PHOTOCATALYST-ASSISTED SINGLE ELECTRON TRANSFER-INDUCED HETEROCYCLE SYNTHESIS AND FUNCTIONALIZATION IN VISIBLE LIGHT

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by

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Dedicated to my beloved family

CERTIFICATE

This is to certify that the thesis entitled, "***Photocatalyst-assisted single electron transfer-induced heterocycle synthesis and functionalization in visible light***" being submitted by **Ms. Shruti Rajput** 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 her. **Ms. Shruti Rajput** has worked under my guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

The results contained in this dissertation have not been submitted in whole or in part, to any other university or institute for award of any degree or diploma.

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ABSTRACT

The thesis entitled "**Photocatalyst-assisted single electron transfer-induced heterocycle synthesis and functionalization in visible light**" explores the application of homogeneous photocatalysts in promoting organic transformations. In recent years, visible light has emerged as an efficient tool to achieve chemical reactions, enabling the generation of highly reactive intermediates formed *in situ* without the need for stoichiometric reagents. It offers a greener and environmentally benign route for the construction and functionalization of organic heterocyclic molecules. We have developed novel protocols involving cyclization, oxidation, and C-H activation strategies for the synthesis of functionalized molecules, enabling the formation of analogous to biologically relevant compounds.

This dissertation comprises five chapters. **Chapter 1** explains the role of photochemistry, focusing on the sophisticated applications of photoredox and dual catalysis for the synthesis and functionalization of heterocycles. It outlines the classification of photocatalysts and an in-depth discussion of photocatalytic processes. A detailed study of homogeneous photocatalysts employed in our research work, and their application in facilitating organic transformations.

In **Chapter 2,** a photoinduced direct synthesis of 3-amino-1-indenones *via* radical cascade cyclization strategy is demonstrated. The methodology involves a domino reaction between 2-alkynylarylnitrile and *N*-aminopyridinium salt and captures the reactivity of *in situ* generated nitrogen-centered radical in visible light. Multiple bond-forming events including C-N, C-C, and C-O take place sequentially on 2-alkynylarylnitrile enabling construction of 3-amino-1-indenone core at room temperature. The transformation exhibits good substrate scope furnishing the products in good yields. A preliminary biological screening of the synthesized compounds is indicative of their potent anti-cancer property.

Building upon our efforts to develop novel strategies under visible light irradiation, in **Chapter 3** we report the visible light-assisted tandem oxidative 5-exo-dig cyclization of 1,6-enynes for the synthesis of aminated C-3 aryloylated benzofuran, furopyridine, benzothiophene, and indole derivatives. Nitrogen-centered radical generated *in situ* from *N*-aminopyridinium salt initiates the consecutive formation of C-N, C-C, and C-O bonds. The methodology exhibits good functional group tolerance and regio-selectivity, furnishing products in good to excellent yields at room temperature. Preliminary biological screening of synthesized molecules reveals their potential as anti-cancer agents.

In **Chapter 4,** a metal-free and photooxidative activation of 2-alkynylarylnitriles in the presence of pyrylium salt as a photocatalyst is reported. The 1,2-diketone intermediate generated in visible light demonstrates base-assisted *ortho*gonality towards cyclization, furnishing 4-aryl-4-hydroxyisoquinoline-1,3-(2*H*,4*H*)-dione and 3-aryl-3-hydroxy-2,3-dihydroazanaphthoquinone derivatives. The reaction has a wide substrate scope, good functional group tolerance, uses an organic photocatalyst, and takes place at room temperature. Preliminary biological screening of synthesized molecules reveals their potential as anti-cancer agents.

In **Chapter 5**, we demonstrate a directing group-assisted decarboxylative *ortho*-benzoylation of *N*-aryl-7-azaindoles with α-keto acids by synergistic visible light promoted photoredox and palladium catalysis. The approach tenders rapid entry to aryl ketone architectures from simple α-keto acid precursors *via* the *in situ* generation of a benzoyl radical intermediate. The transformation provides a range of *ortho*-benzoylated *N*-aryl-7-azaindoles, with excellent site-selectivity and good functional group compatibility under mild reaction conditions. Biological target predictions indicate that these molecules may serve as potential anti-cancer and anti-viral agents.

सार

"**दृश्य प्रकाश में फोटोकैटेलिस्ट-सहायता प्राप्त एकल इलेक्ट्रॉन स्थानांतरण-प्रेरित हेट्रोसाइकिल संश्लेषण और क्रियाशीलता**" शीर्षक वाली थीसिस कार्बनिक परिवर्तनों को बढ़ावा देने में सजातीय फोटोकैटेलिस्ट के अनुप्रयोग की खोज करती है। हाल के वर्षों में, दृश्य प्रकाश रासायनिक प्रतिक्रियाओं को प्राप्त करने के लिए एक कुशल उपकरण के रूप में उभरा है, जो स्टोइकोमेट्रिक अभिकर्मकों की आवश्यकता के बिना सीटू में गठित अत्यधिक प्रतिक्रियाशील मध्यवर्ती की पीढ़ी को सक्षम करता है। यह कार्बनिक हेट्रोसाइक्लिक अणुओं के निर्माण और क्रियाशीलता के लिए एक हरित और पर्यावरण के अनुकूल मार्ग प्रदान करता है। हमने क्रियाशील अणुओं के संश्लेषण के लिए चक्रीकरण, ऑक्सीकरण और C-H सक्रियण रणनीतियों को शामिल करते हुए नए प्रोटोकॉल विकसित किए हैं, जो जैविक रूप से प्रासंगिक यौगिकों के अनुरूप निर्माण को सक्षम करते हैं।

इस शोध प्रबंध में पाँच अध्याय शामिल हैं। **अध्याय 1** फोटोकैमिस्ट्री की भूमिका की व्याख्या करता है, जो हेट्रोसाइकिल के संश्लेषण और क्रियाशीलता के लिए फोटोरेडॉक्स और दोहरे कटैलिसीस के परिष्कृत अनुप्रयोगों पर ध्यान केंद्रित करता है। यह फोटोकैटेलिस्ट के वर्गीकरण और फोटोकैटेलिटिक प्रक्रियाओं की गहन चर्चा को रेखांकित करता है। हमारे शोध कार्य में उपयोग किए जाने वाले सजातीय फोटोकैटेलिस्ट का विस्तृत अध्ययन, तथा कार्बनिक परिवर्तनों को सुविधाजनक बनाने में उनका अनुप्रयोग।

अध्याय 2 में रेडिकल कैस्केड साइक्लाइज़ेशन रणनीति के माध्यम से 3-एमिनो-1-इंडेनोन का फोटो-प्रेरित प्रत्यक्ष संश्लेषण प्रदर्शित किया गया है। कार्यप्रणाली में 2-एल्काइनिलरीलनाइट्राइल और एन-एमिनोपाइरिडिनियम नमक के बीच एक डोमिनो प्रतिक्रिया शामिल है तथा दृश्य प्रकाश में इन-सीटू उत्पन्न नाइट्रोजन-केंद्रित रेडिकल की प्रतिक्रियाशीलता को कैप्चर करता है। सी-एन, सी-सी, तथा सी-ओ सहित कई बॉन्ड-फॉर्मिंग घटनाएँ क्रमिक रूप से 2-एल्काइनिलरीलनाइट्राइल पर होती हैं, जिससे कमरे के तापमान पर 3-एमिनो-1-इंडेनोन कोर का निर्माण संभव होता है। परिवर्तन अच्छे सब्सट्रेट स्कोप को प्रदर्शित करता है, जिससे उत्पाद अच्छी पैदावार देते हैं। संश्लेषित यौगिकों की प्रारंभिक जैविक जांच उनके शक्तिशाली कैंसर-रोधी गुण का संकेत देती है।

दृश्य प्रकाश विकिरण के तहत नई रणनीति विकसित करने के हमारे निरंतर प्रयासों के आधार पर, **अध्याय 3** में हम एमीनेटेड सी-3 एरिलोलेटेड बेंज़ोफ्यूरान, फ्यूरोपाइरीडीन, बेंज़ोथियोफीन और इंडोल डेरिवेटिव के संश्लेषण के लिए 1,6-एनीन के दृश्य प्रकाश से सहायता प्राप्त टेंडेम ऑक्सीडेटिव 5-एक्सो-डिग साइक्लाइज़ेशन की रिपोर्ट करते हैं। एन-एमिनोपाइरीडिनियम नमक से सीटू में उत्पन्न नाइट्रोजन-

केंद्रित रेडिकल सी-एन, सी-सी और सी-ओ बॉन्ड के क्रमिक गठन की शुरुआत करता है। कार्यप्रणाली अच्छी कार्यात्मक समूह सहिष्णुता और क्षेत्र-चयनात्मकता प्रदर्शित करती है, जो कमरे के तापमान पर अच्छे से उत्कृष्ट उपज वाले उत्पाद प्रदान करती है। संश्लेषित अणुओं की प्रारंभिक जैविक जांच से कैंसर विरोधी एजेंट के रूप में उनकी क्षमता का पता चलता है।

अध्याय 4 में फोटोकैटेलिस्ट के रूप में पाइरिलियम नमक की उपस्थिति में 2-एल्काइनिलरीलनाइट्राइल्स के धातु-मुक्त, फोटोऑक्सीडेटिव सक्रियण की रिपोर्ट की गई है। दृश्य प्रकाश में उत्पन्न 1,2-डाइकेटोन मध्यवर्ती चक्रीकरण की दिशा में आधार-सहायता प्राप्त ऑर्थोगोनैलिटी प्रदर्शित करता है, जो 4-एरिल-4-हाइड्रॉक्सीइसोक्विनोलिन-1,3-(2*H*,4*H*)-डायऑन और 3-एरिल-3-हाइड्रॉक्सी-2,3-डायहाइड्रोएज़ानाफ्थोक्विनोन व्युत्पन्न प्रदान करता है। प्रतिक्रिया में व्यापक सब्सट्रेट स्कोप, अच्छी कार्यात्मक समूह सहिष्णुता, एक कार्बनिक फोटोकैटलिस्ट का उपयोग होता है, और यह कमरे के तापमान पर होता है। संश्लेषित अणुओं की प्रारंभिक जैविक जांच से कैंसर विरोधी एजेंट के रूप में उनकी क्षमता का पता चलता है।

अध्याय 5 में हमने खुलासा किया कि α-कीटो एसिड के साथ *N*-एरिल-7-एज़ैनडोल्स के निर्देशन समूह की सहायता से डीकार्बोक्सिलेटिव ऑर्थो-बेंज़ोयलेशन को सहक्रियात्मक दृश्य प्रकाश द्वारा प्रवर्तित फोटोरेडॉक्स और पैलेडियम कटैलिसीस द्वारा प्राप्त किया गया है। यह दृष्टिकोण सरल α-कीटो एसिड अग्रदूतों से बेंज़ोयल रेडिकल इंटरमीडिएट की इन-सीटू पीढ़ी के माध्यम से एरिल कीटोन आर्किटेक्चर में तेजी से प्रवेश करता है। यह परिवर्तन ऑर्थो-बेंज़ोइलेटेड एन-एरिल-7-एज़ैनडोल्स की एक श्रृंखला प्रदान करता है, जिसमें हल्की प्रतिक्रिया स्थितियों के तहत उत्कृष्ट साइट-चयनात्मकता और अच्छी कार्यात्मक समूह संगतता होती है। जैविक लक्ष्य भविष्यवाणियों से संकेत मिलता है कि ये अणु संभावित कैंसर विरोधी और एंटी-वायरल एजेंट के रूप में काम कर सकते हैं।

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GLOSSARY OF SYMBOLS AND ABBREVIATIONS

Ac	Acetyl
Al_2O_3	Aluminium oxide
Ag	Silver
$AgNO_3$	Silver nitrate
$AgSbF_6$	Silver hexafluoroantimonate
Ag_2O	Silver oxide
AgCl	Silver chloride
AgOTf	Silver trifluoromethanesulfonate
BHT	Butylated hydroxytoluene
BQ	Benzoquinone
CCDC	Cambridge crystallographic data centre
$CDCl_3$	Deuterated chloroform
CH_3CN	Acetonitrile
$Cu(OTf)_2$	Copper triflate
CuCl	Copper (II) chloride
CV	Cyclic voltammetry
$Cu(OAc)_2$	Copper acetate
CsOAc	Cesium acetate
Cs_2CO_3	Cesium carbonate
$CuCl_2$	Copper (II) chloride
$CHCl_3$	Chloroform
CF_3CO_2Ag	Silver trifluoroacetate
CuI	Copper (I) iodide
CIDNP	Chemically Induced Dynamic Nuclear Polarization
CdS	Cadmium sulfide
DABCO	1,4-Diazabicylco[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM or CH_2Cl_2	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	Diisopropyl ethyl amine

DMA	Dimethyl acetamide
DMAP	4-dimethylaminopyridine
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMSO-*d6*	Deuterated dimethyl sulfoxide
DIPEA	Disopropylethylamine
DMPO	5,5-Dimethyl-1-pyrroline N-oxide
DMA	Dimethylacetamide
DMEM	Dulbecco's modified Eagle's medium
EPR	Electron paramagnetic resonance
Equiv.	Equivalent
ET	Energy transfer
Et	Ethyl
Et_3N	Triethylamine
EtOH	Ethanol
EtOAc	Ethylacetate
E	Electrophile
EY	Eosin Y
fac	Facial
h	Hour
H_2O_2	Hydrogen peroxide
HAT	Hydrogen atom transfer
HCl	Hydrochloric acid
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
HFIP	Hexafluoroisopropanol
H_2O	Water
HSGC	Headspace gas chromatography
H_2SO_4	Sulfuric acid
IC	Internal conversion
ISC	Intersystem crossing

K_2CO_3	Potassium carbonate
$K_2S_2O_8$	Potassium persulfate
K_3PO_4	Potassium phosphate
KOAc	Potassium acetate
KCl	Potassium chloride
KOH	Potassium hydroxide
KO^tBu	Potassium *tert*-butoxide
LED	Light emitting diode
LUMO	Lowest unoccupied molecular orbital
LiI	Lithium iodide
m/z	Mass by charge ratio
Mpg-CN	Mesoporous graphitic carbon nitride
Me	Methyl
mg	Milligram
min	Minutes
mL	Mililitre
MLCT	Metal to ligand charge transfer
MeCN	Acetonitrile
MHz	Megahertz
MeOH	Methanol
mmol	Millimole
μM	Micromolar
mV/s	Milivolt per second
mA	Miliampere
μL	Microlitre
μs	Microseconds
Na_2SO_4	Sodium sulphate
$NaPF_6$	Sodium hexafluorophosphate
NaOAc	Sodium acetate
NaOH	Sodium hydroxide
$NaHCO_3$	Sodium bicarbonate
NMR	Nuclear magnetic resonance
ND	Not detected

$^nBU_4NOAc$	Tetrabutylammonium acetate
$Na_2S_2O_8$	Sodium persulfate
N_2	Nitrogen
nm	Nanometre
NH_4Cl	Ammonium chloride
NCR	Nitrogen center radical
NHC	N-heterocyclic carbene
Na_2CO_3	Sodium carbonate
Nu	Nucleophile
Ox	Oxidation
O_2	Oxygen
Ph	Phenyl
PCET	Proton-coupled electron transfer
$Pd(OAc)_2$	Palladium acetate
PPh_3AuCl	Chlorido(triphenylphosphine)gold(I)
Pt	Platinum
PPh_3	Triphenylphosphine
$PdCl_2(PPh_3)_2$	Dichlorobis(triphenylphosphine)palladium(II)
PhSH	Thiphenol
$PdCl_2$	Palladium chloride
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium
PhCl	Chlorobenzene
rt	room temperature
RCR	Radical cascade reaction
Red	Reduction
SCE	Standard calomel electrode
SET	Single electron transfer
Sub	Substrate
SCXRD	Single-crystal X-ray diffraction
TEMPO	2,2,6,6-Tetramethylpiperinyloxy
TLC	Thin layer chlromatography
TBHP	*tert*-Butyl hydroperoxide
Ts	Tosyl

TiO_2	Titanium dioxide
tert	Tertiary
THF	Tetrahydrofuran
TMS	Tetramethylsilane
UV	Ultra-violet
V	Volt
W	Watt
$Zn(OTf)_2$	Zinc triflate
ZnO	Zinc oxide
ZnSe	Zinc selenide