PART 1: MECHANISTIC INSIGHTS INTO THE PHOTOCHEMISTRY OF TETRAZOLETHIONES

PART 2: SYNTHESIS OF PHENANTHRIDINE-FUSED QUINAZOLINIMINIUM AND COMPUTATIONAL INVESTIGATION OF THEIR OPTOELECTRONIC PROPERTIES

by

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B.S., Long Island University, 2005

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Department of Chemistry
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Manhattan, Kansas

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Abstract

Research in our laboratory has focused on designing photoactivated DNA cleaving agents based on tetrazolethione scaffolds. The key step in the activation of these involves conversion of tetrazolethione moiety to carbodiimides upon irradiation. However, the mechanism of this reaction was not previously reported. Therefore, we undertook a study to elucidate the mechanism of photodecomposition of tetrazolethione as to identify reactive intermediates involved, that may interfere or aid with the activity of our synthesized DNA cleaving agents under physiological conditions. In Part 1 of this dissertation, we present mechanistic studies on this photodecomposition. Our results indicate the clean photoconversion of tetrazolethiones I to their respective carbodiimides IV via the expulsion of sulfur and dinitrogen. Photoirradiation in the presence of trapping agent (e.g. 1,4-cyclohexadiene) resulted into the formation of their corresponding thioureas. Thus, providing strong evidence for the intermediacy of a 1,3-biradical III, which is believed to be in its triplet spin multiplicity. Further investigations (triplet sensitization and quenching experiments) to determine the precursor of the biradical argued against the involvement of a triplet excited state (T₁). We believe that the mechanistic pathway that leads to the formation of a 1,3-triplet biradical III is a diradicaloid species II – II" generated directly from the singlet excited state of tetrazolethiones (S₁) after the expulsion of dinitrogen. Once formed, this diradicaloid species could be envisioned to undergo intersystem crossing to generate the 1,3triplet biradical III which then undergoes desulfurization to form carbodiimides IV (Chapter 2).
Bridgehead-nitrogen containing fused heterocycles are regarded as “privileged structure” in biology and have found widespread applications in pharmaceutical industry. These heterocycles have also been evaluated in electroluminescent devices and organic dyes. Part II of the dissertation present new, concise and low cost strategies to a unique class of bridgehead nitrogen-containing fused heterocyclic scaffolds which involves two sequential intramolecular cyclizations from heteroene-allenes in the presence of Lewis acids such as SnCl₄ and BF₃·OEt₂, and trace water. The starting heteroene-allenes VI can be prepared from commercially available substrates V in 4 – 5 steps following standard protocols (Chapter 3).

Furthermore, we employed density functional theory to gain insights into the optoelectronic properties of select derivatives of phenanthridine-fused quinazoliniminiums (PNQs) VII and their free base in order to evaluate their scope in OLED technology. Our results show that the energies of the Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied Molecular Orbital (LUMO), the HOMO-LUMO energy gaps, the ionization potentials, electron affinities and the reorganization energies can be finely tuned by varying the substituents on these chromophores. In addition, we found that the introduction of an electron donating group (NMe₂) on the PNQs and their free base increases the energies of the HOMOs and decreases the ionization potentials, relative to its unsubstituted derivative, whereas substitution by an electron withdrawing group (NO₂) decreases the energies of the LUMOs and increases the electron affinities which in turn suggests an improvement in their hole and electron creating abilities, respectively (Chapter 4).
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<th>Substance</th>
<th>E ((\lambda)) / eV (nm)</th>
<th>Oscillator Strength ((f))</th>
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<tr>
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<tr>
<td>Tetrahydrofuran</td>
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<td></td>
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<tr>
<td>Acetonitrile</td>
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<table>
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>1,4-CHD</td>
<td>1,4-Cyclohexadiene</td>
</tr>
<tr>
<td>a</td>
<td>Adiabatic excitation</td>
</tr>
<tr>
<td>ATR</td>
<td>Attenuated total reflectance</td>
</tr>
<tr>
<td>BBr₃</td>
<td>Boron trichloride</td>
</tr>
<tr>
<td>BF₃.OEt₂</td>
<td>Boron trifluoride etherate</td>
</tr>
<tr>
<td>C₂Cl₆</td>
<td>Hexachloroethane</td>
</tr>
<tr>
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</tr>
<tr>
<td>CF₃SO₃Ag</td>
<td>Silver trifluoromethanesulfonate</td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>Methylene Chloride</td>
</tr>
<tr>
<td>CH₃NO₂</td>
<td>Nitromethane</td>
</tr>
<tr>
<td>CT</td>
<td>Charge transfers</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional theory</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
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</tr>
<tr>
<td>DMSO-d₆</td>
<td>Dimethyl sulfoxide-d₆</td>
</tr>
<tr>
<td>E</td>
<td>energy</td>
</tr>
<tr>
<td>EA</td>
<td>Electron affinities</td>
</tr>
<tr>
<td>EDG</td>
<td>Electron donating group</td>
</tr>
<tr>
<td>EEP</td>
<td>Electron extraction potential</td>
</tr>
<tr>
<td>EML</td>
<td>Emissive layer</td>
</tr>
<tr>
<td>ESI MS</td>
<td>Electrospray ionization mass spectrometry</td>
</tr>
<tr>
<td>ET</td>
<td>Energy transfer</td>
</tr>
<tr>
<td>Eₜ</td>
<td>Triplet excited energy</td>
</tr>
<tr>
<td>Et₃N</td>
<td>Triethyl amine</td>
</tr>
<tr>
<td>ETL</td>
<td>Electron-transport layer</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethylacetate</td>
</tr>
<tr>
<td>eV</td>
<td>electron volt</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron Withdrawing group</td>
</tr>
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FeBr₃  Iron(III) bromide
FMOs  Frontier molecular orbitals
FT-IR/IR  Fourier transform infrared spectroscopy/Infrared
HEP  Hole extraction potentials
HMPA  Hexamethylphosphoramide
HOMO  Highly occupied molecular orbitals
HPLC  high-pressure liquid chromatography
HRMS  High resolution mass spectrometry
HTL  Hole-transport layer
Hz  Hertz
hν  Light/Light source/ Photon energy
IC  Internal conversion
IP  Ionization potentials
ISC  Intersystem crossing
J  Coupling constant
K₂CO₃  Potassium carbonate
LEDs  Light-emitting diodes
LUMO  Lowest occupied molecular orbitals
M  molecule
MeOH  Methanol
MgSO₄  Magnesium Sulfate
mHz  mega hertz
MS/MS  Tandem mass spectrometry
n-BuLi  n-Butyllithium
NaSO₄  Sodium sulfate
NH₄Cl  Ammonium chloride
NIR  Near infrared
OLEDs  Organic light-emitting diodes
Pd(PPh₃)₂Cl₂  Bis(triphenylphosphine)palladium(II) dichloride
PDT  Photodynamic therapy
PLEDs  Polymer light-emitter diodes
PNQs  Phenanthridine-\textit{N}-quinazolinimines
PPh$_3$  Triphenylphosphone
ROS  Reactive oxygen species
S$_0$  Singlet ground state
S$_1$  Singlet excited state
SnCl$_4$  Tin tetrachloride
SPE  Singlet photon excitation
t-Bu  \textit{tetra}-Butyl
T$_1$  Triplet excited state
TBABr  Tetrabutylammonium bromide
TDDFT  Time-dependent density functional theory
THF  Tetrahydrofuran
TiCl$_4$  Titanium tetrachloride
TMSA  Trimethylsilyl azide
TMSBr  Trimethylsilyl bromide
TMSCl  Trimethylsilyl chloride
TMSI  Trimethylsilyl iodine
TMSOTf  Trimethylsilyl trifluoromethanesulfonate
TPE  Two-photon excitation
v  Vertical excitation
\Delta E  Change in energy
\lambda(nm)  Wavelength (nanometer \textit{i.e} x 10$^{-9}$)
\lambda_{\text{hole/electron}}  Reorganization energies for hole injection and electron transfer
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Dedication

Dedicated to my incredible mother Iyabo, my queen and lovely wife Safiyyah; two brilliant individuals whom I have learned from to approach life with honor, humility and optimism.
Preface

Research carried out at Kansas State University for this dissertation led to the following publications in peer-reviewed scientific journals:


Chapter 1 - Photochemical Reactions of Tetrazole and its Derivatives

1.1 Introduction

Tetrazole (CN₄H₂) 1 is a five-membered unsaturated heterocyclic ring consisting of one carbon and four nitrogen atoms (Figure 1.1, top). The nitrogen content of this molecule is rated at 80% of its total weight.¹,² These ring systems exhibit annular tautomerism, and co-exist in 1H- and 2H- tautomeric forms (Figure 1.1, bottom).²,³,⁴ There are no known reports of the presence of these heterocyclic scaffolds in natural products, but several tetrazole containing compounds and their derivatives have been synthetically prepared and are known to be relatively stable under different reaction conditions and in the presence of various chemical reagents.¹ These synthetic compounds have attracted considerable attention due to their widely growing applications in many fields, such as chemical,⁵ agricultural⁶ and pharmaceutical industry.⁷

![Structure of 1H-tetrazole 1 (top) and its 1H- and 2H- tautomeric forms (bottom).](image)

Fig. 1.1: Structure of 1H-tetrazole 1 (top) and its 1H- and 2H- tautomeric forms (bottom).¹,²

In chemical industry, tetrazole and its derivatives are employed in the protection of metal surfaces as corrosion inhibitors,⁵,⁸,⁹ and as additives in anti-wear and friction reduction oils.¹⁰ Also, these scaffolds are used as stabilizers in photography and photoimaging.¹,¹¹,¹² The high nitrogen content of tetrazoles makes them excellent sources of environmentally friendly high-energy materials for specialty explosives and pyrotechnics.⁴,¹³,¹⁴ As a result of this property, they
have also found applications as propellants in rockets, and as gas generating agents for airbags.

Furthermore, the tetrazolyl heterocycles have demonstrated applications in coordination chemistry due to their wide range of binding patterns with metal ions. These heterocycles can act as monodentate (N), bidentate (N, N) and/or bridging ligands to form stable complexes with several transition metal ions through coordinate bonding (Figure 1.2). As a result, the tetrazole ring systems have been used in designing polymers and building interesting molecular architectures with a variety of different metal ions and co-ligands. Two examples of metal-organic frameworks are shown below. Figure 1.3 (left) depicts the crystal structure of two independent Mn ions (Mn$^{+1}$ and Mn$^{+2}$) coordinated to three equivalent bridged tetrazaoles and two water molecules. Also, two-dimensional motif of tetradebate 5-methyltetrazole coordinated to Ag (2$^+$, 1$^+$) is shown in Figure 1.3 (right), that further demonstrates the versatility in the coordination properties of tetrazolylic ligand. These compounds have exhibited interesting optical and magnetic properties in material science and have potential applications as mesoporous hydrogen storage material in supramolecular chemistry.

![Figure 1.2: Various coordination modes of tetrazole ligands with Y= N, C.](image)

![Figure 1.3: (a) Triangular [Mn$_3$(µ-OH)] motif and (b) two-dimensional [Ag$_2$(5-methyltetrazolate)]$^+$ motif.](image)
The chelating properties of the tetrazole ring system have been successfully utilized in analytical chemistry for the removal of heavy metal ions from liquids, and biological fluids.\textsuperscript{8,27} Furthermore, tetrazoles have been successfully used as derivatising agents for benzyl alcohols to corresponding ethers prior to hydrogenolysis.\textsuperscript{28} The electron-withdrawing properties of these heterocycles aid in weakening the C-O bond and thus, making the carbon atom more susceptible to nucleophilic attack.

In agriculture, tetrazole moieties are well known for their efficient fungicidal and insecticidal properties that make them excellent candidates for pest management in agriculture (Figure 1.4).\textsuperscript{6,29,30} For example, tetrazole-based compounds 2 and 3 were found to show selective and excellent insecticidal activity against different species of insects,\textsuperscript{6,31} and compounds 4 and 5 both exhibit herbicidal properties and act by inhibiting the plant cell division cycle and chlorophyll biosynthesis, respectively.\textsuperscript{6}

![Figure 1.4: Structures of tetrazole-based insecticides (2 and 3) and herbicides (4 and 5) currently used in agriculture.\textsuperscript{6,29,31}](image)

These nitrogen rich five-membered rings have also demonstrated excellent applications in medicinal chemistry.\textsuperscript{32,33} It is well known that tetrazolic fragment (-CN\textsubscript{4}H) exhibits physical characteristics and abnormally high acidity similar to that of carboxylic acid moiety (-CO\textsubscript{2}H) in biologically active molecules.\textsuperscript{7,34,35} Thus, these are allosteric with the carboxylic acid groups. Furthermore, tetrazole moieties exhibit superior metabolic stability at physiological pH and increased bioavailability than that of the -CO\textsubscript{2}H group.\textsuperscript{7} Therefore, tetrazoles are being employed
as synthetic surrogates of the carboxylic acid moiety in modern drug design. Tetrazole derivatives have found applications in pharmaceuticals as cis-peptide linkers and lipophilic spacers. Tetrazoles containing compounds have also been reported to possess anesthetic, antihypertensive, anti-allergic, antiviral, antibacterial, antibiotic and anti-inflammatory properties. For instance alfentanil is used for short time anesthesia, benzodiazepine analogues 7 and 8, are employed in the treatment of cardiac arrhythmias and Meniere’s disease (an inner ear disorder), and losartan is used as anti-hypertensive drug (Figure 1.5). Furthermore, N-(α-aminoalkyl)tetrazoles (10 – 12) have been proposed to exhibit potential applications in the prevention and treatment of diseases associated with the formation of advanced glycation end products (AGEs) and advanced lipoxidation end products (ALEs) because of their protein synthesis inhibitory properties.

![Figure 1.5: Examples of tetrazole-based therapeutic agents.](image)

### 1.2 Photochemical Reactions of Tetrazole Derivatives

The tetrazolylic ring systems are known to exhibit very strong photochemical reactivity. In the past three decades, there have been a number of reports on the photochemistry of tetrazoles and their derivatives, studied in solution as well as in the gas phase and based on the range of tetrazolyl scaffolds investigated, several decomposition patterns have been established.
that depend upon the reaction conditions (e.g. cryogenic inert matrix or solution), solvent polarity and nature of the substituents present on the tetrazolyl ring.

Figure 1.6 shows general structure of tetrazole derivatives I – III that are discussed in this chapter. The common fragmentation pathway in all derivatives of tetrazoles I – III involves the rapid photorelease of molecular nitrogen (N$_2$) from the ring (referred to as $a$) that further results in the formation of a variety of products depending on the nature of the substituents present on the heterocycle. The second most prevalent pathway in tetrazoles is the ring cleavage through a 1,3-dipolar cycloversion (referred to as $b$) to generate the corresponding photoproducts. This pathway is not observed in annulated derivatives of tetrazoles II, most likely, because of the strain in the putative photoproduct. In case of tetrazole derivatives III with $X = S$, an additional pathway is observed that involves simultaneous loss of molecular nitrogen and sulfur (indicated by $a$ and $c$) (Figure 1.6).

![Figure 1.6: Common ring fragmentation patterns observed for tetrazole and its derivatives in solution or cryogenic matrix.](image)

**1.2.1 Photolysis of unsubstituted tetrazole**

Maier and co-workers described the photochemistry of unsubstituted tetrazole in cryogenic argon matrix.$^{1,45}$ Using IR spectroscopic analysis these researchers were able to identify the reactive intermediates and the mixture of photoproducts generated. The results revealed that the immediate release of N$_2$ led to the formation of resonance stabilized nitrilimine intermediate 14 that tautomerized to afford diazomethane 16 as a photoproduct. The authors reported that nitrilimine 14 also underwent rearrangement to produce HCN···NH complex 15 that decomposed further to give tautomers, carbodiimide 17 and cyanamide 18 (Scheme 1.1).
1.2.2 Photolysis of substituted tetrazole

Fausto and Gómez-Zavaglia described the photochemistry of several substituted tetrazole derivatives using matrix isolated FT-IR spectroscopy and high-level DFT-based quantum mechanical calculations.\textsuperscript{12b,46} The UV-induced photochemistry of alkyloxy-1-phenyl-1\textsubscript{H}-tetrazoles \textsuperscript{19} in argon matrix resulted in two different fragmentation pathways of the ring system. The first pathway involved the production of antiaromatic alkoxy-1-phenyl-1\textsubscript{H}-diazirene \textsuperscript{20} \textit{via} the loss of molecular nitrogen from compound \textsuperscript{19}. The second pathway involved the ring cleavage that led to the formation of alkoxyocyanate \textsuperscript{21} and phenylazide (\textsuperscript{22} as the primary photoproducts \textit{via} 1,3-dipolar cycloversion. Subsequent loss of nitrogen from \textsuperscript{22} resulted into the formation of 1-aza-1,2,4,6-cycloheptatetraene (ACHT) (\textsuperscript{24}), possibly through a singlet phenylnitrene (\textsuperscript{23}) (Scheme 1.2).\textsuperscript{12b,46} The photoproducts obtained were analyzed and identified by IR spectroscopy, and the interpretation of the experimental data was extensively supported by DFT calculations performed at B3LYP/6-311++G(d,p) level of theory.
Cristiano and coworkers investigated the photochemistry of various 1-allyloxy-4-phenyl-1H-tetrazoles 25 in methanol, acetonitrile and cyclohexane solutions with a low-pressure mercury lamp ($\lambda = 254$ nm). The photolysis of these ether compounds resulted in the loss of nitrogen from the tetrazolyl ring to produce triplet 1,3-biradicals 26, which underwent a [1,6] H-shift followed by cyclization to afford two tautomeric N-phenyl-1,3-oxazines 28i-ii as the primary photoproducts (Scheme 1.3). Due to the photosensitive nature of generated oxazines, prolonged irradiation resulted in secondary photoreactions that are discussed below.

The photodecomposition of oxazines 28 followed three pathways in all the solvents (methanol, acetonitrile and cyclohexane), however an additional fourth pathway was observed in methanol. The route A produced phenyl vinyl hydrazine 29 after the photorelease of carbon monoxide (CO) from 28i, and continuous exposure of 29 to UV-irradiation led to the formation of photoproduct 30 and phenyl nitrene 22 that subsequently decomposed to aniline 31. Similarly, route B released CO through a concerted mechanism that transformed 28i to 30 and 22; which eventually decomposed to 31. The route C produced phenyl isocyanate 32 and photoproduct 30 from tautomer 28ii. In methanolic solution, the formation of benzyl carbamate 33 was also observed via route D (Scheme 1.3).
Scheme 1.3: Photodecomposition pathways for the allyloxy tetrazoles 25 in solution.\textsuperscript{37}

Furthermore, Quast and coworkers also investigated the photochemistry of a series of annulated tetrazole derivatives in solution\textsuperscript{47} e.g. 1,4,5-substituted alkylidenedihydrotetrazoles 34. These researchers irradiated diluted, degassed solutions of 34a in toluene-\textit{d}_8 at low temperature (-60 °C) with the filtered focused medium pressure mercury lamp (\(\lambda \geq 320\) nm).\textsuperscript{48} The photodecomposition was diastereoselective involving the release of molecular nitrogen to form the triplet diazatrimethylene methane biradical intermediate 35a followed by ring closure to give the annulated (\textit{E})-iminoaziridines 36a (99\%) with an exocyclic CN double bond. However, at room temperature rapid (\textit{E} \rightleftharpoons (\textit{Z}) equilibration was observed after several days (Scheme 1.4).\textsuperscript{48} In the case of 34b, the photochemical reaction performed in toluene-\textit{d}_8 at -60 °C with \(\lambda \geq 320\) nm similarly resulted in the formation of compound 36b via the biradical intermediate 35b. However, the results indicated poor diastereoselectivity with almost equal amounts of \textit{E} and \textit{Z}
(E/Z, 57:43). Again E/Z ratio changed after sample equilibrated at room temperature (Scheme 1.4). 48

\[
\begin{align*}
\text{Scheme 1.4: Photodecomposition route of 1,4,5-substituted alkylidenedihyrotetrazoles 34 in solution.}^{48}
\end{align*}
\]

Similarly, the photolysis (\(\lambda \geq 320 \text{ nm}\)) of degassed toluene-\(d_8\) solution of geminal tetramethylalkylidenedihyrotetrazole 34c at -60 \(^\circ\)C resulted into a mixture of diastereomers with (Z)-iminoaziridine 36c as the major product (59%). During equilibration at room temperature for several days, diastereomerization to (E)-iminoaziridine 36c was observed (Scheme 1.4). The difference in the diastereoselectivities observed in case of 34a and 34b,c was attributed to the geometric feature of the C=C-N-Me moiety which remained conserved when \(R^1 = \text{H}\), to give exclusively the \(E\)-conformer (34a). However, the steric effect caused by the presence of methyl group (\(R^1 = \text{CH}_3\)) at the C=C bond in 34b or geminal methyls in 34c (\(R^2 = \text{CH}_3\)) resulted in the (E) \(\rightarrow\) (Z) diastereomerization of the biradical intermediates 35b,c before ring closure that afforded a mixture of \(E\) and Z-36b,c. 48

1.2.3 Photolysis of tetrazolone derivatives

In 1975, Quast and Bieber reported that photolysis (\(\lambda \geq 320 \text{ nm}\)) of 1,4-dimethyl-1,4-dihydro-5\(H\)-tetrazol-5-one (38) in acetonitrile-\(d_3\) produced a single photoproduct, the 1,4-dimethylidiaziridinones (39), following the loss of molecular nitrogen (Scheme 1.6, left). 49 Several years later, Quast and Dunkin revisited the photochemistry of 38 in cryogenic matrix and the results indicated the formation of 39 as the major photoproduct, plus a minor photoproduct methyl isocyanate 40. The photodecomposition pathway that led to the formation of compound
40 was thought to involve a different pathway involving 1,3-dipolar cycloversion (Scheme 1.5, right). However, there was no evidence of the second photoproduct of this latter pathway, the methylazide, which was probably due to the sensitivity of the photoproduct to undergo secondary reactions in matrix at prolonged irradiation times.

Scheme 1.5: Photoproducts formed during UV irradiation of 38 in solution and cryogenic matrix.49,50

These researchers also investigated the UV-induced photochemistry (λ = 254 nm) of a series of alkenyldihyrotetrazolones 41a–d in acetonitrile-d$_3$, cyclohexane-d$_{12}$ and methylcyclohexane-d$_{14}$ solutions.51 The photolysis of all derivatives of 41 afforded alkenydiaziridinones 42 as the primary photoproduct in all the solvents via the loss of molecular nitrogen. However, irradiation of 41a,b in acetonitrile-d$_3$ also resulted in the formation of a byproduct 43a,b which was identified as the hydrolyzed form of 42a,b (Scheme 1.6).

Scheme 1.6: Photoconversion of 41 to alkenyl-diaziridinone 42 and its hydrolyzed derivatives 43 in solution.51

Furthermore, it has been shown that modification of the substituents on the tetrazolone ring could lead to the formation of different photoproducts through the common
photodecomposition pathway involving the loss of molecular nitrogen. For example, Quast and Nahr reported that the UV irradiation of a series of phenyl, alkyl phenyl, allylphenyl and diphenyl tetrazolones 44 in acetonitrile, methanol and 2-propanol solutions at 20 °C with 254 nm light (15 W Hg lamp) yielded primarily benzimidazolones 46a–e in quantitative yields via a intermediate 45 formed by the release of molecular nitrogen (Scheme 1.7).^5^2

\[
\text{Ph-}N=NO-N-R \xrightarrow{\text{hv = 254 nm}} \text{N} \xrightarrow{\text{[1,3] H-shift}} \text{R} \\
a: R = H \\
b: R = Me \\
c: R = CH_2CH=CH_2 \\
d: R = CH=CHCH_3 \\
e: R = Ph
\]

Scheme 1.7: Photodecomposition pathway of series of alkyl- phenyltetrazolones 44 in solution.^5^2

Recently, Cristiano and coworkers re-examined the photochemistry of a series of 4-allyltetrazolones in various solvents e.g. acetonitrile, cyclohexane, carbon tetrachloride, methanol, 1-hexanol and 1-propanol.\(^{35,53}\) They showed that photolysis of 4-allyltetrazolones 44c,f,g (254 nm; 16W low pressure Hg lamp; 25 °C) in all the solvents led to the formation of intermediate 47c,f,g after the photorelease of molecular nitrogen, that rapidly underwent ring closure and a [1,2] H-shift to produce pyrimidinones 48c,f,g as the sole primary photoproduct (Scheme 1.8). When the photochemistry was carried out in acetonitrile, cyclohexane and carbon tetrachloride, the primary photoproduct 48 was unstable and underwent secondary photoreactions to afford aniline 31, aminoalkene 49, phenyl and allyl isocyanates 32 and 50, respectively.\(^{35,53}\)
Scheme 1.8: Photocleavage of 4-allyl-1-phenyltetrazolones 44 in solution.\textsuperscript{35,53}

The authors attributed this disparity to different experimental conditions employed. The photostability exhibited by 48 in alcoholic medium was attributed to efficient solvation, which entailed hydrogen bonding with the solvent (Figure 1.7).\textsuperscript{35} This solvent caging was also believed to be responsible for absence of any secondary photoreactions from 48.

Figure 1.7: Stabilization of pyrimidinones 48 by alcohols.\textsuperscript{35}

Note that this study reported the formation of different photoproducts contrary to what was observed by Quast above (Scheme 1.7).

Furthermore, the photochemistry of 44a,c has also been investigated with FT-IR matrix-isolation spectroscopy ($\lambda \geq 235$ nm) and the results revealed the formation of diverse array of photoproducts via three different photodecomposition pathways.\textsuperscript{36,54} Path 1 involved the elimination of molecular nitrogen which afforded the substituted arylidiaziridinones 52a,c. The latter underwent further decomposition to produce 53a via the loss of carbon monoxide, and
rearrangement to produce 1-allyl-1H-benzoimidazol-2(3H)-one 46c as secondary photoproducts. Note that 46c was also observed in solution by Quast (Scheme 1.7). Path 2 followed a retro 1,3-dipolar cycloaddition pathway that produced phenyl isocyanates 32 and allyl azide 53, and path 3 involved a different retro 1,3-dipolar cycloreversion of the tetrazolyl moiety to generate allyl isocyanates 54a,c and phenyl azide 21. The latter decomposed further to produce 1-aza-1,2,4,6-cycloheptatetraene (ACHT) 24 (Scheme 1.9).\textsuperscript{36,54}

Scheme 1.9: Photodecomposition pathways of allyl phenyltetrazolone 44a and 44c in solid matrix.\textsuperscript{36,54}

1.2.4 Photolysis of imino-dihydrotetrazoline derivatives

Quast and coworkers also contributed to the studies involving the UV-induced photochemistry of a number of iminodihydrotetrazoles both in solution and in cryogenic matrix.\textsuperscript{50,55} In the course of their investigation, the authors observed that photolysis of iminotetrazolines both in solution (> 255 nm) and argon matrix (> 200 nm) produced similar results.\textsuperscript{50} Two decomposition pathways were observed. Once again, path 1 involved the initial photorelease of molecular nitrogen that resulted in the formation of singlet
triazamethylenemethane biradicals $^{56,55,56}$ which subsequently produced mixtures of iminodiaziridines $^{57 - 59}$ as the major photoproducts, and path 2 involved a photochemical 1,3-dipolar cycloreversion that yielded small amounts of alkylcarbodiimides $^{50}$. The second product of this latter pathway was alkyl azide $^{61}$ which was highly photolabile and was undetected (Scheme 1.10).$^{55}$

\[ \begin{align*}
\text{Path 1} & \quad > 255 \text{ nm} \quad -60^\circ \text{C} \\
55 & \quad \text{R}^1, \text{R}^2, \text{R}^3 = \text{alkyl group} \\
\text{Path 2} & \quad - \text{N}_2 \\
55 & \quad \text{N} = \text{C} = \text{N} \\
\end{align*} \]

\[ \begin{align*}
\text{Scheme 1.10: Photoproducts generated during irradiation of 55 in solution.}^{55,56}
\end{align*} \]

**1.2.5 Photolysis of tetrazolethione derivatives**

Quast and coworkers investigated the photochemistry ($\geq 254 \text{ nm}$) of a series of 1,4-dialkyl tetrazolethiones $^{62}$ in acetonitrile-$d_3$, dichloromethane, methanol-$d_4$ and methylocyclohexane-$d_{14}$ solutions.$^{1,51}$ The photolysis of $^{62}$ resulted in the simultaneous loss of molecular nitrogen and sulfur to produce the dialkyl carbodiimides $^{63}$, in 50-80% yield. There was no evidence of any alternative photoproduct(s). The formed photoproduct $^{63}$ was unstable in acetonitrile because it was subsequently converted to the corresponding ureas $^{64}$ by reaction with trace amount of water present in solution (Scheme 1.11).

\[ \begin{align*}
\text{R}^1, \text{R}^2 & = \text{alkyl, alkenyl, allyl, aryl, or vinyl}
\end{align*} \]

\[ \begin{align*}
\text{Scheme 1.11: Photodecomposition products of dialkyltetrazolethiones 62 in solution.}^{51}
\end{align*} \]
In a later publication, the same authors described the UV-induced photochemistry (> 200 nm) of alkyl phenyltetrazolethione and dialkyl tetrazolethione in nitrogen matrix. And, the researchers reported the formation of corresponding carbodiimides similar to the solution studies.

Recently, Cristiano and coworkers reported the matrix-isolated photochemistry of 1-methyl-1H-tetrazole-5(4H)-thione (65). Under these reaction conditions, the UV-irradiation (> 235 nm) resulted in the formation of a variety of photoproducts via different decomposition pathways all involving the cleavage of the tetrazolethione ring. The proposed photodecomposition pathways involves (i) simultaneous elimination of molecular nitrogen and sulfur to generate N-methyl carbodiimide 66, (ii) ring cleavage involving 1,3-dipolar cycloreversion to produce methyl isothiocyanate 67 and possibly, the azide 68, (iii) photo-elimination of N₂ that result in the formation of two different conformers of 1-methyl-1H-diazirine-3-thiol 69 that further decomposed to afford E and Z conformers of methyl diazene 71, and (iv) the direct fragmentation of 65 may have yielded 70 through the elimination of carbon monosulfide, that subsequently decomposed to 71 (Scheme 1.12). The results of this study are slightly different from previous report by Dunkin and Quast (Scheme 1.11). This can be attributed to the presence of hydrogen on the N1 of 65 that is expected to allow the formation secondary photoproducts with relative ease, especially 71. The authors believe that the different photolysis conditions employed in the two studies (> 200 nm and > 235 nm), could have also influenced the reaction pathways.
Scheme 1.12: Photoproducts and fragmentation pathways resulting from irradiation of 1-methyl-1H-tetrazole-5(4H)-thione 65 in argon matrix.17

1.3 Concluding Remarks

In contrast to the 5-oxo of derivatives of tetrazoles, the photochemistry of 5-thio derivatives, i.e. the tetrazolethiones has not received much attention. No information is available on the nature of reactive intermediates involved or their photochemical quantum yields. Considering the vast applications of tetrazolethiones in industry, agriculture and medicinal chemistry, the understanding of their mechanism of photodecomposition is critical for designing compounds with improved performance/properties. We were interested in tetrazolethione photochemistry because of our interest in using these scaffolds for designing photoactivated DNA cleaving prodrugs.

Chapter 2 of this dissertation will begin with a brief overview of the photoactivated DNA cleaving agents based on tetrazolethione scaffolds that our laboratory is interested in and will focus on the:

• Synthesis of tetrazolethiones.
• Study of the molecular and electronic properties of tetrazolethiones by theoretical methods.
• Study of photoreactivity of tetrazolethiones and characterization of their photoproducts.
• Study of the mechanism of photodecomposition of these ring systems.
Structures, and Properties.

Coordination Polymers with Bis(tetrazole) compounds (C10H10N4S and C10H9ClN4S) [Cu2(C10H10N4S)2(H2O)2](BF4)2 and [Cu


Klapótké, T. M.; Mayer, P.; Schulz, A.; Weigand, J. J. 1,4-Bis-[1-Methyltetrazol-5-yl]-1,4-Dimethyl-2-Tetrazene: A Stable, Highly Energetic Hexamer of Diazomethane (CH2N2)6. Propellants, Explos., Pyrotech. 2004, 29 (6), 325.


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Chapter 2 - Synthesis and Mechanistic Insights into the Photodecomposition of Tetrazolethiones

2.1 Introduction

The concept of treatment using light has been known for thousands of years. For example, ancient Egyptians, Indian and Chinese civilizations used light to treat various diseases such as psoriasis, rickets, vitiligo and skin diseases.\(^1\),\(^2\),\(^3\) However, it was only in the last century that Niels and Finsen developed phototherapy that involved the use of light in a clinical setting for therapeutic purposes.\(^1\),\(^2\) Finsen described the successful treatment of smallpox pustules and cutaneous tuberculosis by exposing infected patients to red and ultraviolet light.\(^1\),\(^2\)

In 1900, research contribution from Oscar Raab revealed that the combination of acridine red and light induced cytotoxic effects on infusoria (Paramecium caudatum),\(^4\) and several investigations following this discovery subsequently led to the development of Photodynamic therapy or PDT.\(^1\),\(^2\) Today PDT is described as a treatment method that employs a combination of drug (a photosensitizer, usually a porphyrin-based compound) and visible light in the presence of oxygen to kill tumor/cancerous cells.\(^5\),\(^6\) In general, the biochemical mechanism of action in PDT involves irradiation of the sensitizing agent with light, that results in the activation of the sensitizer from a ground state (S\(_0\)) to an excited singlet state (S\(_1\)) followed by intersystem crossing (ISC) to its excited triplet state (T\(_1\)) (Figure 2.1). As the triplet excited state of the sensitizer returns to the ground state, it releases energy that can be used for two pathways: Type I and Type II reactions.\(^1\),\(^2\),\(^3\),\(^5\) The former involves the direct reaction of the triplet excited sensitizer with cellular membrane or biomolecules to produce radicals that interact with oxygen to form reactive oxygen species (ROS; O\(_2^{-}\)). The latter cause localized destruction of the tumor cells. Alternatively, the triplet excited sensitizer can transfer its energy directly to the ground state molecular oxygen (\(^3\)O\(_2\)), subsequently forming the cytotoxic singlet oxygen (\(^1\)O\(_2\)), that causes oxidations of biomolecules resulting in cell death (Figure 2.1).\(^1\),\(^7\) Note that the singlet electronic excited state of molecular oxygen is 94KJ/mole, and therefore for the type II reactions to be thermodynamically favorable the sensitizer’s triplet excited state must be \(\geq\) 94KJ/mole.\(^7\)
Porphyrrins have been widely used as photosensitizers (drugs) for PDT due to their high singlet oxygen quantum yields and high tendency to accumulate in tumor cells. There are three generations of porphyrin based photosensitizers currently known. The first generation PDT sensitizers include Photofrin which is a mixture of hematoporphyrin derived oligomers. However, Photofrin has several limitations such as poor photon absorption at wavelengths used in PDT (> 650 nm), and its administration as a mixture of compounds. Furthermore, it exhibits non-specific biodistribution and prolonged accumulation in healthy tissues that results in sensitivity of the patient to light.

With the discovery of second generation photosensitizers with improved absorption at larger wavelengths (> 650 – 800 nm), an increase in singlet oxygen quantum yield was achieved, which also meant that reduced amount of the drug could be used for PDT. In addition, these new sensitizers are administered as a single compound thus resulting in short photosensitivity of the patients. Recently, third generation photosensitizers have also been reported with selective targeting anchors to increase the drug concentration within the tumor site.

Since its advent, PDT has been used in the treatment of several benign and malignant cancers, age-related macular degeneration, antibiotic-resistant biofilms and wound infections as well as an adjuvant treatment for disseminated diseases. This technique is gaining considerable advancement clinically, because it is minimally invasive with reduced toxicity.

Traditionally, single photon excitation (SPE) is employed for the activation of photosensitizer in PDT (Figure 2.1). However, this method suffers from a number of drawbacks,
particularly, the limited penetration of light (3-10 millimeters) into larger tumors due to optical scattering and absorption by blood and tissue. As a result, PDT is most effective for the treatment of superficial conditions such as skin cancer or the lining of internal organs or cavities. Furthermore, the light that is used for SPE is cytotoxic and mutagenic (because the light source that is used produces broadband radiation), and it is also non-localized, so significant absorption occurs along the path of the beam.

Therefore, the two photon excitation (TPE) of photosensitizers is receiving considerable attention as an alternative to SPE. This process involves simultaneous absorption of two photons of near-infrared (NIR) light from a pulsed laser (750-1000 nm) such that sum of their energy is equal to the first excited state of the photosensitizer ($S_1$), (i.e. $\hbar\nu_1 + \hbar\nu_1$ is equal to $\hbar\nu$ in Figure 2.2). Once $S_1$ is produced, the cellular damage occurs as discussed above and also shown below (Figure 2.2).\textsuperscript{11} TPE provides spatial and precision activation of the sensitizers due to the use of laser as a light source that allows deeper penetration in living tissues than traditional SPE. In addition, the use of NIR wavelengths enables treatment in the tissue transparent window.\textsuperscript{12} Furthermore, this technique allows reduced light scattering, localized absorption and a minimal risk of laser hyperthermia.\textsuperscript{13,14} Despite these benefits, TPE-PDT has been dwarfed by the lack of suitable photosensitizers as the majority of the currently used sensitizers are based on porphyrins that exhibit low two-photon absorption cross-sections ($\delta$).

\textbf{Figure 2.2}: Jablonski diagram illustrating the two photon activation of the photosensitizers and subsequent cellular damage through type I and type II reactions in PDT, ET = energy transfer.\textsuperscript{1}
Some of the proposed approaches to address this drawback include the chemical modification of the existing photosensitizers. For instance, modified photosensitizers in which two-photon absorbing dyes have been covalently attached to the porphyrin-core (photosensitizers) have been put forth to enhance the efficiency of TPE in PDT. These dyes funnel energy to the photosensitizers via the Forster Resonance Energy Transfer (FRET). However, the protocols to synthesize these compounds often involve tedious and complicated steps with less fruitful results. Another method involved the design of conjugated porphyrin dimers (or oligomers) in order to improve their two photon absorption cross-sections. Although, this method demonstrates promising potential in TPE-PDT, it has some limitations such as poor singlet oxygen quantum yields. Note that one of the prerequisite for an efficient photosensitizer is its ability to produce singlet oxygen in high quantum yields. In order to achieve this goal (and as noted above) the triplet excited energy of the photosensitizer must be higher than singlet excited state of the molecular oxygen (>94KJ/mole) (Figures 2.1 and 2.2). In many porphyrin oligomers that have been developed for use in TPE-PDT, the triplet state energy is close to 94KJ/mole and therefore, the quantum yield of singlet oxygen in these systems is compromised.

One way to alleviate the problem of low singlet oxygen quantum yields in TPE-PDT, will be to choose a method of photodestruction in PDT that does not involve the generation of singlet oxygen and one such method may involve photodamage via biradicals. Recently, Popik showed that photoirradiation of $p$-quinoid cyclopropenone-containing enediyne precursor with TPE generated a highly reactive enediyne that was thermally triggered to undergo Bergman cyclization (cycloaromatization), which resulted in the formation of biradicals. The latter abstracts hydrogen from appropriate hydrogen donor as shown below to form. At first glance, this method seems ideal for causing damage through TPE-PDT where could be used to abstract hydrogen atoms from the sugar phosphate backbone of the DNA leading to cell death. However this also has limitations. For example, sensitive and tedious synthetic routes are required for the preparation of the enediyne precursor. Furthermore, the cyclopropenone moieties have poor stability under physiological conditions and the thermal cycloaromatization to produce biradicals requires elevated temperatures (40 °C), which is not feasible under biological conditions. Thus, there is a need to construct a new class of compound that are easy of
synthesize, are stable under physiological conditions and can spontaneously undergo biradical formation upon irradiation which induces DNA cleavage.

Scheme 2.1: TPE generation of reactive enediyne 73 and subsequent cycloaromatization.¹⁸

As a result, we have designed enynyl-1H-tetrazole-5(4H)-thiones 76 as photoactivated DNA cleaving agents for use in PDT. We hypothesized that upon light activation (multiphoton excitation), 76 would undergo two sequential photochemical steps in one pot, involving the decomposition of the tetrazolethione ring system to produce enyne-carbodiimides 77 with the simultaneous loss of molecular nitrogen and sulfur, followed by the Schmittel cyclization of compound 77 to generate the biradical 78. The generated biradical 81 would induce DNA cleavage though H-atom abstraction. Work in our laboratory has already revealed that derivatives of 76 do have the ability to abstract hydrogen atom from the sugar-phosphate backbone of KS' Bluescript super coiled DNA upon light activation through single photon excitation at 350 nm, causing single and double stranded breaks and thus, supporting our hypothesis.²⁰ Future work in the group is targeted toward studying the DNA cleavage by 76 at 800 nm through multiphoton excitation.

Scheme 2.2: Mechanism of action of the proposed enynyl-1H-tetrazole-5(4H)-thiones 76 upon light activation.
At the time, we began our studies on the DNA cleaving abilities of enynyl-1\textit{H}-tetrazole-5(4\textit{H})-thiones 76, the biradical forming Schmittel cyclization of enyne-carbodiimides was well studied in literature,\textsuperscript{21,22} but the mechanism of photodecomposition of tetrazolethiones ring system to carbodiimide was not known. Therefore, it was critical to elucidate the mechanism of this first photochemical step that involved the decomposition of tetrazolethiones (in compound 76) to carbodiimides (in compound 77), and identify any reactive intermediates, or other photoproduct(s) that may interfere with the activation of our proposed prodrug 76 \textit{in vivo} (Scheme 2.2). To achieve this task, model tetrazolethiones 79 were synthesized and their photophysical and photochemical properties were extensively investigated with single photon excitation. As mentioned in Chapter 1, tetrazole and its derivatives have a wide range of applications and therefore, the elucidation of tetrazolethione photodecomposition mechanism would not only provide better understanding of the mode of action of our proposed prodrug 76, but would also aid in the design of new tetrazolethione-based compounds with enhanced performance for application in industry and medicine.

**Scheme 2.3:** Model tetrazolethione compounds 79 employed for photodecomposition studies discussed in this Chapter.

This chapter begins with a study of the electronic, structural and photophysical properties of a series of model tetrazolethiones 79, through a combination of experimental and quantum mechanical methods. This is followed by the discussion of their photochemistry and mechanistic investigations at 254 and 300 nm (single photon excitation). Since our ultimate goal is to be able to induce the chemistry outlined in Scheme 2.2 with multiphoton excitation, we also investigated the photochemical decomposition of tetrazolethiones 79 at 800nm and the preliminary investigations are presented.
2.2 Results and Discussion

2.2.1 Synthesis of tetrazolethiones

The tetrazolethione compounds were all synthesized from commercially available aryl isocyanates. Briefly, the reaction of aryl isocyanates 81 with neat trimethylsilyl azide 82 furnished the 1,3 dipolar cyclized products, the corresponding aryl-1\(H\)-tetrazol-5(4\(H\))-ones 83. Subsequent, methylation employing dimethyl sulfate in sodium hydroxide and a phase transfer catalyst, \(n\)-Bu\(_4\)NBr, resulted into the formation of 1,4-disubstituted tetrazolones 84. The treatment of disubstituted tetrazolones with phosphorus pentasulfide afforded the desired 1-aryl-4-methyl-1\(H\)-tetrazole-5(4\(H\))-thiones 79 (Scheme 2.4).\(^{23,24}\)

![Scheme 2.4: Synthesis of tetrazolethiones 79a–e.\(^{23,24}\)](image)

2.2.2 Absorption spectra of tetrazolethiones

The absorption spectra of tetrazolethiones 79a – e were recorded in cyclohexane, tetrahydrofuran (THF) and acetonitrile.\(^{23c}\) All the five compounds displayed similar absorption characteristics. Herein, we will discuss the data on 79a – c. These compounds exhibited four distinct absorption bands \(\lambda_1\), \(\lambda_2\), \(\lambda_3\) and \(\lambda_4\) in cyclohexane and acetonitrile, however \(\lambda_4\) was not observed in THF because of solvent inference (Figure 2.3). The corresponding values of the energies and molar absorptivities for the bands observed for 79a – c in three solvents are shown in Table 2.1.
Figure 2.3: Absorption spectra of 79a (left), 79b (right) and 79c (center bottom) in cyclohexane (red), THF (green) and acetonitrile (blue).

λ₁ and λ₂ bands for tetrazolethione 79a–c both underwent slight blue shifts as the polarity of the solvent increased from cyclohexane → THF → acetonitrile. However, λ₃ of 79a–c remained practically unchanged from cyclohexane → THF → acetonitrile. λ₄ showed a slight blue shift from cyclohexane to acetonitrile for 79b, but was unchanged for 79a,c with increasing polarity from cyclohexane to acetonitrile (Table 2.1). Overall, the absorption spectra of 79a–c showed no dependence on the polarity of the solvents.

Furthermore, changes in the absorption bands were observed upon varying the substituent from moderate electron donor e.g. -C₆H₅ (79a) to a strong electron donor e.g. –C₆H₄OCH₃ (79b, c), as well as upon changing the position of the methoxy group on the aromatic ring attached to the tetrazolethione rings from meta- (79b) and para- (79c). When λ₁ of 79a was compared to 79b, the absorption band remained unchanged in cyclohexane, while a slight blue shift was observed in THF (5 nm) and slight red shift in acetonitrile (5 nm). Comparing 79a to 79c indicated a slight blue shift in cyclohexane (5 nm) and THF (8 nm), whereas there was no
noticeable change in acetonitrile. \( \lambda_2 \) bands for 79a – c remain unchanged in spite of the change in substituents and their position on the aromatic ring. Similarly, \( \lambda_3 \) was unaffected from 79a to 79b in all the solvents, whereas a slight red shift of 6 nm, 6 nm, 13 nm was observed when comparing 79a to 79c in cyclohexane, THF and acetonitrile, respectively. \( \lambda_4 \) band of 79a – c remain unaffected in acetonitrile whereas in cyclohexane the band produced a red shift when comparing 79a to both 79b (14 nm) and 79c (6 nm). From these studies only a modest effect on the absorption spectra of tetrazolethione compounds was observed upon changing the substituents and their position on the aromatic ring.

**Table 2.1:** Energies (\( \lambda \) (E)) and molar absorptivities (log \( \varepsilon \)) for bands observed in the absorption spectra of 79a – c in cyclohexane, THF and acetonitrile.

<table>
<thead>
<tr>
<th></th>
<th>Cyclohexane</th>
<th>THF</th>
<th>Acetonitrile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \lambda(E)^a )</td>
<td>log ( \varepsilon^b )</td>
<td>( \lambda(E)^a )</td>
</tr>
<tr>
<td>79a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \lambda_1 )</td>
<td>291.0 (4.26)</td>
<td>3.82</td>
<td>290.0 (4.27)</td>
</tr>
<tr>
<td>( \lambda_2 )</td>
<td>267.0 (4.65)</td>
<td>3.97</td>
<td>264.1 (4.69)</td>
</tr>
<tr>
<td>( \lambda_3 )</td>
<td>221.0 (5.63)</td>
<td>4.02</td>
<td>222.0 (5.58)</td>
</tr>
<tr>
<td>( \lambda_4 )</td>
<td>193.0 (6.42)</td>
<td>4.06</td>
<td>195.0 (6.36)</td>
</tr>
<tr>
<td>79b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \lambda_1 )</td>
<td>290.0 (4.27)</td>
<td>3.82</td>
<td>285.0 (4.35)</td>
</tr>
<tr>
<td>( \lambda_2 )</td>
<td>266.0 (4.66)</td>
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<td>264.0 (4.69)</td>
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<tr>
<td>( \lambda_3 )</td>
<td>222.0 (5.58)</td>
<td>4.31</td>
<td>223.0 (5.55)</td>
</tr>
<tr>
<td>( \lambda_4 )</td>
<td>207.0 (5.98)</td>
<td>4.27</td>
<td>196.0 (6.32)</td>
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<tr>
<td>79c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \lambda_1 )</td>
<td>286.0 (4.34)</td>
<td>3.81</td>
<td>282.3 (4.39)</td>
</tr>
<tr>
<td>( \lambda_2 )</td>
<td>267.5 (4.63)</td>
<td>3.96</td>
<td>264.1 (4.69)</td>
</tr>
<tr>
<td>( \lambda_3 )</td>
<td>227.0 (5.46)</td>
<td>4.03</td>
<td>228.0 (5.44)</td>
</tr>
<tr>
<td>( \lambda_4 )</td>
<td>199.0 (6.23)</td>
<td>4.31</td>
<td>197.0 (6.29)</td>
</tr>
</tbody>
</table>

\( ^a \) In nm (eV), \( ^b \) In M\(^{-1}\) cm\(^{-1}\)
2.2.3 Theoretical investigations of the electronic properties of tetrazolethiones

All compounds $79a$–$e$ displayed similar electronic properties. Herein, we discuss only compounds $79a$–$c$.

2.2.3.1 Molecular geometry

To gain insight into the electronic properties of tetrazolethiones $79a$–$c$, quantum mechanical calculations were performed at the density functional level of theory (DFT) employing B3LYP functional and using standard 6-311+G* basis set. The optimized geometries of $79a$–$c$ and their corresponding bond lengths are shown in Figure 2.6. The molecules display $C_1$ symmetry and calculated showed that the dihedral angle between the phenyl substituent and tetrazolethione rings ranged between $41.1^\circ$ to $47.0^\circ$. The calculated gas phase dipole moment for $79a$–$c$ were 1.1, 0.96 and 2.1D, respectively.

![B3LYP/6-311+G* optimized structures showing bond lengths and the dihedral angle (in red) between the tetrazolethione ring and the aryl rings.](image)

Figure 2.4: B3LYP/6-311+G* optimized structures showing bond lengths and the dihedral angle (in red) between the tetrazolethione ring and the aryl rings.

2.2.3.2 Frontier molecular orbitals

The electronic structure of $79a$–$c$ was analyzed in cyclohexane, THF and acetonitrile, and similar results were obtained in three solvents. The isodensity plots of the frontier molecular orbitals that includes HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) obtained at B3LYP/6-311+G* level of theory in acetonitrile indicated that these molecular orbitals exhibit $\pi$-type symmetry (Table 2.2). The HOMO-3 for
79a – c and HOMO-2 of 79a are exclusively localized over the aromatic ring; whereas the HOMO-2 of 79b, c is delocalized over the entire molecule. The HOMO-1 is predominantly localized on the tetrazolethione ring and has major contribution from the C$_5$–S$_{13}$ π bond. The HOMOs of 79a – c are delocalized over the entire molecule showing some bonding contributions from the aromatic ring. All the HOMOs display significant contribution from C$_5$–S$_{13}$ π bond.

The LUMOs exhibit a bonding character at the N$_1$–C$_7$, C$_8$–C$_9$ and C$_{11}$–C$_{12}$ bonds that supports the resonance structures of 79a’ – c’ (Figure 2.5). The LUMO+1 of 79a – c is mostly localized over the tetrazolethione ring, while the LUMO+2 is a π* orbital exclusively localized over the aromatic ring. LUMO+3 of 79a – c is delocalized over the entire molecule. Overall, the molecular orbitals were unaffected by change in the solvent or the substituents and their position. This in turn means that the photoreactivity of tetrazolethione based compounds may not be affected by changing the solvent or the substituent.

![Figure 2.5: Resonance structures of 79a’ – c’.](image-url)
Table 2.2: Frontier molecular orbitals for B3LYP/6-311+G* optimized geometries of 79a – c in acetonitrile.

<table>
<thead>
<tr>
<th></th>
<th>79a</th>
<th>79b</th>
<th>79c</th>
</tr>
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<tbody>
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<tr>
<td>LUMO+2</td>
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<tr>
<td>LUMO+1</td>
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<td><img src="image8" alt="Image" /></td>
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<tr>
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<td>HOMO-2</td>
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<td><img src="image23" alt="Image" /></td>
<td><img src="image24" alt="Image" /></td>
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</table>
2.2.4.3 Vertical excitation energies

In order to determine the nature of the electronic transitions that give rise to bands in the UV spectra of 79a – c, time-dependent density functional calculations (TDDFT) were carried out and thirty low lying singlet excited states were calculated. Figure 2.6 show the absorption spectra of 79a in three solvents). The calculated TDDFT vertical excitations energies are shown as stick spectra (see Figure A.1 – A.2 for 79b,c in all the three solvents. Note that TDDFT predicted excitations matches well with the experimentally obtained absorption spectra.

Figure 2.6: Experimental absorption spectra of 79a in cyclohexane, tetrahydrofuran and acetonitrile, and the vertical excitation calculated with TDDFT/6-311+G*

The vertical excitation energies, corresponding wavelengths, oscillator strengths, molecular orbitals (MO) character and the transition type for the most intense transitions calculated at TDDFT/6-311+G* in cyclohexane, THF and acetonitrile for 79a are provided in Table 2.3. The analysis of TDDFT wave function of 79a indicated that λ₁ experimentally observed at 4.26, 4.27 and 4.49 eV in cyclohexane, THF and acetonitrile (Table 2.1), corresponds to a transition from HOMO-1 or HOMO to the LUMO and is calculated at 4.10 eV, 4.19 eV and 4.23 eV in three solvents (Table 2.3). λ₂ experimentally found at 4.65, 4.69 and 4.78 eV in cyclohexane, THF and acetonitrile, is comprised of one to three excited states consisting of transitions from HOMO-3 → LUMO, HOMO-2 → LUMO, HOMO-1 → LUMO+1/LUMO+2, HOMO → LUMO+1/LUMO+2; it was calculated at 4.71, 4.96 and 5.05 eV in the three solvents, respectively. λ₃ was predicted at 5.51, 5.74 and 5.76 eV (Table 2.3) and observed at 5.63, 5.58 and 5.84 eV in cyclohexane, THF and acetonitrile (Table 2.1).
Table 2.3: TDDFT/6-311+G* vertical excitation energies (E (λ) / eV (nm)), oscillator strengths (f), MO character and transition type of 79a in cyclohexane, tetrahydrofuran and acetonitrile.

<table>
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</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>λ₁</td>
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<tr>
<td>λ₂</td>
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<td>π→π* CT</td>
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<tr>
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<tr>
<td>λ₄</td>
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<tr>
<td></td>
<td>30</td>
<td>6.84</td>
<td>0.132 H₃→L+2; H₂→L+3</td>
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<td>λ₁</td>
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<td>λ₂</td>
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<td>13</td>
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<tr>
<td>λ₄*</td>
<td>17</td>
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<tr>
<td>λ₃</td>
<td>12</td>
<td>5.75</td>
<td>0.101 H₃→L+1; H₂→L+1; H₁→L+3; H→L+3</td>
<td>π→π* CT</td>
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<td></td>
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<td>29</td>
<td>6.92</td>
<td>0.243 H₃→L+3</td>
<td>π→π*</td>
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* experimentally not observed
Similarly, this band is formed by two to three excited states comprising of transitions from several MOs of similar energy that included HOMO-3 → LUMO+1, HOMO-2 → LUMO/LUMO+1, HOMO-1 → LUMO+3 and HOMO → LUMO+3.

λ₄ appears experimentally at 6.42 and 6.63 eV in cyclohexane and acetonitrile and was calculated at 6.65, 6.69 and 6.68 eV, consisting of transitions from HOMO-3 → LUMO+2/LUMO+3 and HOMO-2 → LUMO+2/LUMO+3. Similarly, the calculated values of absorption bands for 79b,c in all the three solvent are shown in Tables A.1 and A.2. As discussed for 79a their UV bands are composed of several excited states consisting of transitions between several molecular orbital of similar energy.

Furthermore, the analysis of the MOs indicate that all bands observed in the UV spectra of 79a-c are of π → π* in nature. Some degree of intramolecular charge transfer from the heterocyclic ring to the phenyl ring was exhibited in λ₁. Note that both HOMO-1 and HOMO are mostly localized on the tetrazolethione ring, whereas LUMO is delocalized over the entire molecule and has bonding characteristics at the N₁-C₇, C₈-C₉ and C₁₁-C₁₂ bonds. Likewise, λ₂ and λ₃ correspond to a π → π* transition, the latter is also associated with some degree of charge transfer within the molecule. λ₄ is a π → π* transition predominantly localized on the phenyl ring.

The experimental and calculated transitions both strongly indicated that solvent polarity only has negligible effect on the photophysical properties of tetrazolethione-based compounds. Also, there was no significant effect on the electronic properties of the tetrazolethione derivatives when the substituents or their position on the aromatic ring was changed.

### 2.2.4 Photochemistry of tetrazolethiones and Mechanistic Studies

The photochemistry of the tetrazolethiones 79 was studied in (i) photochemical reactor vessel with double walled quartz immersion well using a Ace-Hanovia medium pressure mercury lamp producing radiation predominantly at 254 nm and emitting minor photon energy at 265, 297, 303 and 360 nm, and in (ii) Rayonet photochemical reactor (Rayonet RMR- 600) equipped with eight interchangeable lamps emitting radiation at 254 and 300 nm.
2.2.4.1 Photochemical studies using medium pressure Hg lamp

The photochemistry of tetrazolethiones 79b and 79d in tetrahydrofuran and acetonitrile solutions was investigated using medium pressure Hg lamp. The analysis of the irradiated samples was carried out by GCMS, which indicated the formation of corresponding carbodiimides 80, ureas 85 and isocyanates 86 (Scheme 2.5). Based on the work on tetrazolethiones in literature,\textsuperscript{25,26,27} we concluded that the initial photorelease of molecular nitrogen and sulfur from 79b,d produced the corresponding carbodiimide 80b,d as the major photoproduct, which immediately underwent hydrolysis with trace amount of water present in the solvent to form the respective ureas 85b,d. The formation of corresponding isothiocyanates 86b,d occurred through a retro 1,3-dipolar cycloaddition (Scheme 2.5). However, there was no evidence of the azide photoproduct (CH\textsubscript{3}N\textsubscript{3}) of this latter pathway possibly due to further decomposition upon its formation. All attempts towards isolating carbodiimides 80b,d for NMR spectroscopic characterization were unsuccessful.

\begin{center}
\includegraphics[width=\textwidth]{Scheme2.5.png}
\end{center}

Scheme 2.5: Photoproducts formed during irradiation of tetrazolethiones 79b,d in solution with medium pressure Hg lamp.

We performed geometry optimizations on a related derivative, 1-methyl-4-(4-chlorophenyl)-1H-tetrazol-5(4H)-thione 79f at the Restricted Hartree-Fock (RHF) level of theory using the 6-311+G** basis set. Subsequently, Configuration Interaction Singles method (CIS/6-311+G*) was employed to obtain the excited state using the ground state geometry at RHF/6-311+G**. Our computational result predicted a substantial lengthening of the C=S bond in the
excited state (4.117 Å) (Figure 2.7). Thus, suggesting the possible involvement of a heterocyclic carbene in the photodecomposition of tetrazolethiones that would subsequently lose nitrogen to afford carbodiimide as the major photoproduct.

Figure 2.7: Excited State (root = 8) for 1-methyl-4-(4-chlorophenyl)-1H-tetrazol-5(4H)-thione 86f optimized at CIS/6-31+G*.

Based on the computational result obtained above, we experimentally explored the involvement of a heterocyclic carbene in the photodecomposition of tetrazolethiones by carrying out carbene trapping experiments. The photoirradiation of 79b in acetonitrile was carried out in the presence of various alkenes such as cyclohexene, 3-bromocyclohexene, allylbenzene and styrene. Hypothetically, if a heterocyclic carbene intermediate 87b was involved, then photolysis in the presence of these trapping agents would result in the formation of carbene addition products e.g. 88b – 91b (Scheme 2.6).
Scheme 2.6: Proposed carbene addition products possible during photochemical trapping experiments of 87b in various alkenes.

The electrospray ionization mass spectrometric analysis of the irradiated solution of 79b in the presence of cyclohexene showed a [M + H]+ at m/z = 273.0 which suggested the formation of the cyclopropane adduct 88b. The ESI-MS/MS spectrum of the peak at 273.0 is shown in Figure 2.8. The fragmentation pattern was consistent with the structure of trapped carbene product 88b. However, all the attempts to isolate 88b through flash column chromatography, preparative thin-layer chromatography and HPLC were met with failure. This may possibly be due to the instability of the cyclopropane ring in the adduct 88b resulting into its decomposition during isolation. We were also not successful in obtaining any spectroscopic evidence for the formation of 89b – d, in case of trapping reactions with other alkenes. This prompted us to believe that the photodecomposition pathway involving heterocyclic carbene may only be a minor pathway.
2.2.4.2 Photochemical studies using Rayonet photochemical reactor

UV Spectral analyses of the irradiated solutions

The photolyses of argon-saturated acetonitrile solutions of 79a,b were carried out in a Rayonet reactor equipped with 254 and 313 nm lamps in a quartz cuvette, and the progress of the photoreaction was monitored by UV-Vis spectroscopy. The UV spectral changes of 79a,b upon irradiation at 254 nm are shown in Figures 2.9 (left) and 2.10 (left). Similarly, the UV spectral changes upon exposing 79a,b to 313 nm light (obtained by using broadband 300 nm lamp with a chromate filter) is also shown in Figures 2.9 (right) and 2.10 (right), and were found to be identical to that observed at 254 nm, however the photoreaction proceeded much slower. The reason could be attributed to the low molar absorptivity of 79a,b at the region of irradiation (313 nm).
Figure 2.9: Changes in UV absorption spectra of 79a in acetonitrile induced by irradiation at 254 (left) and 313 nm (right), arrows indicate the direction of spectral change upon irradiation.

Figure 2.10: Changes in UV absorption spectra of 79b in acetonitrile induced by irradiation at 254 (left) and 313 nm (right), arrows indicate the direction of spectral change upon irradiation.

Overall, the UV spectra exhibited well-defined isosbestic points in each case 79a,b suggesting the formation of a single photoproduct. This observation was noteworthy as most tetrazolylyl derivatives in literature (Chapter 1) often produce several products upon exposure to UV light.\textsuperscript{25,26,27,28}

NMR spectral analyses of the irradiated solutions

The argon-saturated solutions of tetrazolethione 79a – e in acetonitrile-\textit{d}_3, and of 79a,b in benzene-\textit{d}_6, and methanol-\textit{d}_4 were irradiated at 254 and 300 nm for different time intervals in a quartz NMR tube, and the $^1$H NMR spectra were recorded after each irradiation. The chemical shift values for the obtained photoproduct coincided with those of the independently synthesized carbodiimides 80. Thus, indicating that photodecomposition of tetrazolethiones 79 involves photorelease of nitrogen and sulfur to form carbodiimides 80 (Scheme 2.7). The $^1$H NMR spectra of 79a obtained at 0 and 20 min of irradiation in acetonitrile-\textit{d}_3 is shown in Figure 2.11. The peak corresponding to the methyl (3.89 ppm) group of compound 79a decreased in intensity.
while new peak corresponding to the chemical shift value of methyl group of the carbodiimide 80a emerged (3.14 ppm) and grew quickly with prolonged irradiation (Figure 2.11). This result complied with the UV-Vis spectroscopic studies (Figure 2.9), and corroborated with the previous reports by Quast.\textsuperscript{25,26,27} Similarly, the irradiation of 79b – e in acetonitrile-\textit{d}_3 and of 79a,b in benzene-\textit{d}_6, and methanol-\textit{d}_4 produced carbodiimides 80a – e as indicated by \textsuperscript{1}H NMR spectroscopy (Figure A.19 – A.26). Note that the photochemistry of tetrazolethiones 79a,b at 254 nm proceeded much slower in benzene-\textit{d}_6 because of the competition for UV light between the tetrazolethione substrates and the solvent, (See Figure A.31 – A.32).

**Scheme 2.7:** Photoconversion of tetrazolethiones 79 into their respective carbodiimides 80 in solution using Rayonet reactor.

**Figure 2.11:** \textsuperscript{1}H NMR spectra overlay taken at 0 min (bottom) and 20 min (top) during UV-irradiation of 79a in acetonitrile-\textit{d}_3.

Furthermore, photolysis of tetrazolethiones 79a,b was also studied at 300 nm in acetonitrile-\textit{d}_3, benzene-\textit{d}_6, and methanol-\textit{d}_4 solutions and it resulted in the formation of their
respective carbodiimides 79a, b (Figure A.27 – A.32 in Appendix A). The rate of photoconversion at 300 nm was noticeably slower compared to irradiation at 254 nm, most likely due to reasons noted above.

Since only the formation of carbodiimides was observed in all the solvents this clearly shows that solvent polarity does not influence the photoreactivity of the tetrazolethione derivatives. The hydrolysis of compounds 80a, b to corresponding ureas was not observed with rayonet reactor contrary to irradiation with medium pressure Hg lamp (Scheme 2.5), most likely because of the small amount of solvent used.

Quantification of the photoreaction was carried out by NMR spectroscopy for 79a, b using 1,4-dioxane as an internal standard. The amounts of carbodiimide formed and the starting material remaining after irradiation for 15 min and 60 min at 254 and 300 nm, respectively are shown in Table 2.4.

Table 2.4: Amounts of tetrazolethione 79a, b remaining and photoproduct 80a, b produced after irradiation in acetonitrile-d3 and respective quantum yields (Φ).

<table>
<thead>
<tr>
<th>λ (nm)</th>
<th>Irradiation time (min)</th>
<th>Unreacted 79a, b a</th>
<th>Yield of 80a, b [%]</th>
<th>Φ</th>
</tr>
</thead>
<tbody>
<tr>
<td>79a</td>
<td>254</td>
<td>Ar-purged</td>
<td>57</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>Ar-purged</td>
<td>&gt; 95</td>
<td>trace</td>
</tr>
<tr>
<td>79b</td>
<td>254</td>
<td>Ar-purged</td>
<td>60</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>Ar-purged</td>
<td>&gt; 95</td>
<td>trace</td>
</tr>
</tbody>
</table>

a Amounts calculated using 1,4-dioxane as an internal standard (average of three irradiated samples) with the standard deviation in the range 0.4-2% range.

Note that the exposure of argon purged tetrazolethiones 79a, b to UV light at 254 nm afforded the corresponding carbodiimides 80a, b in 42 – 44% yield, while 57 – 60% of the substrate remained unreacted after irradiation (Table 2.4). There was trace amount of other photoproduct(s) formed which were not identified because the yield was ≤1%. Only trace amounts of corresponding carbodiimides 80a, b were observed after 60 min of photolysis at 300 nm (Table 2.4), while most of the substrate remained unreacted.

In order to rule out the possibility of secondary photoreactions from carbodiimide, and to verify its photostability, synthetically obtained carbodiimides 80a, b were subjected to prolonged
irradiation at 254 nm for 120 min. The results revealed no signs of further decomposition and thus, indicating that carbodiimides once formed were photostable.

Furthermore, azoxybenzene actinometer\textsuperscript{29} was used to calculate the quantum yields for the formation of the carbodiimides at 254 nm (Table 2.4). The low quantum yields suggested that these heterocyclic ring systems might be involved in some radiationless decay or fluorescence mechanisms. Overall, the photochemical decomposition of tetrazolethiones showed modest dependency on the nature of the substituents present on the aromatic ring attached to the tetrazolethione ring.

\textbf{2.2.4.3 Mechanistic considerations}

The photochemical formation of carbodiimides 80 from tetrazolethiones 79 involved the loss of molecular nitrogen and sulfur. In order to adeptly study the photodecomposition mechanism, two possible pathways must be considered. Path A involves the initial desulfurization of the heterocyclic ring to generate a carbene 87 that subsequently, would lose nitrogen to afford the observed photoproduct 80. Whereas, path B would involve the initial photorelease of molecular nitrogen to produce a biradical 92 followed by desulfurization to form the observed photoproduct 80 (Scheme 2.8).

\textbf{Scheme 2.8:} Proposed photodecomposition pathways of tetrazolethione ring systems.
In order to determine the involvement of a heterocyclic carbene \( \text{87} \), the photolyses were performed in acetonitrile-\( d_3 \) with excess cyclohexene (5-10 equiv., see experimental procedure for detailed reaction conditions). If the photodecomposition of tetrazolethiones \( \text{79a,b} \) involved the intermediacy of \( \text{87a,b} \), the presence of a trapping agent would completely or partly obstruct the formation of photoproduct \( \text{80a,b} \) and form the typical carbene addition product \( \text{88a,b} \) (Scheme 2.9). However, the NMR spectroscopic and the mass spectrometry analyses of the reaction mixture did not provide any evidence for the formation of trapped product \( \text{88a,b} \).

\[
\begin{align*}
\text{79a,b} & \quad \text{300 nm} \quad \text{MeCN-}d_3 \\
\text{a; R = H} \\
\text{b; R = m-OCH}_3 \\
\text{89a,b} & \quad \text{88a,b}
\end{align*}
\]

**Scheme 2.9:** Proposed cyclopropane adduct \( \text{88a,b} \) expected during the reaction of 79 with cyclohexene in case of the presence of a carbene intermediate.

Our above result employing a Rayonet photochemical reactor equipped with 300 nm lamp was not consistent with our earlier studies that hinted at the probability of a carbene intermediate. Recall that during the irradiation of tetrazolethiones \( \text{79b} \) with medium pressure Hg lamp, we observed the formation of the trapped carbene product \( \text{88b} \) that was identified by ESI-MS/MS spectrometry (Scheme 2.6 and Figure 2.8). It is plausible that the cyclopropane adduct \( \text{88b} \) in case of \( \text{79b} \) in the previous study was formed as a result of thermal reaction as the temperature generated by the lamp could reach up to 600 – 800 °C.\(^{30} \)

Subsequently, mechanistic studies to explore if biradical intermediate \( \text{92} \) is involved in the formation of carbodiimides were conducted. The photolysis of tetrazolethiones \( \text{79a,b} \) was carried out in acetonitrile-\( d_3 \) in the presence of a hydrogen atom donor, 1,4-cyclohexadiene (1,4-CHD) at 300 nm (Figure A.33 – A.34 in Appendix A). We hypothesized that if the photofragmentation that produced carbodiimide involves the intermediacy of a biradical \( \text{92} \), the photolysis of tetrazolethiones \( \text{79} \) in the presence of 1,4-CHD would consequently produce the reduced product, thiourea \( \text{93} \). Indeed, the \(^1\text{H} \) NMR spectral analysis of the irradiated samples indicated the formation of thioureas \( \text{93a,b} \) as the major products along with trace amounts of
carbodiimides 80a,b (Scheme 2.10) (Figure A.33–34; appendix A). Again, 93a,b were identified by comparing their $^1$H NMR spectra with that of independently synthesized samples.

Scheme 2.10: Trapping experiment to provide support for the involvement of 1,3-biradical intermediate 92 in the photodecomposition of tetrazolethiones 79.

Furthermore, the results indicated that the amount of thiourea produced was directly proportional to the concentration of 1,4-CHD used (Figure 2.12). Thus, clearly confirming that the mechanism of photodecomposition of tetrazolethione scaffolds 79 involves the formation of 1,3-biradical intermediate 92.

Figure 2.12: Plot showing the steady formation of thioureas 93a (left) and 93b (right) with increase in the concentration of 1,4-CHD during irradiation of 79a and 79b in acetonitrile, respectively.
While the biradical trapping experiment strongly revealed the intermediacy of 1,3 biradicals, it does not provide definitive evidence as to whether the biradical exist in its triplet or singlet spin multiplicity. Since the singlet biradicals have a short lifetime ($\sim 10^{-13} - 10^{-11}$ s)$^{31,32}$ it is highly likely that the trapped reactive species was the triplet biradical because only those have a lifetime long enough that allows reaction with external trapping agents.$^{33}$ Moreover, desulfurization from a triplet biradical to afford corresponding carbodiimide $87$ would yield a ground state triplet sulfur atom ($^3P$)$^{34}$ that is energetically more favorable than desulfurization from a singlet biradical, which will lead to the formation of an excited state singlet sulfur atom ($^1D$). The lost sulfur atom becomes $S_8$ as this is the most common allotrope of sulfur.$^{35}$ This argument is further supported by the yellow coloration of the reaction mixture produced after photolysis, which is also suggestive of $S_8$ formation.

Also, an irradiation experiment to study the photodecomposition of thiourea under extended exposure to UV light was preformed. There was no photochemical reaction observed, which inferred that thiourea does not undergo further fragmentation or desulfurization to carbodiimide once formed.

### 2.2.4.4 Identifying the precursor to the triplet biradical

The photodecomposition mechanism of tetrazolethiones $79\text{a,b}$ that led to the formation of 1,3-triplet biradicals $92\text{a,b}$ could possibly involve two pathways: Path A involves the initial excitation of the $79$ from its ground state ($S_0$) to the first excited singlet state ($S_1$). The latter could lose molecular nitrogen to generate excited singlet diradicaloid species $94$, which would subsequently undergo intersystem crossing (ISC) to form the 1,3-triplet biradical $92$ and the loss of sulfur from latter will afford the observed carbodiimide $80\text{a,b}$. Path B would involve intersystem crossing from $S_1$ to the first excited triplet state ($T_1$) of tetrazolethione followed by the loss of nitrogen to afford the 1,3-triplet biradical $92$, which would lose sulfur to produce the desired carbodiimide $80\text{a,b}$ (Scheme 2.11).
In order to investigate the involvement of a triplet excited state in the photodecomposition of the tetrazolethiones 79, we carried out indirect irradiation, i.e. triplet sensitization experiments. An indirect irradiation excites the triplet sensitizer from its ground state $S_0$ to its excited singlet state $S_1$, which rapidly undergo intersystem crossing to its excited triplet state $T_1$. As the sensitizer relaxes to the ground state it undergoes a triplet-triplet energy transfer with an acceptor molecule (photosensitization), which in our case would be the surrounding tetrazolethiones in solution. Therefore, if the mechanism involves a triplet excited state, increase in the yields of the carbodiimides 80, is expected.

The irradiation of argon-purged solutions of 79a,b in acetonitrile-$d_3$ was carried out at 300 nm in the presence of triplet sensitizers of varying energies such as benzophenone ($E_T = 69$ kcal/mol), acetophenone ($E_T = 74$ kcal/mol), and acetone ($E_T = 77$ kcal/mol). However, $^1$H NMR spectroscopic analysis of the irradiated samples after 60 minutes did not indicate the formation of carbodiimide 80a,b. We also attempted the sensitization experiment with varying the amounts of the sensitizers and at different irradiation wavelength (350 nm) but the results were unproductive.

Scheme 2.11: Possible pathways for the formation of 1,3-triplet biradical 92.
In order to rule out the possibility of high lying triplet state, triplet quenching experiments were performed at 300 nm. Similar to previous experiments, tetrazolethiones 79a, b were photolyzed in the presence of triplet quenchers such as trans-1,3-pentadiene, 1,3-cyclohexadiene and biphenyl. The quenching experiments were expected to thwart any triplet photochemical process and result in lower yields of the photoproduct, i.e carbodiimide 80a,b.

However, photolysis of 79 with trans-1,3-pentadiene and 1,3-cyclohexadiene as quenchers showed formation of corresponding thioureas and an increase in the yield of carbodiimides. The thioureas were formed by hydrogen atom abstraction from the dienes similar to 1,4-CHD discussed above (Scheme 2.10). Perhaps, the explanation for the increased carbodiimide yields may involve the formation of exciplex, which influenced the photoreactivity either by aiding the rapid photorelease of nitrogen or sulfur.

The photolysis in the presence of biphenyl as a quencher indicated only a slight decrease in the formation of carbodiimides 80a,b with increasing concentration of biphenyl (Figure 2.13). This modest decrease in yields of the photoproduct can be attributed to a slight competitive absorption between the tetrazolethione and the quencher at irradiating wavelength i.e. at 300 nm.

Figure 2.13: Plots showing modest quenching of carbodiimides 80a (left) and 80b (right) during the photolysis of tetrazolethione 79a,b in the presence of biphenyl.

The inability to detect any photoproducts during the triplet sensitization and the slight inhibition of carbodiimide formation observed in the triplet quenching experiments, does not provide a strong support for the photochemistry from a triplet excited state. Also, the photochemical studies of tetrazolethiones 79a,b (Table 2.5) in oxygen-saturated solutions
showed negligible oxygen effect on product yields, hence further excluding the involvement of a triplet excited state (Compare Tables 2.4 and 2.5).

**Table 2.5**: Amounts of tetrazolethiones remaining and photoproducts produced in acetonitrile-\(d_3\).

<table>
<thead>
<tr>
<th>(\lambda) (nm)</th>
<th>Irradiation time (min)</th>
<th>Unreacted 79a,b (^a)</th>
<th>Yield of 80a,b (^a) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>79a</td>
<td>254</td>
<td>O(_2)-sadt</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>O(_2)-sadt</td>
<td>&gt; 95</td>
</tr>
<tr>
<td>79b</td>
<td>254</td>
<td>O(_2)-sadt</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>O(_2)-sadt</td>
<td>&gt; 95</td>
</tr>
</tbody>
</table>

\(^a\) Amounts calculated using 1,4-dioxane as an internal standard (average of three irradiated samples) with the standard deviation in the range 0.4-2% range.

Therefore, the above experiments suggest that photocleavage of these heterocyclic rings probably follows path A involving the singlet excited state, followed by rapid loss of nitrogen to the diradicaloid species and subsequent, intersystem crossing to 1,3-triplet diradical.

**2.2.4.5 Multiphoton excitation experiment**

Our results above indicate that tetrazolethiones 79 can be cleanly converted into carbodiimides 80 employing single photon excitation at 254 nm or 300 nm \textit{via} the intermediacy of a 1,3-triplet biradical. Next, we examined if we could reproduce this chemistry at 800 nm through a multiphoton excitation process. Irradiation of tetrazolethione 79a in acetonitrile at 800 nm with Ti-Sapphire laser (~800 nm) was carried out to investigate (i) if multiphoton irradiation could be used for the fragmentation of tetrazolethione ring systems and (ii) if multiphoton excitation follows similar photochemical pathways as that observed with single-photon excitation (254 nm). The photolysis of argon-purged solution of 79a in acetonitrile at 800 nm was carried out and the UV spectrum was recorded. Note that the UV spectral changes observed at 30 min of irradiation at 800 nm (Figure 2.14, bottom) were similar to that observed at 20 sec of irradiation at 254 nm (Figure 2.14; top). Thus, indicating that tetrazolethione most likely follows the same decomposition pathway at 800 nm as that observed at 254 nm.
Figure 2.14: UV spectral changes of tetrazolethione 79a in acetonitrile induced by single photon excitation (top, irradiation time 20 sec) and multiphoton excitation (bottom, irradiation time 30 min).

2.3 Summary

A number of model tetrazolethiones were successfully synthesized. UV-Vis absorption spectra of these compounds were recorded and quantum mechanical calculations were employed to determine the nature of the electronic transitions that gave rise to these bands. Our results clearly showed that solvent polarity and substituents have negligible effect on the UV characteristics of these compounds and hence, their photophysical properties.

Photochemical studies indicated a clean conversion of a series of tetrazolethione heterocycles to their respective photostable carbodiimides. Between the two proposed photodecomposition pathways, there was no evidence for the intermediacy of a heterocyclic carbene, wherein desulfurization occurs prior to loss of dinitrogen. Similar to the tetrazolone derivatives the photochemistry of tetrazolethione occurs via a 1,3-biradical intermediate, which was concluded to be in its triplet spin multiplicity.
The photosensitization and triplet-quenching experiments to identify the nature of the precursor that led to the biradical provided no conclusive evidence of a triplet excited state. The most feasible precursor that could lead to the formation of a 1,3-triplet biradical was concluded to be the diradicaloid species generated directly from the singlet excited state of tetrazolethione ring systems after the elimination of molecular nitrogen. Subsequently, these diradicaloid species could be envisioned to undergo intersystem crossing to generate the triplet biradical which would undergo desulfurization to form corresponding carbodiimides. The multiphoton irradiation of the tetrazolethiones suggested the formation of similar photoproducts, *i.e.* carbodiimides.

Our results indicate that the photochemical conversion of the tetrazolethiones to carbodiimides is clean and thus, perfectly suited for use in the designing of photoactivated DNA cleaving agents such as enynyl-1*H*-tetrazole-5(4*H*)-thiones 76. Furthermore, the intermediate 1,3-triplet biradicals 95 are also expected to cause DNA damage through hydrogen atom abstraction (Scheme 2.12). To our knowledge, this is the first reported case where photochemical reaction involves the formation of two different types of biradicals that can be exploited for DNA damage.

![Scheme 2.12: Enynyl-1*H*-tetrazole-5(4*H*)-thiones 76 based photoactivated DNA cleavage agents that generate two different types of biradicals in one pot cellular damage.](image)

**Scheme 2.12:** Enynyl-1*H*-tetrazole-5(4*H*)-thiones 76 based photoactivated DNA cleavage agents that generate two different types of biradicals in one pot cellular damage.

### 2.4 Computational Methods

All calculations were carried out with Gaussian 03 package of programs. B3LYP functional in conjunction with 6-311+G* basis set was used. B3LYP combines Becke’s three-
parameter exchange functional with the correlation functional of Lee, Yang, and Parr. All the geometry optimizations were followed by vibrational analyses to ensure the positive sign of all eigenvalues of the Hessian matrix and to confirm that the stationary point found was a true minimum on the potential energy surface. Vertical excitation energies were computed using time-dependent density functional theory (TDDFT) at optimized geometries. The solvent effects on the ground state geometries and excitation energies were considered using the integral equation formalism of the polarized continuum model (IEFPCM). The molecular orbitals were visualized using Gauss View.

2.5 Experimental

2.5.1 Synthesis

All reactions were carried out under an atmosphere of argon in glassware, which had been oven-dried. Thin layer chromatography was carried out on 250 µm silica gel plates with UV 254 fluorescent indicator and UV-light was used as a visualizing agent. Standard column chromatography was performed using 63–200 µm silica gel. ¹H and ¹³C NMR spectra were recorded at ambient temperature on 400 MHz spectrometers. The carrier frequencies were 399.74 MHz (¹H) and 100.53 MHz (¹³C) respectively. The number of scans used were 64 for ¹H NMR spectra and for ¹³C, those ranged from 3-5 K depending on the sample concentration. Both ¹H and ¹³C spectra were recorded with longer relaxation time (10 s). The data is listed as follows: chemical shifts in parts per million, coupling constants in Hertz, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and integration values. The infrared spectroscopic frequencies are reported in cm⁻¹.

Low-resolution mass spectra (LRMS) were obtained on a mass spectrometer equipped with an electrospray ion source (ESI) operated in positive ion mode and connected to a triple quadrupole mass analyzer. Collision-induced dissociation of mass selected ions was performed using nitrogen as a target gas at collision energy of 25 eV. High resolution mass spectra (HRMS) were acquired on a quadrupole/time-of-flight mass spectrometer. The samples were prepared in methanol/acetonitrile (containing 0.1% formic acid in some cases) and were introduced by continuous infusion into the electrospray ionization (ESI) source at a rate of 30 µL/min. TOF
scans were carried out in positive ionization mode. In most cases, both [M + H]⁺ and [M + Na]⁺ ions were detectable for each species.

### 2.5.2 Photochemistry

All irradiations were carried out either in Ace-photochemical vessel with a 254 nm Ace-Hanovia medium pressure mercury lamp or in a Rayonet reactor (Rayonet RMR-600) equipped with 254 nm and broadband 300 nm UV lamps. Monochromatic 313 nm was obtained by using broad band 300 nm UV lamps and by filtering the radiation through a solution of 0.002 M K₂CrO₄ in 5% Na₂CO₃. All the quantitative analyses of the photolyzed reaction mixtures were performed by NMR spectroscopy with 1,4-dioxane as an internal standard. These experiments were carried out on a 500 MHz NMR spectrometer equipped with a 3 mm triple resonance inverse detection pulse field gradient probe operating at 499.848 MHz for ¹H. The spectra were an accumulation of 64 individual scans. The photoproducts were assigned by comparison of their chemical shift values to that of authentic samples.

**NOTE:** Trimethylsilyl azide, aryl isocyanate and dimethyl sulfate are hazardous and highly toxic compounds. Adequate precaution should be taken when handling these compounds.

### 2.6 General procedure for synthesis of monosubstituted tetrazolones 83

Trimethylsilyl azide (TMSA) (1.5 mmol) was added to a round-bottom flask containing the corresponding aryl isocyanate (1.0 mmol), and then the resulting mixture was refluxed at 100 °C for 24 h. After the reaction mixture was cooled to room temperature, the excess TMSA was removed under reduced pressure. The solid was recrystallized from ethyl acetate-hexane to afford the desired monosubstituted tetrazolone.

#### 2.6.1 1-Phenyl-1H-tetrazol-5(4H)-one, 83a

The general procedure was followed using phenylisocyanate (6.30 mmol), which afforded 83a as a white solid (0.868 g, 85%); Rᵢ = 0.29 (70:30 hexane/ EtOAc). ¹H NMR (DMSO-d₆, 400 MHz): δ 7.42 (t, J = 7.51 Hz, 1H), 7.56 (t, J = 7.60 Hz, 2H), 7.85 (d, J = 7.68 Hz, 2H); ¹³C NMR (DMSO-d₆, 100 MHz): δ 119.5, 127.5, 129.4, 134.1, 150.2.
2.6.2 1-(3-Methoxylphenyl)-1H-tetrazol-5(4H)-one, 83b

The general procedure was followed using 3-methoxyphenylisocyanate (3.35 mmol), which afforded 83b as a pale white solid (0.522 g, 81% yield); R_f = 0.12 (7:3 hexane/EtOAc); m.p. 151–153 °C; 1H NMR (DMSO-d_6, 400 MHz): δ 3.80 (s, 3H), 6.98 (d, J = 4 Hz, 1H), 7.41–7.47 (m, 3H); 13C NMR (DMSO-d_6, 100 MHz): δ 55.4, 105.0, 111.3, 113.0, 130.4, 135.2, 150.1, 159.7. IR (KBr pellet) ν max 3178, 3092, 3019, 2833, 2773, 1709, 1602, 1591, 1501, 1361, 1264, 1155, 1071, 977, 864, 733, 622, 591 cm⁻¹. LRMS (ESI): m/z calculated for C_8H_9N_4O_2 (M⁺) 193.0720, found 193.0727.

2.6.3 1-(4-Methoxylphenyl)-1H-tetrazol-5(4H)-one, 83c

The general procedure was followed using 4-methoxyphenylisocyanate (10.06 mmol), which afforded 83c as a pale white solid (1.12 g, 87% yield); R_f = 0.42 (7:3 hexane/EtOAc); m.p. 177–179 °C; 1H NMR (DMSO-d_6, 400 MHz): δ 3.81 (s, 3H), 7.10 (d, J = 8.98 Hz, 2H), 7.71 (d, J = 9.17 Hz, 2H); 13C NMR (DMSO-d_6, 100 MHz): δ 55.5, 114.5, 122.0, 127.1, 150.5, 158.5.

2.6.4 1-(3-Chlorophenyl)-1H-tetrazol-5(4H)-one, 83d

The general procedure was followed using 3-chlorophenylisocyanate (13.1 mmol) which afforded 83d as a white solid (2.33 g, 90% yield); R_f = 0.22 (7:3 hexane/EtOAc); m.p. 177–179 °C; 1H NMR (DMSO-d_6, 400 MHz): δ 7.46 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 8 Hz), 7.83 (dd, J = 0.8 Hz, J = 8 Hz, 1H), 7.95 (s, 1H); 13C NMR (DMSO-d_6, 100 MHz): δ 117.6, 118.6, 127.2, 131.3, 133.7, 135.5, 150.4.

2.6.5 1-(4-Nitrophenyl)-1H-tetrazol-5(4H)-one, 83e

The general procedure was followed using 4-nitrophenylisocyanate (9.14 mmol) which afforded 83d as a yellow solid (1.53 g, 81% yield); 1H NMR (400 MHz, DMSO): δ 8.21 (d, J = 8.1 Hz, 2H), 8.41 (d, J = 8.2 Hz, 2H); 13C NMR (100 MHz, DMSOC): δ 119.1, 125.3, 139.2, 145.4, 150.0.

2.7 General procedure for synthesis of 1,4-disubstituted tetrazolones 84

To a mixture of monosubstituted tetrazolone, tetrabutylammonium bromide (TBABr), 20% NaOH in methylene chloride was added to a solution of dimethyl sulfate (DMS) in
methylene chloride. The resulting mixture was stirred at room temperature for approximately 3 h (or monitored with TLC until completion). After the completion of the reaction, the organic layer was separated and washed (3x) with water to remove any excess TBABr then dried over Na₂SO₄. The filtrate was concentrated under reduced pressure and dried under vacuum to afford the desired product. The synthesis of compound 84e has been reported from previous work carried out in our lab.

2.7.1 1-Methyl-4-phenyl-1H-tetrazol-5(4H)-one, 84a

The general procedure was followed using 1-phenyl-1H-tetrazol-5(4H)-one (3.08 mmol) to produce 84a as a crystalline colorless solid (0.52 g, 95%); Rₛ = 0.81 (40:60 hexane/EtOAc); ¹H NMR (DMSO-d₆, 400 MHz): δ 3.62 (s, 3H), 7.44 (t, J = 7.40 Hz, 1H), 7.58 (t, J = 7.03 Hz, 2H), 7.85 (d, J = 8.27 Hz, 2H); ¹³C NMR (DMSO-d₆, 100 MHz): δ 31.2, 119.4, 127.7, 129.5, 134.2, 148.8. HRMS (ESI): m/z calculated for C₉H₈N₄ONa (M+Na⁺) 199.0596, found 199.0602.

2.7.2 1-Methyl-4-(3-methoxyphenyl)-1H-tetrazol-5(4H)-one, 84b

The general procedure was followed using 1-(3-Methoxyphenyl)-1H-tetrazol-5(4H)-one (2.60 mmol) to produce 84b as a white crystalline solid (0.482 g, 90% yield); Rₛ = 0.37 (7:3 hexane/EtOAc); m.p. 79–81 °C; ¹H NMR (CDCl₃, 400 MHz): δ 3.70 (s, 3H), 3.86 (s, 3H), 6.89-6.92 (m, 1H), 7.39 (t, J = 8.4 Hz, 1H), 7.52–7.56 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 31.6, 55.7, 104.7, 111.4, 113.9, 130.4, 135.8, 149.4, 160.4. IR (KBr pellet) νmax 3118, 3091, 3012, 2966, 2840, 1729, 1608, 1588, 1502, 1387, 1461, 1299, 1231, 1142, 1042, 866, 782, 727 cm⁻¹. LRMS (ESI): m/z calculated for C₉H₁₁N₄O₂⁺ (M⁺) 207.0877, found 207.0878.

2.7.3 1-Methyl-4-(4-methoxyphenyl)-1H-tetrazol-5(4H)-one, 84c

The general procedure was followed using 1-(4-Methoxyphenyl)-1H-tetrazol-5(4H)-one (2.08 mmol) to produce 84c as a crystalline colorless solid (0.30 g, 91% yield); Rₛ = 0.51 (4:6 hexane/EtOAc); m.p. 119-120 °C; ¹H NMR (CDCl₃, 400 MHz): δ 3.70 (s, 3H), 3.86 (s, 3H), 7.01 (d, J = 9.17 Hz, 2H), 7.80 (d, J = 9.17 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 31.6, 55.7, 114.7, 121.6, 128.0, 149.6, 159.2. IR (KBr pellet) νmax 3088, 3011, 2975, 2945, 2847, 1721, 1618, 1519, 1424, 1357, 1252, 1155, 1048, 1028, 824, 744, 729, 574, 511 cm⁻¹. LRMS (ESI): m/z calculated for C₉H₁₀N₄O₂Na⁺ (M+Na⁺) 229.0702, found 229.0712.
2.7.4 1-(3-Chlorophenyl)-4-methyl-1H-tetrazol-5(4H)-one, 84d

The general procedure was followed using 1-(3-chlorophenyl)-1H-tetrazol-5(4H)-one (2.54 mmol) to produce 84d as a pale white solid (0.51 g, 96% yield); Rf = 0.35 (7:3 hexane/EtOAc); $^1$H NMR (CDCl$_3$, 400 MHz): δ 3.70 (s, 3H), 3.86 (s, 3H), 7.32 (d, $J = 7.8$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 1H), 7.80 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.94$ Hz, 1H), 8.00 (s, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 31.7, 117.0, 119.2, 127.9, 130.7, 135.4, 135.7, 149.1.

2.7.5 1-(4-Nitrophenyl)-4-methyl-1H-tetrazol-5(4H)-one, 84e

The general procedure was followed using 1-(4-nitrophenyl)-1H-tetrazol-5(4H)-one (2.41 mmol) to produce 84e as a yellow solid (0.45 g, 85% yield); $^1$H NMR (400 MHz, DMSO): δ 3.67 (s, 3H, CH$_3$), 8.20 (d, $J = 8.2$ Hz, 2H), 8.46 (d, $J = 8.1$ Hz, 2H); $^{13}$C NMR (100 MHz, DMSO): δ 31.1, 119.0, 125.1, 139.3, 145.6, 148.8.

2.8 General procedure for synthesis of tetrazolethiones, 79

Phosphorus pentasulfide (P$_2$S$_5$) was added to a solution of disubstituted tetrazolone in dry toluene and the resulting reaction mixture was reflux at 110 °C until the starting material disappeared, as indicated by TLC. After cooling, the reaction mixture was filtered, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by column chromatography afforded the product.

2.8.1 1-Methyl-4-phenyl-1H-tetrazole-5(4H)-thione, 79a

The general procedure was followed by using 1-methyl-4-phenyl-1H-tetrazol-5(4H)-one (22.7 mmol) and purification by column chromatography (SiO$_2$, 88:12 hexane/EtOAc) produced 86a as a yellow solid (2.3 g, 53%); Rf = 0.77 (4:6 hexane/EtOAc); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 3.91 (s, 3H) 7.68-7.55 (m, 3H), 7.87 (d, $J = 7.14$ Hz, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 34.7, 124.3, 129.3, 129.8, 134.4, 163.2. HRMS (ESI): $m/z$ calculated for C$_8$H$_9$N$_4$S (M$^+$) 193.0548, found 193.0545.
2.8.2 1-(3-Methoxyphenyl)-4-methyl-1H-tetrazole-5(4H)-thione, 79b

The general procedure was followed by using 1-(3-methoxyphenyl)-4-methyl-1H-tetrazol-5(4H)-one (2.4 mmol) and purification by column chromatography (SiO₂, 93:7 hexane/EtOAc) produced 79b as a white solid (0.42 g, 78% yield): Rf = 0.64 (70:30 hexane/EtOAc); m.p. 52–54°C; 1H NMR (400 MHz, CDCl₃): δ 3.85 (s, 3H), 3.89 (s, 3H), 7.10-7.13 (m, 1H), 7.43-7.46 (m, 1H), 7.49-7.51 (m, 1H), 7.53 (s, 1H); 13C NMR (100 MHz, CDCl₃): δ 35.5, 56.4, 111.0, 116.2, 117.2, 131.2, 137.0, 161.0, 165.0. IR (ZnSe ATR crystal): 1600, 1590, 1492, 1440, 1356, 1324, 1238, 1195, 1160, 1065, 1022, 865, 839, 782, 681 cm⁻¹. HRMS (ESI): m/z calculated for C₉H₁₁N₄OS⁺ (M⁺) 223.0654, found 223.0648; calculated for C₉H₁₀N₄OSNa (M+Na⁺) 245.0473, found 245.0468.

2.8.3 1-(4-Methoxyphenyl)-4-methyl-1H-tetrazole-5(4H)-thione, 79c

The general procedure was followed by using 1-methyl-4-(4-methoxyphenyl)-1H-tetrazol-5(4H)-one (1.46 mmol) and purification by column chromatography (SiO₂, 90:10 hexane/EtOAc) produced 79c as a white crystalline solid (0.24 g, 75% yield): Rf = 0.62 (6:4 hexane/EtOAc); m.p. 134 – 135°C; 1H NMR (200 MHz, CDCl₃): δ 3.88 (s, 3H), 3.98 (s, 3H), 7.05 (d, J = 9.16 Hz, 2H), 7.82 (d, J = 9.16 Hz, 2H); 13C NMR (100 MHz, CDCl₃): δ 35.2, 55.8, 114.6, 125.7, 127.8, 160.5, 163.9. IR (KBr pellet) νmax 3076, 2998, 2965, 2926, 2840, 1612, 1591, 1514, 1446, 1369, 1326, 1302, 1256, 1191, 1114, 1080, 1041, 1028, 825, 742, 561, 543 cm⁻¹; HRMS (ESI): m/z calculated for C₉H₁₁N₄OS⁺ (M⁺) 223.0654, found 223.0645.

2.8.4 1-(3-Chlorophenyl)-4-methyl-1H-tetrazole-5(4H)-thione, 79d

The general procedure was followed by using 1-methyl-4-(3-chlorophenyl)-1H-tetrazol-5(4H)-one (1.90 mmol) and purification by column chromatography (SiO₂, 96:4 hexane/EtOAc) produced 79d as a white solid (0.28 g, 65% yield): Rf = 0.61 (7:3 hexane: EtOAc); 1H NMR (200 MHz, CDCl₃): δ 3.88, 7.55-7.60 (m, 2H), 7.87-7.90 (m, 2H), 8.03 (s, 1H); 13C NMR (100 MHz, CDCl₃): δ 35.5, 123.4, 124.8, 130.6, 131.8, 135.1, 137.0, 165.0.

2.8.5 1-(3-Nitrophenyl)-4-methyl-1H-tetrazole-5(4H)-thione, 79e

The general procedure was followed by using 1-methyl-4-(4-nitrophenyl)-1H-tetrazol-5(4H)-one (3.17 mmol) and purification by column chromatography (SiO₂, 96:4 hexane/EtOAc) produced 79e as a white solid (0.28 g, 65% yield): Rf = 0.61 (7:3 hexane: EtOAc); 1H NMR (400 MHz, CDCl₃): δ 3.85, 7.41-7.48 (m, 2H), 7.56-7.60 (m, 2H), 7.87-7.90 (m, 2H), 8.03 (s, 1H); 13C NMR (100 MHz, CDCl₃): δ 35.5, 123.4, 124.8, 130.6, 131.8, 135.1, 137.0, 165.0.
DMSO): δ 3.91 (s, 3H, CH$_3$), 8.35 (d, $J = 9.4$ Hz, 2H), 8.50 (d, $J = 8$ Hz, 2H); $^{13}$C NMR (100 MHz, DMSO): δ 34.9, 124.7, 125.0, 139.4, 147.4, 163.1.

2.9 General procedure for synthesis of thiourea, 93

To a stirring solution of aromatic amine 96 (16.10 mmol) in methanol (50 mL) was added a commercially obtained methyl isothiocyanate (17.70 mmol), and the reaction mixture was refluxed at 65 °C for 24-30 h. After complete consumption of the starting material the mixture was concentrated under reduced pressure and the crude compound was recrystallized in ethanol to produce the corresponding arylthioureas 93.

2.9.1 1-Methyl-3-phenylthiourea, 93a

Compound 93a was prepared from aniline 96a (16.1 mmol) using the general procedure. White solid (2.46 g, 92% yield): R$_f$ = 0.29 (60:40 hexane/ EtOAc); m.p. 110-112 °C; $^1$H NMR (400 MHz, CD$_3$CN): δ 2.97 (d, $J = 8$ Hz, 3H), 6.56 (s, 1H), 7.22-7.29 (m, 3H), 7.37-7.41 (m, 1H), 8.12 (s, 1H). $^{13}$C NMR (100 MHz, CD$_3$CN): δ 32.1, 126.0, 127.0, 130.4, 138.7, 182.8. IR (ZnSe ATR crystal) 3259, 3155, 2989, 2937, 1515, 1490, 1287, 1246, 1210, 1026, 1001, 723, 689, 640, 602 cm$^{-1}$. HRMS (ESI): $m/z$ calculated for C$_8$H$_{11}$N$_2$S$^+$ (M$^+$) 167.0643, found 167.0637; calculated for C$_8$H$_{10}$N$_2$SNa$^+$ (M+Na$^+$) 189.0462, found 189.0457.

2.9.2 1-(3-Methoxyphenyl)-3-methylthiourea, 93b

Compound 93b was prepared from 3-methoxyaniline 96b (8.12 mmol) using the general procedure. White solid (1.46 g, 92% yield): R$_f$ = 0.15 (70:30 hexane/EtOAc); m.p. 98-100 °C. $^1$H NMR (400 MHz, CD$_3$CN): δ 2.97 (d, $J = 8$ Hz, 3H), 3.78 (s, 3H), 6.62 (s, 1H), 6.78-6.88 (m, 3H), 7.29 (t, 1H), 8.06 (s, 1H). $^{13}$C NMR (100 MHz, CD$_3$CN): δ 32.2, 56.1, 111.4, 112.5, 117.7, 131.3, 139.7, 161.5, 182.7. HRMS (ESI): $m/z$ calculated for C$_9$H$_{12}$N$_2$OS$^+$ (M$^+$) 197.0749, found 197.0743; calculated for C$_9$H$_{12}$N$_2$OSNa$^+$ (M+Na$^+$) 219.0568, found 219.0563.
2.9.3 1-(4-Methoxyphenyl)-3-methylthiourea, 93c

Compound 93c was prepared from 4-methoxyaniline 96c (12.18 mmol) using the general procedure. Crystalline lavender solid (2.08 g, 87% yield); R_f = 0.46 (3:7 hexane/EtOAc); ^1H NMR (400 MHz, CD_3CN): δ 2.94 (d, J = 4.4 Hz, 3H), 3.79 (s, 3H), 6.36 (br s, 1H), 6.94 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 7.96 (br s, 1H); ^13C NMR (100 MHz, CD_3CN): δ 32.1, 56.2, 115.6, 128.6, 159.3, 183.4.

2.9.4 1-(3-Chlorophenyl)-3-methylthiourea, 93d

Compound 93d was prepared from 3-chloroaniline 96d (19.60 mmol) using the general procedure. Brown crystalline colorless solid (3.26 g, 84% yield); R_f = 0.20 (3:7 hexane/EtOAc); ^1H NMR (400 MHz, CD_3CN): δ 2.98 (d, J = 4.4 Hz, 3H), 6.73 (br s, 1H), 7.18-7.23 (m, 2H), 7.16 (t, J = 8 Hz, 1H), 7.44 (br s, 1H), 8.34 (br s, 1H); ^13C NMR (100 MHz, CD_3CN): δ 32.0, 123.7, 125.2, 126.3, 131.5, 134.9, 140.5, 182.6.

2.9.5 1-Methyl-3-(4-Nitrophenyl)-thiourea, 93e

Compound 93e was prepared from 3-nitroaniline 96e (10.86 mmol) using the general procedure. Brownish yellow solid (1.81 g, 79% yield); R_f = 0.17 (6:4 hexane/EtOAc); ^1H NMR (400 MHz, CD_3CN): δ 3.03 (d, J = 4.4 Hz, 1H), 6.92 (s, 1H), 7.72 (d, J = 7.6 Hz, 2H), 8.16 (d, J = 9.2 Hz, 2H), 8.48 (s, 1H).

2.10 General procedure for synthesis of carbodiimides, 80

Mercuric oxide (18.1 mmol) was added to a solution of arylthiourea (6.0 mmol) in CH_2Cl_2:H_2O (4:1, 30 mL), and the reaction mixture was stirred at room temperature for 30 min. After completion the mixture was filtered through Celite, washed with ample amount of CH_2Cl_2 and the filtrate was concentrated under reduced pressure. Purification of the crude compound by a short silica gel flash column chromatography afforded the corresponding carbodiimides.

2.10.1 N-((Methylimino)methylene)aniline, 80a

Compound 80a was prepared from 1-methyl-3-phenylthiourea (93a) (6.0 mmol) using the general procedure. Purification using 5% EtOAc/hexanes afforded a yellow oil (0.10 g, 12% yield): R_f = 0.83 (7:3 hexane/EtOAc); ^1H NMR (400 MHz, CD_3CN): δ 3.14 (s, 3H), 7.09-7.14
(m, 3H), 7.29-7.33 (t, 2H); \(^{13}\)C NMR (100 MHz, CD\(_3\)CN): δ 32.8, 124.4, 125.6, 130.5, 137.0, 142.0. IR (ZnSe ATR crystal) 3059, 3024, 2935, 2879, 2121, 2026, 1592, 1499, 1406, 1282, 1156, 1070, 891 cm\(^{-1}\). HRMS (ESI): \(m/z\) calculated for C\(_9\)H\(_{11}\)N\(_2\)O\(^+\) (M\(^+\)) 163.0871, found 163.0866.

### 2.10.2 3-Methoxy-N-((methylimino)methylene)benzenamine, 80b

Compound 80b was prepared from 1-(3-methoxyphenyl)-3-methylthiourea (93b) (5.1 mmol) using the general procedure. Purification using a 5% EtOAc/hexanes afforded a yellow oil (0.35 g, 42% yield); R\(_f\) = 0.71 (70:30 hexane/EtOAc); \(^1\)H NMR (400 MHz, CD\(_3\)CN): δ 3.14 (s, 3H), 3.76 (s, 3H), 6.63 - 6.70 (m, 3H), 7.20 (t, 1H); \(^{13}\)C NMR (100 MHz, CD\(_3\)CN): δ 32.8, 56.0, 109.9, 111.3, 116.7, 131.1, 136.7, 143.2, 161.6. IR (ZnSe ATR crystal) 2937, 2834, 2123, 1594, 1581, 1493, 1464, 1421, 1281, 1243, 1127, 1038, 945, 840, 769, 684 589 cm\(^{-1}\). HRMS (ESI): \(m/z\) calculated for C\(_9\)H\(_{11}\)N\(_2\)O\(^+\) (M\(^+\)) 163.0871, found 163.0866.

### 2.10.3 4-Methoxy-N-((methylimino)methylene)benzenamine, 80c

Compound 80c was prepared from 1-(4-methoxyphenyl)-3-methylthiourea (93c) (6.11 mmol) using the general procedure. Purification using a 5% EtOAc/hexanes afforded pure 4-methoxy-N-((methylimino)methylene)benzenamine 80c as a pale yellow oil (0.35 g, 42% yield); R\(_f\) = 0.71 (6:4, hexane/EtOAc); \(^1\)H NMR (400 MHz, CD\(_3\)CN): δ 3.10 (s, 3H), 3.75 (s, 3H), 6.86 (d, \(J = 12\)Hz, 2H), 7.02 (d, \(J = 8\)Hz, 2H); \(^{13}\)C NMR (100 MHz, CD\(_3\)CN): δ 33.3, 116.0, 125.7, 134.5, 138.5, 158.3.

### 2.10.4 3-Chloro-N-((methylimino)methylene)benzenamine, 80d

Compound 80d was prepared from 1-(4-methoxyphenyl)-3-methylthiourea (93d) (2.17 mmol) using the general procedure. Purification using 1% EtOAc/hexanes afforded pure 3-chloro-N-((methylimino)methylene)benzenamine 80d as a yellow oil (0.35 g, 42% yield); R\(_f\) = 0.80 (7:3 hexane/EtOAc); \(^1\)H NMR (400 MHz, CD\(_3\)CN): δ 3.16 (s, 3H), 7.01 (d, \(J = 8\)Hz, 1H), 7.12 (s, 2H) 7.27 (t, \(J = 8\)Hz, 1H); \(^{13}\)C NMR (100 MHz, CD\(_3\)CN): δ 32.7, 122.9, 124.4, 125.4, 131.7, 135.3, 143.9.
2.10.5 \(N-((\text{methylimino})\text{methylene})-4\text{-nitrobenzenamine}, \text{80e}\)

Compound \text{80e} was prepared from 1-methyl-3-(4-nitrophenyl)-thiourea (\text{93e}) (3.55 mmol) using the general procedure. Purification using 4% EtOAc/hexanes afforded pure \(N-((\text{methylimino})\text{methylene})-4\text{-nitrobenzenamine} \text{80e}\) as a yellow oil (0.11 g, 26% yield); \(R_f = 0.65\) (6:4, hexane/EtOAc); \(^1\text{H NMR (400 MHz, CD}_3\text{CN):} \delta 3.23\) (s, 3H), 7.21 (d, \(J = 8\text{Hz}, 2\text{H}\)), 8.15 (d, \(J = 8\text{Hz}, 2\text{H}\)); \(^{13}\text{C NMR (100 MHz, CD}_3\text{CN):} \delta 32.5, 124.9, 126.1, 132.3, 145.1, 150.2.\)

2.11 General photochemical procedures: Medium pressure Hg lamp

2.11.1 Photolysis and product identification

An argon purged solution of 1-(3-methoxyphenyl)-4-methyl-1\text{H}-tetrazol-5(4\text{H})-one \text{79b,d} (0.22 mmol) in acetonitrile (125 mL) was irradiated for 60 min at 254 nm in Ace-photochemical vessel using a 100W medium-pressure mercury lamp. GCMS analysis of aliquot of irradiated sample was carried out. The sample was concentrated under reduced pressure and purified with flash column chromatograph to afford the corresponding urea.

2.11.2 Carbene trapping experiment

1-(3-Methoxyphenyl)-4-methyl-1\text{H}-tetrazol-5(4\text{H})-one (0.05g, 0.22 mmol) \text{79b} in acetonitrile (125-130 mL) containing 10 equivalent of carbene trapping agents (cyclohexene, 3-bromocyclohexene, allylbenzene and styrene) was irradiated with medium-pressure mercury lamp (100W; 254 nm) for 60 min in Ace-photochemical vessel. Aliquots of irradiated samples was analyzed by GCMS.

2.12 General photochemical procedures: Rayonet reactor

2.12.1 UV spectral changes

An argon-purged solution of \text{79a} (0.07 mM) and \text{79b} (0.13 mM) in acetonitrile was irradiated in a quartz cuvette at 254 nm. In the case of \text{79a}, a UV spectrum was obtained after each irradiation at 0, 20, 40, 60, 120, 200, 300, and 420s, whereas in the case of \text{79b}, a UV spectrum was obtained after each irradiation at 0, 20, 40, 60, 80, 120, and 150s, respectively. Similarly, the irradiation of an argon-purged solution of \text{79a} (0.2 mM) and \text{79b} (0.075 mM) in
acetonitrile was carried out in a quartz cuvette at 313 nm, and a UV spectrum was obtained after irradiation at different time intervals (at 0, 1, 5, 10, 15, 20, 30, 40, and 50 min for 79a and 0, 5, 10, 15, 20, 25, 25, 30, 35 and 40 min for 79b).

2.12.2 Product identification and Quantitative studies

Irradiation of argon-purged solution of 79a,b (4.63 mM; 0.65 mL) in acetonitrile-d₃ was carried out at 254 and 300 nm in a quartz NMR tube and ¹H NMR spectrum was recorded after photolysis at every 5 min time interval for 15 and 60 min respectively.

2.12.3 Photolysis of carbodiimides and thioureas

Photolysis of compound 79a – b (4.70 mM) in an argon-purged acetonitrile-d₃ was conducted in a quartz NMR tube at 254 for 90 min. Similarly, an argon-purged solution of 93a – b (4.70 mM; 0.7 mL) in acetonitrile-d₃ was irradiated in a quartz NMR tube at 254 for 120 min, and a NMR spectrum was obtained.

2.12.4 Carbene Trapping: Photolysis in the presence of cyclohexene

An argon-purged solution of 79a – b (4.55 mM; 0.7 mL) in acetonitrile-d₃ containing 10 equiv. of cyclohexene was photolyzed at 254 and 300 nm in a quartz NMR tube for 30 and 60 min, respectively, and a NMR spectrum was obtained. For the ESI-MS/MS experiments, 8mL of 1.5 mM tetrazolethione 79a – b solution was irradiated at 254 and 300 nm. The samples were concentrated using rotary evaporator and crude was analyzed.

2.12.5 Biradical Trapping: Photolysis in the presence of 1,4-Cyclohexadiene

Four separate solutions of 79a – b (4.63 mM; 0.7 mL) in acetonitrile-d₃ containing varying amounts of 1,4-CHD (10-50 equiv.) were taken in quartz NMR tubes. The mixture in each tube was purged with argon for 15 min and irradiated with broadband 300 nm UV lamp for 60 min, and the ¹H NMR spectrum was recorded.

2.12.6 Sensitization experiments

The photolysis of three separate argon purged solutions of 79a – b (4.63 mM; 0.7 mL) in acetonitrile-d₃ containing varying amounts (1–20 equiv.) of benzophenone, acetophenone, and
acetone, respectively, was performed with broadband 300 nm UV lamp. Subsequently, the $^1$H NMR spectrum was recorded after 60 min.

2.12.7 Effect of oxygen

An oxygen-purged solution of 79a – b (0.65 mL) in acetonitrile-$d_3$ (approximately in the range 4.63 mM) was irradiated in a quartz NMR tube at 254 and 300 nm for 15 min and 60 min, respectively and NMR spectrum was recorded.

2.12.8 Triplet quenching experiments

A solution of 79a – b (4.02 – 4.64 mM) in acetonitrile-$d_3$ containing trans-1,3-pentadiene and 1,3-cyclohexadiene (10 equiv) respectively, was photolyzed at 300 nm in a quartz NMR tube for 60 min and the $^1$H NMR spectrum was recorded. For the biphenyl experiment, four separate solutions of 79a – b in acetonitrile-$d_3$ (4.63 mM; 0.7 mL) containing varying amounts of biphenyl (0-15 equiv) was purged with argon for 15 min and irradiated with broad band 300 nm UV lamp for 60 min, and NMR spectrum was obtained.

2.13 Actinometry and Quantum yield experiments

A 5.04 mM solution of azoxybenzene in 95% ethanol and a 0.1 M solution of KOH in 95% ethanol were prepared. The azoxybenzene solution was irradiated every 60 sec for 10 min in a quartz cuvette at 254 nm (no purging with Ar required), and 0.1 mL of the irradiated solution was mixed with 1 mL of 0.1 M KOH solution followed by the addition of 23.9 mL of 95% ethanol in a 25 mL volumetric flask. A UV spectrum was subsequently recorded, and the incident light intensity was calculated, as described by Bunce et al., using the equations below:

$$P = (A/\varepsilon) = \text{(moles of X)(dilution factor)} \quad \text{Equation 2.1}$$
$$\text{Extent of reaction} = \{[\text{product concentration}/[\text{initial concentration}]\} \times 100 \quad \text{Equation 2.2}$$
$$I_0 = -[A_o^*\ln(1-(P/A_o))]/\Phi_r t \quad \text{Equation 2.3}$$

Where, $P =$ concentration of product formed at time $t$; $A =$ absorbance; $A_o =$ absorbance at initial concentration; $\varepsilon =$ molar absorptivity of azoxybenzene ($= 7600$); $\Phi_r =$ photosensitivity of azoxybenzene ($\sim 0.02$); $t =$ irradiation time; $I_0 =$ incident light intensity.
An argon-purged solution of 0.25 mM 79a and 0.27 mM 79b in acetonitrile was irradiated every 5 sec for 25 sec (approximately <10% conversions) and the UV spectra were recorded after each irradiation. The progress of the reaction was linear and the photoconversion was analyzed at 5-10% completion. The quantum yields (Φ; in mol/L/s) were calculated using the equations below:

\[
\text{Extent of reaction} = \frac{(A_t - A_o)}{A_o} \times 100 \quad \text{Equation 2.4}
\]

\[
P_{cd} = (\text{Extent of reaction}/100) \times [\text{initial concentration of sample}] \quad \text{Equation 2.5}
\]

\[
\text{Slope} = \frac{P_{cd}}{\text{irradiation time}} \quad \text{Equation 2.6}
\]

\[
\Phi = \frac{\text{slope}}{I_o} \quad \text{Equation 2.7}
\]

Where, \(A_o\) = absorbance at initial concentration; \(A_t\) = absorbance at irradiated time \(t\); \(P_{cd}\) = concentration of product (carbodiimide) formed; \(t\) = irradiation time; slope can also be obtained by plotting \(P_{cd}\) vs \(t\); \(I_o\) = incident light intensity.
References:


20 Gundugola dissertation


Chapter 3 - Synthesis of Phenanthridine-Fused Quinazoliniminium Salts from Heteroenyne-allenes

3.1 Introduction

An important class of \( N \)-heterocyclic moieties that appears in significant number of natural products are \( 4(3\ H) \)-quinazolinones \( 97 \) and their derivatives which demonstrate a wide range of pharmacological activities.\(^1\,\,^2\,\,^3\,\,^4\) Examples of natural products containing this scaffold are chrysogine \( 98 \) isolated from \textit{Penicillium chrysogenum} and febrifugine \( 99 \) obtained from Chinese plant \textit{Dichrofebrifuga}, both of which exhibit potent antimalarial activity,\(^3\) luotonine A \( 100 \) extracted from the Chinese plant \textit{Peganum nigellastrum} acts as a Topoisomerase I inhibitor,\(^3\,\,^5\) and rutaecarpine \( 101 \) isolated from \textit{Evodia rutaecarpa} is used extensively in Chinese medicine for headaches, and for the treatment of cholera and hypertension (Figure 3.1).\(^3\,\,^6\,\,^7\) In addition, many compounds containing quinazolinone scaffold possess a vast range of other biological activities such as antimicrobial, antibacterial, antifungal, antiviral, antidepressant, anti-inflammatory and diuretic.\(^1\,\,^3\,\,^8\,\,^9\,\,^10\) These are also known to act on central nervous system as stimulants, psychotropics, hypnotics and antianxiety drug.\(^1\,\,^3\,\,^4\,\,^11\,\,^12\) Therefore, quinazolinones and their derivatives are interesting structural scaffolds that are capable of interacting with multiple biological receptors and are thus, considered as privileged structures in drug discovery.\(^1\)

![Chemical structures of quinazolinones and biologically active natural products](image)

\textit{Figure 3.1}: \( 4(3\ H) \)-Quinazolinones \( 98 \) and some biologically active natural products containing this scaffold.\(^3\,\,^5\,\,^6\,\,^7\)
4(3H)-Quinazolinimine 102 is a related heterocyclic scaffold that has not received as much attention in biology.\textsuperscript{10,13} For instance, heterocycles 103 – 105 containing this scaffold are known to exhibit cholinesterase inhibitory activity, and therefore, have been proposed for use in the treatment of Alzheimer’s disease (Figure 3.2).\textsuperscript{14,15} Recently, our laboratory reported the antiproliferative activity of 2-halo-3-aryl-4(3H)-quinazoliniminium halides against leukemia (L1210) and breast cancer cell lines (SK-BR-3) and select data is shown in Table 3.1.\textsuperscript{16}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.2}
\caption{4(3H)-quinazolinimine ring structure 102 and synthetic compounds containing this scaffold 104 – 106.\textsuperscript{14,15,16}}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Compd. & \multicolumn{4}{c|}{IC\textsubscript{50} (\textmu M)\textsuperscript{a} in L1210 Cells\textsuperscript{b}} & \multicolumn{2}{c|}{IC\textsubscript{50} (\textmu M)\textsuperscript{a} in SK-BR-3 Cells\textsuperscript{b}} \\
\hline
 & X & R\textsubscript{1} & R\textsubscript{2} & R\textsubscript{3} & R\textsubscript{4} & R\textsubscript{5} \\
\hline
106a & Cl & H & H & H & H & 3.4±0.3 \\
106b & I & H & H & H & H & 3.6±0.2 \\
106c & Cl & H & H & OCH\textsubscript{3} & H & 0.9±0.1 \\
106d & Cl & H & H & Cl & H & 5.9±0.5 \\
106e & Cl & CH\textsubscript{3} & H & H & H & 4.8±0.2 \\
106f & Cl & H & CH\textsubscript{3} & H & H & 5.3±0.2 \\
Daunorubicin & & & & & & 10.3 ± 0.2 nM \\
Mitoxantrone & & & & & & 0.6 ± 0.1 nM \\
\hline
\end{tabular}
\caption{Antiproliferative activity of 2-Halo-3-aryl-4(3H)-quinazoliniminium halides 106 in L1210 and SK-BR-3 tumor cells \textit{in vitro}.}
\end{table}

\textsuperscript{a} mean standard derivation (n=3), \textsuperscript{b} IC\textsubscript{50} reported at day 4
When compared to the known anticancer drugs such as daunorubicin and mitoxantrone, the 2-halo-3-aryl-4(3H)-quinazoliniminium halides 106 showed mediocre activity (Table 3.1), however, our results suggested that careful modification of the quinazoliniminium scaffold may provide more potent analogs. Since rigidification is an important tactic used in medicinal chemistry to increase efficacy and decrease side effects\(^{17,18}\) one way to enhance the antiproliferative activity of quinazolinimines may be by increasing the structural rigidity through the construction of ring-fused quinazoliniminium scaffolds such as 107 (Figure 3.3).

![Quinazoliniminium ring structure](image)

**Figure 3.3:** Quinazoliniminium ring structure in a rigid framework of fused heterocyclic rings.

Previously, we synthesized the 2-halo-3-aryl-4(3H)-quinazoliniminium halides 106 through the intramolecular cyclization of heteroallyne-allenes 108 in the presence of a hydrogen halide generated *in situ* from a Lewis acid and trace water (Scheme 3.1).\(^\text{19}\) The reaction is believed to involve the intermediacy of \(N'\)-(2-cyanophenyl)-\(N\)-phenylcarbamimidic halides A. We envisaged that the presence of a halogen atom at C2 of the quinazoliniminiums 106 may provide the possibility to exploit this functionality into further chemistry, specifically, in an intramolecular Friedel-Crafts type reaction involving C2 and the aryl substituent at N3 to construct a rigid molecular framework of fused heterocyclic rings of the type shown in 107.
Scheme 3.1: Formation of 2-halo-3-aryl-4(3H)-quinazoliniminium halides 106 from heteroenyne-allenes.19

Therefore, through a careful choice of the aryl group on the N1 of the heteroenyne-allenes e.g. a biphenyl, such as in 109, we planned to construct a series of phenanthridine fused quinazoliniminiums 111 through cascade/tandem cyclization via 2-halo-3-biphenyl-4(3H)-quinazoliniminium halides 110 (Scheme 3.2).

Scheme 3.2: Cyclization reaction of heteroenyne-allenes 109 to produce series of phenanthridine fused quinazoliniminiums 111.

Note that the phenanthridine cores 112 and 113 and their derivatives, especially the benzo[c]phenanthridine alkaloids have attracted considerable attention in medicinal chemistry,20,21,22 because of their antitumor, antimicrobial, antifungal, antimalarial and antiviral properties (Figure 3.4).23,24,25,26 For example, the natural product nitidine 114 exhibits antimalarial activity,23,27 lycorine 115 displays antiviral properties,22,28 whereas chelerythrine 116 and NK109 117 both demonstrate potent antitumor activity.23,29,30 Furthermore, molecules containing these core motifs have also been reported to exhibit applications in material science especially in optoelectronic devices.31,32,33
Since phenanthridine serves as a core structure in many drugs or drug-like molecules\textsuperscript{20,23} and a quinazolinimine moiety is also biologically active,\textsuperscript{16} we believe that the combination of these two heterocyclic cores in one molecule \textit{e.g} 111, would increase the number of potential targets and therefore, produce more potent analogs (Figure 3.5). While a number of synthetic methods for the preparation of phenanthridine and quinazolinimine derivatives already exist, the phenanthridine-fused quinazolinimine (PNQ) molecular framework has not been previously constructed or reported.

This chapter describes our work on the development of a quick, versatile and practical protocol for the synthesis of a series of novel phenanthridine-fused quinazolinimines (PNQs) 111.
from heteroene-allenes 109 via two sequential intramolecular cyclizations (also called cascade/tandem cyclization reaction, Scheme 3.2). Our initial investigations focused on streamlining the synthesis of the simplest derivative of the heteroene-allenes 109, the 2-((4’-methylbiphenylimino)methyleneamino) benzonitrile (109a) (R¹ = CH₃; R² = R³ = H) and finding the best reaction conditions for its cyclization to the corresponding PNQ 111a (R¹ = CH₃; R² = R³ = H). Note that the characterization of the cyclized product 111a by NMR spectroscopy was not expected to be trivial because of the presence of heteroatoms and aromatic protons. We hoped that the presence of a methyl group on the biphenyl of 111a and its relative position on the ring would aid in the identification of the cyclized product by NMR spectroscopy. The optimized reaction conditions from this initial study were then employed to obtain a series of heteroene-allenes 109b – k and corresponding PNQ derivatives 111b – k, decorated with different electron donating and electron withdrawing substituents.

3.2 Retrosynthesis of 2-((4’-methylbiphenylimino)methyleneamino) benzonitrile 109a

The ability to successfully synthesize heteroene-allene, 2-((4’-methylbiphenylimino)methyleneamino) benzonitrile 109a was vital to the construction of the PNQ 111a. We envisioned two possible routes (route A and B) to obtain this critical precursor that involved (1) the aza-Wittig-reaction of 4’-methyl-2-biphenylyl isocyanate (118a) with iminophosphorane 119 to directly form the desired isocyanate 109a or (2) the reaction of the isocyanate 118a with anthranilonitrile (120) to afford the substituted urea followed by dehydration to the desired 109a (Scheme 3.3).

Scheme 3.3: Retrosynthetic route showing precursors for the synthesis of heteroene-allenes 109a.
The required isocyanates 118a for routes A and B above would be obtained in two steps involving the Suzuki coupling of 2-bromoaniline (121a) with \( p \)-tolylboronic acid (122a) to produce the 2-aminobiphenyl followed by phosgenation reaction (Scheme 3.4).

**Scheme 3.4:** Retrosynthetic route for the preparation of 4′-methyl-2-biphenylyl isocyanate 118a.

### 3.3 Synthesis of 2-((4′-methylbiphenyylimino)methyleneamino) benzonitrile (109a)

#### 3.3.1 Synthesis of aza-Wittig reagent 119

The reaction of anthranilonitrile (120) with triphenylphosphine in the presence of triethylamine and hexachloroethane in dry methylene chloride at room temperature gave the desired iminophosphorane 119 in good yields (Scheme 3.5).\(^7\)

**Scheme 3.5:** Preparation of aza-Wittig reagent 119.

#### 3.3.2 Synthesis of 2-amino-4′-methylbiphenyl (124a)

4-Bromotoluene (123a) was treated with \( n \)-butyllithium at -78 °C followed by reaction with trimethyl borate to provide the \( p \)-tolylboronic acid (122a).\(^{34,35}\) The latter was then coupled with 2-bromoaniline (121a) using Pd(PPh\(_3\))\(_2\)Cl\(_2\) catalyst under Suzuki reaction conditions to afford 124a in excellent yields (Scheme 3.6).\(^{36}\)
3.3.3 Synthesis of 4′-methyl-2-biphenylyl isocyanate (118a) and attempts towards the synthesis of 2-((4′-methylbiphenylimino)methyleneamino) benzonitrile (109a)

Treatment of a toluene solution of 124a with triphosgene (125) afforded a viscous oily residue,\(^3\) which was purified on a short silica gel column (Scheme 3.7). The IR analysis of the isolated product showed a strong peak at 2249 cm\(^{-1}\) corresponding to a NCO stretch. The formation of 4′-methyl-2-biphenylyl isocyanate (118a) was further confirmed by NMR spectroscopy.

Scheme 3.7: Synthesis of 4′-methyl-2-biphenylyl isocyanate (118a).

Next, we attempted the reaction of the obtained 118a with the iminophosphorane 119 in dry toluene, to produce the desired 2-((4′-methylbiphenylimino)methyleneamino) benzonitrile (109a), however we were unsuccessful (Scheme 3.8).\(^4,9\) Further attempts to synthesize the latter via the modification of the reaction condition by varying relative ratios of the reactants, at different temperatures or reaction times were similarly unsuccessful.
Scheme 3.8: Unsuccessful attempt to form 109a via aza-Wittig reaction (Route A).

We also attempted to obtain 109a through route B outlined in Scheme 3.3 that involved the reaction of the isolated isocyanate 118a with anthranilonitrile (120) followed by its dehydration as shown in Scheme 3.9. However, we failed to form the required urea 126a in the first step. The inability to react 118a with iminophosphorane 119 (Scheme 3.8) or anthranilonitrile 120 (Scheme 3.9) to form heteroenyne-allene 109a or urea 126a, respectively, prompted us to question the stability of the isolated 118a as the latter are notorious for their instability and high reactivity. For instance, isocyanates are known to undergo spontaneous di- or trimerization after isolation, especially at temperature below 30 °C. To avoid these problems, in most literature investigation, the isocyanates have been freshly generated and used in situ for the next synthetic step. We also came across reports that indicated that polymerization of isocyanates can be reversed under high temperature.

Scheme 3.9: Unsuccessful attempted to form 109a involving the coupling of isocyanate with anthranilonitrile (Route B) (Dashed arrow indicate planned reaction that was not attempted).

Therefore, modified reaction conditions were employed during our next attempt that involved preparation of isocyanate 118a at a much higher temperature (175 °C) and subsequently, reacting it with iminophosphorane 119 in situ (Scheme 3.10). To our delight, under these conditions the reaction afforded the much desired heteroenyne-allene 109a in good yields.
3.4 Synthesis of 4’-methyl-phenanthridine-\(N\)-quinazoliniminium salt (111a)

3.4.1 Attempts towards the synthesis of 4’-methyl-phenanthridine-\(N\)-quinazoliniminium salt 111a

Our initial studies were aimed at screening a variety of Lewis acids that can promote cascade cyclization of heteroencyne-allene 109a to the \(N\)-fused heterocycle 111a in order to establish optimal reaction conditions. The influence of temperature and different solvents was also studied and the results are summarized in Table 3.2. In the presence of TMSBr, 2-bromo-3-(4’-methylbiphenyl-2-yl)-quinazolin-4(3\(H\))iminium bromide (110a) was obtained when the reaction was performed either in CH\(2\)Cl\(2\) or in 1,2-dichloroethane (Scheme 3.11; Table 3.1, entries 1 – 3). Note that conducting the reaction for longer time and at slightly elevated temperature (55 °C) for 72 h still led to the formation of 110a (Table 3.1, entry 2).

Scheme 3.11: Formation of 2-bromo-3-(4’-methylbiphenyl-yl)-quinazolin-4(3\(H\))iminium bromide (110a) from 109a with TMSBr.
Similarly, the reaction carried out in the presence of TMSCl (Table 3.1, entry 4) afforded the corresponding chloride salt, 2-chloro-3-(4′-methylbiphenyl)-quinazolin-4(3H)iminium chloride 110a’. However, reaction in the presence of TMSI and FeBr₃ resulted in the formation of a complex mixture of products that was not characterized (Table 3.1, entries 5 – 6). SnCl₄ was found to produce a mixture of 110a’ plus 3,4-dihydro-4-imino-3-(biaryl-2-yl)-quinazolin-2(1H)-one (127a’) (Scheme 3.12; Table 3.1, entry 7). The nucleophilic substitution of the chlorine atom at C2 of 110a’ by water likely resulted in the formation of 127a’.

\[\text{Scheme 3.12: Synthesis of 2-chloro-3-(4′-methylbiphenyl)-quinazolin-4(3H)iminium chloride (110a’) and compound 127a’ (’ indicates a Cl’ counter ion).}\]
Table 3.2: Lewis acid and reaction conditions screened for intramolecular cyclization of 109a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acids&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Solvent</th>
<th>X&lt;sup&gt;-&lt;/sup&gt;</th>
<th>Time [h]</th>
<th>Product (s)</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSBr</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Br</td>
<td>48</td>
<td>110a</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>TMSBr</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Br</td>
<td>72&lt;sup&gt;b&lt;/sup&gt;</td>
<td>110a</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>TMSBr</td>
<td>ClCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>Br</td>
<td>48</td>
<td>110a</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>TMSCl</td>
<td>ClCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>Cl</td>
<td>47</td>
<td>110a'</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>TMSI</td>
<td>ClCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>-</td>
<td>36</td>
<td>None&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>FeBr&lt;sub&gt;3&lt;/sub&gt;</td>
<td>ClCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>-</td>
<td>48</td>
<td>None&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>SnCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>ClCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>Cl</td>
<td>48</td>
<td>110a' + 127a'&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>TMSCl</td>
<td>HMPA</td>
<td>-</td>
<td>20</td>
<td>126a&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>TMSCl</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Cl</td>
<td>5</td>
<td>110a'</td>
<td>76</td>
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<tr>
<td>10</td>
<td>TiCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Cl</td>
<td>10</td>
<td>110a'</td>
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<td>11</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;SO&lt;sub&gt;4&lt;/sub&gt;Ag</td>
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<td>-</td>
<td>36</td>
<td>None&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>BBr&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>12</td>
<td>None&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;OEt&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>BF&lt;sub&gt;4&lt;/sub&gt;</td>
<td>12</td>
<td>111</td>
<td>10</td>
</tr>
</tbody>
</table>

<sup>a</sup> 3.0 equiv. was used, <sup>b</sup> refluxed at 55 °C, <sup>c</sup> complex mixture of products

The two possible mechanisms for the formation 2-halo-3-(4′-methylbiphenyl-2-yl)-quinazolin-4(3H)iminium halide salts (110a,a′) in the above reactions are shown in Scheme 3.14. Path 1 involves the initial formation of hydrogen halide HX (HCl/HBr) from the reaction of Lewis acid with the trace amounts of water in the solvent used. The addition reaction of HX to the heteroenyne-allene 109a would furnish intermediate B, which would subsequently undergo cyclization to give compounds 110a,a′. Another possible pathway, path 2, may involve protonation of the nitrile group by the HX generated in the reaction to produce intermediate C followed by the attack of the halide ion at the heteroenyne-allene moiety and ring closure to form 110a,a′ (Scheme 3.14). The latter were initially characterized by two-dimensional NMR spectroscopy. Eventually, we were also able to obtain a crystal structure of 110a′, which further supported the structural assignment (Figure 3.6).
Scheme 3.13: Possible reaction mechanism for the formation of 110a, a’ (MX = TMSBr, TMSCl, SnCl₄).

Figure 3.6: ORTEP diagram of 110a’.

The failure to obtain the desired 111a,a’ above prompted us to revisit the reaction conditions and we noticed that in the above reactions, 2-halo-3-(4’-methylbiphenyl-2-yl)-quinazolin-4(3H)iminium halide salts (110a,a’) precipitated out of the solution (Table 3.2 entries 1 – 4, 7). Since this compound was expected to be an intermediate in the synthesis of PNQs (Scheme 3.2), we envisioned that the insolubility of 110a,a’ in the solvents used, may be preventing its Friedel Crafts intramolecular cyclization to the desired 111a,a’. Hence, to increase the solubility of 110a,a’, we decided to use more polar solvents, e.g. HMPA and nitromethane.
However, the reaction of 109a in HMPA with TMSCl gave the hydrolyzed product 126a (Scheme 3.13; Table 3.1, entry 8).

Scheme 3.14: Formation of 1-(2-cyanophenyl)-3-(4′-methylbiphenyl) urea 126a from 109a in TMSCl/HMPA.

A series of Lewis acids were screened in nitromethane. This solvent is also known to improve the acidity of the Lewis acids probably by solvation of the cationic intermediate.47,48 Unfortunately, when carbodiimide 109a dissolved in nitromethane was reacted with TMSCl and the result still indicated the formation of the undesired product 110a′ (Table 3.2, entry 9). It is worth mentioning that the use of nitromethane as solvent showed a noticeable influence on the reaction rate resulting into reduced reaction times to form 110a′, most likely, through the stabilization of the charged transition states/intermediates involved in the reaction (compare entries 4 and 9). Similar outcome was obtained when the reaction was performed in the presence of TiCl₄ where 110a′ was isolated (Table 3.2, entry 10). Reactions carried out in the presence of CF₃SO₄Ag and BBr₃ both resulted in the formation of complex mixture of products that were not characterized (Table 3.2, entries 11 – 12). To our delight, the reaction of 109a in with BF₃.OEt₂ in nitromethane furnished the desired PNQ 111a′′, albeit, in very low yield (10%) (Table 3.2, entry 13). The structure of 111a′′ was first confirmed by a series of two-dimensional NMR spectroscopic experiments and finally, by single crystal X-ray analysis (Figure 3.7).
Figure 3.7: ORTEP diagram of N-heterocycle 111a'' ('' indicates a BF$_4^-$ counter ion).

Our future efforts were focused on increasing the yield of 111a'' and determining the optimized reaction conditions. The general reaction is shown in Scheme 3.15 and results are summarized in Table 3.3. The reactions performed using different equivalents of BF$_3$.OEt$_2$ in reagent grade CH$_3$NO$_2$ (≤ 0.05% H$_2$O), all afforded the desired cascade cyclized PNQ 111a'', however in very low yields (Table 3.3, entries 1 – 3). We also investigated the reaction in the presence of a more powerful Lewis acid combination (BF$_3$.OEt$_2$/TMSOTf); but the results were not encouraging (Table 3.3, entry 4).

We noticed that, when the reaction was performed in dry and high-purity CH$_3$NO$_2$ (≤ 0.005% H$_2$O), no product was observed even after extended reaction time (Table 3.3, entry 5), probably because trace amounts of water was necessary for the generation of required hydrogen halide and for the reaction to occur (Schemes 3.14 and 3.2). This premise was validated by adding 4 equivalents of water to the reaction mixture, which gave the expected product 111a'' with improved yields (27%) (Table 3.3, entry 6).

Scheme 3.15: Synthesis of ring-fused N-heterocyclic PNQ 111a',a'' (X=Cl or BF$_4^-$ indicated by ′ or ′′, respectively).
Table 3.3: Optimization of reaction conditions for the synthesis of PNQ 111a′,a′′.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acids</th>
<th>Equiv.</th>
<th>H₂O (equiv.)</th>
<th>X⁻</th>
<th>Time [h]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃.OEt₂</td>
<td>1.5</td>
<td>trace</td>
<td>BF₄</td>
<td>120</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>BF₃.OEt₂</td>
<td>3</td>
<td>trace</td>
<td>BF₄</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>BF₃.OEt₂</td>
<td>5</td>
<td>trace</td>
<td>BF₄</td>
<td>48</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>BF₃.OEt₂/TMSOTf</td>
<td>3:3</td>
<td>trace</td>
<td>-</td>
<td>48</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>BF₃.OEt₂&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3</td>
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<td>BF₄</td>
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<td>None</td>
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<td>6</td>
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<td>3</td>
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<td>BF₄</td>
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<td>27</td>
</tr>
<tr>
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<td>BF₃.OEt₂</td>
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<td>4</td>
<td>4</td>
<td>Cl</td>
<td>24</td>
<td>44</td>
</tr>
</tbody>
</table>

<sup>a</sup> high-purity nitromethane was used.

A further increase in the yields of 111a′′ (39%) was observed when the reaction was performed using slightly higher equivalents of BF₃.OEt₂ and 4 equivalents of water (Table 3.3, entry 7). Furthermore, we found that, SnCl₄ in the presence of 4 equivalents of water can also promote the formation of 111a′ (′ indicates Cl⁻ counter ion) in marginally higher yields (44%) when compared to BF₃.OEt₂ (39%) (Table 3.3, entry 8).

3.4.2 Mechanistic investigations for the formation PNQs 111

As shown in Scheme 3.2, we expected 2-halo-3-(biphenyl-2-yl)-quinazolin-4(3H)iminium halides 110 to be intermediates during the cascade cyclization of heteroenyne-allenes 109 to PNQs 111. To provide evidence in support of this hypothesis, we treated 110a and 110a′ with stoichiometric amounts (5 equiv.) of two different Lewis acids (TMSBr or BF₃.OEt₂) under various reaction conditions. The results are summarized in Scheme 3.16 and Table 3.4. The reaction of 110a at room temperature in the presence of TMSBr for prolong reaction time failed and the unreacted starting material was recovered (Table 3.4, entry 1). However, the treatment of 110a with TMSBr at elevated temperature yielded compound 127a with no trace of the desired 111a (Table 3.4, entry 2). The starting compound was recovered
when the reaction of 110a' was conducted in the presence of TMSBr (Table 3.4, entry 3). Further reaction of 110a' carried out in the presence of BF₃.OEt₂ alone or BF₃.OEt₂/water (Table 3.5, entries 4 and 5 respectively) led to the formation of 127a'. We believe that the direct nucleophilic attack of a water molecule on 110a,a' resulted in the formation of 127a,a'.

Scheme 3.16: Treatment of 110a, a' with Lewis acids.

Table 3.4: Mechanistic study to investigate possible conversion of 110 to N-heterocyclic PNQ 111

<table>
<thead>
<tr>
<th>Entry</th>
<th>110</th>
<th>Lewis acids</th>
<th>Solvent</th>
<th>Time [h]</th>
<th>Products</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>TMSBr</td>
<td>CH₃NO₂</td>
<td>96</td>
<td>Noneᵇ</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>a</td>
<td>TMSBr</td>
<td>CH₃NO₂</td>
<td>72ᶜ</td>
<td>127a</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>a'</td>
<td>TMSBr</td>
<td>CH₃NO₂</td>
<td>48</td>
<td>Noneᵇ</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>a'</td>
<td>BF₃.OEt₂</td>
<td>CH₃NO₂</td>
<td>48</td>
<td>127a'</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>a'</td>
<td>BF₃.OEt₂</td>
<td>CH₃NO₂</td>
<td>72</td>
<td>127a'</td>
<td>29</td>
</tr>
</tbody>
</table>

ᵃ 5 equiv. were used,ᵇ reactant was recoveredᶜ refluxed at 95 °C,ᵈ 4 equiv. H₂O

The failure to convert 2-halo-3-(biphenyl-2-yl)-quinazolin-4(3H)iminium halides 110a, a' to the desired 111a, a' evidently implies that the formation of PNQs does not proceed via...
The three possible reaction mechanisms for the formation of 111 are shown in Scheme 3.17. In Path 1, the heteroene-allene 109a is protonated by trace amounts of acid generated in situ at N3 to give intermediate D which subsequently undergo electrophilic aromatic substitution to form a non-aromatic cyclohexadienyl cation intermediate G; also known as arenium ion. The removal of the proton from the latter would restore aromaticity and result in the formation of compound J that may tautomerize to compound K. Protonation of the cyano group in these tautomers would generate M and N, followed by nucleophilic attack from the nitrogen to generate intermediates O and P, respectively; which would subsequently, undergo loss of a proton to form the imine Q. The acidic medium of the reaction mixture will result in the formation of PNQ salt 111a′, a″.

Path 2 involves the protonation of the N1 of the heteroene-allenes 109 by the trace acid generated in situ to form intermediate E. Similarly, the latter would undergo electrophilic aromatic substitution to produce arenium ion, intermediate H; and the lose of proton from H would generate compound K that may tautomerize to compound J and result in the formation of 111a as discussed above.

Path 3 involves the initial protonation of the cyano group of the heteroene-allenes 109a by trace amounts of acid generated in situ to afford intermediate F, which will be in resonance with species I. This is followed by the nucleophilic attack at the electron deficient carbon by the N1 of heteroene-allenes that in turn activates the carbodiimide carbon towards nucleophilic attack from the biphenyl ring to produce arenium ion, intermediate L. Subsequently, the removal of the proton from the latter would yield imine Q followed by protonation to the desired ring-fused N-heterocycle PNQs 111.

Note that the intermediates J and K formed during the proposed mechanistic pathways 1 and 2, contain phenanthridine moieties that are known to be very stable. The stability of these rings would make it highly difficult for these to attack the carbon atom of protonated nitrile group, such as in intermediates M and/or N as that would involve destruction of the aromaticity in the phenanthridine moiety. To the best of our knowledge, we did not observe the formation of side products corresponding to J and/or K. Therefore, we strongly believe that the formation of PNQs 111 involve path 3.
Scheme 3.17: Plausible mechanism for SnCl₄/BF₃·OEt₂ promoted cascade reaction to produce ring-fused PNQ 111a.
3.4.3 Scope of cascade cyclization reaction

With the optimal reaction conditions in hand, the scope of this protocol was further explored with variously substituted heteroene-alleles 109b – k. These were prepared as shown in Scheme 3.18. Briefly, substituted arylbromides 123 were converted to corresponding arylboronic acids 122 by lithiation followed by treatment with trimethyl borate (note that 122f was purchased). 122 were subjected to Suzuki coupling with 2-bromoanilines 121a – c to obtain biphenyl amines 124b – k. Treatment of the latter with triphosgene generated the isocyanate 118b – k, which was not isolated and reacted with iminophosphorane 119 in situ to yield the desired compounds 109b – k.

![Scheme 3.18: Synthesis of a series of PNQs 109a – k.]

As discussed above that the cascade cyclization of 109a proceeded smoothly in the presence of SnCl₄ to afford 111a' in moderate yields (Table 3.5, entry 1). However, when heteroene-alleles 109b – d were reacted with SnCl₄ or BF₃.OEt₂, their cyclization to corresponding 111b – d did not occur (Table 3.5, entries 2 – 7). It is conceivable that the fluoro, chloro and methoxy substituents destabilize the biphenyl ring towards electrophilic aromatic substitution because these substituents are ortho/para directing in electrophilic aromatic substitution.²² If the mechanism of cyclization involves path 3 as discussed above (Scheme 3.17), then intermediate I for 111b – d is shown in Scheme 3.19 Note that the C-C bond formation to form the expected PNQs in 111b – d need to occur meta to these substituents which
is difficult. Unfortunately, all the reactions of compound 109d performed in the presence of SnCl$_4$ or BF$_3$.OEt$_2$ hydrolyzed the heteroene-allenes and produced the corresponding urea (126d) (Table 3.5, entries 6 – 7). In this case, the strong electron withdrawing inductive effect of the methoxy substituent appears to activate the heteroene-allene carbon toward nucleophilic attack by water to produce the corresponding urea.

\[
\begin{align*}
\text{Intermediate I} & \quad & \text{Resonance structure of substituents (Y = Cl, F and OCH$_3$).}
\end{align*}
\]

**Scheme 3.19:** Resonance structure of substituents (Y = Cl, F and OCH$_3$).

Initial reaction of 109e with SnCl$_4$ led to the formation of trace amounts of product 111e', and when the same reaction was performed under prolonged reaction time the compound decomposed (Table 3.5, entry 8). Interestingly, when substrate 109e was reacted with BF$_3$.OEt$_2$ the result gave the cascade N-heterocycle product 111e'' in moderate yields in less reaction time (Table 3.5, entry 9) compared to 111e'. Furthermore, the reaction of SnCl$_4$ with compound 109f afforded the desired N-heterocycle 111f' in very good yield (Table 3.5, entry 10).

The reaction of 109g in the presence of SnCl$_4$ resulted into the formation of mixture of products with trace amount of 111g' (Table 3.4, entry 11). When the reaction was carried out using BF$_3$.OEt$_2$ and without adding any water, the ring-fused N-heterocyclic compound 111g'' was obtained in good yields (Table 3.4, entry 12). Reaction conducted in the presence of BF$_3$.OEt$_2$ and water only led to the formation of urea, the hydrolyzed form of 109g (126g).$^{53}$

When R$^2$ was a CF$_3$ group, the reaction did not afford the desired products (Table 3.5, entries 13 – 14). Note that the strong electron withdrawing nature of the CF$_3$ is known to deactivate an aromatic ring toward electrophilic aromatic substitution and this effect is most pronounced at ortho and para positions. Unfortunately, the CF$_3$ in 109h is located para to the position where C-C bond formation will have to occur, and thus, no 111h''' was observed.$^{52}$
Table 3.5: Scope of the reaction with cascade cyclization of cyano-ene-carbodiimide 109 to \(N\)-heterocyclic PNQs 111.

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compd.</th>
<th>Lewis acids</th>
<th>(X)</th>
<th>Time [h]</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>(R^3)</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>SnCl(_4)</td>
<td>Cl</td>
<td>24</td>
<td>CH(_3)</td>
<td>H</td>
<td>H</td>
<td>111a(^{\prime}); 44</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>SnCl(_4)</td>
<td>-</td>
<td>-</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>b</td>
<td>BF(_3).OEt(_2)</td>
<td>-</td>
<td>-</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>c</td>
<td>SnCl(_4)</td>
<td>-</td>
<td>-</td>
<td>F</td>
<td>H</td>
<td>H</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>c</td>
<td>BF(_3).OEt(_2)</td>
<td>-</td>
<td>-</td>
<td>F</td>
<td>H</td>
<td>H</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>d</td>
<td>SnCl(_4)</td>
<td>-</td>
<td>-</td>
<td>OCH(_3)</td>
<td>H</td>
<td>H</td>
<td>None (^a)</td>
</tr>
<tr>
<td>7</td>
<td>d</td>
<td>BF(_3).OEt(_2)</td>
<td>-</td>
<td>-</td>
<td>OCH(_3)</td>
<td>H</td>
<td>H</td>
<td>None (^a)</td>
</tr>
<tr>
<td>8</td>
<td>e</td>
<td>SnCl(_4)</td>
<td>Cl</td>
<td>2(^b)</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>111e(^{\prime}); trace(^c)</td>
</tr>
<tr>
<td>9</td>
<td>e</td>
<td>BF(_3).OEt(_2)</td>
<td>BF(_4)</td>
<td>5</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>111e(^{\prime\prime}); 45</td>
</tr>
<tr>
<td>10</td>
<td>f</td>
<td>SnCl(_4)</td>
<td>Cl</td>
<td>30</td>
<td>H</td>
<td>CH(_3)</td>
<td>H</td>
<td>111f(^{\prime}); 81</td>
</tr>
<tr>
<td>11</td>
<td>g</td>
<td>SnCl(_4)</td>
<td>Cl</td>
<td>6</td>
<td>H</td>
<td>OCH(_3)</td>
<td>H</td>
<td>111g(^{\prime}); trace(^c)</td>
</tr>
<tr>
<td>12</td>
<td>g</td>
<td>BF(_3).OEt(_2)(^d)</td>
<td>BF(_4)</td>
<td>40</td>
<td>H</td>
<td>OCH(_3)</td>
<td>H</td>
<td>111g(^{\prime\prime}); 51</td>
</tr>
<tr>
<td>13</td>
<td>h</td>
<td>SnCl(_4)</td>
<td>-</td>
<td>-</td>
<td>H</td>
<td>CF(_3)</td>
<td>H</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>h</td>
<td>BF(_3).OEt(_2)</td>
<td>-</td>
<td>-</td>
<td>H</td>
<td>CF(_3)</td>
<td>H</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>i</td>
<td>SnCl(_4)</td>
<td>Cl</td>
<td>24</td>
<td>H</td>
<td>H</td>
<td>CH(_3)</td>
<td>111i(^{\prime}); 79</td>
</tr>
<tr>
<td>16</td>
<td>j</td>
<td>SnCl(_4)</td>
<td>-</td>
<td>-</td>
<td>H</td>
<td>H</td>
<td>OCH(_3)</td>
<td>None (^a)</td>
</tr>
<tr>
<td>17</td>
<td>j</td>
<td>BF(_3).OEt(_2)</td>
<td>-</td>
<td>-</td>
<td>H</td>
<td>H</td>
<td>OCH(_3)</td>
<td>None (^a)</td>
</tr>
<tr>
<td>18</td>
<td>k</td>
<td>BF(_3).OEt(_2)</td>
<td>BF(_4)</td>
<td>12</td>
<td>H</td>
<td>OCH(_3)</td>
<td>CH(_3)</td>
<td>111k(^{\prime}); 37(^d)</td>
</tr>
</tbody>
</table>

\(^a\) hydrolyzed to the corresponding urea, \(^b\) compound decomposed at prolonged reaction times, \(^c\) mixture of products with trace amount of product observed, \(^d\) no water was needed.
Compound 111i' was prepared in very good yield by reacting 109i with SnCl₄ (Table 3.5, entry 15). The reaction of 109j in the presence both SnCl₄ and BF₃.OEt₂ in water failed to yield the desired product but instead resulted in the formation of the hydrolyzed 126j (Table 3.5, entries 16 – 17). The inability to produce the desired 111j was probably due to the activation of carbon of the heteroenyne-allene 109j via the inductive effect of the methoxy substituent towards nucleophilic attack. The reaction of 109k with BF₃.OEt₂ in the presence of water produced the hydrolyzed product 126k, however, the reaction in the absence of water afforded the ring-fused compound 111k' in modest yields (Table 3.5, entry 18).⁵³

3.5 Conclusion

In summary, we have developed a concise, facile and a versatile protocol for the construction of a novel class of phenanthridine-fused quinazolinimines 111 from heteroenyne-allene 109 via SnCl₄/BF₃.OEt₂ mediated cascade intramolecular cyclization. The reaction conditions are compatible with most of the tested functional groups and effectively afforded the desired product 111 in moderate to excellent yields. Since the electrophilic aromatic substitution is a critical step in the formation of these N-fused heterocycles, the cyclization outcome is strongly dependent on the electronic nature of the substituents and their positioning on the biphenyl ring. Furthermore, this method can provide a new and useful strategy for designing quinazoline precursors. The investigation of the biological relevance of these novel nitrogen fused heterocycles compounds is in progress.

3.6 Experimental

Thin layer chromatography was carried out on 250 µm silica gel plates with a fluorescent indicator and UV-light was used as a visualizing agent. Standard column chromatography was performed using 63–200 µm silica gel. ¹H and ¹³C NMR spectra were recorded at ambient temperature using 400 MHz spectrometers. The carrier frequencies were 399.74 MHz (¹H) and 100.53 MHz (¹³C). The data were recorded as follows: chemical shifts in parts per million, coupling constants in Hertz, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and the number of integrate protons. The infrared spectroscopy frequencies are
reported in cm$^{-1}$. Low-resolution mass spectra (LRMS) were obtained on a mass spectrometer equipped with an electrospray ion source (ESI) operated in positive ion mode and connected to a triple quadrupole mass analyzer. High resolution mass spectra (HRMS) were acquired on a quadrupole/time-of-flight mass spectrometer. TOF scans were carried out in positive ionization mode. In most cases, both [M + H]$^+$ ions were detectable for each species.

3.7 Synthesis of Boronic Acids

3.7.1 General procedure for synthesis of arylboronic acids 122

3.7.2 General Procedure A

$n$-Butyllithium (2.5 M in hexane, 11 mmol) was added dropwise to a stirring solution of aryl bromide (10 mmol) in dry THF:toluene (1:2) at -78 °C under argon. The reaction mixture was stirred at -78 °C for a 1.5 h, and trimethyl borate (12 mmol) was added dropwise. The solution was stirred for an additional 1 h after which the reaction mixture was allowed to warm to room temperature and quenched with saturated NH$_4$Cl. The aqueous and organic layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3x30 mL). The organic layers were combined, dried (Na$_2$SO$_4$), filtered and concentrated under reduce pressure to give the crude solid. The obtained solid was recrystallized from acetonitrile to afford the corresponding arylboronic acids, which were characterized with proton NMR spectroscopy and the data was in agreement with that reported in literature.

3.7.3 General Procedure B

$n$-Butyllithium (2.5 M in hexane, 12 mmol) was added dropwise to a stirring solution of aryl bromide (10 mmol) in dry THF at -78 °C under argon. The solution was slightly warmed up to about -20 °C to allow thorough mixing of the lithium salts, then re-cooled to -78 °C and stirred further for a 1.5 h. Trimethyl borate (12.5 mmol) was added dropwise, after which the solution was stirred for an additional 1 h. Following this, the reaction mixture was warmed to room temperature and quenched with 2N HCl. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (3x20 mL). The organic layers were combined, dried (MgSO$_4$), filtered and concentrated under reduce pressure to give a pale white solid. The obtained solid was recrystallized from ethyl acetate-hexane to afford the corresponding
arylboronic acids, which were characterized with proton NMR spectroscopy and the data was in agreement with that reported in literature.

### 3.7.4 p-Tolylboronic acid 122a

This compound was prepared by following general procedure B from 4-bromotoluene (29.20 mmol, 3.60 mL), in THF (50 mL). White solid (3.45 g, 87% yield). $^1$H NMR (400MHz, CDCl$_3$): δ 2.46 (s, 3H), 7.32 (d, $J$ = 7.6Hz, 2H), 8.14(d, $J$ = 8Hz, 2H).

### 3.7.5 4-Chlorophenylboronic acid 122b

This compound was prepared by following general procedure A from 1-bromo-4-chlorobenzene (26.12 mmol, 5.00 g) in THF:PhCH$_3$ (20:40 mL). White solid (2.95 g, 72% yield). $^1$H NMR (400MHz, DMSO-$d_6$): δ 7.43 (d, $J$ = 8, 2H), 7.84 (d, $J$ = 8.4, 2H).

### 3.7.6 4-Fluorophenylboronic acid 122c

This compound was prepared by following general procedure A from 1-bromo-4-fluorobenzene (34.29 mmol, 3.77 mL) in dry THF:PhCH$_3$ (25:50 mL). White solid (3.04 g, 63% yield). $^1$H NMR (400MHz, DMSO-$d_6$): δ 7.17 (t, $J$ = 8, 2H), 7.91 (t, $J$ = 6.6, 2H).

### 3.7.7 4-Methoxyphenylboronic acid 122d

This compound was prepared by following general procedure B using 4-bromoanisole (26.73 mmol, 3.45 mL) in THF (50 mL). White solid (2.09 g, 51% yield). $^1$H NMR (400MHz, CDCl$_3$): δ 3.90 (s, 3H), 7.03 (d, $J$ = 8.4Hz, 2H), 8.14(d, $J$ = 8.8Hz, 2H).

### 3.7.8 3-Fluorophenylboronic acid 122e

This compound was prepared by following general procedure A using 1-bromo-3-fluorobenzene (28.57 mmol, 3.19 mL) in dry THF:PhCH$_3$ (20:40 mL). White solid (2.79g, 70% yield). $^1$H NMR (400MHz, DMSO-$d_6$): δ 7.20 (dt, $J_1$ = 2.4Hz, $J_2$ = 8.8Hz, 1H), 7.36-7.41 (m, 1H), 7.52 (dd, $J_1$ = 2.4 Hz, $J_2$ = 10, 1H), 7.61 (d, $J$ = 7.2 Hz, 1H), 8.20 (br s, 2H).

### 3.7.9 3-Methylphenyl boronic acid 122f

Purchased from Sigma-Aldrich
3.7.10 3-Methoxyphenylboronic acid 122g

This compound was prepared by following general procedure B from 3-bromoanisole (21.40 mmol, 2.70 mL) in THF (30 mL). White solid (2.5 g, 78% yield). $^1$H NMR (400MHz, DMSO-$d_6$): $\delta$ 3.74 (s, 3H), 6.93-6.97 (m, 1H), 7.25 (t, $J = 8$ Hz, 1H), 7.35-7.30 (m, 2H), 8.06 (br s, 2H).

3.7.11 3-(Trifluoromethyl)phenyl boronic acid 122h

This compound was prepared by following general procedure B from 3-bromo-(trifluoromethyl) benzene (8.90 mmol, 1.20 mL) in THF (30 mL). White solid (1.36 g, 80% yield). $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.69 (t, $J = 8$Hz, 1H), 7.89 (d, $J = 7.6$Hz, 1H), 8.42-8.45 (m, 2H).

3.8 Synthesis of $n$-Tetrabutylammonium tribromide and 2-bromo-4-methoxyaniline

2-Bromoaniline (121$\bar{a}$) and 2-bromo-4-methylaniline (121i) were commercially obtained from Aldrich. $n$-Tetrabutylammonium tribromide was initial prepared as indicated below, then reacted with 4-methoxyaniline to afford 2-bromo-4-methoxyaniline (procedure shown below).

3.8.1 Synthesis of $n$-Tetrabutylammonium tribromide

2.4 mL of bromine (7.44g, 46.98 mmol) was added via syringe to a stirring solution of $n$-tetrabutylammonium bromide (15.1 g, 47 mmol) dissolved in 100 mL methylene chloride. The color of the solution turned orange. The reaction mixture was allowed to stir for an additional 30 minute, and then poured into a flask containing 300 mL ether that caused the product to crystallize. The product was filtered and dried in vacuum, to afford an orange crystalline solid (22.12 g, 98%). m.p = 70–73 °C (lit. m.p = 72-76 °C)

3.8.2 Synthesis of 2-Bromo-4-methoxyaniline 121j

$n$-Tetrabutylammonium tribromide prepared above (9.68g, 20.1 mmol) was added in one portion into a round bottom flask containing $p$-anisidine (2.47 g, 20.1 mmol) dissolved in methanol (40 mL) and CH$_2$Cl$_2$ (80 mL). The reaction mixture was stirred at 25 °C for 35 minutes, then diluted with 100 mL of saturated aqueous Na$_2$SO$_3$ and 100 mL of CH$_2$Cl$_2$. Using separatory funnel, the organic layer was collected then washed with water (2 x 100 mL) and
brane (100 mL). The organic layer was dried over MgSO₄, filtered through a plug of silica and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography (95:5, hexane/EtOAc) to produce 121c as a brown oil (1.47 g, 36%). Rf = 0.58 (8:2, hexane/EtOAc); IR (ZnSe ATR crystal; neat, cm⁻¹): 3435, 3358, 2831, 1598, 1573, 1493, 1272, 1227, 1210, 1024, 837, 806. \(^1\)H NMR (400 MHz, CDCl₃): δ 3.74-3.79 (m, 5H), 6.73-6.74 (m, 2H), 7.02 (dd, \(J_1 = 0.4\) Hz, \(J_2 = 2.4\) Hz); \(^1\)C NMR (100 MHz, CDCl₃): δ 56.1, 109.8, 115.2, 116.8, 117.7, 138.1, 152.9.

3.9 Synthesis of 2-Aminobiphenyls 124

3.9.1 General procedure for synthesis of 2-Aminobiphenyls 124

In a 100 mL round bottom flask, 2-bromoaniline (8.72 mmol), phenylboronic acids (11.34 mmol), K₂CO₃ (34.88 mmol) and Pd(PPh₃)₂Cl₂ (0.69 mmol) were dissolved in toluene (30 mL), water (20 mL) and ethanol (10 mL); then stirred for 18 – 24 h at 95 °C. After cooling, the reaction mixture was diluted with 100 mL of saturated aqueous NH₄Cl and extracted with 100 mL of CH₂Cl₂ (3x). The combine organic layers were dried over Na₂SO₃, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the corresponding products.

3.9.2 2-Amino-4ʹ-methylbiphenyl 124a

The general procedure was followed by reacting 4-methylphenylboronic acid 122a (11.34 mmol) with 2-bromoaniline 121a (8.72 mmol). Purification by column chromatography on silica gel using a gradient eluent of 5% EtOAc in hexane afforded 124a as a clear oil (1.55 g, 97%), Rf = 0.47 (8:2, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm⁻¹): 3460, 3376, 3021, 2918, 1612, 1514, 1487, 1448, 1293, 1004, 818; \(^1\)H NMR (400MHz, CDCl₃): δ 2.46 (s, 3H), 3.80 (s, 2H), 6.81 (dd, \(J_1 = 7.6\) Hz, \(J_2 = 0.8\) Hz, 1H), 6.87 (dt, \(J_1 = 7.6\) Hz, \(J_2 = 1.2\) Hz, 1H), 7.17-7.22 (m, 2H), 7.31 (d, \(J = 8\) Hz, 2H), 7.40-7.42 (m, 2H); \(^1\)C NMR (100 MHz, CDCl₃): δ 21.4, 115.7, 118.8, 127.7, 128.5, 129.1, 129.7, 130.6, 136.7, 137.0, 143.7.

3.9.3 2-Amino-4ʹ-chlorobiphenyl 124b

The general procedure was followed by reacting 4-chlorophenylboronic acid 122b (12.09 mmol) with 2-bromoaniline 121a (9.30 mmol). Purification by column chromatography on silica
gel using a gradient eluent of 6% EtOAc in hexane afforded \textbf{124b} as a waxy pale white solid (1.48 g, 78%), \( R_f = 0.50 \) (9:1, hexane/EtOAc). IR (ZnSe ATR crystal; neat, \( \text{cm}^{-1} \)): 3480, 3382, 1611, 1478, 1451, 1291, 1087, 1002, 823, 743; \(^1\)H NMR (400MHz, CDCl\(_3\))): \( \delta \) 3.74 (s, 3H), 6.78 (dd, \( J_1 = 7.6\text{Hz}, J_2 = 1.2\text{Hz}, 1\text{H} \)), 6.85 (dd, \( J_1 = 7.6\text{Hz}, J_2 = 1.2\text{Hz}, 1\text{H} \)), 7.12 (dd, \( J_1 = 7.6\text{Hz}, J_2 = 1.6\text{Hz}, 1\text{H} \)), 7.17-7.21 (m, 1H), 7.42-7.44 (m, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\))): \( \delta \) 21.4, 115.9, 118.9, 126.5, 129.0, 129.2, 130.5, 130.6, 133.3, 138.1, 143.61.

### 3.9.4 2-Amino-4’-fluorobiphenyl \textbf{124c}

The general procedure was followed by reacting 4-fluorophenylboronic acid \textbf{122c} (12.56 mmol) with 2-bromoaniline \textbf{121a} (10.46 mmol). Purification by column chromatography on silica gel using a gradient eluent of 5% EtOAc in hexane afforded \textbf{124c} as a waxy pale white solid (1.58 g, 81%), \( R_f = 0.47 \) (9:1, hexane/EtOAc). IR (ZnSe ATR crystal; neat, \( \text{cm}^{-1} \)): 3466, 3378, 2993, 1613, 1484, 1449, 1291, 1211, 1155, 831, 807, 747; \(^1\)H NMR (400MHz, CDCl\(_3\))): \( \delta \) 3.73 (s, 2H), 6.79 (dd, \( J_1 = 8\text{Hz}, J_2 = 1.2\text{Hz}, 1\text{H} \)), 6.85 (dt, \( J_1 = 8\text{Hz}, J_2 = 1.2\text{Hz}, 1\text{H} \)), 7.11-7.21 (m, 4H), 7.42-7.46 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\))): \( \delta \) 115.8, 115.9 (d, \( J_{CF} = 21\text{Hz} \)), 118.9, 126.8, 128.8, 130.8 (d, \( J_{CF} = 33\text{Hz} \)), 130.9, 135.6 (d, \( J_{CF} = 3\text{Hz} \)), 143.7, 162.22 (\( J_{CF} = 246\text{Hz} \)).

### 3.9.5 2-Amino-4’-methoxybiphenyl \textbf{124d}

The general procedure was followed by reacting 4-methoxyphenylboronic acid \textbf{122d} (9.90 mmol) with 2-bromoaniline \textbf{121a} (7.07 mmol). Purification by column chromatography on silica gel using a gradient eluent of 6% EtOAc in hexane afforded \textbf{124d} as a brown oil (1.16 g, 82%), \( R_f = 0.55 \) (8:2, hexane/EtOAc). IR (ZnSe ATR crystal; neat, \( \text{cm}^{-1} \)): 3444, 3369, 2957, 1610, 1512, 1487, 1451, 1289, 1238, 1175, 1029, 828, 747; \(^1\)H NMR (400MHz, CDCl\(_3\))): \( \delta \) 3.76 (s, 2H), 3.87 (s, 3H), 6.78 (dd, \( J_1 = 8\text{Hz}, J_2 = 0.8\text{Hz}, 1\text{H} \)), 6.83 (dt, \( J_1 = 7.6\text{Hz}, J_2 = 1.2\text{Hz}, 1\text{H} \)), 6.98-7.02 (m, 2H), 7.12-7.18 (m, 2H), 7.39-7.42 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\))): \( \delta \) 55.5, 114.4, 115.7, 118.8, 127.5, 128.37, 130.4, 130.7, 131.9, 143.8, 158.9.

### 3.9.6 2-Amino-3’-fluorobiphenyl \textbf{124e}

The general procedure was followed by reacting 3-fluorophenylboronic acid \textbf{122e} (15.12 mmol) with 2-bromoaniline \textbf{121a} (11.63 mmol). Purification by column chromatography on silica gel using a gradient eluent of 4% EtOAc in hexane afforded \textbf{124e} as a light yellow oil
(1.72 g, 79%), \( R_f = 0.44 \) (9:1, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm\(^{-1}\)): 3451, 3360, 3035, 1732, 1611, 1582, 1475, 1423, 1291, 1266, 1180, 1155, 879, 747; \(^1\)H NMR (400MHz, CDCl\(_3\)): \( \delta \) 3.75 (br s, 2H), 6.76 (dd, \( J_1 = 7.6\)Hz, \( J_2 = 1\)Hz, 1H), 6.82 (dt, \( J_1 = 7.2\)Hz, \( J_2 = 1\)Hz, 1H), 7.03 (dd, \( J_1 = 8.4\)Hz, \( J_2 = 2.8\)Hz, \( J_3 = 0.8\)Hz, 1H), 7.14 (dd, \( J_1 = 7.6\)Hz, \( J_2 = 1.6\)Hz, 1H), 7.13-7.19 (m, 2H), 7.23-7.25 (m, 1H), 7.37-7.43 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 114 (d, \( J_{CF} = 21\)Hz), 115.95, 116.25 (d, \( J_{CF} = 20\)Hz), 119, 125 (d, \( J_{CF} = 3\)Hz), 126 (d, \( J_{CF} = 2\)Hz), 129.13, 130.50 (d, \( J_{CF} = 9\)Hz), 130.51, 142 (d, \( J_{CF} = 7\)Hz), 144, 163 (d, \( J_{CF} = 246\)Hz).

### 3.9.7 2-Amino-3’-methylbiphenyl 124f

The general procedure was followed by reacting commercially obtained 3-methylphenylboronic acid (13.95 mmol) with 2-bromoaniline 121 (11.63 mmol). Purification by column chromatography on silica gel using a gradient eluent of 5% EtOAc in hexane afforded 124f as a light beige oil (1.75 g, 82%), \( R_f = 0.35 \) (9.5:0.5, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm\(^{-1}\)): 3452, 3371, 3026, 1611, 1478, 1447, 1294, 1156, 869, 787, 742; \(^1\)H NMR (400MHz, CDCl\(_3\)): \( \delta \) 2.46 (s, 3H), 3.78 (s, 2H), 6.80 (dd, \( J_1 = 0.8\)Hz, \( J_2 = 8\)Hz, 1H), 6.87 (dt, \( J_1 = 7.6\)Hz, \( J_2 = 0.8\)Hz, 1H), 7.17-7.22 (m, 3H), 7.29-7.32 (m, 2H), 7.39 (t, \( J = 7.6\)Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 21.7, 115.7, 118.7, 126.2, 127.9, 128.1, 128.5, 128.9, 130.0, 130.6, 138.6, 139.6, 143.7.

### 3.9.8 2-Amino-3’-methoxybiphenyl 124g

The general procedure was followed by reacting 3-methoxyphenylboronic acid 122g (8.09 mmol) with 2-bromoaniline 121 (6.22 mmol). Purification by column chromatography on silica gel using a gradient eluent of 6% EtOAc in hexane afforded 124g as a brown oil (1.11 g, 89%), \( R_f = 0.38 \) (8:2, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm\(^{-1}\)): 3467, 3371, 2956, 2833, 1601, 1498, 1477, 1454, 1418, 1290, 1208, 1175, 1036, 1016, 745; \(^1\)H NMR (400MHz, CDCl\(_3\)): \( \delta \) 3.82-3.85 (s, 5H), 6.78 (dd, \( J_1 = 8\)Hz, \( J_2 = 0.8\)Hz, 1H), 6.84 (dt, \( J_1 = 7.6\)Hz, \( J_2 = 1.2\)Hz, 1H), 6.92 (dd, \( J_1 = 8\)Hz, \( J_2 = 0.8\)Hz, 1H), 7.01-7.03 (m, 1H), 7.07 (td, \( J_1 = 7.6\)Hz, \( J_2 = 1.2\)Hz, 1H), 7.15-7.20 (m, 2H), 7.38 (J = 8Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 55.5, 113.1, 114.6, 115.8, 118.7, 121.6, 127.6, 128.7, 130.0, 130.5, 141.1, 143.7, 160.1.
3.9.9 2-Amino-3′-trifluoromethylbiphenyl 124h

The general procedure was followed by reacting 3-(trifluoromethyl)phenyl boronic acid 122h (14.11 mmol) with 2-bromoaniline 121a (10.85 mmol). Purification by column chromatography on silica gel using a gradient eluent of 4% EtOAc in hexane afforded 124h as a light brown oil (1.52 g, 59%), R_f = 0.42 (8.2 hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm^{-1}): 3465, 3376, 3037, 1615, 1500, 1483, 1425, 1331, 1257, 1159, 1117, 1072, 805, 744; ^1H NMR (400MHz, CDCl_3): δ 3.74 (s, 2H), 6.81 (dd, J_1 = 8Hz, J_2 = 0.8Hz, 1H), 6.87 (dt, J_1 = 7.6Hz, J_2 = 1.2Hz, 1H), 7.14 (dd, J_1 = 7.6Hz, J_2 = 1.6Hz, 1H), 7.20-7.24 (m, 1H), 7.35-7.39 (m, 1H), 7.45-7.51 (m, 4H), 7.68 (d, J = 7.6Hz, 1H), 7.76 (s, 1H). ^13C NMR (100 MHz, CDCl_3): δ 116, 119, 124.2 (q, J_{CF} = 4Hz), 124.3 (q, J_{CF} = 271Hz), 126.1 (t, J_{CF} = 4Hz), 126.2, 129, 130, 131, 131.4 (q, J_{CF} = 32Hz), 132.7 (d, J_{CF} = 2Hz), 141, 144.

3.9.10 2-Amino-4-methylbiphenyl 124i

The general procedure was followed by reacting 2-bromo-4-methylaniline 121i (10.75 mmol) with commercially obtained phenylboronic acid (11.82 mmol). Purification by column chromatography on silica gel using a gradient eluent of 6% EtOAc in hexane afforded 124i as a light yellow solid (1.61 g, 82%), R_f = 0.48 (8:2, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm^{-1}): 3419, 3345, 2970, 1617, 1502, 1487, 1440, 1244, 818, 765, 734; ^1H NMR (400MHz, CDCl_3): δ 2.32 (s, 3H), 3.66 (s, 2H), 6.72 (d, J = 8Hz, 1H), 7.00-7.03 (m, 2H), 7.35-7.39 (m, 1H), 7.45-7.51 (m, 4H); ^13C NMR (100 MHz, CDCl_3): δ 20.6, 116.0, 127.3, 127.9, 128.0, 128.9, 129.2, 129.3, 131.2, 139.9, 141.2.

3.9.11 2-Amino-4-methoxybiphenyl 124j

The general procedure was followed by reacting 2-bromo-4-methoxylaniline 121j (9.90 mmol) with commercially obtained phenylboronic acid (10.89 mmol). Purification by column chromatography on silica gel using a gradient eluent of 7% EtOAc in hexane afforded 124j as a brown oil (1.74 g, 88%), R_f = 0.44 (8:2, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm^{-1}): 3436, 3356, 2933, 2830, 1731, 1601, 1498, 1486, 1414, 1270, 1205, 1038, 809,755; ^1H NMR (400MHz, CDCl_3): δ 4.43 (s, 2H), 3.80 (s, 3H), 6.74-6.82 (m, 3H), 7.36-7.40 (m, 1H), 7.45-7.51 (m, 4H); ^13C NMR (100 MHz, CDCl_3): δ 56.0, 114.6, 115.9, 117.1, 127.4, 128.9, 129.0, 129.2, 137.3, 139.7, 152.9.
3.12 2-Amino-3′-methoxy-4-methyl-biphenyl 124k

The general procedure was followed by reacting commercially obtained 2-bromo-4-
methylaniline 121j (10.75 mmol) with 3-methoxyphenylboronic acid 122g (12.90 mmol).
Purification by column chromatography on silica gel using a gradient eluent of 5% EtOAc in hexane afforded 2-amino-3′-methoxy-4-methyl-biphenyl 124k as a brown oil (1.47 g, 54%), R_f = 0.53 (8:2, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm⁻¹): ¹H NMR (400MHz, CDCl₃): δ 2.42 (s, 3H), 3.69 (s, 2H), 3.87 (s, 3H), 6.71- 6.73 (m, 1H), 6.91-6.94 (m, 1H), 7.00-7.04 (m, 3H), 7.06-7.09 (m, 1H), 7.38 (t, J = 8Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 20.5, 55.4, 113.0, 114.6, 115.9, 121.5, 127.6, 127.8, 129.2, 129.9, 130.9, 141.1, 141.2, 160.0.

3.10 Synthesis of Biphenyllyl Isocyanates 118

CAUTION: Toxic gases (phosgene and hydrogen chloride) may be released, therefore this reaction should be carried out under a well-ventilated hood.

3.10.1 General Procedure A

To a stirring solution of 2-amino biphenyl (2.50 mmol) in dry toluene was added triphosgene at room temperature and the reaction mixture was reflux at 105-110 °C for 12-18 h. After cooling, the reaction mixture was concentrated under vacuum and the corresponding biphenyllyl isocyanates was obtain after purification by column chromatography.

3.10.2 4′-Methyl-2-biphenyllyl Isocyanate 118a

This compound was synthesized according to the general procedure A from 2-amino-4′-methyl biphenyl 124a (5.46 mmol). The crude reaction mixture was purified by a quick flash column chromatography on silica gel using a gradient eluent of 15% CH₂Cl₂ in hexane to afford 118a as a white solid (0.99 g, 86%). R_f = 0.78 (1:1, hexane/CH₂Cl₂); IR (ZnSe ATR crystal; neat, cm⁻¹): 3025, 2920, 2249 (NCO), 1783, 1600, 1502, 1464, 1250, 1184, 1090,1042, 1008, 819, 753; ¹H NMR (400MHz, CDCl₃): δ 2.32 (s, 3H), 7.06-7.09 (m, 1H), 7.12-7.15 (m, 1H), 7.16-7.19 (m, 3H), 7.21-7.25 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 21.5, 124.4, 125.7, 126.1, 128.4, 129.1, 129.5, 130.8, 131.33, 135.5, 137.7, 138.0.
3.10.3 3′-Methoxy-2-biphenylyl Isocyanate 118g

This compound was synthesized according to the general procedure A from 2-amino-3′-methoxy biphenyl 124g (2.50 mmol). The crude reaction mixture was purified by a quick flash column chromatography on silica gel using a gradient eluent of 35% CH₂Cl₂ in hexane to afford 118g as a clear oil (0.32 g, 86%). R_f = 0.65 (1:1, hexane/CH₂Cl₂); IR (ZnSe ATR crystal; neat, cm⁻¹): 2960, 2249 (NCO), 1581, 1509, 1464, 1414, 1257, 1209, 1093, 1019, 863, 792, 753; ¹H NMR (400MHz, CDCl₃): δ 3.85 (s, 3H), 6.95-6.97 (m, 2H), 6.99-7.01 (m, 1H), 7.15-7.18 (m, 1H), 7.22-7.39 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 55.5, 113.8, 114.8, 121.6, 124.5, 125.6, 126.1, 128.7, 129.8, 130.6, 131.4, 137.6, 139.7, 159.8.

3.10.4 3′-Trifluoromethyl-2-biphenylyl Isocyanate 118h

This compound was synthesized according to the general procedure A by reacting 0.43 g 2-amino-3′-trifluoromethyl biphenyl 115h (1.80 mmol). The crude reaction mixture was purified by a quick flash column chromatography on silica gel using a gradient eluent of 20% CH₂Cl₂ in hexane to afford 3′-trifluoromethyl-2-biphenylyl isocyanate 118d as a yellowish brown oil (0.21 g, 46%). IR (ZnSe ATR crystal; neat, cm⁻¹): 3025, 2919, 2263 (NCO), 1603, 1494, 1334, 1245, 1166, 1127, 1073, 1029, 804, 757; ¹H NMR (400MHz, CDCl₃): δ 7.24 (d, J = 8Hz, 1H), 7.28-7.32 (m, 1H), 7.35-7.40 (m, 3H), 7.58-7.62 (m, 1H), 7.65-7.71 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ. 124.1 (q, J_CF = 271Hz), 124.5, 124.9 (q, J_CF = 3.7Hz), 126.1 (q, J_CF = 3.7Hz), 126.3, 126.4, 129.0 (d J_CF = 52Hz), 129.2, 129.4, 130.7, 131.1 (q, J_CF = 32Hz), 131.3, 132.6 (d, J_CF = 1.5Hz), 135.8, 139.1.

CAUTION: Toxic gases (phosgene and hydrogen chloride) maybe released, therefore this reaction should be carried out under a well-ventilated hood.

3.10.5 General Procedure B

Triphosgene 125 (0.40 mmol) was added to a stirring solution of 2-amino biphenyl (1.00 mmol) in dry toluene at 25 °C, resulting in the formation of precipitate and then the reaction mixture was slowly brought to reflux at 175 °C under argon for 2-4 h. Aliquot of the cooled, crude reaction mixture was removed to confirm the formation of corresponding isocyanates using IR
absorption (strong NCO peak at 2250-2290 cm\(^{-1}\)). The crude biphenylyl Isocyanates were used immediately in the next reaction step without further purification.

### 3.10.6 4′-Methyl-2-biphenylyl Isocyanate 118a

This compound was synthesized according to the general procedure B by reacting 1.00 g 2-amino-4′-methyl biphenyl (115a) (5.46 mmol). \( R_f = 0.61 \) (1:1, hexane/CH\(_2\)Cl\(_2\)); IR (ZnSe ATR crystal; NCO, cm\(^{-1}\)): 2249.

### 3.10.7 4′-Chloro-2-biphenylyl Isocyanate 118b

This compound was synthesized according to the general procedure B from 2-amino-4′-chloro biphenyl (124b) (4.91 mmol). \( R_f = 0.88 \) (7:3, hexane/CH\(_2\)Cl\(_2\)); IR (ZnSe ATR crystal; NCO, cm\(^{-1}\)): 2260.

### 3.10.8 4′-Fluoro-2-biphenylyl Isocyanate 118c

This compound was synthesized according to the general procedure B from 2-amino-4′-fluoro biphenyl 124c (4.01 mmol). \( R_f = 0.82 \) (7:3, hexane/CH\(_2\)Cl\(_2\)); IR (ZnSe ATR crystal; NCO, cm\(^{-1}\)): 2252.

### 3.10.9 4′-Methoxy-2-biphenylyl Isocyanate 118d

This compound was synthesized according to the general procedure B from 2-amino-4′-methoxy biphenyl (124d) (5.02 mmol). \( R_f = 0.76 \) (1:1, hexane/CH\(_2\)Cl\(_2\)); IR (ZnSe ATR crystal; NCO, cm\(^{-1}\)): 2253.

### 3.10.10 3′-Fluoro-2-biphenylyl Isocyanate 118e

This compound was synthesized according to the general procedure B from 2-amino-3′-fluoro biphenyl (124e) (5.34 mmol). \( R_f = 0.78 \) (7:3, hexane/CH\(_2\)Cl\(_2\)); IR (ZnSe ATR crystal; NCO, cm\(^{-1}\)): 2251.

### 3.10.11 3′-Methyl-2-biphenylyl Isocyanate 118f

This compound was synthesized according to the general procedure B from 2-amino-3′-methyl biphenyl (124f) (5.46 mmol). \( R_f = 0.93 \) (7:3, hexane/CH\(_2\)Cl\(_2\)); IR (ZnSe ATR crystal; NCO, cm\(^{-1}\)): 2248.
3.10.12 3′-Methoxy-2-biphenyl Isocyanate 118g

This compound was synthesized according to the general procedure B from 2-amino-3′-methoxy biphenyl (124g) (5.17 mmol). R_f = 0.61 (1:1, hexane/CH_2Cl_2); IR (ZnSe ATR crystal; NCO, cm⁻¹): 2255.

3.10.13 3′-Trifluoromethyl-2-biphenyl Isocyanate 118h

This compound was synthesized according to the general procedure B from 2-amino-3′-trifluoromethyl biphenyl (124h) (3.16 mmol). R_f = 0.78 (1:1, hexane/CH_2Cl_2); IR (ZnSe ATR crystal; NCO, cm⁻¹): 2254.

3.10.14 5-Methyl-2-biphenyl Isocyanate 118i

This compound was synthesized according to the general procedure B from 2-amino-4′-methyl biphenyl (124i) (5.46 mmol). R_f = 0.75 (7:3, hexane/CH_2Cl_2); IR (ZnSe ATR crystal; NCO, cm⁻¹): 2260.

3.10.15 5-Methoxy-2-biphenyl Isocyanate 118j

This compound was synthesized according to the general procedure B from 2-amino-4′-methoxy biphenyl (124j) (5.52 mmol). R_f = 0.64 (7:3, hexane/CH_2Cl_2); IR (ZnSe ATR crystal; NCO, cm⁻¹): 2260.

3.10.16 3′-Methoxy-5-Methyl-2-biphenyl Isocyanate 118k

This compound was synthesized according to the general procedure B from 2-amino-4′-methyl-3′-methoxy biphenyl (124k) (4.22 mmol). R_f = 0.64 (7:3, hexane/CH_2Cl_2); IR (ZnSe ATR crystal; NCO, cm⁻¹): 2255.

3.11 Synthesis of aza-Wittig reagent, Iminophosphorane 119

To a solution of anthranilonitrile 118 (12.70 mmol, 1.50 g), PPh_3 (19.10 mmol, 5.01 g), C_2Cl_6 (19.10 mmol, 4.52 g) in dry CH_2Cl_2 (60 mL) cooled to 0 °C was added dropwise Et_3N (63.5 mmol, 6.43 g), causing the solution to quickly turn yellow. The reaction mixture was stirred for 20 h, filtered through short plug of celite and then washed with 100 mL of EtOAc. The filtrate was concentrated under reduced pressure resulting in a yellow solid, which was
recrystallized from CH$_2$Cl$_2$-MeOH (1:5) to afford the iminophosphorane 119 as a white solid (3.97 g, 82%). $R_f = 0.48$ (7:3, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm$^{-1}$): 2209, 1587, 1470, 1445, 1436, 1283, 1154, 1107, 1043, 996, 754; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 6.42 (d, $J = 8.4$ Hz, 1H), 6.61 (t, $J = 7.2$ Hz, 1H), 6.98-7.03 (m, 1H), 7.43-7.58 (m, 10H), 7.79-7.85 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 107.9 (d, $J = 24.9$Hz), 116.8, 120.8, 121.3 (d, $J = 10$Hz), 129.0 (d, $J = 12.4$Hz), 129.6, 130.6, 132.3 (d, $J = 3$Hz), 132.7, 132.8 (d, $J = 10.2$Hz), 133.6 (d, $J = 2$Hz), 155.5.

3.12 Synthesis of 2-((biphenylimino)methyleneamino) benzonitrile

3.12.1 General Procedure for synthesis of 2-((biphenylimino)methyleneamino) benzonitrile

benzonitrile 109

A solution of iminophosphorane (5 mmol) in dry CH$_2$Cl$_2$ (15 mL) was added slowly to a stirring solution of corresponding freshly prepared isocyanates (5 mmol) in toluene (15 mL), and then the resulting reaction mixture was stirred and heated at 65 $^\circ$C under argon for 2-4 h. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by a quick flash column chromatography on silica gel using a EtOAc/hexane gradient elution to afford the corresponding 2-((biphenylimino)methyleneamino) benzonitrile 109.

3.12.2 Synthesis of 2-((4ʹ-methylbiphenylimino)methyleneamino) benzonitrile 109a

The compound was synthesized from crude 4ʹ-methyl-2-biphenylyl isocyanate 118a (5.46 mmol) using general procedure described above. Purification by flash column chromatography on silica gel using a gradient eluent of 7% EtOAc afforded 109a as a viscous yellow oil (1.09 g, 65%), $R_f = 0.48$ (8:2, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm$^{-1}$): 2226, 2138, 2106, 1592, 1570, 1514, 1476, 1441, 1210, 1160, 1103, 1041, 818, 752; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 2.27 (s, 3H), 6.82 (d, $J = 8$Hz, 1H), 7.01-7.15 (m, 3H), 7.23-7.26 (m, 1H), 7.29-7.34 (m, 5H), 7.35-7.39 (m, 1H), 7.51 (dt, $J_1 = 8$Hz, $J_2 = 1.2$Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 21.4, 107.7, 116.9, 124.9, 125.1, 125.7, 126.6, 128.5, 129.2, 129.3, 130.5, 130.8, 133.2, 133.5, 133.8, 135.7, 137.8, 137.9, 142.8. HRMS (ESI): $m/z$ calculated for C$_{21}$H$_{16}$N$_3$ (M$^+$) 310.1339, found 310.1324.
3.12.3 Synthesis of 2-((4'-chlorobiphenyllumino)methyleneamino) benzonitrile 109b

The compound was synthesized from crude 4'-chloro-2-biphenyl isocyanate 118b (4.67 mmol) using general procedure described above. Purification by flash column chromatography on silica gel using a gradient eluent of 7% EtOAc afforded 109b as a viscous yellow oil (0.75 g, 49%), R_f = 0.49 (9:1, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm\(^{-1}\)): 2223, 2138, 2106, 1592, 1570, 1476, 1441, 1210, 1103, 1041, 818, 752; \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 6.93 (d, \(J = 8\)Hz, 1H), 7.19 (dt, \(J_1 = 7.6\)Hz, \(J_2 = 0.8\)Hz, 1H), 7.27-7.38 (m, 6H), 7.40-7.43 (m, 2H), 7.43-7.48 (m, 1H), 7.58 (dd, \(J_1 = 8\)Hz, \(J_2 = 1.6\)Hz, 1H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 107.9, 116.8, 125.1, 126.7, 128.8, 129.1, 130.7, 130.9, 133.5, 133.8, 133.9, 134.1, 136.4, 137.1, 142.4. HRMS (ESI): m/z calculated for C\(_{20}\)H\(_{12}\)N\(_3\)ClNa (M\(^+\)) 352.0612; 354.0589, found 352.0628; 354.0586.

3.12.4 Synthesis of 2-((4'-fluorobiphenyllumino)methyleneamino) benzonitrile 109c

The compound was synthesized from crude 4'-fluoro-2-biphenyl isocyanate 118c (3.81 mmol) using general procedure described above. Purification by flash column chromatography on silica gel using a gradient eluent of 6% EtOAc afforded 109c as a viscous yellow oil (0.67 g, 67%), R_f = 0.41 (9:1, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm\(^{-1}\)): 2225, 2139, 2107, 1733, 1592, 1569, 1509, 1477, 1443, 1211, 1158, 1042, 835, 752; \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 6.95 (dd, \(J_1 = 8\)Hz, \(J_2 = 0.8\)Hz, 1H), 7.04-7.09 (m, 2H), 7.18 (dt, \(J_1 = 7.6\)Hz, \(J_2 = 1.2\)Hz, 1H), 7.28-7.33 (m, 2H), 7.34-7.38 (m, 2H), 7.43-7.47 (m, 3H), 7.56 (dd, \(J_1 = 8\)Hz, \(J_2 = 0.8\)Hz, 1H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 108.0, 115.5 (d, J_{CF} = 21.3Hz), 116.8, 125.1 (d, J_{CF} = 11.7Hz), 126.0, 126.7, 128.9, 130.9, 131.3 (d, J_{CF} = 8.1Hz), 133.6 (d, J_{CF} = 26.3Hz), 136.7, 142.6, 162.7 (d, J_{CF} = 246Hz). HRMS (FAB): m/z calculated for C\(_{20}\)H\(_{13}\)N\(_3\)F (M\(^+\)) 314.1094, found 314.1081.

3.12.5 Synthesis of 2-((4'-methoxybiphenyllumino)methyleneamino) benzonitrile 109d

The compound was synthesized from crude 4'-methoxy-2-biphenyl isocyanate 118d (5.02 mmol) using general procedure described above. Purification by flash column chromatography on silica gel using a gradient eluent of 8% EtOAc afforded 109d as a viscous yellow oil (1.06 g, 65%), R_f = 0.51 (8:2, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm\(^{-1}\)): 2136, 1732, 1592, 1570, 1513, 1477, 1422, 1242, 1210, 1176, 1103, 1032, 828, 757; \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 3.78 (s, 3H), 6.88-6.92 (m, 4H), 7.17 (dt, \(J_1 = 7.6\)Hz, \(J_2 = 0.8\)Hz, 1H), 7.28-
7.31 (m, 1H), 7.34-7.37 (m, 3H), 7.39-7.45 (m, 3H), 7.56 (d, J = 8Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 55.4, 107.7, 114.0, 116.9, 124.9, 124.9, 125.1, 125.8, 126.7, 128.4, 130.6, 130.7, 130.8, 130.9, 133.3, 133.6, 133.9, 137.7, 142.9, 159.4. HRMS (ESI): m/z calculated for C$_{21}$H$_{16}$N$_3$O (M$^+$) 326.1288, found 326.1285.

### 3.12.6 Synthesis of 2-((3′-Fluorobiphenylimino)methyleneamino) benzonitrile 109e

The compound was synthesized from crude 3′-fluoro-2-biphenylyl isocyanate 118e (5.34 mmol) using general procedure described above. Purification by flash column chromatography on silica gel using a gradient eluent of 5% EtOAc afforded 109e as a clear oil (1.04 g, 62%), R$_f$ = 0.43 (9:1, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm$^{-1}$): 2225, 2135, 2109, 1591, 1570, 1473, 1443, 1256, 1212, 1181, 1157, 1104, 882, 753; $^1$H NMR (400MHz, CDCl$_3$): δ 6.95-7.00 (m, 2H), 7.14-7.20 (m, 2H), 7.24-7.38 (m, 6H), 7.42-7.46 (m, 1H), 7.55 (dd, $J_1$ = 8Hz, $J_2$ = 1.6Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 108.0, 114.8 (d, $J_{CF}$ = 21.2Hz), 116.5, 116.8 (d, $J_{CF}$ = 8.8Hz), 125.2 (d, $J_{CF}$ = 4.4Hz), 125.4 (d, $J_{CF}$ = 3Hz), 126.1, 126.7, 129.2, 130.1 (d, $J_{CF}$ = 8.8Hz), 130.4, 130.7, 133.6 (d, $J_{CF}$ = 32.9Hz), 133.9, 136.3 (d, $J_{CF}$ = 2.2Hz), 140.8 (d, $J_{CF}$ = 7.3Hz), 142.4, 162.7 (d, $J_{CF}$ = 245.3Hz). HRMS (ESI): m/z calculated for C$_{20}$H$_{13}$N$_2$F (M$^+$) 314.1094, found 314.1117.

### 3.12.7 Synthesis of 2-((3′-methylbiphenylimino)methyleneamino) benzonitrile 109f

The compound was synthesized from crude 3′-methyl-2-biphenylyl isocyanate 118f (5.46 mmol) using general procedure described above. Purification by flash column chromatography on silica gel using a gradient eluent of 4% EtOAc afforded 109f as a clear oil (1.22 g, 73%), R$_f$ = 0.45 (9:1, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm$^{-1}$): 2225, 2136, 2111, 1592, 1569, 1474, 1442, 1256, 1212, 1104, 906, 793, 752, 730; $^1$H NMR (400MHz, CDCl$_3$): δ $^1$H NMR (400MHz, CDCl$_3$): δ 2.31 (s, 3H), 6.84 (dd, $J_1$ = 8.8Hz, $J_2$ = 0.8Hz, 1H), 7.15 (dt, $J_1$ = 7.6Hz, $J_2$ = 0.8Hz, 1H), 7.24-7.35 (m, 8H), 7.37-7.41 (m, 1H), 7.53 (dd, $J_2$ = 7.6Hz, $J_2$ = 1.2Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 21.6, 107.8, 116.9, 124.9, 125.2, 125.7, 126.5, 128.6, 128.7, 130.2, 130.9, 133.3, 133.6, 133.8, 138.2, 138.3, 138.6, 143.0. HRMS (ESI): m/z calculated for C$_{21}$H$_{16}$N$_3$ (M$^+$) 310.1344, found 310.1369.
3.12.8 Synthesis of 2-((3′-methoxybiphenylimino)methyleneamino) benzonitrile 109g

The compound was synthesized from crude 3′-methoxy-2-biphenylyl isocyanate 118g (4.91 mmol) using general procedure described above. Purification by flash column chromatography on silica gel using a gradient eluent of 5% EtOAc afforded 109g as a viscous yellow oil (0.78 g, 49%). R$_f$ = 0.36 (8:2, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm$^{-1}$): 2146, 2112, 1592, 1443, 1259, 1209, 1108, 1020, 872, 756; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 3.78 (s, 3H), 6.81 (dd, $J_1$ = 8.4Hz, $J_2$ = 1.2Hz, 1H), 6.88 (dd, $J_1$ = 8.4Hz, $J_2$ = 0.8Hz, 1H), 6.98-6.99 (m, 1H), 7.02-7.05 (m, 1H), 7.15 (td, $J_1$ = 7.6Hz, $J_2$ = 0.8Hz, 1H), 7.25-7.43 (m, 6H), 7.54 (dd, $J_1$ = 7.6Hz, $J_2$ = 1.6Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 55.4, 107.8, 113.5, 115.1, 116.8, 121.9, 124.9, 125.2, 125.7, 126.6, 128.8, 129.6, 130.0, 130.7, 133.3, 133.6, 133.8, 137.9, 140.0, 142.8, 159.6. HRMS (ESI): m/z calculated for C$_{21}$H$_{16}$N$_3$O (M$^+$) 326.1293, found.

3.12.9 Synthesis of 2-((3′-trifluoromethylbiphenylimino)methyleneamino) benzonitrile 109h

The compound was synthesized from crude 3′-trifluoromethyl-2-biphenylyl isocyanate 118h (3.16 mmol) using general procedure described above. Purification by flash column chromatography on silica gel using a gradient eluent of 4% EtOAc afforded 109h as a viscous yellow oil (0.48 g, 42%). R$_f$ = 0.45 (9:1, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm$^{-1}$): 2221, 2143, 2113, 1593, 1570, 1478, 1333, 1247, 1163, 1121, 1073, 805, 756; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 6.97 (dd, $J_1$ = 8.4Hz, $J_2$ = 0.8Hz, 1H), 7.29 (dt, $J_1$ = 7.6Hz, $J_2$ = 0.8Hz, 1H), 7.30-7.34 (m, 1H), 7.35-7.47 (m, 4H), 7.54 (dd, $J_1$ = 7.6Hz, $J_2$ = 1.6Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 55.4, 107.8, 113.5, 115.1, 116.8, 121.9, 124.9, 125.2, 125.7, 126.6, 128.8, 129.6, 130.0, 130.7, 133.3, 133.6, 133.8, 137.9, 140.0, 142.8, 159.6. HRMS (ESI): m/z calculated for C$_{21}$H$_{16}$N$_3$O (M$^+$) 364.1062, found 364.1093.

3.12.10 Synthesis of 2-((5-methylbiphenylimino)methyleneamino) benzonitrile 109i

The compound was synthesized from crude 4-methyl-2-biphenylyl isocyanate 118i (5.47 mmol) using general procedure described above. Purification by flash column chromatography
on silica gel using a gradient eluent of 4% EtOAc afforded 109i as a clear viscous oil (1.23 g, 73%), R_f = 0.45 (9:1, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm\(^{-1}\)): 2225, 2131, 2113, 1593, 1570, 1481, 1271, 1213, 1112, 908, 815, 757; \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 2.38 (s, 3H), 6.85 (d, \(J = 8\)Hz, 1H), 7.09-7.16 (m, 3H), 7.22-7.29 (m, 2H), 7.33-7.40 (m, 3H), 7.43-7.46 (m, 2H), 7.51 (dd, \(J_1 = 7.6\)Hz, \(J_2 = 2\)Hz, 1H); \(^13\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 21.2, 107.7, 116.9, 124.8, 125.1, 125.7, 127.8, 128.5, 129.4, 129.5, 130.3, 130.9, 131.5, 133.3, 133.6, 136.6, 137.6, 138.8, 143.2. HRMS (ESI): \(m/\text{z}\) calculated for C\(_{21}\)H\(_{16}\)N\(_3\) (M\(^{+}\)) 310.1344, found 310.1349.

### 3.12.11 Synthesis of 2-((5-methoxybiphenylimino)methyleneamino) benzonitrile 109j

The compound was synthesized from crude 4-methoxy-2-biphenyllyl isocyanate 118j (5.52 mmol) using general procedure described above. Purification by flash column chromatography on silica gel using a gradient eluent of 4% EtOAc afforded 109j as a clear viscous oil (1.38 g, 77%), R_f = 0.52 (8:2, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm\(^{-1}\)): 2225, 2127, 2113, 1594, 1567, 1477, 1443, 1400, 1298, 1207, 1173, 1030, 813, 757; \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 3.83 (s, 3H), 6.85-6.90 (m, 3H), 7.12 (dt, \(J_1 = 8\)Hz, \(J_2 = 1.2\)Hz, 1H), 7.25-7.29 (m, 2H), 7.33-7.41 (m, 3H), 7.44-7.46 (m, 2H), 7.51 (dd, \(J_1 = 8\)Hz, \(J_2 = 1.4\)Hz, 1H); \(^13\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 55.8, 107.7, 114.3, 115.9, 116.9, 124.7, 125.0, 126.2, 128.0, 128.6, 129.4, 130.4, 133.3, 133.6, 138.6, 139.1, 143.5, 158.1. HRMS (ESI): \(m/\text{z}\) calculated for C\(_{21}\)H\(_{16}\)N\(_3\)O (M\(^{+}\)) 326.1293, found 326.1306.

### 3.12.12 Synthesis of 2-((3′-methoxy-5-methylbiphenylimino)methyleneamino) benzonitrile 109k

The compound was synthesized from crude 3′-methoxy-5-methyl-2-biphenyllyl isocyanate 118k (5.47 mmol) using general procedure described above. Purification by flash column chromatography on silica gel using a gradient eluent of 6% EtOAc afforded 109k as a viscous pale yellow oil (1.11 g, 78%), R_f = 0.45 (9:1, hexane/EtOAc). IR (ZnSe ATR crystal; neat, cm\(^{-1}\)): 2226, 2128, 2114, 1593, 1570, 1477, 1429, 1259, 1215, 1161, 1111, 1050, 1032, 820, 757; \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 2.39 (s, 3H), 3.79 (s, 3H), 6.80 (dd, \(J_1 = 8.4\)Hz, \(J_2 = 2.2\)Hz, 1H), 6.88 (d, \(J = 8.4\)Hz, 1H), 6.97-6.98 (m, 1H), 7.02 (dd, \(J_1 = 7.2\)Hz, \(J_2 = 0.8\)Hz, 1H), 7.13-7.18 (m, 3H), 7.22-7.25 (m, 1H), 7.28 (d, \(J = 5.2\)Hz, 1H), 7.40 (dt, \(J_1 = 8\)Hz, \(J_2 = 1.6\)Hz, 1H), 7.53 (dd, \(J_1 = 7.6\)Hz, \(J_2 = 1.2\)Hz, 1H); \(^13\)C NMR (100MHz, CDCl\(_3\)): \(\delta\) 21.2, 55.4, 107.7,
3.13 Synthesis of 2-halo-3-biphenylyl quinazoliniminiums halide salts

3.13.1 General procedure for Lewis acids mediated intramolecular cyclization 110

Lewis acids were added dropwise to a stirring solution of 2-((biphenylimino)methyleneamino) benzonitrile (0.08 g, 0.26 mmol) in the indicated organic solvent (3 mL) at the specified temperature. The reaction mixture was monitored by TLC, after complete consumption of the starting material and the resulting precipitates was filtered and washed with hexane-CH₂Cl₂ to quench the acid. The precipitates are dried under vacuum to afford the corresponding 2-halo-3-biphenylyl quinazoliniminiums halide salts.

3.13.2 2-Bromo-3-(4′-methylbiphenylyl) quinazolin-4(3H)-iminium bromide 110a

The compound was obtained from the reaction of 109a with TMSBr (2.82 mmol) following the general procedure. The solvent used were CH₂Cl₂ or CH₃CH₂CH₂Cl as indicated on Table 3.2. Pale yellow solid (0.077 g, 82%) was obtained. Rᵣ = 0.49 (9.5:0.5, CH₂Cl₂/MeOH). ¹H NMR (400MHz, CH₃OH-d₄): δ 2.24 (s, 3H), 7.12 (d, J = 8Hz, 2H), 7.19-7.22 (m, 2H), 7.69-7.88 (m, 6H), 8.11 (dt, J₁ = 7.2Hz, J₂ = 1.2Hz, 1H), 8.42 (d, J₁ = 8.8Hz, J₂ = 1.2Hz, 1H); ¹³C NMR (100MHz, CH₃OH-d₄): δ 21.2, 114.4, 126.6, 129.1, 129.5, 130.1, 130.6, 131.4, 131.7, 134.1, 134.8, 135.7, 136.1, 139.5, 140.2, 141.7, 147.4, 160.3. LRMS (ESI): m/z calculated for C₂₁H₁₇BrN₃⁺ (M⁺) 390.06, found 390.1 and 390.9.

3.13.3 2-Chloro-3-(4′-methylbiphenylyl) quinazolin-4(3H)-iminium chloride 110a’

Following the general procedure, TMSCl, SnCl₄ or TiCl₄ (3 equiv) was added dropwise to a stirring solution of 2-((4′-methylbiphenylimino)methyleneamino)benzonitrile (109a) (0.15 g, 0.04 mmol) in the specified organic solvent (2-3 mL). White solid (0.077 g, 82%) was obtained. Rᵣ = 0.49 (9.5:0.5, CH₂Cl₂/MeOH). ¹H NMR (400MHz, CH₃OH-d₄): δ 2.24 (s, 3H), 7.12 (d, J = 8Hz, 2H), 7.17 (d, J = 8Hz, 2H), 7.69-7.87 (m, 6H), 8.09-8.14 (m, 1H), 8.43 (d, J₁ = 8.4Hz, J₂ =
0.8Hz, 1H); $^{13}$C NMR (100MHz, CH$_3$OH-$d_4$): δ 21.2, 114.2, 126.7, 129.0, 129.5, 129.8, 130.6, 131.3, 131.7, 134.0, 134.1, 134.8, 139.6, 140.3, 141.7, 144.1, 147.0, 160.9, 129.5, 129.8, 130.6, 131.3, 131.7, 134.0, 134.1, 134.8, 139.6, 140.3, 141.7, 144.1, 147.0, 160.9. HRMS (ESI): $m/z$ calculated for C$_{21}$H$_{17}$ClN$_3$ ($^+$) 346.1, found 346.1.

### 3.14 Synthesis of Phenanthridine fused quinazoliniminiums (PNQs)

#### 3.14.1 General procedure for Lewis acids mediated cascade cyclization of 111

To a stirring solution of 2-((biphenylimino)methyleneamino) benzonitrile 109 (0.50 mmol) in nitromethane (3 mL) was added either SnCl$_4$ or BF$_3$.OEt$_2$ dropwise at 25 °C. In many reactions water (4 equiv.) was also needed as specified. The reaction mixture was stirred for an additional 2-48 h. The product precipitated out of the solution. Upon completion of the reaction, the precipitates were filtered and washed with hexane-CH$_2$Cl$_2$, and then dried under vacuum to afford the corresponding ring-fused phenanthridine N-quinazoliniminiums salt.

#### 3.14.2 Synthesis of 4′-methyl-phenanthidine-N-quinazoliniminiums hydrochloride salt 111a′

The compound was obtained following general procedure by reacting 109a (0.24 mmol) with SnCl$_4$ (0.97 mmol) and water (4 equiv.) to afford a pale green solid (0.08 g, 44%). $R_f = 0.4$ (9.5:0.5, CH$_2$Cl$_2$/MeOH). IR (ZnSe ATR crystal; neat, cm$^{-1}$): 3257, 3151, 1635, 1598, 1566, 1497, 1369, 1309, 1242, 1184, 1008, 821, 754; $^1$H NMR (400MHz, DMSO-$d_6$): δ 2.54 (s, 3H), 7.62-7.70 (m, 2H), 7.75 (d, $J = 8.4$Hz, 1H), 7.81 (dt, $J_1 = 0.8$Hz, $J_2 = 7.6$Hz, 1H), 8.01 (d, $J = 8$Hz, 1H), 8.12 (dt, $J_1 = 8.4$Hz, $J_2 = 1.2$Hz, 1H), 8.42 (dd, $J_1 = 8.4$Hz, $J_2 = 1.6$Hz, 1H), 8.45 (d, $J = 8.4$Hz, 1H), 8.51 (d, $J_1 = 1.6$Hz, $J_2 = 7.6$Hz, 1H), 8.59 (s, 1H), 8.73 (d, $J = 8$Hz, 1H), 11.01 (br s, 1H), 11.34 (br s, 1H); $^{13}$C NMR (100MHz, DMSO-$d_6$): 21.1, 114.8, 121.2, 123.0, 124.6, 124.9, 125.6, 125.9, 127.1, 127.3, 127.9, 128.2, 128.6, 128.7, 130.6, 134.6, 136.9, 139.5, 144.4, 144.5, 158.2. HRMS (ESI): $m/z$ calculated for C$_{21}$H$_{16}$N$_3$O ($^+$) 310.1, found 310.0.
3.14.3 Synthesis of 4′-methyl-phenanthridine-N- quinazoliniminiums tetrafluoroborate Salt 111a**

The compound was obtained following general procedure by reacting 109a (0.69 mmol) with BF₃.OEt₂ (2.77 mmol) and water (4 equiv.) to afford a pale green solid (0.19 g, 70%). R_f = 0.51 (9.5:0.5, CH₂Cl₂/MeOH). IR (ZnSe ATR crystal; neat, cm⁻¹): 3366, 3218, 1660, 1594, 1566, 1474, 1345, 1085, 1053, 1011, 828, 764; ¹H NMR (400MHz, DMSO-d₆): δ 2.54 (s, 3H), 7.63-7.71 (m, 2H), 7.82 (t, J = 8Hz, 1H), 8.02 (d, J = 8.4Hz, 1H), 8.13 (t, J = 7.6Hz, 1H), 8.43 (d, J = 8.4Hz, 1H), 8.47 (d, J = 8Hz, 1H), 8.53 (d, J = 8.4Hz, 1H), 8.47 (d, J = 8Hz, 1H), 8.53 (d, J = 8.4Hz, 1H), 8.60-8.63 (m, 2H), 11.04 (br s, 2H); ¹³C NMR (100MHz, DMSO-d₆): 21.4, 115.4, 121.8, 123.6, 125.5, 126.2, 126.3, 127.8, 128.0, 128.6, 128.8, 129.2, 129.3, 131.2, 135.3, 137.6, 140.1, 145.1, 145.1, 158.8. HRMS (ESI): m/z calculated for C₂₁H₁₆N₃ (M⁺) 310.1339, found 310.1331.

3.14.4 Synthesis of 3′-fluoro-phenanthridine-N-quinazoliniminiums tetrafluoroborate salt 111e**

The compound was obtained following general procedure by reacting 109e (0.77 mmol) with BF₃.OEt₂ (3.08 mmol) and water (4 equiv.) to afford a green solid (0.14 g, 45%). R_f = 0.7 (9.5:0.5; CH₂Cl₂/MeOH). IR (ZnSe ATR crystal; neat, cm⁻¹): 3222, 1685, 1591, 1565, 1475, 1354, 1302, 1201, 1085, 1053, 992, 877, 764. ¹H NMR (400MHz, DMSO-d₆): δ 7.61-7.65 (m, 1H), 7.70-7.33 (m, 2H), 7.82 (t, J = 7.2Hz, 1H), 7.98 (d, J = 8Hz, 1H), 8.12 (t, J = 7.6Hz, 1H), 8.44-8.48 (m, 2H), 8.56-8.61 (m, 2H), 8.82-8.86 (m, 1H), 11.09 (br s, 2H); ¹³C NMR (100MHz, DMSO-d₆): 109.5 (d, J_CF = 24.2Hz), 114.7, 117.5 (d, J_CF = 22.7Hz), 121.3, 122.5 (d, J_CF = 2Hz), 123.8 (d, J_CF = 2Hz), 125.7, 127.3, 128.0, 128.7, 129.7, 130.9 (d, J_CF = 10.3Hz), 131.3, 133.3 (d, J_CF = 9.5Hz), 137.0, 144.0, 144.4, 158.3, 165.4 (d, J_CF = 250Hz). HRMS (ESI): m/z calculated for C₂₀H₁₃N₃F (M⁺) 314.1094, found 314.1078.

3.14.5 Synthesis of 3′-methyl-phenanthridine-N-quinazoliniminiums hydrochloride salt 111f*

The compound was obtained following general procedure by reacting 109f (0.65 mmol) with SnCl₄ (2.59 mmol) and water (4 equiv.) to afford a green solid (0.18 g, 82%). R_f = 0.43 (9.5:0.5, CH₂Cl₂/MeOH). IR (ZnSe ATR crystal; neat, cm⁻¹): 3210, 1674, 1638, 1610, 1560, 1485, 1363, 1263, 1181, 812, 761; ¹H NMR (400MHz, DMSO-d₆): δ 2.58 (s, 3H), 7.58 (t, J =
8.4Hz, 1H), 7.6-7.72 (m, 2H), 7.77-7.81 (m, 1H), 7.96 (d, J = 8Hz, 1H), 8.09-8.13 (m, 1H), 8.39 (s, 1H), 8.43 (dd, J₁ = 7.6Hz, J₂ = 2Hz, 1H), 8.55 (dd, J₁ = 7.6Hz, J₁ = 1.6Hz, 1H), 8.66 (t, J = 7.6Hz, 2H), 10.99 (br s, 1H), 11.19 (br s, 1H). 13C NMR (100MHz, DMSO-d6): 21.5, 114.7, 121.3, 123.0, 123.2, 124.6, 125.1, 125.8, 127.3, 127.7, 128.7, 128.9, 130.5, 130.7, 131.0, 136.9, 144.2, 144.6, 158.2. HRMS (ESI): m/z calculated for C21H16N3O (M⁺) 326.1288, found 326.1286.

3.14.6 Synthesis of 3′-methoxyl-phenanthridine-N-quinazoliniminiums
tetrafluoroborate salt 111g’’

The compound was obtained following general procedure by reacting 109g (1.14 mmol) with BF₃.OEt₂ (4.55 mmol) to afford a green solid (0.24 g, 51%). Rₐ = 0.37 (9.5:0.5, CH₂Cl₂/MeOH). IR (ZnSe ATR crystal; neat, cm⁻¹): 3104, 1680, 1597, 1565, 1506, 1474, 1352, 1314, 1297, 1233, 1170, 1052, 1014, 874, 768; 1H NMR (400MHz, DMSO-d₆): δ 4.02 (s, 3H), 7.32 (dd, J₁ = 8.8Hz, J₂ = 2.8Hz, 1H), 7.67-7.77 (m, 3H), 7.91 (d, J = 7.6Hz, 1H), 7.96 (ds, J = 2.4Hz, 1H), 8.05-8.09 (m, 1H), 8.42-8.45 (m, 1H), 8.55 (d, J = 8Hz, 1H), 8.60-8.62 (m, 1H), 8.65 (d, J = 9.2Hz, 1H), 11.05 (br s, 2H); 13C NMR (100MHz, DMSO-d₆): 55.2, 106.1, 114.4, 117.6, 118.6, 121.4, 124.6, 125.7, 127.2, 127.5, 128.7, 129.2, 129.7, 131.2, 132.7, 137.0, 144.6, 144.9, 158.2, 163.6. HRMS (ESI): m/z calculated for C21H16N3O (M⁺) 326.1288, found 326.1286.

3.14.7 Synthesis of 5-methyl-phenanthridine-N-quinazoliniminiums hydrochloride salt IIIi’

The compound was obtained following general procedure by reacting 109i (0.03 mmol) with SnCl₄ (1.29 mmol) and water (4 equiv.) to afford a pale green solid (0.08 g, 79%). Rₐ = 0.44 (9.5:0.5, CH₂Cl₂/MeOH). IR (ZnSe ATR crystal; neat, cm⁻¹): 3188, 1674, 1634, 1608, 1564, 1541, 1484, 1365, 1264, 1172, 829, 781, 767, 753; 1H NMR (400MHz, DMSO-d₆): δ 2.52 (s, 3H), 7.48 (d, J = 8.8Hz, 1H), 7.74 (t, J = 7.6Hz, 1H), 7.79 (t, J = 8.4Hz, 1H), 7.90 (t, J = 7.2Hz, 1H), 7.96 (d, J = 8Hz, 1H), 8.10 (t, J = 7.2Hz, 1H), 8.29 (d, J = 8.4Hz, 1H), 8.36 (s, 1H), 8.53 (d, J = 8Hz, 1H), 8.75 (t, J = 7.6Hz, 1H), 10.94 (br s, 1H), 11.33 (br s, 1H); 13C NMR (100MHz, DMSO-d₆): 20.7, 114.7, 121.0, 122.9, 124.4, 125.0, 125.6, 125.9, 127.3, 127.4, 127.9, 128.6, 129.4, 129.7, 130.6, 133.4, 136.8, 138.5, 144.4, 144.5, 157.9. HRMS (ESI): m/z calculated for C21H17N3Cl (M⁺) 346.1111, found 346.1101.
3.14.8 Synthesis of 5-methyl-3′-methoxy-phenanthridine-N-quinazoliniminiunms tetrafluoroborate salt 111k

The compound was obtained following general procedure by reacting 109k (0.86 mmol) with BF₃.OEt₂ (3.42 mmol) to afford a pale green solid (0.14 g, 37%). Rf = 0.31 (9.5:0.5, CH₂Cl₂/MeOH). IR (ZnSe ATR crystal; neat, cm⁻¹): 3201, 1658, 1606, 1473, 1411, 1364, 1301, 1235, 1192, 1097, 1051, 1006, 836, 767; ¹H NMR (400MHz, DMSO-d₆): δ 2.54 (s, 3H), 4.05 (s, 3H), 7.34 (dd, J₁ = 8.8Hz, J₂ = 2.8Hz, 1H), 7.50 (dd, J₁ = 8.8Hz, J₂ = 1.2Hz, 1H), 7.76 (t, J₁ = 7.4Hz, J₂ = 1.2Hz, 1H), 7.93 (d, J = 7.6Hz, 1H), 7.98 (ds, J = 2.4Hz, 1H), 8.08 (dt, J₁ = 7.4Hz, J₂ = 1.2Hz, 1H), 8.31 (d, J = 8.4Hz, 1H), 8.46 (s, 1H), 8.56 (d, J = 8Hz, 1H), 8.71 (d, J = 8.8Hz, 1H); ¹³C NMR (100MHz, DMSO-d₆): 20.6, 55.3, 101.6, 113.4, 114.9, 117.0, 121.3, 122.7, 127.3, 127.4, 127.6, 128.6, 128.9, 133.1, 133.8, 136.5, 138.7, 142.2, 153.1, 156.3.

3.15 Formation of 1-(2-cyanophenyl)-3-(biphenyl-2-yl) urea 126

3.15.1 1-(2-cyanophenyl)-3-(5-methoxybiphenyl-2-yl) urea 126j

Compound 126j was obtained from the reaction of SnCl₄ with 109j (0.04 mmol) following the general procedure earlier stated in Section 3.15.1. The reaction yielded a white solid (0.11g, 88%). ¹H NMR (400MHz, DMSO-d₆): δ 3.79 (s, 3H), 6.84 (d, J = 3.2 Hz, 1H), 6.96 (dd, J₁ = 8.8 Hz, J₂ = 3.2 Hz, 1H), 7.14 (dt, J₁ = 8 Hz, J₂ = 1.2 Hz, 1H), 7.37-7.50 (m, 5H), 7.53 (d, J = 8.8 Hz, 1H), 7.57-7.62 (m, 1H), 7.70 (dd, J₁ = 8 Hz, J₂ = 1.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 8.34 (s, 1H), 8.80 (s, 1H); ¹³C NMR (100MHz, DMSO-d₆): 55.3, 101.6, 113.4, 114.9, 117.0, 121.3, 122.7, 127.3, 127.4, 127.6, 128.6, 128.9, 133.1, 133.8, 136.5, 138.7, 142.2, 153.1, 156.3.
References:


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Fukuda, T.; Sudo, E.-I.; Shimokawa, K.; Iwao, M., Palladium-catalyzed cross-coupling of N-benzenesulfonyl-3,4-dibromopyrrole and its application to the total syntheses of lamellarins O, P, Q, and R. Tetrahedron 2008, 64 (2), 328-338;


49 Information obtained from the chemical properties of nitromethane on the bottle and also available at http://www.sigmaaldrich.com/catalog/ProductDetail.do?lang=en&N4=360554%7CSIAL&N5=SEARCH_CONCAT_PNO%7CBRAND_KEY&F=SPEC webpage accessed on 02/10/2012.


53 This reaction was carried out in reagent grade CH3NO2 (≤ 0.05% H2O) and appears that the trace amount of water presence in the nitromethane was sufficient to for the cascade cyclization reaction without the need for additional water.
Chapter 4 - Theoretical Studies on the Optoelectronic Properties of Phenanthridine fused Quinazoliniminiums

4.1 Introduction

There is a growing research interest in the development of more efficient and high performance Organic Light-Emitting Diodes (OLEDs) due to their applications in the development of new electroluminescent components for organic materials.\textsuperscript{1,2} OLEDs have several advantages over conventional LEDs such as greater contrast, superior brightness, broader emission. These are also low weight and offer low-cost display.\textsuperscript{3} Most importantly, the photophysical properties of organic LED molecules can be manipulated by chemical modification to produce materials with tailored optoelectronic properties.\textsuperscript{4} Thus, OLEDs have revolutionized display technologies and are already in use in mobile phones, car radios, digital cameras and personal computers etc.\textsuperscript{5}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4.1.png}
\caption{Basic schematic of multilayer OLED device.}
\end{figure}

OLEDs consist of an electron-transport layer (ETL), emissive layer (EML), hole-transport layer (HTL) sandwiched between two electrodes. The cathode is metallic and anode is usually made of indium tin oxide (Figure 4.1).\textsuperscript{6,7} The mechanism of electroluminescence is well established and involves the injection of electrons from the low work function metallic cathode into the LUMO (Lowest Unoccupied Molecular Orbital) of the electron-transport layer (ETL) and simultaneous, injection of holes (extraction of electrons) into the HOMO (Highest Occupied Molecular Orbital) of the hole-transport layer (HTL) at the anode under an applied current (Figure 4.2). The electron-hole pairs migrate and recombine in the emissive layer (EML) to form excitons, which relax to the ground state by emitting light.\textsuperscript{7,8,9,10} The energy difference (band gap) between the HOMO and LUMO levels (HOMO-LUMO gap) of EML determines the color
of light emitted and influences the charge transport and injection, which in turn determines the efficiency of OLEDs.

It is believed that for an efficient hole-injection from the anode, the HOMO level of HTL should be in 5 – 6 eV range, whereas for an efficient electron injection from the cathode, the LUMO energy level of ETL must be in the range 2–3 eV. A band gap of 0.5 eV or smaller is desired in the EML for high performance in electroluminescent applications, which is a considerable challenge.

![Energy Level Diagram for a Multilayer OLED](image)

**Figure 4.2**: Schematic of energy level diagram for a multilayer OLED.

There are two types of organic materials (chromophores) commonly used for OLEDs. Those that are based on small molecules and polymers, both of which have demonstrated significant advantages in OLED technology, and have also contributed to the basic understanding of current electroluminescent materials. Some examples of small compounds commonly used as hole transporters are shown in Figure 4.3 that includes 4,4′,4′′-tris(3-methylphenylphenylamino) triphenylamine (MT-DATA) (128) N,N′-diphenyl-N,N′-(3-methylphenyl)-1,1′-biphenyl-4,4′-diamine (TPD) (129) and its analog 1,4-bis(1-naphtylphenylamino) biphenyl (NPB) (130). Tris(8-hydroxyquinolinato)aluminum (Alq₃) (131) and 2-(4-biphenyl)-5-(4-tert-butylphenyl)-1,3,4-oxadiazole (PBD) (132), both are normally used as electron transporters. 131 is also a widely used emitter.
Recently, bridgehead-nitrogen containing fused heterocyclic molecules have attracted interest as highly efficient chromophores for the development of OLEDs (Figure 4.4). For instance, imidazole[1,5-a]pyridines\(^1\) (128) and pyrrolo[1,2-b] pyridines\(^1\) (129) both emit intense blue light whereas pyrrolo[1,2-b]cinnolines (130) emit blue light whereas pyrrolo[1,2-b]cinnolines (130) as well as benzo[f]pyridazines[6,1-a]isoindole-5,10-diones (131) both emit green light.\(^1\) Similarly, indolizino[3,4,5-ab]isoindoles (132) chromophores are excellent light-emitting compounds that emit different colors ranging from blue to green.\(^1\) The presence of N-atom at the ring fusion is known to impart unique photophysical properties to these compounds, such as excellent luminescence and easily tunable emission colors for device fabrication. Furthermore, these small organic molecules exhibit considerable advantages such as broad emission spectra, and easy fabrication into multilayer devices.\(^1\)
Figure 4.4: Bridgehead-nitrogen containing chromophores proposed for use in OLEDs.\textsuperscript{13-15}

Polymeric materials used for the fabrication of OLEDs are usually conjugated in order to increase conductance. These polymer LEDs (PLEDs) are lightweight and flexible, therefore, can easily be employed for image display technology.\textsuperscript{19,20} Poly(9,9-dioctylfluorene (141) and its analog, the poly(9,9-dioctylfluorene-co-benzothiadiazole) (142), and poly(9,9-dioctylfluorene-co-N-(4-butylphenyl)diphenylamine) (143), poly(p-phenylenevinylene) (144), poly(ethylene dioxythiophene) (145), poly(N-vinylcarbazole) (146) and poly(styrene sulfonic acid) (147) are interesting examples of electroluminescent polymers used in PLED displays (Figure 4.5).\textsuperscript{21,22}

Figure 4.5: Chemical structure of some polymeric materials used in OLEDs.\textsuperscript{21,22}

Although, many chromophores based on small molecules or polymers have been designed for potential OLEDs, only a few to date have been particularly successful in these
applications. There are many drawbacks of the existing OLED molecules\textsuperscript{23,24,25}. For instance, current OLEDs are composed of multilayers of hole transporting layer, an emissive layer, an electron transporting layer sandwiched between two electrodes (Figure 2.1). The fabrication of very thin OLEDs with one or two layers is still a major challenge as only a limited number of molecules are available to date that can function as an emitter as well as either a hole- or electron-transport material\textsuperscript{26,27,28}. In addition, chromophores that offer the possibility of tuning emission color and HOMO-LUMO energy levels without compromising the fluorescence are scarce. Therefore, more compounds with finer properties are needed that overcome these aforementioned limitations and to broaden the range of available properties\textsuperscript{29} so as to obtain improved performance.

We evaluated derivatives of phenanthridine-fused quinazolininimiums, PNQs (\textit{148}_{n}-X and \textit{148}_{n}-Y) and their free base (\textit{149}_{n}-X and \textit{149}_{n}-Y) for potential applications in OLED technology. Note that “X” refers to the presence of an electron donating group (EDG) e.g. NMe\textsubscript{2} while “Y” refers to the presence of an electron withdrawing groups (EWG) e.g. Cl, NO\textsubscript{2}, and the subscript “n” refers to their position on the chromophore. The substitution at C3, C6 and C12 was considered on A, B and C rings respectively, therefore “n” was equal to 3, 6, 12 (Figure 4.6). We believed that due to the presence of a bridgehead nitrogen atom, analogous to the OLED molecules shown in Figure 4.4, these would exhibit optical properties desired for application in electroluminescent devices. Since computational methods have provided indispensible tools in gaining insight into the optoelectronic properties of organic compounds and subsequently, guiding experimental research, we decided to use density functional theory to identify lead structures with promise in organic materials and the results are presented and discussed.
Figure 4.6: Structure of phenanthridine-fused quinazoliniminiums $148_n$-X,Y and their free base $149_n$-X,Y.

4.2 Computational Methods

All calculations have been performed using the Gaussian 09 package of program. The geometry optimizations employed B3LYP functional in conjunction with 6-311+G* basis set. All geometry optimizations were followed by vibrational analyses to confirm that each structure corresponded to a stationary point on the potential energy surface. Vertical excitation energies were computed using Time Dependent Density Functional Theory (TDDFT) at the optimized geometries. The molecular orbitals were visualized using Gaussview. The vertical and adiabatic Ionization Potentials (IP) and Electron Affinities (EA), Hole Extraction Potentials (HEP), Electron Extraction Potentials (EEP), reorganization energies for hole ($\lambda_{\text{hole}}$) and electron ($\lambda_{\text{electron}}$) were calculated using the equations below, and as described by Rang and Fang. $^3$0 $M$ refers to $148_n$-X,Y or $149_n$-X,Y.

\[
\text{IP (v)} = E^+ (M) - E (M) \quad \text{Equation 4.1}
\]
\[
\text{IP (a)} = E^+ (M^+) - E (M) \quad \text{Equation 4.2}
\]
\[
\text{EA (v)} = E (M) - E^- (M) \quad \text{Equation 4.3}
\]
\[
\text{EA (a)} = E (M) - E^- (M^+) \quad \text{Equation 4.4}
\]
\[
\text{HEP} = E^+ (M^+) - E (M^+) \quad \text{Equation 4.5}
\]
$$\text{EEP} = E (M) - E^+ (M')$$  \quad \text{Equation 4.6}

$$\lambda_{\text{hole}} = \text{IP} (v) - \text{HEP}$$  \quad \text{Equation 4.7}

$$\lambda_{\text{electron}} = \text{EEP} - \text{EA} (v)$$  \quad \text{Equation 4.8}

### 4.3 Results and Discussion

#### 4.3.1 Frontier Molecular Orbitals

In order to determine the optoelectronic properties of PNQs 148\textsubscript{n}-X, Y and 149\textsubscript{n}-X,Y, the HOMOs, LUMOs and their corresponding energy gaps were examined for the optimized geometries at B3LYP /6-311+G*. The isodensity plots of the Frontier Molecular Orbitals (FMOs) for 148\textsubscript{n}-X, Y all exhibit \(\pi\)-type characteristics. The FMOs of the unsubstituted 148-H are shown in Figure 4.7 (top). In general, the HOMO exhibits a bonding character whereas the LUMO display an antibonding character. The HOMO orbital is delocalized over the entire molecule, while the LUMO orbital is mainly localized over the quinazoliniminium moiety. The FMOs of all other the derivatives of 148\textsubscript{n}-X and 148\textsubscript{n}-Y considered in this study demonstrate similar characteristics as that of 148-H, with the exception of 148\textsubscript{3}-NO\textsubscript{2} in which the LUMOs exhibit a bonding character at the N-C\textsubscript{16}, C\textsubscript{1}-C\textsubscript{2}, C\textsubscript{3}-N and C\textsubscript{4}-C\textsubscript{17}, bonds (Figure 4.7, bottom right) and supports the resonance structure 148\textsubscript{3}-NO\textsubscript{2}' (Scheme 4.1).

![Figure 4.7: Selected FMOs of 148H and 148\textsubscript{3}-NO\textsubscript{2}](image)
Scheme 4.1: Resonance structure of 1483-NO₂.

The FMOs of the unsubstituted free base PNQ 149-H is shown below (Figure 4.8). Similar to 148-H, the HOMO and LUMO exhibit a bonding and antibonding characteristics, respectively and are delocalized over the entire molecule. The LUMOs exhibit a bonding character at the C₅-C₁₈, C₇-C₈, C₉-C₁₉, N-C₂₀, C₁₅-N, C₁₀-C₁₁ and C₁₃-C₁₄ bonds that supports the resonance structures 149-H' and 149-H'' (Scheme 4.2).

Figure 4.8: FMOs of 149H.

Scheme 4.2: Resonance structures of 149-H.

The FMOs of all other derivatives of PNQs 149ₙ-X and 149ₙ-Y considered in this study demonstrate similar characteristics as that of 149-H, except the LUMO of 149₃-NO₂, 149₆-NO₂ and 149₁₂-NO₂, which is exclusively localized on the A, B and C rings of the PNQ scaffold,
respectively (Figure 4.9), indicating significant contributions from the corresponding resonance structures $149_3$-$NO_2$, $149_6$-$NO_2'$ and $149_{12}$-$NO_2'$ (Scheme 4.3).

Figure 4.9: Selected FMOs of $149_6$-$NO_2$. 
The HOMO, and LUMO energies and corresponding gaps ($\Delta E_{H-L}$) are listed in Table 4.1. Our results revealed that the HOMO energies increase with the incorporation of EDG (NMe$_2$) on PNQs 148 and their free bases 149, suggesting an improved hole creating ability, while the LUMO energies decrease upon substitution with EWG (Cl, NO$_2$) implying an improved electron accepting ability (Figure 4.2). Overall, the HOMO-LUMO energy gaps are influenced by the nature of the substituent and its position, which indicates the tunability in the electronic properties of these PNQs chromophores. Furthermore, the HOMO (~5-6 eV) and LUMO energies (~2-3 eV) of the free base PNQs 149 are in the range desired for efficient hole and electron injection in OLEDs devices.$^{10}$

**Scheme 4.3:** Resonance structures of 149$_n$-NO$_2$'.

![Resonance structures of 149$_n$-NO$_2$'](image-url)
Table 4.1: HOMOs, LUMOs energies and energy gaps (ΔE) calculated for PNQs 148 and its free base 149.

<table>
<thead>
<tr>
<th>X, Y</th>
<th>148</th>
<th>149</th>
</tr>
</thead>
<tbody>
<tr>
<td>-H</td>
<td>9.57</td>
<td>5.93</td>
</tr>
<tr>
<td>Substitution at C3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMe₂</td>
<td>8.53</td>
<td>5.54</td>
</tr>
<tr>
<td>Cl</td>
<td>9.67</td>
<td>6.03</td>
</tr>
<tr>
<td>NO₂</td>
<td>9.93</td>
<td>6.40</td>
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<tr>
<td>Substitution at C6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMe₂</td>
<td>8.36</td>
<td>5.56</td>
</tr>
<tr>
<td>Cl</td>
<td>9.58</td>
<td>6.01</td>
</tr>
<tr>
<td>NO₂</td>
<td>9.99</td>
<td>6.24</td>
</tr>
<tr>
<td>Substitution at C12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMe₂</td>
<td>8.52</td>
<td>5.58</td>
</tr>
<tr>
<td>Cl</td>
<td>9.60</td>
<td>6.08</td>
</tr>
<tr>
<td>NO₂</td>
<td>9.92</td>
<td>6.40</td>
</tr>
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</table>

4.3.2 Ionization potentials and Electron affinities

Since the performance of OLED devices depend on the injection and mobility of holes and electrons as well as the charge balance, we evaluated the energy barrier for the injection of holes and electrons by investigating the ionization potentials (IP) and electron affinities (EA) of PNQs 148 and their free bases 149. The rate of charge transfer and balance was estimated by calculating reorganization energies (λ). Table 4.2 shows a list of the calculated vertical (v) and adiabatic (a) IP and EA as well as the hole extraction potentials (HEP), electron extraction potentials (EEP), reorganization energies for hole injection (λ_{hole}) and electron transfer (λ_{electron}) for 148_n-X and 148_n-Y.
Our results reveal that IP for $148_3\text{-NMe}_2$ are lower (9.92 eV) than $148\text{-H}$ (10.93 eV), which indicates that the presence of EDG (NMe$_2$) improves the hole creating ability of the chromophore. In case of $148_3\text{-NO}_2$, EA values (5.07 eV) are higher than $148\text{-H}$ (4.51 eV), thus demonstrating that incorporation of a strong EWG increases the electron accepting abilities of the chromophore. Similar results were obtained for other derivatives of $148$ ($148_6\text{-X}, 148_6\text{-Y}, 148_{12}\text{-X}, 148_{12}\text{-Y}$).

Table 4.2: Calculated Ionization Potentials (IP), Electron affinities (EA), Extraction Potentials (EP) and reorganization energies for $148_n\text{-X}$ and $148_n\text{-Y}$.

<table>
<thead>
<tr>
<th>Structure</th>
<th>IP (v)</th>
<th>IP (a)</th>
<th>HEP</th>
<th>EA (v)</th>
<th>EA (a)</th>
<th>EEP</th>
<th>$\lambda_{\text{hole}}$</th>
<th>$\lambda_{\text{electron}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$148\text{-H}$</td>
<td>10.93</td>
<td>10.84</td>
<td>10.74</td>
<td>4.51</td>
<td>4.81</td>
<td>5.13</td>
<td>0.19</td>
<td>0.62</td>
</tr>
<tr>
<td>$148_3\text{-NMe}_2$</td>
<td>9.92</td>
<td>9.83</td>
<td>9.71</td>
<td>4.18</td>
<td>4.48</td>
<td>4.81</td>
<td>0.21</td>
<td>0.64</td>
</tr>
<tr>
<td>$148_3\text{-Cl}$</td>
<td>10.99</td>
<td>10.90</td>
<td>10.81</td>
<td>4.63</td>
<td>4.92</td>
<td>5.24</td>
<td>0.18</td>
<td>0.61</td>
</tr>
<tr>
<td>$148_3\text{-NO}_2$</td>
<td>11.27</td>
<td>11.16</td>
<td>11.06</td>
<td>5.07</td>
<td>5.29</td>
<td>5.55</td>
<td>0.21</td>
<td>0.48</td>
</tr>
<tr>
<td>$148_6\text{-NMe}_2$</td>
<td>9.68</td>
<td>9.61</td>
<td>9.54</td>
<td>4.20</td>
<td>4.52</td>
<td>4.87</td>
<td>0.14</td>
<td>0.66</td>
</tr>
<tr>
<td>$148_6\text{-Cl}$</td>
<td>10.90</td>
<td>10.80</td>
<td>10.69</td>
<td>4.60</td>
<td>4.90</td>
<td>5.23</td>
<td>0.20</td>
<td>0.63</td>
</tr>
<tr>
<td>$148_6\text{-NO}_2$</td>
<td>11.32</td>
<td>11.21</td>
<td>11.11</td>
<td>4.89</td>
<td>5.12</td>
<td>5.45</td>
<td>0.21</td>
<td>0.56</td>
</tr>
<tr>
<td>$148_{12}\text{-NMe}_2$</td>
<td>9.85</td>
<td>9.74</td>
<td>9.61</td>
<td>4.23</td>
<td>4.53</td>
<td>4.84</td>
<td>0.24</td>
<td>0.61</td>
</tr>
<tr>
<td>$148_{12}\text{-Cl}$</td>
<td>10.91</td>
<td>10.81</td>
<td>10.70</td>
<td>4.69</td>
<td>4.99</td>
<td>5.31</td>
<td>0.21</td>
<td>0.62</td>
</tr>
<tr>
<td>$148_{12}\text{-NO}_2$</td>
<td>11.27</td>
<td>11.17</td>
<td>11.06</td>
<td>5.03</td>
<td>5.28</td>
<td>5.58</td>
<td>0.21</td>
<td>0.54</td>
</tr>
</tbody>
</table>

We also calculated the IP and EA for free bases of PNQs $149$. Analogous to $148$, the presence of EDG in case of $149_3\text{-NMe}_2$, $149_6\text{-NMe}_2$, $149_{12}\text{-NMe}_2$ decreases the IPs relative to $149\text{-H}$ (6.52 eV, 6.63 eV, 6.48 eV Vs 7.15 eV), while the incorporation of EWG such as in $149_3\text{-NO}_2$, $149_6\text{-NO}_2$, $149_{12}\text{-NO}_2$ increases the EAs (1.40 eV, 1.69 eV, 1.61 eV Vs 0.77 eV)
confirming an improvement in the hole creating and electron accepting abilities relative to the unsubstituted free base 149-H, respectively.

Table 4.3: Calculated Ionization Potentials (IP), Electron affinities (EA), Extraction Potentials (EP) and reorganization energies for 149n-X and 149n-Y.

<table>
<thead>
<tr>
<th>Structure</th>
<th>IP (v)</th>
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In order to gain insight into the mobility of the hole injection and electron transport for these PNQs chromophores we calculated the reorganization energies (λ) using equations 4.7 and 4.8.30 The calculated hole injection (λ_hole) and the electron acceptance (λ_electron) values for PNQs 148n-X,-Y and its free base 149n-X,-Y are listed on Tables 4.2 and 4.3, respectively. Note that lower the λ values, the bigger the charge-transport rate. Our results revealed that for all the PNQs considered in this study, the λ_hole values are smaller than their respective λ_electron values, suggesting that PNQs can serve as a better hole transporting organic molecules than the electron transporting organic molecules.
4.4 Conclusion

These studies show that the optoelectronics properties of the PNQ derivatives \(148_{\alpha-X,Y}\) and their free bases \(149_{\alpha-X,Y}\) such as HOMOs, LUMOs and energy gaps can be fine tuned by varying the nature and positions of the substituents. The HOMO and LUMO levels of the free base derivatives, \(149_{\alpha-X,Y}\) are in the range desired for applications in organic materials (\(\sim 5 – 6\) eV and \(2 – 3\) eV, respectively). The presence of electron donating group on these ring systems increases the energies of the HOMOs while the presence of electron withdrawing group decrease energies of the LUMOs. And, similarly the ionization potentials decreases and electron affinities increase upon incorporation of electron donating group and electron withdrawing group, which indicates an improvement in the hole creating and electron accepting capabilities, respectively. The results of the reorganization energy (\(\lambda\)) suggest that PNQs and their free bases can serve as efficient hole transporting materials in OLEDs.
Reference:

2. (a) Shirota, Y.; Organic materials for electronic and optoelectronic devices; *J. Mater. Chem.* **2000**, *10*, 1; (b) Zou, L. Y.; Ren, A. M.; Feng, J. K.; Liu, Y. L.; Ran, X. Q.; Sun, C. C.; Theoretical Study on Photophysical Properties of Multifunctional Electroluminescent Molecules with Different \( \pi \)-Conjugated Bridges; *J. Phys. Chem. A.*, **2008**, *112*, 12172.


Appendix
Appendix A - Absorption spectra, TDDFT data, NMR spectra of synthesized compounds and reaction mixtures during photochemical experiments
Figure A.1: Experimental absorption spectra of 79b in cyclohexane, tetrahydrofuran and acetonitrile. The vertical excitations calculated at TDDFT/6-311+G* are shown as stick spectra.
**Figure A.2:** Experimental absorption spectra of 79c in cyclohexane, tetrahydrofuran and acetonitrile. The vertical excitations calculated at TDDFT/6-311+G* are shown as stick spectra.
Table A.1: TDDFT/6-311+G* vertical excitation energies (E (λ) / eV (nm)), oscillator strengths (f), MO character and transition type of 79b in cyclohexane, tetrahydrofuran and acetonitrile.

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*a* experimentally not observed
Table A.2: TDDFT/6-311+G* vertical excitation energies (E(\(\lambda\)) / eV (nm)), oscillator strengths (f), MO character and transition type of 79c in cyclohexane, tetrahydrofuran and acetonitrile

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Figure A.3: $^1$H and $^{13}$C NMR of 83b
Figure A.4: $^1$H and $^{13}$C NMR of 84b
Figure A.5: $^1$H and $^{13}$C NMR of 79b
Figure A.6: $^1$H and $^{13}$C NMR of 83c
Figure A.7: $^1$H and $^{13}$C NMR of 84c
Figure A.8: $^1$H and $^{13}$C NMR of 79c
Figure A.9: $^1$H and $^{13}$C NMR of 93a
Figure A.10: $^1$H NMR of 93b
Figure A.11: $^1$H and $^{13}$C NMR of 93c
Figure A.12: $^1$H and $^{13}$C NMR of 93d
Figure A.13: $^1$H NMR of 93e
Figure A.14: $^1$H and $^{13}$C NMR of 80a
Figure A.15: $^1$H and $^{13}$C NMR of 80b
Figure A.16: $^1$H and $^{13}$C NMR of 80c
Figure A.17: $^1$H and $^{13}$C NMR of 80d
Figure A.18: $^1$H and $^{13}$C NMR of 80e
Figure A.19: $^1$H NMR spectra of 79b in acetonitrile-$d_3$ taken at 0 (bottom), 10 (middle) and 20 (top) min of UV-irradiation at 254 nm, respectively.
Figure A.20: $^1$H NMR spectra of 79c in acetonitrile-$d_3$ taken at 0 (bottom), 15 (middle) and 30 (top) min of UV-irradiation at 254 nm, respectively.
**Figure A.21:** $^1$H NMR spectra of 79d in acetonitrile-$d_3$ taken at 0 (bottom), 15 (middle) and 30 (top) min of UV-irradiation at 254 nm, respectively.
Figure A.22: $^1$H NMR spectra of 79e in acetonitrile-$d_3$ taken at 0 (bottom), 15 (middle) and 30 (top) minute of UV-irradiation at 254 nm, respectively.
Figure A.23: $^1$H NMR spectra of 79a in methanol-$d_4$ taken at 0 (bottom), 10 (middle) and 20 (top) min of UV-irradiation at 254 nm, respectively.
Figure A.24: $^1$H NMR spectra of 79b in methanol-$d_4$ taken at 0 (bottom), 10 (middle) and 20 (top) min UV-irradiation in 254 nm, respectively.
Figure A.25: $^1$H NMR spectra of 79a in benzene-$d_6$ taken at 0 (bottom) and 20 (top) min of UV-irradiation at 254 nm, respectively.
Figure A.26: \(^1\)H NMR spectra of 79b in benzene-\(d_6\) taken at 0 (bottom) and 20 (top) min of UV-irradiation at 254 nm, respectively.
**Figure A.27**: $^1$H NMR spectra of 79a in acetonitrile-$d_3$ taken at 0 (bottom) and 60 (top) min of UV-irradiation at 300 nm at 300 nm, respectively.
**Figure A.28:** $^1$H NMR spectra of 79b in acetonitrile-$d_3$ taken at 0 (bottom) and 60 (top) min of UV-irradiation at 300 nm, respectively.
Figure A.29: $^1$H NMR spectra of 79a in methanol-$d_4$ taken at 0 (bottom) and 60 (top) min of UV-irradiation at 300 nm, respectively.
**Figure A.30:** $^1$H NMR spectra of 79b in methanol-$d_4$ taken at 0 (bottom), 30 (middle) and 60 (top) min of UV-irradiation at 300 nm, respectively.
Figure A.31: $^1$H NMR spectra of 79a in benzene-$d_6$ taken at 0 (bottom) and 60 (top) minutes of UV-irradiation at 300 nm, respectively.
Figure A.32: $^1$H NMR spectra of 79b in benzene-$d_6$ taken at 0 (bottom) and 60 (top) min of UV-irradiation at 300 nm, respectively.
Figure A.33: $^1$H NMR spectra of 79a and 1,4-CHD in acetonitrile-$d_6$ taken at 0 (bottom) and 60 (top) min of UV-irradiation at 300 nm, respectively.
Figure A.34: $^1$H NMR spectra of 79b and 1,4-CHD in acetonitrile-$d_6$ taken at 0 (bottom) and 60 (top) min of UV-irradiation at 300 nm, respectively.
Appendix B - NMR Spectra for 2-bromo-4-methoxyaniline, substituted biphenyl amines, biphenylyl isocyanates, 2-((biphenylimino)methyleneamino)benzonitrile, 2-halo-3-biphenylyl quinazolinimininium halides and phenanthridine-fused quinazolinimininium salts
Figure B.1: $^1$H and $^{13}$C NMR of 121j
Figure B.2: $^1$H and $^{13}$C NMR of 124a
Figure B.3: $^1$H and $^{13}$C NMR of 124b
Figure B.4: $^1$H and $^{13}$C NMR of 124c
Figure B.5: $^1$H and $^{13}$C NMR of 124d
Figure B.6: $^1$H and $^{13}$C NMR of 124e
Figure B.7: $^1$H and $^{13}$C NMR of 124f
Figure B.8: $^1$H and $^{13}$C NMR of 124g
Figure B.9: $^1$H and $^{13}$C NMR of 124h
Figure B.10: $^1$H and $^{13}$C NMR of 124i
Figure B.11: $^1$H and $^{13}$C NMR of 124j
Figure B.12: $^1$H and $^{13}$C NMR of 124k
Figure B.13: $^1$H and $^{13}$C NMR of 115a
Figure B.14: $^1$H and $^{13}$C NMR of 115g
Figure B.15: $^1$H and $^{13}$C NMR of 115h
Figure B.16: $^1$H and $^{13}$C NMR of 119
Figure B.17: $^1$H and $^{13}$C NMR of 109a
Figure B.18: $^1$H and $^{13}$C NMR of 109b
Figure B.19: $^1$H and $^{13}$C NMR of 109c
Figure B.20: $^1$H and $^{13}$C NMR of 109d
Figure B.21: $^1$H and $^{13}$C NMR of 109e
Figure B.22: $^1$H and $^{13}$C NMR of 109f
Figure B.23: $^1$H and $^{13}$C NMR of 109g
Figure B.24: $^1$H and $^{13}$C NMR of 109h
Figure B.25: $^1$H and $^{13}$C NMR of 109i
Figure B.26: $^1$H and $^{13}$C NMR of 109j
Figure B.27: $^1$H and $^{13}$C NMR of 109k
Figure B.28: $^1$H and $^{13}$C NMR of 110a

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</tbody>
</table>
Figure B.29: $^1$H and $^{13}$C NMR of 110a'
Figure B.30: $^1$H and $^{13}$C NMR of 111a'
Figure B.31: $^1$H and $^{13}$C NMR of 111a''
Figure B.32: $^1$H and $^{13}$C NMR of 111e''
Figure B.33: $^1$H and $^{13}$C NMR of 111f
Figure B.34: $^1$H and $^{13}$C NMR of 111g''
Figure B.35: $^1$H and $^{13}$C NMR of 111i'
Figure B.36: $^1$H and $^{13}$C NMR of 111k''
Figure B.37: $^1$H and $^{13}$C NMR of 126j
Figure B.38: $^1$H and $^{13}$C NMR of 127a