SUPPORTING INFORMATION

Triazole Ureas act as Diacylglycerol Lipase Inhibitors and Prevent Fasting-induced Refeeding

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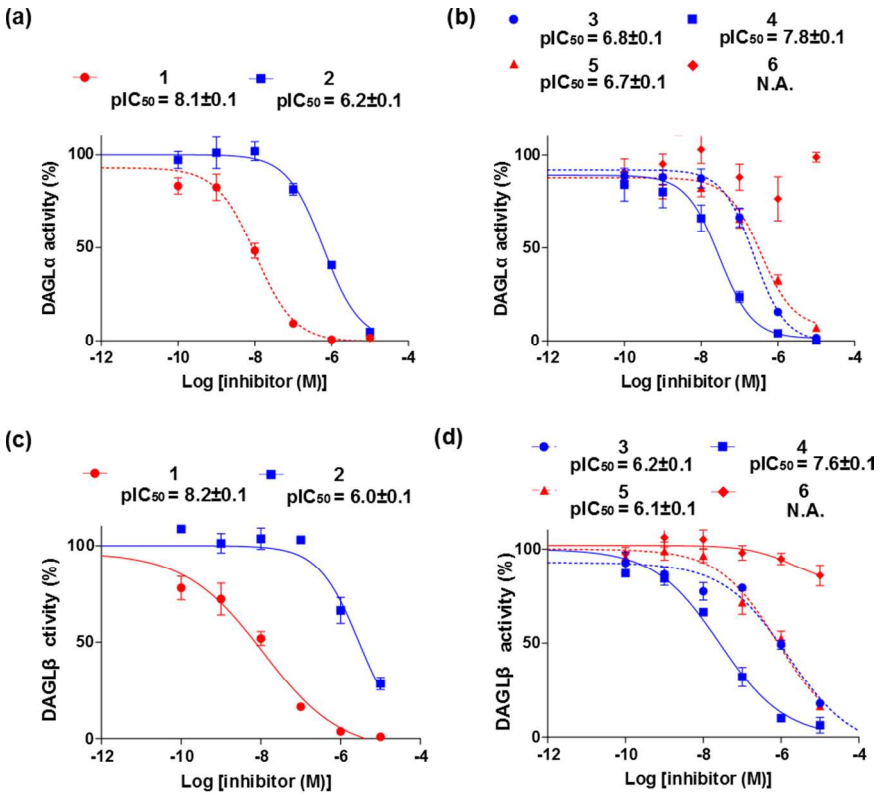


Figure S.1. Concentration-dependent inhibition curves of recombinant human DAGLα (a, b) and human DAGLβ (c, d) as determined with competitive ABPP labeled by DH379 (representative gels in Figure 1f and g). Data represent average values ± SEM; n = 3 per group .

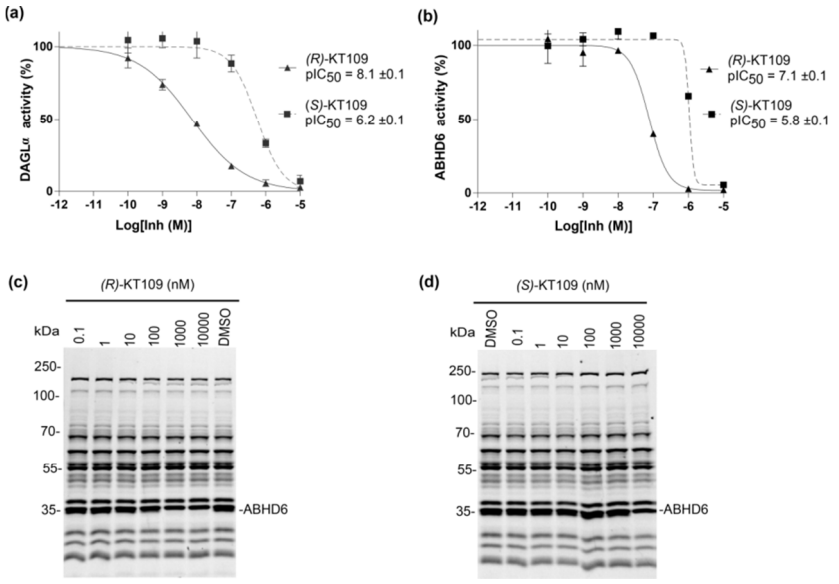


Figure S.2. *In vitro* characterization of *(R)*-KT109 and *(S)*-KT109 in mouse brain membrane proteome. (a-b) Dose response curves of DAGLα (a) and ABHD6 (b) inhibition as determined with competitive ABPP labeled by MB064 (Figure 2d and e). Data represent average values ± SEM; n = 3 per group. (c-d) Selectivity profiles of *(R)*-KT109 (c) and (*S*)-KT109 (d) across mouse brain serine hydrolases as determined by competitive ABPP using broad-spectrum probe FP-TAMRA (0.5 µM, 20 min). Of note, in these gel profiles for FP-TAMRA labeling, ABHD6 and MAGL signals were not resolved from one another, and DAGLs are not visualized .

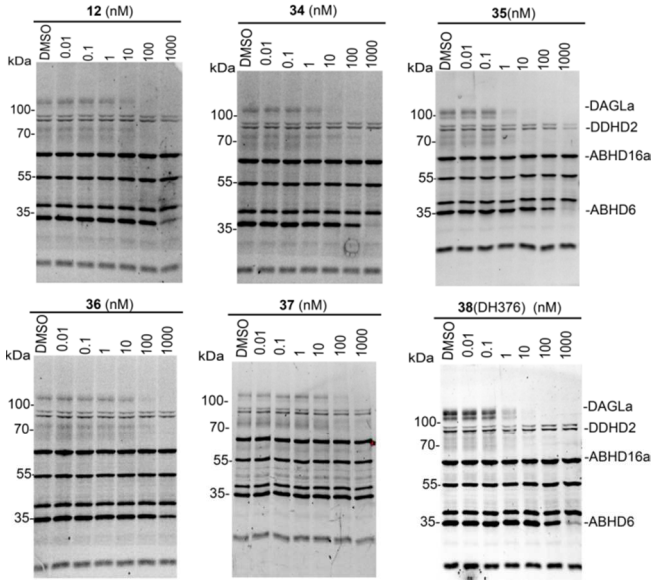


Figure S.3., related to Figure 3b. Full gels of *in vitro* competitive ABPP for compounds **34-38**, and **12** in mouse brain membrane proteome using probe MB064 (0.25 µM, 20 min).

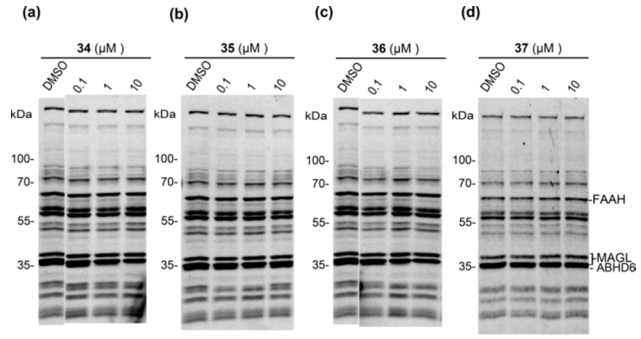


Figure S.4. Selectivity profiles of compounds **34-37** across mouse brain serine hydrolases as determined by competitive ABPP using broad-spectrum probe FP-TAMRA (0.5 μM, 20 min).

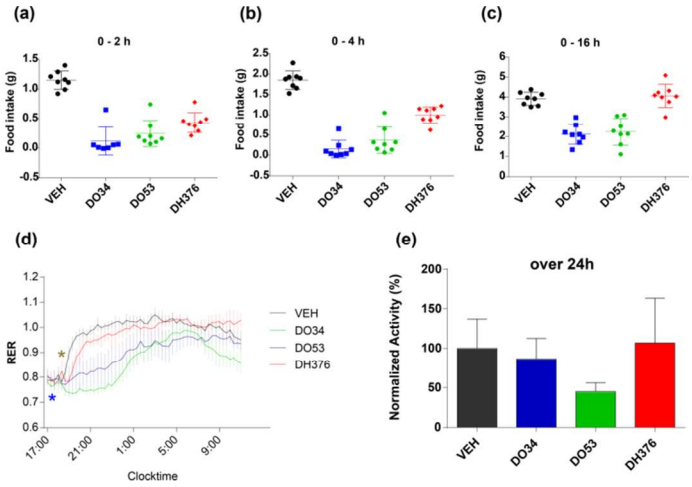


Figure S.5 *In vivo* effects of DAGL inhibitors DH376 (**38**), DO34 and control compound DO53 on food intake (a-c), respiratory exchange ratio (RER) (d) and locomotor activity (e, 0-24h) in mice. After 18h of fasting, the mice received a single intraperitoneal injection of vehicle (black), or DH376 (red), DO34 (blue), and DO53 (green) (50 mg/kg) 30 min before the start of refeeding and the testing period. Cumulative food intake was measured for different period of time (2h, 4h and 16h). The respiratory exchange ratio of the animals were measured (in 20 min bins) and calculated from the ratio of O_2 consumption and CO_2 production in metabolic cages, and the locomotor activity over 24h of the animals were measured by infrared beam breaks in Y and Z axis. Data represent average values ± SEM; n = 8 mice per group. $^{**}P < 0.01$; $^{***}P < 0.001$ for all groups vs. the vehicle-treated group.

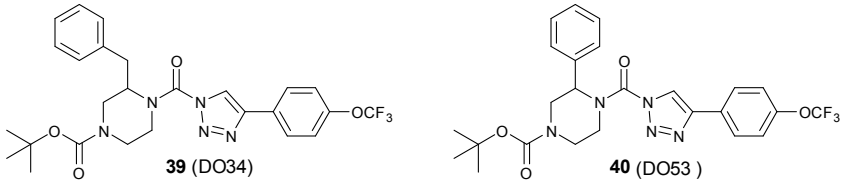


Figure S.6 Structures of DAGL inhibitor **39** and control compound **40**.

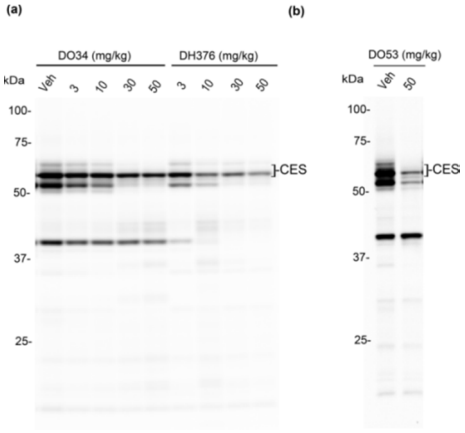


Figure S.7 *Ex vivo* selectivity profile of DAGLs inhibitors (DH376 and DO34) and control compound (DO53) in mouse liver. (a) Competitive ABPP analysis in mouse liver from mice treated with various dose (3-20-30-50 mg/kg, i.p., 4h) of DAGLs inhibitors DH376 and DO34 using FP-TAMRA (1 μM, 30 min) as a broad-spectrum probe. (b) Competitive ABPP analysis in mouse liver from DO53-treated mice (50 mg/kg, i.p., 4h) using FP-TAMRA (1 μM, 30 min) as a probe.

Table S.1 pIC_{50} values of compounds **1-6** against DAGLα and DAGLβ as determined by the colorimetric assay with PNP butyrate as substrate and competitive ABPP assay. Data represent average values ± SEM; n = 4 per group for substrate assay, and n = 3 per group for ABPP assay.

	Substrate assay (PNP butyrate)		**ABPP** (DH379)	
	hDAGLα	mDAGLβ	hDAGLα	hDAGLβ
1	8.9±0.1	7.1±0.2	8.1±0.1	8.2±0.1
2	7.2±0.1	4.9±0.3	6.2±0.1	6.0±0.1
3	7.6±0.1	7.1±0.1	6.8±0.1	6.2±0.1
4	8.6±0.1	7.9±0.1	7.8±0.1	7.6±0.1
5	7.7±0.1	4.7±0.2	6.7±0.1	6.1±0.1
6	5.4±0.1	N.A.	N.A.	N.A.

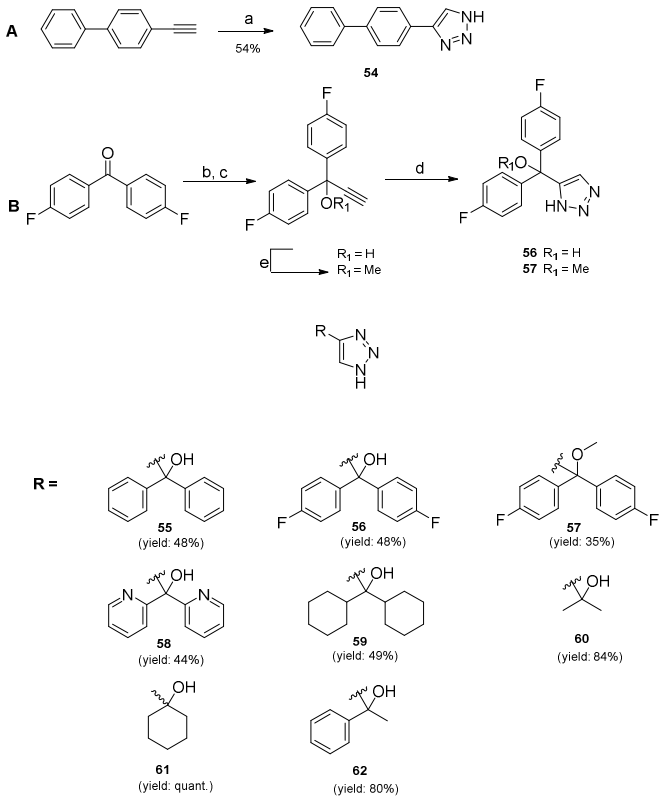
II. Experimental Section

General Synthetic Methods. All Reagents were purchased from Sigma Aldrich, Acros or Merck and used without further purification unless noted otherwise. All moisture sensitive reactions were performed under an argon atmosphere. Traces of water were removed from starting compounds by co-evaporation with toluene. Reactions were performed using oven or flame-dried glassware and dry solvents. Liquid chromatography was performed on a Finnigan surveyor LC/MS system, equipped with a C18 column. Optical rotations were measured on a Propol automatic polarimeter (Sodium D-line, λ = 589 nm). Flash chromatography was performed using SiliCycle silica gel type SilicaFlash P60 (230 – 400 mesh). TLC analysis was performed on Merck silica gel 60/Kieselguhr F254, 0.25 mm. Compounds were visualized using either Seebach's reagent (a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H_2O (500 mL) and H_2SO_4 (25 mL)) or a $KMnO_4$ stain (K_2CO_3 (40 g), $KMnO_4$ (6 g), H_2O (600 mL) and 10% NaOH (5 mL)).

(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(2-benzylpiperidin-1-yl)methanone (1, KT109). A solution of 2-benzylpiperidine (90.0 mg, 0.513 mmol) in THF was treated with DIPEA (0.269 mL, 1.54 mmol) and bis(trichloromethyl) carbonate (76.0 mg, 0.257 mmol) and the reaction mixture was stirred for 30 min at 0 ^oC. After that the reaction mixture was poured into water and extracted with ethyl acetate (3 x 10 mL).The organic layer was washed with water, brine and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The intermediate was dissolved in THF and DIPEA (0.269 mL, 1.54 mmol), DMAP (62.7 mg, 0.513 mmol) and 4-([1,1'-biphenyl]-4-yl)-1*H*-1,2,3-triazole (125 mg, 0.565 mmol) were added to the solution. The mixture was stirred for 2h at 60 ^oC and poured into saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with ethyl acetate (3 x 20 mL), washed with water, brine, dried over $MgSO_4$ and filtered. The solvents are removed under reduced pressure to yield the crude triazole urea as a mixture of N1- and N2-carbamoylated regioisomers. The N1-carbamoyl triazole was isolated by silica gel chromatography (pentane/EtOAc 100:1 → 5:1) to afford KT109 (**1**) (99.0 mg, 0.234 mmol, 46% yield). LC-MS m/z: calculated for $C_{27}H_{26}N_4O$ $[M+H]^+$ 423.22, found: 423.04. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 2H), 7.74 – 7.60 (m, 4H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.42 – 7.34 (m, 1H), 7.22 (br s, 4H), 7.01 (br s, 1H), 4.86 (br s, 1H), 4.37 (br d, *J* = 13.6 Hz, 1H), 3.43 – 3.18 (m, 2H), 2.70 (br s, 1H), 2.07 – 1.67 (m, 6H).

(2-Ethylpiperidin-1-yl)(4-(hydroxydiphenylmethyl)-2*H*-1,2,3-triazol-2-yl)methanone (2, ML226). The title compound was synthesized from 2-ethylpiperidine (0.057 mL, 0.430 mmol) and diphenyl(1*H*-1,2,3-triazol-4-yl)methanol (90.0 mg, 0.358 mmol) according to the procedures described for compound **1**. The N2-carbamoyl triazole was isolated by silica gel chromatography (pentane/EtOAc 100:1 → 5:1) to afford 2,4-triazole urea ML226 (76.0 mg, 0.195 mmol, 54% yield). LC-MS m/z: calculated for $C_{23}H_{26}N_4O_2$ $[M+H]^+$ 391.49, found: 391.14. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.39 – 7.24 (m, 10H), 4.22 (br s, 1H), 3.98 – 3.03 (m, 3H), 1.84 – 1.50 (m, 8H), 1.11 – 0.58 (m, 3H).

Scheme S.1. Synthesis of triazole building blocks (A and B).



Reagents and conditions: (a) CuI, azidotrimethylsilane, DMF:MeOH = 5:1, 100 ^{o}C; (b) butyllithium, ethynyltrimethylsilane, THF, -10 ^{o}C; (c) NaOH, MeOH; (d) MeI, K_2CO_3, DMF, 60 ^{o}C.

4-([1,1'-Biphenyl]-4-yl)-2*H*-1,2,3-triazole (**54**)**.** In a 50 mL 2-neck round-bottom flask, a solution of 4-ethynyl-1,1'-biphenyl (415 mg, 2.30 mmol) in DMF (20 mL) and MeOH (6 mL) was purged with argon three times. To this solution was added N_3-TMS (0.772 mL, 5.82 mmol) and CuI (100 mg, 0.538 mmol). The reaction mixture was stirred for 2 days at 120 °C. The reaction was allowed to cool to room temperature and H_2O (30 mL) was added after removal of the solvents. Products were extracted with DCM (3 x 75 mL). Organic fractions were combined, washed with brine (30 mL), and dried over $MgSO_4$. After filtering and removal of the solvents, the crude material was purified over silica gel using pentane/ethyl acetate (1:1, 1% Et_3N) and yielded **54** (277 mg, 1.25 mmol, 54%). ^{1}H NMR (400 MHz, DMSO) δ: 8.42 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.75 – 7.68 (m, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.38 (t, J = 7.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 139.73, 139.46, 129.38, 129.02, 127.58, 127.12, 126.48, 126.14.

1,1-Diphenylprop-2-yn-1-ol. To a solution of ethynyltrimethylsilane (0.430 mL, 3.10 mmol) in anhydrous THF (10 mL) under nitrogen atmosphere was added slowly butyllithium (1.92 mL, 3.02 mmol) (1.6 M in hexane) at -10 °C and the solution was

stirred 1h at – 10 °C. A solution of benzophenone (500 mg, 2.74 mmol) in dry THF 5 mL was then added at -10 °C. After 3h stirring at -10 °C, the temperature was raised to 0°C and a solution of NaOH (143 mg, 3.57 mmol) in MeOH (2.80 mL) was added. After warming the solution to room temperature, the solution was neutralized to pH 7 with acetic acid and the resulting solution poured into water (38 mL). The organic layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography over silica gel using pentane/ethyl acetate and finished the title compound (1.08 g, 4.42 mmol, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 4H), 7.25 – 7.11 (m, 6H), 3.16 (s, 1H), 2.70 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.38, 128.22, 127.74, 126.00, 86.36, 75.70, 74.22.

Diphenyl(1*H*-1,2,3-triazol-4-yl)methanol (55). 1,1-Diphenylprop-2-yn-1-ol (260 mg, 1.25 mmol) and CuI (12.0 mg, 0.062 mmol) were dissolved in DMF/MeOH (5:1, 36 mL), azidotrimethylsilane (0.250 mL, 1.87 mmol) was added and the reaction mixture was stirred at 100 °C over the weekend. The reaction mixture was quenched with H_2O, and the organic layer was extracted with DCM. The combined organic layers were washed with H_2O and brine, dried on $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel using pentane/ethyl acetate (1:1) with 1% Et_3N, yielding **55** (151 mg, 0.599 mmol, 48% yield). ^{1}H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 7.36 – 7.26 (m, 10H).

Bis(4-fluorophenyl)(1*H*-1,2,3-triazol-4-yl)methanol (56). This compound was prepared and characterized as previously described [1].

4-(Bis(4-fluorophenyl)(methoxy)methyl)-1H-1,2,3-triazole (57). (1,1'-Bis(4-fluorophenyl)prop-2-yn-1-ol) (50.0 mg, 0.205 mmol) was dissolved in anhydrous THF (5 mL) and purged with argon 3 times. NaH (60%, 10 mg, 0.25 mmol;) was added and the reaction mixture was stirred for 30 min at 0°C. Subsequently, MeI (16.0 µL, 0.250 mmol) was added and the mixture was stirred for 3h at 0 °C. The mixture was washed with NH_4Cl solution (10 mL), H_2O (5 mL) and extracted with DCM (3 x 20 mL). Organic fractions were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified with pentane/ethyl acetate (1:1, 1% Et_3N) and obtained the methylated compound (45.0 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.48 (m, 4H), 7.11 – 6.98 (m, 4H), 3.37 (s, 3H), 2.94 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.32 (d, *J* = 246.9 Hz), 138.63 (d, *J* = 3.2), 128.38 (d, *J* = 7.7 Hz), 115.12 (d, *J* = 21.6 Hz), 82.03, 79.75, 78.01, 52.42. The obtained intermediate (46.0 mg, 0.178 mmol) was converted into 1,2,3-triazole according to the same procedures described for compound **55** (20.0 mg, 35%). LC-MS m/z: calculated for $C_{16}H_{13}N_3O$ $[M+H]^+$ 302.10, found 302.52. ^{1}H NMR (400 MHz, MeOD) δ 7.56 (s, 1H), 7.53 – 7.42 (m, 4H), 7.14 – 7.01 (m, 4H), 3.17 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 163.42 (d, *J* = 245.4 Hz), 144.20, 140.83, 130.91 (d, *J* = 8.2 Hz), 123.55, 115.62 (d, *J* = 21.7 Hz), 93.33, 52.63.

1,1-Di(pyridin-2-yl)prop-2-yn-1-ol. To a solution of ethynyltrimethylsilane (0.850 mL, 6.00 mmol) in anhydrous THF (20 mL) under nitrogen atmosphere was added slowly butyllithium (3.69 mL, 5.90 mmol) (1.6 M in hexane) at -10 °C and the solution was stirred 1h at -10 °C. A solution of di(pyridin-2-yl)methanone (1.00 g, 5.43 mmol) in

dry THF (10 mL) was then added at -10 °C. After 3h stirring at -10 °C, the temperature was raised to 0 °C and a solution of NaOH (238 mg, 5.95 mmol) in MeOH (4.60 mL) was added. After the solution was warmed to room temperature, the solution was neutralized to pH 7 with acetic acid and the resulting solution poured into water (38 mL). The organic layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography over silica gel using pentane/ethyl acetate (1:1) with 1% Et_3N. Yielding 1,1-di(pyridin-2-yl)prop-2-yn-1-ol (690 mg, 3.27 mmol, 60% yield). LC-MS m/z: calculated for $C_{13}H_{10}N_2O$ $[M+H]^+$ 211.08, found: 211.11. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.72 (td, *J* = 7.8, 4.0 Hz, 2H), 7.25 – 7.21 (m, 2H), 6.79 (br s, 1H), 2.75 (s, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 160.44, 148.06, 137.49, 123.22, 121.37, 85.85, 75.73, 73.66.

Di(pyridin-2-yl)(1*H*-1,2,3-triazol-4-yl)methanol (58). The title compound was synthesized from 1,1-di(pyridin-2-yl)prop-2-yn-1-ol (1.10 g, 5.23 mmol) according to the same procedures described for compound **55**. This furnished di(pyridin-2-yl)(1*H*-1,2,3-triazol-4-yl)methanol **58** (580 mg, 2.30 mmol, 44% yield). LC-MS m/z: calculated for $C_{13}H_{11}N_5O$ $[M+H]^+$ 254.10, found: 254.32. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 – 8.51 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.72 (s, 1H), 7.67 (td, *J* = 7.8, 1.8 Hz, 2H), 7.20 – 7.17 (m, 2H), 4.99 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.30, 159.55, 147.58, 136.98, 130.82, 122.75, 121.98, 75.87.

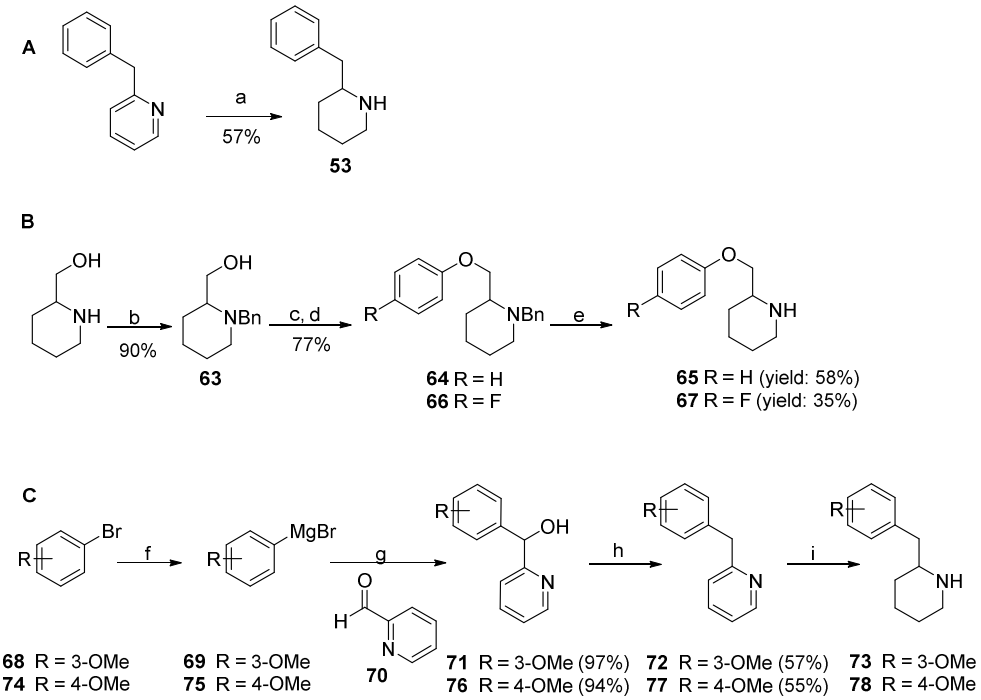
Dicyclohexyl(2*H*-1,2,3-triazol-4-yl)methanol (59). Following the procedure that was described for 1,1-diphenylprop-2-yn-1-ol, dicyclohexylmethanone (0.990 mL, 5.20 mmol) was reacted with ethynyltrimethylsilane (0.710 mL, 5.66 mmol), n-BuLi (3.33 mL, 5.66 mmol) and NaOH (206 mg, 5.15 mmol, in 5 mL MeOH) to obtain 1,1-dicyclohexylprop-2-yn-1-ol (1.06 g, 94%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 1H), 1.93 – 1.25 (m, 22H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 85.8, 73.43, 43.4, 27.7, 26.5, 26.5, 26.3, 26.0. The obtained 1,1-dicyclohexylprop-2-yn-1-ol (804 mg, 3.65 mmol) was converted into its 1,2,3-triazole according to the same procedures described for compound **55**. This furnished **59** (469 mg, 49%). LC-MS m/z: calculated for $C_{15}H_{25}N_3O$ $[M+H]^+$ 264.20, found: 264.24. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.37 (m, 1H), 1.98 – 0.68 (m, 22H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.53, 139.29, 44.11, 29.72, 27.13, 26.54, 26.38, 26.22

2-(2*H*-1,2,3-Triazol-4-yl)propan-2-ol (60). The title compound was synthesized from 2-methyl-3-butyn-2-ol (581 µL, 5.94 mmol) according to the same procedures described for compound **55**. This furnished **60** (635 mg, 84% yield). LC-MS m/z: calculated for $C_5H_9N_3O$ $[M+Na]^+$ 150.06, found: 150.21. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 1.59 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.52, 131.53, 68.48, 30.12.

1-(2*H*-1,2,3-Triazol-4-yl)cyclohexan-1-ol (61). The title compound was synthesized from 1-ethynyl-1-cyclohexanol (642 µL, 5.00 mmol) according to the same procedures described for compound **55**. This furnished **61** (843 mg, quant.). LC-MS m/z: calculated for $C_8H_{13}N_3O$ $[M+Na]^+$ 190.10, found: 190.41. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 1.91 (dt, *J* = 9.2, 4.7 Hz, 4H), 1.81 – 1.71 (m, 2H), 1.68 – 1.52 (m, 3H), 1.42 – 1.23 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.42, 123.03, 76.33, 69.82, 38.24, 38.15, 25.28, 21.90.

1-Phenyl-1-(1*H*-1,2,3-triazol-4-yl)ethan-1-ol (62). The title compound was synthesized from 2-phenylbut-3-yn-2-ol (500 mg, 3.42 mmol) according to the same procedures described for compound **55**. This furnished 1-phenyl-1-(1*H*-1,2,3-triazol-4-yl)ethan-1-ol **62** (453 mg, 2.40 mmol, 80% yield). LC-MS m/z: calculated for $C_{10}H_{11}N_3O$ $[M+H]^+$ 212.08, found 212.10. ^{1}H NMR (400 MHz, MeOD) δ 7.67 (d, *J* = 16.0 Hz, 1H), 7.53 (m, 2H), 7.39 – 7.15 (m, 3H), 2.00 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 156.22, 146.91, 132.63, 127.89, 126.92, 125.10, 75.92, 29.69.

Scheme S.2. Synthesis of 2-substituent piperidine building blocks.



Reagents and conditions: (a) PtO_2, H_2 (1.6 bar), HCl/EtOH (1:25), r.t., 1.5h; (b) $NaBH_4$, AcOH, benzylaldehyde, THF, r.t.; (c) tosylchloride, Et_3N, DMAP, DCM, 0 °C; (d) NaH, corresponding phenol, THF, 0 °C (30 min), reflux (16h); (e) Pd/C (10 mol%), H_2, DCM/MeOH=1:2, r.t; (f) Mg, I_2, dry THF, 60 °C, 15 min; (g) pyridine-2-aldehyde, dry THF, r.t., overnight; (h) H_2 (1 bar), Pd/C, H_2SO_4 (98%)/MeOH (1:5), r.t., 3.5 – 5.5h; (i) H_2 (1.6 bar), PtO_2, HCl/EtOH (1:25), r.t., 1.5h.

2-Benzylpiperidine (53). To a solution of 2-benzylpyridine (3.00 mL, 18.7 mmol) in EtOH (25 mL) was added HCl ((37% in H_2O), 1 mL) and PtO_2 (170 mg, 0.750 mmol, 0.04%). The suspension was purged with hydrogen three times and was put under 1.2 bar of H_2. The reaction was shaken vigorously for 1 hour after which the hydrogen had been absorbed. Repeating this step twice led to the desired hydrogenated adduct. The mixture was filtered and washed with EtOH (2 x 5 mL) and solvents were removed under reduced pressure. The residue was further washed with 10% Na_2CO_3, water, brine and dried over $MgSO_4$, and concentrated under reduced pressure to yield the crude product **53** (1.93 g, 11.0 mmol, 57%), which was used for the next step without further purification. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 5H), 3.20 – 3.09 (m, 1H), 2.71 – 2.59 (m, 2H), 2.59 – 2.47 (m, 2H), 1.98 (br s, 1H), 1.81 – 1.22 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.60, 128.51, 128.12, 127.48, 58.12, 46.44, 42.23, 32.97, 25.82, 24.93.

(1-Benzylpiperidin-2-yl)methanol (63). $NaBH_4$ (1.97 g, 52.1 mmol) was treated with AcOH (10.4 mL, 174 mmol) in anhydrous THF (50 mL) for 30 min at 0 °C. To this solution was added 2-hydroxymethyl piperidine (2.00 g, 17.4 mmol) in anhydrous THF (10 mL), and benzaldehyde (5.30 mL, 51.9 mmol). The reaction mixture was stirred overnight at room temperature. The mixture was filtered and concentrated *in vacuo*. Purification by column chromatography over silica gel (pentane/EtOAc = 10:1 → 1:1) yielded **63** (1-benzyl)2-hydroxymethyl piperidine as yellow oil (3.19 g, 15.5 mmol, 90%). LC-MS *m/z*: calculated for $C_{13}H_{19}NO$ $[M+H]^+$ 206.15, found: 206.16. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.21 (m, 5H), 4.11 (d, *J* = 13.4 Hz, 1H), 3.86 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.61 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.35 (d, *J* = 13.4 Hz, 1H), 3.21 (s, 1H), 2.89 (d, *J* = 11.5 Hz, 1H), 2.47 (s, 1H), 2.14 (t, *J* = 10.5 Hz, 1H), 1.83 – 1.24 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 139.02, 129.01, 128.45, 127.12, 62.48, 61.32, 57.91, 51.13, 27.6, 24.29, 23.52.

1-Benzyl-2-(phenoxymethyl)piperidine (64). ((1-Benzyl)2-hydroxymethyl piperidine) (200 mg, 0.975 mmol) was dissolved in DCM (2 mL) and cooled to 0 °C. To this were added Et_3N (215 µL, 2.93 mmol), DMAP (24.0 mg, 0.195 mmol) and *p*-toluenesulfonyl chloride (558 mg, 2.93 mmol). The reaction mixture was stirred at 0°C for 16h, warming up to room temperature 20 °C overnight. The mixture was concentrated *in vacuo* and dissolved in DCM (50 mL). The organic layer was washed with H_2O (25 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was obtained. Phenol (175 mg, 1.86 mmol) was reacted with NaH (60% dispersion, 74.3 mg, 1.86 mmol) in anhydrous THF (2 mL) at 0 °C for 30 min. After which the crude product from above (139 mg, 0.62 mmol) was added and the mixture heated to reflux for 16h. The reaction mixture was concentrated *in vacuo* and dissolved in DCM (25 mL). Organic layer was washed with 1M NaOH (2 x 10 mL), brine (10 mL), and dried over $MgSO_4$, filtered,. concentrated and purified over silica gel (pentane/EtOAc 10:1 → 1:1), yielding **64** (134 mg, 0.477 mmol, 77%). LC-MS m/z: calculated for $C_{19}H_{23}NO$ $[M+H]^+$ 282.18, found: 282.34. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.22 (m, 7H), 7.03 – 6.86 (m, 3H), 4.23 (dd, *J* = 9.8, 4.9 Hz, 1H), 4.14 (d, *J* = 13.7 Hz, 1H), 4.04 (dd, *J* = 9.8, 4.7 Hz, 1H), 3.44 (d, *J* = 13.7 Hz, 1H), 2.90 – 2.74 (m, 2H), 2.20 – 2.09 (m, 1H), 1.92 – 1.83 (m, 1H), 1.79 – 1.37 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.89, 129.43, 128.92, 128.13, 126.75, 120.67, 118.90, 114.64, 70.32, 60.45, 59.03, 52.04, 29.45, 25.42, 23.46.

2-(Phenoxymethyl)piperidine (65). 1-Benzyl-2-(phenoxymethyl)piperidine (118 mg, 0.420 mmol) was treated with 10% palladium on carbon (44.0 mg, 0.042 mmol) in MeOH/DCM (2:1, 1.5 mL) under hydrogen atmosphere for 16h at room temperature. After reaction was completed, solvents were removed under reduced pressure and mixture was dissolved in EtOAc (30 mL). Organic layer was washed with H_2O (10 mL), sat. $NaHCO_3$ (10 mL), and brine (10 mL) before dried over $MgSO_4$, concentrated and purified over silica gel (pentane/EtOAc 10:1 → 1:1) yielding **65** (47.0 mg, 0.246 mmol, 58%). LC-MS *m/z*: calculated for $C_{12}H_{17}NO$ $[M+H]^+$ 192.13, found: 192.15. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 2H), 6.97 – 6.85 (m, 3H), 3.89 (dd, *J* = 9.0, 3.6 Hz,

1H), 3.80 (t, J = 9.0 Hz, 1H), 3.15 – 3.06 (m, 1H), 3.00 – 2.90 (m, 1H), 2.69 (td, J = 11.6, 2.7 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.71 – 1.59 (m, 2H), 1.55 – 1.19 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 129.4, 120.8, 114.9, 72.54, 53.1, 46.6, 28.7, 26.3, 24.4.

2-((4-Fluorophenoxy)methyl)piperidine (67). ((1-Benzyl)2-hydroxymethyl piperidine) (200 mg, 0.974 mmol) was dissolved in DCM (2 mL) and cooled to 0 °C. To this were added Et_3N (407 µL, 2.92 mmol), DMAP (24.0 mg, 0.196 mmol) and *p*-toluenesulfonyl chloride (558 mg, 2.90 mmol). The reaction mixture was stirred at 0 °C for 16h, slowly warming up to room temperature. The mixture was concentrated *in vacuo* and dissolved in DCM (50 mL). The organic layer was washed with H_2O, brine, dried over $MgSO_4$, filtrated and the crude tosylate product was obtained. 4-Fluorophenol (752 mg, 6.71 mmol) was reacted with NaH (60% dispersion, 179 mg, 4.47 mmol) over 30 min at 0 °C in anhydrous DMF (5 mL). The crude tosylate product from above in anhydrous DMF (2 mL) was added to the reaction mixture and stirred at 70 °C for 18h. The mixture was cooled to room temperature, diluted with H_2O (50 mL) and extracted with DCM (3 x 75 mL). Organic fractions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude **66** was then dissolved in MeOH/DCM (6 mL, 2:1), 10% Pd/C (200 mg) was added and the mixture was flushed with hydrogen gas three times. The reaction mixture was stirred under hydrogen atmosphere for 16h. Purification over silica gel using pentane : EtOAc = 1:1 as the eluent with 1% Et_3N to yield product **67** (71.0 mg, 0.340 mmol, 35%). LC-MS m/z: calculated for $C_{12}H_{16}FNO$ $[M+H]^+$ 210.12, found: 210.41. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (t, J = 8.7 Hz, 2H), 6.85 – 6.79 (m, 2H), 3.84 (dd, J = 8.9, 3.6 Hz, 1H), 3.74 (t, J = 8.6 Hz, 1H), 3.09 (d, J = 11.8 Hz, 1H), 2.98 – 2.88 (m, 1H), 2.68 (td, J = 11.7, 2.7 Hz, 1H), 1.88 – 1.78 (m, 1H), 1.68 – 1.59 (m, 2H), 1.55 – 1.31 (m, 2H), 1.30 – 1.17 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.32 (d, J = 238.2 Hz), 155.01 (d, J = 2.1 Hz), 115.68 (d, J = 23.0 Hz), 115.52 (d, J = 7.9 Hz), 73.31, 55.82, 46.53, 28.62, 26.28, 24.32.

(3-Methoxyphenyl)(pyridin-2-yl)methanol (71). After flame-drying and flushing with argon, the flask containing magnesium turnings (156 mg, 6.50 mmol) was charged, dry THF (2.5 mL) and a catalytic amount of iodine were added under argon atmosphere. Then, 1/10 of a argon flushed solution of 1-bromo-3-methoxybenzene **68** (0.675 mL, 5.33 mmol) in dry THF (2.5 mL) was added at room temperature. The mixture was heated with a heating gun until initiation of the reaction was observed. The rest of the 1-bromo-3-methoxybenzene solution was then added dropwise, and the reaction mixture was stirred under reflux for 15 min, after which it was allowed to cool to room temperature. The solution containing Grignard reagent **69** was cooled to 0 °C and pyridine-2-aldehyde **70** (0.430 mL, 4.52 mmol) was added dropwise under argon atmosphere. Extra dry THF was added (2.5 mL) and the reaction mixture was allowed to warm to room temperature while stirring overnight. After quenching with aqueous saturated NH_4Cl (35 mL), the aqueous layer was extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane/EtOAc = 10:1 → 2:1) afforded compound **71** (940 mg, 4.37 mmol, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, J = 4.8 Hz, 1H), 7.52 (td, J = 7.7, 1.7 Hz, 1H), 7.21 – 7.17 (m, 2H), 7.10 – 7.05 (m, 1H), 6.95 – 6.93 (m, 2H), 6.78 – 6.74 (m, 1H), 5.72 (s, 1H), 5.56 (br s, 1H), 3.69 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

161.16, 159.64, 147.75, 144.76, 136.81, 129.40, 122.31, 121.11, 119.20, 113.19, 112.20, 75.03, 55.02. LC-MS m/z: calculated for $C_{13}H_{13}NO_2$ $[M+H]^+$ 216.10, found 215.73.

2-(3-Methoxybenzyl)pyridine (72). A hydrogenation flask containing compound **71** (100 mg, 0.465 mmol) in a mixture of H_2SO_4 (98%)/MeOH (1:5, 5.6 mL) was flushed with argon. Pd/C (10%, 250 mg) was added and the mixture was hydrogenated at 1 bar at room temperature for 4h. The reaction mixture was then filtered, concentrated *in vacuo* and neutralize with aqueous NaOH solution (1.0 M). The aqueous layer was extracted with DCM (3 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane/EtOAc = 10:1 → 4:1) afforded compound **72** (51.0 mg, 0.256 mmol, 57%). LC-MS m/z: calculated for $C_{13}H_{13}NO$ $[M+H]^+$ 200.10, found 200.41. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 7.3 Hz, 1H), 7.56 (td, *J* = 7.7, 1.8 Hz, 1H), 7.27 – 7.18 (m, 1H), 7.14 – 7.06 (m, 2H), 6.87 – 6.80 (m, 2H), 6.76 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.13 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.88, 159.83, 149.36, 141.08, 136.66, 129.62, 123.22, 121.57, 121.36, 114.87, 111.87, 55.22, 44.79.

2-(3-Methoxybenzyl)piperidine (**73**). A hydrogenation flask containing compound **72** (51.0 mg, 0.256 mmol) in a mixture of HCl/EtOH (1:25, 6.7 mL) was flushed with argon. PtO_2 (4.60 mg, 20.3 μmol) was added and the mixture was hydrogenated at 1 bar at room temperature for 2h. The reaction mixture was filtered, concentrated *in vacuo* and coevaporated with EtOH (3 x 10 mL) and with toluene (3 x 10 mL) to give crude compound **73**, which was used in the following step without any further purification. LC-MS m/z: calculated for $C_{13}H_{19}NO$ $[M+H]^+$ 206.10, found 206.21. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.08 (m, 1H), 6.96 – 6.58 (m, 3H), 3.79 (s, 3H), 3.57 (d, *J* = 7.0 Hz, 2H), 3.28 (br s, 1H), 2.97 (d, *J* = 5.3 Hz, 2H), 2.08 – 1.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.46, 137.00, 129.48, 121.67, 114.95, 112.34, 58.50, 55.38, 49.03, 39.91, 29.32, 27.39, 22.25.

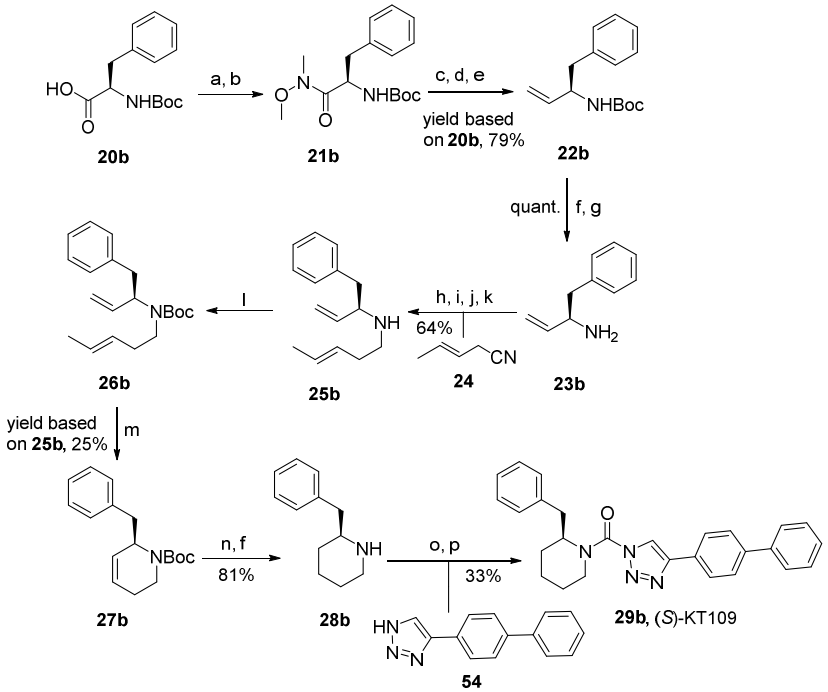
(4-Methoxyphenyl)(pyridin-2-yl)methanol (**76**). After flame-drying and flushing with argon, the flask containing magnesium turnings (156 mg, 6.50 mmol) was charged dry THF (2.5 mL) and a catalytic amount of iodine were added. Then, 1/10 of a argon flushed solution of 1-bromo-4-methoxybenzene **74** (0.675 mL, 5.33 mmol) in dry THF (2.5 mL) was added at room temperature. The mixture was heated with a heating gun until initiation of the reaction was observed. The rest of the 1-bromo-4-methoxybenzene solution was added dropwise, and the reaction mixture was stirred under reflux for 15 min, after which it was allowed to cool to room temperature. The solution containing Grignard reagent **75** was then further cooled to 0 °C and pyridine-2-aldehyde **70** (0.430 mL, 4.52 mmol) was added dropwise under argon atmosphere. Extra dry THF(2.5 mL) was added and the reaction mixture was allowed to warm to room temperature while stirring overnight. After quenching with aqueous saturated NH_4Cl (35 mL), the aqueous layer was extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane/EtOAc = 10:1 → 2:1) afforded compound **76** (910 mg, 4.23 mmol, 94%). LC-MS m/z: calculated for $C_{13}H_{13}NO_2$ $[M+H]^+$ 216.10, found: 215.73. ^{1}H NMR (400 MHz, MeOD) δ 8.45 – 8.37 (m, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.25 (m, 3H), 6.89 – 6.81 (m, 2H), 5.76 (s, 1H), 4.91 (s, 1H), 3.75

(s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 164.75, 160.65, 149.06, 138.84, 136.64, 129.19, 123.73, 122.06, 114.76, 77.06, 55.66.

2-(4-Methoxybenzyl)pyridine (77). The title compound was prepared from compound **76** (100 mg, 0.465 mmol) and Pd/C (10%, 250 mg) in H_2SO_4/MeOH (1:5, 8.4 mL) according to the same procedures described for compound **72**. Purification by column chromatography (pentane/EtOAc = 10:1 → 4:1) afforded compound **77** (80.0 mg, 0.404 mmol, 55%) as a yellow oil. LC-MS m/z: calculated for $C_{13}H_{13}NO$ $[M+H]^+$ 200.11, found: 199.87. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 3.8 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 7.7 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.09 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.39, 158.19, 149.27, 136.55, 131.60, 130.07, 122.99, 121.17, 114.01, 55.22, 43.81.

2-(4-Methoxybenzyl)piperidine (78). The title compound was prepared from compound **77** (68.0 mg, 0.342 mmol) and PtO_2 (6.20 mg, 27.3 μmol) in HCl/EtOH (1:25, 10 mL) according to the same procedures described for compound **72**. This furnished crude compound **78**, which was used in the following steps without any further purification. LC-MS m/z: calculated for $C_{13}H_{19}NO$ $[M+H]^+$ 206.16, found 205.93. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 2H), 6.82 (s, 2H), 3.77 (s, 3H), 3.50 (br s, 2H), 3.17 (br s, 1H), 2.93 (br s, 2H), 2.03 – 1.66 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.59, 130.67, 127.72, 114.14, 58.91, 55.37, 45.58, 39.03, 29.64, 27.53, 22.45.

Scheme S.3. Enantioselective synthesis of (*S*)-KT109



Reagents and conditions: (a) Me(OMe)NH·HCl; (b) EDCI, NMM; (c) $LiAlH_4$; (d) H_3O^+; (e) $(Ph)_3P{=}CH_2$; (f) MeOH, HCl; (g) NaOH; (h) compound **24**, diethyl ether, DIBAL-H, -80 °C to 0 °C; (i) MeOH, -90 °C; (j) corresponding amine **23b** (3 equiv), r.t., 20h; (k) $NaBH_4$, 0 °C to r.t., 5h; (l) Boc_2O, Et_3N, THF, 50 °C, 20h; (m) Grubbs I cat. 4 mol %,

DCM, reflux, 48h; (n) H_2, Pd/C, MeOH; (o) DIPEA, Triphosgene, THF, 0 ^oC; (p) DIPEA, DMAP, triazole , THF, 60 ^oC.

***(S,E)*-N-(1-Phenylbut-3-en-2-yl)pent-3-en-1-amine (25a)**. Under an argon atmosphere, a flame dried three necked reaction flask was charged with a solution of 3-pentene nitrile **24** (285 mg, 3.34 mmol) in dry diethyl ether. At -78 °C a 1.0 M solution of DIBAL-H (12 mL, 12 mmol) in toluene was added drop wise. The reaction was warmed slowly on the cooling bath until 0 °C in circa 2h. After re-cooling to -90 °C, dry MeOH (10 mL) was added at once. After 5 min followed by a solution of (*S*)-1-phenylbut-3-en-2-amine [1, 2] **23a** (1.80 g, 12.2 mmol, e.e. = 99%) in MeOH (10 mL). The cooling bath was removed and the mixture stirred at room temperature for 6h. Subsequently, an excess of $NaBH_4$ (870 mg, 22.9 mmol) was added at 0 °C in two portions with a five minute interval. The reaction was left stirring on the ice bath and slowly warmed up to room temperature overnight. The reaction mixture was poured into 0.8 M aqueous NaOH solution (80 mL) and extracted with diethyl ether (3 x 30 mL). The organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as an orange oil that was purified by silica gel column chromatography using pentane: EtOAc : TEA = 9 : 1 : 0 → 90 : 10 : 5 → 85 : 15 : 5 as the eluent to give the target compound (315 mg, 1.47 mmol, 44% yield). $[\alpha]_D^{23}$ = -9.2 (c = 1.0, $CHCl_3$). HRMS calculated for $C_{15}H_{21}N$ $[M+H]^+$ 202.1590; found: 202.1593. IR (film) 3063, 3026, 2967, 2918, 2818, 1495, 1554, 1111, 966, 918. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 2H), 7.20 (m, 3H), 5.65 (ddd, *J* = 16.9, 10.5, 8.1 Hz, 1H), 5.58 – 5.36 (m, 2H), 5.16 – 5.00 (m, 2H), 3.31 (m, 1H), 3.25 – 3.14 (m, 1H), 3.03 – 2.95 (m, 1H), 2.77 (d, *J* = 6.9 Hz, 2H), 1.64 (dd, *J* = 6.0, 1.2 Hz, 3H), 1.42 – 1.34 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.65, 138.51, 129.38, 129.29, 128.31, 127.09, 126.25, 116.14, 62.27, 49.09, 42.45, 17.77.

***tert*-Butyl *(S,E)*-pent-3-en-1-yl(1-phenylbut-3-en-2-yl)carbamate (26a)**. The amine from above **25a** (315 mg, 1.47 mmol) was dissolved in a mixture of THF (20 mL) and Et_3N (1 mL). Boc_2O (450 mg, 2.06 mmol) was added and the reaction refluxed overnight. TLC analysis confirmed complete conversion of the amine and after evaporation of the solvents and silica gel column chromatography using pentane: EtOAc = 98 : 2 as the eluent afforded the Boc-protected amine (425 mg, 1.35 mmol, 92% yield). $[\alpha]_D^{22}$ = -58 (c =1.0, $CHCl_3$). HRMS calculated for $C_{20}H_{29}NO_2$ $[M+H]^+$: 316.2271; found: 316.2272. IR (film) 3029, 2980, 2936, 1690, 1456, 1396, 1371, 1308, 1256, 1211, 1169, 1117, 1069. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 – 6.77 (m, 5H), 5.96 (ddd, *J* = 16.6, 10.5, 6.0 Hz, 1H), 5.55 – 5.20 (m, *J* = 33.4 Hz, 2H), 5.17 – 5.07 (m, 2H), 4.48 (m, 1H), 3.41 – 2.69 (m, 4H), 2.38 – 1.92 (m, 2H), 1.62 (d, *J* = 6.1 Hz, 3H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.09, 138.59, 137.32, 129.26, 129.20, 128.16, 128.11, 126.62, 126.13, 115.91, 79.16, 61.12, 45.76, 38.24, 33.12, 28.32, 17.93.

***tert*-Butyl *(S)*-6-benzyl-3,6-dihydropyridine-1(2H)-carboxylate (27a)**. The diene from above (425 mg, 1.35 mmol) was dissolved in DCM (10 mL) and purged with argon. After the addition of Grubb's 1st generation catalyst (42.0 mg, 0.050 mmol, 3.6 mol%) and refluxing overnight TLC analysis confirmed complete conversion. The solvent was evaporated and the crude product purified by silica gel column chromatography using pentane : EtOAc = 97 : 3 as the eluent to afford the title compound (252 mg, 0.920 mmol, 68% yield). $[\alpha]_D^{21}$ = +161 (c = 1.0, $CHCl_3$). HRMS calculated for $C_{17}H_{23}NO_2$ $[M+H]^+$:

274.1802; found: 274.1802. ^{1}H NMR (400 MHz, $CDCl_3$, 60 ^{o}C) δ 7.28 – 7.21 (m, 2H), 7.20 – 7.14 (m, 3H), 5.79 (dd, *J* = 10.3, 6.1 Hz, 1H), 5.54 (dt, *J* = 10.3, 3.3 Hz, 1H), 4.54 (s, 1H), 4.11 (s, 1H), 2.89 (dd, *J* = 13.0, 6.2 Hz, 1H), 2.83 – 2.67 (m, 2H), 2.15 (m, 1H), 1.88 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, 60 ^{o}C) δ 154.28, 138.23, 129.36, 128.10, 127.94, 126.06, 125.38, 79.17, 53.47, 40.20, 36.30, 28.29, 24.85.

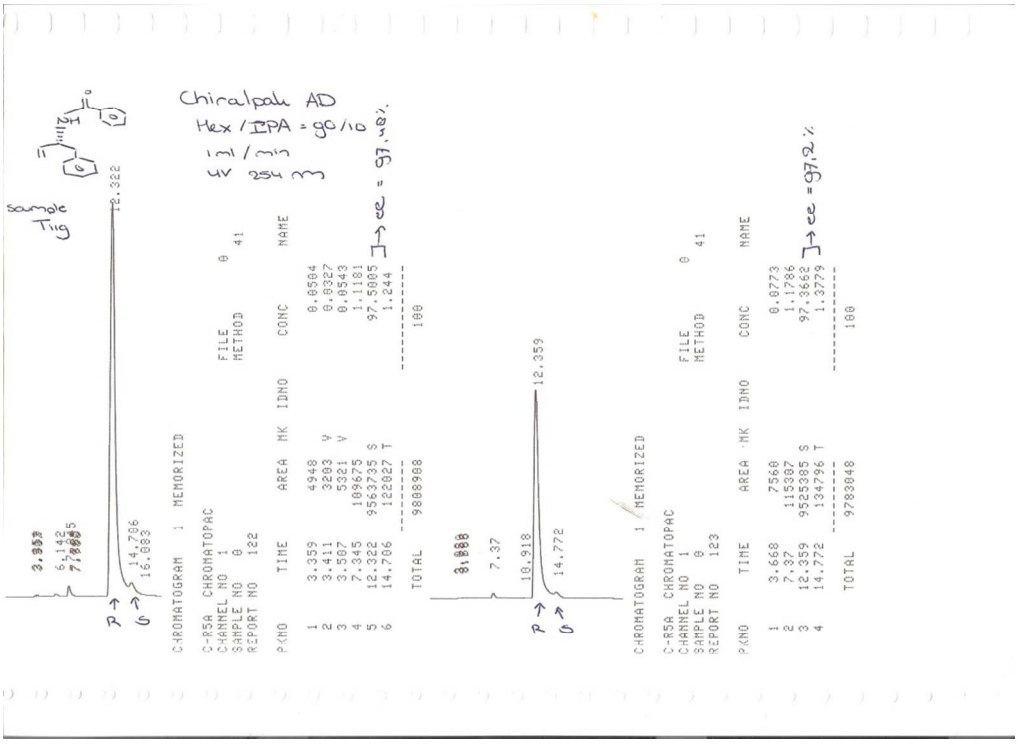
***(R)*-2-Benzylpiperidine (28a)**. The compound from above **27a** (680 mg, 2.49 mmol) was dissolved in MeOH (10 mL) and an aqueous 6.0 M HCl solution (1 mL) and Pd/C-10% (24 mg) were added subsequently. The reaction was stirred overnight under a balloon of hydrogen. After filtering over a Whatman® filter and evaporation of the solvents, (*R*)-2-benzylpiperidine hydrochloride was obtained. The salt from above was dissolved in water (20 mL) and washed with EtOAc (2 x 10 mL). The water layer was basified with an aqueous 4.0 M NaOH solution (4 mL) and extracted with $CHCl_3$ (4 x 10 mL). The combined $CHCl_3$ layers were dried over Na_2SO_4, filtered and concentrated to give the crude material as a yellow oil that was purified by silica gel column chromatography (pentane : EtOAc : Et_3N = 80 : 15 : 5) to afford *(R)*-2-benzylpiperidine (306 mg, 1.75 mmol, 70%). $[\alpha]_D^{23}$ = -13 (c = 0.5, $CHCl_3$). HRMS calculated for $C_{12}H_{17}N$ $[M+H]^+$ 176.1432; found: 176.1434. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.23 – 7.16 (m, 3H), 2.98 (d, *J* = 11.5 Hz, 1H), 2.74 – 2.62 (m, 2H), 2.61 – 2.44 (m, 2H), 1.89 – 1.72 (m, 2H), 1.68 (d, *J* = 12.7 Hz, 1H), 1.57 (d, *J* = 12.5 Hz, 1H), 1.43 (m, 1H), 1.36 – 1.13 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.11, 129.12, 128.27, 126.06, 58.15, 47.05, 43.83, 32.83, 26.10, 24.77.

***(R)*-(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(2-benzylpiperidin-1-yl)methanone (29a**, *(R)*-KT109**)**. A solution of *(R)*-2-benzylpiperidine (40.0 mg, 0.229 mmol) in THF was treated with DIPEA (0.120 mL, 0.685 mmol) and bis(trichloromethyl) carbonate (33.9 mg, 0.114 mmol) and the reaction mixture was stirred for 30 min at 0 ^{o}C. The mixture was poured into water and extracted with ethyl acetate (3 times). The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The intermediate was dissolved in THF and DIPEA (0.120 mL, 0.685 mmol), DMAP (27.9 mg, 0.228 mmol) and triazole (55.5 mg, 0.251 mmol) were added to the solution. The mixture was stirred for 2h at 60 ^{o}C and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flush column chromatography (pentane/EtOAc = 100 : 1 → 8 : 1) to afford 1,4-triazole urea *(R)*-KT109 (24.0 mg, 0.057 mmol, 30% yield) as top TLC spot. $[\alpha]_D^{22}$ = -14 (*c* = 0.1, $CHCl_3$). The enantiomeric purity was determined on a Daicel Chiralcel OD-H column (4.6 X 250 mm, 20:80 IPA/Hex, flow rate of 1 mL/min): 14.4 min, e.e.>95%. HRMS calculated for $C_{27}H_{26}N_4O$ $[M+H]^+$ 423.2179, found: 423.2179. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (br s, 1H), 7.75 – 7.67 (m, 4H), 7.53 – 7.48 (m, 2H), 7.43 – 7.04 (m, 6H), 4.90 (br s, 1H), 4.40 (br d, *J* = 16.0 Hz, 1H), 3.39 – 3.26 (m, 2H), 2.74 (br s, 1H), 2.07 – 1.69 (m, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 146.14, 141.28, 140.49, 137.99, 129.20, 128.88, 128.74, 128.64, 127.61, 127.57, 127.03, 126.63, 126.18, 120.56, 57.20, 40.80, 36.41, 29.65, 25.44, 18.75.

(*R*)-1-phenylbut-3-en-2-amine (23b). Compound **22b** was prepared according the procedure reported [2] on 48 mmol scale, affording 9.40 g of compound **22b** (79%, $[\alpha]_D^{23}$ = -34 (*c* = 1.0, $CHCl_3$); Lit [2]: $[\alpha]_D^{25}$ = -37 (*c* = 0.28, $CHCl_3$)). The Boc-protetected amine

22b (9.40 g, 38.1 mmol) was dissolved in a mixture of MeOH (100 mL) and aqueous 6.0 M HCl (20 mL). After TLC confirmed total conversion of compound **22b**, evaporation of the solvents afforded a white solid that was dissolved in water (50 mL). After addition of aqueous 8.0 M NaOH (10 mL), extraction with chloroform (4 x 30 mL), drying ($MgSO_4$), filtering and evaporation of the solvent, amine **23b** was obtained as a pale brown liquid that was used without further purification. $[\alpha]_D^{20}$ = -14 (*c* = 1.0, $CHCl_3$); Lit[3] $[\alpha]_D^{25}$ = -15 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 5H), 5.88 (ddd, *J* = 17.2, 10.3, 6.3 Hz, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 5.03 (d, *J* = 10.3 Hz, 1H), 3.59 (q, *J* = 6.3 Hz, 1H), 2.82 (dd, *J* = 13.3, 5.3 Hz, 1H), 2.61 (dd, *J* = 13.3, 8.3 Hz, 1H), 1.28 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.30, 138.65, 129.29, 128.28, 126.22, 113.52, 55.36, 44.23. For chiral HPLC analysis amine **23b** was derivatized as its benzoate, followed by analysis on a Daicel Chiralpak AD column (250 x 4.5 mm, 10µm particle size). Eluent hexane / 2-propanol = 90 /10, 1.0 mL / min., detection UV 254 nm. (*R*)-Enantiomer, R_t = 12.3 min (97.4%); (*S*)-enantiomer, R_t = 14.7 min (1.3%). See figure below.

*Chiral HPLC analysis for N-benzoylated compound **23b**.*



***tert*-Butyl *(R,E)*-pent-3-en-1-yl(1-phenylbut-3-en-2-yl)carbamate (26b)**. *(R,E)*-N-(1-Phenylbut-3-en-2-yl)pent-3-en-1-amine **25b** was prepared from 3-pentene nitrile **24** (586 mg, 7.23 mmol) and (*R*)-1-phenylbut-3-en-2-amine **23b** (e.e. = 97%, 3.50 g, 13.8 mmol) in 64% yield (1.24 g, ≈80% purity, 4.61 mmol) following the procedure as described for **25a**. This material was converted into Boc-protected compound **26b** as described for **26a**. The Boc-protected amine **26b** was obtained as colorless oil contaminated with circa 40 mol% Boc_2O (1.22 g). Analytical data from a pure sample: $[\alpha]_D^{22}$ = +66 (c =1.0 $CHCl_3$). HRMS calculated for $[C_{20}H_{29}NO_2+H]^+$: 316.2271; found: 316.2272. IR 2972, 2930, 1690, 1454, 1404, 1366, 1252, 1169, 1136, 966. ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.33 – 7.15 (m, 5H), 5.96 (ddd, *J* = 16.7, 10.7, 6.0 Hz, 1H), 5.48 – 5.25 (m, 2H), 5.19 – 5.01 (m, 2H), 4.67 – 4.28 (m, 1H), 3.16 – 2.80 (m, 4H), 2.32 – 1.85 (m, 2H), 1.62 (d, *J* = 6.1 Hz, 3H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.09, 138.61, 137.41, 129.27, 129.21, 128.18, 128.13, 126.63, 126.14, 115.92, 79.31, 77.32, 77.00, 76.68, 60.18, 45.80, 38.25, 28.34, 17.93.

***tert*-Butyl *(R)*-6-benzyl-3,6-dihydropyridine-1(2*H*)-carboxylate (27b)**. Prepared as described for **27a**. The Boc-protected diene from above (1.22 g, 3.87 mmol) afforded the title compound in 25% overall yield (491 mg, 1.80 mmol). $[\alpha]_D^{21}$ = -172 (c =1.0 $CHCl_3$). HRMS calculated for $C_{17}H_{23}NO_2$ $[M+H]^+$: 274.1802; found: 274.1803. IR 2974, 2926, 1690, 1454, 1416, 1391, 1364, 1337, 1279, 1250, 1171, 1107. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.08 (m, 5H), 5.81 (s, 1H), 5.63 – 5.48 (m, 1H), 4.68 – 4.42 (m, 1H), 4.33 – 3.94 (m, 1H), 2.99 – 2.82 (m, 1H), 2.84 – 2.67 (m, 2H), 2.19 (m, 1H), 2.02 – 1.83 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.34, 138.25, 129.40, 128.22, 127.70, 126.15, 125.63, 79.33, 53.84, 40.27, 35.87, 28.29, 24.85.

(*S*)-2-Benzylpiperidine (28b). A solution of *tert*-butyl *(R)*-6-benzyl-3,6-dihydropyridine-1(2*H*)-carboxylate **27b** (277 mg, 1.01 mmol) in methanol (10 mL) and 6.0 M HCl (1 mL) was purged with argon and Pd/C 10% (100 mg) was added subsequently. The flask was sealed with a septum, placed under a balloon of hydrogen, and stirred vigorously overnight. The mixture was filtered over a Whatman® filter and the solvents evaporated to afford the hydrochloride as a white foam that was dissolved in methanol (1 mL) and loaded onto a flash silica gel column that was eluted subsequently with pentane/EtOAc/Et_3N = 97:3:0 → 9:1:0 → 85:10:5 → 75:20:5 to yield the target compound as a pale yellow oil (142 mg, 81%). $[\alpha]_D^{27}$ = +14 (c = 1.0, $CHCl_3$). HRMS calculated for $[C_{12}H_{17}N+H]^+$: 176.1434; found: 176.1433. IR 3026, 2928, 2851, 2799, 1495, 1452, 1441, 1331, 1319, 1119, 1053. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.20 (dt, *J* = 7.1, 2.9 Hz, 3H), 2.99 (ddt, *J* = 11.5, 3.9, 2.1 Hz, 1H), 2.76 – 2.63 (m, 2H), 2.63 – 2.46 (m, 1H), 2.04 (s, 1H), 1.83 – 1.74 (m, 1H), 1.68 (d, *J* = 12.7 Hz, 1H), 1.62 – 1.52 (m, 1H), 1.44 (qt, *J* = 12.2, 3.7 Hz, 1H), 1.37 – 1.13 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.10, 129.14, 128.30, 126.08, 58.17, 47.03, 43.80, 32.79, 26.08, 24.76.

***(S)*-(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(2-benzylpiperidin-1-yl)methanone (29b**, (*S*)-KT109**)**. The title compound was synthesized from (*S*)-2-benzylpiperidine **28b** (40.0 mg, 0.229 mmol) according to the procedures described for *(R)*-KT109. This yielded (*S*)-(4-([1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)(2-benzylpiperidin-1-yl)methanone (*S*)-KT109 (66.0 mg, 0.156 mmol, 33 % yield). $[\alpha]_D^{22}$ = 13 (*c* = 1.0, $CHCl_3$). The enantiomeric purity was determined on a Daicel Chiralcel OD-H column (4.6 X 250 mm, 20:80 IPA/Hex, flow rate of 1 mL/min): 18.4 min, e.e.>95%. HRMS calculated for $C_{27}H_{27}N_4O$ $[M+H]^+$ 423.2179, found: 423.2179. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (s, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 4.0 Hz, 2H), 7.49 – 7.41 (m, 3H), 7.39 – 7.33 (m, 1H), 7.21 – 7.01 (m, 5H), 4.85 (s, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 3.35 (br d, *J* = 12.0 Hz, 1H), 3.21 (s, 1H), 2.69 (s, 1H), 1.93 – 1.69 (m, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 146.13, 142.13, 141.37, 140.55, 138.05, 129.25, 128.94, 128.79, 128.74, 127.67, 127.62, 127.08, 126.68, 126.24, 120.61, 50.75, 40.28, 36.47, 28.67, 25.50, 19.08.

(*3R,6S*)-6-Benzyl-3-((*tert*-butyldiphenylsilyl)oxy)-1,2,3,6-tetrahydropyridine (45). To a solution of *tert*-butyl (*3R,6S*)-6-benzyl-3-((*tert*-butyldiphenylsilyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate **44** [1] (120 mg, 0.227 mmol) in DCM was added 20% TFA, the reaction mixture was stirred at r.t. for 2.5h until TLC showed the reaction was completed. When the reaction is finished, the mixture was co-evaporated with toluene (3 times), the residue was diluted with ethyl acetate and washed with 10% Na_2CO_3, water, brine and dried over $MgSO_4$, and concentrated under reduced pressure. Filtering and concentration under reduced pressure afforded the crude product that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.59 (m, 4H), 7.45 – 7.29 (m, 8H), 7.28 – 7.18 (m, 3H), 5.72 – 5.61 (m, 2H), 4.18 (br s, 1H), 4.09 (br s, 1H), 3.29 (br d, *J* = 31.9 Hz, 2H), 3.09 (br d, *J* = 48.0 Hz, 2H), 1.02 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.86, 135.72, 134.10, 132.91, 132.42, 130.36, 130.24, 129.69, 129.12, 128.39, 128.11, 127.91, 127.74, 126.24, 61.00, 54.53, 48.13, 38.18, 26.75, 19.01.

***tert*-Butyl *(2R,5R)*-2-benzyl-5-methoxypiperidine-1-carboxylate (51)**. To a solution of *tert*-butyl *(2R,5R)*-2-benzyl-5-hydroxypiperidine-1-carboxylate **50** [1]. (100 mg, 0.343 mmol) and NaH (60%, 34.3 mg, 0.858 mmol) in DMF (3 mL) at 0 °C, MeI (0.064 mL, 1.03 mmol) was added dropwise with continuous stirring, and the mixture was allowed to stand at room temperature for 24h. The mixture was diluted with water (10 mL), and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/ethyl acetate = 20:1 → 5:1) to furnish *tert*-butyl (*2R,5R*)-2-benzyl-5-methoxypiperidine-1-carboxylate (87.0 mg, 0.285 mmol, 83% yield). $[\alpha]_D^{22}$ = -31 (*c* = 0.8, $CHCl_3$). LC-MS m/z: calculated for $C_{18}H_{27}NO_3$ $[M+H]^+$ 306.20, found: 306.27. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 7.18 – 7.12 (m, 3H), 4.39 (br s, 2H), 3.41 (s, 3H), 3.18 (t, *J* = 4.0 Hz, 1H), 2.97 – 2.87 (m, 1H), 2.74 – 2.58 (m, 2H), 1.96 (br s, 1H), 1.66 – 1.49 (m, 3H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.82, 139.12, 129.22, 128.47, 126.29, 79.61, 75.89, 56.33, 52.24, 42.06, 35.94, 26.25, 26.21, 25.84.

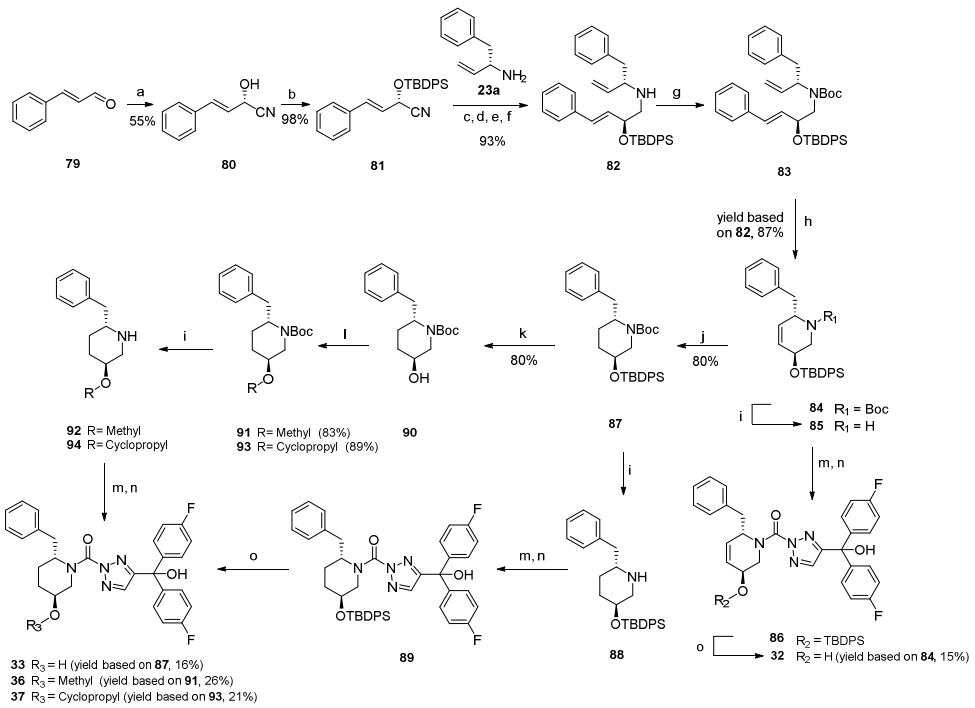
***(2R,5R)*-2-Benzyl-5-methoxypiperidine.** To a solution of compound *tert*-butyl *(2R,5R)*-2-benzyl-5-methoxypiperidine-1-carboxylate **51** (44.0 mg, 0.144 mmol) in DCM was added 20% TFA, the reaction mixture was stirred at r.t. for 2.5h until TLC showed the reaction was completed. When the reaction is finished, the mixture was co-evaporated with toluene (3 times), the residue was diluted with ethyl acetate and washed with 10% Na_2CO_3, water, brine and dried over $MgSO_4$, and concentrated under reduced pressure. Filtering and concentration under reduced pressure afforded the crude product *(2R,5R)*-2-benzyl-5-methoxypiperidine that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 3H), 7.18 (d, *J* = 6.5 Hz, 2H), 3.57 (s, 1H), 3.46 (br s, 1H), 3.33 (s, 4H), 3.17 (br d, *J* = 11.6 Hz, 1H), 3.03 (br s, 1H), 2.84 (br s, 1H), 2.07 (d, *J* = 15.0 Hz, 1H), 1.92 – 1.73 (m, 1H), 1.61 (d, *J* = 13.4 Hz, 1H), 1.53 – 1.41 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.33, 129.47, 128.91, 127.35, 70.16, 58.07, 56.12, 47.01, 39.64, 25.73, 22.63.

***tert*-Butyl *(2R,5R)*-2-benzyl-5-(cyclopropylmethoxy)piperidine-1-carboxylate (52)**. To a solution of *tert*-butyl *(2R,5R)*-2-benzyl-5-hydroxypiperidine-1-carboxylate (100 mg, 0.343 mmol) and NaH (60%, 24.7 mg, 1.03 mmol) in DMF (3 mL) at 0 °C,

(bromomethyl)cyclopropane (139 mg, 1.03 mmol) was added dropwise with continuous stirring, and the mixture was allowed to stand at room temperature for 24h. The mixture was diluted with water (10 mL), and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/ethyl acetate = 20:1 → 5:1) to furnish *tert*-butyl *(2R,5R)*-2-benzyl-5-(cyclopropylmethoxy)piperidine-1-carboxylate (96.0 mg, 0.277 mmol, 81% yield). $[\alpha]_D^{22} = -32$ (*c* = 0.9, $CHCl_3$). LC-MS m/z: calculated for $C_{21}H_{31}NO_3$ $[M+H]^+$ 346.23, found: 346.40. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 2H), 7.20 – 7.15 (m, 3H), 4.58 – 4.11 (m, 2H), 3.37 (d, *J* = 4.0 Hz, 2H), 3.30 – 3.20 (m, 1H), 2.96 – 2.85 (m, 1H), 2.71 (t, *J* = 8.0 Hz, 2H), 1.93 (br s, 1H), 1.62 (br s, 2H), 1.39 (br s, 1H), 1.28 (s, 9H), 1.12 – 1.03 (m, 1H), 0.54 (br d, *J* = 8.0 Hz, 2H), 0.21 (br d, *J* = 4.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.79, 138.71, 129.23, 128.46, 126.27, 79.56, 74.18, 73.72, 52.25, 42.57, 36.01, 28.26, 26.44, 26.11, 11.02, 3.21.

***(2R,5R)*-2-Benzyl-5-(cyclopropylmethoxy)piperidine** To a solution of compound *tert*-butyl *(2R,5R)*-2-benzyl-5-(cyclopropylmethoxy)piperidine-1-carboxylate (30.0 mg, 0.087 mmol) in DCM was added 20% TFA, the reaction mixture was stirred at r.t. for 2.5h until TLC showed the reaction was completed. When the reaction is finished, the mixture was co-evaporated with toluene (3 times), the residue was diluted with ethyl acetate and washed with 10% Na_2CO_3, water, brine and dried over $MgSO_4$. Filtering and concentration under reduced pressure afforded the crude product that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.18 (m, 5H), 3.75 (s, 1H), 3.47 (s, 1H), 3.41 – 3.17 (m, 2H), 3.17 (d, *J* = 10.1 Hz, 2H), 3.06 (d, *J* = 12.1 Hz, 1H), 2.88 (d, *J* = 7.7 Hz, 1H), 2.03 (d, *J* = 11.7 Hz, 1H), 1.85 (d, *J* = 11.5 Hz, 1H), 1.62 (d, *J* = 14.2 Hz, 1H), 1.26 (br s, 1H), 1.02 (br s, 1H), 0.52 (d, *J* = 8.0 Hz, 2H), 0.16 (d, *J* = 4.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.43, 129.50, 128.89, 127.30, 73.27, 68.20, 57.92, 47.49, 39.39, 26.29, 22.70, 10.49, 3.08, 3.04.

S. Scheme 4. Enantioselective synthesis of chiral compounds.



Reagents and conditions: (a) HCN, EtOAc, 0.1M aq. citrate buffer, pH 5.4, Hydroxynitrile lyase; (b) TBDPS-Cl, imidazole, DMF, 0 ^{o}C; (c) diethyl ether, DIBAL-H, -80 ^{o}C to 0 ^{o}C; (d) MeOH, -90 ^{o}C; (e) *(S)*-amine (**23a**) (3 equiv), r.t., 20h; (f) $NaBH_4$; (g) Boc_2O, TEA, THF, 50 ^{o}C, 20h; (h) Grubbs I cat. 4 mol %, DCM, reflux, 48h; (i) 25% TFA, DCM, r.t.; (j) Hydrazine, $CuSO_4$, EtOH, 0 ^{o}C to 70 ^{o}C; (k) TBAF, THF, r.t.; (l) NaH, corresponding bromide; (m) DIPEA, Triphosgene, THF, 0 ^{o}C; (n) DIPEA, DMAP, triazole, THF, 60 ^{o}C; (o) HF-pyridine, THF : pyridine = 1:1 (v/v).

(*S,E*)-2-((*tert*-Butyldiphenylsilyl)oxy)-4-phenyl-*N*-((*S*)-1-phenylbut-3-en-2-yl)but-3-en-1-amine (82). Under an argon atmosphere cyanohydrin **81**[4, 5] (2.80 g, 7.05 mmol) was dissolved in dry diethyl ether (40 mL) and at -78 °C a 1.0 M solution of DIBAL-H in toluene (11.0 mL, 11.0 mmol) was added dropwise in 15 min. The mixture was slowly warmed on the cooling bath to 5 °C. After re-cooling to -90 °C methanol (10 mL) was added at once, followed by a solution of *(S)*-1-phenylbut-3-en-2-amine **23a** (3.00 g, 20.4 mmol) in methanol (10 mL). The cooling bath was removed and the remaining mixture stirred at room temperature, under a light flow of argon, for 28h. The remaining mixture was cooled on an ice-bath and $NaBH_4$ (880 mg, 23.0 mmol) was added in three portions with five minute intervals. The mixture was stirred overnight while slowly warming to room temperature. The reaction was quenched with a 0.8 M NaOH solution (150 mL) and the resulting mixture extracted with diethyl ether (3 x 60 mL). The combined organic layers were washed subsequently with 1.0 M HCl solution (2 x 30 mL) and 0.8 M NaOH solution, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product that was purified by silica gel column chromatography (pentane/EtOAc = 97 : 3 → 9 : 1) to give the target amine **82** as a colorless oil (3.50 g, 93%). $[\alpha]^{23}_{D}$ = +116 (*c* = 1.0, $CHCl_3$). HRMS calculated for $C_{36}H_{41}NOSi$ $[M+H]^+$: 532.3030 found: 532.3021. IR: 3071,

3026, 2930, 2893, 2857, 1495, 1454, 1427, 1362, 1109, 1059, 962, 918. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.61 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.42 – 7.05 (m, 16H), 6.09 – 5.91 (m, 2H), 5.59 (ddd, *J* = 17.0, 10.3, 8.0 Hz, 1H), 5.07 – 4.92 (m, 2H), 4.37 (app. q, *J* = 6.1 Hz, 1H), 3.23 (app q, *J* = 7.7 Hz, 1H), 2.76 – 2.61 (m, 4H), 1.59 (br s, 1H), 1.00 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.67, 138.36, 136.66, 135.89, 135.88, 134.05, 133.95, 131.00, 130.58, 129.54, 129.41, 129.28, 128.30, 128.22, 127.47, 127.34, 127.30, 126.38, 126.21, 116.00, 74.22, 62.69, 53.55, 42.40, 26.99, 19.25.

The acidic water layer was basified with 8.0 M NaOH (12 mL) and extracted with $CHCl_3$ (4 x 30 mL). After drying ($MgSO_4$), filtering and evaporation of the solvent, excess (*S*)-1-phenylbut-3-en-2-amine (2.02 g, 13.7 mmol) was recovered.

***tert*-Butyl ((*S*,*E*)-2-((*tert*-butyldiphenylsilyl)oxy)-4-phenylbut-3-en-1-yl)((*S*)-1-phenylbut-3-en-2-yl)carbamate (83)**. The amine from above (3.30 g, 6.21 mmol) was dissolved in THF (50 mL), Boc_2O (2.80 g, 12.8 mmol) and Et_3N (2 mL) were added subsequently. The mixture was refluxed overnight upon which TLC confirmed complete conversion. Concentration *in vacuo* and purification by silica gel column chromatography (pentane/EtOAc = 99 : 1 → 97 : 3) afforded the title compound (5.10 g) as a mixture with unseparated Boc_2O. Analytical data are from a pure fraction. $[\alpha]_D^{21}$ = -4.6 (c =1.0, $CHCl_3$). HRMS calculated for $C_{41}H_{49}NO_3Si$ $[M+H]^+$: 632.3555; found: 632.3555. IR 3069, 3028, 2963, 2930, 2859, 1694, 1454, 1427, 1410, 1366, 1250, 1167, 1113, 964. ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers (2:1 ratio): δ 7.75 (d, *J* = 6.8 Hz, 2H),7.68 (d, *J* = 6.8 Hz, 2H), 7.47 – 7.29 (m, 6H), 7.29 – 7.11 (m, 8H), 7.08 – 6.95 (m, 2H), 6.10 (s, 0.35H), 6.06 (s, 0.65H), 5.92 – 5.63 (m, 2H), 4.93 (d, *J* = 10.5 Hz, 1H), 4.88 (d, *J* = 17.4 Hz, 1H), 4.33 (br s, 0.4H), 4.12 (br s, 1H), 3.91 (br s, 0.6H), 3.53 – 3.15 (m, 1H), 3.13 – 2.64 (m, 3H), 1.23 (s, 3H), 1.19 (s, 6H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) mixture of rotamers (2:1 ratio): δ 154.77, 138.63, 137.93, 137.23, 137.01, 135.98, 135.88, 134.16, 133.59, 130.73, 130.41, 129.66, 129.30, 128.22, 128.16, 127.59, 127.47, 127.11, 126.35, 126.17, 115.87, 79.34, 73.59 (minor CHO), 72.58 (major CHO), 62.70 (major CHN), 61.71 (minor CHN), 53.02 (major CH_2N), 50.99 (minor CH_2N), 38.64 (minor CH_2Ph), 38.12 (major CH_2Ph), 28.13, 27.03, 19.27.

***tert*-Butyl *(3S,6S)*-6-benzyl-3-((*tert*-butyldiphenylsilyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (84)**. The Boc-protected diene **83** (max 6.21 mmol) from above was dissolved in DCM under argon. Grubbs I catalyst (309 mg, 0.375 mmol) was added and the mixture refluxed overnight after which TLC confirmed complete conversion. The solvent was evaporated and the crude product purified by silica gel column chromatography (pentane/EtOAc = 99 : 1 → 96 : 4) to afford the target cyclic alkene as a colorless oil (2.84 g, 5.39 mmol, 76% over two steps). $[\alpha]_D^{21}$ = +159 (c =1.0, $CHCl_3$). HRMS calculated for $C_{33}H_{41}NO_3Si$ $[M+H]^+$: 528.2929; found: 528.2922. IR 3028, 2971, 2931, 2858, 1810, 1756, 1692, 1454, 1448, 1417, 1364, 1112, 1072. ^{1}H NMR (400 MHz, $CDCl_3$, 60 ^{o}C) δ 7.70 (d, *J* = 7.4 Hz, 2H), 7.64 (d, *J* = 7.7 Hz, 2H), 7.41 – 7.27 (m, 6H), 7.24 – 7.09 (m, 5H), 5.62 (dd, *J* = 10.1, 3.7 Hz, 1H), 5.59 – 5.52 (m, 1H), 4.69 (br s, 1H), 4.23 (br s, 1H), 4.07 – 3.98 (m, 1H), 2.82 (dd, *J* = 12.9, 5.9 Hz, 1H), 2.77 – 2.67 (m, 2H), 1.44 (s, 9H), 1.04 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, 60 ^{o}C) δ 154.73, 138.04, 135.80, 134.65, 134.22, 131.16, 129.60, 129.46, 128.22, 127.61, 127.42, 126.53, 126.25, 79.35, 64.08, 38.95, 28.44, 26.95, 19.20.

***tert*-Butyl *(2R,5S)*-2-benzyl-5-((*tert*-butyldiphenylsilyl)oxy)piperidine-1-carboxylate (87)**. A suspension of substrate *tert*-butyl *(3S,6S)*-6-benzyl-3-((tert-butyldiphenylsilyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (500 mg, 0.947 mmol) and copper (II) sulfate (1.50 g, 9.47 mmol) in ethanol (2 mL) was cooled on an ice bath. Hydrazine (3.01 mL, 96.0 mmol) was added drop wise and the reaction was subsequently stirred for 15 min. After that, the reaction mixture was stirred at 70 °C for 24h until TLC showed the reaction was completed. The mixture was filtered over celite and concentrated *in vacuo*. The residue was diluted with ethyl acetate and washed with water, brine and dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/EtOAc = 99 : 1 → 90 : 10) to furnish *tert*-butyl *(2R,5S)*-2-benzyl-5-((*tert*-butyldiphenylsilyl)oxy)piperidine-1-carboxylate **87** (400 mg, 0.756 mmol, 80 % yield) as a colorless oil. LC-MS m/z: calculated for $C_{33}H_{43}NO_3Si$ $[M+H]^+$ 530.30, found 530.81. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 4H), 7.42 – 7.33 (m, 6H), 7.27 – 7.20 (m, 2H), 7.18 – 7.14 (m, 3H), 4.56 (br s, 1H), 4.09 (br d, *J* = 7.0 Hz, 1H), 3.91 (br s, 1H), 2.94 – 2.78 (m, 2H), 2.72 – 2.61 (m, 1H), 2.19 (br, 1H), 1.72 – 1.47 (m, 3H), 1.35 (s, 9H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.20, 139.35, 135.97, 135.79, 134.52, 133.99, 129.72, 129.66, 129.27, 128.36, 127.69, 127.64, 126.16, 79.04, 65.79, 50.37, 44.02, 35.99, 28.41, 27.04, 26.24, 20.28, 19.38.

***(2R,5S)*-2-Benzyl-5-((*tert*-butyldiphenylsilyl)oxy)piperidine (88)**. To a solution of *tert*-butyl *(2R,5S)*-2-benzyl-5-((*tert*-butyldiphenylsilyl)oxy)piperidine-1-carboxylate **87** (120 mg, 0.226 mmol) in DCM was added 20% TFA, the reaction mixture was stirred at r.t. for 2.5h until TLC showed the reaction was completed. When the reaction is finished, the mixture was co-evaporated with toluene (3 times), the residue was diluted with ethyl acetate and washed with 10% Na_2CO_3, water, brine and dried over $MgSO_4$, and concentrated under reduced pressure. Filtering and concentration under reduced pressure afforded the crude product that was used without further purification. $[\alpha]_D^{20}$ = -13 (c =1.0, $CHCl_3$). HRMS calculated for $C_{28}H_{35}NOSi$ $[M+H]^+$: 430.2554; found: 430.2555. IR 3069, 3026, 2930, 2855, 2805, 1495, 1454, 1427, 1288, 1103, 1082, 1030, 993. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.9 Hz, 4H), 7.42 – 7.29 (m, 6H), 7.26 – 7.18 (m, 3H), 7.08 – 7.03 (m, 2H), 4.00 (br s, 1H), 3.19 (br d, *J* = 10.0 Hz, 1H), 3.14 – 2.90 (m, 2H), 2.73 (br d, *J* = 10.2 Hz, 1H), 2.63 – 2.49 (m, 1H), 1.86 (br s, 1H), 1.69 (br s, 1H), 1.38 (br t, *J* = 11.3 Hz, 2H), 1.02 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.63, 135.57, 135.46, 133.41, 133.00, 130.17, 130.07, 129.29, 128.89, 127.96, 127.84, 127.36, 66.03, 57.45, 49.28, 39.12, 32.21, 26.91, 26.04, 19.20.

***tert*-Butyl *(2R,5S)*-2-benzyl-5-hydroxypiperidine-1-carboxylate (90)**. A solution of TBAF (2.83 mL, 2.83 mmol) was added to a solution of *tert*-butyl *(2R,5S)*-2-benzyl-5-((*tert*-butyldiphenylsilyl)oxy)piperidine-1-carboxylate **87** (1.00 g, 1.89 mmol) in THF (15 mL) with ice cooling and the mixture was stirred at r.t. for 2.5h, After being diluted with water, the mixture was extracted with ethyl acetate (3 times), the organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under *in vacuo*. The residue was purified by flash chromatography (pentane/EtOAc = 99 : 1 → 80 : 20) to furnish *tert*-butyl *(2R,5S)*-2-benzyl-5-hydroxypiperidine-1-carboxylate (440 mg, 1.51 mmol, 80% yield) as a colorless oil. $[\alpha]_D^{22}$ = -33 (*c* = 1.0, $CHCl_3$). LC-MS m/z: calculated for $C_{17}H_{25}NO_3$ $[M+H]^+$ 292.18, found: 292.71. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.21 – 7.15 (m, 3H), 4.35 (br s, 1H), 4.25 (br s, 1H), 3.64 – 3.57 (m, 1H), 2.91

(dd, *J* = 13.1, 8.1 Hz, 1H), 2.75 (dd, *J* = 12.8, 10.8 Hz, 2H), 1.90 (br s, 1H), 1.66 -1.59 (m, 3H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.78, 138.98, 129.20, 128.44, 126.26, 79.72, 67.03, 53.90, 45.69, 35.81, 28.26, 28.12, 26.28.

***tert*-Butyl (*2R,5S*)-2-benzyl-5-methoxypiperidine-1-carboxylate (91)**. To a solution of *tert*-butyl *(2R,5S)*-2-benzyl-5-hydroxypiperidine-1-carboxylate (70.0 mg, 0.240 mmol) and NaH (60%, 17.3 mg, 0.721 mmol) in DMF (3 mL) at 0 °C, MeI (0.045 mL, 0.721 mmol) was added dropwise with continuous stirring, and the mixture was allowed to stand at room temperature for 24h. The mixture was diluted with water (10 mL), and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/EtOAc = 99 : 1 → 90 : 10) to furnish *tert*-butyl *(2R,5S)*-2-benzyl-5-methoxypiperidine-1-carboxylate (61.0 mg, 0.200 mmol, 83% yield). $[\alpha]_D^{22}$ = -36 (*c* = 0.6, $CHCl_3$). LC-MS m/z: calculated for $C_{18}H_{27}NO_3$ $[M+H]^+$ 306.20, found: 306.82. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.19 – 7.14 (m, 3H), 4.43 (br s, 1H), 4.33 (br d, *J* = 13.5 Hz, 1H), 3.41 (br s, 1H), 3.34 (s, 3H), 2.97 – 2.82 (m, 2H), 2.74 (dd, *J* = 13.1, 8.3 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.88 – 1.72 (m, 2H), 1.34 (s, 9H), 1.31 – 1.28 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.27, 139.22, 129.28, 128.48, 126.28, 79.35, 73.19, 56.08, 52.47, 40.38, 36.00, 28.42, 23.84, 21.47.

***(2R,5S)*-2-Benzyl-5-methoxypiperidine (92).** To a solution of compound *tert*-butyl *(2R,5S)*-2-benzyl-5-methoxypiperidine-1-carboxylate (30.0 mg, 0.098 mmol) in DCM was added 20% TFA, the reaction mixture was stirred at r.t. for 2.5h until TLC showed the reaction was completed. When the reaction is finished, the mixture was co-evaporated with toluene (3 times), the residue was diluted with ethyl acetate and washed with 10% Na_2CO_3, water, brine and dried over $MgSO_4$, and concentrated under reduced pressure. Filtering and concentration under reduced pressure afforded the crude product *(2R,5S)*-2-benzyl-5-methoxypiperidine **92** that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 3H), 7.19 – 7.13 (m, 2H), 3.69 – 3.46 (m, 2H), 3.36 (s, 3H), 3.25 – 2.95 (m, 2H), 2.77 – 2.71 (m, 1H), 2.66 – 2.62 (m, 1H), 2.21 (br s, 1H), 1.98 – 1.83 (m, 1H), 1.71 – 1.52 (m, 1H), 1.34 – 1.16 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.46, 129.34, 128.99, 127.47, 72.84, 57.81, 56.77, 47.10, 39.13, 28.58, 25.86.

***tert*-Butyl *(2R,5S)*-2-benzyl-5-(cyclopropylmethoxy)piperidine-1-carboxylate (93).** To a solution of *tert*-butyl *(2R,5S)*-2-benzyl-5-hydroxypiperidine-1-carboxylate **90** (100 mg, 0.344 mmol) and NaH (60%, 24.7 mg, 1.03 mmol) in DMF (3 mL) at 0 °C, (bromomethyl)cyclopropane (139 mg, 1.03 mmol) was added dropwise with continuous stirring, and the mixture was allowed to stand at room temperature for 24h. The mixture was diluted with water (10 mL), and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (pentane/EtOAc = 99 : 1 → 90 : 10) to furnish *tert*-butyl *(2R,5S)*-2-benzyl-5-(cyclopropylmethoxy)piperidine-1-carboxylate **93** (110 mg, 0.318 mmol, 89% yield). $[\alpha]_D^{22}$ = -38 (*c* = 1.0, $CHCl_3$). LC-MS m/z: calculated for $C_{21}H_{31}NO_3$ $[M+H]^+$ 346.18, found 346.40. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.22 – 7.15 (m, 3H), 4.44 (br s, 1H), 4.28 (d, *J* = 13.9 Hz, 1H), 3.54 (s, 1H), 3.40 – 3.20 (m, 2H), 2.96 – 2.84 (m, 2H), 2.74 (dd, *J* = 13.2, 8.1 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.89 – 1.67 (m, 2H), 1.34 (s, 9H), 1.29 – 1.24 (m, 1H), 1.08 – 0.98 (m, 1H), 0.50 –

0.47 (m, 2H), 0.30 – 0.10 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.17, 139.27, 129.27, 128.33, 126.23, 79.20, 72.66, 71.08, 51.90, 40.42, 36.08, 28.40, 24.50, 21.74, 10.83, 3.18, 2.92.

***(2R,5S)*-2-Benzyl-5-(cyclopropylmethoxy)piperidine (94)**. To a solution of solution of *tert*-butyl *(2R,5R)*-2-benzyl-5-(cyclopropylmethoxy)piperidine-1-carboxylate **93** (50.0 mg, 0.145 mmol) in DCM was added 20% TFA, the reaction mixture was stirred at r.t. for 2.5h until TLC showed the reaction was completed. When the reaction is finished, the mixture was co-evaporated with toluene (3 times), the residue was diluted with ethyl acetate and washed with 10% Na_2CO_3, water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure afforded the crude product that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 3H), 7.20 – 7.10 (m, 2H), 3.70 (s, 1H), 3.51 (s, 1H), 3.31 (p, *J* = 9.9 Hz, 2H), 3.16 (s, 2H), 2.74 (br s, 2H), 2.17 (br d, *J* = 11.6 Hz, 1H), 1.87 (br d, *J* = 13.4 Hz, 1H), 1.62 (br d, *J* = 11.5 Hz, 1H), 1.32 (br d, *J* = 11.7 Hz, 1H), 0.99 (br s, 1H), 0.51 (d, *J* = 7.7 Hz, 2H), 0.16 (d, *J* = 4.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.38, 129.33, 128.98, 127.46, 74.17, 71.12, 57.86, 47.58, 39.23, 29.26, 26.09, 10.82, 3.12, 3.07.

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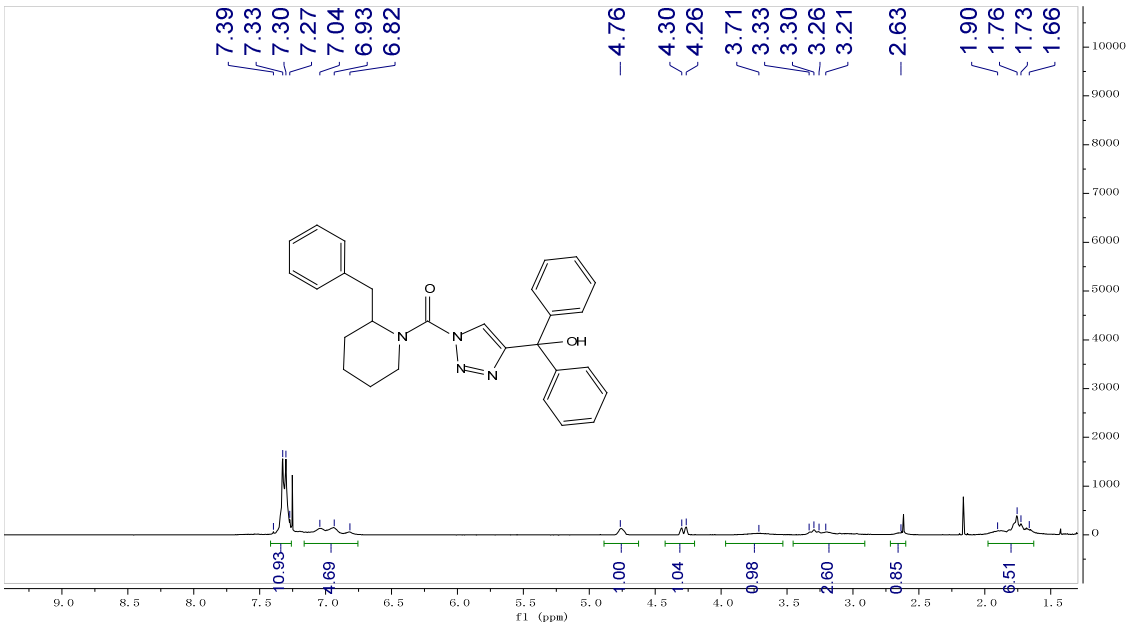
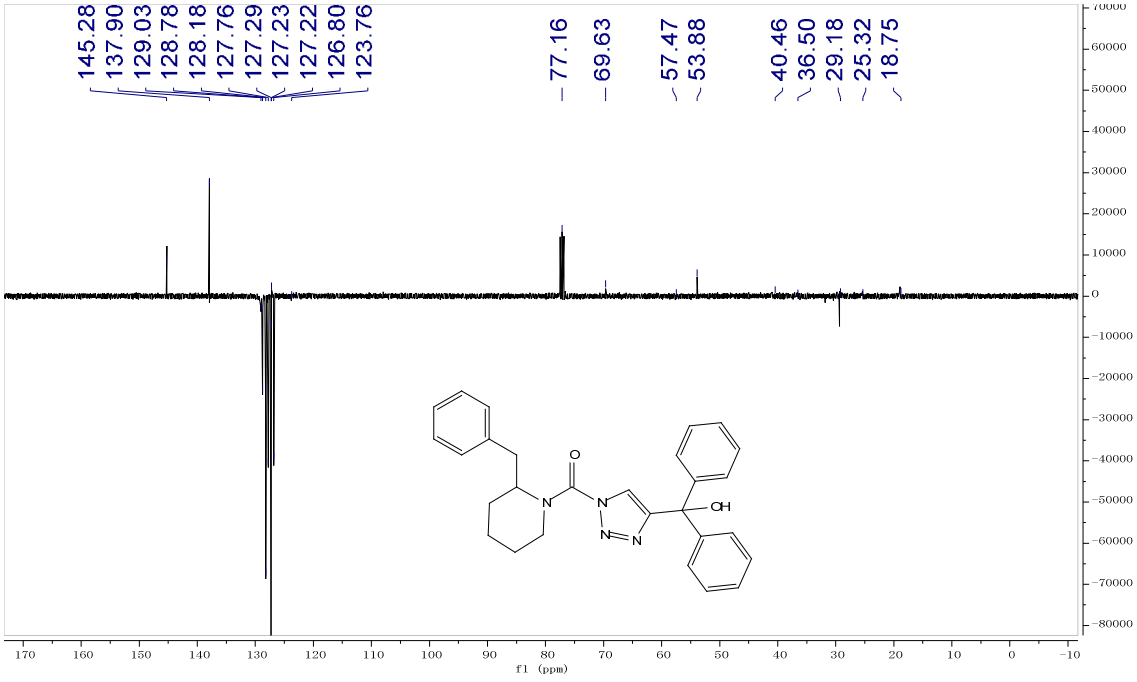
^{1}H and ^{13}C NMR ($CDCl_3$)

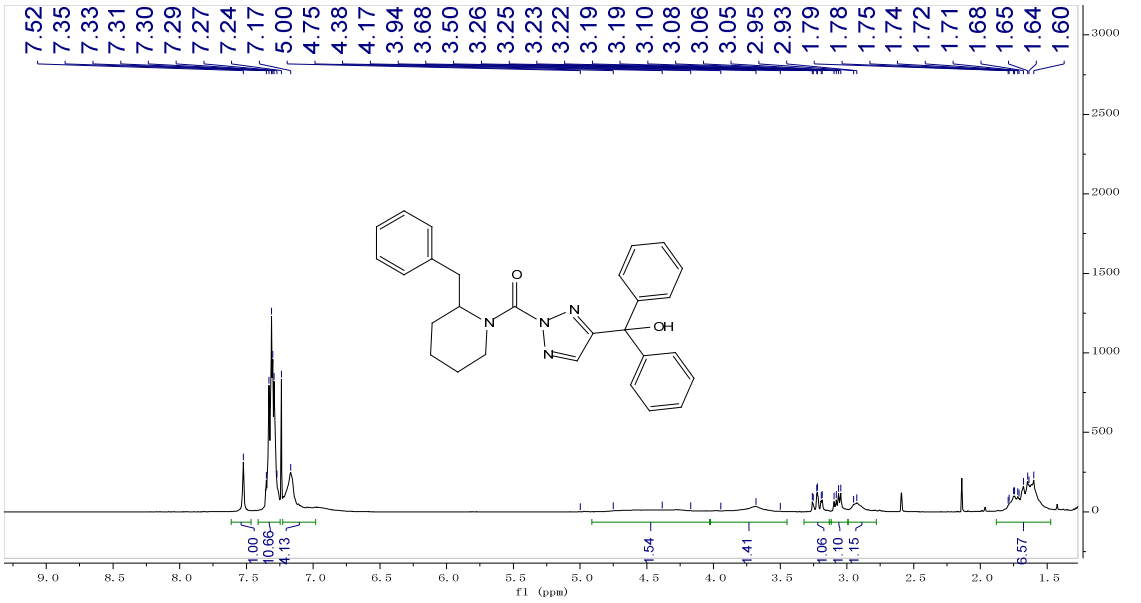
(2-Benzylpiperidin-1-yl)(4-(hydroxydiphenylmethyl)-1*H*-1,2,3-triazol-1-yl)methanone (**3**)

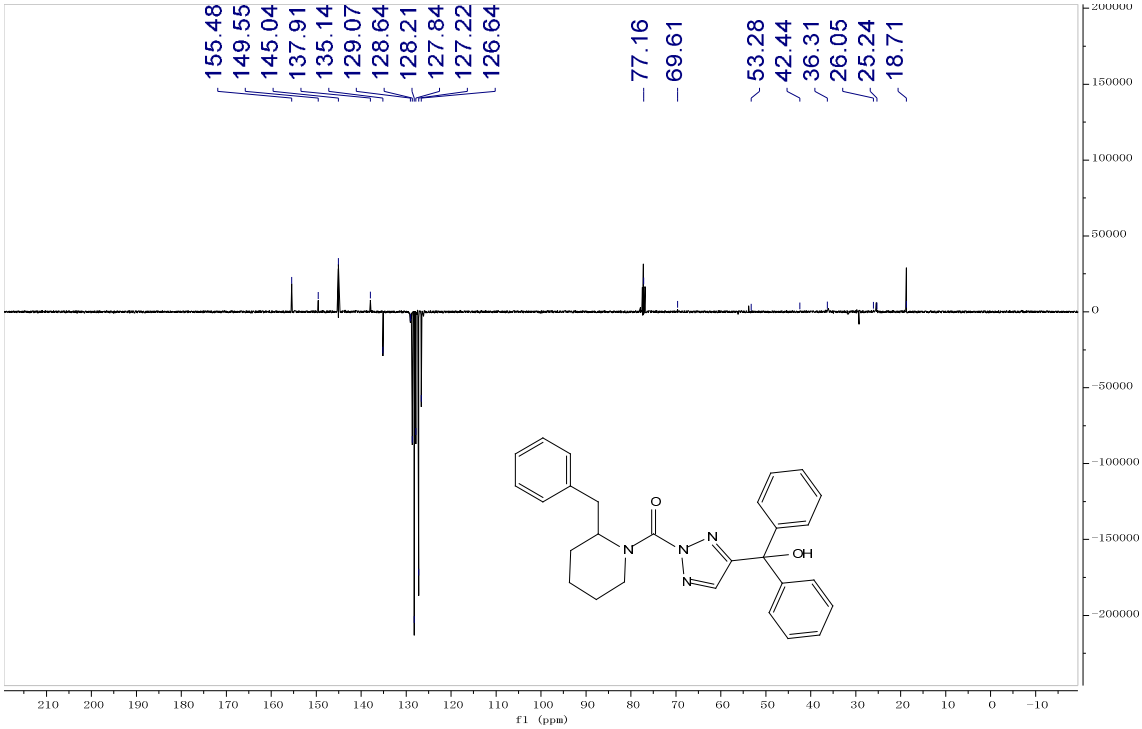




^{1}H and ^{13}C NMR ($CDCl_3$)

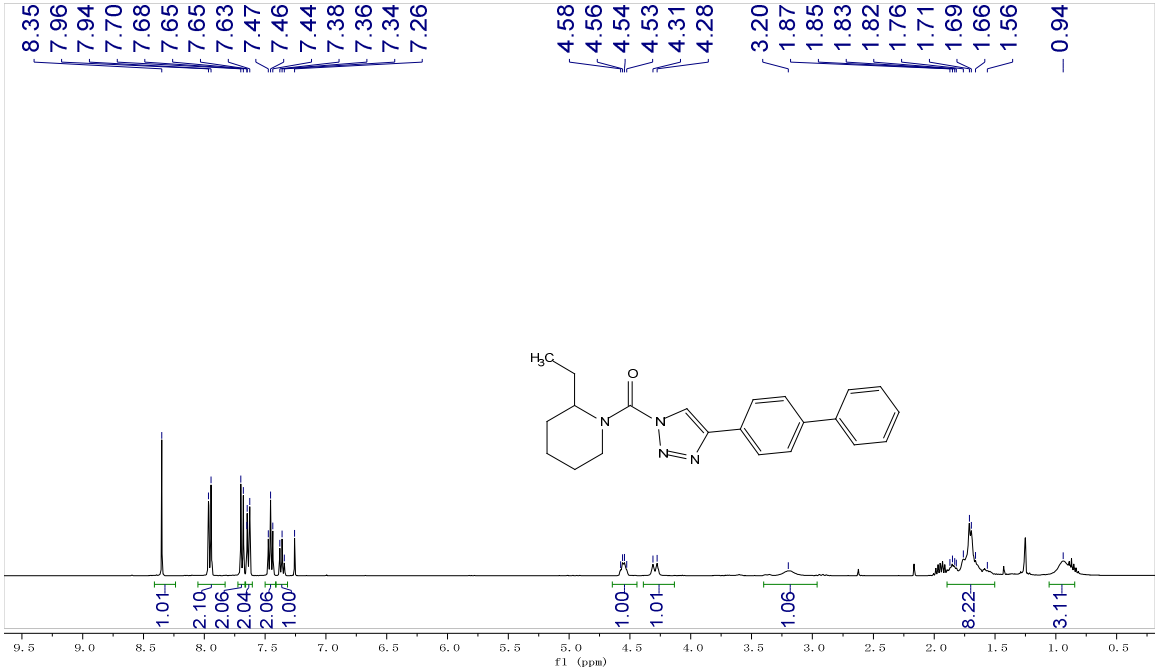
(2-Benzylpiperidin-1-yl)(4-(hydroxydiphenylmethyl)-2*H*-1,2,3-triazol-2-yl)methanone (**4**)

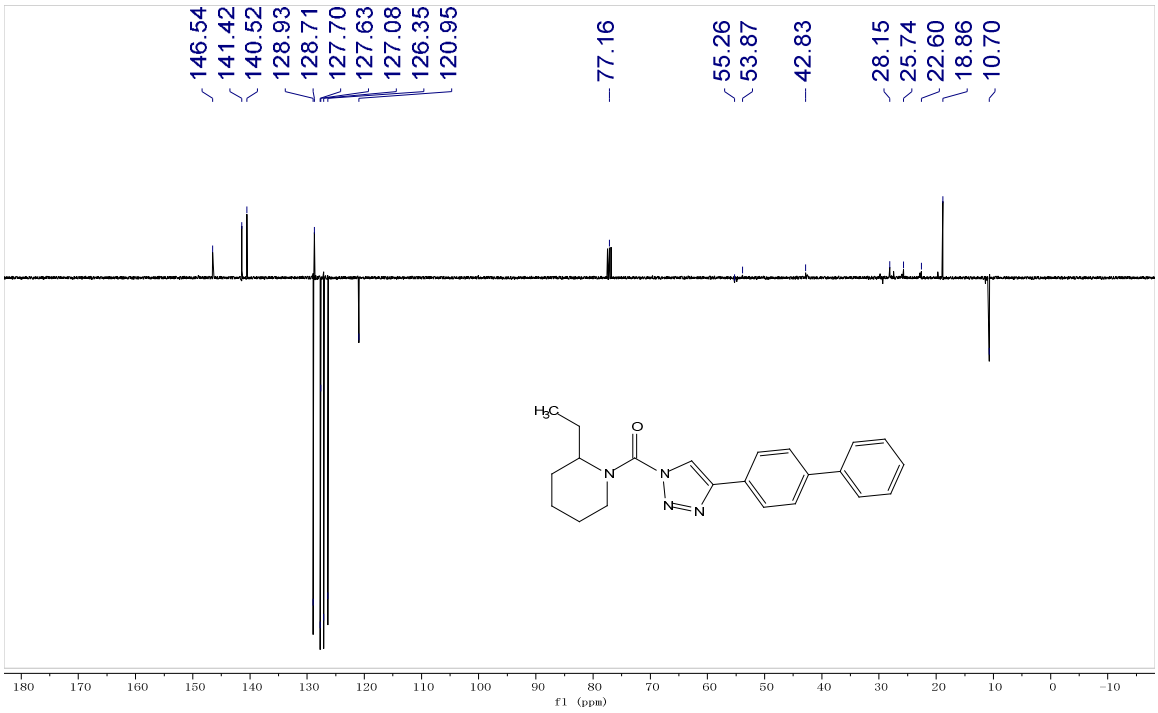




^{1}H and ^{13}C NMR ($CDCl_3$)

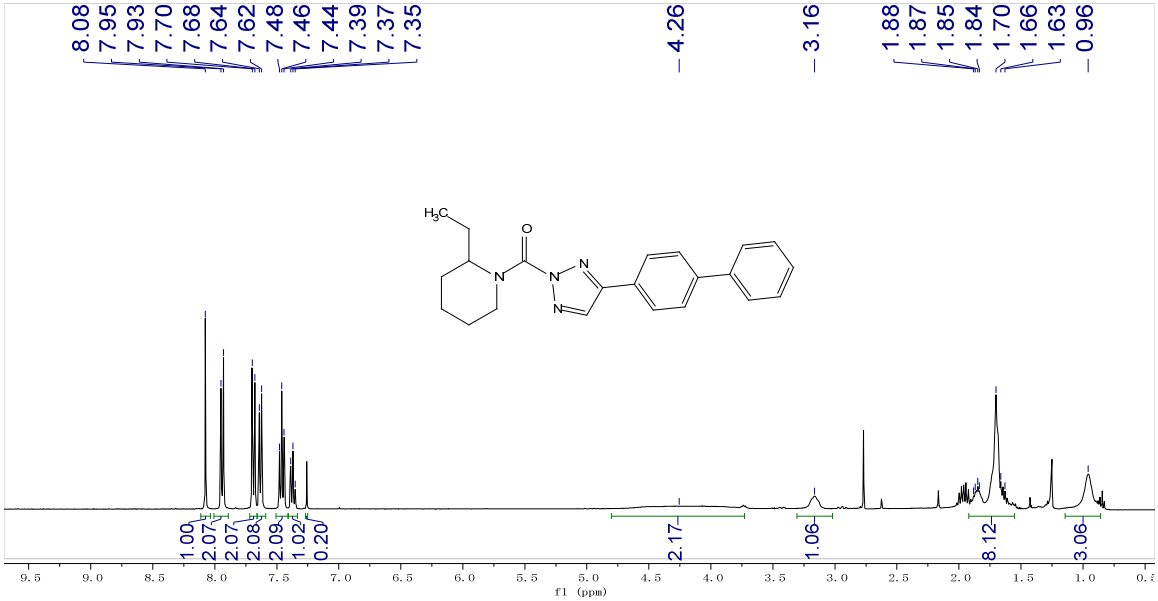
(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(2-ethylpiperidin-1-yl)methanone (**5**)

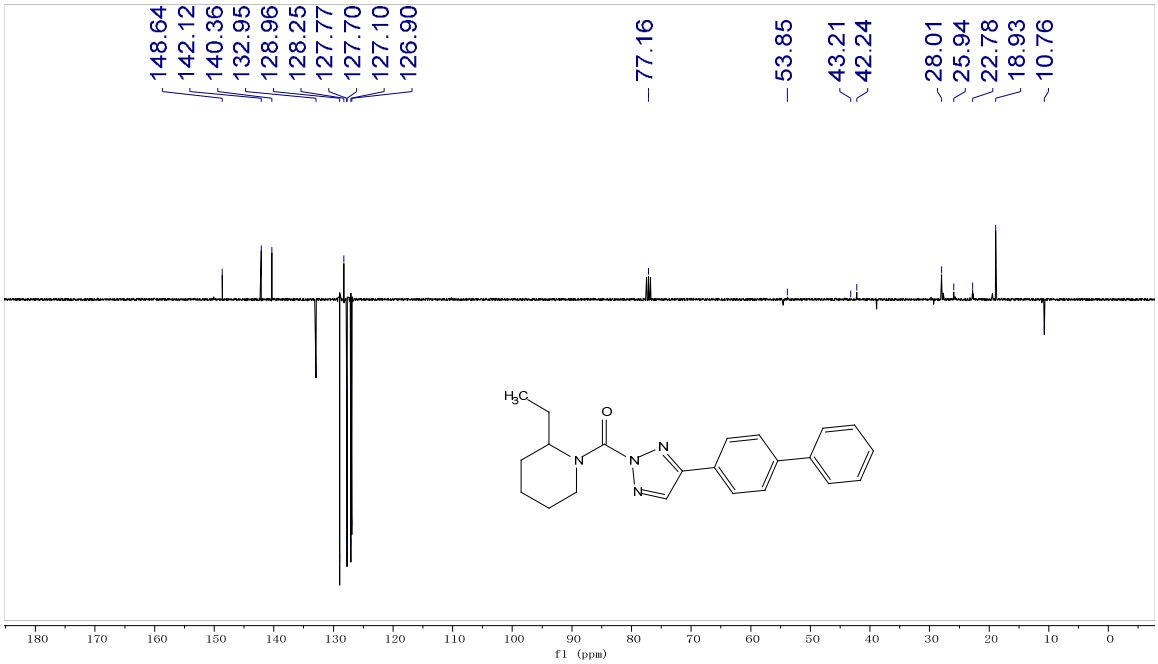




^{1}H and ^{13}C NMR ($CDCl_3$)

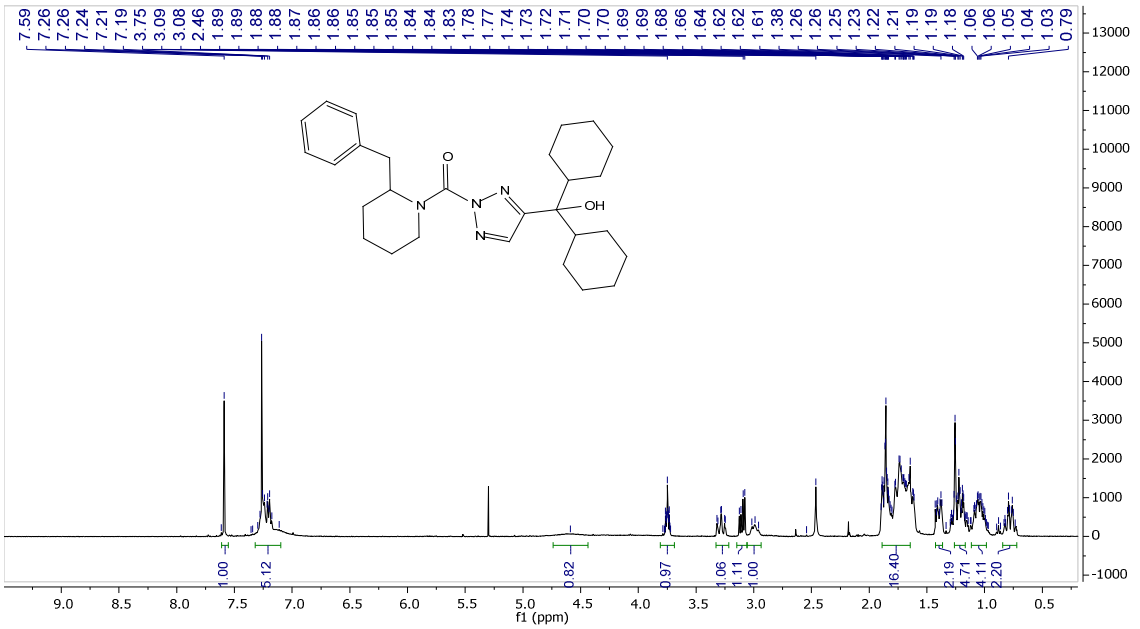
(4-([1,1'-Biphenyl]-4-yl)-2*H*-1,2,3-triazol-2-yl)(2-ethylpiperidin-1-yl)methanone (**6**)

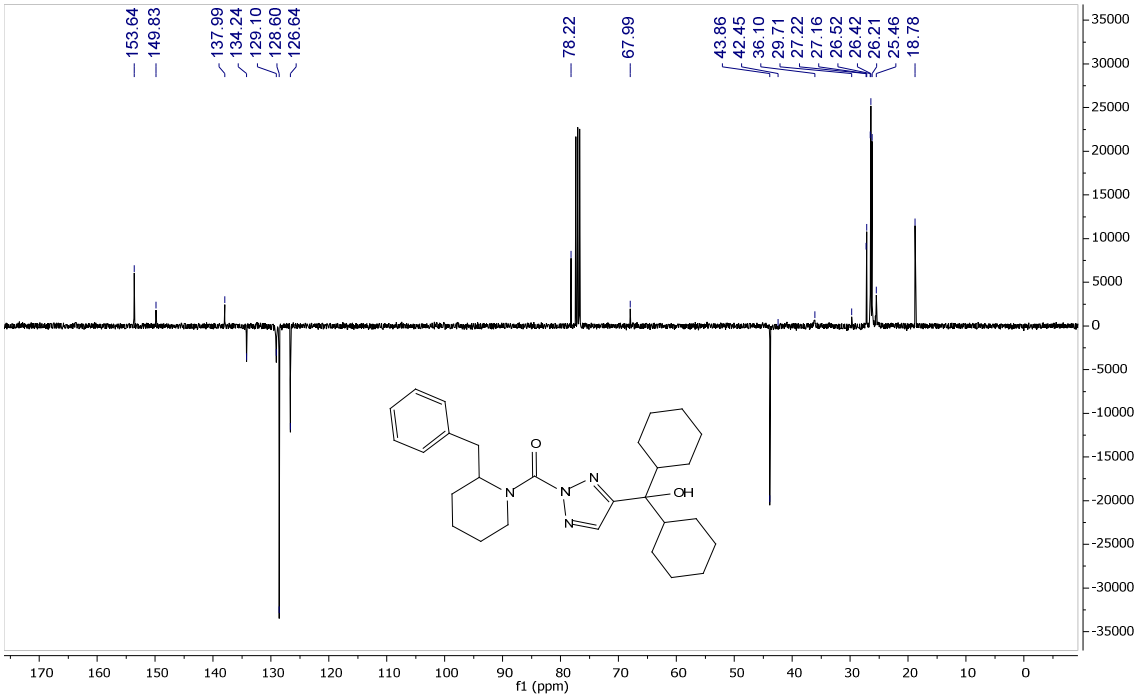




^{1}H and ^{13}C NMR ($CDCl_3$)

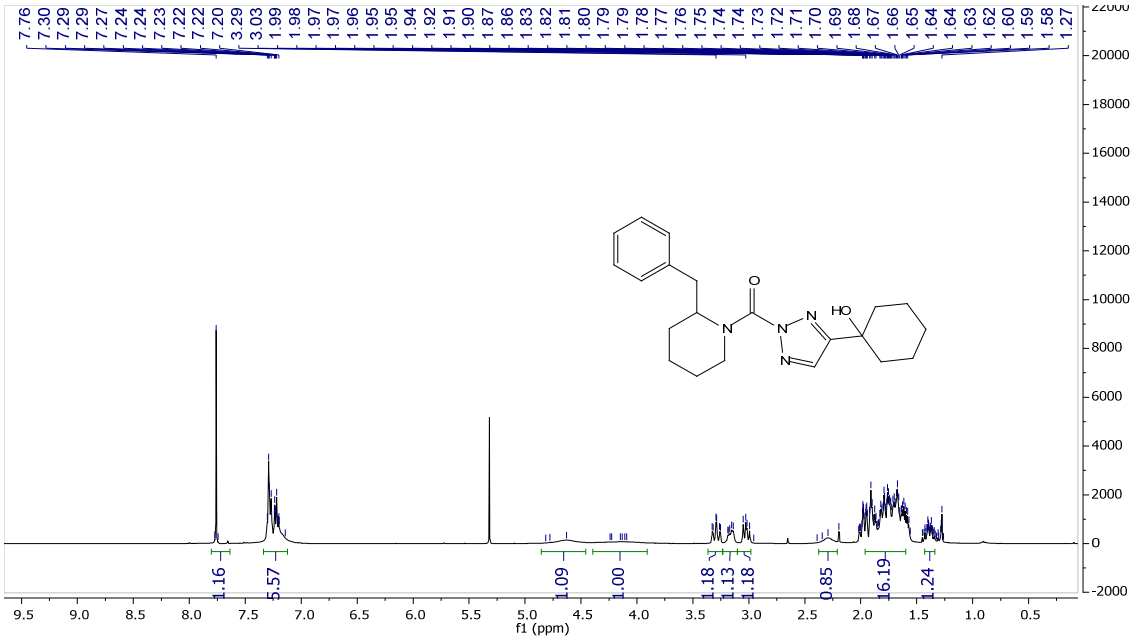
(2-Benzylpiperidin-1-yl)(4-(dicyclohexyl(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)methanone (**7**)

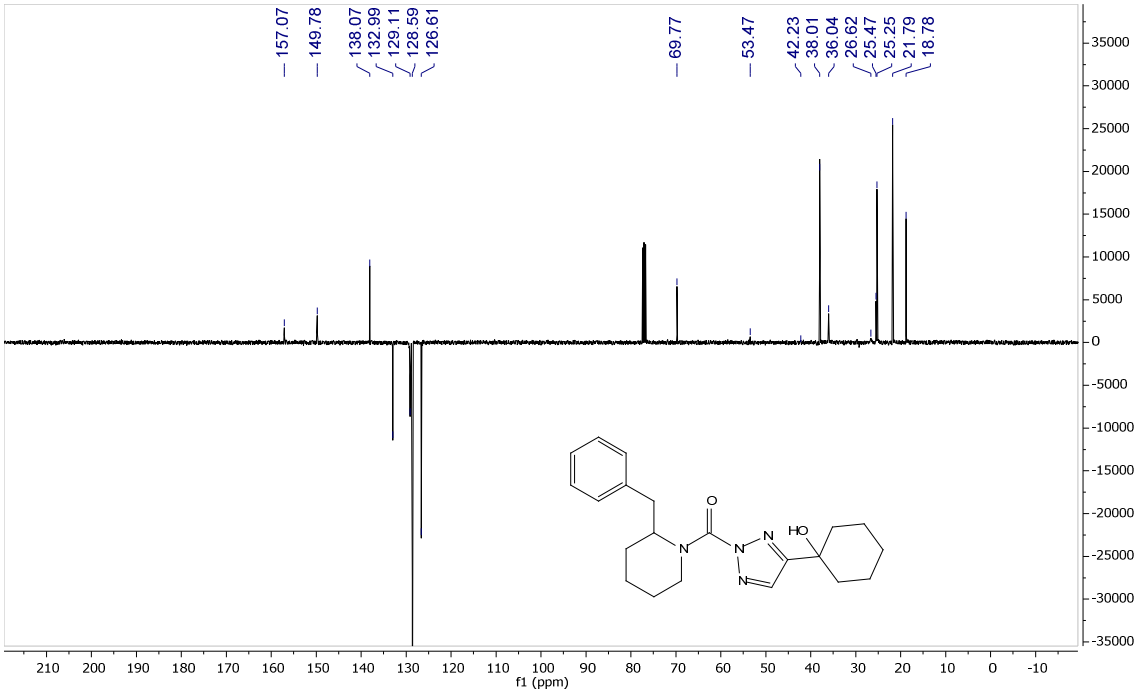




^{1}H and ^{13}C NMR ($CDCl_3$)

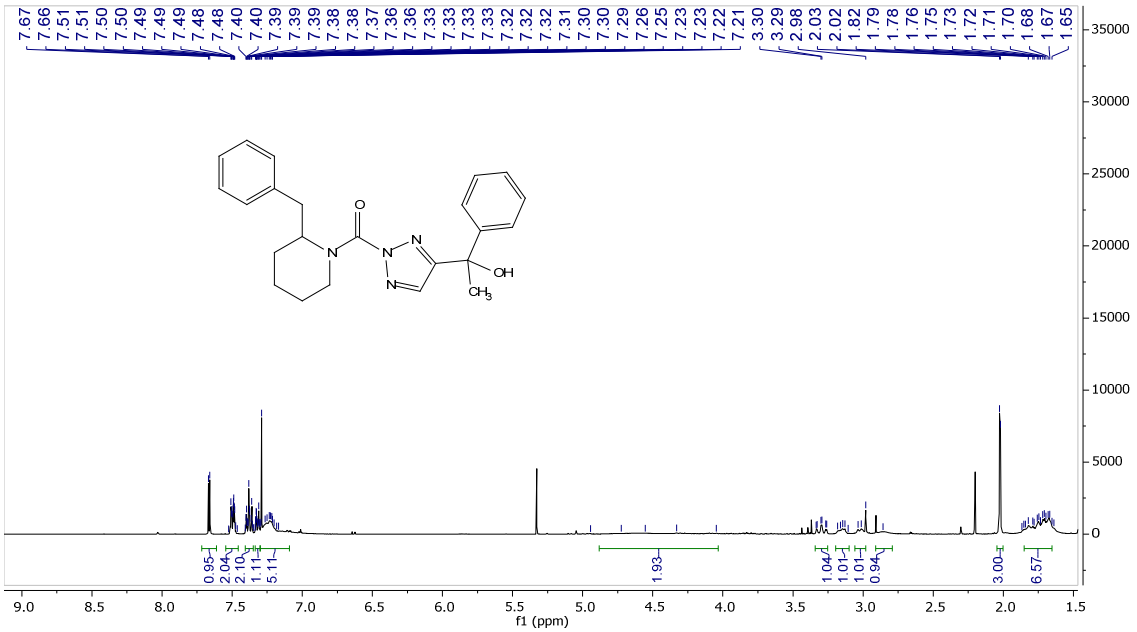
(2-Benzylpiperidin-1-yl)(4-(1-hydroxycyclohexyl)-2*H*-1,2,3-triazol-2-yl)methanone (**8**)

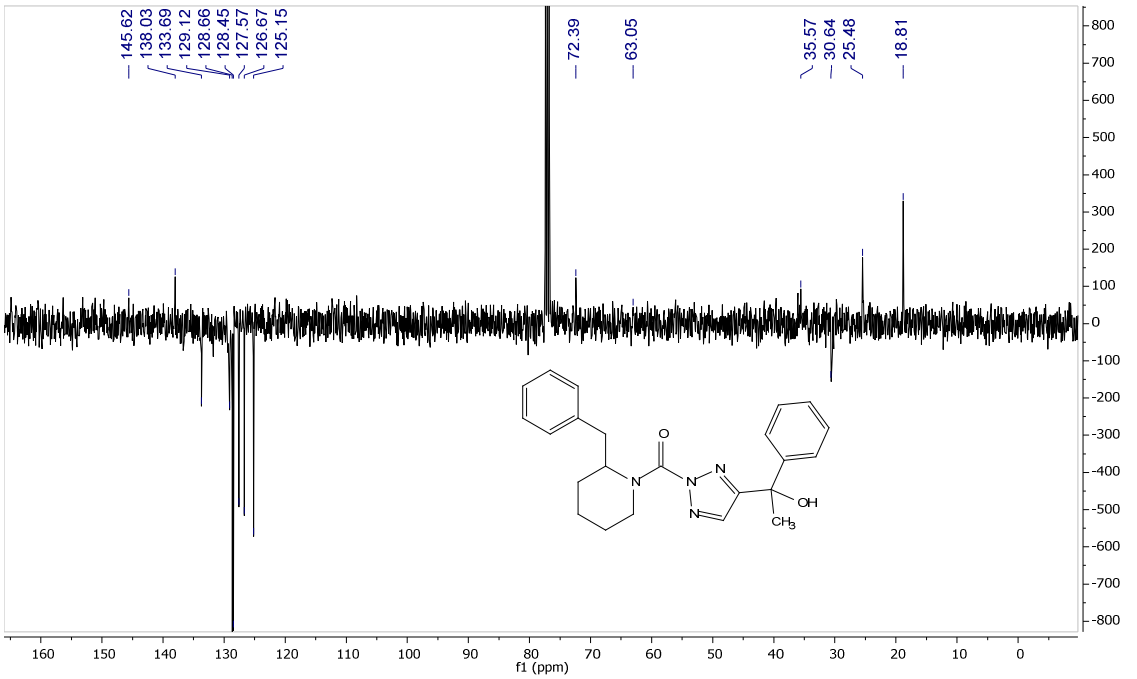




^{1}H and ^{13}C NMR ($CDCl_3$)

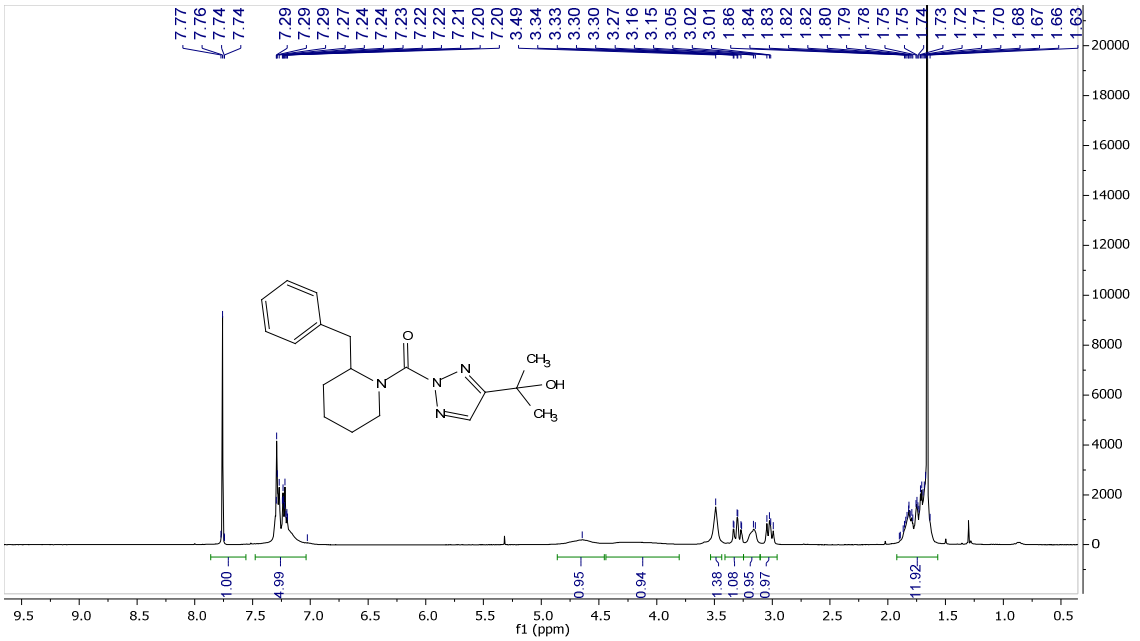
(2-Benzylpiperidin-1-yl)(4-(1-hydroxy-1-phenylethyl)-2*H*-1,2,3-triazol-2-yl)methanone (**9**)

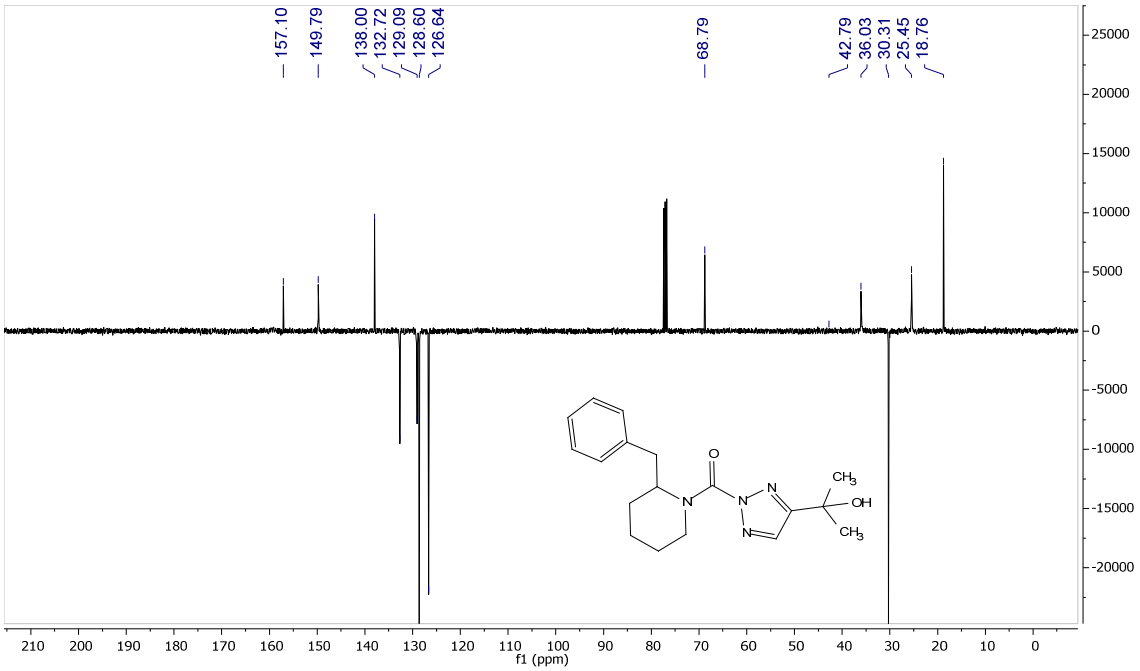




^{1}H and ^{13}C NMR ($CDCl_3$)

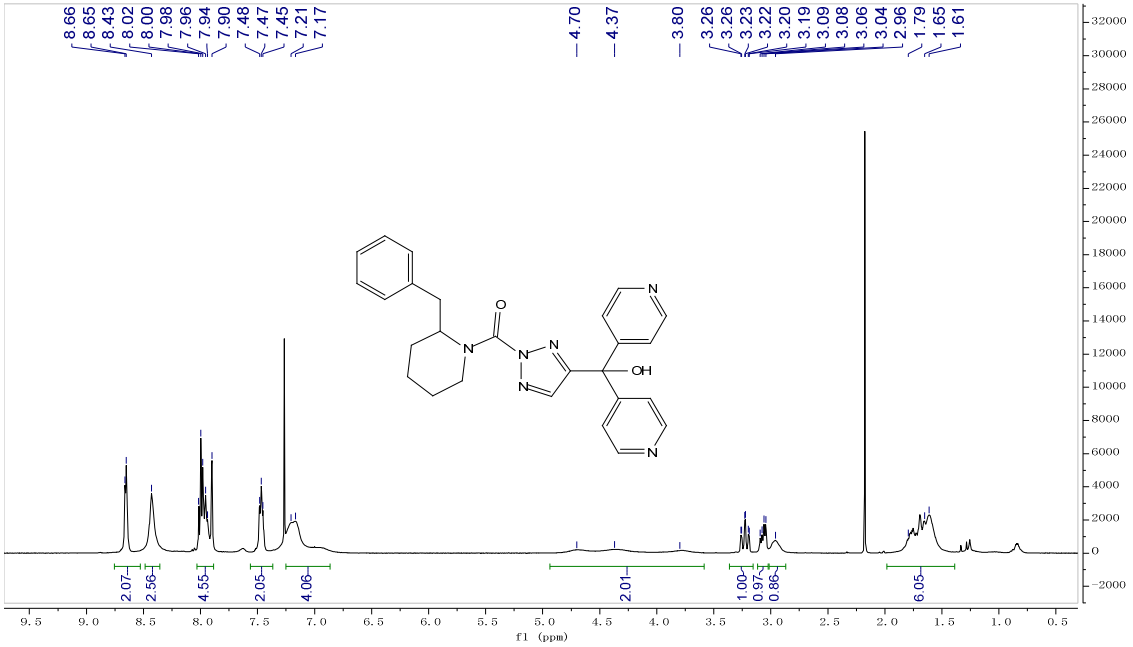
(2-Benzylpiperidin-1-yl)(4-(2-hydroxypropan-2-yl)-2*H*-1,2,3-triazol-2-yl)methanone (**10**)

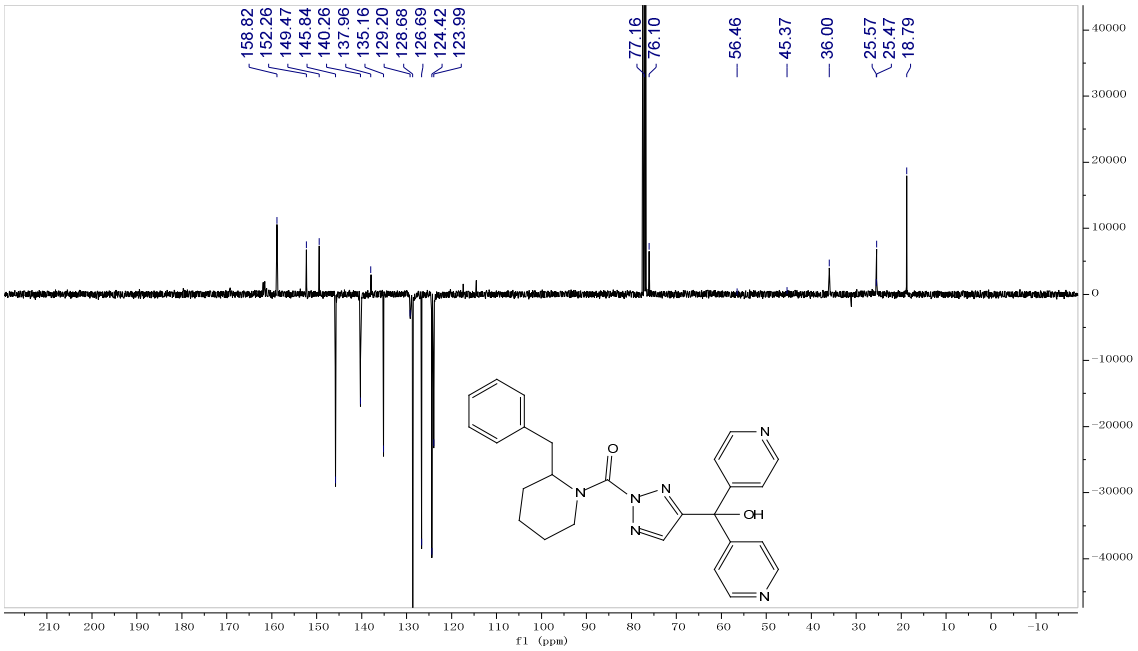




^{1}H and ^{13}C NMR ($CDCl_3$)

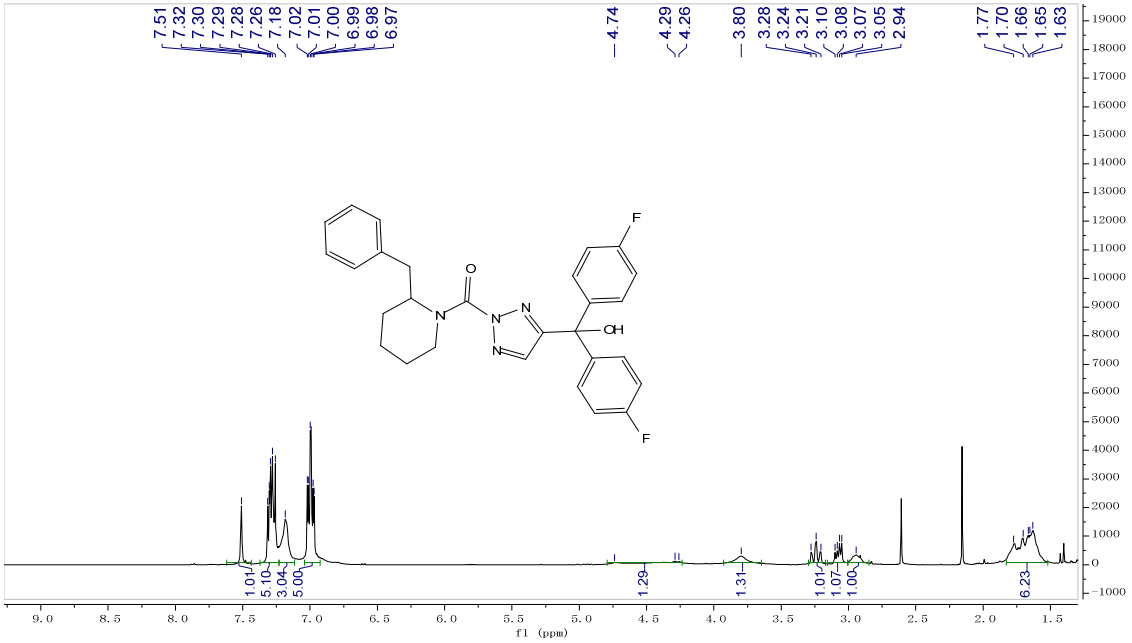
(2-Benzylpiperidin-1-yl)(4-(hydroxydi(pyridin-2-yl)methyl)-2*H*-1,2,3-triazol-2-yl)methanone (**11**)

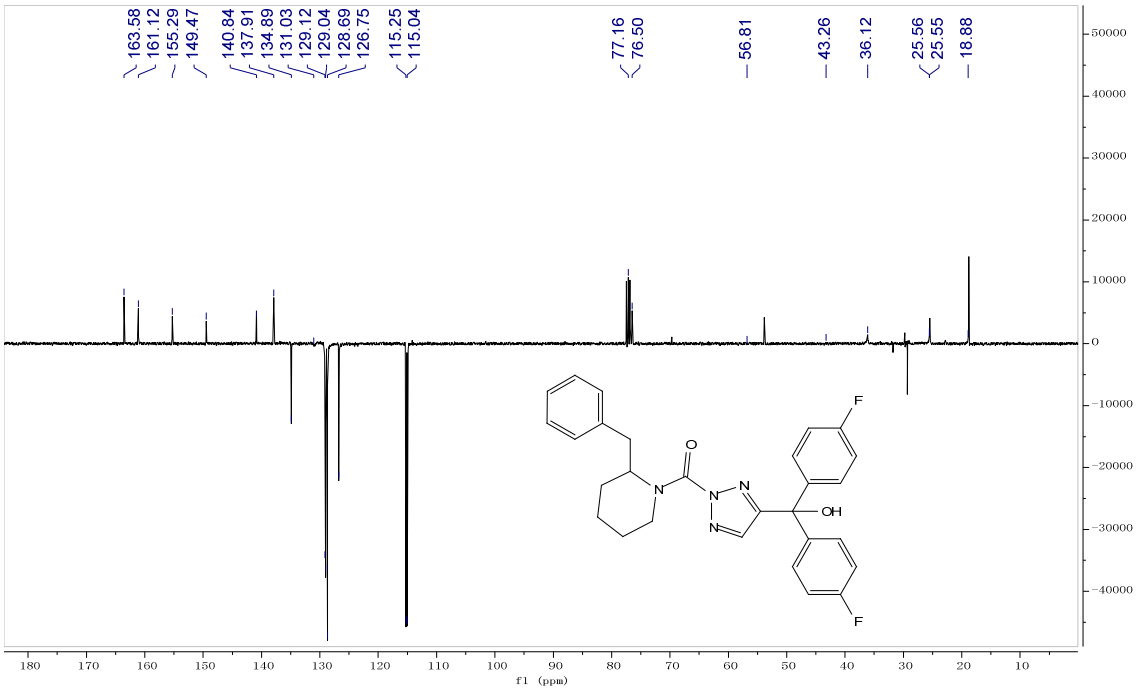




^{1}H and ^{13}C NMR ($CDCl_3$)

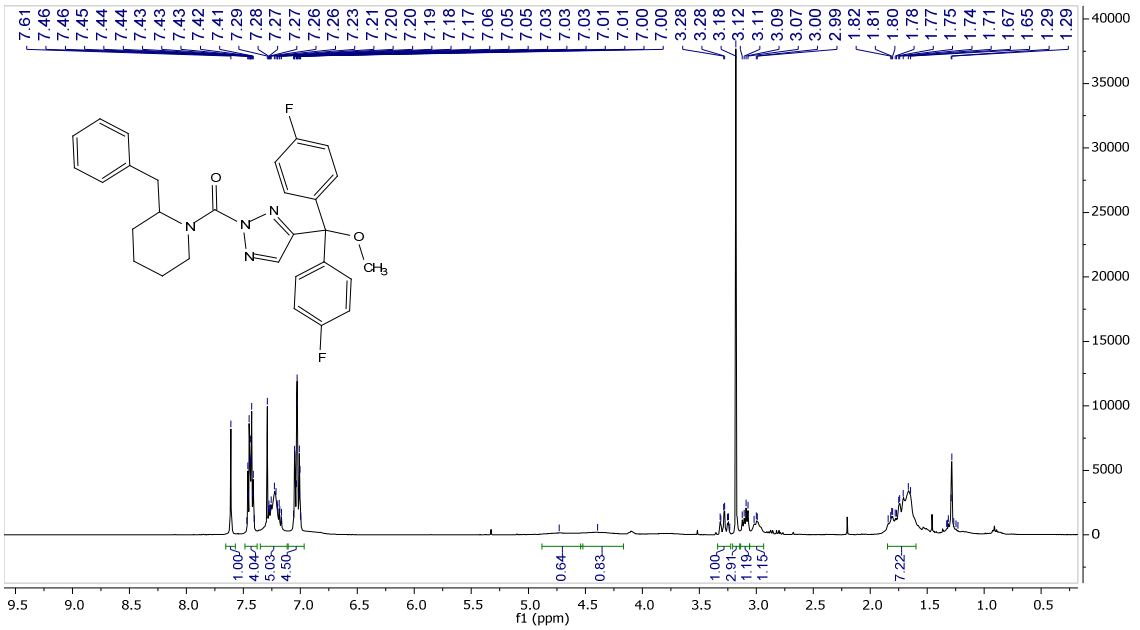
(2-Benzylpiperidin-1-yl)(4-(bis(4-fluorophenyl)(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)methanone (**12**)

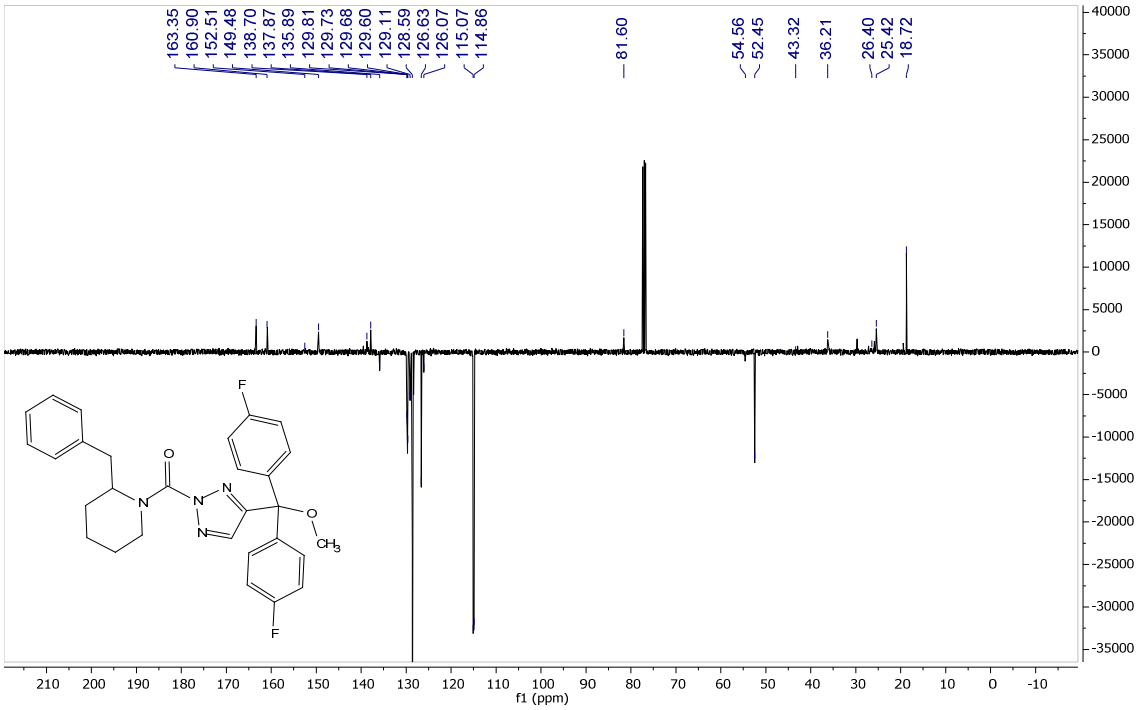




^{1}H and ^{13}C NMR ($CDCl_3$)

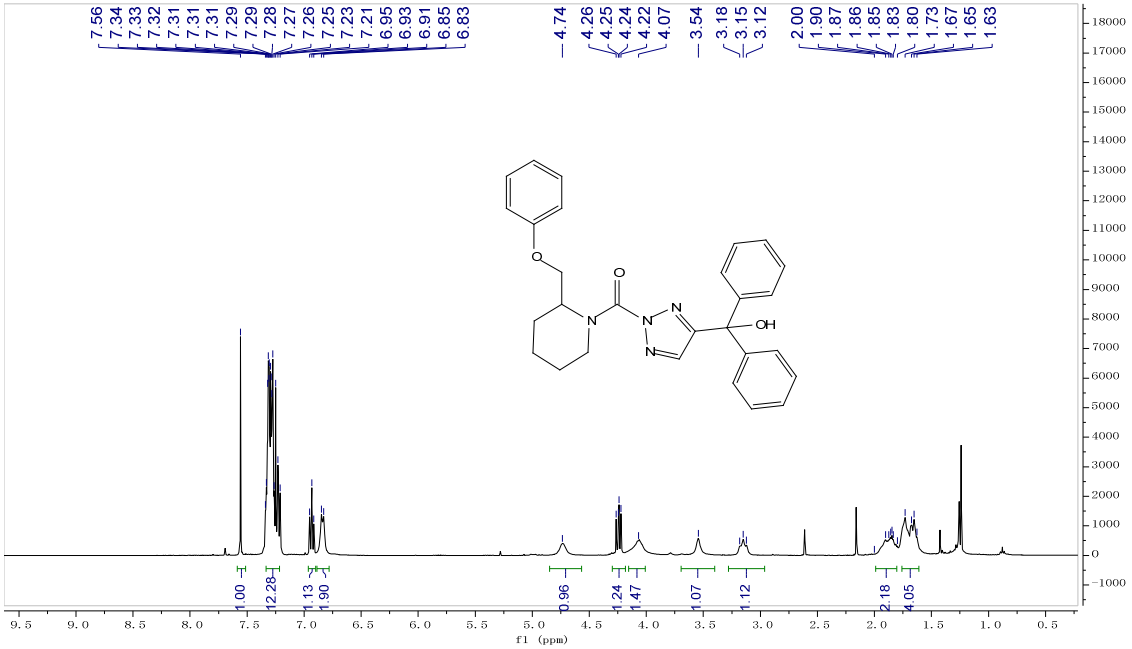
(2-Benzylpiperidin-1-yl)(4-(bis(4-fluorophenyl)(methoxy)methyl)-2*H*-1,2,3-triazol-2-yl)methanone (**13**)

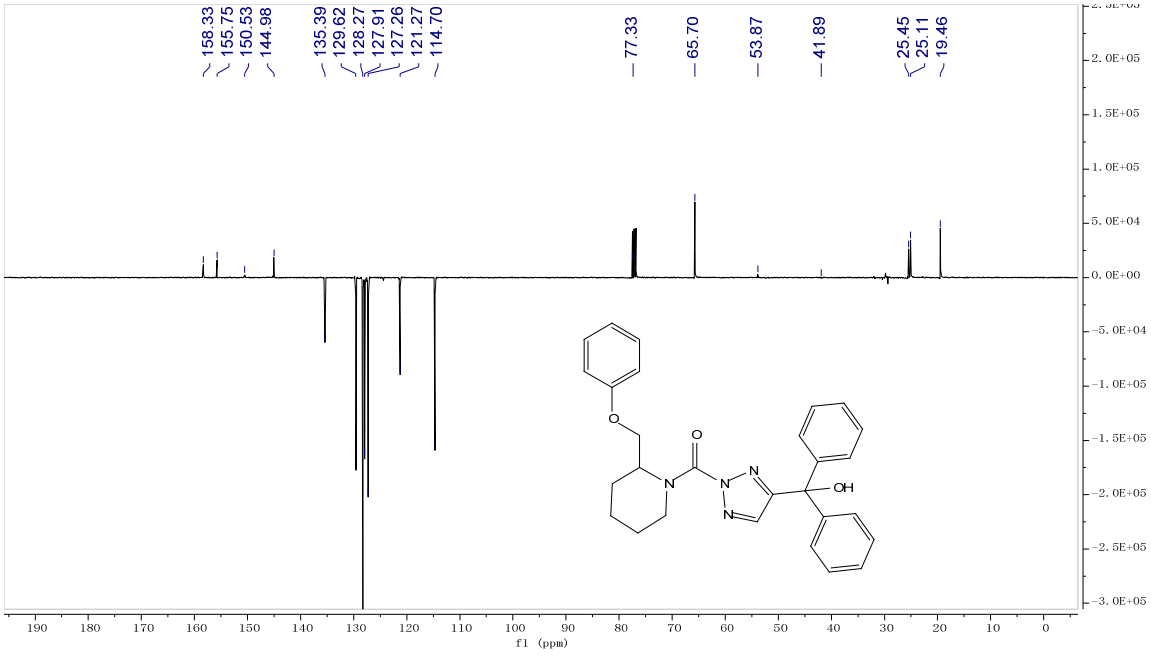




^{1}H and ^{13}C NMR ($CDCl_3$)

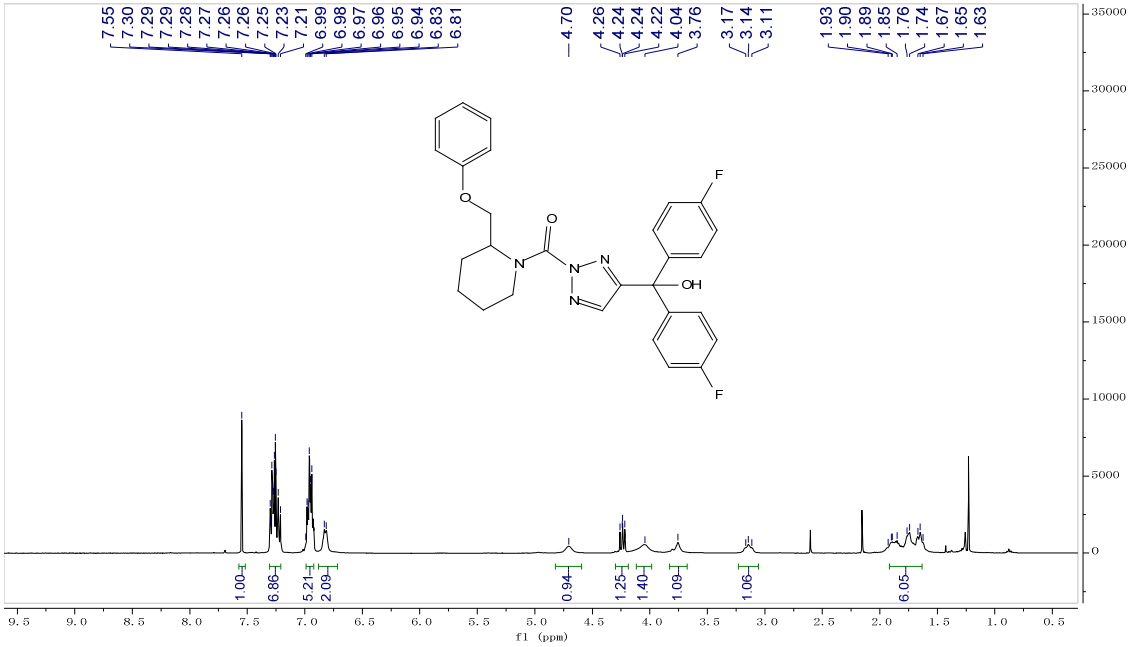
(4-(Hydroxydiphenylmethyl)-2*H*-1,2,3-triazol-2-yl)(2-(phenoxymethyl)piperidin-1-yl)methanone (**14**)

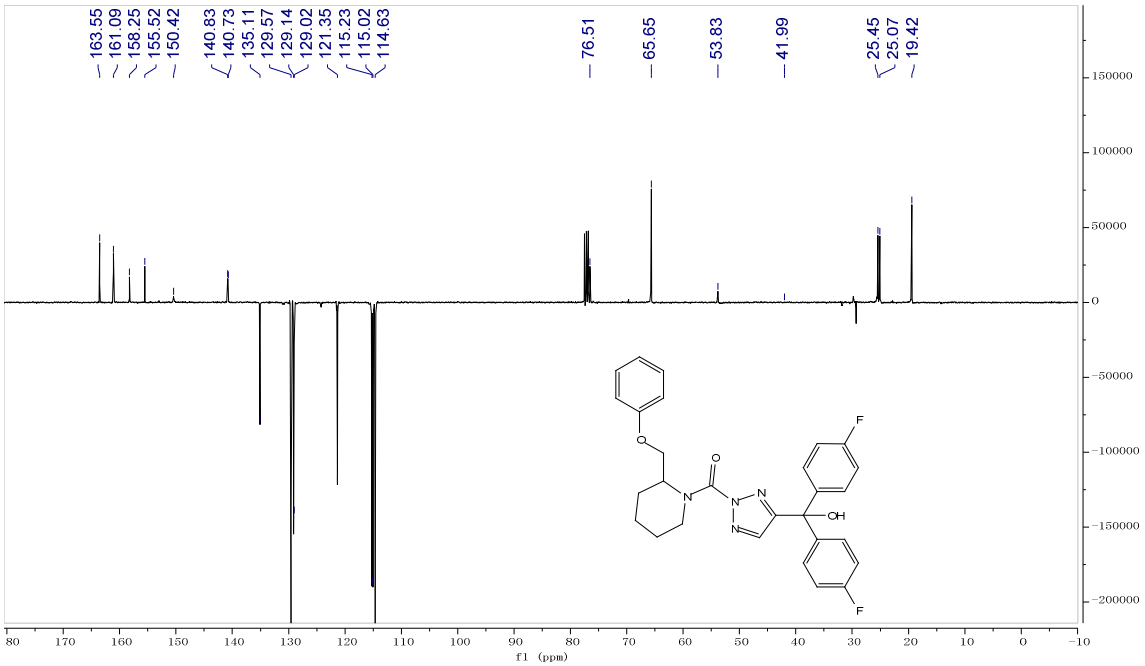




^{1}H and ^{13}C NMR ($CDCl_3$)

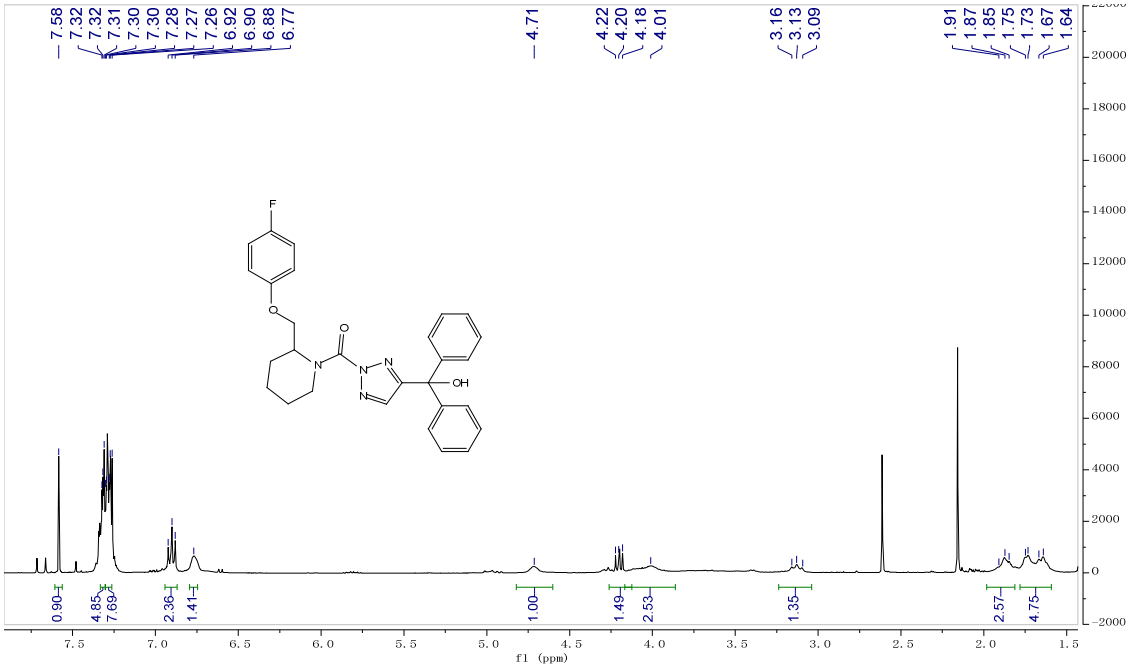
(4-(Bis(4-fluorophenyl)(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)(2-(phenoxymethyl)piperidin-1-yl)methanone (**15**)

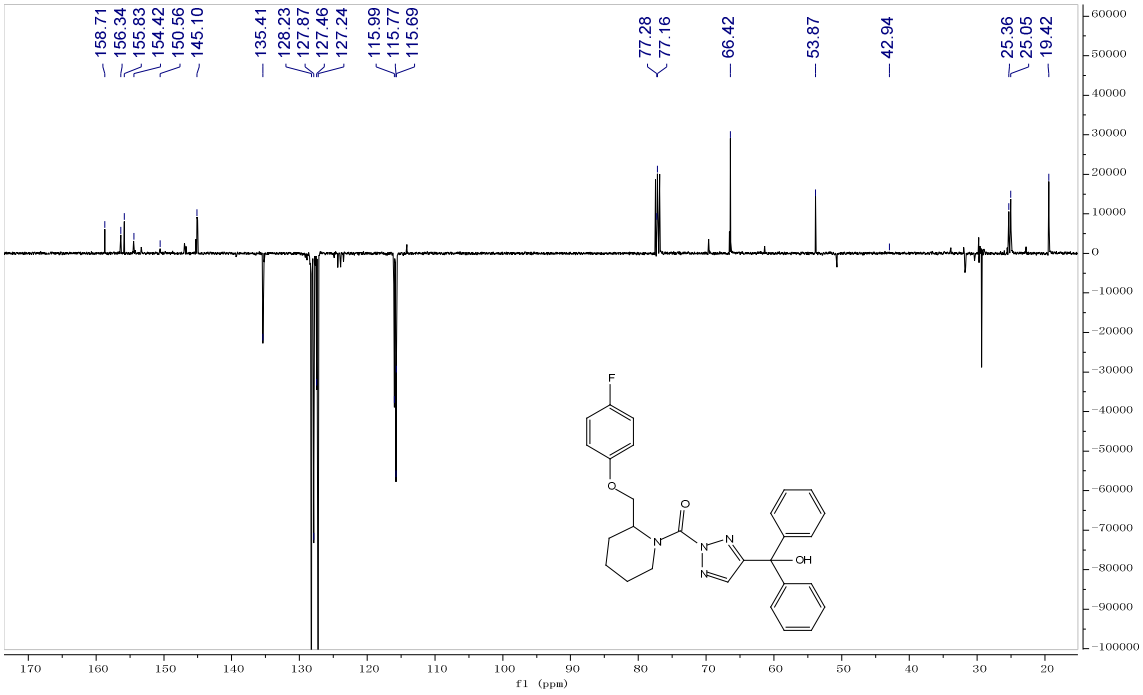




^{1}H and ^{13}C NMR ($CDCl_3$)

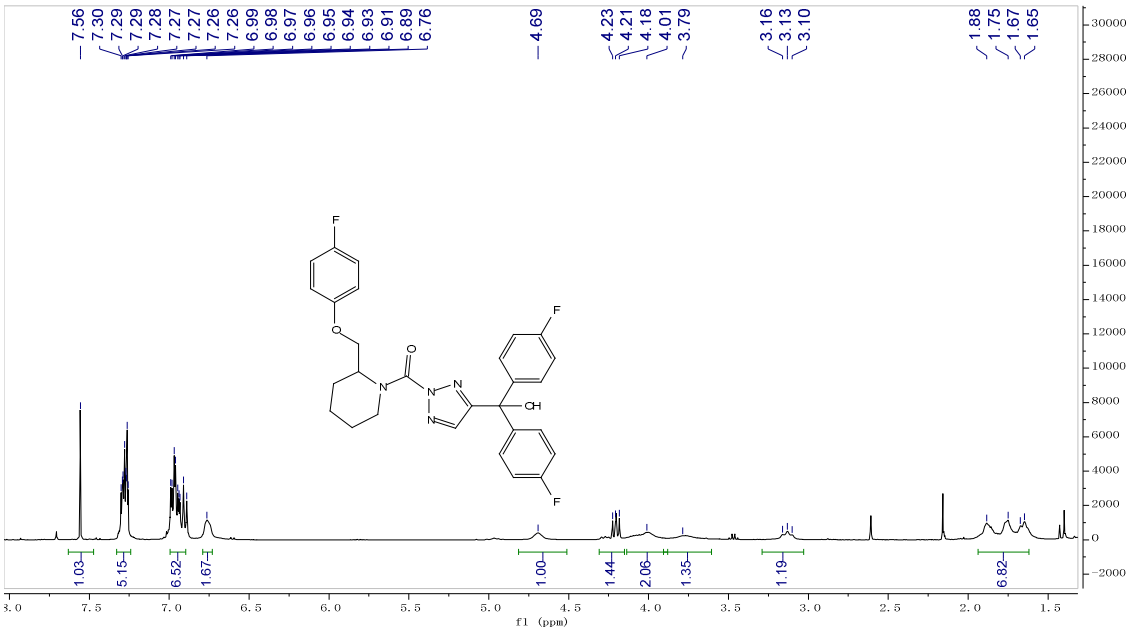
(2-((4-Fluorophenoxy)methyl)piperidin-1-yl)(4-(hydroxydiphenylmethyl)-2*H*-1,2,3-triazol-2-yl)methanone (**16**)

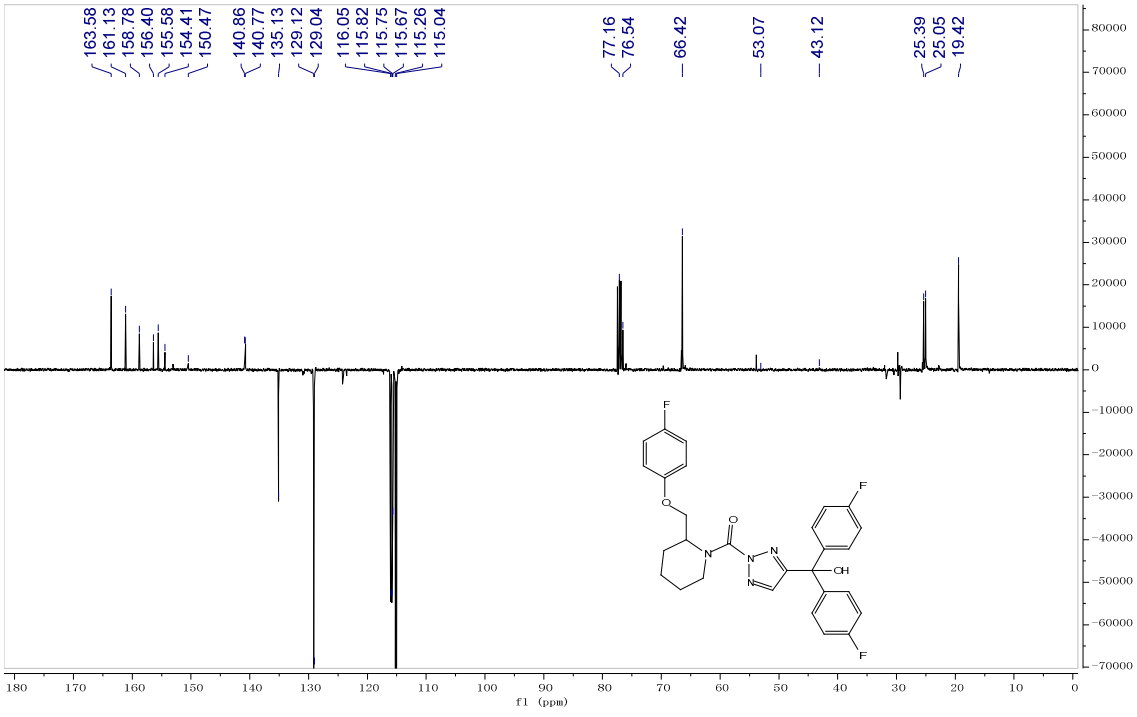




^{1}H and ^{13}C NMR ($CDCl_3$)

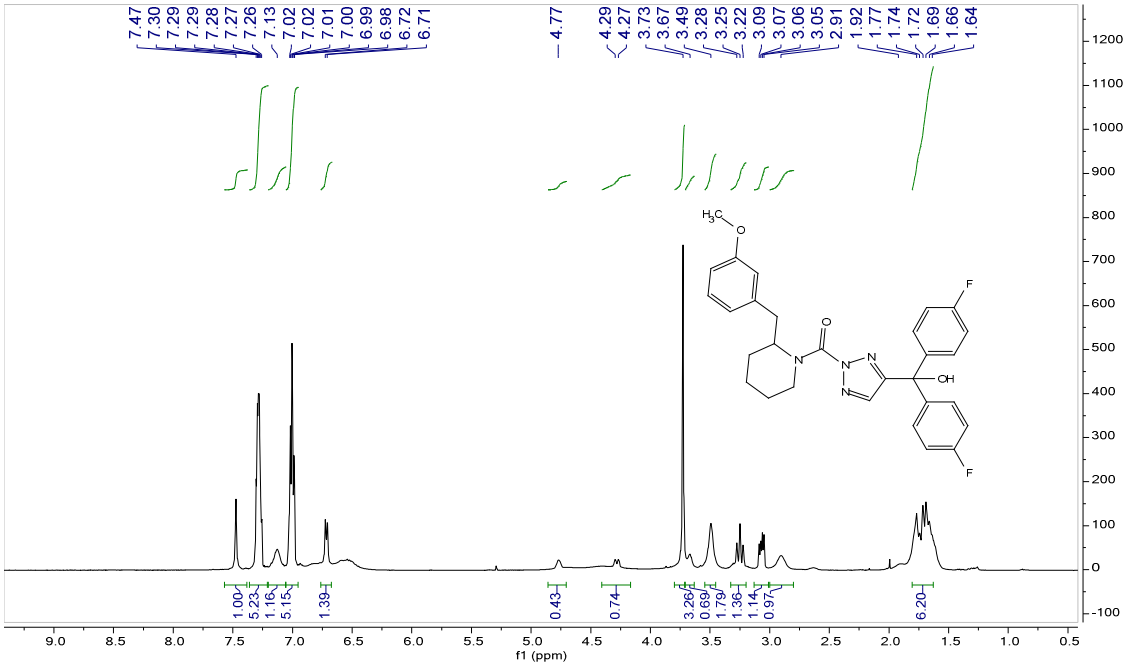
(4-(Bis(4-fluorophenyl)(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)(2-((4-fluorophenoxy)methyl)piperidin-1-yl)methanone (**17**)

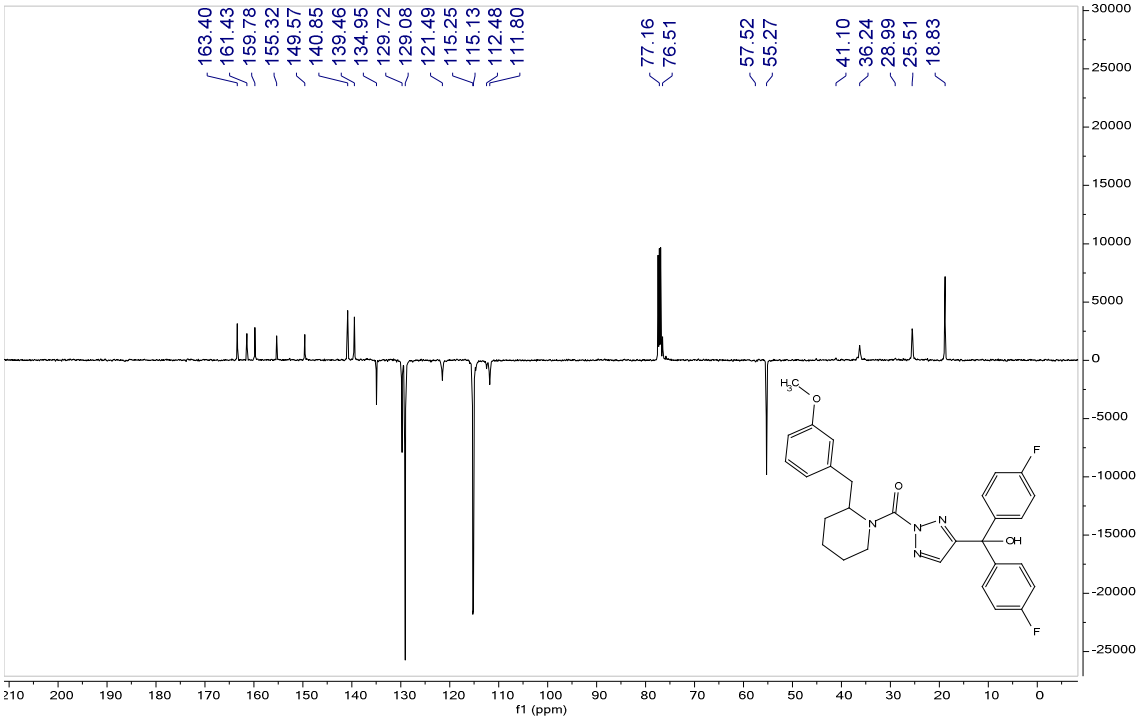




^{1}H and ^{13}C NMR ($CDCl_3$)

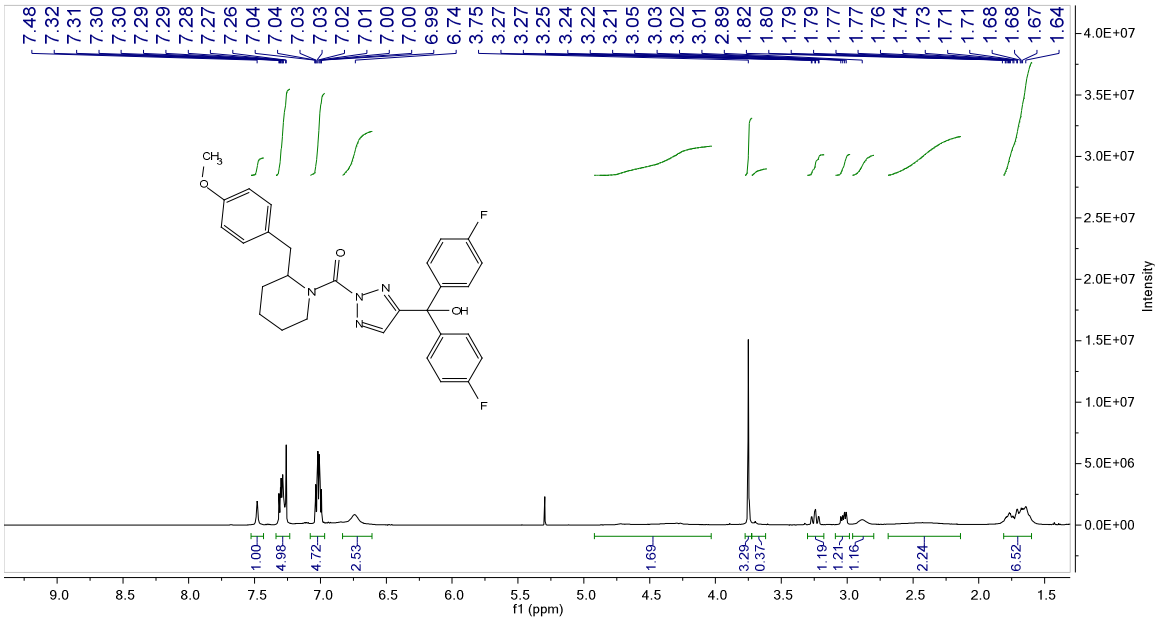
(4-(Bis(4-fluorophenyl)(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)(2-(3-methoxybenzyl)piperidin-1-yl)methanone (**18**)

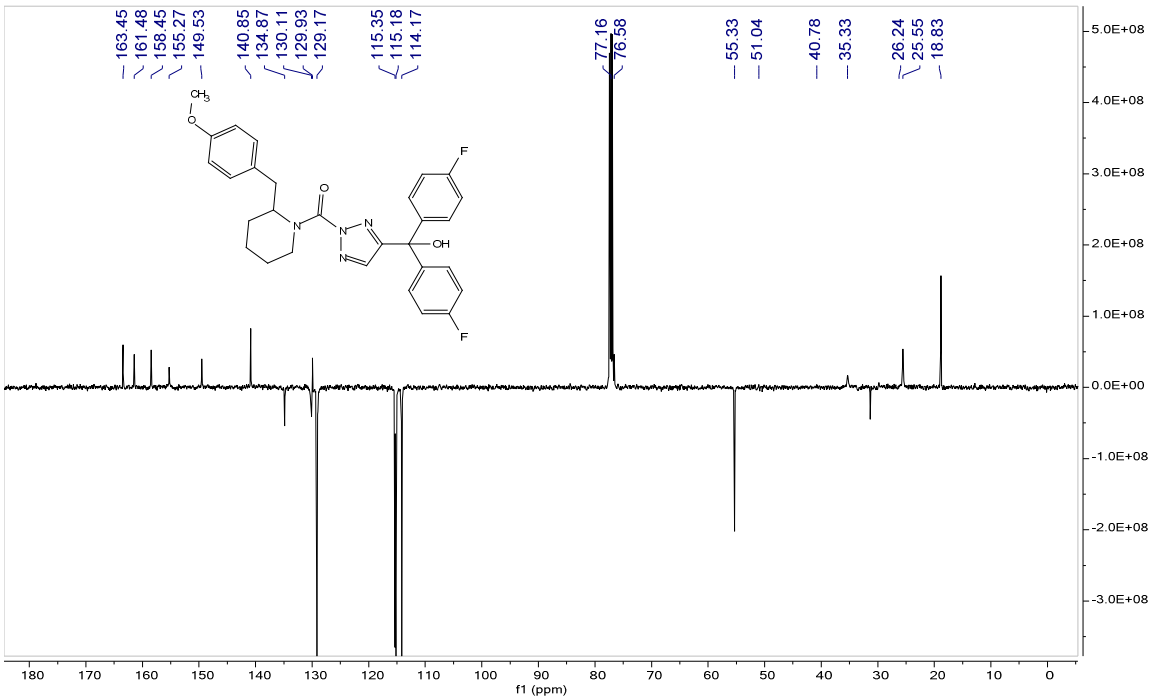




^{1}H and ^{13}C NMR ($CDCl_3$)

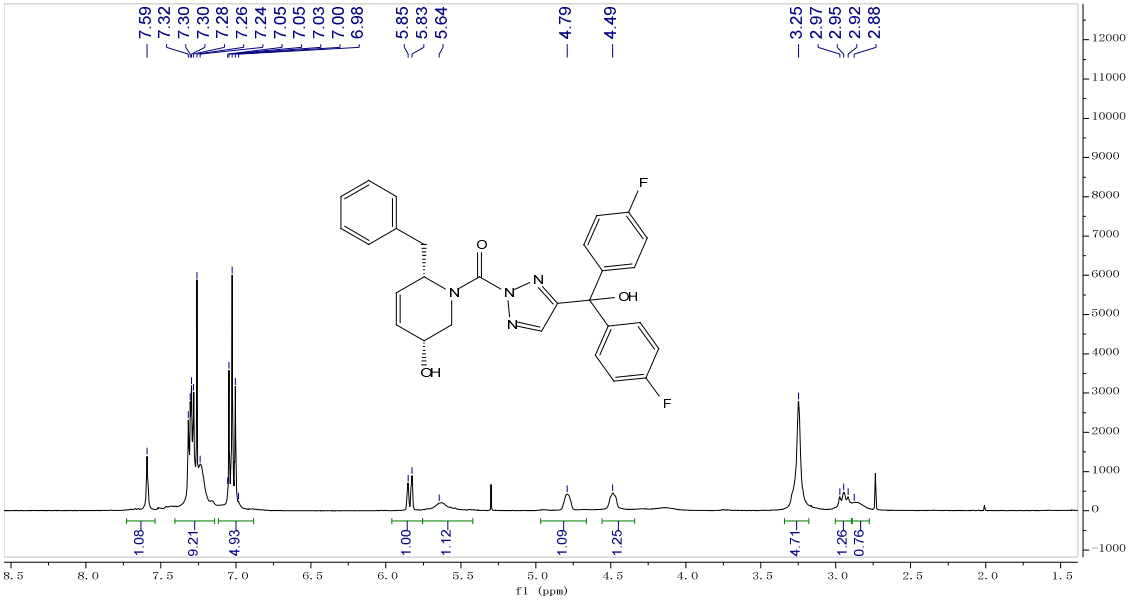
(4-(Bis(4-fluorophenyl)(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)(2-(4-methoxybenzyl)piperidin-1-yl)methanone (**19**)

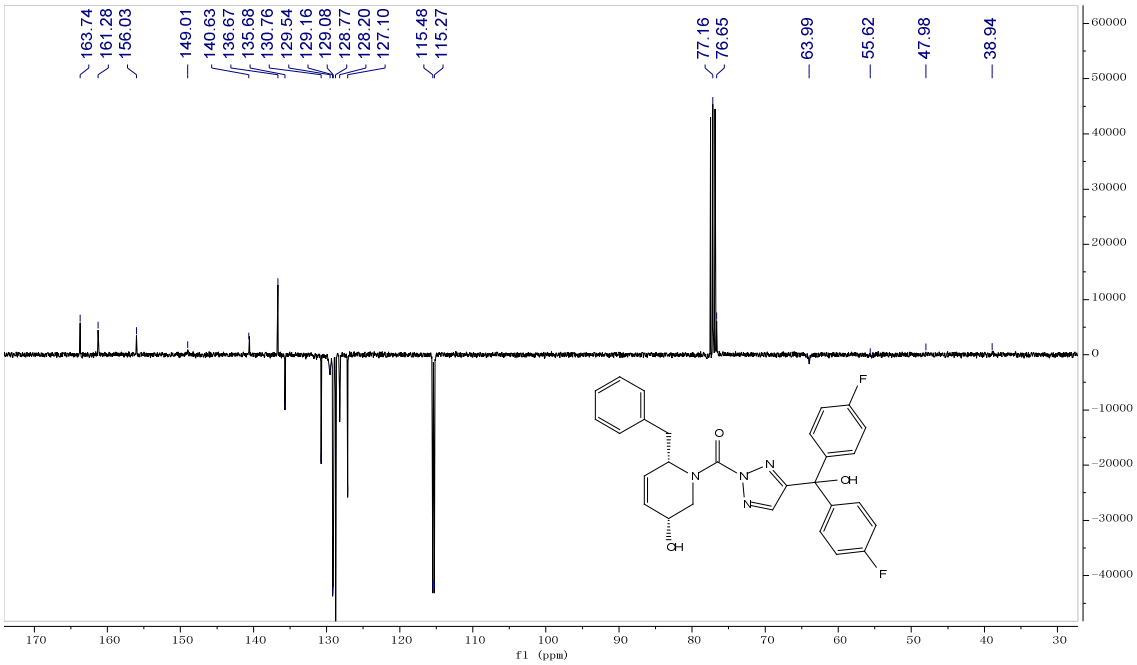




^{1}H and ^{13}C NMR ($CDCl_3$)

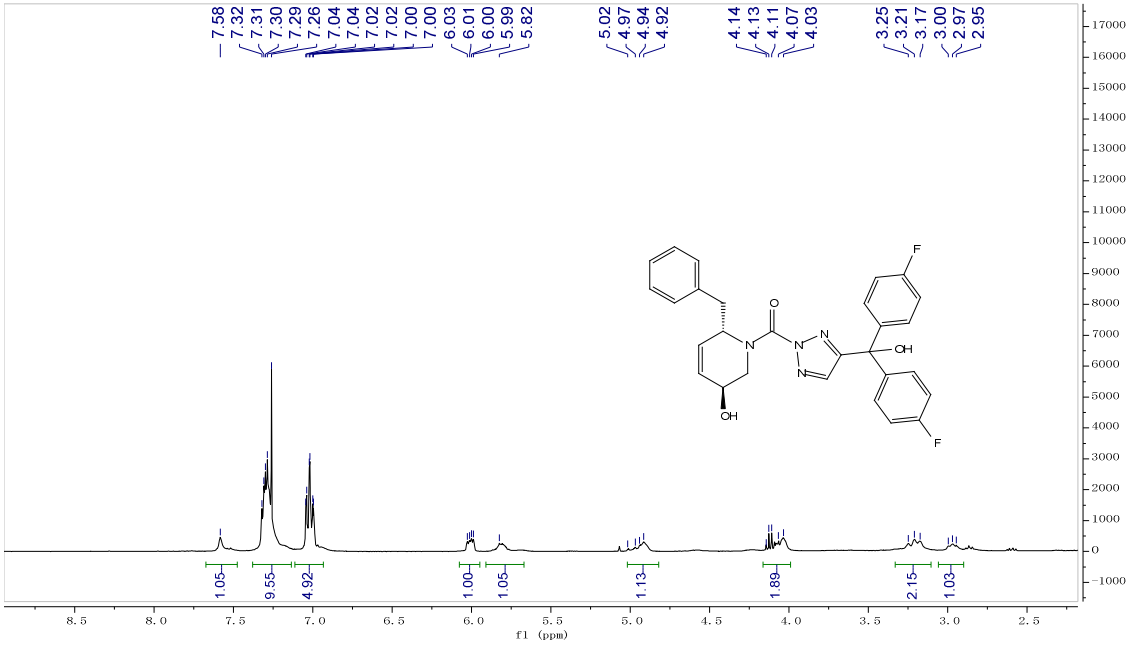
(*(3R,6S)*-6-Benzyl-3-hydroxy-3,6-dihydropyridin-1(2H)-yl)(4-(bis(4-fluorophenyl)(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)methanone (**30**)

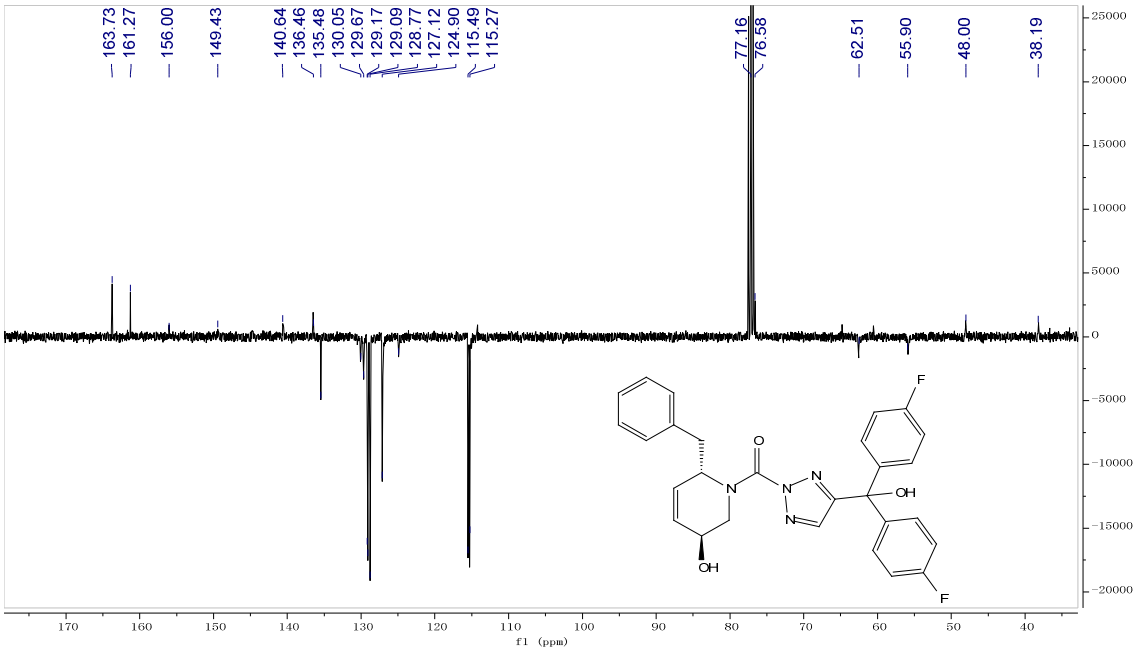




^{1}H and ^{13}C NMR ($CDCl_3$)

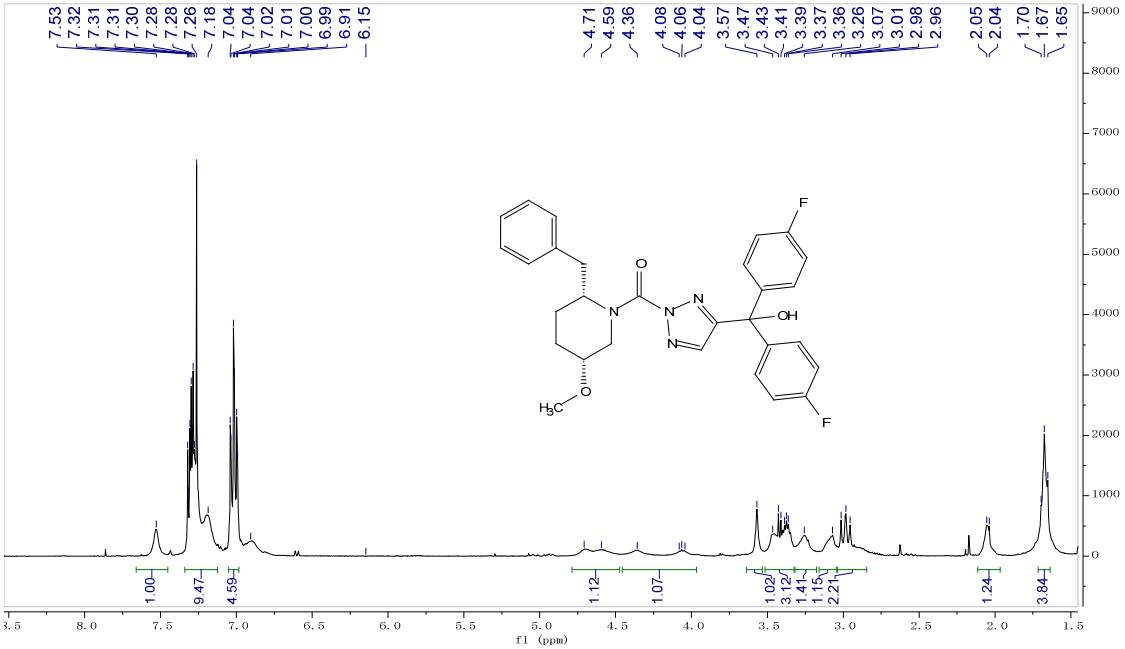
((*3S,6S*)-6-Benzyl-3-hydroxy-3,6-dihydropyridin-1(2H)-yl)(4-(bis(4-fluorophenyl)(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)methanone (**32**)

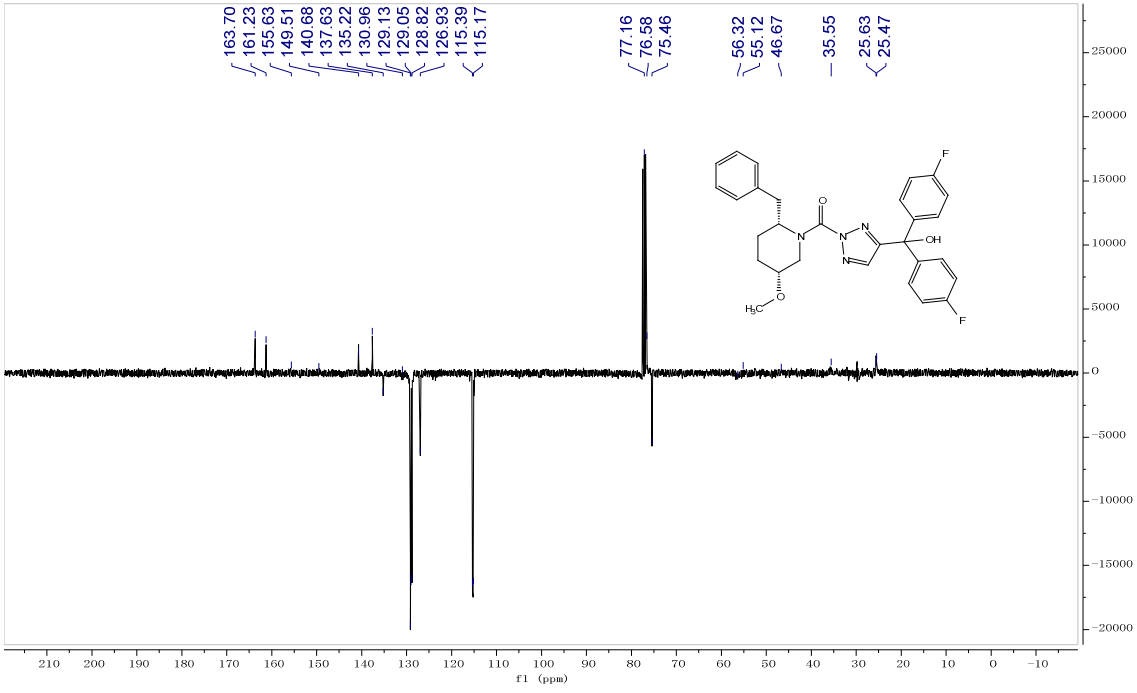




^{1}H and ^{13}C NMR ($CDCl_3$)

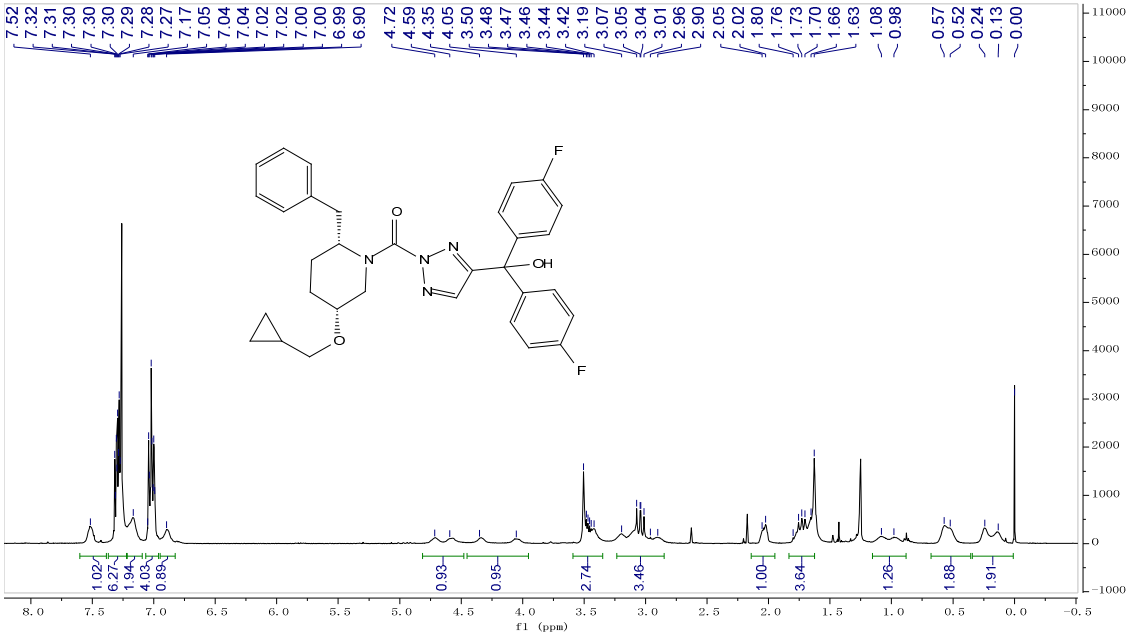
((*2R,5R)*-2-Benzyl-5-methoxypiperidin-1-yl)(4-(bis(4-fluorophenyl)(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)methanone (**34**)

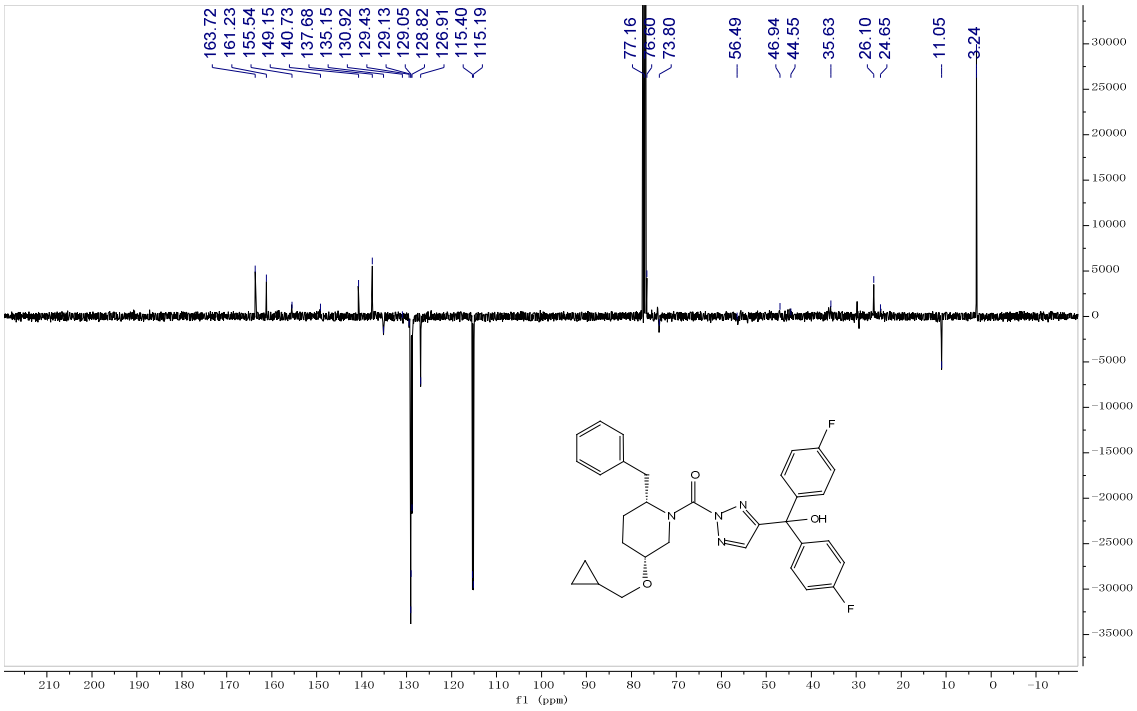




^{1}H and ^{13}C NMR ($CDCl_3$)

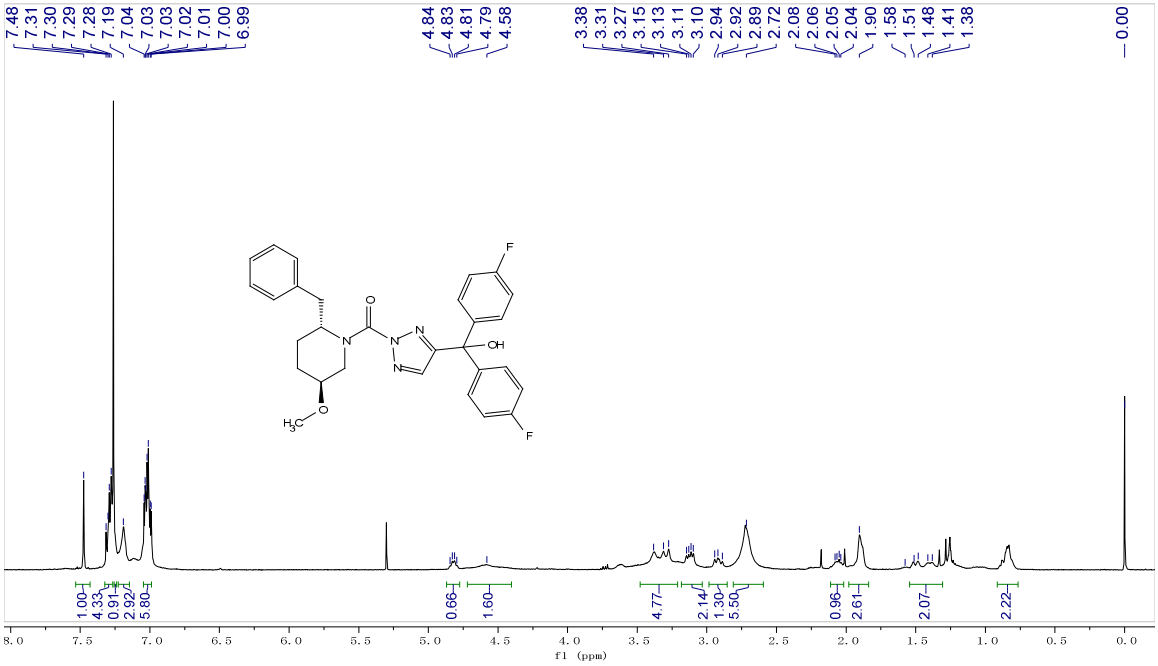
((*2R,5R)*-2-Benzyl-5-(cyclopropylmethoxy)piperidin-1-yl)(4-(bis(4-fluorophenyl)(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)methanone (**35**)

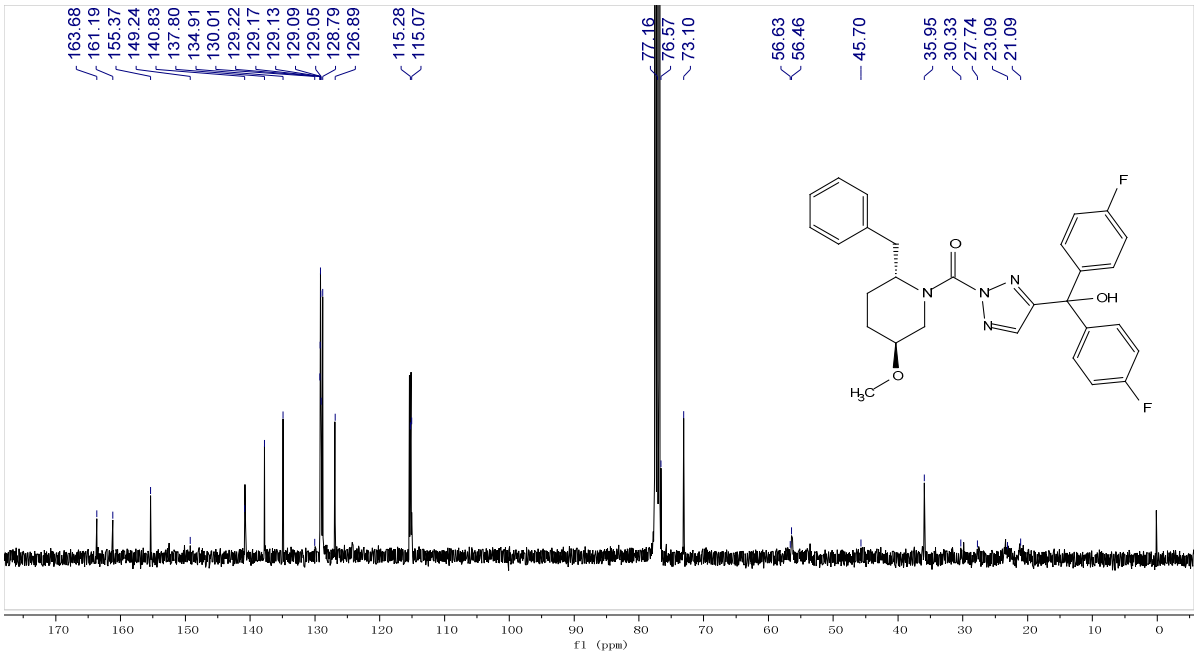




^{1}H and ^{13}C NMR ($CDCl_3$)

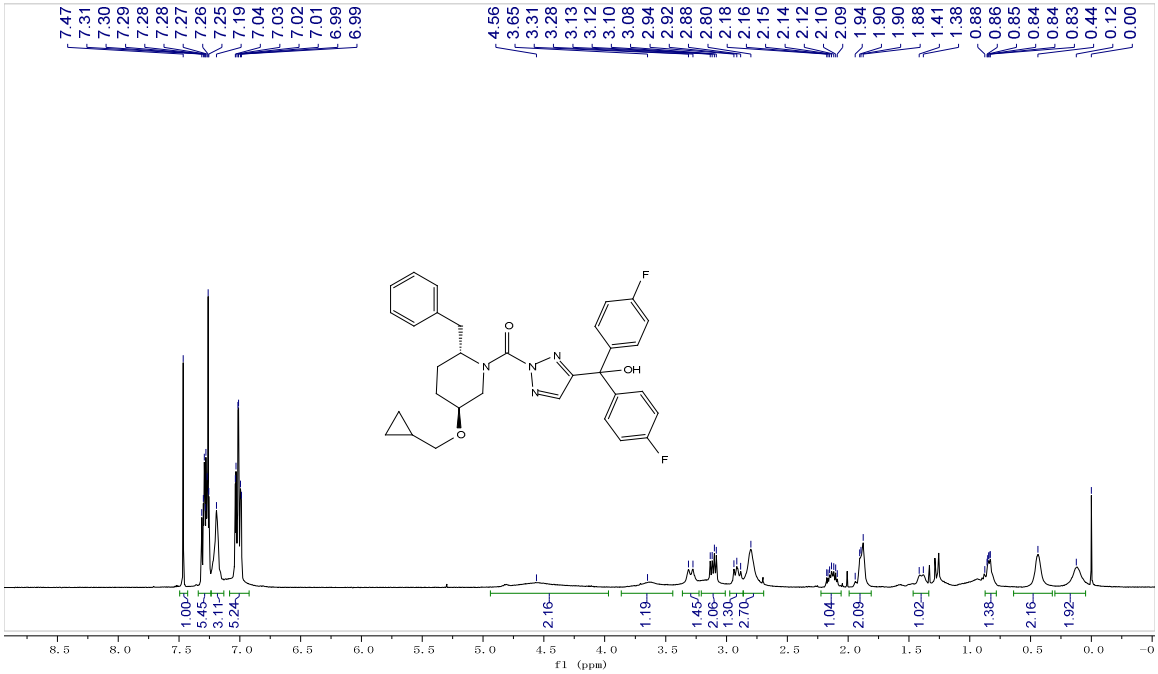
(*(2R,5S)*-2-Benzyl-5-methoxypiperidin-1-yl)(4-(bis(4-fluorophenyl)(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)methanone (**36**)

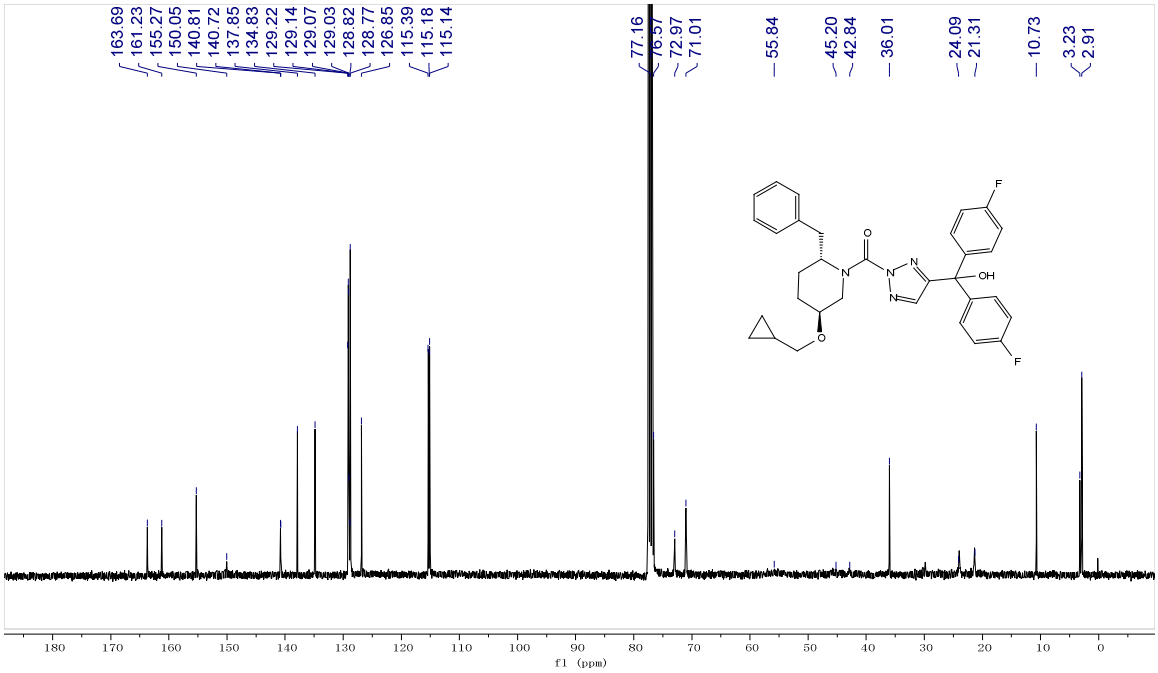




^{1}H and ^{13}C NMR ($CDCl_3$)

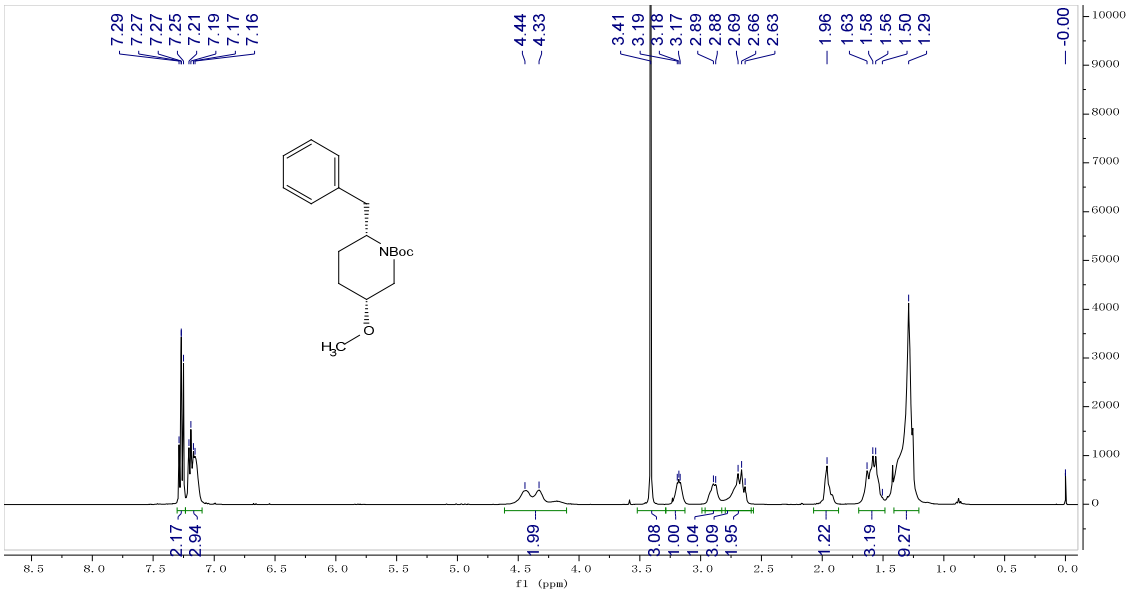
(*(2R,5S)*-2-Benzyl-5-(cyclopropylmethoxy)piperidin-1-yl)(4-(bis(4-fluorophenyl)(hydroxy)methyl)-2*H*-1,2,3-triazol-2-yl)methanone (**37**)

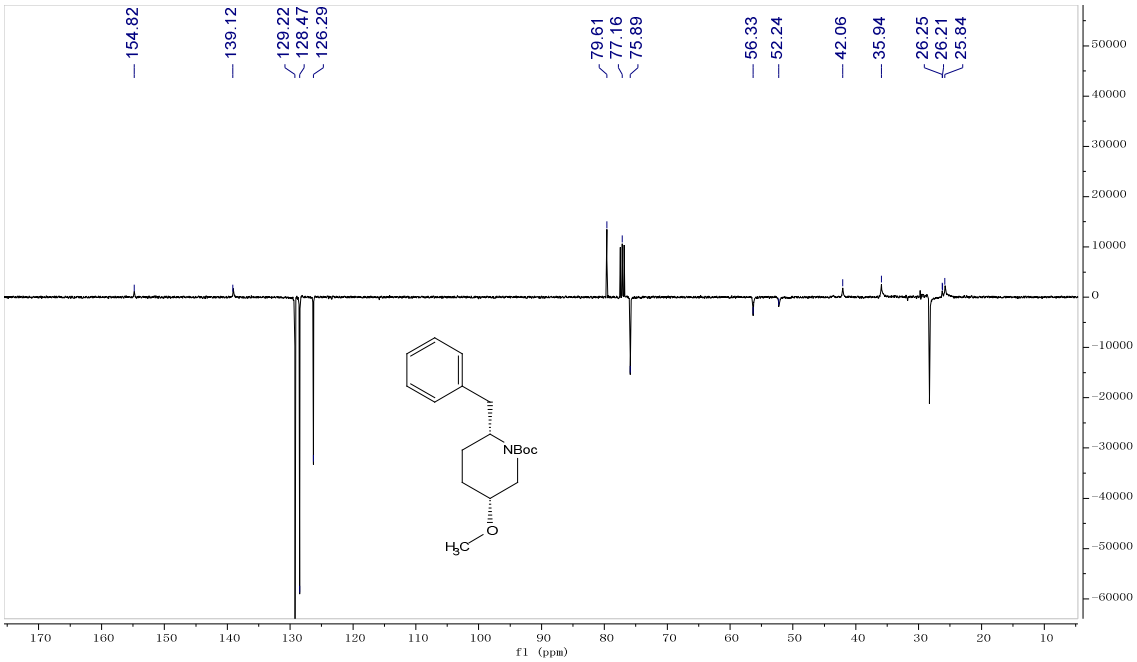




^{1}H and ^{13}C NMR ($CDCl_3$)

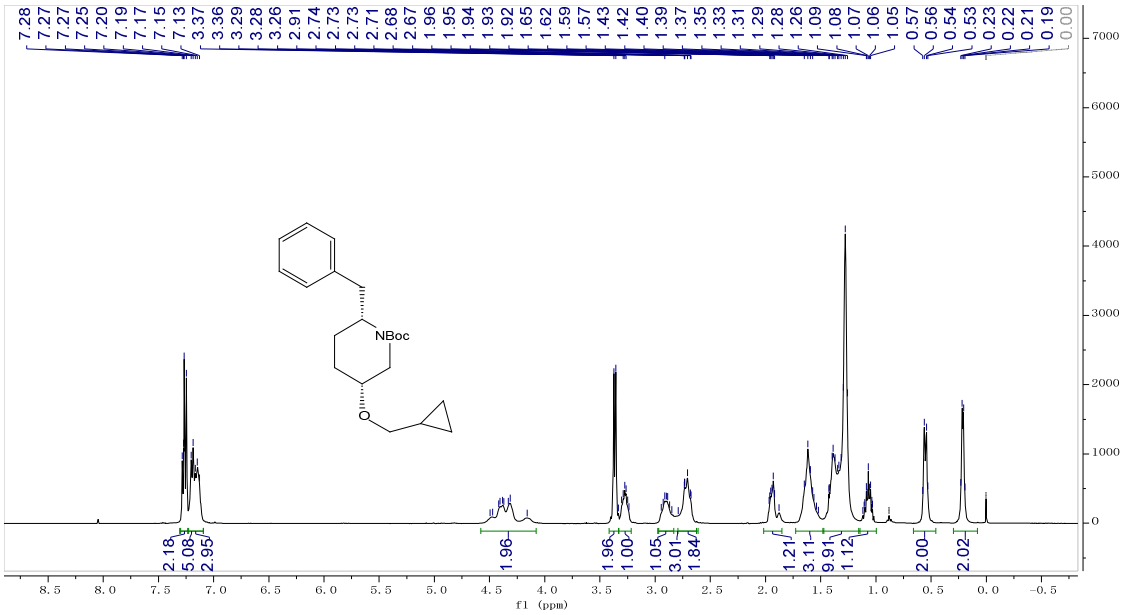
tert-Butyl *(2R,5R)*-2-benzyl-5-methoxypiperidine-1-carboxylate (**51**)

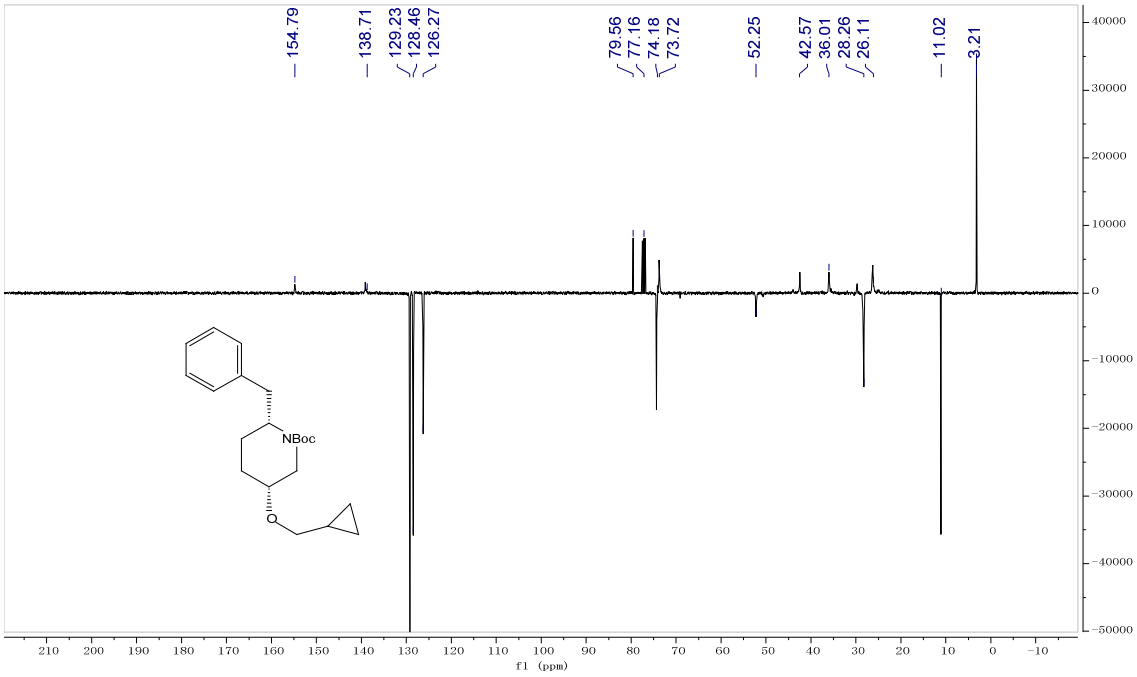




^{1}H and ^{13}C NMR ($CDCl_3$)

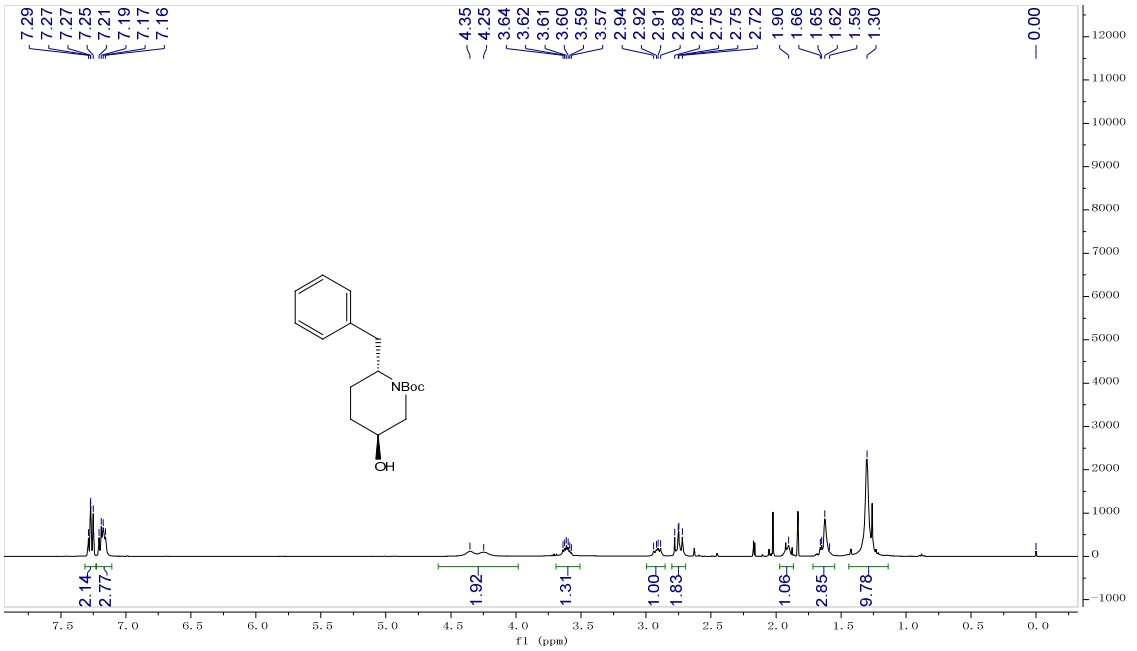
tert-Butyl *(2R,5R)*-2-benzyl-5-(cyclopropylmethoxy)piperidine-1-carboxylate (**52**)

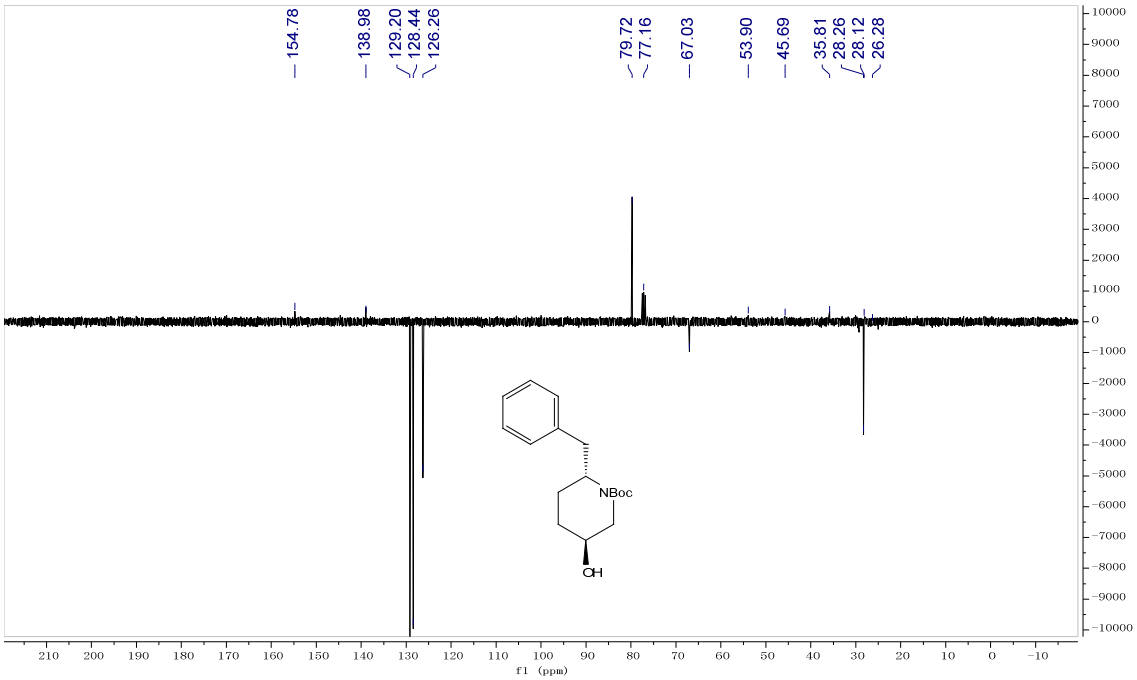




^{1}H and ^{13}C NMR ($CDCl_3$)

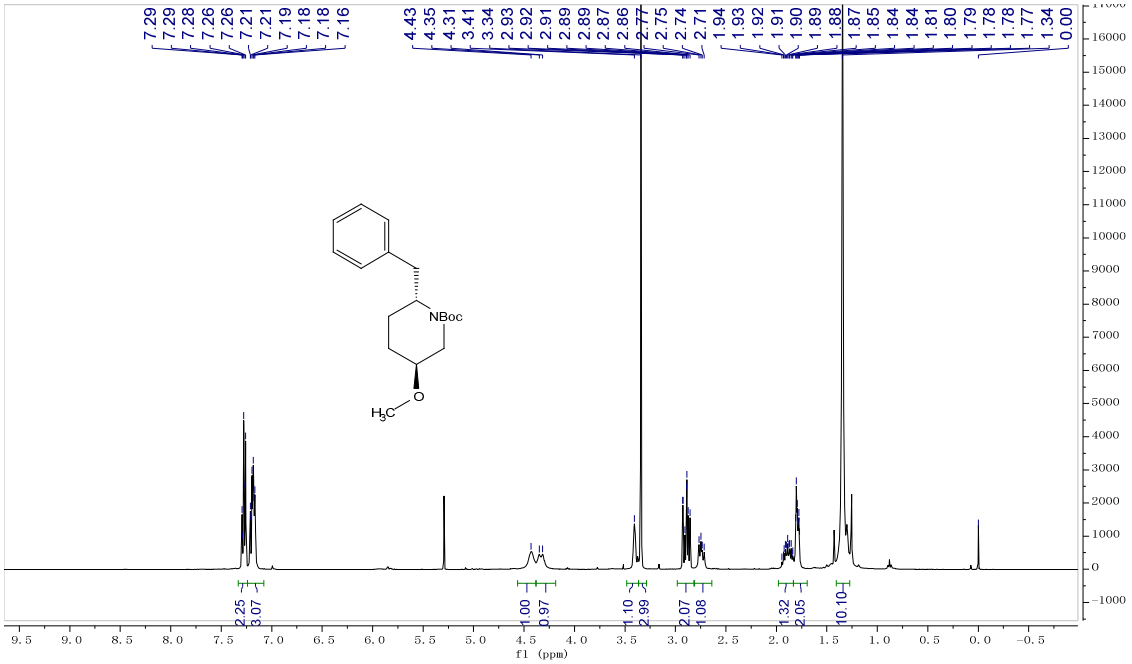
tert-Butyl *(2R,5S)*-2-benzyl-5-hydroxypiperidine-1-carboxylate (**90**)

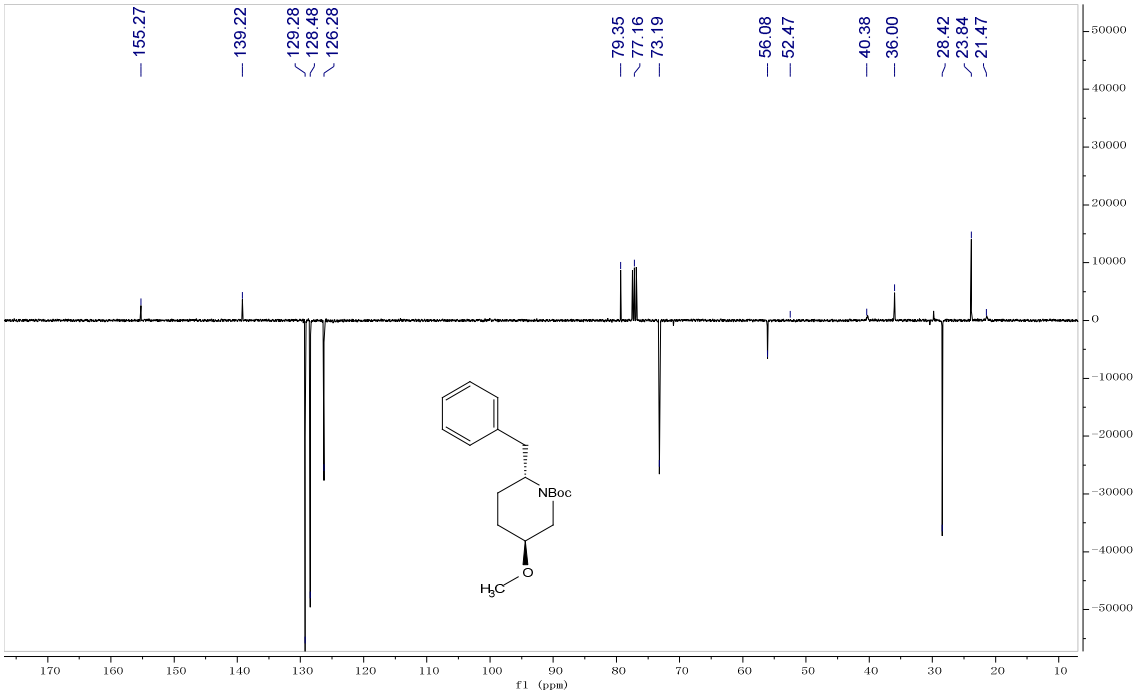




^{1}H and ^{13}C NMR ($CDCl_3$)

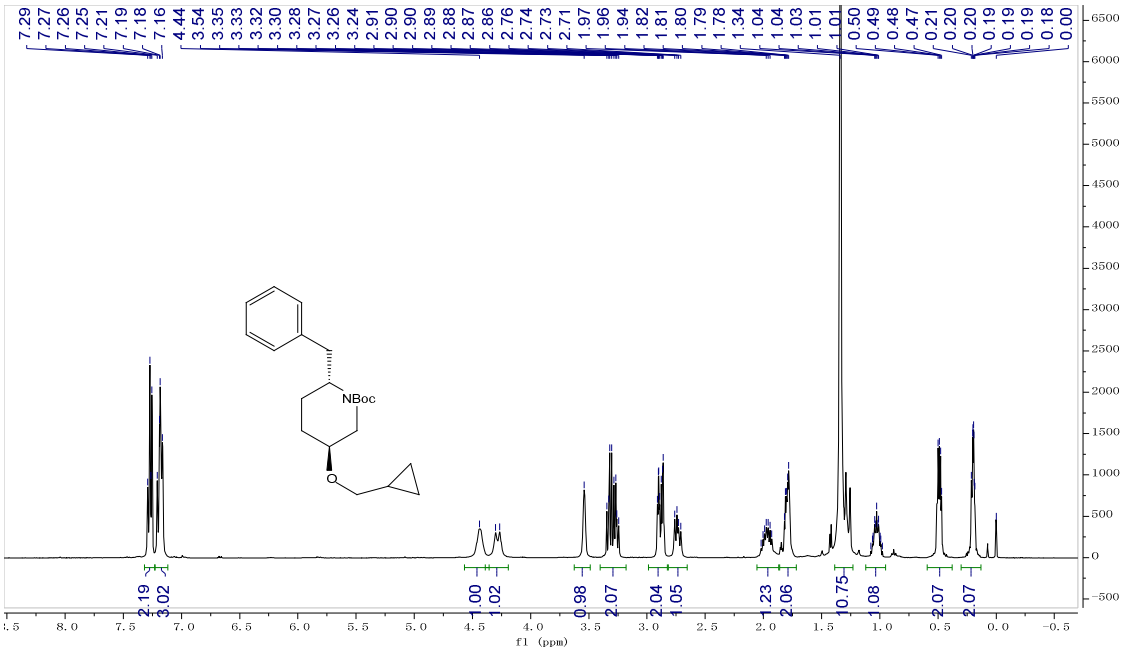
tert-Butyl (*2R,5S*)-2-benzyl-5-methoxypiperidine-1-carboxylate (**91**)

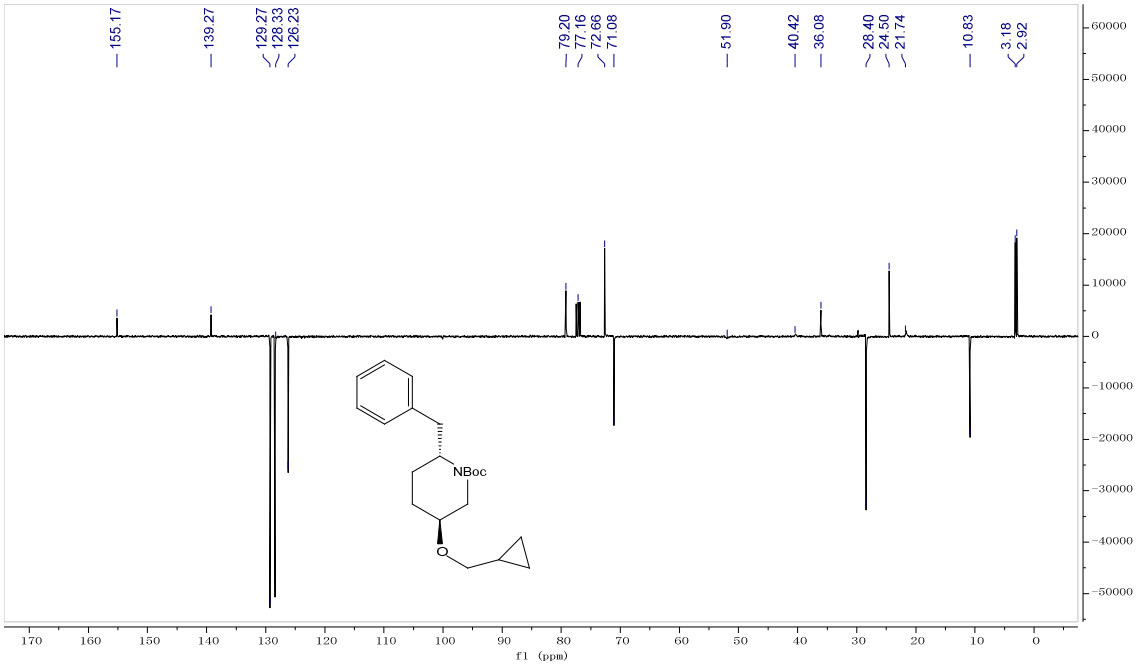




^{1}H and ^{13}C NMR ($CDCl_3$)

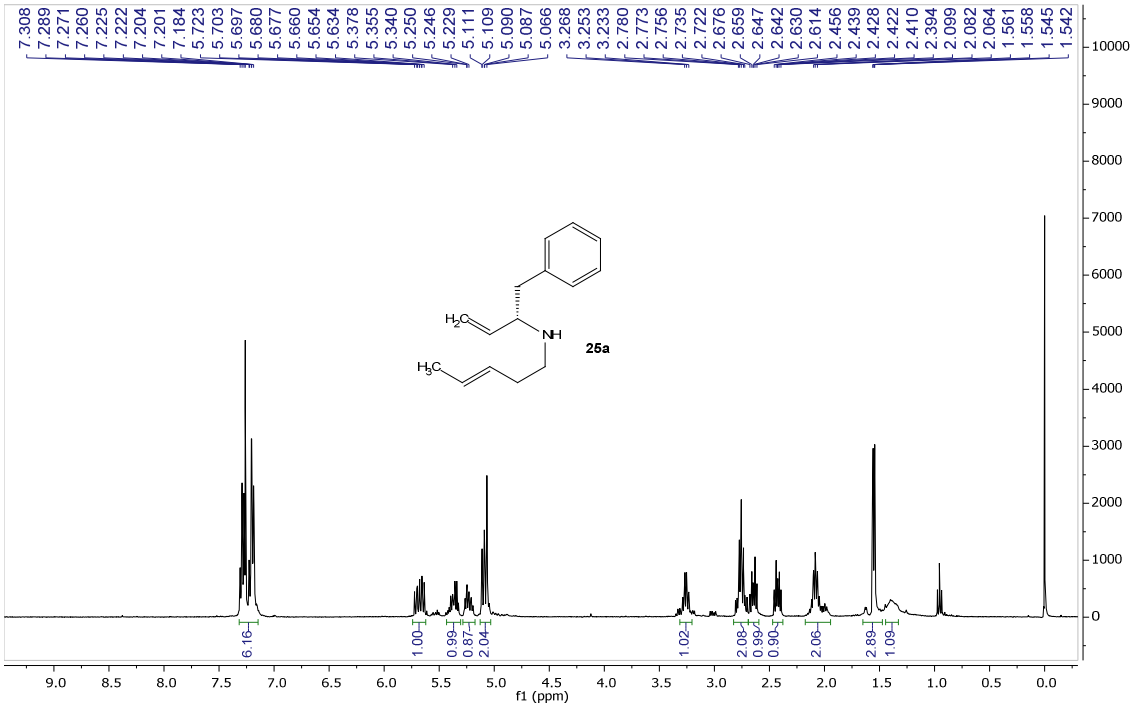
tert-Butyl *(2R,5S)*-2-benzyl-5-(cyclopropylmethoxy)piperidine-1-carboxylate (**93**)

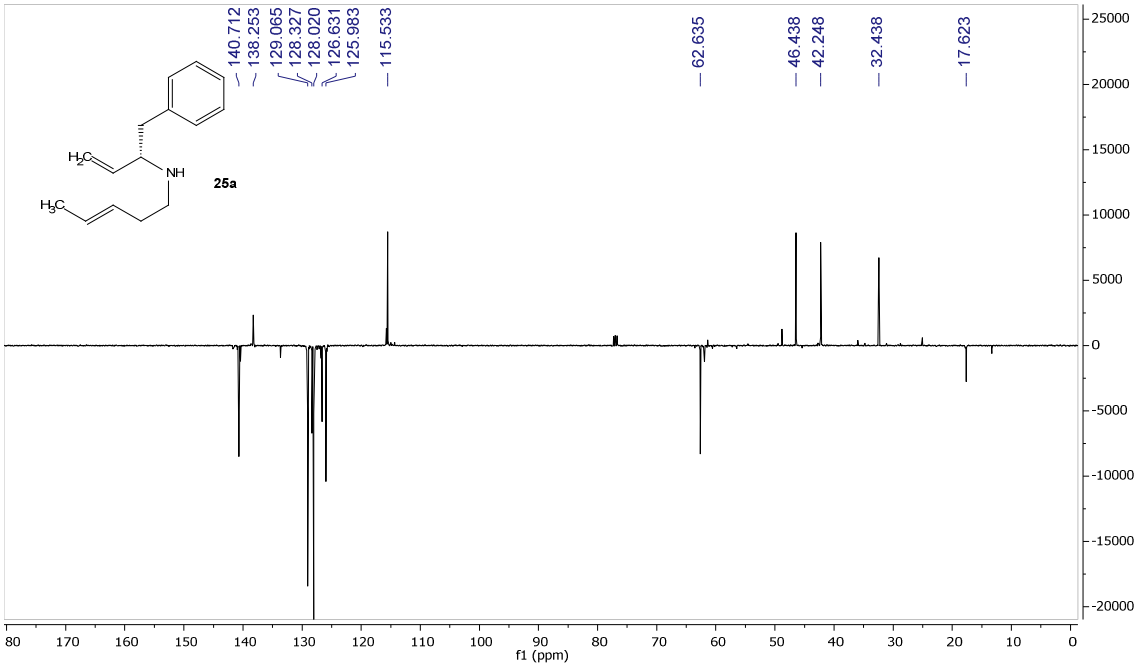




^{1}H and ^{13}C NMR ($CDCl_3$)

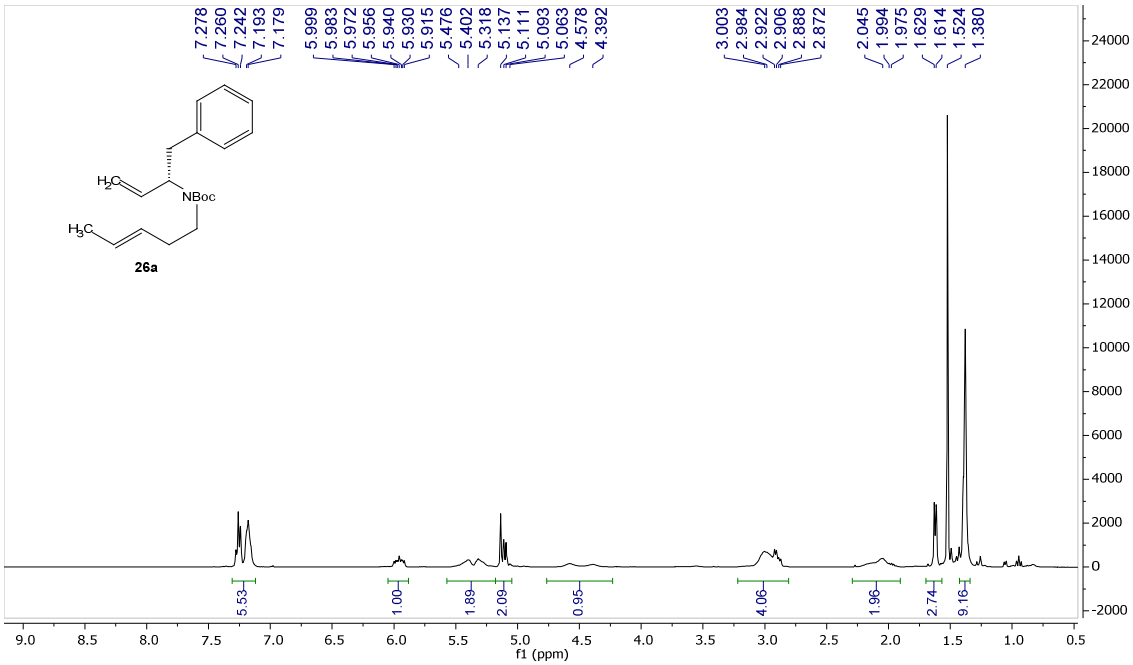
(S,E)-N-(1-Phenylbut-3-en-2-yl)pent-3-en-1-amine (**25a**)

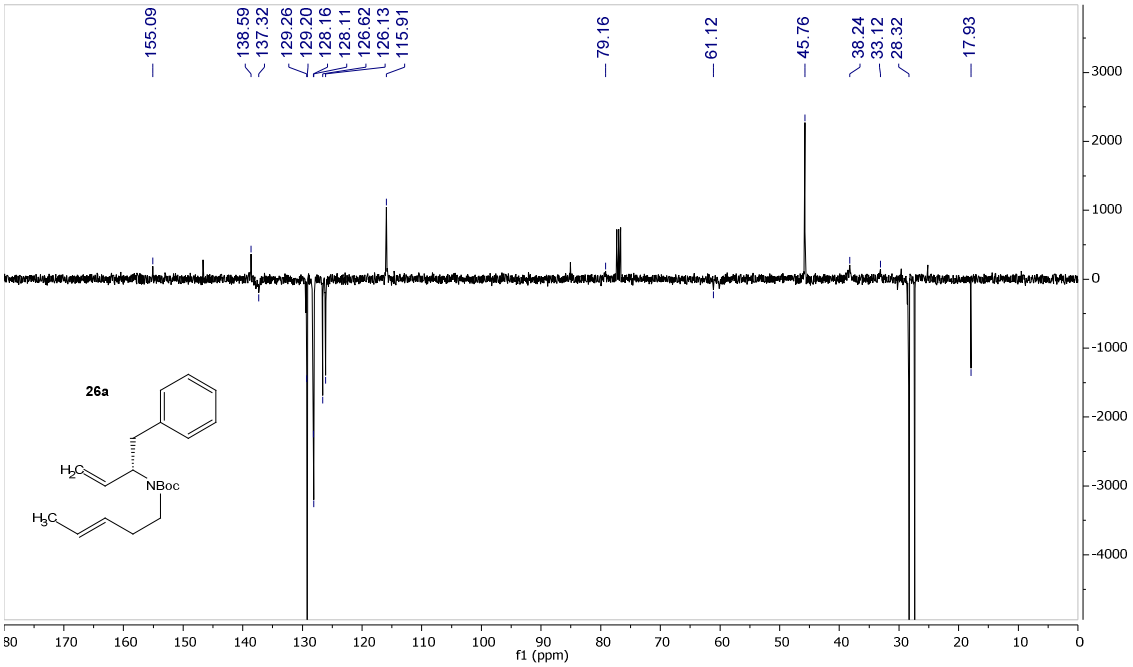




^{1}H and ^{13}C NMR ($CDCl_3$)

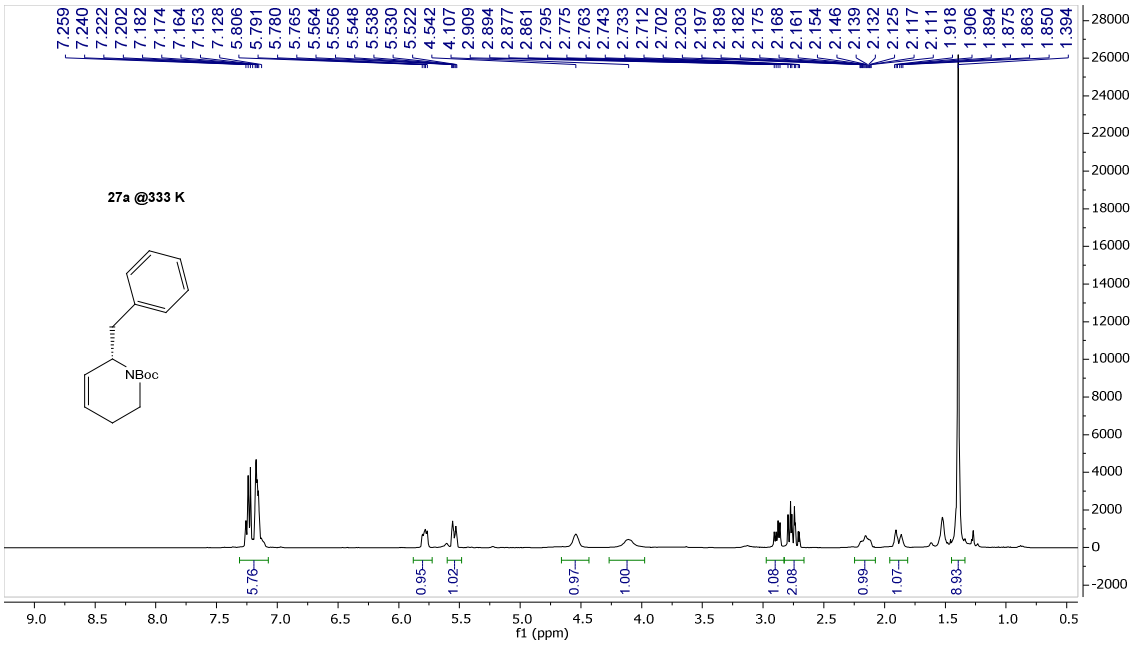
tert-Butyl *(S,E)*-pent-3-en-1-yl(1-phenylbut-3-en-2-yl)carbamate (**26a**)

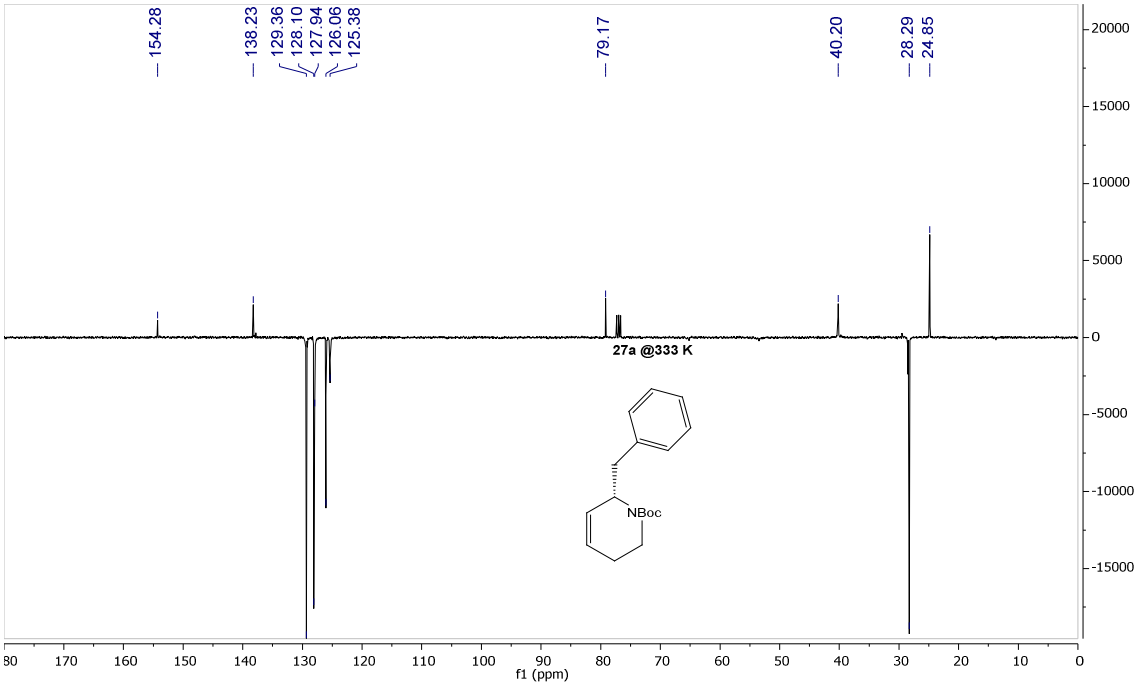




^{1}H and ^{13}C NMR ($CDCl_3$)

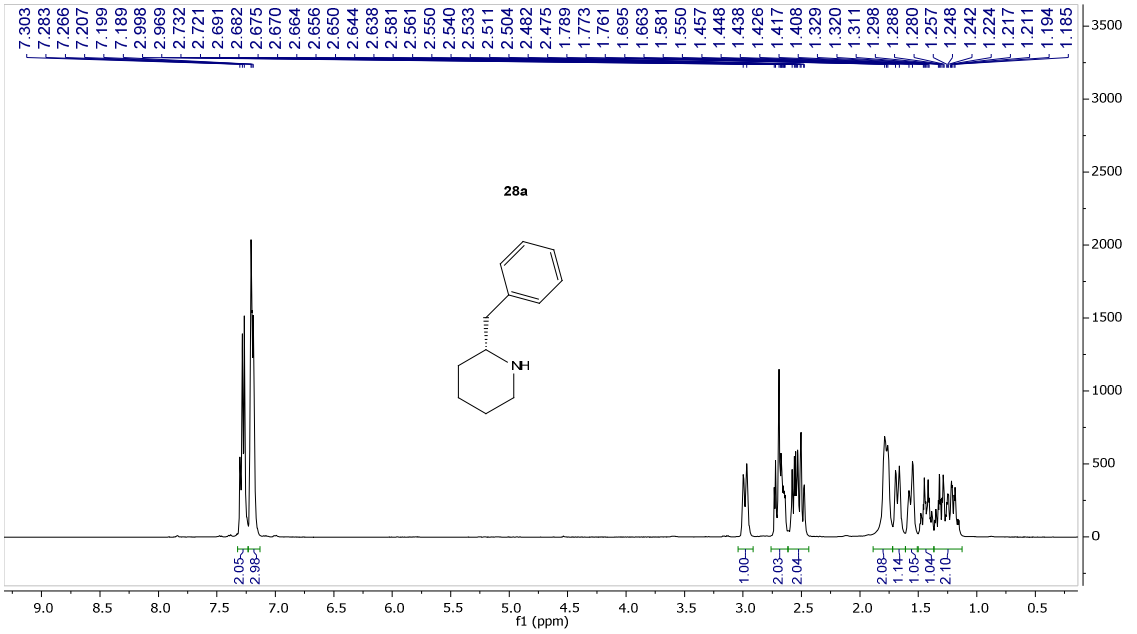
tert-Butyl *(S)*-6-benzyl-3,6-dihydropyridine-1(2H)-carboxylate (**27a**).

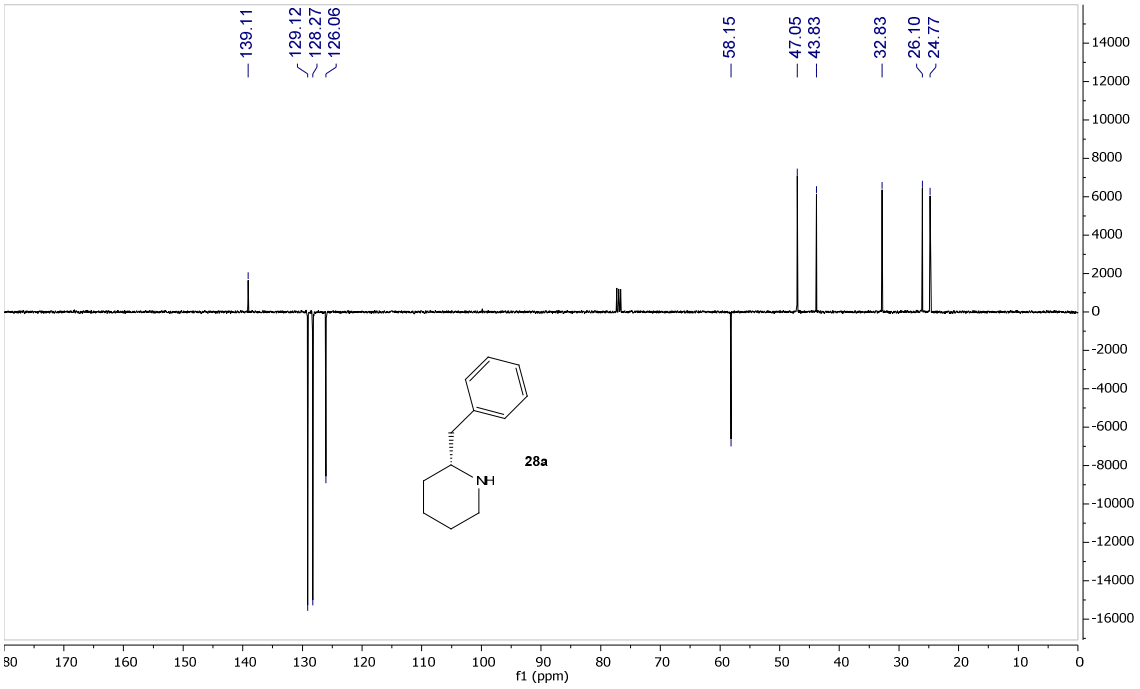




^{1}H and ^{13}C NMR ($CDCl_3$)

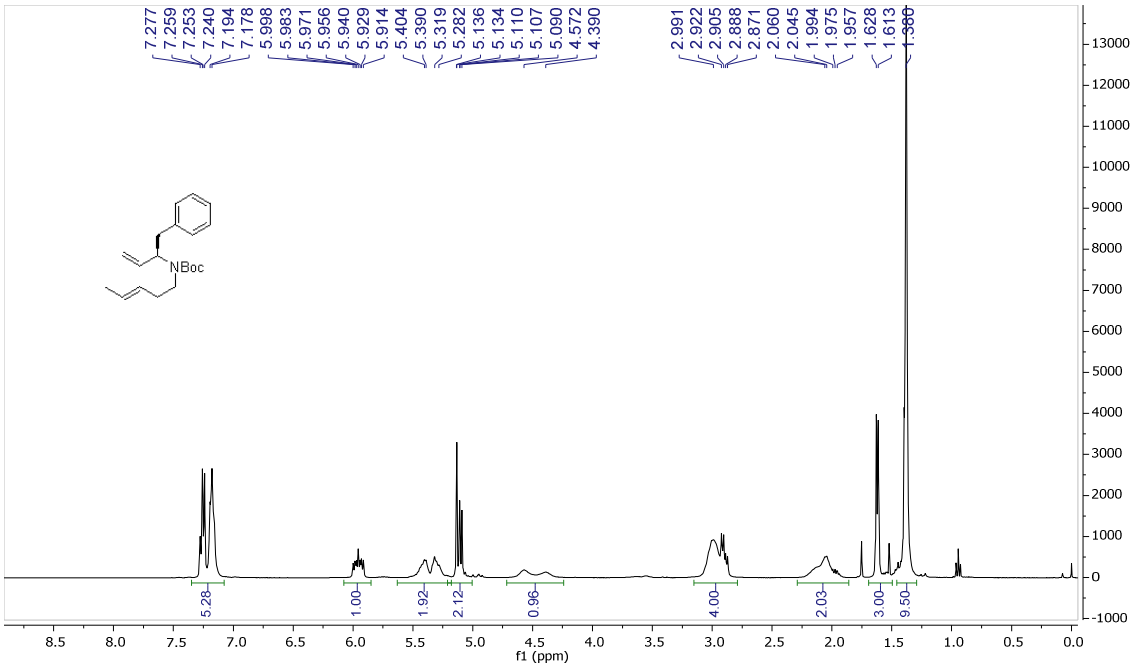
(R)-2-Benzylpiperidine (**28a**)

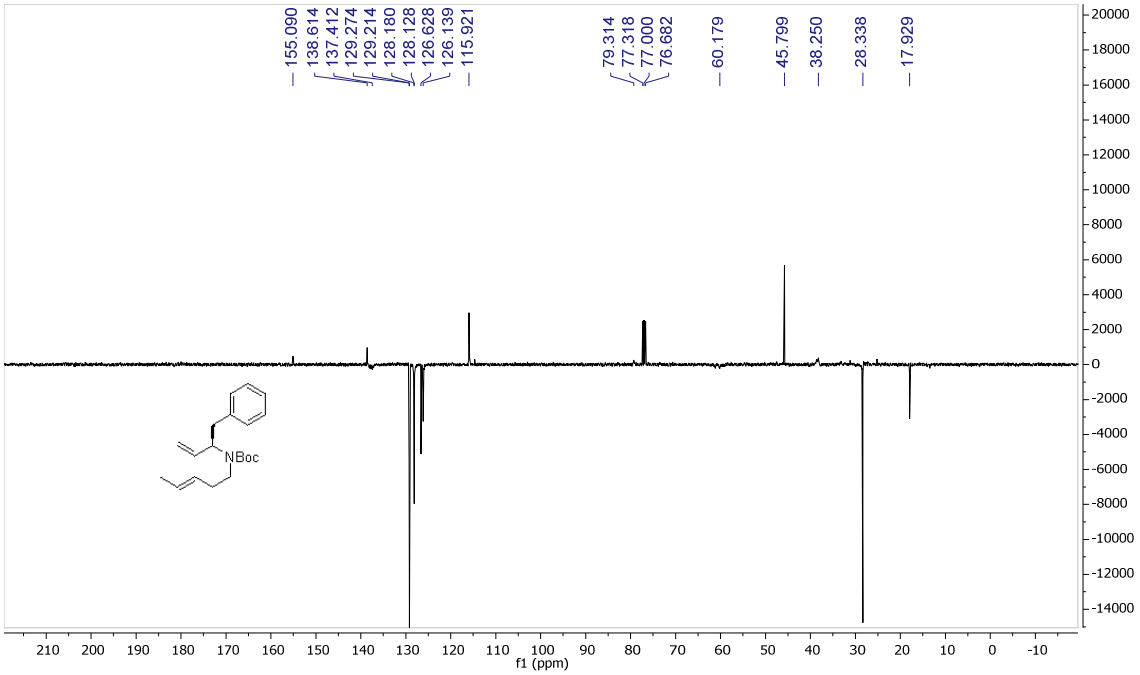




^{1}H and ^{13}C NMR ($CDCl_3$)

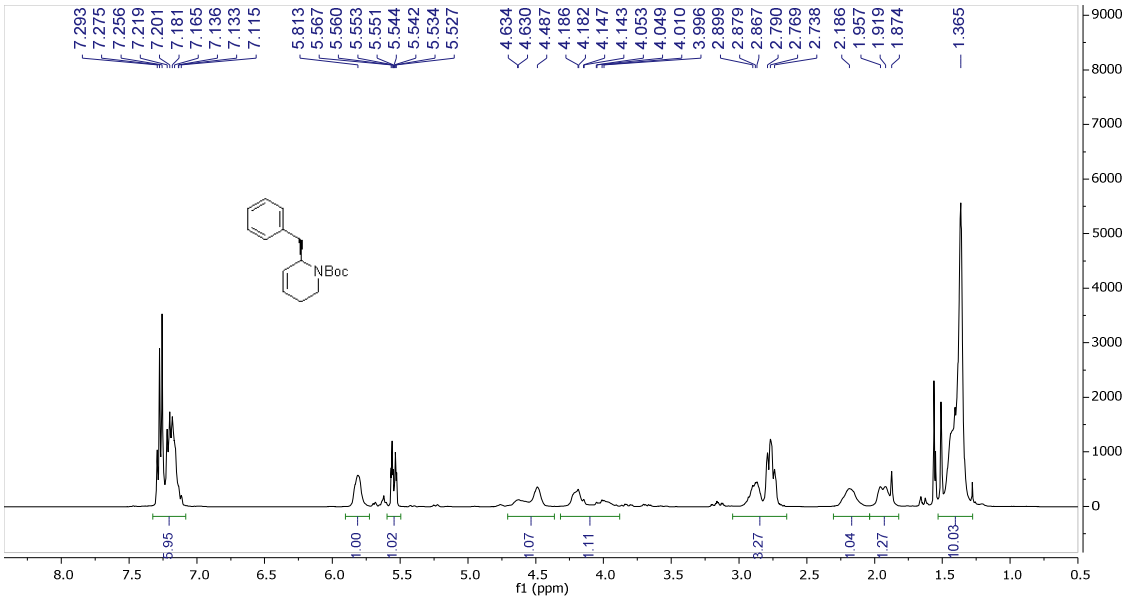
tert-Butyl *(R,E)*-pent-3-en-1-yl(1-phenylbut-3-en-2-yl)carbamate (**26b**)

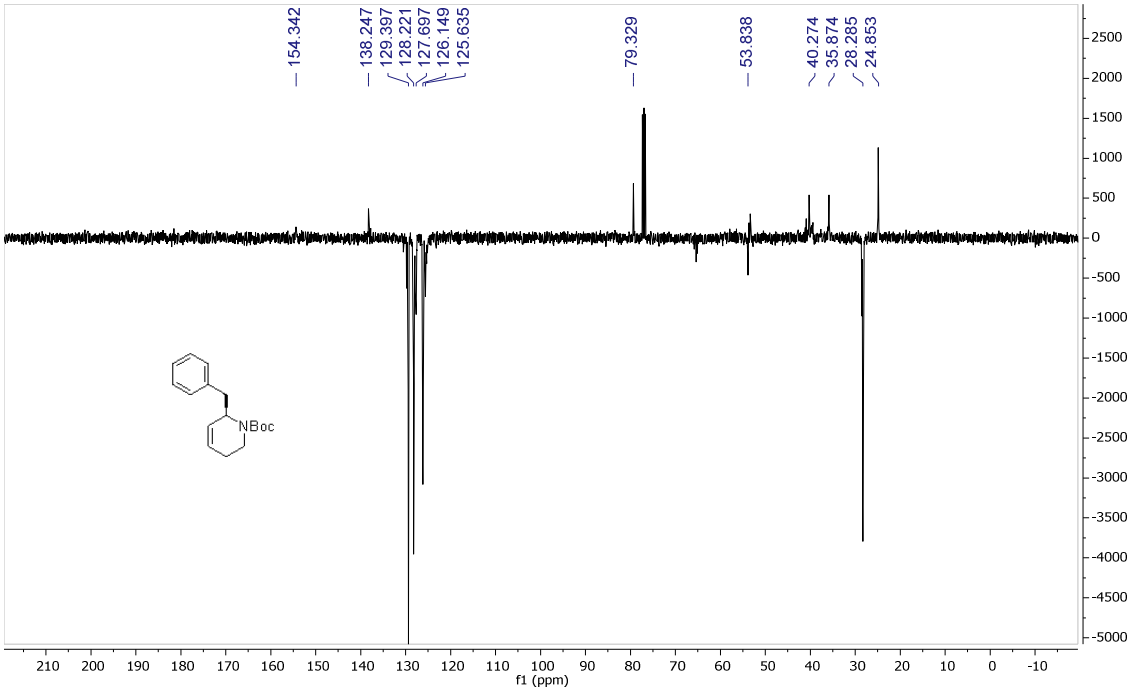




^{1}H and ^{13}C NMR ($CDCl_3$)

tert-Butyl *(R)*-6-benzyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**27b**)





^{1}H and ^{13}C NMR ($CDCl_3$)

(*S*)-2-Benzylpiperidine (**28b**)