TOTAL SYNTHESIS OF (−)-HYGROPHORONE A[12], 4-*epi*-2,3-DIHYDROHYGROPHORONE H[12] AND DISCOVERING POTENT QUORUM SENSING INHIBITORS THROUGH IN SILICO STUDIES

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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

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Dedicated to

All the inside-outside voices,
That uttered it could not be done,
Nothing can be won.

To all the children, away from school,
Hoping for their Jolly Pool.
Envisioning for their lives to fuel,
And to those dreaming for their debut in the classroom,
Where they'll undoubtedly bloom.

To all the girls out there,
Who dream,
Have vision, ambition, ignition,
And have already taken their first step,
For their new, to pursue, adept.

To all the outstanding teachers of the country,
For shaping the lives of millions.
And finally,

To all the parents who worked & works day-night.
For providing the moral wings,
To their offspring.

Submitting to the premiere institute hoping for its ten-fold growth in upcoming years!

CERTIFICATE

This is to certify that thesis entitled **"Total synthesis of (−)-hygrophorone A^{12}, 4-*epi*-2,3-dihydrohygrophorone H^{12} and discovering potent quorum sensing inhibitors through *in silico* studies",** being submitted by **ANU DALAL** 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 her. **Ms Anu Dalal** has worked under my supervision and guidance. She has fulfilled all the requirements for the submission of a PhD thesis, which to my knowledge, has reached the requisite standard and is worthy of consideration for the award of a PhD degree.

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

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ABSTRACT

The thesis titled "**Total synthesis of (−)-hygrophorone A[12], 4-*epi*-2,3-dihydrohygrophorone H[12] and discovering potent quorum sensing inhibitors through *in silico* studies"** presents the work carried out on the total synthesis (−)-hygrophorone A[12], 4-*epi*-2,3-dihydrohygrophorone H[12] and using *in silico* tools to discover potent quorum sensing inhibitors

Chapter 1 describes the stereoselective total synthesis of anti-fungal cyclopentenone (−)-hygrophorone A[12] and cyclopentanone 4-*epi*-2,3-dihydrohygrophorone H[12] in high overall yields from D-ribose. The key step of this syntheses is an aqueous KOH mediated diastereoselective intramolecular aldol reaction to form *β*-hydroxy ketone with three contiguous chiral centres, which was further elaborated to (−)-hygrophorone A[12] and (+)-hygrophorone B[12].

Chapter 2 This chapter consists of three subsections discussing three classes of molecules namely, hygrophorones, pentenomycins, and crown ethers to be potential inhibitors for the LasR protein in the QS pathway of *P. aeuriginosa* bacteria. In the hygrophorone class, we found 8 molecules from a pool of 64 different molecules, while from the crown ethers only 5 out of 54 molecules have shown promising results. Hygrophorones seem to be the structural analog of autoinducer AHL (natural ligand for LasR). Most of the top scored molecules of hygrophorone series reflect higher binding energy than the rest of the molecules of different classes. On the contrary, the pentenomycin class molecules have poor binding efficiency due to their small size and the lack of the alkyl chain. However, previous literature reports and our simulations results confirm that the addition of an alkyl chain to the pentenomycin molecules will enhance their interaction with the LasR active site residues (coherence with *in vitro* studies reported).

Crown ethers seem to be the intermediate candidate for LasR inhibition. C5-5, C5-10, and C5-11 are some of the best candidates among 54 chosen ligands. This macrocyclic crown moiety of the crown ethers gets stabilized in the polar pocket of the LasR protein, while the aromatic or alkyl chain gets stabilised in the non-polar pocket of LasR. In summary, comparable, and higher binding energies of the lead compounds obtained from our study from that of naturally occurring autoinducer AHL reflect these molecules to be potential candidates as inhibitors for the LasR target. We hope our work will spur further experimental studies that would lead to the discovery of new antibiotics for *P. aeruginosa* infections.

Chapter 3 This chapter unravels the molecular level insights and the binding mechanism for pentenomycin to behave as a broad range antibiotic. In our computational study, we found that pentenomycin binds with the LuxP protein and can even bind with the LuxP homologue, LsrB. Based on molecular docking, molecular dynamics simulations, and MMPBSA calculations, it was observed that pentenomycin induces conformational changes of LsrB/LuxP from its closed to open state. Pentenomycin ligand prevents domain closure (as seen in the cases of 1TJY, 3EJW, 3T95) thereby blocking PBP signals and ultimately shutting down the QS cascade and virulence factors. For other proteins, it was observed that pentenomycin occupies the active binding site without causing much of the structural change in protein and preventing binding with AI-2, hence again shutting QS cascade (as seen in the cases of 5BQ3, 5BRA, 5GTA, 6DSP). Through these computational studies, we predict that pentenomycin would prove to be a better antibiotic in the case of bacteria having periplasmic binding proteins (such as LuxP or LsrB). Because PBPs share a common architecture and hinge motion upon opening and closing and we anticipate that pentenomycin takes the exact binding site and prevents domain closure in some while in others it may occupy active site thereby preventing the binding of AI-2.

सार

थीसिस शीर्षक **"(-)-हाइग्रोफोरोन ए[12], 4-एपी-2,3-डायहाइड्रोहाइग्रोफोरोन एच[12] और इनसिलिको स्टडीज के माध्यम से शक्तिशाली कोरम सेंसिंग इनहिबिटर की खोज"** कुल संश्लेषण (-)-हाइग्रोफोरोन ए[12] पर किए गए कार्य को प्रस्तुत करता है। , 4-एपी-2,3-डायहाइड्रोहाइग्रोफोरोन और शक्तिशाली कोरम सेंसिंग इनहिबिटर की खोज के लिए इनसिलिको टूल्स का उपयोग करना।

अध्याय 1 डी-राइबोज से उच्च समग्र पैदावार में एंटी-फंगल साइक्लोपेंटेनोन (-)-हाइग्रोफोरोन ए[12] और साइक्लोपेंटेनोन 4-एपी-2,3-डायहाइड्रोहाइग्रोफोरोन एच[12] के स्टीरियोसेलेक्टिव कुल संश्लेषण का वर्णन करता है। इस संश्लेषण का मुख्य चरण एक जलीय KOH मध्यस्थता डायस्टेरियोसेलेक्टिव इंट्रामोल्युलर एल्डोल प्रतिक्रिया है जो तीन सन्निहित चिरल केंद्रों के साथ β-हाइड्रॉक्सी कीटोन बनाता है, जिसे आगे (-)-हाइग्रोफोरोन ए[12] और (+)-हाइग्रोफोरोन बी[12] के लिए विस्तृत किया गया था।

अध्याय 2 इस अध्याय में तीन उपखंड हैं जिनमें तीन वर्गों के अणुओं पर चर्चा की गई है, जैसे कि हाइग्रोफोरोन, पेंटेनोमाइकिन्स, और क्राउन ईथर, पी. एयूरिगिनोसा बैक्टीरिया के क्यूएस मार्ग में एलएसआर प्रोटीन के संभावित अवरोधक होने के लिए। हाइग्रोफोरोन वर्ग में, हमने 64 विभिन्न अणुओं के एक पूल से 8 अणु पाए, जबकि क्राउन ईथर से 54 में से केवल 5 अणुओं ने आशाजनक परिणाम दिखाए हैं। हाइग्रोफोरोन ऑटोइंड्यूसर AHL (LasR के लिए प्राकृतिक लिगैंड) का संरचनात्मक एनालॉग प्रतीत होता है। हाइग्रोफोरोन श्रृंखला के अधिकांश शीर्ष अणु विभिन्न वर्गों के बाकी अणुओं की तुलना में उच्च बाध्यकारी ऊर्जा को दर्शाते हैं। इसके विपरीत, पेंटेनोमाइसिन वर्ग के अणुओं में उनके छोटे आकार और

अल्काइल श्रृंखला की कमी के कारण खराब बाध्यकारी दक्षता होती है। हालाँकि, पिछले साहित्य रिपोर्ट और हमारे सिमुलेशन परिणाम इस बात की पुष्टि करते हैं कि पेंटेनोमाइसिन अणुओं के लिए एक एल्काइल श्रृंखला के अलावा लासआर सक्रिय साइट अवशेषों (इन-विट्रो अध्ययनों के साथ सुसंगतता) के साथ उनकी बातचीत में वृद्धि होगी। क्राउन ईथर LasR निषेध के लिए मध्यवर्ती उम्मीदवार प्रतीत होते हैं। C5-5, C5-10, और C5-11 54 चुने हुए लिगेंड में से कुछ सर्वश्रेष्ठ उम्मीदवार हैं। क्राउन ईथर का यह मैक्रोसाइक्लिक क्राउन मोइविटी LasR प्रोटीन के ध्रुवीय पॉकेट में स्थिर हो जाता है, जबकि सुगंधित या एल्काइल श्रृंखला LasR के गैर-ध्रुवीय पॉकेट में स्थिर हो जाती है। संक्षेप में, प्राकृतिक रूप से पाए जाने वाले ऑटोइंड्यूसर एएचएल से हमारे अध्ययन से प्राप्त प्रमुख यौगिकों की तुलनीय और उच्च बाध्यकारी ऊर्जा इन अणुओं को लासआर लक्ष्य के अवरोधक के रूप में संभावित उम्मीदवारों के रूप में दर्शाती है। हमें उम्मीद है कि हमारा काम आगे के प्रायोगिक अध्ययनों को बढ़ावा देगा जिससे पी. एरुगिनोसा संक्रमण के लिए नई एंटीबायोटिक दवाओं की खोज हो सकेगी।

अध्याय 3 यह अध्याय आणविक स्तर की अंतर्दृष्टि और पेंटेनोमाइसिन के लिए एक व्यापक श्रेणी के एंटीबायोटिक के रूप में व्यवहार करने के लिए बाध्यकारी तंत्र को उजागर करता है। हमारे कम्प्यूटेशनल अध्ययन में, हमने पाया कि पेंटेनोमाइसिन लक्सपी एंजाइम के साथ बांधता है और यहां तक कि लक्सपी होमोलॉग, एलएसआरबी के साथ भी जुड़ सकता है। आणविक डॉकिंग, आणविक गतिकी सिमुलेशन और एमएमपीबीएसए गणनाओं के आधार पर, यह देखा गया कि पेंटेनोमाइसिन एलएसआरबी/लक्सपी के बंद से खुले राज्य में गठनात्मक परिवर्तनों को प्रेरित करता है। पेंटेनोमाइसिन लिगैंड डोमेन को बंद होने से रोकता है (जैसा कि 1TJY, 3EJW, 3T95 के मामलों में देखा गया है) जिससे PBP सिग्नल अवरुद्ध

हो जाते हैं और अंततः QS कैस्केड और पौरुष कारकों को बंद कर देते हैं। अन्य प्रोटीनों के लिए, यह देखा गया कि पेंटेनोमाइसिन प्रोटीन में अधिक संरचनात्मक परिवर्तन किए बिना सक्रिय बाध्यकारी साइट पर कब्जा कर लेता है और एआई-2 के साथ बंधन को रोक सकता है, इसलिए फिर से क्यूएस कैस्केड बंद कर देता है (जैसा कि 5BQ3, 5BRA, 5GTA के मामलों में देखा गया है) , 6DSP)। इन कम्प्यूटेशनल अध्ययनों के माध्यम से, हम अनुमान लगाते हैं कि पेरिप्लास्मिक बाइंडिंग प्रोटीन (जैसे लक्सपी या एलएसआरबी) वाले बैक्टीरिया के मामले में पेंटेनोमाइसिन एक बेहतर एंटीबायोटिक साबित होगा। क्योंकि पीबीपी खोलने और बंद होने पर एक सामान्य वास्तुकला और काज गति साझा करते हैं और हम अनुमान लगाते हैं कि पेंटेनोमाइसिन सटीक बाध्यकारी साइट लेता है और कुछ में डोमेन बंद होने से रोकता है जबकि अन्य में यह सक्रिय साइट पर कब्जा कर सकता है जिससे एआई-2 के बंधन को रोका जा सकता है।

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CHAPTER 2:

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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 an inert atmosphere was freed from oxygen prior to entry into the reaction vessel.

Commercially sourced TLC plates were used, and the spots were visualized by exposure to iodine or by dipping in $KMnO_4$. Column chromatography was carried out on silica gel (230–400 mesh) using hexane and ethyl acetate mixtures 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).

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

^{1}H-NMR spectra were recorded on 300 MHz or 400 MHz, or 500 MHz Bruker Spectrospin DPX FT-NMR instruments. The solvents employed were $CDCl_3$ or CD_3OD 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 100 MHz, or 125 MHz instruments. 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.

SOFTWARE

For chapter 2 and 3, structures were drawn in ChemDraw and saved in SDF file format. The molecules were minimized using the Steepest Descent algorithm with the Universal Force Field (uff) as implemented in the PyRx software. The coordinates of the proteins were downloaded from the RCSB protein data bank. Hydrogen atoms were added, and structure optimization was done using the clean geometry module of discovery studio (Accelerys San Diego, CA, USA). In the docking technique, all water molecules were removed. Subsequently, hydrogen atoms were added to the protein residues, and Kollman atomic charges were assigned to the protein atoms using AutoDock MGL Tools 1.5.6.

All simulations were carried out using the GROMACS 5.1.4 software provided by HPC IIT Delhi. The force field used is GROMOS96 43a1. Ligand topology files were created with the help of the PRODRG server. The long-range electrostatic interactions were described by the Particle Ewald Mesh method. Using the LINCS algorithm, all bonds involving hydrogen atoms were restrained. The system's temperature is controlled at 300 K using the Berendsen thermostat while the pressure is maintained at 1 bar using the Parrinello-Rahman barostat. The GROMACS g_mmpbsa module was used to calculate the binding free energies. The configurations collected every 100 ps of the last 10 ns of the MD simulations were used for these analyses.

LIST OF ABBREVIATIONS

Ac	:	acetyl
Ac_2O	:	acetic anhydride
Anhyd.	:	anhydrous
Ar	:	aryl
aq	:	aqueous
AI	:	autoinducer
Bn	:	benzyl
brs	:	broad singlet
C	:	concentration
calcd	:	calculated
cat.	:	catalytic
cm	:	centimeter
DCM	:	dichloromethane
dd	:	doublet of a doublet
ddd	:	doublet of a doublet of a doublet
ddt	:	doublet of a doublet of a triplet
dt	:	doublet of a triplet
DIPA	:	*N*, *N*-diisopropylamine
DIPEA	:	*N*, *N*-diisopropylethylamine
DMF	:	*N*, *N*-dimethylformamide
DMAP	:	4-(*N*,*N*-dimethylamino)pyridine
2,2-DMP	:	2,2-dimethoxy propane
DMP	:	Dess-Martin periodinane
DMSO	:	dimethylsulfoxide
dr	:	diastereomeric ratio
dt	:	doublet of a triplet
ent	:	enantiomer
eq.	:	equivalents
Et	:	ethyl
Fig.	:	figure
g	:	gram(s)

h	:	hour(s)
HRMS	:	high resolution mass spectrum
Hz	:	hertz
IC_{50}	:	half maximal inhibitory concentration
^{i}Pr	:	isopropyl
IR	:	infrared
liq	:	liquid
Lit.	:	literature
LiHMDS	:	lithium hexamethyldisilazide
m	:	multiplet
m-CPBA	:	*meta*-chloroperbenzoic acid
Me	:	methyl
mg	:	milligram(s)
MHz	:	megahertz
min	:	minute(s)
mL	:	milliliter(s)
mmol	:	millimole
MOM	:	methoxymethyl
M.p.	:	melting point
MS	:	Molecular sieves
MD	:	molecular dynamics
NMR	:	Nuclear Magnetic Resonance
p	:	para
Ph	:	phenyl
ppm	:	parts per million
PPTS	:	pyridinium para-toluenesulphonate
p-TSA	:	*para*-toluenesulfonic acid
py	:	pyridine
pent.	:	pentet
q	:	quartet
QS	:	quorum sensing
rt	:	room temperature
RMSD	:	root mean square deviation

RMSF	:	root mean square fluctuation
Rg	:	radius of gyration
s	:	singlet
sat.	:	saturated
SASA	:	solvent accessible surface area
^{t}Bu	:	*tertiary*-Butyl
t	:	triplet
td	:	triplet of a doublet
TBAF	:	tetra-*n*-butylammonium fluoride
TBS	:	*tertiary*-butyldimethylsilyl
TBDMSCl	:	*tertiary*-butyldimethylsilyl chloride
TBDMSOTf	:	*tertiary*-butyldimethylsilyl trifluromethanesulfonate
tert	:	*tertiary*
TFA	:	trifluoroacetic acid
THF	:	tetrahydrofuran
TLC	:	thin layer chromatography
UV	:	ultraviolet