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Matthew G. Smentek Date

TARGETING MIXED LINEAGE LEUKEMIA AS ANTICANCER THERAPY FOR INFANTILE ACUTE LYMPHOBLASTIC LEUKEMIA THROUGH THE SYNTHESIS OF NOVEL COMPOUNDS

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Matthew G. Smentek
B.A., Wake Forest University, 2008

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

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By: Matthew G. Smentek

The synthesis of novel pharmaceutical compounds for anticancer therapy is a major focus for medicinal synthetic chemists. Recently, a novel compound (**SM7**) was discovered which could be used to develop a method to inhibit Acute Lymphoblastic Leukemia (ALL) translocation in the leukemia gene by targeting a variety of inhibitors for inducing cytotoxicity in a variety of MLL-leukemia cell lines.[1] The biological evaluations for this compound may be specific for Mixed Lineage Leukemia (MLL) cell lines, but since the MLL transcription factor is found in 70-80% of infant ALL cases it may have clinical ramifications for the treatment of ALL.[1]

The ultimate goal is to design a set of analogues of **SM7** and have our collaborators test their biological efficacy. The chemistry used to synthesize these compounds has been well established and offers a simple pathway to establish molecular complexity rapidly. Nearly thirty different analogues were synthesized and tested for their biological efficacy. Of this small library of compounds, three showed promising levels of activity against MLL cell lines. These promising results suggest that the pursuit of further analogues may eventually yield an effective compound that may be used in future biological tests.

Another important series of analogues was also conceived which contained a heterocyclic moiety similar to that in compound **SM7**. Testing these molecules will be interesting because they offer an alternative molecular structure that bears a cyclopropyl moiety prevalent in a variety of biologically active compounds.[2-9]

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LIST OF ABBREVIATIONS

AcOH – Acetic Acid

ALL – Acute Lymphoblastic Leukemia

APCI – Atmospheric Pressure Chemical Ionization

aq. – Aqueous

Cat. – Catalyst

CH_2Cl_2 or DCM – Dichloromethane

DMB – 2,2-Dimethylbutane

DMF – Dimethylformamide

DMSO – Dimethylsulfoxide

DOSP – Tetrakis-N-(p-dodecylphenylsulfonyl)prolinato]dirhodium (II)

ee % – Enantiomeric Excess

Et_2O – Diethyl Ether

EtOH – Ethanol

Equiv. – Equivalents

HCl – Hydrochloric Acid

HRMS – High Resolution Mass Spectroscopy

IR – Infrared Spectroscopy

KI – Potassium Iodide

LAH or $LiAlH_4$ – Lithium Aluminum Hydride

M – Molar

μM – Micromolar

Me – Methyl Substituent

$MgSO_4$ – Magnesium Sulfate

MLL – Mixed Lineage Leukemia

$NaHCO_3$ – Sodium Bicarbonate

$NaIO_4$ – Sodium Periodate

NaOAc – Sodium Acetate

nd – Not Determined

NMR – Nuclear Magnetic Resonance Spectroscopy

NOE – Nuclear Overhauser Effect

OMe – Methoxy Substituent

OTf – Triflate Substituent

Ph – Phenyl Substituent

RT – Room Temperature

TBAF – Tetra-n-butylammonium Fluoride

TBS – tert-Butyl Dimethyl Silyl Substituent

THF – Tetrahydrofuran

Acknowledgments:

I would first and foremost give special thanks to my parents Genevieve (Donnelly) Smentek and Gregory Smentek for being my proud supporters over the past twenty-three years. Life has not been as easy-going for us since the loss of my beloved sister Kelly nearly four years ago. This document is an expression of my career as a professional student that I would like to formally dedicate in her honor.

I would also like to thank Dr. Huw M.L. Davies for exhibiting unwavering patience with my progression as a graduate student. Although I may have made the process tedious at times, he has been a wonderful mentor who has sympathized with my complications and repeatedly reinforced my self-esteem as a student-researcher.

As for my peers, none has shown more support than Gregory Goschy. He has been the colleague with whom I have shared most of my shortcomings and frustrations. I believe to have gained a lifelong friendship that will prove to be invaluable as I move onward. It is also important that I recognize my fellow colleagues including: Eric Miller, Edo Mwenda, Brendan Parr, Pablo Guzman, and Felicia Fullilove. These are my dear friends and were integral to my professional success and my personal development here at Emory.

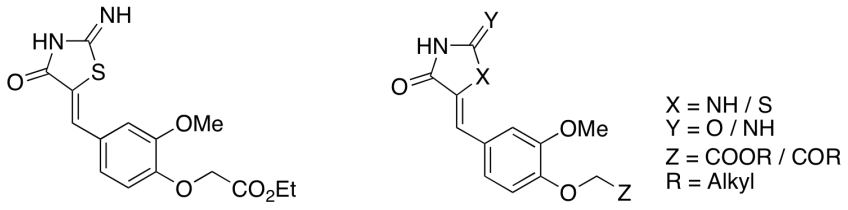
I also would like to thank Dr. Daniel Morton and the rest of the Davies group for continuously aiding me in my experiments and giving numerous tips on how to refine my chemistry during my two year stay at Emory.

Finally, I would like to thank our collaborators headed by Dr. Cally Burkhart at Cleveland Biolabs Inc. located in Buffalo, New York. Without them it would be impossible to have had the biological data necessary to make this an innovative project.

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a form of leukemia whose primary symptoms are similar to those exhibited by other diseases that are responsible for defective blood cells. These symptoms include: weakness, fatigue, anemia, and frequent illness due to a dysfunctional blood cell formation. ALL is found in both adults and children, but it is far more prevalent in children and has a long-term survival rate of 30-50%.[1] Current treatments for ALL are inefficient and highly toxic due to the fact that they also target healthy, non-leukemia-produced blood cells. In order to produce compounds that are viable treatments for ALL it was decided that inhibition of Mixed Lineage Leukemia (MLL) transcription factors would be targeted since they are present in 70-80% of infant ALL cases.[1] If MLL transcription could be selectively targeted, then it could also be possible to stunt the ability of ALL cells to replicate.

Figure 1. Lead Compound and General Structure of Initial Targets



SM7 *Initial Target*

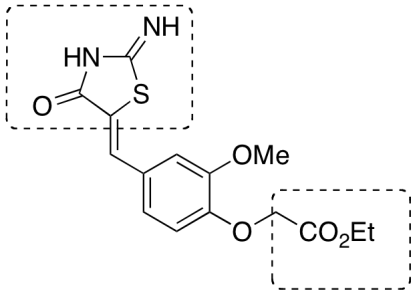
After screening a library of compounds, a promising lead compound (**SM7**) was discovered by collaborators in a research group at Cleveland BioLabs Inc. headed by Dr. Catherine Burkhart. This target was structurally unique, effective, and relatively small

(Figure 1). Modifications of this structure can be synthesized with relative ease and offer a wide range of initial targets for additional screening at Cleveland BioLabs Inc.

Fitting a biological receptor that has not been fully evaluated is a significant challenge for medicinal chemists. It is important to note that the development of novel therapeutic agents involves the design of analogues with regard to their functionalities as opposed to their molecular framework.[10] Analogues which exhibit similar functionalities will have similar bonding affinities even if they lack structural similarity.[10] Developing a compound that properly fits this ambiguous site requires full understanding of the analogues that exhibit the desired effect and utilizing molecular recognition to further modify the structure.

Hydrogen bonding interactions within moieties similar to pseudothiohydantoin are known to have a crucial influence on a wide variety of biological receptors.[11-15] This may be due to the fact that hydantoin heterocycles are also well-established kinase inhibitors in many biological systems.[16,17] This can be attributed to hydrogen bonding interactions which are critical in the binding and docking process because they restrict the orientation of the pharmacophore in the binding cavity.[2,18,19] For this project, the heterocycle was designed to be structurally similar to the effective pseudothiohydantoin moiety in order to facilitate this docking process. Making moderate alterations to the hydrogen bond donating/accepting capacity of the heterocycle within the lead compound would alter the ligand's orientation as it approached the receptor and would thus affect its ability to conform to the active site.

Figure 2. Crucial Functionalities Within SM7



SM7

Figure 2 highlights the functionalities and bonds that can be used for retrosynthetic analysis of the target. The heterocycle features one hydrogen bond donor, which is the amidic site, and one hydrogen bond acceptor, which is the carbonyl group. The sulfur site on the heterocycle also has the capacity to function as a hydrogen bond acceptor, but will not participate as strongly as will the carbonyl group because it is a much weaker Lewis base. The imine group is intriguing because it could function as both a hydrogen bond donor and an acceptor. Although it is formally recognized as a Lewis base, it is also a hydrogen bond donor due to the proton bonded to the nitrogen atom. Since the nature of the hydrogen bonding associated with these two sites is relatively ambiguous in terms of how the sites will interact with the receptor, there may be difficulty in modifying the heterocycle for a better fit.

While the hydrogen bonding interactions of the heterocycle helps to restrict the vast array of conformations a compound may have, the other components of the ligand remain an important issue.[20] Searching for these analogous tethers of the lead compound proved to be as ambiguous as establishing the necessary core functionality. It is possible

that effective ligands may differ in both structure and functionality, which requires further investigation to establish a connection between the two.

The aromatic tether of **SM7**, which contains an ester functionality, was the foundation on which the first set of compounds was conceived. The efficacy of both of the crucial functionalities was probed separately while keeping one constant. That is, the aromatic tether was left unaltered while a different a different heterocycle was installed in the same position as the pseudothiohydantoin moiety. This would help to identify the most effective heterocycle by leaving that region as the only variable in the analogue. Any increase or decrease in biological activity could then be solely attributed to the heterocyclic moiety. Likewise, the pseudothiohydantoin moiety was left unaltered as a variety of different aromatic tethers were employed to find the most effective side chain. By keeping either of the crucial functionalities as a constant, it was possible probe the receptor in order to isolate the most effective heterocycle and aromatic tether separately in order to create a more effective lead compound.

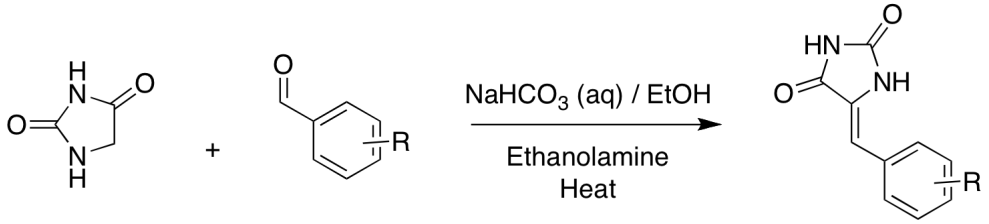
Methods of Preparation for Analogues of SM7:

In order to create the necessary functional groups on the aromatic system, a simple base-promoted alkylation could be performed on the corresponding phenol (vanillin) with a wide range of alkyl substituents bearing an ample leaving group. This chemistry is well established and is a fundamental reaction within the field of organic chemistry. Designing a set of parameters to facilitate the alkylation process would involve little analysis and leaves only the heterocyclic moiety to be added to complete the synthesis.

The most practical method for installing this heterocyclic moiety is a modification of the Knoevenagel condensation.[11-15] The general mechanism for the Knoevenagel condensation was discovered in 1904 and is an amine base-catalyzed aldol-type reaction between a doubly activated methylene site and a ketone or aldehyde.[21] The exact mechanism is dependent on the type of amine used and the product recovered is the alkene in the *Z* orientation.[21]

Synthetic chemists have taken advantage of other compounds containing acidic protons centered between two electron withdrawing substituents to create an array of analogous condensations. In 2004, Thenmozhiyal, Wong, and Chui used a variation of this reaction to synthesize a series of aryl-heterocyclic compounds that exhibited anticonvulsant activity related to epilepsy (Figure 3).[11]

Figure 3. Method A: Condensation of Aldehydes with Hydantoin

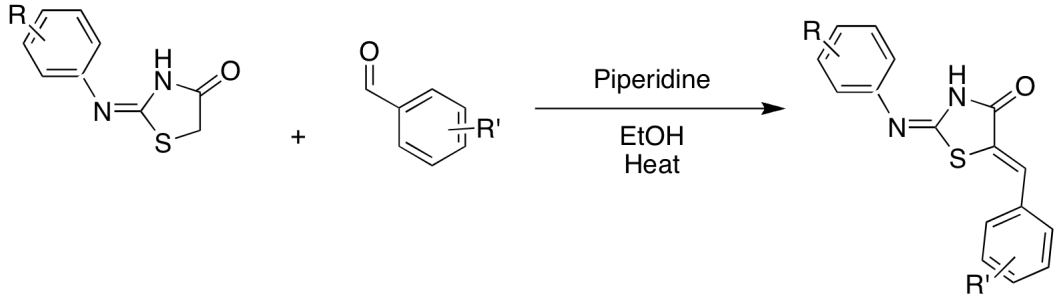


1

R = Alkyl, Alkoxyl, N-Alkyl, OH, X, CN, CF_3, NO_2

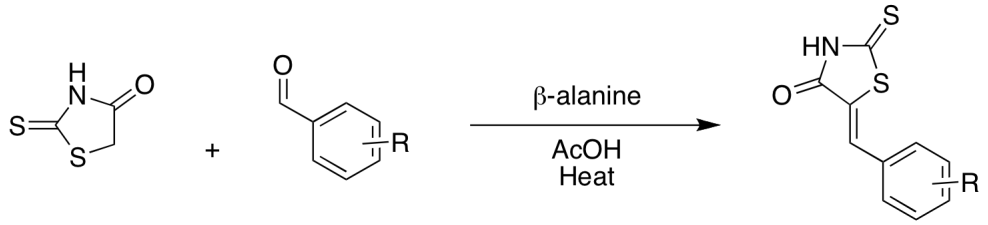
Using hydantoin (**1**) they were able to synthesize over fifty different analogues exclusively as the *Z*-isomer.[11] For the condensation they used ethanolamine as the catalyst and sodium bicarbonate as a base in an aqueous ethanol solution. The primary amine could readily attack the carbonyl group of the aldehyde and allow for attack by the deprotonated hydantoin heterocycle to create the necessary carbon-carbon bond. It may be inferred that these same reagents could be used to install the hydantoin moiety to a large variety of aldehydes similar to those for the synthesis of analogues of **SM7**. Zhou *et al.* utilized a similar method in 2008 when synthesizing compounds for drug-resistant lung cancer cells by using piperidine as the amine catalyst and ethanol as the solvent (Figure 4).[12]

Figure 4. Method B: Condensation of Aldehydes with N-Aryl Pseudothiohydantoin



Another variation of the Knoevenagel condensation between 2-thioxo-thiazolidin-4-one and selected aldehydes was performed by Bursavich *et al.* in 2007 to synthesize over thirty compounds which targeted the inhibition of osteoarthritis (Figure 5).[13]

Figure 5. Method C: Condensation of Aldehydes with 2-thioxo-thiazolidin-4-one

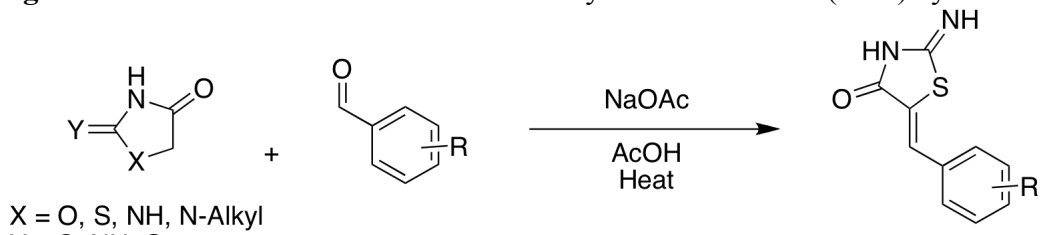


In this reaction β-alanine is used as the amine catalyst for the condensation in the absence of a base. It can be inferred that deprotonation of the heterocycle could occur by the presence of excess amine in the solution. One can infer that using acetic acid as the solvent allowed for facile protonation during the condensation and/or the dehydration. By using a different heterocycle, this allows for further diversity in compounds that are able to perform the necessary condensation.

A final method that has proven effective for the condensation of pseudothiohydantoin with a variety of aldehydes was also demonstrated by Unangst *et al.*

in 1994 as well as Irvine, Patrick, Kewney, Hastings, and MacKenzie in 2008 (Figure 6).[14,15]

Figure 6. Method D: Condensation of Aldehydes with Various (Thio)Hydantoins



X = O, S, NH, N-Alkyl
Y = S, NH, O
2 = Pseudothiohydantoin when X = S and Y = NH

This method, which does not use an amine base as a catalyst, is entirely dependent on the acidity of the pseudothiohydantoin (**2**). Since a variety of analogues were synthesized with viable biological activity under these conditions, it is apparent that an amine is not entirely necessary to perform the desired condensation. This method provides an efficient route to obtaining the desired product with a wide scope of reagents and could be included in the potential routes to analogues of **SM7**.

Potentially Biologically Active Cyclopropyl Analogues:

Figure 7. General Structure of the Cyclopropyl Target

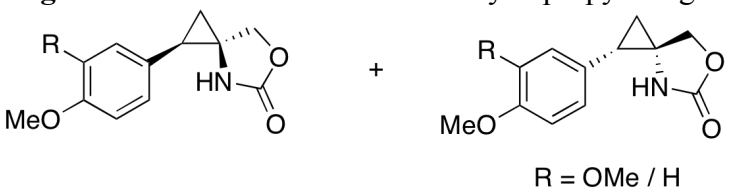
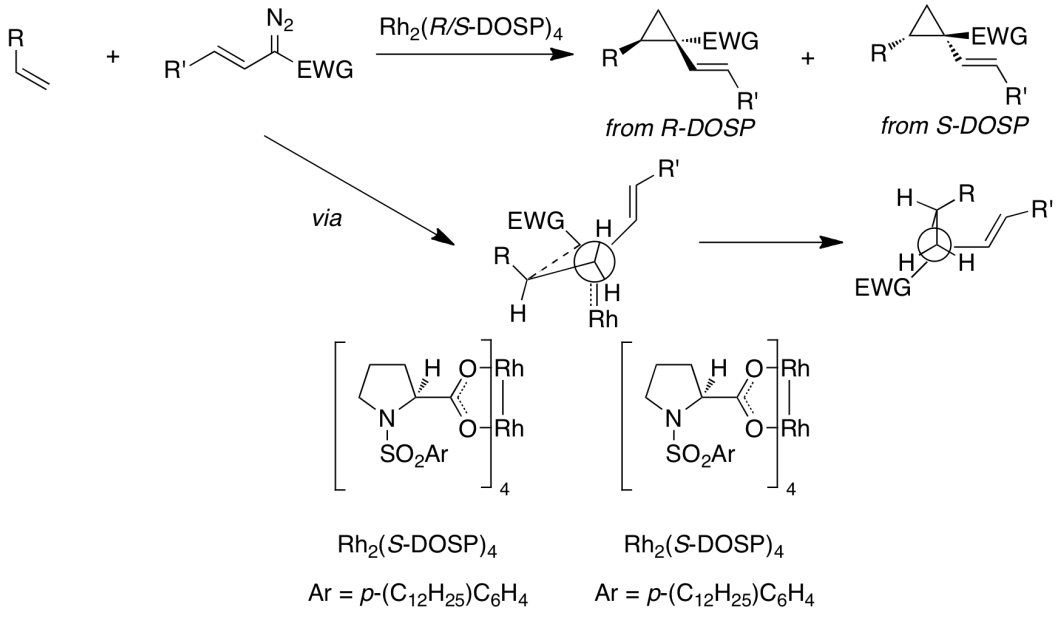


Figure 7 depicts two potentially biologically active cyclopropanes with functional similarities to **SM7** derived from an intriguing synthetic pathway. The approach to these analogues involves using cyclopropanation chemistry, which has been well documented within the Davies group.[22-24] In particular, the rhodium(II) catalyzed decomposition of arylvinyldiazoacetates through a fixed transition state allows for asymmetric synthesis of aromatic cyclopropanes which could potentially have biological significance (Figure 8).[22]

Figure 8. Illustration of the Cyclopropanation of Methyl Styryldiazoacetates



The chirality of the cyclopropane targets is of high interest because they have the ability to probe the receptor in terms of its geometry as opposed to functionality. This differs from the hydantoin analogues because their core is planar and lacks chiral sites. The cyclopropanation step determines the absolute configuration of the targets that would be formed. That is, all modifications of the compound performed after cyclopropanation will retain the previously introduced stereochemistry. This would lead to a variety of enantiomerically pure compounds that can be easily synthesized in a short number of steps. Since chiral cyclopropanes are synthetically intriguing and have a wide variety of biological applications, they should be seriously considered as novel candidates for screening against MLL cell lines.

Summary:

All of the methods described provide intriguing routes to potentially biologically active compounds for the inhibition of ALL/MLL transcription. Each class of compounds offers a different set of functionalities that will provide for a wide variety of analogues for biological screening. The hydantoin moieties are well known to be effective kinase inhibitors and biologically active agents.[11-17] However, the analogues containing these moieties are restricted in their geometry due to their lack of a chiral center and may not be optimal for the designated receptor. The cyclopropyl analogues, which lack the exact functionality of the **SM7** analogues, may prove to be effective because of this reason. However, the heterocycle contained in the proposed cyclopropyl

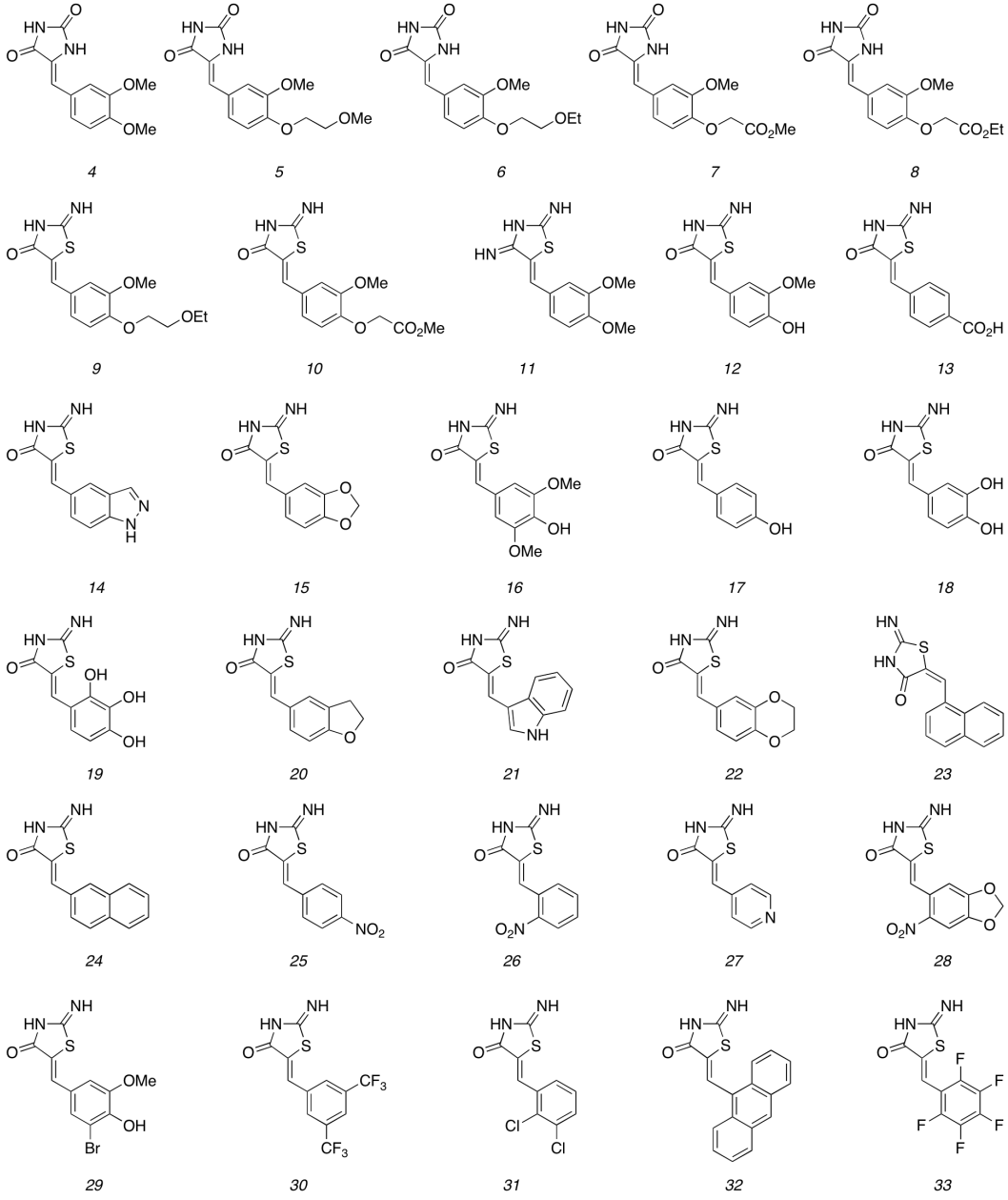
targets may not have as strong of an affinity for the receptor site as does the one present in **SM7**.

A large variation of compounds will allow for a more thorough analysis of the receptor as well as give valuable data about which functionalities seem to be most effective in the inhibition of MLL cell transcription. Realization of effective functionalities will eventually lead to better molecular design and further analogues that should be more effective. The ultimate goal of this design process is to reveal a highly effective compound that is more efficient and not as toxic as those currently available for therapeutic treatment.

RESULTS AND DISCUSSION

The ultimate goal of the project was to synthesize a variety of analogues of **SM7** for biological assays. Nearly thirty different analogues of **SM7** were successfully synthesized as single stereoisomers and are shown in Figure 9.

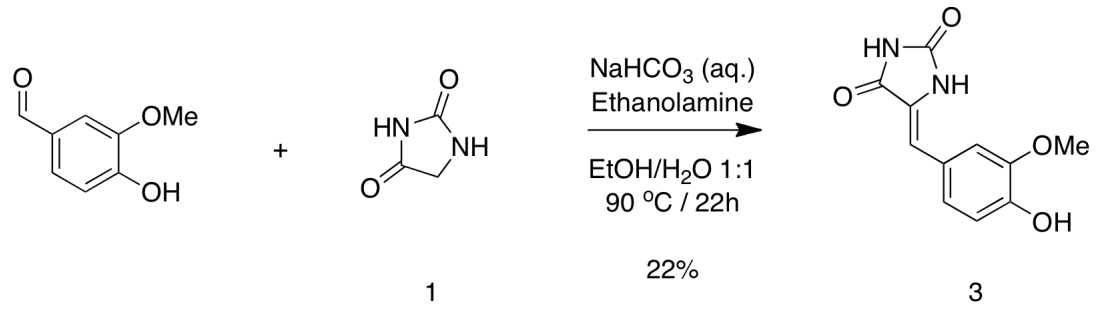
Figure 9. Synthesized Analogues of Lead Compound SM7



Two potential pathways were deemed feasible for the synthesis of analogues of **SM7**. The first pathway called for the condensation of the heterocycle before performing an alkylation reaction on the phenolic hydroxyl substituent. Using the precedent set by

Thenmozhiyal, Wong, and Chui, the condensation between vanillin and hydantoin was performed with moderate yield (Figure 10).[11]

Figure 10. Condensation Reaction Between Vanillin and Hydantoin

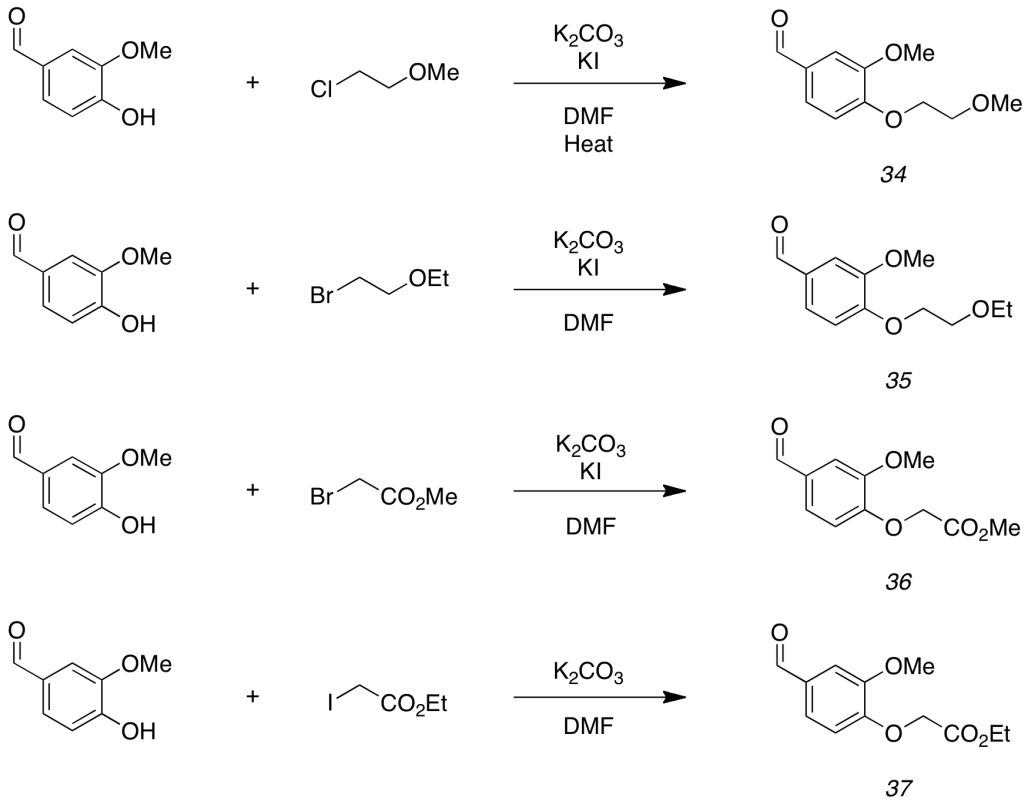


Although the reaction yielded the desired product, attempts at O-alkylation of compound **3** were unsuccessful. The substrate **3** was only soluble in DMF and DMSO and the reactions conducted in these solvents were inconclusive. Due to these important factors, it was decided to perform the condensation of the heterocycle after the O-alkylation of vanillin.

Four different O-alkylations were performed before the condensation to yield the desired aldehydes **34-37** (Figure 11). Each of these O-alkylations was a relatively facile process that involved the use of a single base and halogenated alkyl ester or ether as the alkylating reagent.

Analogues Prepared From O-Alkylation:

Figure 11. O-Alkylation of Vanillin with Varying Reagents



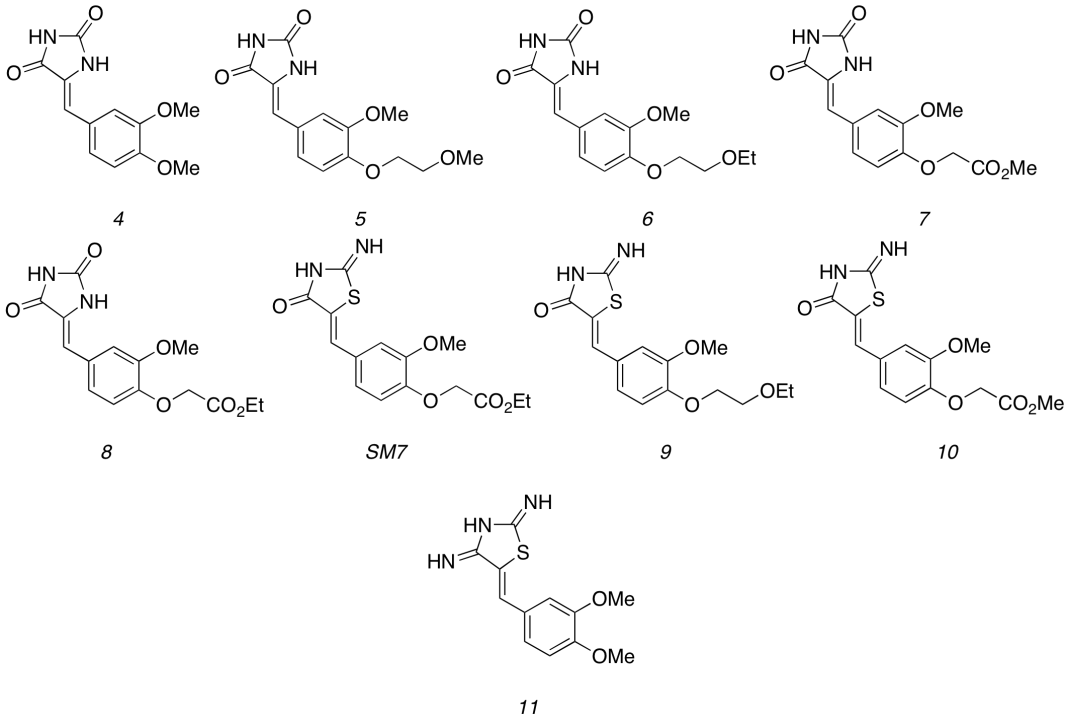
Aldehyde	K_2CO_3 (equiv.)	Cat. (equiv.)	Temp (°C)	Time (h)	Yield (%)
34	1.25	KI (10%)	60	40	56
35	1.25	KI (10%)	RT	21	70
36	1.25	KI (10%)	RT	18	73
37	1.25	-	RT	22	81

3,4-Dimethoxybenzaldehyde and aldehydes **34-37** were condensed with either hydantoin or pseudothiohydantoin to yield the desired analogues **4-11** and **SM7** (Figure 12). To synthesize compounds **4-6** and **11**, which involved the condensation of hydantoin with the selected aldehydes, the precedent set by Thenmozhiyal, Wong, and Chui (**Method A**)

was used.[11] The NOE data for the products were consistent with the supposition submitted by the authors that all of the products are in the Z orientation.[11,21]

The synthesis of analogues **7-10** and **SM7** was also attempted through this same precedent, but these reactions failed to yield the desired products. Compounds **7** and **8** were synthesized by the method established by Zhou *et al*., which used piperidine as the amine catalyst (**Method B**).[12] Analogues **9**, **10**, and **SM7** had to be synthesized according to the protocol set forth by Unangst *et al*. and Irvine, Patrick, Kewney, Hastings, and MacKenzie (**Method D**).[14,15] This method, which employed the use of sodium acetate as a base without the use of an amine catalyst, proved to be successful in synthesizing the analogues which could not be assembled by the method set forth by Thenmozhiyal, Wong, and Chui.[11]

Figure 12. Synthesized Analogues **4-11** and **SM7**



Compound	Aldehyde	Method	Aldehyde : Hetereocycle	Heterocycle	Time (h)	Yield (%)
4	**-**	A	1 : 1.1	Hydantoin	21	66
5	**34**	A	1 : 1.1	Hydantoin	20	37
6	**35**	A	1 : 1.1	Hydantoin	16	33
7	**36**	B	1 : 1.1	Hydantoin	18	40
8	**37**	B	1 : 1.1	Hydantoin	17	21
9	**37**	D	1 : 1.1	Pseudothiohydantoin	16	48
10	**36**	D	1 : 1.1	Pseudothiohydantoin	17	54
11	**-**	A	1 : 1.1	Pseudothiohydantoin	11	23
SM7	**37**	B	1 : 1.1	Pseudothiohydantoin	16	92

While the yields were modest, enough product was obtained from each reaction to run biological assays against MLL cell lines. Other than the lead compound **SM7**, none of these compounds exhibited the desired biological efficacy against MLL cell transcription (Figure 13).

Figure 13. Biological Activity of Analogues **4-11** and **SM7**

Analogue	IC50 MV4-11 MLL leukemia cells (μM)	IC50 MCF7 breast cancer cells (μM)	IC50 HeLa cervical cancer cells (μM)	IC50 NKE "normal" kidney cells (μM)
SM7	11.1	inactive	inactive	31.4
4	inactive	inactive	nd	nd
5	inactive	inactive	inactive	inactive
6	inactive	inactive	inactive	inactive
7	>40	nd	inactive	inactive
8	39.7	nd	inactive	inactive
9	>40	inactive	inactive	inactive
10	nd	nd	nd	nd
11	inactive	inactive	inactive	inactive

Poor biological activity led to modification of the functionalities and structures of further analogues. Since all of the analogues containing ether linkages proved to be inefficient at inducing biological activity, these aldehydes were abandoned as condensation reagents in favor of those with ester functionalities. **SM7** continued to exhibit biological activity upon further testing which supported the presumption that ester functionalities opposite to the heterocycle would most likely yield the desired biological activity.

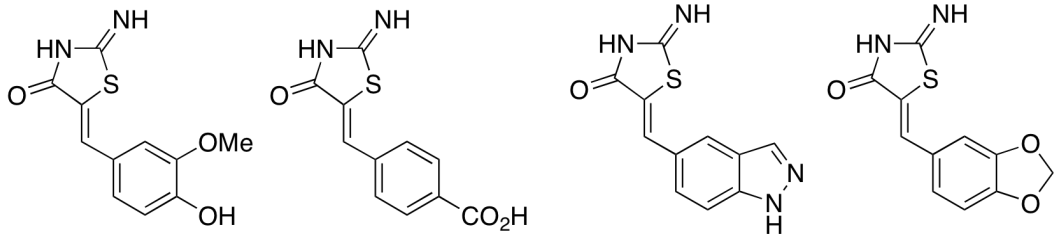
Although both compounds **7** and **8** were relatively ineffective at inducing the desired biological activity, analogue **8** was slightly more active than **7**. These compounds differed by the length of the ester attached to the aromatic tether, thus it can be inferred that shortening the side chain on the ester also has an adverse effect on the overall biological activity. The ineffectiveness of compound **8** also led to the conclusion that the pseudothiohydantoin would be a more effective heterocycle than hydantoin. This inference can be made because both compounds **SM7** and **8** contain the exact same

aromatic tether and differ only by their heterocycle. This means that the pseudothiohydantoin heterocycle was necessary for the induction of biological activity and that future analogues should contain this moiety. Much had yet to be determined regarding the optimized functionality and structure of the aromatic tether.

Analogues Prepared From Commercially Available Material:

Analogues **12-15** were established to evaluate a variety of commercially available aldehydes that were not readily available via alkylation (Figure 13). All of the analogues contain the pseudothiohydantoin moiety attached to the aromatic ring as well as acidic protons that may participate in hydrogen bonding with the biological receptor. All of these compounds were synthesized according to the procedure set forth by Unangst *et al*. and Irvine *et al.* (**Method D**).[14,15]

Figure 14. Synthesized Analogues **12-15**



12 *13* *14* *15*

Entry	Method	Aldehyde : Heterocycle	Heterocycle	Time (h)	Yield (%)
12	D	1.1 : 1	Pseudothiohydantoin	18	33
13	D	1.1 : 1	Pseudothiohydantoin	19	74
14	D	1.1 : 1	Pseudothiohydantoin	24	14
15	D	1.1 : 1	Pseudothiohydantoin	24	49

Of these analogues, only two showed significant biological activity towards MLL transcription (Figure 15). Analogues **12** and **15** were both more active than the lead compound **SM7**, but differed in their molecular structure slightly. Analogue **12**, which was the less active of the two against MLL cell lines, contained a hydroxy functionality para to the heterocycle. Analogue **15** did not contain a similar functionality, but rather bore a cyclic acetal.

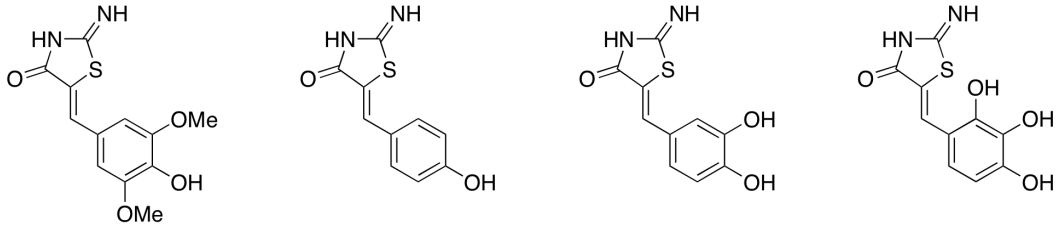
Figure 15. Biological Activity of Analogues **12-15** and **SM7**

Analogue	IC50 MV4-11 MLL leukemia cells (μM)	IC50 MCF7 breast cancer cells (μM)	IC50 HeLa cervical cancer cells (μM)	IC50 NKE "normal" kidney cells (μM)
SM7	11.1	inactive	inactive	31.4
12	10.25	31.5	34.7	29.1
13	inactive	inactive	nd	nd
14	37.5	inactive	nd	nd
15	4.44	7.28	nd	nd

The difference in acidity between **12** and **15** is enormous, a pK_a of ~9.9 for **12** and a pK_a of >40 for the cyclic acetal in **15**, initially suggesting that acidity of the aromatic substituents opposite of the heterocycle may not be a primary factor in their biological efficacy. While the carboxylic acid **13** has a far lower pKa, its location one carbon away from the aromatic ring may interfere with its ability to orientate properly at the receptor site. The acidic phenol **12** still remained interesting due to its activity and it was decided that this functionality would be further studied to facilitate the development of a relationship amongst functionalities that elicited a biological response.

In order to probe whether or not acidic hydroxyl substituents directly attached to the aromatic ring was advantageous, a set of phenols were condensed with pseudothiohydantoin by **Method D** to give compounds **16-19** (Figure 16).[14,1]

Figure 16. Synthesized Analogues **16-19**



16 *17* *18* *19*

Entry	Method	Aldehyde : Heterocycle	Heterocycle	Time (h)	Yield (%)
16	D	1.1 : 1	Pseudothiohydantoin	24	50
17	D	1.1 : 1	Pseudothiohydantoin	24	40
18	D	1.1 : 1	Pseudothiohydantoin	20	4
19	D	1.1 : 1	Pseudothiohydantoin	24	24

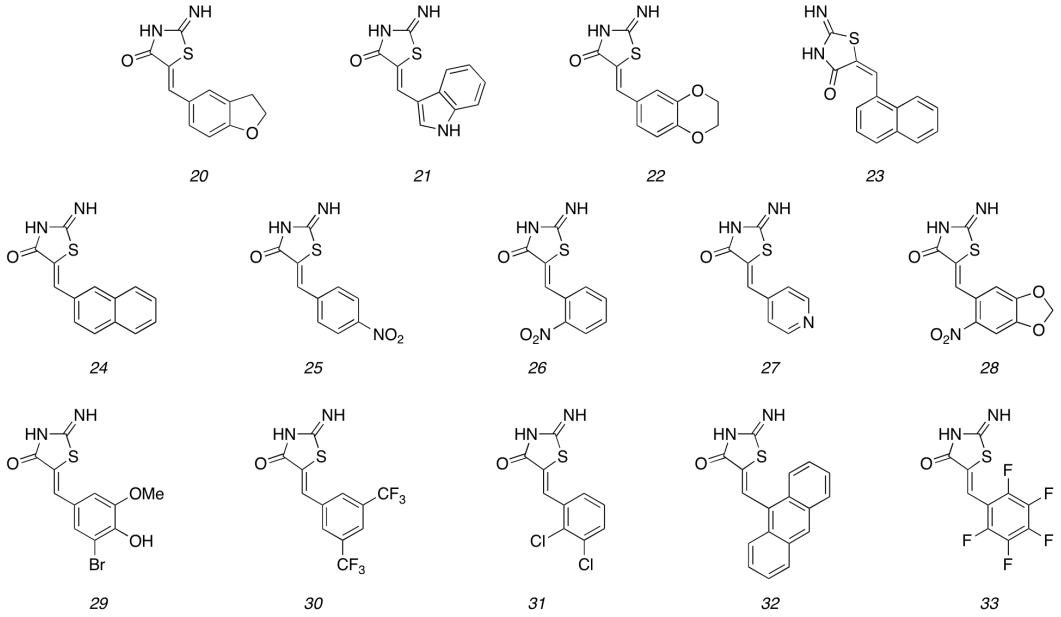
Analogues **16** and **19** were biologically inefficient and inactive, respectively, while results for **17** and **18** are still pending (Figure 17). The inactivity of these compounds containing acidic aromatic tethers allows one to infer that an acidic proton opposite of the heterocycle is not likely to induce the desired biological activity in MLL cell screenings. This hypothesis is further supported by the fact that these compounds all have functionalities with pKa's of less than **12**.

Figure 17. Biological Activity of Analogues **16-19** and **SM7**

Analogue	IC50 MV4-11 MLL leukemia cells (μM)	IC50 MCF7 breast cancer cells (μM)	IC50 HeLa cervical cancer cells (μM)	IC50 NKE "normal" kidney cells (μM)
SM7	11.1	inactive	inactive	31.4
16	42.2	inactive	nd	nd
17	nd	nd	nd	nd
18	nd	nd	nd	nd
19	inactive	inactive	nd	nd

Since a firm relation between the aromatic tether and biological activity had not been firmly established, new sets of analogues with varying characteristics were synthesized. The synthesis of a variety of cyclic ethers was then performed to determine whether or not cyclic ethers similar to **15** bear a functionality that elicits the desired biological effect. Analogues **20-33** were also prepared from a variety of commercially available aldehydes by **Method D** (Figure 18).[14,15]

Figure 18. Synthesized Analogues **20-33**



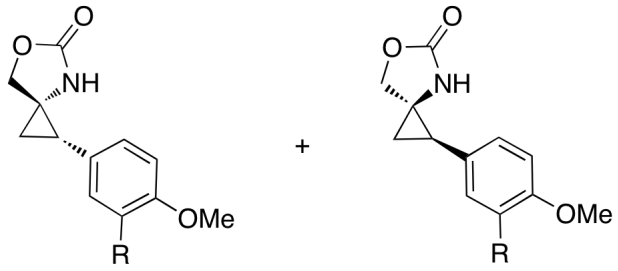
Entry	Method	Aldehyde : Heterocycle	Heterocycle	Time (h)	Yield (%)
20	D	1.1 : 1	Pseudothiohydantoin	24	43
21	D	1.1 : 1	Pseudothiohydantoin	24	11
22	D	1.1 : 1	Pseudothiohydantoin	24	68
23	D	1.1 : 1	Pseudothiohydantoin	24	18
24	D	1.1 : 1	Pseudothiohydantoin	20	41
25	D	1.1 : 1	Pseudothiohydantoin	24	50
26	D	1.1 : 1	Pseudothiohydantoin	15	68
27	D	1.1 : 1	Pseudothiohydantoin	20	39
28	D	1.1 : 1	Pseudothiohydantoin	21	61
29	D	1.1 : 1	Pseudothiohydantoin	14	49
30	D	1.1 : 1	Pseudothiohydantoin	14	28
31	D	1.1 : 1	Pseudothiohydantoin	15	82
32	D	1.1 : 1	Pseudothiohydantoin	15	21
33	D	1.1 : 1	Pseudothiohydantoin	17	15

Compounds **20**, **22**, and **28** were similar to compound **15** due to the presence of cyclic ethers tethered to the aromatic ring. It was conjectured that these similarities in functionality might induce the desired biological activity in MLL cell lines. Compounds **28** and **29** were synthesized for similar reasoning in order to validate the biological

expression of the functionalities within **15** and **12**, respectively. If these compounds prove to be effective then a correlation between structure, functionality, and biological efficacy may begin to emerge. However, data on the biological activity of analogues **20-33** has yet to be made available at this time.

Cyclopropyl Analogues:

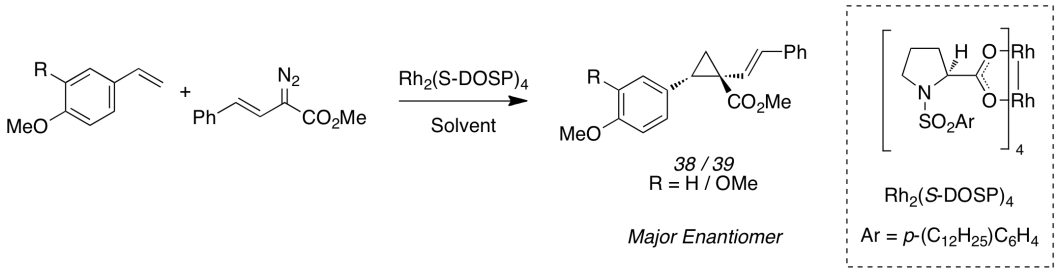
Figure 19. Cyclopropyl Targets



R = OMe / H

The final two analogues are cyclopropanes that bear a heterocycle similar to the hydantoin and pseudothiohydantoin moieties (Figure 19). Because of this structural similarity it can be inferred that these molecules hold promise for biological activity. The first step in the synthetic scheme for these molecules was a rhodium(II) catalyzed cyclopropanation reaction that yielded the desired chiral products **38** and **39** in modest yields (Figure 20).

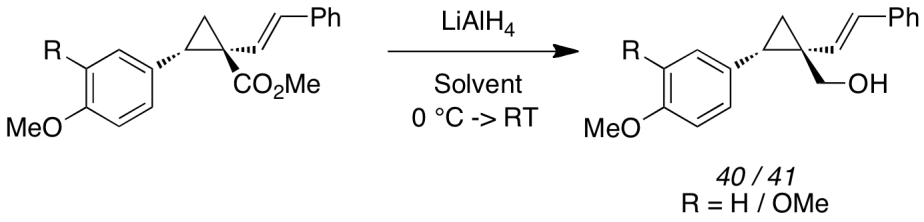
Figure 20. Cyclopropanation of Electron-Rich Styrenes



Entry	R	Solvent	Time (h)	Styrene (equiv.)	Yield (%)
38	H	DMB	3	1	Trace
38	H	DCM	4	1	46
38	H	Hexanes	4	1	17
38	H	Hexanes	5	1	48
38	H	Pentane	4	4	70
39	OMe	DMB	3.5	1	27
39	OMe	Hexanes	6.5	1	2
39	OMe	Hexanes	8	1	40
39	OMe	Hexanes	6	1	14
39	OMe	Pentane	4	4	52

The enantiomeric excess (ee %) was 84% and 82% for compounds **38** and **39**, respectively. The next step was to reduce the esters in both of these compounds through a lithium aluminum hydride reduction. These reactions were successfully performed but gave modest yield of compounds **40** and **41** (Figure 21).

Figure 21. LAH Reduction of Cyclopropyl Esters

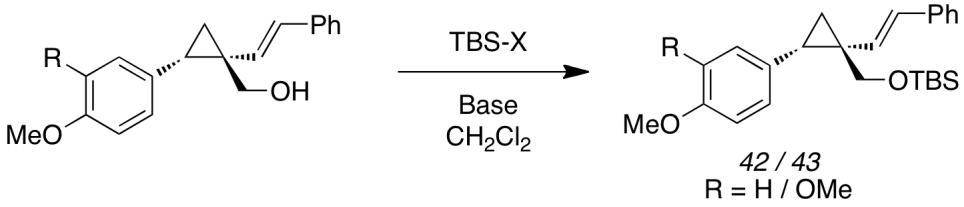


40 / 41
R = H / OMe

Entry	R	Solvent	$LiAlH_4$ (equiv.)	Time (h)	Yield (%)
40	H	Et_2O	3	15	59
41	OMe	THF	8	12	86

Since the yield and recovery of starting material were low for entry **40**, it can be inferred that product must have remained trapped within the lithium salts during workup. Future attempts at this reduction must employ further dilution of the reaction mixture and slower addition of the quenching agent to avoid complications with aluminum salt formation. Subsequent silyl protection of the primary alcohols gave compounds **42** and **43** and leaves the compounds three steps away from submission for biological evaluation (Figure 22).

Figure 22. Silyl Protection of the Primary Alcohol

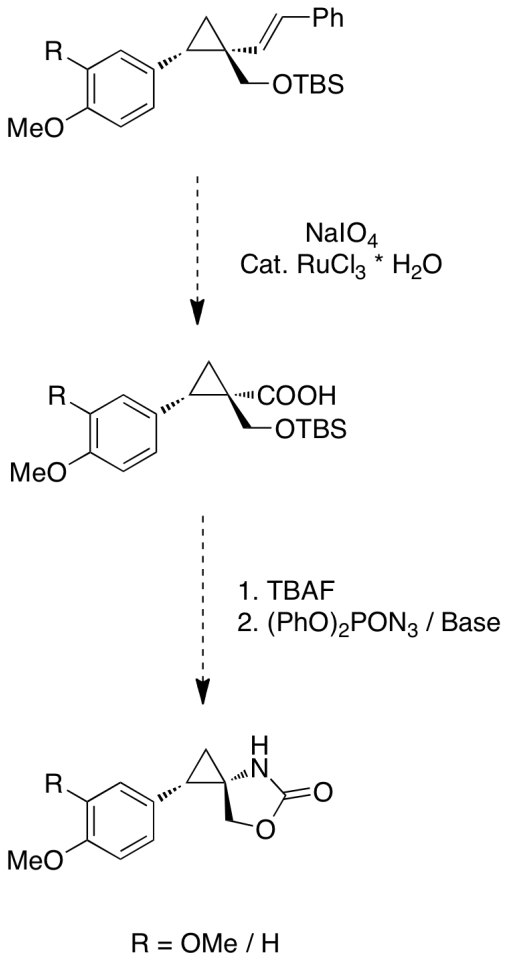


42 / 43
R = H / OMe

Entry	R	X	Base (equiv.)	Time (h)	Yield (%)
42	H	OTf	2,6-lutidine (2)	4	67
43	OMe	Cl	Imidazole (5)	15	87

The final three steps to reach the desired analogues involve a ruthenium catalyzed oxidative cleavage of the alkene to produce the carboxylic acid (Figure 23). Silyl deprotection followed by an intramolecular Curtius rearrangement would eventually lead to the desired analogues (Figure 23).

Figure 23. Endgame of the Cyclopropyl Analogue Synthesis



Biological evaluation of these molecules will lead to further structural modifications pending the results. Thus far all attempts at the ruthenium catalyzed oxidative cleavage of have proven unsuccessful in creating the desired carboxylic acids.

Even upon running these reactions a relatively large scale, isolation of the various products after column chromatography revealed insignificant amounts of the desired carboxylic acid. The reason for these difficulties is not understood, especially as closely related compounds have been converted successfully under these conditions.

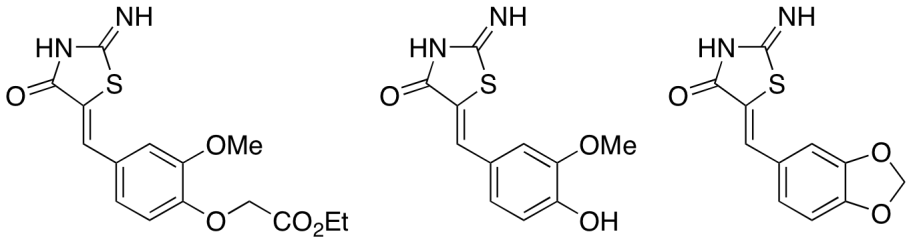
Conclusions:

The synthetic process for the cyclopropyl analogues may need to be refined in order to reach the desired analogues. While the planarity of these molecules will be interesting to test in relation to the receptor site, it seems that the pseudothiohydantoin moiety is necessary to encourage strong binding affinities. It is hoped that increasing the scale of the oxidative ruthenium cleavage will yield the desired carboxylic acid. Otherwise, alternative methods at oxidative cleavage of the alkene may need to be evaluated. The proceeding silyl deprotection should be fairly straightforward, leaving only the intramolecular Curtius rearrangement to be performed to attain these analogues. If the biological assays prove inactive then the cyclopropyl analogues will most likely be disregarded since there is little evidence for their efficacy other than the similarities between heterocycles with **SM7**. Otherwise, further structural modifications may be made to the structure in order to enhance reactivity in search of a new class of MLL inhibitors.

Nearly thirty different analogues of **SM7** were successfully synthesized and screened for biological activity against MLL cell lines. Of these, only analogues **12** and

15 showed promise in terms of their biological activity in comparison to the lead compound **SM7** (Figure 24).

Figure 24. Biologically Active Compounds



SM7 *12* *15*

Analogue	IC50 MV4-11 MLL leukemia cells (μM)	IC50 MCF7 breast cancer cells (μM)	IC50 HeLa cervical cancer cells (μM)	IC50 NKE "normal" kidney cells (μM)
SM7	11.10	inactive	inactive	31.40
12	10.25	31.50	34.70	29.10
15	4.44	7.28	nd	nd

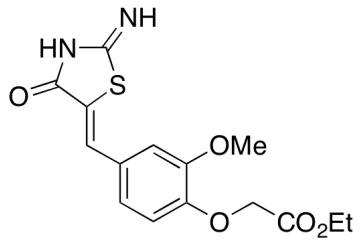
Figure 24 shows that analogues **12** and **15** were more effective in MLL cell screens than was the original lead compound **SM7**. Analogue **12** was only slightly more active than the lead in MLL cell screens, but **15** was two and a half times as effective. Intriguingly, compound **15** was also active against breast cancer cells. This demonstrates its potential diversity as a chemotherapeutic agent.

Although the functionality of the aromatic tether within each of these compounds differs significantly, their efficacy is not surprising. These compounds have quite different functionalities and their ability to exhibit high levels of cytotoxicity within MLL cell screens can be at least partly explained by the pseudothiohydantoin moiety. The inactivity of the hydantoin analogues can be explained by the fact that the heterocycles

differ greatly in their ability to participate in hydrogen bonding. The pseudothiohydantoin moiety must strongly participate in the orientation of the molecular structure as the compound participates in binding with the biological receptor. All of the future targets should undergo condensation with pseudothiohydantoin, but other heterocycles with similar features should not be overlooked simply because the lead compound contains this functionality.

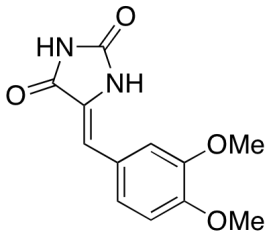
The diversity of functionality within the aromatic tether is a source of concern that deserves future probing due to ambiguous results. That is, each effective compound lacks the distinguishing features necessary to make progressive structural modifications. Each set of submitted analogues helps to better define the binding affinities of the receptor and creates a more complete model of the functionalities necessary in the pharmacophore. Although the system responsible for initiating cytotoxicity in MLL cell lines is not completely refined, these analogues make a strong statement with their biological efficacy. It is entirely possible that further probing of the functionalities within these effective compounds could eventually lead to a novel compound which can be employed as an effective agent for chemotherapy for those afflicted with ALL and MLL.

EXPERIMENTAL



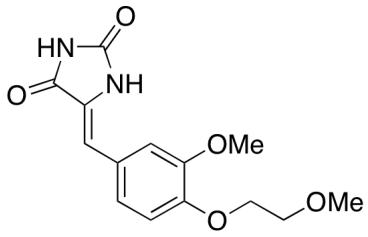
Ethyl 2-(4-((2-imino-4-oxothiazolidin-5-ylidene)methyl)-2-methoxyphenoxy)acetate (SM7):

Pseudothiohydantoin (0.40 g, 3.47 mmol), ethyl 2-(4-formyl-2-methoxyphenoxy)acetate (**37**) (0.75 g, 3.15 mmol), and sodium acetate (0.92 g, 11.3 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 16h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), ethanol (10 mL), hexane (50 mL), and pentane (10 mL). This process yielded the desired product (0.98 g, 92%) as a deep orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.35 (s, 1H), 9.07 (s, 1H), 7.52 (s, 1H), 7.18 (s, 1H), 7.10-7.07 (d, *J* = 8.8 Hz, 1H), 7.01-6.98 (d, *J* = 8.8 Hz, 1H), 4.81 (s, 2H), 4.18-4.11 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 1.21-1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.1, 176.1, 169.1, 150.0, 149.2, 130.0, 128.4, 127.9, 123.6, 115.2, 114.9, 65.8, 61.7, 56.1, 14.7. IR (neat) 1739, 1365, 1228, 1217 cm^{-1}. HRMS (+APCI): calc'd for $C_{12}H_{12}N_2O_4S$ [+H], *m/z*: 281.0597, found *m/z*: 281.0588.

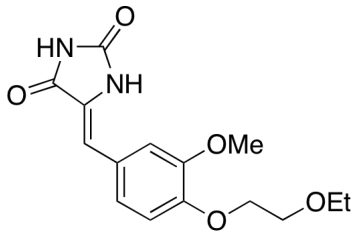


5-(3,4-dimethoxybenzylidene)imidazolidine-2,4-dione (4):

Hydantoin (1.00 g, 10.0 mmol) was dissolved in deionized water (10 mL) and was heated to 70 °C. Aqueous sodium bicarbonate was then added to the solution until it reached a pH of 7. Ethanolamine (0.9 mL, 14.9 mmol) was then added to the flask and was then heated to 90 °C. 3,4-Dimethoxybenzaldehyde (1.66 g, 10.0 mmol) was then dissolved in ethanol (10 mL) and added quickly to the flask and heated to 120 °C. After refluxing for 21h a precipitate was formed and 6 M HCl (10 mL) was then added to the solution to facilitate further precipitation. The resulting suspension was then vacuum filtered and washed with a 5:1 water:ethanol solution. Recrystallization was performed in methanol to yield the desired product (1.63 g, 66%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.18 (s, 1H), 10.48 (s, 1H), 7.22-7.15 (d, J = 8.1 Hz, 1H), 7.11 (s, 1H), 6.98-6.92 (d, J = 8.1 Hz, 1H), 6.36 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 166.2, 156.4, 150.1, 149.4, 126.8, 126.3, 123.7, 113.2, 112.4, 109.9, 56.3, 56.1. IR (neat): 1760, 1708, 1648, 1516, 1376, 1277, 1255, 1019, 802, 781 cm^{-1}. HRMS (+APCI): calc'd for $C_{12}H_{12}N_2O_4$ [+H], *m/z*: 249.0876, found *m/z*: 249.0868.

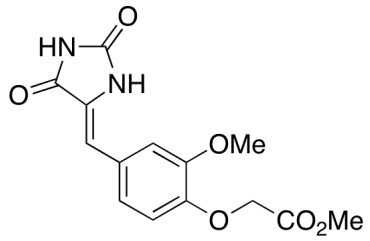


5-(3-methoxy-4-(2-methoxyethoxy)benzylidene)imidazolidine-2,4-dione (5): Hydantoin (0.24 g, 2.35 mmol) was dissolved in deionized water (2.4 mL) and was heated to 70 °C. Aqueous sodium bicarbonate was then added to the solution until it reached a pH of 7. Ethanolamine (0.2 mL, 3.31 mmol) was then added to the flask and was then heated to 90 °C. 3-Methoxy-4-(2-methoxyethoxy)benzaldehyde (**34**) (0.45 g, 2.14 mmol) was then mixed with ethanol (2.4 mL) to form a suspension and added quickly to the flask and heated to 120 °C. After refluxing for 16h a precipitate was formed and 6 M HCl (2.5 mL) was then added to the solution to facilitate further precipitation. The resulting suspension was then vacuum filtered and washed with a 5:1 water:ethanol solution. Recrystallization was performed in methanol to yield the desired product (0.23 g, 37%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.81 (s, 2H), 7.19-7.14 (d, *J* = 8.1 Hz, 1H), 7.12 (s, 1H), 6.98-6.92 (d, *J* = 8.1 Hz, 1H), 6.37 (s, 1H), 4.12-4.08 (t, *J* = 4.2 Hz, 2H) 3.82 (s, 3H), 3.68-3.62 (t, *J* = 4.2 Hz, 2H), 3.29 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 166.3, 156.3, 149.6, 149.2, 126.9, 126.5, 123.7, 113.5, 113.4, 109.9, 71.0, 68.2, 58.9, 56.3. IR (neat): 1738, 1366, 1228 cm^{-1}. HRMS (+APCI): calc'd for $C_{14}H_{16}N_2O_5$ [+H], *m/z*: 293.1138, found *m/z*: 293.1130.



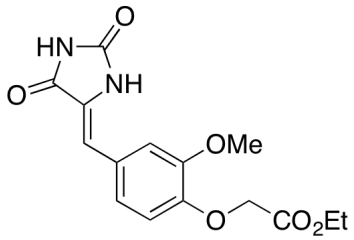
5-(4-(2-ethoxyethoxy)-3-methoxybenzylidene)imidazolidine-2,4-dione (6):

Hydantoin (0.24 g, 2.35 mmol) was dissolved in deionized water (2.4 mL) and was heated to 70 °C. Aqueous sodium bicarbonate was then added to the solution until it reached a pH of 7. Ethanolamine (0.2 mL, 3.31 mmol) was then added to the flask and was then heated to 90 °C. 4-(2-Ethoxyethoxy)-3-methoxybenzaldehyde (**35**) (0.48 g, 2.15 mmol) was then mixed with ethanol (2.4 mL) to form a suspension and added quickly to the flask and heated to 120 °C. After refluxing for 16h a precipitate was formed and 6 M HCl (2.5 mL) was then added to the solution to facilitate further precipitation. The resulting suspension was then vacuum filtered and washed with a 5:1 water:ethanol solution. Recrystallization was performed in ethanol to yield the desired product (0.22 g, 33%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.18 (s, 1H), 10.55 (s, 1H), 7.17-7.13 (d, *J* = 8.4 Hz, 1H), 7.11 (s, 1H), 6.96-6.94 (d, *J* = 8.4 Hz, 1H), 6.36 (s, 1H), 4.11-4.04 (t, *J* = 4.5 Hz, 2H), 3.81 (s, 3H), 3.70-3.64 (t, *J* = 4.5 Hz, 2H), 3.53-3.43 (q, *J* =6.9 Hz, 2H), 1.19-1.05 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 166.3, 156.4, 149.6, 149.3, 126.9, 126.5, 123.8, 113.6, 113.5, 109.9, 69.0, 68.5, 66.4, 56.3, 15.8. IR (neat): 1751, 1713, 1650, 1517, 1255, 1024 cm^{-1}. HRMS (+APCI): calc'd for $C_{15}H_{18}N_2O_5$ [+H], *m/z*: 307.1295, found *m/z*: 307.1286.

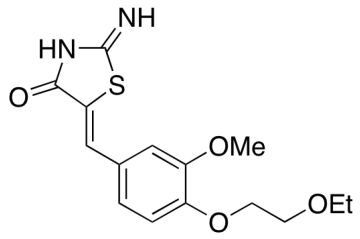


Methyl 2-(4-((2,5-dioxoimidazolidin-4-ylidene)methyl)-2-methoxyphenoxy)acetate (7):

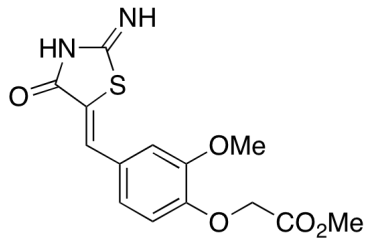
Hydantoin (0.10 g, 0.98 mmol) and methyl 2-(4-formyl-2-methoxyphenoxy)acetate (**36**) (0.20 g, 0.89 mmol) were dissolved in methanol (5 mL). Piperidine (0.13 mL, 1.34 mmol) was then added to the solution rapidly. The contents of the flask were then heated to reflux for a period of 18h. The solution was then allowed to cool to RT and 1 M HCl (5 mL) was added in order to facilitate precipitation of the desired product. The resulting suspension was filtered and washed with diethyl ether (5 mL) and water (5 mL). After washing, a pale yellow solid (0.12 g, 40%) was obtained as the desired product. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.18 (s, 1H), 10.54 (s, 1H), 7.16-7.10 (m, 2H), 6.90-6.84 (d, *J* = 8.7 Hz, 1H), 6.36 (s, 1H), 4.81 (s, 2H), 3.83 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 169.8, 166.3, 156.5, 149.6, 148.1, 127.3, 127.1, 123.3, 113.9, 113.7, 109.5, 65.8, 56.2, 52.2. IR (neat): 1766, 1731, 1712, 1651, 1515, 1383, 1277, 1240, 1217, 1155, 1101, 1039 cm^{-1}. HRMS (+APCI): calc'd for $C_{14}H_{14}N_2O_6$ [+H], *m/z*: 307.0931, found *m/z*: 307.0923.



Ethyl 2-(4-((2,5-dioxoimidazolidin-4-ylidene)methyl)-2-methoxyphenoxy)acetate (8): Hydantoin (0.11 g, 1.1 mmol) and ethyl 2-(4-formyl-2-methoxyphenoxy)acetate (**37**) (0.24 g, 1.0 mmol) were dissolved in ethanol (5 mL). Piperidine (0.15 mL, 1.5 mmol) was then added to the solution rapidly. The contents of the flask were then heated to reflux for a period of 17h. The solution was then allowed to cool to RT and 1 M HCl (5 mL) was added in order to facilitate precipitation of the desired product. The resulting suspension was filtered and washed with diethyl ether (5 mL) and water (5 mL). After washing, a pale yellow solid (0.07 g, 21%) was obtained as the desired product. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.19 (s, 1H), 10.48 (s, 1H), 7.14-7.08 (m, 2H), 6.86-6.82 (d, J = 8.4 Hz, 1H), 6.35 (s, 1H), 4.78 (s, 2H), 4.19-4.12 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 1.20-1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 169.2, 166.1, 156.3, 149.5, 148.2, 127.2, 127.1, 123.3, 113.9, 113.7, 109.4, 65.8, 61.2, 56.2, 14.8. IR (neat): 1738, 1434, 1365, 1228, 1216 cm^{-1}. HRMS (+APCI): calc'd for $C_{15}H_{16}N_2O_6$ [+H], *m/z*: 321.1087, found *m/z*: 321.1080.

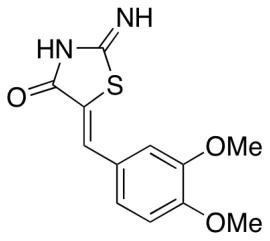


5-(4-(2-ethoxyethoxy)-3-methoxybenzylidene)-2-iminothiazolidin-4-one (9): Pseudothiohydantoin (0.12 g, 1.0 mmol), 4-(2-ethoxyethoxy)-3-methoxybenzaldehyde (**37**) (0.20 g, 0.90 mmol), and sodium acetate (0.26 g, 3.2 mmol) were all added to a round bottom flask. Acetic acid (5 mL) was then added and the solution was heated to 135 °C. After refluxing for 17h, the solution was cooled to RT and rapidly added to deionized water (25 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (25 mL) and deionized water (25 mL). Recrystallizaiton was performed in ethanol to yield the desired product (0.16 g, 54%) as a pale orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.35 (s, 1H), 9.03 (s, 1H), 7.57 (s, 1H), 7.16-7.14 (d, *J* = 8.4 Hz, 1H), 7.09-7.07 (d, *J* = 8.4 Hz, 1H) 7.08 (s, 1H), 4.13-4.08 (t, *J* = 4.8 Hz, 2H), 3.79 (s, 3H), 3.69-3.64 (t, *J* = 4.8 Hz, 2H), 3.50-3.39 (q, *J* = 7.2 Hz, 2H), 1.12-1.07 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.6, 176.4, 149.9, 149.6, 130.2, 127.6, 127.3, 123.3, 113.8, 113.6, 68.9, 68.5, 66.5, 56.0, 15.9. IR (neat): 1738, 1509, 1447, 1365, 1229, 1216, 1122 cm^{-1}. HRMS (+APCI): calc'd for $C_{15}H_{18}N_2O_4S$ [+H], *m/z*: 323.1066, found *m/z*: 323.1059.



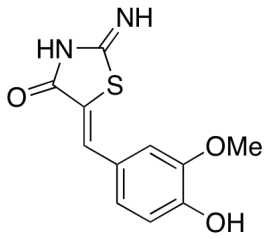
Methyl 2-(4-((2-imino-4-oxothiazolidin-5-ylidene)methyl)-2-methoxyphenoxy)acetate (10):

Pseudothiohydantoin (0.11 g, 0.98 mmol), methyl 2-(4-formyl-2-methoxyphenoxy)acetate (**36**) (0.20 g, 0.89 mmol), and sodium acetate (0.26 g, 3.17 mmol) were all added to a round bottom flask. Acetic acid (5 mL) was then added and the solution was heated to 135 °C. After refluxing for 15h, the solution was cooled to RT and rapidly added to deionized water (25 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (25 mL), ethyl acetate (25 mL), methanol (5 mL) hexane (25 mL), and pentane (5 mL). This process yielded the desired product (0.12 g, 40%) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.37 (s, 1H), 9.09 (s, 1H), 7.52 (s, 1H), 7.20-6.90 (m, 3H), 4.83 (s, 2H), 3.81 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.2, 176.1, 169.6, 149.7, 148.9, 130.0, 128.3, 127.8, 123.2, 114.2, 113.9, 65.5, 56.2, 52.6.



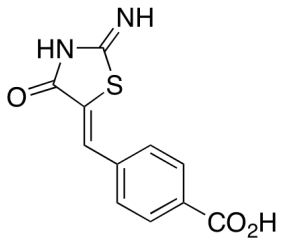
5-(3,4-dimethoxybenzylidene)-2-iminothiazolidin-4-one (11):

Pseudothiohydantoin (0.36 g, 2.35 mmol) was dissolved in deionized water (2.4 mL) and was heated to 70 °C. Aqueous sodium bicarbonate was then added to the solution until it reached a pH of 7. Ethanolamine (0.2 mL, 3.31 mmol) was then added to the flask and was then heated to 90 °C. 3,4-Dimethoxybenzaldehyde (0.36 g, 2.15 mmol) was then dissolved in ethanol (2.4 mL) and added quickly to the flask and heated to 120 °C. After refluxing for 11h a precipitate was formed and 6 M HCl (2.5 mL) was then added to the solution to facilitate further precipitation. The resulting suspension was then vacuum filtered and washed with a 5:1 water:ethanol solution. Recrystallization was performed in methanol to yield the desired product (0.13 g, 23%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.85-9.01 (s, 2H), 7.72 (s, 1H), 7.18-7.13 (m, 2H), 7.12-7.07 (d, *J* = 8.4 Hz, 1H), 3.82-3.79 (s, 3H), 3.78-3.75 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 168.7, 168.1, 151.6, 149.8, 133.0, 126.3, 124.5, 121.1, 114.1, 112.8, 56.3, 56.2. IR (neat): 1738, 1365, 1228, 1217 cm^{-1}. HRMS (+APCI): calc'd for $C_{12}H_{12}N_2O_3S$ [+H], *m/z*: 265.0648, found *m/z*: 265.0640.



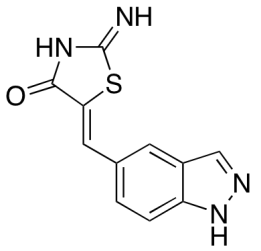
5-(4-hydroxy-3-methoxybenzylidene)-2-iminothiazolidin-4-one (12):

Pseudothiohydantoin (3.02 g, 26.0 mmol), vanillin (2.81 g, 28.0 mmol), and sodium acetate (7.63 g, 73.0 mmol) were all added to a round bottom flask. Acetic acid (40 mL) was then added and the solution was heated to 135 °C. After refluxing for 18h, the solution was cooled to RT and rapidly added to deionized water (200 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (200 mL) and deionized water (200 mL). Recrystallizaiton was performed in methanol to yield the desired product (2.17 g, 33%) as a dark orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.71 (s, 1H), 9.28 (s, 1H), 9.03 (s, 1H), 7.48 (s, 1H), 7.13 (s, 1H), 7.05-6.98 (d, *J* = 8.4 Hz, 1H), 6.89-6.82 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.1, 176.1, 149.3, 148.5, 130.6, 130.5, 126.2, 126.1, 124.0, 118.4, 117.1, 53.8. IR (neat): 1738, 1641, 1461, 1378, 1315, 1270, 1230, 1217, 1204, 1141 cm^{-1}. HRMS (+APCI): calc'd for $C_{11}H_8N_2O_3S$ [+H], *m/z*: 251.0491, found *m/z*: 251.0485.



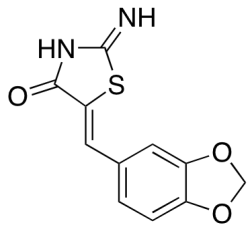
4-((2-imino-4-oxothiazolidin-5-ylidene)methyl)benzoic acid (13):

Pseudothiohydantoin (0.21 g, 1.78 mmol), 4-formylbenzoic acid (0.29 g, 1.96 mmol), and sodium acetate (0.52 g, 6.34 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 19h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (10 mL). This process yielded the desired product (0.37 g, 74%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.53 (s, 1H), 9.24 (s, 1H), 8.04-7.98 (d, *J* =8.4 Hz, 2H), 7.68-7.63 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 0.63 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 180.8, 179.3, 176.1, 138.9, 132.5, 131.6, 130.7, 130.7, 130.1, 130.1, 128.4. IR (neat): 3070, 2358, 1738, 1365, 1228 cm^{-1}. HRMS (+APCI): calc'd for $C_{11}H_{10}N_2O_3S$ [+H], *m/z*: 249.0335, found *m/z*: 249.0327.



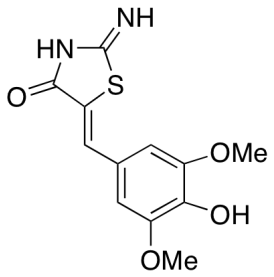
5-((1*H*-indazol-5-yl)methylene)-2-iminothiazolidin-4-one (14):

Pseudothiohydantoin (0.21 g, 1.78 mmol), 1*H*-indazole-5-carbaldehyde (0.29 g, 1.96 mmol), and sodium acetate (0.52 g, 6.34 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 24h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (10 mL). This process yielded the desired product (0.06 g, 14%) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.40 (s, 1H), 9.10 (s, 1H), 8.18 (s, 1H), 7.97 (s, 1H), 7.71 (s, 1H), 7.66-7.62 (d, *J* = 8.4 Hz, 1H), 7.56-7.52 (d, *J* = 8.4 Hz, 1H), 0.80 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.1, 176.1, 140.5, 135.4, 130.8, 127.9, 127.7, 127.3, 124.1, 123.6, 111.7. IR (neat): 1738, 1365, 1228, 1216 cm^{-1}. HRMS (+APCI): calc'd for $C_{11}H_8N_4OS$ [+H], *m/z*: 245.0498, found *m/z*: 245.0490.



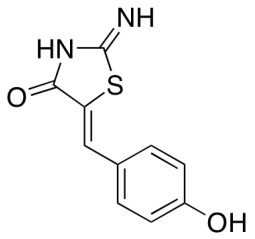
5-(benzo[*d*][1,3]dioxol-5-ylmethylene)-2-iminothiazolidin-4-one (15):

Pseudothiohydantoin (0.21 g, 1.78 mmol), piperonal (0.29 g, 1.96 mmol), and sodium acetate (0.52 g, 6.34 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 24h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (10 mL). This process yielded the desired product (0.22 g, 49%) as a pale orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.38 (s, 1H), 9.08 (s, 1H), 7.49 (s, 1H), 7.12-7.02 (m, 3H), 6.08 (s, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.1, 176.1, 149.2, 148.9, 130.0, 129.1, 127.9, 125.6, 109.8, 109.4, 102.4. IR (neat): 1738, 1484, 1442, 1365, 1274, 1229, 1217, 1204, 1145, 1125, 1097, 1033 cm^{-1}. HRMS (+APCI): calc'd for $C_{11}H_8N_4OS$ [+H], *m/z*: 249.0335, found *m/z*: 249.0326.



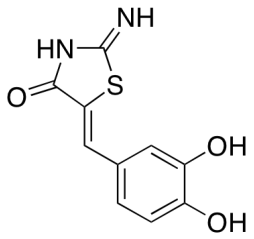
5-(4-hydroxy-3,5-dimethoxybenzylidene)-2-iminothiazolidin-4-one (16):

Pseudothiohydantoin (0.21 g, 1.78 mmol), syringaldehyde (0.36 g, 1.96 mmol), and sodium acetate (0.52 g, 6.34 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 24h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (10 mL). This process yielded the desired product (0.25 g, 50%) as a pale orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.31 (s, 1H), 9.10 (s, 1H), 9.02 (s, 1H), 7.50 (s, 1H), 6.85 (s, 2H), 3.87 (s, 6H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.1, 176.1, 148.2, 148.2, 137.6, 130.2, 125.8, 124.3, 107.3, 107.3, 56.0, 56.0. IR (neat): 1651, 1610, 1581, 1514, 1456, 1424, 1371, 1332, 1301, 1266, 1209, 1186, 1157, 1113, 1095, 1037 cm^{-1}. HRMS (+APCI): calc'd for $C_{12}H_{12}N_2O_4S$ [+H], *m/z*: 281.0597, found *m/z*: 281.0588.



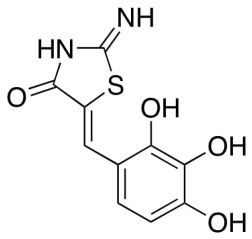
5-(4-hydroxybenzylidene)-2-iminothiazolidin-4-one (17):

Pseudothiohydantoin (0.21 g, 1.78 mmol), 4-hydroxybenzaldehyde (0.24 g, 1.96 mmol), and sodium acetate (0.52 g, 6.34 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 24h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (10 mL). This process yielded the desired product (0.16 g, 40%) as a bright orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.29 (s, 1H), 9.02 (s, 1H), 7.48 (s, 1H), 7.41-7.37 (d, *J* = 8.4 Hz, 2H), 6.88-6.84 (d, *J* = 8.4 Hz, 2H), 3.37 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.1, 176.1, 170.5, 149.6, 149.1, 130.2, 128.0, 127.8, 123.2, 113.9. IR (neat): 1571, 1508, 1485, 1365, 1293, 1229, 1175, 1147, 1013 cm^{-1}. HRMS (+APCI): calc'd for $C_{10}H_8N_2O_2S$ [+H], *m/z*: 221.0385, found *m/z*: 221.0378.



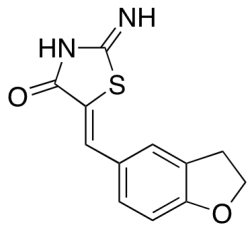
5-(3,4-dihydroxybenzylidene)-2-iminothiazolidin-4-one (18):

Pseudothiohydantoin (0.21 g, 1.78 mmol), 3,4-dihydroxybenzaldehyde (0.27 g, 1.96 mmol), and sodium acetate (0.52 g, 6.34 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 20h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (10 mL). This process yielded the desired product (0.02 g, 4%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.62 (s, 1H), 9.34 (s, 1H), 9.24 (s, 1H), 9.02 (s, 1H), 7.37 (s, 1H), 6.94 (s, 1H), 6.89-6.85 (d, J = 8.4 Hz, 1H), 6.83-6.79 (d, J = 8.4 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.1, 176.1, 148.3, 146.4, 130.7, 126.0, 125.9, 123.7, 117.1, 116.9. IR (neat): 3134, 1577, 1522, 1508, 1500, 1298 cm^{-1}. HRMS (+APCI): calc'd for $C_{10}H_8N_2O_3S$ [+H], *m/z*: 237.0335, found *m/z*: 237.0327.



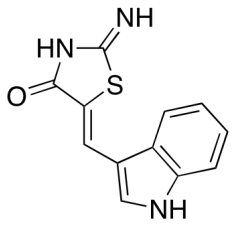
2-imino-5-(2,3,4-trihydroxybenzylidene)thiazolidin-4-one (19):

Pseudothiohydantoin (0.17 g, 1.50 mmol), 2,3,4-trihydroxybenzaldehyde (0.23 g, 1.50 mmol), and sodium acetate (0.44 g, 5.30 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 24h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.09 g, 24%) as a deep red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.25-6.97 (d, J = 8.5 Hz, 1H), 6.74-6.70 (d, J = 8.5 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 173.2, 159.7, 151.4, 143.3, 142.8, 132.9, 119.5, 117.8, 113.8, 113.0. IR (neat): 3139, 1683, 1601, 1566 cm^{-1}. HRMS (ESI): calc'd for $C_{10}H_8N_2O_4S$ [+Na], *m/z*: 275.0103, found *m/z*: 275.1440. This calc'd value is consistent with the molecular weight of the compound $C_{10}H_8N_2O_4S$ (252.0205) plus a sodium (+Na) counterion (22.9898) = 275.0103.



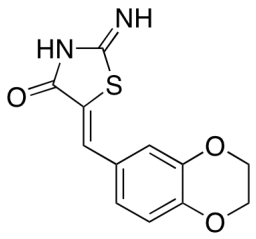
5-((2,3-dihydrobenzofuran-5-yl)methylene)-2-iminothiazolidin-4-one (20):

Pseudothiohydantoin (0.17 g, 1.50 mmol), 2,3-dihydrobenzofuran-5-carbaldehyde (0.22 g, 1.50 mmol), and sodium acetate (0.44 g, 5.30 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 24h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.16 g, 43%) as a bright orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.28 (s, 1H), 9.04 (s, 1H), 7.50 (s, 1H), 7.41 (s, 1H), 7.34-7.29 (d, J = 8.5 Hz, 1H), 6.90-6.85 (d, J = 8.5 Hz, 1H), 4.61-4.53 (t, J = 8.4 Hz, 2H), 3.25-3.16 (t, J = 8.4 Hz, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.3, 176.1, 161.8, 131.2, 130.2, 129.5, 127.2, 126.9, 126.4, 110.4, 72.4, 29.3. IR (neat): 3168, 2922, 1667, 1600, 1581, 1491 cm^{-1}. HRMS (+APCI): calc'd for $C_{12}H_{10}N_2O_2S$ [+H], *m/z*: 247.0542, found *m/z*: 247.0536.



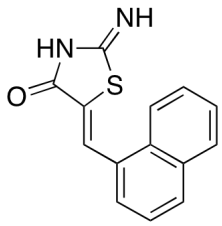
5-((1*H*-indol-3-yl)methylene)-2-iminothiazolidin-4-one (21):

Pseudothiohydantoin (0.17 g, 1.50 mmol), 1-indole-3-carbaldehyde (0.22 g, 1.50 mmol), and sodium acetate (0.44 g, 5.30 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 24h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.04 g, 11%) as a deep red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.82 (s, 1H), 8.93 (s, 1H), 8.11 (s, 1H), 7.93-7.88 (d, J = 15.5 Hz, 1H), 7.84 (s, 1H), 7.80 (s, 1H), 7.54-7.49 (d, J = 15.5 Hz, 1H), 7.27-7.22 (t, J = 12.9 Hz, 1H), 7.22-7.16 (t, J = 12.9 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.3, 176.1, 159.9, 137.1, 129.1, 127.6, 124.0, 121.9, 121.7, 121.1, 119.2, 113.3. IR (neat): 2925, 1668, 1591, 1574, 1545, 1513 cm^{-1}. HRMS (+APCI): calc'd for $C_{12}H_9N_3OS$ [+H], *m/z*: 244.0545, found *m/z*: 244.0538.



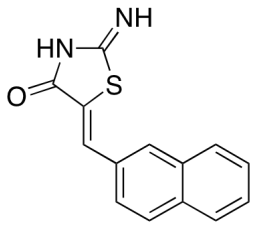
5-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)methylene)-2-iminothiazolidin-4-one (22):

Pseudothiohydantoin (0.17 g, 1.50 mmol), 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (0.25 g, 1.50 mmol), and sodium acetate (0.44 g, 5.30 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 24h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.26 g, 68%) as a dark orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.40-9.00 (s, 2H), 7.45 (s, 1H), 7.07-7.01 (m, 2H), 6.98-6.92 (m, 1H), 4.28-4.22 (m, 4H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.2, 176.1, 145.5, 144.3, 129.6, 128.0, 127.8, 123.8, 118.8, 118.6, 65.1, 64.7. IR (neat): 3241, 2941, 2803, 1655, 1594, 1578, 1500 cm^{-1}. HRMS (+APCI): calc'd for $C_{12}H_{10}N_2O_3S$ [+H], *m/z*: 263.0491, found *m/z*: 263.0485.



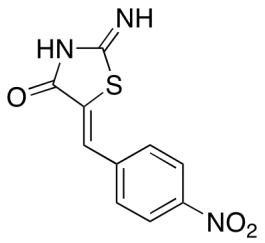
2-imino-5-(naphthalen-1-ylmethylene)thiazolidin-4-one (23):

Pseudothiohydantoin (0.21 g, 1.78 mmol), 1-napthaldehyde (0.24 mL, 1.78 mmol), and sodium acetate (0.52 g, 6.54 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 24h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.08 g, 18%) as a ruddy orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.45 (s, 1H), 9.17 (s, 1H), 8.21 (s, 1H), 8.11-8.06 (d, J = 7.3 Hz, 1H) 8.02-7.96 (d, J = 7.3 Hz, 1H), 7.70-7.66 (d, J = 6.8 Hz, 1H), 7.64-7.56 (m, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 180.4, 176.7, 133.9, 132.4, 131.7, 130.6, 129.5, 127.9, 127.3, 126.4, 126.3, 126.2, 126.1, 124.0. IR (neat): 3212, 2991, 1670, 1597, 1506 cm^{-1}. HRMS (+APCI): calc'd for $C_{14}H_{10}N_2OS$ [+H], *m/z*: 255.0593, found *m/z*: 255.0586.



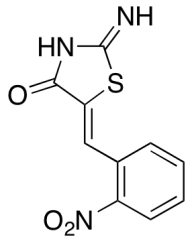
2-imino-5-(naphthalen-2-ylmethylene)thiazolidin-4-one (24):

Pseudothiohydantoin (0.21 g, 1.78 mmol), 2-napthaldehyde (0.28 g, 1.78 mmol), and sodium acetate (0.52 g, 6.54 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 20h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.18 g, 41%) as a bright yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.48 (s, 1H) 9.20 (s, 1H), 8.12 (s, 1H), 8.05-8.00 (d, J = 8.6 Hz, 1H), 8.00-7.92 (m, 2H), 7.74 (s, 1H), 7.70-7.65 (d, J = 8.6 Hz, 1H), 7.60-7.55 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.1, 176.3, 133.6, 133.5, 132.4, 130.5, 130.4, 129.7, 129.4, 129.1, 128.4, 128.1, 127.7, 126.6. IR (neat): 3184, 2959, 1678 cm^{-1}. HRMS (+APCI): calc'd for $C_{14}H_{10}N_2OS$ [+H], *m/z*: 255.0593, found *m/z*: 255.0586.



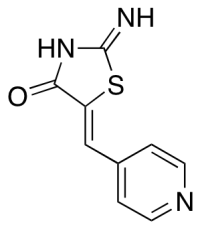
2-imino-5-(4-nitrobenzylidene)thiazolidin-4-one (25):

Pseudothiohydantoin (0.21 g, 1.78 mmol), 4-nitrobenzaldehyde (0.27 g, 1.78 mmol), and sodium acetate (0.52 g, 6.54 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 24h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.22 g, 50%) as a bright yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 1H), 9.38 (s, 1H), 8.33-8.29 (d, J = 8.9 Hz, 2H), 7.82-7.77 (d, J = 8.9 Hz, 2H), 7.67 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 180.5, 175.9, 147.6, 141.4, 134.5, 131.5, 130.4, 127.7, 125.0, 124.8. IR (neat): 3197, 2942, 1673, 1520 cm^{-1}. HRMS (+APCI): calc'd for $C_{10}H_7N_3O_3S$ [+H], *m/z*: 250.0287, found *m/z*: 250.0281.



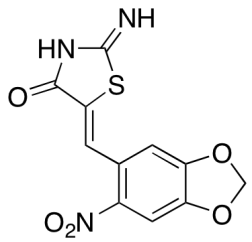
2-imino-5-(2-nitrobenzylidene)thiazolidin-4-one (26):

Pseudothiohydantoin (0.21 g, 1.78 mmol), 2-nitrobenzaldehyde (0.27 g, 1.78 mmol), and sodium acetate (0.52 g, 6.54 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 15h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.30 g, 68%) as a golden solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.56 (s, 1H), 9.24 (s, 1H), 8.16-8.10 (d, J = 8.3 Hz, 1H), 7.90-7.82 (t, J = 8.3 Hz, 1H), 7.77-7.72 (m, 2H), 7.70-7.62 (t, J = 8.3 Hz, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 179.9, 176.3, 148.7, 135.4, 134.9, 130.9, 130.8, 129.8, 125.8, 125.3. IR (neat): 3214, 2980, 1692, 1654, 1601, 1567, 1522 cm^{-1}. HRMS (+APCI): calc'd for $C_{10}H_7N_3O_3S$ [+H], *m/z*: 250.0287, found *m/z*: 250.0279.

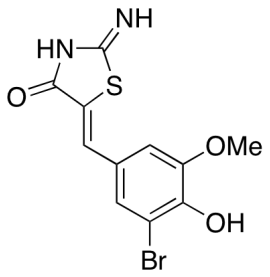


2-imino-5-(pyridin-4-ylmethylene)thiazolidin-4-one (27):

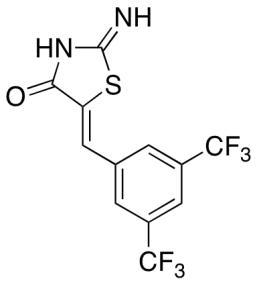
Pseudothiohydantoin (0.21 g, 1.78 mmol), isonicotinaldehyde (0.17 mL, 1.78 mmol), and sodium acetate (0.52 g, 6.54 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 20h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.14 g, 39%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.66-12.60 (s, 2H), 8.73-8.66 (d, J = 6.1 Hz, 2H), 7.72-7.67 (d, J = 6.1 Hz, 2H), 6.24 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 177.4, 161.5, 151.4, 150.8, 139.0, 139.0, 122.5, 122.5, 105.4. IR (neat): 3070, 3042, 2523, 2362, 1683, 1569 cm^{-1}. HRMS (+APCI): calc'd for $C_9H_7N_3OS$ [+H], *m/z*: 206.0389, found *m/z*: 206.0382.



2-imino-5-((6-nitrobenzo[*d*][1,3]dioxol-5-yl)methylene)thiazolidin-4-one (28): Pseudothiohydantoin (0.21 g, 1.78 mmol), 6-nitropiperonal (0.35 g, 1.78 mmol), and sodium acetate (0.52 g, 6.54 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 21h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.32 g, 61%) as a gold colored solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.48 (s, 1H), 9.18 (s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 7.16 (s, 1H), 6.27 (s, 2 H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 179.9, 176.1, 152.8, 149.1, 143.3, 134.5, 127.5, 126.2, 107.9, 106.4, 104.7. IR (neat): 2915, 2359, 1682, 1613, 1595, 1516, 1500 cm^{-1}. HRMS (+APCI): calc'd for $C_{11}H_7N_3O_5S$ [+H], *m/z*: 294.9965, found *m/z*: 294.9957.

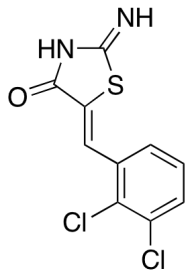


5-(3-bromo-4-hydroxy-5-methoxybenzylidene)-2-iminothiazolidin-4-one (29): Pseudothiohydantoin (0.21 g, 1.78 mmol), 5-bromovanillin (0.41 g, 1.78 mmol), and sodium acetate (0.52 g, 6.54 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 14h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.28 g, 49%) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.18 (s, 1H), 9.40 (s, 1H), 9.05 (s, 1H), 7.48 (s, 1H), 7.29 (s, 1H), 7.18 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.1, 175.9, 149.2, 145.9, 129.0, 128.0, 127.1, 126.2, 113.2, 110.4, 56.9. IR (neat): 3428, 3293, 3071, 2362, 1664, 1587, 1530, 1500 cm^{-1}. HRMS (+APCI): calc'd for $C_{11}H_9{}^{79}BrN_2O_3S$ [+H], *m/z*: 328.9596, found *m/z*: 328.9589.



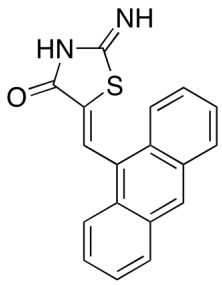
5-(3,5-bis(trifluoromethyl)benzylidene)-2-iminothiazolidin-4-one (30):

Pseudothiohydantoin (0.21 g, 1.78 mmol), 3,5-bis(trifluoromethyl)benzaldehyde (0.43 g, 1.78 mmol), and sodium acetate (0.52 g, 6.54 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 14h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.16 g, 28%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65 (s, 1H), 9.26 (s, 1H), 8.20 (s, 1H), 8.13 (s, 1H), 7.78 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 180.3, 175.5, 137.8, 134.4, 131.6 (q, J = 33.2 Hz, 2C), 129.9, 129.9, 126.3, 123.8 (q, J = 231 Hz, 2C), 123.0 (m, 1C). IR (neat): 2993, 1673, 1605, 1540 cm^{-1}. HRMS (+APCI): calc'd for $C_{12}H_6F_6N_2OS$ [+H], *m/z*: 341.0184, found *m/z*: 341.0176.



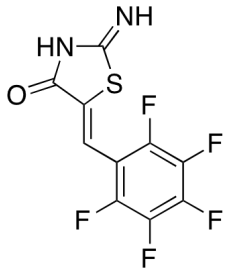
5-(2,3-dichlorobenzylidene)-2-iminothiazolidin-4-one (31):

Pseudothiohydantoin (0.21 g, 1.78 mmol), 2,3-dichlorobenzaldehyde (0.31 g, 1.78 mmol), and sodium acetate (0.52 g, 6.54 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 15h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.40 g, 82%) as a bright yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 1H), 9.30 (s, 1H), 7.80-7.65 (m, 2H), 7.60-7.46 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 180.2, 176.3, 135.7, 135.3, 133.5, 131.8, 129.6, 127.8, 124.9, 124.8. IR (neat): 3228, 2956, 1692, 1653, 1522 cm^{-1}. HRMS (+APCI): calc'd for $C_{10}H_6Cl_2N_2O_3S$ [+H], *m/z*: 272.9657, found *m/z*: 272.9650.



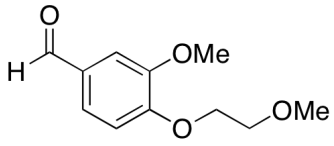
5-(anthracen-9-ylmethylene)-2-iminothiazolidin-4-one (32):

Pseudothiohydantoin (0.21 g, 1.78 mmol), 2,3-dichlorobenzaldehyde (0.37 g, 1.78 mmol), and sodium acetate (0.52 g, 6.54 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 15h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.12 g, 21%) as a dark orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.40 (s, 1H), 8.95 (s, 1H), 8.69 (s, 1H), 8.34 (s, 1H), 8.19-8.12 (d, J = 9.3 Hz, 2H), 8.00-7.92 (d, J = 9.3 Hz, 2H), 7.62-7.55 (m, 4H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 179.5, 176.2, 139.6, 131.5, 131.5, 130.1, 129.7, 129.7, 128.8, 128.5, 128.5, 127.5, 127.5, 126.4, 126.4, 125.9, 125.9, 124.2. IR (neat): 2957, 1673, 1623, 1575 cm^{-1}. HRMS (+APCI): calc'd for $C_{18}H_{12}N_2OS$ [+H], *m/z*: 305.0749, found *m/z*: 305.0741.



2-imino-5-((perfluorophenyl)methylene)thiazolidin-4-one (33):

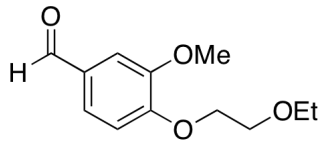
Pseudothiohydantoin (0.21 g, 1.78 mmol), pentafluorobenzaldehyde (0.35 g, 1.78 mmol), and sodium acetate (0.52 g, 6.54 mmol) were all added to a round bottom flask. Acetic acid (10 mL) was then added and the solution was heated to 135 °C. After refluxing for 17h, the solution was cooled to RT and rapidly added to deionized water (50 mL). The resulting suspension was filtered and the solid was washed with diethyl ether (50 mL), ethyl acetate (50 mL), methanol (10 mL), hexane (50 mL), and pentane (50 mL). This process yielded the desired product (0.08 g, 15%) as a peach colored solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65 (s, 1H), 9.30 (s, 1H), 7.30 (s, 1H). ^{19}F NMR (400 MHz, DMSO-d_6): δ -4.65 to -4.83 (d, J = 24.6 Hz, 2F), -19.44 to -19.61 (t, J = 24.6 Hz, 2F), -28.55 to -28.75 (m, 1F). IR (neat): 3226, 2980, 1655 cm^{-1}. HRMS (+APCI): calc'd for $C_{10}H_3F_5N_2OS$ [+H], *m/z*: 294.9965, found *m/z*: 294.9957.



3-methoxy-4-(2-methoxyethoxy)benzaldehyde (34):

Vanillin (1.52g, 10.0 mmol), potassium iodide (0.17 g, 1.0 mmol), and potassium carbonate (1.72 g, 12.5 mmol) were added to a flask along with DMF (15 mL). 1-chloro-2-methoxyethane (1.83 mL, 20.0 mmol) was then added dropwise to the solution over 1h.

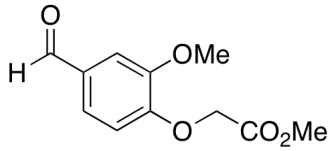
The solution was then heated to 60 °C and after 40h the reaction was quenched with 1 M HCl (15 mL). The resulting solution was extracted with ethyl acetate (3 x 15 mL) and then washed with 5% LiCl solution (10 x 15 mL) followed by an additional wash with 0.5 M HCl (10 x 15 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The remaining solid was purified by column chromatography (SiO_2, EtOAc/Hexane = 2:3) and dried to yield the desired product (1.25 g, 56%) as an off-white solid. ^{1}H NMR (300 MHz, $CdCl_3$): δ 9.83 (s, 1H), 7.48-7.38 (m, 2H), 7.05-6.99 (d, *J* = 8.4 Hz, 1H), 4.29-4.23 (t, *J* = 4.8 Hz, 2H), 3.83-3.77 (t, *J* = 4.8 Hz, 2H), 3.92 (s, 3H), 3.86-3.80 (t, *J* = 4.8 Hz, 2H), 3.45 (s, 3H). ^{13}C NMR (400 MHz, $CdCl_3$): δ 191.3, 154.1, 150.2, 130.5, 112.1, 109.5, 70.9, 68.6, 59.5, 56.3. IR (neat): 1679, 1585, 1507, 1265, 1136 cm^{-1}. HRMS (+APCI): calc'd for $C_{12}H_{16}O_4$ [+H], *m/z*: 211.0971, found *m/z*: 211.0964.



4-(2-ethoxyethoxy)-3-methoxybenzaldehyde (35):

Vanillin (1.52g, 10.0 mmol), potassium iodide (0.17 g, 1.0 mmol), and potassium carbonate (1.72 g, 12.5 mmol) were added to a flask along with DMF (15 mL). 1-bromo-2-ethoxyethane (2.26 mL, 20.0 mmol) was then added dropwise to the solution over 1h. After 21h the reaction was quenched with 1 M HCl (15 mL). The resulting solution was extracted with ethyl acetate (3 x 15 mL) and then washed with 5% LiCl solution (10 x 15 mL) followed by an additional wash with 0.5 M HCl (10 x 15 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The remaining solid

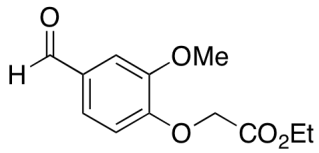
was purified by column chromatography (SiO_2, EtOAc/Hexane = 1:1) and dried to yield the desired product (1.56 g, 70%) as a peach colored solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.40-7.35 (d, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 6.90-6.85 (d, *J* = 8.0 Hz, 1H), 4.23-4.17 (t, *J* = 4.8 Hz, 2H), 3.83-3.77 (t, *J* = 6.8 Hz, 2H), 3.59-3.51 (q, *J* = 6.8 Hz, 2H), 1.22-1.18 (t, *J* = 5.7 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 191.0, 154.1, 150.1, 130.4, 126.7, 112.0, 109.5, 68.7, 68.7, 67.0, 56.1, 15.3. IR (neat): 1670, 1594, 1582, 1510, 1458, 1427, 1396, 1267, 1239, 1160, 1137, 1115, 1055, 1025 cm^{-1}. HRMS (+APCI): calc'd for $C_{12}H_{16}O_4$ [+H], *m/z*: 225.1128, found *m/z*: 225.1120.



Methyl 2-(4-formyl-2-methoxyphenoxy)acetate (36):

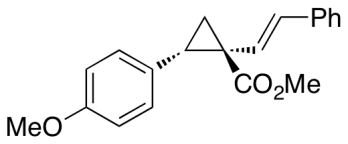
Vanillin (1.52 g, 10.0 mmol), potassium iodide (0.17 g, 1.0 mmol), and potassium carbonate (1.72 g, 12.5 mmol) were added to a flask along with DMF (15 mL). methyl 2-bromoacetate (2.28 mL, 24.2 mmol) was then added dropwise to the solution over 1h. After 24h the reaction was quenched with 1 M HCl (15 mL). The resulting solution was extracted with ethyl acetate (3 x 15 mL) and then washed with 5% LiCl solution (10 x 15 mL) followed by an additional wash with 0.5 M HCl (10 x 15 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The remaining solid was purified by column chromatography (SiO_2, EtOAc/Hexane = 1:1) and dried to yield the desired product (1.43 g, 73%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.46-7.38 (m, 2H), 6.90-6.85 (d, *J* = 8.1 Hz, 1H), 4.79 (s, 2H), 3.95 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 191.0, 168.7, 152.6, 150.1, 131.4, 126.4,

112.5, 110.0, 66.0, 56.3, 52.6. IR (neat): 1736, 1449, 1365, 1227, 1216 cm^{-1}. HRMS (+APCI): calc'd for $C_{11}H_{12}O_5$ [+H], *m/z*: 225.0764, found *m/z*: 225.0756.



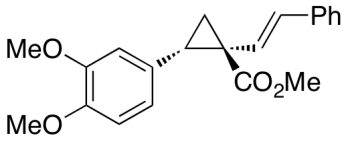
Methyl 2-(4-formyl-2-methoxyphenoxy)acetate (37):

Vanillin (1.52g, 10.0 mmol) and potassium carbonate (1.72 g, 12.5 mmol) were added to a flask along with DMF (15 mL). Ethyl iodoactetate (3.54 mL, 30.0 mmol) was then added dropwise to the solution over 1h. After 22h the reaction was quenched with 1 M HCl (15 mL). The resulting solution was extracted with ethyl acetate (3 x 15 mL) and then washed with 5% LiCl solution (10 x 15 mL) followed by an additional wash with 0.5 M HCl (10 x 15 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The remaining solid was purified by column chromatography (SiO_2, EtOAc/Hexane = 2:3) and dried to yield the desired product (1.93 g, 81%) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.38-7.33 (m, 3H), 6.84-6.79 (d, *J* = 8.4 Hz, 1H), 4.71 (s, 2H), 4.23-4.16 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 1.24-1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 191.0, 168.2, 153.8, 150.1, 131.2, 126.3, 112.5, 110.0, 66.1, 61.8, 56.2, 14.3. IR (neat): 1743, 1365, 1228, 1216 cm^{-1}. HRMS (+APCI): calc'd for $C_{12}H_{14}O_5$ [+H], *m/z*: 239.0920, found *m/z*: 239.0913.



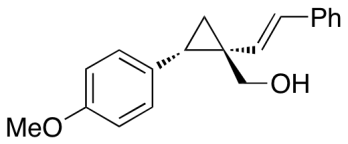
Methyl 2-(4-methoxyphenyl)-1-styrylcyclopropanecarboxylate (38):

Rhodium (II) S-DOSP (0.053 g, 0.056 mmol) was added to a flask along with 4-methoxystyrene (1.0 mL, 7.48 mmol) which was dissolved in degassed pentane (5 mL). Phenyl vinyl diazoacetate (methyl 2-diazo-4-phenylbut-3-enoate) (0.38 g, 1.86 mmol) was then dissolved in an additional degassed pentane (5 mL) and added dropwise over 1h. The resulting solution was stirred for 4h at RT and the solvent was removed by use of rotary evaporator. The remaining oil was purified by column chromatography (SiO_2, Et_2O/Pentane = 1:8) and dried to yield the desired product (0.40 g, 70%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.14 (m, 5H), 7.08-7.03 (d, *J* = 8.4 Hz, 2H), 6.79-6.74 (d, *J* = 8.4 Hz, 2H), 6.38-6.31 (d, *J* = 16.0 Hz, 1H), 6.19-6.13 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.00-2.94 (t, *J* =8.0 Hz, 1H), 2.04-1.98 (dd, *J* = 7.6 Hz, *J* = 5.2 Hz, 1H), 1.79-1.75 (dd, *J* = 7.6 Hz, *J* = 3.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.4, 148.7, 148.1, 137.2, 133.2, 128.7, 128.3, 127.6, 126.4, 124.4, 121.4, 112.5, 111.9, 66.1, 56.1, 56.0, 52.6, 35.1, 33.5, 19.2. IR (neat): 1716, 1516, 1243, 1136, 1026, 909, 727 cm^{-1}. HPLC analysis: 84% ee, OD-H, 1 % isopropanol/hexanes, 0.02 mL/min, UV: 230 nm, t_R(major): 41.2 min, t_R (minor) 28.5 min.



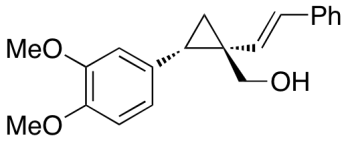
Methyl 2-(2-(3,4-dimethoxyphenyl)-1-styrylcyclopropyl)acetate (39):

Rhodium (II) S-DOSP (0.066 g, 0.035 mmol) was added to a flask along with 3,4-dimethoxystyrene (2.11 mL, 14.2 mmol) which was dissolved in degassed pentane (5 mL). Phenyl vinyl diazoacetate (methyl 2-diazo-4-phenylbut-3-enoate) (0.72 g, 3.56 mmol) was then dissolved in an additional degassed pentane (5 mL) and added dropwise over 1h. The resulting solution was stirred for 4h at RT and the solvent was removed by use of rotary evaporator. The remaining oil was purified by column chromatography (SiO_2, Et_2O/Pentane = 1:4) and dried to yield the desired product (0.63 g, 52%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.13 (m, 5H), 6.69-6.65 (d, J = 8.0 Hz, 1H), 6.64-6.60 (d, J = 8.0 Hz, 1H), 6.63 (s, 1H), 6.40-6.34 (d, J = 16.4 Hz, 1H), 6.18-6.12 (d, J = 16.4 Hz, 1H), 2.98-2.91 (t, J = 8.0 Hz, 1H), 2.04-1.97 (dd, J = 7.2 Hz, J = 4.8 Hz, 1H) 1.79-1.74 (dd, J = 9.5 Hz, J = 5.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.4, 148.6, 148.1, 137.2, 133.2, 128.6, 128.6, 128.3, 128.3, 127.6, 126.4, 126.4, 124.4, 121.4, 112.4, 110.9, 56.1, 56.0, 52.6, 35.0, 33.5, 19.2. HPLC analysis: 82% ee, OD-H, 1 % isopropanol/hexanes, 0.02 mL/min, UV: 230 nm, t_R(major): 40.8 min, t_R (minor) 28.2 min. IR (neat): 1716, 1516, 1243, 1136, 1026, 909, 727 cm^{-1}.



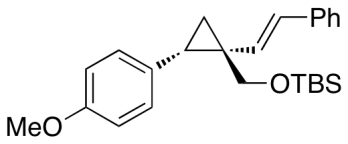
(2-(4-methoxyphenyl)-1-styrylcyclopropyl)methanol (40):

Methyl 2-(4-methoxyphenyl)-1-styrylcyclopropanecarboxylate (0.07 g, 0.22 mmol) and diethyl ether (2 mL) were added to a flask and allowed to cool to 0 °C. Lithium aluminum hydride (0.03 g, 0.66 mmol) was then added portionwise to the reaction. The resulting mixture was stirred for 30 minutes at 0 °C and allowed to warm an additional 14h to RT. Diethyl ether (20 mL) was then added to dilute the reaction mixture as a pre-quench. After stirring for 10 minutes, 1M HCl (2 mL) was added to quench the reaction and the suspension was extracted with diethyl ether (3 x 30 mL). The salts remaining in the flask were also washed with diethyl ether (3 x 30 mL). The organic layers were combined, dried with $MgSO_4$, and dried *in vacuo*. The resulting oil was purified by column chromatography (SiO_2, Et_2O/Pentane = 1:2) and dried to yield the desired product (0.03 g, 59%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.17 (d, *J* = 8.4 Hz, 2H), 7.16-7.08 (m, 5H), 6.83-6.77 (d, *J* = 8.4 Hz, 2H), 6.58-6.51 (d, *J* = 16.4 Hz, 1H), 5.69-5.61 (d, *J* = 16.4 Hz, 1H), 3.88-3.84 (d, *J* = 10.4 Hz, 1H) 3.79-3.75, (d, *J* = 10.4 Hz, 1H), 3.75 (s, 3H), 2.38-2.31 (t, *J* = 7.2 Hz, 1H), 1.80 (s, 1H), 1.34-1.27 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (600 MHz, $CDCl_3$): δ 158.2, 137.6, 130.3, 130.1, 130.0, 129.9, 128.7, 128.5, 127.2, 126.1, 114.2, 113.8, 68.9, 55.5, 32.3, 30.5, 29.9, 29.0, 17.4. IR (neat): 2359, 2341, 1514, 1246, 1034, 694 cm^{-1}.

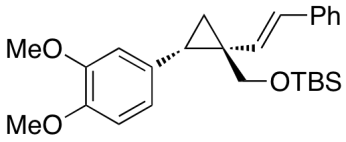


(2-(3,4-dimethoxyphenyl)-1-styrylcyclopropyl)methanol (41):

Methyl 2-(2-(3,4-dimethoxyphenyl)-1-styrylcyclopropyl)acetate (1.52 g, 4.48 mmol) and THF (25 mL) were added to a flask and allowed to cool to 0 °C. Lithium aluminum hydride (1.36 g, 25.86 mmol) was then added portionwise to the reaction. The resulting mixture was stirred for 30 minutes at 0 °C and allowed to warm an additional 11h to RT. Diethyl ether (10 mL) was then added to dilute the reaction mixture as a pre-quench. After stirring for 10 minutes, Rochelle's salt (10 mL) followed by 1 M HCl (50 mL) were added to quench the reaction and the suspension was extracted with diethyl ether (3 x 25 mL). The salts remaining in the flask were also washed with diethyl ether (3 x 25 mL). The organic layers were combined, dried with $MgSO_4$, and dried *in vacuo*. The resulting oil was purified by column chromatography (SiO_2, Et_2O/Pentane = 3:1) and dried to yield the desired product (1.20 g, 86%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.10 (m, 5H), 6.78-6.70 (m, 3H), 6.60-6.54 (d, *J* = 16.4 Hz, 1H), 5.72-5.64 (d, *J* = 16.4 Hz, 1H), 3.88-3.84 (d, *J* = 10.4 Hz, 1H), 3.84 (s, 3H), 3.81-3.79 (d, *J* = 10.4 Hz, 1H), 3.81 (s, 3H), 2.39-2.32 (t, *J* = 7.2 Hz, 1H), 1.84 (s, 1H), 1.32-1.28 (m, 2H). ^{13}C NMR (600 MHz, $CDCl_3$): δ 148.8, 147.7, 137.6, 130.6, 130.3, 130.2, 128.7, 128.7, 127.3, 126.1, 126.1, 121.3, 112.6, 111.1, 68.8, 56.2, 56.1, 32.4, 29.3, 17.6. IR (neat): 1514, 1252, 1233, 1139, 1025, 728 cm^{-1}. HRMS (+APCI): calc'd for $C_{20}H_{22}O_3$ [+H], *m/z*: 311.1648, found *m/z:* 311.1646.



***Tert*-butyl((2-(4-methoxyphenyl)-1-styrylcyclopropyl)methoxy)dimethylsilane (42):** (2-(4-methoxyphenyl)-1-styrylcyclopropyl)methanol (0.05 g, 0.18 mmol) was dissolved in 1 mL of dichloromethane and placed in an ice bath which allowed it to cool to 0 °C. 2,6-Lutidine (0.04 mL, 0.36 mmol) was then added quickly to the solution and was allowed to stir for 5 minutes. Tert-butyldimethylsilyl trifluoromethanesulfonate (0.06 mL, 0.27 mmol) was then added dropwise over 1h and allowed to stir for 1h at 0 °C. The ice bath was then removed and the reaction was allowed to stir for an additional 3h. 1 M HCl (1 mL) was then added to the reaction and the resulting solution was extracted with dichloromethane (3 x 5 mL). The mixture was then dried with $MgSO_4$ and concentrated by rotary evaporator. The resulting oil was purified by column chromatography (SiO_2, Et_2O/Pentane = 4:96) and dried to yield the desired product (0.05 g, 67%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.18 (d, *J* = 9.0 Hz, 2H), 7.16-7.10 (m, 5H), 6.84-6.78 (d, *J* = 9.0 Hz, 2H), 6.36-6.30 (d, *J* = 16.2 Hz, 1H), 5.74-5.66 (d, *J* = 16.2 Hz, 1H), 3.95-3.90 (d, *J* = 9.9 Hz, 1H), 3.70-3.65 (d, *J* = 9.9 Hz, 1H), 3.77 (s, 3H), 2.42-2.35 (t, *J* = 7.2 Hz, 1H), 1.24-1.19 (t, *J* = 7.2 Hz, 1H), 0.94 (s, 9H), 0.94-0.85 (t, *J* = 6.6 Hz, 1H), 0.10 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (600 MHz, $CDCl_3$): δ 158.0, 138.2, 131.4, 131.0, 130.3, 130.3, 129.3, 128.6, 128.6, 126.8, 126.8, 125.9, 113.7, 113.7, 67.2, 55.5, 31.2, 29.9, 27.6, 26.2, 26.2, 26.2, 18.5, 16.5, 16.5. IR (neat): 1513, 1246, 1090, 832, 773, 745 cm^{-1}.



***Tert*-butyl((2-(3,4-dimethoxyphenyl)-1-styrylcyclopropyl)methoxy)dimethylsilane (43):**

(2-(3,4-dimethoxyphenyl)-1-styrylcyclopropyl)methanol (1.20 g, 4.27 mmol) was dissolved in 10 mL of dichloromethane and placed in an ice bath which allowed it to cool to 0 °C. Imidazole (1.45 g, 21.37 mmol) was then added quickly to the solution and was allowed to stir for 5 minutes. Tert-butylchlorodimethylsilane (2.58 g, 17.04 mmol) was dissolved in 10 mL of dichloromethane and then added dropwise over 1h and allowed to stir for 1h at 0 °C. The ice bath was then removed and the reaction was allowed to stir for an additional 15h. 1 M HCl (20 mL) was then added to the reaction and the resulting solution was extracted with dichloromethane (3 x 20 mL). The mixture was then dried with $MgSO_4$ and concentrated by rotary evaporator. The resulting oil was purified by column chromatography (SiO_2, Et_2O/Pentane = 4:96) and dried to yield the desired product (1.58 g, 87%) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24-7.12 (m, 5H), 6.79-6.74 (m, 3H), 6.50-6.45 (d, *J* = 16.2 Hz, 1H), 5.74-5.68 (d, *J* = 16.2 Hz, 1H), 4.00-3.97 (d, *J* = 10.0 Hz, 1H), 3.79-3.65 (d, *J* = 10.0 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.44-2.39 (t, *J* = 7.2 Hz, 1H), 1.34-1.30 (m, 1H), 1.24-1.20 (t, *J* = 7.2 Hz, 1H), 0.96 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (600 MHz, $CDCl_3$): δ 148.6, 147.4, 138.1, 131.6, 131.3, 130.3, 130.1, 129.3, 128.6, 128.6, 127.3, 126.9, 126.1, 125.9, 125.9, 121.2, 112.8, 111.0, 67.3, 56.2, 56.0, 31.4, 28.1, 26.2, 18.5, 16.8. IR (neat): 2929, 2856, 1516, 1253, 1139, 1093, 1029, 835, 774, 746 cm^{-1}.

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