

**GLYCAL BASED APPROACH TO THE SYNTHESIS OF (+)-KIRKAMIDE, AMINO-  
POLYHYDROXY CARBOCYCLES AND SUGAR-IMINOSUGAR HYBRID  
MOLECULES**

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**DEPARTMENT OF CHEMISTRY  
INDIAN INSTITUTE OF TECHNOLOGY DELHI  
JULY 2025**

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*by*

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DEPARTMENT OF CHEMISTRY

*Submitted*  
*in fulfillment of the requirements of the degree of*

**DOCTOR OF PHILOSOPHY**

to the



**INDIAN INSTITUTE OF TECHNOLOGY DELHI**  
**HAUZ KHAS, NEW DELHI-110016**  
**INDIA**

**July, 2025**

*This thesis is dedicated to my beloved parents*

**Mr. Ashok Kulshrestha and Mrs. Praveena Kulshrestha**

*For their love, endless support, and encouragement*

## CERTIFICATE

This is to certify that the thesis entitled “**GLYCAL BASED APPROACH TO THE SYNTHESIS OF (+)-KIRKAMIDE, AMINO-POLYHYDROXY CARBOCYCLES AND SUGAR-IMINOSUGAR HYBRID MOLECULES**”, being submitted by **Mr. ABHISHEK KULSHRESTHA** to the Indian Institute of Technology Delhi for the award of the degree of **Doctor of Philosophy**, is a record of bonafide research work carried out by him. **Mr. ABHISHEK KULSHRESTHA** has worked under my supervision and guidance and has fulfilled all the requirements for the submission of a Ph.D. thesis, which to my knowledge has reached the requisite standard and is worthy of consideration for the award of Ph.D. degree.

The work embodied in this thesis has not been submitted, in part or full, to other University or Institute for the award of any degree or diploma.

**Prof. N. G. Ramesh**

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## ACKNOWLEDGEMENTS

*I would like to express my sincere gratitude to my advisor, **Prof. N. G. Ramesh**, Department of Chemistry, Indian Institute of Technology, Delhi, who provided me the opportunity to pursue my Ph.D. research in his laboratory. I am grateful for his logistical support, constant motivation, invaluable guidance through every step, timely support and supervision throughout being an excellent supervisor and for your support and guidance during these years. His guidance helped during all my research as well as during writing of this thesis. I would also like to thank him for arranging all modern facilities and chemicals available whenever it needed.*

*I would like to acknowledge **Prof. S. Nagendran**, head of the department for providing basic facilities of the department for my research.*

*I also extend my heartfelt gratitude to **Prof. Nalin Pant**, **Prof. Ravi. P. Singh** for their valuable guidance and interest in my research. I am also grateful to **Prof. Josemon Jacob**, **Prof. Narayanan Kurur**, **Prof. Chinmoy Kumar Hazra** and other faculty members for their help and support during my tenure at IIT, Delhi.*

*I thank to all seniors Dr. Rahul Vilas Salunke, Dr. Venkatesan S, Dr. Vimal Kant Harit, Dr. Umesh Kumar Mishra, Ms. Adrika Banerjee, Md. Abu Zaid and Dr. Ghanshyam Tiwari for their co-operation during my research work and I also extend my thanks to seniors Dr. Vipin Kumar (late), Dr. Nagarajan, Dr. Ganesan, Dr. Sathish Kannan and Dr. Inderpreet Arora.*

*I would like to DST, DBT, CSIR, UGC and IIT Delhi, India for research fellowships (JRF/SRF) for funding my doctoral work.*

*I would like to thank IIT Delhi for providing facilities of the institute. I am extremely grateful for the help rendered to me by staffs of NMR lab, instrumentation lab, glass blowing facility, central research facility.*

*Last, but not the least, I would like to take this opportunity to offer my sincere regards to my ever supportive parents, **Mr. Ashok Kulshrestha** and **Mrs Praveen Kulshrestha** for their graceful sacrifices made to nurture our family. Today, this thesis is fruitful because I have been nurtured incessantly with moral support, love, encouragement and discipline from my parents throughout my life and at this juncture today. I dedicate my thesis to my parents. Thank you for your unconditional support with my studies. I am honoured and blessed to have you as my parents. I also thank my sisters, **Ms. Priyanka Kulshrestha** and **Ms. Dimpi Kulshrestha** for their moral support and appreciation.*

**(ABHISHEK KULSHRESTHA)**

## ABSTRACT

The thesis titled “**GLYCAL BASED APPROACH TO THE SYNTHESIS OF (+)-KIRKAMIDE, AMINO-POLYHYDROXY CARBOCYCLES AND SUGAR-IMINOSUGAR HYBRID MOLECULES**” presents the research work carried out on the synthesis of (+)-kirkamide, amino-polyhydroxy carbocycles and sugar-iminosugar hybrid molecules utilizing precursors derived from tri-*O*-benzyl-D-glucal.

The research work embodied in the thesis has been divided into three chapters.

**Chapter I** describes the synthesis of the C7N aminocyclitol natural product (+)-kirkamide. Two distinct synthetic strategies were explored: (a) ring-closing metathesis (RCM) and (b) the Baylis–Hillman reaction. Both strategies commenced from tri-*O*-benzyl-D-glucal. The RCM approach facilitates the formation of a C7N aminocyclitol, while the Baylis–Hillman strategy used to synthesize (+)-kirkamide through an alternative route provided an unexpected product.

**Chapter II** describes the use of the ring-closing metathesis approach to the synthesis of the core analogue of C6N aminocyclitol (–)-neplanocin A. This approach highlights the utility of metathesis in C6N aminocyclitol synthesis and offers a versatile platform for the development of (–)-neplanocin A analogues with potential biological applications.

**Chapter III** A few sugar-iminosugar hybrid molecules comprising oxa-aza fused skeletons were designed and synthesized using the diversity-oriented synthetic (DOS) approach from tri-*O*-benzyl-D-glucal derived common intermediate involving ring-closing metathesis as a key step along with the Wittig reaction, Grignard reaction, Barbier reaction and dihydroxylation reaction. These sugar-iminosugar oxa-aza hybrid molecules are pyrrolidino-pyran, pyrrolidino-oxepane and pyrrolidino-oxocane. The interesting thing in all these hybrid molecules is that one of the

common moiety in all these molecules is a five-membered pyrrolidino ring while other moieties are different, such as -pyran, a six-membered ring, -oxepane, a seven-membered ring and -oxocane, an eight-membered ring.

## सारांश

थीसिस शीर्षक “ग्लाइकल आधारित (+)-किर्कोमाइड, एमिनो-पॉलीहाइड्रॉक्सी कार्बोसाइक्ल्स और शुगर-इमिनोशुगर हाइब्रिड अणुओं का संश्लेषण” उस अनुसंधान कार्य को प्रस्तुत करता है जो (+)-किर्कोमाइड, एमिनो-पॉलीहाइड्रॉक्सी कार्बोसाइक्ल्स तथा शुगर-इमिनोशुगर हाइब्रिड अणुओं के संश्लेषण पर आधारित है। इस कार्य में संश्लेषण के लिए ट्राई-ओ-बेंज़िल-डी-ग्लूकाल से प्राप्त अग्रद्रव्यों का उपयोग किया गया है।

इस शोध कार्य को तीन अध्यायों में विभाजित किया गया है।

**अध्याय I** में C7N एमिनोसाइक्लिटोल प्राकृतिक उत्पाद (+)-किर्कोमाइड के संश्लेषण का वर्णन किया गया है। इसमें दो भिन्न संश्लेषणीय रणनीतियों का अन्वेषण किया गया: (क) रिंग-क्लोज़िंग मेटाथेसिस (RCM) (ख) बेइलिस-हिलमैन प्रतिक्रिया। दोनों ही रणनीतियाँ ट्राई-ओ-बेंज़िल-डी-ग्लूकाल से प्रारंभ होती हैं। RCM पद्धति C7N एमिनोसाइक्लिटोल के निर्माण को सुगम बनाती है, जबकि बेइलिस-हिलमैन रणनीति का उपयोग वैकल्पिक मार्ग से (+)-किर्कोमाइड के संश्लेषण हेतु किया गया, लेकिन इस प्रक्रिया में एक अप्रत्याशित उत्पाद प्राप्त हुआ।

**अध्याय II** में रिंग-क्लोज़िंग मेटाथेसिस (RCM) पद्धति का उपयोग करके C6N एमिनोसाइटोल (-)-नेप्लैनोसिन A के कोर एनालॉग का संश्लेषण प्रस्तुत किया गया है। यह पद्धति C6N एमिनोसाइटोल के संश्लेषण में मेटाथेसिस की उपयोगिता को दर्शाती है तथा संभावित जैविक गतिविधियों वाले (-)-नेप्लैनोसिन A के विभिन्न एनालॉग्स को विकसित करने का एक बहुआयामी मंच प्रदान करती है।

**अध्याय III** में कुछ शुगर-इमिनोशुगर हाइब्रिड अणुओं का डिज़ाइन और संश्लेषण किया गया है, जिनमें ऑक्सा-एज़ा संयुक्त कंकाल हैं। ये अणु डाइवर्सिटी-ओरिएंटेड सिंथेटिक (DOS) दृष्टिकोण द्वारा ट्राई-ओ-बेंज़िल-डी-ग्लूकाल से प्राप्त एक सामान्य मध्यवर्ती से बनाए गए हैं। इसमें रिंग-

क्लोज़िंग मेटाथेसिस को एक मुख्य चरण के रूप में अपनाया गया, और इसके साथ-साथ विटिग प्रतिक्रिया, ग्रिगनार्ड प्रतिक्रिया, बार्बियर प्रतिक्रिया तथा डायहाइड्रोक्सीलेशन प्रतिक्रिया का भी प्रयोग किया गया। इन शुगर-इमिनोशुगर ऑक्सा-एज़ा हाइब्रिड अणुओं में पाइरोलिडिनो-पाइरान, पायरोलीडिनो-ऑक्सेपेन और पायरोलीडिनो-ऑक्सोकैन शामिल हैं। सभी हाइब्रिड अणुओं में एक रोचक तथ्य यह है कि इनमें एक सामान्य अणु पाँच-सदस्यीय पाइरोलिडिनो रिंग पाया गया, जबकि अन्य रिंग संरचनाएँ भिन्न थीं, जैसे की: पाइरान (छह-सदस्यीय रिंग), ऑक्सेपेन (सात-सदस्यीय रिंग), तथा ऑक्सोकैन (आठ-सदस्यीय रिंग)।

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### CHAPTER 1

**Diversity-Oriented attempt towards the synthesis of (+)-kirkamide through two different approaches: (a) ring-closing metathesis and (b) Baylis–Hillman reaction starting from tri-*O*-benzyl-D-glucal.**

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## GENERAL EXPERIMENTAL CONSIDERATIONS

All solvents employed were purified by standard procedures. Anhydrous solvents were dried over sodium wire (THF, diethyl ether, toluene) or molecular sieves ( $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ , DMF,  $\text{CH}_3\text{CN}$ ).

Nitrogen or Argon gas used for creating inert atmosphere was freed from oxygen prior to entry into the reaction vessel.

Thin-layer chromatography (TLC) was performed on Merck silica gel pre-coated on aluminium plates and the spots were visualized by exposure to UV light, iodine, or by dipping in  $\text{KMnO}_4$  solution. Column chromatography was carried out on silica gel (230–400 mesh) using mixtures of hexane and ethyl acetate as eluent unless otherwise mentioned.

Optical rotations were recorded on an Autopol V (Rudolph Research Flanders, NJ) instrument. All the rotations were measured at 589 nm (sodium D' line).

Freeze-drying of samples was done on a Freezone 2.5 (Labconco, USA) lyophilizer.

IR spectra were taken within the range  $4000\text{--}600\text{ cm}^{-1}$  as KBr pellets on a Nicolet (Madison, USA) FT-IR spectrophotometer (Model Protégé 460).

$^1\text{H}$ -NMR spectra were recorded on 300 MHz, 400 MHz, 500 MHz Bruker Spectrospin DPX FT-NMR instruments or 400 MHz Jeol instrument. The solvents employed were  $\text{CDCl}_3$ ,  $\text{D}_2\text{O}$  or  $\text{DMSO-d}_6$  with  $\text{Me}_4\text{Si}$  as the internal standard. The multiplicities are denoted as s-singlet, br s-broad singlet, d-doublet, t-triplet, q-quartet, dt-doublet triplet, dd-doublet of doublet.  $^{13}\text{C}$ -NMR spectra were recorded at 75 MHz, 100 MHz or 125 MHz instruments. The chemical shifts are reported in  $\delta$  values (parts per million, ppm) relative to the internal standard  $\text{Me}_4\text{Si}$ . High-resolution mass spectra were recorded with a Q-TOF Bruker instrument, using electrospray ionization (ESI) as the ionization method and on Xevo G2-XS QToF.



## COMMON ABBREVIATIONS

|                   |   |                                        |
|-------------------|---|----------------------------------------|
| Ac                | : | Acetyl                                 |
| Ac <sub>2</sub> O | : | acetic anhydride                       |
| AcOH              | : | acetic acid                            |
| ADMP              | : | aminodeoxy-DMDP                        |
| AIBN              | : | Azobisisobutyronitrile                 |
| Atm               | : | atmospheric pressure                   |
| Aq                | : | Aqueous                                |
| Bn                | : | Benzyl                                 |
| Boc               | : | tertiary-butoxycarbonyl                |
| <sup>t</sup> Bu   | : | tertiary butyl                         |
| <i>C</i>          | : | Concentration                          |
| Cat               | : | Catalyst                               |
| Cbz               | : | Carbobenzyloxy                         |
| COSY              | : | correlation spectroscopy               |
| CSA               | : | camphor-10-sulfonic acid               |
| DCC               | : | <i>N, N'</i> -dicyclohexylcarbodiimide |
| DCM               | : | Dichloromethane                        |
| DEAD              | : | diethyl azodicarboxylate               |
| DMAP              | : | 4-dimethylaminopyridine                |

|                        |   |                                                 |
|------------------------|---|-------------------------------------------------|
| DMF                    | : | <i>N, N'</i> -dimethylformamide                 |
| DMSO                   | : | Dimethylsulfoxide                               |
| Dr                     | : | diastereomeric ratio                            |
| Equiv                  | : | Equivalent                                      |
| ESI                    | : | electrospray ionization                         |
| Et                     | : | Ethyl                                           |
| EtOAc                  | : | ethyl acetate                                   |
| G                      | : | Gram                                            |
| GalNAcase              | : | <i>N</i> -acetyl- $\alpha$ -D-galactosaminidase |
| Hr                     | : | Hour                                            |
| HRMS                   | : | high resolution mass spectrometry               |
| HSQC                   | : | heteronuclear single quantum coherence          |
| Hz                     | : | Hertz                                           |
| IC <sub>50</sub>       | : | half maximal inhibitory concentration           |
| Imi                    | : | Imidazole                                       |
| <sup><i>i</i></sup> Pr | : | Isopropyl                                       |
| IR                     | : | Infrared                                        |
| LAH                    | : | lithium aluminum hydride                        |
| LDA                    | : | lithium diisopropylamide                        |
| LiHMDS                 | : | lithium hexamethyldisilamide                    |

|                |   |                                            |
|----------------|---|--------------------------------------------|
| <i>m</i> -CPBA | : | meta-chloro perbenzoic acid                |
| Me             | : | Methyl                                     |
| Mg             | : | Milligrams                                 |
| Min            | : | Minute                                     |
| mL             | : | Milliliters                                |
| mM             | : | Millimolar                                 |
| Mmol           | : | Millimoles                                 |
| M.P            | : | melting point                              |
| Ms             | : | Mesyl                                      |
| MS             | : | molecular sieves                           |
| MHz            | : | Megahertz                                  |
| m/z            | : | mass-to-charge ratio                       |
| NAc            | : | <i>N</i> -acetyl                           |
| NCS            | : | <i>N</i> -chlorosuccinimide                |
| NIS            | : | <i>N</i> -iodosuccinimide                  |
| NMO            | : | <i>N</i> -methylmorpholine <i>N</i> -oxide |
| NMR            | : | nuclear magnetic resonance                 |
| NOESY          | : | nuclear overhauser effect spectroscopy     |
| Nu             | : | Nucleophile                                |
| Pd/C           | : | palladium on activated carbon              |

|                      |   |                                          |
|----------------------|---|------------------------------------------|
| PPh <sub>3</sub>     | : | triphenyl phosphine                      |
| Ph                   | : | Phenyl                                   |
| Py                   | : | Pyridine                                 |
| <i>p</i> -TSA        | : | para-toluenesulfonic acid                |
| RCM                  | : | ring closing metathesis                  |
| <i>R<sub>f</sub></i> | : | retention factor                         |
| Ref                  | : | Reference                                |
| Rt                   | : | room temperature                         |
| TBAF                 | : | tetra- <i>N</i> -butyl ammonium fluoride |
| TBS                  | : | tertiary-butyldimethyl silyl             |
| TCDI                 | : | 1,1'-thiocarbonyldiimidazole             |
| TFA                  | : | trifluoroacetic acid                     |
| THF                  | : | Tetrahydrofuran                          |
| TLC                  | : | thin layer chromatography                |
| TMS                  | : | trimethyl silyl                          |
| Tr                   | : | trityl (triphenyl methyl)                |
| Ts                   | : | tosyl ( <i>p</i> -toluenesulfonyl)       |