# Green Synthesis of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles and Biological Testing Against *Staphylococcus epidermidis*.

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**Abstract:**

Oxadiazoles and thiadiazoles are privileged scaffolds—compounds known to interact with a wide array of receptors—with known activity against gram-positive bacterial strains. In this paper, we attempted to synthesize a variety of semicarbazones, thiosemicarbazones, and their corresponding 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. The oxadiazoles were tested to determine their biological activity against a Biosafety Level I strain of *Staphylococcus epidermidis*. To make the reactions green, the semicarbazones and thiosemicarbazones were synthesized using ethyl lactate as the solvent, as it has been designated as a green solvent by the American Chemical Society. Ultimately, we successfully synthesized benzaldehyde semicarbazone (**A1**), 4-bromobenzaldehyde semicarbazone, (**A2**), 4-chlorobenzaldehyde semicarbazone (**A3**), 4-hydroxybenzaldehyde semicarbazone (**A4**), 4-isopropylbenzaldehyde semicarbazone (**A5**), green benzaldehyde oxadiazole (**B1**), standard benzaldehyde oxadiazole (**B1.1**), 4-bromobenzaldehyde oxadiazole (**B2**), 4-chlorobenzaldehyde oxadiazole (**B3**), 4-hydroxybenzaldehyde oxadiazole (**B4**), and 4-isopropylbenzaldehyde oxadiazole (**B5**). Benzaldehyde thiosemicarbazone (**A6**), 4-bromobenzaldehyde thiosemicarbazone (**A7**), 4-chlorobenzaldehyde thiosemicarbazone (**A8**), 4-hydroxybenzaldehyde thiosemicarbazone (**A9**), and 4-isopropylbenzaldehyde thiosemicarbazone (**A10**) were also successfully made. All 6 synthesized oxadiazoles tested were determined to be ineffective—up to 128 µg/mL—against *Staphylococcus epidermidis*. Ultimately, a novel green synthetic route was presented for 5 oxadiazoles (**B1** – **B5**), replacing toxic $Br_2$ with the more environmentally friendly pyridinium tribromide.

**Introduction:**

The chemical industry is a significant contributor to global warming as the industry is currently ranked as third-largest emitter of greenhouse gases.[1] In an effort to address the negative impact that the chemical industry has had on the environment and on human health, the 12 Principles of Green Chemistry were published by Anastas and Werner in 1998.[2] The 12 Principles of Green Chemistry present a variety of factors that should be considered when running a chemical reaction, including the use of less hazardous chemical synthesis methods (Principles 3), the employment of safer solvents (Principle 5), and designing reactions to maintain energy efficiency (Principle 6).[3] In our research, we have employed these principles in our efforts to synthesize semicarbazones, thiosemicarbazones, oxadiazoles, and thiadiazoles.

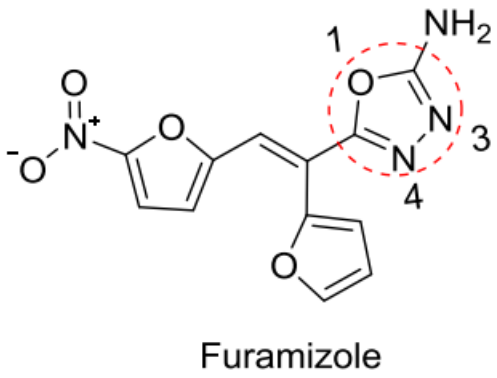
Oxadiazoles are a five-membered heterocyclic ring system that have been designated as privileged scaffolds for their biological activity against a variety of diseases. Oxadiazole derivatives have been found to have antibacterial, antiviral, blood pressure lowering, antifungal, antineoplastic, anticancer, antioxidant, anti-inflammatory and analgesic properties[4], making them a useful scaffold for drug development. Oxadiazoles can be useful in drugs because of their ability to contribute to ligand binding. Some drugs incorporate the oxadiazole scaffold for its ability to act as an aromatic linker that helps place substituents in the correct orientation or to replace carbonyl-containing compounds.[5] Four oxadiazole regioisomers exist (Figure 1), although the 1,2,3-oxadiazole is unstable in the cyclic form and will generally tautomerize with itself.[6] The 1,2,4 and 1,3,4 oxadiazole scaffolds are the most common regioisomers, and are the subject of most papers that investigate the medicinal potential of the oxadiazole scaffold. The 1,2,5-oxadiazole does appear in medicine, although it interacts with different targets than the 1,3,4 and 1,2,4-oxadiazole isomers, and will therefore not be discussed in this paper.


Figure 1. Four regioisomers of the oxadiazole scaffold.[6]

When comparing the 1,2,4 and 1,3,4 oxadiazole scaffolds, many similarities become apparent between the two structures. Both the 1,2,4 and 1,3,4 oxadiazoles allow substituents to be placed in similar positions on the oxadiazole so that they can maintain similar bond angles.[7] Despite having slight differences in substituent electronic environment, these two oxadiazole regioisomers generally result in comparable 3D arrangements and are therefore expected to bind similarly to their targets—compared to the 1,2,5 regioisomer—due to their ability to fit into receptors with wider pockets. Despite these similarities, the 1,3,4-oxadiazoles demonstrate more favorable lipophilicity (logD), aqueous solubility, and metabolic stability than their 1,2,4-counterparts. Drug candidates need to have lipophilicity to pass through the cell membrane, although a logD value that is too high indicates that the compound will be too hydrophobic to be able to interact with its molecular targets, so a logD less than 5 is generally preferred. 1,3,4-oxadiazoles also have lower affinity towards the hERG receptor, which indicates that they will

be associated with fewer cardiac side effects. hERG is a voltage-gated potassium channel, and drug candidates that have demonstrated a high affinity for the hERG receptor are typically associated with cardiac arrhythmias due to the inhibition of the cardiac potassium channel.[7] Therefore, 1,3,4-oxadiazoles generally demonstrate greater success as drug candidates and were the focus of our synthetic efforts in this research project.

The 1,3,4-oxadiazole regioisomer has been a well-known structure for the past 85 years and is used frequently in biological and chemical fields.[6] One area where oxadiazoles have shown biological promise is as antibacterial agents. Oxadiazoles are a relatively new class of non-β-lactam antibiotics capable of targeting cell-wall biosynthesis[8] and they have been designated as privileged scaffolds in part for their sustained efficacy against gram-positive bacterial strains. Oxadiazoles have even shown promise against a variety of gram-positive bacteria that have been historically difficult to treat—like multi-drug resistant strains of *Mycobacterium tuberculosis*—although they have no established effect against Gram-negative strains. [8] Furamizole is a current antibiotic containing the 1,3,4-oxadiazole ring (Figure 2).[9] The development of this antibiotic has encouraged other research groups to pursue drug development and synthetic projects incorporating the 1,3,4-oxadiazole scaffold.




Furamizole

Figure 2. Molecular structure of the antibiotic Furamizole.[7]

Another factor supporting the use of oxadiazoles in drug development is the rise of antibiotic resistant bacterial strains, and the subsequent need for new scaffolds in drug development. The World Health Organization (WHO) has classified the rise of microbial resistance as a significant threat to public development and global health.[10] This resistance has been driven by the overuse and/or misuse of antibiotics, which has resulted in an increase of bacteria that are unable to be treated with standard first-line antibiotics, known as superbugs.[11] The WHO estimates that in 2019 bacterial antimicrobial resistance was involved in 4.95 million deaths, and directly contributed to 1.27 million deaths.[10]

One disease that has been negatively impacted by the rise of antibiotic resistance is Tuberculosis (TB), which has seen a steady increase in the number of multi-drug resistant cases (MDR)—resistant to both first-line antibiotics isoniazid and rifampicin—over the past decade.[12] The rise of MDR among *Mycobacterium tuberculosis*, the bacteria that causes TB, has led to the push for the development of new anti-TB medications. Oxadiazoles are a scaffold that has

exhibited promise as a new anti-TB agent, primarily because of its ability to serve as a substitute for the hydrazide moiety that is crucial for the activity of the anti-TB drug isoniazid. Oxadiazoles have also been reported to interact with new and different anti-TB targets[7], indicating that they may have the capability to treat MDR-TB cases when traditional first-line drugs fail. In De, *et al.* the authors reviewed a variety of papers that were focused on the synthesis of oxadiazole-containing molecules for their potential use against TB.[7]

One group highlighted in the review was able to successfully synthesize 2-((5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl) sulfanyl)-N-phenethylacetamide (Figure 4) that had minimum inhibitory concentration values as low as 0.38 μM against an MDR strain of *M. tuberculosis*.[13] The authors proposed that the compound acted by inhibiting the enzyme decaprenylphosphoryl-β-D-ribofuranose-2'-oxidase (DprE1), which synthesizes an essential component of the bacterial cell wall. The 1,3,4-oxaidazole ring is generally thought to provide crucial hydrogen bonding interactions that allow the drug to bind to the target enzyme.[13]

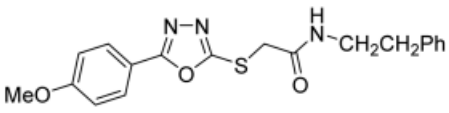



Figure 4: Structure of a 2-((5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl) sulfanyl)-N-phenethylacetamide that was shown to have 0.38 μM activity against at least one MDR strain of *M. tuberculosis*.[7]

One potential synthetic route for 1,3,4-oxadiazoles, is to start with semicarbazones, which themselves are made when an aldehyde or ketone is reacted with an amine, specifically an amine that is part of a semicarbazide ($H_2N - NH - CO - NH_2$).[14] Current synthesis methods for semicarbazones commonly use ethanol as the solvent, and generally require heat for the reaction to go forward. To make the reactions greener, we dissolved the aldehydes in ethyl lactate, and dissolved the semicarbazide HCl in water. Ethyl lactate has been designated as a green solvent by the American Chemical Society, as the production of the solvent is a closed loop—it is produced and broken down entirely by plants—and it has no significant negative effects towards the environment. Additionally, our semicarbazone synthesis reactions were run at room temperature, which increases the energy efficiency of the syntheses as well.

Common synthesis methods of oxadiazoles from semicarbazones utilize $Br_2$ which is a chemical that is hazardous for human health and dangerous for the environment.[15,16] $Br_2$ is categorized as a corrosive, environmentally hazardous, and acutely toxic chemical that can be deadly if inhaled. As $Br_2$ is a potent oxidizer, it can cause severe tissue damage if an individual is exposed for any length of time, and it is incredibly toxic to aquatic life as well.[17] To address Green Chemistry Principle number three, $Br_2$ was replaced with Pyridinium tribromide in our syntheses. Pyridinium tribromide is significantly less toxic than $Br_2$, both regarding human health and the environment, and so by making this substitution we greatly increased the safety of this synthesis.[18]

After successfully synthesizing and characterizing a variety of semicarbazones and oxadiazoles, the oxadiazoles were tested for their biological activity against a Biosafety Level 1 strain of *Staphylococcus epidermidis*. *S. epidermidis* is a gram-positive bacterial strain, and so we were interested in seeing whether the oxadiazoles that we synthesized had any antibacterial activity against this strain.[19]

In addition to 1,3,4-oxadiazoles, thiadiazoles are another five-membered heterocyclic ring system that has demonstrated promising biological activity. Like oxadaizoles, thiadiazoles also exist in four isomeric forms, with 1,3,4-thiadiazole considered to have the most biological potential[20]. Cefazolin and Cefazedone are two FDA-approved drugs that contain the 1,3,4-thiadiazole ring[20] Thiadiazoles are also thought to be good hydrogen-bond acceptors and electron donors and are thought to have even better lipophilicity (allowing them to easily cross the cell membrane) due to their mesoionic nature and the sulfur atom in the ring.[21] Mesoionic compounds have a neutral electronic charge while also being dense and polarizable, allowing them to cross the cellular membrane easily while still being able to interact with their targets once inside the cell. In addition to their antibacterial activity, 1,3,4-thiadiazoles also show up in anticancer drugs—like in the FDA approved drug Azetepa[20] (Figure 5)—and are a promising scaffold in anti-cancer drug design.


Figure 5: Azetepa, an anti-cancer drug, containing the 1,3,4-thiadiazole ring, that acts as an alkylating agent.[20]

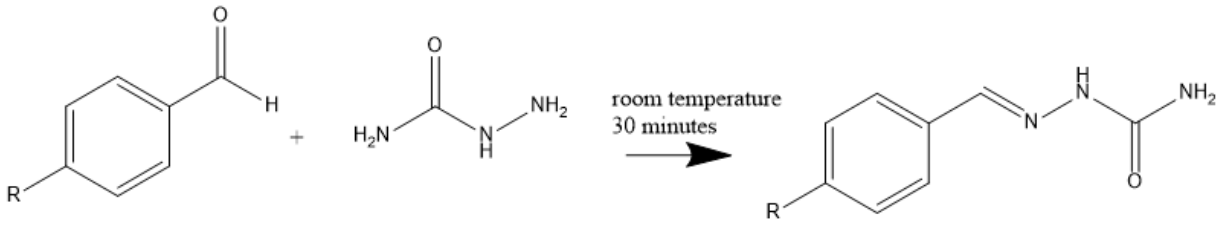
One area of anti-cancer drug development research is the synthesis of carbonic anhydrase inhibitors. Carbonic anhydrase is an enzyme whose activity has been shown to be upregulated in cancer cells, and thus has become a target for cancer therapies. [20] Supuran *et al.* successfully synthesized a 1,3,4-thiadiazole containing molecule that was shown to have promising activity against Carbonic Anhydrase II (CA II)[22], and molecular docking studies confirmed that the activity was in part due to the ability of the two nitrogens to act as hydrogen bond acceptors or to chelate zinc metal ions necessary for CA II function.[20]

1,3,4-thiadiazoles can be synthesized from thiosemicarbazones, and the same synthetic route was followed as for the 1,3,4-oxadiazoles, but the semicarbazide HCl was replaced with thiosemicarbazide HCl.

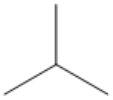
In this project, we successfully synthesized 5 semicarbazones and thiosemicarbazones using greener methods. 5 known oxadiazoles were also synthesized with a novel synthetic route utilizing Pyridinium tribromide in place of toxic $Br_2$.

**Results/Discussion:**

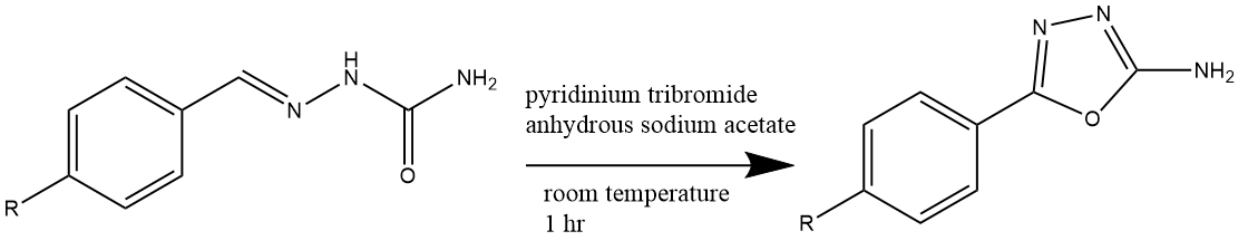
We were able to successfully synthesize a variety of semicarbazones and oxadiazoles (synthetic routes shown in Schemes 1 and 2, respectively) and tested them for their antibacterial activity against a BSL-1 strain of *Staphylococcus epidermidis* via a minimum inhibitory concentration (MIC) assay. Analysis data—NMR, IR, melting point—confirmed that we had the most success with the synthesis of **A1**, **A2**, **A3**, **A4**, **A5**, **B1.1**, **B1**, **B2**, **B3**, **B4**, and **B5**. Semicarbazones **A1** – **A5** all contained IR peaks around 3400, 3000, and 1640 – 1670 $cm^{-1}$, as would be expected for the functional groups present on the molecule (Figure 6 shows IR of compound **A2**). **B1.1**, **B1**, **B2**, **B3**, **B4**, and **B5** all contained the imine peak around 1690 $cm^{-1}$, the benzene C-H peak around 3100 $cm^{-1}$, and the primary amine peak at 3400 $cm^{-1}$. Another indication that the oxadiazole had been made was the loss of the amide peak at 1670 $cm^{-1}$, that was present in all the semicarbazone compounds' IR spectra (Figure 7 shows IR of compound **B2**). Some of the sample melting points were slightly (approx. 10° C) below the published melting points (**A1**, **A2**, **A5**, and **B4**), which could have been because of some light impurities in the samples (Table 2). Most of the samples were white in color, however, compounds **B1.1** and **B4** were yellow, which could have been because of sample impurities. Some of the yellow color was removed via recrystallization with 95% ethanol. Nuclear Magnetic Resonance (NMR) data was collected for all oxadiazole samples (**B1** – **B5**) and peaks were observed in the $^{1}H$ NMR spectra that corresponded to the primary amino group, the hydrogen on the imine, and benzene ring on those molecules, the three peaks necessary to confirm that all 1,3,4-oxadiazoles were successfully synthesized (Figure 8 shows NMR for compound **B3**). We were able to bring the reaction time of these syntheses down from 12 hours for the second step to 1 hour. This was accomplished by dissolving all the reagents together—in glacial acetic acid—instead of waiting for them to dissolve in glacial acetic acid before combining them. Currently, the total reaction time for these syntheses is approximately 1.5 hours start to finish, down from about 13 hours last semester. The success of these syntheses is significant because it improves the sustainability of these reactions. Most current synthetic routes for 1,3,4-oxadiazoles utilize strong acids and high temperatures, which decreases the safety and sustainability of these reactions.[5] In the past decade alone, 686 patent applications were filed for drug discovery compounds that include the oxadiazole scaffold.[23] Despite the increased prevalence of 1,3,4-oxadiazoles in drug development, few green syntheses have been proposed for the scaffold, and there are no published syntheses that utilize pyridinium tribromide as a reagent. The success of these reactions provides another synthetic route that could be adapted to produce 1,3,4-oxadiazoles for use in therapeutics and in drug discovery programs.



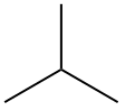

R =

| | | |
|---|---|---|
| **A1** | H— | (2*E*)-2-(phenylmethylene)hydrazinecarboxamide |
| **A2** | Br— | (2*E*)-2[(4-bromophenyl)methylene]hydrazinecarboxamide |
| **A3** | Cl— | (2*E*)-2[(4-chlorophenyl)methylene]hydrazinecarboxamide |
| **A4** | HO— | (2*E*)-2[(4-hydroxyphenyl)methylene]hydrazinecarboxamide |
| **A5** |  | (2*E*)-2[(4-isopropylphenyl)methylene]hydrazinecarboxamide |

*Scheme 1: Synthesis of substituted semicarbazones with corresponding R groups:* **A1**, **A2**, **A3**, **A4**, **A5**.




R =

| | | |
|---|---|---|
| **B1** | H— | 2-amino-5-phenyl-1,3,4-oxadiazole |
| **B1.1** | | (compound **B1** with $Br_2$ as reagent) |
| **B2** | Br— | 2-amino-5-(4-bromophenyl)-1,3,4-oxadiazole |
| **B3** | Cl— | 2-amino-5-(4-chlorophenyl)-1,3,4-oxadiazole |
| **B4** | HO— | 2-amino-5-(4-hydroxyphenyl)-1,3,4-oxadiazole |
| **B5** |  | 2-amino-5-(4-isopropylphenyl)-1-3,4-oxadiazole |

*Scheme 2: Synthesis of substituted 1,3,4-oxadiazoles with corresponding R groups:* **B1**, **B1.1**, **B2**, **B3**, **B4**, **B5**.

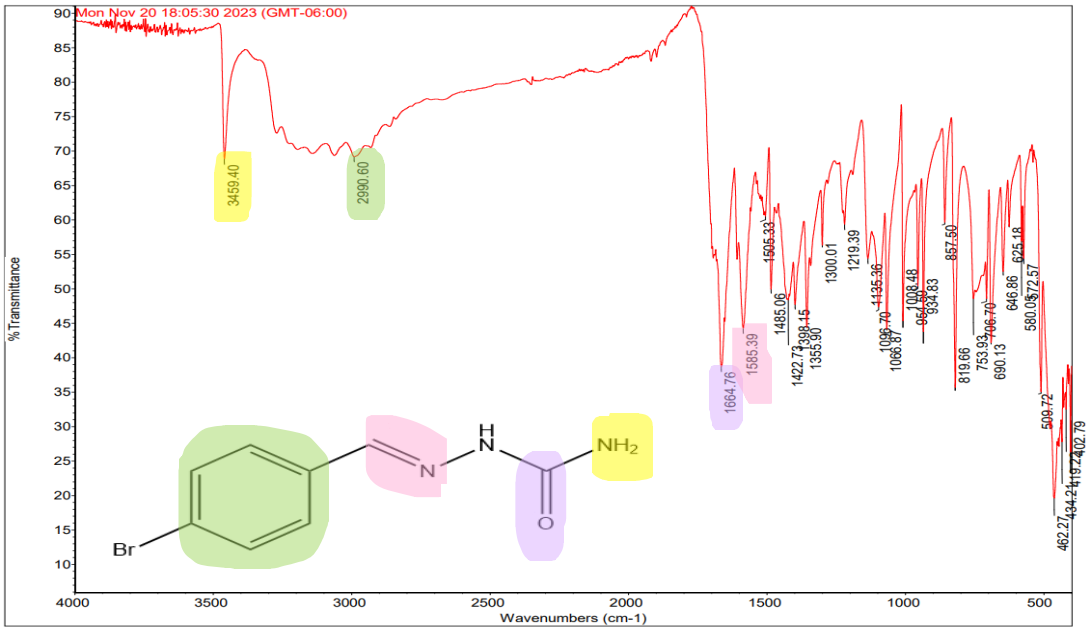



Figure 6: IR spectra for compound **A2**.

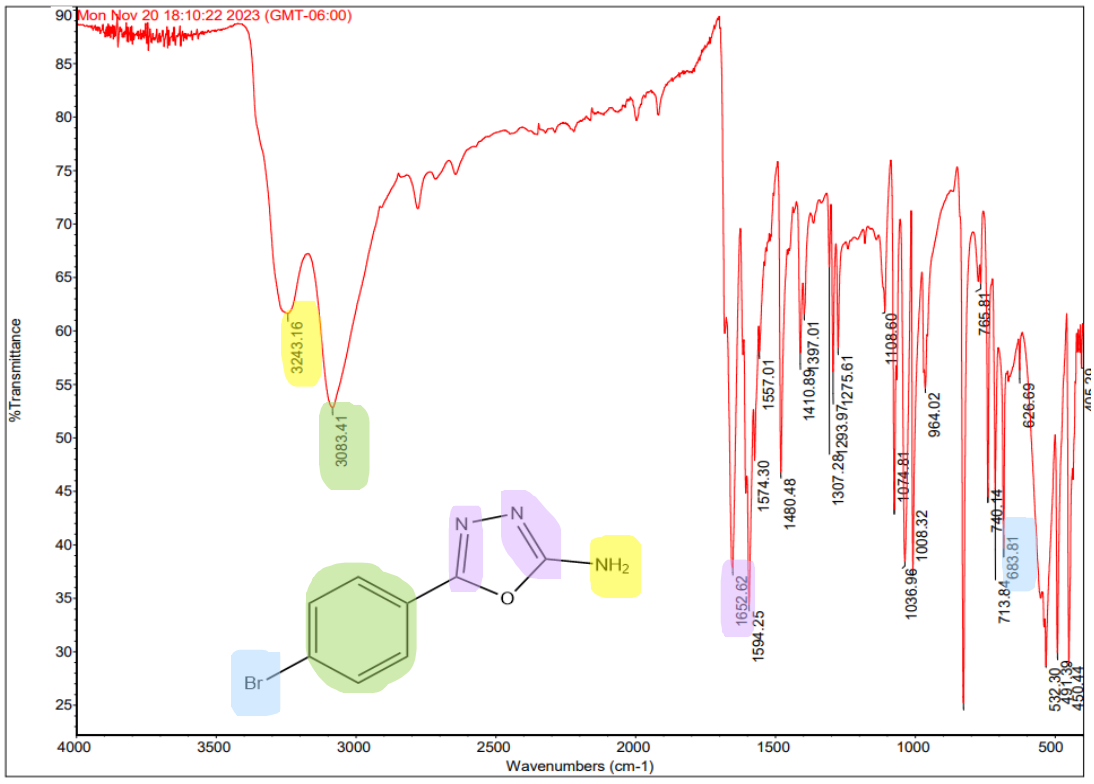



Figure 7: IR spectra for compound **B2**.

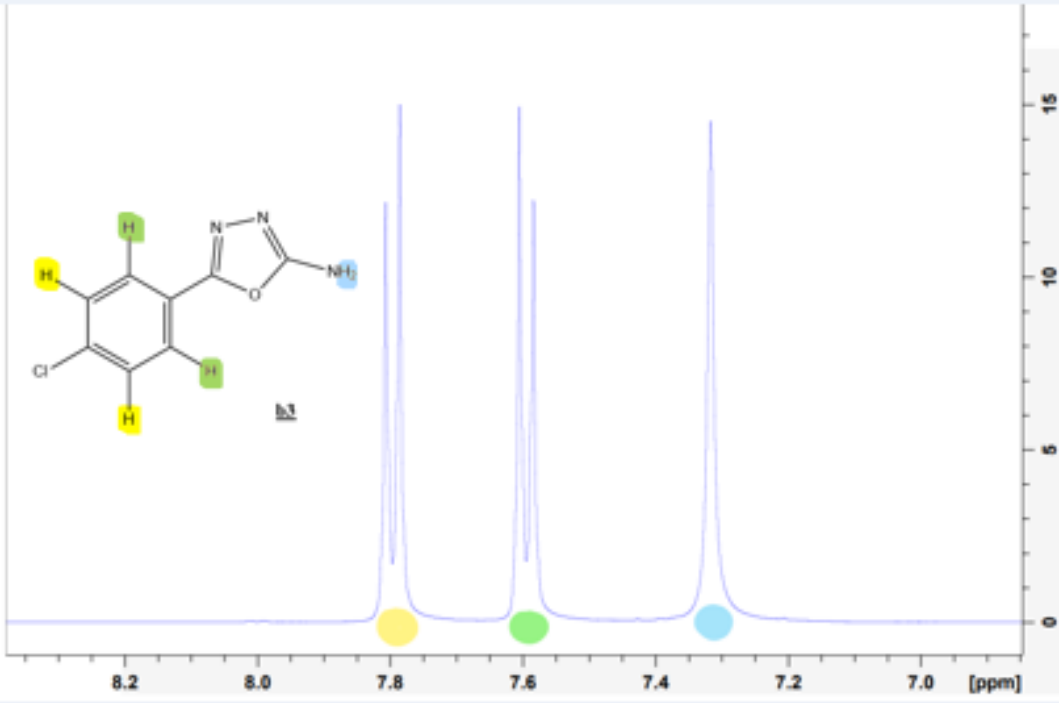



Figure 8: $^{1}$H NMR spectrum for compound **B3**.

Following the synthesis of the semicarbazones and oxadiazoles, an MIC assay was run to test the oxadiazoles for antibacterial activity against *S. epidermidis* (Figure 9). The MIC value for a compound is the lowest concentration (in µg/mL) that can inhibit the growth of a bacterial strain.[24] In the MIC assay, *S. epidermidis* was incubated in a 96 well-plate in the presence of increasing concentrations of either a test compound or a control. Linezolid was used as the positive control, as it is a known antibiotic that is effective against *S. epidermidis*.[25] Dimethyl sulfoxide (DMSO) was used as the negative control, as it has no established effect against *S. epidermidis*, and it was also the solvent used to dissolve all the test samples. All plates were run successfully—Linezolid showed activity against *S. epidermidis* at approx. 0.75 µg/mL and DMSO had no activity—but none of the tested compounds (**B1.1**, **B1**, **B2**, **B3**, **B4**, **B5**) demonstrated any level of activity against *S. epidermidis*, even at the highest concentration of 128 µg/mL (Table 1). There is a possibility that the compounds were not large enough to induce any biological effect, as most published anti-bacterial oxadiazoles utilize a much larger scaffold than the compounds that we tested.[26]

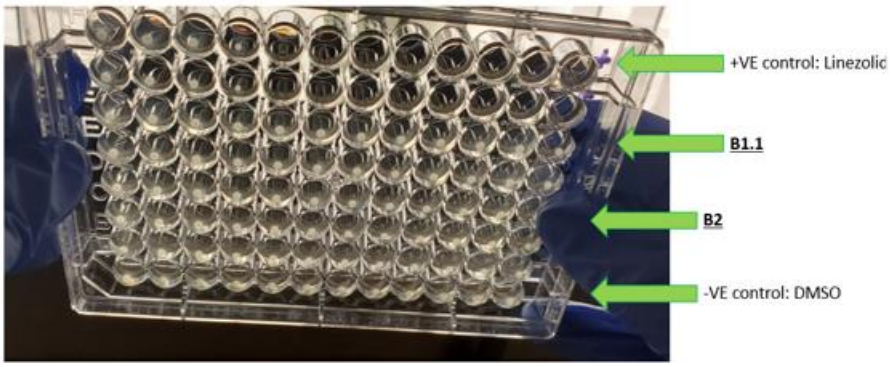



Figure 9: MIC assay of two compounds—B1.1. and B2—against a gram-positive strain of *S. epidermidis*.

**Table 1:** Biological activity of each synthesized oxadiazole against BSL-1 strain of *S. epidermidis*, determined via an MIC assay.

| **Compounds** | **Active against *Staphylococcus Epidermidis*?** |
|---|---|
| **B1** | No |
| **B1.1** | No |
| **B2** | No |
| **B3** | No |
| **B4** | No |
| **B5** | No |

For the thiosemicarbazones, **A6**, **A7**, **A8**, **A9**, and **A10** were all able to be successfully synthesized (Scheme 3). All compounds had IR peaks at 3400, 3000, and 1600 $cm^{-1}$, corresponding to the functional groups on those compounds (Figure 11 shows IR of compound **A7**). $^1$H NMR was collected for **A6** – **A10**, further confirming that those compounds were synthesized correctly. **A6** – **A10** all had the necessary $^1$H NMR peaks corresponding to the primary amine, imine, and benzene ring in the thiosemicarbazones. The melting point data collected for compounds **A6** – **A10** also indicated that the correct compounds were made, as they all relatively matched the melting points reported in SciFinder for each of the thiosemicarbazones (Table 2).

IR and $^1$H NMR spectra for the thiadiazoles indicates that those compounds were not successfully synthesized (Scheme 4). Sulfur and oxygen undergo different chemistry in many cases, and so it is not completely surprising that the 1,3,4-thiadiazole synthesis reaction did not work the same way as the 1,3,4-oxadaizole synthesis. Sulfur, unlike oxygen, can form more than two covalent bonds and so the 1,3,4-thiadiazole ring is sometimes known to react at the sulfur heteroatom to add an additional substituent there. The C=S bond in the thiosemicarbazone is weaker and less polar than the C=O bond in the semicarbazones, which could lead to the C=S

bond being more reactive, although it depends on the reaction conditions used. Research into 1,3,4-thiadiazoles has demonstrated that they are stable in acidic conditions—not very susceptible to attack by acids—but are easily cleaved by bases and are sensitive to nucleophilic attack.[21] Our 1,3,4-thiadiazole synthesis reactions were run in glacial acetic acid, which is a weak acid. To improve the synthesis in the future, we will use a stronger acid—such as sulfuric acid—to try and stabilize the 1,3,4-thiadiazole product once it is formed. Additionally, 2-amino-1,3,4-thiadiazoles—the compounds that we have been making—have been shown to readily undergo rearrangements at 150 °C into isomeric triazolinethiones.[21] Other 1,3,4-thiadiazoles have been shown to rearrange as well, as shown in Figure 10. We do not believe that this has happened in our case as our reactions were kept at room temperature, but it is worth noting that a rearrangement of the 2-amino-1,3,4-thiadiazole product could have occurred, which might be contributing to the issues that we are facing with this reaction.

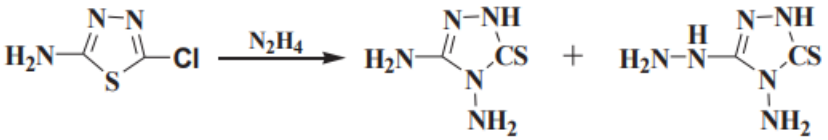
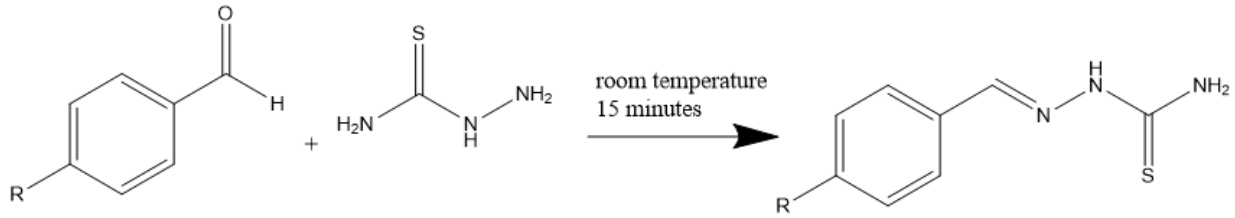
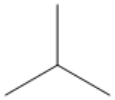
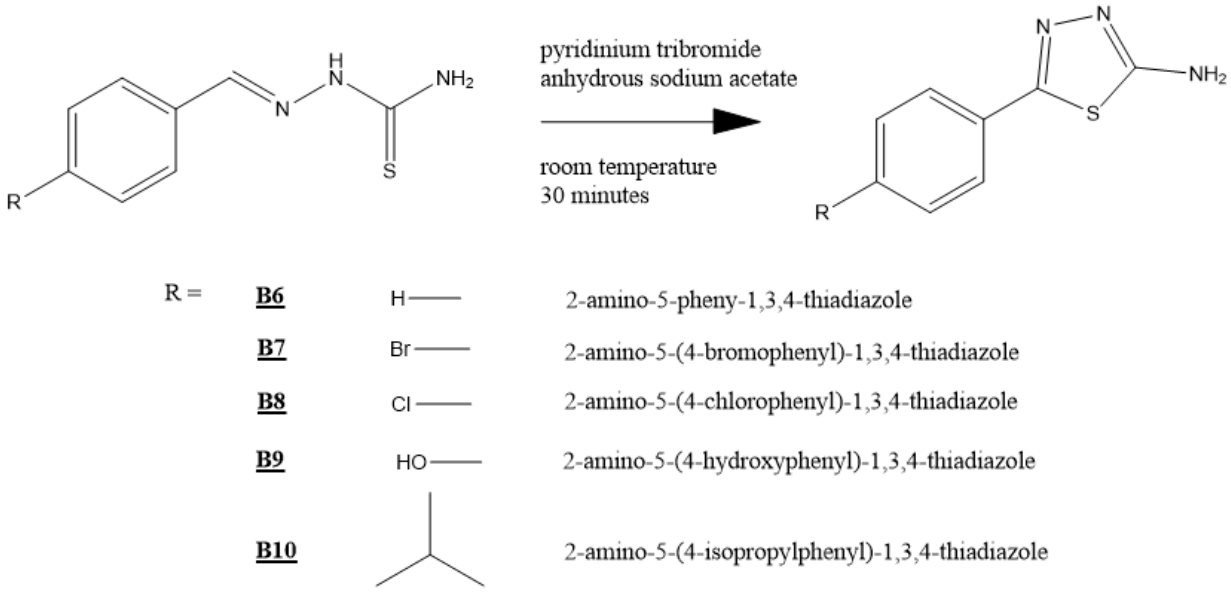



Figure 10: Example of a common 1,3,4-thiadiazole rearrangement.




| R = | | | |
|---|---|---|---|
| **A6** | H— | (2*E*)-2-(phenylmethylene)hydrazinethiocarboxamide |
| **A7** | Br— | (2*E*)-2[(4-bromophenyl)methylene]hydrazinethiocarboxamide |
| **A8** | Cl— | (2*E*)-2[(4-chlorophenyl)methylene]hydrazinethiocarboxamide |
| **A9** | HO— | (2*E*)-2[(4-hydroxyphenyl)methylene]hydrazinethiocarboxamide |
| **A10** |  | (2*E*)-2[(4-isopropylphenyl)methylene]hydrazinethiocarboxamide |

*Scheme 3: Synthesis of substituted thiosemicarbazones:* **A6**, **A7**, **A8**, **A9**, **A10**.




*Scheme 4: Synthesis of substituted thiadiazoles:* **B6**, **B7**, **B8**, **B9**, **B10**.

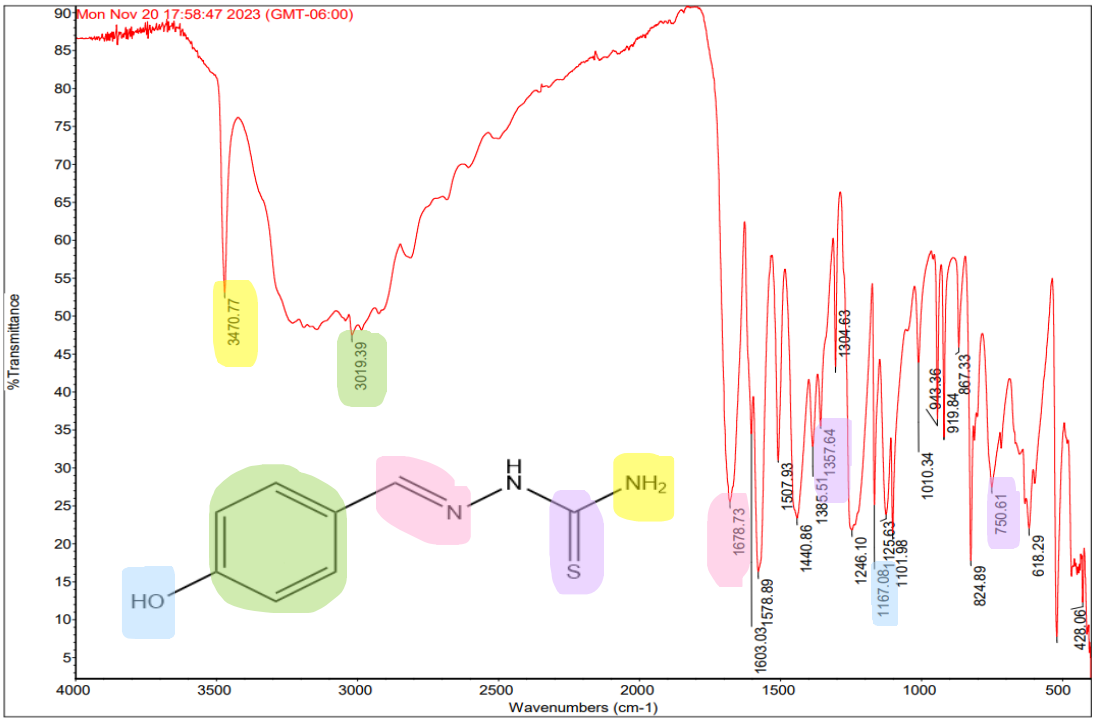



Figure 11: IR spectra for compound **A9**.

**Table 2:** Melting point (experimental and literature) and percent yield data for all synthesized semicarbazones, thiosemicarbazones, and oxadiazoles.

| **Compound** | **Percent Yield** (%) | **Experimental Melting Point** (°C) | **Literature Melting Point** (°C) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **A1** | 100 | 199.3 – 200.4 | 212-213[27] |
| **A2** | 100 | 207.8 – 210.9 | 227 – 228[28] |
| **A3** | 97.84 | 199.3 – 200.4 | 202 – 204[29] |
| **A4** | 100 | 181.9 – 182.3 | 186[30] |
| **A5** | 75.83 | 182.6 – 186.6 | 210 – 211[31] |
| **A6** | 38.84 | 155 | 156[32] |
| **A7** | 88.44 | 203 – 204 | 202 – 203.5[33] |
| **A8** | 93.60 | 203 | 201 – 203[34] |
| **A9** | 92.20 | 218 – 219 | 210.7 – 212.1[35] |
| **A10** | 38.81 | 144 – 147 | 145 – 150[36] |
| **B1** | 57.37 | 219 – 220 | 220 – 222[37] |
| **B1.1** | 61.17 | 219 – 220 | 220 – 222 |
| **B2** | 86.21 | 253.2 – 260.1 | 259 – 260[38] |
| **B3** | 37.37 | 247.1 – 248.1 | 243 – 245[39] |
| **B4** | 52.55 | 258 – 262 | 274 – 276[40] |
| **B5** | 47.51 | 236 – 239.9 | unknown |

**Conclusion:**

We were successfully able to synthesize 5 semicarbazones (**A1**, **A2**, **A3**, **A4**, **A5**) and 5 thiosemicarbazones (**A6**, **A7**, **A8**, **A9**, **A10**) by using a green solvent system and running the reactions at room temperature. Reactions times and yields comparable to the literature values were achieved for these compounds. Additionally, we were able to successfully replicate a published synthesis of benzaldehyde oxadiazole using standard regents (**B1.1**)[15] and were also able to successfully synthesize five oxadiazoles (**B1**, **B2**, **B3**, **B4**, **B5**) while replacing $Br_2$ with pyridinium tribromide to make the reactions more green. The reaction time for the 1,3,4-oxadiazole synthesis was also improved, resulting in a total run time (first step to final step) that was comparable to literature syntheses. Ultimately, this reaction scheme could be applied to other 1,3,4-oxadiazole derivatives in drug discovery and development processes, to improve the sustainability of those reactions.

By running an MIC assay with our compounds against *S. epidermidis*, we determined that, unfortunately, our compounds do not have any activity against this BSL-1 strain. It is likely that additional modifications to the 1,3,4-oxadiazole structure will address this with an aim to improve activity.

**Experimental:**

**Synthesis of benzaldehyde semicarbazone, A1:**

5.486 g (0.0492 mol) of semicarbazide HCl was dissolved in the minimum amount of water (9.0 mL). 5 mL (0.0492 mol) of benzaldehyde was then mixed with 7.5 mL 80:20 ethyl lactate: water. The benzaldehyde solution was then added to the semicarbazide solution, and the reaction ran for approximately 15 minutes at room temperature. The reaction mixture was then gravity filtered and left to dry in the oven overnight. Product was obtained in 100% yield as a white solid: mp 199.3 – 200.4 °C; $R_f$ 0.213 (60:40 ethyl acetate: hexane); IR (ATR, diamond, neat, $cm^{-1}$) 3457, 3631, 3063, 2989, 1644.

**Synthesis of 4-bromobenzaldehyde semicarbazone, A2:**

0.686 g (0.00615 mol) of semicarbazide HCl was dissolved in 1.9 mL of water. 1.138 g (0.00615 mol) of 4-bromobenzaldehyde was dissolved in a minimum amount of 80:20 ethyl lactate: water (3.25 mL). The 4-bromobenzaldehyde solution was then added to the semicarbazide solution, and the reaction ran for approximately 15 minutes at room temperature. The reaction mixture was then gravity filtered and left to dry in the oven overnight. Product was obtained in 100% yield as a white solid: mp 207.8 – 210.9 °C; $R_f$ 0.319 (60:40 ethyl acetate: hexane); IR (ATR, diamond, neat, $cm^{-1}$) 3459, 2991, 1664.

**Synthesis of 4-chlorobenzaldehyde semicarbazone: A3:**

2.743 g (0.0246 mol) of semicarbazide HCl was dissolved in 6.5 mL of water. 3.458 g (0.0246 mol) of 4-chlorobenzaldehyde was then dissolved in the minimum amount of 80:20 ethyl lactate: water (8.5 mL). The 4-chlorobenzaldehyde solution was then added to the semicarbazide solution, and the reaction ran for approximately 15 minutes at room temperature. The reaction mixture was then gravity filtered and left to dry in the oven overnight. Product was obtained in 97.84% yield as a white solid: mp 199.3 – 200.4 °C; $R_f$ 0.196 (60:40 ethyl acetate: hexane); IR (ATR, diamond, neat, $cm^{-1}$) 3460, 3139, 1662.

**Synthesis of 4-hydroxybenzaldehyde semicarbazone, A4:**

2.744 g (0.0246 mol) of semicarbazide HCl was dissolved in 7.5 mL of water. 3.004 g (0.0246 mol) of 4-hydroxybenzaldehyde was then dissolved in the minimum amount of 80:20 ethyl lactate: water (7.5 mL). The 4-hydroxybenzaldehyde solution was then added to the semicarbazide solution, and the reaction ran for approximately 15 minutes at room temperature. The reaction mixture was then gravity filtered and left to dry in the oven overnight. Product was obtained in 97.84% yield as a white solid: mp 181.9 – 182.3 °C; $R_f$ 0.164 (60:40 ethyl acetate: hexane); IR (ATR, diamond, neat, $cm^{-1}$) 3470, 3019, 1678.

**Synthesis of 4-isopropylbenzaldehyde semicarbazone, A5:**

2.551 g (0.0246 mol) of semicarbazide HCl was dissolved in 7.5 mL of water. 3.657 g (0.0246 mol) of 4-isopropylbenzaldehyde was then dissolved in the minimum amount of 80:20 ethyl lactate: water (7.5 mL). The 4-isopropylbenzaldehyde solution was then added to the semicarbazide solution, and the reaction ran for approximately 15 minutes at room temperature. The reaction mixture was then gravity filtered and left to dry in the oven overnight. Product was

obtained in 75.83% yield as a white solid: mp 182.6 – 186.6 °C; $R_f$ 0.154 (60:40 ethyl acetate: hexane); IR (ATR, diamond, neat, $cm^{-1}$) 3460, 3229, 3163, 3067, 2954, 2861, 1679, 1644.

**Synthesis of benzaldehyde thiosemicarbazone, A6:**

3.19 g (0.025 mol) of thiosemicarbazide HCl was dissolved in 7.5 mL of water. 2.551 mL (0.025 mol) of benzaldehyde was then dissolved in the minimum amount of 80:20 ethyl lactate: water (7.5 mL). The benzaldehyde solution was then added to the thiosemicarbazide solution, and the reaction ran for approximately 15 minutes at room temperature. The reaction mixture was then gravity filtered and left to dry in the oven overnight. Product was obtained in 38.84% yield as a white solid: mp: 155 °C; IR (ATR, diamond, neat, $cm^{-1}$) 3388, 3235, 3152, 3024, 2984, 1597, 1531. $^1$H NMR (400 MHz, DMSO-d6) δ 11.41 (s, 1H), 8.20 (s, 1H), 7.99 (d, 2H), 7.79 (d, 2H), 7.40 (d, 3H).

**Synthesis of 4-bromobenzaldehyde thiosemicarbazone, A7:**

1.5312 g (0.012 mol) of semicarbazide HCl was dissolved in 7.5 mL of water. 2.1846 g (0.012 mol) of 4-bromobenzaldehyde was dissolved in 7.5 m: of 80:20 ethyl lactate: water. The 4-bromobenzaldehyde solution was then added to the semicarbazide solution, and the reaction ran for approximately 15 minutes at room temperature. The reaction mixture was then gravity filtered and left to dry in the oven overnight. Product was obtained in 88.44% yield as a white solid: mp: 203 – 204 °C IR (ATR, diamond, neat, $cm^{-1}$) 3433, 3283, 3163, 2982, 1588, 1520 $^1$H NMR (400 MHz, DMSO-d6) δ 11.43 (s, 1H), 8.19 (s, 1H), 8.02 (s, 2H), 7.71 (d, 2H), 7.55 (d, 2H)

**Synthesis of 4-chlorobenzaldehyde thiosemicarbazone: A8:**

1.816 g (0.0142 mol) of thiosemicarbazide HCl was dissolved in 7.5 mL of water. 2.00 g (0.0142 mol) of 4-chlorobenzaldehyde was then dissolved in 7.5 mL of 80:20 ethyl lactate: water. The 4-chlorobenzaldehyde solution was then added to the thiosemicarbazide solution, and the reaction ran for approximately 15 minutes at room temperature. The reaction mixture was then gravity filtered and left to dry in the oven overnight. Product was obtained in 93.60% yield as a white solid: mp: 203 °C; IR (ATR, diamond, neat, $cm^{-1}$) 3434, 3275, 3161, 2984, 1598, 1522. $^1$H NMR (400 MHz, DMSO-d6) δ 11.43 (s, 1H), 8.18 (s, 1H), 7.98 (s, 2H), 7.80 (d, 2H), 7.41 (d, 2H).

**Synthesis of 4-hydroxybenzaldehyde thiosemicarbazone, A9:**

1.9140 g (0.015 mol) of thiosemicarbazide HCl was dissolved in 7.5 mL of water. 1.8318 mL (0.015 mol) of 4-hydroxybenzaldehyde was then dissolved in the minimum amount of 80:20 ethyl lactate: water (7.5 mL). The 4-hydroxybenzaldehyde solution was then added to the thiosemicarbazide solution, and the reaction ran for approximately 15 minutes at room temperature. The reaction mixture was then gravity filtered and left to dry in the oven overnight. Product was obtained in 92.20% yield as a yellow solid: mp: 218 – 219 °C IR (ATR, diamond, neat, $cm^{-1}$) 3464, 3357, 3113, 1608, 1581. $^1$H NMR (400 MHz, DMSO-d6) δ 11.20 (s, 1H), 9.81 (s, 1H), 7.91 – 8.00 (s, 2H), 7.77 (s, 1H), 7.57 (d, 2H), 7.34 (d, 2H).

**Synthesis of 4-isopropylbenzaldehyde thiosemicarbazone, A10:**

1.9140 g (0.015 mol) of thiosemicarbazide HCl was dissolved in 7.5 mL of water. 2.2230 g (0.015 mol) of 4-isopropylbenzaldehyde was then dissolved in the minimum amount of 80:20 ethyl lactate: water (7.5 mL). The 4-isopropylbenzaldehyde solution was then added to the thiosemicarbazide solution, and the reaction ran for approximately 15 minutes at room temperature. The reaction mixture was then gravity filtered and left to dry in the oven overnight. Product was obtained in 38.81% yield as a white solid: mp: 144 – 147 °C; IR (ATR, diamond, neat, $cm^{-1}$) 3406, 3272, 3151, 2956, 2924, 1587, 1533. $^1$H NMR (400 MHz, DMSO-d6) δ 11.332 (s, 1H), 8.12 (s, 1H), 7.97 (s, 1H), 7.88 (s, 1H), 7.65 (d, 2H), 7.22 (d, 2H), 2.83 – 2.87 (m, 1H), 1.16 (d, 6H).

**Standard synthesis of benzaldehyde oxadiazole, <u>B1.1</u>:**

0.75 g of benzaldehyde semicarbazone and 1.6 g of anhydrous sodium acetate were dissolved in 5 mL of glacial acetic acid. 0.3 mL of $Br_2$ was added to 1 mL of glacial acetic acid with stirring, and the solution was added to the mixture of benzaldehyde semicarbazone/sodium acetate in glacial acetic acid. The reaction ran for approximately 1 hour at room temperature and then was poured into 12.5 mL of distilled water. The mixture was then gravity filtered and left to dry in the oven overnight. Product was obtained in 61.17% yield as a yellow solid: mp 219 – 220 °C; IR (ATR, diamond, neat, $cm^{-1}$) 3260, 3105, 1708, 1651; $^1$H NMR (400 MHz, DMSO-d6) δ 7.78 – 7.80 (d, 2H), 7.51 – 7.54 (m, 3H), 7.32 (s, 2H).

**Green synthesis of benzaldehyde oxadiazole, <u>B1</u>:**

1.7533 g of pyridinium tribromide was dissolved in 12.5 mL of glacial acetic acid (may not completely dissolve). 0.75 g of benzaldehyde semicarbazone and 1.6 g of anhydrous sodium acetate are then dissolved in 5 mL of glacial acetic acid (may not dissolve). The solution containing the dissolved semicarbazone/sodium acetate was then added to the solution containing the dissolved pyridinium tribromide and the reaction ran for approximately 1 hour at room temperature. The reaction mixture was then poured into a beaker with 12.5 mL of water, allowing the product to fall out of solution. The solution was then gravity filtered and recrystallized with 100% ethanol. Product was obtained in 57.37% yield as a white solid: mp 228 – 229 °C; $R_f$ 0.383 (60:40 ethyl acetate: hexane); IR (ATR, diamond, neat, $cm^{-1}$) 3262, 3106, 1651; $^1$H NMR (400 MHz, DMSO-d6) δ 7.83 (d, 2H), 7.49 – 7.55 (m, 3H), 7.26 (s, 2H).

**Green synthesis of 4-bromobenzaldehyde oxadiazole, <u>B2</u>:**

1.7533 g of pyridinium tribromide was dissolved in 12.5 mL of glacial acetic acid (may not completely dissolve). 0.75 g of 4-bromobenzaldehyde semicarbazone and 1.6 g of anhydrous sodium acetate are then dissolved in 5 mL of glacial acetic acid (may not dissolve). The solution containing the dissolved 4-bromobenzaldehyde semicarbazone/sodium acetate was then added to the solution containing the dissolved pyridinium tribromide and the reaction ran for approximately 1 hour at room temperature. The reaction mixture was then poured into a beaker with 12.5 mL of water, allowing the product to fall out of solution. The solution was then gravity filtered and recrystallized with 100% ethanol. Product was obtained in 86.21% yield as a white solid: mp 253.2 – 260.1 °C; $R_f$ 0.319 (60:40 ethyl acetate: hexane); IR (ATR, diamond, neat, $cm^{-}$

$^{-1}$) 3243, 3083, 2779, 1652, 1108, 627; $^{1}$H NMR (400 MHz, DMSO-d6) δ 7.72 (m, 4H), 7.31 (s, 2H).

**Green synthesis of 4-chlorobenzaldehyde oxadiazole, B3:**

1.7533 g of pyridinium tribromide was dissolved in 12.5 mL of glacial acetic acid (may not completely dissolve). 0.75 g of 4-chlorobenzaldehyde semicarbazone and 1.6 g of anhydrous sodium acetate are then dissolved in 5 mL of glacial acetic acid (may not dissolve). The solution containing the dissolved 4-chlorobenzaldehyde semicarbazone/sodium acetate was then added to the solution containing the dissolved pyridinium tribromide and the reaction ran for approximately 1 hour at room temperature. The reaction mixture was then poured into a beaker with 12.5 mL of water, allowing the product to fall out of solution. The solution was then gravity filtered and recrystallized with 100% ethanol. Product was obtained in 37.37% yield as a white solid: mp 247.1– 248.1 °C; $R_f$ 0.5 (60:40 ethyl acetate: hexane); IR (ATR, diamond, neat, cm$^{-1}$) 3242, 3081, 2777, 1651, 1109; $^{1}$H NMR (400 MHz, DMSO-d6) δ 7.78 – 7.80 (d, 2H), 7.58 – 7.60 (d, 2H), 7.32 (s, 2H).

**Green synthesis of 4-hydroxybenzaldehyde oxadiazole, B4:**

1.7533 g of pyridinium tribromide was dissolved in 12.5 mL of glacial acetic acid (may not completely dissolve). 0.75 g of 4-hydroxybenzaldehyde semicarbazone and 1.6 g of anhydrous sodium acetate are then dissolved in 5 mL of glacial acetic acid (may not dissolve). The solution containing the dissolved 4-hydroxybenzaldehyde semicarbazone/sodium acetate was then added to the solution containing the dissolved pyridinium tribromide and the reaction ran for approximately 1 hour at room temperature. The reaction mixture was then poured into a beaker with 12.5 mL of water, allowing the product to fall out of solution. The solution was then gravity filtered and recrystallized with 100% ethanol. Product was obtained in 52.55% yield as a yellow solid: mp 258 – 262 °C; $R_f$ 0.1 (60:40 ethyl acetate: hexane); IR (ATR, diamond, neat, cm$^{-1}$) 3501, 3388, 2981, 1668, 1110; $^{1}$H NMR (400 MHz, DMSO-d6) δ 10.14 (d, 2H), 7.95 (s, 2H), 7.70 (s, 1H), 6.57 (s, 2H).

**Green synthesis of 4-isopropylbenzaldehyde oxadiazole, B5:**

1.7533 g of pyridinium tribromide was dissolved in 12.5 mL of glacial acetic acid (may not completely dissolve). 0.75 g of benzaldehyde semicarbazone and 1.6 g of anhydrous sodium acetate are then dissolved in 5 mL of glacial acetic acid (may not dissolve). The solution containing the dissolved semicarbazone/sodium acetate was then added to the solution containing the dissolved pyridinium tribromide and the reaction ran for approximately 1 hour at room temperature. The reaction mixture was then poured into a beaker with 12.5 mL of water, allowing the product to fall out of solution. The solution was then gravity filtered and recrystallized with 100% ethanol. Product was obtained in 47.15% yield as a white solid: mp 236 – 239.9 °C; $R_f$ 0.25 (60:40 ethyl acetate: hexane); IR (ATR, diamond, neat, cm$^{-1}$) 3304, 3112, 2963, 1651, 1098; $^{1}$H NMR (400 MHz, DMSO-d6) δ 7.71 (d, 2H), 7.38 (d, 2H), 2.93 (m, 1H), 1.20 (d, 6H).

IR data collected via the Thermo-Scientific Nicolet iS20 Infrared Spectroscopy machine. NMR data collected via JEOL 400 MHz NMR.

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