GLYCAL BASED DIVERSITY ORIENTED APPROACH TO THE SYNTHESIS OF (–)-CONDURAMINE F-4, (–)-CONDURAMINE B-2, *ent*-CONDURAMINE F-2, (+)-ANISOMYCIN, AMINOCYCLITOLS AND IMINOCYCLITOLS

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INDIAN INSTITUTE OF TECHNOLOGY DELHI
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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

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This thesis is dedicated to my beloved parents

(Late) ***Mr. Keshraj Singh*** *and* ***Mrs. Shashi Kanta***

CERTIFICATE

This is to certify that the thesis entitled "**Glycal Based Diversity Oriented Approach to the Synthesis of (–)-Conduramine F-4, (–)-Conduramine B-2, *ent*-Conduramine F-2, (+)-Anisomycin, Aminocyclitols and Iminocyclitols",** being submitted by **Mr. VIMAL KANT HARIT** 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. VIMAL KANT HARIT 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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(Vimal Kant Harit)

ABSTRACT

The thesis titled "**Glycal Based Diversity Oriented Approach to the Synthesis of (–)-Conduramine F-4, (–)-Conduramine B-2, *ent*-Conduramine F-2, (+)-Anisomycin, Aminocyclitols and Iminocyclitols"** presents the work carried out on the synthesis of all titled molecules starting from tri-*O*-benzyl-D-glucal. Enzyme inhibition studies against five commercially available glycosidases were also carried out.

Chapter I describes 'reagent-based diversity' strategy on a tri-*O*-benzyl-D-glucal derived 'common precursor' for the synthesis of three distinct target molecules of pharmacological relevance. In this chapter, for the first time, application of McMurry coupling for the construction of the six-membered carbocyclic aminocyclitols has been demonstrated. The first carbohydrate based approach towards the total synthesis of (–)-conduramine F-4 is reported. The chapter also describes the synthesis of amino-azepanes using double nucleophilic substitution which provided access to a collection of a few *N*-substituted azepane derivatives.

Chapter II describes a common strategy towards the synthesis of three structurally distinct target molecules, namely 1,4-Dideoxy-1,4-imino-L-xylitol (L-DIX), deacetyl (+)-anisomycin and amino-substituted piperidine iminosugars of biological and medicinal significance. The synthesis of common intermediate pyrrolidine was achieved through a novel concomitant ring closure upon oxidative cleavage of a vicinal diol derived in a few steps from tri-*O*-benzyl-D-glucal.

Chapter III describes a ring closing metathetical (RCM) approach for the synthesis of six membered and five membered aminocyclitols. This chapter also reports a novel glycosylation reaction on a tri-*O*-benzyl-D-glucal derived 2-iodo-2-deoxy-1-(*p*-

toluenesulfonamido) derivative for the synthesis of methyl-2-deoxy-2-(*p*-toluenesulfonamido)-β-D-glucoside, which was taken forward to synthesize a common formyl-olefin intermediate. Through RCM of appropriate substrates, synthesized from the common intermediate, three structurally different types of molecules were obtained.

सार

थीसिस का शीर्षक "ग्लाइकॉल आधारित विविधता ओरिएंटेड एप्रोच टू द सिन्थेसिस ऑफ़ (–)-कॉन्ड्यूरामाइन F-4, (–)-कॉन्ड्यूरामाइन B-2, कॉन्ड्यूरामाइन F-2, (+)-एनिसोमाइसिन, अमीनोसायक्लिटोल्स और इमिनोसायक्लिटोल्स है। त्रि-ओ-बेंजाइल-डी-ग्लुकल से शुरू होने वाले सभी शीर्षक वाले अणुओं के संश्लेषण पर किए गए कार्य को प्रस्तुत करता है। पांच व्यावसायिक रूप से उपलब्ध ग्लाइकोसिडेसिस के खिलाफ एंजाइम निषेध अध्ययन भी किए गए।

अध्याय I, औषधीय प्रासंगिकता के तीन अलग-अलग लक्ष्य अणुओं के संश्लेषण के लिए त्रि-ओ- बेंजाइल -डी-ग्लुकल व्युत्पन्न 'सामान्य अग्रदूत' पर 'अभिकर्मक-आधारित विविधता' रणनीति का वर्णन करता है। इस अध्याय में, पहली बार, छह-सदस्यीय कार्बोसाइक्लिक एमिनोसाइक्लिटोल्स के निर्माण के लिए मैकमरी कपलिंग के उपयोग का प्रदर्शन किया गया है। (–)-कॉन्ड्यूरामाइन F-4 के कुल संश्लेषण के प्रति पहला कार्बोहाइड्रेट आधारित दृष्टिकोण बताया गया है। अध्याय में डबल न्यूक्लियोफिलिक प्रतिस्थापन का उपयोग करते हुए अमीनो-एजेपेंस के संश्लेषण का भी वर्णन किया गया है।

अध्याय II, में तीन संरचनात्मक रूप से अलग लक्ष्य अणुओं के संश्लेषण की दिशा में एक सामान्य रणनीति का वर्णन किया गया है, जैविक और औषधीय महत्व के अणुओं, क्रमशः 1,4-डिडॉक्सी-1,4-इमिनो-एल-ज़ाइलिटोल (एल-डीक्स), डीएसेटाइल (+)-एनिसोमाइसीन और एमिनो-प्रतिस्थापित पिपेरिडीन इमिनोसुगर शामिल हैं। त्रि-ओ-बेंजाइल-डी-ग्लुकल से कुछ ही चरणों में व्युत्पन्न एक विसीनल डायोल के ऑक्सीडेटिव क्लैवेज पर एक सहचारी रिंग क्लोजर के माध्यम से सामान्य मध्यवर्ती पाइरोलिडीन के संश्लेषण को प्राप्त किया गया।

अध्याय III, में छह सदस्यीय और पांच सदस्यीय अमीनोसायक्लिटोल्स के संश्लेषण के लिए एक रिंग क्लोजिंग मेटाथैटिकल (RCM) दृष्टिकोण का वर्णन किया गया है। इस अध्याय में त्रि-ओ-बेंजाइल-डी-ग्लुकल व्युत्पन्न 2-आयोडो-2-डीऑक्सी-1-(पी-टोलुइनसल्फोनोमीडो)-D-ग्लूकोज पर एक नई ग्लाइकोसिलेशन प्रतिक्रिया का वर्णन किया गया है, फिर जिसे एक सामान्य फॉर्मेल-ओलेफिन मध्यवर्ती

को संश्लेषित करने के लिए किया गया। सामान्य मध्यवर्ती से संश्लेषित, उपयुक्त सब्सट्रेट्स के आरसीएम के माध्यम से, तीन संरचनात्मक रूप से विभिन्न प्रकार के अणु प्राप्त किए गए।

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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, benzene) or molecular sieves (CH_2Cl_2, $CHCl_3$, 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 $KMnO_4$ 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).

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^{-1} as KBr pellets on a Nicolet (Madison, USA) FT-IR spectrophotometer (Model Protégé 460).

^{1}H-NMR spectra were recorded on a 300 MHz or 400 MHz Bruker Spectrospin DPX FT-NMR instruments. The solvents employed were $CDCl_3$, D_2O or DMSO-d_6 with Me_4Si 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. ^{13}C-NMR spectra were recorded at 75 MHz or at 100 MHz instrument. The chemical shifts are reported in δ values (parts per million, ppm) relative to the internal standard Me_4Si.

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

COMMON ABBREVIATIONS

aq	:	Aqueous
Bn	:	Benzyl
BnBr	:	Benzyl bromide
BnOH	:	Benzyl alcohol
Boc	:	Tertiary-butoxycarbonyl
n-BuLi	:	*n*-Butyllithium
BzCl	:	Benzoyl chloride
c	:	Concentration
Cat	:	Catalyst
Cbz	:	Carbobenzyloxy
CbzCl	:	Carboxybenzyl chloride
Conc.	:	Concentrated
COSY	:	Correlation Spectroscopy
mCPBA	:	Meta chloro perbenzoic acid
CSA	:	Camphor sulphonic acid
CSO	:	Carbonyl sulfide
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	:	*N*, *N*'-dicyclohexylcarbodiimide
DCN	:	1,4-dicyanonaphthalene
de	:	Diastereomeric excess
DEAD	:	Diethyl azodicarboxylate
DIBAL-H	:	Diisobutylaluminium hydride
DIPEA	:	*N*,*N*-Diisopropylethylamine
DMAP	:	4-Dimethylaminopyridine
DME	:	Dimethoxyethane
DMF	:	*N*, *N*'-dimethylformamide
DMP	:	2,2-Dimethoxy propane
DMSO	:	Dimethylsulfoxide
dr	:	Diastereomeric ratio
ee	:	Enantiomeric excess

ent	:	Enantiomer
Et_3SiH	:	Triethylsilane
epi	:	Epimer
equiv	:	Equivalent
g	:	Gram
GalNAcase	:	*N*-acetyl-α-D-galactosaminidase
G_{M1}	:	Monosialotetrahexosylganglioside
h	:	Hour
HRMS	:	High Resolution Mass Spectrometry
HSQC	:	Heteronuclear Single Quantum Coherence
Hz	:	Hertz
IC_{50}	:	Half maximal Inhibitory Concentration
Imd	:	Imidazole
IR	:	Infrared
K_i	:	Inhibition Constant
KHMDS	:	Potassium *bis*(trimethylsilyl)amide
LAH	:	Lithium aluminium hydride
LDA	:	Lithium diisopropyl amide
liq	:	Liquid
Martin sulfurane	:	Bis[α,α-bis(trifluoromethyl)benzyloxy]diphenylsulfur
Me	:	Methyl
MeCN	:	Acetonitrile
mg	:	Milligrams
MHz	:	Megahertz
min	:	Minute
mL	:	Milliliters
mM	:	Millimolar
mmol	:	Millimoles
μM	:	Micromolar
MOMI	:	Methoxymethyl iodide
M.P.	:	Melting Point
Ms	:	Mesyl

MS	:	Molecular sieves
MsCl	:	Methanesulfonyl chloride
MW	:	Microwave
m/z	:	mass-to-charge ratio
NaH	:	Sodium hydride
NHC	:	*N*-Heterocyclic carbene
nM	:	Nanomolar
NMO	:	4-Methylmorpholine *N*-oxide
NMR	:	Nuclear magnetic resonance
Nu	:	Nucleophile
PDC	:	Pyridinium Dichromate
Pd/C	:	Palladium on activated carbon
Ph	:	Phenyl
PivCl	:	Pivaloyl chloride
ppm	:	Parts per million
PPTS	:	Pyridinium *p*-toluenesulfonate
^{i}Pr	:	Isopropyl
Py	:	Pyridine
R_f	:	Retention factor
ref	:	Reference
rt	:	Room temperature
TBATB	:	Tetrabutylammonium tribromide
TFA	:	Trifluoroacetic acid
Ts	:	Para-toluenesulfonyl
)))	:	Sonication