Rowan University
Rowan Digital Works

Theses and Dissertations

2-8-2019

Synthesis of novel library of cyanopyrrolidinyl beta-amino alcohols and matrine alkaloids

Xiaotian Chen
Rowan University

Follow this and additional works at: https://rdw.rowan.edu/etd

 Part of the Medicinal and Pharmaceutical Chemistry Commons

Recommended Citation

Chen, Xiaotian, "Synthesis of novel library of cyanopyrrolidinyl beta-amino alcohols and matrine alkaloids" (2019). *Theses and Dissertations*. 2632.
https://rdw.rowan.edu/etd/2632

This Thesis is brought to you for free and open access by Rowan Digital Works. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of Rowan Digital Works. For more information, please contact graduateresearch@rowan.edu.

SYNTHESIS OF NOVEL LIBRARY OF CYANOPYRROLIDINYL β-AMINO ALCOHOLS AND MATRINE ALKALOIDS

by

Xiaotian Chen

A Thesis

Submitted to the
Department of Chemistry and Biochemistry
College of Science and Mathematics
In partial fulfillment of the requirement
For the degree of
Master of Science in Pharmaceutical Sciences
at
Rowan University
October 11, 2018

Thesis Chair: Gustavo Moura-Letts

© 2019 Xiaotian Chen

Dedications

This thesis is dedicated to my parents. For their love, support and encouragement.

Acknowledgments

I would first like to thank Professor Subash and Professor Wu of the Chemistry Department at Rowan University, who constantly gave me academic advice to help me achieve academic success.

I would also like to thank my research partners Joe Lizza, Brittany Gallagher for their help with synthesis. And everyone in the GML group.

A very special gratitude goes to my graduate program mentor Dr. Gustavo Moura-Letts. In the past four years, I have learned a lot chemistry knowledge and synthetic skills from him and it was fantastic to have the opportunity to work with him.

Abstract

Xiaotian Chen
SYNTHESIS OF NOVEL LIBEARY OF CYANOPYRROLIDINYL β-AMINO ALCOHOLS AND MATRINE ALKALOIDS
2018-2019
Dr. Gustavo Moura-Letts
Master of Science in Pharmaceutical Sciences

Cyanopyrrolidines and β-Amino alcohols are molecular scaffolds that highly found in commercially available drugs. We developed a multi-step synthetic method to form novel library of compounds as inhibitors that share both scaffolds toward potent and selective diabetes therapeutics. Despite the ease for the synthesis of cyanopyrrolidines, the difficulty of forming high selective β-Amino alcohols is challenging. We successfully find the best condition for the preference of highly selective mono-alkylation and double-alkylation products and product them with high yield.

Matrine is an alkaloid found in plants from the genus Sophora and can produce some pharmacological effects such as anti-cancer and anti-tumor effects. We modified the structure of matrine compound by adding aminonitriles and β-Amino alcohols scaffolds to its 1st and 2nd generation analogues to produce potential drug therapy.

Table of Contents

Table of Contents (Continued)

List of Figures

List of Tables

Chapter 1

Synthesis of Cyanopyrrolidinyl β-Amino Alcohols

1.1 Introduction

Diabetes has become one of the most lethal diseases in the world. Over 110 million people have diabetes world-widely. There are three main types of diabetes and Type 2 Diabetes is one of them. Dipeptidyl-peptidase (DPP)-4 is a degrading enzyme found playing an important role in Type 2 Diabetes. Some Cyanopyrrolidines contained DPP4 inhibitors such as Saxagliptin and Vildagliptin have been recently approved by FDA (2), which can serve as a new class of anti-diabetic drugs and will not trigger hypoglycemic episodes and cause weight gaining side effect.

Cyanopyrrolidine is a scaffold that found in natural products and commonly used in commercial drugs. It's also contained in the structure of DPP4 inhibitors such as Vildagliptin, Saxagliptin and Denaglipti. An amine group was also observed and located next to the cyanopyrrolidine. We envisioned to convert the amine group into a β-amino alcohol which is also an important class of scaffold in pharmaceutical chemistry and drug discovery. β-amino alcohol has been widely used as inhibitors for protein kinase C, glycosidase or β-adrenergic blockers and antimalarial agents. We hypothesized the combination of β-amino alcohol and the existing cyanopyrrolidine could act as more potent and selective diabetes therapeutics.

We are able to synthesize cyanopyrrolidines from naturally available amino acid proline through different synthetic approaches. However, synthesis of selective β-Amino

alcohols difficult. Epoxide ring could be opened up by primary amines with selective mono and double alkylation products.

We envision to constructed a proposed cyanopyrrolidinyl β-amino alcohol scaffold by reacting cyanopyrrolidines with phenyl glycidyl ethers (Figure 1). In order to obtain the cyanopyrrolidine, L-proline was chosen as starting material. After a three steps synthesis, L-proline was successfully converted into cyanopyrrolidinyl amine.

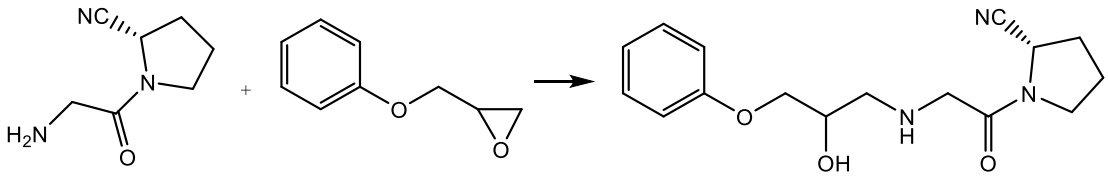


Figure 1. Inhibitor Design

1.2 Synthesis Approach

1.2.1 Synthesis of cyanopyrrolidinyl amine. L-proline was first reacted with chloroacetyl chloride and a N-acetylation product was obtained. Then an addition of DCC (dicyclohexylcarbodiimide) followed with NH4HCO3 converted the carboxylic acid into amide. TFAA (trifluoroacetic anhydride) mediated the elimination of amide and the product was reacted with a cold ammonium hydroxide. Eventually, cyanopyrrolidinylamine product was obtained with a 55% overall yield after 3 steps.

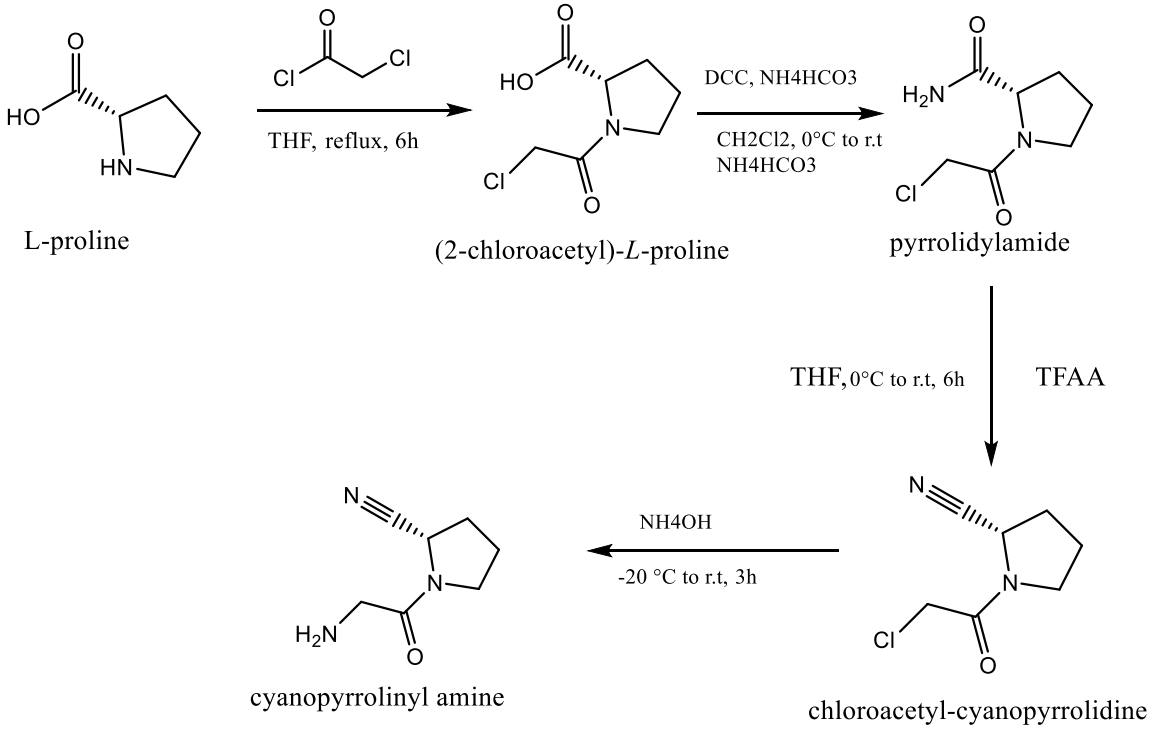


Figure 2. Cyanopyrrolidinyl Amine Synthesis

1.2.2 Epoxide opening reaction discovery and optimization. Once the Cyanopyrrolidinyl amine intermediate was successfully formed, we used them to open epoxide rings. The nucleophile would attack the less substituted carbon because it's less hindered. Selectivity of products for this reaction was also expected. In order to figure out the best reaction condition for high selectivity of epoxide opening product, we chose phenylgylcidyl ether and allylamine as proof of principle substrate (Table 1) Based on the observations, we found that polar aprotic solvents could accelerate the reaction. We obtained a significant increase of reaction conversion with 3:1 mono-alkylation / double alkylation product in ethanol (Entry 5) and a better conversion with 2:3 mono-alkylation /

double alkylation product in H2O (Entry 6). Under neat condition, a 3:1 Selectivity ratio was observed. Only mono-alkylation product was produced for highly polar solvents ACN and DMF because mono-alkylation is kinetically favored. Meanwhile, low conversion of reactions was observed (Entry 8&9). We also found higher conversion could be obtained by increasing reaction temperature to provide more energy. (Entry 10 - 12). Selectivity of products declined while the conversion remained steady at higher temperature. The desired balance between selectivity and conversion was achieved when using DMF as solvent with excess of H2O. We observed 98% conversion of reaction and over 95% selectivity of mono-alkylation product when mixed excess of H2O with DMF solution at 60°C, and a high conversion and selectivity of double-alkylation product using H2O if using amine as limiting reagent. (Entry 20).

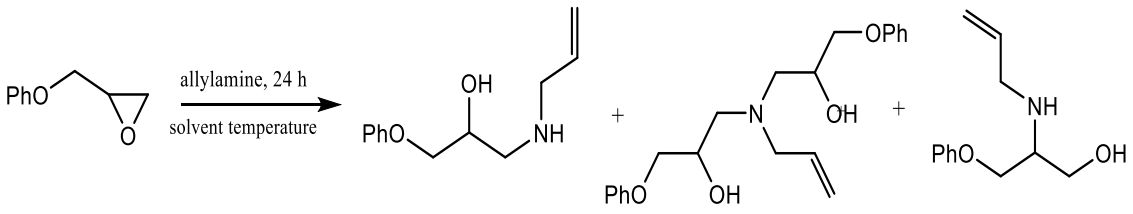


Figure 3. Reaction Discovery and Optimization

Table 1

Reaction Discovery and Optimization of Epoxide Opening Reaction

Entry	Solvent	Temperature	Conversion	Yield (Mono-alkylation)	Yield (Double - alkylation)
1	Toluene	room temp.	5%	73%	25%
2	Et2O	room temp.	5%	71%	24%
3	CH2Cl2	room temp.	5%	75%	24%
4	THF	room temp.	10%	70%	29%
5	EtOH	room temp.	85%	70%	30%
6	H2O	room temp.	>99%	40%	59%
7	neat	room temp.	>99%	71%	28%
8	ACN	room temp.	15%	90%	0%
9	DMF	room temp.	25%	95%	0%
10	DMF	40 °C	27%	91%	9%
11	DMF	50 °C	31%	89%	8%
12	DMF	60 °C	40%	90%	9%
13	DMF	80 °C	47%	75%	23%
14	DMF	100 °C	53%	79%	20%
15	DMF	120 °C	65%	72%	28%
16	DMF/H20	room temp.	35%	96%	<2%
17	DMF/H2O	40 °C	81%	95%	<2%
18	DMF/H2O	60 °C	98%	94%	5%
19	DMF/H20	60 °C	96%	96%	<2%
20	H2O	room temp.	>99%	<2%	97%

(Entry 19: 50 equiv. H2O, Entry 20: 0.5 equiv. amine)

1.2.3 Synthesis of cyanopyrrolidinyl β-amino alcohols. To form the cyanopyrrolidine amino alcohol scaffolds, we began with styrene oxides as electrophile and obtained expected mono and double alkylation product with high selectivity in different conditions (Entry 19&20, Table 1). Then we react our cyanopyrrolidinyl with fluorine, chlorine and bromine substituted styrene oxides, similar results were observed (Entry 2-4). Moreover, o-toyl, benzyl and p-methoxy-phenyl cyanopyrrolidinyl amino

alcohol scaffold were successfully obtained (Entry 7-9). We also expand the structural profile of the scaffold by synthesizing naphthyl, benzyl and furfuryl cyanopyrrolidinyl amino alcohols with high yield (Entry 13-15).

Table 2

Library of Cyanopyrrolidinyl β-Amino Alcohol

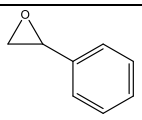
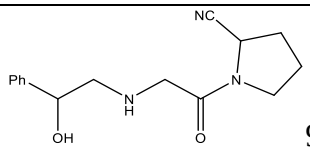
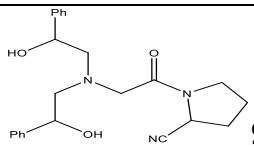
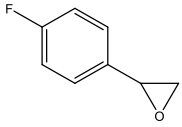
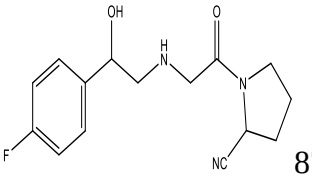
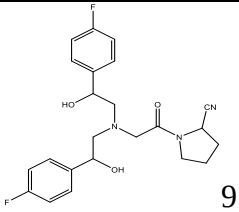
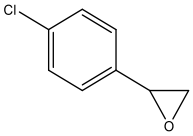
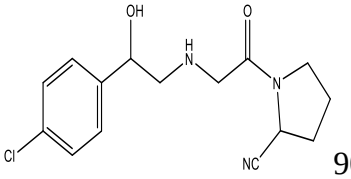
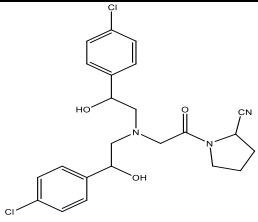
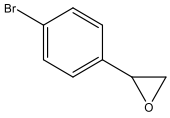
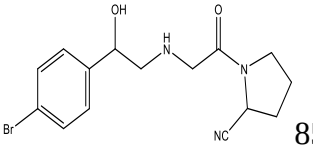
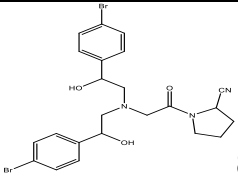
Entry	Epoxide	Product a (Yield)	Product b (Yield)
1		 91%	 90%
2		 87%	 91%
3		 90%	
4		 85%	 83%

Table 2 (continued)

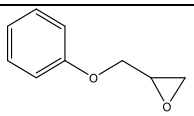
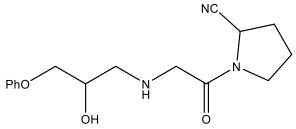
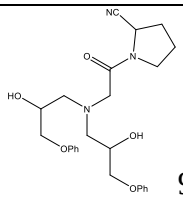
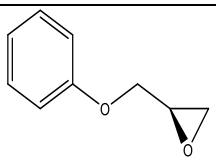
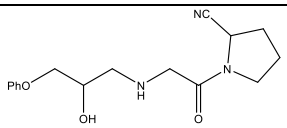
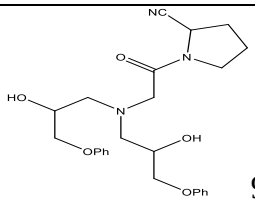
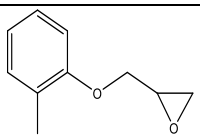
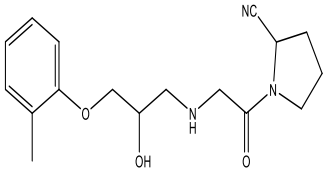
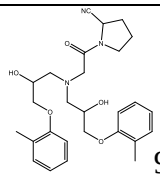
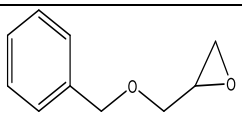
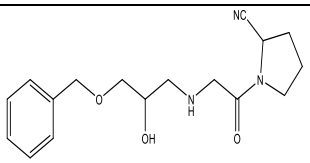
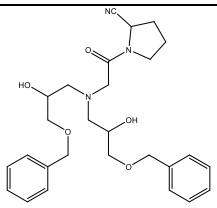
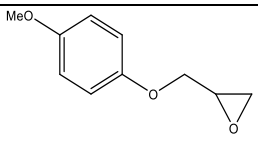
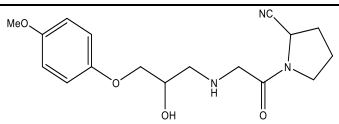
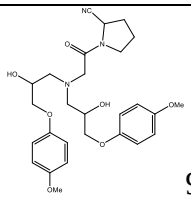
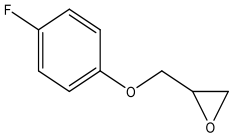
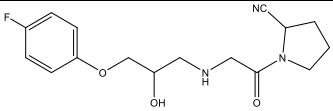
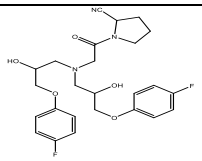
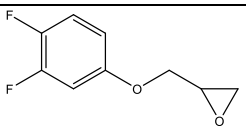
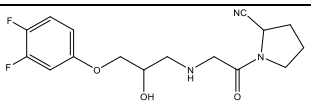
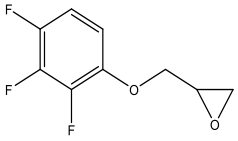
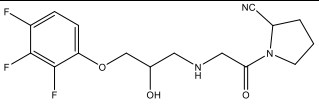
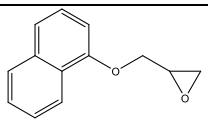
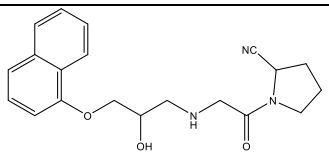
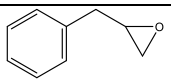
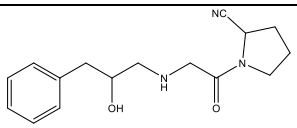
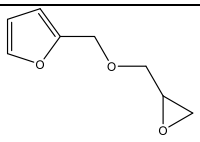
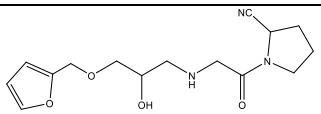
Entry	Epoxide	Product a & Yield	Product b & Yield
5		 97%	 91%
6		 94%	 94%
7		 93%	 91%
8		 87%	 90%
9		 93%	 95%

Table 2 (continued)

Entry	Epoxide	Product a & Yield	Product b & Yield
10		 93%	
11		 90%	
12		 89%	
13		 94%	
14		 90%	
15		 86%	

1.2.4 DPP4 inhibitor activity. We conducted our inhibitor assay against enzymes to test their potential inhibitory properties. Inhibition potency of our synthetic products were measured by monitoring the hydrolytic reaction of Gly-Pro-7-amniomethylcoumarin (Gly-Pro-AMC) by human DPP4. We incubated our compounds with DPP4 to observe whether the cleavage of the substrate would occur. A significant inhibitory potency was observed for our mono alkylated product styrene oxide opening with cyanopyrrolidinyl amine (42nM). Other substituted aromatic analogues such as Chlorine and brominephenyl analogues (Entry 3,4) also displayed good inhibitory effect but not as great as the unsubstituted version (Entry 1). However, flurophenyl analogue shown much lower inhibition (>10k nM, Entry 2). Phenoxy, o-methylphenoxy, benzyloxy and p-methoxy were available to produce similar inhibitory effective but still not efficient as non-substituted aromatic analogue (Entry 5-9). Fluorophenoxy inhibitors also displayed some effect, 4,5- difluorophenoxy had better inhibitory effect than p-fluorophenoxy and 4,5,6-trifluorophenoxy analogues (Entry 10 -12). Benzyloxy and heterocyclic analogues displayed very low inhibitory effect (Entry 14,15).

Table 3

DPP4 Inhibitor Activity

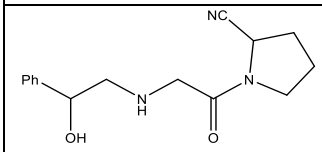
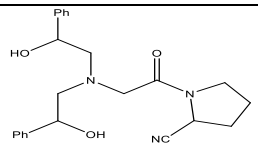
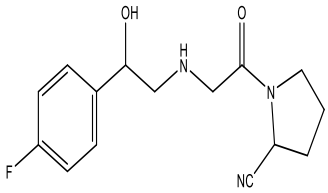
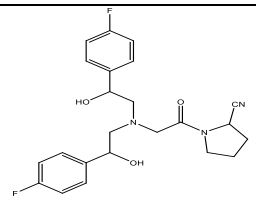
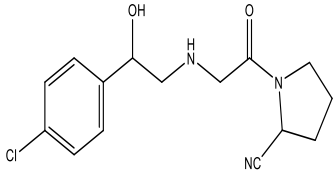
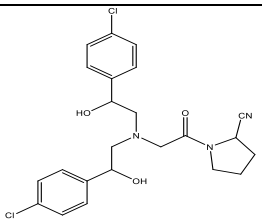
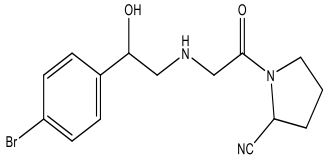
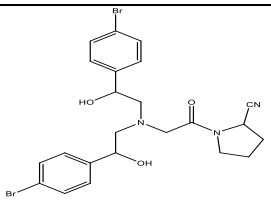
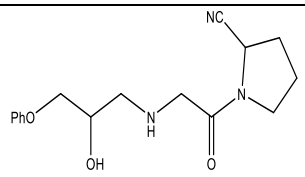
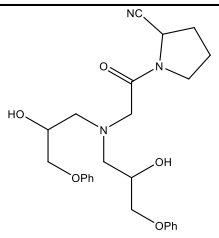
Inhibitor (mono-alky)	IC50 [nM]^[a]	Inhibitor (double-alky)	IC50 [nM]^[a]
	42		>10k
	6511		>10k
	124		>10k
	160		>10k
	91		>10k

Table 3 (continued)

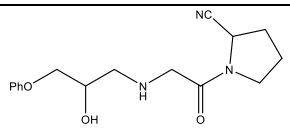
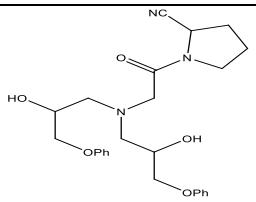
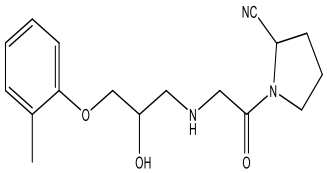
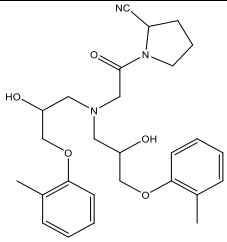
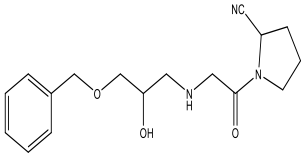
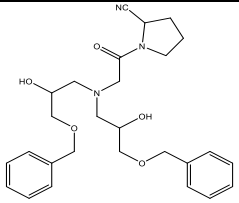
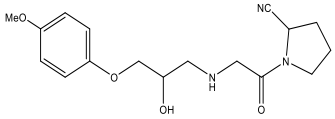
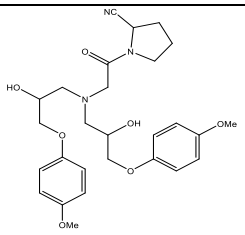
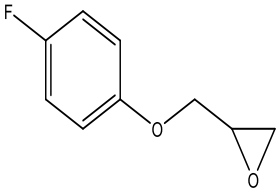
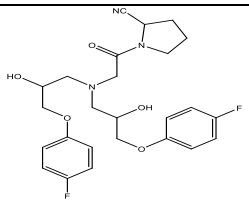
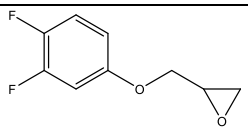
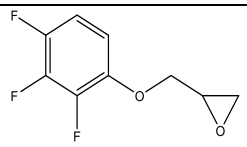
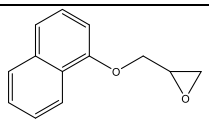
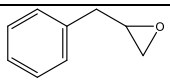
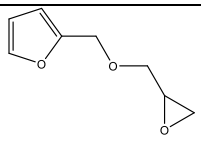
Inhibitor (mono-alky)	IC50 [nM]^[a]	Inhibitor (double-alky)	IC50 [nM]^[a]
	82		>10k
	98		>10k
	80		>10k
	74		>10k
	112		>10k

Table 3 (continued)

Inhibitor (mono-alky)	IC50 [nM]^[a]	Inhibitor (double-alky)	IC50 [nM]^[a]
	78		
	141		
	101		
	2555		
	>10k		

[a] All IC50 values are the mean SD of at least triplicate determinations.

1.3 Conclusion

We developed a novel synthesis method to produce cyanopyrrolidinyl amino alcohol compounds and further proved their efficiency as DPP4 inhibitors. We also discovered the optimized condition for epoxide opening reaction to form high selectivity

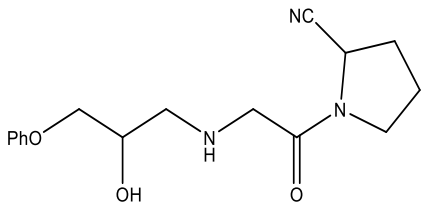
of either mono or double alkylation products. The biochemical test on our mono-alkylation products have shown their potential as DPP4 inhibitors.

1.4 Experimental

1.4.1 General method for the synthesis of mono-alkylated amino alcohols. In a 20 mL vial at room temperature, epoxide (1.0 mmol, 1.0 equiv.) and amine (1.5 mmol, 1.5 equiv.) were added to 6.7 mL of DMF. The reaction was stirred at 60°C for 12 hours then the reaction mixture received DI water (50 equiv.). The reaction was allowed to stir at 60 °C for another 12 hours. The solvent was removed on rotavapor and the remaining residue loaded directly onto a silica gel column.

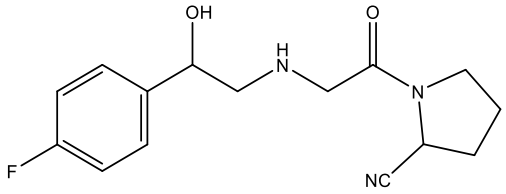
1.4.2 General method for the synthesis of double-alkylated amino alcohols. In a 20 mL vial at room temperature, epoxide (2.0 mmol, 2.0 equiv.) and amine (1 mmol, 1 equiv.) were added to 5 mL of DI water. The reaction was stirred at room temperature for 12 hours. Then solvent was removed on rotavapor and the remaining residue loaded directly onto a silica gel column.

1.4.3 H-NMR and C-NMR of mono/double-alkylated amino alcohols. H and C NMR data are listed below.



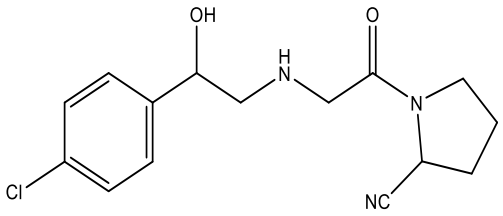
(2S)-1-[(2-Hydroxy-2-phenylethyl)glycyl]pyrrolidine-2-carbo-nitrile (1a): Method A. Styrene oxide (150 mg, 1.25 mmol) and amine (287 mg, 1.87 mmol). Purification by

silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 1aa(311 mg, 91 %) as a clear oil. TLC: Rf= 0.25 (1:9 MeOH/CHCl3). IR(thin film): ν˜= 3332, 2241, 1658 cm–1.1H NMR (400 MHz, CDCl3):δ = 7.41–7.25 (m, 5 H), 4.77–4.75 (m, 2 H), 3.53–3.51 (m, 1 H), 3.49(s, 2 H), 3.38–3.31 (m, 2 H), 2.99 (dd, J = 7.3, 6.8 Hz, 1 H), 2.76 (dd,J = 7.1, 6.8 Hz, 1 H), 2.26–2.06 (m, 4 H) ppm.13C NMR (100 MHz,CDCl3): δ = 170.3, 142.3, 128.3, 127.4, 127.3, 125.8, 118.2, 71.9, 57.4,51.0, 46.4, 45.3, 29.7, 25.0 ppm. ESI-MS m/z (rel. int.): (pos.) 274.1([M+H]+, 100); (neg) 272.1 ([M – H]–, 100). HRMS (ESI): Calc d. for: C15H20N3O2+: 274.15500, found 274.15447. Absolute difference(ppm): 1.96

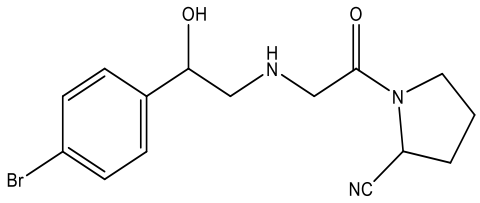


(2S)-1-{[2-(4-Fluorophenyl)-2-hydroxyethyl]glycyl}pyrrolidine-2carbonitrile (2a): Method A. 2-(4-fluorophenyl)oxirane (150 mg,1.09 mmol) and amine a (250 mg, 1.63 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 2aa (275 mg, 87 %) as a clear oil. TLC: Rf = 0.24 (1:9 MeOH/ CHCl3). IR (thin film): ν ˜ = 3322, 2243, 1639 cm–1. 1H NMR (400 MHz, CDCl3): δ = 7.38 (dd, J = 5.9, 1.6 Hz, 2 H), 7.01 (dd, J = 5.7, 1.5 Hz, 2 H), 4.79 (dd, J = 7.1, 6.8 Hz, 1 H), 4.69 (dd, J = 7.2, 7.1 Hz, 1 H), 3.59–3.52 (m, 1 H), 3.49 (s, 2 H), 3.45–3.38 (m, 1 H), 2.99 (dd, J = 7.1, 6.8 Hz, 1 H), 2.75 (dd, J = 7.3, 7.1 Hz, 1 H), 2.32–2.12 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 162.7 (d, J = 244 Hz, 1 C), 138.0, 127.5,

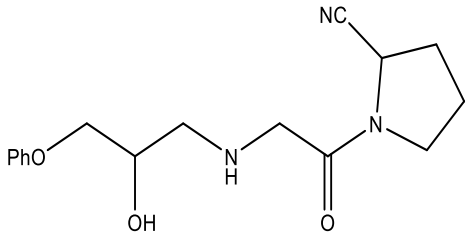
118.1, 115.2, 71.3, 57.5, 51.1, 46.7, 45.3, 29.8, 25.1 ppm. ESI-MS m/z (rel. int.): (pos.) 292.1 ([M + H]+, 100); (neg) 290.1 ([M – H]–, 100). HRMS (ESI): Calcd. for: C15H19FN3O2+: 292.14558, found 292.14578. Absolute difference (ppm): 0.68.



(2S)-1-{[2-(4-Chlorophenyl)-2-hydroxyethyl]glycyl}pyrrolidine2-carbonitrile (3a): Method A. 2-(4-chlorophenyl)oxirane (150 mg, 0.97 mmol) and amine a (223 mg, 1.46 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 3aa (269 mg, 90 %) as a clear oil. TLC: Rf = 0.26 (1:9 MeOH/ CHCl3). IR (thin film): ν ˜ = 3334, 2244, 1659 cm–1. 1H NMR (400 MHz, CDCl3): δ = 7.29 (d, J = 5.9 Hz, 2 H), 7.23 (d, J = 5.7 Hz, 2 H), 4.75 (dd, J = 7.3, 6.6.6 Hz, 1 H), 4.68 (dd, J = 7.1, 6.6 Hz, 1 H), 3.55–3.50 (m, 1 H), 3.45 (s, 2 H), 3.41–3.34 (m, 1 H), 2.99 (dd, J = 7.1, 6.4 Hz, 1 H), 2.73 (dd, J = 7.1, 6.8 Hz, 1 H), 2.28–2.08 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 1704, 140.8, 133.0, 128.4, 127.2, 118.1, 71.3, 57.3, 51.0, 46.4, 45.3, 29.8, 25.0 ppm. ESI-MS m/z (rel. int.): (pos.) 308.1 ([M + H]+, 100); (neg) 306.1 ([M – H]–, 100). HRMS (ESI): Calc. for: C15H19ClN3O2+: 308.11603, found 308.11633. Absolute difference (ppm): 0.93.

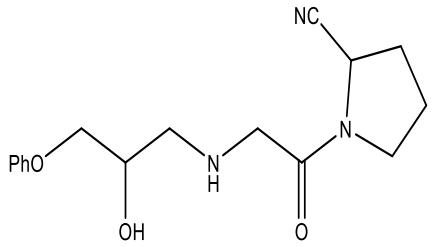


(2S)-1-{[2-(4-Bromophenyl)-2-hydroxyethyl]glycyl}pyrrolidine2-carbonitrile (4a): Method A. 2-(4-bromophenyl)oxirane (150 mg, 0.75 mmol) and amine a (173 mg, 1.13 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 4aa (226 mg, 85 %) as a clear oil. TLC: Rf = 0.25 (1:9 MeOH/CHCl3). IR (thin film): ν ˜ = 3321, 2240, 1658 cm–1. 1H NMR (400 MHz, CDCl3): δ = 7.49 (d, J = 6.2 Hz, 2 H), 7.23 (d, J = 6.2 Hz, 2 H), 4.75 (dd, J = 7.1, 6.8 Hz, 1 H), 4.71 (dd, J = 7.2, 7.1 Hz, 1 H), 3.55–3.49 (m, 1 H), 3.45 (s, 2 H), 3.41–3.34 (m, 1 H), 2.97 (dd, J = 7.1, 6.8 Hz, 1 H), 2.71 (dd, J = 7.3, 7.1 Hz, 1 H), 2.28–2.24 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.3, 141.2, 131.4, 127.5, 121.2, 118.1, 71.3, 57.3, 51.0, 46.5, 45.3, 29.8, 25.1 ppm. ESI-MS m/z (rel. int.): (pos.) 352.1 ([M + H]+, 100); (neg) 350.1 ([M – H]–, 100). HRMS (ESI): Calc. for: C15H19BrN3O2+: 352.06552, found 352.06628. Absolute difference (ppm): 2.18.



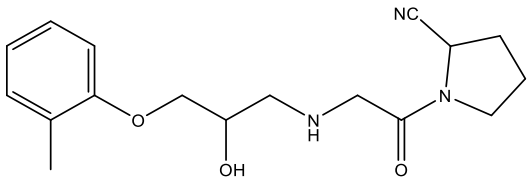
(2S)-1-[(2-Hydroxy-3-phenoxypropyl)glycyl]pyrrolidine-2carbonitrile (5a): Method A. 2-(phenoxymethyl)oxirane (150 mg, 1.00 mmol) and amine a (230 mg, 1.50 mmol).

Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 5aa (294 mg, 97 %) as a clear oil. TLC: Rf = 0.26 (1:9 MeOH/ CHCl3). IR (thin film): ν ˜ = 3321, 2243, 1653 cm–1. 1H NMR (400 MHz, CDCl3): δ = 7.52–7.50 (m, 2 H), 6.95–6.91 (m, 3 H), 4.75 (t, J = 6.8 Hz, 1 H), 4.08 (ddt, J = 7.1, 6.8, 6.6 Hz, 1 H), 3.98 (d, J = 6.8 Hz, 2 H), 3.51–3.49 (m, 1 H), 3.43 (s, 2 H), 3.32–3.29 (m, 1 H), 2.93 (dd, J = 7.1, 6.4 Hz, 1 H), 2.77 (dd, J = 6.6, 6.4 Hz, 1 H), 2.26–2.08 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 158.5, 129.3, 120.7, 118.2, 114.4, 70.0, 68.4, 52.2, 52.1, 46.3, 45.2, 29.6, 24.9 ppm. ESI-MS m/z (rel. int.): (pos.) 304.2 ([M + H]+, 100); (neg) 302.2 ([M – H]–, 100). HRMS (ESI): Calcd. for: C16H22N3O3+: 304.16557, found 304.16591. Absolute difference (ppm): 1.11.

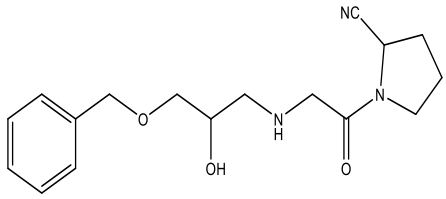


(S)-1-{[(S)-2-Hydroxy-3-phenoxypropyl]glycyl}pyrrolidine-2carbonitrile (6a): Method A. (S)-2-(phenoxymethyl)oxirane (150 mg, 1.00 mmol) and amine a (230 mg, 1.50 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 6aa (285 mg, 94 %) as a clear oil. TLC: Rf = 0.28 (1:9 MeOH/CHCl3). IR (thin film): ν ˜ = 3331, 2241, 1656 cm–1. 1H NMR (400 MHz, CDCl3): δ = 7.32–7.28 (m, 2 H), 6.95–6.89 (m, 3 H), 4.77 (t, J = 6.8 Hz, 1 H), 4.11 (ddt, J = 7.1, 6.8, 6.6 Hz, 1 H), 3.98 (d, J = 6.8 Hz, 2 H), 3.53–3.51 (m, 1 H), 3.45 (s, 2 H),

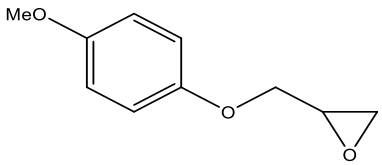
3.37–3.27 (m, 1 H), 2.93 (dd, J = 7.1, 6.3 Hz, 1 H), 2.82 (dd, J = 6.6, 6.3 Hz, 1 H), 2.28–2.08 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.3, 158.5, 129.3, 120.7, 118.2, 114.4, 70.0, 68.4, 52.1, 51.1, 46.3, 45.2, 29.6, 25.0 ppm. ESI-MS m/z (rel. int.): (pos.) 304.2 ([M + H]+, 100); (neg) 302.2 ([M– H]–, 100).HRMS (ESI): Calcd. for:C16H22N3O3+: 304.16557, found 304.16516. Absolute difference (ppm): 1.34.



(2S)-1-{[2-Hydroxy-3-(o-tolyloxy)propyl]glycyl}pyrrolidine-2carbonitrile (7a): Method A. 2-[(o-tolyloxy)methyl]oxirane (150 mg, 0.91 mmol) and amine a (210 mg, 1.37 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 7aa (270 mg, 93 %) as a clear oil. TLC: Rf = 0.25 (1:9 MeOH/CHCl3). IR (thin film): ν ˜ = 3335, 2242, 1657 cm–1. 1H NMR (400 MHz, CDCl3): δ = 7.14–7.09 (m, 2 H), 6.84–6.80 (m, 2 H), 4.76 (dd, J = 6.8, 6.6 Hz, 1 H), 4.08–4.04 (m, 1 H), 3.98 (dd, J = 7.1, 6.9 Hz, 1 H), 3.96 (dd, J = 7.2, 6.9 Hz, 1 H), 3.52–3.49 (m,1 H), 3.41 (s, 2 H), 3.38–3.34 (m, 1 H), 2.91 (dd, J = 7.1, 6.5 Hz, 1 H), 2.82 (dd, J = 7.1, 6.4Hz,1H),2.22 (s,3H),2.20–2.06(m,4H)ppm. 13CNMR (100MHz, CDCl3): δ = 170.4, 156.6, 130.6, 126.7, 126.6, 120.6, 118.2, 111.0, 70.0, 68.6, 52.3, 51.3, 46.3, 45.3, 29.7, 25.0, 16.2 ppm. ESI-MS m/z (rel. int.): (pos.) 318.2 ([M + H]+, 100); (neg) 316.2 ([M – H]–, 100). HRMS (ESI): Calcd. for: C17H24N3O3+: 318.18122, found 318.18104. Absolute difference (ppm): 0.55.

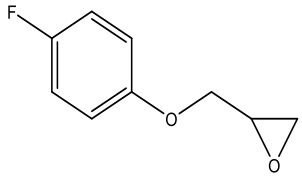


(2S)-1-{[3-(Benzyloxy)-2-hydroxypropyl]glycyl}pyrrolidine-2scarbonitrile (8a): Method A. 2-[(benzyloxy)methyl]oxirane (150 mg, 0.91 mmol) and amine a (210 mg, 1.37 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 8aa (252 mg, 87 %) as a clear oil. TLC: Rf = 0.29 (1:9 MeOH/CHCl3). IR (thin film): ν ˜ = 3333, 2242, 1657 cm–1. 1H NMR (400 MHz, CDCl3): δ = 7.38–7.32 (m, 5 H), 4.77 (dd, J = 6.8, 6.6 Hz, 1 H), 4.57 (s, 2 H), 3.87–3.81 (m, 1 H), 3.54–3.47 (m, 3 H), 3.41 (s, 2 H), 3.38–3.34 (m, 1 H), 2.80 (dd, J = 7.1, 6.6 Hz, 1 H), 2.68 (dd, J = 7.3, 6.6 Hz, 1 H), 2.28–2.13 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 138.0, 128.3, 127.7, 127.6, 118.2, 73.3, 72.6, 69.0, 52.3, 51.2, 46.3, 45.3, 29.7, 25.0 ppm. ESI-MS m/z (rel. int.): (pos.) 318.2 ([M + H] +, 100); (neg) 316.2 ([M – H]–, 100). HRMS (ESI): Calcd. for: C17H24N3O3+: 318.18122, found 318.18179. Absolute difference (ppm): 1.81.



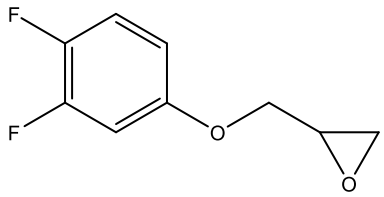
(2S)-1-{[2-Hydroxy-3-(4-methoxyphenoxy)propyl]glycyl}pyrrolidine-2-carbonitrile (9a): Method A. 2-[(4-methoxyphenoxy)methyl]oxirane (150 mg, 0.83 mmol) and amine a (191 mg, 1.25 mmol). Purification by silica gel chromatography (isocratic, 4 %

MeOH/CHCl3) produced amino alcohol 9aa (258 mg, 93 %) as a clear oil. TLC: Rf = 0.28 (1:9 MeOH/CHCl3). IR (thin film): ν ˜ = 3332, 2241, 1658 cm–1. 1H NMR (400 MHz, CDCl3): δ = 6.88–6.78 (m, 4 H), 4.75 (dd, J = 7.1, 6.8 Hz, 1 H), 4.04–4.00 (m, 1 H), 3.96 (s, 2 H), 3.76 (s, 3 H), 3.52 (dt, J = 6.8, 6.6 Hz, 1 H), 3.41 (s, 2 H), 3.38 (dt, J = 6.8, 6.6 Hz, 1 H), 2.93–2.84 (m, 2 H), 2.78–2.72 (m, 2 H), 2.26–2.08 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.5, 153.9, 152.7, 118.2, 115.5, 115.4, 114.6, 114.5, 70.8, 68.6, 55.6, 52.2, 51.3, 46.4, 45.3, 29.8, 25.0 ppm. ESI-MS m/z (rel. int.): (pos.) 334.2 ([M + H]+, 100); (neg) 332.2 ([M– H]–, 100).HRMS (ESI): Calcd. for:C17H24N3O4+: 334.17613, found 334.17552. Absolute difference (ppm): 1.84.

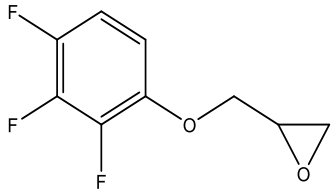


(2S)-1-{[3-(4-Fluorophenoxy)-2-hydroxypropyl]glycyl}pyrrolidine-2-carbonitrile (10a): Method A. 2-[(4-fluorophenoxy)methyl]oxirane (150 mg, 0.89 mmol) and amine a (205 mg, 1.34 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 10aa (267 mg, 93 %) as a clear oil. TLC: Rf = 0.28 (1:9 MeOH/CHCl3). IR (thin film): ν ˜ = 3331, 2441, 1655 cm–1. 1H NMR (400 MHz, CDCl3): δ = 6.88–6.73 (m, 4 H), 4.73 (dd, J = 6.9, 6.8 Hz, 1 H), 4.04–4.00 (m, 1 H), 3.85 (s, 2 H), 3.52 (dt, J = 6.8, 6.6 Hz, 1 H), 3.37 (s, 2 H), 3.38 (dt, J = 6.8, 6.6 Hz, 1 H), 2.82 (dd, J = 6.9, 6.6 Hz, 1 H), 2.73 (dd, J = 7.1, 6.6 Hz, 2 H), 2.18– 2.06 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 157.6 (d, J = 237 Hz, 1 C), 154.7, 118.2,

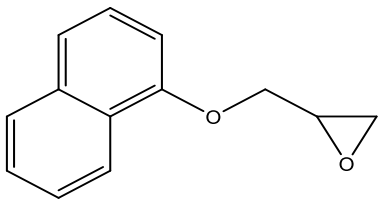
115.7, 115.5, 115.4, 70.8, 68.5, 52.2, 51.2, 46.3, 45.3, 29.6, 24.9 ppm. ESI-MS m/z (rel. int.): (pos.) 322.1 ([M + H] +, 100); (neg) 320.1 ([M – H]–, 100). HRMS (ESI): Calcd. for: C16H21FN3O3+: 322.15615, found 322.15596. Absolute difference (ppm): 0.59.



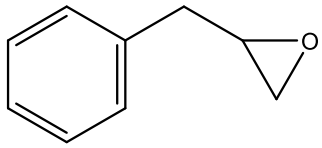
(2S)-1-{[3-(3,4-Difluorophenoxy)-2-hydroxypropyl]glycyl}pyrrolidine-2-carbonitrile (11a): Method A. 2-[(3,4-difluorophenoxy)methyl]oxirane (150 mg, 0.81 mmol) and amine a (185 mg, 1.21 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 11aa (246 mg, 90 %) as a clear oil. TLC: Rf = 0.28 (1:9 MeOH/CHCl3). IR (thin film): ν ˜ = 3332, 2243, 1653 cm–1. 1H NMR (400 MHz, CDCl3): δ = 6.96 (dd,J = 9.3, 5.7 Hz, 1 H), 6.68 (ddd, J = 9.3, 6.4, 5.8 Hz, 1 H), 6.55 (dd, J = 6.4, 5.6 Hz, 1 H), 4.71 (dd, J = 7.1, 6.6 Hz, 1 H), 3.96 (ddt, J = 7.1, 6.8, 6.6 Hz, 1 H), 3.81 (d, J = 6.8 Hz, 2 H), 3.50 (dt, J = 6.8, 6.4 Hz, 1 H), 3.41 (s, 2 H), 3.32 (dt, J = 6.8, 6.4 Hz, 1 H), 2.80 (dd, J = 7.1, 6.4 Hz, 1 H), 2.71 (dd, J = 6.6, 6.4 Hz, 1 H), 2.24–2.06 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 154.9, 149.7 (d, J = 246 Hz, 1 C), 144.3 (d, J = 238 Hz, 1 C), 118.2, 117.1,116.9, 109.8, 109.7, 104.2, 70.9, 68.3, 52.1, 51.2, 46.3, 45.3, 29.7, 24.9 ppm. ESI-MS m/z (rel. int.): (pos.) 340.2 ([M + H]+, 100); (neg) 338.2 ([M – H]–, 100). HRMS (ESI): Calcd. for: C16H20F2N3O3+: 340.14672, found 340.14725. Absolute difference (ppm): 1.53.



(2S)-1-{[2-Hydroxy-3-(3,4,5-trifluorophenoxy)propyl]glycyl}pyrrolidine-2-carbonitrile (12a): Method A. 2-[(3,4,5trifluorophenoxy)methyl]oxirane (150 mg, 0.73 mmol) and amine a (169 mg, 1.10 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 12aa (234 mg, 89 %) as a clear oil. TLC: Rf = 0.26 (1:9 MeOH/CHCl3). IR (thin film): ν ˜ = 3317, 2245, 1657 cm–1. 1H NMR (400 MHz, CDCl3): δ = 6.53 (dd, J = 9.5, 5.9 Hz, 2 H), 4.73 (dd, J = 7.1, 6.8 Hz, 1 H), 4.04 (ddt, J = 7.1, 6.8, 6.4 Hz, 1 H), 3.87 (d, J = 6.8 Hz, 2 H), 3.50 (dt, J = 6.8, 6.4 Hz, 1 H), 3.45 (s, 2 H), 3.32 (dt, J = 6.8, 6.4 Hz, 1 H), 2.88 (dd, J = 7.1, 6.4 Hz, 1 H), 2.73 (dd, J = 6.8, 6.4 Hz, 1 H), 2.31–2.11 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 152.8 (d, J = 240 Hz, 1 C), 151.2 (d, J = 233 Hz, 1 C), 134.6 (d, J = 224 Hz, 1 C), 118.2, 99.3, 99.2, 71.0, 68.1, 52.0, 51.2, 46.4, 45.3, 29.7, 25.0 ppm. ESI-MS m/z (rel. int.): (pos.) 358.1 ([M + H]+, 100); (neg) 356.1 ([M – H]–, 100). HRMS (ESI): Calcd. for: C16H19F3N3O3+: 358.13730, found 358.13691. Absolute difference (ppm): 3.9.

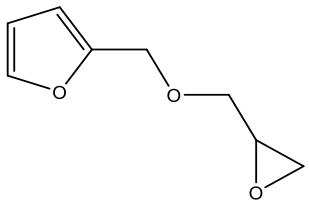


(2S)-1-{[2-Hydroxy-3-(naphthalen-1-yloxy)propyl]glycyl}pyrrolidine-2-carbonitrile (13a): Method A. 2-[(naphthalen-1-yloxy)methyl]oxirane (150 mg, 0.75 mmol) and amine a (172 mg, 1.12 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 13aa (249 mg, 94 %) as a yellow oil. TLC: Rf = 0.25 (1:9 MeOH/CHCl3). IR (thin film): ν ˜ = 3320, 2239, 1658 cm–1. 1H NMR (400 MHz, CDCl3): δ = 8.26 (d, J = 5.8 Hz, 1 H), 7.76 (d, J = 5.8 Hz, 1 H), 7.49–7.45 (m, 2 H), 7.41 (d, J = 6.4 Hz, 1 H), 7.29 (t, J = 6.4 Hz, 1 H), 6.79 (d, J = 5.8 Hz,1 H), 4.68 (dd, J = 7.1, 6.2 Hz, 1 H), 4.22 (dd, J = 7.1, 6.8 Hz, 2 H), 4.15 (dddd, J = 7.1, 6.8, 6.6, 6.4 Hz, 1 H), 3.45–3.41 (m, 3 H), 3.19–3.15 (m, 1 H), 3.05 (dd, J = 7.1, 6.6 Hz, 1 H), 2.93 (dd, J = 6.8, 6.6 Hz, 1 H), 2.22–1.98 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 154.2, 134.3, 127.4, 126.3, 125.8, 125.4, 125.2, 121.8, 120.4, 118.2, 104.9, 70.2, 68.6, 52.3, 51.3, 46.3, 45.2, 29.6, 24.9 ppm. ESI-MS m/z (rel. int.): (pos.) 354.2 ([M + H] +, 100); (neg) 352.2 ([M – H]–, 100). HRMS (ESI): Calc. for: C20H24N3O3+: 354.18122, found 354.18062. Absolute difference (ppm): 1.69.



(2S)-1-[(2-Hydroxy-3-phenylpropyl)glycyl]pyrrolidine-2-carbonitrile (14a): Method A. 2-benzyloxirane (150 mg, 1.12 mmol) and aminea(257 mg, 1.68 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 14aa (289 mg, 90 %) as a clear oil. TLC: Rf = 0.26 (1:9 MeOH/CHCl3). IR (thin film): ν ˜ = 3334, 2241, 1655 cm–1. 1H NMR (400 MHz, CDCl3): δ = 7.29–7.18 (m, 5 H), 4.73 (dd,

J = 6.9, 6.6 Hz, 1 H), 3.89 (dt, J = 6.8, 6.4 Hz, 1 H), 3.54–3.50 (m, 2 H), 3.38 (s, 2 H), 2.82–2.73 (m,4 H), 2.59 (dd, J = 6.9, 6.6 Hz, 1 H), 2.37–2.13 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 138.4, 129.3, 128.2, 126.1, 118.2, 70.7, 54.9, 51.0, 46.3, 45.2, 41.3, 29.7, 24.9 ppm. ESI-MS m/z (rel. int.): (pos.) 288.2 ([M + H]+, 100); (neg) 286.2 ([M – H]–, 100). HRMS (ESI): Calc. for: C16H22N3O2+: 288.17065, found 288.17032. Absolute difference (ppm): 1.17.



(2S)-1-{[3-(Furan-2-ylmethoxy)-2-hydroxypropyl]glycyl}pyrrolidine-2-carbonitrile (15a): Method A. 2-[(oxiran-2-ylmethoxy)methyl]furan (150 mg, 0.97 mmol) and amine a (224 mg, 1.46 mmol). Purification by silica gel chromatography (isocratic, 4 % MeOH/CHCl3) produced amino alcohol 15aa (257 mg, 86 %) as a clear oil. TLC: Rf = 0.28 (1:9 MeOH/CHCl3). IR (thin film): ν ˜ = 3363, 2243, 1652 cm–1. 1H NMR (400 MHz, CDCl3): δ = 7.38 (s, 1 H), 6.28– 6.26 (m, 2 H), 4.71 (dd, J = 6.9, 6.5 Hz, 1 H), 4.42 (s, 2 H), 3.78 (ddt, J = 7.1, 6.8, 6.4 Hz, 1 H), 3.52–3.49 (m, 2 H), 3.43–3.41 (m, 2 H), 3.38 (s, 2 H), 2.71 (dd, J = 6.9, 6.2 Hz, 1 H), 2.60 (dd, J = 6.5, 6.2 Hz, 1 H), 2.24–2.08 (m, 4 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 170.4, 168.1, 157.3, 151.4, 142.7, 118.2, 110.2, 109.4, 72.3, 68.9, 65.1, 56.5, 52.1, 51.2, 46.4, 45.3, 29.7, 25.0 ppm. ESI-MS m/z (rel. int.): (pos.) 308.2 ([M + H]

Chapter 2

Semi-Synthesis of a Novel Library of Matrine Alkaloids

2.1 Background

Matrine type alkaloids extracted from Chinese herb Sephora Tonkinese's has been used clinically in China for many years. (3) It has been proved that matrine and oxymatrine are the principle constituents can behave as potent antiviral agent to against hepatitis B virus (HBV), Coxsackie virus B3 (CVB3), B5 (CVB5) and respiratory syncytial virus (RSV) (1). Although matrine's molecular mechanism is unclear, it still successfully grabbed our attention to discover a new synthetic approach to make potent anti-cancer or anti-tumor agent by applying structural modification.

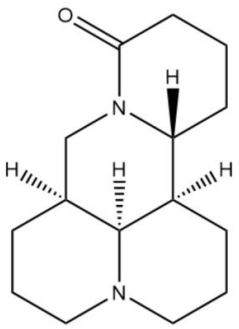


Figure 4. Matrine Compound structure

2.2 Synthetic Approach

2.2.1 Synthesis of 1st generation matrine analogue. In order to modify matrine compound and make more reactive derivative. Structural modification was applied. Lactam ring opening with concentrated HCl to form a modified matrine analogue with an exposed secondary amine. The remaining carboxylic acid terminal underwent esterification and converted into an methyl ester by stirring in excess of methanol.

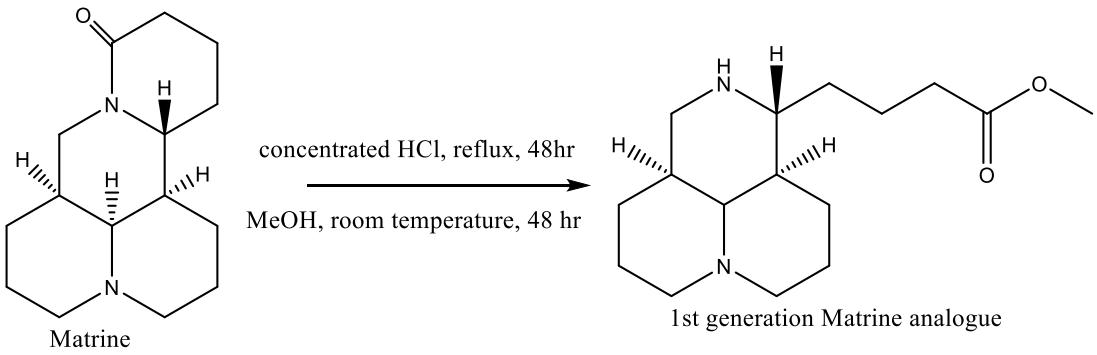


Figure 5. Formation of 1st Generation Matrine Analogue

2.2.2 Synthesis of aminonitrile matrine analogue. Amino nitriles contained pharmaceutical therapy drugs have been commonly used. The importance of nitrogen containing agents have been reported especially their role as small molecule inhibitors. Nitrile group has also been mentioned as a key functional group for molecular recognition. (2) They can be metabolized by human body and could be excreted easily.

We decided to continue our matrine analogue modification by adding a nitrile group based on amino nitrile's significant biological properties.

The first step of Strecker reaction is known as preparation of α-aminonitriles by reacting amine and ketone or aldehyde in the presence of cyanide salts. Since our modified 1st generation matrine derivative has an exposed secondary amine group, which was used as nucleophile to produce a library of aminonitrile matrine analogue products.

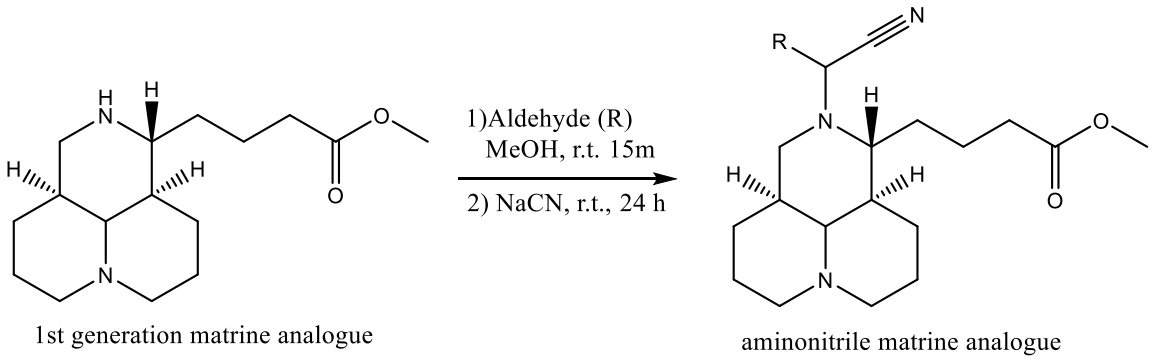
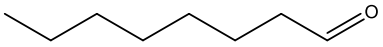
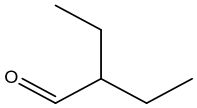
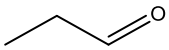
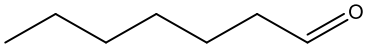
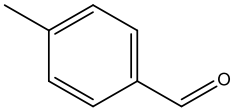
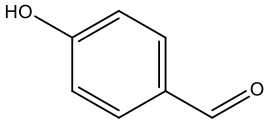
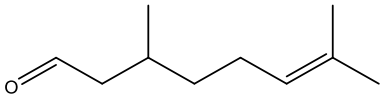


Figure 6. Synthesis of 1st Generation Matrine Aminonitrile Analogue

Table 4

Aminonitrile Matrine Analogue

Entry	**Aldehyde (R)**	**Percent Yield**
1		75.9
2		50.4
3		47.6
4		43.7
5		41.9
6		36.7
7		33.1

2.2.3 Synthesis of 2nd generation matrine analogue. Even though our modified 1st generation matrine worked fine with aldehydes. We still observed a major byproduct been produced and the yield of aminonitriles wasn't high enough. We quantitatively analyzed the byproduct fraction through NMR and LC-MS and discovered that the major byproduct was original matrine compound which meant the opened lactam ring of 1st generation matrine compound was spontaneously closed up again during the aminonitrile formation. Thus, in order to obtain higher yield of modified matrine products, we further reduced the methyl ester portion with borane and refluxed in THF for 24 hours to prevent

the secondary amine group reacting with the ester terminal, then we applied acid base extraction to obtain 2nd generation matrine analogue.

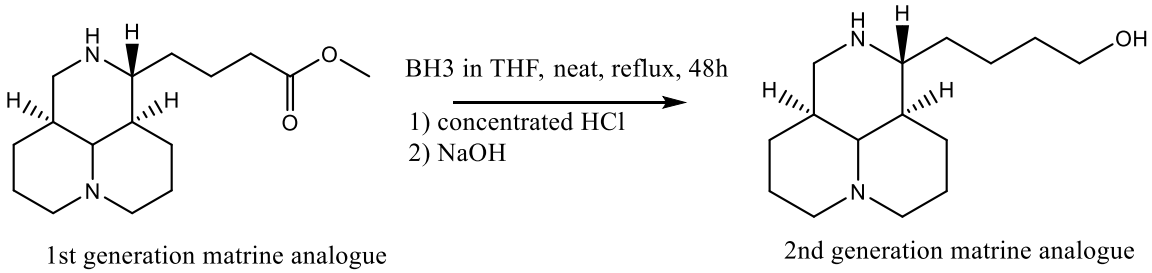
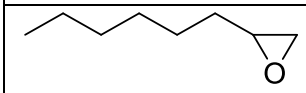
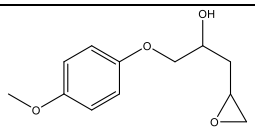
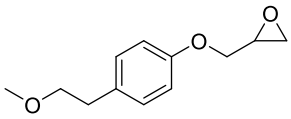
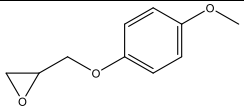
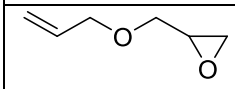
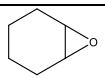
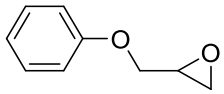
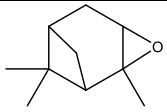
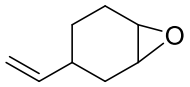
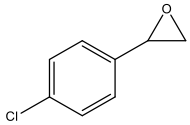
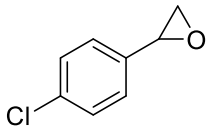
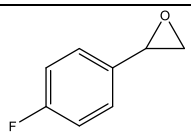
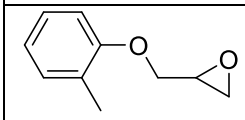
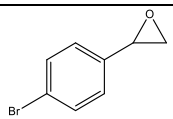
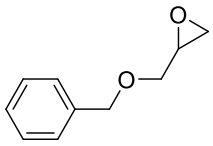
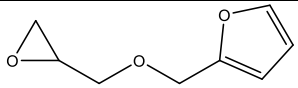
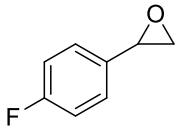
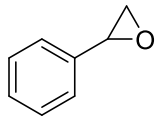


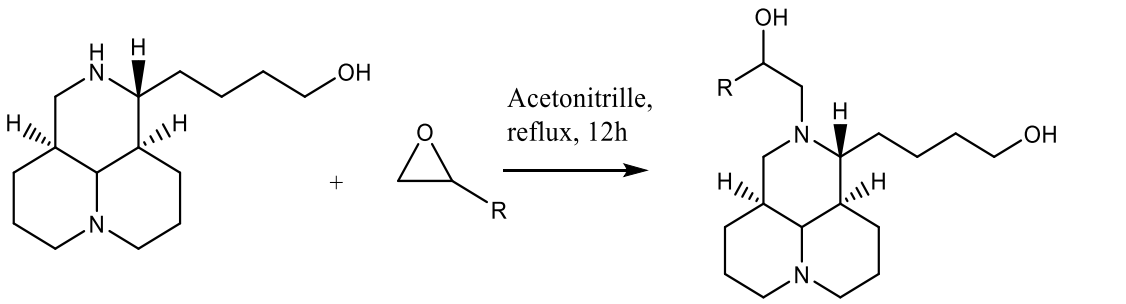
Figure 7. Synthesis of 2nd Generation Matrine Analogue

2.2.4 Synthesis of β-amino alcohol matrine analogue. β-amino alcohol is functional group that has been widely used as inhibitors for protein kinase C, glycosidase or β-adrenergic blockers and antimalarial agents. We envision combine our 2nd generation matrine analogue and β-amino alcohol to form a potent pharmacological effective drug or stronger anticancer agent.

Table 5

Epoxide Opening of 2nd Generation Matrine Analogue

Epoxide	**Percent Yield**	**Epoxide**	**Percent Yield**
	**65.2**		**53.8**
	**55.3**		**46.8**
	**57**		**46.8**
	**59.6**		**45.3**
	**61**		**45.3**
	**54.5**		**43.6**
	**51.4**		**42.6**
	**57**		**37.6**
	**50.3**		**41.2**



2nd generation matrine analogue epoxide ß-amino alcohol matrine analogue

Figure 8. Synthesis of Amino Alcohol Matrine Analogue

2.3 Conclusion

Two different Matrine modifications were successfully applied to form aminonitrile and β-amino matrine analogues. Pharmacological activity test also indicated that our modified productions have the anti-Leukemia potential. However, they're still not good enough to work as drugs due to their low anti-Leukemia efficiency.

2.4 Experimental

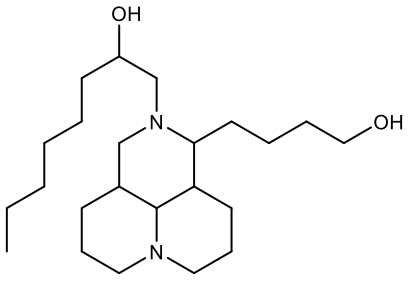
2.4.1 Synthesis of 1st generation matrine analogue. In a 250 mL round bottom flask, 2.94 g of matrine was dissolved in 118.37 ml of concentrated hydrochloric acid. The reaction was refluxed for 48 hours. The solvent was dried and the residue was added methanolic hydrogen chloride. The mixture was stirred at room temperature and refluxed for another 48 hours. The resulting solution was dried then rinsed with methanol three times. The remaining residue in isopropyl alcohol was added diethyl ether. Filtration was applied to the resulting precipitate. Ether washing was repeated until product turned into white solid.

2.4.2 Synthesis of aminonitrile matrine analogue. In a 250 mL round bottom flask, 1 equiv. of 1st generation matrine analogue and 2 equiv. of aldehyde was stirred in Methanol for about 15 minutes then 3 equiv. of sodium cyanide was added into the mixture. The crude was stripped of solvent and the residue loaded directly onto a silica gel column.

2.4.3 Synthesis of 2nd generation matrine analogue. Over dried 3 neck round bottom flask was filled with a stir bar, reflux condenser, flushed with argon, and charged with borane -THF complex. To this stirring solution was added matrine M.E, dihydrochloride as a solid under argon portionwise. The flask heated at reflux 48Hrs. Rxn was quenched with methanol, rotavappoed with 3x chassing of fresh methanol. The residue was applied acid base extraction. Aqueous fraction was extracted with DCM and then precipitate in ethyl acetate.

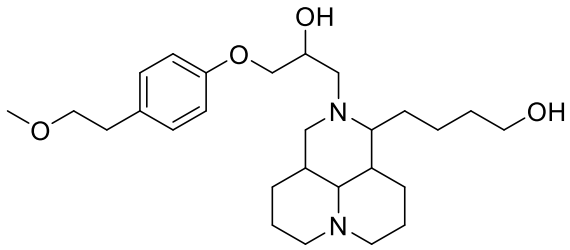
2.4.4 Synthesis of β-amino alcohol matrine analogue. In a 250 mL round bottom flask, 1 equiv. of 2nd generation matrine analogue and 2 equiv. of epoxide were stirred in acetonitrile and the reaction was then refluxed for 12 hours. The crude was stripped of solvent and the residue loaded directly onto a silica gel column.

2.4.5. H-NMR and C-NMR of amino alcohol matrine analogue.



1-(1-(4-hydroxybutyl)octahydro-1H,4H-pyrido[3,2,1-ij][1,6]naphthyridin-2(3H)-yl)octan-2-ol, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.26 – 6.17 (m, 2H), 5.60 (ddd, *J* = 12.4, 7.9, 6.1 Hz, 2H), 5.44 – 5.30 (m, 1H), 4.98 – 4.84 (m, 2H), 4.78 – 4.57 (m, 3H), 4.45 (ddd, *J* = 9.8, 7.6, 5.2 Hz, 4H), 4.43 – 4.30 (m, 2H), 4.34 – 4.19 (m, 6H), 4.23 – 4.08 (m, 4H), 4.13 – 3.93 (m, 4H), 3.95 (s, 3H), 3.98 – 3.84 (m, 2H), 3.80 – 3.61 (m, 2H), 3.58 (td, *J* = 8.7, 7.7, 4.8 Hz, 4H).

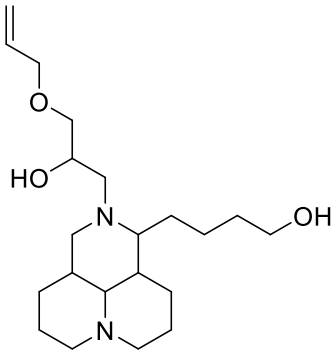
^{13}C NMR (101 MHz, Chloroform-*d*) δ 69.09, 66.66 , 63.19 , 61.96 , 59.77 , 57.04 , 56.27 , 55.16 , 42.10 , 37.11 , 35.60 , 33.03 , 31.50 , 29.30 , 29.17 , 28.58 , 26.37 , 25.57 , 24.98 , 23.40 , 23.15 , 22.86 , 14.13 .



4-(2-(2-hydroxy-3-(4-(2-methoxyethyl)phenoxy)propyl)decahydro-1H,4H-pyrido[3,2,1-ij][1,6]naphthyridin-1-yl)butan-1-ol, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 – 7.07 (m, 4H), 6.84 (dt, *J* = 8.7, 1.5 Hz, 4H), 4.14 – 3.88 (m, 5H), 3.68 – 3.48 (m, 8H), 3.36 – 3.31 (m, 5H), 3.35 – 3.09 (m, 3H), 2.98 (dd, *J* = 12.5, 10.2 Hz, 1H), 2.92 – 2.83 (m, 2H), 2.79 (dt, *J* = 15.8, 8.4 Hz, 11H), 2.71 – 2.51 (m, 3H), 2.27 (dd, *J* = 12.4, 3.7 Hz, 1H), 2.10 – 2.00 (m, 3H), 1.99 – 1.75 (m, 6H), 1.66 (t, *J* = 12.8 Hz, 2H), 1.50 (dd, *J* = 11.5, 6.8 Hz, 3H), 1.44 – 1.32 (m, 1H), 1.39 (s, 3H), 1.35 – 1.20 (m, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 131.23 , 129.80 , 129.70 , 114.49 , 73.84 , 73.81 ,

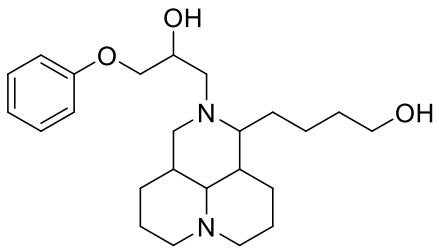
70.62 , 70.37 , 66.14 , 65.38 , 64.55 , 64.03 , 62.47 , 62.23 , 62.11 , 58.60 , 57.56 , 57.50 , 57.46 , 57.42 , 57.26 , 57.23 , 57.18 , 57.05 , 54.23 , 52.45 , 51.90 , 50.33 , 46.02 , 38.93 , 37.05 , 36.85 , 35.27 , 35.25 , 34.87 , 32.81 , 32.62 , 32.53 , 32.21 , 31.34 , 28.58 , 28.32 , 28.20 , 28.06 , 27.95 , 27.39 , 27.20 , 21.58 , 21.48 , 21.45 , 21.38 , 21.18 , 21.08 , 20.75 , 19.55 .



4-(2-(3-(allyloxy)-2-hydroxypropyl)decahydro-1H,4H-pyrido[3,2,1-ij][1,6]naphthyridin-1-yl)butan-1-ol, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.97 – 5.82 (m, 2H), 5.30 – 5.21 (m, 3H), 5.16 (d, *J* = 10.3 Hz, 2H), 4.05 – 3.98 (m, 4H), 3.87 (ddt, *J* = 21.7, 9.5, 4.5 Hz, 2H), 3.61 (q, *J* = 6.1, 5.5 Hz, 6H), 3.46 (dp, *J* = 19.5, 5.3, 4.5 Hz, 4H), 3.25 – 3.07 (m, 3H), 2.96 – 2.78 (m, 2H), 2.80 (s, 4H), 2.80 – 2.63 (m, 4H), 2.56 (ddd, *J* = 22.4, 12.0, 4.2 Hz, 2H), 2.38 – 2.25 (m, 1H), 2.03 (d, *J* = 4.1 Hz, 2H), 1.98 – 1.74 (m, 7H), 1.74 – 1.54 (m, 3H), 1.55 – 1.48 (m, 1H), 1.48 (s, 2H), 1.39 (dddd, *J* = 15.4, 11.9, 8.5, 3.7 Hz, 8H), 1.33 – 1.20 (m, 1H), 1.24 (s, 1H).

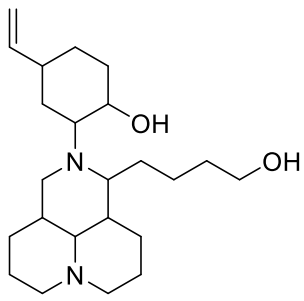
^{13}C NMR (101 MHz, Chloroform-*d*) δ 134.71, 117.05 , 73.01 , 72.63 , 72.46 , 66.69 , 66.00 , 64.59 , 64.05 , 62.40 , 61.87 , 57.50 , 57.25 , 57.04 , 54.27 , 52.43 , 51.72 , 50.13 ,

36.92 , 34.86 , 32.65 , 32.56 , 31.09 , 28.53 , 28.20 , 27.93 , 27.38 , 27.21 , 21.59 , 21.43 , 20.80 , 19.35 .



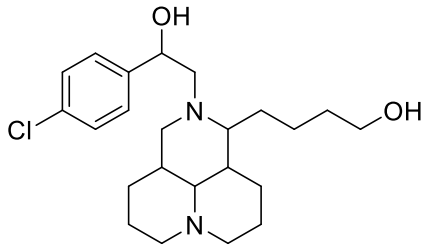
4-(2-(2-hydroxy-3-phenoxypropyl)decahydro-1H,4H-pyrido[3,2,1-ij][1,6]naphthyridin-1-yl)butan-1-ol, H NMR (400 MHz, Chloroform-*d*) δ 7.26 (s, 1H), 7.01 – 6.89 (m, 1H), 3.72 (s, 6H), 3.70 (dd, *J* = 6.3, 4.0 Hz, 1H), 3.65 (dq, *J* = 11.7, 5.1 Hz, 4H), 3.44 (t, *J* = 12.3 Hz, 3H), 3.08 (s, 2H), 2.78 (dd, *J* = 21.7, 9.2 Hz, 7H), 2.33 (s, 3H), 2.12 (s, 2H), 2.03 – 1.87 (m, 9H), 1.48 – 1.38 (m, 7H).

^{13}C NMR (101 MHz Chloroform-*d*) δ 129.57, 121.47 , 114.93 , 69.63 , 67.91 , 66.66 , 63.19 , 61.96 , 57.55 , 57.04 , 56.27 , 55.16 , 42.10 , 37.11 , 33.03 , 29.17 , 28.58 , 26.37 , 24.98 , 23.40 , 23.15 . Molecular Weight: 402.58



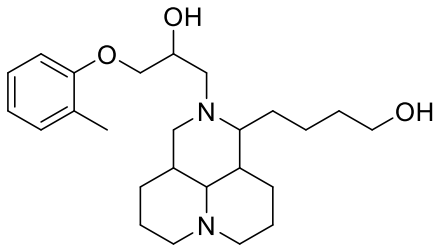
2-(1-(4-hydroxybutyl)octahydro-1H,4H-pyrido[3,2,1-ij][1,6]naphthyridin-2(3H)-yl)-4-vinylcyclohexan-1-ol, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.59 (tt, *J* = 6.4, 3.2 Hz, 2H), 3.21 (t, *J* = 12.1 Hz, 1H), 3.08 (td, *J* = 9.5, 3.2 Hz, 1H), 2.77 (ddd, *J* = 18.4, 11.2, 3.6 Hz, 2H), 2.60 (dd, *J* = 11.9, 4.3 Hz, 1H), 2.09 – 1.98 (m, 1H), 1.91 (pt, *J* = 11.9, 7.0 Hz, 3H), 1.82 – 1.22 (m, 8H), 1.19 (ddd, *J* = 18.4, 9.0, 4.4 Hz, 1H).

3-^{13}C NMR (101 MHz, Chloroform-*d*) δ 144.82 , 112.39 , 69.63 , 65.35 , 64.19 , 62.81 , 61.96 , 57.04 , 56.27 , 53.32 , 42.26 , 41.49 , 36.95 , 33.03 , 29.95 , 29.77 , 28.54 , 28.09 , 27.90 , 25.87 , 24.98 , 22.27 , 21.95 .



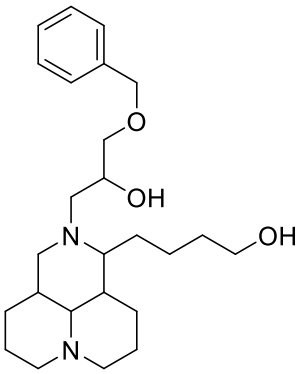
4-(2-(2-(4-chlorophenyl)-2-hydroxyethyl)decahydro-1H,4H-pyrido[3,2,1-ij][1,6]naphthyridin-1-yl)butan-1-ol, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.31 (m, 4H), 5.07 (t, *J* = 7.0 Hz, 1H), 3.62 – 3.50 (m, 2H), 3.37 (dd, *J* = 12.4, 7.0 Hz, 1H), 2.97 – 2.84 (m, 2H), 2.58 (dd, *J* = 12.4, 6.9 Hz, 1H), 2.48 – 2.31 (m, 2H), 2.03 (dq, *J* = 12.6, 7.3 Hz, 2H), 1.82 – 1.24 (m, 15H), 1.29 – 1.08 (m, 1H), 1.00 (dq, *J* = 13.8, 7.0 Hz, 1H), 0.77 (dq, *J* = 13.8, 7.1, 6.6 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 128.58 , 128.22 , 70.33 , 66.66 , 63.19 , 61.96 , 60.29 , 57.04 , 56.27 , 55.16 , 42.10 , 37.11 , 33.03 , 29.17 , 28.58 , 26.37 , 24.98 , 23.40 , 23.15 .



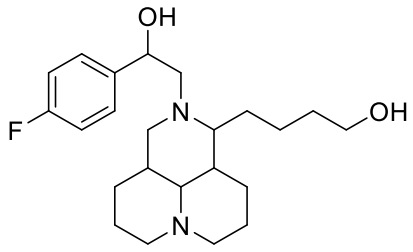
4-(2-(2-hydroxy-3-(o-tolyloxy)propyl)decahydro-1H,4H-pyrido[3,2,1-ij][1,6]naphthyridin-1-yl)butan-1-ol, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 (s, 1H), 7.13 (dd, *J* = 9.4, 6.6 Hz, 4H), 6.93 – 6.76 (m, 4H), 4.15 (dd, *J* = 9.7, 5.3 Hz, 1H), 4.15 – 3.92 (m, 5H), 3.66 – 3.53 (m, 4H), 3.26 – 3.12 (m, 2H), 3.02 (dd, *J* = 12.5, 10.3 Hz, 1H), 2.95 – 2.72 (m, 7H), 2.71 – 2.46 (m, 3H), 2.34 (dd, *J* = 12.6, 3.6 Hz, 1H), 2.23 (s, 5H), 2.05 (dt, *J* = 5.9, 3.0 Hz, 2H), 2.02 – 1.76 (m, 6H), 1.77 – 1.62 (m, 3H), 1.52 (dtd, *J* = 17.4, 10.8, 5.9 Hz, 9H), 1.45 – 1.37 (m, 3H), 1.38 – 1.20 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 130.61 , 126.78 , 126.76 , 120.53 , 111.02 , 110.99 , 77.22 , 76.73 , 70.40 , 70.38 , 66.27 , 65.45 , 64.59 , 64.05 , 62.59 , 62.34 , 57.51 , 57.43 , 57.27 , 57.24 , 57.21 , 56.94 , 54.73 , 52.43 , 51.86 , 50.22 , 39.02 , 36.98 , 34.90 , 32.93 , 32.60 , 31.23 , 28.63 , 28.58 , 28.21 , 27.95 , 27.39 , 27.20 , 21.60 , 21.45 , 21.39 , 21.07 , 20.80 , 19.77 , 16.23 .



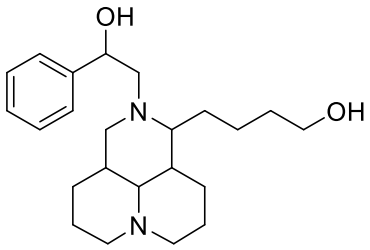
4-(2-(3-(benzyloxy)-2-hydroxypropyl)decahydro-1H,4H-pyrido[3,2,1-ij][1,6]naphthyridin-1-yl)butan-1-ol, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.24 (m, 5H), 4.54 (s, 2H), 4.13 – 4.05 (m, 1H), 3.87 (d, *J* = 19.6 Hz, 1H), 3.54 (td, *J* = 10.7, 5.6 Hz, 2H), 3.46 (s, 2H), 3.14 (s, 1H), 2.82 – 2.69 (m, 4H), 2.53 (s, 1H), 2.13 (d, *J* = 4.5 Hz, 2H), 2.01 (d, *J* = 4.4 Hz, 2H), 1.61 (s, 4H), 1.48 (s, 6H), 1.37 (s, 5H), 1.23 (t, *J* = 6.6 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 138.22 , 128.31 , 128.30 , 127.71 , 127.69 , 127.68 , 127.57 , 127.54 , 77.26 , 73.46 , 73.44 , 73.06 , 72.69 , 66.74 , 66.00 , 64.53 , 64.01 , 62.31 , 61.85 , 60.35 , 57.48 , 57.40 , 57.37 , 57.23 , 57.21 , 57.05 , 54.42 , 52.44 , 51.79 , 50.31 , 38.93 , 36.96 , 34.82 , 32.66 , 32.57 , 31.16 , 29.65 , 28.59 , 28.30 , 28.17 , 27.90 , 27.34 , 27.16 , 21.55 , 21.40 , 21.36 , 21.04 , 20.83 , 19.53 , 14.16 .



4-(2-(2-(4-fluorophenyl)-2-hydroxyethyl)decahydro-1H,4H-pyrido[3,2,1-ij][1,6]naphthyridin-1-yl)butan-1-ol, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.13 (m, 4H), 7.07 – 6.88 (m, 5H), 4.77 – 4.55 (m, 2H), 3.60 (ddt, *J* = 29.7, 11.6, 7.8 Hz, 4H), 3.50 (s, 2H), 3.22 (ddt, *J* = 41.3, 27.0, 6.6 Hz, 1H), 2.80 (dt, *J* = 19.7, 6.6 Hz, 2H), 2.71 (s, 3H), 2.77 – 2.54 (m, 2H), 2.36 – 2.15 (m, 1H), 2.08 – 1.86 (m, 2H), 1.90 – 1.80 (m, 2H), 1.66 – 1.49 (m, 2H), 1.47 (t, *J* = 9.0 Hz, 2H), 1.34 (s, 1H), 1.21 (qd, *J* = 11.8, 7.1, 5.8 Hz, 1H).

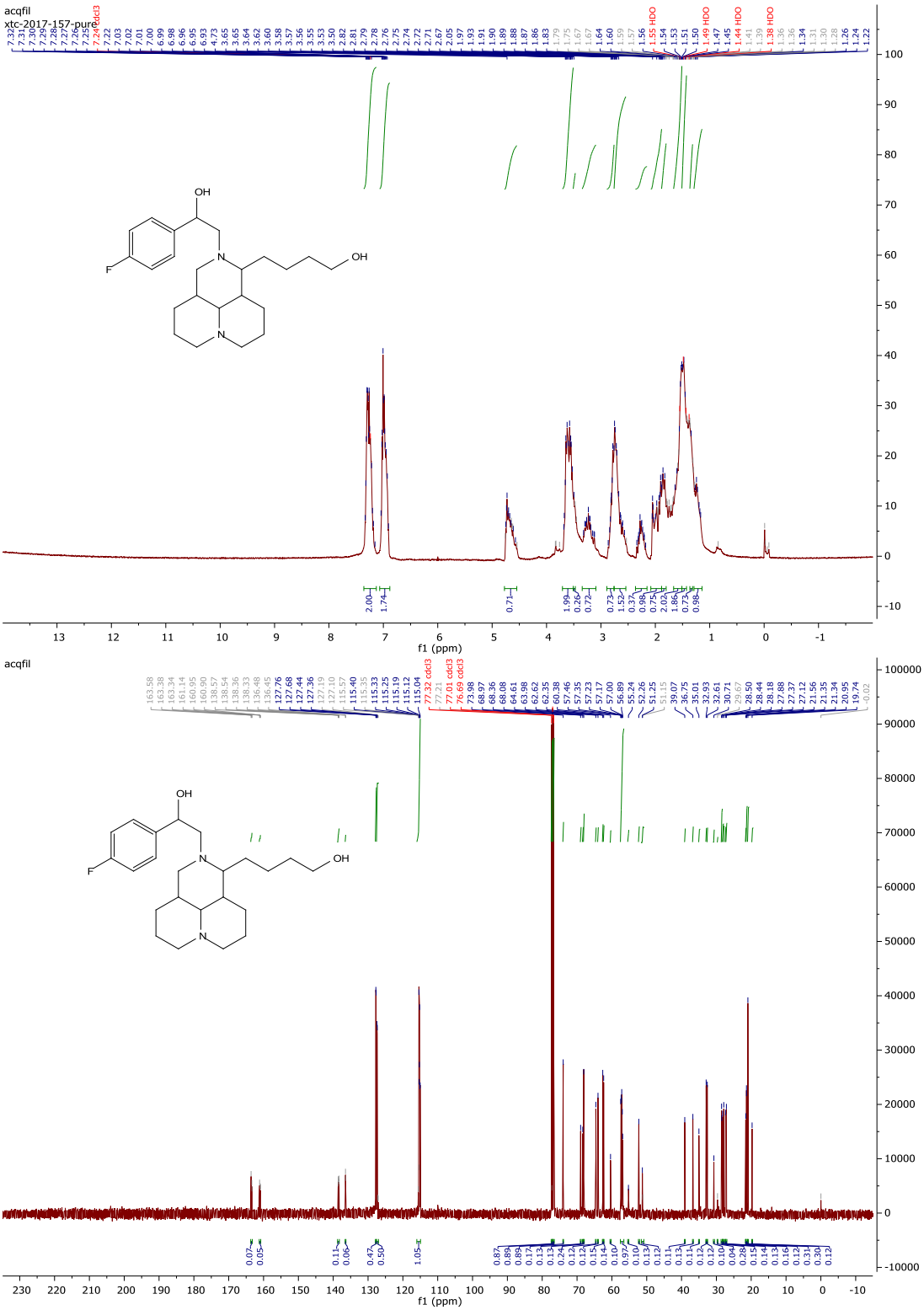
^{13}C NMR (101 MHz, Chloroform-*d*) δ 127.76 , 127.68 , 127.44 , 127.36 , 115.40 , 115.33 , 115.25 , 115.19 , 115.12 , 115.04 , 73.98 , 68.97 , 68.36 , 68.08 , 64.61 , 63.98 , 62.62 , 62.35 , 60.38 , 57.46 , 57.35 , 57.23 , 57.17 , 57.00 , 56.89 , 55.24 , 52.26 , 51.25 , 39.07 , 36.75 , 35.01 , 32.93 , 32.61 , 30.71 , 28.50 , 28.44 , 28.18 , 27.88 , 27.37 , 27.12 , 21.56 , 21.35 , 21.34 , 20.95 , 19.74 .

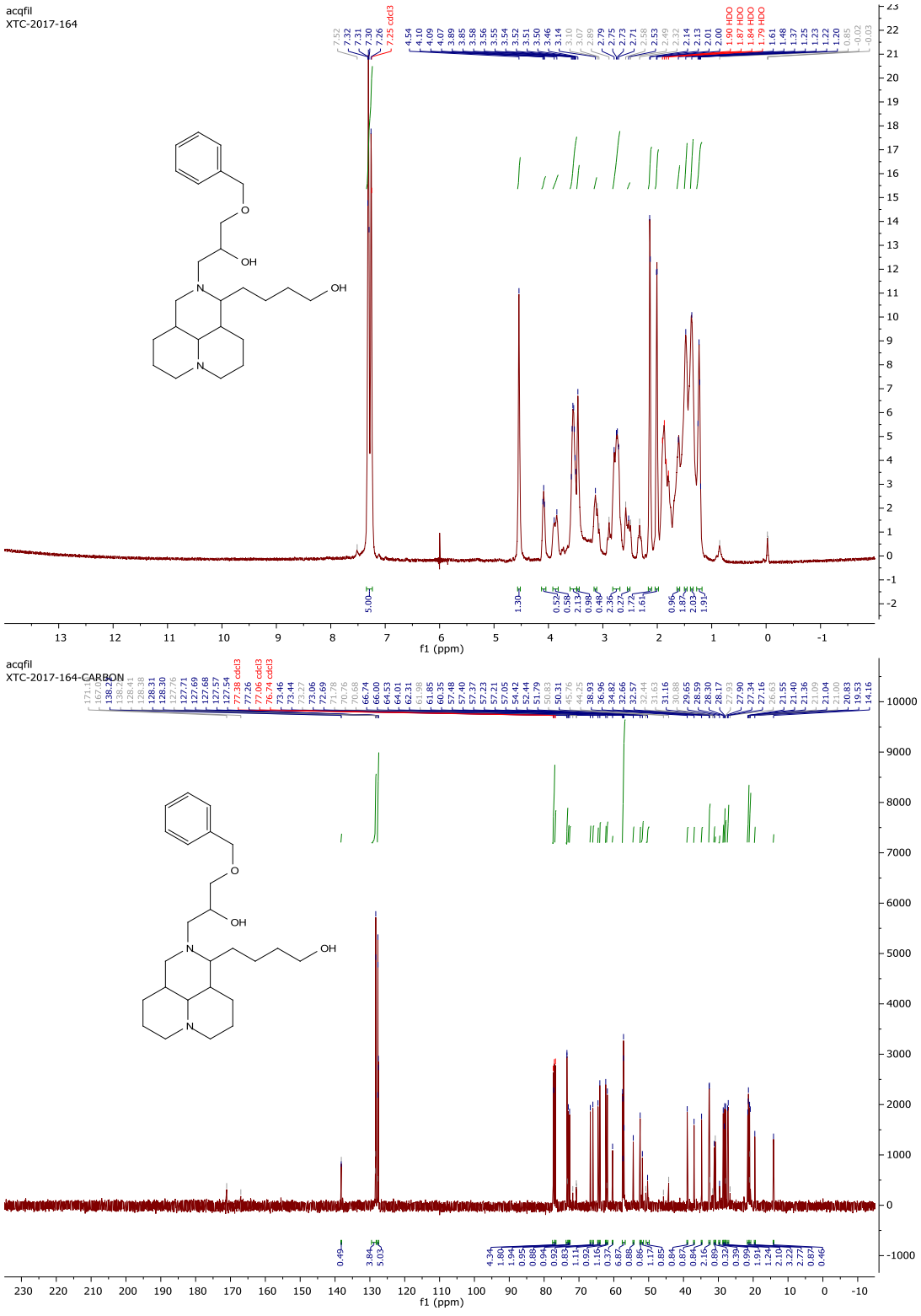


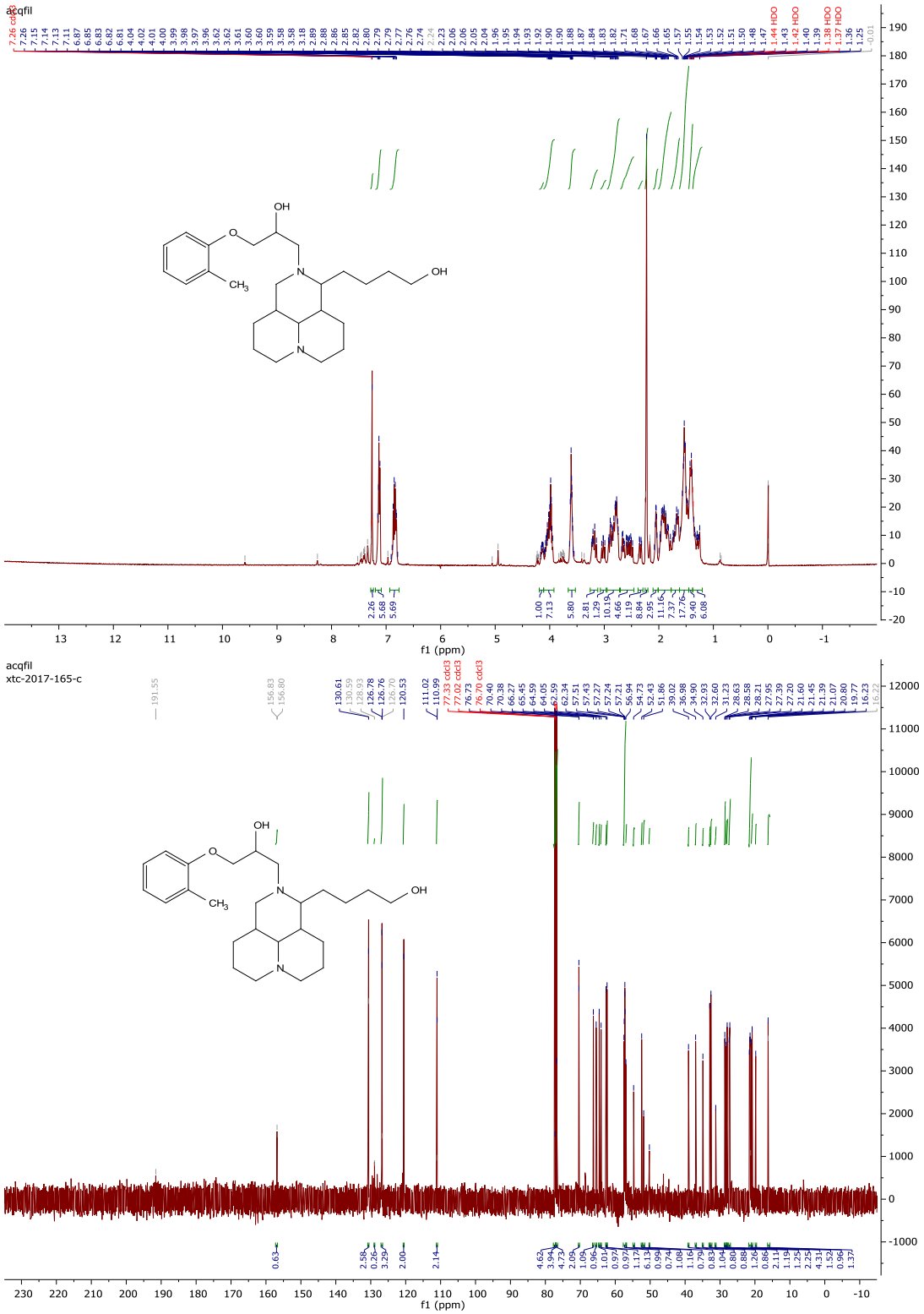
4-(2-(2-hydroxy-2-phenylethyl)decahydro-1H,4H-pyrido[3,2,1-ij][1,6]naphthyridin-1-yl)butan-1-ol, Molecular Weight: 372.55, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.28 (m, 11H), 7.31 – 7.19 (m, 2H), 4.75 (ddd, *J* = 14.2, 9.5, 3.6 Hz, 1H), 3.75 – 3.53 (m, 5H), 3.35 – 3.16 (m, 1H), 2.80 (dddt, *J* = 27.8, 15.4, 10.9, 4.2 Hz, 6H), 2.42 – 2.25 (m, 1H), 2.11 – 1.69 (m, 5H), 1.72 – 1.53 (m, 2H), 1.50 (dd, *J* = 12.5, 4.3 Hz, 2H), 1.43 (s, 2H), 1.38 (td, *J* = 13.5, 11.8, 6.4 Hz, 2H).

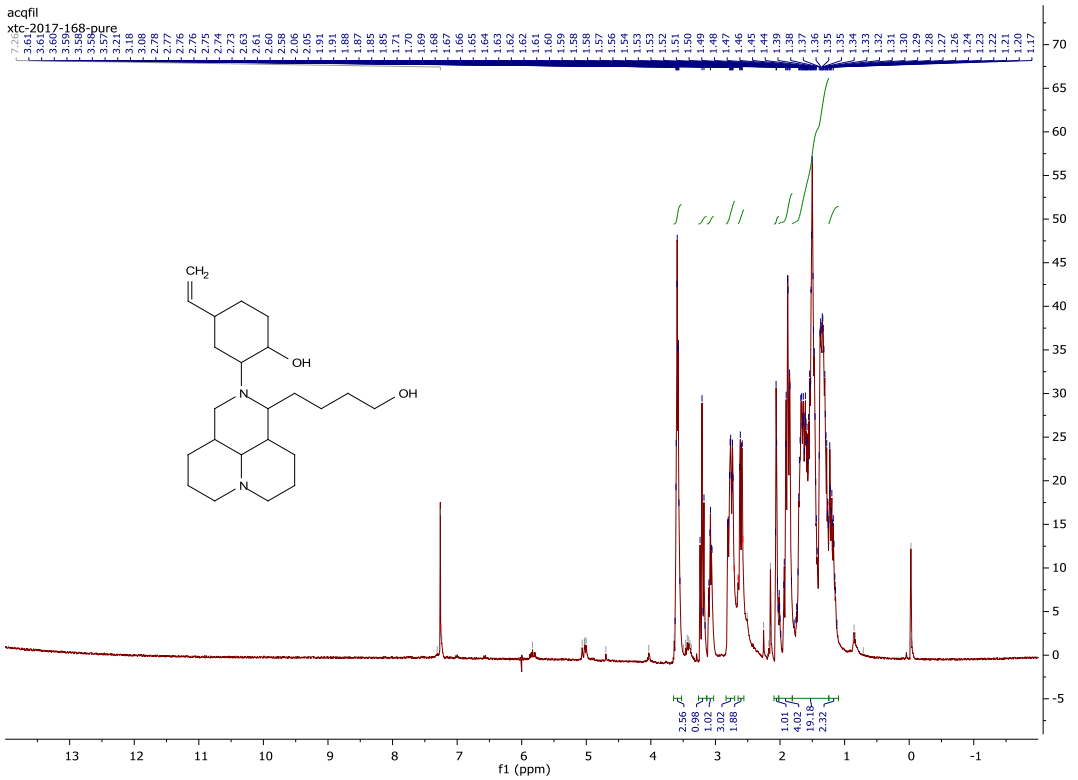
^{13}C NMR (101 MHz, Chloroform-*d*) δ 128.41 , 128.39 , 128.32 , 127.81 , 127.36 , 126.06 , 125.83 , 125.80 , 74.62 , 68.95 , 68.12 , 64.71 , 64.07 , 62.63 , 62.36 , 60.40 , 57.49 , 57.39 , 57.26 , 57.21 , 56.95 , 56.81 , 52.27 , 51.27 , 39.11 , 36.74 , 35.07 , 32.97 , 32.67 , 30.72 , 28.44 , 28.22 , 27.91 , 27.40 , 27.13 , 21.59 , 21.37 , 20.93 , 19.70 .

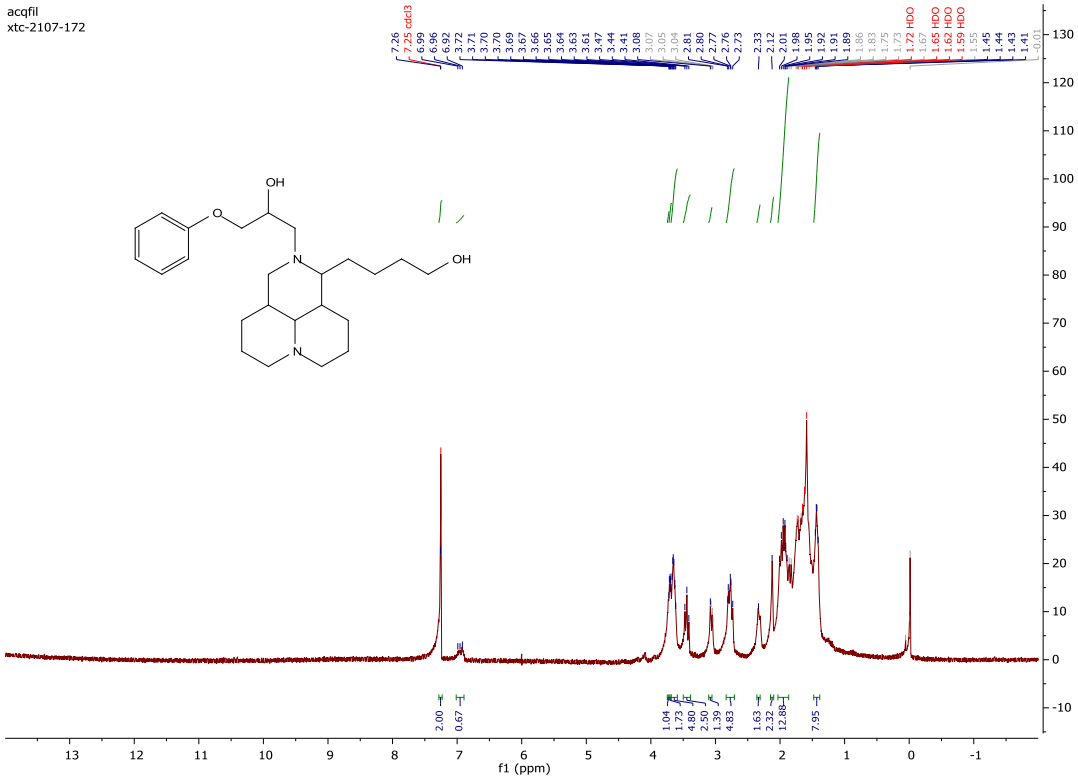
H NMR & C NMR

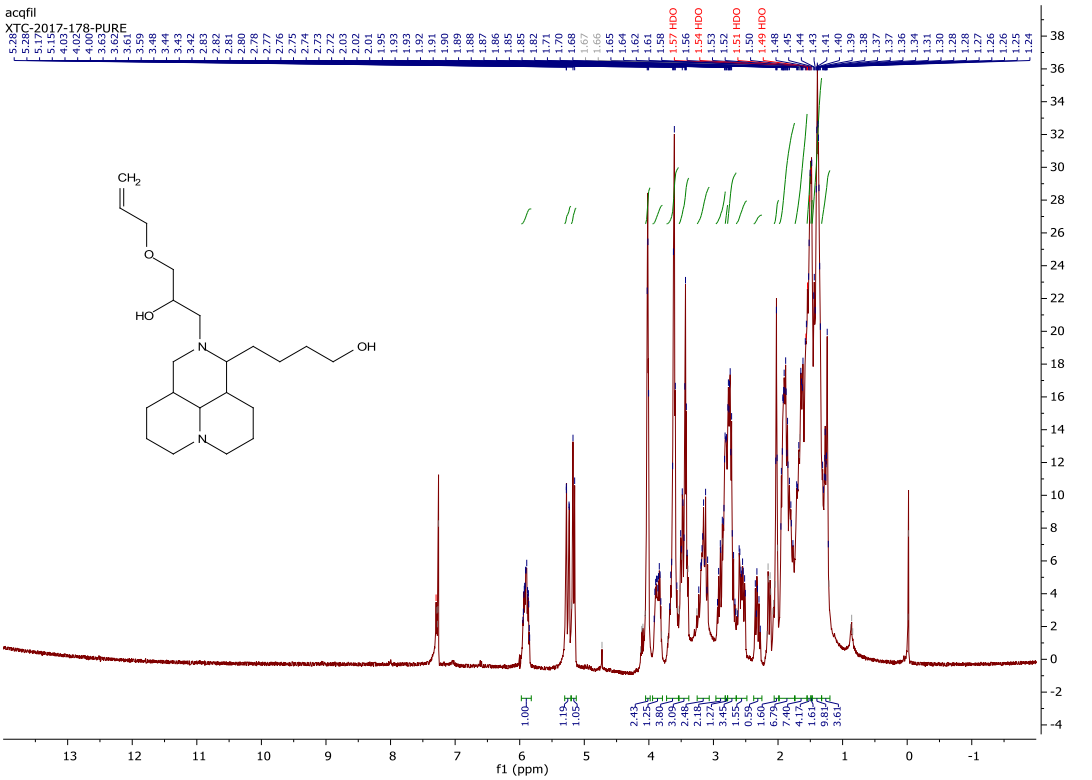


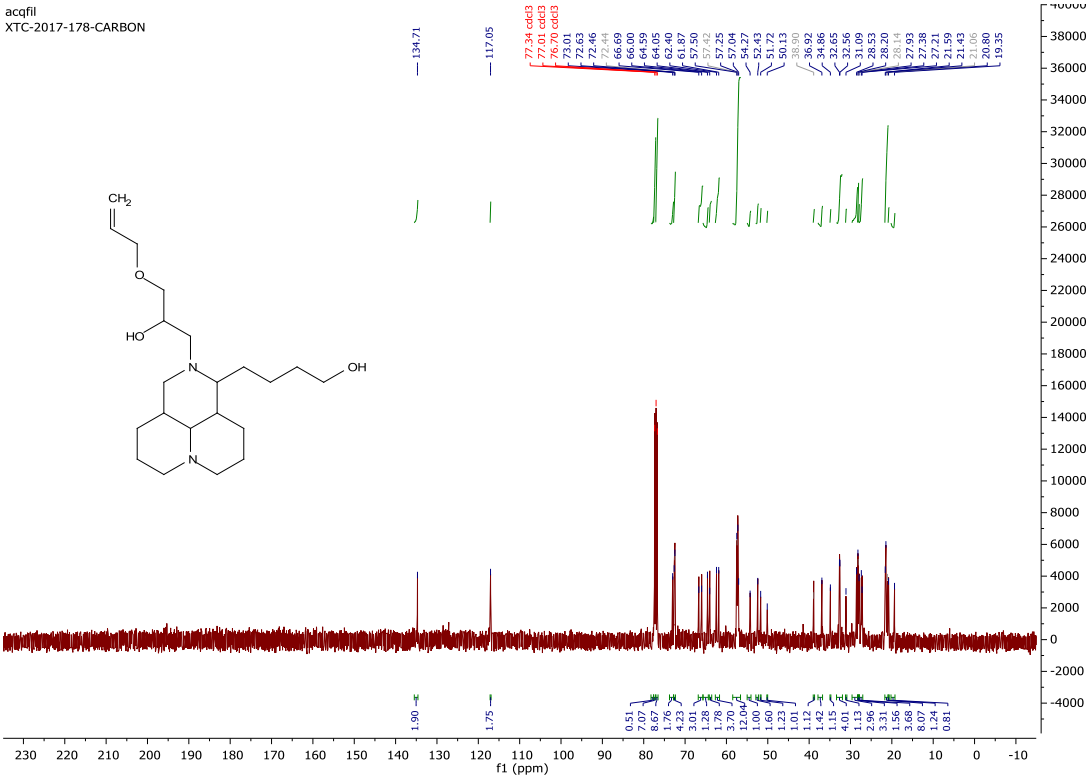

acqfil
XTC-2017-164
f1 (ppm)
acqfil
XTC-2017-164-CARBON
f1 (ppm)

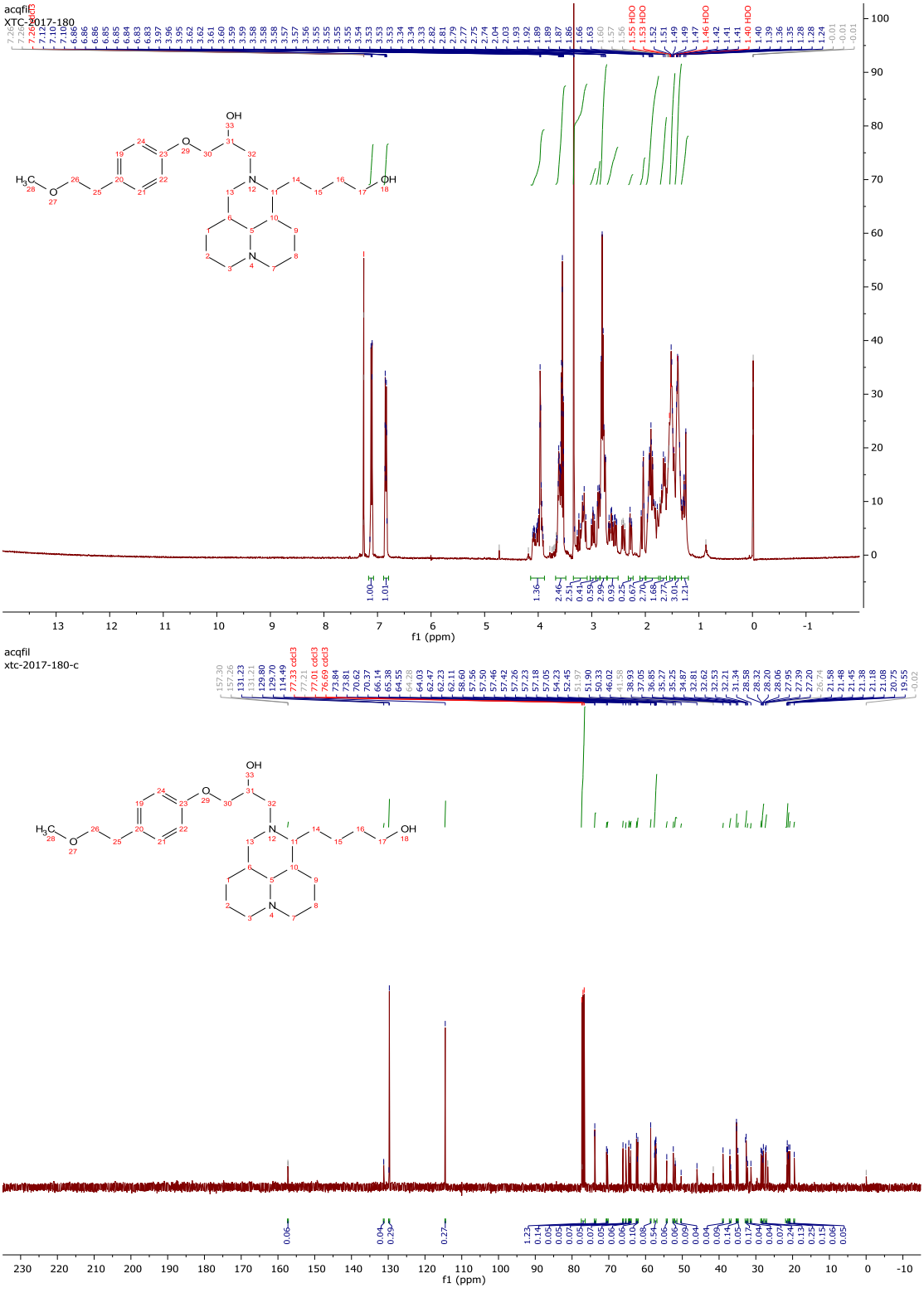

acqfil
OH
O
CH3
N
OH
N
f1 (ppm)
acqfil
xtc-2017-165-c
OH
O
CH3
N
OH
N
f1 (ppm)


acqfil
xtc-2017-168-pure
f1 (ppm)


acqfil
xtc-2107-172
f1 (ppm)


acqfil
XTC-2017-178-PURE
CH2
O
HO
N
OH
N
f1 (ppm)


acqfil
XTC-2017-178-CARBON
CH2
O
HO
N
OH
N
f1 (ppm)


acqfil
XTC-2017-180
f1 (ppm)
acqfil
xtc-2017-180-c
f1 (ppm)

References

1. DPP-4 inhibitors in the treatment of type 2 diabetes. Duez H1, Cariou B, Staels B. Biochem Pharmacol. 2012 Apr 1;83(7):823-32. doi: 10.1016/j.bcp.2011.11.028. Epub 2011 Dec 13.

2. Lizza, J. R., Patel, S. V., Yang, C. F., & Moura-Letts, G. (2016). Direct Synthesis of Cyanopyrrolidinyl β-Amino Alcohols for the Development of Diabetes Therapeutics. European Journal of Organic Chemistry,2016(30), 5160-5168. doi:10.1002/ejoc.201600969

3. Green, B., Flatt, P., & Bailey, C. (2006). Dipeptidyl peptidase IV (DPP IV) inhibitors: a newly emerging drug class for the treatment of type 2 diabetes. *Diabetes and Vascular Disease Research*, *3*(3), 159-165.

4. Pan, Q., Li, Y., Hua, J., Huang, F., Wang, H., & Liang, D. (2015). Antiviral Matrine-Type Alkaloids from the Rhizomes of Sophora tonkinensis. *Journal of Natural Products*, *78*(7), 1683-1688.

5. Fleming, F., Yao, L., Ravikumar, P., Funk, L., & Shook, B. (2010). Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *Journal of Medicinal Chemistry*, *53*(22), 7902-7917.

6. Qing, Z., Yang, P., Tang, Q., Cheng, P., Liu, X., Zheng, Y., Liu, Y., & Zeng, J (2003). Isoquinoline Alkaloids and Their Antiviral, Antibacterial, and Antifungal Activities and Structure-activity Relationship. Retrieved October 2017

7. Moura-Letts, G., Ph.D., (n.d.). Moura-Letts Group. Retrieved October. 2017, from https://www.gmlresearchgroup.com/projects

8. Moura-letts, Gustavo, Ph.D., Department of Chemistry and Biochemistry, Rowan University