4-26-2018

Synthesis and cytotoxicity evaluation of functionalized betulin derivatives

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SYNTHESIS AND CYTOTOXICITY EVALUATION OF FUNCTIONALIZED BETULIN DERIVATIVES

by

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A Thesis

Submitted to the
Department of Chemistry & Biochemistry
College of Science & Mathematics
In partial fulfillment of the requirement
For the degree of
Master of Science in Pharmaceutical Sciences
at
Rowan University
December 11, 2017

Thesis Chair: Subash Jonnalagadda, Ph.D.

Dedications

I dedicate my monograph work to my parents Ghanshyam Patel and Mina Patel, and my spouse Shruti Patel, who has been a consistent source of support and inspiration during the challenges of graduate school and the life. I am truly thankful for having you in my life and for having always loved me unconditionally. I also dedicate this monograph to my brother Varshil Patel and my son Prince Patel. I will always welcome all they have done for me.

Acknowledgments

I would like to express my appreciation to Prof. Subash Jonnalagadda for his guidance and help throughout this research. The skills and knowledge that I have gained are things that I will take with me into my next professional endeavour. I look forward to whatever challenges that come my way knowing that I am prepared to take them on. I would also like to thank Dr. Suman Pathi for his kind support through this journey.

Abstract

Amardeep Patel
SYNTHESIS AND CYTOTOXICITY EVALUATION OF FUNCTIONALIZED BETULIN DERIVATIVES
2017-2018
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Master of Science in Pharmaceutical Sciences

Betulin and betulinic acid are complex natural compounds that can be readily extracted in high quantities from external bark of yellow and white birch trees. Birch tree is native to northern New Jersey and is also commonly available for purchase as firewood. Betulinic acid is found to exhibit very good activity against few cancer cell lines, and is relatively non-toxic to normal cells. The ready availability and selective cytotoxicity coupled with the favorable therapeutic index have made betulinic acid an attractive and promising anticancer agent. However, this molecule is almost insoluble in water and shows anti-cancer activity only on very few cell lines.

This thesis details our efforts on the development of novel synthetic methodologies for the synthesis of functionalized betulin derivatives as potential anti-cancer agents. We initiated the synthesis of betulin conjugates starting from betulinic acid employing reactions such as Baylis-Hillman reaction and click reaction. Further functionalization of these conjugates was achieved via reduction and succinylation. The cytotoxicity evaluation of these compounds showed good potential as anti-cancer agents.

Table of Contents

Table of Contents (Continued)

List of Figures

List of Figures (Continued)

Figure Page

List of Figures (Continued)

Figure Page

List of Figures (Continued)

Figure Page

List of Figures (Continued)

Figure Page

List of Tables

Chapter 1

Introduction

Betulin/Betulinic Acid

Betulin **1** and betulinic acid (B/BA) are pentacyclic lupane –type triterpenoids that are found as secondary metabolites in various types of plants distributed across of plant kingdom (**Figure 1**).[1-2] Betulin is abundantly available in the outer part of the birch bark and these trees are native to northern America and various parts of Europe. Betulonic acid **2** and betulinic acid **3** can be easily synthesized from betulin via simple redox chemistry. Betulinic acid exhibits significant cytotoxicity against various cancer such as melanoma, gliblastoma pancreatic cancer, breast, and prostate cancer, etc.[3] Further their derivatives also exhibit diverse range of pharmacological properties ranging from anti-HIV, anti-micotic, anti-inflammatory, anti-parasitic, and antioxidants.[4-13] There have been several reports on the synthesis and development of the betulin derivatives as potential medicinal agents.[4-13] One of the recognized analogs of betulinic acid is bevirimat **4**, which shows excellent anti-HIV activity with a new mechanism of action known as virus maturation inhibition. This molecule was developed by Panacos Pharmaceuticals and it reached Phase IIb clinical trials for the treatment of HIV. While the mechanism of action is unclear, several reports indicate that betulinic acid triggers apoptosis via direct regulation of mitochondrial pathways and increased production of caspase-3.[4-14] Betulinic acid is also known to produce an anti-angiogenic response as well as affect the immuno-regulation *in-vivo* and arrest the cell cycle in the G2/M phase. [4-13]

Further, betulinic acid has been evaluated for the *in vivo* protective effect on dexamethasone-induced thymocyte apoptosis via reduction of oxidative stress.[15] Betulin also inhibits TLR4/NF-kB pathway which results in reduction of kidney,[16] liver, and lung[17] injuries in rats. It also exhibits protective effects against colitis in mice.[18]

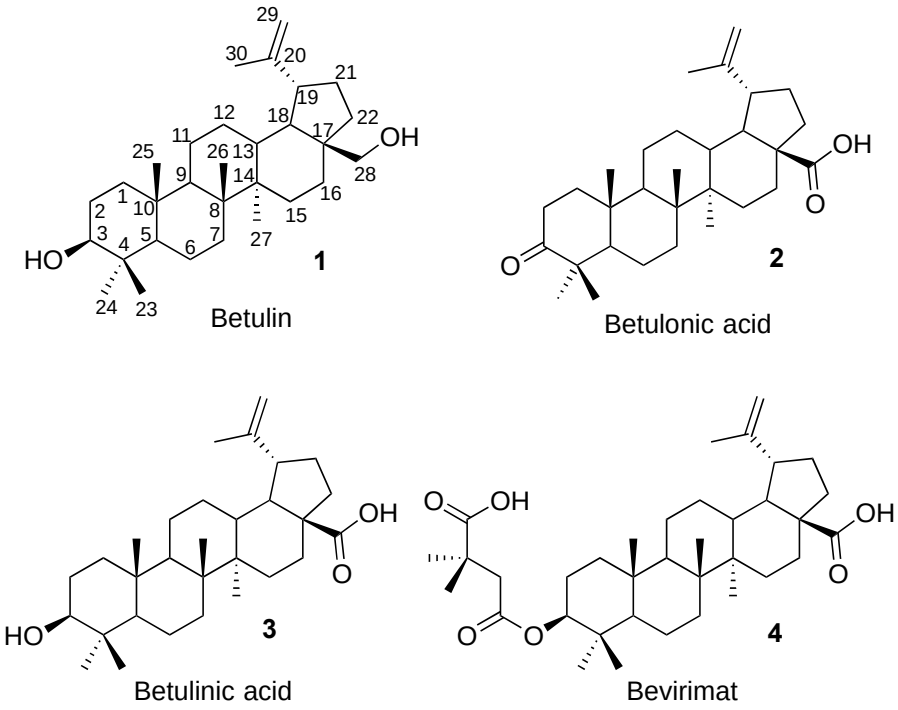


Figure 1. Betulinic acid analogs.

Multicomponent Reactions

Multi-component coupling reactions involve the combination of three or more precursors to form complex products. These reactions are highly atom, economical and exhibit excellent chemo selectivity. These reactions offer wide range of benefits in drug development as these are usually highly convergent one pot reactions which offer

high diversity in the product formation. There have been several examples of the use of MCRs for the development of medicinal compounds such as kinase inhibitors, tubulin inhibitors, aspartyl protease inhibitors, serine protease inhibitors, metaloprotease inhibitors, GPCR inhibitors and so on.[19]

Some of the famous examples of MCRs include alkyne trimerization, Biginelli reaction, Bucherer-Bergs reaction, Gewald reaction, Greico three component coupling, Hantzsch pyridine synthesis, Mannich reaction, Passerini reaction, Pauson-Khand reaction, Petasis reaction, Ugi reaction, Strecker synthesis, etc.[20]

Passerini reaction involves the coupling of an isocyanide **7** with an aldehhyde **5** or ketone and a carboxylic acid **6** to yield an α-acyloxy amide product **8**;[21] similarly the Ugi reaction involves four components coupling between an isocyanide **7**, and aldehyde/ketone **5**, an amine **9**, and a carboxylic acid **6** to furnish α-carboamido amides **10** (**Figure 2**).[22]

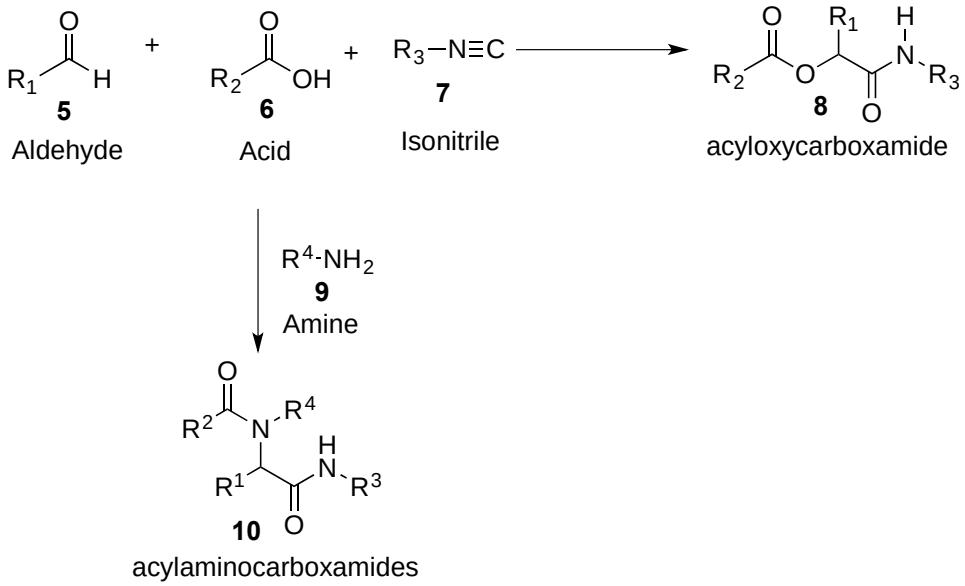


Figure 2. Passerini and Ugi multicomponent coupling reactions.

Prior to the current work, our group has synthesized several betulinic acid analogs via multicomponent coupling reactions such as reductive amination, aldol condensation, and Passerini reaction.[23]

Synthesis of Betulin-Chalcone Conjugates

The betulin-chalcone analog **15** was synthesized starting from betulin in five steps. Initially, betulin **1** was esterified as C_3-C_{28} diester, which was then selectively hydrolyzed with aluminum isopropoxide to furnish the primary alcohol and subsequently oxidized with PCC to generate the aldehyde **11**. Reaction of **11** with acetophenone **12** in the presence of potassium *tert*-butoxide in THF yielded the chalcone **13** with the concomitant hydrolysis of C_3 ester. This compound was further converted to the target compound succinic acid hemi ester **14** upon heating with succinic anhydride **14** in the presence of DMAP (**Figure 3**).

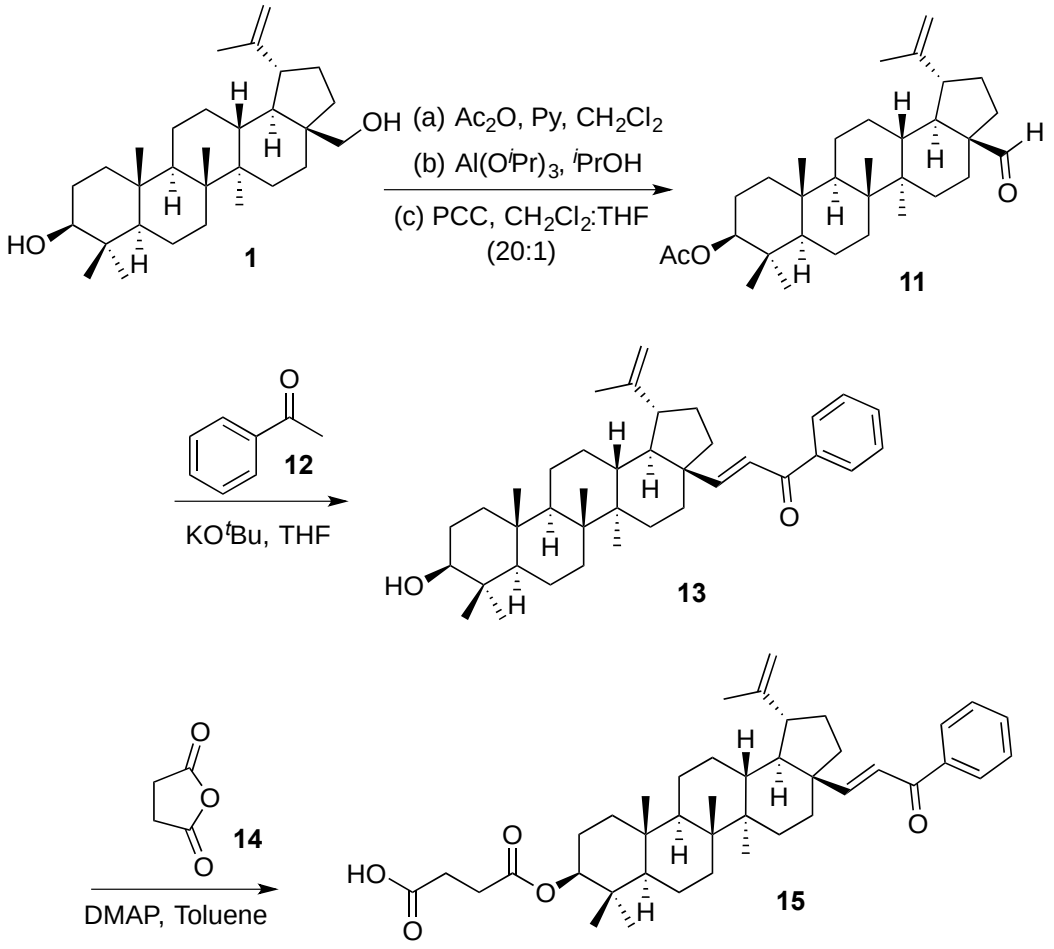


Figure 3. Preparation of betulin-chalcone conjugates.

Synthesis of Betulin Conjugates via Passerini Reaction

The betulin aldehyde **11** was reacted with variety of carboxylic acids and isocyanides to furnish the C_{28} acetoxyamide derivatives **16** and **17**. We were also able to synthesize a fluorescent BODIPY- betulin conjugate **19** via this protocol (**Figure 4**).

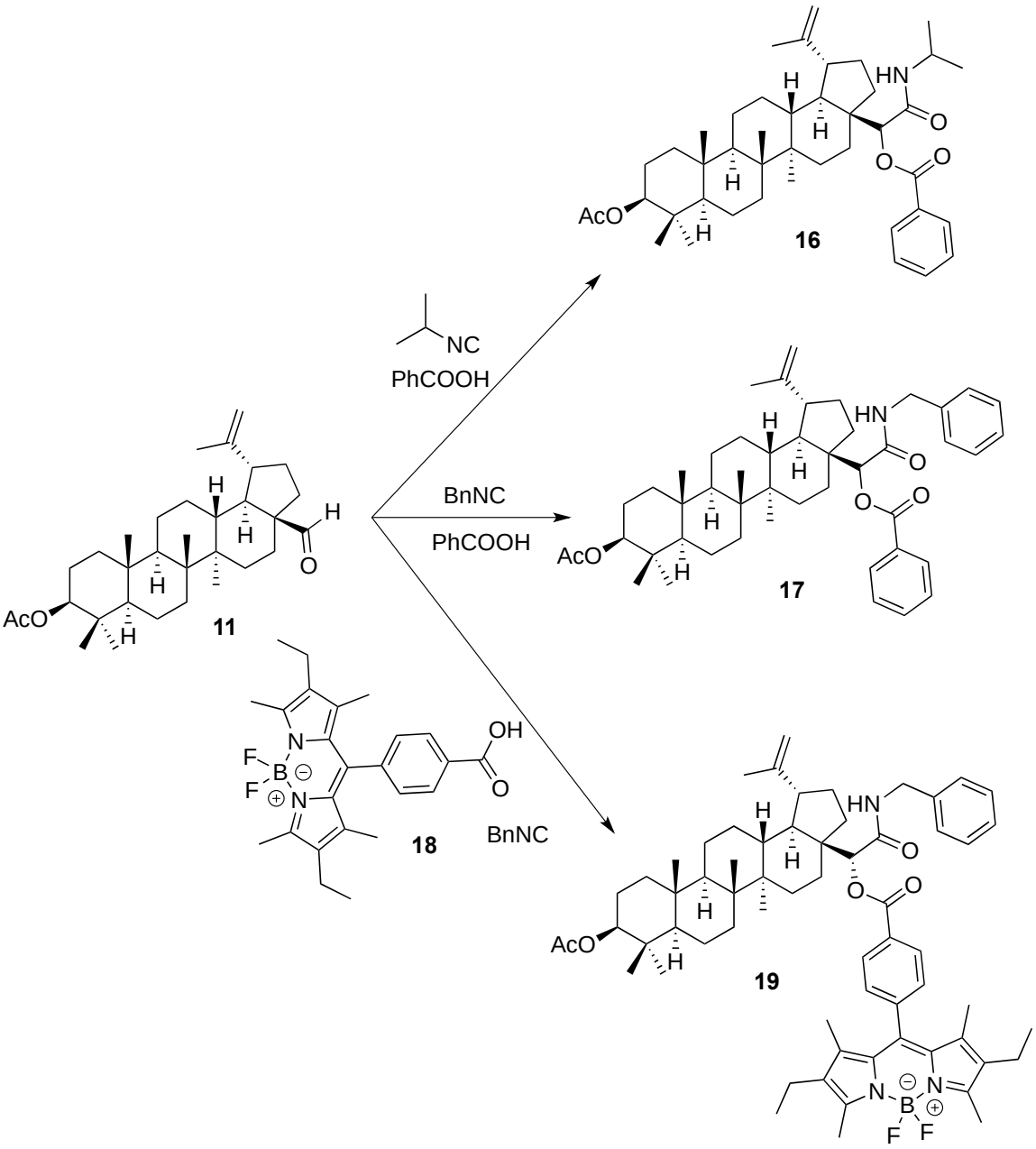


Figure 4. Preparation of betulin conjugates via Passerini reaction.

Synthesis of Betulin Conjugates via Reductive Amination

The betulin aldehyde **20** was subjected to reductive amination with benzyl amine and sodium borohydride to yield secondary amine, which was then treated with benzyl

bromide to furnish the tertiary amine **21** (**Figure 5**).

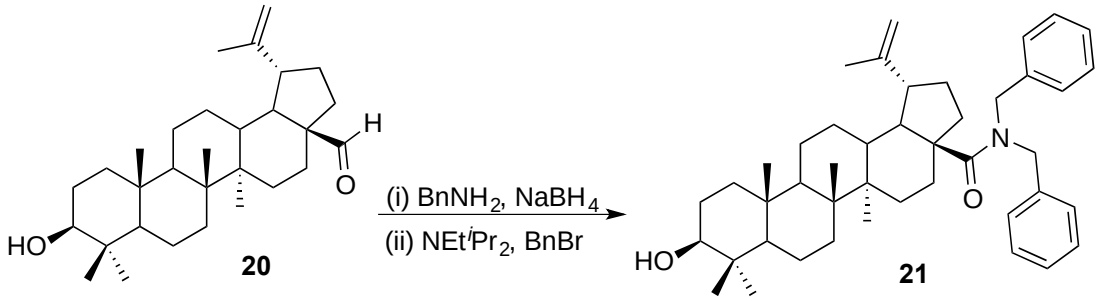


Figure 5. Preparation of betulin conjugates via reductive amination.

Synthesis of Betulin Conjugates via Click Reaction

The click reaction is a 1,3-dipolar cycloaddition reaction involving the coupling of azides **22** and alkynes **23** in the presence of copper catalyst which results in the formation of 1,4 disubstituted 1,2,3 triazoles **24** (**Figure 6**).[24] The product triazoles have wide range of medicinal application and are heavily used in natural product drug discovery,[25] biopolymers,[26] nano-technology,[27-28] and other biomaterials.[29] Click chemistry has been used extensively in high throughput synthesis and assembly of the chemical libraries.

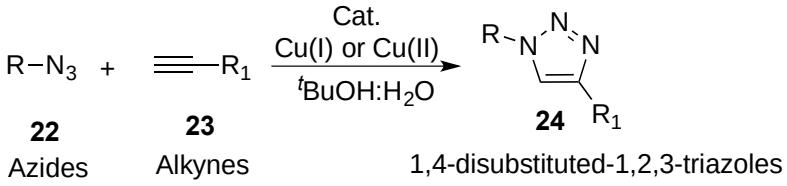


Figure 6. Click reaction.

Several betulin conjugates have been developed via click chemistry *albeit*

with limited biological success. Bori *et al.* described an efficient strategy to link azidothymidine with betulin/betulinic acid via click chemistry. Selective monoproteciton of C_{28} primary alcohol in **1** with TBS chloride was achieved followed by the propargylation of C_3 secondary alcohol to provide the ether **25a**. Alternatively, betulin propargyl carbonate **25b** was also obtained via the reaction of C_{28} silyl betulin ether with triphosgene followed by the addition of propargyl alcohol. Theses alkynes **25a-b** were subjected to click coupling with azidothymidine to yield the triazoles **26a-b** (**Figure 7**).[30]

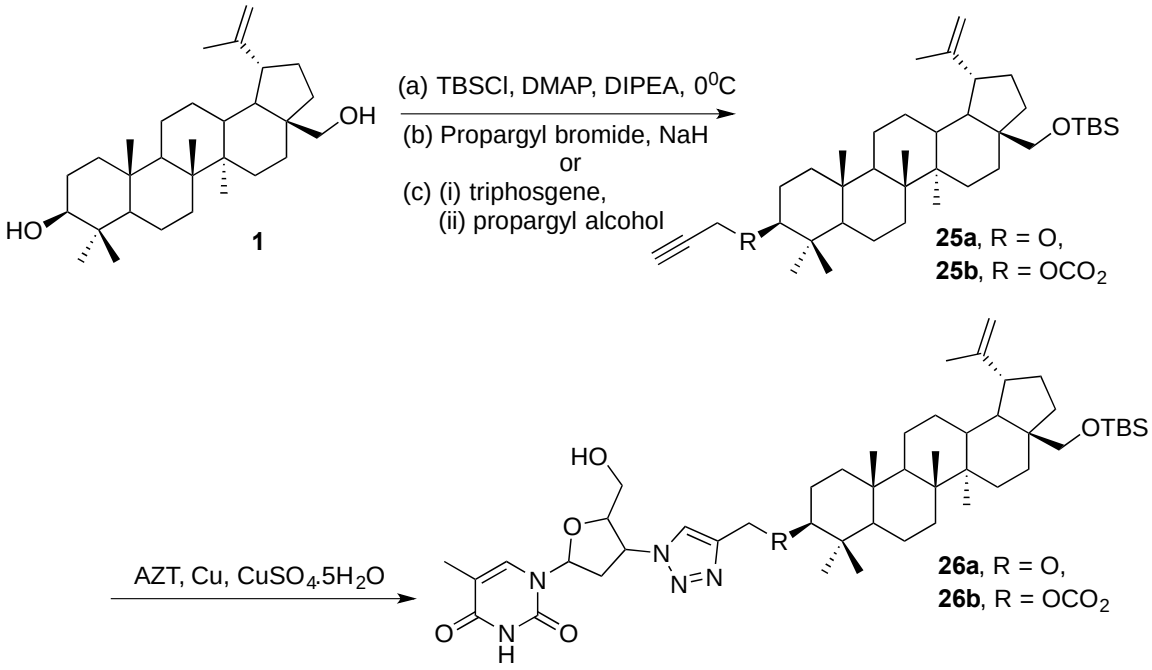


Figure 7. Betulin-AZT conjugates via click chemistry.

Bori and co-workers were also able to synthesize Betulinic acid-AZT conjugate **29** via the succinylation of betulinic acid **3** with dimethylsuccinic anhydride **27** to yield the diacid **28**. Esterification of C_{28} acid in **28** with propargyl bromide followed by click coupling with AZT resulted in the formation of the target compound **29**

(**Figure 8**). Some of these compounds showed efficacy as anti-AIDS agents with EC50 values ~0.1 μM.

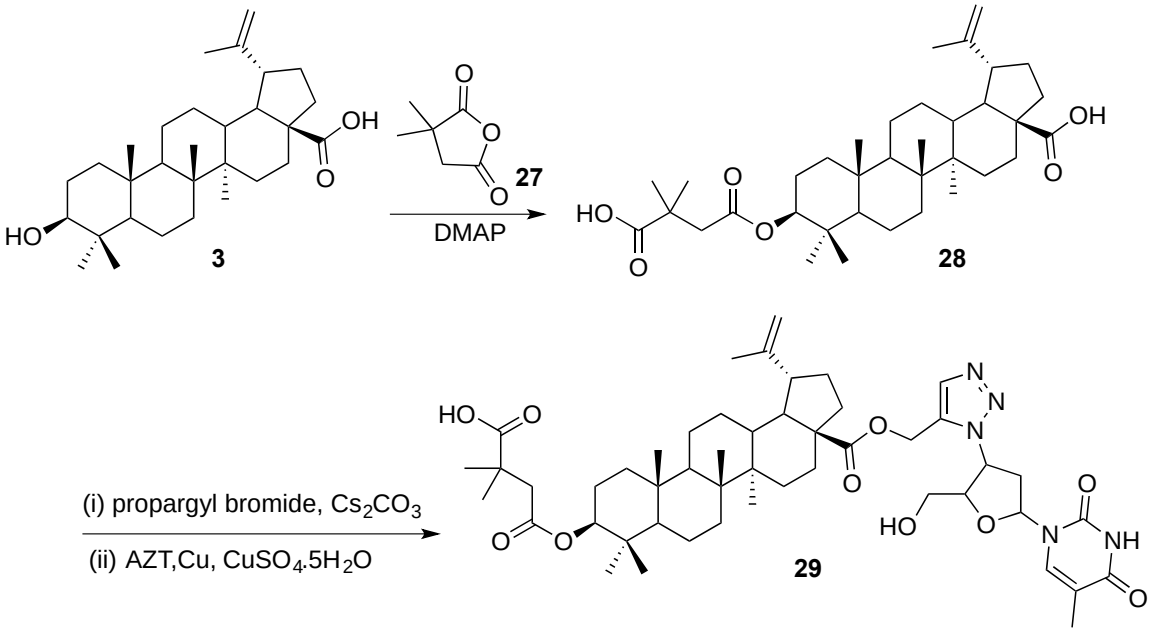


Figure 8. Betulinic acid-AZT conjugates via click chemistry.

Similarly, Khan and co-workers synthesized *N*-aryl triazole conjugates **30** of betulinic acid **3** under identical conditions **(Figure 9)**. Some of these analogs showed better potency against four human cancer cell lines (HL-60, MiaPaCa-2, PC-3, and A549) when compared to the parent natural products of betulinic acid. [31]

Dang Thi *et al* reported betulinic acid AZT conjugates **32,** which showed moderate cytotoxicity on KB and Hep-G2 cancer cells (**Figure 10**).[32]

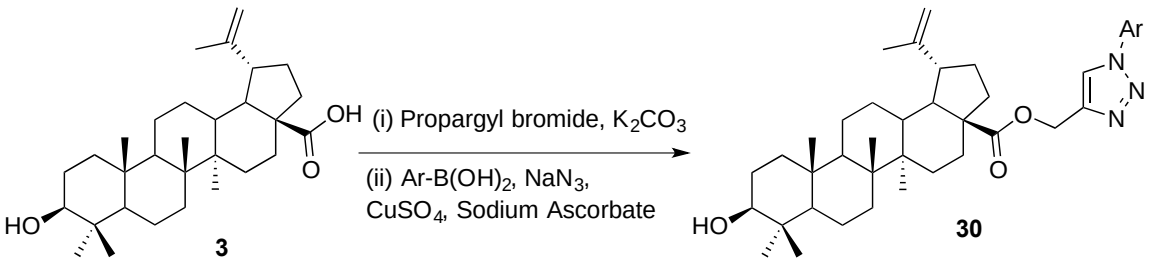


Figure 9. Betulinic acid-triazole conjugates via click chemistry.

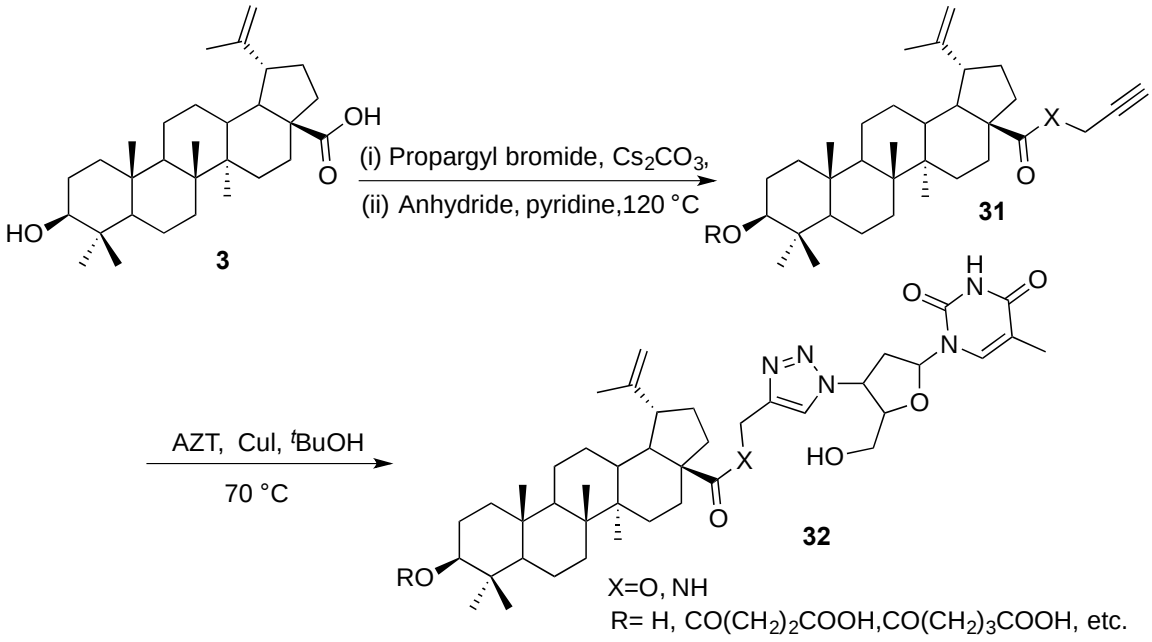


Figure 10. Betulinic acid-AZT conjugates as anti-cancer agents.

Csuk *et al* reacted the aldehyde **33** with lithium acetylide followed by the oxidation of the resulting alcohol to furnish the diketone **34**, which was then coupled with *p*-azidobenzoic acid or ethyl azidoacetate to yield the triazoles **35**. Some of these molecules showed moderate cytotoxicity as established via fifteen human cancer cell line assay (**Figure 11**).[33]

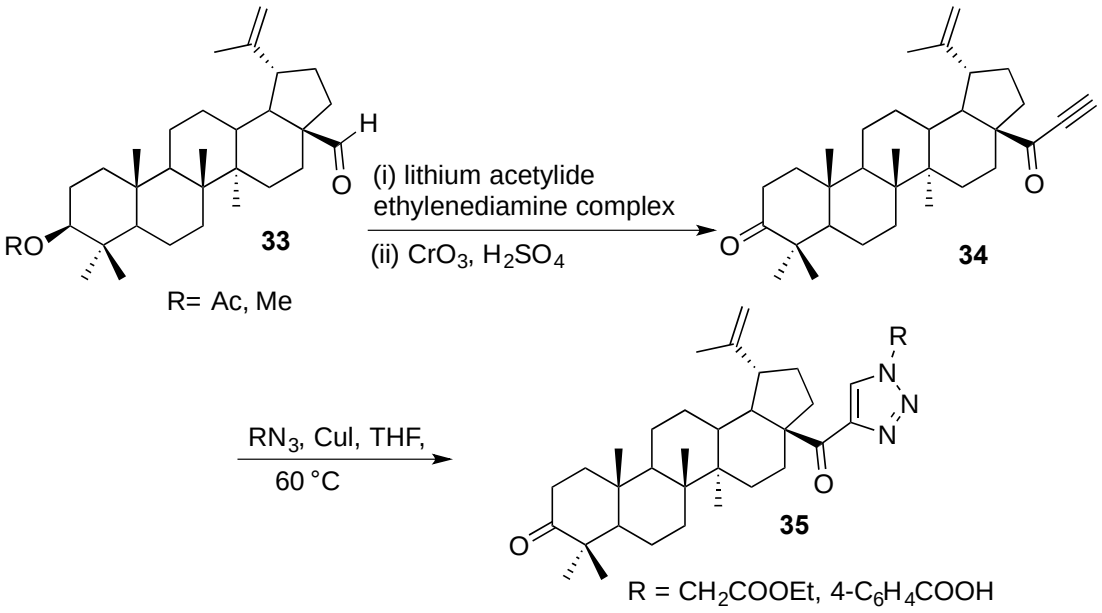


Figure 11. Betulonic acid-triazole conjugates via click chemistry.

Shi *et al* synthesized the triazoles **37** via modification at the C_{30} position of betulin **1**. Initial diesterification of betulin **1** followed by the selective monodeprotection of the primary alcohol and allylic bromination with NBS yielded the bromide **36**. The bromide **36** was converted to azide and further subjected to click coupling with variety of terminal alkynes in a one-pot transformation to yield the target compounds **37.** These compounds showed anticancer activity against Leukemia cell lines HL60 (**Figure 12)**. Under similar condition the C_{30} triazoles **39** of betulinic acid **3** were also synthesized (**Figure 13**).[34]

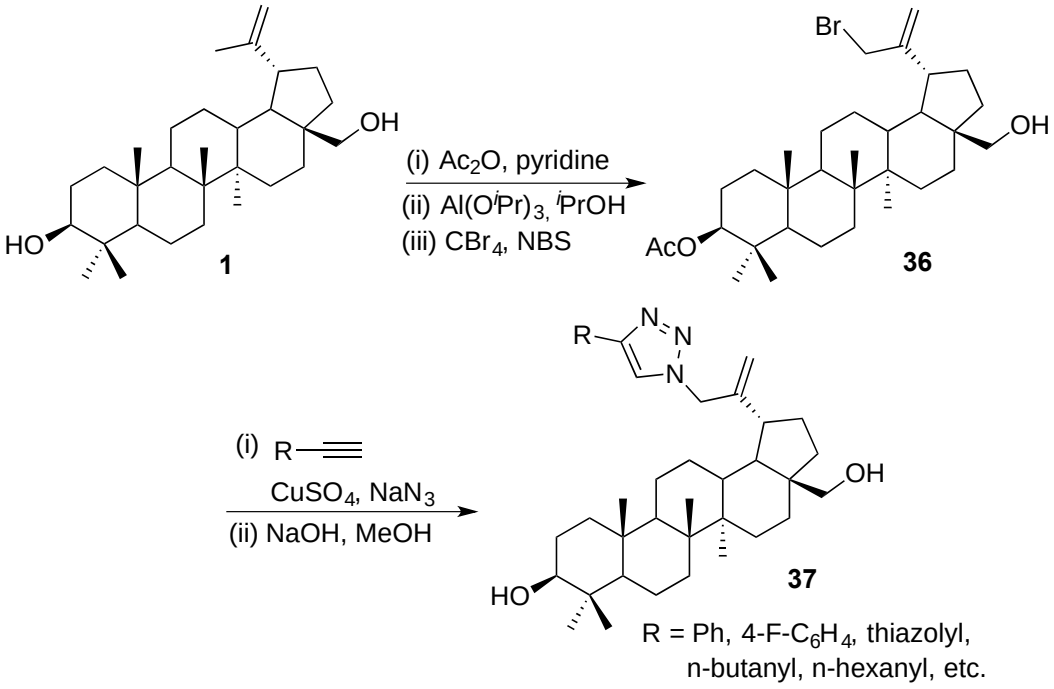


Figure 12. Betulin-C30 triazole conjugates via click chemistry.

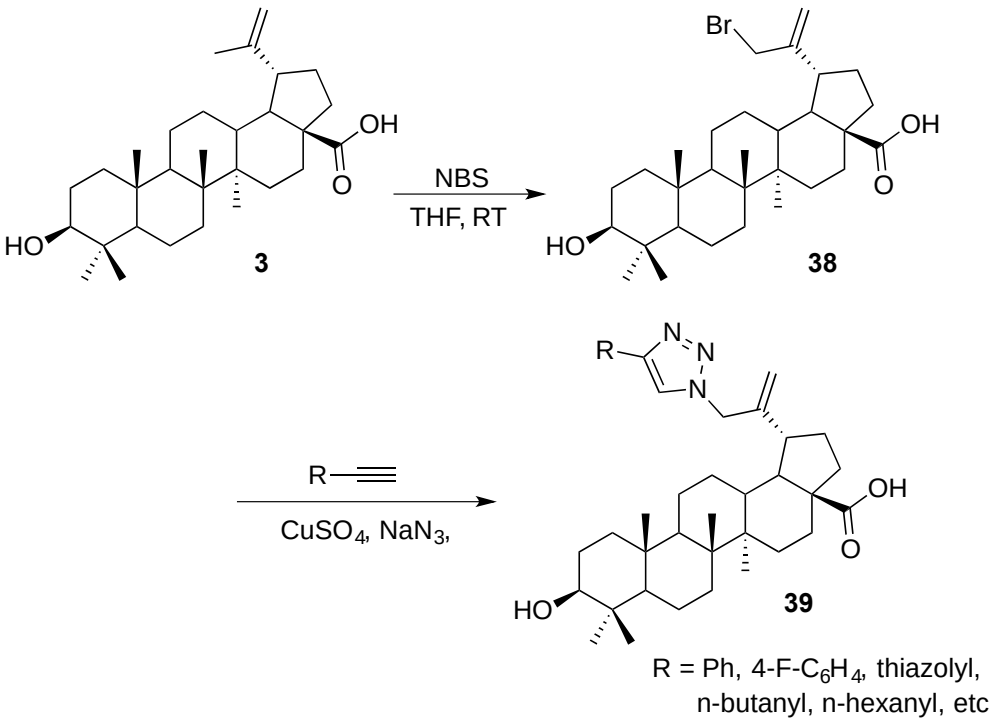


Figure 13. Betulinic acid-C30 triazole conjugates via click chemistry.

Chakrabarty *et al* converted the C_3 alcohol of betulinic acid **3** as the chloroacetyl ester followed by the treatment with sodium azide to yield the azido acid **40** which was then subjected to click coupling with different alkynes to furnish the target compounds **41** (**Figure 14**). The biological evaluation of these molecules showed anticancer activity in HT29 cell lines via induction of apoptosis and activation of caspase-3.[35]

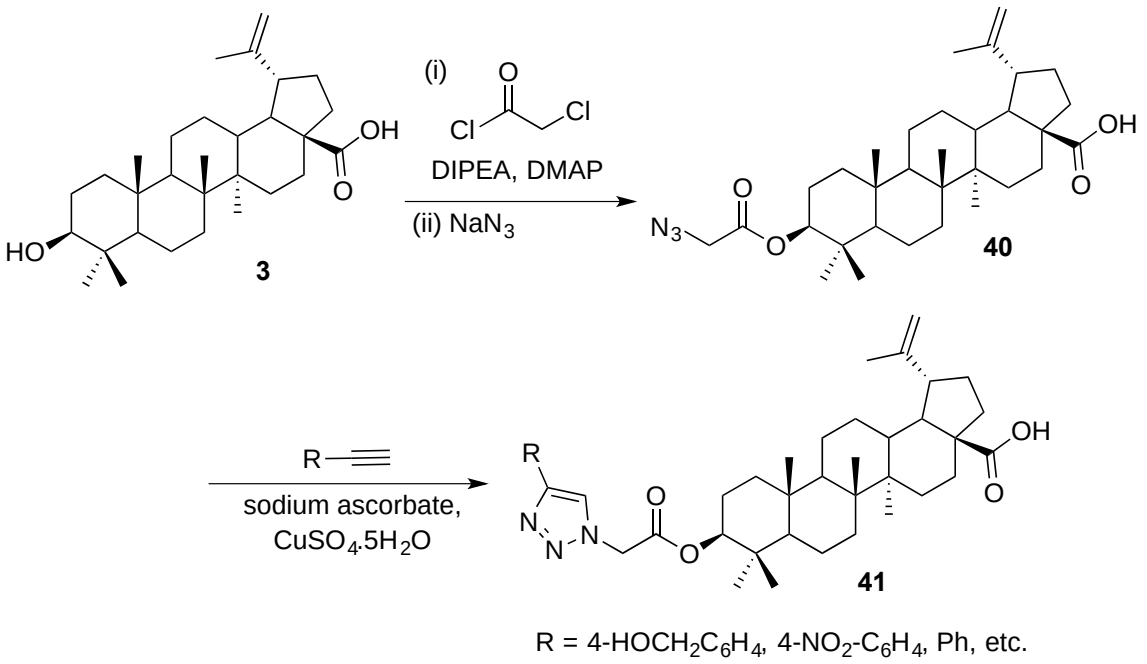


Figure 14. Betulinic acid-C3 triazole ester conjugates via click chemistry.

Majeed and co-workers synthesized O-propargyl betulinic acid and coupled it with various azides using click chemistry resulting in the formation of triazolylbetulinic acid conjugates **42** (**Figure 15**). Some of these compounds showed potential as apoptotic agents.[36]

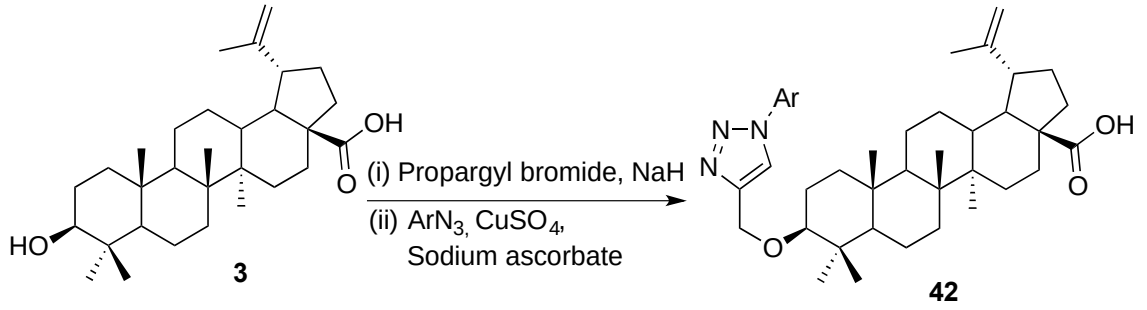


Figure 15. Betulinic acid-C3 triazole ether conjugates via click chemistry.

Baylis-Hillman Reaction

Baylis-Hillman reaction was first reported in 1972 by German scientist A.B. Baylis and M.E.D. Hillman.[37] This reaction is highly robust and involves in the coupling of activated alkenes with carbonyl or imine moieties resulting in the formation of densely functionalized allylic alcohols and amines.[38] BH reaction involves the Michael addition of DABCO on an activated alkene followed by an aldol addition of the resulting enolate to the carbonyl compound. This reaction is quite versatile and has attracted the attention of several synthetic chemists worldwide. One of the minor drawbacks of this reaction deals with the slow rate of reaction. Accordingly, several approaches have been reported for the acceleration of the rate including the use of reactive activated olefins/electrophiles,[39,40] microwave irradiation,[41] enhanced hydrogen bonding capabilities,[42] use of aqueous medium,[43] and high pressures.[44,45,46] Variety of activated olefins such as alkyl vinyl ketone,[47,48,49] acrylates,[50,51] acrylamides,[41] acrylonitriles,[47,52] acrolein,[53] vinyl sulfones,[54] vinyl sulfoxides,[55] vinyl phosphonates, and allenyl esters,[56,57] etc. have been used for the effective coupling with an array of aliphatic, alicyclic, aromatic, and heteroaromatic aldehydes and the corresponding allylic alcohols **46a-h** have been obtained in high selectivity and yields (**Figure 16**). Baylis-Hillman template offers another significant advantage because of the presence of multiple sites for further functionalization, which gains importance especially in medicinal chemistry in terms of the determination of structure activity relationship (SAR) profile.

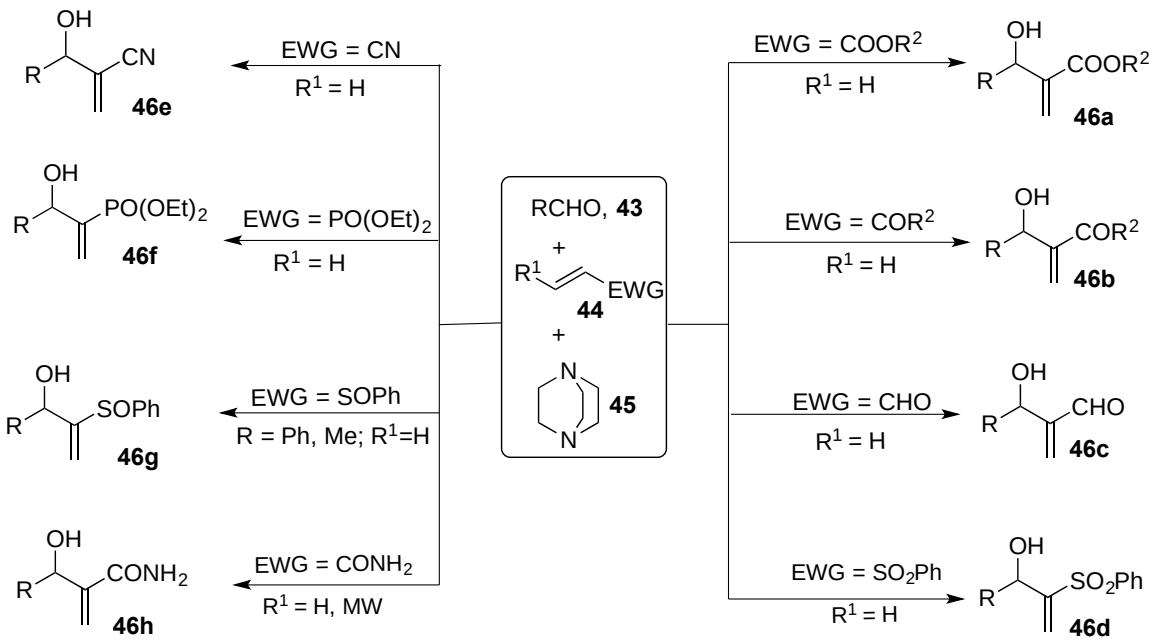


Figure 16. Baylis-Hillman reaction.

Chapter 2

Preparation of Betulin-Triazole Conjugates

In this project, we envisioned the preparation of betulinic acid-triazole conjugates using Baylis-Hillman reaction and click chemistry so as to improve the biological efficacy. Herein, we provide an account of our synthetic and biological evaluation results.[58] We started our synthesis with the preparation of the two precursors for click chemistry namely the azides and alkynes. We contemplated the synthesis of azides utilizing Baylis-Hillman reaction and the alkynes starting from betulinic acid.

Synthesis of Azides via Baylis-Hillman Reaction

Under Baylis-Hillman reaction conditions, benzaldehyde **47** reacted with methyl acrylate **48** in the presence of DABCO at room temperature to afford the corresponding allylic alcohol **49** (**Figure 17**) as the colorless liquid in 78% yield. The three Baylis-Hillman motif derived allylic azides **51a-c** were then prepared from the alcohol **49**. Nucleophilic substitution of allylic alcohol **49** with HBr in the presence of H_2SO_4 at 0°C yielded the corresponding allylic bromide **50** in 74% yield. Conversion of the allylic bromide to allylic azide **51a** was achieved using sodium azide in acetone: H_2O solvent medium at room temperature. The corresponding carboxylic acid derivative **52** was easily obtained upon hydrolysis in the presence of aq. NaOH in a mixture of THF/methanol solvent. Two other allylic azides **51b-c** were synthesized by employing conventional amide coupling of the carboxylic acid **52** with *N*,*N*,*N*-trimethyl ethylenediamine **53** or *N*-methyl piperazine **54** in the presence of 2-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent and

diisopropylethylamine (DIPEA) as the base in dimethylformamide (DMF) as solvent (**Figure 17**).

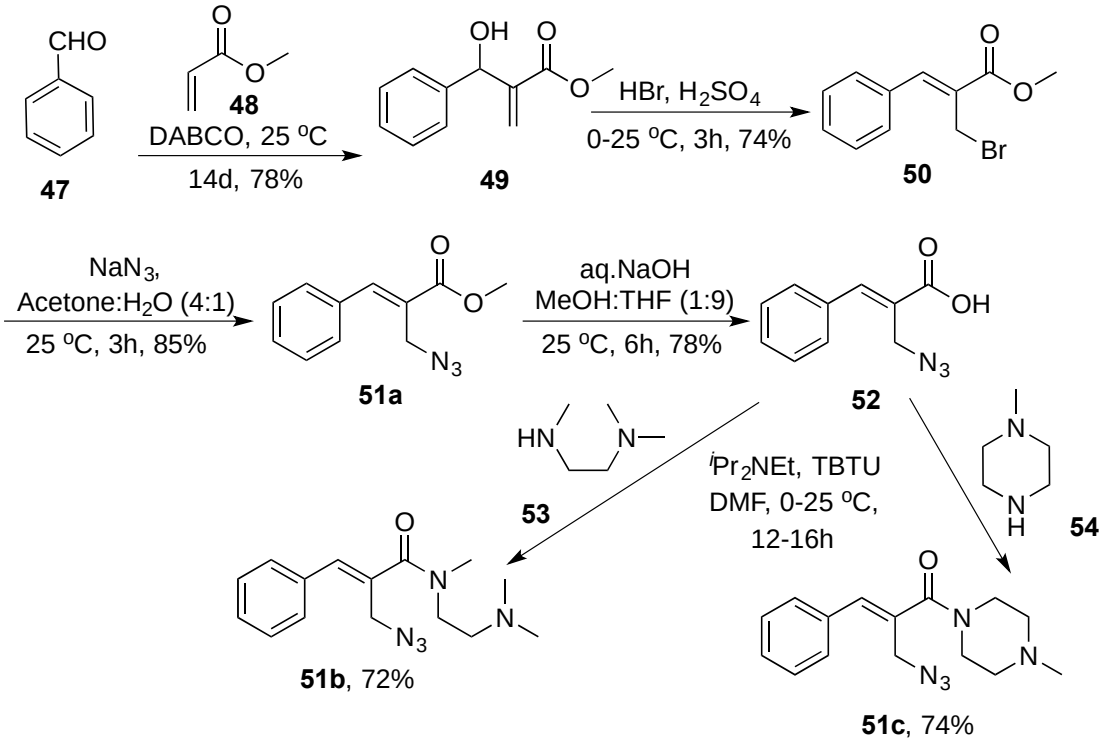


Figure 17. Preparation of α-azidomethylcinnamamides.

After succeeding in the synthesis of three Baylis-Hillman derived allylic azides **51a-c**, we ventured into the synthesis of three β-azidoethylamides **51d-f**. The two β-azidoethylamides **51d-e** were prepared from BH allylic alcohol **49** (**Figure 18**). Reaction of **49** with acetic anhydride in the presence of triethylamine in dichloromethane (CH_2Cl_2) yielded corresponding acetate **55** in very good yield. The nucleophilic substitution (S_N2') of acetate **55** with *N,N,N′*-trimethylethylenediamine **53** in the presence of potassium carbonate (K_2CO_3) in DMF furnished the allylic amine **56** in 77% yield. Alkaline hydrolysis of **56** and the coupling of the resulting acid **57** with 2-azido ethylamine

in the presence of 1-ethyl-3-(-3-dimethylamino propyl) carbodimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt) and Hünig's base yielded β-azidoethylamide **51d** in 74% yield. The β-azidoethylamide **51e** was obtained following a similar procedure by replacing *N*,*N*,*N*-trimethylethylendiamine **53** with *N*-methyl piperazine **54** for coupling with acetate **55** followed by hydrolysis and amide coupling with 2-azido ethylamine (**Figure 18**).

The coupling of cinnamic acid **60** with 2-azidoethylamine under HOBt conditions furnished β-azidoethyl-cinnamamide **51f** as a white solid in 73% yield (**Figure 19**). All of these compounds were characterized using proton, carbon, and mass spectral analysis**.**

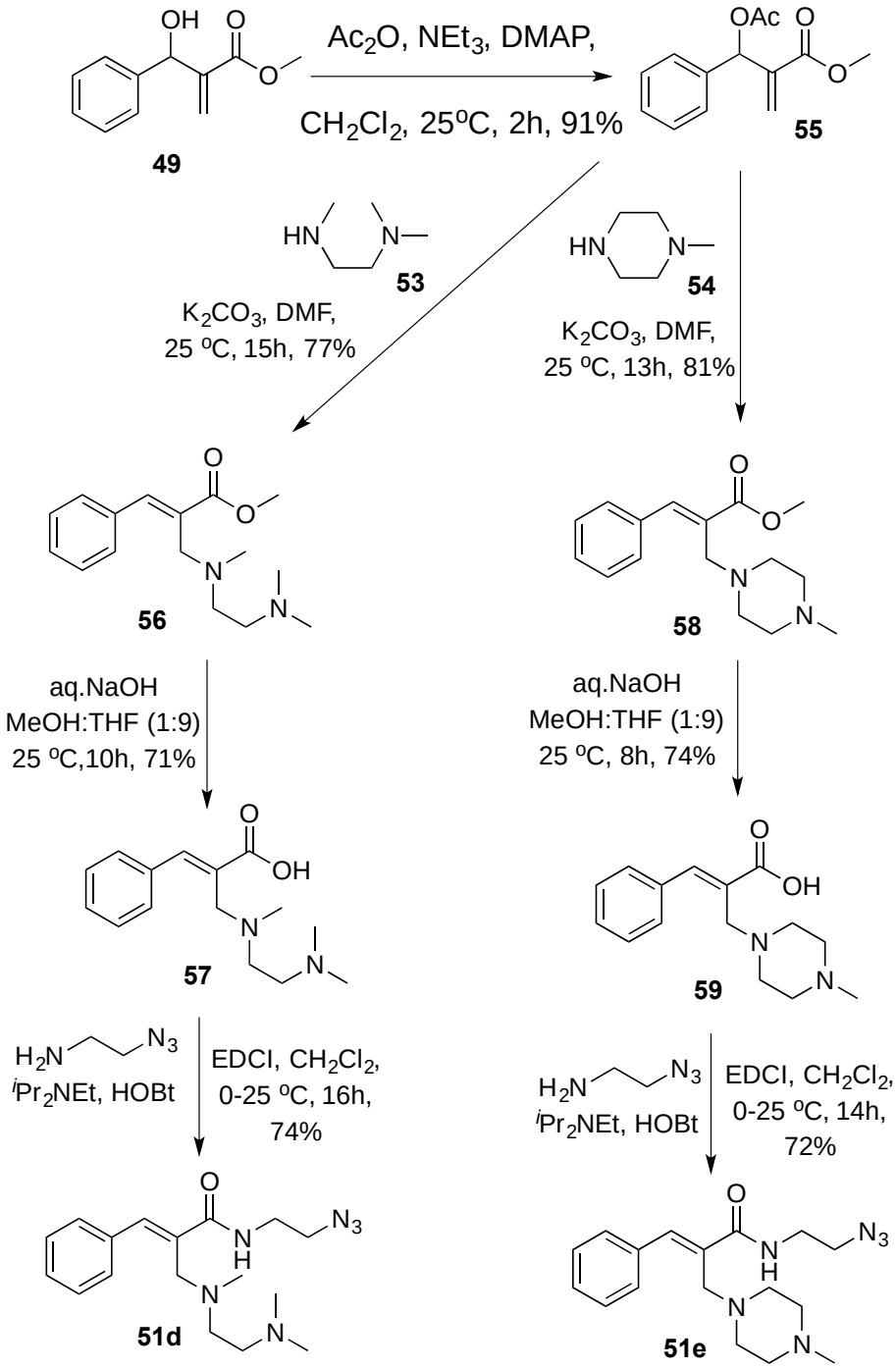


Figure 18. Preparation of α-aminomethyl *N*-azidoethylcinnamamides.

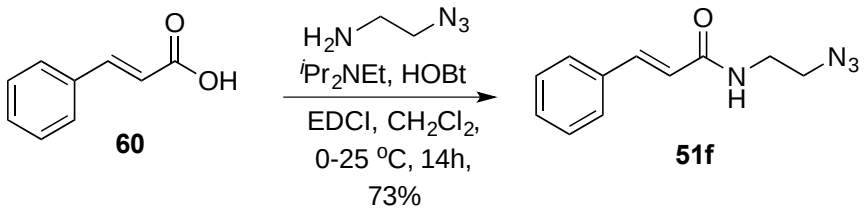


Figure 19. Preparation of *N*-azidoethylcinnamamide.

Synthesis of *N*-Propargyl Betulonamide

Having prepared the azides from BH template, we focused our efforts on the functionalization of betulin for the preparation of click reaction counterpart. We initiated the synthesis of *N*-propargyl betulonamide **61** using Jones oxidation (CrO_3 in acetone, conc. H_2SO_4) of betulin **1**, resulting in the formation of betulonic acid **2** as a white solid. The coupling of betulonic acid **2** with propargyl amine using TBTU and Hünigs base furnished *N*-propargyl betulonamide **16** in 73% yield upon recrystallization from hexane (**Figure 20**).

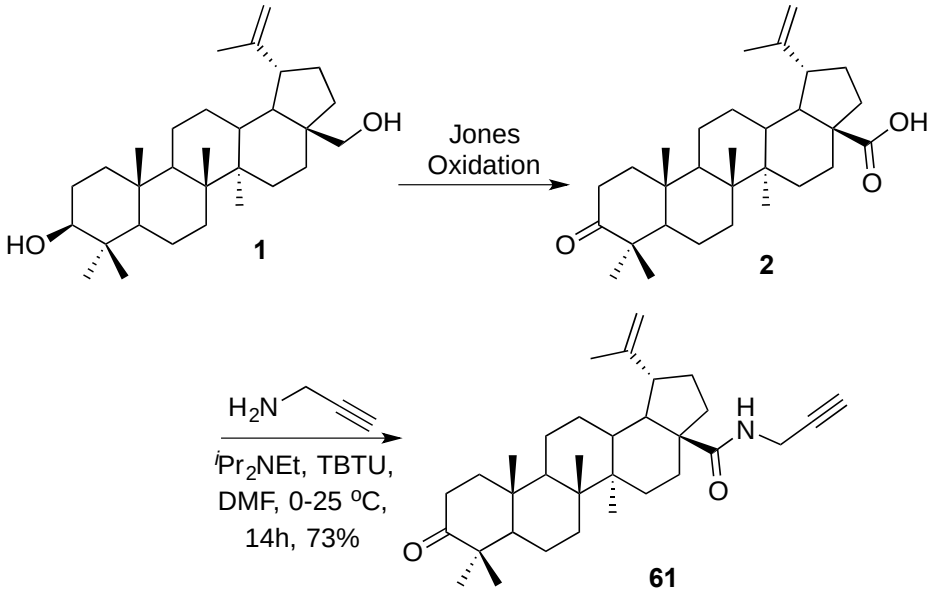


Figure 20. Preparation of *N*-propargyl betulonamide.

Synthesis of Betulinic Acid-Triazole Conjugates

After preparing the key intermediates *N*-propargyl betulonamide **61** and Baylis-Hillman motif-derived azides **51a-f**, we undertook the click coupling of these precursors for the synthesis of 1,2,3-triazoles (**Figure 21**).

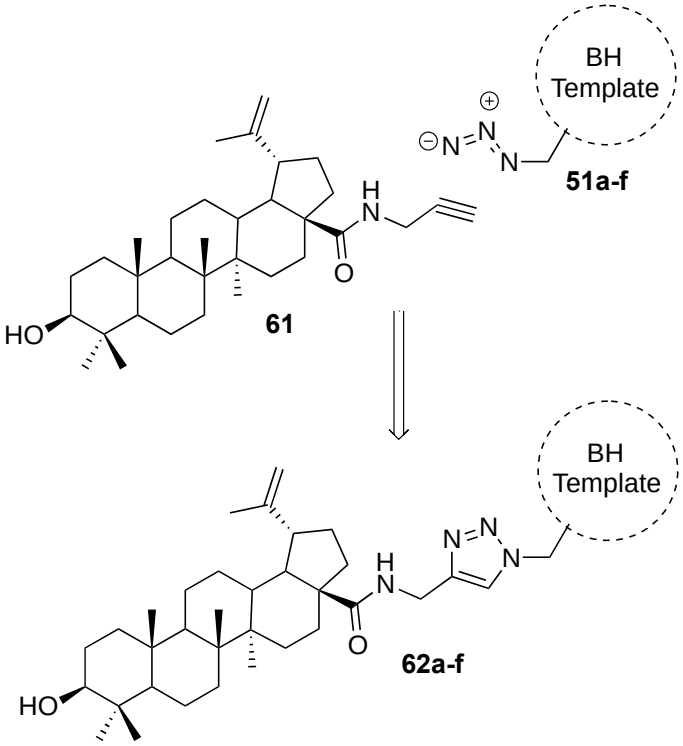


Figure 21. Target betulinic acid-triazole conjugates.

Click Coupling of *N*-Propargylbetulonamide with Azides

Initially, we attempted click coupling of methyl α-azidomethylcinnamate **51a** with *N*-propargyl-betulonamide **61** using copper iodide. Under these conditions, we were unable to obtain the product triazole **62a** in decent yield even after performing the reaction in different solvents at room temperature or reflux conditions. Switching from copper iodide to copper sulfate and sodium ascorbate mediated cycloaddition in *t*-butyl alcohol/water resulted in the formation corresponding 1,2,3-triazole derivative **62a** as a cream solid in 89% yield (**Figure 22**). The compound **62a** was confirmed by the characteristic triazole proton signal δ 7.74 (1H, s) in ^{1}H NMR spectrum as well as by

ESI-MS spectral peak at 709.55 $(M+H)^+$.

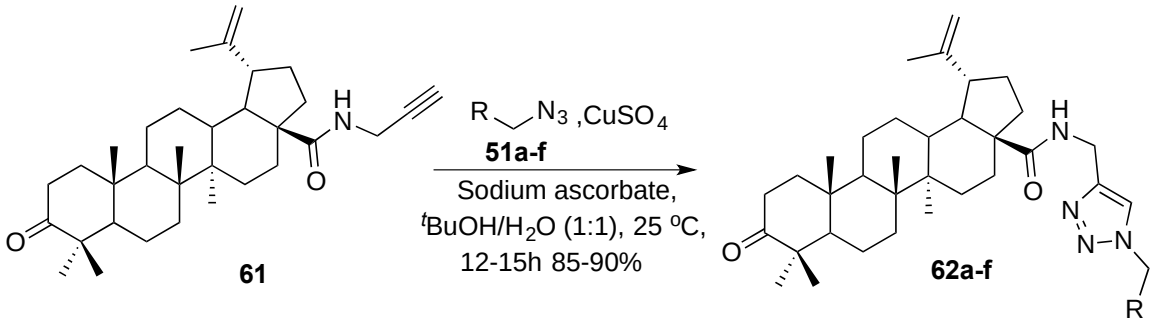


Figure 22. Coupling of *N*-propargylbetulonamide with azides.

After synthesizing the betulinic acid-triazole conjugate **62a**, under identical conditions, the reaction of the remaining Baylis-Hillman motif derived azides **51b-f** with *N*-propargyl betulonamide **61** furnished the corresponding triazoles **62b-f** in high yield (**Figures 22** and **23**). All the compounds were well characterized using NMR and mass spectrometric analyses.

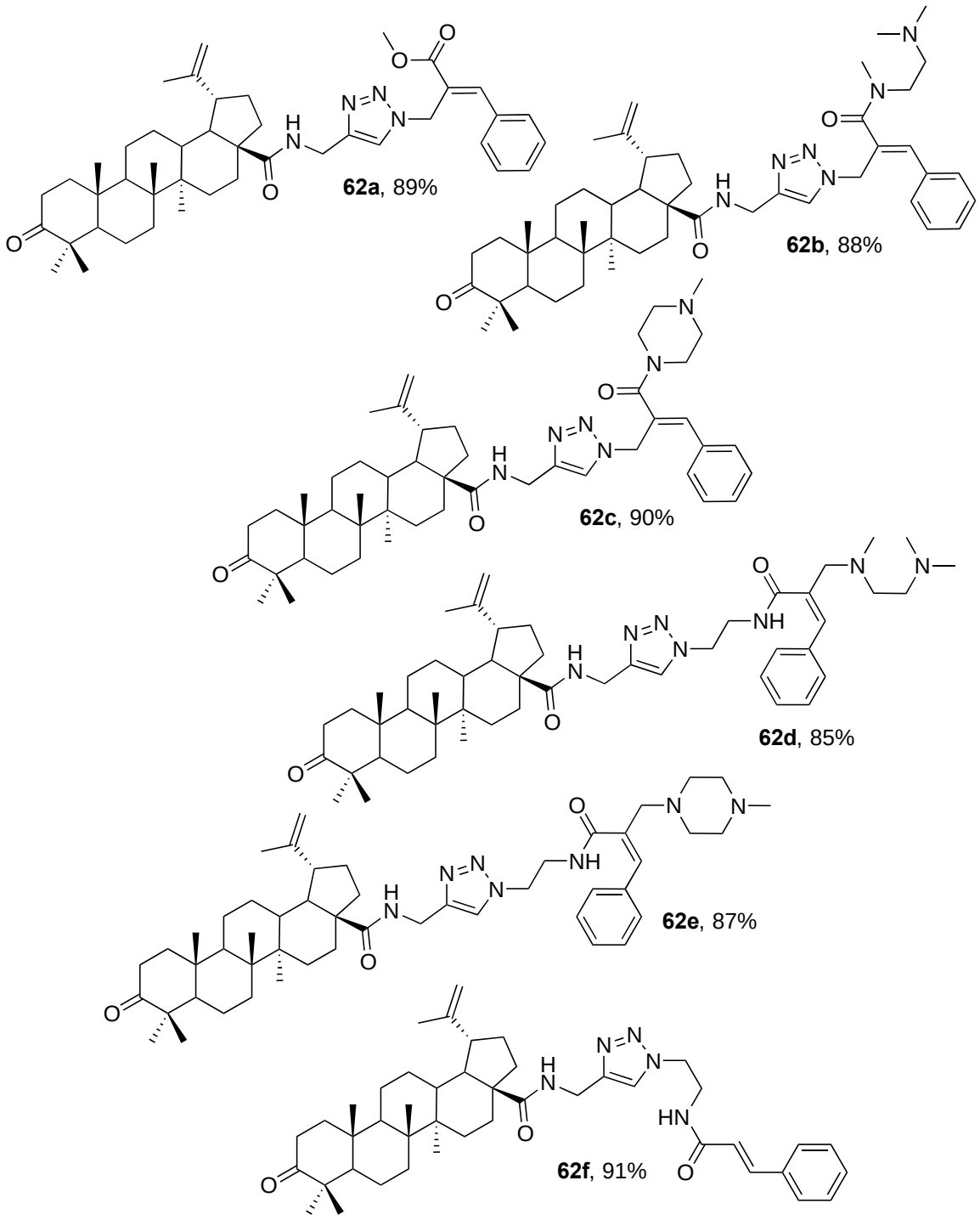


Figure 23. Triazoles obtained from *N*-propargylbetulonamide.

Reduction of Betulonamide-Triazole Conjugates

We then reduced the C_3 ketone of **62a-f** to the corresponding alcohol **63a-f** using $NaBH_4$ in methanol. Under these conditions, the betulinic acid-triazoles **63a-f** were obtained in good yield (**Figures 24** and **25**). All the compounds were well characterized using NMR and mass spectrometric analyses.

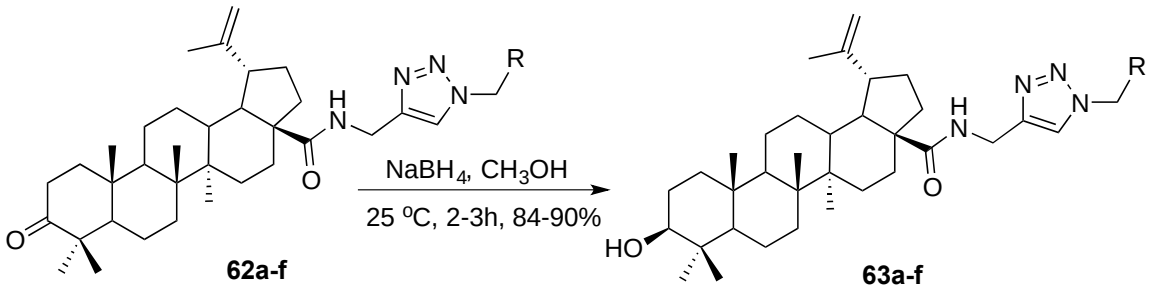


Figure 24. Reduction of betulonamide-triazole conjugates.

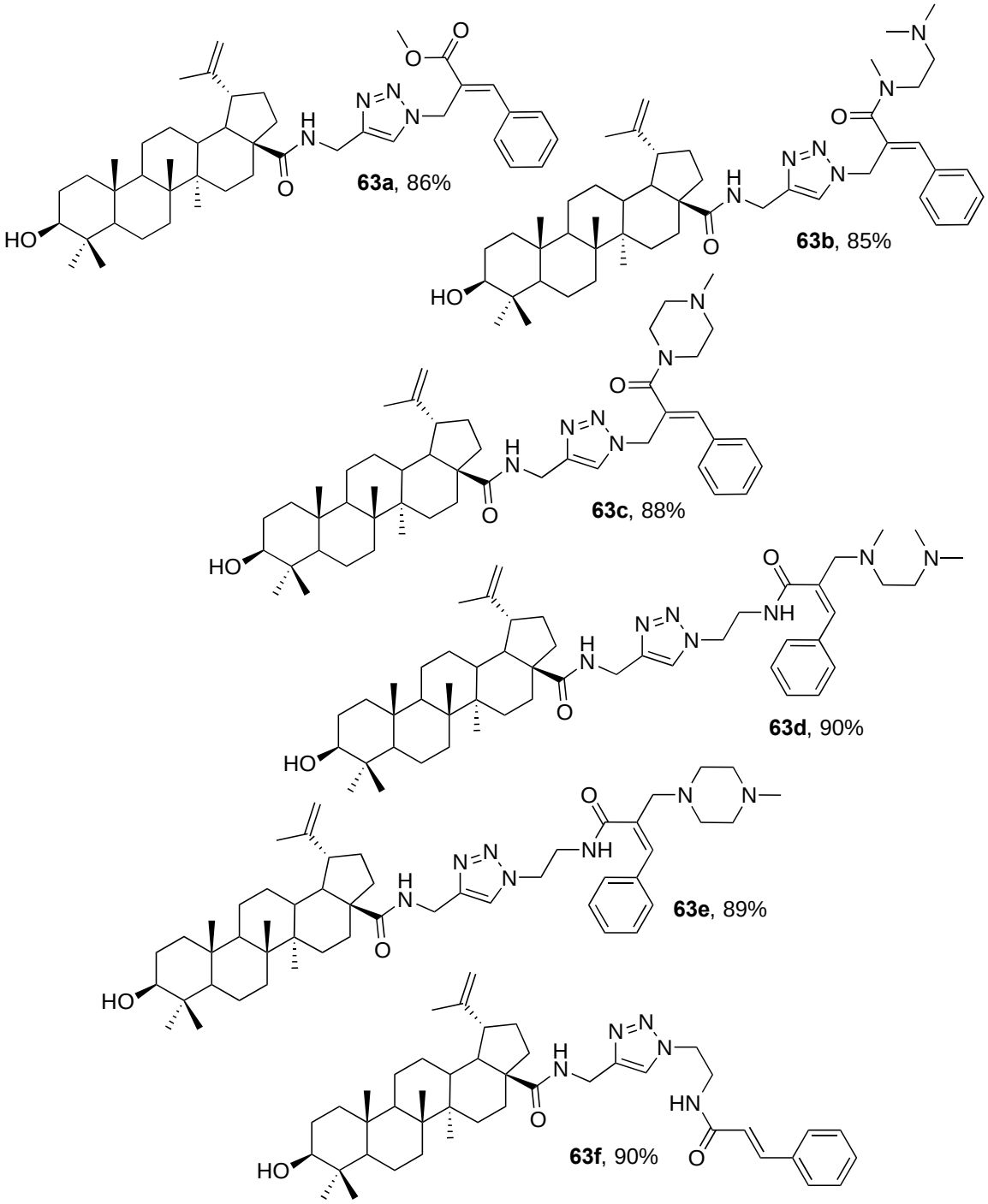


Figure 25. Triazoles obtained via reduction of betulonamide conjugates.

Succinylation of Betulinamide-Triazole Conjugates

Having prepared a series of C_3 alcohol betulinic acid-triazoles **63a-f**, in an effort towards increasing the hydrophilicity of these compounds, these alcohols were heated with succinic anhydride in toluene to yield the corresponding succinic acid hemiesters **64a-f** in 80-87% yield (**Figures 26** and **27**). All the compounds were well characterized using NMR and mass spectrometric analyses.

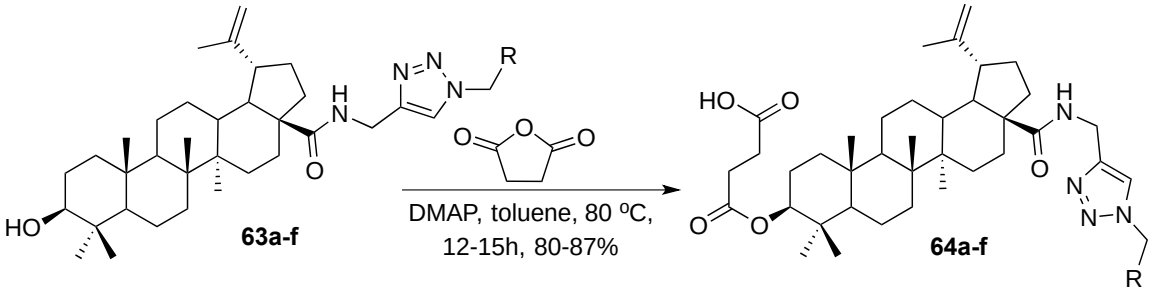


Figure 26. Succinylation of betulinamide-triazole conjugates.

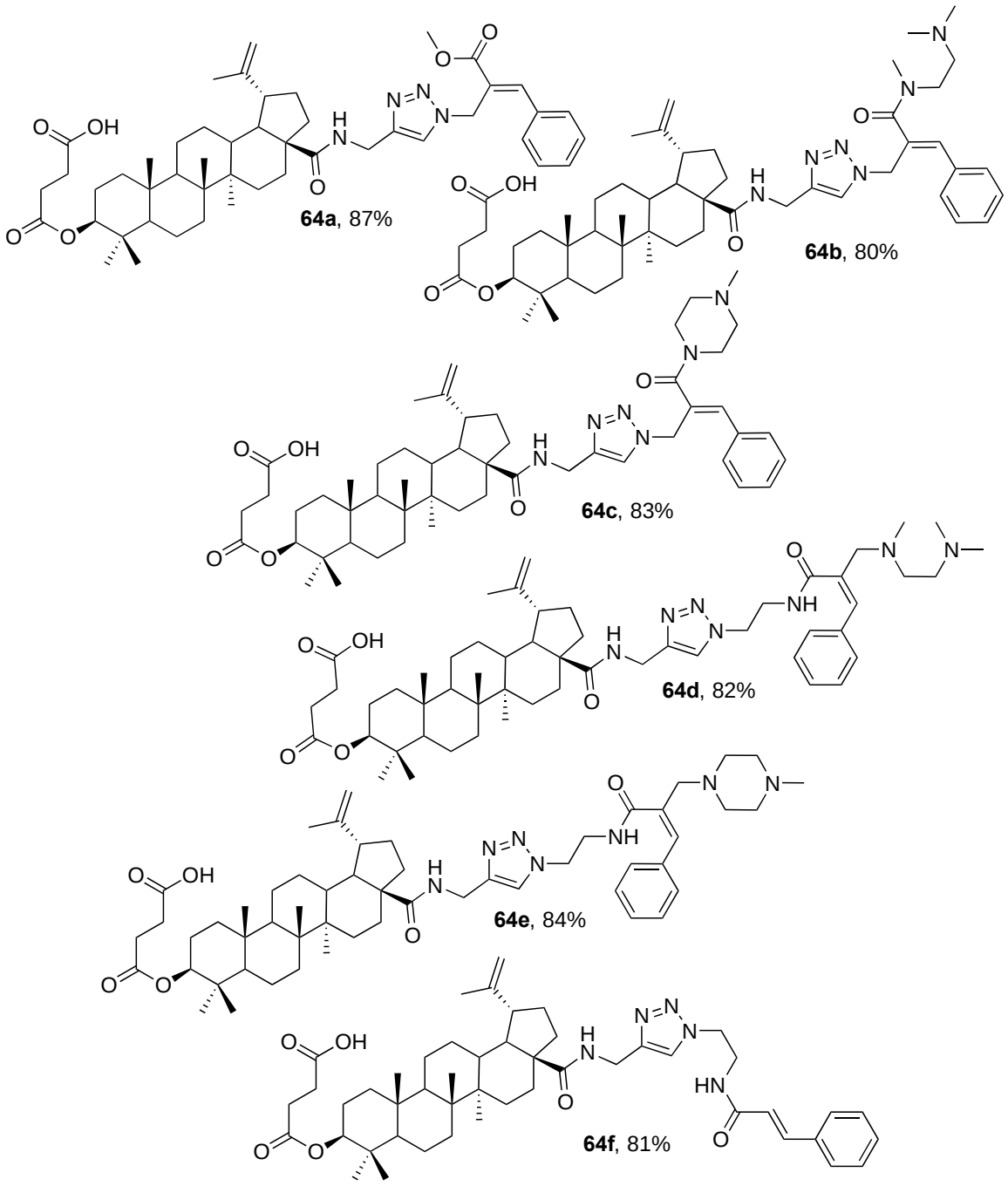


Figure 27. Triazoles obtained via succinylation of betulinamide conjugates.

Biological Evaluation

All the synthetic analogs, as well as some of the intermediates, were evaluated for their cytotoxicity against murine breast cancer (4T1) and pancreatic cancer (MIA PaCa-2) cell lines. The cells were purchased from ATCC, and the assays were performed using standard conditions by seeding the cells in 96 well plates, and the cell viability was determined using MTT assay. Primary screening was carried out at concentrations of 50 μM, 12.5 μM and 1.5 μM on two tumor cell lines as the parent natural product betulinic acid showed moderate activity (~60% inhibition of 4T1 and ~40% of MIAPaCa-2 cells) at 12.5 μM, and majority of betulinic acid-triazole conjugates that were assayed, also displayed promising activity at this concentration (>90% inhibition of 4T1 and ~80-90% MIA PaCa-2 cells). The IC_{50} values were determined for the compounds that displayed moderate to good cytotoxicity. As shown in Table 1, the cytotoxicity profile of C3-alcohol containing betulinic acid-triazoles **63a-f** proved to be better relative to the C3-ketone based analogs **62a-f**. Interestingly, conversion of C_3-alcohol to succinic acid hemi ester, i.e., compounds **64a-f**, resulted in a slight reduction in anticancer activity. Two compounds (**63d-e**) in the C_3-alcohol series displayed good anti-cancer activity against 4T1 (2-3 μM) and MIA PaCa-2 (1-3 μM) cell lines when compared to their analogous C_3-ketones **62d-e** (4T1, 5-6 μM; MIA PaCa-2, 5-9 μM) and C_3-hemi esters **64d-e** (4T1, 4-8 μM; MIA PaCa-2, 10-27 μM).

Based on these results, we perceive the significance of C_3-alcohol unit and *N,N,N'*-trimethylethylenediamine/*N*-methylpiperazine motif at α-position of cinnamamides for improving the biological action of these molecules. It should also be

noted that none of the intermediates tested showed any toxicity, which leads us to believe that the BH motif is also required for the activity. Efforts are currently underway to identify the mechanism of action for the lead derivatives as well as for the identification of potent candidate for further development.

Table 1

In vitro cytotoxicity of betulinic acid-triazole conjugates.

#	Compound	4T1 [IC_{50} (μM)]	MIA PaCa-2 [IC_{50} (μM)]
1	**62a**	NT	NT
2	**62b**	6.93 ± 1.09	9.87 ± 0.79
3	**62c**	7.15 ± 0.18	14.99 ± 2.12
4	**62d**	5.67 ± 0.10	8.11 ± 1.54
5	**62e**	5.17 ± 0.60	5.98 ± 0.99
6	**62f**	NT	NT
7	**63a**	39.75 ± 9.45	NT
8	**63b**	3.97 ± 0.73	2.44 ± 0.36
9	**63c**	4.37 ± 0.43	8.69 ± 0.33
10	**63d**	**2.38 ± 0.45**	**1.36 ± 0.21**
11	**63e**	**2.62 ± 0.24**	**1.64 ± 0.20**
12	**63f**	27.26 ± 12.2	32.50 ± 7.92
13	**64a**	5.26 ± 0.65	47.58 ± 5.51
14	**64b**	7.48 ± 0.59	21.73 ± 5.12
15	**64c**	6.13 ± 0.81	14.44 ± 3.44
16	**64d**	4.13 ± 0.22	9.66 ± 0.51
17	**64e**	7.05 ± 0.53	24.28 ± 3.24
18	**64f**	8.61 ± 2.27	NT

Table 1 (Continued)

#	Compound	4T1 [IC_{50} (μM)]	MIA PaCa-2 [IC_{50} (μM)]
19	**3** (betulinic acid)	6.29 ± 0.96	25.63 ± 3.79

NT = Not toxic

Conclusions

In conclusion, we have prepared betulinic acid-triazole derivatives utilizing Baylis-Hillman reaction and click chemistry as the key protocols in our synthesis. These compounds were tested for their biological efficacy against murine breast cancer cell line (4T1) and human pancreatic cancer cell line (MIA PaCa-2). Based on these *in vitro assays*, we have been able to identify two series of betulin derivatives for further SAR and pre-clinical studies. The ready availability of betulin from natural resources as well as the great chemical diversity afforded by the Baylis-Hillman template imparts significance to this class of compounds for potential development as *anti*-cancer agents.

Chapter 3

Experimental Procedures

Materials and Methods

All the reactants were of reagent grade, purchased from Acros Organics, Alfa Aesar or Sigma Aldrich, and used without further purification. All solvents were used without further drying or purification and were of ACS grade purchased from Fisher Scientific. All operations were carried out under an inert atmosphere of nitrogen. Glassware for all reactions was oven dried at 125 °C and cooled under nitrogen prior to use. Liquid reagents and solvents were introduced by oven-dried syringes or cannulas through septa sealed flasks under a nitrogen atmosphere.

Instrumentation

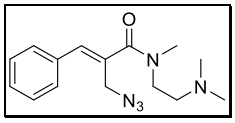
Nuclear Magnetic Spectroscopy (NMR) spectra were produced using a Varian 400 MHz spectrophotometer. The instrument was maintained at 25^{o} C operating at 400 MHz for ^{1}H NMR, and 101 MHz for ^{13}C NMR. The deuterated solvent ($CDCl_3$, DMSO-d_6) used for each respective spectrum is referenced to the appropriate literature peak shift.

Procedures

General amide-coupling procedure A. To a stirred solution of the appropriate acid (1.0 mmol) in dimethylformamide (10.0 mL), was added *N*,*N*-diisopropylethylamine (2.0 mmol) followed by TBTU (1.1 mmol) at 0 °C and stirred for 30 min. The appropriate amine (1.0 mmol) was then added in one portion and stirred overnight at room temperature. Upon completion (as indicated by TLC), the reaction mixture was quenched by the addition of saturated $NaHCO_3$ and extracted with dichloromethane (2 x 10.0 mL). The combined extracts were washed with cold water (10.0 mL) and brine (10.0

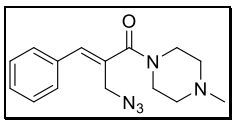
mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography (silica gel, hexanes:ethyl acetate) to obtain pure amides.

General amide-coupling procedure B. *N,N*-diisopropylethylamine (2.0 mmol), HOBt (1.1 mmol), and EDCI (1.1 mmol) were added at 0 °C to a stirred solution of the appropriate acid (1.0 mmol) in dichloromethane (10.0 mL) and the reaction was stirred for 30 min. The appropriate amine (1.0 mmol) was added in one portion and the reaction was stirred overnight at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution and worked up with dichloromethane (2 x 10.0 mL). The combined extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography (silica gel, hexanes:ethyl acetate) to obtain pure amides in good yields.

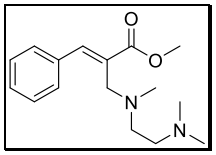


(E)-2-(azidomethyl)-N-(2-(dimethylamino)ethyl)-N-methyl-3-phenylacrylamide: The reaction of (*E*)-2-(azidomethyl)-3-phenylacrylic acid (1.0 g, 4.9 mmol) with *N,N,N'*-trimethylethylenediamine (602 mg, 5.9 mmol) as per the general amide coupling ***procedure A*** yielded 1.02 g (72%) of **51b** as a pale brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 – 7.44 (m, 3H), 7.26 – 7.31 (m, 2H), 6.78 (s, 1H), 4.30 (s, 2H), 3.61 (t, *J* = 7.1 Hz, 2H), 3.15 (s, 3H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.28 (s, 6H); ^{13}C NMR

(101 MHz, $CDCl_3$): δ (ppm) 169.5 134.4, 133.5, 131.6, 128.8, 128.6, 128.4, 49.4, 45.7. ESIMS: m/z calculated for $C_{15}H_{21}N_5O$ $(M+H)^+$ 288.18, found 288.38.

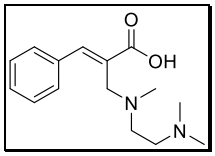


(E)-2-(azidomethyl)-1-(4-methylpiperazin-1-yl)-3-phenylprop-2-en-1-one: The reaction of (*E*)-2-(azidomethyl)-3-phenylacrylic acid (1.0 g, 4.92 mmol) with *N*-methylpiperazine (590 mg, 5.90 mmol) as per the general amide coupling ***procedure A*** furnished 1.04 g (74%) of **51c** as a pale brown liquid. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.24 – 7.41 (m, 5H), 6.69 (s, 1H), 4.26 (s, 2H), 3.61 – 3.80 (m, 4H), 2.37 – 2.50 (m, 4H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.9, 134.3, 134.0, 131.2, 129.0, 128.9, 128.8, 55.0, 49.5, 46.2. ESIMS: m/z calculated for $C_{15}H_{19}N_5O$ $(M+H)^+$ 286.16, found 286.30.



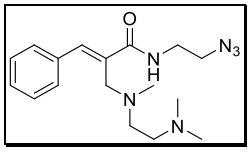
Methyl (E)-2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)-3-phenylacrylate: *N,N,N'*-Trimethylethylenediamine (521 mg, 5.1 mmol) and K_2CO_3 (883 mg, 6.40 mmol) were added to a stirred solution of **55** (1.0 g, 4.27 mmol) in *N,N*-dimethylformamide (10.0 mL) at room temperature and the reaction mixture was stirred overnight. Upon completion (TLC), the reaction was quenched with cold water and extracted with ethyl acetate (2 x 20.0 mL). The combined organic layers were washed thoroughly

with cold water (2 x 10.0 mL), brine (2 x 10.0 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate was concentrated *in vacuo* and purified by column chromatography (silica gel, hexanes: ethyl acetate, 1:4) to obtain **56** as brown liquid (912 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.80 (s, 1H), 7.57 – 7.61 (m, 2H), 7.29 – 7.41 (m, 3H), 3.82 (s, 3H), 3.39 (s, 2H), 2.48 – 2.54 (m, 2H), 2.37 – 2.44 (m, 2H), 2.21 (s, 6H), 2.18 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 168.9, 142.6, 135.3, 130.4, 130.2, 128.7, 128.3, 57.2, 55.5, 53.1, 51.9, 45.8, 41.9. ESIMS: m/z calculated for $C_{16}H_{24}N_2O_2$ $(M+H)^+$ 277.19, found 277.38.

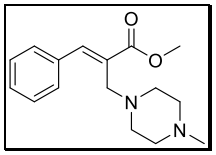


(E)-2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)-3-phenylacrylic acid: *aq.* NaOH (2.9 mL, 2.5 M, 7.3 mmol) was added to a solution of **56** (1.0 g, 3.6 mmol) in THF:MeOH (9:1, 20.0 mL) at 0 °C and the reaction was stirred overnight at room temperature. Upon completion (TLC), the solution was acidified to pH 6 with 1N HCl. The solution was concentrated *in vacuo* and the resulting slurry was dissolved in isopropyl alcohol to effect the precipitation of sodium chloride. The reaction was then filtered and the filtrate was concentrated *in vacuo* to yield 671 mg (71%) of **57** as pale cream-colored semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96 (s, 1H), 7.33 – 7.42 (m, 3H), 7.26 – 7.31 (m, 2H), 3.81 (s, 2H), 3.45 (m, 2H), 3.19 (m, 2H), 2.89 (s, 6H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 169.5, 142.9, 134.9, 130.4, 129.5, 129.1, 52.9, 52.7, 51.3, 42.6, 41.4. ESIMS: m/z calculated for $C_{15}H_{22}N_2O_2$ $(M+H)^+$

263.17, found 263.37.

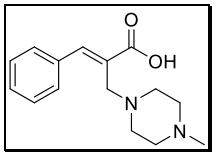


(E)-N-(2-azidoethyl)-2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)-3-phenylacrylamide 7c: The reaction of **57** (500 mg, 1.90 mmol) with 2-azidoethylamine (180 mg, 2.09 mmol) as per the general amide-coupling ***procedure B*** yielded 460 mg (74%) of **51d** as a pale orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.10 (s, 1H), 7.96 (s, 1H), 7.21 – 7.41 (m, 5H), 3.49 – 3.53 (m, 4H), 3.39 (s, 2H), 2.43 – 2.51 (m, 2H), 2.34 – 2.42 (m, 2H), 2.24 (s, 6H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 168.6, 140.1, 136.1, 131.0, 129.2, 128.4, 128.0, 56.8, 54.6, 53.1, 50.8, 45.6, 42.0, 39.7. ESIMS: m/z calculated for $C_{17}H_{26}N_6O$ $(M+H)^+$ 331.22, found 331.35.

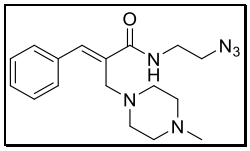


Methyl (E)-2-((4-methylpiperazin-1-yl)methyl)-3-phenylacrylate: The reaction of **55** (1.0 g, 4.3 mmol) with *N*-methylpiperazine (512 mg, 5.1 mmol) and K_2CO_3 (883 mg, 6.4 mmol) provided 943 mg (81%) of **58** as a pale cream liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.84 (s, 1H), 7.63 – 7.68 (m, 2H), 7.32 – 7.41 (m, 3H), 3.81 (s, 3H), 3.35 (s, 2H), 2.31 – 2.63 (m, 8H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.3, 143.6, 135.6, 130.7, 129.9, 129.1, 128.6, 55.5, 53.4, 52.8, 52.3, 46.3. ESIMS: m/z

calculated for $C_{16}H_{22}N_2O_2$ $(M+H)^+$ 275.17, found 275.10.

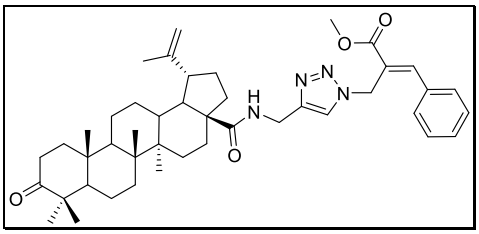


(E)-2-((4-methylpiperazin-1-yl)methyl)-3-phenylacrylic acid: The reaction of **58** (1.0 g, 3.6 mmol) and aq. NaOH (2.9 mL, 2.5 M, 7.3 mmol) yielded 710 mg (74%) of **59** as a pale cream-colored solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.02 (s, 1H), 7.38 – 7.42 (m, 3H), 7.30 – 7.32 (m, 2H), 3.66 (s, 2H), 2.95 – 3.10 (m, 8H), 2.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.5, 142.9, 134.6, 129.5, 128.8, 128.3, 127.9, 53.2, 52.9, 49.4, 43.4. ESIMS: m/z calculated for $C_{15}H_{20}N_2O_2$ (M^+) 260.15, found 260.80.

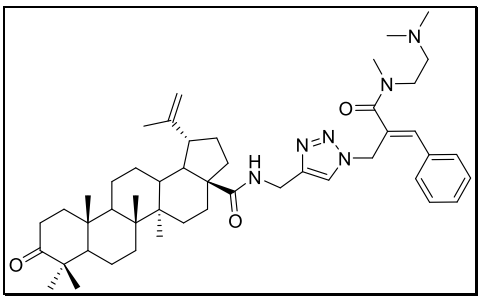


(E)-N-(2-azidoethyl)-2-((4-methylpiperazin-1-yl)methyl)-3-phenylacrylamide: The reaction of **59** (250 mg, 0.96 mmol) with 2-azidoethylamine (90 mg, 1.05 mmol) as per the general amide-coupling ***procedure B*** yielded 226 mg, (72%) of **51e** as a pale orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.04 (s, 1H), 7.92 (s, 1H), 7.18 – 7.36 (m, 5H), 3.50 – 3.56 (m, 2H), 3.45 – 3.49 (m, 2H), 3.39 (s, 2H), 2.33 – 2.68 (m, 8H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 168.6, 140.7, 135.7, 129.8, 129.2, 128.5, 128.2, 55.3, 54.9, 52.5, 51.2, 46.2, 38.9. ESIMS: m/z calculated for $C_{17}H_{24}N_6O$ $(M+H)^+$

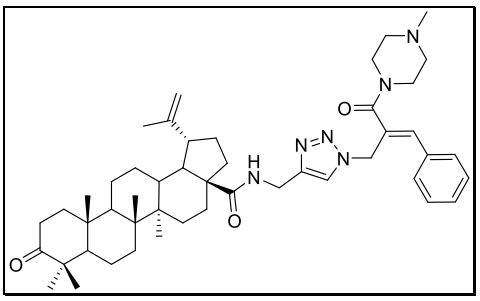
329.20, found 329.33.



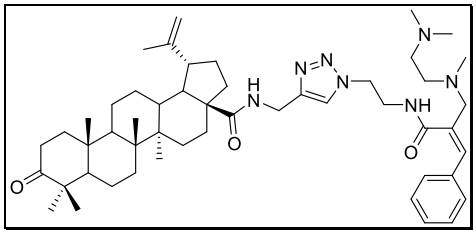
Preparation of triazole 62a. To a stirred solution of alkyne **61** (450 mg, 0.9 mmol) and azide **51a** (198 mg, 0.9 mmol) in a mixture of *t*-butanol/water (1:1, 8.0 mL), was added $CuSO_4$ (23 mg, 0.1 mmol) and sodium ascorbate (36 mg, 0.2 mmol). The reaction mixture was stirred overnight at room temperature. Upon completion (TLC), the reaction was concentrated *in vacuo* and diluted with water to effect precipitation. The resulting solid was filtered, washed with water, and further purified via column chromatography (silica gel, methanol:dichloromethane, 2:3) to obtain 528 mg (89%) of 1,2,3-triazole **62a** as a white solid. Mp 124 – 126 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07 (s, 1H), 7.74 (s, 1H), 7.62 (d, *J* = 7.4 Hz, 2H), 7.39 – 7.46 (m, 3H), 6.36 (t, *J* = 5.2 Hz, 1H), 5.35 (s, 2H), 4.72 (s, 1H), 4.58 (s, 1H), 4.40 – 4.56 (m, 2H), 3.84 (s, 3H), 3.11 (dt, *J* = 4.2, 11.0 Hz, 1H), 2.33 – 2.49 (m, 3H), 0.70 – 2.04 (m, 21H), 1.66 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.83 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.4, 176.5, 167.2, 151.1, 146.2, 145.2, 133.7, 130.2, 129.9, 129.2, 125.1, 123.4, 109.6, 55.8, 55.1, 52.8, 50.2, 50.1, 47.5, 47.1, 46.9, 42.6, 40.8, 39.8, 38.4, 37.9, 37.0, 34.8, 34.3, 33.7, 33.6, 31.0, 29.5, 26.8, 25.8, 21.6, 21.2, 19.8, 19.7, 16.1, 15.8, 14.7; ESIMS: m/z calculated for $C_{44}H_{60}N_4O_4$ $(M+H)^+$ 709.47, found 709.55.



Preparation of triazole 62b**:** Procedure similar to that of **62a**. This compound was prepared by the reaction of alkyne **61** with azide **51b**. Yield: 88%; cream color solid; mp 98 – 101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (s, 1H), 7.33 – 7.46 (m, 5H), 6.92 (s, 1H), 6.25 (t, *J* = 5.3 Hz, 1H), 5.31 – 5.42 (m, 2H), 4.73 (s, 1H), 4.55 – 4.61 (m, 1H), 4.50 (dd, *J* = 5.5, 15.0 Hz, 1H), 4.44 (dd, *J* = 5.5, 15.2 Hz, 1H), 3.42 – 3.50 (m, 2H), 3.12 (dt, *J* = 4.3, 11.2 Hz, 1H), 3.00 (brs, 3H), 2.33 – 2.52 (m, 5H), 2.24 (brs, 6H), 0.78 – 2.01 (m, 21H), 1.67 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.0, 176.2, 150.8, 145.0, 134.8, 134.0, 130.2, 128.8 (2C), 128.7, 123.2, 109.4, 55.5, 54.9, 50.0, 49.9, 48.5, 47.2, 46.6, 45.6, 42.4, 40.6, 39.6, 38.2, 37.7, 36.8, 34.7, 34.1, 33.6, 33.4, 30.8, 29.6, 29.3, 26.6, 25.6, 21.4, 20.9, 19.6, 19.4, 15.9, 15.6, 14.5; ESIMS: m/z 779.70 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{70}N_6O_3$ $[M+H]^+$ 779.5582, found 779.5578.

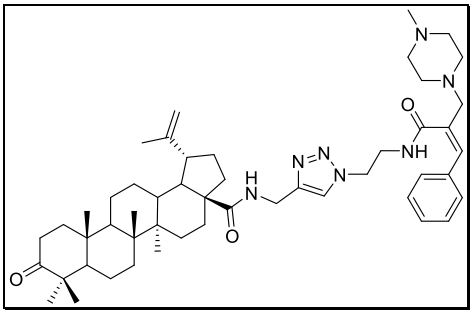


Preparation of triazole 62c: Procedure similar to that of **62a**. This compound was prepared by the reaction of alkyne **61** with azide **51c**. Yield: 90%; cream color solid; mp 134 – 137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (s, 1H), 7.34 – 7.43 (m, 5H), 6.87 (s, 1H), 6.25 (m, 1H), 5.35 (s, 2H), 4.73 (s, 1H), 4.59 (s, 1H), 4.52 (dd, *J* = 4.0, 16.0 Hz, 1H), 4.42 (dd, *J* = 4.0, 16.0 Hz, 1H), 3.63 (m, 4H), 3.12 (dt, *J* = 4.3, 11.2 Hz, 1H), 2.34 – 2.52 (m, 3H), 2.17 – 2.30 (m, 4H), 2.25 (s, 3H), 0.77 – 1.94 (m, 21H), 1.67 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.4, 176.5, 169.0, 150.9, 145.3, 134.8, 134.1, 129.9, 129.1, 129.0, 128.9, 123.7, 109.6, 55.8, 55.2, 54.9, 50.3, 50.1, 48.8, 47.5, 46.9, 46.2, 42.7, 40.9, 39.8, 38.4, 37.9, 37.1, 34.9, 34.3, 33.8, 33.7, 31.0, 29.6, 26.8, 25.8, 21.6, 21.2, 19.8, 19.7, 16.2, 15.8, 14.8; ESIMS: m/z 777.65 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{68}N_6O_3$ $[M+Na]^+$ 799.5245, found 799.5239.



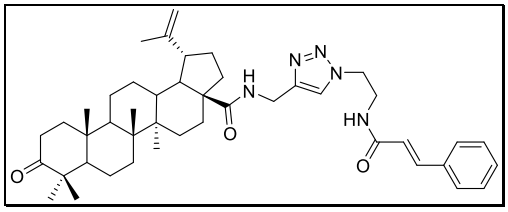
Preparation of triazole 62d: Procedure similar to that of **62a**. This compound was

prepared by the reaction of alkyne **61** with azide **51d**. Yield: 85%; cream color solid; mp 108 – 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.89 (brs, 1H), 7.94 (s, 1H), 7.59 (s, 1H), 7.22 – 7.40 (m, 5H), 6.37 (brs, 1H), 4.73 (s, 1H), 4.56 – 4.60 (m, 3H), 4.51 (dd, *J* = 5.4, 15.0 Hz, 1H), 4.44 (dd, *J* = 5.5, 15.0 Hz, 1H), 3.65 – 3.82 (m, 2H), 3.34 (s, 2H), 3.12 (dt, *J* = 4.2, 11.1 Hz, 1H), 2.34 – 2.52 (m, 7H), 2.19 (brs, 3H), 2.07 (s, 6H), 0.82 – 1.97 (m, 21H), 1.67 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.1, 176.4, 168.5, 150.8, 145.0, 140.1, 135.6, 130.5, 128.9, 128.3, 127.9, 122.9, 109.4, 55.9, 55.5, 54.9, 53.8, 52.7, 50.0, 49.9, 49.2, 47.3, 46.7, 44.9, 42.4, 41.6, 40.6, 39.9, 39.6, 38.2, 37.7, 36.9, 34.7, 34.1, 33.6, 33.4, 30.8, 29.6, 29.3, 26.6, 25.6, 21.4, 21.0, 19.7, 19.4, 15.9, 15.6, 14.5; ESIMS: m/z 822.65 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{50}H_{75}N_7O_3$ $[M+Na]^+$ 844.5824, found 844.5831.

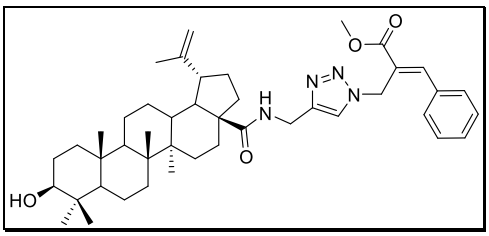


Preparation of triazole 62e: Procedure similar to that of **62a**. This compound was prepared by the reaction of alkyne **61** with azide **51e**. Yield: 87%; cream color solid; mp 118 – 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.87 (s, 1H), 7.92 (s, 1H), 7.61 (s, 1H), 7.22 – 7.37 (m, 3H), 7.20 – 7.25 (m, 2H), 6.23 – 6.29 (m, 1H), 4.73 (s, 1H), 4.59 (s, 1H), 4.38 – 4.55 (m, 4H), 3.79 – 3.92 (m, 2H), 3.34 (s, 2H), 3.08 – 3.15 (m, 1H), 2.29 – 2.52 (m, 11H), 2.25 (s, 3H), 0.76 – 1.92 (m, 21H), 1.75 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H),

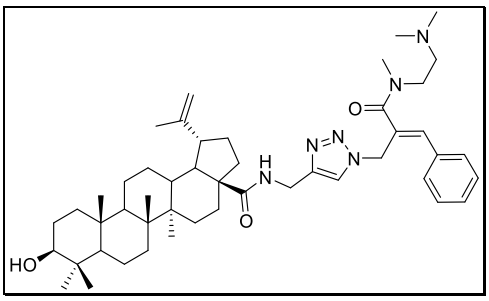
0.94 (s, 3H), 0.90 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.3, 176.7, 168.9, 150.9, 145.5, 140.9, 135.4, 129.5, 129.2, 128.5, 128.3, 123.2, 109.7, 55.7, 55.2, 54.9, 54.9, 52.3, 50.2, 50.1, 49.9, 47.5, 46.9, 45.9, 42.7, 40.9, 39.8, 39.4, 38.4, 38.0, 37.1, 35.0, 34.3, 33.8, 33.7, 31.0, 29.6, 26.8, 25.8, 21.6, 21.2, 19.8, 19.7, 16.2, 15.8, 14.8; ESIMS: m/z 820.70 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{50}H_{73}N_7O_3$ $[M+H]^+$ 820.5848, found 820.5877.



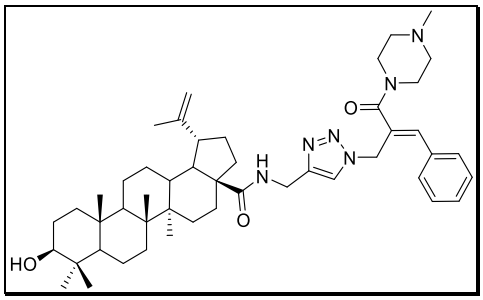
Preparation of triazole 62f: Procedure similar to that of **62a**. This compound was prepared by the reaction of alkyne **61** with azide **51f**. Yield: 91%; white solid; mp 139 – 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (d, *J* = 15.6 Hz, 1H), 7.60 (s, 1H), 7.46 – 7.51 (m, 2H), 7.32 – 7.36 (m, 3H), 6.26 – 6.42 (m, 3H), 4.70 (s, 1H), 4.57 (s, 1H), 4.46 – 4.54 (m, 3H), 4.40 (dd, *J* = 5.7, 15.0 Hz, 1H), 3.85 – 3.94 (m, 2H), 3.12 (dt, *J* = 4.4, 11.1 Hz, 1H), 2.32 – 2.51 (m, 3H), 0.75 – 1.95 (m, 21H), 1.64 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.5, 176.9, 166.7, 150.8, 145.7, 141.7, 134.8, 130.1, 129.0, 128.0, 123.6, 120.3, 109.8, 55.8, 55.1, 50.2, 50.1, 49.9, 47.5, 46.9, 42.7, 40.8, 39.8, 38.4, 37.9, 37.1, 35.0, 34.4, 33.8, 33.6, 31.0, 29.6, 26.8, 25.8, 21.6, 21.2, 19.8, 19.6, 16.2, 15.9, 14.7; ESIMS: m/z 708.55 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{44}H_{61}N_5O_3$ $[M+H]^+$ 708.4847, found 708.4833.



Preparation of alcohol 63a. To a stirred solution of the appropriate ketone **62a** (180 mg, 0.2 mmol) in methanol at 0 °C, was added $NaBH_4$ (14 g, 0.4 mmol), and stirred for 2 h at room temperature. Upon completion of reaction (as monitored by TLC), the reaction mixture was concentrated *in vacuo,* diluted with water and extracted with ethyl acetate (2 x 10.0 mL). The combined organic extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, concentrated under vacuum and purified via column chromatography (silica gel, hexane:ethyl acetate, 1:2) to obtain 155 mg (86%) of pure alcohol **63a** as a white solid. Mp 123 – 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (s, 1H), 7.72 (s, 1H), 7.57 – 7.64 (m, 2H), 7.39 – 7.46 (m, 3H), 6.49 (m, 1H), 5.33 (s, 2H), 4.70 (s, 1H), 4.56 (s, 1H), 4.50 (dd, *J* = 5.7, 15.0 Hz, 1H), 4.41 (dd, *J* = 5.5, 15.0 Hz, 1H), 3.82 (s, 3H), 3.03 – 3.22 (m, 2H), 2.34 (dt, *J* = 3.5, 12.7 Hz, 1H), 0.59 – 2.02 (m, 24H), 1.64 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H), 0.72 (s, 3H), 0.70 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.5, 167.2, 151.2, 146.2, 145.2, 133.8, 130.2, 129.9, 129.2, 125.1, 123.3, 109.6, 79.1, 55.8, 55.5, 52.8, 50.8, 50.3, 47.1, 47.0, 42.6, 40.9, 39.0, 38.9, 38.4, 37.9, 37.4, 34.8, 34.5, 33.7, 31.1, 29.6, 28.2, 27.6, 25.8, 21.1, 19.7, 18.5, 16.3, 16.0, 15.6, 14.8; ESIMS: m/z calculated for $C_{44}H_{62}N_4O_4$ $(M+H)^+$ 711.48, found 711.70.

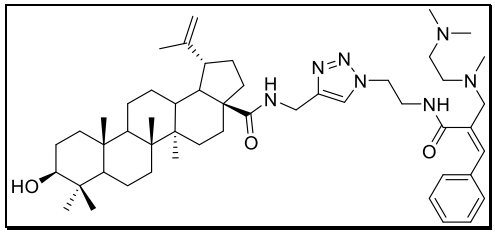


Preparation of 63b: Procedure similar to that of **63a**. Yield: 85%; cream color solid; mp 118 – 121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (s, 1H), 7.33 – 7.43 (m, 5H), 6.99 (s, 1H), 6.25 – 6.34 (m, 1H), 5.35 (s, 2H), 4.72 (s, 1H), 4.58 (s, 1H), 4.49 (dd, *J* = 5.6, 15.1 Hz, 1H), 4.42 (dd, *J* = 5.6, 15.1 Hz, 1H), 3.61 (brs, 2H), 3.05 – 3.18 (m, 5H), 2.29 – 2.77 (m, 10H), 0.63 – 1.94 (m, 23H), 1.66 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.77 (s, 3H), 0.76 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.4, 150.8, 135.1, 133.9, 129.8, 128.84, 128.80, 128.78, 123.3, 109.4, 78.9, 55.6, 55.3, 50.5, 50.1, 48.6, 46.8, 44.9, 44.8, 42.4, 40.7, 38.8, 38.7, 38.2, 37.7, 37.1, 34.8, 34.3, 33.5, 30.8, 29.4, 27.9, 27.4, 25.6, 20.9, 19.4, 18.3, 16.1, 15.8, 15.4, 14.6; ESIMS: m/z 781.70 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{72}N_6O_3$ $[M+Na]^+$ 803.5558, found 803.5558.



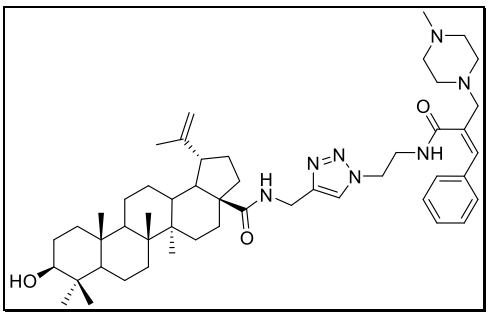
Preparation of 63c: Procedure similar to that of **63a**. Yield: 88%; white solid; mp 134 – 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (s, 1H), 7.34 – 7.42 (m, 5H),

6.86 (s, 1H), 6.24 (t, *J* = 5.6 Hz, 1H), 5.34 (s, 2H), 4.73 (s, 1H), 4.58 (s, 1H), 4.52 (dd, *J* = 5.6, 15.1 Hz, 1H), 4.42 (dd, *J* = 5.6, 15.1 Hz, 1H), 3.66 (m, 4H), 3.06 – 3.19 (m, 2H), 2.17 – 2.35 (m, 5H), 2.26 (s, 3H), 0.63 – 1.93 (m, 24H), 1.67 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.76 (s, 6H), 0.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.3, 168.8, 150.8, 145.1, 134.6, 133.8, 129.6, 128.8, 128.8, 128.7, 123.5, 109.3, 78.8, 55.7, 55.3, 54.7, 50.5, 50.1, 48.5, 46.7, 45.8, 42.4, 40.7, 38.8, 38.7, 38.2, 37.7, 37.1, 34.7, 34.3, 33.5, 30.8, 29.4, 27.9, 27.4, 25.6, 20.9, 19.5, 18.3, 16.1, 15.8, 15.4, 14.6; ESIMS: m/z 779.70 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{70}N_6O_3$ $[M+Na]^+$ 801.5402, found 801.5443.

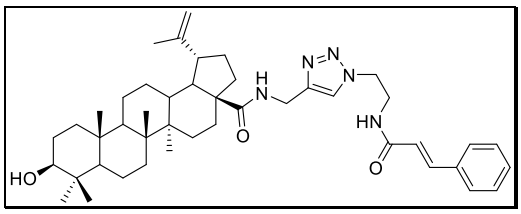


Preparation of 63d: Procedure similar to that of **63a**. Yield: 90%; cream color solid; mp 119 – 122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.95 (s, 1H), 7.96 (s, 1H), 7.58 (s, 1H), 7.24 – 7.41 (m, 5H), 6.33 (s, 1H), 4.72 (s, 1H), 4.55 – 4.64 (m, 3H), 4.51 (dd, *J* = 5.5, 15.0 Hz, 1H), 4.43 (dd, *J* = 5.5, 15.0 Hz, 1H), 3.69 – 3.83 (m, 2H), 3.33 (s, 2H), 3.06 – 3.20 (m, 2H), 2.29 – 2.42 (m, 4H), 2.07 (brs, 3H), 2.07 (s, 6H), 0.63 – 1.95 (m, 25H), 1.67 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.80 (s, 3H), 0.79 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.4, 168.5, 150.8, 144.9, 140.1, 135.6, 130.5, 129.0, 128.2, 127.9, 122.9, 109.4, 78.9, 56.1, 55.6, 55.3, 54.0, 52.5, 50.6, 50.1, 49.2, 46.8, 45.0, 42.4, 41.7, 40.7, 39.9, 38.8, 38.7, 38.2, 37.7, 37.2, 34.7, 34.3, 33.5, 30.9, 29.4,

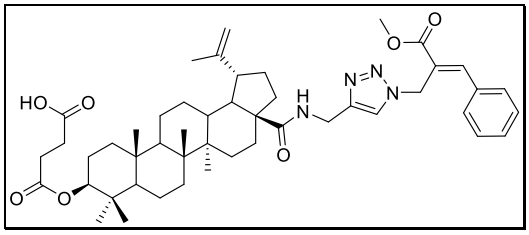
27.9, 27.4, 25.6, 20.9, 19.4, 18.2, 16.1, 15.8, 15.4, 14.6; ESIMS: m/z 824.75 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{50}H_{77}N_7O_3$ $[M+Na]^+$ 846.5980, found 846.5983.



Preparation of 63e: Procedure similar to that of **63a**. Yield: 89%; cream color solid; mp 130 – 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.86 (t, *J* = 4.0 Hz, 1H), 7.92 (s, 1H), 7.58 (s, 1H), 7.20 – 7.39 (m, 5H), 6.26 (t, *J* = 5.7 Hz, 1H), 4.73 (s, 1H), 4.58 (s, 1H), 4.46 – 4.56 (m, 3H), 4.40 (dd, *J* = 5.6, 15.0 Hz, 1H), 3.79 – 3.91 (m, 2H), 3.34 (s, 2H), 3.08 – 3.18 (m, 2H), 2.21 – 2.48 (m, 10H), 2.25 (s, 3H), 0.64 – 1.92 (m, 25H), 1.67 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.5, 168.7, 150.8, 145.3, 140.8, 135.2, 129.3, 128.9, 128.3, 128.0, 123.1, 109.4, 78.8, 55.6, 55.3, 54.8, 54.6, 52.1, 50.5, 50.1, 49.7, 46.8, 45.7, 42.4, 40.7, 39.2, 38.8, 38.7, 38.2, 37.8, 37.2, 34.7, 34.3, 33.5, 30.8, 29.4, 27.9, 27.4, 25.6, 20.9, 19.4, 18.2, 16.2, 15.8, 15.4, 14.6; ESIMS: m/z 822.70 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{50}H_{75}N_7O_3$ $[M+Na]^+$ 844.5824, found 844.5852.

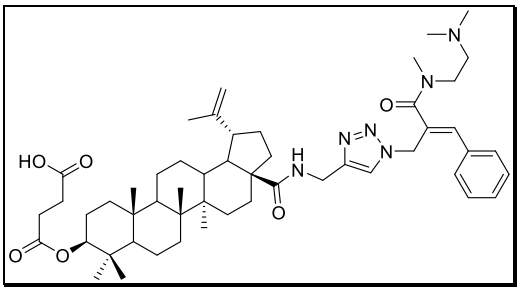


Preparation of 63f: Procedure similar to that of **63a**. Yield: 90%; gray color solid; mp 185 – 187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63 (d, *J* = 15.6 Hz, 1H), 7.60 (s, 1H), 7.45 – 7.53 (m, 2H), 7.33 – 7.60 (m, 3H), 6.38 (d, *J* = 15.6 Hz, 1H), 6.24 – 6.35 (m, 2H), 4.71 (s, 1H), 4.57 (s, 1H), 4.38 – 4.54 (m, 4H), 3.86 – 3.93 (m, 2H), 3.06 – 3.17 (m, 2H), 2.26 – 2.39 (m, 1H), 0.62 – 1.94 (m, 24H), 1.65 (s, 3H), 0.92 (s, 6H), 0.78 (s, 3H), 0.75 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.7, 166.4, 150.7, 145.5, 141.6, 134.6, 129.8, 128.8, 127.8, 123.4, 120.0, 109.4, 78.9, 55.6, 55.3, 50.5, 50.1, 49.7, 46.7, 42.4, 40.7, 39.5, 38.8, 38.7, 38.2, 37.8, 37.1, 34.7, 34.3, 33.4, 30.8, 29.4, 27.9, 27.4, 25.6, 20.9, 19.4, 18.2, 16.1, 15.8, 15.4, 14.6; ESIMS: m/z calculated for $C_{44}H_{63}N_5O_3$ $(M+H)^+$ 710.50, found 710.65.



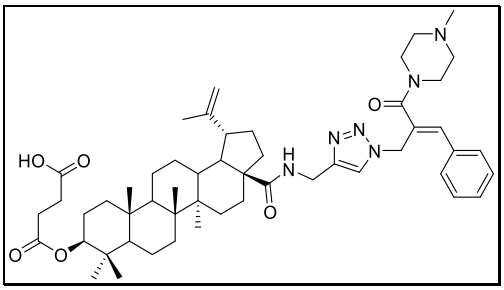
Preparation of succinic acid hemiester 64a. A stirred solution of alcohol **63a** (110 mg, 0.1 mmol), DMAP (19 mg, 0.1 mmol), and succinic anhydride (31 mg, 0.3 mmol) in toluene (4.0 mL) was refluxed overnight. Upon completion (TLC), the

reaction mixture was concentrated *in vacuo*, diluted with water, and extracted with ethyl acetate (2 x 10.0 mL). The combined extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified using column chromatography (silica gel, hexanes:ethyl acetate, 1:3) to obtain 109 mg (87%) of pure succinic acid hemi ester **64a** as a white solid. Mp 122 – 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07 (s, 1H), 7.73 (s, 1H), 7.58 – 7.63 (m, 2H), 7.41 – 7.47 (m, 3H), 6.71 (t, *J* = 5.9 Hz, 1H), 5.34 (s, 2H), 4.71 (s, 1H), 4.57 (s, 1H), 4.43 – 4.50 (m, 3H), 3.84 (s, 3H), 3.10 (dt, *J* = 4.3, 11.1 Hz, 1H), 2.57 – 2.69 (m, 4H), 2.32 (dt, *J* = 3.6, 12.3 Hz, 1H), 0.65 – 1.98 (m, 23H), 1.66 (s, 3H), 0.92 (s, 3H), 0.80 (s, 3H), 0.78 (s, 3H), 0.75 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.6, 176.3, 171.9, 166.9, 150.9, 146.1, 144.9, 133.5, 130.0, 129.7, 128.9, 124.7, 123.4, 109.3, 81.4, 55.6, 55.5, 52.6, 50.4, 50.1, 46.9, 46.8, 42.4, 40.6, 38.4, 38.1, 37.8, 37.7, 37.0, 34.2, 34.0, 33.3, 30.8, 29.4, 29.3, 29.1, 27.8, 25.5, 23.6, 20.9, 19.4, 18.1, 16.5, 16.1, 15.7, 14.6; ESIMS: m/z 811.65 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{66}N_4O_7$ $[M+H]^+$ 811.5004, found 811.5038.



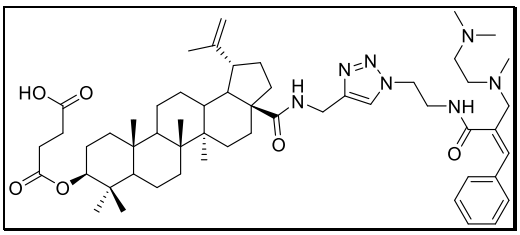
Preparation of succinic acid hemiester 64b: Procedure similar to that of **64a**. Yield: 80%; cream color solid; mp 130 – 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (s,

1H), 7.33 – 7.43 (m, 5H), 6.99 (s, 1H), 6.29 (m, 1H), 5.33 (s, 2H), 4.72 (s, 1H), 4.58 (s, 1H), 4.39 – 4.50 (m, 3H), 3.55 – 3.70 (m, 2H), 3.07 – 3.18 (m, 1H), 3.05 (brs, 3H), 2.70 (m, 1H), 2.29 – 2.77 (m, 8H), 2.24 – 2.40 (m, 4H), 0.63 – 1.94 (m, 23H), 1.66 (s, 3H), 0.92 (s, 3H), 0.80 (s, 6H), 0.76 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.5, 176.3, 172.6, 150.8, 145.4, 135.1, 133.8, 129.8, 129.7, 128.9, 128.7, 113.9, 109.5, 80.9, 55.6, 55.4, 50.4, 50.1, 48.6, 46.8, 43.8, 42.4, 40.7, 38.3, 38.2, 37.8, 37.7, 37.0, 34.6, 34.2, 33.4, 30.8, 30.1, 30.0, 29.7, 29.4, 27.9, 25.5, 23.6, 20.9, 19.4, 18.1, 16.5, 16.2, 15.8, 14.6; ESIMS: m/z calculated for $C_{52}H_{76}N_6O_6$ $(M+H)^+$ 881.59, found 881.58.

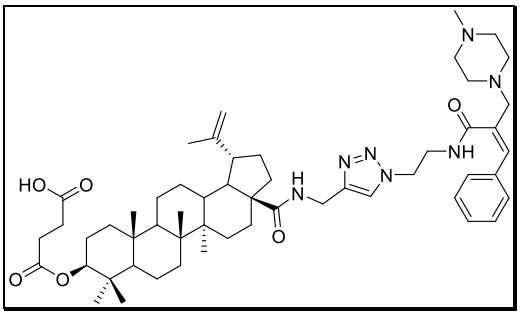


Preparation of succinic acid hemiester 64c: Procedure similar to that of **64a**. Yield: 83%; cream color solid; mp 142 – 145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (s, 1H), 7.36 – 7.44 (m, 5H), 6.88 (s, 1H), 6.58 (t, *J* = 5.7 Hz, 1H), 5.34 (s, 2H), 4.72 (s, 1H), 4.58 (s, 1H), 4.43 – 4.50 (m, 3H), 3.73 (brs, 4H) 3.12 (dt, *J* = 5.4, 11.0 Hz, 1H), 2.57 – 2.65 (m, 4H), 2.26 – 2.53 (m, 5H), 2.36 (s, 3H), 0.72 – 1.96 (m, 23H), 1.67 (s, 3H), 0.93 (s, 3H), 0.82 (s, 3H), 0.81 (s, 3H), 0.77 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.6, 175.8, 172.3, 168.9, 150.8, 145.4, 135.1, 133.7, 129.1, 128.9, 128.9, 128.7, 123.5, 109.4, 81.1, 55.6, 55.4, 53.8, 50.4, 50.1, 48.6, 46.8, 44.7, 42.4, 40.7, 38.4, 38.1, 37.8, 37.7, 37.0, 34.5, 34.2, 33.4, 30.8, 29.8, 29.6, 29.6, 29.4, 27.9, 25.5, 23.6,

20.9, 19.4, 18.1, 16.5, 16.2, 15.8, 14.6; ESIMS: m/z calculated for $C_{52}H_{74}N_6O_6$ $(M+H)^+$ 879.57, found 879.65.

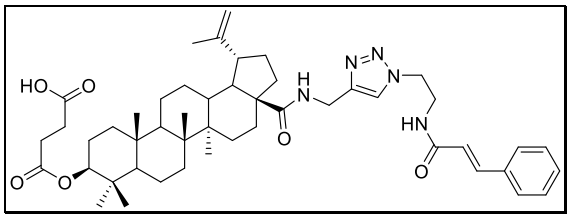


Preparation of succinic acid hemiester 64d: Procedure similar to that of **64a**. Yield: 82%; white solid; mp 114 – 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.68 (s, 1H), 7.91 (s, 1H), 7.60 (s, 1H), 7.27 – 7.39 (m, 3H), 7.20 – 7.25 (m, 2H), 6.66 (t, *J* = 5.5 Hz, 1H), 4.72 (s, 1H), 4.58 (s, 1H), 4.40 – 4.57 (m, 5H), 3.73 – 3.85 (m, 2H), 3.34 (s, 2H), 3.12 (dt, *J* = 4.2, 10.8 Hz, 1H), 2.40 – 2.68 (m, 8H), 2.34 (m, 1H), 2.28 (s, 6H), 2.05 (s, 3H), 0.72 – 1.98 (m, 23H), 1.66 (s, 3H), 0.92 (s, 3H), 0.81 (s, 9H), 0.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.5 (2C), 172.7, 168.5, 150.8, 145.3, 140.3, 135.5, 130.3, 129.0, 128.3, 127.9, 123.0, 109.4, 80.9, 55.6, 55.4, 55.2, 53.9, 53.5, 53.1, 50.6, 50.5, 50.1, 49.4, 46.7, 44.1, 42.4, 41.4, 40.7, 39.6, 38.4, 38.2, 37.8, 37.7, 37.1, 34.6, 34.2, 33.4, 30.9, 29.4, 27.9, 25.5, 23.7, 20.9, 19.4, 18.1, 16.5, 16.2, 15.8, 14.6; ESIMS: m/z calculated for $C_{54}H_{81}N_7O_6$ $(M+H)^+$ 924.63, found 924.70.



Preparation of succinic acid hemiester 64e: Procedure similar to that of **64a**. Yield:

84%; cream color solid; mp 132 – 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (m, 1H), 7.94 (s, 1H), 7.64 (s, 1H), 7.28 – 7.40 (m, 3H), 7.19 – 7.23 (m, 2H), 6.52 (t, *J* = 5.0 Hz, 1H), 4.72 (s, 1H), 4.59 (s, 1H), 4.38 – 4.51 (m, 5H), 3.88 – 3.92 (m, 2H), 3.38 (s, 2H), 3.11 (dt, *J* = 4.4, 11.0 Hz, 1H), 2.40 – 2.76 (m, 10H), 2.44 (s, 3H), 2.33 (m, 3H), 0.71 – 1.95 (m, 23H), 1.67 (s, 3H), 0.93 (s, 3H), 0.81 (s, 6H), 0.79 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.7 (2C), 172.6, 168.5, 150.7, 145.7, 141.5, 134.9, 128.9, 128.7, 128.5, 128.3, 123.5, 109.5, 80.9, 55.6, 55.4, 54.2, 53.3, 50.6, 50.4, 50.1, 50.0, 46.8, 44.0, 42.4, 40.7, 39.0, 38.3, 38.2, 37.8, 37.7, 37.1, 34.6, 34.3, 33.4, 30.8, 29.7, 29.4, 27.9, 25.5, 23.6, 20.9, 19.4, 18.1, 16.5, 16.2, 15.8, 14.6; ESIMS: m/z calculated for $C_{54}H_{79}N_7O_6$ $(M+H)^+$ 922.62, found 922.75.



Preparation of succinic acid hemiester 64f: Procedure similar to that of **64a**. Yield: 81%; yellow solid; mp 141 – 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (d, *J* = 15.6 Hz, 1H), 7.63 (s, 1H), 7.46 – 7.52 (m, 2H), 7.34 – 7.38 (m, 3H), 6.60 – 6.69 (m, 1H), 6.40 (d, *J* = 15.5 Hz, 1H), 6.26 – 6.34 (m, 1H), 4.70 (s, 1H), 4.57 (s, 1H), 4.39 – 4.54 (m, 5H), 3.80 – 3.97 (m, 2H), 3.09 (dt, *J* = 4.1, 11.0 Hz, 1H), 2.59 – 2.70 (m, 4H), 2.22 – 2.33 (m, 1H), 0.66 – 1.91 (m, 23H), 1.65 (s, 3H), 0.91 (s, 3H), 0.80 (s, 3H), 0.79 (s, 6H), 0.71 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.9 (2C), 172.2, 166.6, 150.7, 145.3, 141.8, 134.5, 129.9, 128.8, 127.9, 123.6, 119.9, 109.5, 81.4, 55.6, 55.4, 50.4, 50.0, 49.8,

46.8, 42.4, 40.7, 39.5, 38.3, 38.1, 37.8, 37.7, 37.0, 34.3, 34.2, 33.3, 30.8, 29.6, 29.3, 27.8, 25.5, 23.6, 20.9, 19.4, 18.1, 16.5, 16.2, 15.7, 14.6; ESIMS: m/z 810.75 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{67}N_5O_6$ $[M+H]^+$ 832.4984, found 832.5026.

Chapter 4

Spectral Characterization

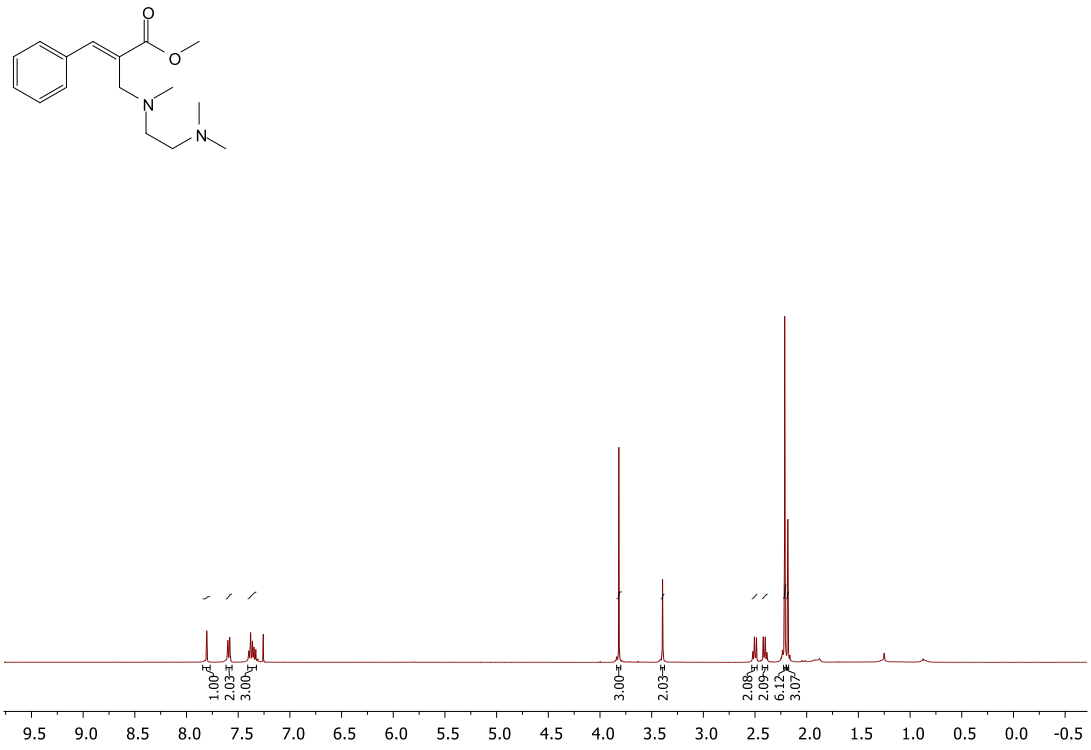


Figure 28. 400 MHz ^{1}H NMR of Compound **56** in $CDCl_3$

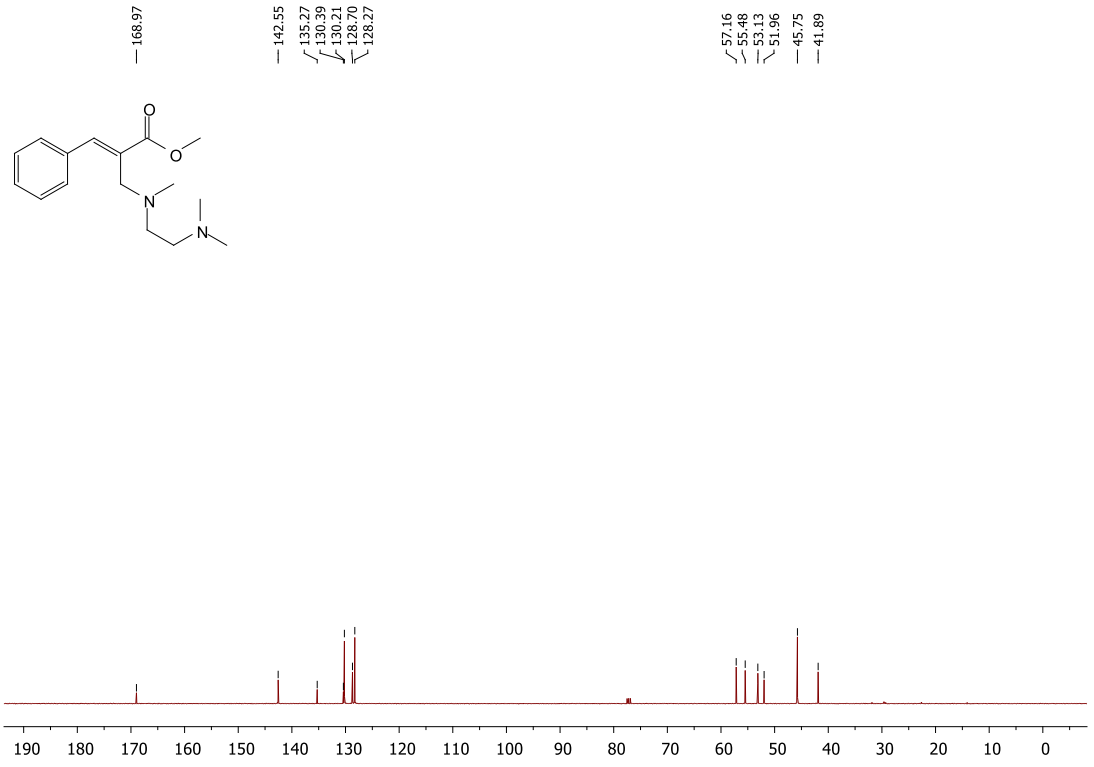


Figure 29. 101 MHz ^{13}C NMR of Compound **56** in $CDCl_3$

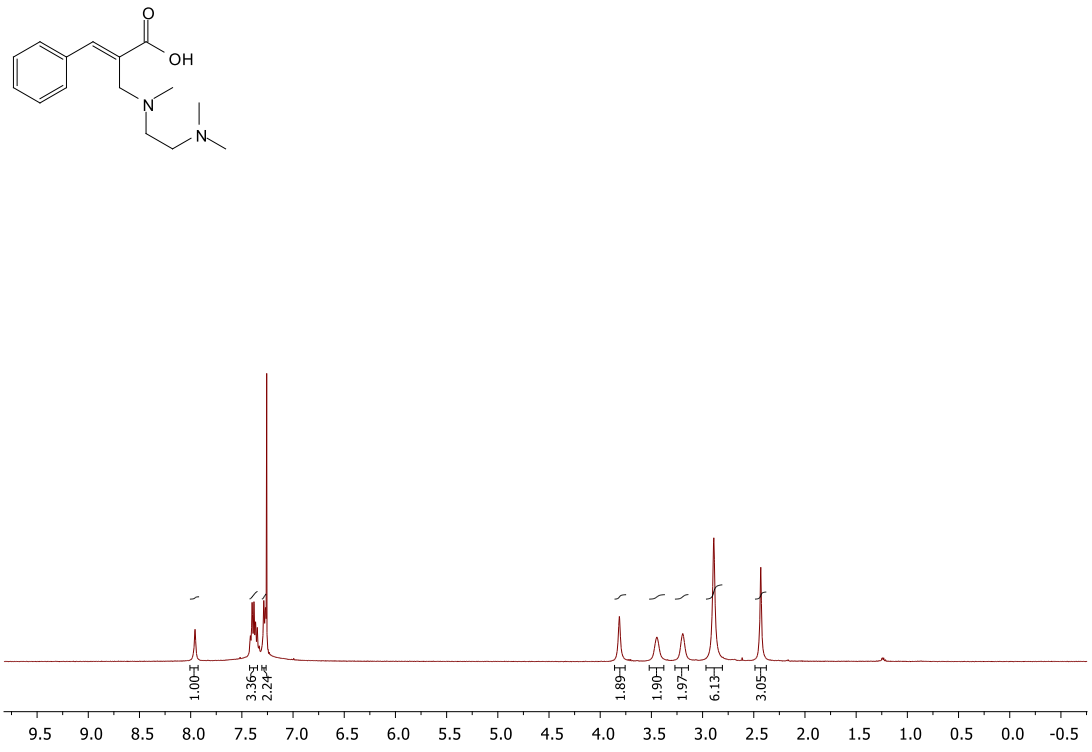


Figure 30. 400 MHz ^{1}H NMR of Compound **57** in DMSO-d_6

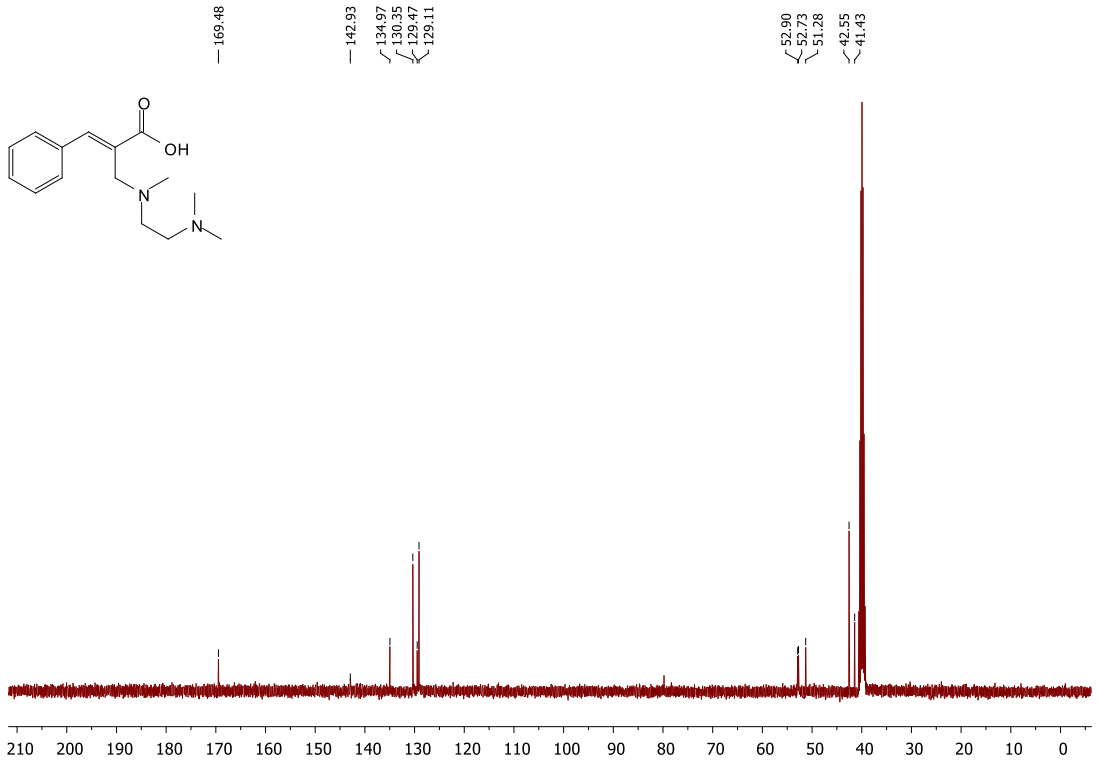


Figure 31. 101 MHz ^{13}C NMR of Compound **57** in DMSO-d_6

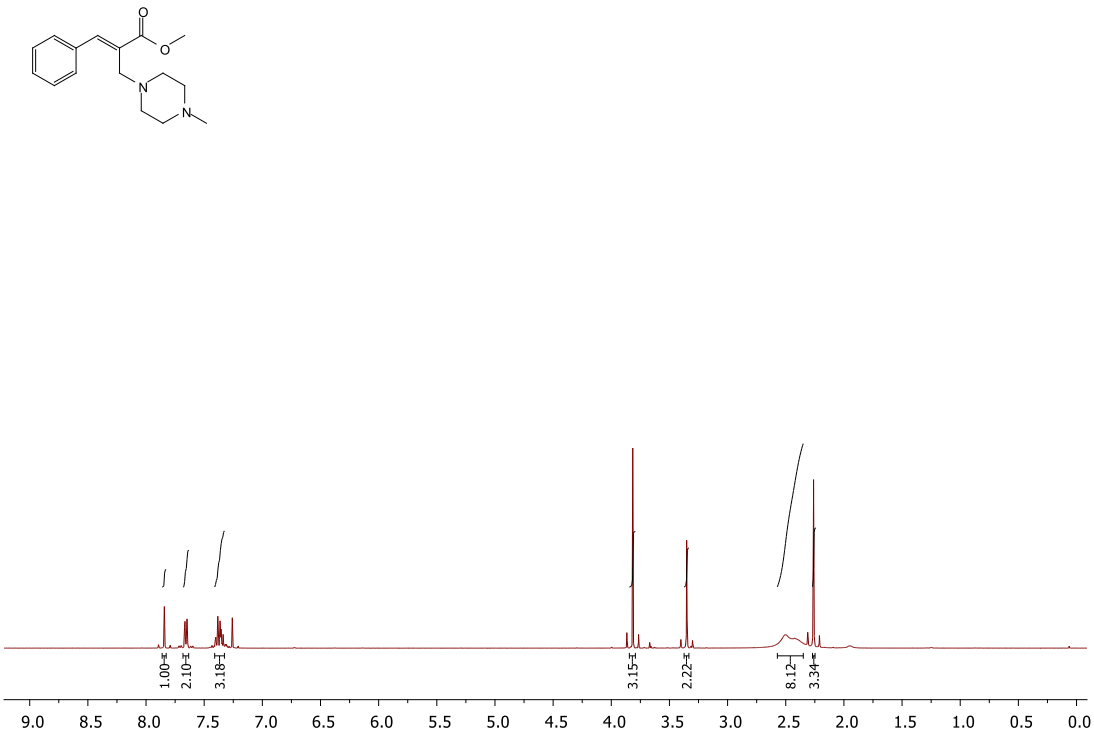


Figure 32. 400 MHz ^{1}H NMR of Compound **58** in $CDCl_3$

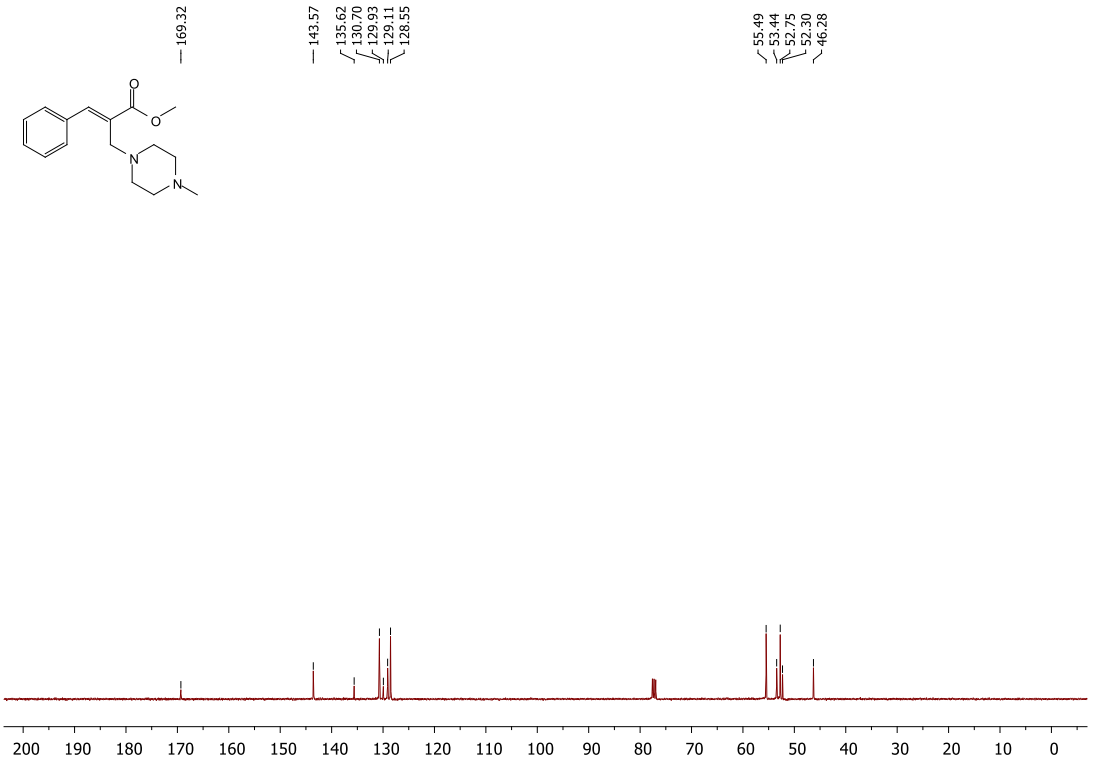
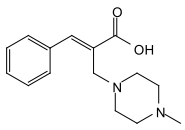


Figure 33. 101 MHz ^{13}C NMR of Compound **58** in $CDCl_3$



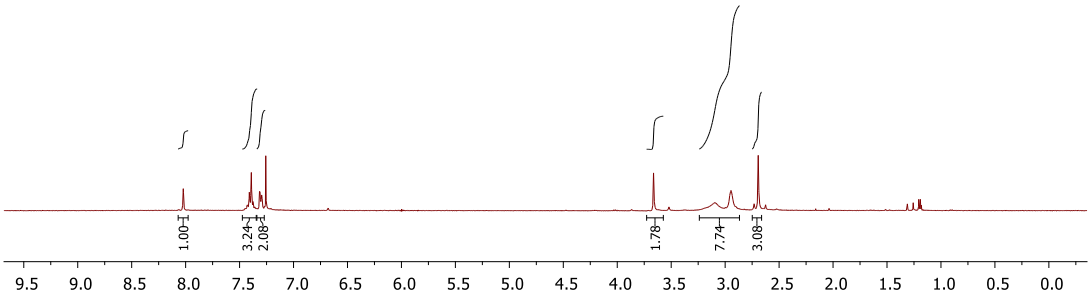


Figure 34. 400 MHz ^{1}H NMR of Compound **59** in $CDCl_3$

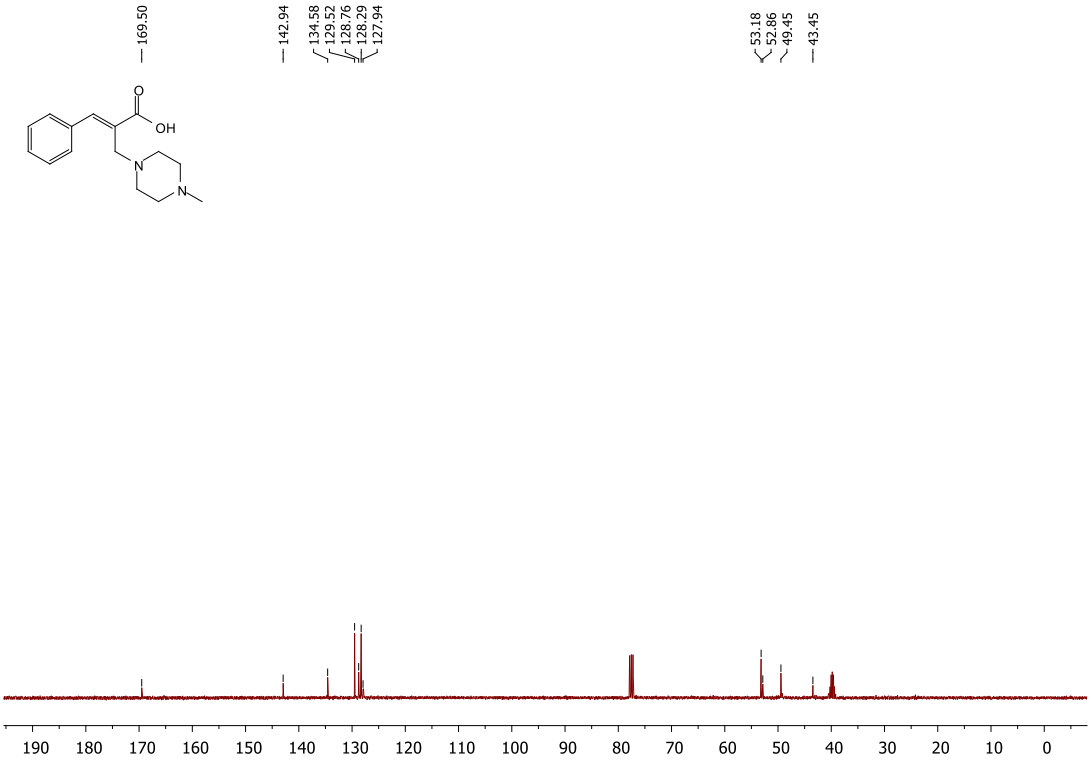


Figure 35. 101 MHz ^{13}C NMR of Compound **59** in $CDCl_3$

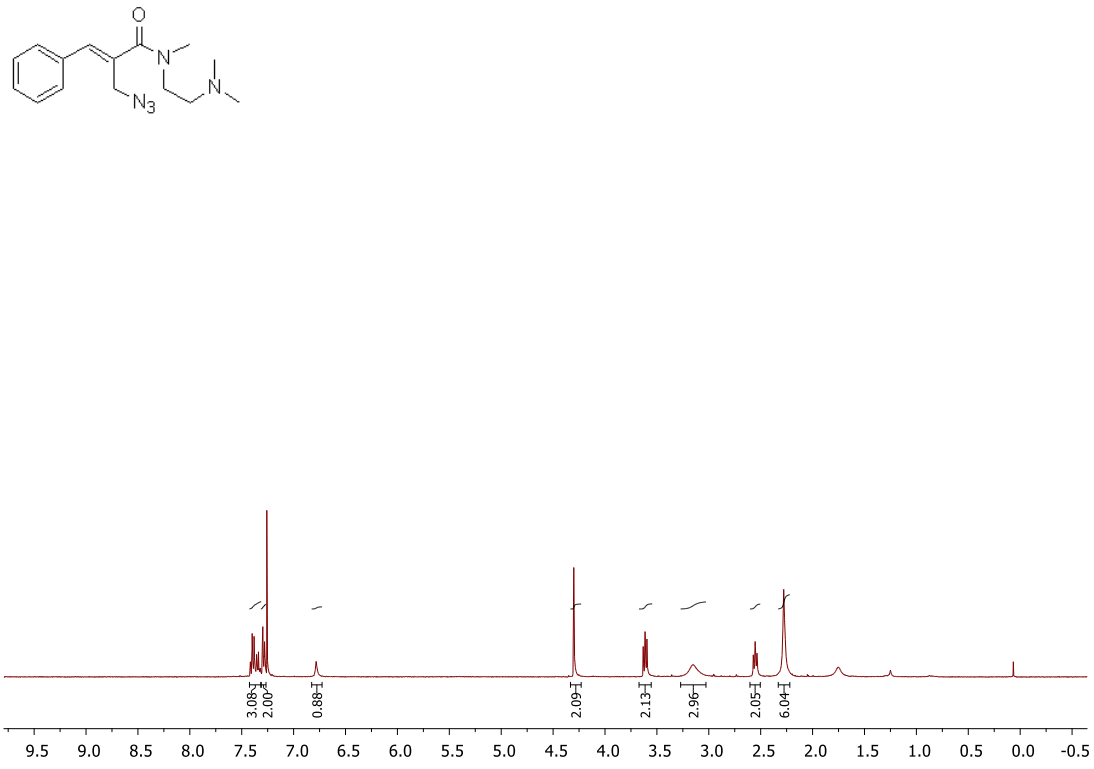


Figure 36. 400 MHz ^{1}H NMR of Compound **51b** in $CDCl_3$

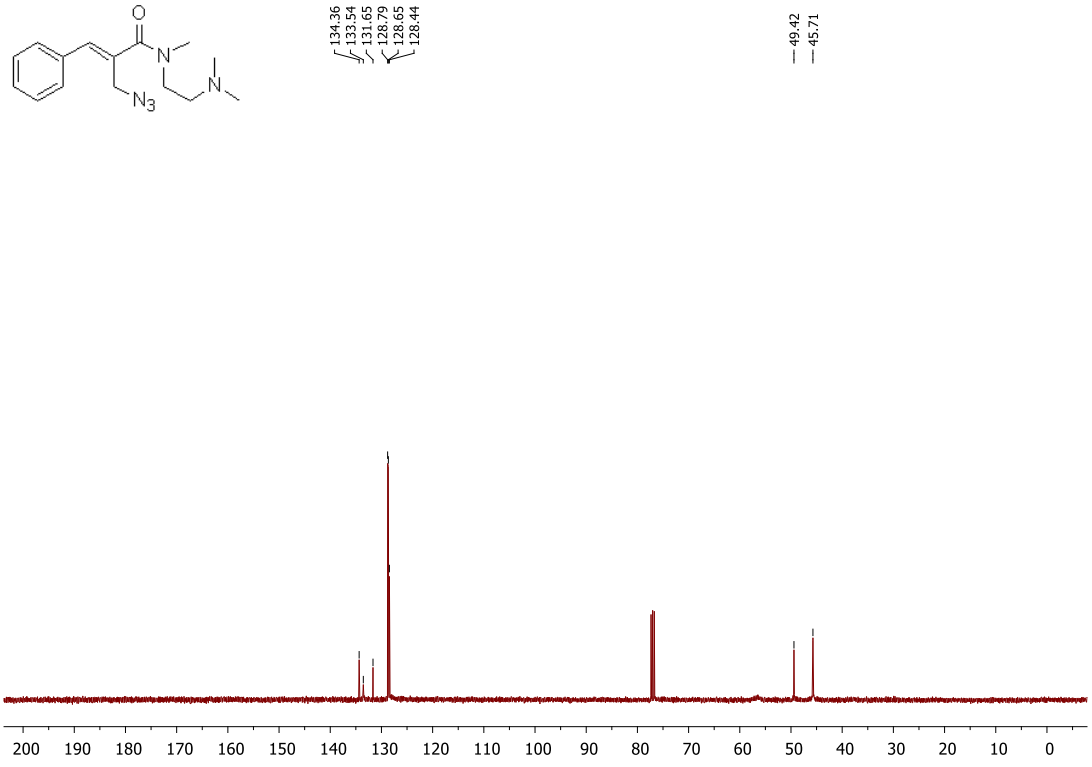


Figure 37. 101 MHz ^{13}C NMR of Compound **51b** in $CDCl_3$

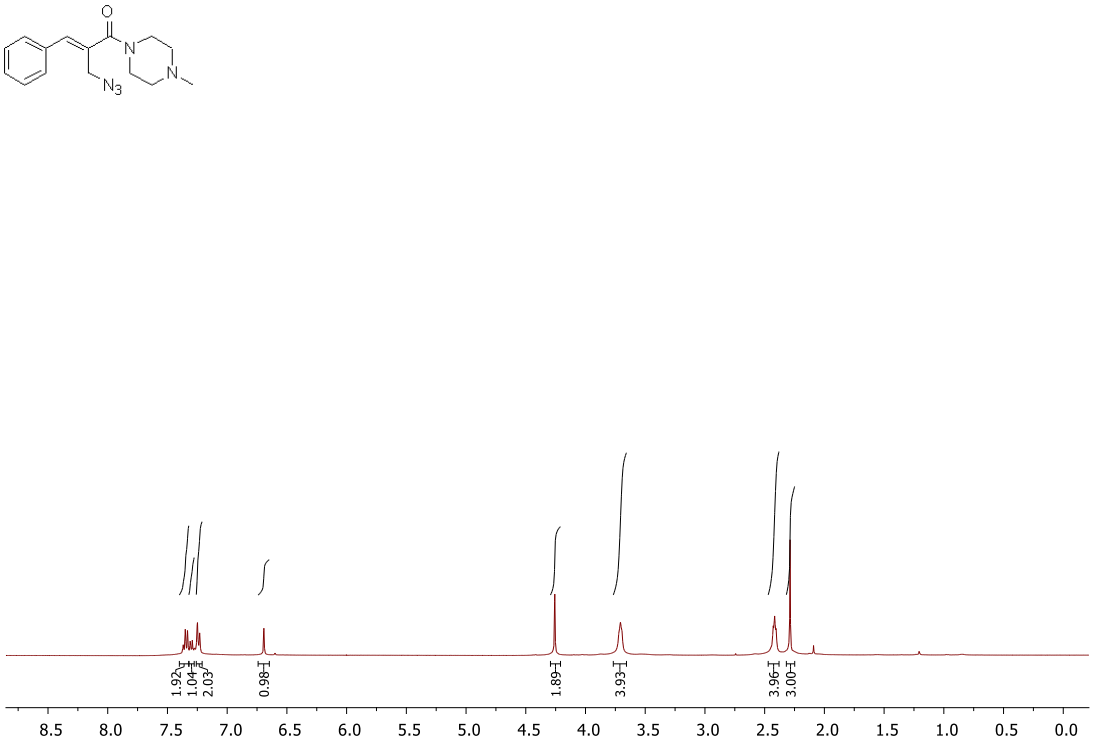


Figure 38. 400 MHz ^{1}H NMR of Compound **51c** in $CDCl_3$

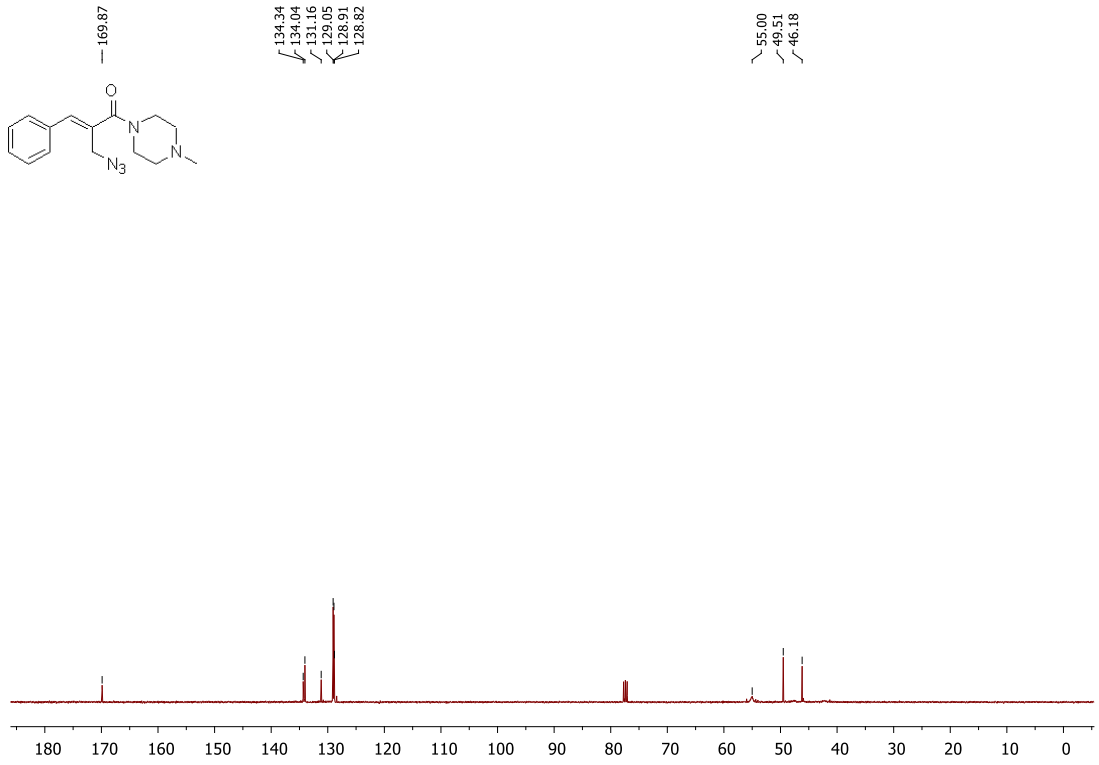


Figure 39. 101 MHz ^{13}C NMR of Compound **51c** in $CDCl_3$

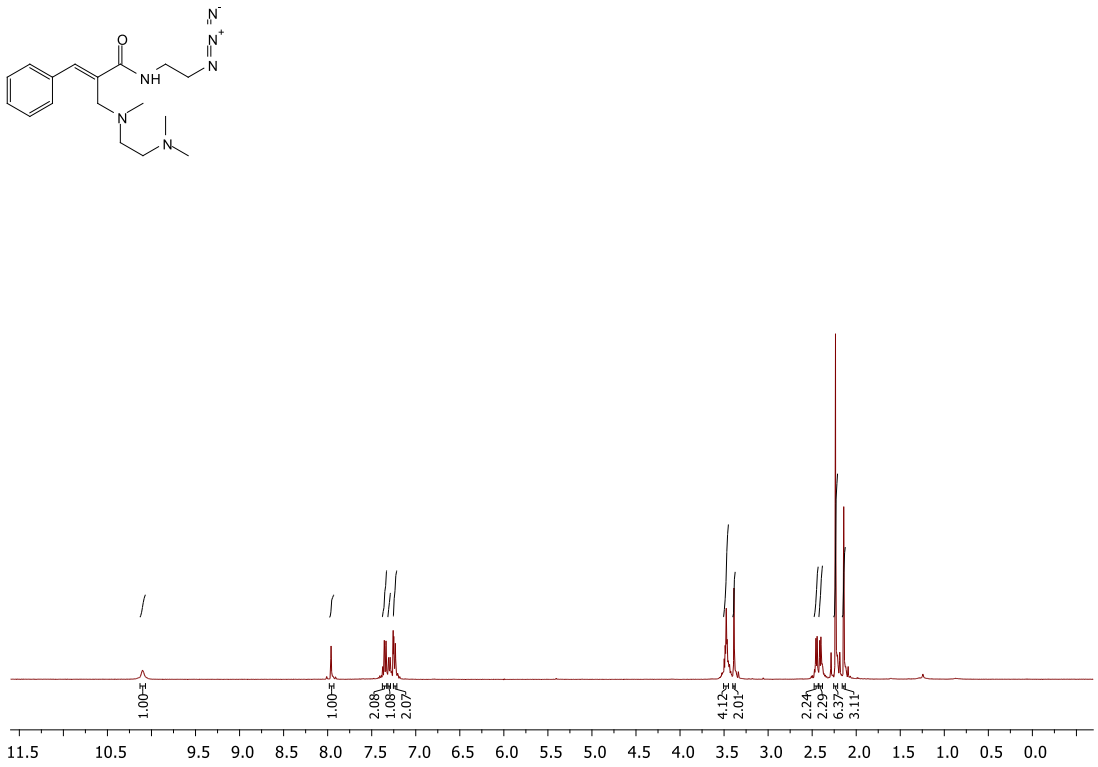


Figure 40. 400 MHz ^{1}H NMR of Compound **51d** in $CDCl_3$

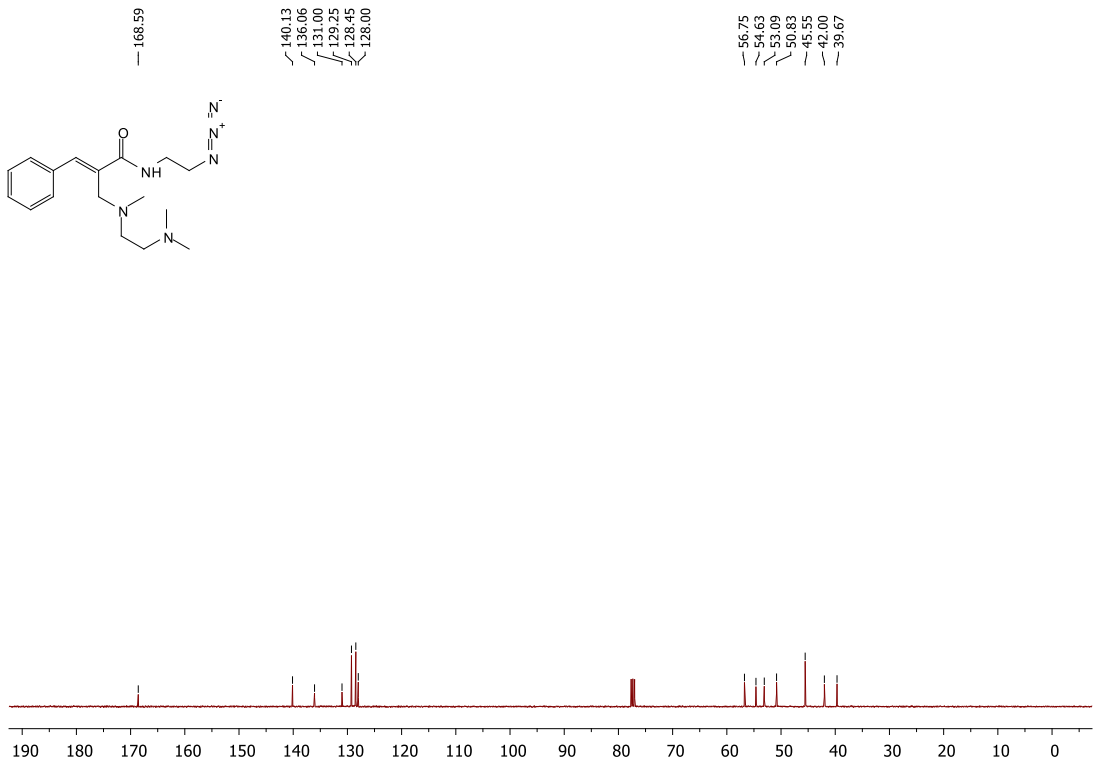


Figure 41. 101 MHz ^{13}C NMR of Compound **51d** in $CDCl_3$

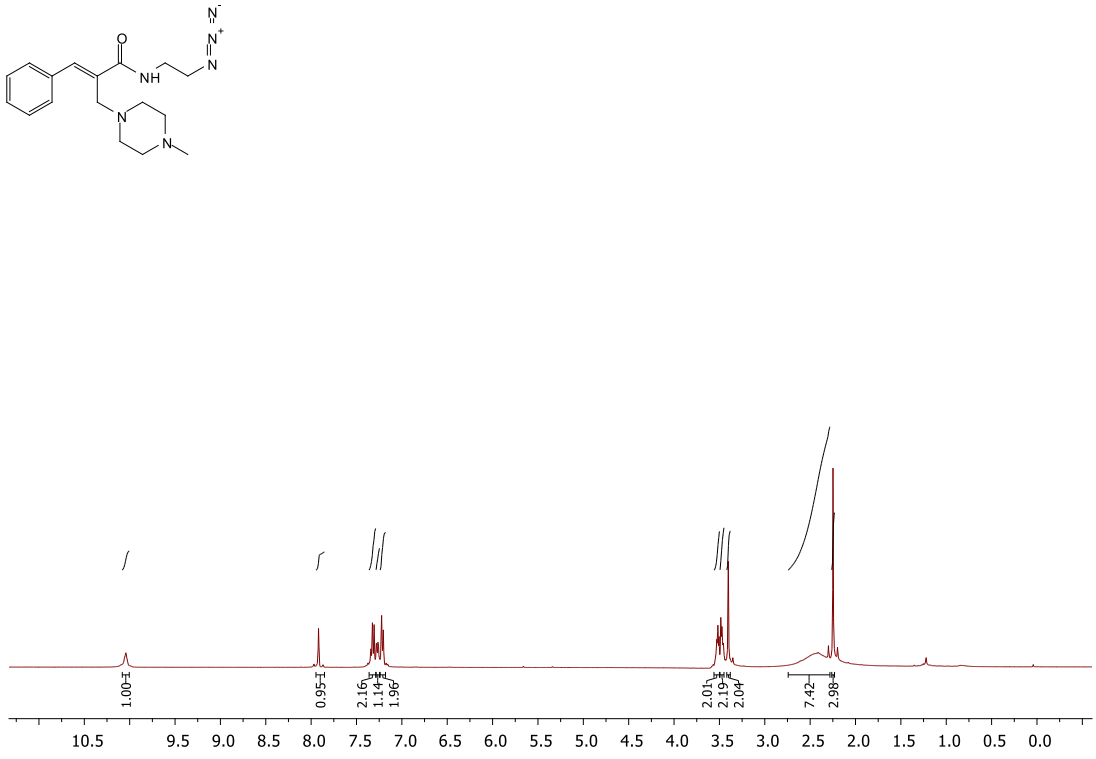


Figure 42. 400 MHz ^{1}H NMR of Compound **51e** in $CDCl_3$

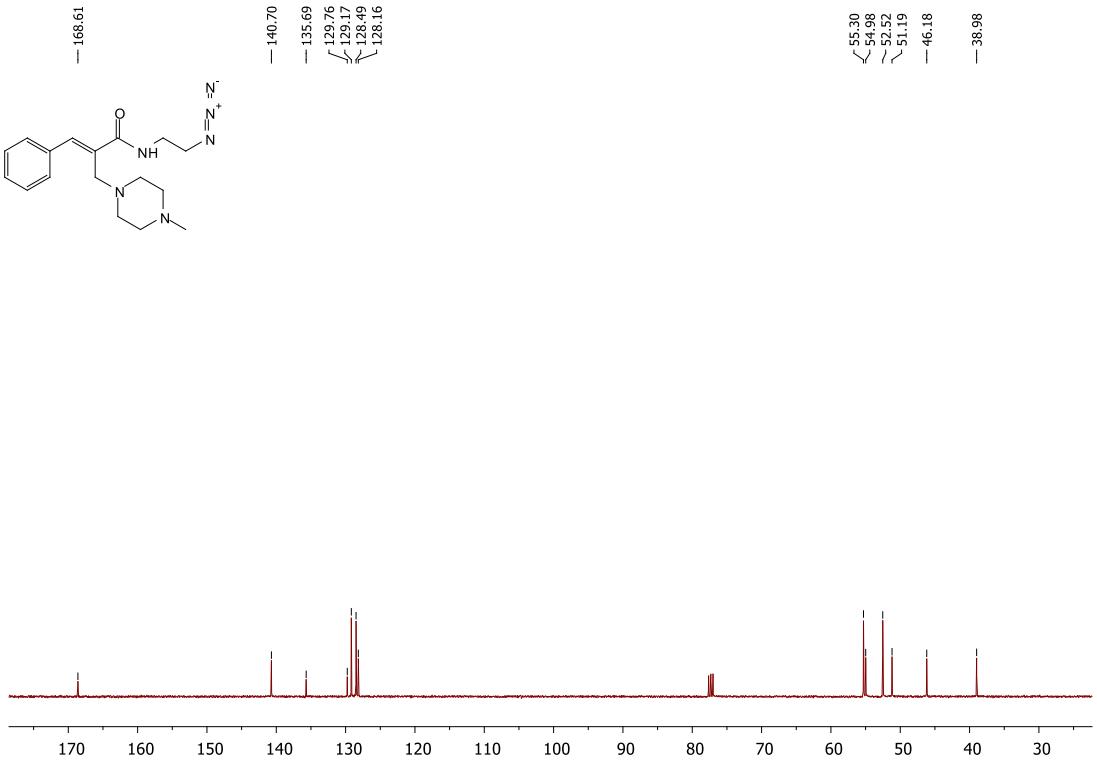


Figure 43. 101 MHz ^{13}C NMR of Compound **51e** in $CDCl_3$

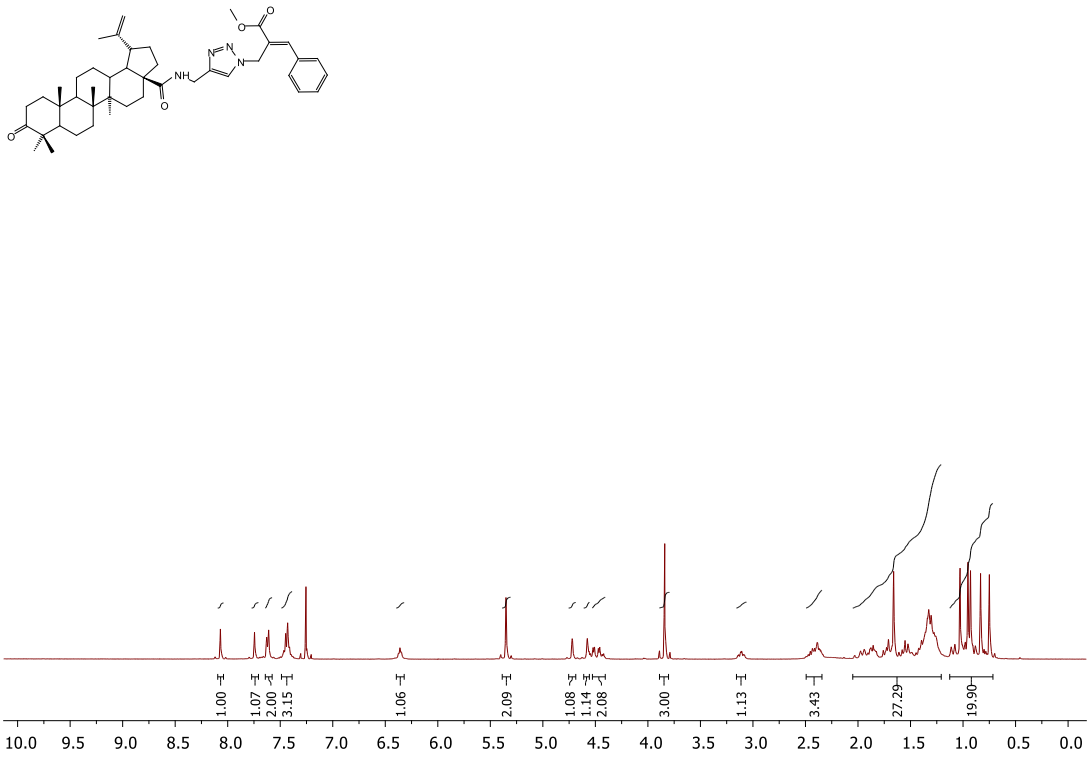


Figure 44. 400 MHz ^{1}H NMR of Compound **62a** in $CDCl_3$

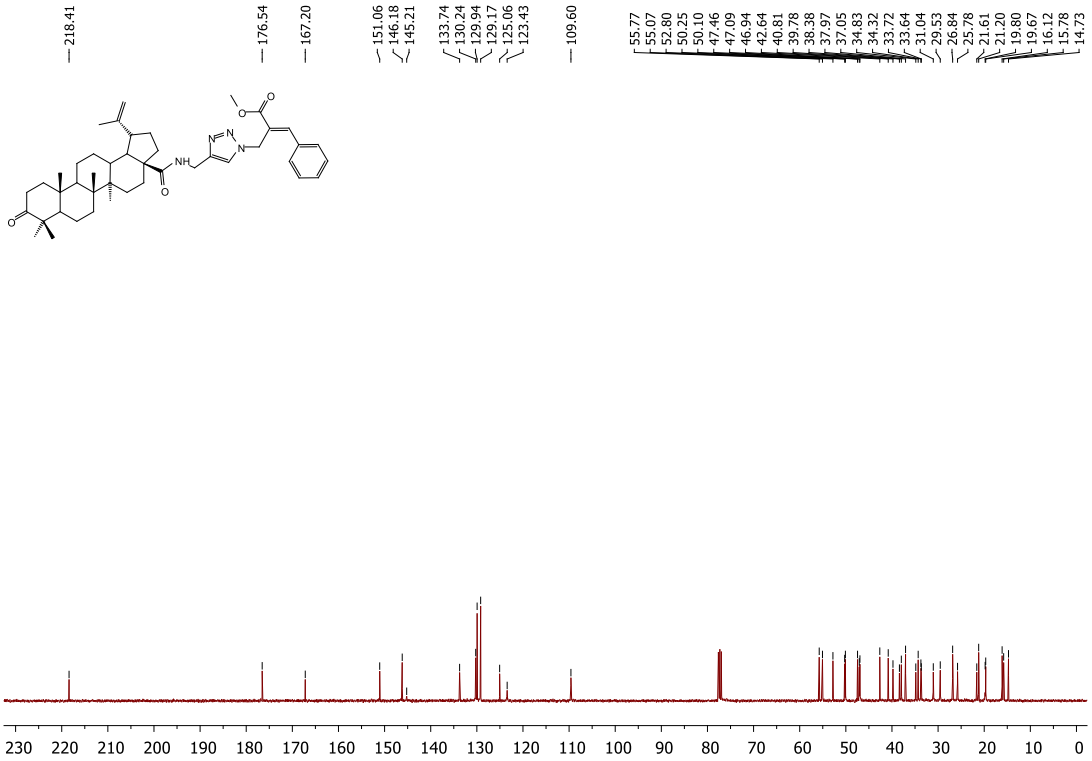


Figure 45. 101 MHz ^{13}C NMR of Compound **62a** in $CDCl_3$

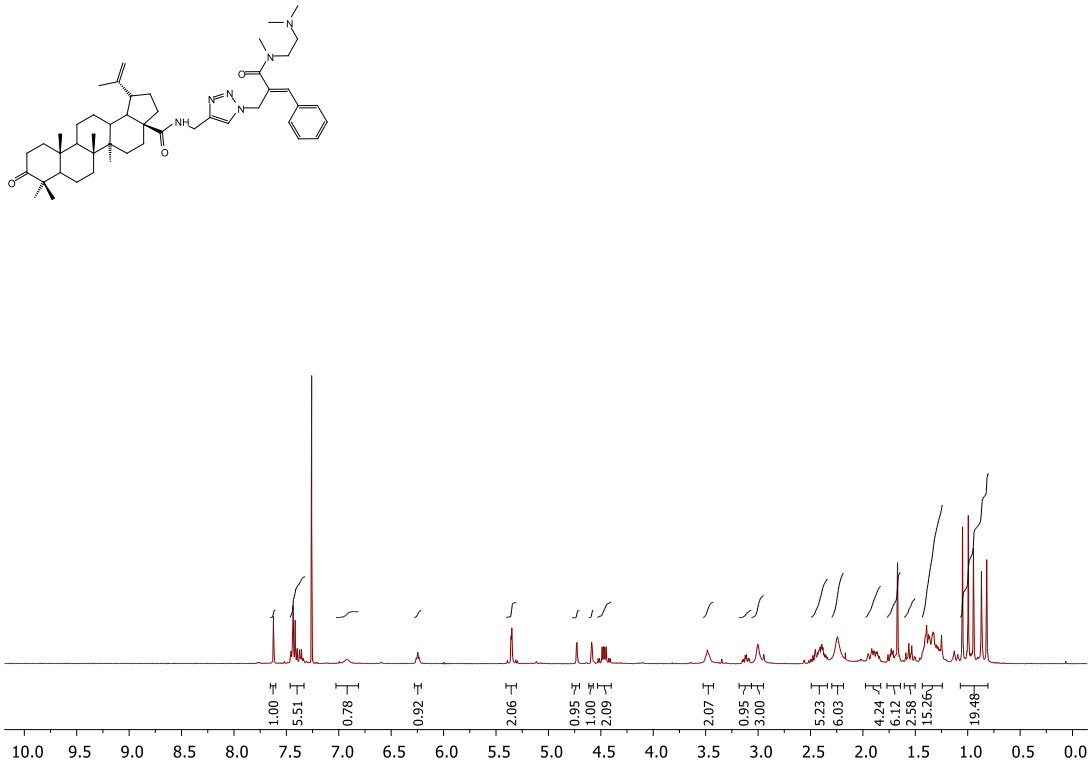


Figure 46. 400 MHz ^{1}H NMR of Compound **62b** in $CDCl_3$

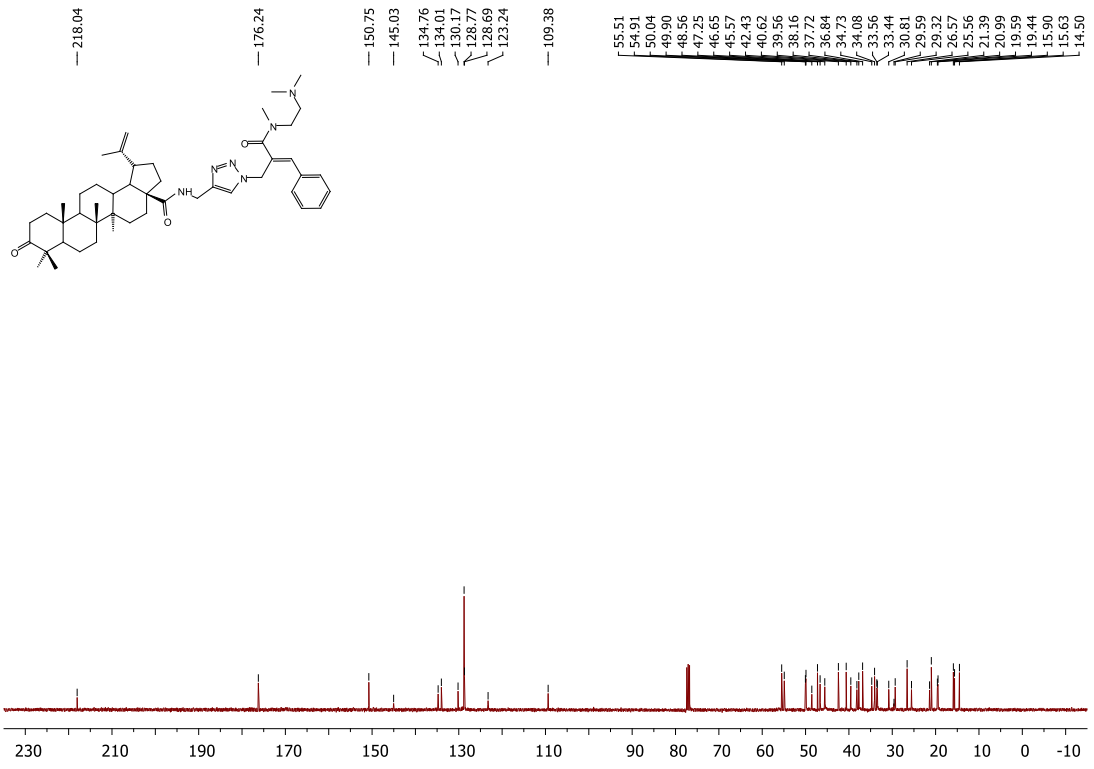


Figure 47. 101 MHz ^{13}C NMR of Compound **62b** in $CDCl_3$

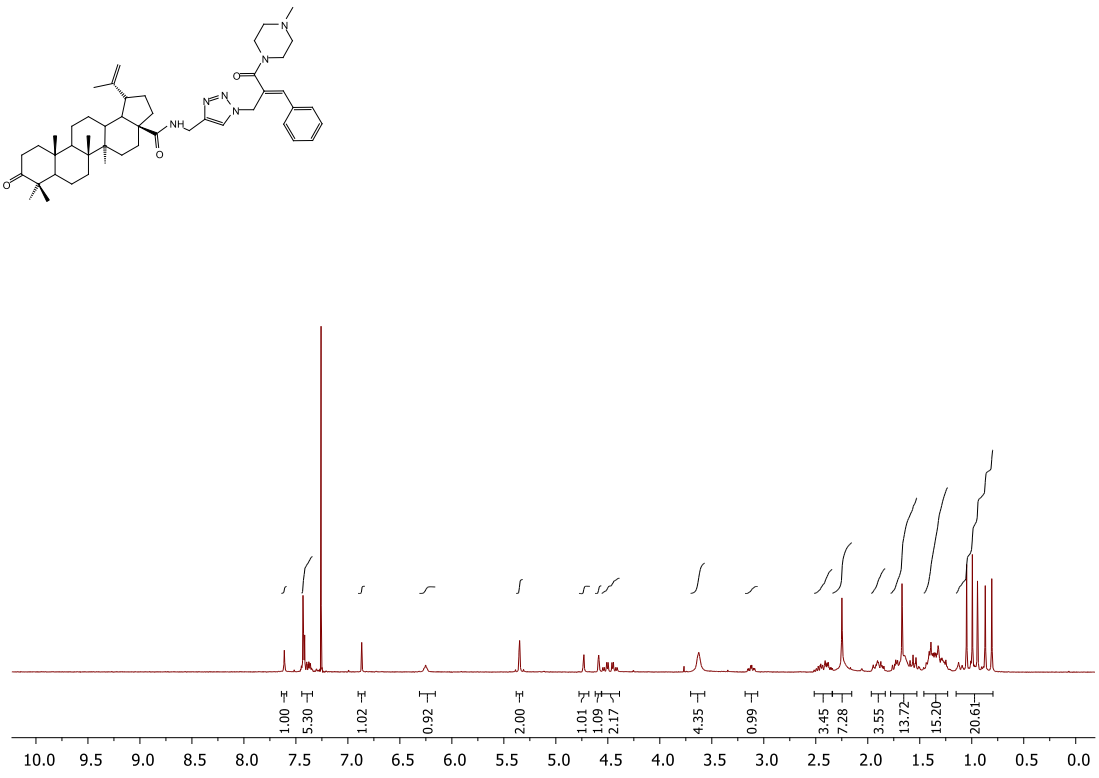


Figure 48. 400 MHz ^{1}H NMR of Compound **62c** in $CDCl_3$

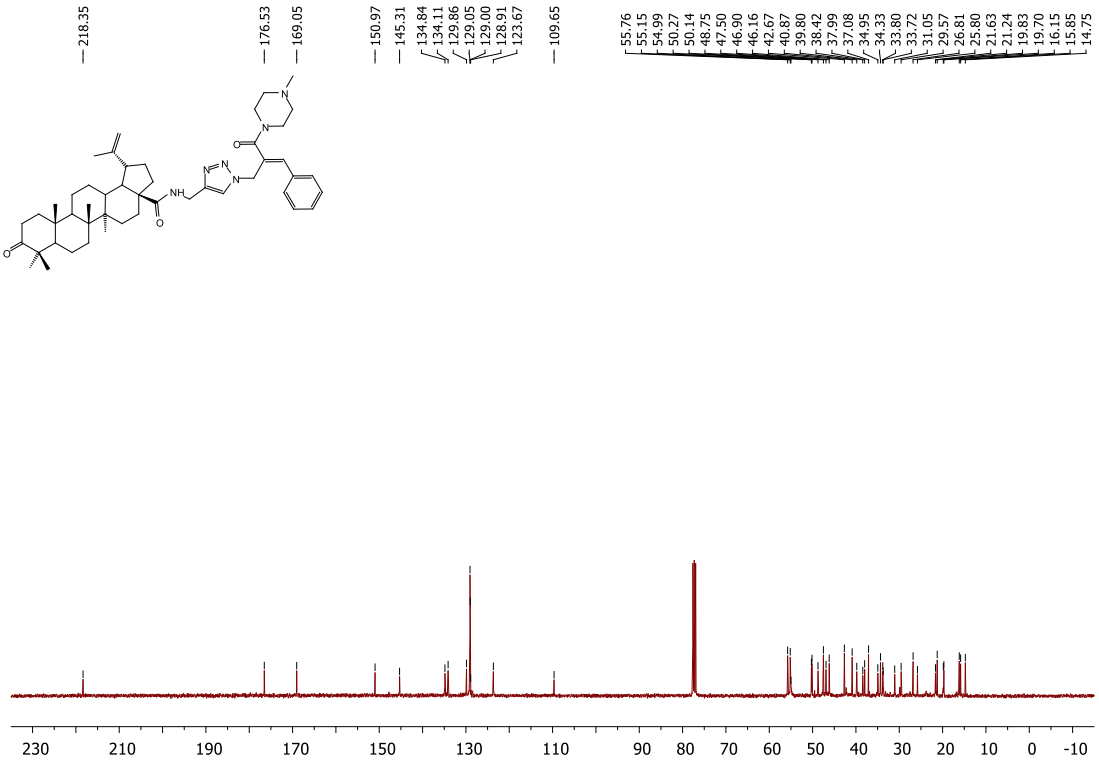


Figure 49. 101 MHz ^{13}C NMR of Compound **62c** in $CDCl_3$

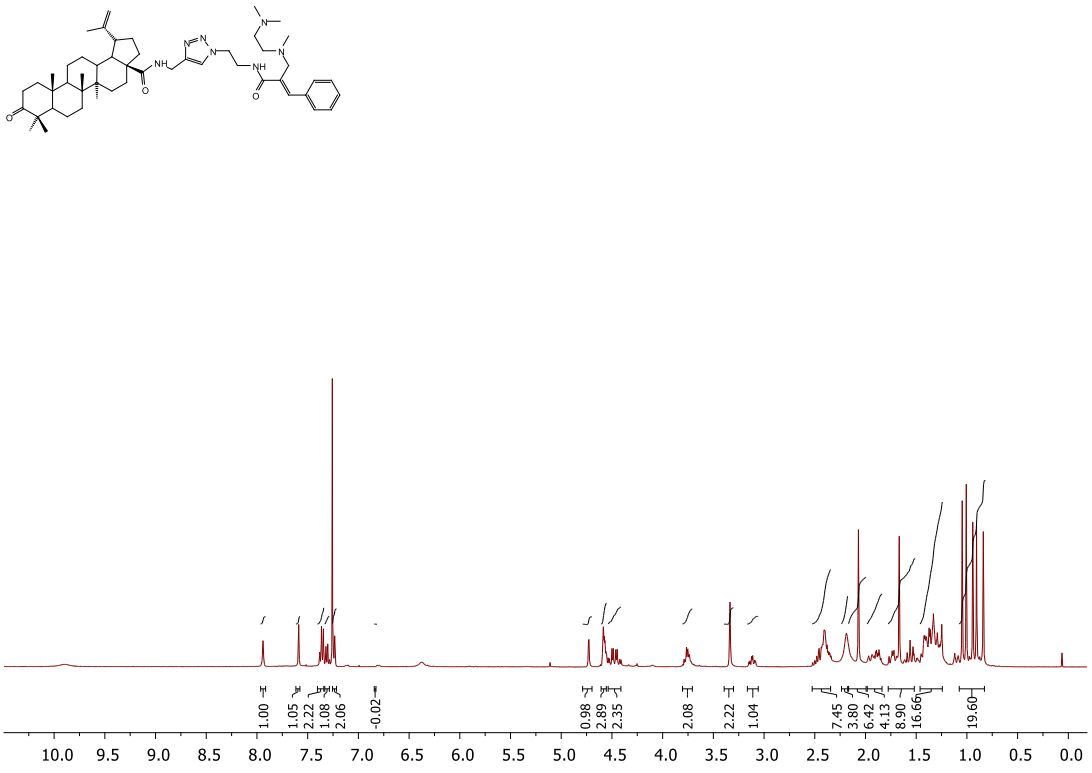


Figure 50. 400 MHz ^{1}H NMR of Compound **62d** in $CDCl_3$

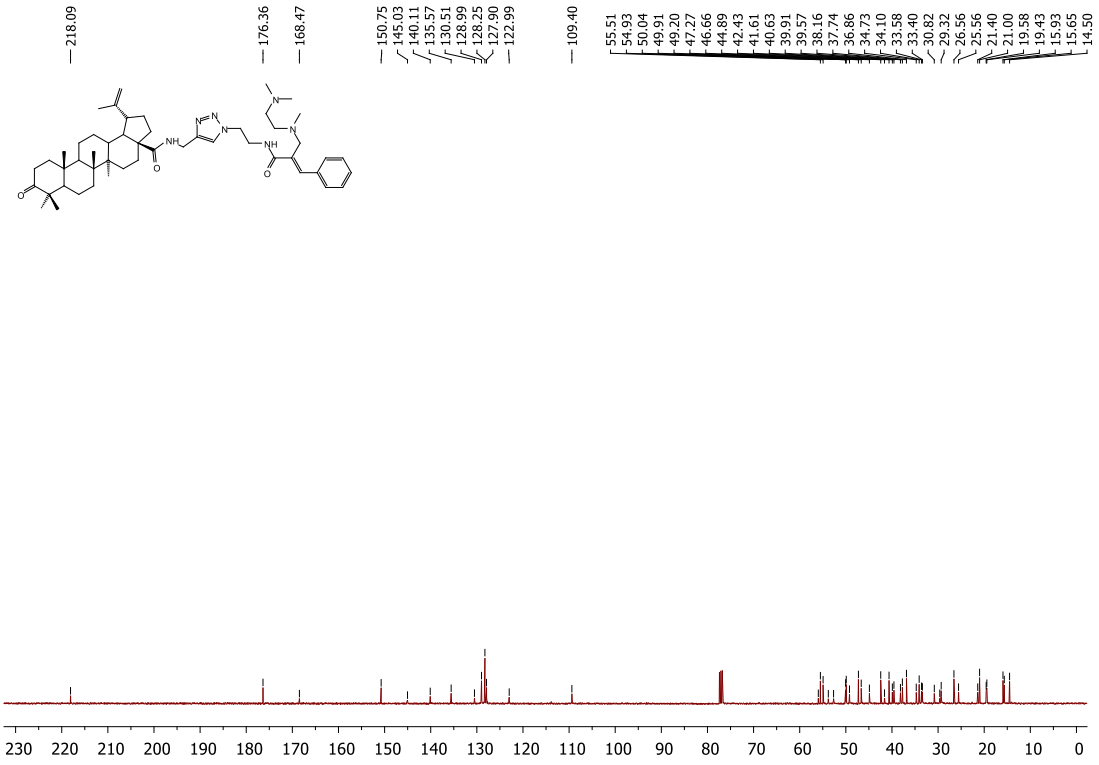


Figure 51. 101 MHz ^{13}C NMR of Compound **62d** in $CDCl_3$

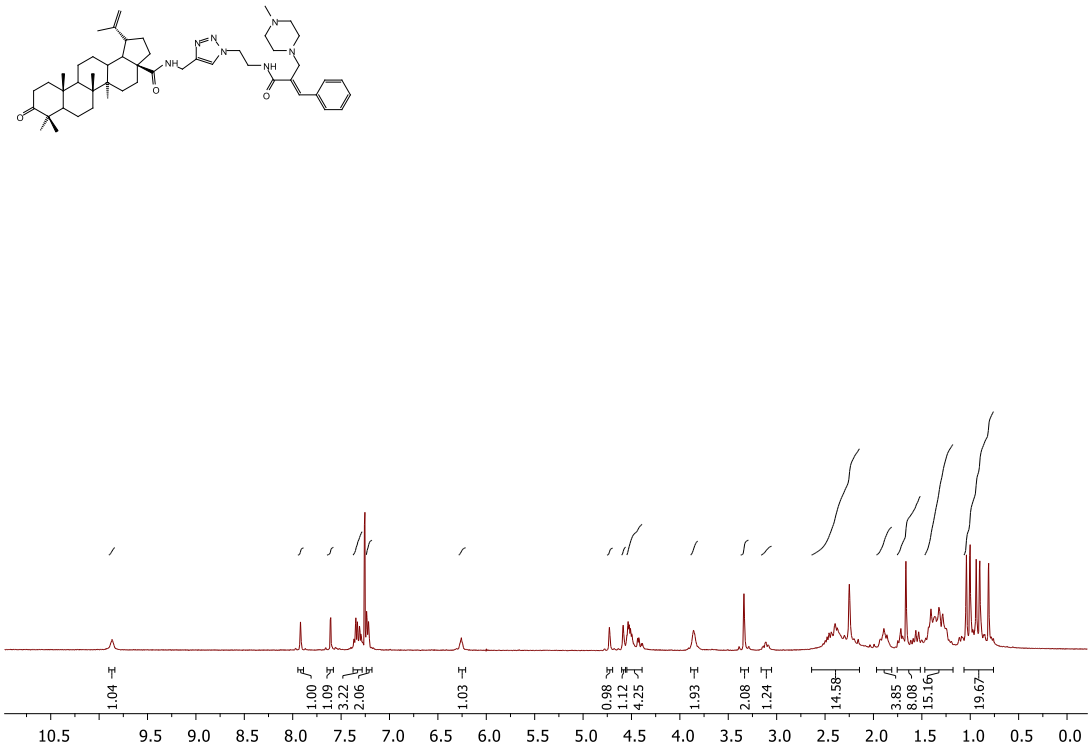


Figure 52. 400 MHz ^{1}H NMR of Compound **62e** in $CDCl_3$

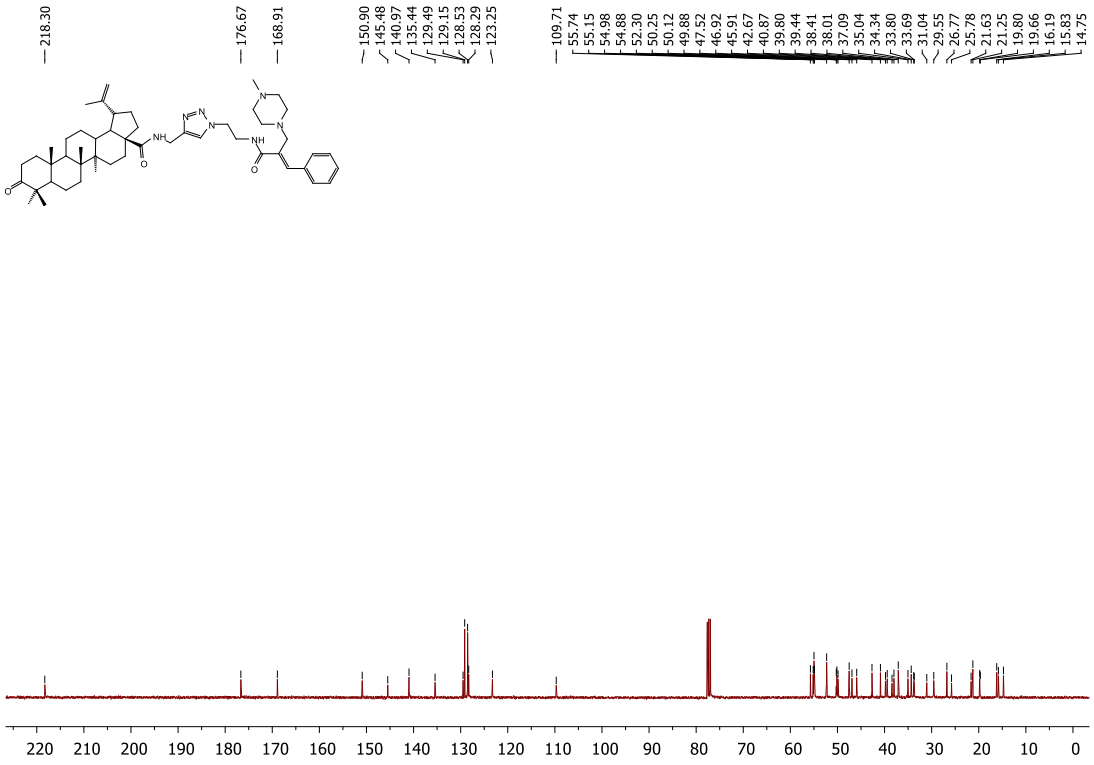


Figure 53. 101 MHz ^{13}C NMR of Compound **62e** in $CDCl_3$

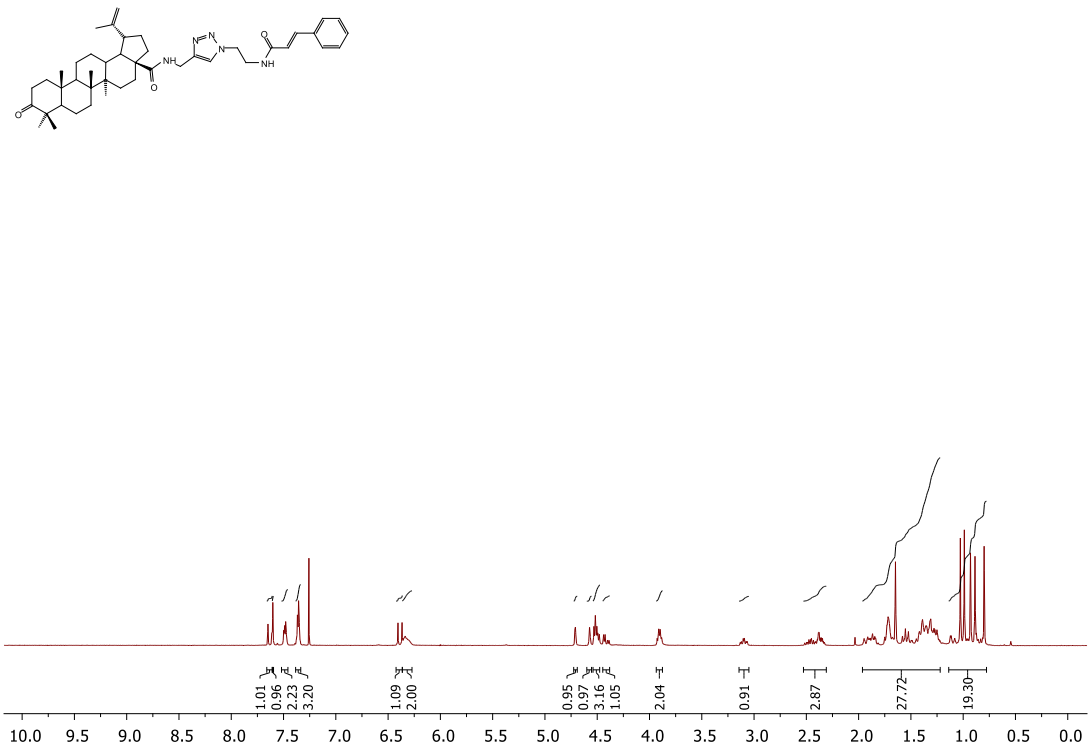


Figure 54. 400 MHz ^{1}H NMR of Compound **62f** in $CDCl_3$

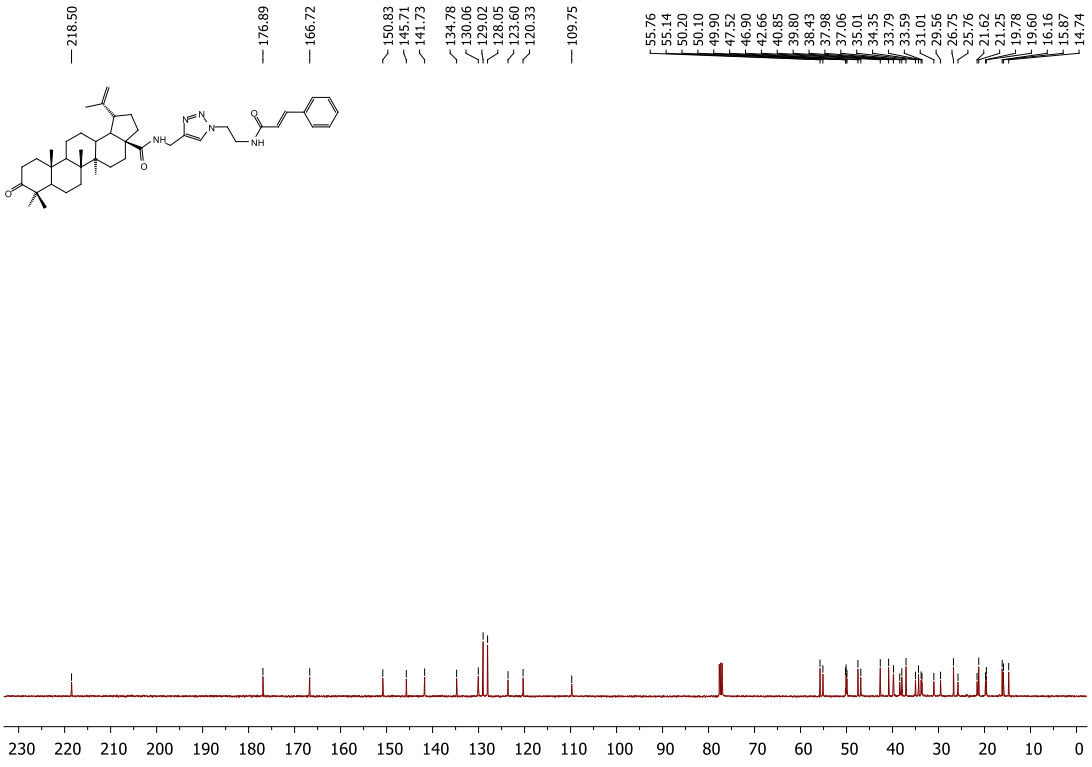


Figure 55. 101 MHz ^{13}C NMR of Compound **62f** in $CDCl_3$

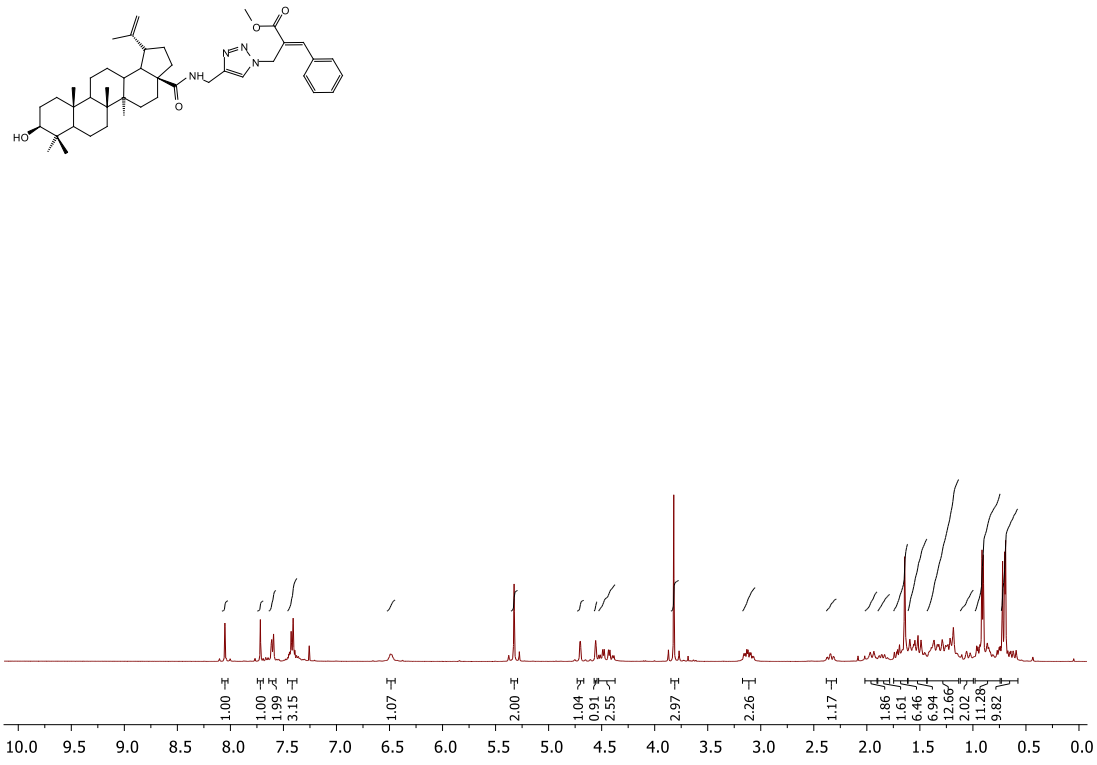


Figure 56. 400 MHz ^{1}H NMR of Compound **63a** in $CDCl_3$

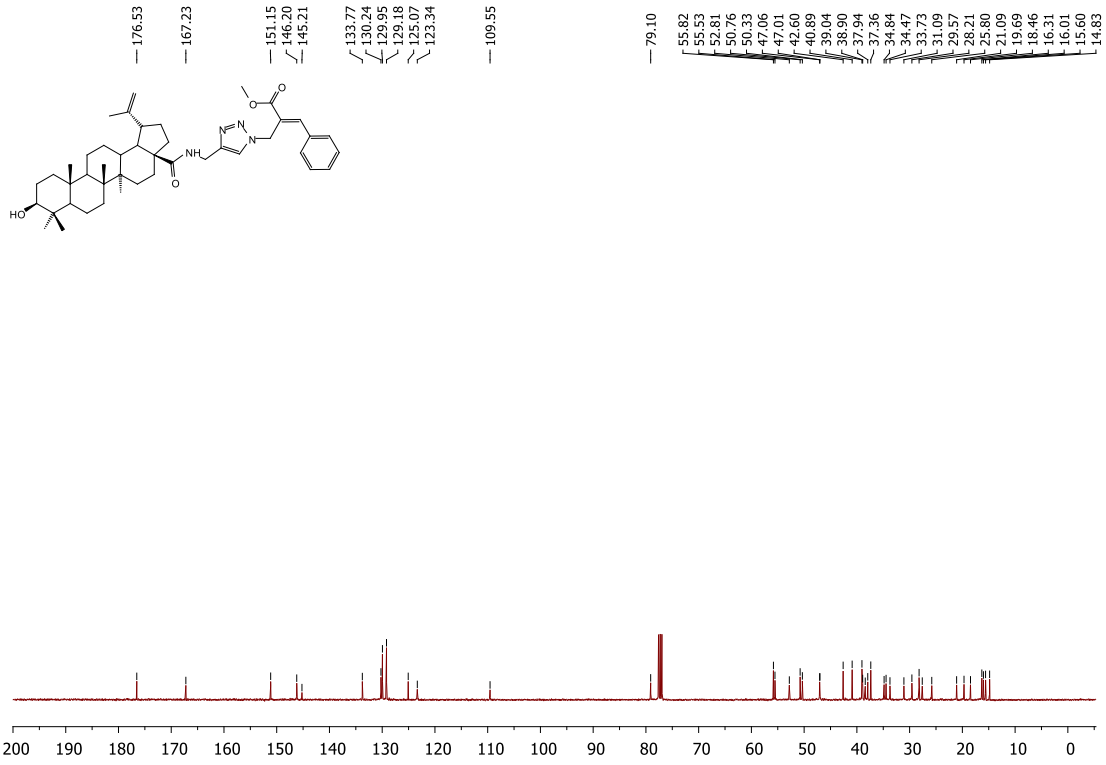


Figure 57. 101 MHz ^{13}C NMR of Compound **63a** in $CDCl_3$

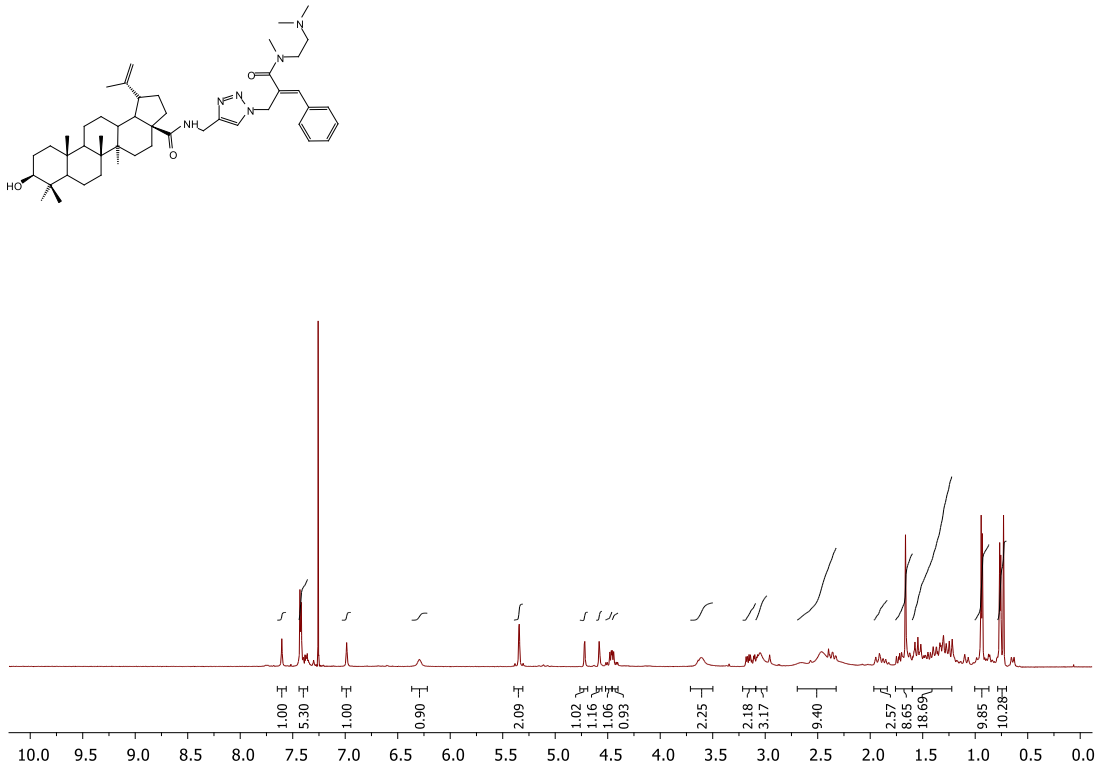


Figure 58. 400 MHz ^{1}H NMR of Compound **63b** in $CDCl_3$

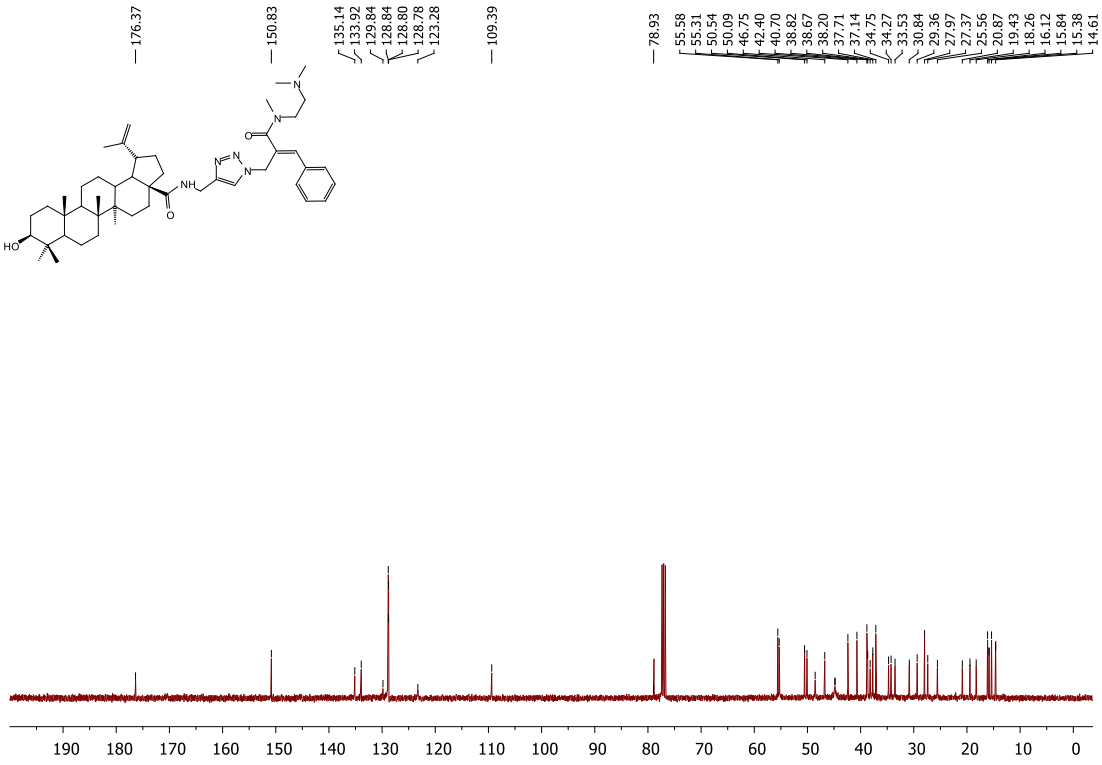


Figure 59. 101 MHz ^{13}C NMR of Compound **63b** in $CDCl_3$

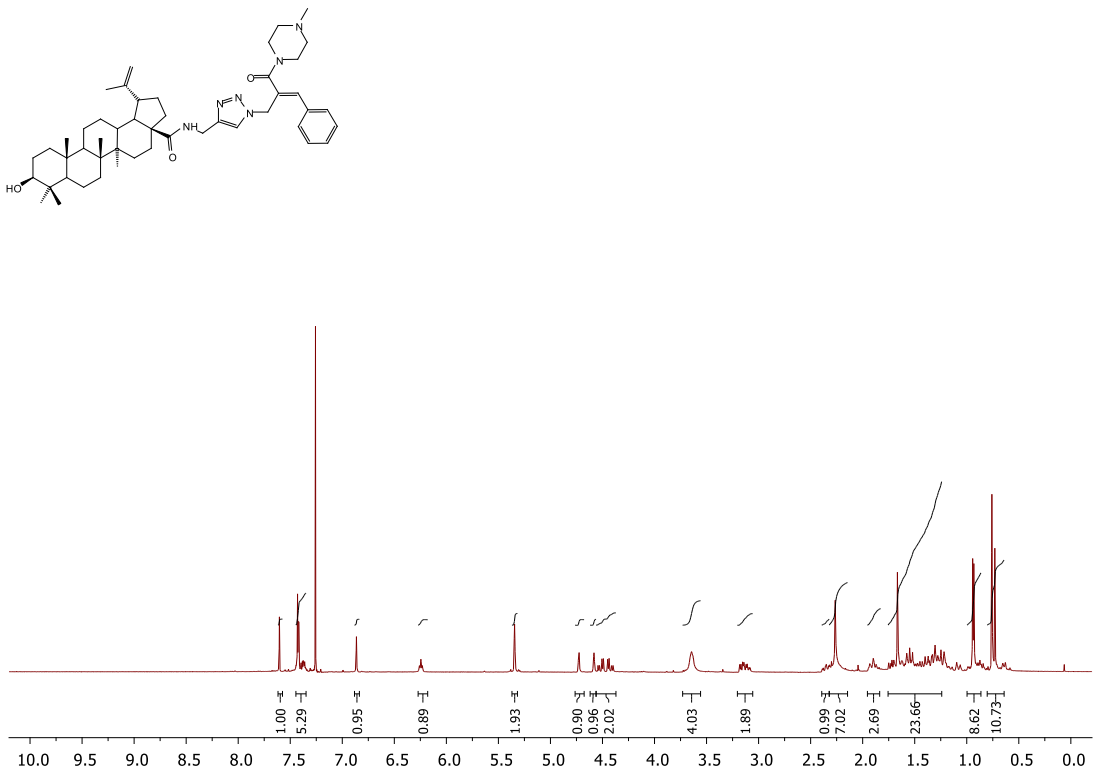


Figure 60. 400 MHz ^{1}H NMR of Compound **63c** in $CDCl_3$

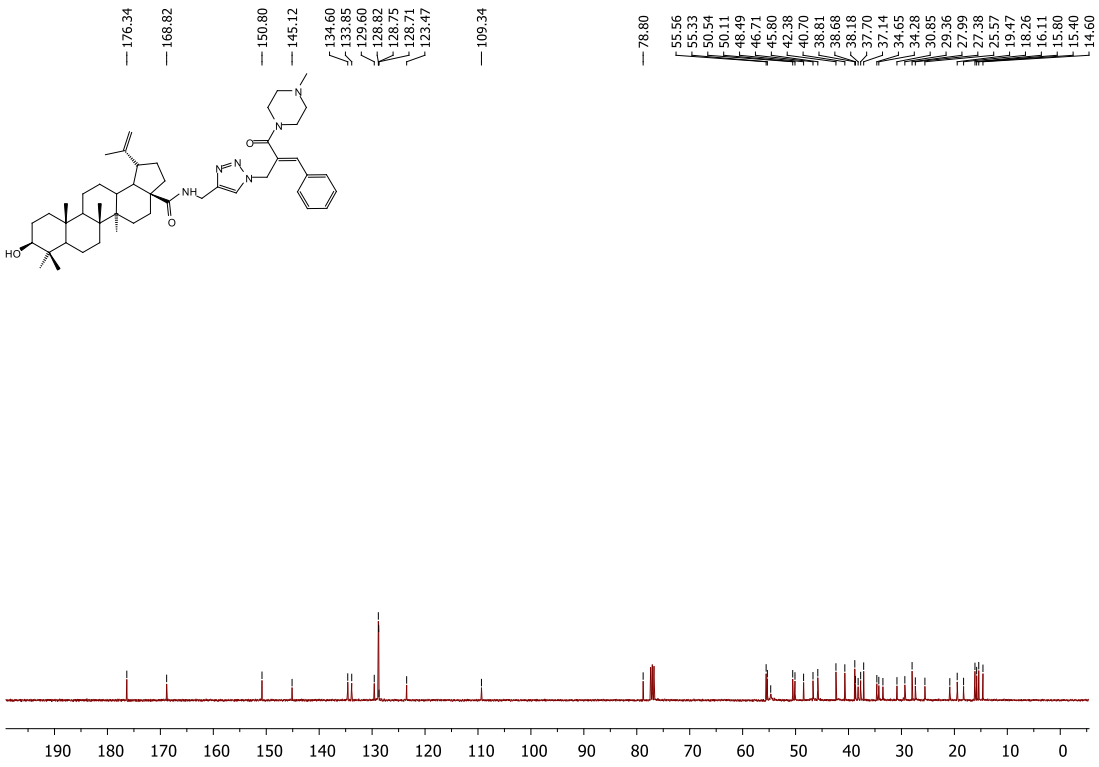


Figure 61. 101 MHz ^{13}C NMR of Compound **63c** in $CDCl_3$

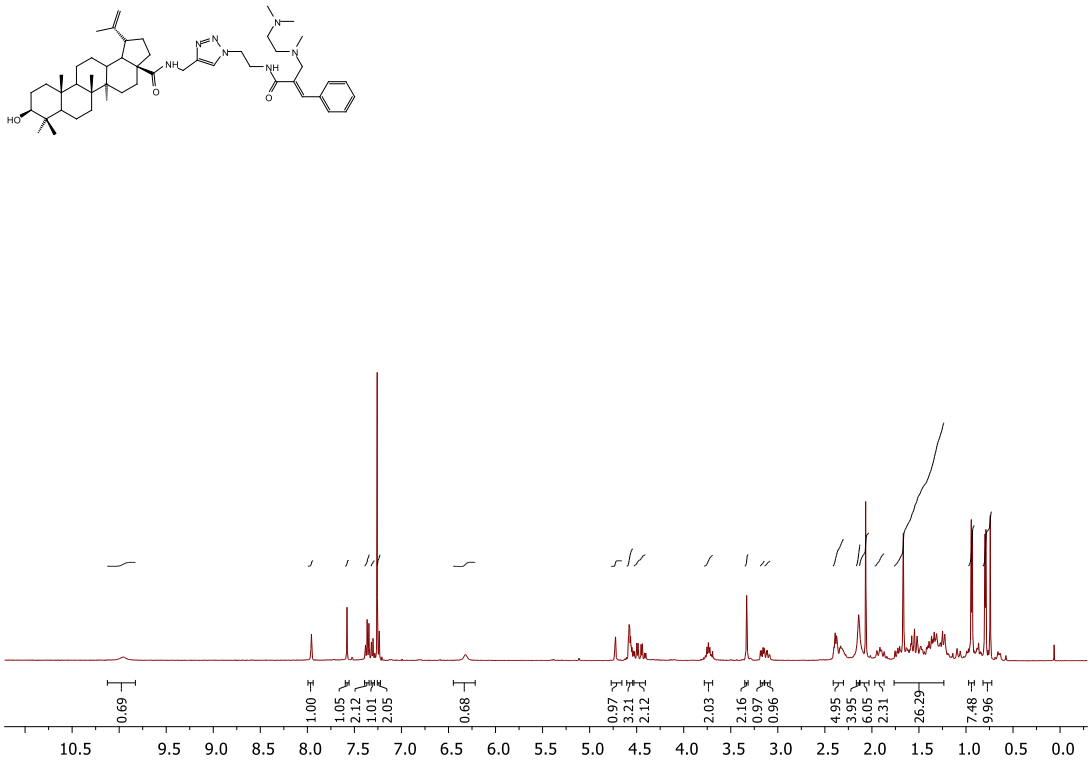


Figure 62. 400 MHz ^{1}H NMR of Compound **63d** in $CDCl_3$

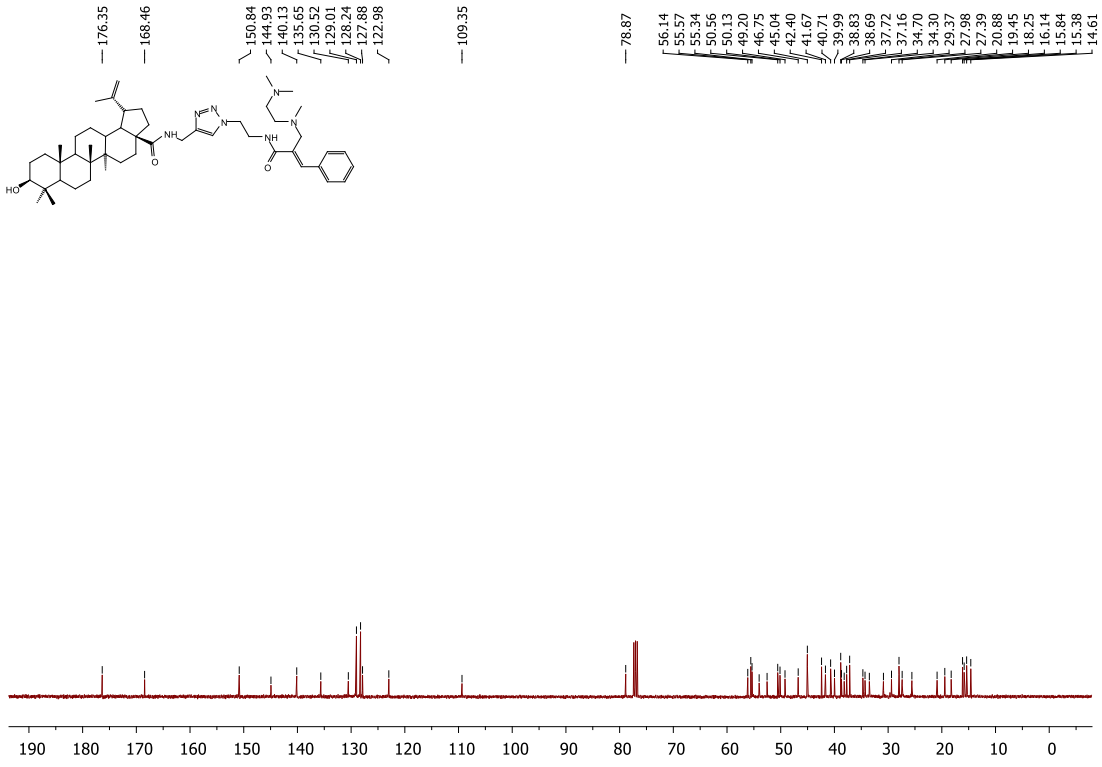
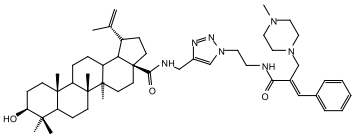


Figure 63. 101 MHz ^{13}C NMR of Compound **63d** in $CDCl_3$



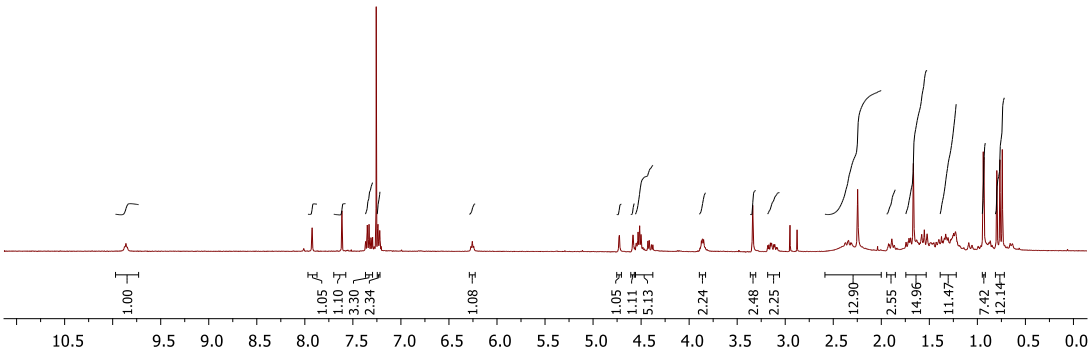


Figure 64. 400 MHz ^{1}H NMR of Compound **63e** in $CDCl_3$

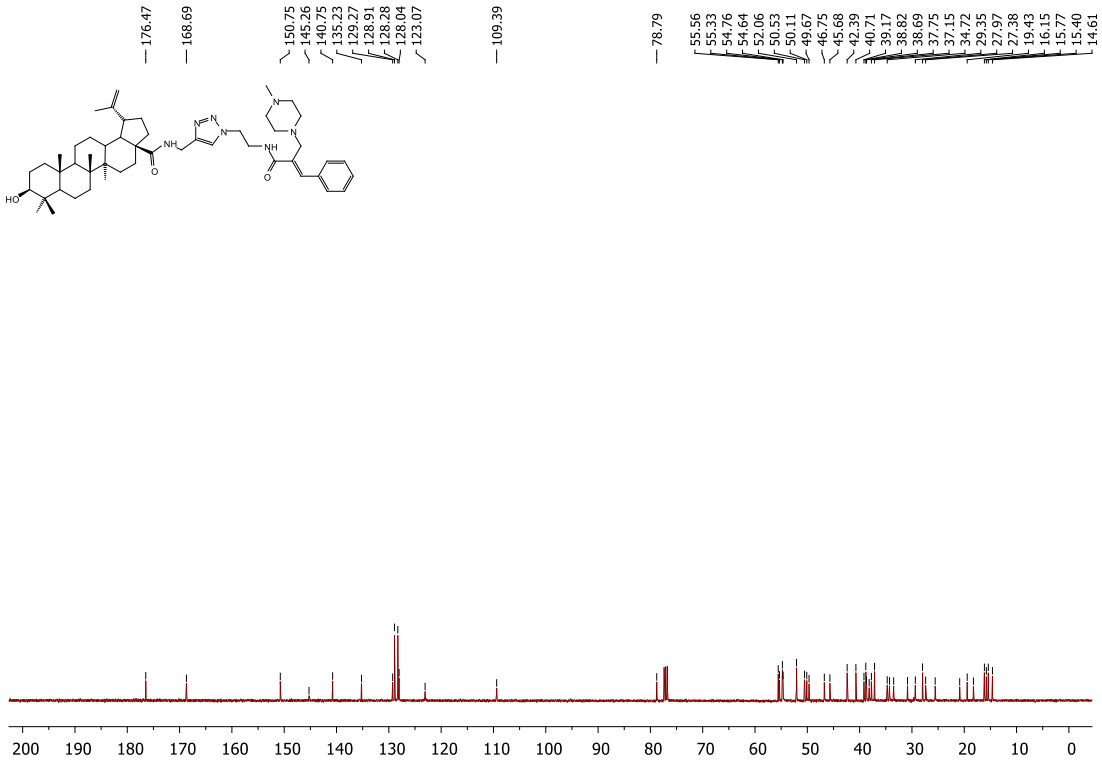


Figure 65. 101 MHz ^{13}C NMR of Compound **63e** in $CDCl_3$

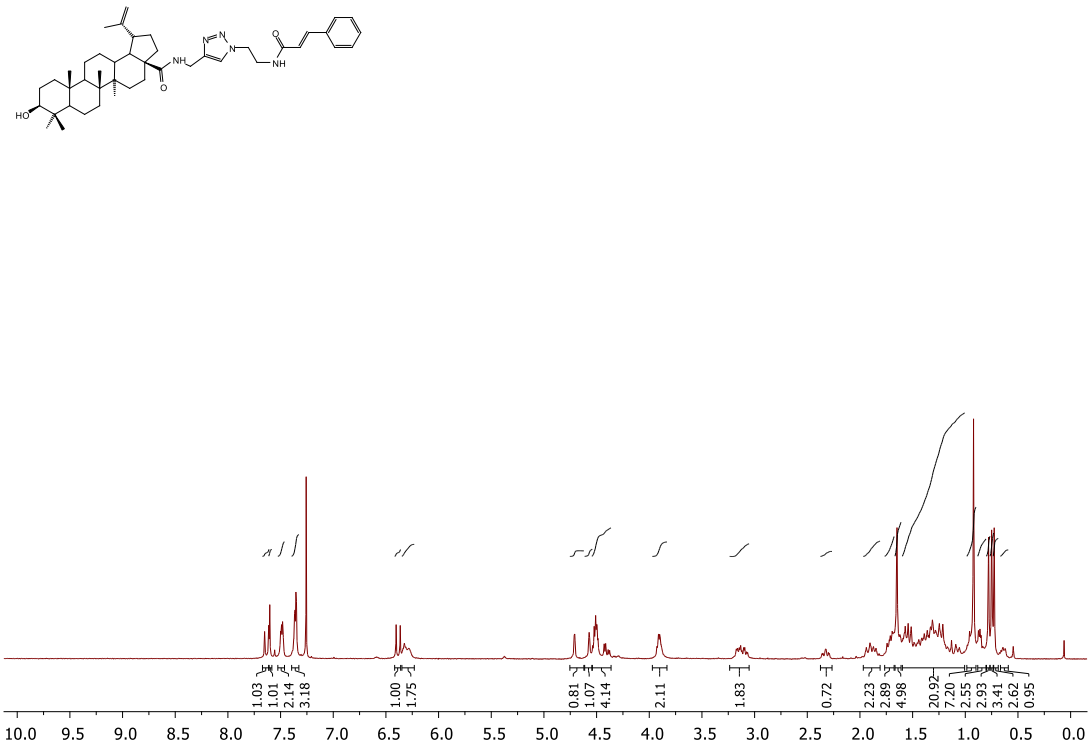


Figure 66. 400 MHz ^{1}H NMR of Compound **63f** in $CDCl_3$

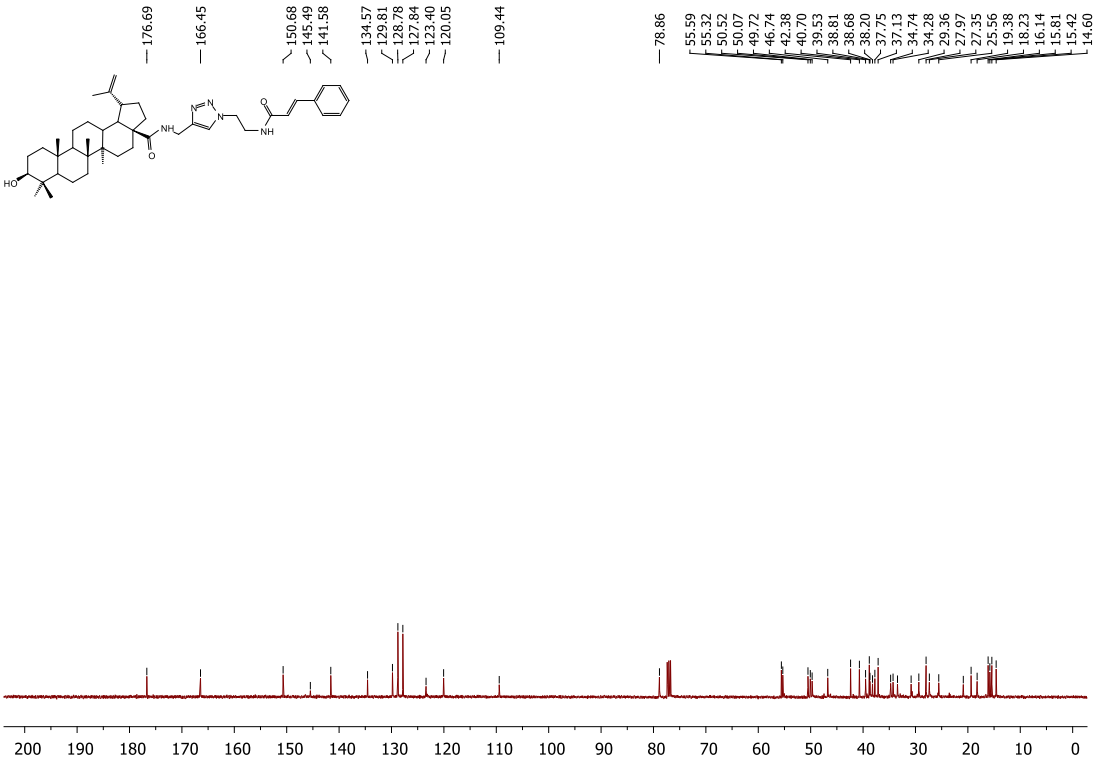


Figure 67. 101 MHz ^{13}C NMR of Compound **63f** in $CDCl_3$

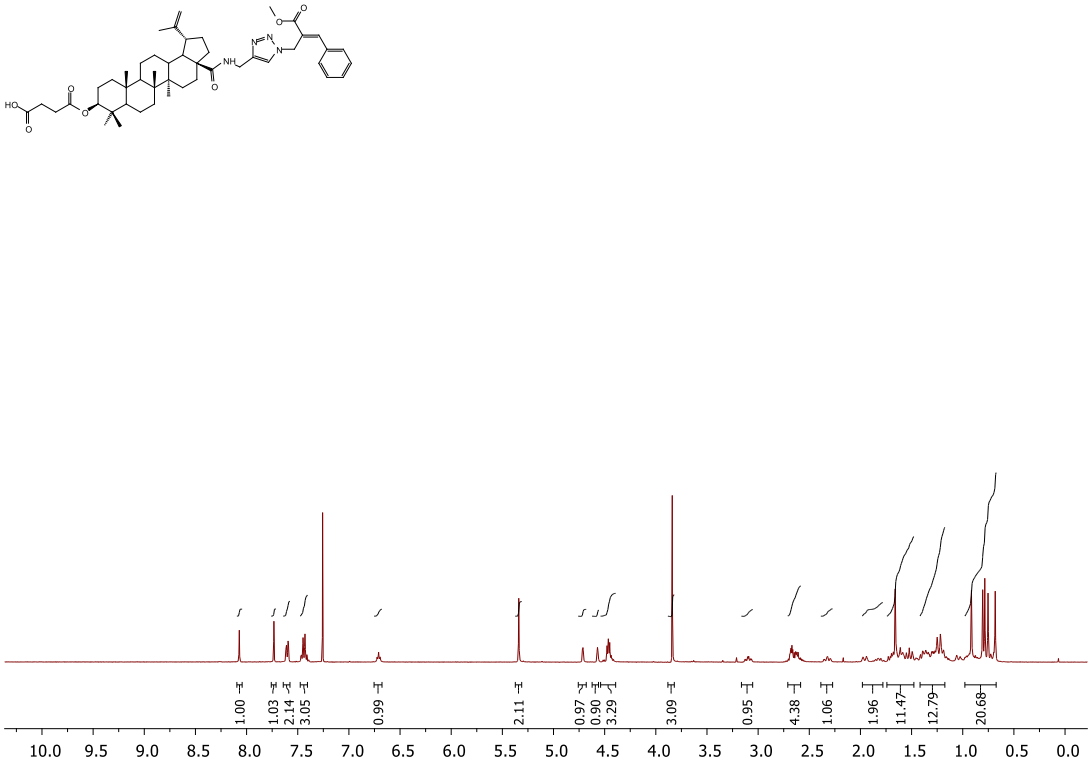


Figure 68. 400 MHz ^{1}H NMR of Compound **64a** in $CDCl_3$

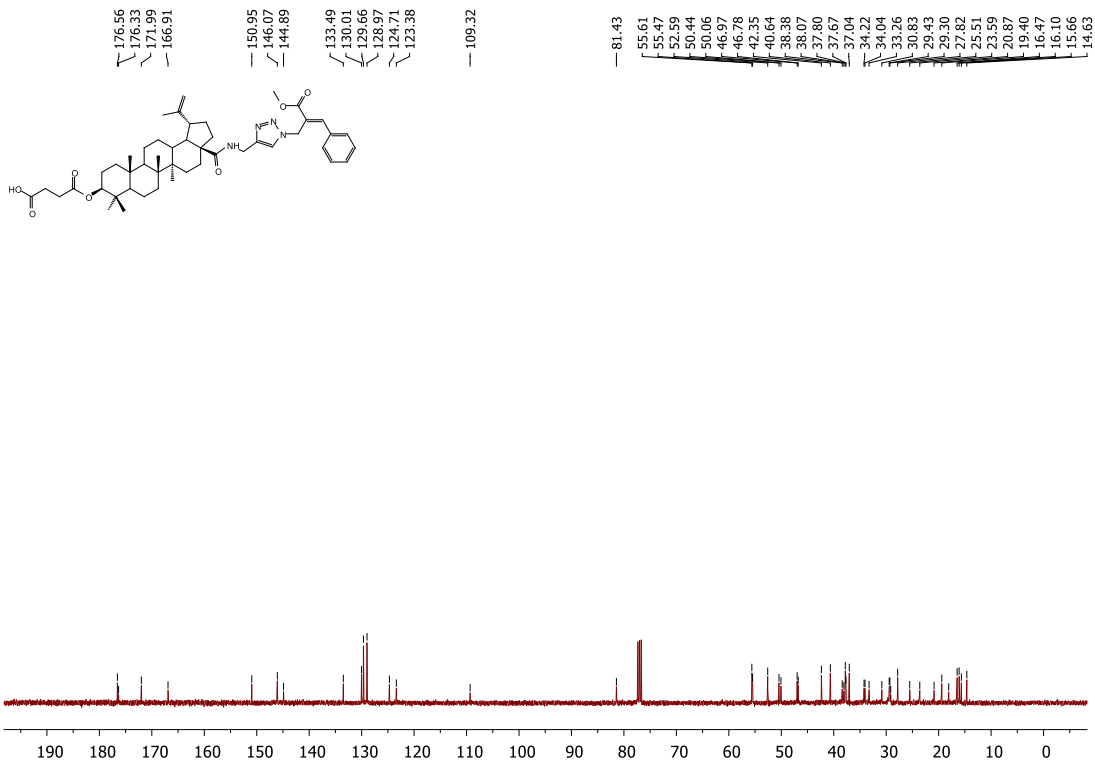


Figure 69. 101 MHz ^{13}C NMR of Compound **64a** in $CDCl_3$

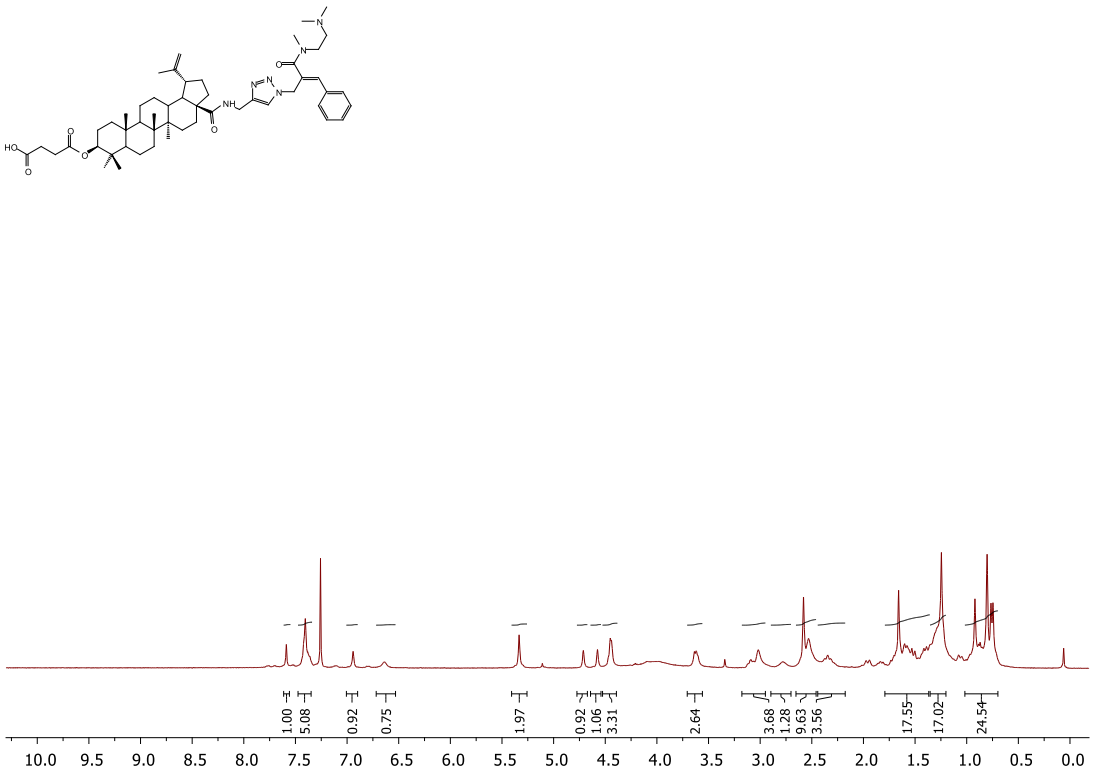


Figure 70. 400 MHz ^{1}H NMR of Compound **64b** in $CDCl_3$

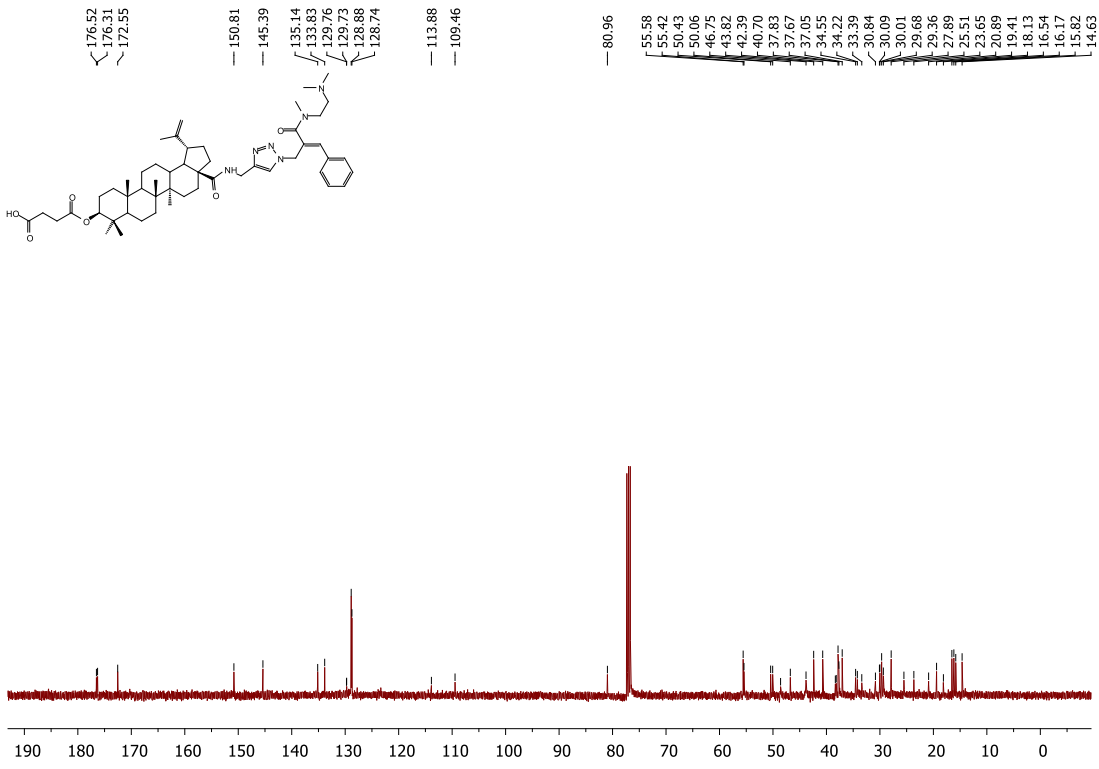


Figure 71. 101 MHz ^{13}C NMR of Compound **64b** in $CDCl_3$

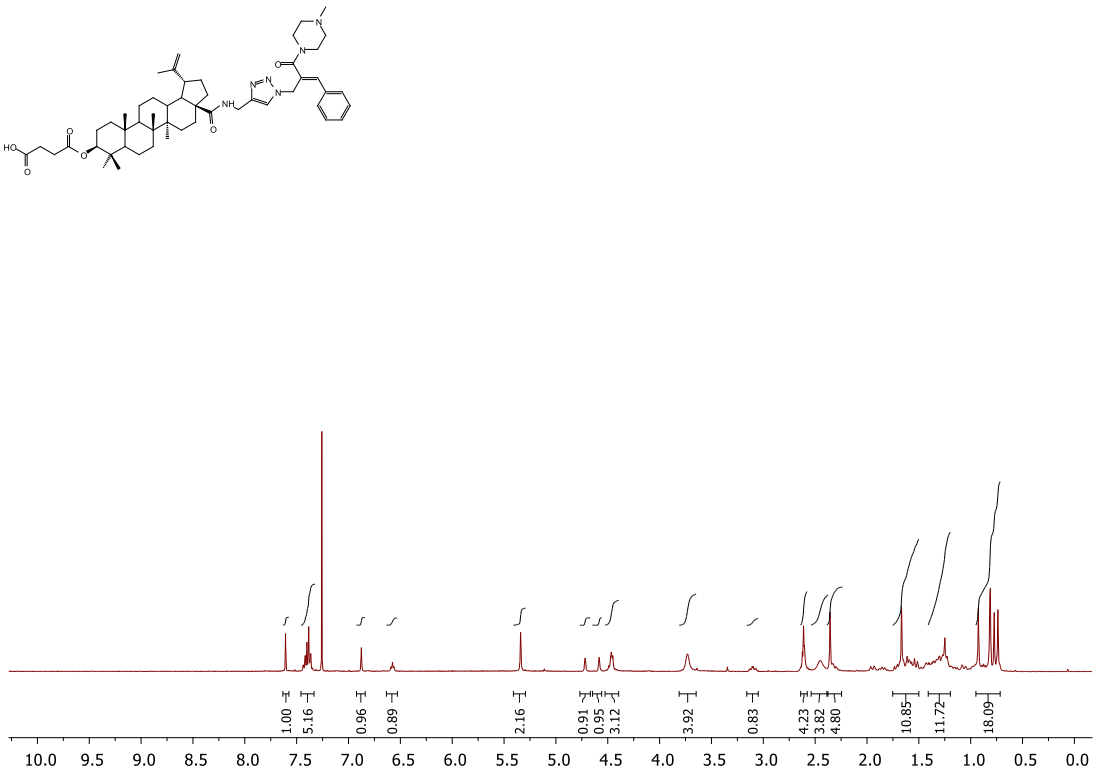


Figure 72. 400 MHz ^{1}H NMR of Compound **64c** in $CDCl_3$

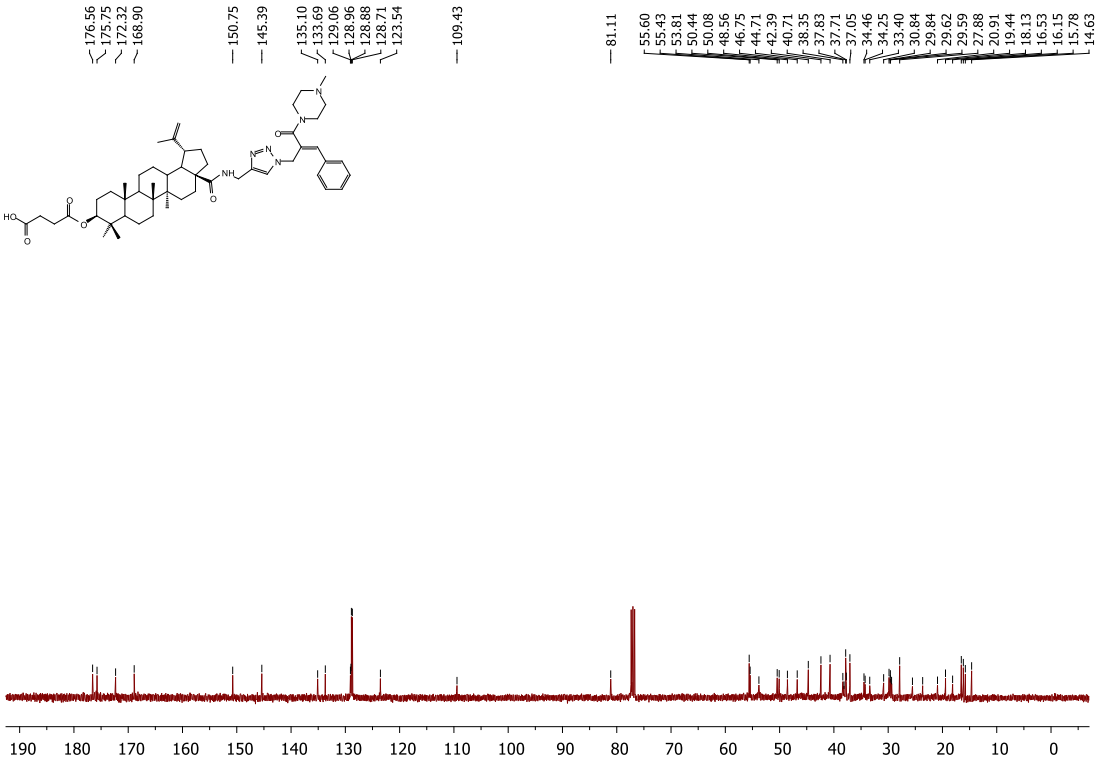


Figure 73. 101 MHz ^{13}C NMR of Compound **64c** in $CDCl_3$

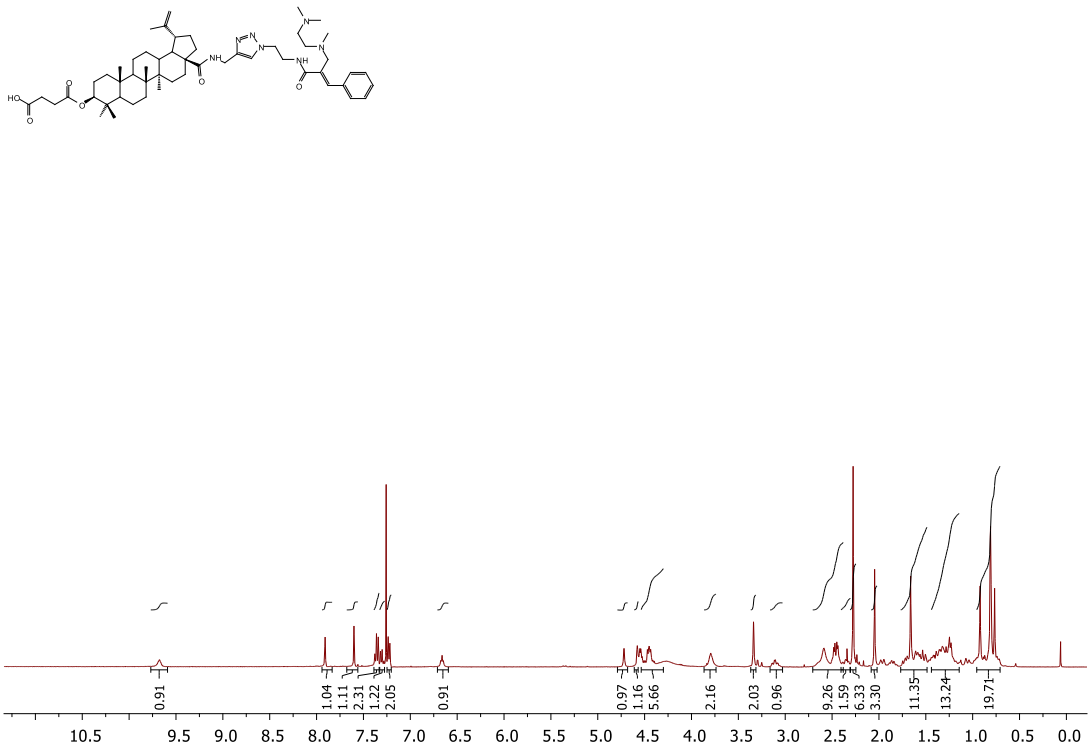


Figure 74. 400 MHz ^{1}H NMR of Compound **64d** in $CDCl_3$

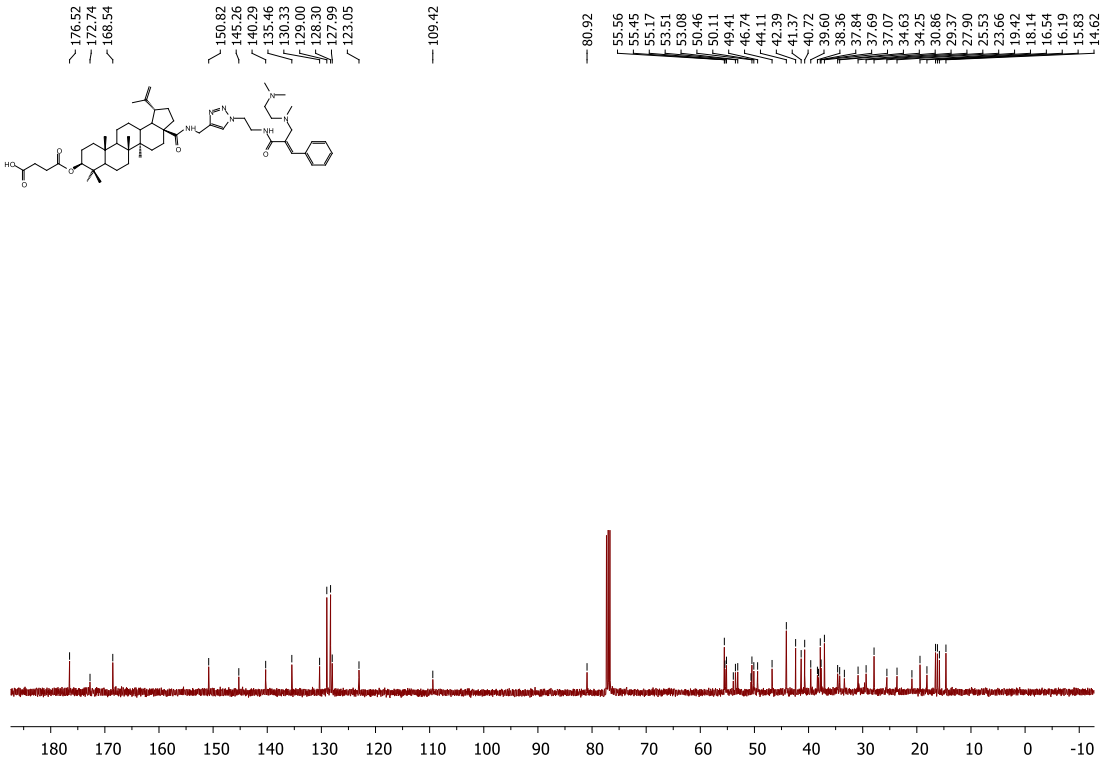
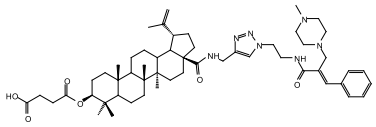


Figure 75. 101 MHz ^{13}C NMR of Compound **64d** in $CDCl_3$



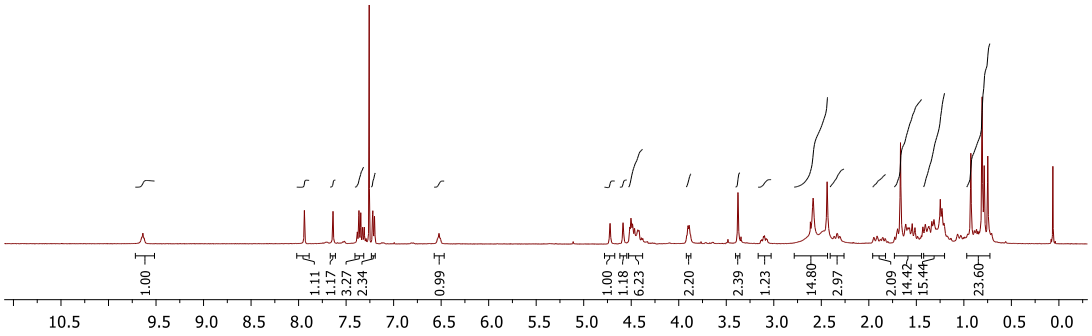


Figure 76. 400 MHz ^{1}H NMR of Compound **64e** in $CDCl_3$

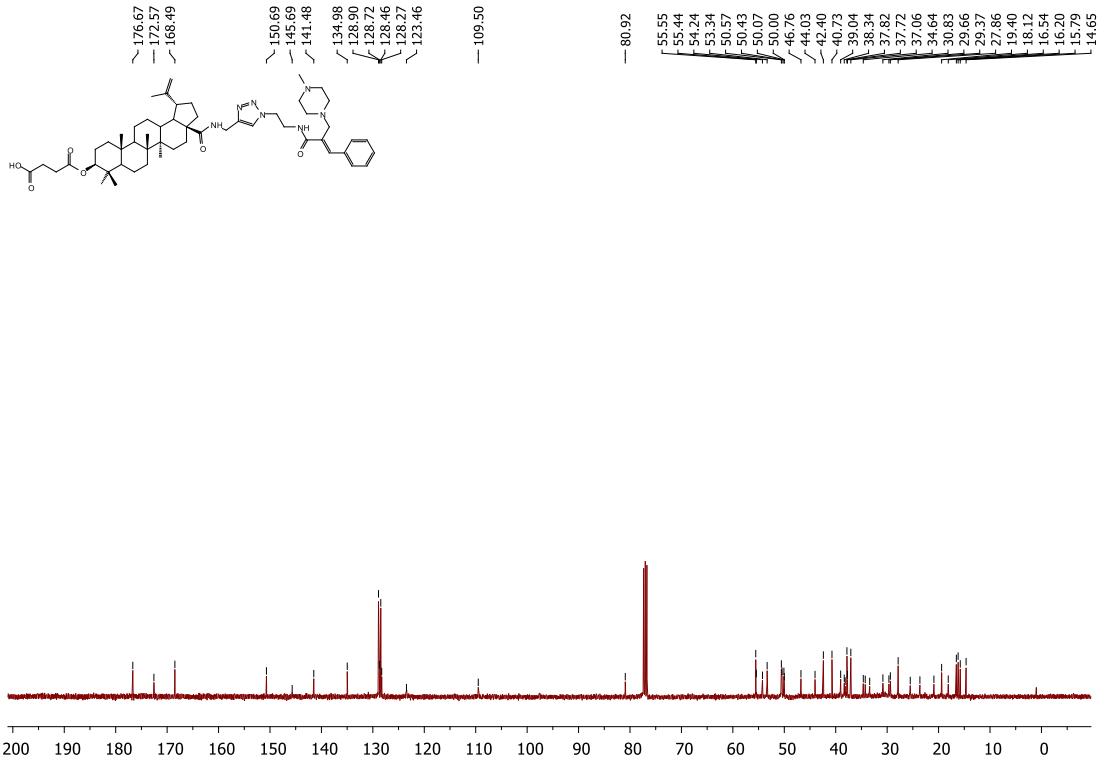


Figure 77. 101 MHz ^{13}C NMR of Compound **64e** in $CDCl_3$

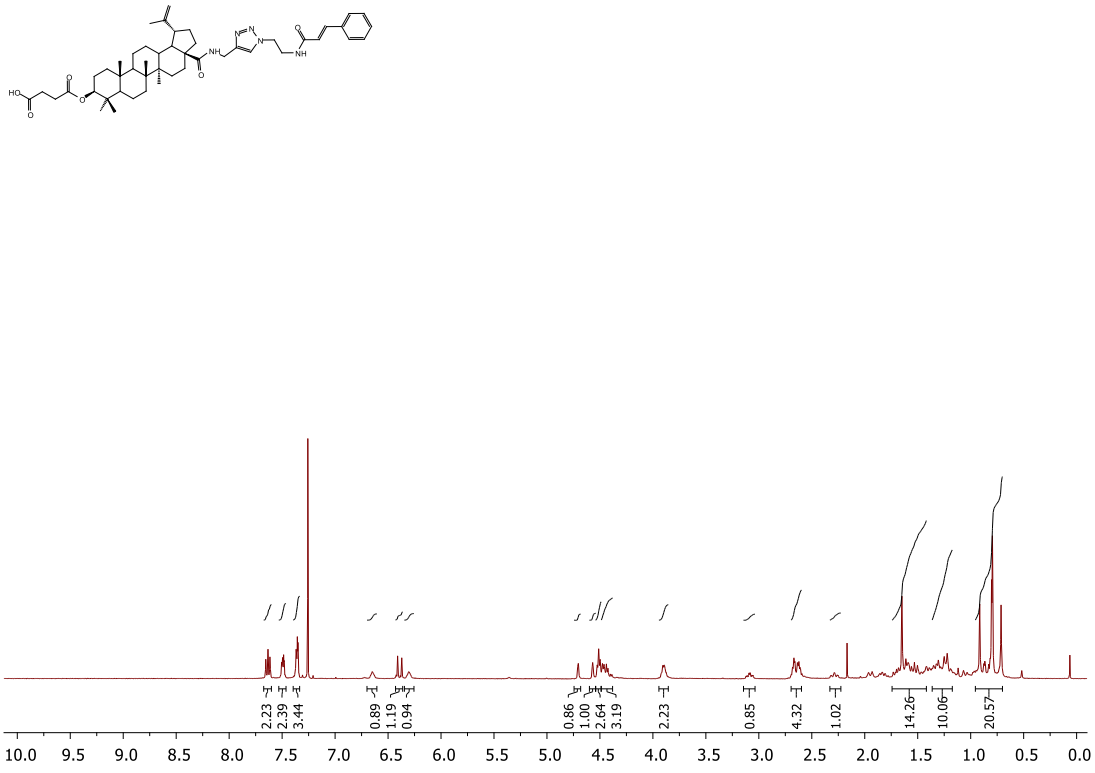


Figure 78. 400 MHz ^{1}H NMR of Compound **64f** in $CDCl_3$

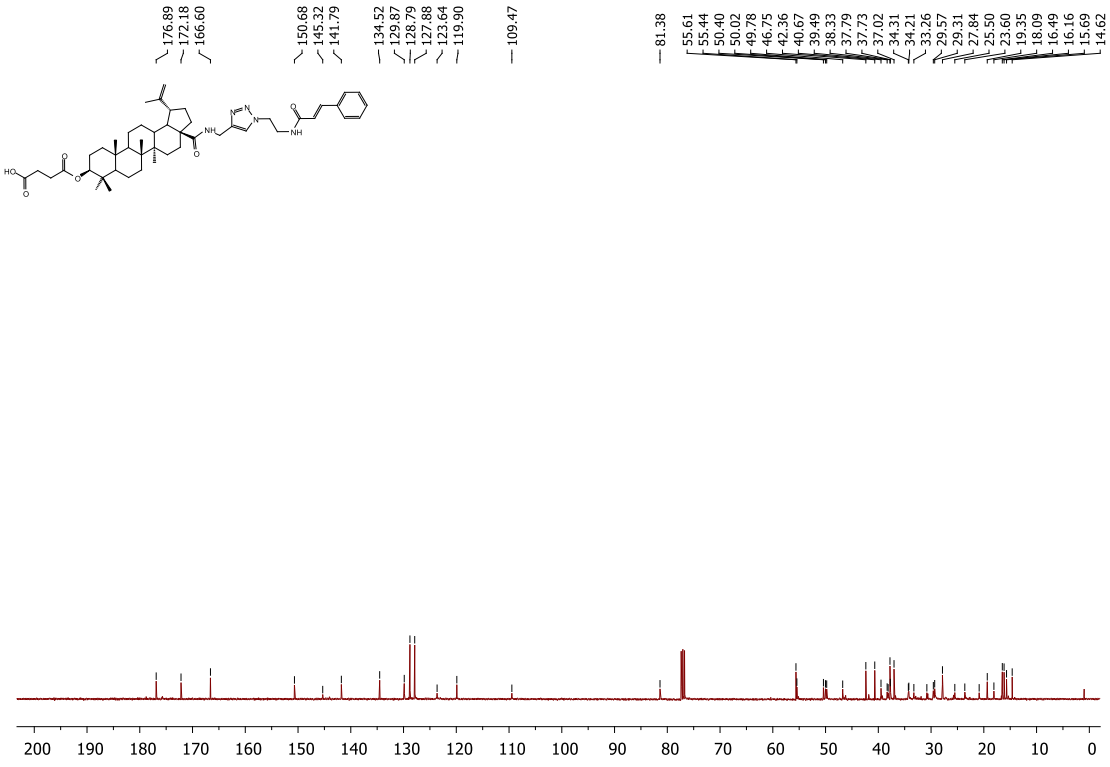


Figure 79. 101 MHz ^{13}C NMR of Compound **64f** in $CDCl_3$

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