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# Designing Synthetic Pathways for Several 2-Thio-Substituted-3H-Phenothiazin-3-ones in Preparation for Testing in Treatment of Central Nervous System Disorders

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**ABSTRACT**

This paper investigates possible synthetic pathways for two 2-thio-substituted-3H-phenothiazin-3-ones **(7)**. A two step reaction in which 1,4-benzoquinone **(1)** is first reacted with an alkylthiol **(2)** in the presence of sodium periodate ($NaIO_4$) and then treated with 2-aminothiophenol **(5)** followed by a second oxidation with sodium periodate was demonstrated to be effective in synthesizing 2-(phenylthio)-3H-phenothiazin-3-one **(12)**. The same synthetic approach was shown to be ineffective in the synthesis of 2-(cyclopentylthio)-3H-phenothiazin-3-one **(16)** due to the fact that the first step was incapable of synthesizing 2-(cyclopentylthio)-1,4-benzoquinone **(14)**. Several other synthetic routes were also proven to be ineffective. This investigation is part of a larger effort to create a vast library of 2-thio-substituted-3H-phenothiazin-3-ones **(7)** for testing in leukotriene inhibition and treatment of neurodegenerative disorders.

**TABLE OF CONTENTS**

## INTRODUCTION

According to Girard *et al.,* work on derivatives of phenothiazine have historically led to the development of drugs capable of treating central nervous system (CNS) disorders.[1] Examples of these drugs include Ethopropazine, an anti-Parkinson drug, and Chlorpromazine, an early anti-psychotic.[1] Observations in their lab have also indicated that derivatives of 3H-phenothiazin-3-one, which have since been demonstrated effective in the treatment of neurodegenerative disorders[2], also have the potential to treat diseases caused by leukotrienes.[1] Leukotrienes are classic mediators of inflammation[3] produced by leukocytes and other immune cells.[4] Their inflammatory effects are most notably thought to play a role in asthma[5] and allergic rhinitis,[6] but leukotriene-mediated inflammation also plays a significant role in inflammatory conditions ranging from conjunctivitis[7] to traumatic brain injury.[8] Fortin *et al.* have concluded that work on inhibition of leukotriene biosynthesis and/or antagonism of leukotriene action will remarkably benefit the range of patients suffering from leukotriene-mediated diseases.[9] In the present paper, we aim to describe our work towards synthesizing two 2-thio-substituted-3H-phenothiazin-3-ones **(7)** in preparation for testing their efficacy in the inhibition of leukotrienes and treatment of neurodegenerative disorders.

The initially proposed dual step synthetic approach for both molecules (**Figure 1)** adapted from previous work done on the compilation of this molecular library[10] follows two steps. First, the 2-alkylthio-1,4-benzoquinone **(3)** would be formed by reacting 1,4-benzoquinone **(1)** with an alkylthiol **(2)** in the presence of sodium periodate ($NaIO_4$) and distilled water. Second, the 2-thio-substituted-3H-phenothiazin-3-one **(7)** would be formed by reacting 2-alkylthio-1,4-benzoquinone **(3)** with 2-aminothiophenol **(5)** in the presence of sodium periodate and distilled water.

The initially proposed dual step synthetic approach worked well for 2-(phenylthio)-3H-phenothiazin-3-one **(12)**. First, the 2-(phenylthio)-1,4-benzoquinone **(9)** was formed by reacting 1,4-benzoquinone **(1)** with thiophenol **(8)** in the presence of sodium periodate and distilled water. Second, 2-(phenylthio)-3H-phenothiazin-3-one **(12)** was formed by reacting 2-(phenylthio)-1,4-benzoquinone **(9)** with 2-

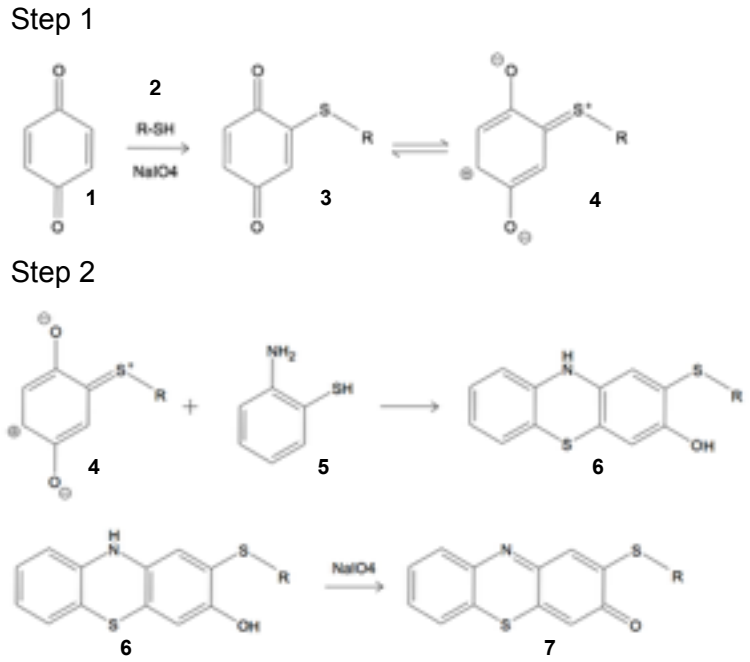



**Figure 1.** Initially proposed dual step approach to synthesizing 2-thio-substituted-3H-phenothiazin-3-ones

aminothiophenol **(5)** in the presence of sodium periodate in distilled water as shown in **Figure 2.**

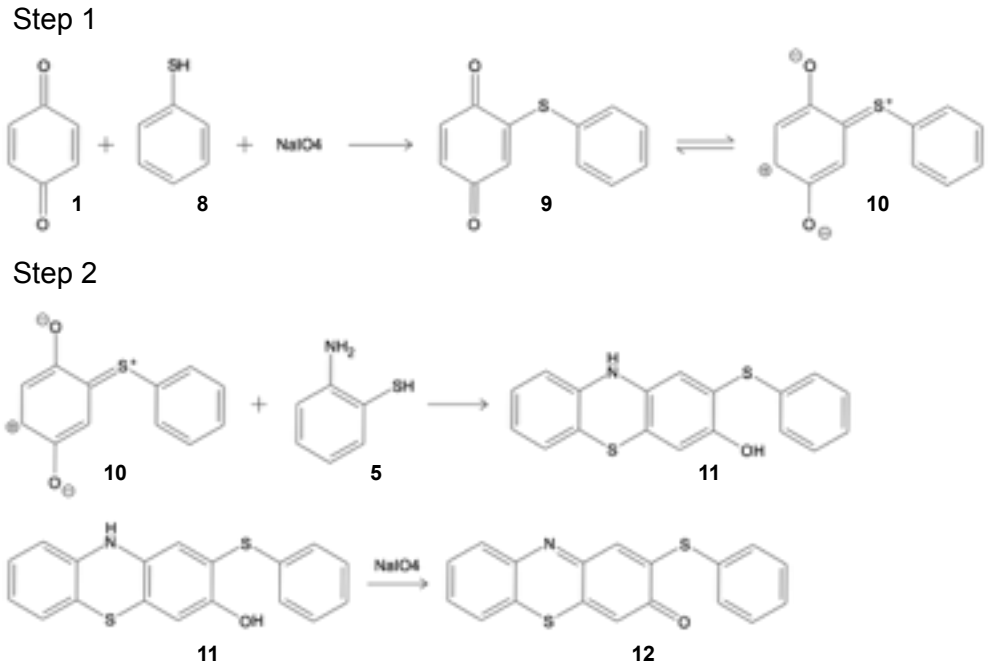



**Figure 2.** Initially proposed dual step approach to synthesizing 2-(phenylthio)-3H-phenothiazin-3-one

No 2-(cyclopentylthio)-1,4-benzoquinone **(14)** was able to be formed, however, when the initially proposed dual step synthetic approach **(Figure 3)** was applied to the formation of 2-(cyclopentylthio)-3H-phenothiazin-3-one **(Figure 4).** A new synthetic approach for 2-(cyclopentylthio)-1,4-benzoquinone **(14)**, therefore, had to be devised.

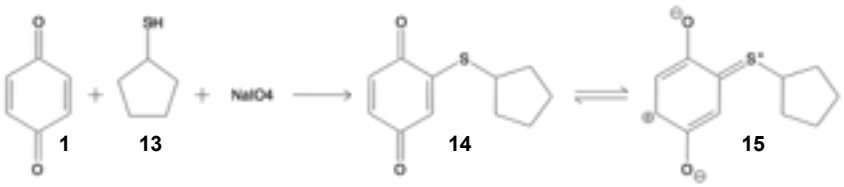



**Figure 3.** First step of initially proposed dual step approach to synthesizing 2-(cyclopentylthio)-3H-phenothiazin-3-one

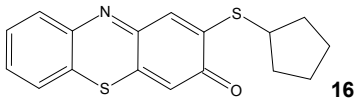
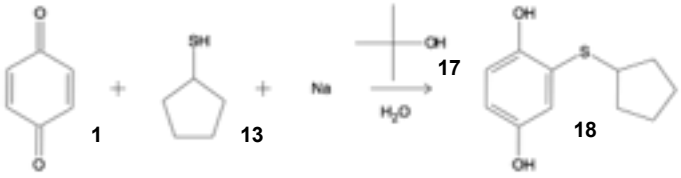



**Figure 4.** 2-(cyclopentylthio)-3H-phenothiazin-3-one

The second proposed synthetic approach for 2-(cyclopentylthio)-1,4-benzoquinone **(14)** follows two steps **(Figure 5)**. First, 2-(cyclopentylthio)-hydroquinone **(18)** would be formed by attacking 1,4-benzoquinone **(1)** with thiocyclopentane **(13)** deprotonated by sodium tert-butoxide. Second, the 2-(cyclopentylthio)-3H-hydroquinone **(18)** would be oxidized using sodium periodate to form 2-(cyclopentylthio)-1,4-benzoquinone **(14)**. This procedure resulted in a bis-alkylation of benzoquinone and had to be abandoned as well.

Step 1




Step 2

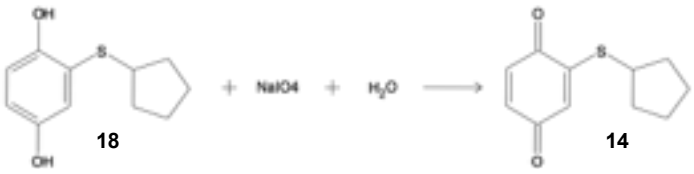



**Figure 5.** Second proposed approach to synthesizing 2-(cyclopentylthio)-1,4-benzoquinone

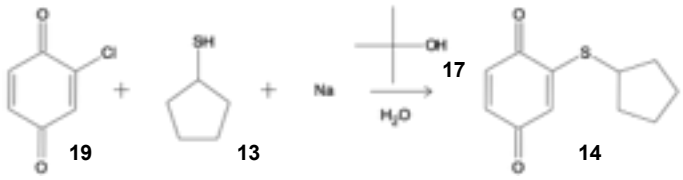



**Figure 6.** Third proposed approach to synthesizing 2-(cyclopentylthio)-1,4-benzoquinone

The third proposed synthetic approach for 2-(cyclopentylthio)-1,4-benzoquinone **(14)** follows a single step **(Figure 6)**. The 2-(cyclopentylthio)-1,4-benzoquinone **(14)** would be formed by performing an addition-elimination reaction between 2-chloro-1,4-benzoquinone **(19)** and thiocyclopentane **(13)** deprotonated by sodium tert-butoxide. The third synthetic approach resulted in the formation of new product but requires further purification and identification by NMR to establish its success.

## EQUIPMENT AND METHODOLOGY

### Synthesis of 2-(phenylthio)-3H-phenothiazin-3-one - Initially Proposed Dual Step Synthetic Approach - Step I

To synthesize 2-(phenylthio)-1,4-benzoquinone **(9)**, 0.2703 g of 1,4-benzoquinone **(1)** were added to 12.50 mL of dichloromethane (DCM) and 2.50 mL of methanol (MeOH). Then, 0.0256 mL of the thiophenol **(8)** were added to the reaction vessel using a 500um Hamilton precision syringe. In a separate reaction vessel, 1.069 g of sodium periodate were added to 5.00 mL of distilled water and then poured drop-wise into the main reaction vessel. The main reaction vessel was then shaken gently for about thirty seconds, a stir-bar was added, and the reaction vessel was placed on the stir plate (CG-1994 Chemglass Optimag Magnetic Hot Plate Stirrer) at 350 RPM and room temperature (r.t.) overnight. The reaction was monitored with a ten-minute thin-layer chromatography (TLC) using a 7:3 hexanes:ethyl acetate (H:E) under 254 nm ultra-violet (UV) light to confirm the formation of a new compound **(Figure 7A)**. The next day, the solid was extracted from the reaction solution using the extraction procedure outlined below. The dried crude was then placed in a refrigerator for storage. The following week, the desired product was isolated using the flash column

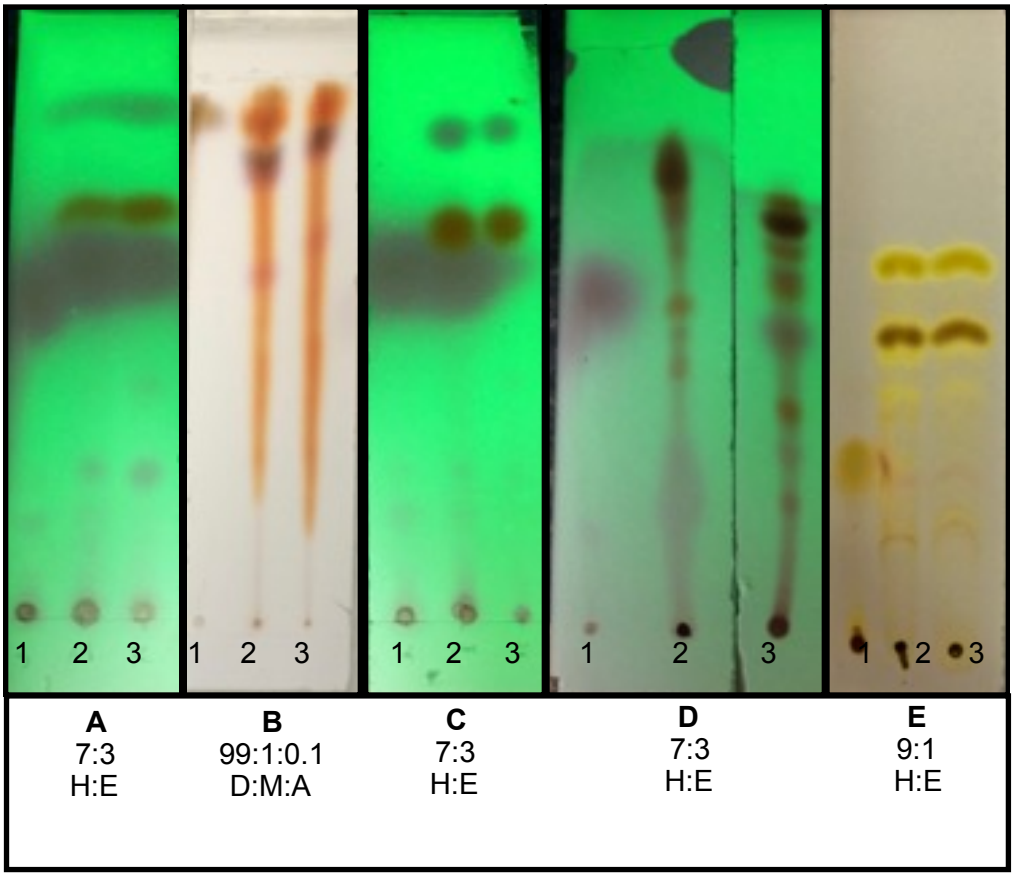



**Figure 7.** Ten minute thin-layer chromatography plates. In each frame, column 1 represents starting material. Columns 2 and 3 show new product.

chromatography procedure defined below with a 95:5 hexanes:ethyl acetate solvent system. Fractions 8-34 were collected, and the solvent is then stripped under reduced pressure and heat (WG-HB03 Wilmad LabGlass Heat Bath) in a rotary evaporator (RE11 Buchi Rotavapor). Finally, the isolated 2-(phenylthio)-1,4-benzoquinone **(12)** was refrigerated. The identity of final product was successfully confirmed using $^{1}$H NMR (400 Hz Jeol FT-NMR).

**Synthesis of 2-(phenylthio)-3H-phenothiazin-3-one - Initially Proposed Dual Step Synthetic Approach - Step II**

To synthesize 2-(phenylthio)-3H-phenothiazin-3-one **(12)**, 0.025 mL of 2-aminothiophenol **(5)** were added to 0.0491 g of 2-(phenylthio)-1,4-benzoquinone **(10)** in 1.14 mL DCM and 0.227 mL of MeOH. In a separate reaction vessel, 0.097 g of sodium periodate were added to 0.455 mL of distilled water and then poured drop-wise into the main reaction vessel. The main reaction vessel was then shaken gently for about thirty

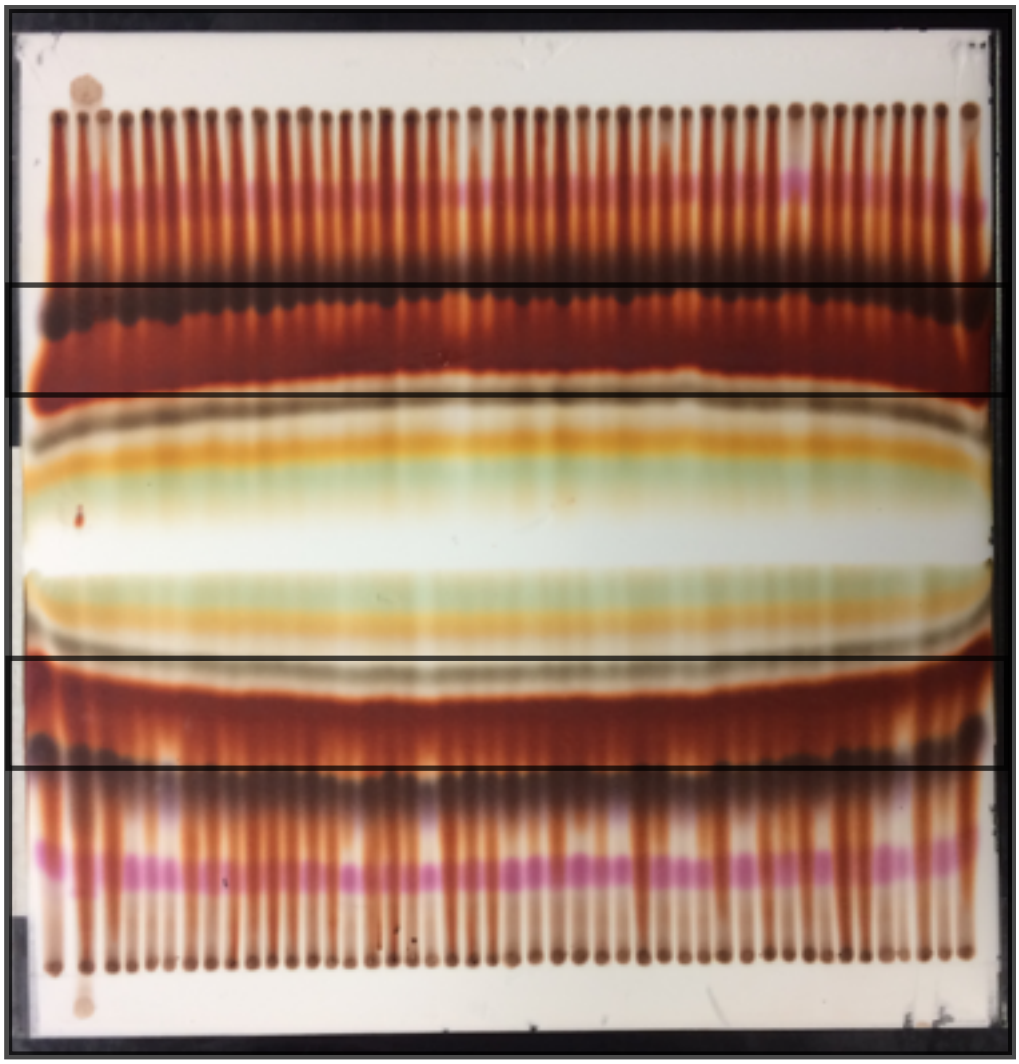


**Figure 8.** Preparative TLC (500um 20x20cm) run with 99:1:0.1 DCM:MeOH:ammonia solvent to isolate 2-(phenylthio)-3H-phenothiozin-3-one. Desired band indicated by black boxes.

seconds, a stir-bar was added, and the reaction vessel was placed on the stir plate at 350 RPM and r.t. overnight. The reaction was monitored with a ten-minute TLC with a 99:1:0.1 DCM:methanol:ammonia (D:M:A) solvent system to establish the formation of a new compound **(Figure 7B)**. The next day, the solid was extracted, and the dried crude was placed in a refrigerator for storage. The following week, the desired product was isolated using the preparative TLC procedure outlined below with a 99:1:0.1 DCM:MeOH:ammonia solvent system **(Figure 8)**. The identity of the final product was later confirmed using $^{1}H$ NMR.

**Synthesis of 2-(cyclopentylthio)-3H-phenothiazin-3-one - Initially Proposed Dual Step Synthetic Approach - Step I**

In accordance with the first step of the proposed general synthetic approach, 0.2703 g of 1,4-benzoquinone **(1)** were added to a reaction vessel containing 12.50 mL of DCM and 2.50 mL of MeOH. Next, 0.267 mL of 97% cyclopentanethiol **(13)** were added to the reaction vessel using a 500 uL Hamilton precision syringe. In a separate reaction vessel, 1.069 g of sodium periodate were added to 5.00 mL of distilled water. This mixture was then added to the main reaction vessel drop-wise. The entire reaction was shaken gently for about 30 seconds, a stir bar was added, and the reaction was monitored with a ten-minute TLC with a 99:1:0.1 DCM:methanol:ammonia solvent system under 254 nm ultra-violet (UV) light to establish the formation of a new compound **(Figure 7C)**. The reaction vessel was placed on the stir plate running at 350 RPM at r.t. overnight. The next day, the crude was extracted using the extraction procedure and refrigerated. One week later, a flash chromatography column was run using a 95:5 hexanes:ethyl acetate solvent system. Fractions 5-13 were collected, stripped, and the purified product was refrigerated. The identity of the final product was later investigated using $^{1}$H NMR.

**Synthesis of 2-(cyclopentylthio)-1,4-benzoquinone - Second Proposed Synthetic Approach - Step I**

First, 0.072 g of sodium metal (Na) were added to 8.33 mL of 2-methyl-2-propanol **(17)**, a stir bar was added, and the reaction was stirred on a hot plate (Isotemp Fisher Scientific) for 1 hour under gentle heat (~100$^{o}$C) and 350 RPM. Then, 0.267 mL of the 97% cyclopentanethiol **(13)** were added to the reaction vessel using a 500 um Hamilton precision syringe, and the reaction was stirred for another hour under gentle heat at 350 RPM. Finally, 0.2703 g of 1,4-benzoquinone **(1)** were added, and the reaction was then left on the stir plate to stir at 350 RPM at r.t. for five days. After five days the reaction vessel was refrigerated. Two days later, the reaction vessel was gently thawed and 0.090 mL of distilled water were added. The reaction was then monitored with a ten-minute TLC with a 7:3 hexanes:ethyl acetate solvent system under 254 nm ultra-violet (UV) light to establish the formation of a new compound **(Figure 7D**

**2)**. The reaction was stirred for 10 more minutes at r.t., the solvent was stripped, and the crude was refrigerated.

**Synthesis of 2-(cyclopentylthio)-1,4-benzoquinone - Second Proposed Synthetic Approach - Step II**

The crude from step I was dissolved with 12.5 mL of DCM and 2.5 mL of MeOH. In a separate reaction container, 1.069 g of sodium periodate were added to 5.00 mL of distilled water, and the mixture was added drop-wise to the main reaction vessel. The main reaction vessel was then stirred for 10 minutes at r.t. and the reaction was monitored with a ten-minute TLC using a 7:3 hexanes:ethyl acetate solvent system under 254 nm ultra-violet (UV) light to establish the formation of a new compound

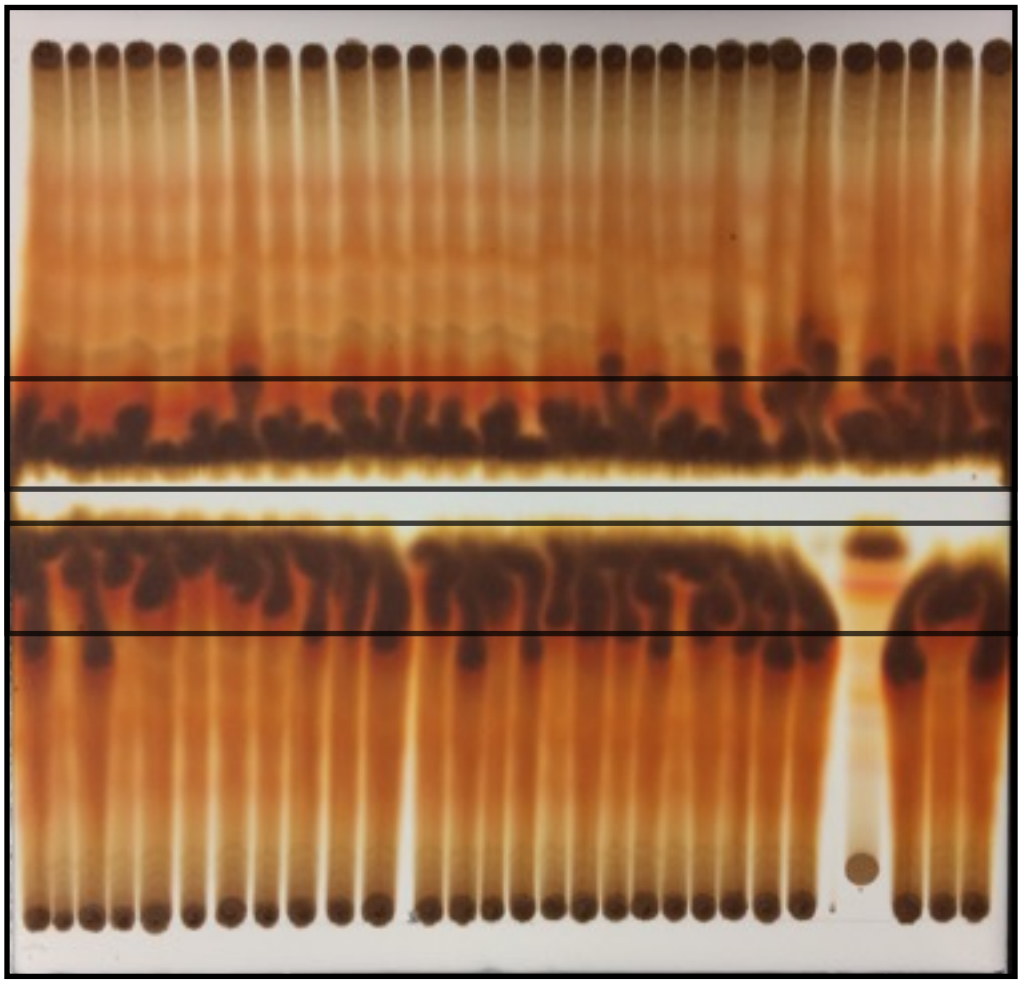


**Figure 9.** First preparative TLC (500um 20x20cm) run with 7:3 hexanes:ethyl acetate solvent to isolate 2-(cyclopentylthio)-1,4-benzoquinone. Desired band indicated by black boxes.

**(Figure 7D 3)**. The solid was extracted, and the dried crude was placed in a refrigerator for storage. One week later, the desired product was isolated using preparative TLC and a 7:3 hexanes:ethyl acetate solvent system **(Figure 9)**. A second preparative TLC was run on the isolated compound using a 9:1 hexanes:ethyl acetate solvent system **(Figure 10)**, and the identity of the final product was later determined using $^{1}$H NMR.

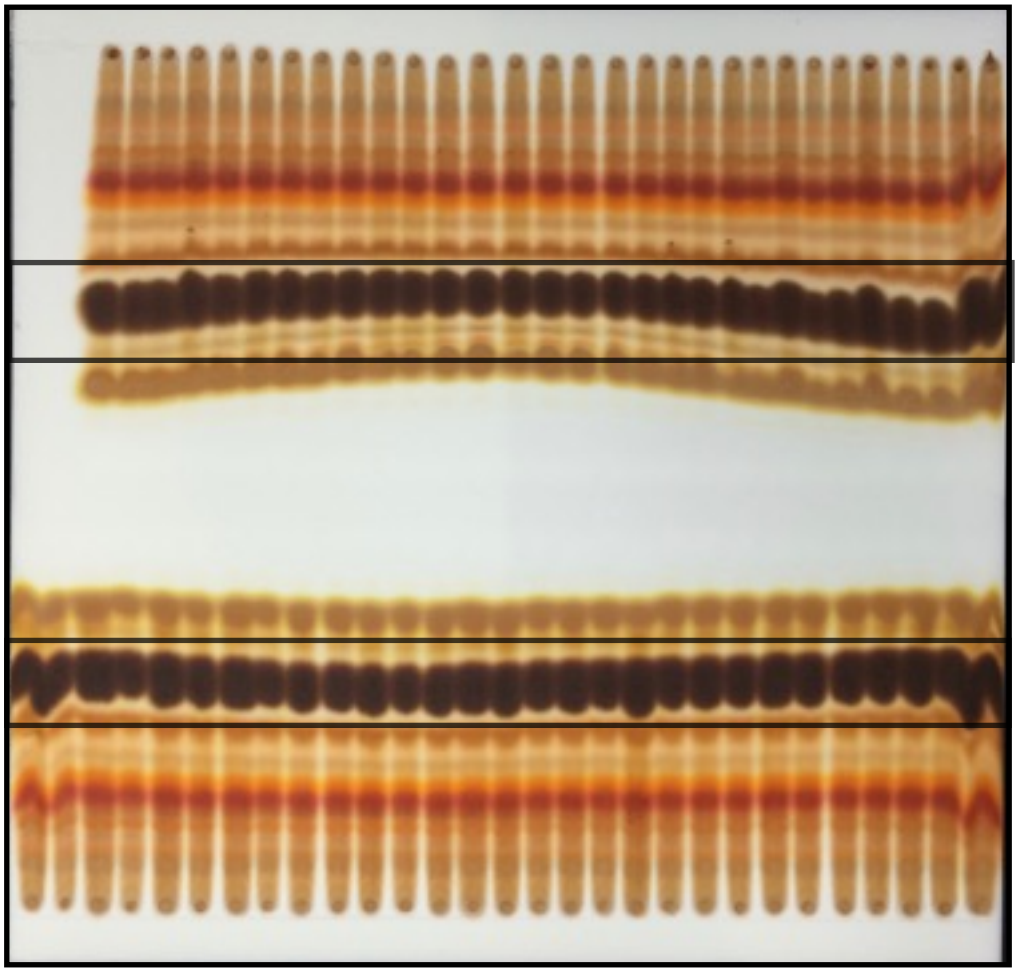


**Figure 10.** Second preparative TLC (500um 20x20cm) run with 9:1 hexanes:ethyl acetate solvent to isolate 2-(cyclopentylthio)-1,4-benzoquinone. Band collected indicated by black boxes. The desired product may, in fact, have existed in the red band.

**Synthesis of 2-(cyclopentylthio)-1,4-benzoquinone - Third Proposed Synthetic Approach**

First, 0.072 g of sodium metal were added to 8.33 mL of 2-methyl-2-propanol **(17)**, and the reaction was stirred under gentle heat until the sodium metal dissolved.

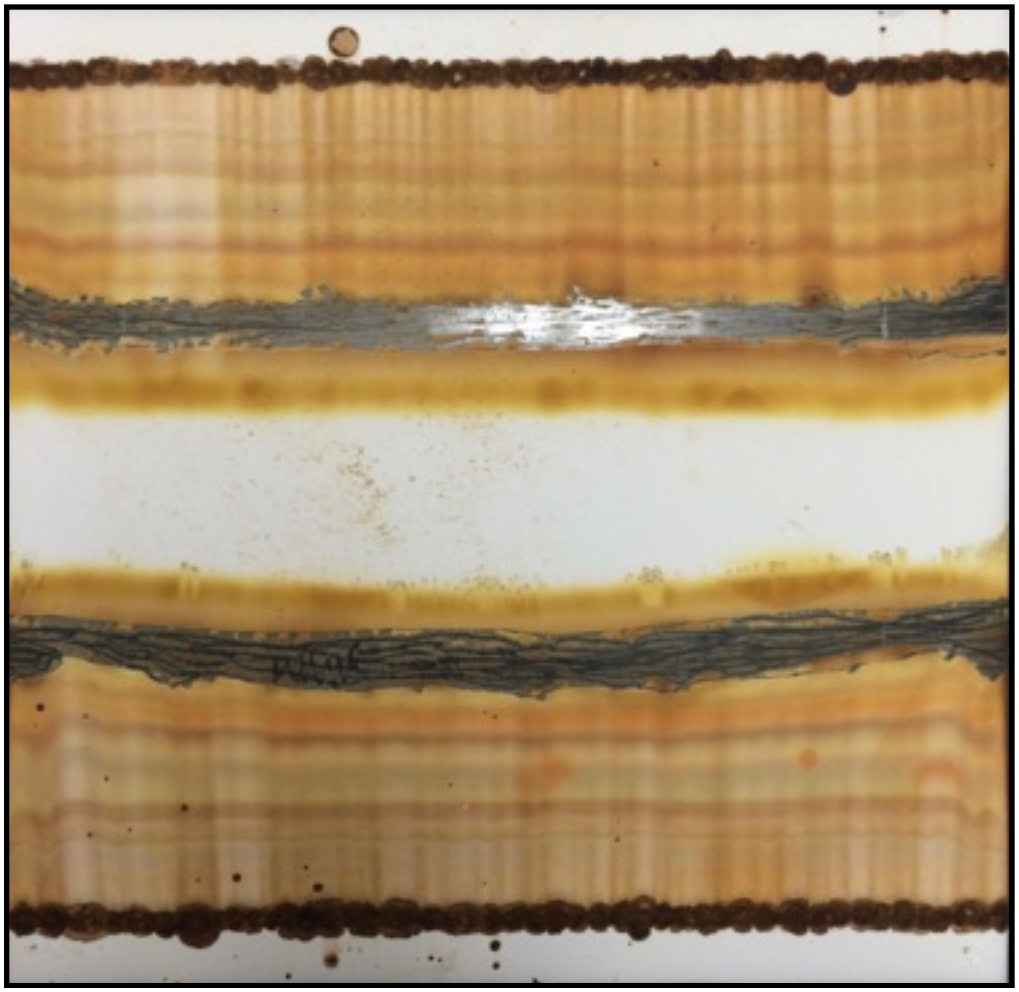


**Figure 11.** Preparative TLC (500um 20x20cm) run with 9:1 hexanes:ethyl acetate solvent to isolate 2-(cyclopentylthio)-1,4-benzoquinone. Unfortunately, the picture was taken after the desired bands were scraped off. The band collected was a light brown.

Then, 0.267 mL of the 97% cyclopentanethiol **(13)** were added to the reaction vessel, and the reaction was placed on the hot plate to stir for five minutes under gentle heat. Finally, 0.3564 g of 2-chloro-1,4-benzoquinone **(19)** were added to the reaction vessel, and the reaction was stirred at r.t. for one day. After refrigerating for a week, the crude was thawed, and 0.090 mL of distilled water were added to the reaction vessel. The reaction vessel was then stirred at 350 RPM for 30 minutes. At that time, a ten-minute TLC with a 9:1 hexanes:ethyl acetate solvent system was run to establish the formation of a new compound before the addition of water **(Figure 7E 2)** and after the addition of water **(Figure 7E 3)**. One week later, the desired product was isolated using preparative TLC and a 9:1 hexanes:ethyl acetate solvent system **(Figure 11)** with a slight alteration

in procedure. During the spotting step of the preparative TLC procedure, the interaction between the product and the silica gel seemed to cause the silica gel to peel off the plate, so rather than spotting the entire amount, only a portion of the product was actually spotted onto the TLC plate limiting our ability to know exactly how much was applied. The identity of the final product was later determined using $^{1}H$ NMR.

**Extraction Procedure**

The reaction mixture is vacuum filtered through celite (diatomacious earth) in a fritted funnel to remove solid contaminants. 5 mL of $H_2O$ are used to rinse the celite. The aqueous layer is then washed three times with 5 mL of DCM. The non-polar layer is then extracted from the aqueous layer using a separatory funnel and dried with sodium sulfate, which is then vacuum filtered using a Buchner funnel. The solvent is then stripped under reduced pressure and heat (WG-HB03 Wilmad LabGlass Heat Bath) in a rotary evaporator (RE11 Buchi Rotavapor).

**Flash Chromatography Column Procedure**

A flash chromatography column (Kontes 250 mL) is filled with 20 times the mass of the crude in silica gel (230-400 Mesh, Grade 60). The silica gel is then packed three times using the least polar component of the solvent system and a nitrogen gas propellant. The dried crude is dissolved in ~3 mL of DCM and 5 drops of MeOH. It is then mixed with 2 times its mass in silica gel and stripped again using the rotary evaporator. The crude/silica gel powder is added to a flash chromatography column on top of the packed silica gel, and small boluses of the solvent system are used in coordination with the nitrogen gas propellant to push the crude into the packed silica gel. Once the crude has entered the packed silica gel, 20 mL fractions are collected until all the product has been pushed through the column. A 10 minute TLC with the same solvent system is run to determine which fractions contain the desired compound. The desired fractions are collected and combined. The solvent is removed using the rotary evaporator.

**Preparative TLC Procedure**

The dried crude is dissolved in ~3 mL of DCM and 5 drops of MeOH. The entirety of the crude is then spotted in parallel lines running the length of the edge of a preparative TLC (500um 20x20cm) plate on two opposing ends about 1 cm away from the border. The plate is then lowered into a TLC vessel filled with 35 mL of solvent with the spotted side tilted towards the bottom. The TLC is left to run for about 15 minutes on one end. When the product travels about half the length of the plate, the plate is then flipped, 15 mL more of solvent are added, and the TLC is run for 15 more minutes. Once complete, the plate is withdrawn and the band containing the desired compound is scraped off the plate. The collected powder is flushed with 5 mL of 9:1 DCM:MeOH using a 10 mL syringe containing a filtration frit. The solvent is then removed using the rotovap.

**RESULTS**

Final products were confirmed using $^{1}$H NMR (400 Hz Jeol FT-NMR). $^{1}$H NMR predictions were also created for each compound as a means of comparison with the actual $^{1}$H NMR findings.

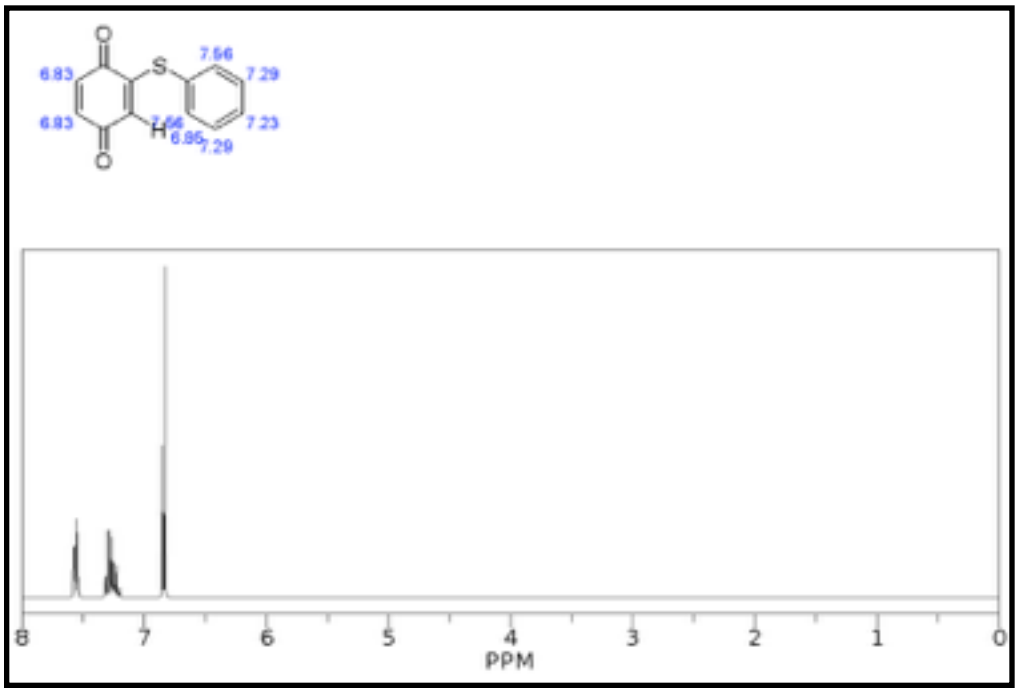



**Figure 12.** $^{1}$H NMR prediction for 2-(phenylthio)-1,4-benzoquinone

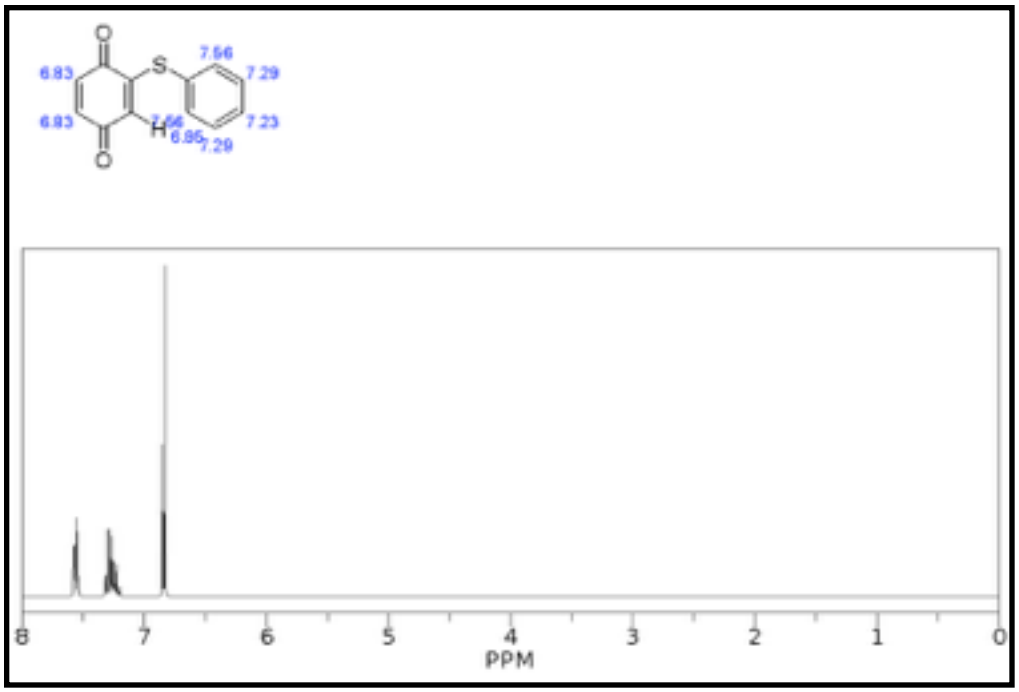



**Figure 12.** $^{1}$H NMR prediction for 2-(phenylthio)-1,4-benzoquinone

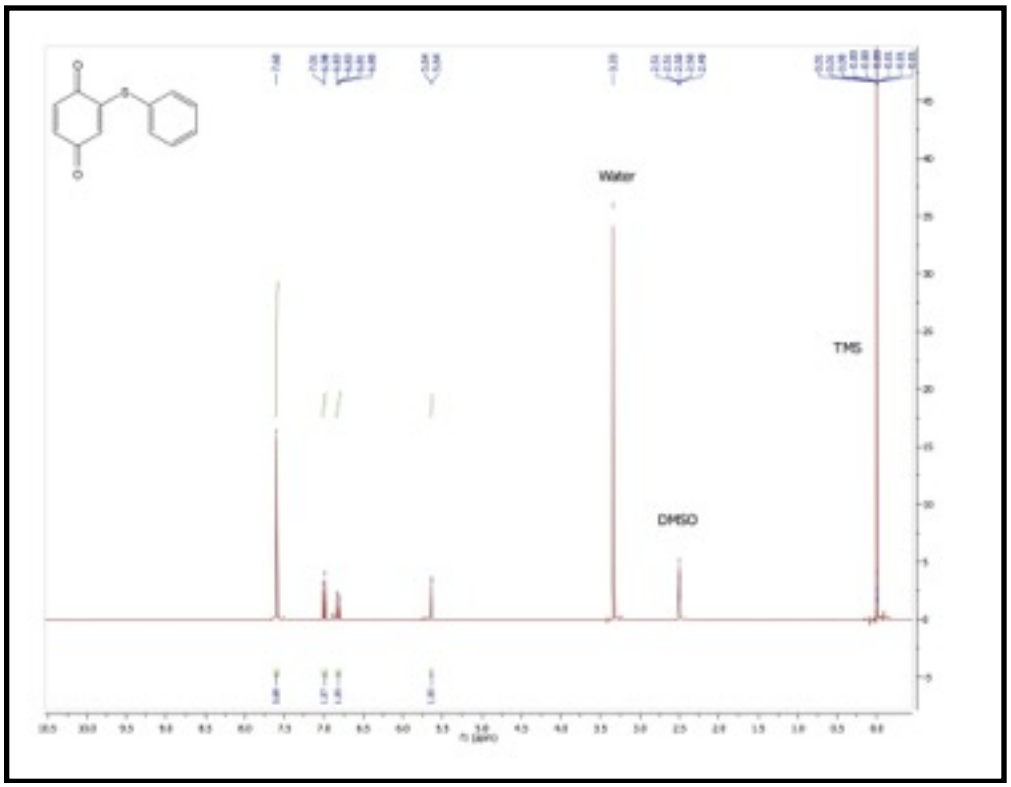



**Figure 13.** Experimental $^{1}$H NMR findings for first step of initially proposed dual step approach to synthesizing 2-(phenylthio)-3H-phenothiazin-3-one. Demonstrates presence of 2-(phenylthio)-1,4-benzoquinone.

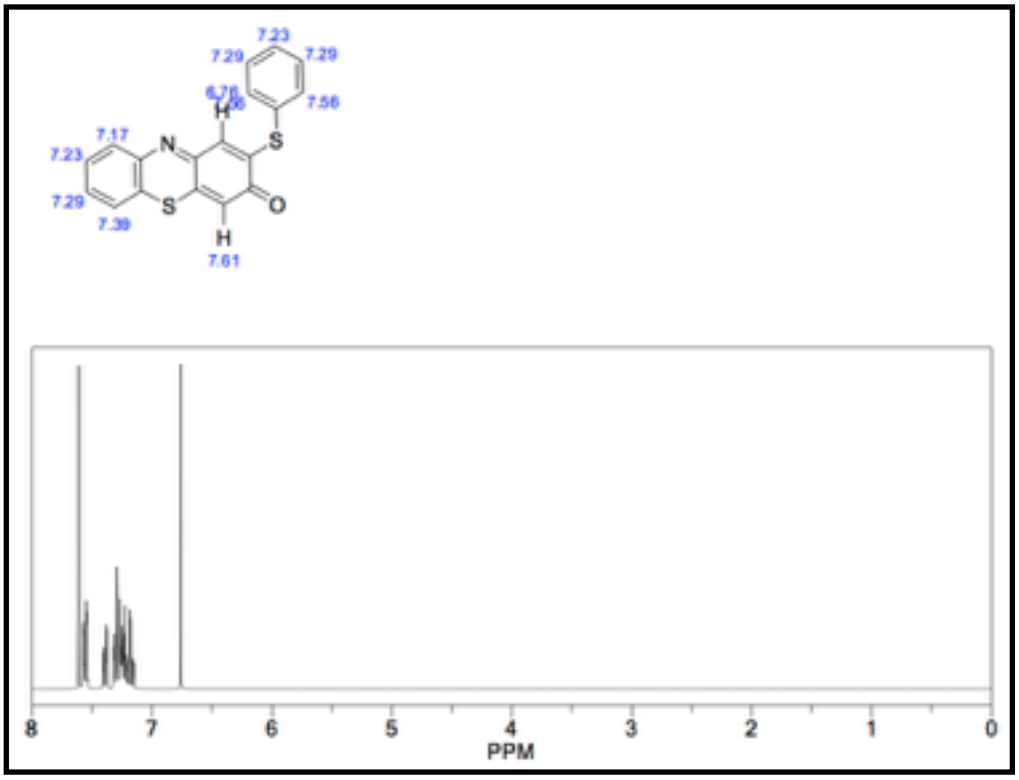



**Figure 14.** $^{1}$H NMR prediction for 2-(phenylthio)-3H-phenothiazin-3-one

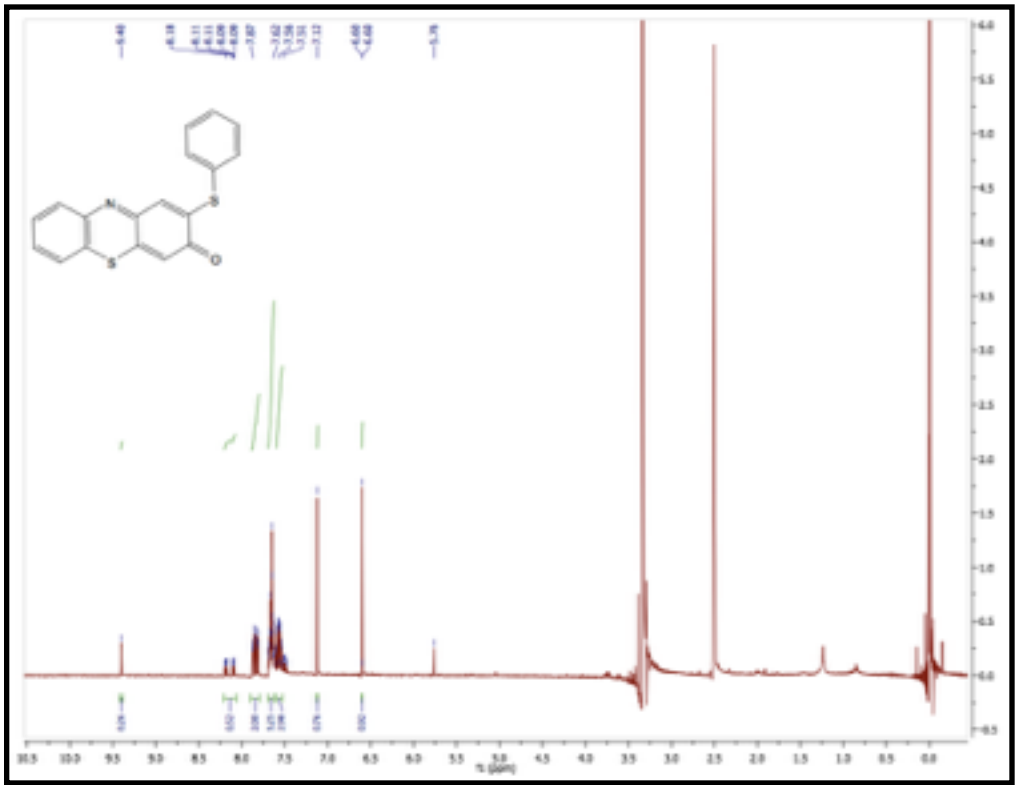


**Figure 15.** Experimental $^{1}$H NMR findings for first step of initially proposed dual step approach to synthesizing 2-(phenylthio)-3H-phenothiazin-3-one. Demonstrates presence of 2-(phenylthio)-3H-phenothiazin-3-one.

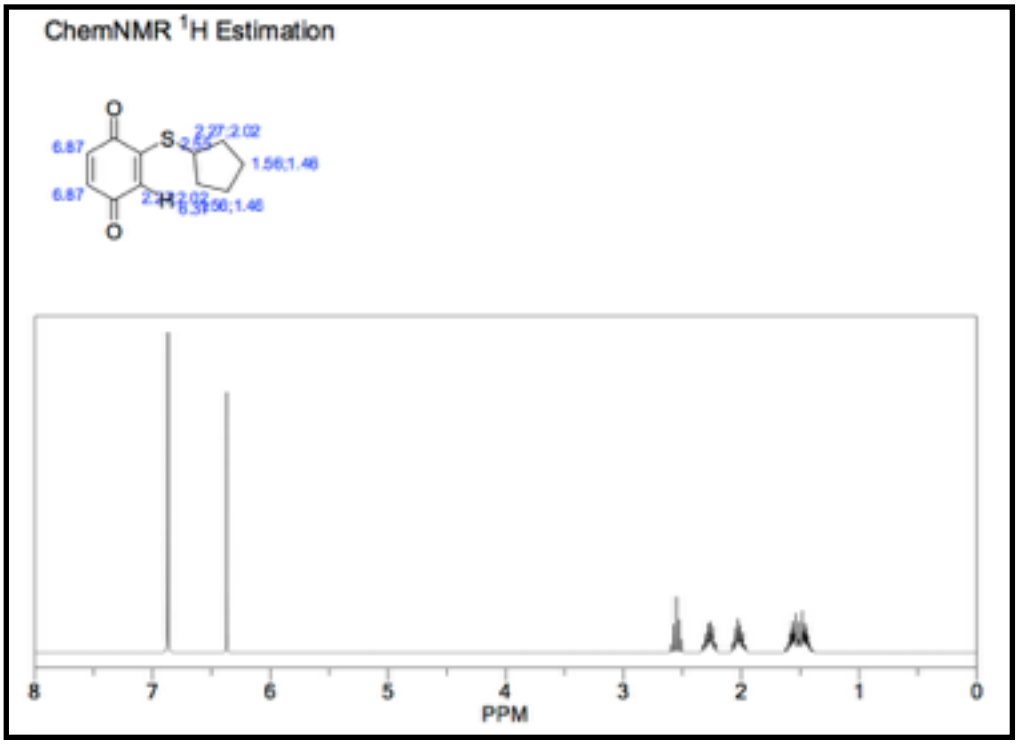



**Figure 16.** $^{1}$H NMR prediction for 2-(cyclopentylthio)-1,4-benzoquinone

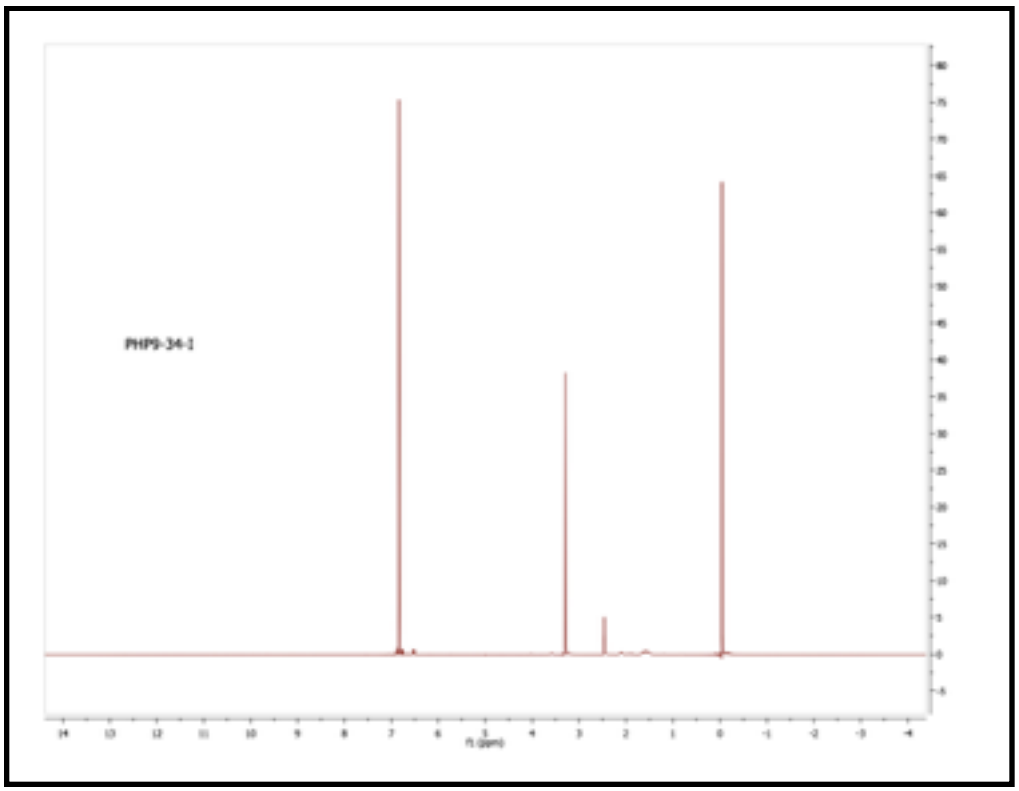



**Figure 17.** Experimental $^{1}$H NMR findings for first step of initially proposed dual step approach to synthesizing 2-(cyclopentylthio)-3H-phenothiazin-3-one. Data indicates presence of 1,4-benzoquinone.

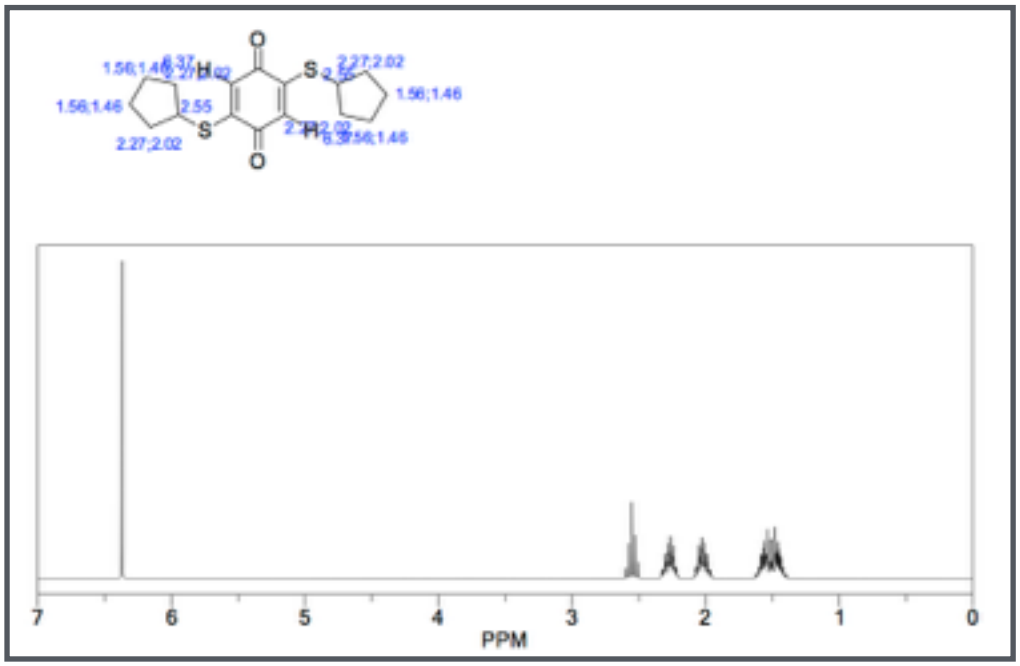



**Figure 18.** $^{1}$H NMR prediction for 2,5-(dicyclopentylthio)-1,4-benzoquinone

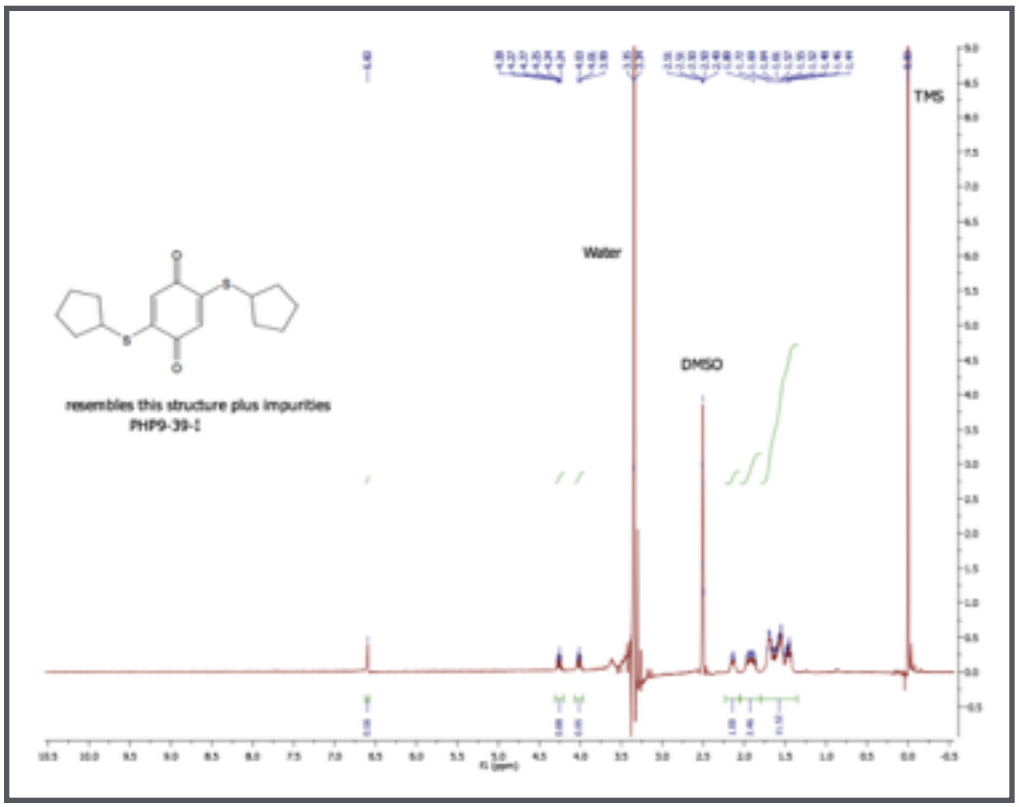



**Figure 19.** Experimental $^{1}$H NMR findings for second proposed approach to synthesizing 2-(cyclopentylthio)-1,4-benzoquinone. Data indicates presence of 2,5-(dicyclopentylthio)-1,4-benzoquinone.

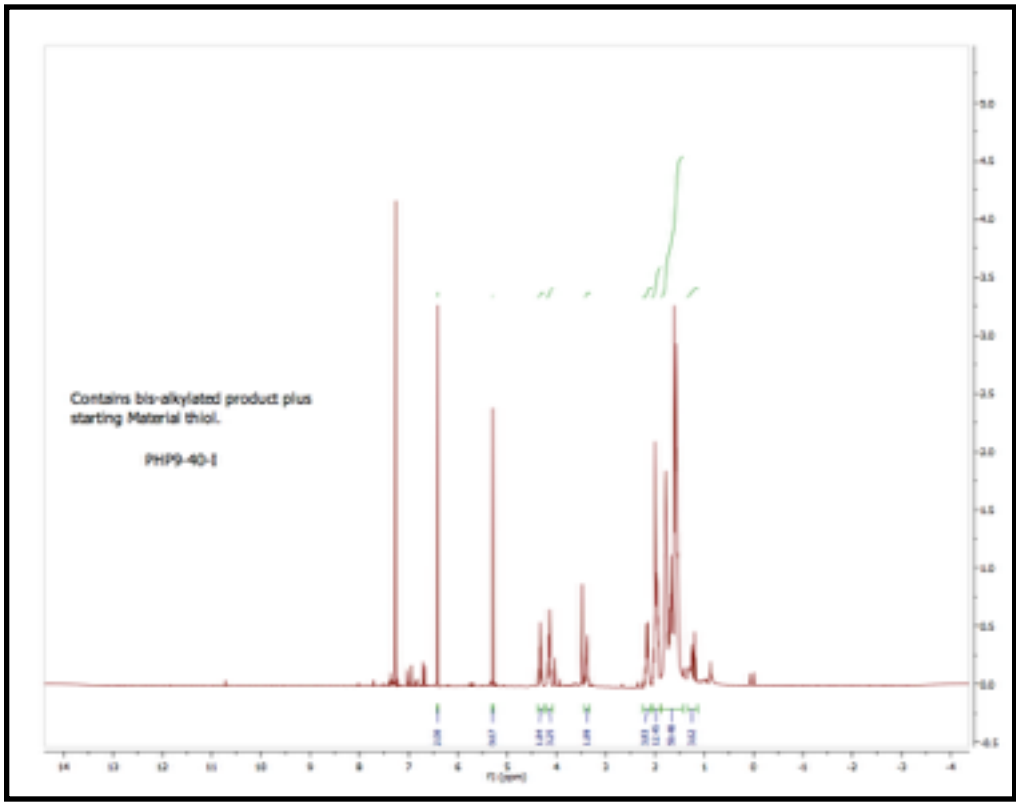



**Figure 20.** Experimental $^{1}H$ NMR findings for Third proposed approach to synthesizing 2-(cyclopentylthio)-1,4-benzoquinone. Data seems to indicate presence of 2,5-(dicyclopentylthio)-1,4-benzoquinone and a significant amount of thiocyclopentane.

## DISCUSSION

### Synthesis of 2-(phenylthio)-3H-phenothiazin-3-one - Initially Proposed Dual Step Synthetic Approach - Step I

After completely isolating and purifying the target compound, 0.379 g remained. A comparison between the predicted $^{1}H$ NMR results for 2-(phenylthio)-1,4-benzoquinone **(Figure 12)** and the experimental $^{1}H$ NMR results **(Figure 13)** indicate that the correct compound was indeed collected. This was confirmed by the fact that the three peaks between 6.75 ppm and 7.75 ppm in **Figure 13** match up with the predicted peaks in **Figure 12**. The percent yield of 2-(phenylthio)-1,4-benzoquinone **(9)** was 70.1%.

**Synthesis of 2-(phenylthio)-3H-phenothiazin-3-one - Initially Proposed Dual Step Synthetic Approach - Step II**

After completely isolating and purifying the target compound, 0.0198 g remained. A comparison between the predicted $^{1}$H NMR results for 2-(phenylthio)-3H-phenothiazin-3-one **(Figure 14)** and the experimental $^{1}$H NMR results **(FIgure 15)** indicate that the correct compound was indeed collected. This was confirmed by the fact that the three peaks between 6.50 ppm and 8.50 ppm in **Figure 15** match up with the predicted peaks in **Figure 14**. The two peaks that most definitively indicate the correct compound are the two peaks between 6.50 ppm and 7.5 ppm in **Figure 15**. There were, however, a significant amount of contaminants. The yield of 2-(phenylthio)-3H-phenothiazin-3-one **(12)** was somewhat lower than expected at 48.5%. A better job could have been done washing the compound with DCM to remove any ammonia, methanol, water, or acetone. Further care could have also been taken in employing the quantitative techniques that ensure the highest yield.

**Synthesis of 2-(cyclopentylthio)-3H-phenothiazin-3-one - Initially Proposed Dual Step Synthetic Approach - Step I**

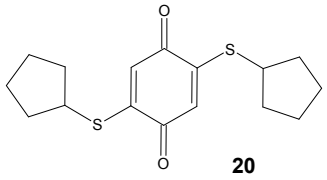
After attempting to completely isolate and purify the target compound, 0.111 g remained. A comparison between the predicted $^{1}$H NMR results for 2-(cyclopentylthio)-1,4-benzoquinone **(Figure 16)** and the experimental $^{1}$H NMR data **(Figure 17)** indicates that no 2-(cyclopentylthio)-1,4-benzoquinone **(14)** existed in the target compound. The experimental $^{1}$H NMR data **(Figure 17)** seems to show several contaminants and a single peak around 7ppm that identifies the compound as 1,4-benzoquinone **(1)**. It also appears to be missing the essential peaks between 1 ppm and 3 ppm seen in the predicted results. The percent yield of 1,4-benzoquinone **(1)** was 41.1%. The failure to synthesize a new product may have occurred because 1,4-benzoquinone **(1)** acts as a base to deprotonate cyclopentanethiol **(13)**.

**Synthesis of 2-(cyclopentylthio)-1,4-benzoquinone - Second Proposed Synthetic Approach**

After completely isolating and purifying the target compound, 0.0591 g remained. A comparison between the predicted $^{1}H$ NMR results for 2-(cyclopentylthio)-1,4-benzoquinone **(Figure 16)** and the experimental $^{1}H$ NMR findings **(Figure 19)** indicate the desired compound was not collected. The experimental $^{1}H$ NMR findings **(Figure 19)** reveal that there is second peak missing between 6 ppm and 7 ppm that would have existed in a 2:1 ratio with the neighboring peak. The single peak between 6 ppm and 7 ppm suggests that we instead bis-alkylated the compound and now have 2,5-(dicyclopentylthio)-1,4-benzoquinone **(Figure 21)** with a percent yield of 19.2%. This is confirmed by comparing the experimental $^{1}H$ NMR findings **(Figure 19)** with the predicted $^{1}H$ NMR results **(Figure 18)** for 2,5-dicyclopentanethio-1,4-benzoquinone **(20)**.

**Synthesis of 2-(cyclopentylthio)-1,4-benzoquinone - Third Proposed Synthetic Approach**

After completely isolating and purifying the target compound, 0.0238 g remained. An unknown portion of the product was applied to the plate limiting the ability to obtain a percent yield. A comparison between the predicted $^{1}H$ NMR results for 2-(cyclopentylthio)-1,4-benzoquinone **(Figure 16)** and the experimental $^{1}H$ NMR findings




**20**

**Figure 21.** 2,5-(dicyclopentylthio)-1,4-benzoquinone

**(Figure 20)** indicate the desired compound was not collected. The experimental $^{1}H$ NMR findings **(Figure 20)** indicate, instead, the presence of 2,5-(dicyclopentylthio)-1,4-benzoquinone **(20)**, which is confirmed by consultation with the expected $^{1}H$ NMR results for 2,5-(dicyclopentylthio)-1,4-benzoquinone **(Figure 18).** A significant amount of thiocyclopentane was also present.

## CONCLUSION

The current investigation into synthetic pathways for two 2-thio-substituted-3H-phenothiazin-3-ones **(7)** successfully establishes a synthetic approach for 2-(phenylthio)-3H-phenothiazin-3-one **(12)**. The next step will be to determine whether this specific approach can be repeated on a larger scale. This investigation also contains significant work towards the synthesis of 2-(cyclopentylthio)-3H-phenothiazin-3-one **(16)**. A successful synthetic approach has not yet been established for 2-(cyclopentylthio)-3H-phenothiazin-3-one **(16)**, but testing will continue to determine an efficient and effective pathway. One significant obstacle to this endeavor appears to be the inclination of 1,4-benzoquinone **(1)** to be bis-alkylated by the cyclopentanethiol **(13)**. A proposed method for overcoming this obstacle is to adjust the molar ratio of 1,4-benzoquinone **(1)** to cyclopentanethiol **(13)** from 1:1 to 3:1 while adding the cyclopentanethiol **(13)** drop-wise to the 1,4-benzoquinone **(1)** during the reaction. This would keep the 1,4-benzoquinone **(1)** from being overwhelmed by the cyclopentanethiol **(13).** Future work will also include finding synthetic pathways for new 2-thio-substituted-3H-phenothiazin-3-ones **(7)** since our ultimate goal is to create a vast library of 2-thio-substituted-3H-phenothiazin-3-ones **(7)** for testing in inhibition of leukotrienes.

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