DESIGN AND SYNTHESIS OF BIOLOGICALLY RELEVANT HETEROCYCLES

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by

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CERTIFICATE

This is to certify that the thesis entitled, **"DESIGN AND SYNTHESIS OF BIOLOGICALLY RELEVANT HETEROCYCLES"** being submitted by **Mr. Deshmukh Mahesh Subhashrao** to the Indian Institute of Technology, Delhi, for the award of the degree of **Doctor of Philosophy** in chemistry, is a record of bonafide research work carried out by him. He has worked under my guidance and supervision. He has fulfilled all the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

The results embodied in this thesis have not been submitted, in part or in full, to any other university or institute for award of any degree or diploma.

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ABSTRACT

Chapter 1: An overview of the importance of heterocyclic compounds in different fields such as natural products, transition metal-ligands, organocatalysts and medicines has been provided. Further, different approaches used for their synthesis have also been discussed.

Chapter 2: An unprecedented one-pot synthesis of substituted 1,2,3,4-tetrahydroquinoxalines, 2,3-dihydro-1,4-benzoxazines, and 1,4-benzodioxines from activated *ortho*-halonitrobenzenes has been discussed. The reaction proceeds by dual nucleophilic aromatic substitution (S_NAr) of halogen followed by substitution of the nitro group by secondary diamines, secondary amino alcohols, and diols respectively.

Chapter 3: An unprecedented zinc triflate catalyzed selective C-benzylation of anilides and heteroaryl amides with benzyl chlorides having electron-donating group at *para*-position has been demonstrated. The methodology offers moderate to high yield of para-amido substituted diaryl and arylheteroarylmethanes, uses cheap and easily available benzyl chlorides as the benzylating agent, catalytic amount of zinc triflate, and takes place under ambient conditions. The methodology has also been applied for preparing dimethoxydiarylmethanes in good yields, which are the key precursors for synthesis of phenolic natural products.

Chapter 4: Design, synthesis and antibacterial evaluation of a series of novel oxazolidinone derivatives with diverse fused heteroaryl C-rings bearing hydrogen bond donor and hydrogen bond acceptor functionalities has been carried out. The detailed structure activity relation obtained by modifications at C-ring as well as C5-side chain has been discussed. Further, the drug-like properties of the selected compounds have also been determined. Docking studies of selected compounds has been performed to understand the increased activity of the synthesized compounds.

सार

अध्याय 1: विभिन्न उत्पादों जैसे कि प्राकृतिक उत्पादों, संक्रमण धातु-अंगों, कार्बनिक पदार्थों और दवाइयां जैसे विभिन्न क्षेत्रों में हेरोर्काइक्लिक यौगिकों के महत्व का अवलोकन किया गया है। इसके अलावा, उनके संश्लेषण के लिए इस्तेमाल किए गए विभिन्न तरीकों पर भी चर्चा हुई है।

अध्याय 2: एवजी 1,2,3,4-tetrahydroquinoxalines, 2,3-dihydro-1,4-benzoxazines, और सक्रिय ऑर्थो-halonitrobenzenes से 1,4-benzodioxines की एक अभूतपूर्व एक पॉट संश्लेषण चर्चा की गई। क्रमशः द्वितीयक नायकों, माध्यमिक अमीनो अल्कोहल, और डायल द्वारा नाइट्रो ग्रुप के प्रतिस्थापन के बाद दोहरे न्यूक्लियोफ़िलिक सुगन्धित प्रतिस्थापन (एसएनएआर) के हलोजन द्वारा प्रतिक्रिया की गई।

अध्याय 3: पैरामीशन में इलेक्ट्रान-दान देने वाले समूह वाले बेंज़िल क्लोराइड के साथ अनियमित जस्ता ट्रिपलेट ने चयनात्मक सी-बेंज़िलेशन और अनियमितों के हेटेरोअल एमिड्स का प्रदर्शन किया है। पद्धति, पैरा-amido की उच्च उपज के लिए उदार diaryl और arylheteroarylmethanes प्रतिस्थापित प्रदान करता है benzylating एजेंट के रूप में सस्ते और आसानी से उपलब्ध बेंजाइल क्लोराइड, जस्ता triflate के उत्प्रेरक राशि का उपयोग करता है, और परिवेश की स्थिति के तहत जगह लेता है। फीनोलॉजिकल प्राकृतिक उत्पादों के संश्लेषण के लिए महत्वपूर्ण पूर्ववर्ती हैं, जो अच्छी पैदावार में डायमिथॉक्सीडायरीमिथेन्स तैयार करने के लिए भी कार्यप्रणाली लागू की गई है।

अध्याय 4: डिज़ाइन, संश्लेषण और विभिन्न फ्यूज़ हेटरोराइल सी-रिंग्स वाले हाइड्रोजन बांड दाता और हाइड्रोजन बांड स्वीकर्ता कार्यात्मकताओं के साथ उपन्यास ऑक्सोजोलिकिनन डेरिवेटिव की एक श्रृंखला का एंटिबेक्टीयर मूल्यांकन। सी-अंगूठी और सी 5-साइड चैन पर संशोधनों से प्राप्त विस्तृत संरचना गतिविधि संबंध पर चर्चा की गई है। इसके अलावा, चयनित यौगिकों की दवा जैसे गुणों को भी निर्धारित किया गया है। संश्लेषित यौगिकों की वृद्धि की गतिविधि को समझने के लिए चुने हुए यौगिकों के अध्ययन को डॉकिंग किया गया है।

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GLOSSARY OF SYMBOLS AND ABBREVIATIONS

Ac	:	Acetyl
acac	:	Acetylacetonate
ADME	:	Absorption, Distribution, Metabolism and Excretion
Al/MCM-41	:	Aluminium grafted mesoporous silica
Aq.	:	Aqueous
Ar	:	Aryl
ATCC	:	American type culture collection
BArF	:	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
9-BBN	:	9-Borabicyclononane
BINAP	:	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	:	1,1'-Bi-2-naphthol
Bn	:	Benzyl
BOC	:	*tert*-Butyloxycarbonyl
BOD	:	Biochemical oxygen demand
BOX	:	Bis(oxazoline)
B/P ratio	:	Blood to Plasma ratio
bpy	:	2,2'-Bipyridine
Bz	:	Benzoyl
CAMHB	:	Cation-adjusted Mueller-Hinton broth
Cat.	:	Catalyst
CAP	:	Community-acquired pneumonia
CBZ	:	Carboxybenzyl

CETP	:	Cholesteryl ester transfer protein
CFL	:	Compact fluorescent lamp
cfu	:	Colony-forming unit
CLSI	:	Clinical and laboratory standards institute
COD	:	1,5-Cyclooctadiene
Cp*	:	Pentamethylcyclopentadienyl
Cy	:	Cyclohexyl
CYP	:	Cytochrome
dba	:	Dibenzylideneacetone
DCE	:	Dichloroethane
DCM	:	Dichloromethane
DEPT	:	Distortionless enhancement of polarization transfer
Difluorophos	:	5,5′-Bis(diphenylphosphino)-2,2,2′,2′-tetrafluoro-4,4′-bi-1,3-benzodioxole
DME	:	Dimethoxyethane
DMF	:	*N*,*N*-Dimethylformamide
DMSO	:	Dimethyl sulfoxide
DNA	:	Deoxyribonucleic acid
dppf	:	1,1’-Bis(diphenylphosphino)ferrocene
DPPPent	:	1,5-Bis(diphenylphosphino)pentane
dr	:	Diastereomeric ratio
dtbbpy	:	4,4’-Di-*tert*-butyl-2,2’-dipyridyl
ee	:	Enantiomeric excess
Equiv.	:	Equivalent

ESI	:	Electron spray ionization
EtOAc	:	Ethyl acetate
EtOH	:	Ethanol
Et_2O	:	Diethyl ether
EWG	:	Electron withdrawing group
FDA	:	Food and Drug adminstration
Fmoc	:	Fluorenylmethyloxycarbonyl
GSK	:	GlaxoSmithKline
h	:	Hour
HBA	:	Hydrogen bond acceptor
HBD	:	Hydrogen bond donor
HetAr	:	Heteroaryl
HIV	:	Human immunodeficiency virus
H-mont	:	Proton-exchanged montmorillionite
HMDS	:	Hexamethyldisilazane
HMPA	:	Hexamethylphosphoramide
HMQC	:	Heteronuclear multiple-quantum correlation spectroscopy
HPLC	:	High performance liquid chromatography
HRMS	:	High resolution mass spectroscopy
HTM	:	*Haemophilus* test medium
H_8-BINAPO	:	2,2'-Bis((diphenylphosphino)oxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene
IDSA	:	Infectious disease society of America

LZD	:	Linezolid
MAO	:	Monoamine oxidase
Me-DuPhos	:	1,2-Bis(2,5-dimethylphospholano)benzene
MeOH	:	Methanol
mg	:	Milligram
MHz	:	Megahertz
MIC	:	Minimum inhibitory concentration
min	:	Minutes
mL	:	Millilitre
mmol	:	Millimole
MRSA	:	Methicillin-resisitant *staphylococcus aureus*
Ms	:	Methane sulfonyl
M. TB.	:	Mycobacterium tuberculosis
MW	:	Microwave
NADPH	:	Nicotinamide adenine dinucleotide phosphate
NBE	:	Norbornene
NCEs	:	New chemical entities
NHC	:	*N*-Heterocyclic carbene
NMP	:	*N*-Methylpyrrolidine
NMR	:	Nuclear magnetic resonance
Nu	:	Nucleophile
PDB	:	Protein data bank
PEG	:	Poly(ethylene glycol)

PG	:	Protecting group
Ph	:	Phenyl
Physchem	:	Physicochemical properties
Pin	:	Pinacol
PipPhos	:	(3,5-Dioxo-4-phosphacyclohepta[2,1-a:3,4-a']dinaphthalen-4-yl) piperidine
Piv	:	Pivaloyl
ppm	:	Parts per million
PTC	:	Phase transfer catalyst
PTFE	:	Ploytetrafluoroethylene
p-TSA	:	*para*-Toluene sulfonic acid
Py	:	Pyridine
Q-Phos	:	1,2,3,4,5-Pentaphenyl-1'-(di-*tert*-butylphophino)ferrocene
rt	:	Room temperature
RNA	:	Ribonucleic acid
SEM	:	2-(Trimethylsilyl)ethoxymethyl
S_NAr	:	Nucleophilic aromatic substitution
S-Phos	:	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TADDOL	:	2,2-Dimethyl-α,α,α',α'-tetraphenyl-dioxolan-4,5-dimethanol
TBAB	:	Tetra-n-butylammonium bromide
TBAF	:	Tetra-n-butylammonium fluoride
TBAI	:	Tetra-n-butylammonium iodide
TBS	:	*tert*-Butyldimethylsilyl

TEMPO	:	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TEG	:	Triethylene glycol
tert	:	Tertiary
TFA	:	Trifluoroacetic acid
TfO	:	Trifluoromethanesulphonate
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
TMEDA	:	*N,N,N',N'*-Tetramethylethylenediamine
TMS	:	Trimethylsilyl
TPPMS	:	Sodium triphenylphosphino-*m*-sulfonate
Ts	:	*para*-Tolunesulfonyl
UPLC	:	Ultra performance liquid chromatography
uSSSI	:	Uncomplicated skin and skin structure infections
UV	:	Ultraviolet
Vis	:	Visible
VRE	:	Vancomycin-resistant *Enterococcus faecalis*
WHO	:	World health organization
WT	:	Wild type
X-Phos	:	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
µL	:	Microlitre

MATERIAL AND METHODS

Physical Measurement

NMR spectra (^{1}H and ^{13}C) were measured on a Bruker Varian Unity 400 MHz spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz). HRMS were recorded on MICROTOF-Q ll 228888.10262 using electrospray ionization (ESI) as the ionization method. UV-vis spectroscopy was recorded on Lambda Bio 20, Perkin Elmer. HPLC analysis was performed on Alliance HPLC system (Waters, Milliford, USA), using Kromasil C18 HPLC column (5.0 mm, 4.6 mm x 250 mm). Optical rotation was measured on an Autopol V, serial number 80121, manufactured by Rudolph research analytical, Hackettstown, NJ, USA.

Analytical Information

All the isolated compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS using $CDCl_3$, D_2O and DMSO as the solvents with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are given in δ (ppm) relative to TMS, the coupling constants (*J)* are given in hertz (Hz).

Chemicals and Reagents

All the solvents were bought from commercial vendors (Aldrich, Spectrochem, Alfa-aesar etc) and were used as received. Pre-packed silica gel columns from Biotage and Agela were used for column chromatography. A gradient elution using ethyl acetate: Hexanes or MeOH: DCM were performed on Merck aluminium TLC sheets (silica gel 60F254).