DIVERGENT SYNTHESIS OF NOVEL FIVE-MEMBERED, SIX-MEMBERED AND BRIDGED BICYCLIC IMINOCYCLITOLS

by

GANESAN M

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submitted

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INDIA

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This thesis is dedicated to my beloved parents

Mr. Muthupandian *and* ***Mrs. Palanithai***

for their love, endless support

and encouragement

CERTIFICATE

This is to certify that the thesis entitled "**DIVERGENT SYNTHESIS OF NOVEL FIVE-MEMBERED, SIX-MEMBERED AND BRIDGED BICYCLIC IMINOCYCLITOLS**", being submitted by **Mr. GANESAN M** 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. GANESAN M 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.

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ABSTRACT

The thesis titled "**Divergent Synthesis of Novel Five-membered, Six-membered and Bridged Bicyclic Iminocyclitols**" presents the research work carried out on the synthesis of novel skeletally diverse iminocyclitols from a single starting material viz., tri-*O*-benzyl-D-glucal. Their inhibition studies against commercially available glycosidases are also discussed.

Iminosugars are polyhydroxylated alkaloids and can be viewed as sugar derivatives in which the endocyclic oxygen atom has been replaced with a basic nitrogen atom. These compounds are highly medically relevant and their biological activities mainly orient towards inhibition of glycosidases, due to which they find immense applications as drug molecules against various diseases. This is clearly evident from the fact that quite a few iminosugar based drugs have already hit the market and many more are in their earlier/advanced clinical trials.

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

Chapter I highlights a brief general overview on the history, natural occurrence and therapeutic applications of iminosugars.

Chapter II describes design, synthesis and glycosidase inhibition studies of novel amino-modified polyhydroxypyrrolidines. This is the first glycal based approach reported for the synthesis of such class of iminocyclitols. The synthesis is one of the shortest reported so far and requires only 4–6 steps from readily available tri-*O*-benzyl-D-glucal with high yields in all the steps. Quite interestingly, two of the amino-modified five-membered iminocyclitols reported in this chapter have been found to very specifically inhibit α–galactosidase among the various

glycosidases that have been considered for inhibition studies. Since inhibitors of α–galactosidase have been found to be promising chemical chaperones for Fabry's disease, these two compounds are likely to find potential applications in this direction as well.

Chapter III discusses a new and short synthesis of naturally occurring 1-deoxy-L-*gulo*nojirimycin from tri-*O*-benzyl-D-glucal in high yield. With the help of single crystal X-ray structure of one of the intermediates, it was unambiguously proved that the naturally occurring *gulo*-DNJ indeed belongs to the L-family, which was reported to be belonging to D-family when it was isolated.

Divergent synthesis of novel (1*S*,4*R*,5*S*,8*R*)-2,6-diaza-bicyclo[3.2.1]octane-4,8-diol and 6-amino-1,6-dideoxy-L-*gulo*nojirimycin from a single starting material, through protecting group dictated regio-divergent cyclization strategy constitute the research work described in **Chapter IV**. The bicyclic diazasugar, namely, 2,6-diaza-bicyclo[3.2.1]octane-4,8-diol was obtained through an unprecented one-pot three step domino "*intramolecular cyclization-benzoyl migration-cyclization*" process. Synthesis of hitherto unreported amino-analogue of DNJ, viz. 6-amino-1,6-dideoxy-L-*gulo*nojirimycin was also accomplished. The inhibition studies of these compounds revealed that they selectively inhibit *N*-acetyl-β-hexosaminidase among a few commercially available glycosidases that were tested upon.

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