

2015

Innovative Synthesis of Diltiazem/Clentiazem Analogs

David Chang

Follow this and additional works at: <https://knowledge.e.southern.edu/jiur>

Recommended Citation

Chang, David (2015) "Innovative Synthesis of Diltiazem/Clentiazem Analogs," *Journal of Interdisciplinary Undergraduate Research*: Vol. 7, Article 5.

Available at: <https://knowledge.e.southern.edu/jiur/vol7/iss1/5>

This Article is brought to you for free and open access by the Peer Reviewed Journals at KnowledgeExchange@Southern. It has been accepted for inclusion in *Journal of Interdisciplinary Undergraduate Research* by an authorized editor of KnowledgeExchange@Southern. For more information, please contact jspears@southern.edu.

Innovative Synthesis of Diltiazem/Clentiazem Analogs

David Chang

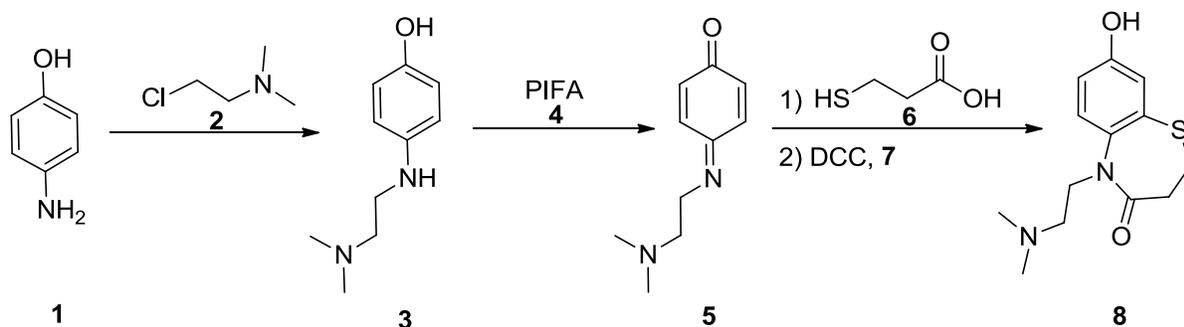
Southern Adventist University, Collegedale, TN 37315

CHEM 497 –Intro to Research

Research Advisor: Dr. Herman H. Odens

Abstract

The nucleophilic addition of 4-aminophenol **1** to 2-chloro-*N,N*-dimethylethylamine **2** generated intermediate **3**. Following oxidation facilitated by [bis(trifluoroacetoxy)iodo]benzene (PIFA, **4**) created quinoneimine **5**. Then, Compound **5** went under nucleophilic Michael Addition with 3-mercaptopropionic acid and subsequent cyclization with coupling reagent *N,N'*-dicyclohexylcarbodiimide (DCC) **7**, to generate the desired analogs of Diltiazem/Clentiazem **8**. This four-step total synthesis approach provides a high yielding novel synthesis methodology.



Scheme 1. General Synthesis of Analogs of Diltiazem/Clentiazem

Introduction

In today's society, cardiovascular diseases are rampant. According to the World Health Organization, cardiovascular disease accounts for 30% of all global deaths¹. Therefore, researchers put a big effort into trying to find a drug that will cure these diseases. Drugs containing a benzothiazepinone core structure are known to be potent in treating cardiovascular diseases.² Thus, researchers have synthesized benzothiazepinones such as Diltiazem and Clentiazem and their analogs, Figure 1. A Chinese team synthesized benzothiazepinone derivatives from 1,5-difluoro-2,4-dinitrobenzene.³ Whereas, a Japanese team synthesized benzothiazepinone derivatives through fusion of the halogen-substituted 2-aminothiophenol with the trans-3-arylglycidic ester.⁴ Just like these scientists, the purpose of this research is to propose a new synthetic route to benzothiazepinones that will have shorter reaction steps with cheaper starting materials. To test the potency of the drug, the final product will be tested as a potential vasodilator or calcium antagonist at a later determined time. By creating a shorter and more affordable route to benzothiazepinone, we hope to impact society with a more effective cardiovascular drug.

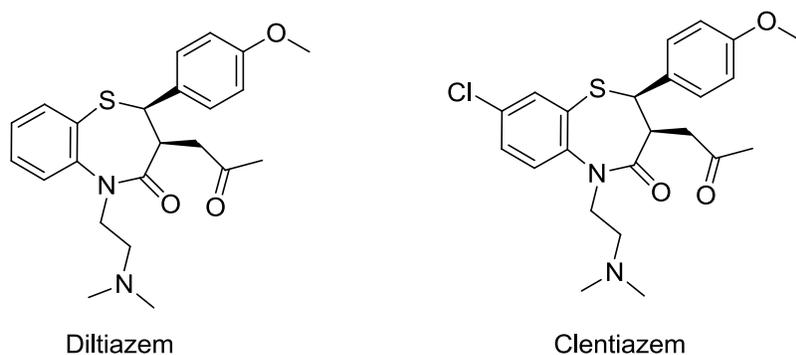
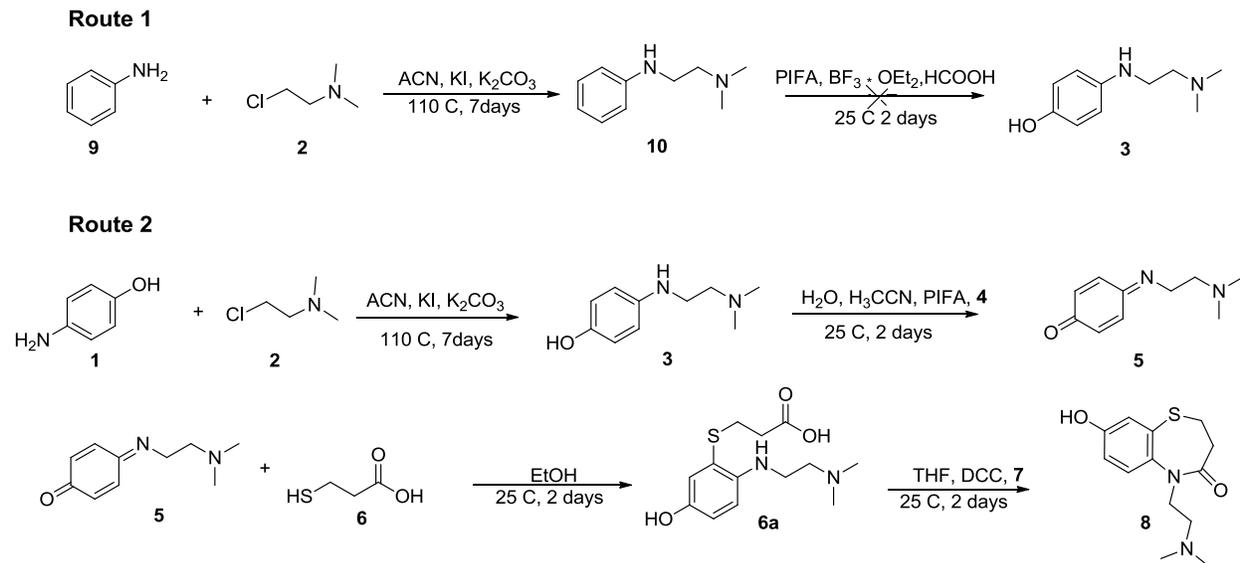


Figure 1. Diltiazem and Clentiazem structures

Methods



The total synthesis of Diltiazem/Clentiazem analogs had two different pathways: **Route 1** and **Route 2** which are demonstrated in Figure 2. Bold numbers from the following passage and figures refer to their corresponding compounds as it is listed in Figure 2. In **Route 1**, nucleophilic addition of aniline **9**, to 2-chloro-*N,N*-dimethylethylamine **2**, successfully generated dimethyl[2-(phenylamino)ethyl]amine **10**. However, oxidation of compound **10** was unsuccessful which led to the design of an alternative pathway. Therefore, in **Route 2**, nucleophilic addition of 4-aminophenol **1**, to 2-chloro-*N,N*-dimethylethylamine **2**, generated intermediate **3**. This intermediate was oxidized by PIFA, followed by nucleophilic Michael addition of 3-mercaptopropionic acid **6**. Lastly, cyclization with DCC **7** generated the Diltiazem/Clentiazem analogs **8**.

Nucleophilic addition of 4-aminophenol to 2-chloro-*N,N*-dimethylethylamine⁵

In the nucleophilic addition, 12 mL of acetonitrile (ACN) was added to 0.5 mmol of potassium iodide (KI). Then, 5 mmol of potassium carbonate (K_2CO_3), and 15 mmol of 4-

aminophenol **1** were added respectively to the solution. Lastly, 5 mmol of 2-chloro-*N, N*-dimethylethylamine **2** were added to the mixture, and the reaction was left heating for 7 days at 110C. Then, the mixture was purified through flash column chromatography using ethyl acetate: methanol: and ammonia (85:15:0.1) as a solvent system. The resulting product was dried *in vacuo* and (4-{[2-(dimethylamino)ethyl]amino}phenol), compound **3**, was formed.

Oxidation of (4-{[2-(dimethylamino)ethyl]amino}phenol)⁶

In the oxidation step, 0.227 mmol of the compound **3** was dissolved into acetonitrile:water (2:1, 0.680mL). Then, 0.227 mmol of PIFA **4** was added to the solution. The reaction vial was covered in aluminum foil and left stirring in room temperature for a week. This reaction produced *in situ* 4-{[2-(dimethylamino)ethyl]imino}cyclohexa-2,5-dien-1-one **5**. The reaction mixture was used onto the next step without further purification and monitored by thin layer chromatography (TLC). Once TLC detected a new spot and the starting material was consumed, the solvent was dried *in vacuo* and stored to be used onto the following step.

Michael addition of 3-mercaptopropionic acid⁷

To a solution of 0.227 mmol of oxidized compound dissolved in 1.89 mL of ethanol (EtOH), a solution of 0.227 mmol of 3-mercaptopropionic acid was added and the mixture was stirred at room temperature for two days. Like the previous reaction, the addition of 3-mercaptopropionic acid was monitored through TLC. This reaction produced 3-[(2-{[2-(dimethylamino)ethyl]amino}-5-hydroxyphenyl)sulfanyl]propanoic acid, compound **6a**, which was evaporated *in vacuo* as well.

Cyclization of 3-[(2-[[2-(dimethylamino)ethyl]amino]-5-hydroxyphenyl)sulfanyl]propanoic acid⁷

A solution of 0.227 mmol of compound **6a** was dissolved into 1 mL of tetrahydrofuran (THF). Then, 0.227 mmol of DCC **7** was added to the solution. The solution was left stirring at room temperature for four days. On the fourth day, TLC detected the presence of a new spot, so flash column chromatography was performed. The eluent solvent system was ethyl acetate: methanol: and ammonia (85:15:0.1). The compound was isolated and the solvent was evaporated in *vacuo*. This reaction should have produced 5-[2-(dimethylamino)ethyl]-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepin-4-one **8**, which is a Diltiazem/Clentiazem analog. Data analysis of this step is in progress.

Results and Discussion

Nucleophilic addition of 4-aminophenol to of 2-chloro-N, N-dimethylethylamine

This reaction was run in two different ways: a front-run and a large scale. The front-run produced 0.316g, 1.75 mmol, 35% yield. Whereas, the large scale yielded 3.500g, 18.6 mmol, 93% yield. The yield in the large scale run improved greatly due to having more material to work with and an increase in technical knowledge and laboratory ability. The same purification procedure was conducted for the column chromatography of both runs. Furthermore, both runs isolated desired products and were analyzed by Dr. Herman H. Odens, the lead researcher, with the courtesy of University of Tennessee at Chattanooga. Samples were analyzed by ¹H and ¹³C NMR using a Jeol 400MHz NMR. The ¹H NMR spectrum of the front-run is illustrated in Figure 3. Likewise, the large scale reaction ¹H NMR spectrum is illustrated in Figure 4.

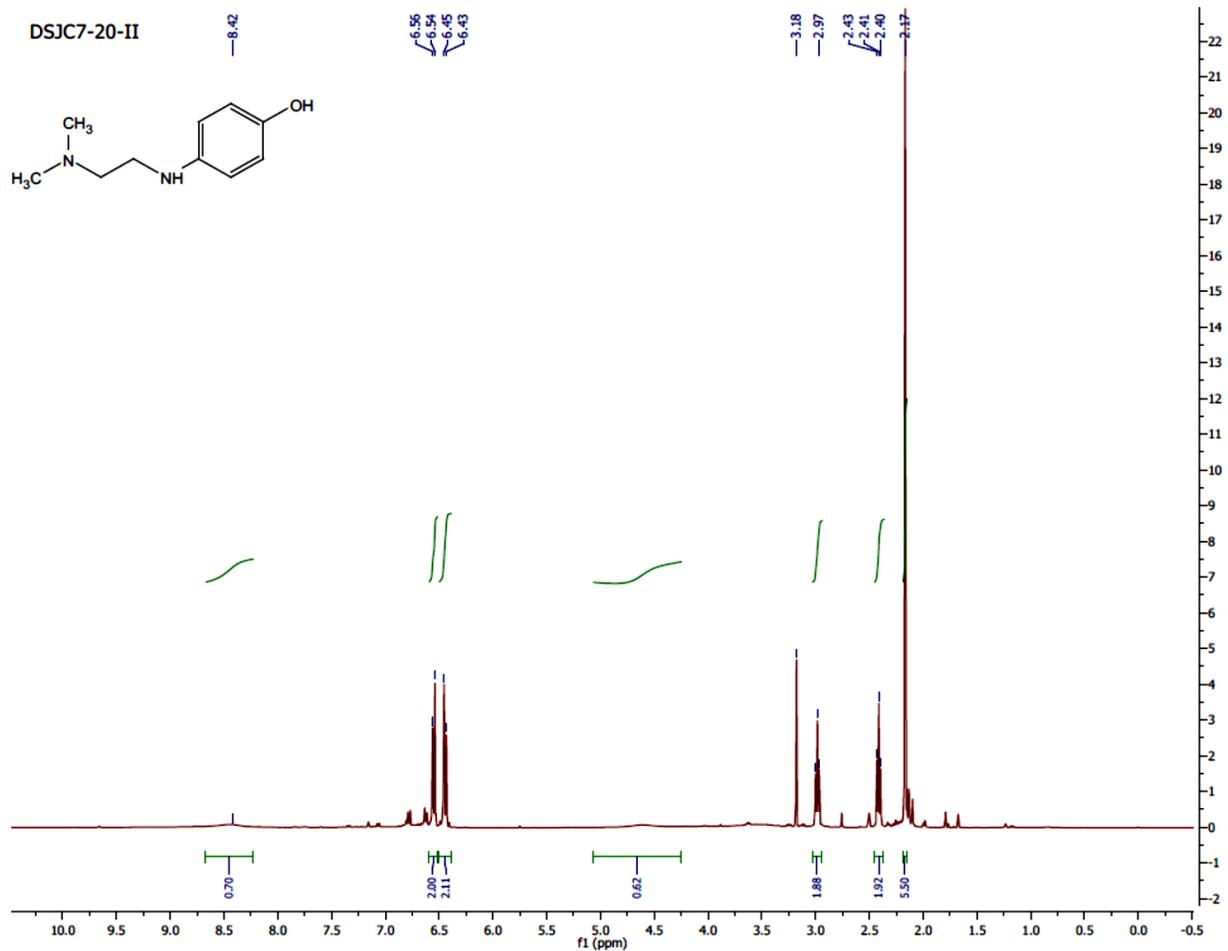


Figure 3. ^1H NMR of the front-run of compound **3**

^1H NMR of the front-run and of the large scale are just as anticipated. All the expected peaks are present and very few impurities are shown. Thus, the nucleophilic addition reaction was conducted successfully. However, from the oxidation step onward, the researchers carried out the total synthesis with no purification. Therefore, the results for the final synthesis of Diltiazem and Clentiazem analogs are still in progress.

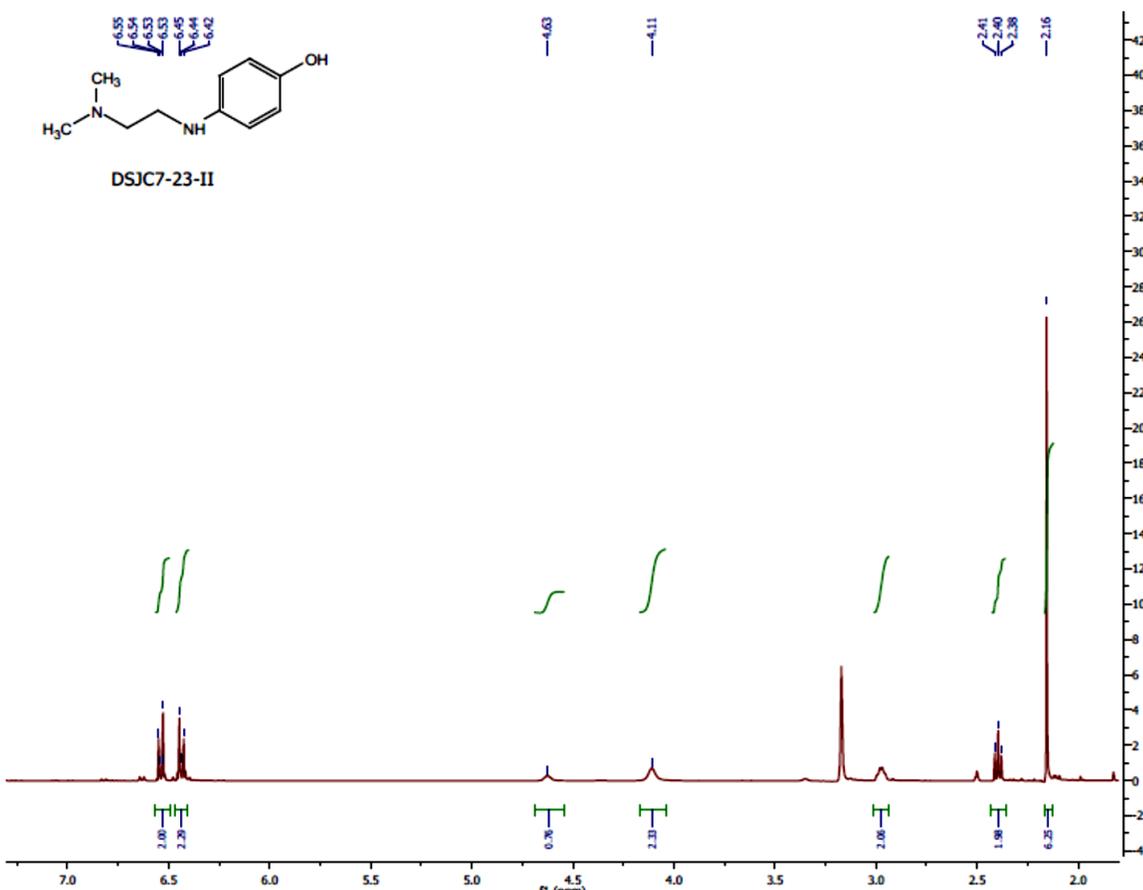


Figure 4. ^1H NMR of DSJC7-23 from large scale

In the nucleophilic step, there was a possibility of O-alkylation instead of N-alkylation. However, both TLC and ^1H NMR revealed that no such alkylation occurred. In fact, NMR showed no trace of O-alkylation. This trend is consistent with common nucleophilicity knowledge. Nitrogen is less electronegative and a better base than the oxygen atom, which makes N-alkylation much more likely to happen.

This successful $\text{S}_{\text{N}}2$ reaction is masked by the failure of **Route 1**, Figure 2, synthesis. As in **Route 2** nucleophilic reaction, the **Route 1** nucleophilic reaction was fundamentally successful and produced N^1 -ethyl- N^2 , N^2 -dimethyl- N^1 -phenyl-1,2-ethanediamine, **11**. However, the insertion of a hydroxyl group to this molecule was unsuccessful. The TLC revealed a

breakdown of product and ^1H NMR showed too many peaks to have any meaningful interpretation. Thus, realizing the difficulty of inserting a hydroxyl group to N^1 -ethyl- N^2,N^2 -dimethyl- N^1 -phenyl-1,2-ethanediamine **11**, the same reaction conditions were used in **Route 2** with 4-aminophenol instead of aniline. This strategy not only gave a better result but also cut down on total synthetic steps.

In the second step of Route 2, the oxidation of (4-{[2(dimethylamino)ethyl]amino}phenol) compound **3** had several problems. The compound is heat and light sensitive, and also breaks down in silica gel. Thus, no purification was done from this oxidation step onward because flash column chromatography requires silica gel. Because of these sensitivities, four different oxidizing agents were tried to find the best one, Figure 5. According to TLC, treatment of compound **3** with PIFA **4** was the only reaction that successfully oxidized the (4-{[2(dimethylamino)ethyl]amino}phenol) **3**. However, an attempt to isolate compound **5** by column chromatography was unsuccessful.

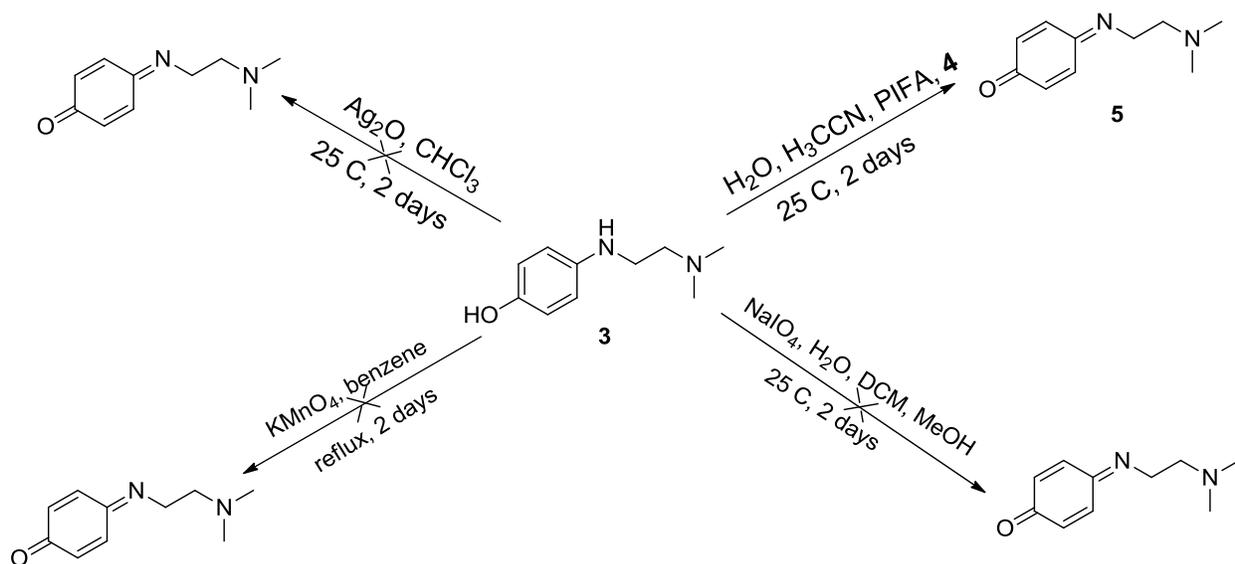


Figure 5. Explosion chart of various oxidizing agents

The oxidation steps show that redox reactions are usually substrate specific and not all oxidants can oxidize the same molecule. Compound **3** seems to favor PIFA **4** over the others. When Ag₂O, KMnO₄, and NaIO₄ were used as oxidants, TLC showed many spots which are an indication of multiple product formation. Possible causes for this would be over oxidation and degradation of compounds, which was evident from TLC data of these three reactions. However, exact reason why compound **3** favors PIFA is unclear.

Conclusion:

Although the research was slow in the beginning, a new methodology, **Route 2**, has been successfully developed for the synthesis of Diltiazem/Clentiazem analogs. In the future, addition of chiral groups to the 7-member ring of 5-[2-(dimethylamino)ethyl]-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepin-4-one **8** can be tested to understand how chirality and different functional groups affect the biological activity. Lastly, **Route 2** seems to be a viable procedure for the synthesis of Diltiazem or Clentiazem analogs because the starting materials and reagents used are relatively inexpensive and the procedure is mild.

References

1. World Health Organization . Accessed on Dec. 9, 2013.
2. Brauns, T., Cai, Z., Kimball, D., Kang, H., Haugland, R. P., Berger, W., Berjukov, S., Hering, S., Glossmann, H., and Striessnig, J. (1995) Benzothiazepinone binding domain of purified L-type calcium channels: direct labeling using a novel fluorescent diltiazem analogue, *Biochemistry* 34, 3461-3469.
3. Zhao, H., and Liu G. (2007) Solution-phase parallel synthesis of 2,3-dihydro-1,5-benzothiazepin-4(5H)-ones, *Journal of Combinatorial Chemistry* 9, 756-772
4. Inoue, H., Konda, M., Hashiyama, T., Otsuka, H., Takahashi, K., Gaino, M., Date, T., Aoe, K., Takeda, M., Murata, S., Narita, H., and Nagao, T. (1991) Synthesis of halogen-substituted 1,5-benzothiazepine derivatives and their vasodilating and hypotensive activities, *Journal of Medicinal Chemistry* 34, 675-687.
5. Romera, J. L., Cid, J. M., and Trabanco A. A. (2004) Potassium iodide catalysed monoalkylation of anilines under microwave irradiation, *Tetrahedron Letters* 45, 8797–8800.
6. Morin, C., Besset, T., Moutet, J-C., Fayolle, M., Brückner, M., Limosin, D., Becker, K., Davioud-Charvet, E. (2008) The aza-analogues of 1,4-naphthoquinones are potent substrates and inhibitors of plasmodial thioredoxin and glutathione reductases and of human erythrocyte glutathione reductase, *Org. Biomol. Chem.* 6, 2731-2742.
7. Katrizky, A. R., Odens, H. H., and Zhang, S. (2001) Novel synthesis of 2,3-dihydro-1,5-benzothiazepin-4(5H)-ones and 2H-1,4-Benzothiazin-3(4H)-ones, *Journal of Organic Chemistry* 66, 6792-6796.