Supporting Information

A Scalable Route for the Regio- and Enantioselective Preparation of a Tetrazole Prodrug: Application to the Multi-Gram Scale Synthesis of a PCSK9 Inhibitor

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Table of Contents

Experimental Data

Alternative method to prepare **10**: To a solution of 4-iodo-1-methyl-1*H*-pyrazole-5-carbonitrile **8** (500 mg, 2.15 mmol) in 2-MeTHF (4 mL) was added P_2S_5 (24 mg, 0.11 mmol) followed by hydrazine monohydrate (523 μL, 10.7 mmol). The reaction mixture was heated in a sealed vial at 70 °C for 17 h. The reaction mixture was added slowly to heptane with vigorous stirring until an oily precipitate formed. The mother liquor was decanted away and the residue triturated with heptane and dried under vacuum to afford a light yellow solid (520 mg). The residue was dissolved in EtOH (5 mL). HCl (2.0 mL, 3.0 M aqueous solution) was added followed by $NaNO_2$ (405 mg, 5.88 mmol) dissolved in water (1.5 mL) dropwise to control exotherm and gas evolution. The reaction mixture was concentrated in vacuo to a volume of ~3 mL. Water (20 mL) and CH_2Cl_2 (15 mL) were added, followed by saturated aqueous $NaHCO_3$ (5 mL) to adjust the solution to pH > 7. The reaction mixture was partitioned and the organic layer discarded. The aqueous layer was acidified to pH 1 with 6M HCl. The reaction mixture was extracted with EtOAc (2x 40 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo to afford 5-(4-iodo-1-methyl-1*H*-pyrazol-5-yl)-2*H*-tetrazole as an off-white solid (390 mg, 66%). ^{1}H NMR (MeOH-d_4) δ: 7.69 (s, 1H), 4.08 (s, 3H). UPLC (UPLC-MS Method 1): t_R = 0.52 min. MS (ES+): 276.9 $(M+H)^+$.

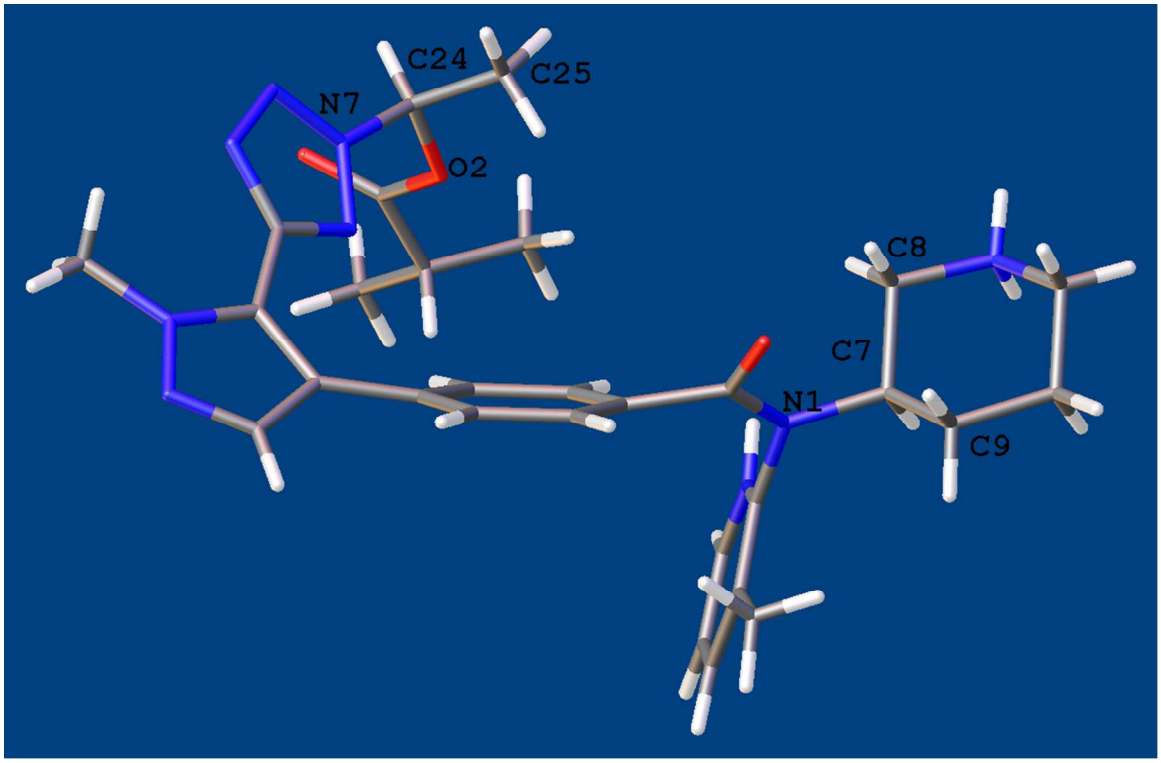


Figure S1: Structure Solution and Refinement for (*R*,R)-3

The submitted compound crystallizes in the chiral monoclinic space group *P*21 with two target molecules and one disordered solvent molecule (*i*PrOH) per asymmetric unit.

The structure was solved with direct methods using the program SHELXT[4] and refined against *F*2 on all data with SHELXL[5] using established refinement techniques[6]. All non-hydrogen atoms were refined anisotropically. All carbon-bound hydrogen atoms were placed in geometrically calculated positions and refined using a riding model while constraining their *Uiso* to 1.2 times the *Ueq* of the atoms to which they bind (1.5 times for methyl groups). Coordinates for the hydrogen atoms on nitrogen were taken from the difference Fourier synthesis. Those hydrogen atoms were subsequently refined semi-freely with the help of N—H distance restraints (target value 0.91(2) Å for the hydrogen atoms on N3 and N12 and 0.88(2) Å for hydrogen atoms on N2 and N11) while constraining their *Uiso* to 1.2 times the *Ueq* of the corresponding nitrogen atom.

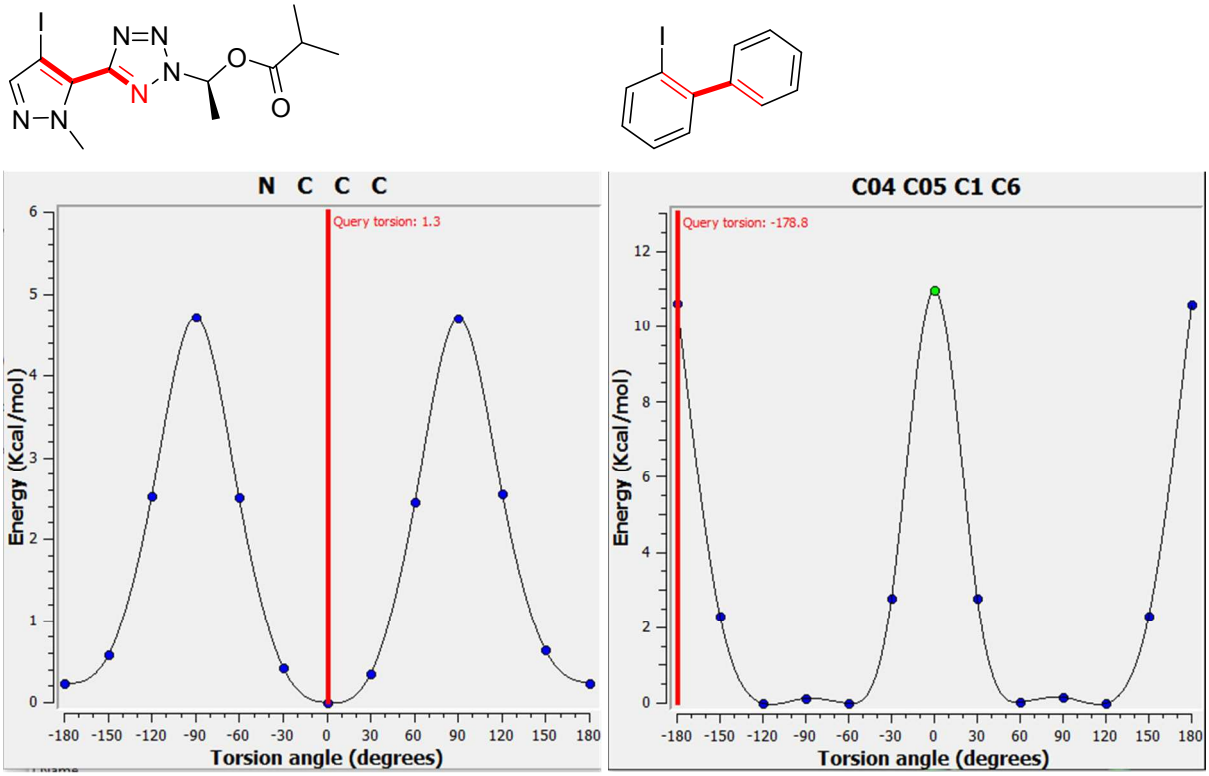
The diffraction data, show significant anomalous signal and the absolute structure could be established with confidence. The configurations of the compound's four crystallographically independent chiral carbon atoms (two per independent molecule) are as follows: C7: R, C24: R in the first molecule and the corresponding atoms in the second molecule have the same conformation (C37: R, C54: R).

Table S1: Crystal data and structure refinement for (*R*)-1-(5-(1-methyl-4-(4-((3-methylpyridin-2-yl)((*R*)-1λ2-piperidin-3-yl)carbamoyl)phenyl)-1*H*-pyrazol-5-yl)-2*H*-tetrazol-2-yl)ethyl isobutyrate dihydrochloride (CCDC 1571688)

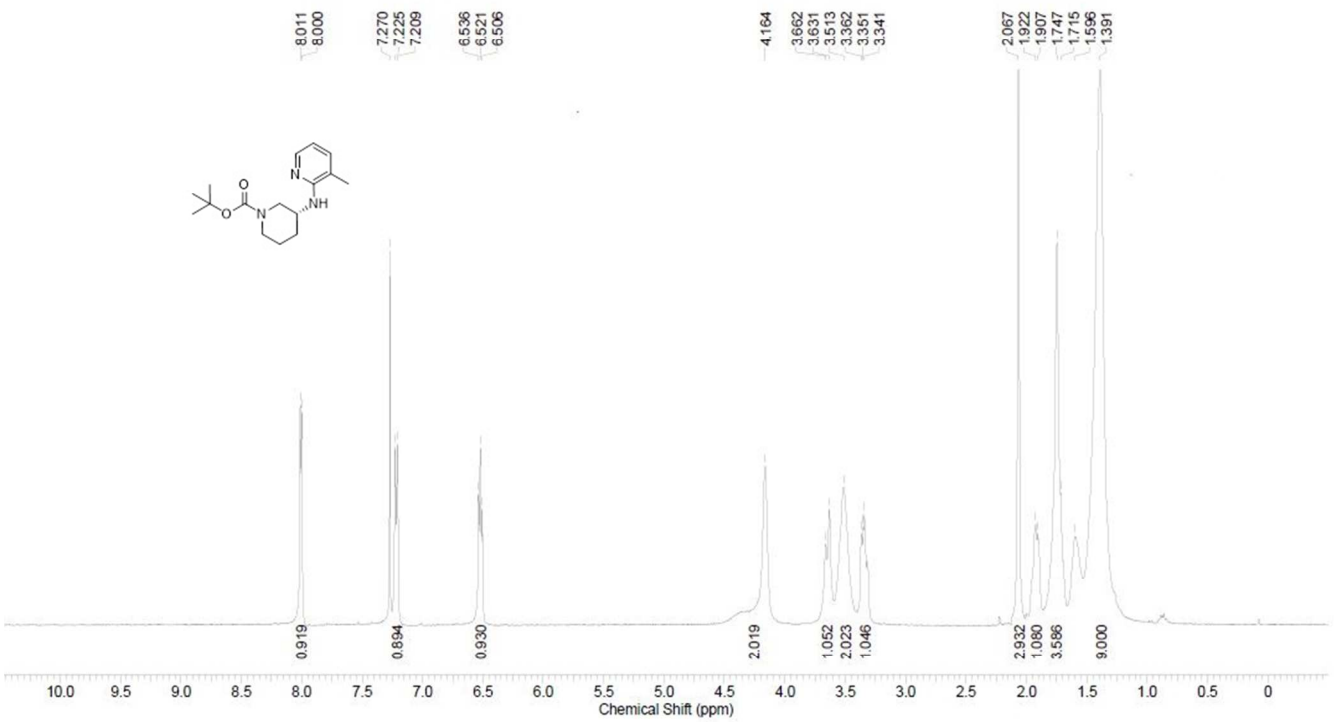
Empirical formula	C30.50H41Cl2N9O3.50	
Formula weight	660.62	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	*P*21	
Unit cell dimensions	*a* = 9.0796(2) Å	α = 90°.
	b = 14.0908(3) Å	β = 98.6028(17)°.
	c = 26.9425(7) Å	γ = 90°.
Volume	3408.21(14) Å3	
Z	4	
Density (calculated)	1.287 Mg/m3	
Absorption coefficient	2.097 mm-1	
F(000)	1396	
Crystal size	0.110 x 0.100 x 0.010 mm3	
Theta range for data collection	3.318 to 68.245°.	
Index ranges	-10<=*h*<=10, -16<=*k*<=16, -32<=*l*<=32	
Reflections collected	120204	
Independent reflections	12910 [*Rint* = 0.0845]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.753269 and 0.675301	
Refinement method	Full-matrix least-squares on *F*2	

Data / restraints / parameters	12910 / 654 / 959
Goodness-of-fit on *F*2	1.080
Final *R* indices	[$I>2\sigma(I)$] $R1 = 0.0458$, $wR2 = 0.0946$
R indices (all data)	$R1 = 0.0544$, $wR2 = 0.0988$
Absolute structure parameter	0.014(6)
Largest diff. peak and hole	0.283 and -0.205 e.Å-3

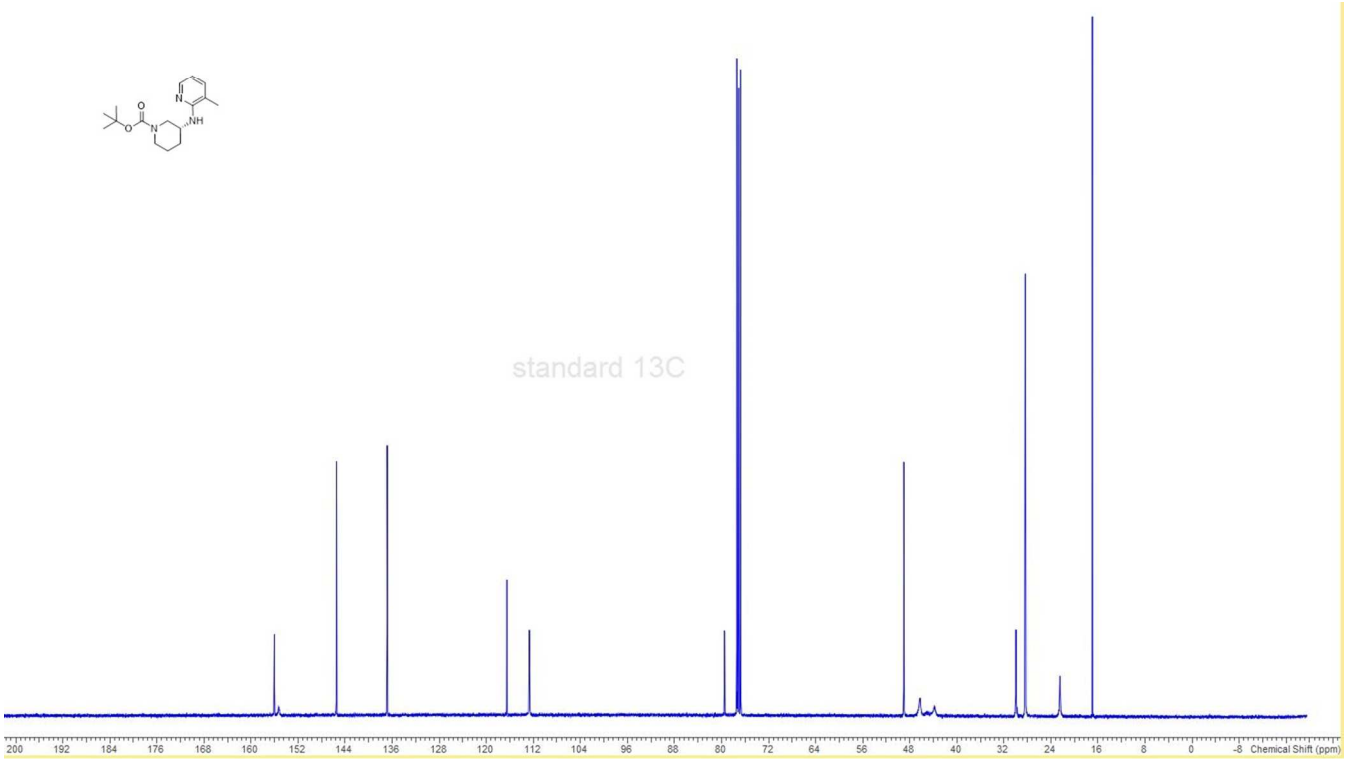
Figure S2. Ligand Torsion Scan of (S)-**12** and 2-iodobiphenyl.



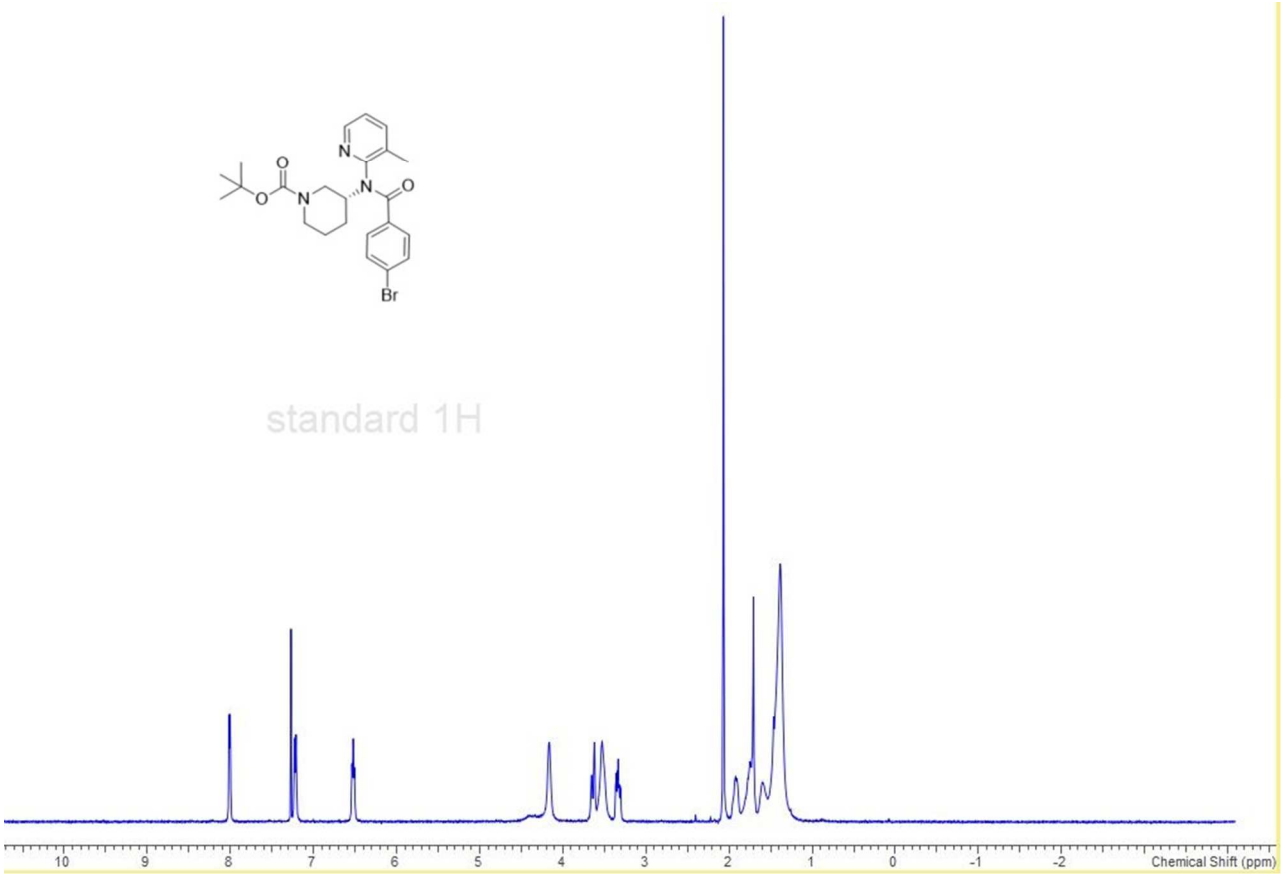
A torsion angle scan of (S)-**12** shows the maximum barrier to rotation around (red) atoms is about 4.8 kcal/mol. For comparison, 2-iodobiphenyl is shown to have a barrier to rotation of about 11.0 kcal/mol. This is in good agreement with calculated (B3LYP/6-311+G* and HF/6-31G*) values for 2-bromo and 2-iodobiphenyl (*J. Phys. Chem. A* **2002,** *106,* 3823-3827). A minor amount of hindered rotation might exist for (S)-**12**, but the obtained value for the ligand torsion scan is several kcal/mol less than the typical barrier associated with hindered rotation/isolable atropisomers (23 kcal/mol).



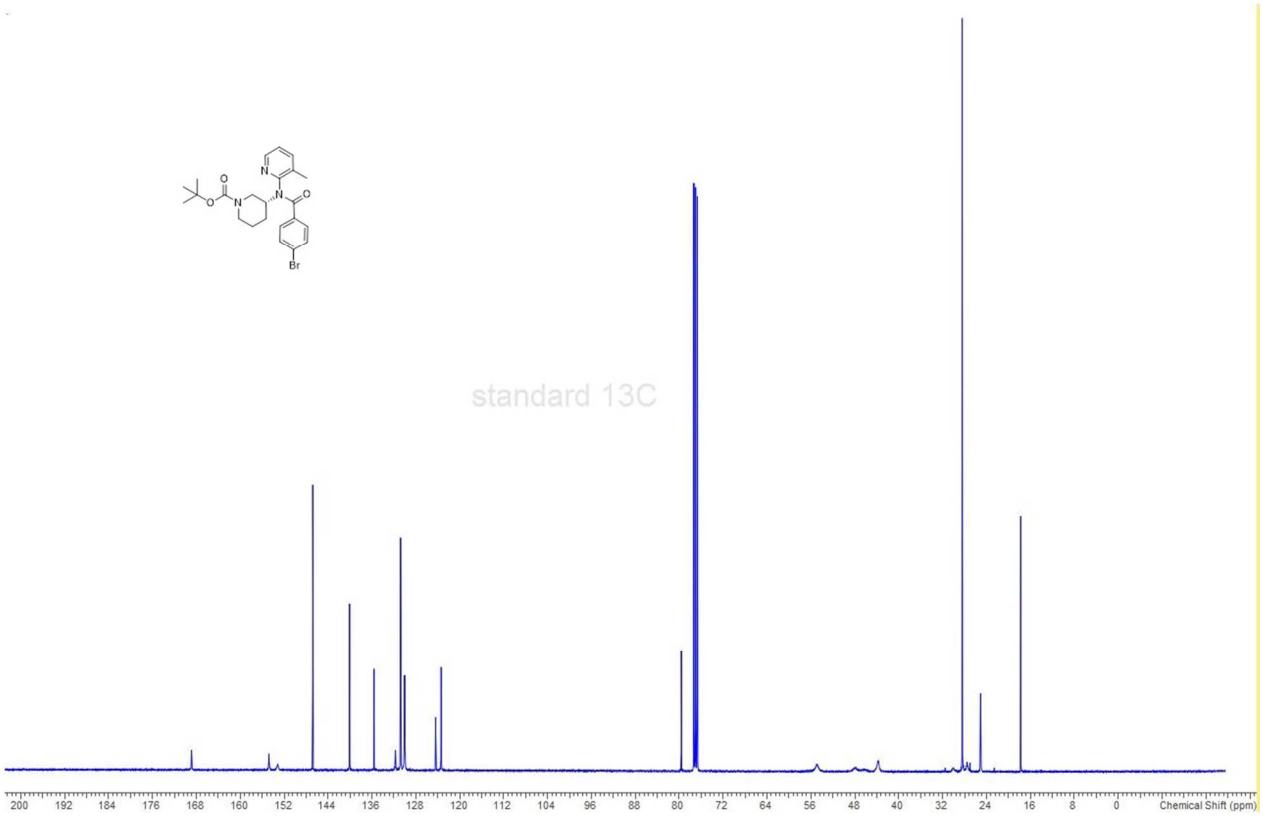
^{1}H NMR ($CDCl_3$) spectrum of *tert*-butyl (3*R*)-3-[(3-methylpyridin-2-yl)amino]piperidine-1-carboxylate (**S1**)



^{13}C NMR ($CDCl_3$) spectrum of *tert*-butyl (3*R*)-3-[(3-methylpyridin-2-yl)amino]piperidine-1-carboxylate (**S1**)



^{1}H NMR ($CDCl_3$) spectrum of *tert*-butyl (3*R*)-3-[(4-bromobenzoyl)(3-methylpyridin-2-yl)amino]piperidine-1-carboxylate (**5**)



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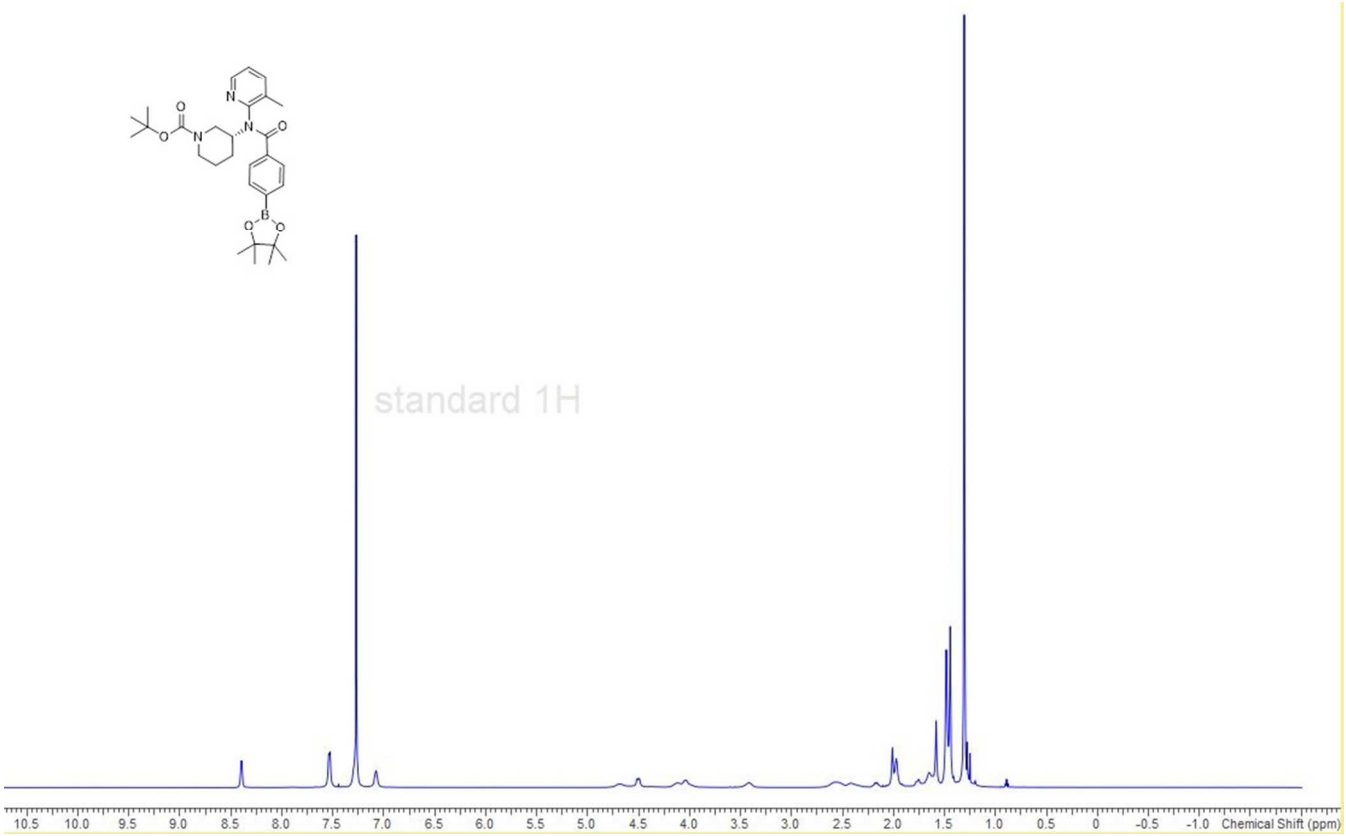
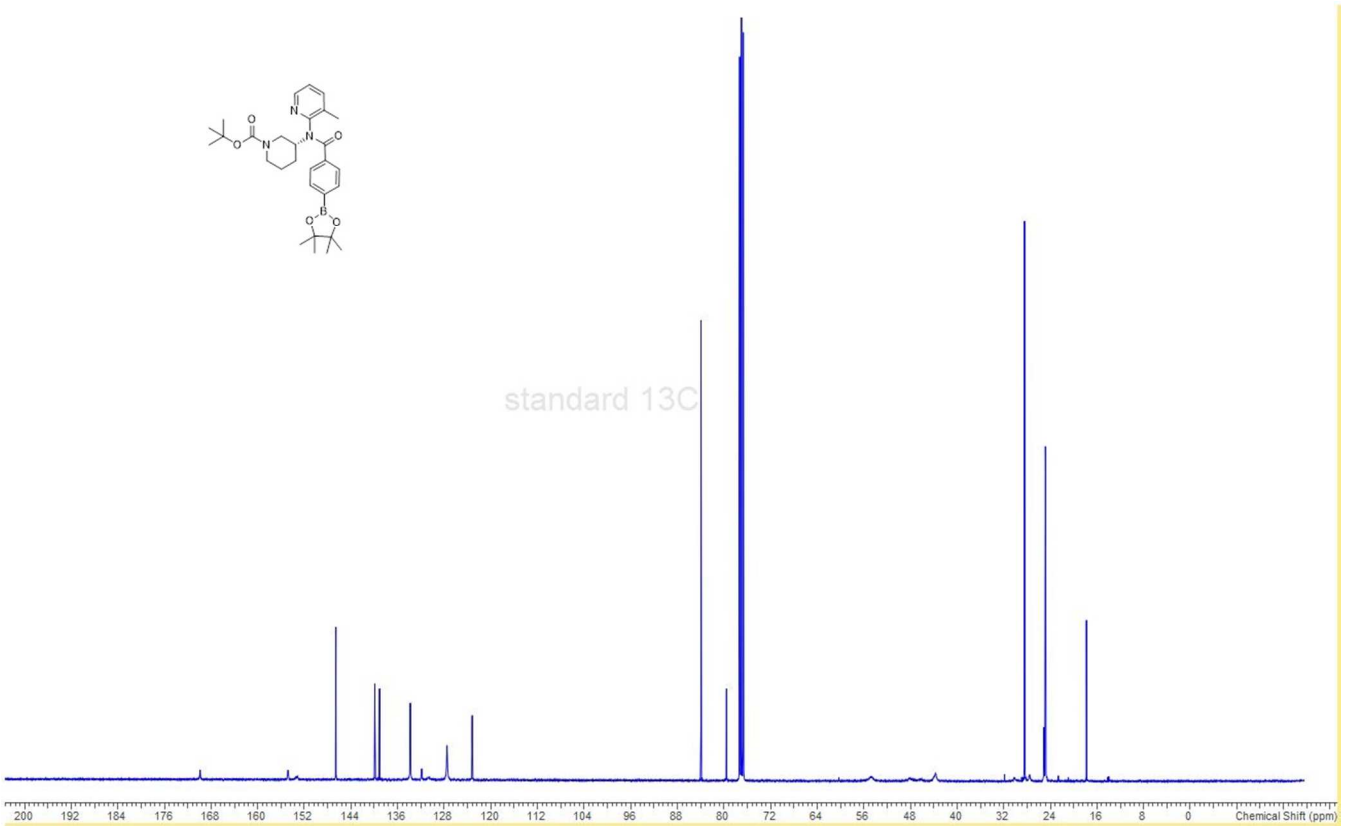


^{1}H NMR ($CDCl_3$) spectrum of *tert*-butyl (3*R*)-3-{(3-methylpyridin-2-yl)[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl]amino}piperidine-1-carboxylate (**6**)



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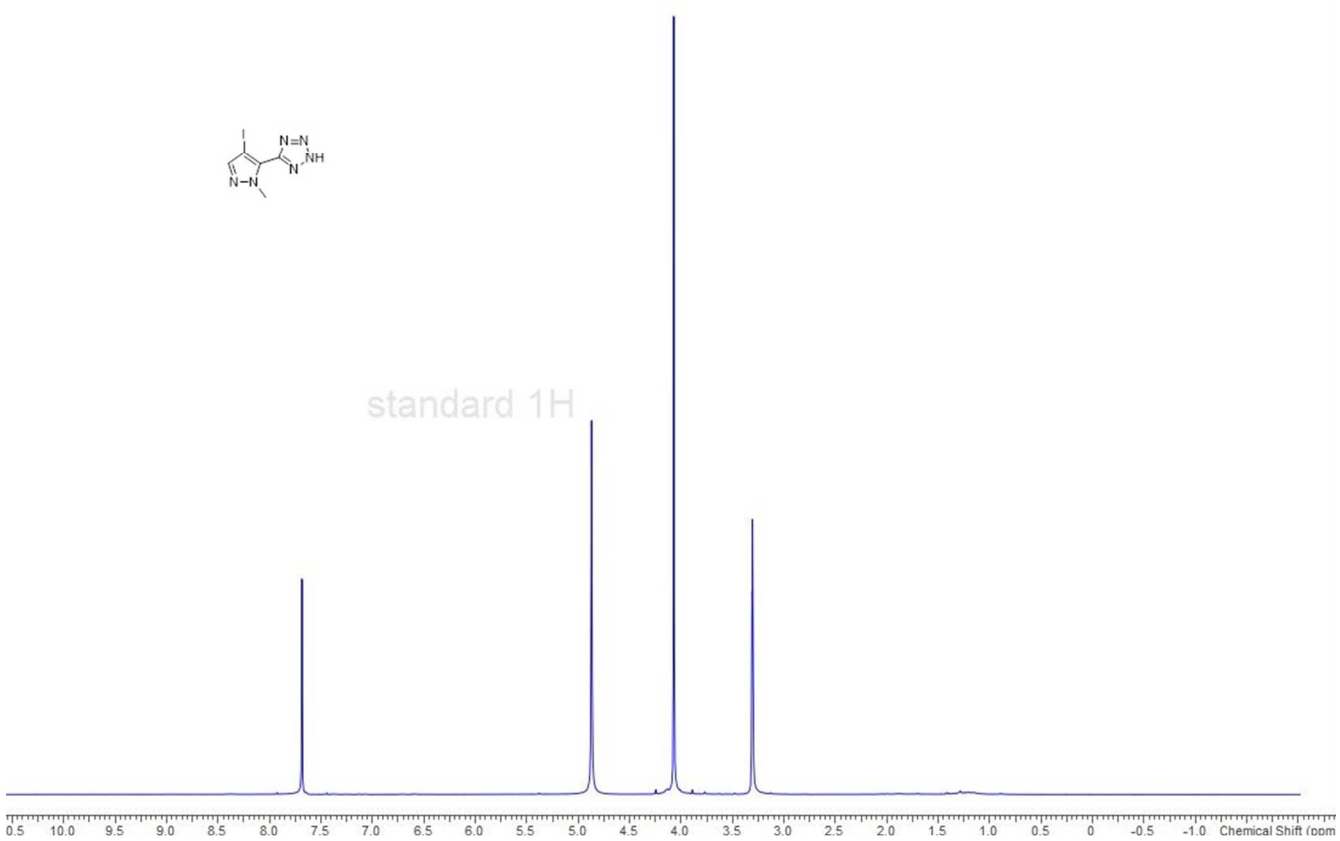
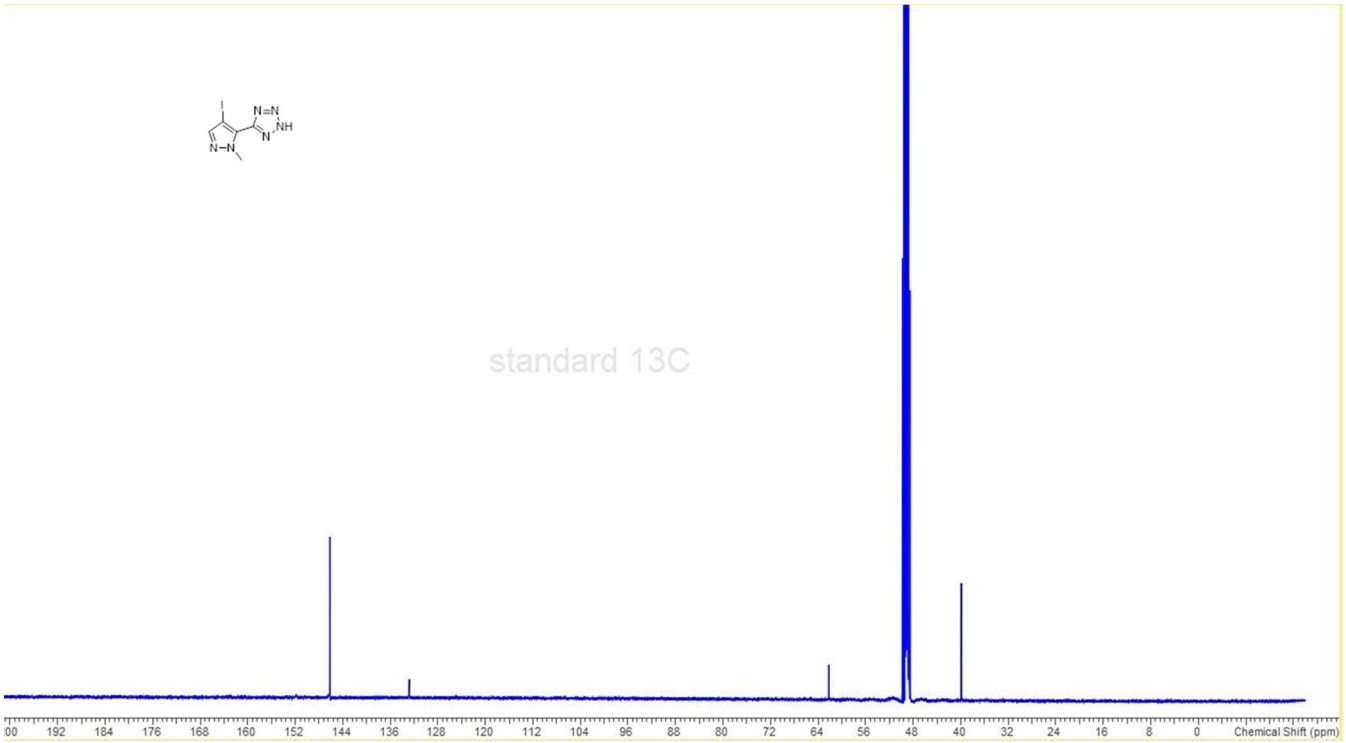


^{1}H NMR (MeOH-d_4) spectrum of 5-(4-iodo-1-methyl-1*H*-pyrazol-5-yl)-2*H*-tetrazole (**10**)



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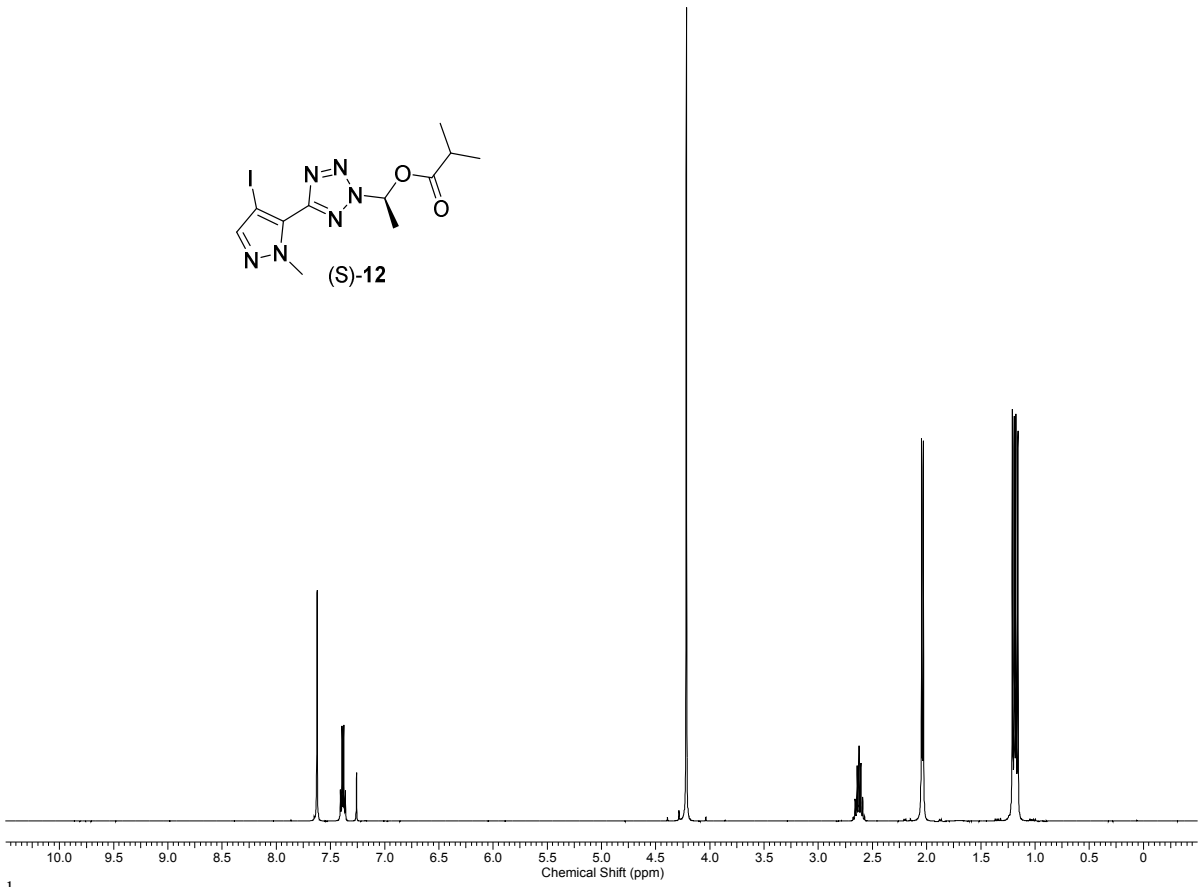
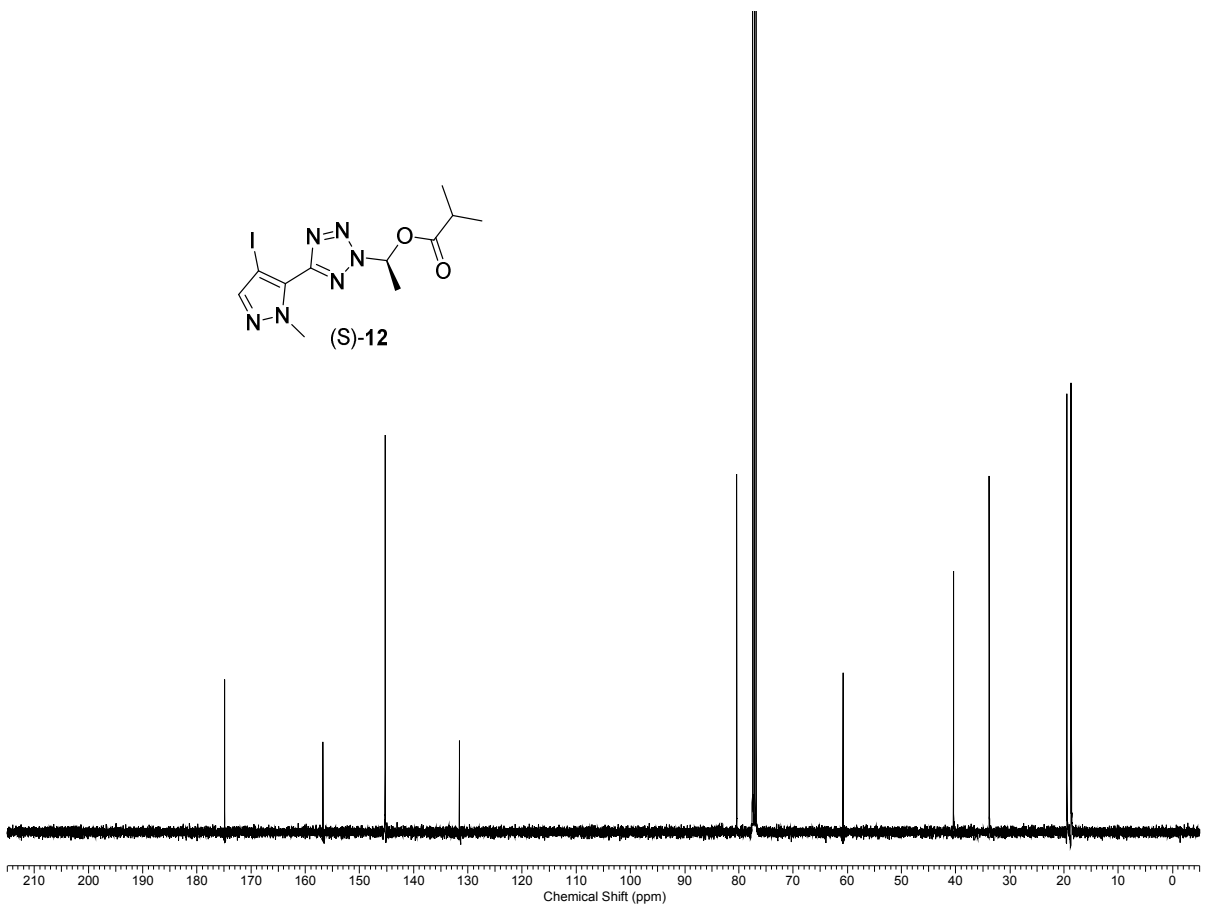


^{1}H NMR ($CDCl_3$) (*S*)-1-(5-(4-Iodo-1-methyl-1*H*-pyrazol-5-yl)-2*H*-tetrazol-2-yl)ethyl isobutyrate ((*S*)-**12**)



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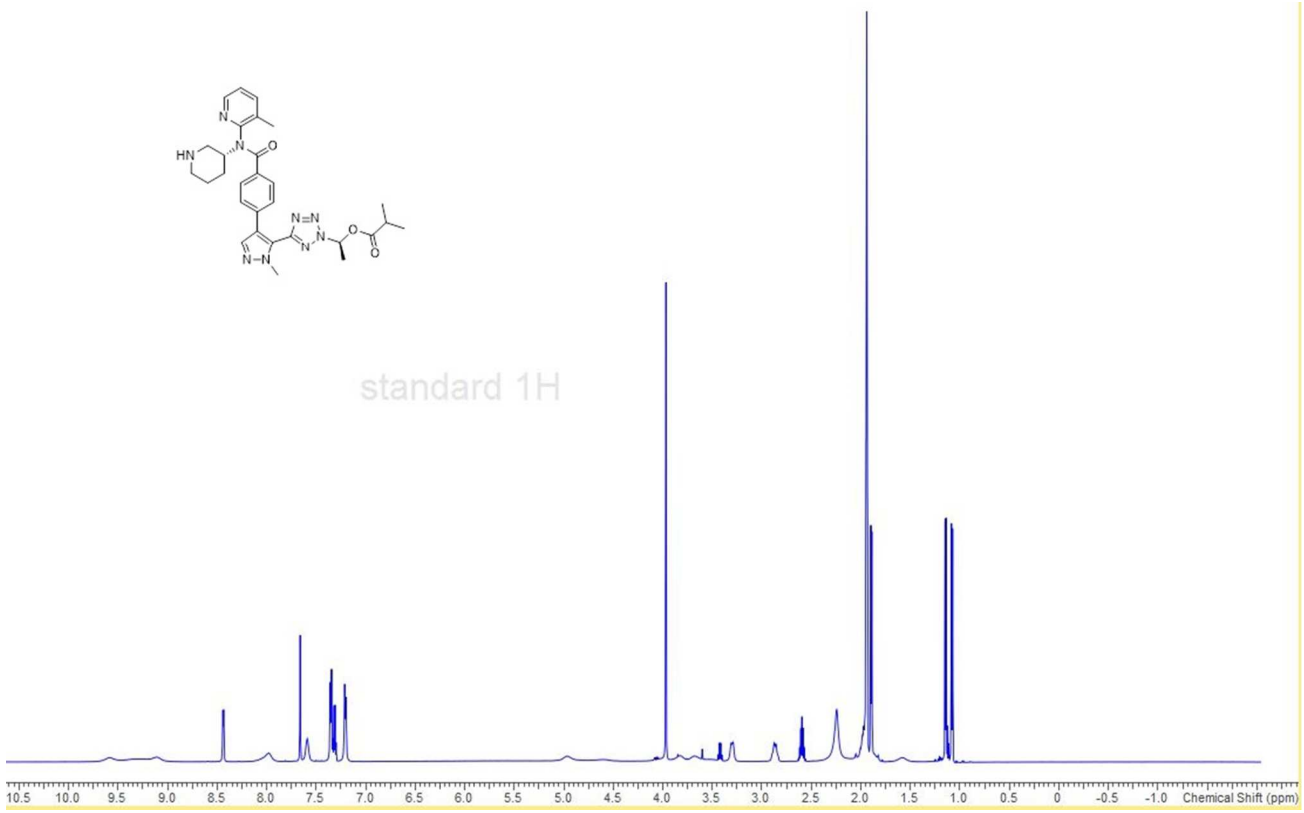

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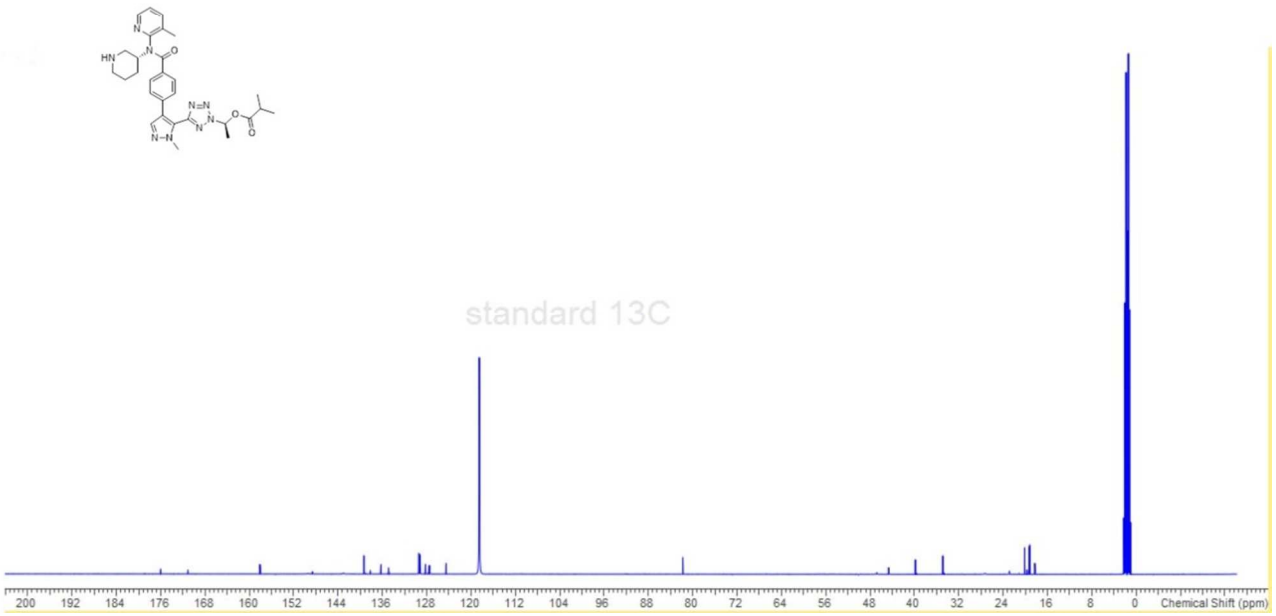

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