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Approaches Toward Novel 1,2,3-Triazole Sensors for the Detection of Anions and Heavy Metal Cations

Richard D. Govan

APPROACHES TOWARD NOVEL 1,2,3-TRIAZOLE SENSORS FOR THE DETECTION OF ANIONS AND HEAVY METAL CATIONS

by

RICHARD GOVAN

(Under The Direction of Karelle Aiken)

ABSTRACT

Cations and anions play pivotal roles in biological and physiological processes, however an imbalance in concentration of any ion can be detrimental. Therefore, research into the selective recognition of anions and heavy metal cations has acquired much attention. One approach in particular involves the use of chemosensors. Upon interaction with targeted analytes, chemosensors produce a distinct response, such as a fluorescent or colorimetric signal. The 1,2,3-triazole unit has much potential as a chemical sensor due to its unique photophysical properties. The specificity, selectivity, and signaling mechanism of triazole sensors can be tuned with conjugation in the motif and choice and placement of substituents in the structure. The utility of the motif is extensive with significant applications in toxicological assessments, therapeutics, and materials science. Herein we report the synthesis and analytical investigations of novel 1,2,3-triazole sensors tuned for intense color and fluorescent changes with specific analytes. Our current studies include a 1,2,3-triazole based copper (II) sensor and a dual sensor, able to detect both cations and anions. The sensors are synthesized by copper-mediated approaches with 1) azides and alkynes in the copper (I)-catalyzed azide-alkyne cycloaddition (CuAAC), a “click” reaction, or 2) N-tosylhydrazone and aniline substrates. Ultraviolet-Visible (UV-Vis), Fluorescence, and Nuclear

Magnetic Resonance (NMR) Spectroscopy are used to investigate the selectivity and specificity of the sensors with their respective analytes.

INDEX WORDS: 1,2,3-Triazole, Chemosensor, Copper (II), Fluoride, Cations, Anions

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RICHARD GOVAN

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RICHARD GOVAN

Major Professor:	Karelle Aiken
Committee:	Shainaz Landge
	Weihua Ming

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CHAPTER 1

INTRODUCTION

Anions and cations are unquestionably of fundamental importance to environmental and physiological processes. The regulation of these ions is often a topic of concern since an imbalance in concentration of any ion can have devastating effects on a system. While an ion may be essential in certain situations, the same ion can be considered xenobiotic, or even an indicator of damaging conditions under different circumstances.[1]

For instance, sodium,[2] potassium,[3] and magnesium[4] play key roles in the central nervous system but irregularities in these ion concentrations are implicated in heart diseases[5] and bone disorders.[6] A number of heavy metals such as magnesium[7, 8] and copper[9] serve as co-factors for many enzymes, though acute and chronic overexposure to heavy metals has been linked to multiple cancers and disease conditions. For example overexposure of copper, especially in people with Wilson's Disease, leads to the aggregation of copper in the liver, kidney, and brain.[10] Moreover, excessive exposure to many ions induces oxidative stress and apoptosis leading to a number of harmful conditions in organisms.[11] The therapeutic agents used to treat disease conditions related to anion and heavy metal cation imbalances are often expensive.[12] The ability to detect and quantify these ions in a timely manner could alternatively offer preventative measures eliminating the need for costly treatments.

For detection purposes, scientists can employ the use of chemosensors. These molecules are designed to produce a measurable response, for example optical or electrochemical signals, in the presence of a targeted analyte (Figure 1).[13, 14] In many cases the receptor is covalently bonded to the signaling sub-unit and in the design of the probe, the response can made reversible.[15] The signals allow scientists to identify and quantify the sensor's selectivity and specificity for the target

species.[16] The nature of this analyte is determined by the structural make-up of the probes, whether it be supra-[17] or small molecule sensing.[18] Our current studies focus on small molecular sensors involving the use of the 1,2,3-triazole scaffold.

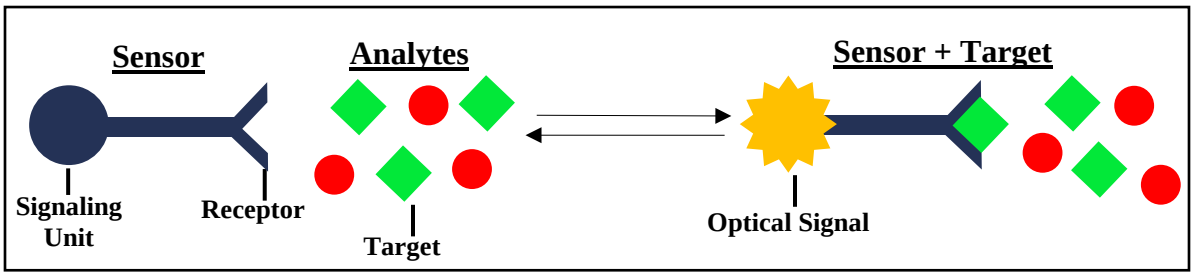


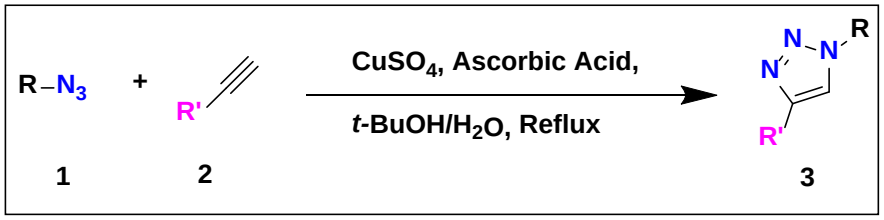
Figure 1. General schematic of a reversible mechanism for a chemosensor's detection of a targeted analyte.

Synthetic Approach Towards 1,2,3-Triazoles

Unfortunately, the seemingly simplistic approach of an analyte binding to a receptor is typically complicated with difficult and expensive synthetic procedures to create the probes. However, various investigations have synthesized triazole molecules using "Click Chemistry",[19-21] azide-free,[22] and metal-free approaches.[23-27] These methodologies can provide relatively quick synthetic access to the triazole-based sensors.

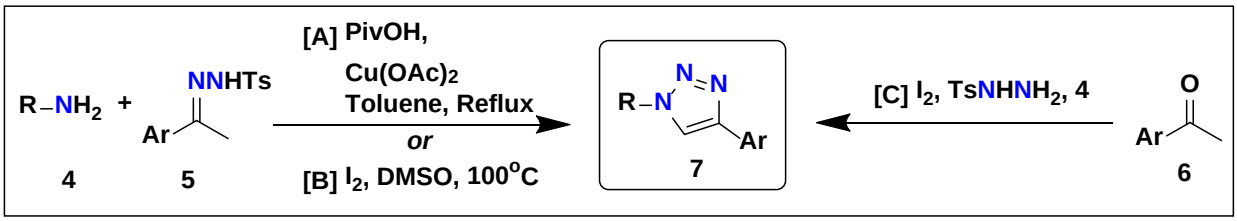
The most popular method is the "Click Chemistry" approach. Click chemistry describes a group of reactions with high yields, good atom-economy and easy purifications.[28] Of all Click reactions, the copper catalyzed azide-alkyne cycloaddition (CuAAC) is most extensively used (Scheme 1).[29] The CuAAC method was developed by Fokin, Sharpless, and Meldal and it is a copper-mediated version of another reaction, the Azide-alkyne Huisgen Cycloaddition.[30] In CuAAc, the azide precursor **1** is "clicked" with the acetylene **2** using Cu (I) catalyst. The result is a 1,4-disubstituted 1,2,3-triazole **3**. The Cu (I) catalyst can be generated in situ from the reaction of a Cu (II) salt with a reducing agent like sodium ascorbate. The CuAAC reaction has high

functional group compatibility and is not considerably affected by the electronic or steric properties of the groups on the alkynes and azides. This reaction is also regiospecific as it only produces the 1,4-disubstituted triazoles. The chemistry can be performed at low temperatures and most products are easily purified by recrystallization. It should be noted that the Azide-alkyne Huisgen Cycloaddition requires high temperatures and produces both 1,4 and 1,5-disubstituted triazole regioisomers. Indeed, the CuAAC is one of the best click reactions to date.



Scheme 1. General mechanism of 1,2,3-triazoles *via* Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC).[31]

In separate reports, Zhang and colleagues have described azide-free approaches with,[32] and without copper catalysts.[22] The former involves the coupling of an aniline **4** and a N-tosylhydrazone precursor **5**. The metal-free approach is iodine-mediated. This procedure uses the anilines **4**, ketones **6**, and N-tosylhydrazone **5** to form the 1,4-disubstituted 1,2,3-triazoles **7**. These reactions are also regiospecific and only produce 1,4-disubstituted products.



Scheme 2. Zhang's azide-free approaches to 1,2,3-triazoles.[22, 32]

In our investigations we have used two approaches for the synthesis of the chemosensors, the CuAAC (Scheme 1) and Zhang's copper-catalyzed azide-free procedure (Scheme 2).

Triazoles in Sensing

The unique photophysical and structural properties of the triazole have attracted much attention in the area of organic sensors.[33] These units enable scientists to design small molecular sensors for a number of applications. The versatility of the triazole unit has led to sensing in environmental toxicology,[34] materials science,[35] medical imaging,[36] and pharmaceuticals.[37-39]

In sensors, the triazole scaffolds can serve as a part of the receptor, a signaling unit, or as a ligature, linking the binding site to the reporter.[33] As a receptor in ion-sensing, triazoles can bind both cations and anions (Figure 2). With cations, the heterocycle is a nitrogen-donor, *i. e.*, chelation occurs via lone pairs on one of the π-bonded nitrogen atoms.[40, 41] For anions, triazoles are H-bond donors on which binding occurs *via* the partially positive C_{sp}^2-H site (Figure 2).[18, 35, 42, 43] As a part of the signaling unit, these molecules can be tuned for fluorescence or intense color changes by making modifications in their structures, for example adding moieties that serve to extend conjugation and/or varying the functional group appendages.[44]

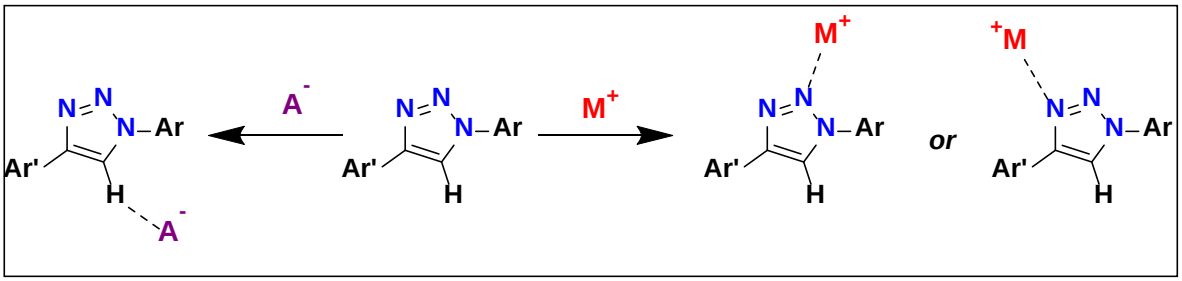
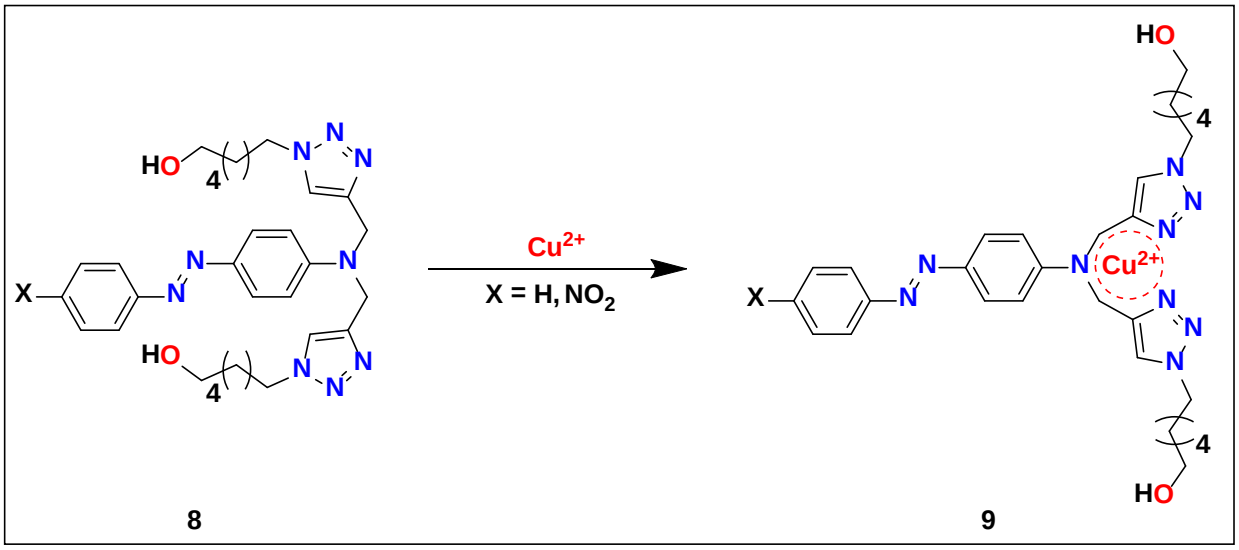


Figure 2. General Schematic of the binding sites for anions (**A**$^-$) and heavy metal cations (**M**$^+$) with 1,2,3-triazoles

Examples of Triazoles in Sensing

The multifunctionalilty of the triazole unit for sensing is quite advantageous. For instance, the bis-triazole-appended azobenzene, compound **8**, designed and synthesized by the Kannan Group is a chromophore that is selective for Cu^{2+} in acetonitrile/water solution (Scheme 3).[45] The

triazoles serve as parts of the receptor and rotate to facilitate chelation to the Cu^{2+}, depicted by compound **9**. Upon binding, the color shifts from bright red-orange to yellow. The Erdemir Group has developed a "turn-on" fluorescent triazole sensor **10** (Figure 3).[40] Sensor **10**, a 1,2,4-triazole, is shown to be selective of F^- in acetonitrile, binding the fluorine anion through OH^- group. Sensor **10** also has an affinity for Al^{3+} in an acetonitrile-water solution through the complexation with the OH^-, hydrazide, and triazole groups.



Scheme 3. Proposed binding schematic of **8** with Cu^{2+} (**9**). Compound **9** depicts the rotation of the triazole motif to facilitate binding of Cu^{2+}. X=H, NO_2.[45]

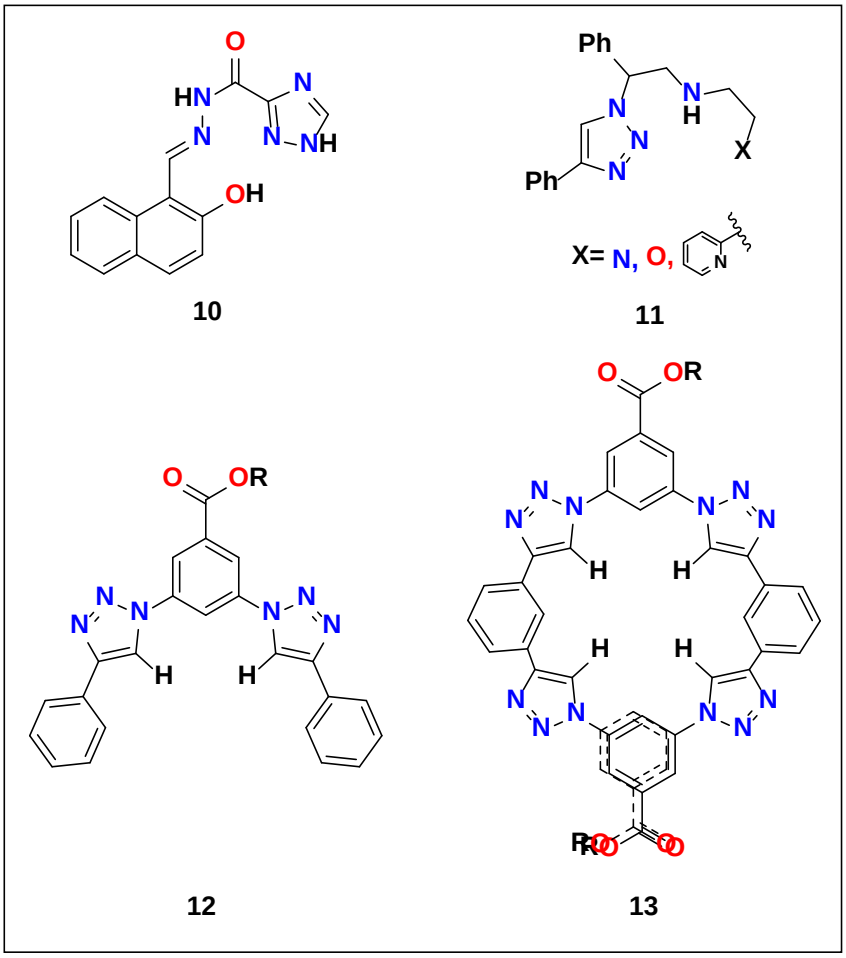


Figure 3. Examples of triazole-based compounds as seen throughout the literature.[40, 46, 47]

Franc Požgan and colleagues have prepared 1,2,3-triazole based sensors **11** able to chelate both Zn^{2+} and Ni^{2+}.[46] Metal complexation between the cations and sensor **11** can involve the use of both triazole and 2-pyridyl groups. Hemraj Juwarker and coworkers synthesized a class of short aryl triazoles, **12** and **13,** with a high affinity for various anions (Figure 3).[47] The aryl triazole oligomer **13** has an exceptionally high specificity for Cl^- binding that anion via the $C_{sp}{}^2$-H atoms of the triazole units.

The literature clearly shows that the cavity size as well as the moieties attached to the 1,2,3-triazole scaffold play a significant role in role in sensing. These properties determine the chemosensors' specificity, selectivity, and signaling response when detecting analytes.

Prior Results

In previous work, our lab has reported studies on the fluorophore 2-(4-phenyl-1,2,3-triazol-1-yl) phenol, **PTP**, (**14**)[34] and chromophore 2,2-bis((1-(2-hydroxyphenyl)-1,2,3-triazol-4-yl)methyl)-5,5-dimethylcyclohexane-1,3-dione, **BPT**, (**15**).[48] Once synthesized, sensors **14** and **15** were screened against various cations and anions to examine the sensors' selectivity and signaling response to the analytes.

Sensor **14** has a strong affinity for the F^- anion. UV-Vis Absorbance, Fluorescence, and NMR titration studies were used to quantify the selectivity and specificity for F^- and to decipher the specific properties of **PTP**. The binding pocket of **PTP** for the anion consists of the proton of the OH group and the C_{sp}^2-H on the triazole ring (Figure 4). It was discovered that the OH group of **PTP** is initially located near the triazole nitrogens. When the F^- anion is introduced to the system the phenol group rotates around the nitrogen-phenol bond, allowing **PTP** to bind the anion in a 1:1 ratio, **PTP** to fluoride. A prominent, blue, turn-on fluorescence indicates the detection of F^- anion even at submolar concentrations.

Sensor **15**, **BPT**, showed promise for the detection of the Cu^{2+}. Sensor **15,** unlike **14,** displayed a colorimetric response, clear to yellow, upon the addition of the cation. The change in color and increased absorption in UV-Vis spectroscopy were observed. NMR titration and computational studies were employed to determine how the cations chelated with **BPT**. Job's and Benesi-Hildebrand plots indicate a 2:1 binding complex of **15** with Cu^{2+} (Figure 4). The

colorimetric signal seen in **BPT** binding to Cu^{2+} is subtle though visible. Current efforts are focused on the design of analogues that can provide a more pronounced colorimetric response.

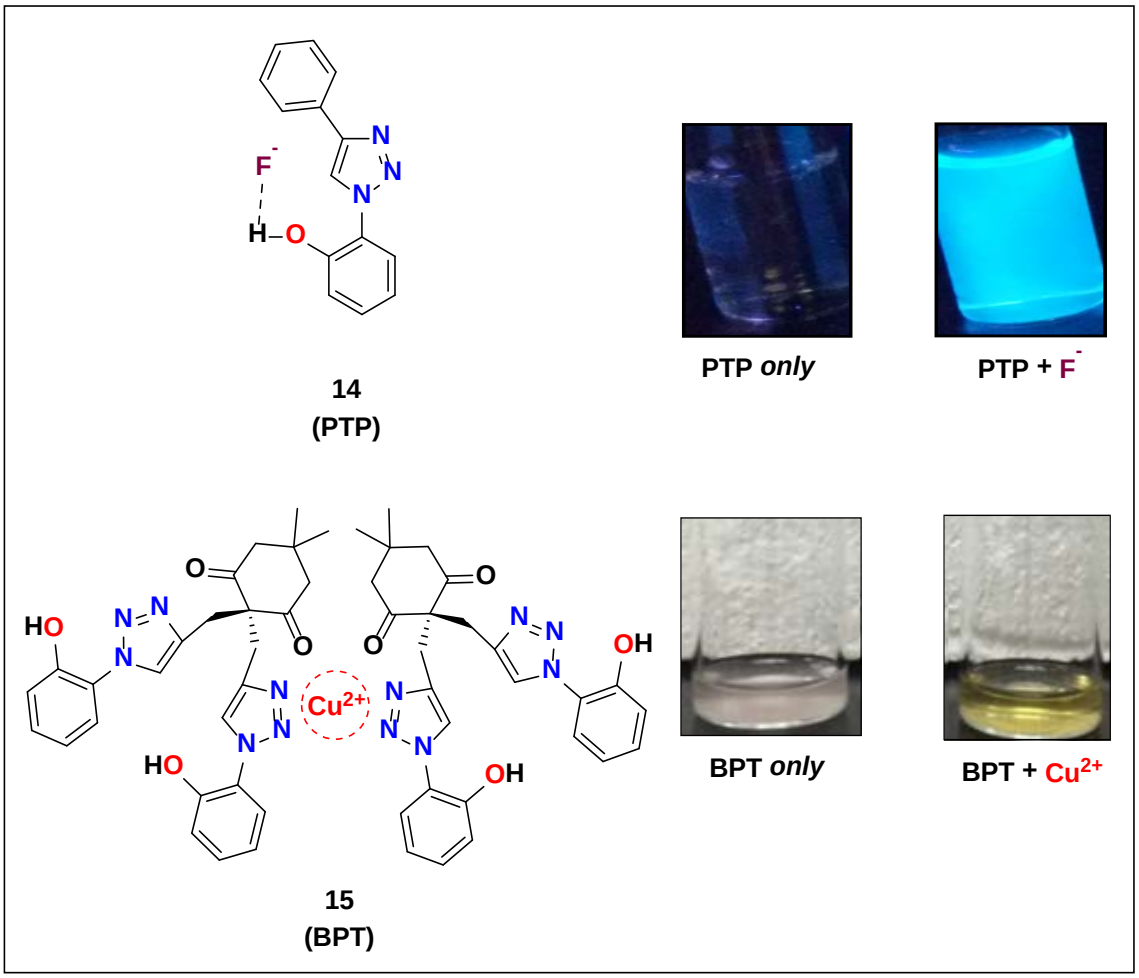


Figure 4. Proposed binding for **PTP** with fluorine (F^-) and **BPT** with copper (Cu^{2+}). Images of solutions of **PTP** and **BPT** with and without ion under UV-light and ambient light, respectively. [34, 48]

The ongoing study is directed toward the synthesis of more extensively conjugated and functionalized triazole probes, effectively improving on the design of **14** and **15**. Increased conjugation in the sensor should allow for more intense signals and greater possibility for responses in the visible light realm. Varying the functional group will tune the sensor for ion specificity, and potentially contribute to intensifying the signal as well (Figure 5). Nuclear

Magnetic Resonance Spectroscopy (NMR), and Infrared Spectroscopy are used to confirm the sensors' structures. Investigations with UV-Vis absorption, fluorescence, and NMR spectroscopy, are employed to understand the selectivity and binding mechanism of the triazole chemosensors with their analytes.

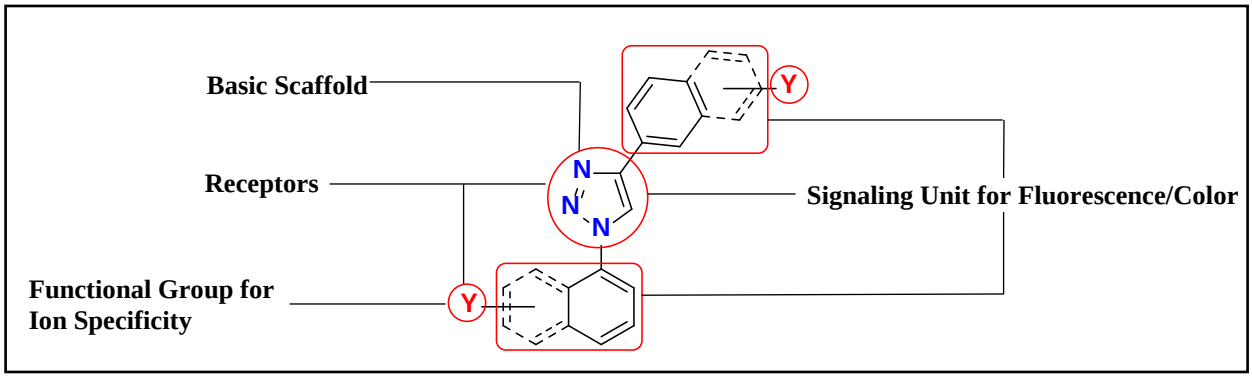


Figure 5. General structure of the 1,2,3-Triazole motif displaying extended conjugations for signal tuning and functionalization for ion specificity.

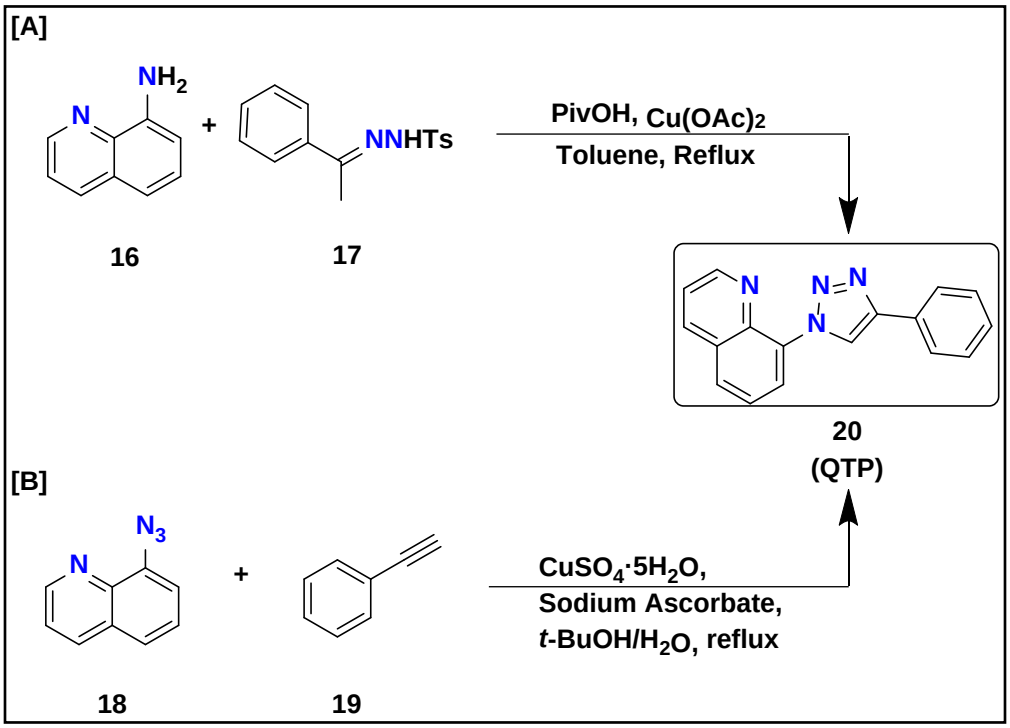
CHAPTER 2

RESULTS AND DISCUSSION

Copper (II) Sensor: 8-(4-Phenyl-1,2,3-Triazol-yl)Quinoline [QTP]

Herein, we report the synthesis of the copper (II) 1,2,3-triazole based sensor 8-(4-phenyl-1*H*-1,2,3-triazol-*yl*)quinoline (**QTP**), a known compound (Scheme 4). The concept for synthesizing this molecule targeted cation detection but with a more prominent response than the "clear to yellow" color change of **BPT** (Figure 4). To achieve this, the design of the probe focused on incorporating more extensive conjugation throughout the molecule. In contrast to **BPT**, **QTP**s conjugated system spans the entire structure. The molecule has as bicyclic quinoline appendage and a donor group for binding at that ring's nitrogen. The conjugation in **BPT** only occurs across the phenol and the triazole scaffolds (Figure 4).

Initial attempts to make this molecule using the CuAAC procedure resulted in a 27% yield (Scheme 4). A more efficient approach was achieved with Zhang's method, the copper-mediated coupling of 8-aminoquinoline and acetophenone *N*-tosylhydrazone (Scheme 4).[32] With Zhang's procedure, the chemosensor was obtained in 62 % yield in our studies.



Scheme 4. Synthesis of probe 8-(4-phenyl-1*H*-1,2,3-triazol-*yl*)quinoline (**QTP**) using the copper-mediated aniline and N-tosylhydrazone coupling approach [A] and the CuAAC approach [B].

Treatment of **QTP** with various metal ions (Fe^{3+}, Fe^{2+}, Cu^{2+}, Ag^{+}, Cr^{3+}, Al^{3+}, Co^{2+}, Ni^{2+}, Cd^{2+}, Mg^{2+}, Li^{+}) revealed a selectivity for the copper (II) ion. Nuclear Magnetic Resonance (NMR) Spectroscopy, UV-Vis absorption, and fluorescence spectroscopy were used to quantify the response of the probe to the cation and to decipher its binding mode. Overall, our results suggest coordination between Cu^{2+} and the **QTP**'s triazole and quinoline nitrogens in a stoichiometric ratio of 1 : 1, sensor : metal.

The Response of QTP to Metal Perchlorate Salts under Visible and Ultraviolet Light

Screening studies under UV (365 nm) and ambient light were carried out in acetonitrile with the metal perchlorate salts at a molar ratio of 1: 10, **QTP**: salt. Upon illumination with the UV lamp, the probe fluoresces bright blue in acetonitrile (Figure 6). Changes in this fluorescence

were only observed with the addition of Cu^{2+}, Al^{3+}, Fe^{2+}, and Fe^{3+}. Varying degrees of green were obtained with Fe^{3+} and Al^{3+}. A complete "turn-off" response was induced by Cu^{2+} while Fe^{2+} only generated a slight reduction in the intensity. Visible changes in the **QTP**-acetonitrile solution were not observed under ambient light with any of the perchlorates.

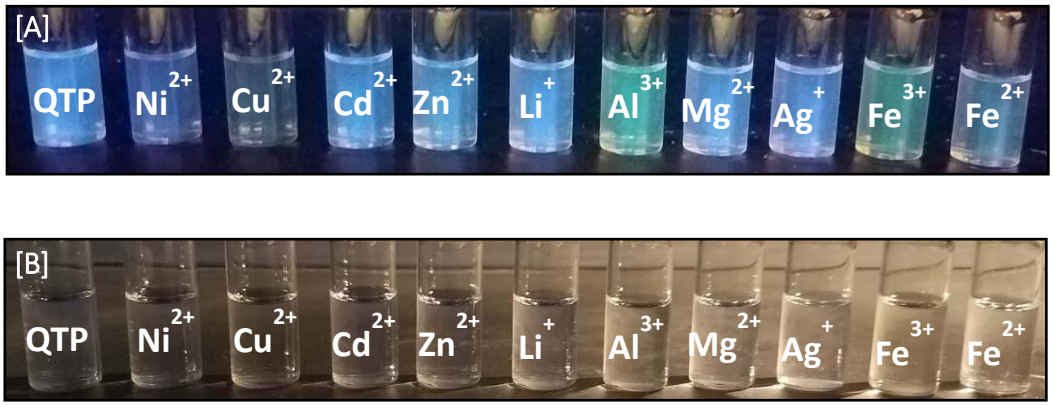


Figure 6. Response of **QTP** (2.94×10^{-4} mol dm^{-3}) treated with metal perchlorate salts (~2×10^{-3} mol dm^{-3}) in acetonitrile under (a) ultraviolet (365 nm) and (b) ambient light.

Investigations with Fluorescence Spectroscopy

QTP's response to the metal salts was examined with fluorescence spectroscopy. The maximum fluorescence of the probe occurred at 411 nm for excitation at 294 nm (Figure 7). In this experiment, 65 a.u. was the highest intensity value for **QTP**. When treated with 10 equivalents of perchlorates, the Cu^{2+} and Fe^{2+} salts reduced the intensity (Figure 8). In line with our observations under UV-light (Figure 6), this spectroscopic change was far more distinct with Cu^{2+} (Figure 8). Cu^{2+} caused a reduction by about four-fold, 63 a.u. to 15 a.u., while Fe^{2+} only reduced the value to 55 a.u. For the other ions, the addition of Al^{3+} or Fe^{3+} induced a bathochromic shift, 411 nm to 477 nm for both salts with an intensity of 25 a.u. for Al^{3+} and 16 a.u. for Fe^{3+}. The remaining salts (Ni^{2+}, Cd^{2+}, Zn^{2+}, Mg^{2+}, Li^{+}, and Ag^{+}) enhanced the fluorescence at 411 nm by different orders of magnitude (Figure 8).

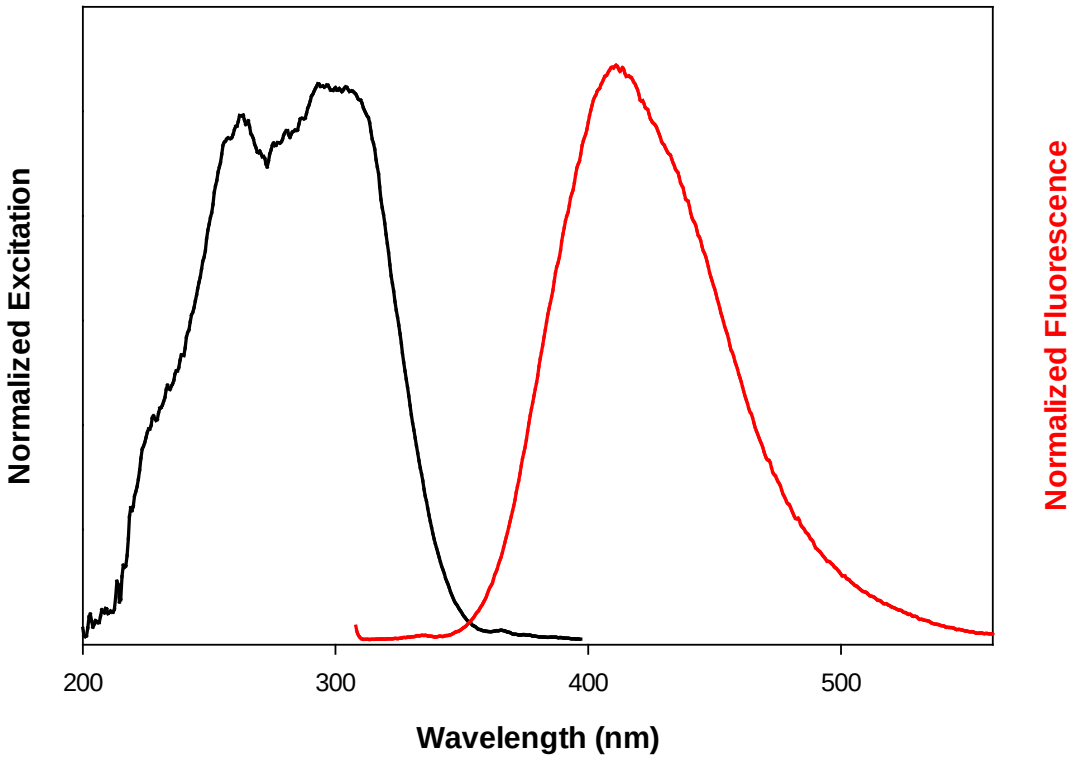


Figure 7. Normalized emission and fluorescence excitation spectra of QTP (2.94×10^{-4} mol dm^{-3}) in acetonitrile (for emission spectrum the excitation wavelength is 294 nm and for the excitation spectrum the monitored emission wavelength is 411 nm).

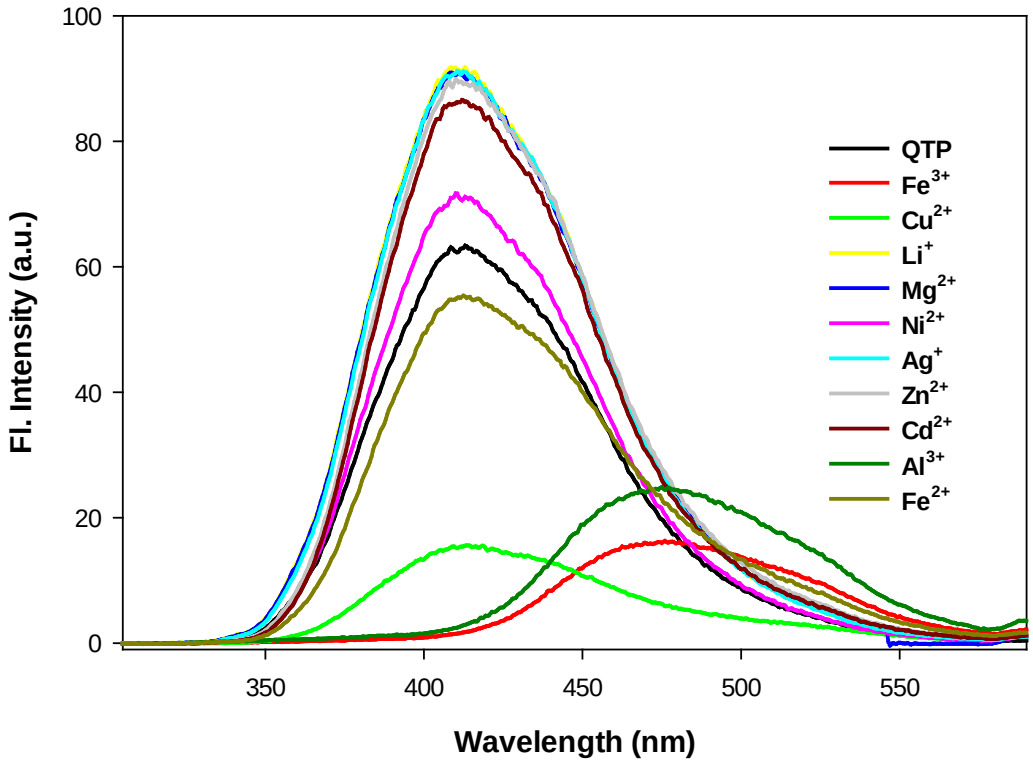


Figure 8. Fluorescence spectra of **QTP** sensor (2.94×10^{-4} mol dm^{-3}) treated with perchlorate salts (~3×10^{-3} mol dm^{-3}) in acetonitrile. *Exc*. at 294 nm.

A fluorescence titration study was performed to determine the binding stoichiometry between Cu^{2+} and **QTP** (Figure 9). Changes in the fluorescence at 411 nm were monitored while varying the equivalents of the perchlorates relative to the sensor. For the Job's plot, the product of difference in fluorescence intensity (ΔF) and the mole fraction (X), ΔF·X, was plotted against X (Figure 10) where:

- $\Delta F = F_x - F_0$ for F_0: initial intensity of **QTP** and F_x: final intensity
- $X = \frac{[\mathbf{QTP}]}{[\mathbf{QTP}]+[Cu^{2+}]}$ for $[Cu^{2+}]$: molar concentration of Cu^{2+} and [**QTP**]: molar concentration of **QTP**

A non-linear curve fit parameter went through a maximum $\Delta F \cdot X$ at X = 0.51. This indicated a 1:1 ratio for **QTP** : Cu^{2+}.

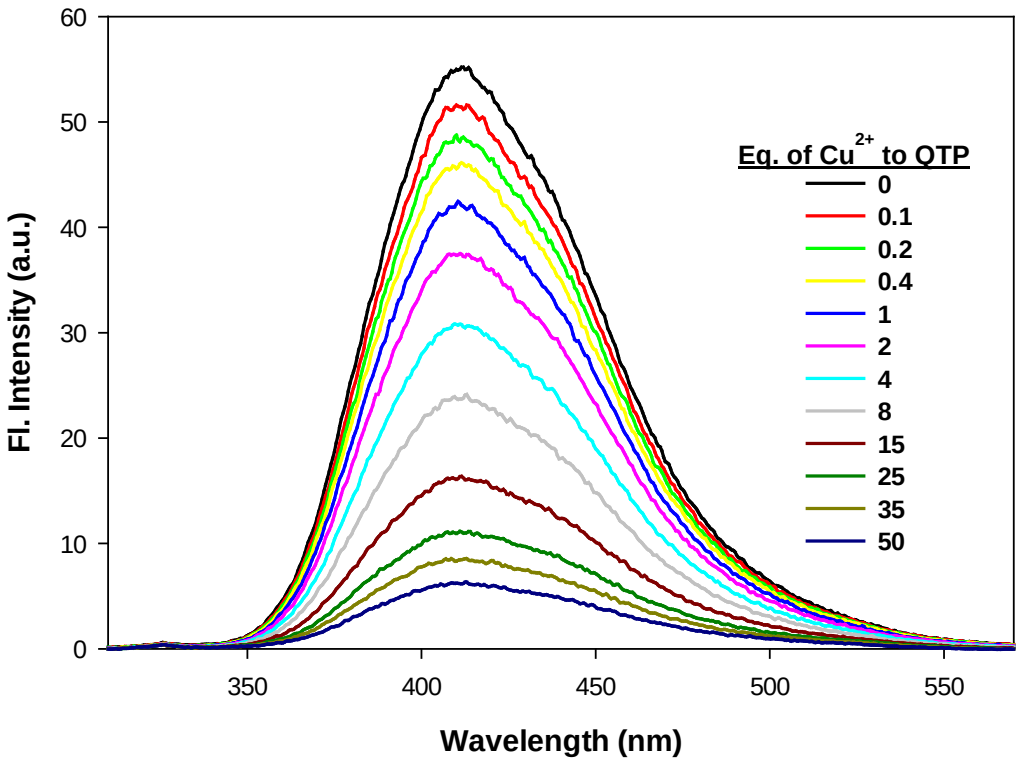


Figure 9. Fluorescence titration of **QTP** sensor (2.95×10^{-4} mol dm^{-3}) with the addition of Copper perchlorate hexahydrate (3.70×10^{-2} mol dm^{-3}) in acetonitrile. *Exc*. at 294 nm.

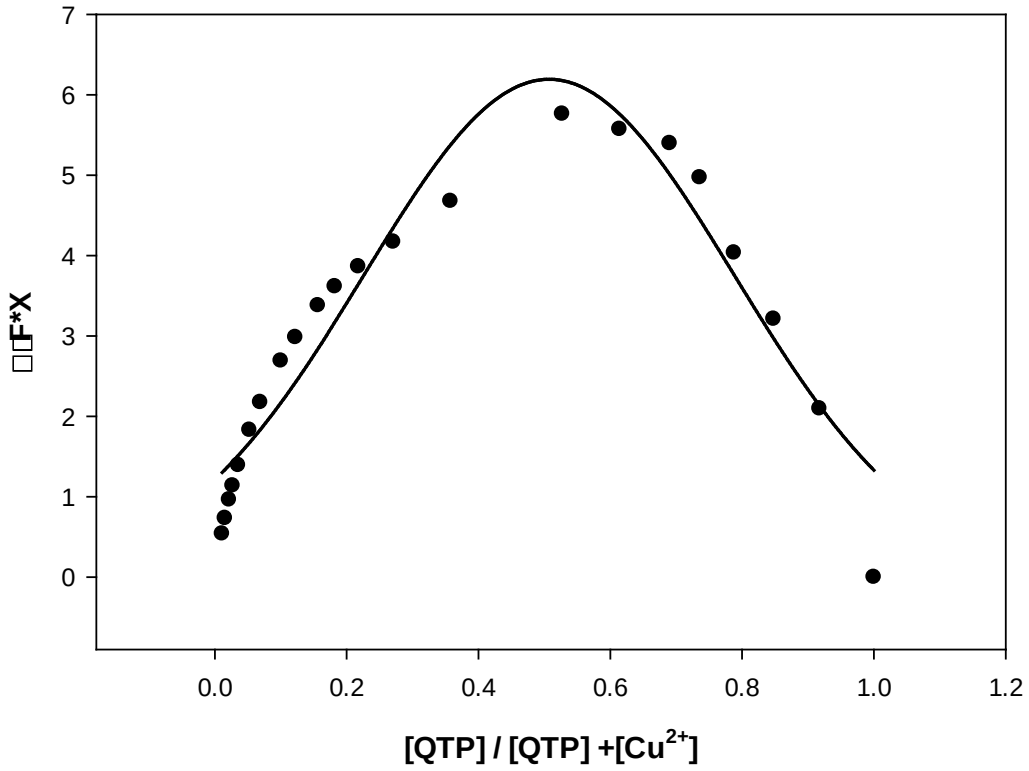


Figure 10. Job's plot of **QTP** with Cu (II) perchlorate salt in acetonitrile, emission monitored at 411 nm. *Exc*. at 294 nm.

Investigations with UV-Vis Absorption Spectroscopy

QTP in acetonitrile has two maxima at 210 nm and 303 nm (Figure 11). A decrease in the absorbance at both 210 nm and 303 nm was observed with Cd^{2+}, Al^{3+}, Co^{2+}, Zn^{2+}, and Fe^{2+} while an enhancement was obtained with Fe^{3+} and Cr^{3+} (Figure 11). It should be noted that the latter results with Fe^{3+} and Cr^{3+} are deemed inconclusive as the absorbance of the salts themselves overwhelm the spectra. Isobestic points were not generated with Cd^{2+}, Al^{3+}, Co^{2+}, Zn^{2+}, and Fe^{2+}. Hence, the UV-Vis absorption studies did not point to the formation of complexes between **QTP** and these ions.

In the presence of Cu^{2+}, the absorbance of **QTP** increases at 210 nm but decreases at 303 nm. An absorbance titration study with **QTP** and Cu^{2+} yielded two isosbestic points at 276 nm and 308 nm (Figure 12). This indicated the formation of new species, a complex between Cu (II) and the probe. Increasing equivalents of copper perchlorate enhances the band at 210 nm. However, at 303 nm, the addition of Cu^{2+} lowers the absorbance and causes a bathochromic shift of about 12 nm.

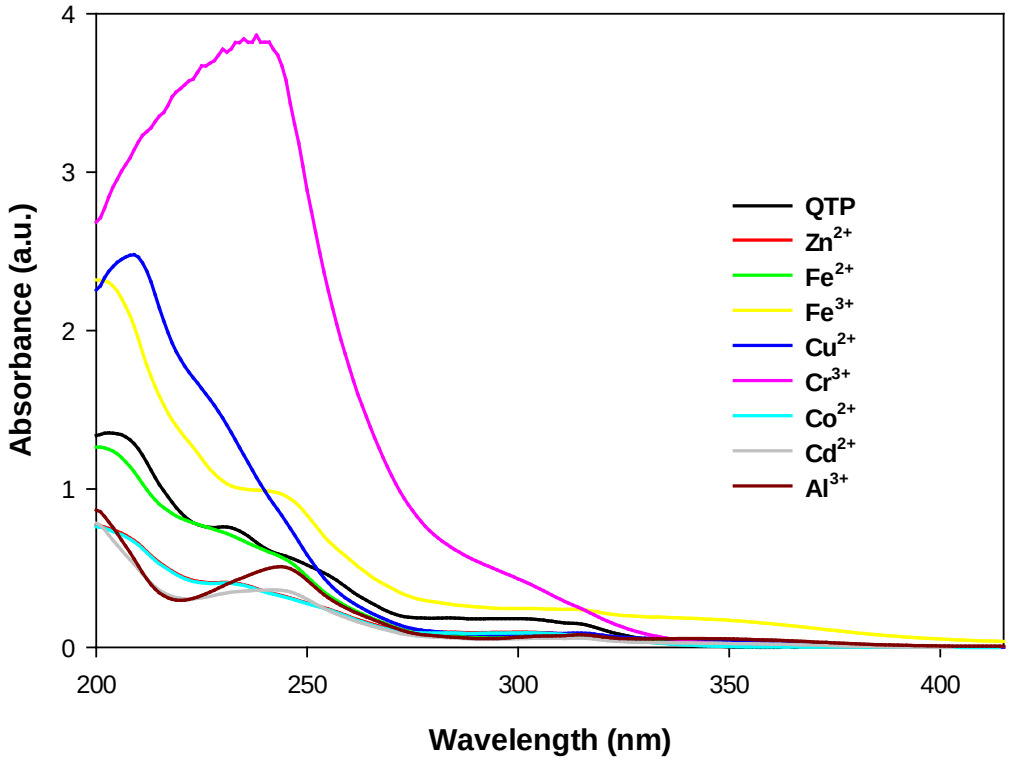


Figure 11. Absorption spectra of **QTP** (2×10^{-5} mol dm^{-3}) with the addition of 3.0×10^{-5} mol dm^{-3} metal perchlorate salts in acetonitrile.

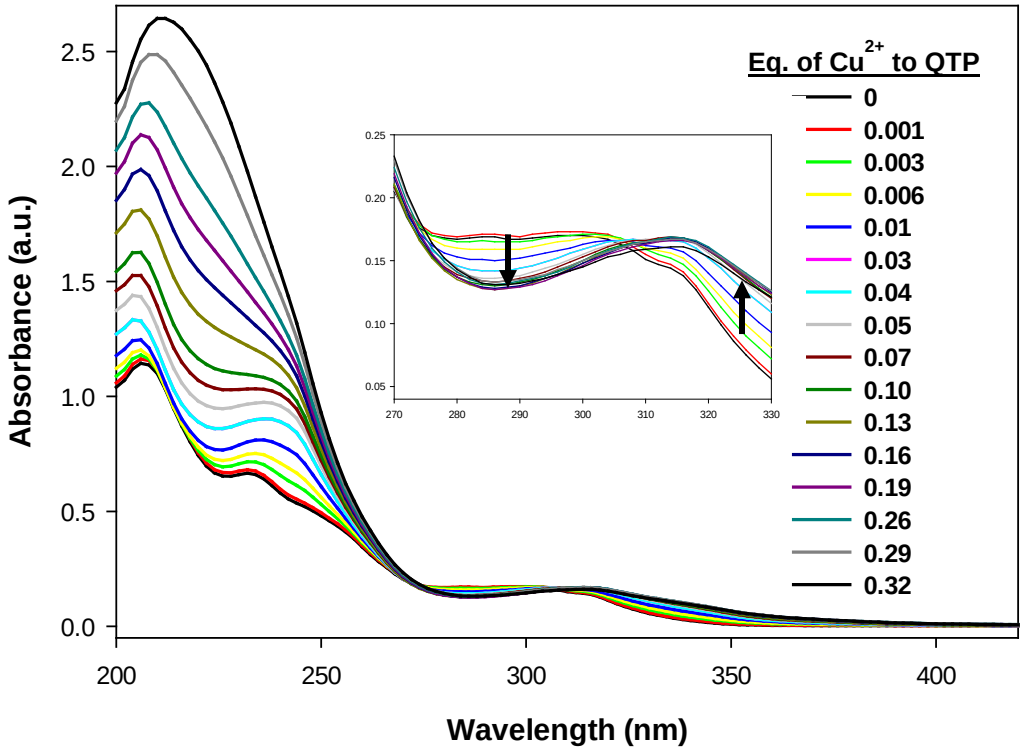


Figure 12. Absorbance spectrum of **QTP** (2×10^{-5} mol dm^{-3}) with the addition (µl) of copper perchlorate salt (2.67×10^{-5} mol dm^{-3}) in acetonitrile.

Investigations with NMR Spectroscopy

^{1}H-NMR experiments were performed to further understand the binding mechanism of **QTP** with copper (II) and its interaction with other cations (Fe^{3+}, Fe^{2+}, Cr^{3+}, Al^{3+}, Co^{2+}, Ni^{2+}, Cd^{2+}) (Figure 13). Results with Al^{3+} and Zn^{2+} indicated that there is some coordination between these ions and the probe's triazole and quinoline units. In the presence of Zn^{2+} there is an upfield shift of the triazole proton H-7 and a downfield shift for H-1 on the quinoline unit. With Al^{3+}, all of the proton signals move downfield except the triazole's H-7 and the phenyl group's H-9 and H-10. The signal for H-7 occurs at a lower chemical shift while those for H-9 and H-10 remain unchanged. The proton resonances for **QTP** are unaffected by the addition of Cd^{2+}. The spectra with Cu^{2+}, Fe^{2+}, and Fe^{3+} showed a broadening of the signals due to the paramagnetic properties

of these cations. As a result, the interaction between Cu^{2+}, Fe^{2+}, and Fe^{3+} and the probe could not be determined in this experiment.

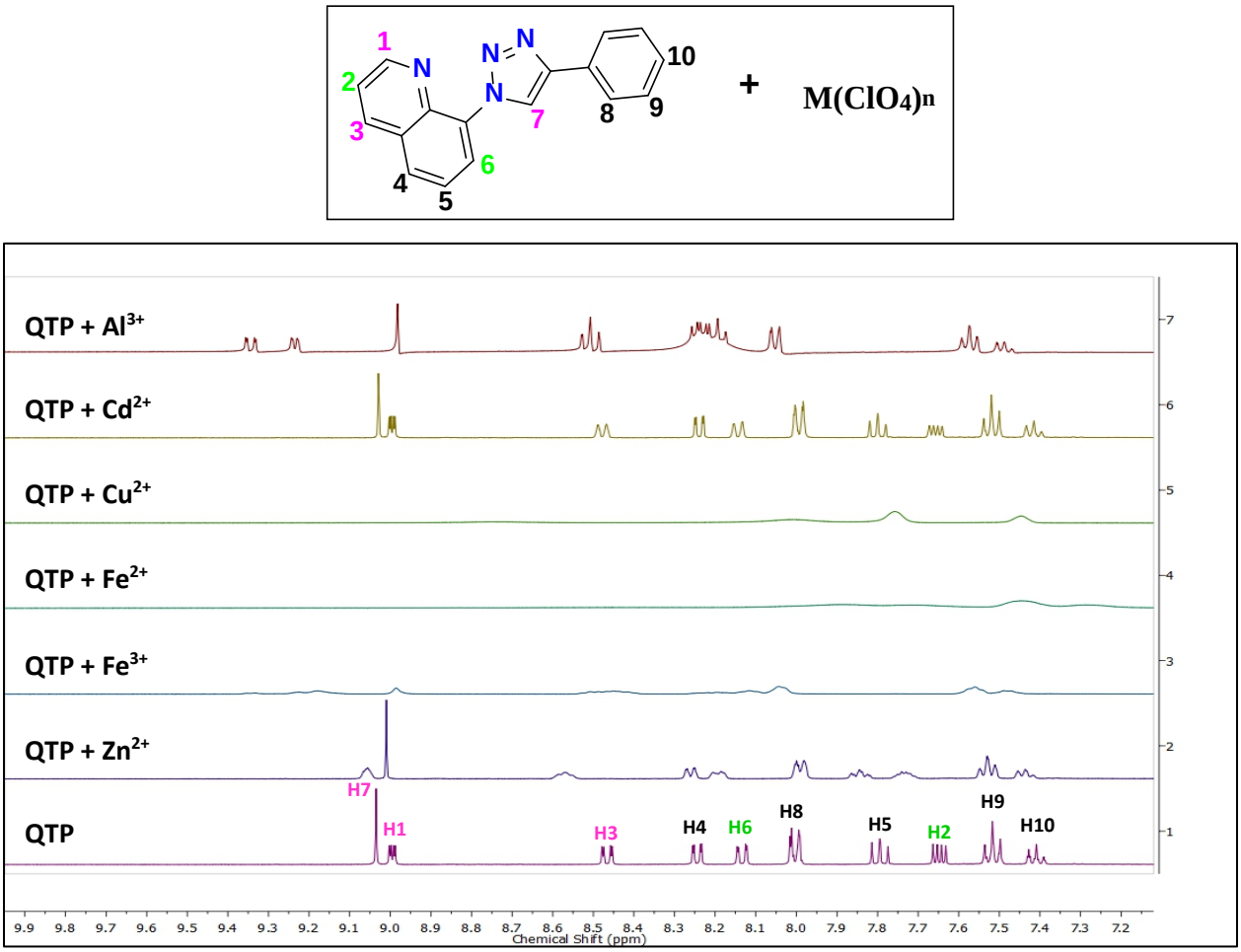


Figure 13. Changes in the ^{1}H-NMR spectra **QTP** (1.47×10^{-2} mol dm^{-3}) with equivalent additions of metal perchlorate salts in acetonitrile.

In the ^{1}H-NMR titration of **QTP** with Cu^{2+}, increasing the amount of Cu^{2+} resulted in downfield shifts for the triazole's H-7 and the quinoline's H-1 and H-3 (Figure 14). The maximum observable change occurred with H-3, a difference of 0.15 ppm, from 8.45 ppm at 0 eq of Cu (II) to 8.60 ppm with 0.50 eq of Cu (II). The deshielding effect on H-1, H-3 and H-7 suggests that both the triazole and quinoline nitrogen's are directly involved in binding Cu^{2+}. This hypothesis is further substantiated by the severe broadening and subsequent disappearance of signals for protons

that are in close proximity to the proposed binding pocket: H-2 and H-6 at 0.15 eq of Cu (II), and H-1 at 0.10 eq of Cu (II). Not much could be discerned at 0.75eq and beyond. However, the information obtained at lower equivalents suggests the existence of a probe-metal complex similar to the structure shown in Figure 14.

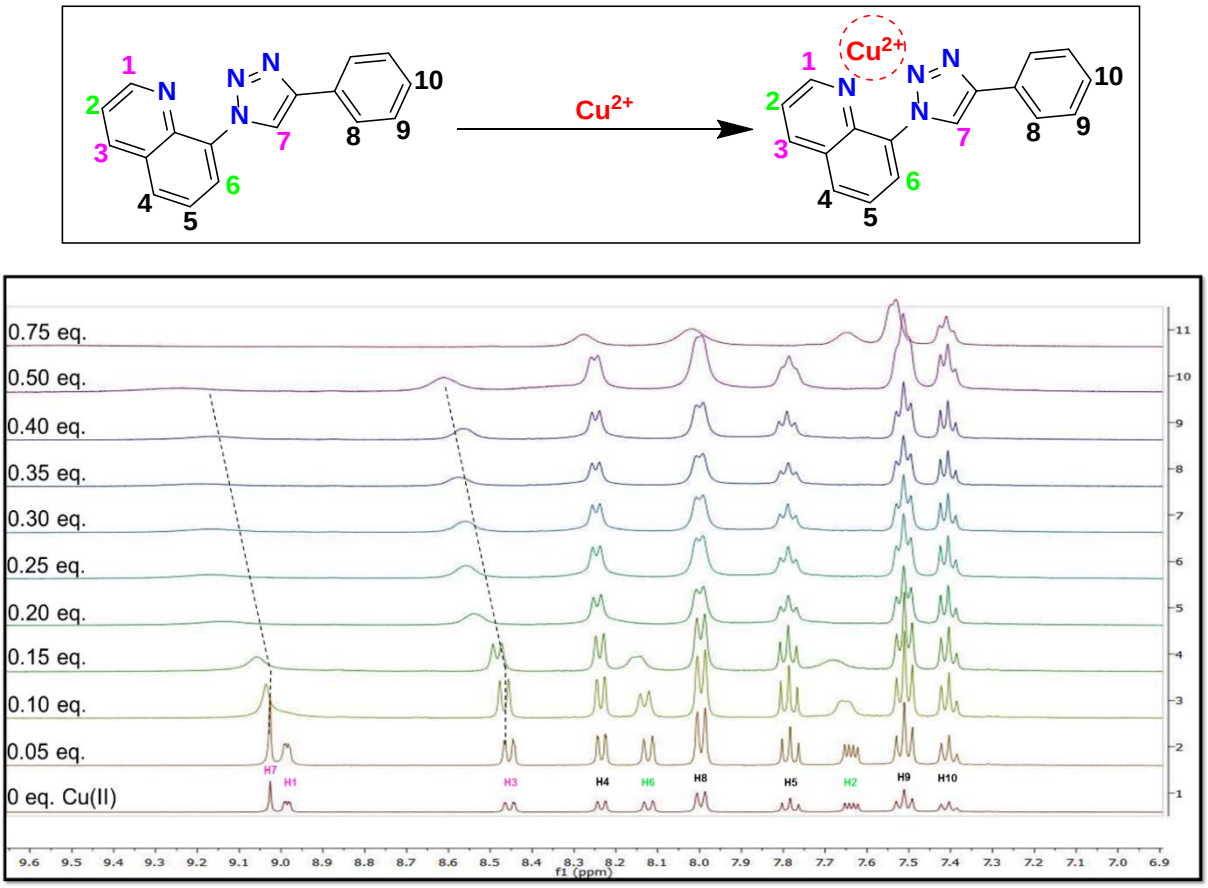


Figure 14. Changes in partial ^{1}H-NMR spectra of **QTP** sensor (3.68×10^{-2} mol dm^{-3}) upon increasing equivalents of Cu (II) perchlorate salt in acetonitrile.

Conclusion and Future Direction for QTP

QTP was found to produce a "turn off" response in the presence of copper (II). NMR studies confirmed that the binding interaction between the probe and the copper (II) cation occurs inside the cavity located between the triazole and quinoline nitrogens. UV-absorption studies

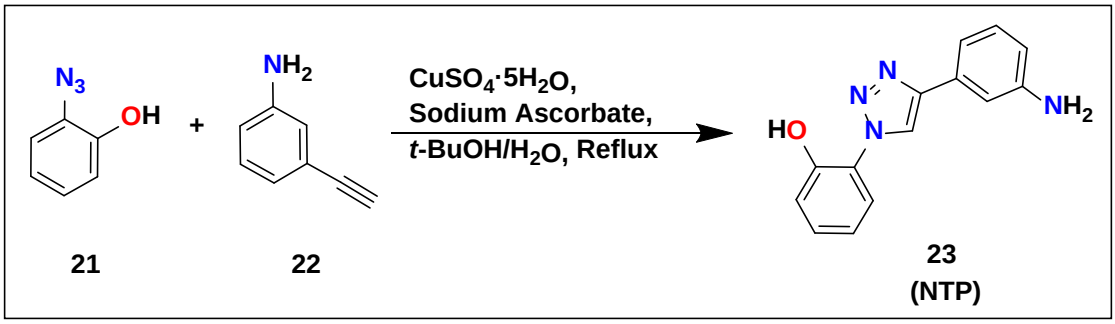
revealed the development of a new species through the formation of isosbestic points, a metal-ligand complex between Cu^{2+} and the chemosensor. Fluorescence titration studies confirm a 1:1 stoichiometric binding ratio. To confirm a specificity for Cu (II), the probe **QTP** will be investigated using interference studies with other cations (Fe^{3+}, Fe^{2+}, Ag^{+}, Cr^{3+}, Al^{3+}, Co^{2+}, Ni^{2+}, Cd^{2+}, Mg^{2+}, and Li^{+}).

Dual Sensor: 2-(4-(3-Aminophenyl)-1,2,3-Triazole-1-yl)Phenol [NTP]

2-(4-(3-Aminophenyl)-1H-1,2,3-triazole-1-yl)phenol (**NTP**) was designed with both cation and anion sensing in mind. The following discussion focuses on initial results for the anion-sensing properties of this chemosensor and preliminary screening with the metal perchlorate salts.

NTP (Scheme 5) is an amino substituted analogue of **PTP**, a fluoride sensor (Figure 4). The incorporation of an electron donating amino group in **NTP** was intended to enhance the sensitivity and signaling response of the sensor. A distinct selectivity for fluoride was obtained by mimicking the binding pocket of **PTP**, i. e., the ortho-placement of the phenol's OH group relative to the triazole unit. The sensor is also sensitive to Cu (II). The binding mode between **NTP** and this cation is currently being studied.

NTP is synthesized from 2-azidophenol and 3-aminophenylacetylene with the copper catalyzed azide-alkyne cycloaddition (CuAAC) (Scheme 5). The molecule was obtained in 74% yield and it is new to the literature.



Scheme 5. Synthesis of 2-(4-(3-aminophenyl)-1H-1,2,3-triazole-1-yl)phenol (NTP).

Screening was performed with tetrabutylammonium salts (Br^-, Cl^-, $H_2PO_4^-$, OAc^-, F^-, BF_4^- and ClO_4^-) and the perchlorates of metal cations (Fe^{3+}, Fe^{2+}, Cu^{2+}, Cr^{3+}, Al^{3+}, and Cd^{2+}). For the anions, UV-Vis absorbance and fluorescence spectroscopy were used to investigate the mode of binding and the affinity of the anions for **NTP**. Thus far, preliminary results show that the sensor responds to $H_2PO_4^-$, OAc^- and F^-. However, the signal induced by F^- is the most intense. Under UV-light, it is a bright blue fluorescence. In the case of the cations, the sensor displays a selectivity and sensitivity for copper (II) with a clear to purple colorimetric response.

The Response of NTP to Tetrabutylammonium Salts under Visible and Ultraviolet Light

NTP in acetonitrile faintly fluoresces when illuminated with a 365 nm lamp (Figure 15). Treatment with tetrabutylammonium salts in a 1:1 molar ratio, **NTP** to salt, reveals that the fluorescence is intensified by $H_2PO_4^-$, OAc^-, and F^- (Figure 15). The fluoride anion gives the most

pronounced response. All others, Br^-, Cl^-, BF_4^- and ClO_4^-, do not have an effect on the sensor. In addition, changes cannot be detected under visible light with any of the anions.

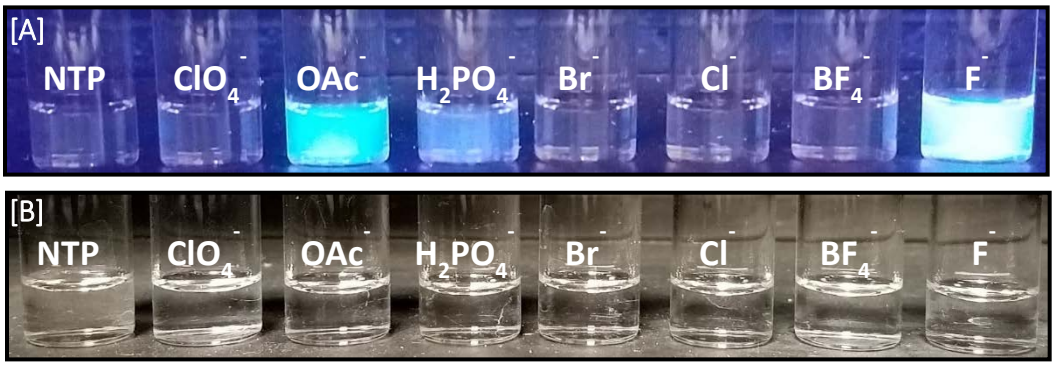


Figure 15. Response of NTP (1.98×10^{-3} mol dm^{-3}) treated with equivalent amounts of tetrabutylammonium salts in acetonitrile under (a) ultraviolet (365 nm) and (b) ambient light.

Investigations with Fluorescence Spectroscopy

The results for the fluorescence studies are consistent with observations from the screening study under UV-light (Figure 15). Excitation of **NTP** at 298 nm produces the maximum fluorescence intensity at 471 nm (Figure 16). The addition of $H_2PO_4^-$, OAc^-, or F^- causes a shift of 46 nm to a new maximum at 425 nm. The intensity of the fluorescent was also enhanced six-fold by $H_2PO_4^-$, ten-fold by OAc^- and twelve-fold by F^-. Spectroscopic data shows that **NTP**'s fluorescence was somewhat diminished by Br^-, Cl^-, BF_4^-, and ClO_4^-. However, in comparison to $H_2PO_4^-$, OAc^-, and F^-, the effects of the other salts on **NTP**'s emission were inconsequential.

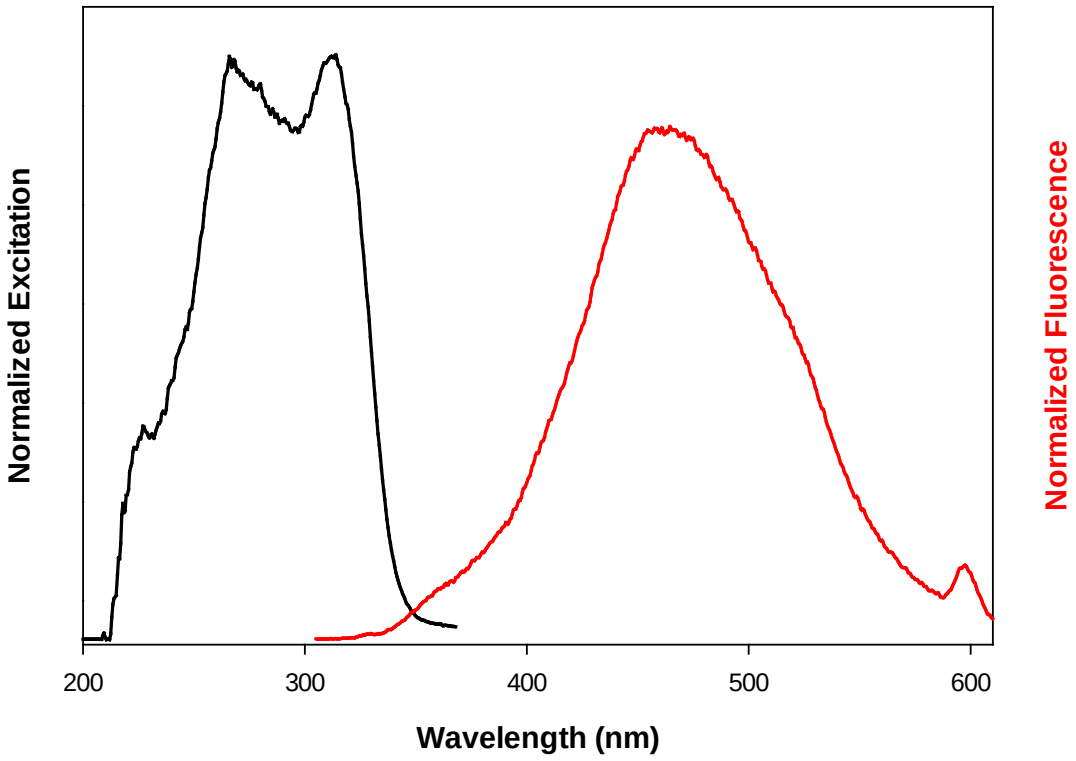


Figure 16. Normalized emission and fluorescence excitation spectra of NTP (1.98×10^{-4} mol dm^{-3}) in acetonitrile (for emission spectrum the excitation wavelength is 298 nm and for excitation spectrum the monitoring wavelength is 471 nm of the emission spectrum).

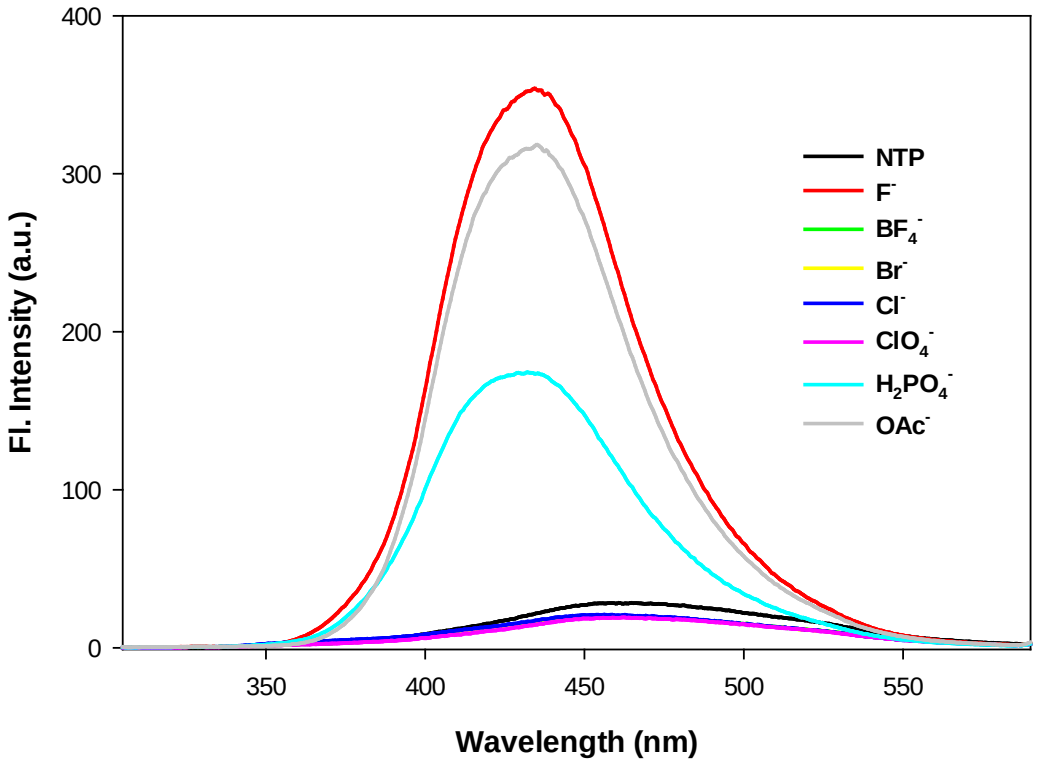


Figure 17. Fluorescence spectra of NTP sensor (1.98×10^{-4} mol dm^{-3}) treated with tetrabutylammonium salts (~2×10^{-4} mol dm^{-3}) in acetonitrile. *Exc*. at 298 nm.

The Response of NTP to Metal Perchlorate Salts under Visible and Ultraviolet Light

The probe **NTP** was treated with metal perchlorate salts (Fe^{3+}, Fe^{2+}, Cu^{2+}, Cr^{3+}, Al^{3+}, and Cd^{2+}) in acetonitrile in a 1 : 1 ratio, **NTP** to salt (Figure 18). In the presence of Cu (II), **NTP** produces a clear to purple colorimetric response after approximately one hour. There is an immediate clear to pale brown color response when **NTP** is treated with Cu^{2+}, Fe^{3+}, Fe^{2+}, and Cr^{3+}. However, the response of **NTP** with Cu (II) is the most distinct amongst the metal perchlorate cations, suggesting a selectivity and specificity for sensing Cu (II). These results are promising

and future work will involve computational and spectroscopic studies to understand the mechanism behind the response obtained with Cu (II).

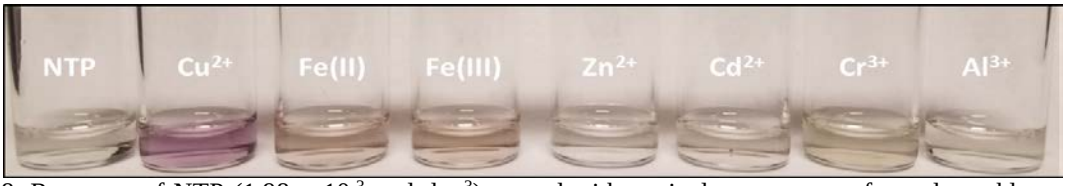


Figure 18. Response of NTP (1.98×10^{-3} mol dm^{-3}) treated with equivalent amounts of metal perchlorate salts in acetonitrile under ambient light after an hour.

Conclusion and Future Direction for NTP

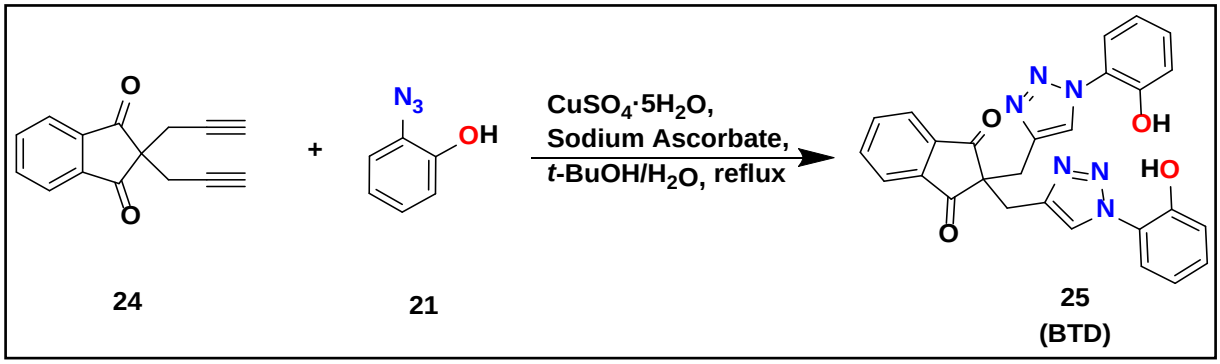
Using "click chemistry" we have synthesized a novel chemosensor **NTP**. This molecule can serve as a "dual sensor," able to detect both cations and anions. It produces "turn-on" fluorescence with fluoride and a colorimetric signal with Cu (II). As an anion sensor, the probe also detects dihydrogen phosphate and acetate, however with weaker responses. For cation detection, preliminary screening shows a distinct color change, colorless to purple, upon treating **NTP** with copper (II). Further investigations into the behavior of anions and metal cations with **NTP** need to be performed. This will include the fluorescence, UV-Vis and NMR spectroscopic studies in tandem with computational calculations.

Additional Approaches to Chemosensors

A Novel 1,2,3-Triazole Based Sensor: 2,2-Bis-((1-(2-Hydroxyphenyl) -1,2,3-Triazol-4-yl)Methyl)-Indene-1,3-Dione [BTD]

The novel 1,2,3-triazole probe **BTD** was synthesized from 2-azidophenol and dipropargylated indandione using the CuAAC approach. The molecule was obtained in 40% yield, and is not known. **BTD** was designed in an attempt to intensify the signaling response seen in our previous sensors. In contrast to **BPT** (Figure 4), **BTD** has a more conjugated backbone, the

replacement of dimedone with 1,3-indanedione. Upon treating **BTD** with metal perchlorate salts and tetrabutylammonium salts of anions in dimethyl sulfoxide (DMSO) there was no observed fluorescent or colorimetric change under UV or ambient light, respectively. Unlike **BPT** which is colorless in solution, the probe **BTD** is already highly colored (deep yellow) which may contribute the lack of an observable color change in the presence of anions and heavy metal cations. Notably, the deep yellow color of **BTD** is caused by the dimedone backbone which is not in conjugation with units that could function as binding motifs. Since we did not observe any distinct fluorescent or colorimetric change we chose not to investigate the probe any further. However, results for **BTD** compared to those for **PTP, NTP,** and **QTP,** underscores the importance of incorporating conjugation throughout the entire structure of our 1,2,3-triazole based sensors in our current approach.



Scheme 6. Synthesis of 2,2-Bis-((1-(2-hydroxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-indene-1,3(2H)-dione [BTD].

CHAPTER 3

CONCLUSION

Overall, our current work to manipulate 1,2,3-triazole probes to improve on the design of our previous sensors has proven successful. We have synthesized two 1,2,3-triazole based chemosensors **QTP** and **NTP** using copper-mediated arylamine and tosylhydrazone cycloaddition and the azide-alkyne reaction, CuAAC, respectively. **QTP** is selective for the detection of Cu (II), binding in a 1 : 1 ratio, producing a “turn-off” fluorescent response with the cation. **NTP** is a dual sensor producing a colorimetric signal, colorless to purple, for Cu (II) and a “turn-on” fluorescence response with the fluoride anion.

CHAPTER 4

EXPERIMENTAL

Materials and Methods

All chemicals and reactants were obtained through commercial sources (Alfa Aeser, OXCHEM, Sigma Aldrich, Acros, and Fisher) without further purification. Column chromatography was performed with Selecto Scientific Silica Gel (particle size 100-200 microns). FT-IR spectra were recorded on Nicolet iS10 FT-IR spectrometer, signals recorded in cm^{-1}.

NMR spectra was recorded on Agilent MR4000DD2 spectrometer: 1H-NMR: 400 MHz and ^{13}C-NMR:100 MHz. Deuterated acetonitrile (CD_3CN), chloroform ($CDCl_3$) and dimethyl sulfoxide ($(CD_3)_2SO$) were used as solvents. Signals were recorded in parts per million (*ppm*). References in the corresponding solvents were set according to residual CH_3CN at 1.94 ppm for ^{1}H-NMR and 1.32 ppm [$\underline{C}H_3$] & 118.26 [$\underline{C}N$] for ^{13}C-NMR, $(CH_3)_2SO$ at 2.50 ppm for ^{1}H-NMR and 30.37 ppm for ^{13}C-NMR and $CHCl_3$ at 7.26 ppm for ^{1}H-NMR and 77.16 ppm for ^{13}C-NMR . Signals for the ^{1}H-NMR multiplicity are described as: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), multiplet (m), coupling constants (*J*, Hz).

Absorption and steady state fluorescence measurements were performed using a Shimadzu UV-2450 spectrophotometer and PerkinElmer LS55 with well plate reader fluorimeter respectively. All of these experiments were performed at ambient temperature (27°C).

Synthesis and Characterization of Novel 1,2,3-Triazole Sensors

Synthesis and Characterization of the Probe 8-(4-Phenyl-1,2,3-Triazol-yl)Quinoline (QTP) [20]

CuAAC approach:

8-azidoquinoline (438 mg, 2.58 mmol) and phenylacetylene (283 ml, 2.58 mmol) were suspended in *t*-BuOH/ H_2O (50 ml, 1:1 v/v) and stirred in a round bottom flask. A mixture of $CuSO_4 \cdot 5H_2O$ (32 mg, 0.13 mmol) and water (2ml) was added to the reaction, followed by sodium ascorbate (102 mg, 0.52 mmol). After 24 hours of reflux and stirring, the reaction was cooled to room temperature. Ethyl acetate (200 ml) was added to the crude product. The resulting organic layer was washed with water (2 × 200 ml), brine (2 × 200 ml), dried over anhydrous Na_2SO_4, then the solvent removed under vacuum to provide the crude product. The crude product was then purified by column chromatography (45% ethyl acetate in hexanes) yielding a brown solid 120 mg (27%).

Azide-Free Approach[32]*:*

Acetophenone tosylhydrazone (2.01 g, 6.94 mmol) and 8-aminoquinoline (2.00 g, 13.71 mmol) were suspended in toluene (70 ml). Pivalic acid (1.41 g, 13.71 mmol) was added to the reaction vessel, followed by the addition of copper (II) acetate anhydrous (1.26 g, 6.94 mmol). After 32 hours of stirring while refluxing the reaction was cooled and the solvent removed in vacuo. The crude product was dissolved in acetonitrile (70 ml), then disodium ethylenediaminetetraacetate (EDTA) dihydrate solution (70 ml) was added to the product and stirred for 10 mins. The organic layer was removed, and the solvent evaporated. Ethyl acetate (200 ml) was added to the crude product, then washed with water (2 × 200 ml), brine (2 × 200 ml), then dried over anhydrous sodium sulfate. After evaporation of the solvent the product was purified

with column chromatography (20% ethyl acetate in hexanes followed by 60% ethyl acetate in hexanes) resulting in off white-beige powder 2.50 g (67%). **^{1}H-NMR** (400MHz, CD_3CN) δ 9.04 (s, 1-H), 8.99 (d, 1-H, J = 4.4, 1.9), 8.46 (d, 1-H, J = 8.4), 8.24 (d, 1-H, J = 7.2), 8.14 (d, 1-H, J = 8.4), 8.01 (d, 2-H, J = 7.3), 7.79 (t, 1-H, J = 7.7), 7.65 (dd, 1-H, J = 8.5, 4.2), 7.52 (t, 2-H, J = 7.8), 7.41 (t, 1-H, J = 7.5); **^{13}C-NMR** (100MHz, CD_3CN) δ 151.30, 148.60, 143.16, 136.59, 136.38, 128.97, 128.09, 127.02, 126.26, 125.97, 125.52, 124.88, 124.30, 122.40, 121.94, 121.49, 117.36, 115.78.

Synthesis and Characterization of the Probe 2-(4-(3-Aminophenyl)-1,2,3-Triazole-1-yl)Phenol (NTP) [23]

2-Azidophenol (231 mg, 1.71 mmol) and aminophenylacetylene (200 mg, 1.71 mmol) were suspended in *t*-BuOH/ H_2O (25 ml, 1:1 v/v) and stirred in a round bottom flask. A mixture of $CuSO_4 \cdot 5H_2O$ (0.004 mg, 0.02 mmol) and water (2ml) was added to the reaction, followed by sodium ascorbate (0.03 g, 0.17 mmol). After 24 hours of reflux and stirring, the reaction was cooled to room temperature and placed in an ice bath. Ethyl acetate (200 ml) was added to the crude product. The resulting organic layer was washed with water (2 × 200 ml), brine (2 × 200 ml), and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the product was recrystallized from methylene chloride/hexanes: The crude product was dissolved in boiling methylene chloride (~10 ml). The resulting solution was cooled to room temperature followed by the addition of ice-cold hexane (~40 ml) to induce precipitation. The purified compound, a tan-brown powder, was collected by vacuum filtration, 157 mg (76%). **^{1}H-NMR** (400MHz, CD_3CN) δ 8.79 (s, HO), 8.55 (s, 1-H), 7.67 (dd, 1-H, J = 8.7, 1.7), 7.38 (m, 1-H), 7.35 (s, 1-H), 7.27-7.06 (m, 4-H), 6.67 (dt, 1-H, J = 6.3, 4.6, 2.5), 4.29 (s, H_2N); **^{13}C-NMR** (100MHz, CD_3CN) δ 149.16,

148.56, 147.34, 131.12, 131.00, 129.75, 123.16, 120.79, 120.43, 117.84, 117.31, 114.61, 114.48, 111.26.

Synthesis and Characterization of the Probe 2,2-Bis-((1-(2-hydroxyphenyl)-1,2,3-Triazol-4-yl)methyl)-Indene-1,3-Dione (BTD) [25]

2,2-dipropynyl-1H-indene-1,3(2H)-dione (400 mg, 1.80 mmol) and 2-azidophenol (559 mg, 4.14 mmol) were suspended in *t*-BuOH/ H_2O (40 ml, 1:1 v/v) and stirred in a round bottom flask. A mixture of $CuSO_4 \cdot 5H_2O$ (44 mg, 0.18 mmol) and water (2ml) was added to the reaction, followed by sodium ascorbate (356 mg, 1.79 mmol). After 24 hours of reflux and stirring, the reaction was cooled to room temperature. Ethyl acetate (200 ml) was added to the crude product. The resulting organic layer was washed with water (2 × 200 ml), brine (2 × 200 ml), and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to provide the crude product. The crude product was then purified by column chromatography (60% ethyl acetate in hexanes) yielding a tan powder 260 mg (40%).**^{1}H-NMR** (400MHz, $CDCl_3$) δ 9.65 (s, HO), 7.91 (dd, 1-H, J = 5.9, 3.2 Hz), 7.85 (s, 1-H), 7.75 (dd, 1-H, J = 5.9, 3.2 Hz), 7.29 (m, 2-H), 7.27 (dd, 1-H, J = 8.3, 1.2), 7.11-6.92 (m, 1-H), 3.43 (s, 2-H); **^{13}C-NMR** (100MHz, DMSO) δ 202.05, 149.72, 142.21, 141.24, 136.16, 125.02, 124.98, 124.68, 123.18, 119.82, 117.44, 30.48.

Synthesis and Characterization of 8-Azidoquinoline (18)

8-Aminoquinoline (1.03 g, 7.16 mmol) was suspended in acetonitrile (14 ml) and placed in an ice bath. Then *t*-butyl nitrate (1.29 ml, 10.74 mmol) and $TMSN_3$ (1.13 ml, 8.60 mmol) were carefully added to the reaction. After 2 hrs of vigorously stirring ethyl acetate (50 ml) was added to the mixture. The resulting organic layer was washed with water (2 × 200 ml), brine (2 × 200 ml), and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to provide the

crude product. The crude product was purified by column chromatography (20% ethyl acetate in hexanes) yielding an orange-brown solid 400 mg, (20%). **IR** (cm^{-1}) 2114, 1567, 1325; **^{1}H-NMR** (400MHz, CD_3CN) δ 8.87 (dd, 1-H, J = 4.7, 1.8), 8.11 (dd, 1-H, J = 8.5, 1.9), 7.55 (dd, 1-H, J = 8.5, 1.9), 7.48-7.40 (m, 2-H), 7.35 (dd, 1-H, J = 7.3, 1.1); **^{13}C-NMR** (100MHz, $CDCl_3$) δ 149.31, 141.32, 136.93, 136.02, 129.15, 126.38, 124.08, 121.81, 118.08.

Synthesis and Characterization of 2-Azidophenol [21]

2-Aminophenol (2.00 g, 18.33 mmol)) was suspended in water (50 ml) and cooled to 0°C. HCl conc. (4.48 ml) was added to the suspension dropwise, then $NaNO_2$ (1.24 g, 18.33 mmol) was dissolved in water (5 ml) and added to the reaction. The reaction was stirred for 10 mins at 0-5°C, then sodium azide (1.41 g, 21.99 mmol) was added dropwise to the reaction. After 24 hrs of stirring at room temperature ethyl acetate (50 ml) was added to the mixture. The resulting organic layer was washed with water (2 × 200 ml), brine (2 × 200 ml), and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to provide the crude product. The crude product was then purified by column chromatography (30% ethyl acetate in hexanes) yielding an orange-brown solid 2.21 g, (50%). **IR** (cm^{-1}) 3350, 2117, 1507, 1293, 765; **^{1}H-NMR** (400MHz, CD_3CN) δ 6.99 (m, 2-H,), 6.88 (m, 2-H), 5.97 (s, HO); **^{13}C-NMR** (100MHz, CD_3Cl) δ 147.20, 126.05, 125.93, 121.21, 118.29, 116.00.

Synthesis and Characterization of 2,2-Dipropynyl-Indene-1,3-Dione [24]

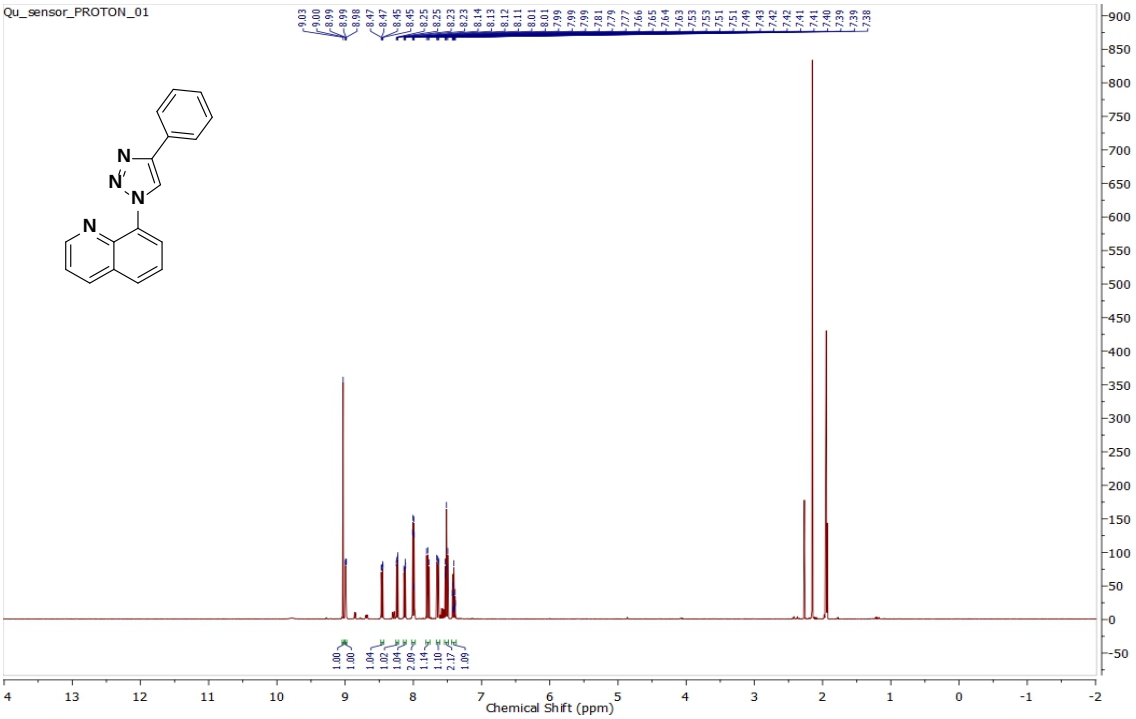
1,3-indanedione (2.00 g, 13.69 mmol), propargyl bromide (4.57 ml, 41.07 mmol), and potassium carbonate anhydrous (5.67 g, 41.07 mmol) were suspended in dry acetone (60 ml) and flushed with N_2. The reaction was allowed to stir under N_2 at room temperature, for 24 hrs. The solvent was removed under vacuum and ethyl acetate (60 ml) was added to the mixture. The

resulting organic layer was washed with water (2 × 200 ml), brine (2 × 200 ml), and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to provide the crude product. The crude product was then purified by column chromatography (15% ethyl acetate in hexanes) yielding a bright orange solid 1.68 g, (54%). **^{1}H-NMR** (400MHz, $CDCl_3$) δ 8.00 (dd, 1-H, J = 5.6, 3.1), 7.86 (dd, 1-H, J = 5.6, 3.1), 2.65 (d, 2-H, J = 2.6), 1.75 (t, 1-H, J = 2.7); **^{13}C-NMR** (100MHz, $CDCl_3$) δ 200.49, 142.28, 136.01, 123.32, 77.64, 71.87, 55.08, 22.81.

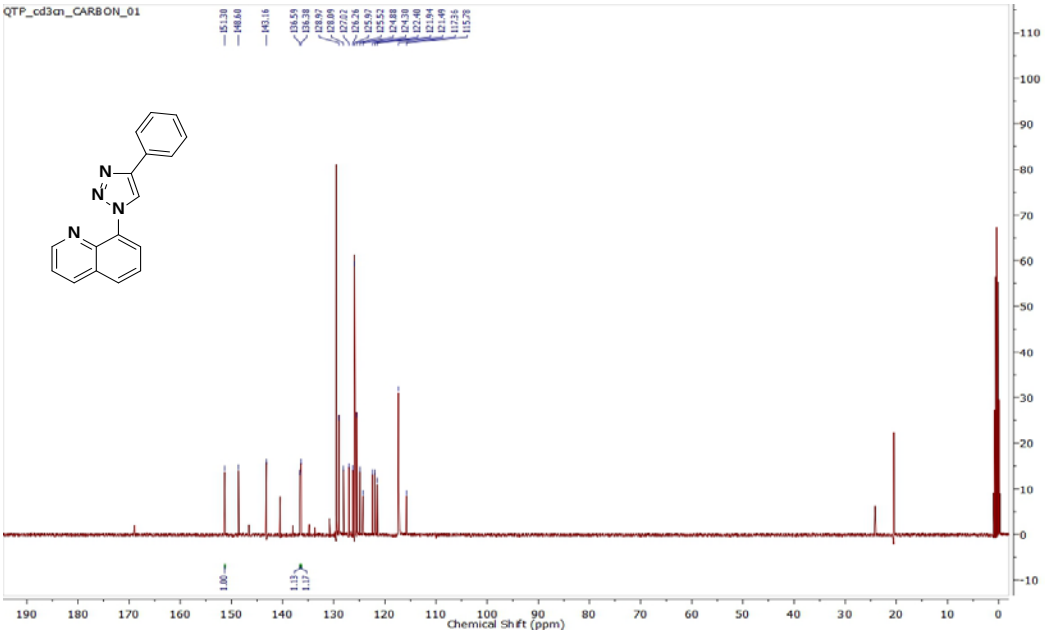
CHAPTER 5

SPECTRA FOR 1,2,3-TRIAZOLE SENSORS AND PRECURSORS

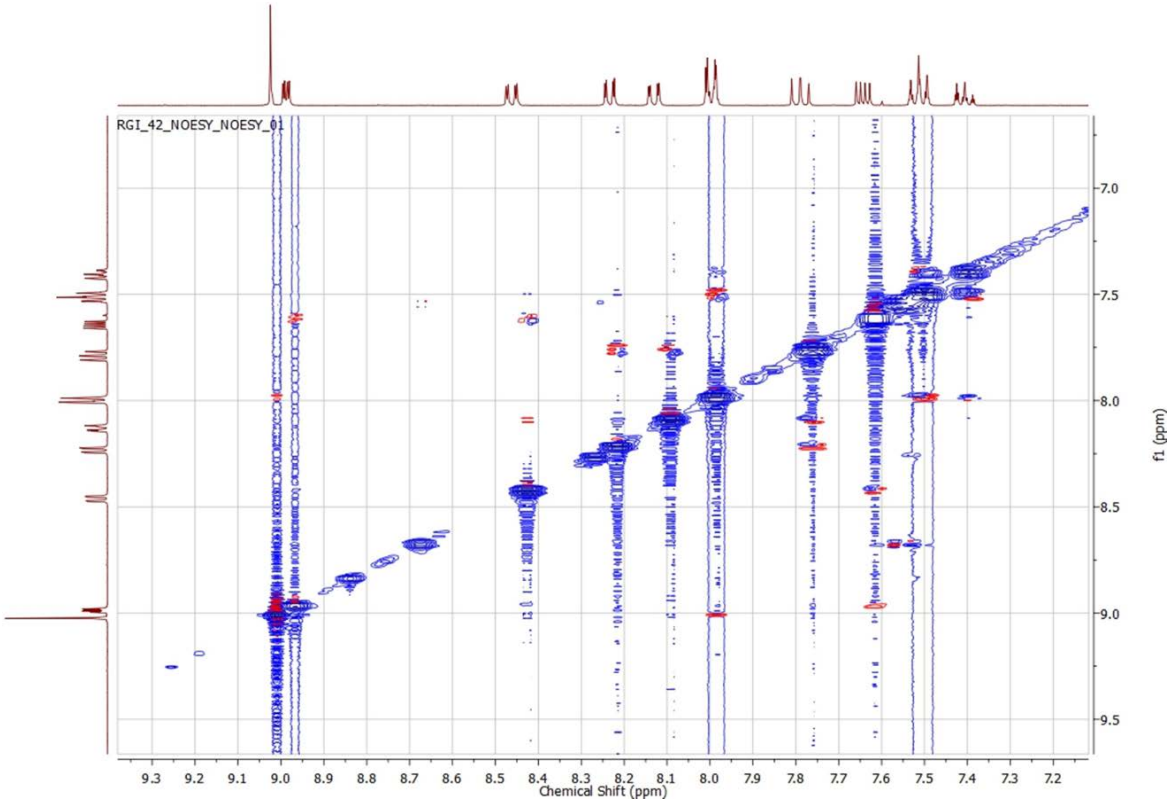
Compound **20,** ^{1}H-NMR Spectrum



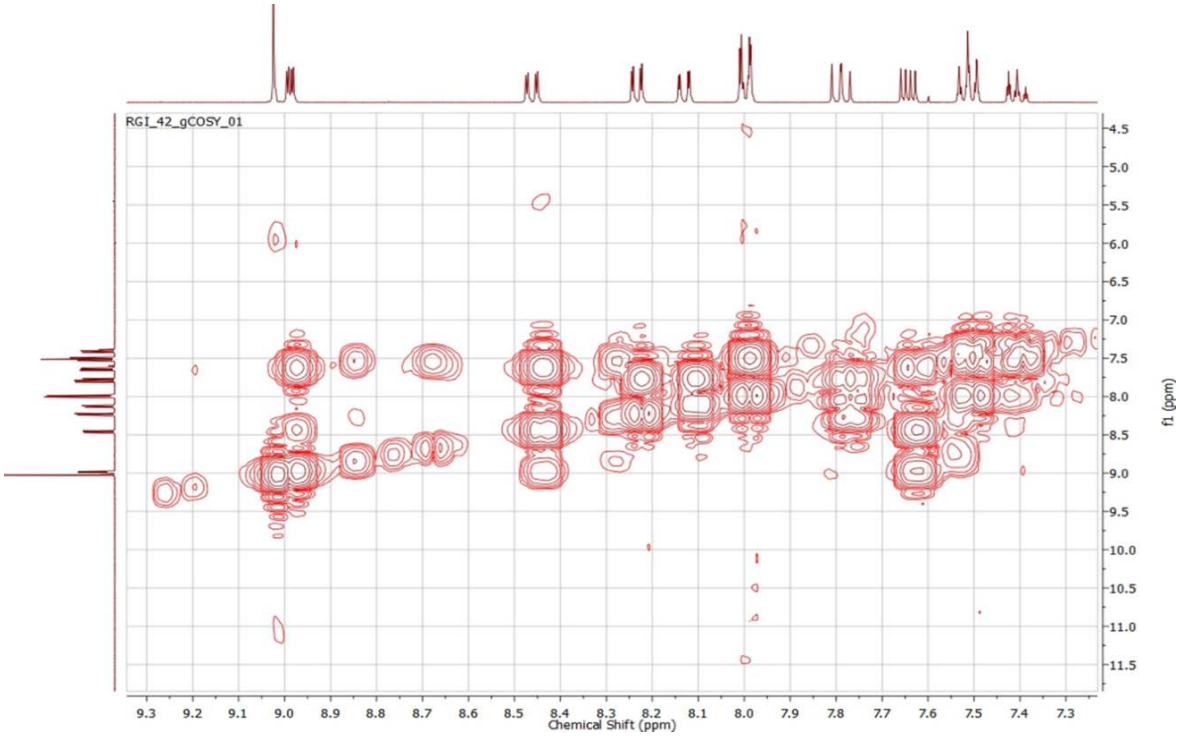
Compound **20,** ^{13}C-NMR Spectrum



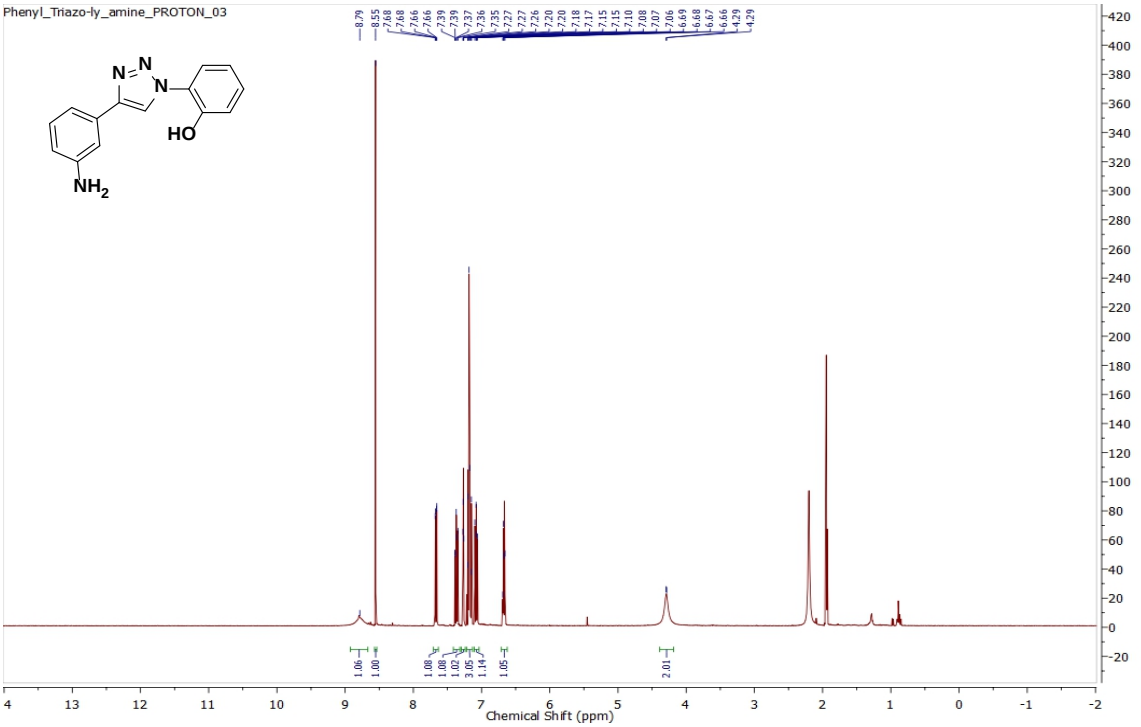
Compound **20,** 2D NOESY Spectrum



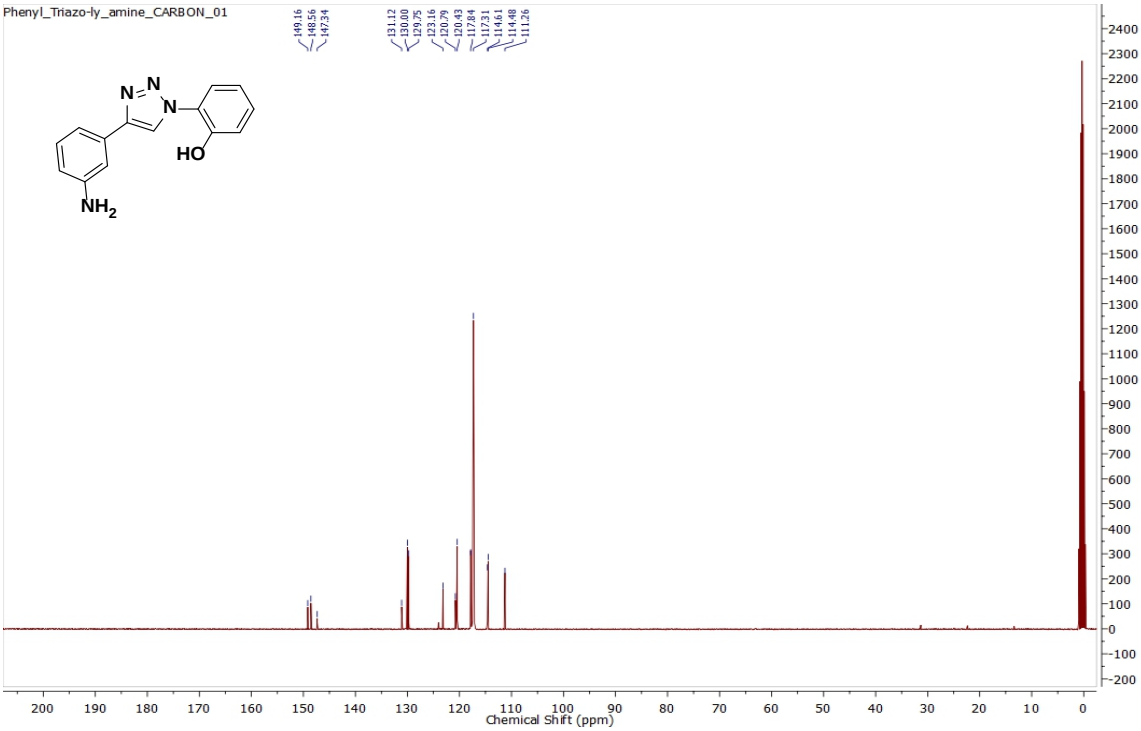
Compound **20,** 2D COSY Spectrum



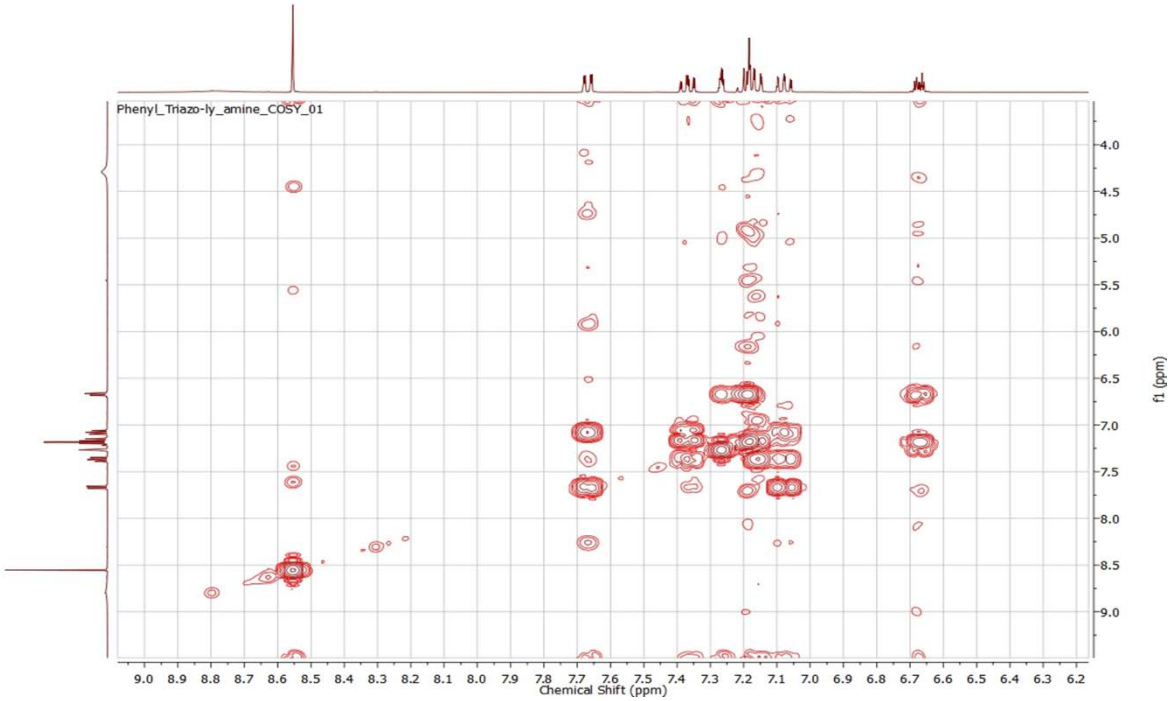
Compound **23**, ^{1}H-NMR Spectrum



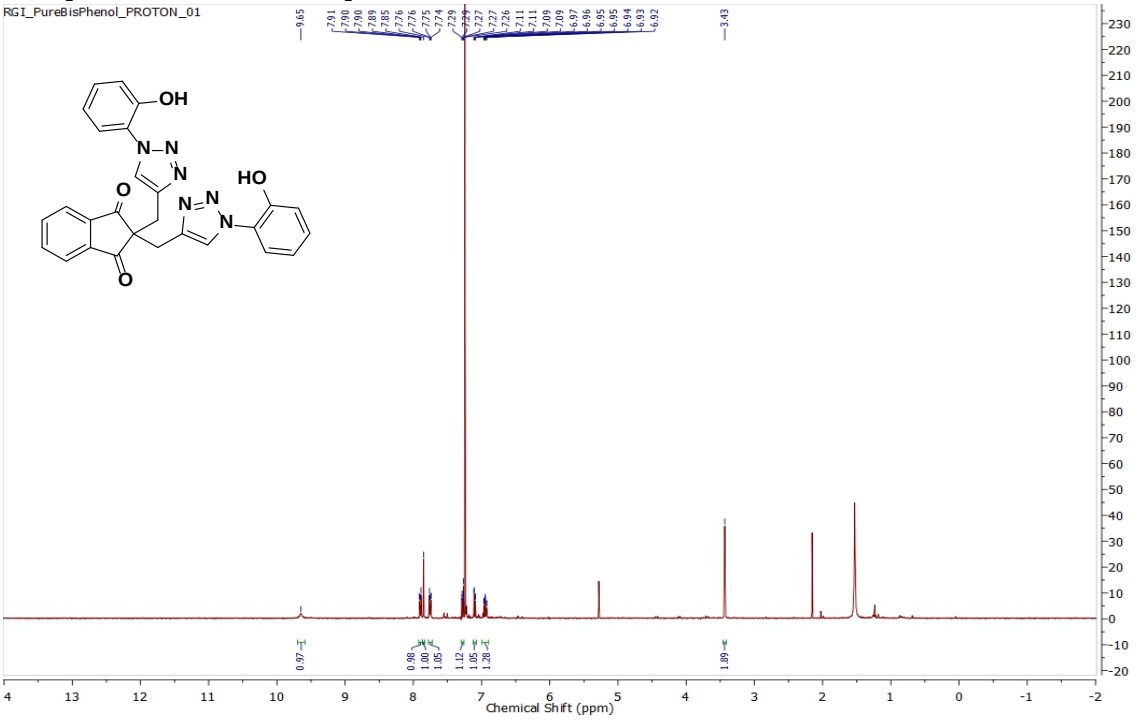
Compound **23**, ^{13}C-NMR Spectrum



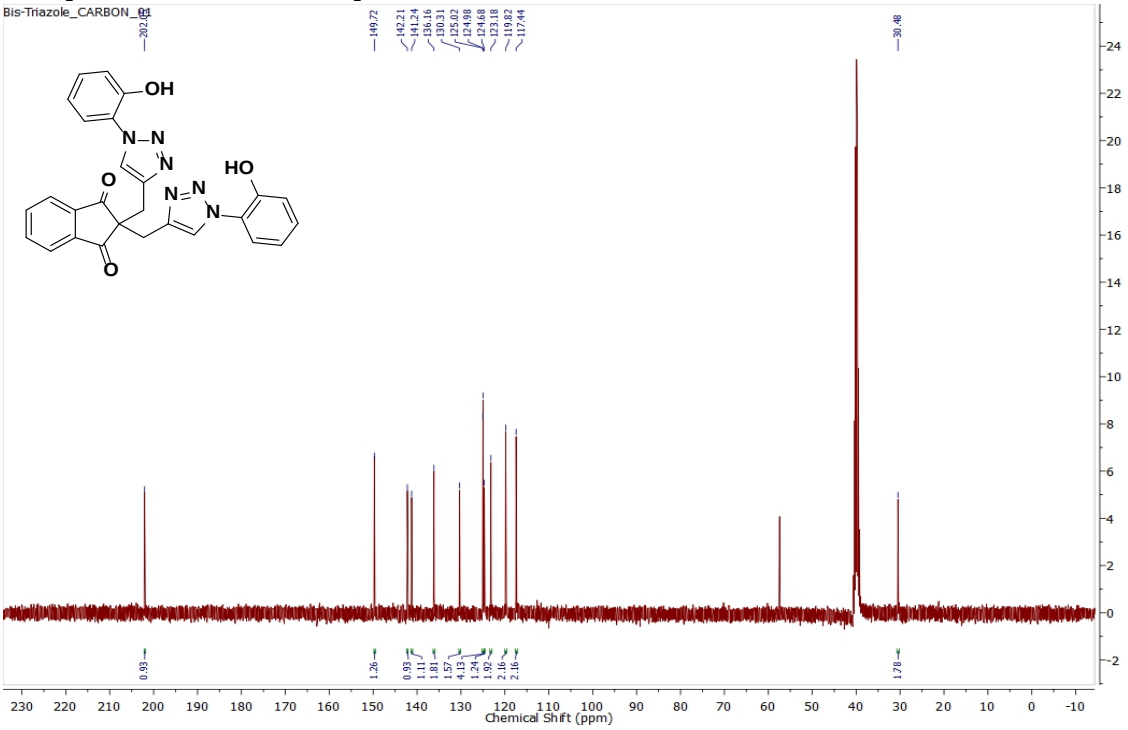
Compound **23**, 2D COSY Spectrum



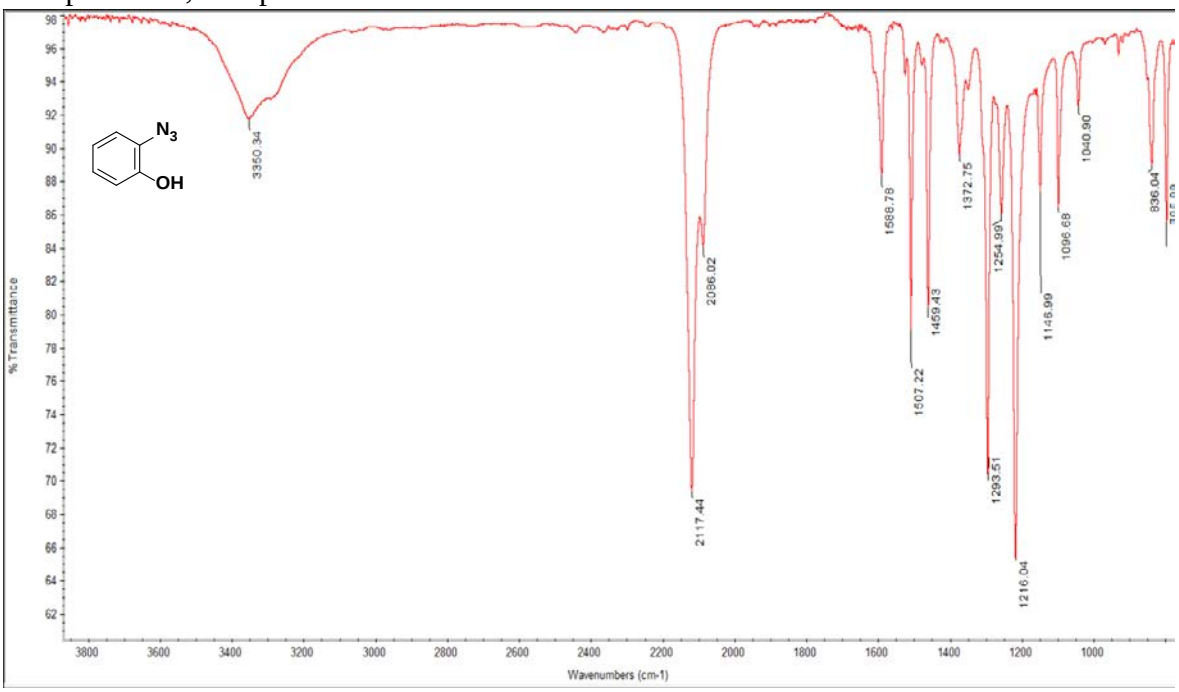
Compound **25**, ^{1}H-NMR Spectrum



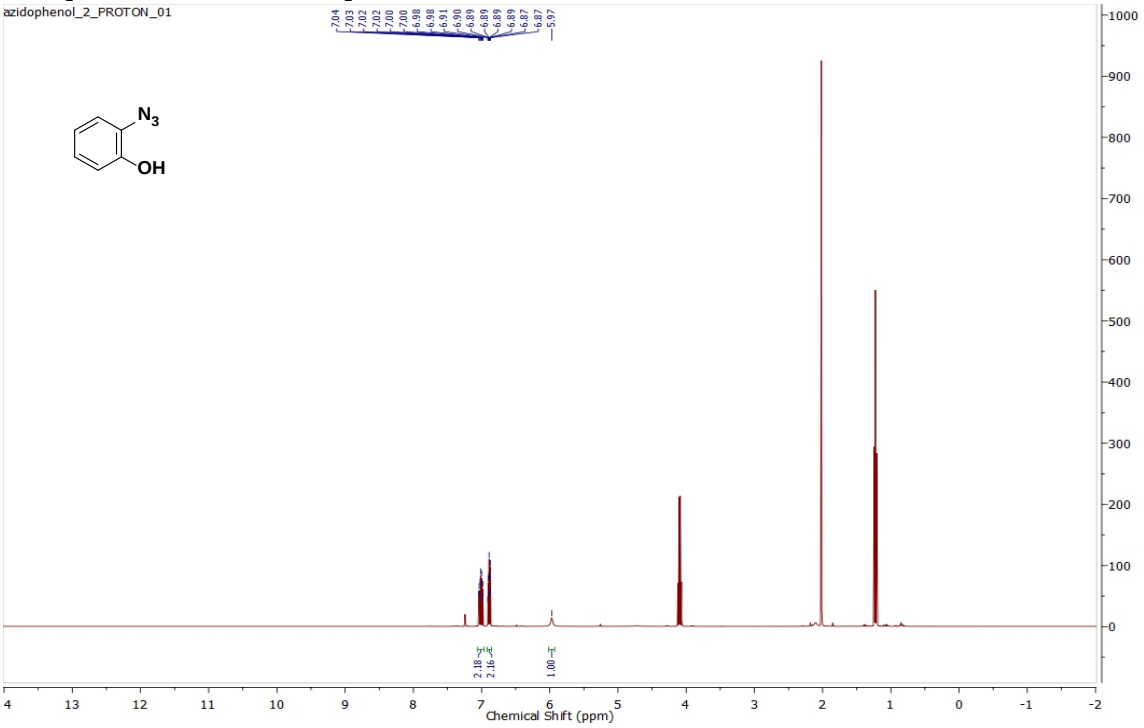
Compound **25**, ^{13}C-NMR Spectrum



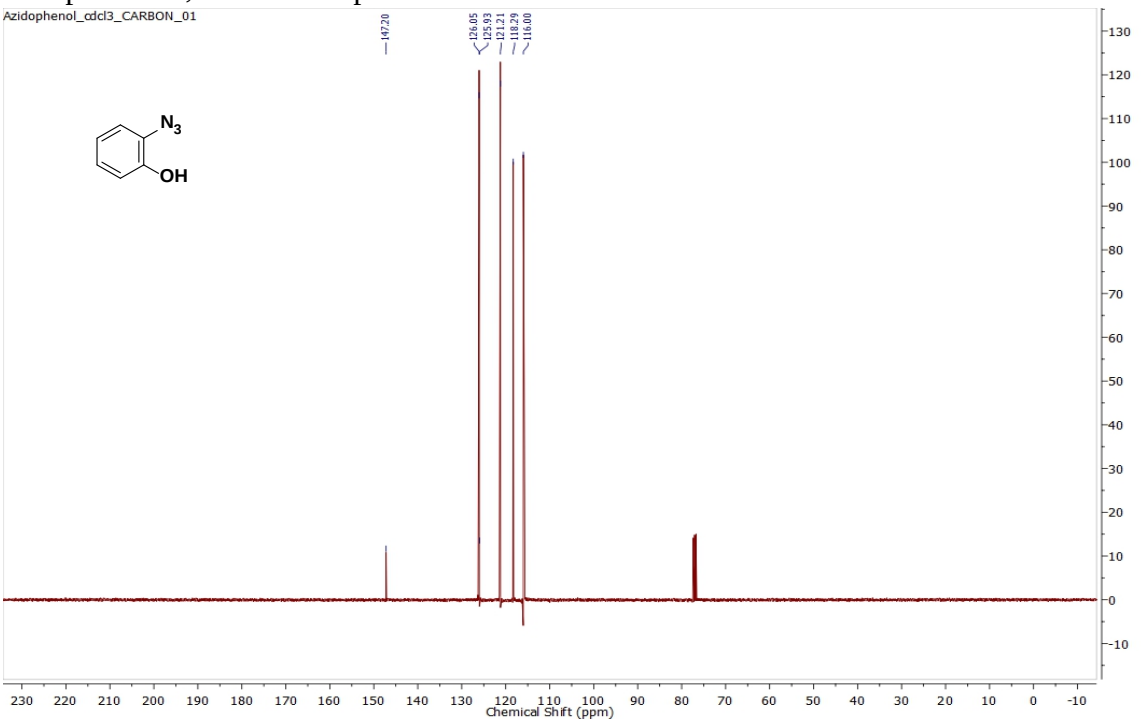
Compound **21**, IR Spectrum



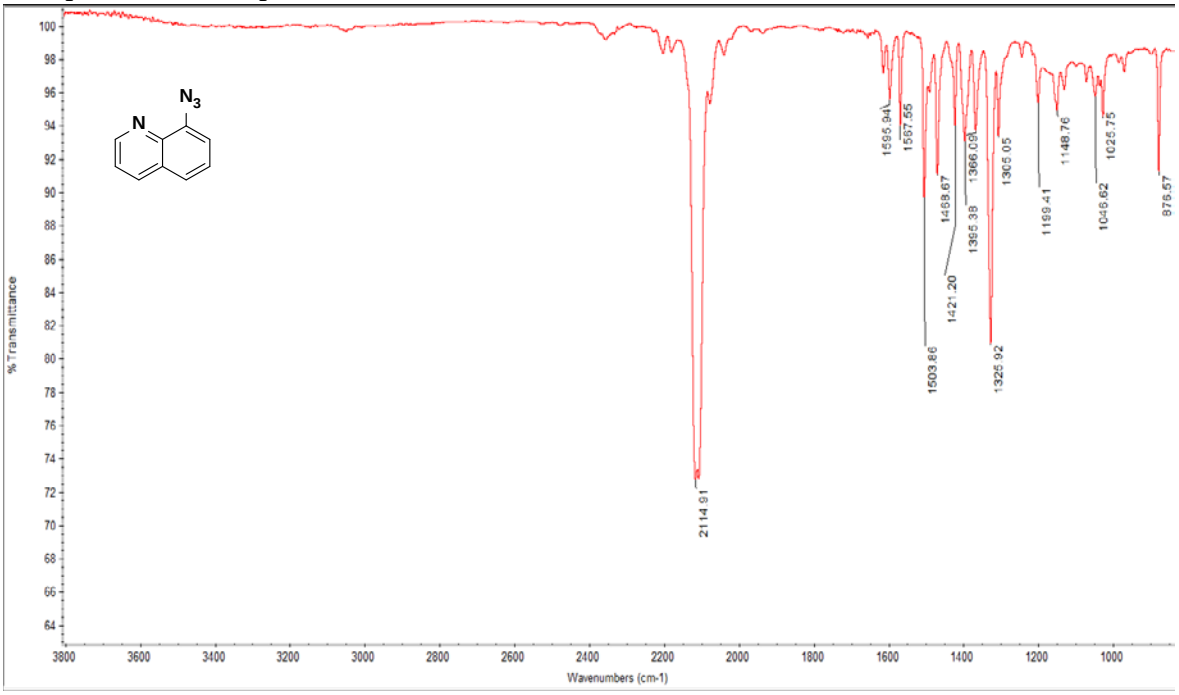
Compound **21**, ^{1}H-NMR Spectrum



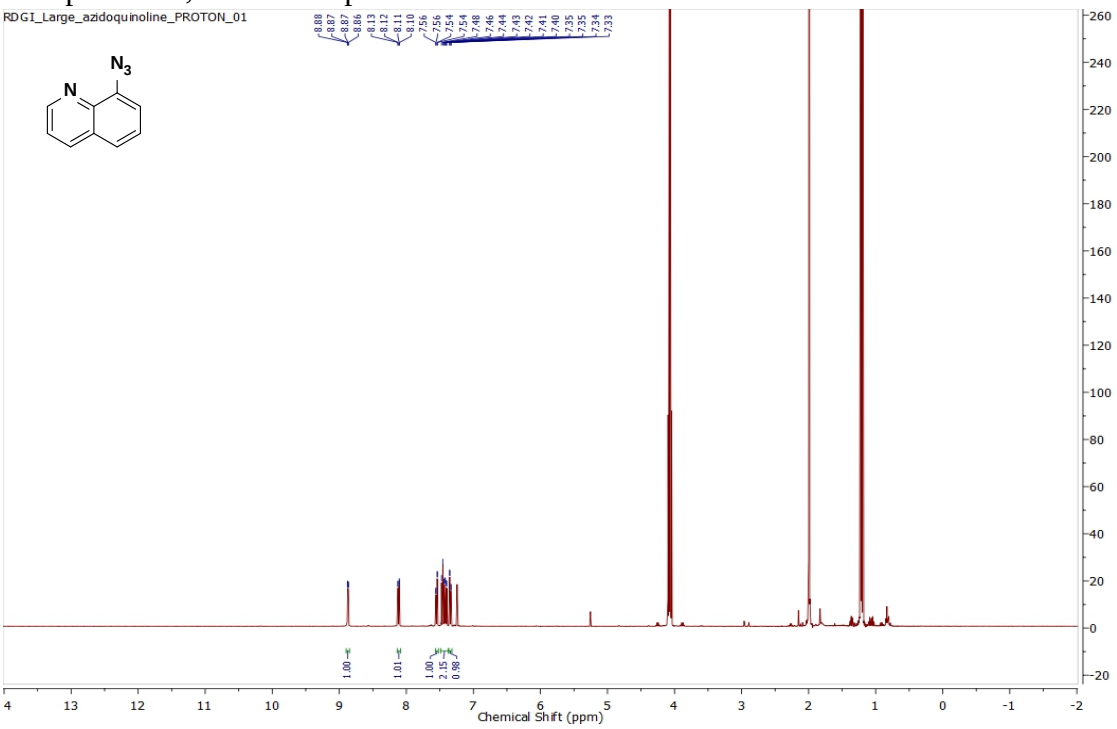
Compound **21**, ^{13}C-NMR Spectrum



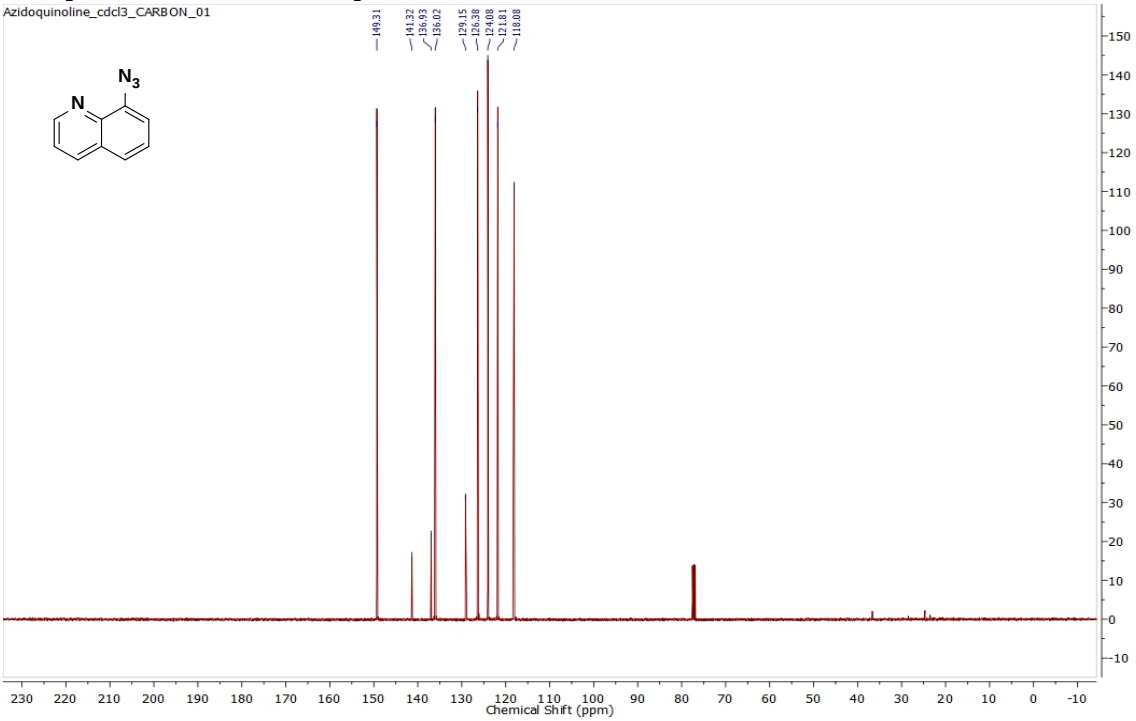
Compound **18**, IR Spectrum



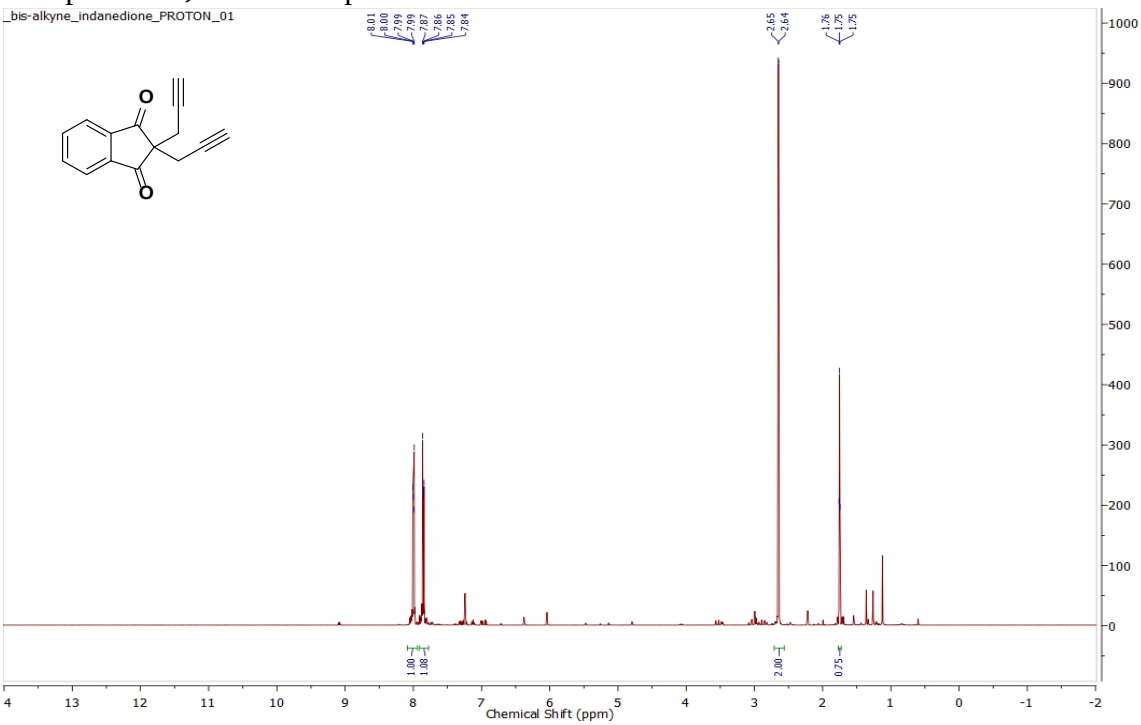
Compound **18**, ^{1}H-NMR Spectrum



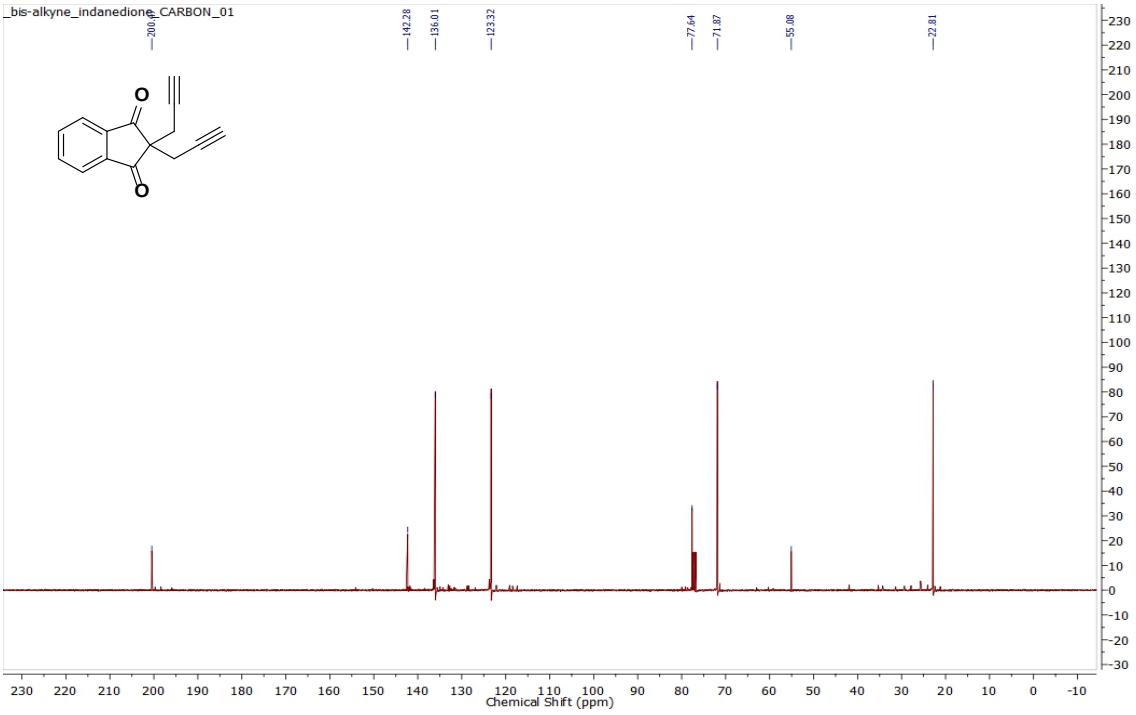
Compound **18**, ^{13}C-NMR Spectrum



Compound **24,** ^{1}H-NMR Spectrum



Compound **24**, ^{13}C-NMR Spectrum



CHAPTER 6

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