

**SYNTHESIS OF NOVEL AZA-NUCLEOSIDES AND A  
NEW STRATEGY TO (+)-BULGECININE, *TRANS*-4-  
HYDROXY-D-PROLINE**

**UMESH KUMAR MISHRA**



**DEPARTMENT OF CHEMISTRY  
INDIAN INSTITUTE OF TECHNOLOGY DELHI  
DECEMBER 2019**

© Indian Institute of Technology Delhi (IITD), New Delhi, 2019

**SYNTHESIS OF NOVEL AZA-NUCLEOSIDES AND A  
NEW STRATEGY TO (+)-BULGECININE, *TRANS*-4-  
HYDROXY-D-PROLINE**

*by*

**UMESH KUMAR MISHRA**

**DEPARTMENT OF CHEMISTRY**

*Submitted*

*In fulfillment of the requirements of the degree of DOCTOR OF PHILOSOPHY*

to the



**INDIAN INSTITUTE OF TECHNOLOGY DELHI**

**DECEMBER 2019**

*This thesis is dedicated to  
my beloved parents  
**Mr. Ram Sagar Mishra**  
and  
**Mrs. Sarojni Mishra***

## CERTIFICATE

This is to certify that the thesis entitled “**SYNTHESIS OF NOVEL AZA-NUCLEOSIDES AND A NEW STRATEGY TO (+)-BULGECININE, TRANS-4-HYDROXY-D-PROLINE**”, being submitted by **Mr. UMESH KUMAR MISHRA** to 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. Umesh Kumar Mishra 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**  
Supervisor  
Department of Chemistry  
Indian Institute of Technology Delhi  
Hauz Khas, New Delhi-110016  
India.

## **ACKNOWLEDGEMENTS**

*I wish to express my sincere appreciation to those who have contributed to this thesis and supported me in one way or the other during this amazing journey.*

*I would like to express my sincere gratitude and respect for my supervisor **Prof. N. G. Ramesh** for his able and inspiring guidance, continuous support and practical suggestions to overcome all the difficulties during my research work. If it was not his painstaking efforts, invaluable suggestions and constant encouragement throughout the execution of my research, the thesis would definitely not have seen the light of day. I am extremely thankful to his immense knowledge which enriched my scientific experience as well.*

*My sincere thanks also goes to Prof. Anil J. Elias, head of the department for providing departmental facilities.*

*Besides my advisor, I would like to thank my thesis committee Prof. Nalin Pant, Prof. V. Haridas and Prof. Josemon Jacob for their insightful comments and encouragement. I am also grateful to Prof. Shivajirao L. Gholap, Prof. A. Ramanan, Prof. S. Nagendran, Prof. N. D. Kurur, Prof. Ravi Shankar, Prof. Ashok K. Ganguli and other faculties for their help and support during my research period at IIT Delhi.*

*Very special thanks to Dr. Yogesh S. Sanghvi, Rasayan Inc. for his in valuable insights and suggestions. I really appreciate his willingness to meet me at short notice every time and for their financial support.*

*My sincere gratitude is reserved for Prof. Egli Martin, Vanderbilt University, Nashville, for their very helpful comments and suggestions.*

*My heartfelt thanks to my seniors Dr. Nagarajan, Dr. Rahul Vilas Salunke, Dr. S. Venkatesan, Dr. Vimal Kant Harit and Dr. Sathis Kannan for their guidance and*

*moral support. They always helped me out when I got into any problem or queries regarding experiments. It is my privilege to acknowledge to labmates, Abhishek, Abu Zaid, Adrika and Danish for always standing by my side and sharing a great relationship as compassionate friends.*

*IIT Delhi for providing institute facilities, I am thankful to Mr. Keshav, Mr. Alok of the NMR lab, Mr. Virender of glass blowing section and all the members of instrument lab and chemistry office. Very special thanks to DST, CSIR and IIT Delhi, India for their financial support.*

*I would like to acknowledge my friend Dr. Rituraj Mishra for their help in NMR experiment and Dr. Mahendra Sharma, Dharmendra and Pritam for their help to do single-crystal X-ray experiment.*

*Ph.D. students frequently talk about loneliness during the course of their study but this is something which I never experienced at IIT Delhi. A heartfelt thanks to all my really supportive and active friends who made the IIT Delhi experience something special, in particular, Pawan Mishra, Saurabh Mishra, Rituraj Mishra, Ashish Pandey, Vipin Tiwari, Shailendra Singh, Bhawna, Uma, Ajay Verma and Komal Kumar. I wish to thank my friends from graduation (Digvijay, Deepak, Amardeep, Ashish, Ashish Tiwari) and from post-graduation (Manish, Rahul and Munendra) for helping me to get through the difficult times, and for all the emotional support.*

*I am also indebted to my brothers and friends Mr. Vinay Shukla, Mr. Udit Shukla, Arvind Mishra, Mr. Atma Prakash, Mr. Dinesh Singh, Anupam Mishra, Rajkishore, Devanshu Pandey, Sandeep Dixit and Shivam Mishra not only for all their useful suggestions but also for being there to listen when I needed an ear.*

*Last, but not the least, my deep and sincere gratitude to my family for their continuous and unparalleled love, help and support. I am grateful to my sisters (Rekha,*

*Soni and Neha) for always being there for me as a friend. I am forever indebted to my parents (Mr. Ram Sagar Mishra and Mrs. Sarojni Mishra) for giving me the opportunities and experiences that have made me who I am. They selflessly encouraged me to explore new directions in life and seek my own destiny. This journey would not have been possible without them, and I dedicate this milestone to them. Finally, I thank with love to Jyoti Shukla, my wife, for understanding me best. Her presence has always been a really great consolation and support to me.*

*Finally, my thanks go to all the people who have supported me to complete the research work directly or indirectly.*

Umesh Kumar Mishra

## ABSTRACT

The thesis titled “**SYNTHESIS OF NOVEL AZA-NUCLEOSIDES AND A NEW STRATEGY TO (+)-BULGECININE, TRANS-4-HYDROXY-D-PROLINE**” present the research work carried out on the synthesis of novel aza-nucleosides starting material tri-*O*-benzyl-D-glucal. On the other hand, (+)-Bulgecinine, polyhydroxypyrrolidine and *trans*-4-hydroxy-D-proline were synthesized from tri-*O*-acetyl-D-glucal as the convenient starting material.

Aza-nucleosides are nucleoside analogues wherein the oxygen atom of the furanose ring has been replaced with a nitrogen atom. Synthesis and development of aza-nucleosides have been the focus of attention, due to the vital role played by carbohydrates in a variety of biological process. A variety of novel nucleoside analogues have been discovered, which are potential inhibitors of glycosidases and purine nucleoside phosphorylase (PNP) enzyme. PNP catalyses the reversible phosphorylation of purine nucleosides to produce the corresponding purine base and ribose-1-phosphate.

**Chapter I** describes the synthesis of aza-nucleosides. This is the first example of the synthesis of double headed aza-nucleosides, wherein two nucleobases (either same or complimentary) were coupled with polyhydroxypyrrolidine. Single crystal X-ray structure of three compounds were obtained and their supramolecular assembly was investigated. The PNP inhibition of the purine based aza-nucleosides is in progress and the outcome of the results is awaited.

**Chapter II** describes the synthesis of four molecules namely (+)-bulgecinine, 3-hydroxy-2,5-dihydroxymethylpyrrolidine and two stereoisomers of 2-oxapyrrolizidin-3-one starting from 4,6-di-*O*-benzyl-D-glucal through divergent approach involving a

common intermediate. This is the first carbohydrate based approach to the synthesis of (+)-bulgecinine that proceeds with complete stereochemical integrity.

**Chapter III** describes a straight-forward, high yielding, highly stereoselective synthesis of *trans*-4-hydroxy-D-proline and *trans*-4-hydroxy-D-prolinol starting from 4,6-di-*O*-benzyl-D-glucal. This is perhaps the first carbohydrate based approach to the synthesis of *trans*-4-hydroxy-D-proline and prolinol that proceeds with complete stereochemical integrity.

## सार

थिसिस शीर्षक “नॉवेल एजा-न्यूक्लियोसाइड और एक नई रणनीति (+)-बुलजेसिनीन, ट्रांस 4-हाइड्रॉक्सी-डी-प्रोलीन का संश्लेषण” प्रस्तुत शोध कार्य नॉवेल एजा-न्यूक्लियोसाइड के संश्लेषण पर शुरू किया जो सामग्री त्रिकोणीय-ओ-बेंजिल-डी-ग्लुकल है। दूसरी ओर, सुविधाजनक शुरुआत सामग्री के रूप में ट्राई-ओ-एसिटाइल-डी-ग्लुकल से (+)-बुलजेसिनीन, पॉलीहाइड्रॉक्सीपिरोलिडीन और ट्रांस-4-हाइड्रॉक्सी-डी-प्रोलीन को संश्लेषित किया गया था।

एजा-न्यूक्लियोसाइड न्यूक्लियोसाइड एनालॉग्स हैं, जहां फूरेनोज रिंग के ऑक्सीजन परमाणु को नाइट्रोजन परमाणु के साथ बदल दिया गया है। विभिन्न जैविक प्रक्रिया में कार्बोहाइड्रेट द्वारा निर्भाई गई महत्वपूर्ण भूमिका के कारण, एजा-न्यूक्लियोसाइड का संश्लेषण और विकास ध्यान का केंद्र बिंदु रहा है। नॉवेल न्यूक्लियोसाइड एनालॉग्स की एक किस्म की खोज की गई है, जो ग्लाइकोसिडेस और प्यूरिन न्यूक्लियोसाइड फॉस्फोराइलेज (पीएनपी) एंजाइम के संभावित अवरोधक हैं। पीएनपी, इसी प्यूरिन बेस और राइबोस-1-फॉस्फेट के उत्पादन के लिए प्यूरिन न्यूक्लियोसाइड के प्रतिवर्ती फॉस्फोराइलेशन को उत्प्रेरित करता है।

**अध्याय I** एजा-न्यूक्लियोसाइड के संश्लेषण का वर्णन करता है। यह डबल हेडेड एजा-न्यूक्लियोसाइड्स के संश्लेषण का पहला उदाहरण है, जिसमें दो न्यूक्लियोबेस (या तो समान या मानार्थ) पॉलीहाइड्रॉक्सीपिरोलिडीन के साथ मिलकर किए गए थे। तीन यौगिकों के एकल क्रिस्टल एक्स-रे संरचना प्राप्त किए गए थे और उनकी सुपरमॉलेक्यूलर असेंबली की जांच की गई थी। प्यूरिन के बेस एजा-न्यूक्लियोसाइड का पीएनपी निषेध प्रगति पर है और परिणामों का इंतजार है।

**अध्याय II** में चार अणुओं के संश्लेषण का वर्णन है, (+)-बुलजेसिनीन, 3-हाइड्रॉक्सी-2,5-डायहाइड्रॉक्सीमिथाइलपिरोलिडीन और 2-ऑक्सापायरोलिजिडिन-3-ओन के दो स्टीरियोइसोमर्स 4,6-डाई-ओ-बेन्जिल-डी-ग्लुकल से शुरू होते हैं। ग्लुकल गर्त विचलन दृष्टिकोण जिसमें एक सामान्य मध्यवर्ती शामिल है। यह (+)-बुलजेसिनीन के संश्लेषण के लिए पहला कार्बोहाइड्रेट आधारित दृष्टिकोण है जो पूर्ण स्टीरियोकेमिकल अखंडता के साथ आगे बढ़ता है।

**अध्याय III** में ट्रांस 4-हाइड्रॉक्सी-डी प्रोलीन और ट्रांस-4-हाइड्रॉक्सी-डी-प्रोलिनोल के 4,6- डाई-ओ-बेंजिल-डी-ग्लुकल से शुरू होने वाले एक सीधे-आगे, उच्च उपज, अत्यधिक स्टीरोसेलेक्टिव संश्लेषण का वर्णन है। यह ट्रांस-4-हाइड्रॉक्सी-डी-प्रोलीन और प्रोलिनोल के संश्लेषण के लिए शायद पहला कार्बोहाइड्रेट आधारित दृष्टिकोण है जो पूर्ण स्टीरियोकेमिकल अखंडता के साथ आगे बढ़ता है।

# TABLE OF CONTENTS

<b>CERTIFICATE</b>	i
<b>ACKNOWLEDGEMENTS</b>	iii
<b>ABSTRACT</b>	vii
<b>TABLE OF CONTENTS</b>	xi
<b>LIST OF FIGURES</b>	xiii
<b>LIST OF TABLES</b>	xix
<b>GENERAL EXPERIMENTAL CONSIDERATIONS</b>	xxi
<b>COMMON ABBREVIATIONS</b>	xxiii
<b>CHAPTER 1: Synthesis of novel double-headed aza-nucleosides and nucleoside analogues of (+)-anisomycin</b>	
1.1 Introduction	3
1.1.2 Objective	38
1.1.3 Results and discussion	40
1.1.4 Conclusion	51
1.2.2 Objective	52
1.2.3 Results and discussion	53
1.2.4 Conclusion	60
1.5 Experimental section	61
1.6 Reference	115
1.7 Spectra of compounds	120
<b>CHAPTER 2: A glycal based approach to (+)-bulgecinine, 3-hydroxy-2,5-dihydroxymethylpyrrolidine and 2-oxapyrrolizidin-3-one</b>	

2.1	Introduction	165
2.2	Objective	180
2.3	Results and discussion	181
2.4	Conclusion	188
2.5	Experimental section	189
2.6	References	214
2.7	Spectra of Compounds	218

**CHAPTER 3: A new strategy to the synthesis of *trans*-4-hydroxy-D-proline and prolinol**

3.1	Introduction	241
3.2	Objective	249
3.3	Results and discussion	250
3.4	Conclusion	252
3.5	Experimental section	253
3.6	References	261
3.7	Spectra of compounds	265

**A BRIEF BIO-DATA OF THE AUTHOR**

## LIST OF FIGURES

CHAPTER I	PAGE
<b>Figure 1.1</b> Description of nucleosides	3
<b>Figure 1.2</b> Description of nucleotides	4
<b>Figure 1.3</b> Chemical structure of DNA	5
<b>Figure 1.4</b> Structures of primary nucleobases	5
<b>Figure 1.5</b> Structures of modified nucleobases	6
<b>Figure 1.6</b> Structure of natural nucleosides present in DNA and RNA	6
<b>Figure 1.7</b> Structure of nucleosides active against antiviral and antibacterial	7
<b>Figure 1.8</b> Structure of nucleosides and aza-nucleoside	8
<b>Figure 1.9</b> Transition states of PNP catalysed phosphorolysis of inosine and Imm-H	9
<b>Figure 1.10</b> Catalytic site contacts between human PNP and the Imm-H	9
<b>Figure 1.11</b> Examples of aza-nucleosides	10
<b>Figure 1.12</b> Double headed nucleotides.	11
<b>Figure 1.13</b> Structure of anisomycin and deacetylanisomycin	33
<b>Figure 1.14</b> Crystal structure of compound <b>225</b>	43
<b>Figure 1.15</b> Crystal structure of compound <b>218</b>	45
<b>Figure 1.16</b> Crystal structure of compound <b>236</b>	50
<b>Figure 1.17</b> Crystal structure of compound <b>248</b>	54
<b>Figure 1.18</b> <sup>1</sup> H-NMR spectrum of compound <b>222</b>	120
<b>Figure 1.19</b> <sup>13</sup> C-NMR spectrum of compound <b>222</b>	120
<b>Figure 1.20</b> <sup>1</sup> H-NMR spectrum of compound <b>223</b>	121
<b>Figure 1.21</b> <sup>13</sup> C-NMR spectrum of compound <b>223</b>	121
<b>Figure 1.22</b> <sup>1</sup> H-NMR spectrum of compound <b>220</b>	122
<b>Figure 1.23</b> <sup>13</sup> C-NMR spectrum of compound <b>220</b>	122
<b>Figure 1.24</b> <sup>1</sup> H-NMR spectrum of compound <b>224</b>	123
<b>Figure 1.25</b> <sup>13</sup> C-NMR spectrum of compound <b>224</b>	123
<b>Figure 1.26</b> <sup>1</sup> H-NMR spectrum of compound <b>225</b>	124
<b>Figure 1.27</b> <sup>13</sup> C-NMR spectrum of compound <b>225</b>	124
<b>Figure 1.28</b> <sup>1</sup> H-NMR spectrum of compound <b>217</b>	125

<b>Figure 1.29</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>217</b>	125
<b>Figure 1.30</b>	$^1\text{H}$ -NMR spectrum of compound <b>226</b>	126
<b>Figure 1.31</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>226</b>	126
<b>Figure 1.32</b>	$^1\text{H}$ -NMR spectrum of compound <b>227</b>	127
<b>Figure 1.33</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>227</b>	127
<b>Figure 1.34</b>	$^1\text{H}$ -NMR spectrum of compound <b>228</b>	128
<b>Figure 1.35</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>228</b>	128
<b>Figure 1.36</b>	$^1\text{H}$ -NMR spectrum of compound <b>218</b>	129
<b>Figure 1.37</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>218</b>	129
<b>Figure 1.38</b>	$^1\text{H}$ -NMR spectrum of compound <b>229</b>	130
<b>Figure 1.39</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>229</b>	130
<b>Figure 1.40</b>	$^1\text{H}$ -NMR spectrum of compound <b>231</b>	131
<b>Figure 1.41</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>231</b>	131
<b>Figure 1.42</b>	$^1\text{H}$ -NMR spectrum of compound <b>232</b>	132
<b>Figure 1.43</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>232</b>	132
<b>Figure 1.44</b>	$^1\text{H}$ -NMR spectrum of compound <b>233</b>	133
<b>Figure 1.45</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>233</b>	133
<b>Figure 1.46</b>	$^1\text{H}$ -NMR spectrum of compound <b>234</b>	134
<b>Figure 1.47</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>234</b>	134
<b>Figure 1.48</b>	$^1\text{H}$ -NMR spectrum of compound <b>235</b>	135
<b>Figure 1.49</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>235</b>	135
<b>Figure 1.50</b>	$^1\text{H}$ -NMR spectrum of compound <b>236</b>	136
<b>Figure 1.51</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>236</b>	136
<b>Figure 1.52</b>	$^1\text{H}$ -NMR spectrum of compound <b>237</b>	137
<b>Figure 1.53</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>237</b>	137
<b>Figure 1.54</b>	$^1\text{H}$ -NMR spectrum of compound <b>219</b>	138
<b>Figure 1.55</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>219</b>	138
<b>Figure 1.56</b>	$^1\text{H}$ -NMR spectrum of compound <b>242</b>	139
<b>Figure 1.57</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>242</b>	139
<b>Figure 1.58</b>	$^1\text{H}$ -NMR spectrum of compound <b>246</b>	140
<b>Figure 1.59</b>	$^{13}\text{C}$ -NMR spectrum of compound <b>246</b>	140
<b>Figure 1.60</b>	$^1\text{H}$ -NMR spectrum of compound <b>247</b>	141

<b>Figure 1.61</b>	<sup>13</sup> C-NMR spectrum of compound <b>247</b>	141
<b>Figure 1.62</b>	<sup>1</sup> H-NMR spectrum of compound <b>248</b>	142
<b>Figure 1.63</b>	<sup>13</sup> C-NMR spectrum of compound <b>248</b>	142
<b>Figure 1.64</b>	<sup>1</sup> H-NMR spectrum of compound <b>249</b>	143
<b>Figure 1.65</b>	<sup>13</sup> C-NMR spectrum of compound <b>249</b>	143
<b>Figure 1.66</b>	<sup>1</sup> H-NMR spectrum of compound <b>250</b>	144
<b>Figure 1.67</b>	<sup>13</sup> C-NMR spectrum of compound <b>250</b>	144
<b>Figure 1.68</b>	<sup>1</sup> H-NMR spectrum of compound <b>251</b>	145
<b>Figure 1.69</b>	<sup>13</sup> C-NMR spectrum of compound <b>251</b>	145
<b>Figure 1.70</b>	<sup>1</sup> H-NMR spectrum of compound <b>252</b>	146
<b>Figure 1.71</b>	<sup>13</sup> C-NMR spectrum of compound <b>252</b>	146
<b>Figure 1.72</b>	<sup>1</sup> H-NMR spectrum of compound <b>253</b>	147
<b>Figure 1.73</b>	<sup>13</sup> C-NMR spectrum of compound <b>253</b>	147
<b>Figure 1.74</b>	<sup>1</sup> H-NMR spectrum of compound <b>254</b>	148
<b>Figure 1.75</b>	<sup>13</sup> C-NMR spectrum of compound <b>254</b>	148
<b>Figure 1.76</b>	<sup>1</sup> H-NMR spectrum of compound <b>255</b>	149
<b>Figure 1.77</b>	<sup>13</sup> C-NMR spectrum of compound <b>255</b>	149
<b>Figure 1.78</b>	<sup>1</sup> H-NMR spectrum of compound <b>256</b>	150
<b>Figure 1.79</b>	<sup>13</sup> C-NMR spectrum of compound <b>256</b>	150
<b>Figure 1.80</b>	<sup>1</sup> H-NMR spectrum of compound <b>257</b>	151
<b>Figure 1.81</b>	<sup>13</sup> C-NMR spectrum of compound <b>257</b>	151
<b>Figure 1.82</b>	<sup>1</sup> H-NMR spectrum of compound <b>258</b>	152
<b>Figure 1.83</b>	<sup>13</sup> C-NMR spectrum of compound <b>258</b>	152
<b>Figure 1.84</b>	<sup>1</sup> H-NMR spectrum of compound <b>259</b>	153
<b>Figure 1.85</b>	<sup>13</sup> C-NMR spectrum of compound <b>259</b>	153
<b>Figure 1.86</b>	<sup>1</sup> H-NMR spectrum of compound <b>260</b>	154
<b>Figure 1.87</b>	<sup>13</sup> C-NMR spectrum of compound <b>260</b>	154
<b>Figure 1.88</b>	<sup>1</sup> H-NMR spectrum of compound <b>261</b>	155
<b>Figure 1.89</b>	<sup>13</sup> C-NMR spectrum of compound <b>261</b>	155
<b>Figure 1.90</b>	<sup>1</sup> H-NMR spectrum of compound <b>263</b>	156
<b>Figure 1.91</b>	<sup>13</sup> C-NMR spectrum of compound <b>263</b>	156
<b>Figure 1.92</b>	<sup>1</sup> H-NMR spectrum of compound <b>264</b>	157

<b>Figure 1.93</b>	<sup>13</sup> C-NMR spectrum of compound <b>264</b>	157
<b>Figure 1.94</b>	<sup>1</sup> H-NMR spectrum of compound <b>265</b>	158
<b>Figure 1.95</b>	<sup>13</sup> C-NMR spectrum of compound <b>265</b>	158
<b>Figure 1.96</b>	<sup>1</sup> H-NMR spectrum of compound <b>266</b>	159
<b>Figure 1.97</b>	<sup>13</sup> C-NMR spectrum of compound <b>266</b>	159
<b>Figure 1.98</b>	<sup>1</sup> H-NMR spectrum of compound <b>268</b>	160
<b>Figure 1.99</b>	<sup>13</sup> C-NMR spectrum of compound <b>268</b>	160
<b>Figure 1.100</b>	<sup>1</sup> H-NMR spectrum of compound <b>269</b>	161
<b>Figure 1.101</b>	<sup>13</sup> C-NMR spectrum of compound <b>269</b>	161
<b>Figure 1.102</b>	<sup>1</sup> H-NMR spectrum of compound <b>271</b>	162
<b>Figure 1.103</b>	<sup>13</sup> C-NMR spectrum of compound <b>271</b>	162
<b>CHAPTER II</b>		
<b>Figure 2.1</b>	Structures of bulgecinine, bulgecins and iminocyclitols	165
<b>Figure 2.2</b>	General mechanism of hydrolysis by glycosidases	174
<b>Figure 2.3</b>	Mimicry of transition state of glycosidic hydrolysis	176
<b>Figure 2.4</b>	Examples of piperidine iminosugar.	176
<b>Figure 2.5</b>	Examples of pyrrolidine based iminosugar	177
<b>Figure 2.6</b>	Examples of pyrrolizidine and indoizilidine iminosugar	178
<b>Figure 2.7</b>	Crystal structure of compound <b>92</b>	185
<b>Figure 2.8</b>	<sup>1</sup> H-NMR spectrum of compound <b>83</b>	218
<b>Figure 2.9</b>	<sup>13</sup> C-NMR spectrum of compound <b>83</b>	218
<b>Figure 2.10</b>	<sup>1</sup> H-NMR spectrum of compound <b>79</b>	219
<b>Figure 2.11</b>	<sup>13</sup> C-NMR spectrum of compound <b>79</b>	219
<b>Figure 2.12</b>	<sup>1</sup> H-NMR spectrum of compound <b>84</b>	220
<b>Figure 2.13</b>	<sup>13</sup> C-NMR spectrum of compound <b>84</b>	220
<b>Figure 2.14</b>	<sup>1</sup> H-NMR spectrum of compound <b>78</b>	221
<b>Figure 2.15</b>	<sup>13</sup> C-NMR spectrum of compound <b>78</b>	221
<b>Figure 2.16</b>	<sup>1</sup> H-NMR spectrum of compound <b>85</b>	222
<b>Figure 2.17</b>	<sup>13</sup> C-NMR spectrum of compound <b>85</b>	222
<b>Figure 2.18</b>	<sup>1</sup> H-NMR spectrum of compound <b>86</b>	223
<b>Figure 2.19</b>	<sup>13</sup> C-NMR spectrum of compound <b>86</b>	223
<b>Figure 2.20</b>	<sup>1</sup> H-NMR spectrum of compound <b>87</b>	224

<b>Figure 2.21</b>	<sup>13</sup> C-NMR spectrum of compound <b>87</b>	224
<b>Figure 2.22</b>	<sup>1</sup> H-NMR spectrum of compound <b>88</b>	225
<b>Figure 2.23</b>	<sup>13</sup> C-NMR spectrum of compound <b>88</b>	225
<b>Figure 2.24</b>	<sup>1</sup> H-NMR spectrum of compound <b>89</b>	226
<b>Figure 2.25</b>	<sup>13</sup> C-NMR spectrum of compound <b>89</b>	226
<b>Figure 2.26</b>	<sup>1</sup> H-NMR spectrum of compound <b>90</b>	227
<b>Figure 2.27</b>	<sup>13</sup> C-NMR spectrum of compound <b>90</b>	227
<b>Figure 2.28</b>	<sup>1</sup> H-NMR spectrum of compound <b>91</b>	228
<b>Figure 2.29</b>	<sup>13</sup> C-NMR spectrum of compound <b>91</b>	228
<b>Figure 2.30</b>	<sup>1</sup> H-NMR spectrum of compound <b>92</b>	229
<b>Figure 2.31</b>	<sup>13</sup> C-NMR spectrum of compound <b>92</b>	229
<b>Figure 2.32</b>	<sup>1</sup> H-NMR spectrum of compound <b>3</b>	230
<b>Figure 2.33</b>	<sup>13</sup> C-NMR spectrum of compound <b>3</b>	230
<b>Figure 2.34</b>	<sup>1</sup> H-NMR spectrum of compound <b>76</b>	231
<b>Figure 2.35</b>	<sup>13</sup> C-NMR spectrum of compound <b>76</b>	231
<b>Figure 2.36</b>	<sup>1</sup> H-NMR spectrum of compound <b>93</b>	232
<b>Figure 2.37</b>	<sup>13</sup> C-NMR spectrum of compound <b>93</b>	232
<b>Figure 2.38</b>	<sup>1</sup> H-NMR spectrum of compound <b>94</b>	233
<b>Figure 2.39</b>	<sup>13</sup> C-NMR spectrum of compound <b>94</b>	233
<b>Figure 2.40</b>	<sup>1</sup> H-NMR spectrum of compound <b>95</b>	234
<b>Figure 2.41</b>	<sup>13</sup> C-NMR spectrum of compound <b>95</b>	234
<b>Figure 2.42</b>	<sup>1</sup> H-NMR spectrum of compound <b>96</b>	235
<b>Figure 2.43</b>	<sup>13</sup> C-NMR spectrum of compound <b>96</b>	235
<b>Figure 2.44</b>	<sup>1</sup> H-NMR spectrum of compound <b>97</b>	236
<b>Figure 2.45</b>	<sup>13</sup> C-NMR spectrum of compound <b>97</b>	236
<b>Figure 2.46</b>	<sup>1</sup> H-NMR spectrum of compound <b>75</b>	237
<b>Figure 2.47</b>	<sup>13</sup> C-NMR spectrum of compound <b>75</b>	237
<b>Figure 2.48</b>	<sup>1</sup> H-NMR spectrum of compound <b>77</b>	238
<b>Figure 2.49</b>	<sup>13</sup> C-NMR spectrum of compound <b>77</b>	238
<b>CHAPTER III</b>		
<b>Figure 3.1</b>	Structure of the hydroxyproline bound <i>O</i> -glycans	241
<b>Figure 3.2</b>	Examples of drug molecule derived from hydroxyproline	242

<b>Figure 3.3</b>	Stereoisomers of hydroxyproline	243
<b>Figure 3.4</b>	<sup>1</sup> H-NMR spectrum of compound <b>44</b>	265
<b>Figure 3.5</b>	<sup>13</sup> C-NMR spectrum of compound <b>44</b>	265
<b>Figure 3.6</b>	<sup>1</sup> H-NMR spectrum of compound <b>41</b>	266
<b>Figure 3.7</b>	<sup>13</sup> C-NMR spectrum of compound <b>41</b>	266
<b>Figure 3.8</b>	<sup>1</sup> H-NMR spectrum of compound <b>42</b>	267
<b>Figure 3.9</b>	<sup>13</sup> C-NMR spectrum of compound <b>42</b>	267
<b>Figure 3.10</b>	<sup>1</sup> H-NMR spectrum of compound <b>47</b>	268
<b>Figure 3.11</b>	<sup>13</sup> C-NMR spectrum of compound <b>47</b>	268
<b>Figure 3.12</b>	<sup>1</sup> H-NMR spectrum of compound <b>9</b>	269
<b>Figure 3.13</b>	<sup>13</sup> C-NMR spectrum of compound <b>9</b>	269
<b>Figure 3.14</b>	<sup>1</sup> H-NMR spectrum of compound <b>43</b>	270
<b>Figure 3.15</b>	<sup>13</sup> C-NMR spectrum of compound <b>43</b>	270

## LIST OF TABLES

<b>CHAPTER I</b>		<b>PAGE</b>
<b>Table 1.1</b>	Crystal data and structure refinement parameters for <b>225</b>	61
<b>Table 1.2</b>	Crystal data and structure refinement parameters for <b>218</b>	62
<b>Table 1.3</b>	Crystal data and structure refinement parameters for <b>236</b>	63
<b>Table 1.4</b>	Crystal data and structure refinement parameters for <b>225</b>	64

  

<b>CHAPTER II</b>		
<b>Table 2.1</b>	Crystal data and structure refinement parameters for <b>92</b>	189

## GENERAL EXPERIMENTAL CONSIDERATIONS

All solvents employed were purified by standard procedures. Anhydrous solvents were dried over sodium wire (THF, diethyl ether, benzene) or molecular sieves (CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, DMF).

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

Commercially sourced TLC plates were used, and the spots were visualized by exposure to iodine, or by dipping in KMnO<sub>4</sub> and ninhydrin 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).

All melting points reported in this thesis are uncorrected and were taken on an electric melting point apparatus (Ambassador, India).

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

Inhibition studies were carried out on Biotek Synergy 2 microplate reader.

IR spectra were taken within the range 4000–600 cm<sup>-1</sup> either as KBr pellets or neat on a Nicolet (Madison, USA) FT-IR spectrophotometer (Model Protégé 460).

<sup>1</sup>H-NMR spectra were recorded on a 300 MHz or 400 MHz Bruker Spectrospin DPX FT-NMR instruments. The solvents employed were CDCl<sub>3</sub>, CD<sub>3</sub>OD, D<sub>2</sub>O or

DMSO-*d*<sub>6</sub> with Me<sub>4</sub>Si as the internal standard. The multiplicities are denoted as s-singlet, brs-broad singlet, d-doublet, brm-broad multiplet, t-triplet, q-quartet, dt-doublet triplet and m-multiplet. <sup>13</sup>C-NMR spectra were recorded at 75 MHz or at 100 MHz instrument. The chemical shifts are reported in  $\delta$  values (parts per million, ppm) relative to the internal standard Me<sub>4</sub>Si.

High-resolution mass spectra were recorded with a Q-TOF Bruker instrument, using electrospray ionization (ESI) as the ionization method.

### **X-ray crystallography**

Suitable crystal of compounds, have been carried out using BRUKER AXS SMART-APEX diffractometer equipped with CCD area detector ( $K\alpha=0.71073\text{\AA}$ , monochromator: graphite). Frames were collected at T=298K by  $\omega$ ,  $\phi$  and  $2\theta$ -rotation with full quadrant data collection strategy (four domains each with 600 frames) at 10s per frame with SMART. The measured intensities were reduced to  $F^2$  and corrected for absorption with SAINT. Structure solution and refinement were carried out with the SHELXTL package by direct methods. Non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in idealized positions, and a riding model was used for the refinement.

## COMMON ABBREVIATIONS

<b>ent</b>	<b>Enantiomer</b>
<b>Cbz</b>	Carbobenzyloxy
<b>2,2-DMP</b>	2,2-Dimethoxy propane
<b>Boc</b>	Tertiary-butoxycarbonyl
<b>epi</b>	Epimer
<b>aq</b>	Aqueous
<b>Bn</b>	Benzyl
<b>Conc.</b>	Concentrated
<b>LDA</b>	Lithium diisopropyl amide
<b>c</b>	Concentration
<b>cat</b>	Catalyst
<b>COSY</b>	Correlation Spectroscopy
<b>HSQC</b>	Heteronuclear Single Quantum Coherence
<b>NOESY</b>	Nuclear Overhauser Effect Spectroscopy
<b>HMBC</b>	Heteronuclear Multiple Bond Correlation
<b>HETCOR</b>	Heteronuclear Correlation
<b>DCC</b>	<i>N, N'</i> -dicyclohexylcarbodiimide
<b>DCM</b>	Dichloromethane
<b>DEAD</b>	Diethyl azodicarboxylate
<b>DMAP</b>	4-dimethylaminopyridine
<b>DMF</b>	<i>N, N'</i> -dimethylformamide
<b>DMSO</b>	Dimethylsulfoxide
<b>ppm</b>	Parts per million
<b>dr</b>	Diastereomeric ratio
<b>DEPT</b>	Distortionless Enhancement by Polarization Transfer
<b>equiv</b>	Equivalent
<b>ESI</b>	Electrospray ionization
<b>CSA</b>	Camphor sulphonic acid

<b>g</b>	Gram
<b>GalNAcase</b>	<i>N</i> -acetyl- $\alpha$ -D-galactosaminidase
<b>h</b>	Hour
<b>HRMS</b>	High Resolution Mass Spectrometry
<b>Hz</b>	Hertz
<b>IC<sub>50</sub></b>	Half maximal Inhibitory Concentration
<b><sup>i</sup>Pr</b>	Isopropyl
<b>IR</b>	Infrared
<b>K<sub>i</sub></b>	Inhibition Constant
<b>LAH</b>	Lithium Aluminum Hydride
<b>Me</b>	Methyl
<b>mg</b>	Milligrams
<b>min</b>	Minute
<b>mL</b>	Milliliters
<b>mM</b>	Millimolar
<b>mmol</b>	Millimoles
<b><math>\mu</math>M</b>	Micromolar
<b>M.p.</b>	Melting Point
<b>Ms</b>	Mesyl
<b>MS</b>	Molecular sieves
<b>MHz</b>	Megahertz
<b>m/z</b>	mass-to-charge ratio
<b>NBS</b>	<i>N</i> -Bromosuccinimide
<b>NIS</b>	<i>N</i> -Iodosuccinimide
<b>nM</b>	Nanomolar
<b>NMO</b>	<i>N</i> -Methylmorpholine <i>N</i> -oxide
<b>NMR</b>	Nuclear magnetic resonance
<b>Nu</b>	Nucleophile
<b>Pd/C</b>	Palladium on activated carbon
<b>Ph</b>	Phenyl
<b><i>p</i>-TSA</b>	Para-toluenesulfonic acid
<b>TsCl</b>	Para-toluenesulfonyl chloride

<b>Ts</b>	Para-toluenesulfonyl
<b>R<sub>f</sub></b>	Retention factor
<b>ref</b>	Reference
<b>rt</b>	Room temperature
<b>TBAF</b>	Tertiary-butyldimethylsilyl fluoride
<b>TBS</b>	Tertiary-butyldimethylsilyl
<b>TBSCI</b>	Tertiary-butyldimethylsilyl chloride
<b>TBSOTf</b>	Tertiary-butyldimethylsilyltriflate
<b>TBDPS</b>	Tertiary-butyl diphenylsilyl
<b>TMSCN</b>	Trimethylsilyl cyanide
<b>THF</b>	Tetrahydrofuran
<b>TLC</b>	Thin layer chromatography
<b>TMS</b>	Tetramethylsilane
<b>liq</b>	Liquid
<b>DIPEA</b>	Diisopropyl ethyl amine
<b>Py</b>	Pyridine
<b>DNA</b>	Deoxyribonucleic acid
<b>RNA</b>	Ribonucleic acid
<b>ATP</b>	Adenosine triphosphate
<b>HIV</b>	Human immunodeficiency virus
<b>AIDS</b>	Acquired immunodeficiency syndrome
<b>US FDA</b>	United states Food and Drug Administration
<b>HBV</b>	<i>Hepatitis B</i> virus
<b>HCV</b>	<i>Hepatitis C</i> virus
<b>mRNA</b>	Messenger Ribonucleic acid
<b>AON</b>	Antisense oligonucleotide
<b>PNP</b>	Purine nucleoside phosphorylase
<b>Ipc</b>	Diisopinocampyl
<b>de</b>	Diastereomeric excess
<b>mCPBA</b>	Meta chloroperbenzoic acid
<b>TFA</b>	Trifluoroacetic acid
<b>Fmoc</b>	Fluorenylmethoxycarbonyl

<b>DMTrCl</b>	Dimethoxytrityl chloride
<b>CbzCl</b>	Carboxybenzyl chloride
<b>DAST</b>	Diethylaminosulfurtrifluoride
<b>cAMP</b>	Cyclic adenosine mono phosphate
<b>cGMP</b>	Cyclic guanosine mono phosphate
<b>NAD<sup>+</sup></b>	Nicotinamide adenine dinucleotide
<b>NADP<sup>+</sup></b>	Nicotinamide adenine dinucleotide phosphate
<b>FAD</b>	Flavin adenine dinucleotide
<b>FMN</b>	Flavin mono nucleotide
<b>dGTP</b>	Deoxyguanosine triphosphate