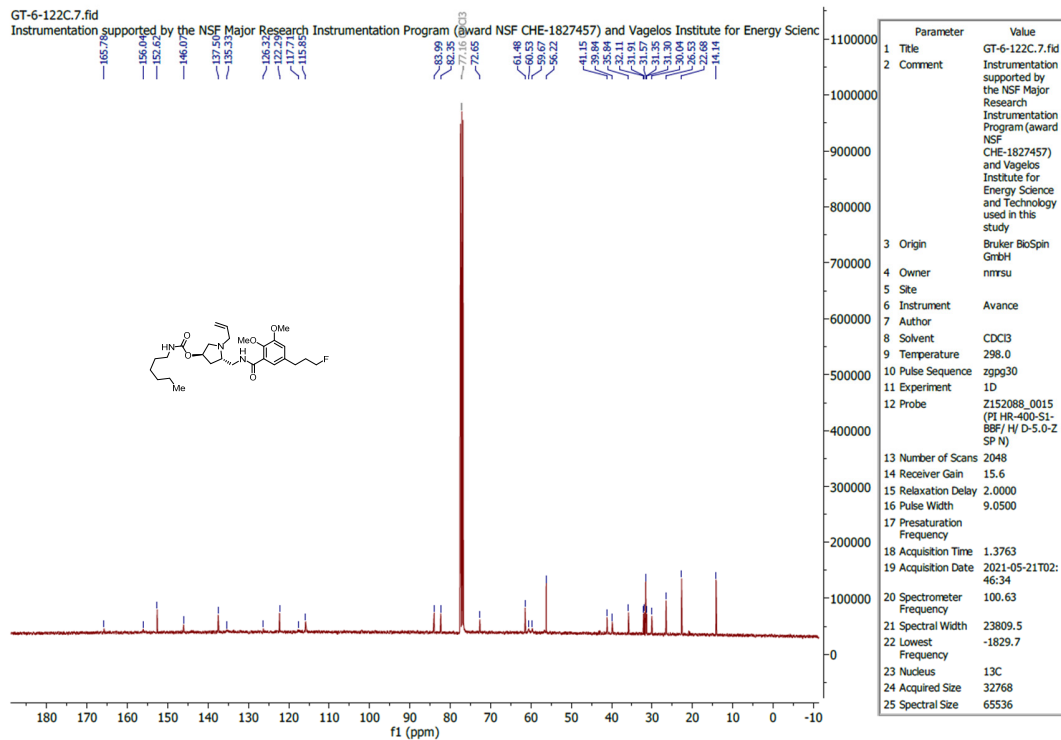
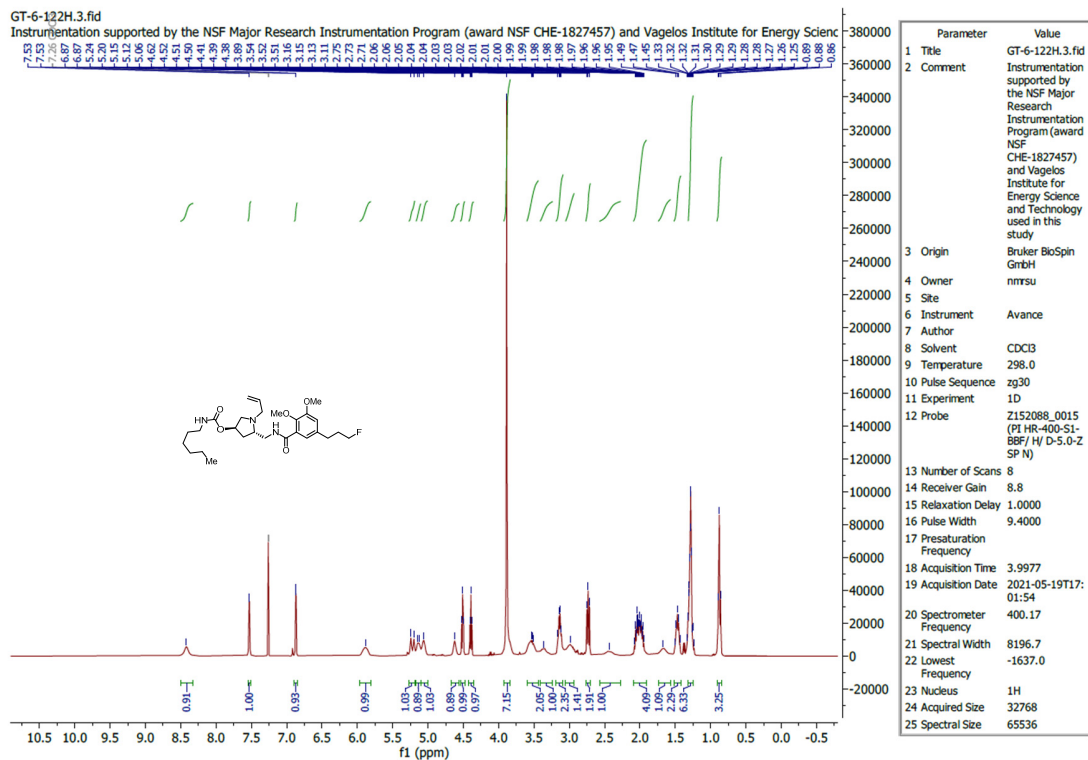


GT-1_122C.5.fid

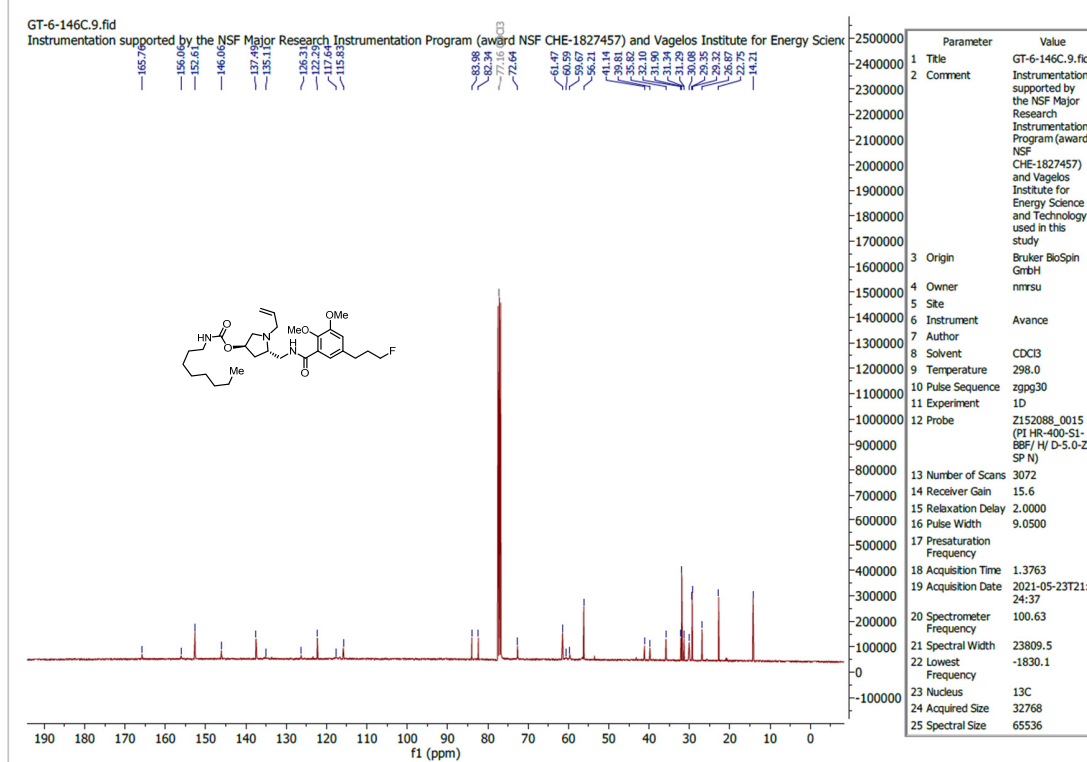
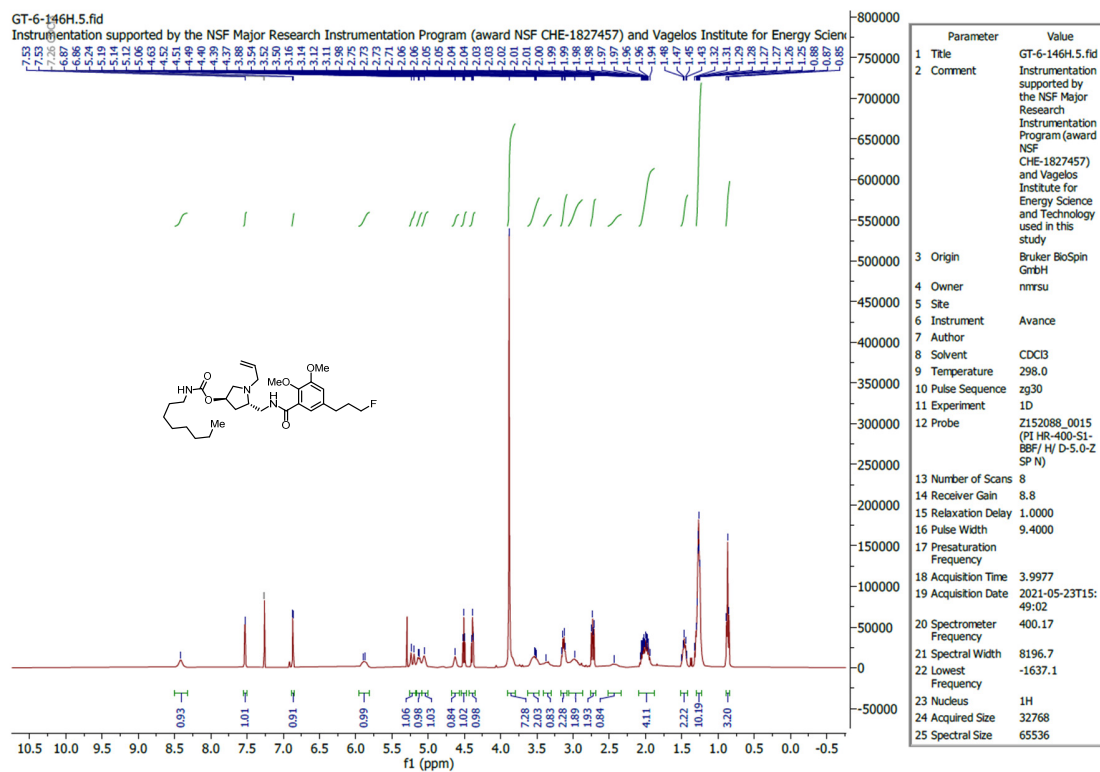
Instrumentation supported by the NSF Major Research Instrumentation Program (award NSF CHE-1827457) and Vagelos Institute for Energy Science



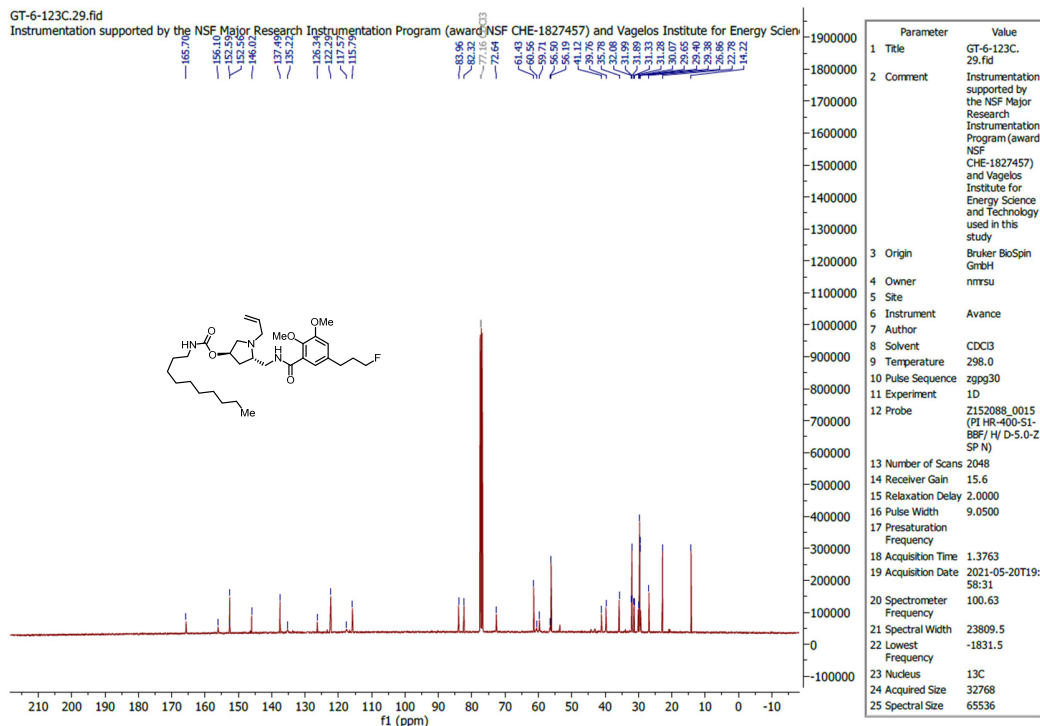
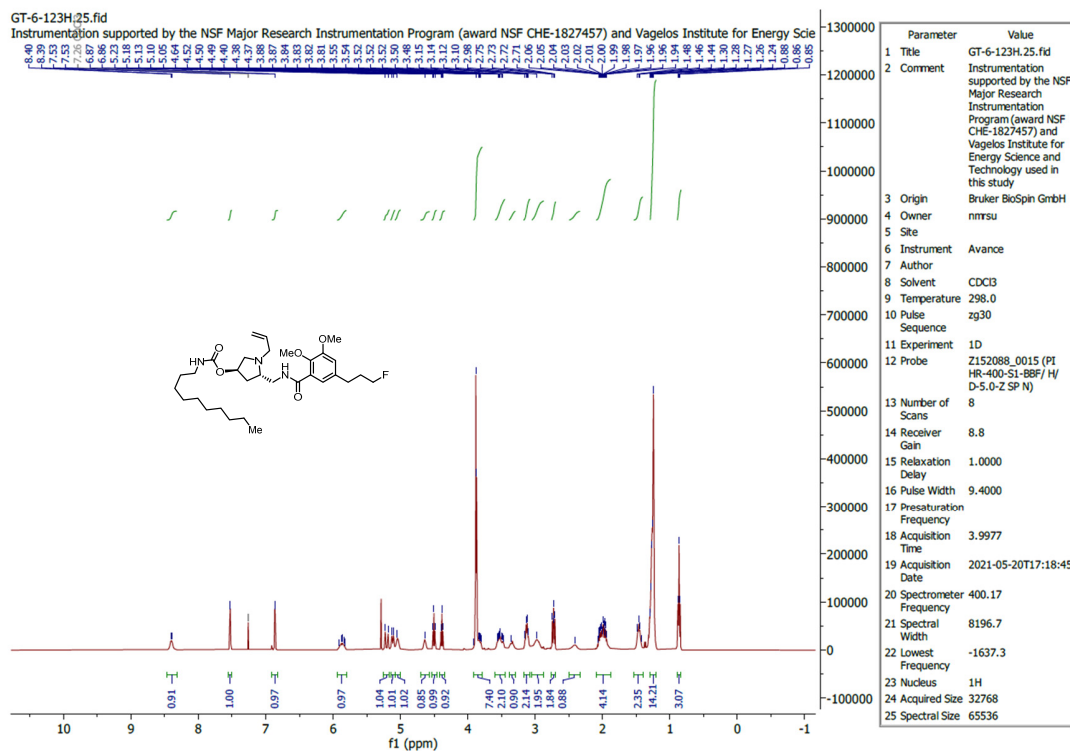
(3*R*,5*S*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl hexylcarbamate ((*R,S*)-*trans*-2b**). GT-6-122**



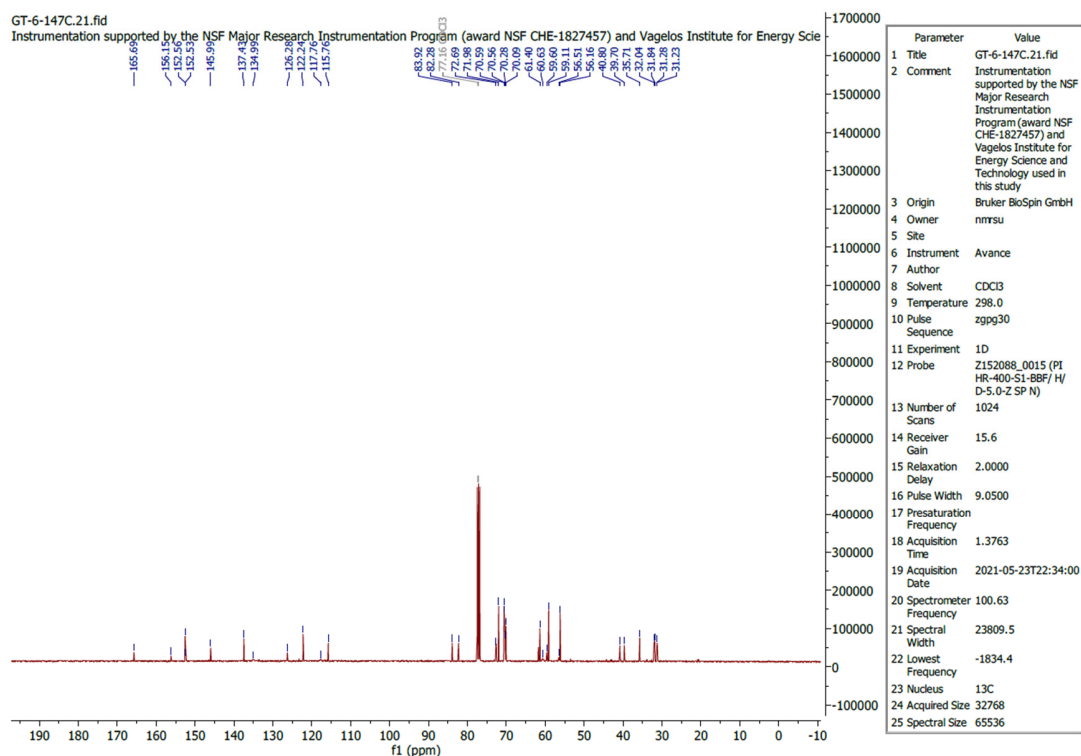
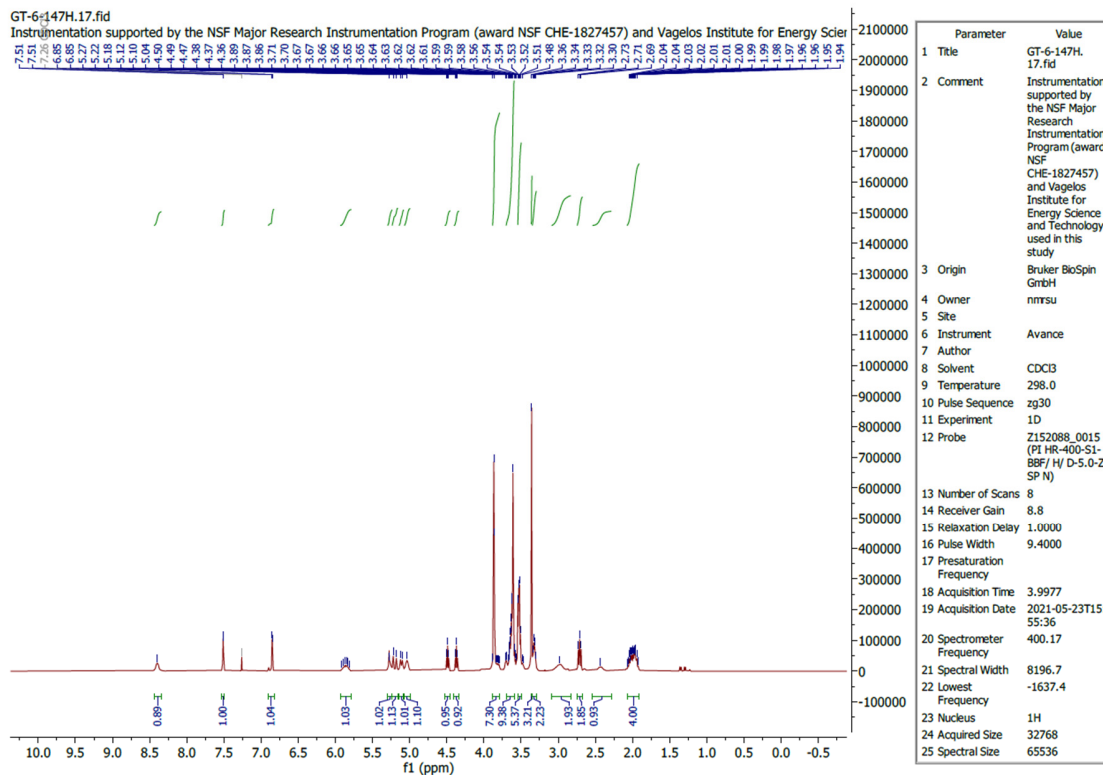
(3*R*,5*S*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl octylcarbamate
(*R,S*)-**trans-2c**. GT-6-146



(3*R*,5*S*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl decylcarbamate
((*R*,*S*)-trans-2d) GT-6-123 and (3*S*,5*R*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl decylcarbamate **((*S*,*R*)-trans-2d)**. GT-7-50

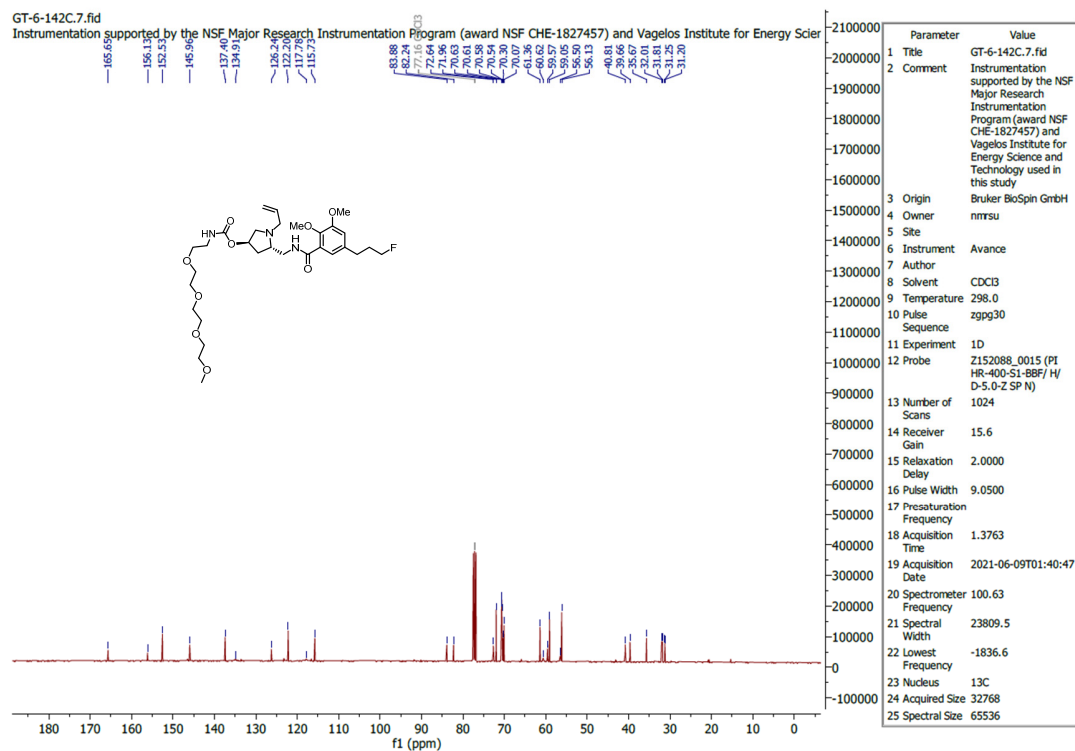
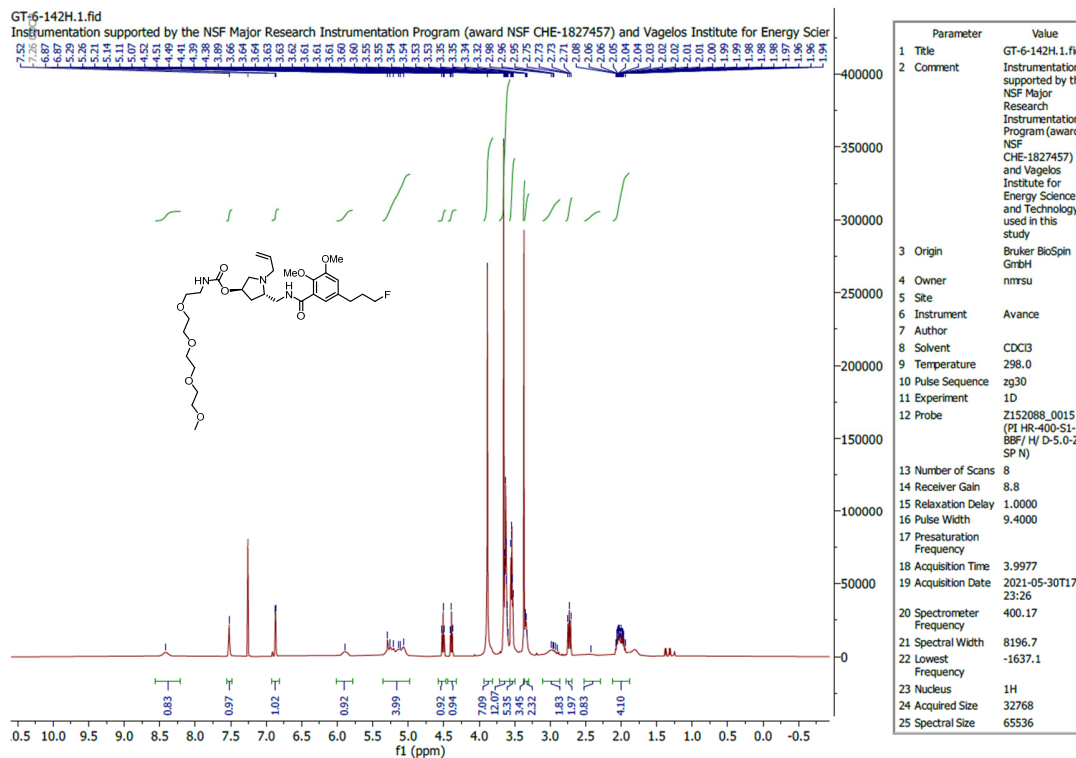


(3*R*,5*S*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl (2-(2-(2-methoxyethoxy)ethoxy)ethyl)carbamate ((*R,S*)-*trans*-2*e*). GT-6-147

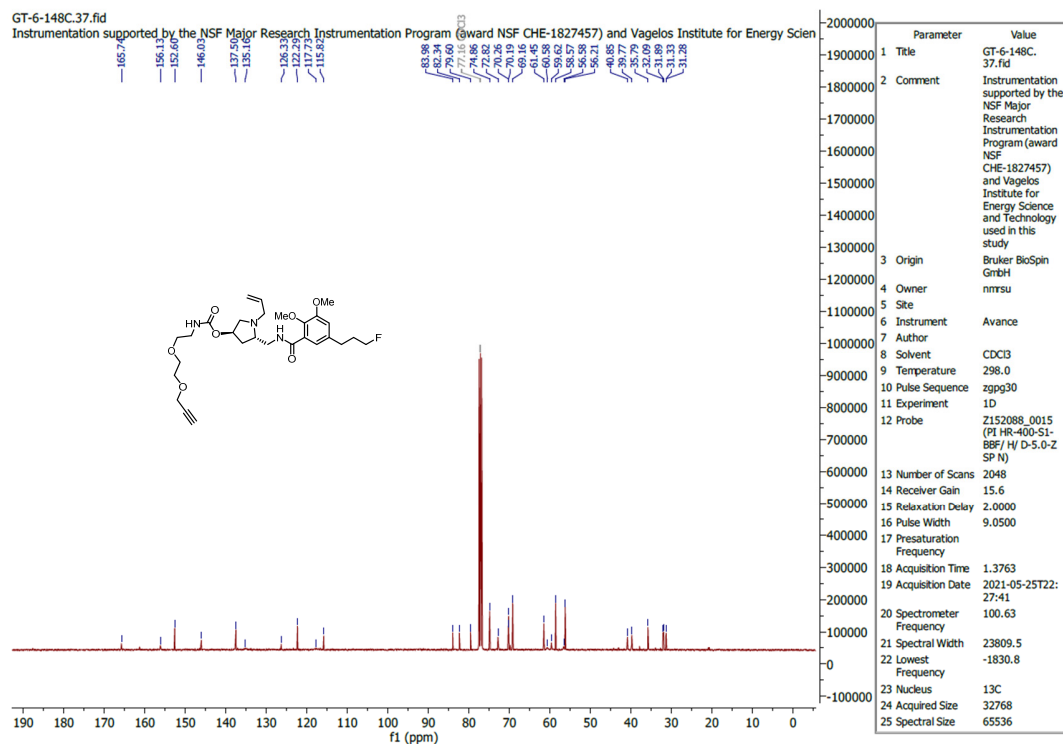
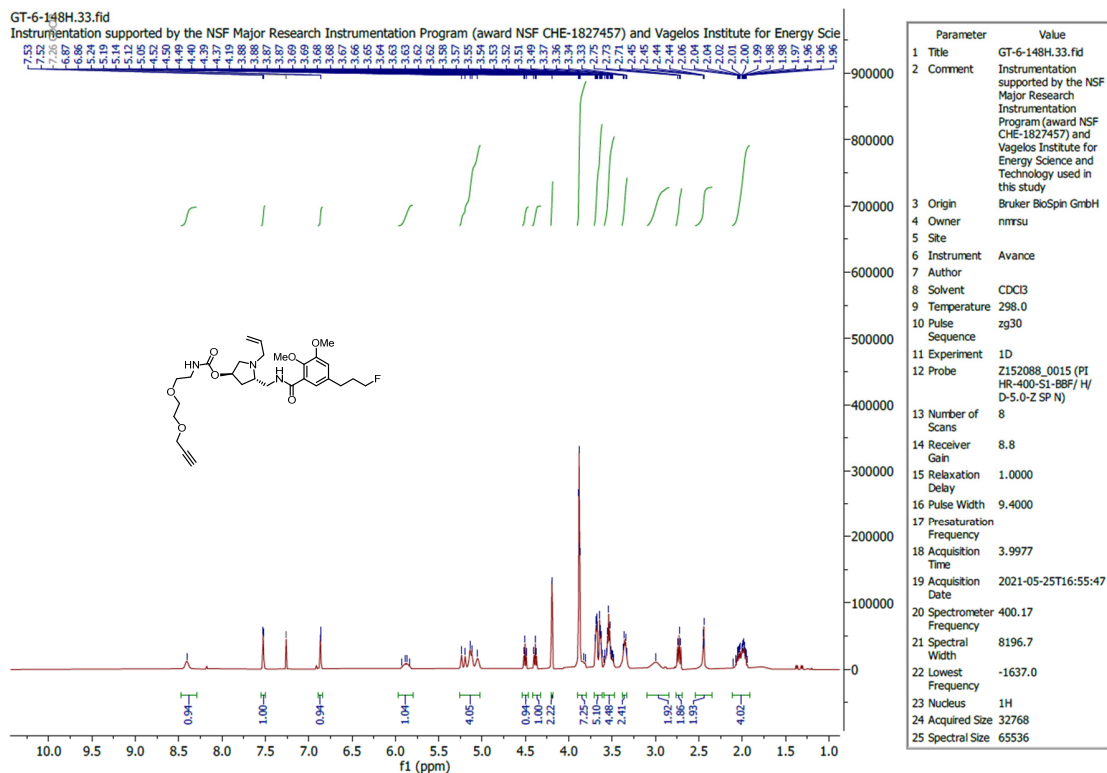


(3*R*,5*S*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl
tetraoxatridecan-13-yl)carbamate ((*R,S*)-*trans*-2*f*). GT-6-142

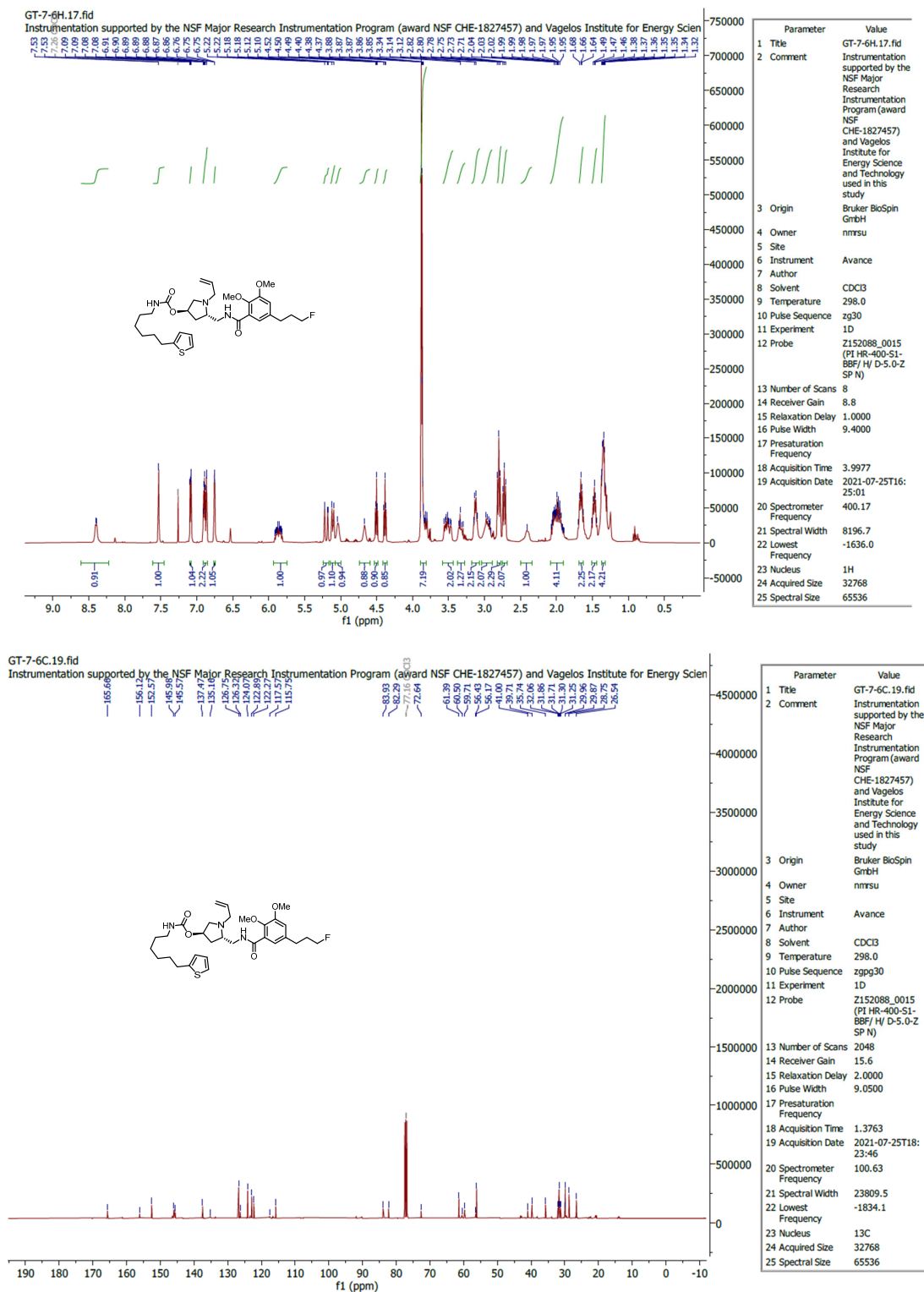
(2,5,8,11-



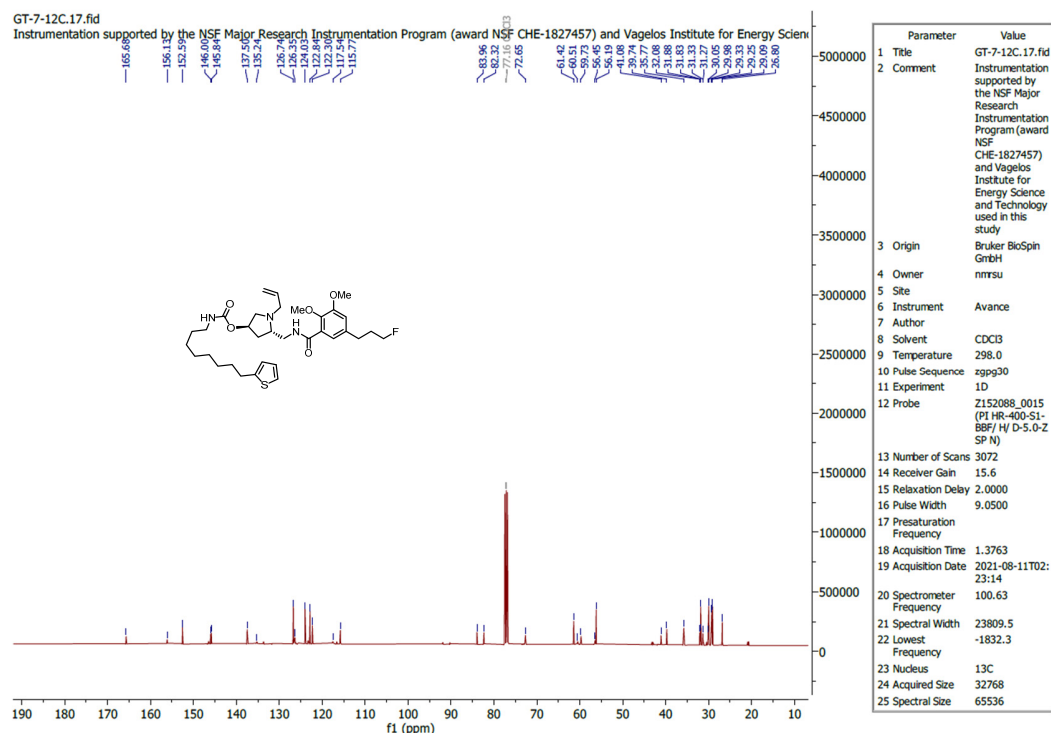
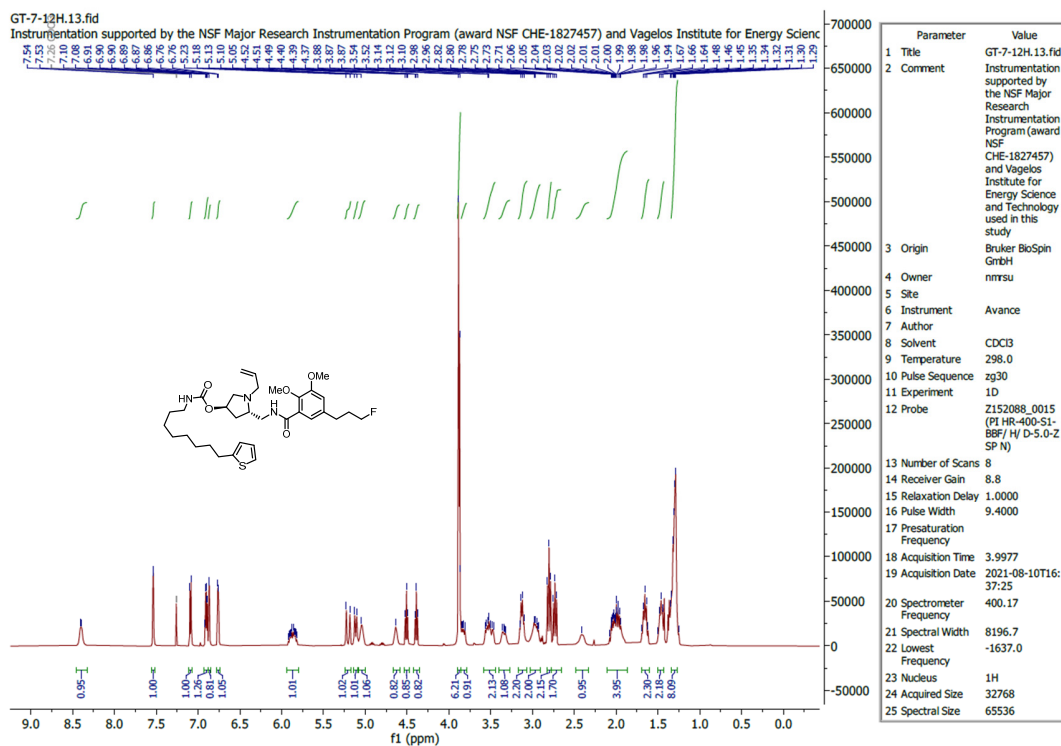
(3*R*,5*S*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl (2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)carbamate ((*R,S*)-*trans*-2*g*). GT-6-148



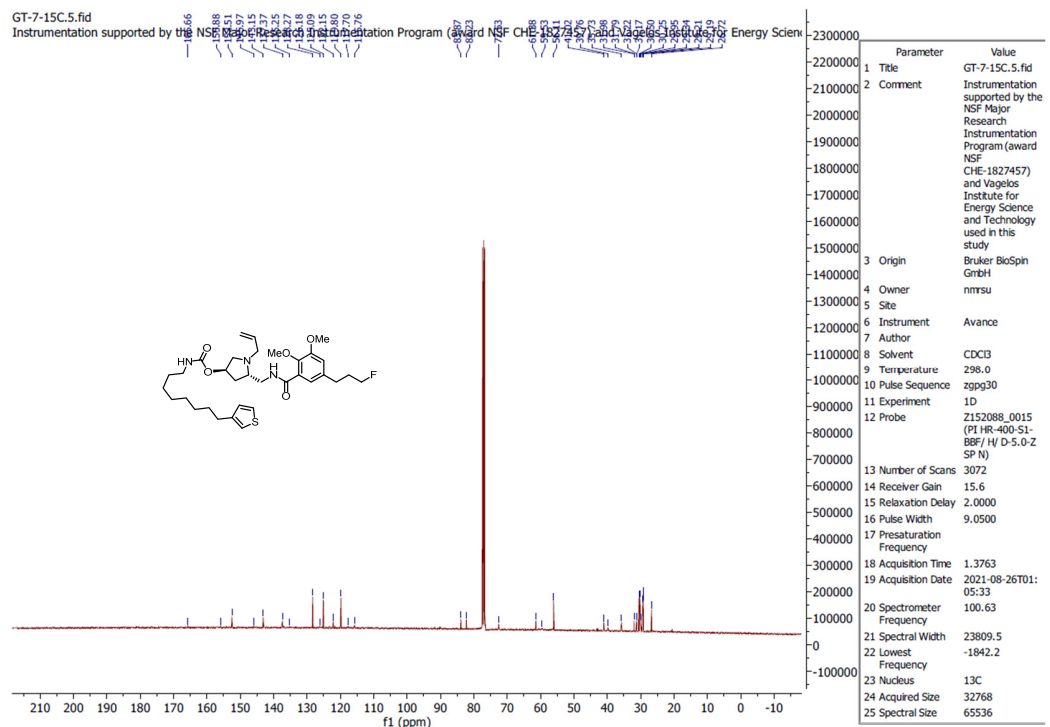
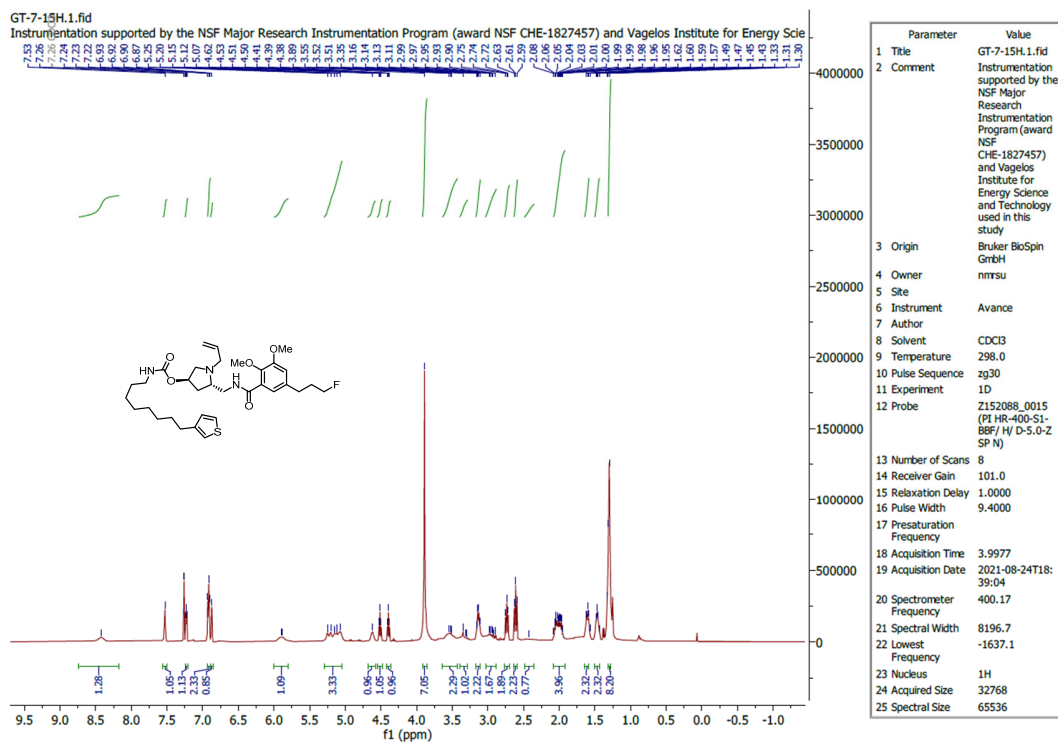
(3*R*,5*S*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl (6-(thiophen-2-yl)hexyl)carbamate (**(*R,S*)-trans-2h**) GT-7-6



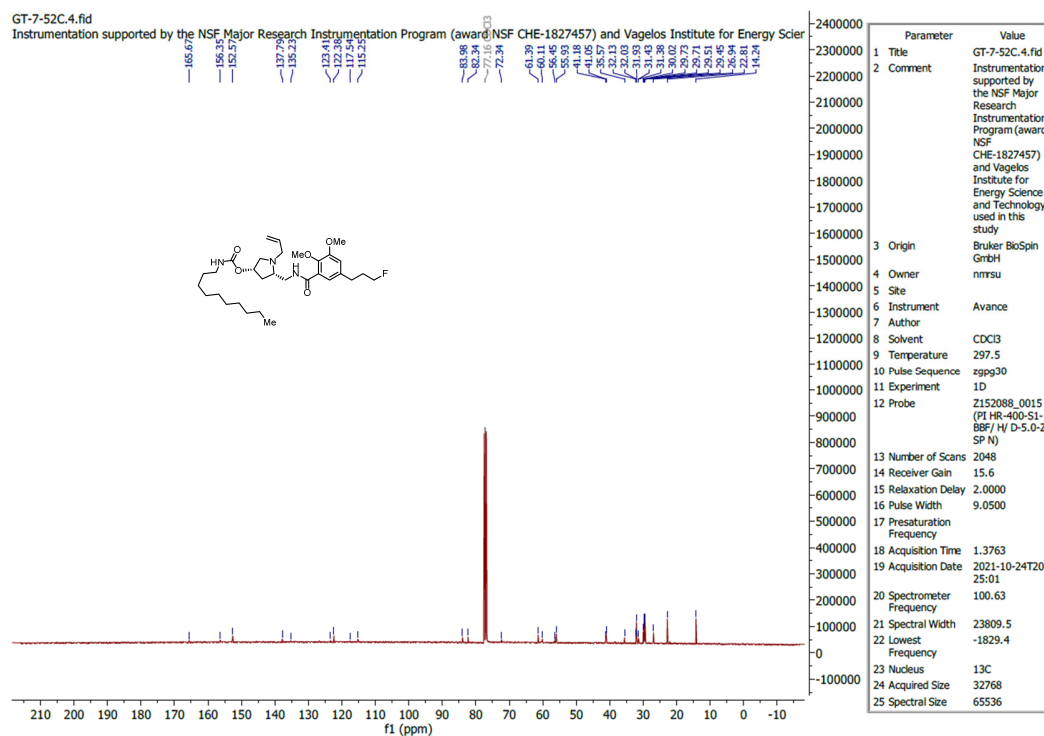
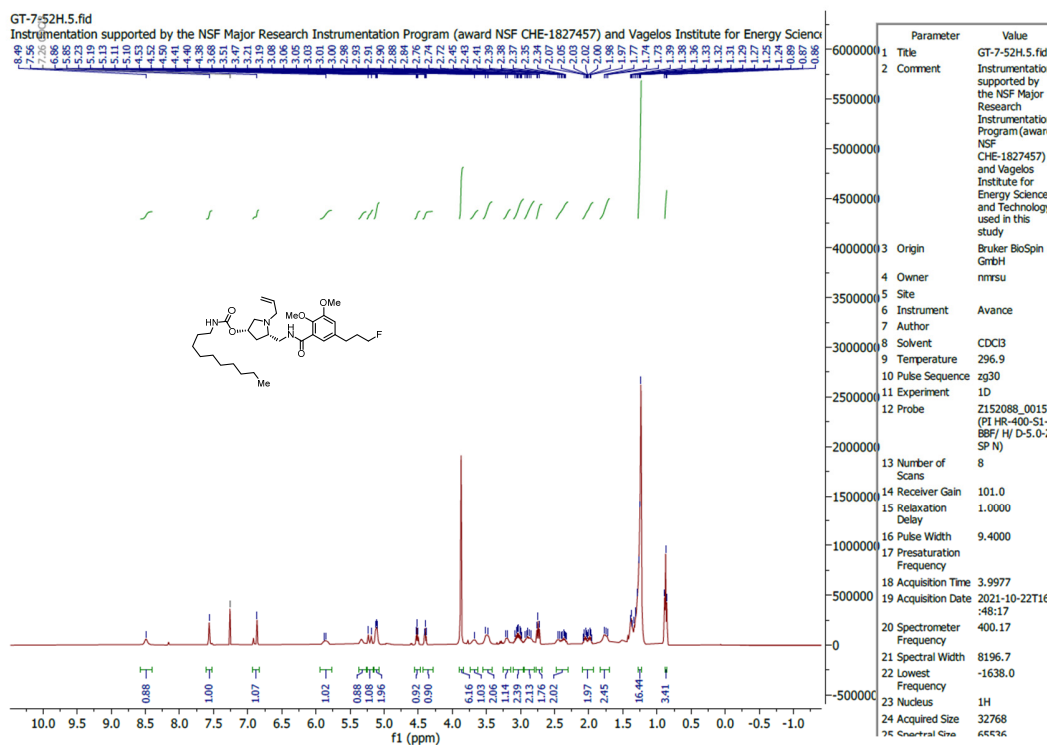
(3*R*,5*S*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl (8-(thiophen-2-yl)octyl)carbamate ((*R,S*)-*trans*-2i) GT-7-12 or (3*S*,5*R*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl (8-(thiophen-2-yl)octyl)carbamate ((*S,R*)-*trans*-2i). GT-7-51



(8-(thiophen-3-



(3*S*,5*S*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl decylcarbamate ((*S*, *S*)-*cis*-**2d**) GT-7-52 and (3*R*,5*R*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl decylcarbamate ((*R*, *R*)-*cis*-**2d**). GT-7-54



(3*S*,5*S*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl (8-(thiophen-2-yl)octyl)carbamate ((*S*, *S*)-*cis*-2*i*) GT-7-53 and (3*R*,5*R*)-1-allyl-5-((5-(3-fluoropropyl)-2,3-dimethoxybenzamido)methyl)pyrrolidin-3-yl (8-(thiophen-2-yl)octyl)carbamate ((*R*, *R*)-*cis*-2*i*). GT-7-55

