2017

Synthesis Of Oxadeazoles With Electron Withdrawing Groups And The Analysis Of Product Yield With Bond Length

Elizabeth Ann Hall Peters
Otterbein University, elizabeth.peters@otterbein.edu

Synthesis of Oxadiazoles with Electron Withdrawing Groups and the Analysis of Product Yield with Bond Length

By

Elizabeth Ann Hall Peters
Department of Chemistry
Otterbein University
Westerville, Ohio 43081

March 24th, 2017

Submitted in partial fulfillment of the requirement for graduation with Honors

Dr. Robin Grote	_____
Honors Advisor	Honors Advisor's Signature
Dr. Dean Johnston	_____
Second Reader	Second Reader's Signature
Dr. Stephanie Patridge	_____
Honors Representative	Honors Representative's Signature

Abstract

2,5-disubstituted 1,3,4-oxadiazoles are a class of organic compound that are widely used and successful in pharmaceutical chemistry because they demonstrate strong biological activity. They are part of a larger class of compound called heterocycles, which make up most pharmaceutical drugs today. When synthesizing the compounds, higher yield means higher reactivity of the compound, and this is important for pharmaceuticals that need to have a strong biological activity. Per past studies, electron withdrawing groups on the compound allow higher, product yields. Along with electron withdrawing group addition, the bond length from electron withdrawing group and its corresponding carbon is analyzed to look for positive correlation between high product yield and electron withdrawing group addition. The objective of this research is clarified by two phases: synthesis of 1,3,4-oxadiazoles with different electron withdrawing groups and analysis of yield and bond length. The conclusion of these phases demonstrates a trend between bond length and yield of the para oxadiazoles. As product yield increases, the bond length of the electron withdrawing group to carbon shortens. This trend is not observed in the ortho products because of other unknown factors, including steric hindrances that may limit the strength of the electron withdrawing group.

Table of Contents

List of Tables

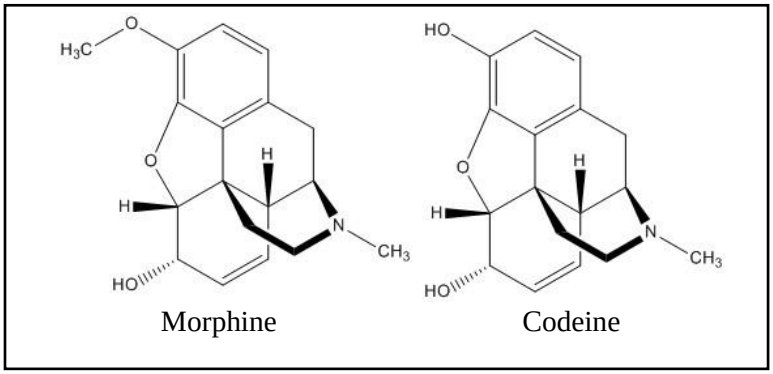
Page

List of Figures

Page

Introduction

1,3,4-oxadiazoles are a class of heterocycle, meaning a carbon ring with additional atoms like nitrogen, sulfur and oxygen. Oxadiazoles are widely used in medicinal chemistry because of their strong biological applications. These applications include, but are not limited to, antibacterial and antifungal activity, as well as being useful pesticides.[1] Some well-known heterocyclic compounds represented by Figure 1 are morphine and codeine, which are successful pain relievers. These two compounds differ by one methyl group attached to the top benzene ring. According to recent studies, more than 90% of new drugs are composed of some form of heterocycle.[1] In 2006, eight of the top ten most used prescription drugs were heterocycles.[2] Some of those compounds, Lipitor, Prevacid, and Singulair are shown in Figure 2. Although these compounds are all heterocycles, they differ greatly in biological activity. Lipitor is used to lower cholesterol levels while Prevacid treats acid reflux and Singulair treats asthmas and allergies.[2] Other heterocycles that naturally occur in the body are riboflavin, biotin, vitamin C, and the neurotransmitters serotonin and melatonin. Those structures are shown in Figure 2. Along with these naturally occurring heterocycles are those commonly found in pesticides like diazinon, which is also shown in Figure 2. Heterocycles allowed for advancements in medicine and have changed the pharmaceutical industry with their strong biological effects. This project explores



Morphine Codeine

Figure 1: Heterocycles in pharmaceuticals

the synthesis of a class of heterocycle, oxadiazoles, and analyzes their reactivity through product yield and bond length comparison.

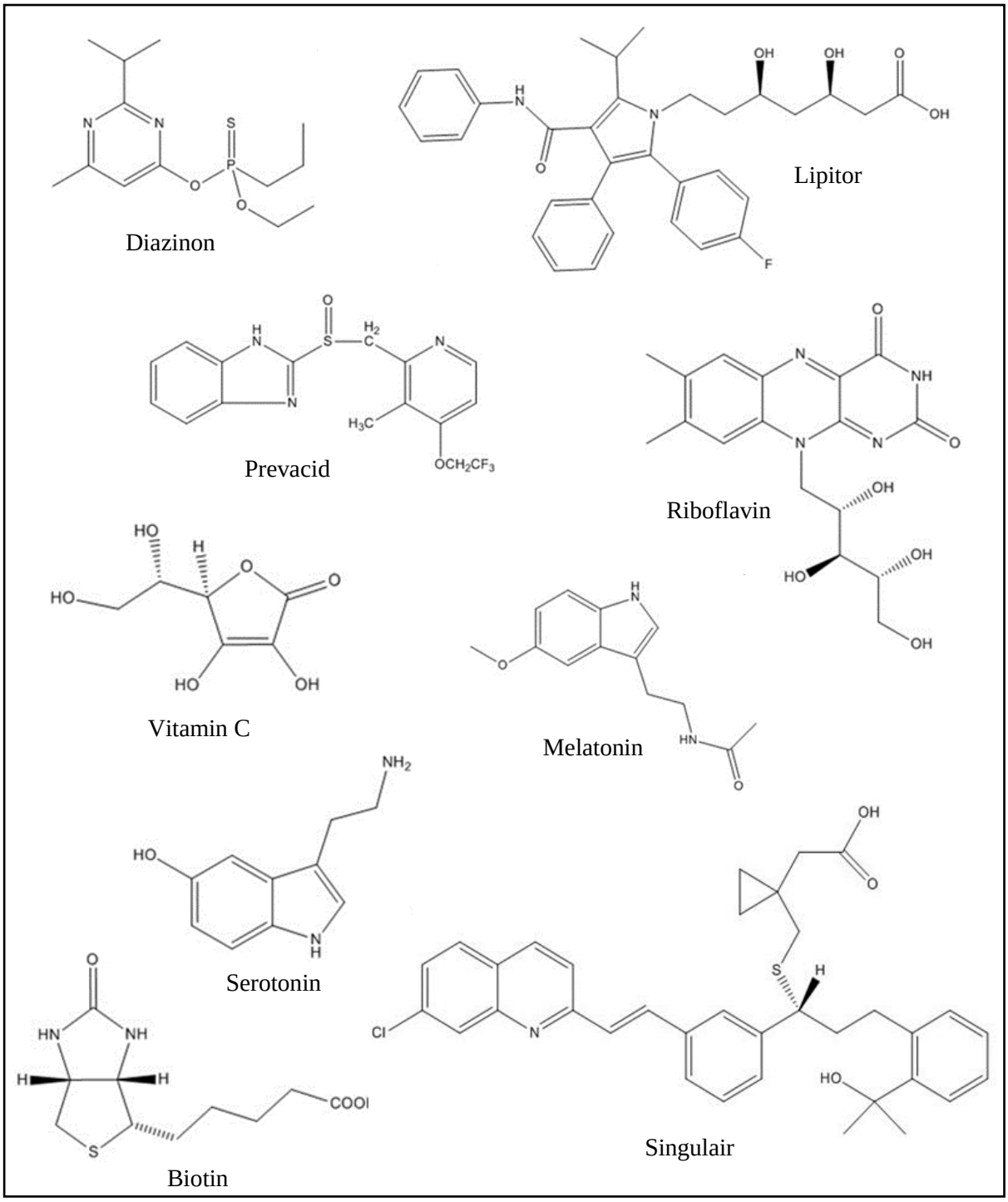


Figure 2: Synthetic and natural occurring heterocycles

An oxadiazole consists of a five-membered ring containing two nitrogens, two carbons, and one oxygen[3], as shown in Figure 3. This compound allows substituents to bond easily around the core scaffold[1,4], making it pliable for structural additions like electron withdrawing groups and aromatics. The pliable aspects of the oxadiazole are what make it biologically active.[1,4] This project employed cyclodehydration as the method used to synthesize 1,3,4-oxadiazoles.

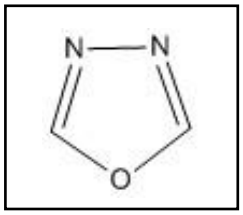


Figure 3: Oxadiazole

This method reacts a hydrazide with a R-substituted benzoic acid.[5] Reagents dibromo triphenyl phosphorane and DIPEA were used. Dibromotriphenylphosphorane is highly reactive with water and needs to be added quickly to the flask to ensure high activity of the reactant. Diisopropylethylamine, or DIPEA, is used as a base. Figure 4 demonstrates the general reaction, with **a**, **b**, and **c** representing the hydrazide, benzoic acid derivative, and oxadiazole, respectively. The longer side chains of compounds **a** and **b** cyclize to form the oxadiazole.

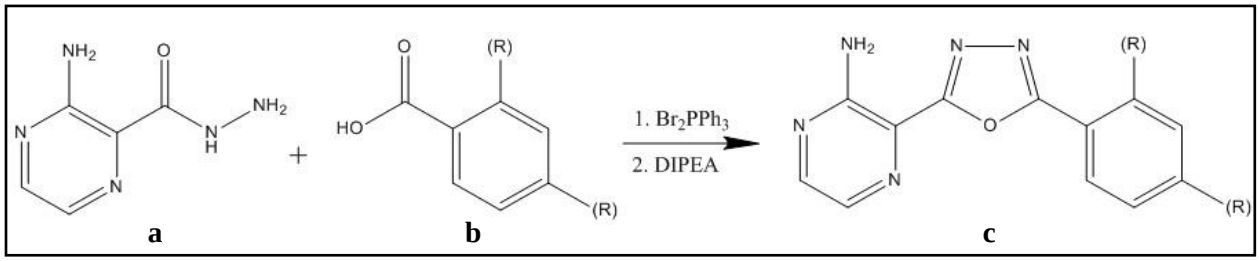


Figure 4: Synthesis of R-substituted oxadiazole

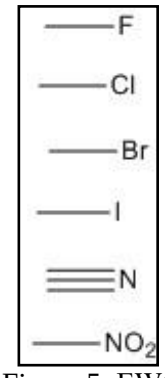


Figure 5: EWG's

Electron withdrawing groups (EWG's) are a class of molecule that pull electrons away from the reaction center called the resonance withdrawing effect; some examples of these compounds are halogens, nitro groups, and nitriles[6] depicted in Figure 5. The reaction center is the main carbon involved in the reaction. By pulling electrons away from the main center of the compound, the reaction center will become slightly more positive and is more susceptible

to nucleophilic attack.[6] An electrophile is a molecule with a slightly positive carbon that is vulnerable to attack by a nucleophile. A typical nucleophilic attack can be seen in Figure 6. In this reaction, the electrophile is the R-substituted benzoic acid and the nucleophile is the hydrazide. When an EWG is added to the electrophile, the withdrawing effect pulls electrons away from the attack center and the attackable carbon becomes slightly more positive. Figure 7 shows how EWG's can destabilize the carbon. By becoming more positive, the carbon becomes more susceptible to nucleophilic attack by the more negatively charged nucleophile. This idea that we can induce a more reactive electrophile may be demonstrated through high product yield. If the product yield is high, then there were more nucleophilic attacks on the benzoic acid, thus forming more product, the oxadiazole. Another benefit of EWG's is that they can resonance stabilize due to the number of available electrons and promote very stable intermediates. The abundance of pi bonding around the benzene ring coupled with the EWG allow the compound to shift electrons around the ring with stability and ease. An example of resonance stabilization can be seen in Figure 8, where bromine is the electron withdrawing group. The positive charge is changing around the benzene ring because the electrons are flowing around the compound. By adding these R-groups to the oxadiazole, I propose there will be increased reactivity of the compound demonstrated through high product yield. Other studies have shown that when adding electron withdrawing side groups to the structure of the oxadiazole, there is an increase in anti-microbial activity.[7] This demonstrates the

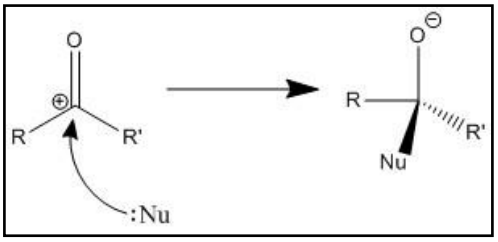


Figure 6: Nucleophilic attack

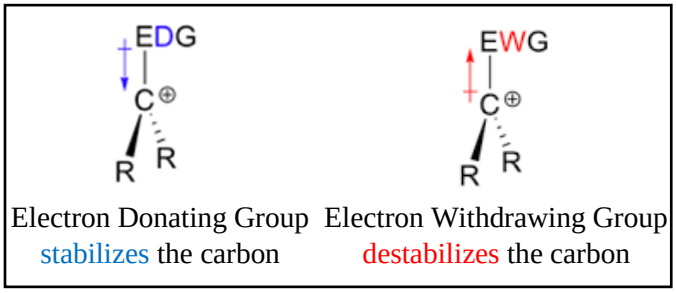


Figure 7: EDG and EWG interactions with carbon

increased biological activity of the oxadiazole containing EWG's. In contrast, there are other studies that added electron donating groups to the scaffold of the molecule and results showed decreased electronic activity.[8] Donor groups stabilize the reaction carbon and make it less likely to be attacked by the nucleophile.[6]

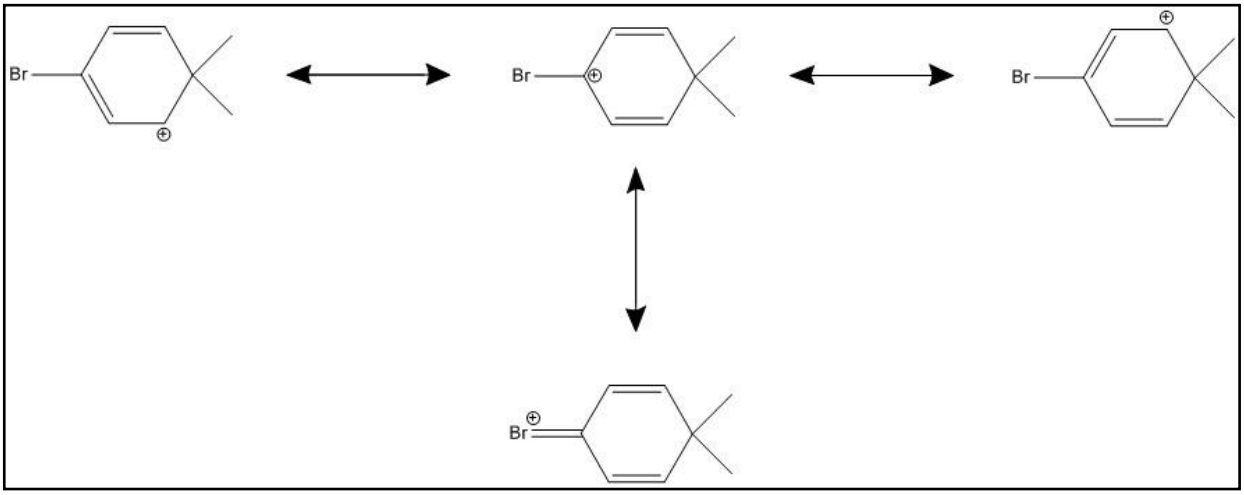


Figure 8: Stabilization of compound through resonance

Structure Activity Relationship (SAR) is the idea that there is a positive correlation between the structural aspects of a molecule and its observed biological activity. Oxadiazoles are shown to have antibacterial and anticancer applications, and through SAR, biological activity can be amplified or diminished. Already proposed is that electron withdrawing groups stabilize through their resonance withdrawing effects, and produce higher product yields. Other studies have already demonstrated that structural addition of electron donating groups produce very poor yields.[8,9,10] According to another thesis project in this lab, the addition of electron donating groups would lead to no reaction or yields as low as 3.5%.[10] The lowest, credible yield from the electron withdrawing groups in this investigation is 55.5%. Understanding how product yield and reactivity are related, electron withdrawing groups are a better choice to amplify biological activity of the oxadiazole.

Bond length may be another indicator of reactivity. This project focuses on the bond distance between the electron withdrawing group and adjacent carbon of the R-substituted benzoic acid. It is important to remember that there are dipole forces present in the bond between the EWG and adjacent carbon. A dipole is a force between two atoms, when the electrons creating the bond between them are not being shared evenly.[6] The bond length between two carbon atoms, atoms that equally share a pair of electrons in the bond and exhibit no dipole moment, is 1.54 angstroms.[6] When one of those carbons is replaced by a EWG, the length of the bond may change as the electrons are now being shared differently and have a different dipole moment.

The periodic trend atomic radius plays a role in bond length. Atomic radius increases across the periodic table and going down each column.[6] As the size of the molecule increases, the shorter the bond becomes because of its want for electrons. Therefore, when we consider electron withdrawing groups, the further down a column an EWG is, the shorter the bond length.[6] The trend between the shorter bond lengths and stronger EWG's should reflect higher product yields, and this is the main question in this investigation. Product yields should be higher because the strong EWG is pulling electrons away from the reaction center and making the reaction carbon more partially positive and susceptible for nucleophilic attack. The more nucleophilic attacks that occur correspond with more product being formed, and thus a higher yield.

One effective method to measure the bond length between electron withdrawing groups and their adjacent carbon is to use the computer program Mercury. This is a crystal structure visualization tool used to measure different structural components of compounds from The Cambridge Crystallographic Data Centre. The following are just a few applications of this

program: 3D structure visualization, statistical analysis, and bond length measurement.[11] Each benzoic acid derivative is within the database, and bond length of the crystal structure can be easily calculated. From that, conclusions can be drawn between bond length, electron withdrawing group, and product yield. The conditions that represent a biologically active species would result in short bond length coupled with strong EWG and high product yield.

There are two stages to this research: Synthesis of oxadiazoles and analysis of product yield with bond length. This project investigates how the strength of the electron withdrawing group compares to product yield and bond length.

Results and Discussion

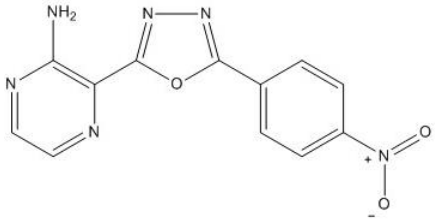
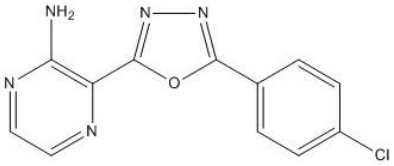
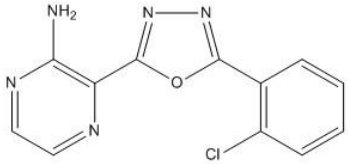
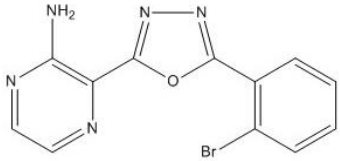
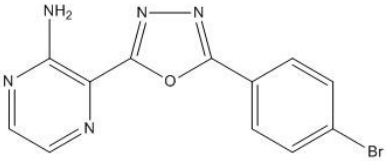
This project focused on the synthesis and characterization of 1,3,4-oxadiazoles. Electron withdrawing group addition is the main focus for the synthesis portion of this investigation, mainly how the addition affects biological activity as reflected through product yield. I propose this biological activity may also be analyzed through bond length. For the highest biological activity, product yield of the 1,3,4-oxadiazole will be high while bond length between EWG and adjacent carbon is shorter.

1,3,4-oxadiazole product yield

Final product yield results are depicted in Table 1 below. There is a sum of five oxadiazole derivatives, with different electron withdrawing group orientation. Yields vary from 45% up to 89.1%. It is important to note that the lowest yield, 30%, was an experimenter error. While setting up the product to dry on manifold overnight, most of the product sucked into the instrument and was lost. Therefore, 30% is not a true yield and will not be considered when looking at overall, average yields. Another note to examine, is the duplicate results of ortho-

chloro yields. The first reaction yielded the highest yield of the project, 89.1%. However, the duplicate yielded half that value at 45%. There is nothing that went wrong procedurally, but this gap in yields suggest there is something wrong. Due to the fact that no other experimental yields were lower than 55.5%, the 45% yield appears to be the error yield. Although, that is not to say the 89.1% yield may not be higher due to impurities. This situation could be a combination of both.

The general trend with yield shows the para-positioned electron withdrawing groups producing higher yields. These results start to show a positive correlation with my original hypothesis. Because the group is farther away from the reaction center in the para position, the electron withdrawing group will be pulling the density of electrons farther away from the reaction center. By pulling those electrons towards the other end of the molecule, the reaction carbon becomes even more partially positive and more susceptible to nucleophilic attack by the nucleophile. When more nucleophilic attacks occur, there is more product being produced, thus a higher yield. Relating this to oxadiazole reactivity, the more reactive the compound during synthesis, the more biologically active it will be.

oxadiazole	yield 1	yield 2	average yield
	71.1%		71.1%
	69.4%	69.9%	69.7%
	89.1%	45% ***1**	67.1%
	64.6%	70.3%	67.5%
	55.5%	30% ***2**	55.5%

***1 experimental error**

Table 1: List of oxadiazole yields

***2much of product sucked into manifold, value thrown out of average**

Product yield versus bond length

When comparing yield and bond length, ortho and para products will be analyzed separately due to other structural features that interfere with the different structural placements. The para position is two carbon atoms further away from the rest of the molecule, and is showing the beginnings of a trend in terms of the length of that bond.

My proposal is that a shorter bond length between the electron withdrawing group and its corresponding carbon will be shorter as the product yield of that oxadiazole is high. Depicted in Table 2 is the beginnings of a trend following this hypothesis. The para-nitro oxadiazole shows both a high yield and one of the shortest bond lengths of the electron withdrawing groups. For para-bromo derivative, as the bond length increases up to 1.899 angstroms, the average yield fell to 55.5%. This trend shows how electron withdrawing groups play a role in the synthesis of these oxadiazoles. By having a shorter bond length, the electron withdrawing nitro group has a greater pull on the electrons in the molecule. This effect allows the carbon of interest to become slightly more positive for nucleophilic attack, the results being a higher product yield.

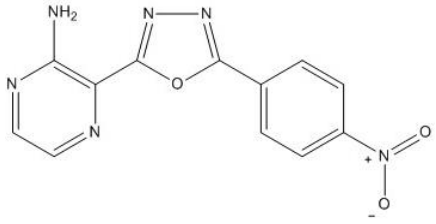
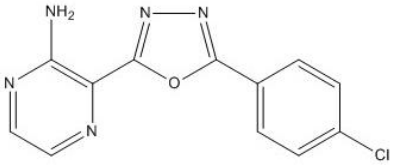
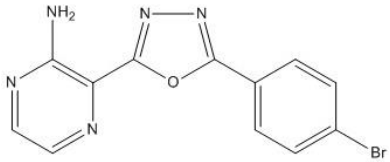
oxadiazole	**product yield**	**bond length**
	71.1%	1.479
	69.7%	1.744
	55.5 %	1.899

Table 2: Para products: yield vs bond length

As shown in Table 3, there is not much difference in the ortho product yields. Although, there is a considerable difference between the bond lengths of the chlorine and bromine. Both oxadiazoles have a 67% product yield. One possible explanation for this may be due to steric effects. Chlorine's and bromine's atoms require more space, and in the restricted ortho position this could affect how there is no correlation between bond length and product yield. The pull of electrons by the electron withdrawing group does not have the same effect in the ortho position as it does further away in the para position. In a smaller space provided by the ortho position, there is more concentration of electrons per space, as opposed to the para position at the end of the molecule. When in para position, the EWG has a much longer distance to pull the electrons over, and more space to fit which eliminates steric effects.

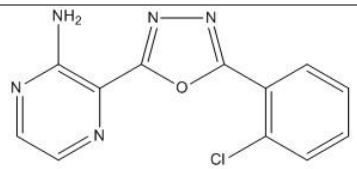
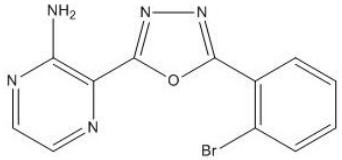
oxadiazole	yield	bond length
	67.1%	1.743
	67.5%	1.901

Table 3: Ortho products: yield vs bond length

Solubility of Oxadiazoles

When conducting solubility tests at room temperature, I noticed that there were very little the compounds were soluble in, if anything at all. They were not soluble in water, ethanol, ethyl

acetate, dichloromethane, or acetone. Some of the vials became puffed up solutions, like the compounds were beginning to break up, but no homogeneous solutions could be made. Nuclear magnetic resonance (NMR) is an integral part of characterizing one's compounds, but due to the solubility issues with the oxadiazoles, they would not go into solution for analysis. Mass spectrometry is another characterization technique that was not used due to solubility issues. When a sonicator was used, no change in solubility was observed.

Past research has also shown high insolubility of oxadiazoles. Because of this limitation, BOC protecting groups were added to the amino group to increase the oxadiazole's solubility and gather additional data[12], including NMR and X-ray. In future work, it will be very beneficial to add protecting groups to the oxadiazoles and gather additional, structural information on them.

Conclusions

This project investigated the relationship between bond length and product yield for synthesized oxadiazoles. It was already known that electron withdrawing groups increase product yield, and this project confirmed those results. The para oxadiazole derivatives showed a trend between bond length and product yield. The oxadiazole with the highest product yield, 71.1%, also had the shortest bond length between the EWG and its adjacent carbon, 1.479 angstroms. There is no correlation between product yield and bond length for the ortho products. This may be due to steric hindrances or other unknown factors.

Materials and Methods

All reagents, with exception to synthesized hydrazide, were purchased from Sigma Aldrich. All solvents used for reactions and recrystallization were purchased. All products were characterized using Nicolet 380 FT-IR with ATR attachment.

General Procedure of Hydrazide Synthesis

The reaction was conducted in a 70°C oil bath and topped with a rubber stopper with air vent needle at joint of 250 mL round bottom flask (RBF). 2.0 g of methyl-3-amino-2-pyrazine carboxylate, 87 mL of ethanol, 3.8 mL hydrazine monohydrate, and stir bar was added to RBF. The reaction was heated and stirred for 1.5 hours. RBF was promptly removed from oil bath and allowed to cool to room temperature for 20 minutes. After RBF was cooled, product was filtered using vacuum filtration with sintered glass funnel and washed with water and ethanol, sequentially. Theoretical yield of product is 2.0 g. There was a 74% (1.48 g) product yield. The general reaction to produce hydrazide reagent is shown below in Figure 9.[13]

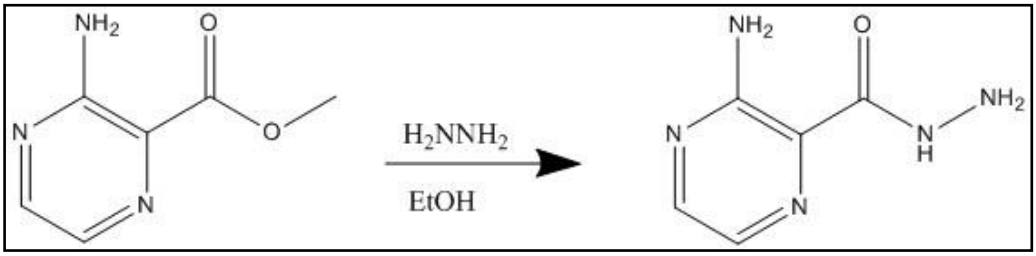


Figure 9: Synthesis of hydrazide

General Procedure of Oxadiazole Synthesis

Reaction was conducted at room temperature under nitrogen conditions. In a 25 mL RBF, 0.132 g of hydrazide and 0.178 g of benzoic acid derivative were added together with a micro stir bar. The flask was flushed with nitrogen and a rubber stopper placed in neck joint. Using a syringe, 4 mL of acetonitrile were added through the rubber stopper and stirring began. Immediately added 1.75 g of dibromo triphenyl phosphorane into the reaction flask, and replaced stopper to ensure integrity of nitrogen conditions. The mixture was stirred for 1 hour. Then 0.9 mL of DIPEA was added through the stopper with a syringe and left to stir overnight for 16 hours.[13]

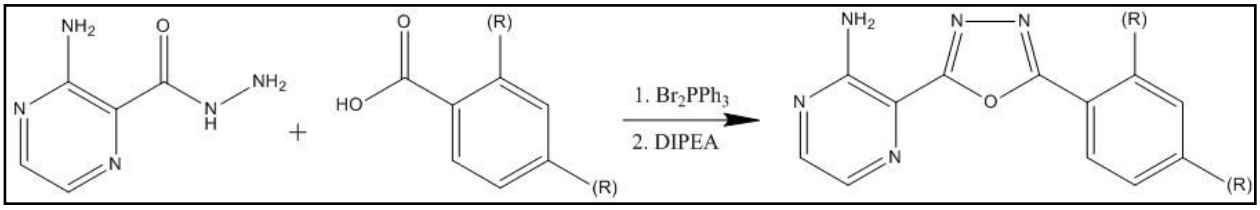


Figure 10: Synthesis of oxadiazole

After stirring for 16 hours, RBF was removed from stir plate and filtered through a sintered glass funnel via vacuum filtration. Next, the product was washed sequentially with 20 mL of acetonitrile and 10 mL of hexanes. Product was transferred to clean filter paper and allowed to air dry for 20 minutes. Then, product was transferred again to a clean 25 mL RBF and pumped with phosphorus pentoxide on high vacuum overnight. The reaction below depicts the synthesis for each oxadiazole.[13] There is one electron withdrawing group, R, per reaction, and whether it is ortho or para is controlled based on the starting material.

4-bromobenzoic acid derivative

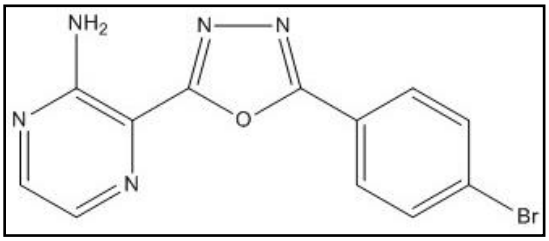


Figure 11: Para-bromo oxadiazole

The procedure was carried out in manner described above.[13] Both products appeared light yellow in color and gave 55.5% (0.152 g) and 30% (0.0626 g) yields for two reactions, respectively. It is important to note that the second reaction was mostly sucked into the glassware of manifold during overnight dry time. Therefore, the 30% yield is not accurate. The observed melting point is 193^{o}, which is when the compound began to decompose. The IR shows aromatics around 1700 cm^{-1} and an amino peak at 3359.9 cm^{-1}. The broad peak at 2500 cm^{-1} is an ammonium peak, which may come from a hydrated amino group.

2-bromobenzoic acid

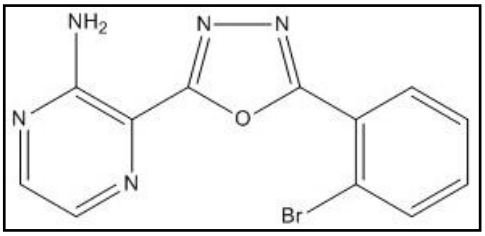


Figure 12: Ortho-bromo oxadiazole

This procedure was carried out in manner described above.[13] Both products appeared pale yellow in color and gave 64.6% (0.1769) and 70.26% (0.1467 g) yields for two reactions, respectively.

4-chlorobenzoic acid

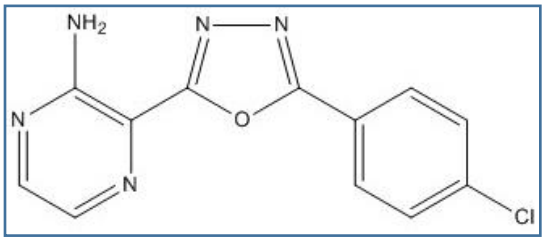


Figure 13: Para-chloro oxadiazole

The procedure was carried out in manner described above. Both products appeared light beige in color and gave 69.41% (0.1638 g) and 69.9% (0.165 g) yields for two reactions, respectively.

2-chlorobenzoic acid

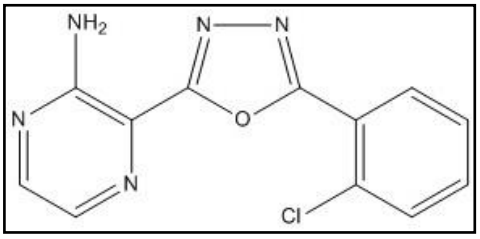


Figure 14: Ortho-chloro oxadiazole

The procedure was carried out in manner discussed above. The products appeared a deep golden tan color and gave 89.1% (0.2129 g) and 45% (0.1062 g) yields for two reactions, respectively. Observed melting point is 165º, which was when compound began decomposing.

4-nitrobenzoic acid

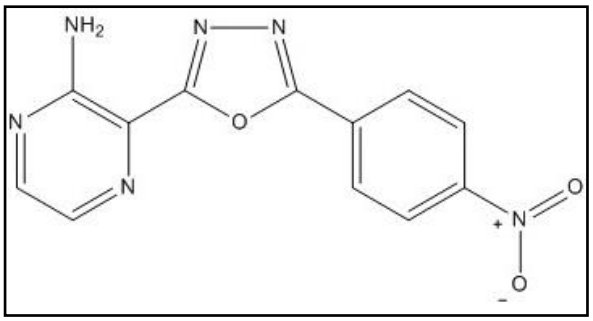


Figure 15: Para-nitro oxadiazole

This procedure was carried out in manner described above. The product appeared mustard yellow in color and gave a 71.1% (0.1742 g) yield. IR show an amino peak at 3419.19 cm^{-1}.

Computational Studies

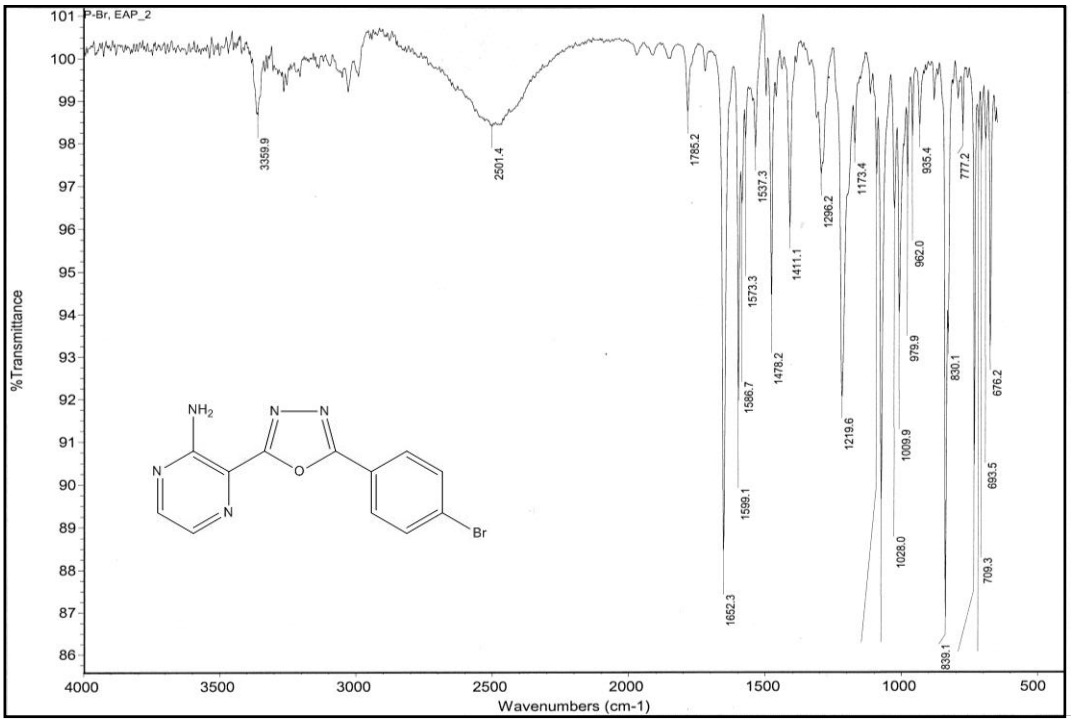
All benzoic acid derivatives were analyzed with the program Mercury. This extensive tool allows structural characterization of the compounds of interest. I made a rough sketch of the benzoic acid derivative that contains the electron withdrawing group, and then searched the crystal database for likeness. Once a structure was identified, I was able to measure bond length between the EWG and adjacent carbon. This was conducted for all five benzoic acid derivatives.

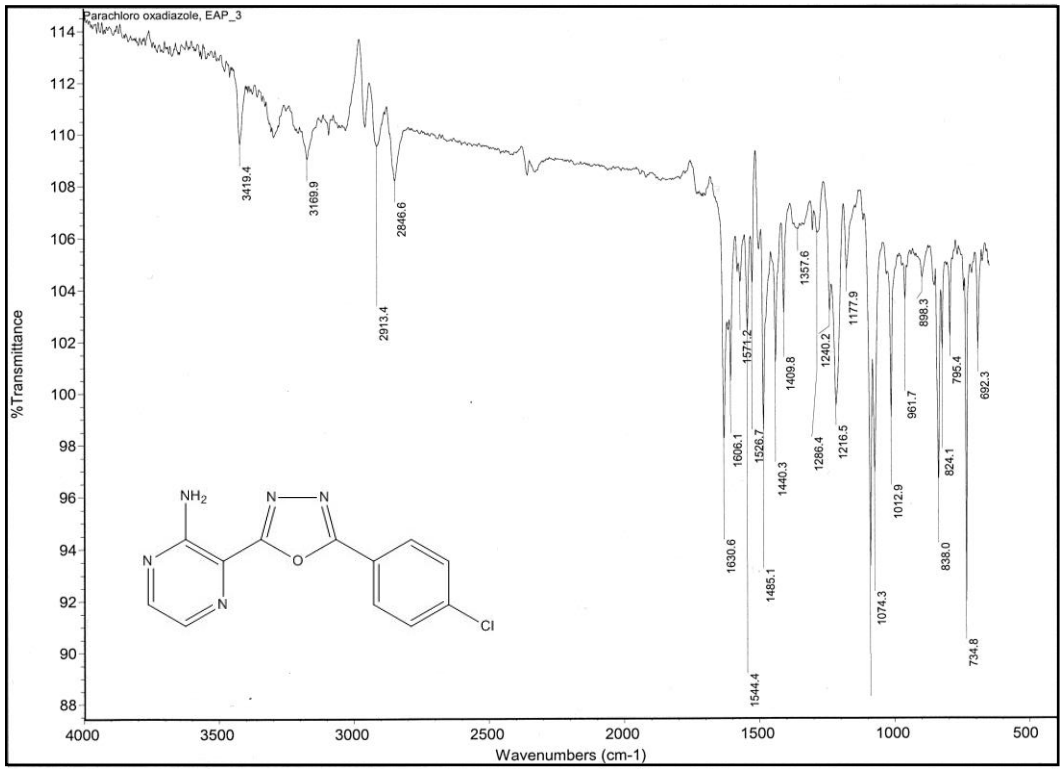
References

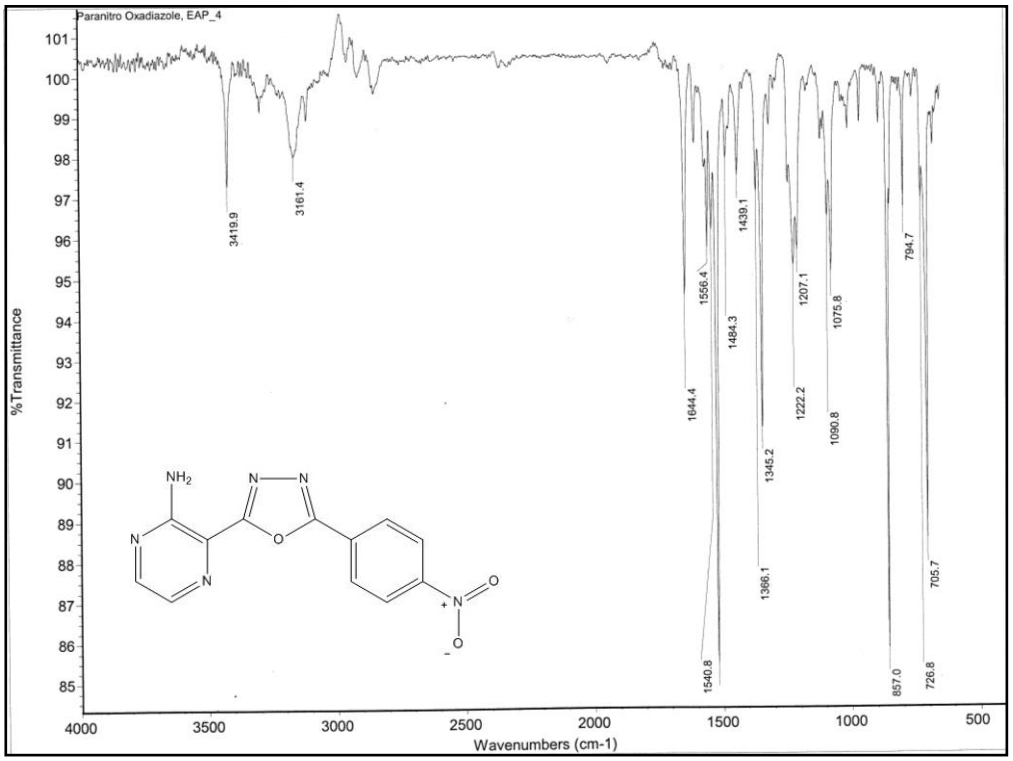
1. Dua, R.; Shrivastava, S.; Sonwane, S. K.; Srivastava, S. K. Pharmacological Significance of Synthetic Heterocycles Scaffold: A Review. *Advances in Biological Research*. **2011**, 5, pp 120-144.
2. Joule, J. A.; Mills, K. In Synthesis of aromatic heterocycles; Heterocyclic Chemistry; Blackwell Science Ltd: Oxford. **2000**. pp 4.
3. Kumar, K. A.; Jayaroopa, P.; Kumar, G. V. Comprehensive Review on the Chemistry of 1, 3, 4-Oxadiazoles and their Applications. *International Journal of Chem Tech Research*. **2012**. 4. pp 1782-1791.
4. Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Bahramnejad, M. A Facile Procedure for the One-Pot Synthesis of Unsymmetrical 2, 5-Disubstituted 1, 3, 4-Oxadiazoles. *Tetrahedron letters*. **2006**, 47, 6983-6986.
5. Charrier, J. et al. International Patent WO2011/143426 A1, November 17, **2011**. Iv
6. Silberberg, M. A.; Amateis, P. G. *Chemistry: The Molecular Nature of Matter and Change.* McGraw-Hill Education. **2015**. Pp 369-373.
7. Parikh, K. Synthesis, Antimicrobial Evaluation, and Structure Activity Relationship: Studies of New Biphenyl-2-Carbonitrile Clubbed 1,3,4-Oxadiazole Derivatives. *Pharmaceutical Chemistry Journal*. **2015**, 49, 523-529.
8. Agrawal, A. K.; Jenekhe, S. A. Synthesis and Processing of Heterocyclic Polymers as Electronic, Optoelectronic, and Nonlinear Optical Materials. 3. New Conjugated Polyquinolines with Electron-Donor Or-Acceptor Side Groups. *Chemistry of Materials.* **1993**, 5, 633-640.
9. Childers, K. Investigating the Synthesis of Heterocycles via Gold Catalyzed Cyclations and Cyclo-Dehydrating Reactions. Honors Thesis, Otterbein University. **2015.**
10. Merringer, K. Substituent Strength vs Reactivity: A Study of 1,3,4-Oxadiazoles and Electron Donating Groups. Honors Thesis, Otterbein University. **2017.**
11. Cambridge Crystallographic Data Centre. Mercury – Crystal Structure Visualization, Exploration and Analysis Made Easy. https://www.ccdc.cam.ac.uk/solutions/csd-system/components/mercury/ (accessed Mar 1, 2017).

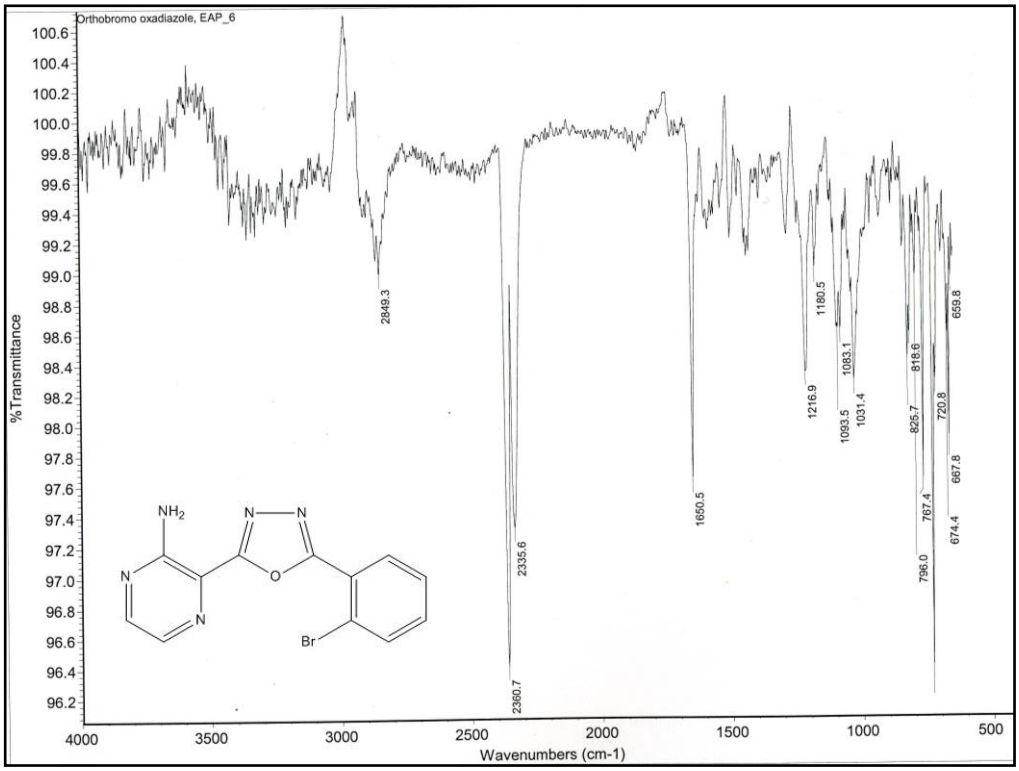
12. Webber, A. E. Transition Metal Catalysis and the Synthesis of Biologically Interesting Heterocycles: A Study of Gold-Catalyzed Intermolecular Cyclization and Palladium-Catalyzed Suzuki Cross-Coupling. Honors thesis, Otterbein University. **2015**.
13. Charrier, J. et al. International Patent WO2011/143426 A1, November 17, **2011**.

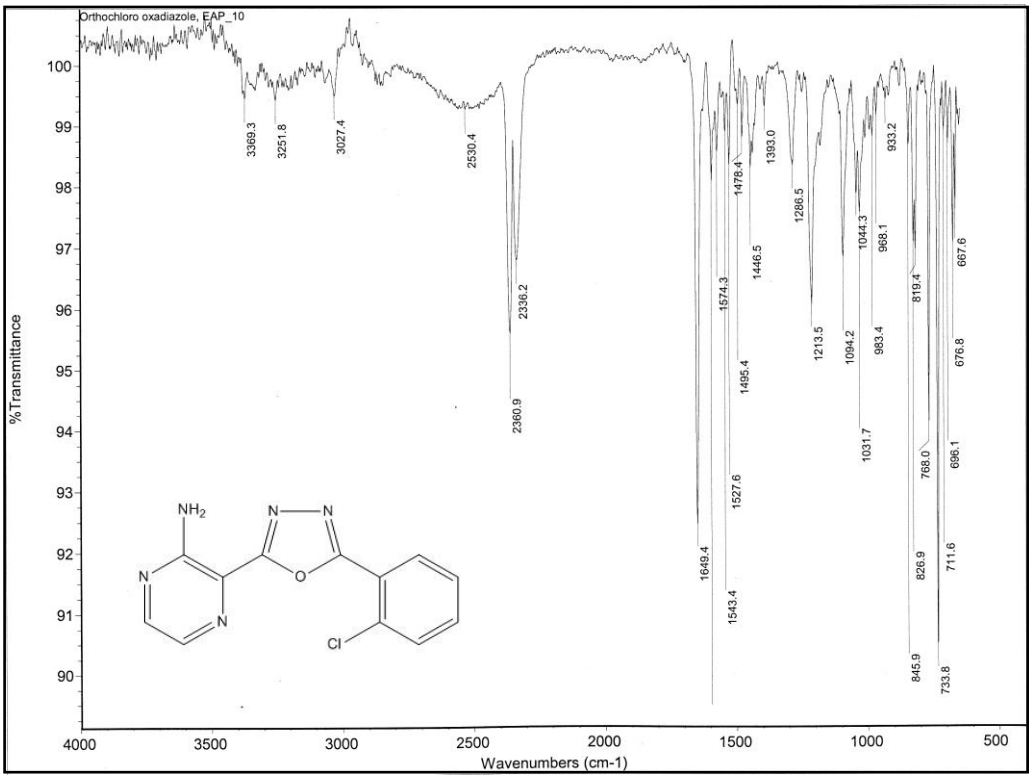
Appendix


P-Br, EAP_2
%Transmittance
Wavenumbers (cm-1)
3359.9
2501.4
1785.2
1652.3
1599.1
1586.7
1573.3
1537.3
1478.2
1411.1
1296.2
1219.6
1173.4
1028.0
1009.9
979.9
962.0
935.4
839.1
830.1
777.2
709.3
693.5
676.2
NH2
N
O
Br


Parachloro oxadiazole, EAP_3
%Transmittance
Wavenumbers (cm-1)
3419.4
3169.9
2846.6
2913.4
1630.6
1606.1
1571.2
1544.4
1526.7
1485.1
1440.3
1409.8
1357.6
1286.4
1240.2
1216.5
1177.9
1074.3
1012.9
961.7
898.3
838.0
824.1
795.4
734.8
692.3
NH2
N
O
Cl


Paranitro Oxadiazole, EAP_4
%Transmittance
Wavenumbers (cm-1)
3419.9
3161.4
1644.4
1556.4
1540.8
1484.3
1439.1
1366.1
1345.2
1222.2
1207.1
1090.8
1075.8
857.0
794.7
726.8
705.7
NH2
N
O
+
-


Orthobromo oxadiazole, EAP_6
%Transmittance
Wavenumbers (cm-1)
2849.3
2360.7
2335.6
1650.5
1216.9
1180.5
1093.5
1083.1
1031.4
825.7
818.6
796.0
767.4
720.8
674.4
667.8
659.8
NH2
N
O
Br


Orthochloro oxadiazole, EAP_10
%Transmittance
Wavenumbers (cm-1)
3369.3
3251.8
3027.4
2530.4
2360.9
2336.2
1649.4
1574.3
1543.4
1527.6
1495.4
1478.4
1446.5
1393.0
1286.5
1213.5
1094.2
1044.3
1031.7
983.4
968.1
933.2
845.9
826.9
819.4
768.0
733.8
711.6
696.1
676.8
667.6
NH2
N
O
Cl