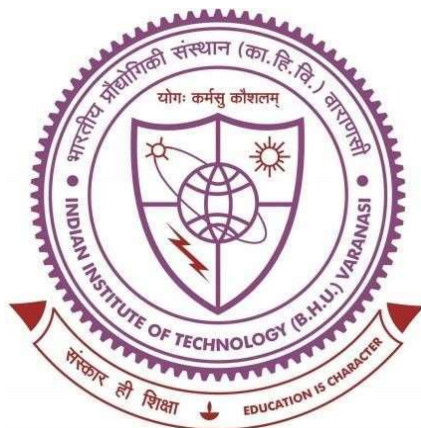


Multicomponent Synthesis of N-Containing Heterocyclic Compounds



THESIS SUBMITTED IN PARTIAL FULFILLMENT FOR THE
AWARD OF DEGREE

DOCTOR OF PHILOSOPHY

By

HIMANSHU KUMAR SINGH

Department of Chemistry
Indian Institute of Technology
(Banaras Hindu University)
Varanasi-221005

Roll No: 17051017

Year of Submission: 2023

**Copyright ©
Department of Chemistry,
Indian Institute of Technology,
Banaras Hindu University, Varanasi-221005, India,
2023.
All rights reserved.**



*Dedicated to
my
loving family...*

CERTIFICATE

It is certified that the work contained in the thesis titled "*Multicomponent Synthesis of N-Containing heterocyclic Compounds*" by "*Himanshu Kumar Singh*" has been carried out under our joint supervision and this work has not been submitted elsewhere for a degree.

It is further certified that the student has fulfilled all the requirements of Comprehensive, Candidacy, and SOTA.



Supervisor

Dr. (Mrs.) Sundaram Singh
Department of Chemistry
IIT (BHU), Varanasi-221005



Co-Supervisor

Dr. Vandana Srivastava
Department of Chemistry
IIT (BHU), Varanasi-221005

DECLARATION BY THE CANDIDATE

I, "**Himanshu Kumar Singh**" certify that the work embodied in this thesis is my own bonafide work and carried out by me under the joint supervision of "**Dr. (Mrs.) Sundaram Singh**" and "**Prof. Vandana Srivastava**" from "**July 2017**" to "**June 2023**" at the "**Department of Chemistry**," Indian Institute of Technology, Banaras Hindu University, Varanasi. The matter embodied in this thesis has not been submitted for the award of any other degree/diploma. I declare that I have faithfully acknowledged and given credits to the research workers wherever their works have been cited in this thesis. I further declare that I have not willfully copied any other's work, paragraphs, text, data, results, etc., reported in journals, books, magazines, reports, dissertations, theses, etc., or available at websites and have not included them in this thesis and have not cited as my own work.

Date : 01/07/2023

Place : Varanasi


Signature of the Student

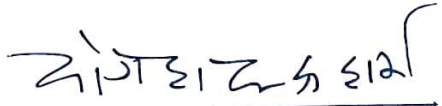
(Himanshu Kumar Singh)

CERTIFICATE BY THE SUPERVISOR(S)

It is certified that the above statement made by the student is correct to the best of our knowledge.


Supervisor
(Department of Chemistry)


Co-Supervisor
(Department of Chemistry)


Signature of Head of Department
(Department of Chemistry)

रसायन विज्ञान विभाग
Department of Chemistry
भारतीय प्रौद्योगिकी संस्थान (का.हि.वि.ति.)
Indian Institute of Technology
वाराणसी-221005 IV

COPYRIGHT TRANSFER CERTIFICATE

Title of the Thesis: **“Multicomponent Synthesis of N-Containing heterocyclic Compounds”**

Name of the Student: **Himanshu Kumar Singh**

Copyright Transfer

The undersigned hereby assigns to the Indian Institute of Technology (Banaras Hindu University) Varanasi all rights under copyright that may exist in and for the above thesis submitted for the award of the “*Doctor of Philosophy*” degree.

Date: 01/07/2023
Place: Varanasi


Signature of the Student
(Himanshu Kumar Singh)

Note: However, the author may reproduce or authorize others to reproduce material extracted verbatim from the thesis or derivative of the thesis for the author's personal use provided that the source and the Institute's copyright notice are indicated.

ACKNOWLEDGEMENTS

I give honor to God, the creator, and sustainer of life, for blessing me to be able to pursue and complete this milestone. I thank God for giving me much knowledge, wisdom, and health to complete this work on time.

Foremost, I “**Mr. Himanshu Kumar Singh**” would like to thank my Research Supervisor “**Dr. (Mrs.) Sundaram Singh**” Department of Chemistry, Indian Institute of Technology (Banaras Hindu University), Varanasi, for her wide experience, unrivaled knowledge of chemistry, learned guidance, stimulating discussion, and unstinting moral support which helped me immensely in completing this work in time. I thank her for putting up with my shortcomings and helping me to improve and overcome the same. Particularly, in the final stages, she has sustained me with her paternal care and thoughtful advice. I am beholden to my Co-Supervisor **Prof. Vandana Srivastava** who had been a constant source of support and encouragement.

I am thankful to **Prof. Yogesh Chandra Sharma** Head of the Department and **Prof. Rashmi Bala Rastogi**, and **Prof. Dhanesh Tiwary**, former Head of the Department of Chemistry, Indian Institute of Technology (Banaras Hindu University), for providing necessary lab facilities and a congenial working atmosphere in the Department.

I would also like to thank my RPEC members, **Prof. Vandana Srivastava**, Department of Chemistry, Indian Institute of Technology (Banaras Hindu University), **Dr. Jeyakumar Kandasamy** (former Internal subject expert), **Dr. Manisha Malviya** (Internal subject expert) Department of Chemistry, Indian Institute of Technology (Banaras Hindu University), and **Dr. Abha Mishra** (External subject expert), Department of Biochemical

Engineering, Indian Institute of Technology (Banaras Hindu University), for their valuable suggestions throughout this work.

I'm highly indebted to CIFIC, Indian Institute of Technology (BHU) for providing NMR Spectroscopy facility, Department of Chemistry, Banaras Hindu University (BHU) for Mass Spectrometry.

I also wish to thank all the non-teaching staff of the Department of Chemistry, Indian Institute of Technology (BHU) for their cooperation and timely help.

I am thankful to all lab members Dr. Savita Kumari, Dr. Dharendra Kumar, Dr. Arsala Kamal, Dr. Suresh Kumar Maury, Ambuj Kumar Kushwaha, and Shikha Pandey for their kind cooperation and friendly environment during the entire period of my research.

I would like to express my deepest affection to my father “Mr. Vijay Bahadur Singh”, my mother, “Mrs. Prem Lata Singh”, younger brother “Shubhanshu Singh”, and other family members for their unconditional love, concern, continuous moral support, and encouragement which enabled me to perform my liabilities. I also would like to thank my friends Alok Kumar Singh, Nivedita Shukla, Dr. Suresh Kumar Pandey, Sushant Singh, and Vishal Singh for their affection, prayer, and support as well as hard scolds to focus on my aim.

At the last but not least, I thank to all my well-wishers whose names I may have failed to mention here unintentionally.

Himanshu Kumar Singh

Research Scholar

CONTENTS

	Page No.
Acknowledgements	vi
List of Titles	viii
List of Schemes	xi
List of Figures	xiii
List of Tables	xv
List of Abbreviations	xvi
General Experimental Considerations	xx
Preface	xxi

LIST OF TITLES

Titles	Page No.
CHAPTER-1	
Introduction	
1.1 Multicomponent Reactions	1
1.2 Nitrogen-Containing Organic Compound	4
1.2.1 Nitrogen-containing five-membered cyclic compounds	5
1.2.1.1 Pyrrole	5
1.2.1.2 Triazoles	7
1.2.2 Nitrogen-containing six-membered cyclic compounds	9
1.2.2.1 Pyridine	9
1.2.3 Nitrogen-containing seven-membered cyclic compounds	11
1.2.3.1 Azepines	11
1.2.4 Nitrogen-containing fused heterocyclic compounds	13
1.2.4.1 Benzimidazole	13
1.2.4.2 Benzothiazole	15
1.2.4.3 Benzoxazole	17
1.2.4.4 Indole	19
1.3 Multicomponent Synthesis of N-containing Compounds	21
1.3.1 Microwave-Assisted Reaction	21
1.3.2 Ultrasound-Assisted Reactions	23
1.3.3 Mechanochemical Synthesis of N-Heterocyclic Compounds	25
1.3.4 Visible Light-Mediated Synthesis of N-Heterocyclic Compounds	28
1.3.4.1 Catalyst-free Multicomponent Synthesis under Visible Light	29
1.3.4.2 Visible-light Photo-redox Catalyzed Organic Synthesis	31

1.3.5	Transition metal Catalyzed Synthesis of N-Heterocyclic Compounds	33
1.3.6	Nanoparticle Catalyzed Synthesis of N-Heterocyclic Compounds	35
1.4	References	38

CHAPTER-2

Eosin Y-Catalyzed Synthesis of 3-Aminoimidazo[1,2-*a*]Pyridines via the HAT Process under Visible Light through Formation of the C-N Bond

2.1	Introduction	50
2.2	Results and Discussion	54
2.3	Control Experiment	61
2.3.1	UV-Vis absorption experiment	63
2.4	Proposed Mechanism	64
2.5	Conclusion	65
2.6	Experimental Procedures	66
2.6.1	General procedure for the preparation of compound 4a-4t	66
2.7	Characterization of products	67
2.8	Spectral Data of Product 4a	76
2.9	FT-IR Spectra	79
2.10	References	80

CHAPTER-3

Visible-Light-Promoted Synthesis of Fused Imidazoheterocycle by Eosin Y under Metal-Free and Solvent-Free Conditions

3.1	Introduction	86
3.2	Results and Discussion	88
3.3	Control Experiment	95
3.3.1	ON/OFF Experiments	97
3.4	Proposed Mechanism	98
3.5	Conclusion	99
3.6	Experimental Procedures	100
3.6.1	General Procedure for Synthesis of 3-Aminoimidazo-fused Heterocycles	100
3.7	Characterization of products	100
3.8	Spectral Data of Few Products	114
3.9	References	116

CHAPTER-4

Green Synthesis of Pyrimido[4,5-*b*]Quinolines and Pyrido [2,3-*d*] Pyrimidines via mechanochemical approach

4.1	Introduction	121
4.2	Results and Discussion	125

4.3	Proposed Mechanism	135
4.4	Conclusion	137
4.5	Experimental Procedures	137
4.5.1	General procedure for the preparation of compound 4a-4w & 5a-5q	137
4.6	Characterization of products	138
4.7	Spectral Data of few products	158
4.8	HRMS Spectra	162
4.9	References	164

CHAPTER-5

Transition metal-free Synthesis of Pyrido[2,3-d]pyrimidines via Csp³/Csp²-H functionalization using K₂S₂O₈ as Oxidant

5.1	Introduction	169
5.2	Results and Discussion	172
5.3	Control Experiment	178
5.4	Proposed Mechanism	181
5.5	Conclusions	182
5.6	Experimental Procedures	183
5.5.1	General procedure for the preparation of compound 4a-4zf	183
5.7	Characterization of the products.	183
5.8	Spectral Data of few Products	199
5.9	HRMS spectra	201
5.10	References	205

CHAPTER-6

Summary and Conclusion

6.1	Summary and conclusion	208
-----	------------------------	-----

List of research publications

List of Schemes

Scheme	Page No.
1.1 Multicomponent synthesis of purine	4
1.2 Synthesis of pyrrole and its derivatives.	7
1.3 Synthesis of Triazole and its derivatives	9
1.4 Synthesis of pyridine and its derivatives	11
1.5 Synthesis of azepines and its derivatives	13
1.6 Synthesis of benzimidazole and its derivatives	15
1.7 Synthesis of benzothiazole and its derivatives	17
1.8 Synthesis of Benzoxazoles and their Derivatives	19
1.9 Synthesis of Indole and its derivatives	21
1.10 Synthesis of phenanthrene-fused tetrahydrodibenzoacridinones	22
1.11 Synthesis of Pyridines derivatives	22
1.12 Synthesis of Pyrazolo pyrimidine derivatives	23
1.13 Synthesis of polysubstituted pyrroles	24
1.14 Synthesis of pyrazolo quinolone	24
1.15 Synthesis of benzodiazepine	25
1.16 Synthesis of indoloindolpyrimidine	26
1.17 Mechanochemical multicomponent synthesis of Pyrrolo[2,1a]isoquinolines	27
1.18 Synthesis of pyrimidine derivatives	27
1.19 Machenochemical synthesis of indolizines	28
1.20 Synthesis of phenanthridines	30
1.21 Synthesis of 5-substituted indole chromeno[2,3-b]pyridines	31
1.22 Synthesis of 4-oxo-tetrahydroindoles	31
1.23 Synthesis of pyrimidoindazole	32
1.24 Synthesized 3- aminoimidazo[1,2-a]pyridines	32
1.25 Synthesis of 3-aminoimidazoheterocycles	32
1.26 Multicomponent synthesis of fused N-heterocycles	34
1.27 Three-component synthesis of 3-(diarylmethylene)oxindoles	34
1.28 Three-component synthesis of quinolines	35
1.29 Multicomponent synthesis of 2-aminoimidazoles and 2-iminoimidazoles	35
1.30 One-pot synthesis of 1, 4-dihydropyridine derivatives	36
1.31 Synthesis of 1,4-dihydropyridin	36
1.32 Synthesis of 1,2,4,5-tetrasubstituted imidazoles	37
2.1 Synthesis of 3-aminoimidazo[1,2-a]pyridines via one-pot multicomponent reaction	54
2.2 Control experiments	61
2.3 Control experiments	62
2.4 Plausible mechanism	65
3.1 Synthesis of 3-Aminoimidazo[1,2-a]pyrimidines via One-Pot Multicomponent Reaction	88

3.2	Control reaction experiments	95
3.3	Control experiments	96
3.4	Plausible mechanism	99
4.1	Solution-Phase and Mechanochemical Solvent-free Approaches towards Pyrimido [4,5-b]quinolones and Pyrido [2,3-d] pyrimidines	124
4.2	Plausible mechanism	136
4.3	Stepwise reaction for the synthesis of 4a	137
5.1	Various Procedures for Synthesis of Pyrido[2,3-d]pyrimidine	172
5.2	The gram-scale reaction	178
5.3	Control experiment for mechanistic investigation	180
5.4	Plausible mechanism	182

List of Figures

Figure	Page No.
1.1 A divergent one-component reaction and convergent two- and multi-component reactions	2
1.2 N-Heterocyclic containing some main class of organic compounds	5
1.3 Few biologically active compounds containing pyrrole moiety	6
1.4 Triazoles containing marketed drugs and pharmacologically active molecules.	8
1.5 Representative compounds containing pyridine substructure	10
1.6 Benzoazepines based potent molecules	12
1.7 Few biologically active compounds containing imidazole moiety	14
1.8 Few biologically active compounds containing Benzothiazole moiety	16
1.9 Few biologically active compounds containing benzoxazoles moiety	18
1.10 Representatives of substituted indoles	20
1.11 Photocatalytic pathway via EDA complex	30
2.1 Photochemical and Electrochemical Properties of Eosin Y	52
2.2 Some biologically active compounds containing imidazo[1,2-a]pyridineframework.	53
2.3 Yield (%) vs visible light intensity for the preparation of N-(tert-butyl)-2-phenylimidazo[1,2-a]pyridin-3-amine	59
2.4 UV-Vis spectrum of 2-Amino Pyridine in chloroform (Conc. 1.0×10^{-4} mol/L)	63
2.5 UV-Vis spectrum of 4-Methoxybenzyl amine in chloroform (Conc. 1.25×10^{-4} mol/L)	63
2.6 ^1H NMR of product 4a	76
2.7 ^{13}C NMR of product 4a	77
2.8 D_2O exchange ^1H NMR of product 4a	78
2.9 FT-IR spectrum of compound 4p	79
3.1 Examples of biologically relevant imidazo[1,2-a]pyridines	87
3.2 Visible-light irradiation on/off experiment	97
3.3 ^1H NMR of product 4a	114
3.4 ^{13}C NMR of product 4a	115
4.1 Effect of the ball (a) material and (b) mass on the mechanochemical synthesis of pyrimido [4,5-b] quinolines and pyrimido [2,3-d] pyrimidines	134
4.2 ^1H NMR of product 4a	158
4.3 ^{13}C NMR of product 4a	159
4.4 ^1H NMR of product 5c	160
4.5 ^{13}C NMR of product 5c	161
4.6 HRMS Spectra of 4b	162
4.7 HRMS Spectra of 5a	162
4.8 HRMS Spectra of 4l	163
5.1 Most representative biologically active 1,4-dihydropyridines	170

5.2	^1H NMR of product 4a	199
5.3	^{13}C NMR of product 4a	200
5.4	HRMS Spectra of 6a	201
5.5	HRMS Spectra of 6b	202
5.6	HRMS Spectra of 6c	203
5.7	HRMS Spectra of 6d	204

List of Tables

Table	Page No.
2.1 Optimization of the Reaction Conditions	55
2.2 Effect of the visible light intensity on the reaction	58
2.3 Substrate scope and versatility of reaction	60
3.1 Optimization of the Reaction Conditions	90
3.2 Substrate scope and versatility of reaction of 2-aminopyrimidine	93
3.3 Substrate scope and versatility of reaction of 2-aminopyridine	94
4.1 Optimization of the Reaction Conditions	127
4.2 Substrate scope of Pyrimido [4,5-b]quinolines	129
4.3 Substrate scope of Pyrido [2,3-d] pyrimidines	131
4.4 Effect of number of milling balls on the yield of the product 4a	133
4.5 Effect of Milling Ball material and ball mass on the product 4a	134
5.1 Optimization of the Reaction Conditions	175
5.2 Three-component reaction of 6-aminouracil with different methyl arene and active methylene compound	176

List of Notations, Symbols and Abbreviations

Notations	Abbreviations
%	Percentage
<	Less than
>	More than
°	Degree
Å	Angstrom
Ac	Acetyl
Ac ₂ O	Acetic anhydride
AcOH	Acetic acid
Bn	Benzyl
Bz	Benzoyl group
Boc	Di- <i>tert</i> -butyl dicarbonate
brs	Broad singlet
Obser.	Observed
Calc.	Calculated
©	Copyright
CHCl ₃	Chloroform
CD ₃ OD	Methanol-d ₄
CDCl ₃	Deuterated chloroform
cm	Centimeter
<i>J</i>	Coupling constant
DMF	Dimethylformamide
DMSO- <i>d</i> ₆	Deuterated dimethyl sulfoxide
D ₂ O	Deuterated water
°C	Degree Celsius
d	Doublet
DMAP	4-Dimethylaminopyridine
DCE	Dichloroethane
DCM	Dichloromethane

dd	Doublet of doublet
ddd	Doublet of doublet of doublet
ddt	Doublet of doublet of triplet
DMSO	Dimethyl sulfoxide
dq	Doublet of quartet
dt	Doublet of triplet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DABCO	1,4-Diazabicyclo[2.2.2]octane
equiv.	Equivalent
EtOH	Ethanol
EtOAc	Ethyl acetate
EDG	Electron donating group
EWG	Electron withdrawing group
EY	Eosin Y
equiv.	Equivalent
g	Gram; Gravitational force
BAs	Barbituric acids
h	Hour
Sc(OTf) ₃	Scandium (III) Trifluoromethanesulfonate
H ₂ DEBA	Diethylbarbituric acid
Hz	Hertz
IR	Infra-Red
LDA	Lithium diisopropylamide
m	Multiplet
H ₃ BA	Barbituric acid
MeOH	Methanol
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mm	Millimeter
mmol	Millimole
μm	Micrometer

M.p.	Melting point
nm	Nanometer
NMR	Nuclear Magnetic Resonance
<i>n</i> -BuLi	<i>n</i> -Butyllithium
KOH	Potassium hydroxide
pH	Potential of hydrogen
ppm	Parts per million
RT	Room temperature
NaCl	Sodium chloride
s	Singlet
NMP	N-Methyl-2-pyrrolidone
<i>t</i> -Bu	Tertiary butyl
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMS	Tetramethylsilane
CF ₃ COOH	Trifluoroacetic acid
UV	Ultraviolet
XRD	X-ray Diffraction
α	Alpha
β	Beta
γ	Gamma
δ	Chemical shift
[ox]	Oxidation
R _f	Refractive Index
i.e.	that is
<i>o</i>	Ortho
<i>m</i>	Meta
<i>p</i>	Para
H ₂ O ₂	Hydrogen peroxide
H ₂ SO ₄	Sulfuric acid
Et ₃ N	Triethylamine
Cu(OTf) ₂	Copper (II) trifluoromethanesulfonate
Yb(OTf) ₃	Ytterbium (III) trifluoromethanesulfonate

TBHP	<i>tert</i> -Butylhydroperoxide
BHT	Butylatedhydroxytoluene
Ag ₂ O	Silver(I) oxide
LiAlH ₄	Lithium aluminium hydride
ZnCl ₂	Zinc chloride
Ni(OTf) ₂	Nickel (II) trifluoromethanesulfonate
KMnO ₄	Potassium permanganate
K ₂ S ₂ O ₈	Potassium persulfate
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxidanyl
ZnO	Zinc oxide
CH ₃ COOH	Acetic acid
<i>p</i> -TSA	<i>p</i> -Toluenesulfonic acid
TiO ₂	Titanium dioxide
CuCl	Copper (I) chloride
AlCl ₃	Aluminium chloride
NaBH ₄	Sodium borohydride
DTBP	Di- <i>tert</i> -butyl peroxide
et al.	et alia, Latin for “and others”
i.e.	that is
e.g.	Example
equiv.	Equivalents

General Experimental Considerations

All the chemicals were procured from Aldrich, USA, and E. Merck, Germany, and were used as received. The solvents were purchased from Merck, India, and Ranbaxy, India, and were purified before their use. The preparation and particulars of the substrates employed for the work undertaken are given in their respective chapters. **Melting points** were measured using Stuart Melting point apparatus SPM10 in open capillary tubes and are uncorrected. **UV-visible spectroscopy** of the reaction solution was recorded on a SHIMADZU UV-3600 UV-visible spectrophotometer. **Infrared (IR)** spectra were recorded on the Perkin-Elmer FT-IR-5300 spectrophotometer (ν_{max} expressed in cm^{-1}). The ^1H (500 MHz) and ^{13}C (126 MHz) **NMR** ^{19}F (126 MHz) **NMR** spectra were run on a Bruker Advance 500 MHz FT-NMR at 500 MHz spectrometers. Chemical shifts are given in δ ppm, using tetramethylsilane (TMS) as an internal standard **HRMS (m/z)** and were recorded in an electron ionization or electrospray ionization (ESI) mode on Waters-Q-TOF Premier-HAB213 and Sciex X500R QTOF instruments. The **elemental microanalyses** were performed on Exeter Analytical Inc Model, CE-440 elemental analyzer.

Thin-layer Chromatography (TLC) was performed on glass plates (7.5×2.5 and 7.5×5.0 cm) coated with Merck silica gel GF 254 using various combinations of ethyl acetate and n-hexane as an eluent. Visualization of spots was accomplished either in an iodine chamber or by exposure to UV light. Merck silica gel (100-200 mesh) was used for column chromatography (approximately 15-20 g per 1 g of the crude product).

Preface

The fundamental goal of this thesis is to create novel synthetic methodologies for the synthesis of N-Containing heterocyclic Compounds.

The effective green synthesis of Nitrogen-containing heterocyclic compounds is embodied in the thesis titled "**Multicomponent Synthesis of N-Containing Heterocyclic Compounds**". **Chapter 1** provides a detailed explanation of multicomponent synthesis and its significance in organic synthesis, N-Containing heterocycles and its importance, and different methods for the synthesis of Nitrogen Containing Compounds.

Chapter 2 will describe the Eosin Y-Catalyzed Synthesis of 3-Aminoimidazo[1,2-*a*]Pyridines via the HAT Process under Visible Light through Formation of the C-N Bond. **Chapter 3** will disclose Visible-Light-Promoted Synthesis of Fused Imidazoheterocycle by Eosin Y under Metal-Free and Solvent-Free Conditions. **Chapter 4** will highlight a Green Synthesis of Pyrimido[4,5-*b*]Quinolines and Pyrido [2,3-*d*] Pyrimidines via mechanochemical approach. **Chapter 5** will present Transition metal-free Synthesis of Pyrido[2,3-*d*]pyrimidines via Csp³/Csp²-H functionalization using K₂S₂O₈ as Oxidant finally, **Chapter 6** will summarize and conclude the total thesis work.