Synthesis of Thiazol-2-yl Urea Derivatives, Antibacterial Agents

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Master research report
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Front cover: Methicillin resistant Staphylococcus aureus (MRSA)
http://www.hygiset.eu/images/MRSA.jpg

“Organic chemistry nowadays almost drives me mad. To me it appears like a primeval tropical forest full of the most remarkable things, a dreadful endless jungle into which one does not dare enter for there seems to be no way out.”

Friedrich Wöhler, 1835

Contents

Abbreviations

EtOAc	ethyl acetate
DMSO	methyl sulfoxide
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
Boc	tert-butoxycarbonyl
Boc_2O	di-tert-butyldicarbonate
RT	room temperature
15-crown-5	crown ether (1,4,7,10,13-pentaoxacyclopentadecane)
THF	tetrahydrofuran
HPLC	high performance liquid chromatography
TLC	thin layer chromatography
PMA	phosphomolybdic acid
^{1}H-NMR	proton nuclear magnetic resonance
RP	reversed phase
m-CPBA	3-chloroperbenzoic acid
Oxone	potassium monoperoxymonosulfate ($2\ KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)
TMANO	trimethylamine N-oxide

Chapter 1 Introduction

1.1 Organic Synthesis

The history of organic synthesis is lengthy and can be traced back to ancient times. On the other hand, as a science, organic chemistry is relatively young, its beginning being marked by the synthesis of urea [$CO(NH_2)_2$] by Wöhler in 1828.[1] This was followed by other milestone syntheses such as those of acetic acid[2] (Kolbe, 1845), glucose[3] (Fischer, 1890) and quinine[4] (Woodward and Doering, 1944).

Figure 1.1 *Wöhler, Kolbe, Fischer, Woodward and Doering*

Organic synthesis is involved in many applications of everyday life. Some examples of these applications are: insecticides, pesticides, cosmetics, pharmaceuticals that can prevent or cure diseases and polymers.
The goal of organic synthesis is to assemble a given organic compound from readily available starting materials and reagents in the most efficient way. Organic synthesis can be divided in two areas: 'methods oriented synthesis' and 'target oriented synthesis', as depicted in Figure 1.2.

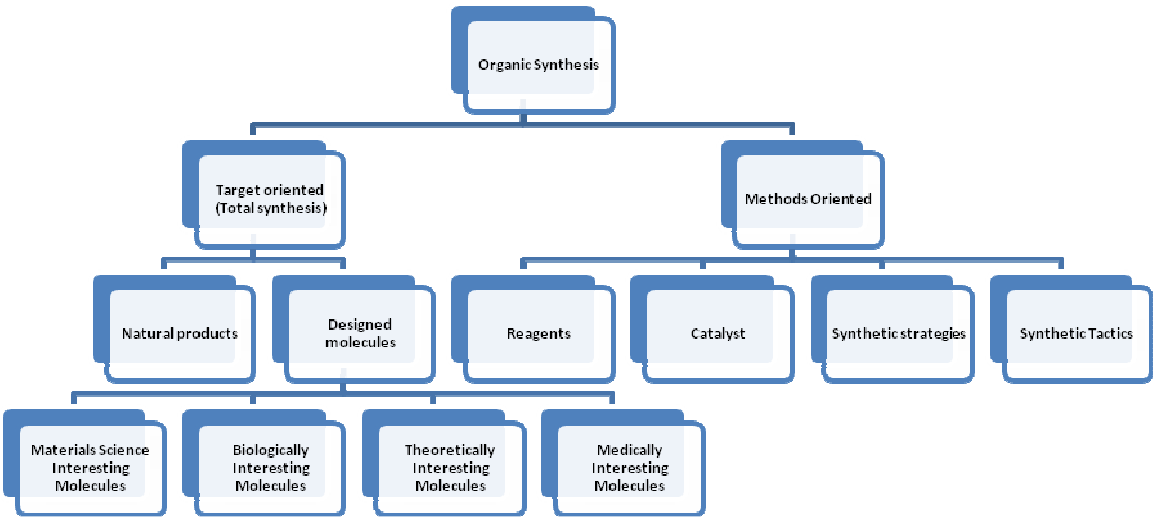


Figure 1.2 *Organic Synthesis in perspective* [5]

‘Methods oriented synthesis’ includes the invention, discovery and development of new synthetic reactions, enabled with the aid of new reagents and catalysts or by applying new strategies or different tactics. However, the synthetic pursuit of a defined molecule, natural or designed, is classified under ‘target oriented synthesis’. This method is more commonly referred to as “Total Synthesis”.
Both areas of the organic chemistry are heavily connected with one another. The development of new reactions, reagents and catalysts has greatly contributed to the ‘target oriented synthesis’ (also called total synthesis). As a result of the invention and discovery of new strategies, ‘method oriented synthesis’ benefits from the field of ‘target oriented synthesis’.

1.2 Total Synthesis

The goal of ‘total synthesis’ (target oriented) is to synthesize a given organic compound, the target molecule (a natural product or a designed molecule), *via* a sequence of reactions starting from simple and readily available starting materials. A total synthesis usually starts with design of a synthetic strategy; various reactions in a certain sequence to synthesize the target molecule.
An important method for design of a synthetic strategy is the concept “Retrosynthetic analysis”. In this analysis method the synthesis of the target molecule is carried out in thought backwards. It starts with the product, the target molecule, and breaks it down one step at a time to end at simple, readily available starting materials. This concept of retrosynthetic analysis was developed by E.J. Corey for which he received the Nobel Prize in Chemistry in 1990. The development of this method and theories has made it possible to synthesize a large variety of biologically highly active or complicated natural products.[6]

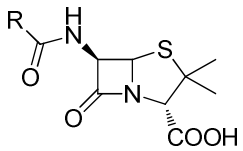
Figure 1.3 *E.J. Corey*

Some important points of interest for a planned synthetic strategy are: 1) the synthetic reactions have to be effective; 2) the starting materials have to be inexpensive and readily available; 3) the reactions have to be practical and convenient; 4) the strategy has to be flexible for modification in case of pitfalls; and 5) the strategy has to be adaptable to the synthesis of other members of the structural family. [5]

1.3 Antibiotics

1.3.1 Introduction

An antibiotic (derived from the Ancient Greek: ἀντί – *anti* meaning "against" and βίος – *bios* meaning "life") is a substance or compound that kills or inhibits the growth of bacteria or kills bacteria by interfering with the major cellular function processes that are essential for their survival. The development of antibacterial agents has significantly reduced the morbidity and mortality associated with bacterial infections over the last century, particularly in developed countries.
The first antibiotic, Penicillin was discovered by Alexander Fleming in 1928.

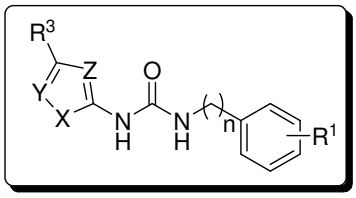


Penicillin

Penicillin antibiotics are historically significant because they are the first drugs that were effective against many previously serious diseases such as syphilis and Staphylococcus infections. Penicillins are still widely used today, though many types of bacteria are now resistant.
There are many different classes of antibiotics. Nowadays, most antibiotics are semisynthetic (modified chemically from original compounds found in nature,[7] as is the case with beta-lactams. This includes the penicillins, produced by fungi in the genus *Penicillium*, the cephalosporins, and the carbapenems. Some antibiotics are still produced and isolated from living organisms, such as the aminoglycosides. Others have been created through purely synthetic means: the sulfonamides, the quinolones and the oxazolidinones.
In addition to this origin-based classification into natural, semisynthetic, and synthetic, antibiotics may be divided into two broad groups according to their effect on microorganisms. Bactericidal agents; antibiotics that kill bacteria and bacteriostatic agents; antibiotics that only impair bacterial growth. Many antibiotics are relatively small molecules with a molecular weight less than 2000 Da.
The appearance of drug-resistant strains of pathogenic bacteria has revived interest in the development of novel antibacterial compounds.[8] However, the emergence of drug-resistant bacterial strains threatens the resurgence of bacterial-borne diseases long thought to have been conquered.
Therefore the pharmaceutical industry was interested in the search of new class of antibiotic. This study describes the synthesis of 2-aminothiazole urea derivatives, which was initiated by a project for Replidyne Inc.

1.3.2 Biological applications and therapeutic applications

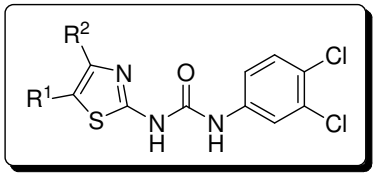
In the literature, the biological activity of several heterocyclic urea derivatives is well described.[9,10] The ureas fitting the general structure are either a 5-aminopyrazole urea or a 2-aminothiazole urea derivative as shown in Figure 1.4. These showed promising activity versus *Staphylococcus aureus*.[11] The *S. aureus* may occur on the human skin. If the bacteria enters the body through the skin, the bacteria can cause skin infections. Ureas of 2-aminothiazoles are well known in literature and are active as antivirals[12], VLA-4 inhibitors[13] and antitumor agents[14].



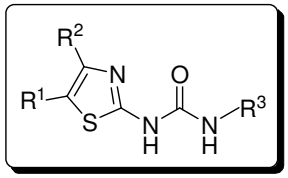
$X = NR^2$, $Y = N$, $Z = CR^4$
$X = S$, $Y = CR^5$, $Z = N$
$n = 0, 1$

Figure 1.4 *General structure of 5-aminopyrazole or 2-aminothiazole urea derivatives*

The 2-aminothiazole urea derivatives fitting the general structure in Figure 1.5 showed good antibacterial activity against methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococcus* (VRE) and penicillin resistant *Streptococcus pneumoniae* (PRSP).[15]



$R^1 = H$; $R^2 = H$, CN
$R^1 = CN$; $R^2 = H$, *t*-Bu, O*i*-Bu, OEt, Cl, OMe, morpholino
$R^1 = NO_2$; $R^2 = H$



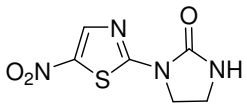
$R^1 = CN$; $R^2 = t$-Bu; R^3 = 3,4-diMePh, 3,4-diFPh, 3-CNPh, 3-Py, 3,4-diClPhCH_2
$R^1 = CN$; $R^2 = H$; R^3 = 3,4-diFPh, 3,4-diClPhCH_2

Figure 1.5 *General structure of 2-aminothiazole urea derivatives*

Enterococcus can cause endocarditis, as well as infections in bladder, prostate and epididymitis (the curved structure at the back of the testicals). *S. pneumoniae* is also a bacteria that occurs in humans, and normally causes no diseases. However, if infection takes place the illness can be severe. The bacteria can cause, for example the following diseases; pneumonia, sinusitis, arthritis, meningitis, otitis and peritonitis.

1.3.3 Mechanism of action

All penicillins are beta-lactam antibiotics and they work by inhibiting the formation of peptidoglycan cross-links in the bacterial cell wall. The beta-lactam moiety of penicillin binds to the enzyme (DD-transpeptidase) that links the peptidoglycan molecules in bacteria. This weakens the cell wall of the bacteria and causes cytolysis (is the bursting of the cell due to an osmotic imbalance).
A similar thiazole urea derivative with antibacterial activity is niridazole (Ambilhar^R). The antibacterial activity of niridazole has been known since 1969.[16] Niridazole is a bactericidal antibiotic. Bactericidal antibiotics kill the bacteria by inhibition of the cell wall synthesis.



Niridazole

In the case of niridazole, it is the nitrothiazole ring moiety that contains the antimicrobially active site.[17] Unfortunally, the mode of action of nitrothiazole derivatives is not yet fully understood. It might that after passage into the the bacterial cell, the bactericidal causes damage of the bacterial DNA resulting in the death of the bacterial cell.[18,19]
Niridazole has for example antibacterial activity against *Campylobacter* species, *Escherichia coli* and *Sammonella typhimurium*.
There are similarities in the structure of niridazole and the thiazole-2-yl urea derivatives. Possibly, these novel molecules have a similar mechanism of action.

1.4 Aim and outline of this report

The aim of this research project is the development of a new and convenient route to novel thiazol-2-yl urea derivatives in order to synthesize easily a large library. Literature describes antibacterial activity of thiazol-2-yl urea derivatives.[9-15] With the synthesis of a library of novel derivatives it is the goal to find a new thiazol-2-yl urea derivative with large antibacterial activity against clinically relavant pathogens.
For the synthesis of the library the left and right-side of the target compound is varied, marked by the circles in Figure 1.6. The part within the dotted cirle is the core-structure, which is kept constant within the library.

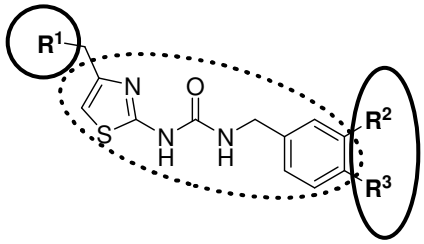


Figure 1.6 *Variations in the left and right-side of the target compounds*

The variations on the left-side consist of different ether, amine, thiol, sulfoxide and sulfone chains connected to the thiazole-ring. On the right-side the variations consist of different substituents on the benzyl-ring.

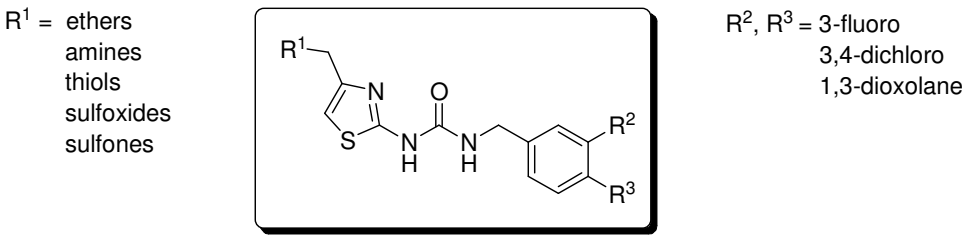
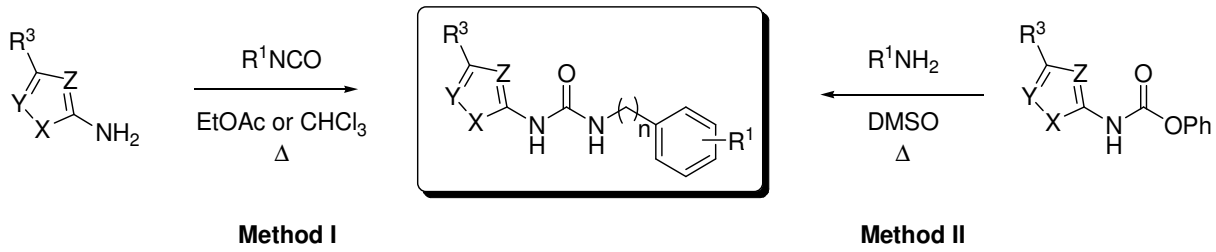


Figure 1.7 *General structure of thiazol-2-yl urea derivatives*

The thiazol-2-yl urea derivatives contain alkoxymethyl-, aminomethyl-, thiomethyl-, sulfoxymethyl- and sulfonylmethyl thiazol-2-yl urea derivatives. For the complete library see Figure 1.7 and Appendix A - I.
Chapter 2 provides some background information on the derivatives and the applications thereof. This is followed by the first strategy for the synthesis of the thiazol-2-yl urea derivatives and the actual synthesis of the thiazol-2-yl urea derivatives.
In Chapter 3, the second synthetic strategy for the synthesis of the thiazol-2-yl urea derivatives will be described and the actual synthesis used for the thiazol-2-yl urea derivatives including the improvements that were made compared to the first route.
The final chapter contains an alternative synthetic route towards the sulfonylmethyl thiazol-2-yl urea derivatives.

1.5 Synthesis of 5-aminopyrazole and 2-aminothiazole urea derivatives

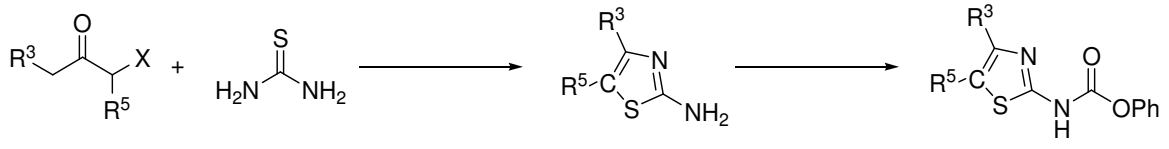
The synthesis of the 5-aminopyrazole and 2-aminothiazole urea derivatives (see Figure 1.4) is straightforward and involves the formation of the urea-linkage using one of the two methods depicted in Scheme 1.8.[20] Method I involves the coupling of the heterocyclic amine and the corresponding isocyanate in a suitable solvent. The mechanism of the reaction between the aminopyrazole or aminothiazole and the corresponding isocyanate is described in Chapter 2 (section 2.3.3).



Scheme 1.8 *Methods for the formation of the urea-linkage*

Alternatively (Method II), the heterocyclic phenylcarbamate was coupled with the corresponding amine.[21]

Both methods require the synthesis of the heterocyclic amine (the 2-aminothiazoles). These were synthesized *via* the Hantzsch procedure from α-haloketones and thiourea.[22] The mechanism of the Hantzsch procedure is described in more detail in Chapter 2 (section 2.3.1).

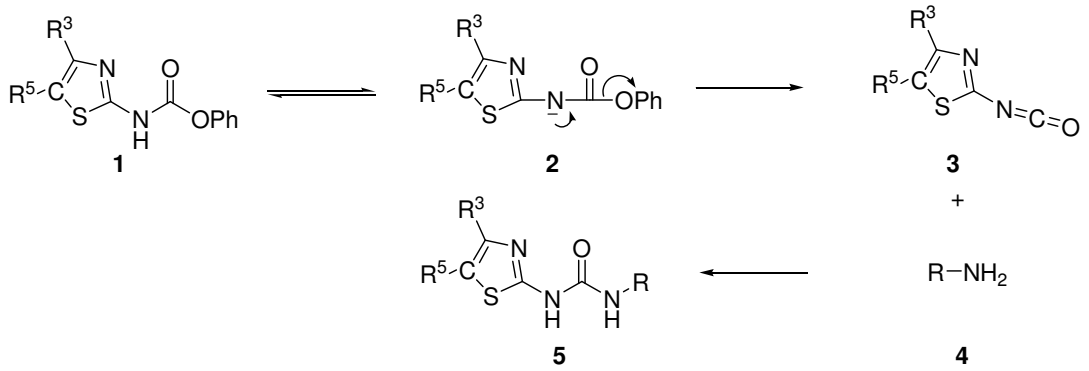


Scheme 1.9 *Formation of the hetreocyclic phenylcarbamate*

In Method II the following step is the formation of the phenylcarbamate.[23] The phenylcarbamate was synthesized by treatment of the corresponding amine with benzyl

chloroformate under basic conditions. The heterocyclic phenylcarbamates were isolated in 80-95% yield.

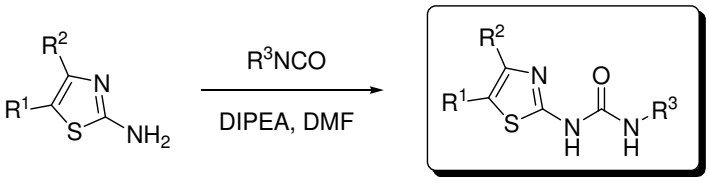
The last step is the formation of the urea from the phenylcarbamate and the corresponding amine. The mechanism of the urea formation has been controversial.[21] A possible mechanism could involve the *in situ* formation of the isocyanate.[24,25,26,27]



Scheme 1.10 *Possible mechanism of the formation of thiazole urea derivative using a phenylcarbamate*

The *N*-phenyl carbamate **1** is weakly acidic and has an equilibrium with **2**. After elimination of the phenolate-moiety, the isocyanate **3** was formed. The isocyanate **3** will react with the corresponding amine **4** to afford the thiazole urea derivative **5**. The last step is the formation of the thiazole urea derivative, the mechanism of this is described in more details inChapter 2 (section 2.3.3).

A variation on Method II is depicted in Scheme 1.11. The synthesis of the 2-aminothiazole urea derivatives (see Figure 1.5) is also straightforward and involves the formation of the urea-linkage from the substituted 2-aminothiazole and the corresponding isocyanate in the presence of Hunig's base in DMF.[28]



Scheme 1.11 *Method for the formation of the urea-linkage*

The mechanism of the reaction between the substituted 2-aminothiazole and the corresponding isocyanate is described in more detail in Chapter 2 (section 2.3.3).

1.6 Notes and references

[1] Wöhler, F. *Ann. Phys. Chem.* **1828**, *12*, 253
[2] Kolbe, H. *Ann. Chem. Pharm.* **1845**, *54*, 145
[3] Fischer, E. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 799
[4] Woodward, R.B.; Doering, W.E. *J. Am. Chem. Soc.* **1944**, *66*, 849
[5] Nicolaou, K.C.; Sorensen, E.J. In *Classics in Total Synthesis*, Ed.; VCH, Weinheim: **1996**
[6] See the website of the Nobel Committees for Physics and Chemistry, http://nobelprize.org/nobel_prizes/chemistry/laureates/1990/press.html
[7] von Nussbaum F. *et al. Angew. Chem. Int. Ed.* **2006**, *45*, 31, 5072–5129
[8] Bronson, J.J.; Barrett, J.F. *Annu. Rep. Med. Chem.* **2001**, *36*, 89
[9] Siddiqui, H.L.; Zia-ur-Rehman, M.; Ahmad, M.; Weaver, G.W; Lucas, P.D. *Chem. Pharm. Bull* **2007**, *55*, 7, 1014-1017
[10] Yonova, P.A.; Stoilkova, G.M. *J. Plant Growth Regul.* **2005**, *23*, 280-291
[11] Kane, J.L.; Hirth, B.H.; Liang, B.; Gourlie, B.B.; Nahill, S.; Barsomian, G. *Bioorg. and Med. Chem. Letters.* **2003**, *13*, 4463
[12] Liebig, H.; Pfetzing H.; Grafe, A. *Arzneim.-Forsch.* **1974**, *24*, 887
[13] Baldwin, J.J.; Mc Donald, E.; Moriarty, K.J.; Sarko, C.R.; Machinaga, N.; Nakyama, A.; Chiba, J.; Iimura, S.; Yoneda, Y. *Chem. Abstr.* **2001**, *134*, 86149; WO Patent 2001/0100206
[14] Pevarello, P.; Amici, R.; Traquandi, G.; Villa, M.; Vulpetti, A.; Isacchi, A. *Chem. Abstr.* **2000**, *132*, 334455; WO Patent 2000/0026203
[15] Francisco, G.D.; Li, Z.; Albright, D.; Eudy, N.H.; Katz, A.H.; Petersen, P.J.; Labthavikul, P.; Singh, G.; Yang, Y.; Rasmussen, B.A.; Lin, Y.; Mansour, T.S. *Bioorg. and Med. Chem. Letters.* **2004**, *14*, 235
[16] Kradolfer F.; Jarumilinta, R.; Sackmann, W. *Ann. N. Y. Acad. Sci.* **1969**, *160*, 740
[17] Hof, H.; Eisenbarth, B.; Denzler, A.; Zak, O.; Schweizer, E. *Journal of Antimicrobial Chemotherapy* **1985**, *16*, 205
[18] Hof, H.; Zak, O; Schweizer, E.; Denzler, A. *Journal of Antimicrobial Chemotherapy* **1984**, *14*, 31
[19] Hof, H.; Rieffert, M.; Sticht-Groh, V.; Zak, O.; Schweizer, E.H. *Antimicrobial Agents and Chemotherapy* **1984**, *26*, 4, 498
[20] Kane, J.L.; Hirth, B.H.; Liang, B.; Gourlie, B.B.; Nahill, S.; Barsomian, G. *Bioorg. and Med. Chem. Letters.* **2003**, *13*, 4463
[21] Thavonekham, B. *Synthesis* **1997**, *10*, 1189
[22] Wiley, R.H.; England D.C.; Behr, L.C. In *Organic Reactions*; Adams, R., Ed.; Wiley & Sons: New York, **1951**, p367
[23] Stevens, C.M.; Watanabe, R. *J. Am. Chem. Soc.* **1950**, *72*, 725
[24] Hegarty, A.F.; Frost, L.N. *J. Chem. Soc., Chem. Commun.* **1972**, 500
[25] Bender, M.L.; Homer, R.B. *J. Org. Chem.* **1965**, *30*, 3975
[26] Ellman, J.A. *Acc. Chem. Res.* **1996**, *29*, 132
[27] Hegarty, A.F.; Frost, L.N.; Coy, J.H. *J. Org. Chem.* **1974**, *39*, 8, 1089
[28] Francisco, G.D.; Li, Z.; Albright, D.; Eudy, N.H.; Katz, A.H.; Petersen, P.J.; Labthavikul, P.; Singh, G.; Yang, Y.; Rasmussen, B.A.; Lin, Y.; Mansour, T.S. *Bioorg. and Med. Chem. Letters.* **2004**, *14*, 235
[29] Wikipedia was used for general information

Chapter 2 First strategy for the synthesis of the alkoxymethyl thiazol-2-yl urea derivatives

2.1 Introduction

In this chapter the synthesis of the alkoxymethyl thiazol-2-yl urea derivatives fitting the general structure in Figure 2.1 will be described.

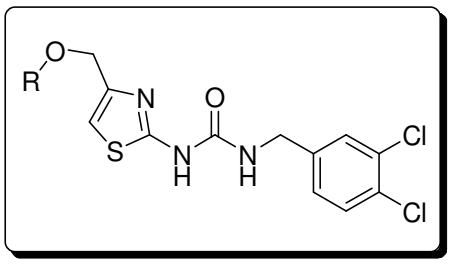
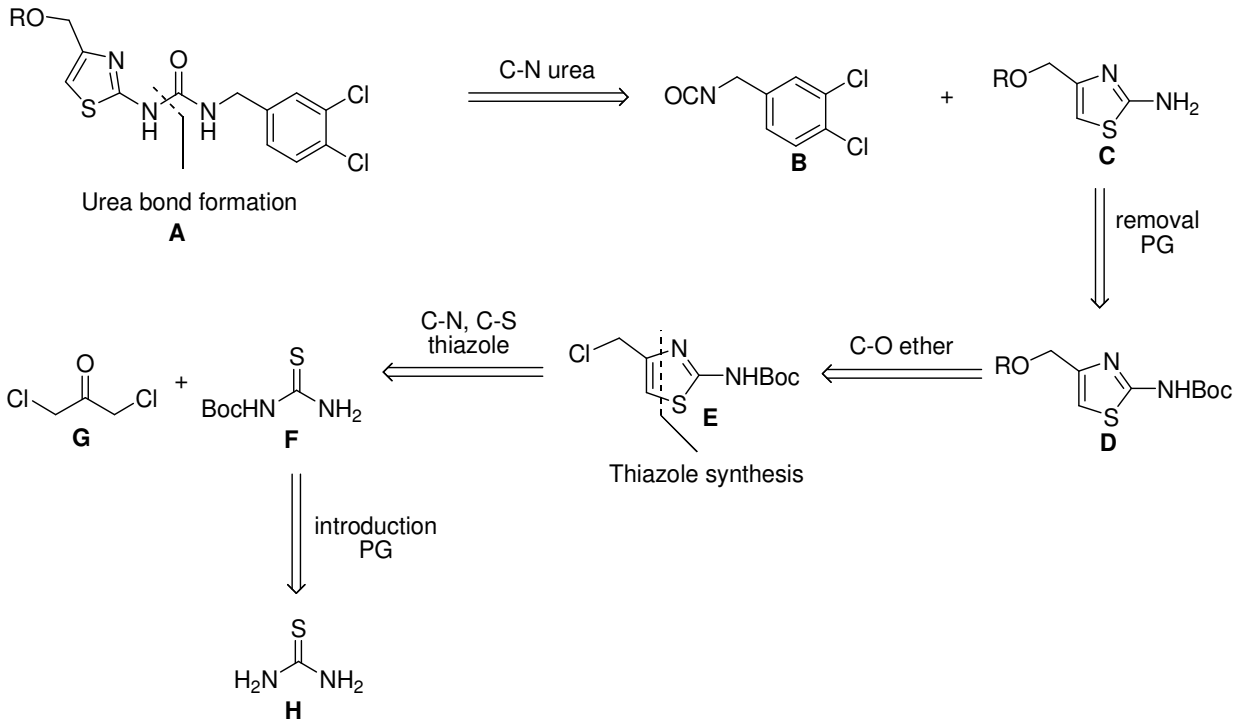


Figure 2.1 *General structure of the alkoxymethyl thiazol-2-yl urea derivatives*

This chapter will at first describe the retrosynthetic analysis and strategy, followed by the developed synthetic route. Finally there is a discussion and a conclusion about the developed synthetic strategy and the found results. The experimental details of the synthetic strategy are described in the experimental section.
An overview of all the alkoxymethyl thiazol-2-yl urea derivatives that were prepared are depicted in Appendix A and B.

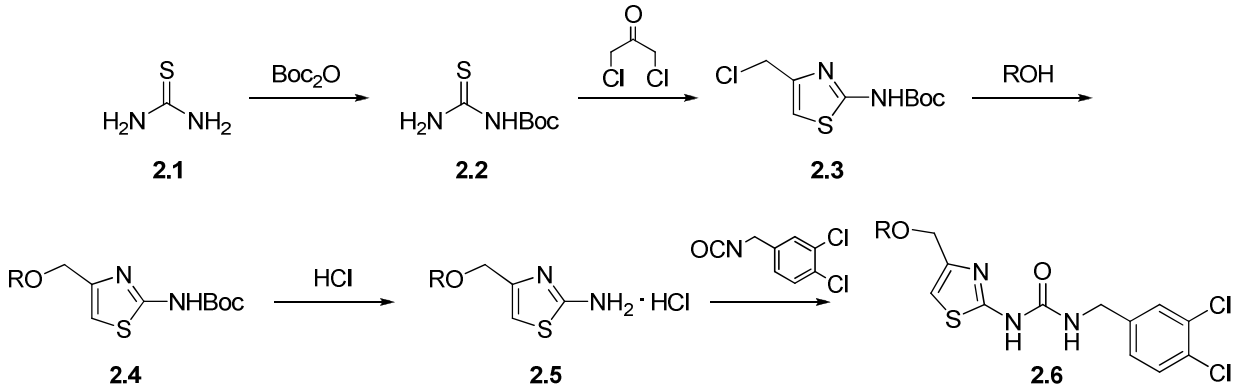
2.2 Retrosynthetic analysis and strategy

The alkoxymethyl thiazol-2-yl urea derivatives were analyzed retrosynthetically, and a possible synthetic route was developed. The retrosynthetic analysis and the synthetic route are depicted in Scheme 2.1 and 2.2 respectively.
The retrosynthetic analysis of the alkoxymethyl thiazol-2-yl urea derivative **A**, translated into accessible starting materials, reveals two synthetic fragments, isocyanate **B** and alkoxymethyl aminothiazole **C**. The isocyanates **B** are commercially available and the alkoxymethyl aminothiazoles **C** have to be prepared.



Scheme 2.1 *Retrosynthetic analysis of thiazol-2-yl urea derivatives.*

Because the chloromethyl aminothiazole **E** has to undergo a functional group inversion, the amine-group has to be protected. As a protecting group a Boc-group was chosen. A protected amine-group of chloromethyl aminothiazole **E** was necessary to eliminate side-reactions during the formation of alkoxymethyl aminothiazole **D**. The Boc-protected alkoxymethyl aminothiazole **D** can be synthesized from the corresponding alcohol and the Boc-protected chloromethyl aminothiazole **E**. Aminothiazole **E** can be synthesized from the commercially available 1,3-dichloroacetone **G** and Boc-protected thiourea **F** *via* the Hantzsch thiazole synthesis.[1] Boc-protected thiourea **F** is commercially available but it can also be synthesized from the commercially available thiourea **H** and di-*tert*-butyldicarbonate.
The synthetic route that was developed after the retrosynthetic analysis is depicted in Scheme 2.2. The synthesis consist of five steps; a protection step, a thiazole synthesis, formation of the methylalkoxy functionality, a deprotection step and finally the formation of a urea-linkage.



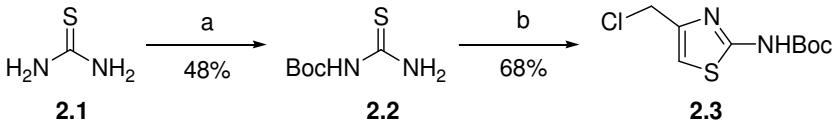
Scheme 2.2 *Synthetic route towards the alkoxymethyl thiazole urea derivatives*

In the following subchapters the synthesis of the alkoxymethyl thiazol-2-yl urea derivatives will be thoroughly described. First the synthesis of the *N*-Boc-4-(chloromethyl)thiazol-2-amine **2.3** will be discussed, followed by the synthesis of the alkoxymethyl thiazol-2-amine derivatives **2.5** and last the synthesis of the alkoxymethyl thiazol-2-yl urea derivatives **2.6**.

2.3 Synthesis

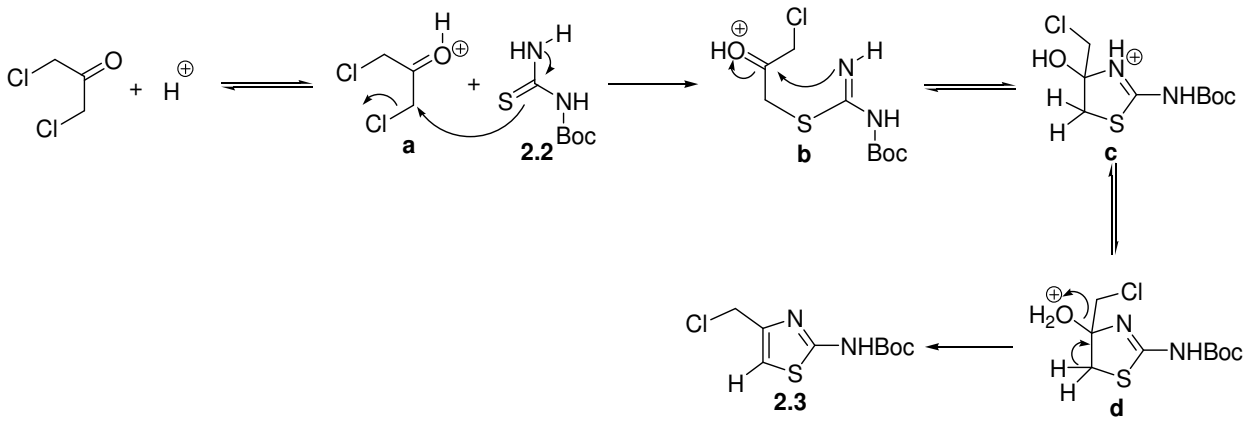
2.3.1 Preparation of the *N*-Boc-4-(chloromethyl)thiazol-2-amine

The *N*-Boc-4-(chloromethyl)thiazol-2-amine **2.3** was prepared in two steps with an overall yield of 33%, starting from the commercially available thiourea **2.1**[2], see Scheme 2.3.



Scheme 2.3 *Reagents and conditions: (a) NaH, Boc_2O, THF, RT, 1 hour; (b) 1,3-dichloroacetone, acetone, RT, 72 hours.*

The first step is the protection of one of the amine-groups of the thiourea **2.1** with a Boc-group. The amine-group of the thiourea **2.1** was deprotonated with NaH as a base, and protected with a Boc-group using Boc_2O. A statistical mixture is formed of the thiourea **2.1**, Boc-protected thiourea **2.2** and bis-Boc-protected thiourea. The Boc-protected thiourea **2.2** and bis-Boc-protected thiourea were separated from the thiourea **2.2** *via* crystallization. The thiourea **2.2** was removed to eliminate side-reactions. 1,3-Dichloroacteone can otherwise react with both amino-groups of the thiourea and the formed side-product has to removed. The second step of the synthesis of *N*-Boc-4-(chloromethyl)thiazol-2-amine **2.3** proceeds *via* the Hantzsch thiazole synthesis, which is a reaction between thioamides and haloketones.[1][3] In this case the reaction is between 1,3-dichloroacetone and Boc-protected thiourea **2.2** in acetone as the solvent.
The mechanism of the Hantzsch thiazole synthesis is depicted in Scheme 2.4.



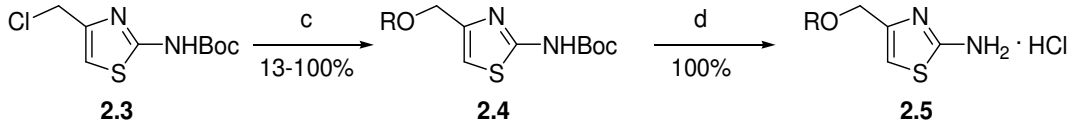
Scheme 2.4 *Mechanism of the Hantzsch thiazole synthesis*

In this case the reaction is acid catalyzed. First the carbonyl of 1,3-dichloroacetone was protonated. In the next step the lone pair of the nitrogen shifts to form a double bond, followed by the formation of a bond between the sulfur of the Boc-thiourea **2.2** and the carbon of the protonated 1,3-dichloroacetone **a** next to the carbonyl and finally the chloride eliminates. After a proton shift intermediate **b** is formed. This intermediate **b** is in equilibrium with intermediate **c**. Intermediate **c** is formed after the lone pair of the nitrogen

attacks the carbonyl carbon and forms a five-membered ring. After a proton shift intermediate **d** is formed. This is followed by elimination of H_2O and formation of a double bond, affording *N*-Boc-4-(chloromethyl)thiazol-2-amine **2.3**.

2.3.2 Preparation of the alkoxymethyl thiazol-2-amine derivatives

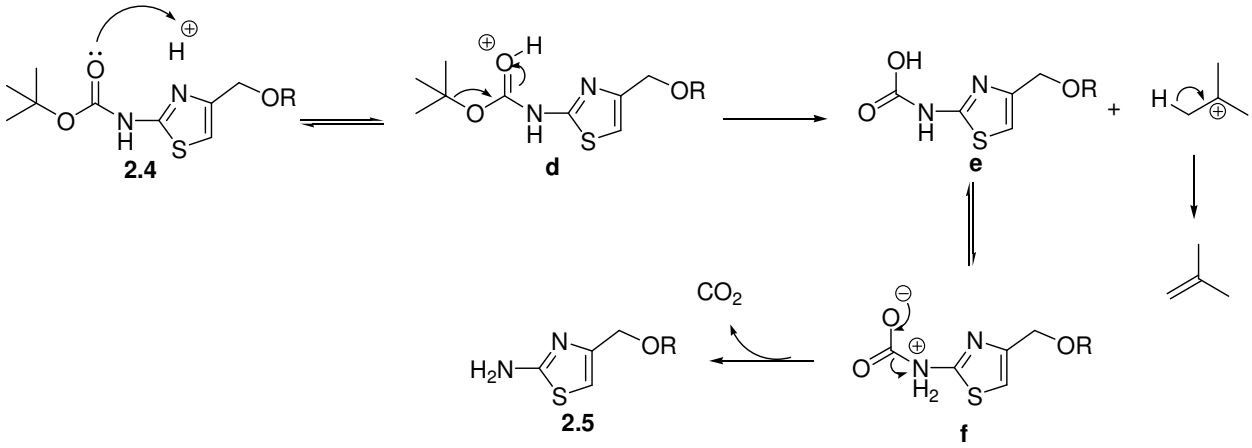
The alkoxymethyl thiazol-2-amine derivatives **2.5** could be prepared in two steps from *N*-Boc-4-(chloromethyl)thiazol-2amine **2.3** in a total yield of 13-100%, see Scheme 2.5.



2.3 **2.4** **2.5**

Scheme 2.5 *Reagents and conditions: (c) NaH, ROH, 15-crown-5, THF, RT, 18 hours or K_2CO_3, ROH, 70-80°C, 2 hours; (d) HCl, 1,4-dioxane, RT, 18 hours.*

The yield of the first step varies from poorly to excellent. A main cause for the large variation in yield can be explained by the ease of the purification of the crude reaction mixture. Some of the derivatives had to be purified by column chromatography or prepative-HPLC.
The first step is the coupling of the *N*-Boc-4-(chloromethyl)thiazol-2-amine **2.3** with the corresponding alcohol to form the *N*-Boc-4-(alkoxymethyl)thiazol-2-amine derivatives **2.4** using two different methods.[4][5] The first method makes use of NaH as a base, the corresponding alcohol as the reagent and THF as the solvent. 15-Crown-5 ether was added for better solubility of the NaH in THF. The second method makes use of K_2CO_3 as a base and uses the corresponding alcohol not only as the reagent but also as the solvent. The NaH-method has the advantage that it affords the desired compound in higher yields than the K_2CO_3-method. An advantage of the K_2CO_3-method is the short reaction time and the easy work-up, which includes only the removal of the solids by filtration and removal of the volatiles. The crude material can then be purified by column chromatography.
The second step is the removal of the Boc-group using 4N HCl in 1,4-dioxane, which was chosen as the reagent for the deprotection step owing to the easy work-up procedure. After full conversion the only work-up step is removal of the volatiles and the material can be used as such in the next step.
The mechanism of the Boc-deprotection of *N*-Boc-4-(alkoxymethyl)thiazol-2-amine derivatives **2.4** is depicted in Scheme 2.8, using HCl as the reagent.

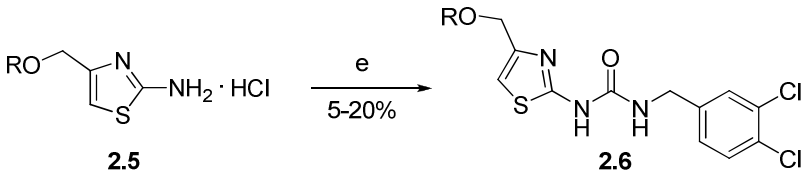


Scheme 2.8 *Mechanism of the Boc-deprotection*

At first the carbonyl-group of alkoxymethyl thiazole-2-amine derivative **2.4** is protonated by the hydrochloric acid. This is followed by the elimination of the *tert*-butyl cation, which forms isobutene. After a proton-shift in alkoxymethyl(thiazol-2-yl)carbamic acid derivative **e**, decarboxylation takes place and alkoxymethyl aminothiazol-2-amine derivative **2.5** is formed.

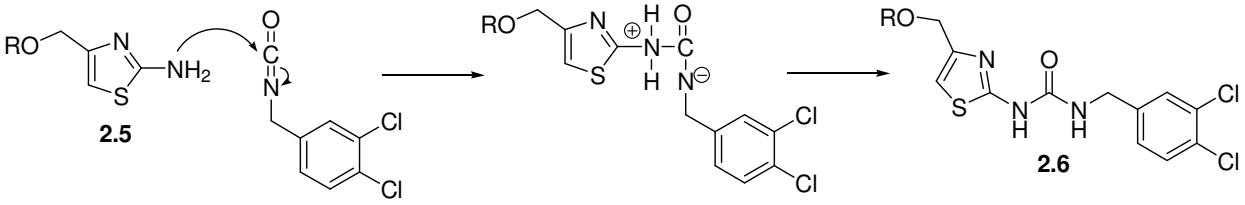
2.3.3 Preparation of the alkoxymethyl thiazol-2-yl urea derivatives

The alkoxymethyl thiazol-2-yl urea derivatives **2.6** could be prepared in a single step from the alkoxymethyl thiazol-2-amine derivatives **2.5** in 5-20% yield, see Scheme 2.9.



Scheme 2.9 *Reagents and conditions: (e) Et_3N or DIPEA, 3,4-dichlorobenzylisocyanate, THF or CH_2Cl_2, RT, 18-72 hours.*

Also the last step has a yield that is somewhat poorly. This is mainly caused by the fact that the purification is troublesome. All compounds need purification by column chromatography and sometimes even preperative-HPLC.
The final step is the formation of an urea bond between the amino-thiazole **2.5** and the 3,4-dichlorobenzylisocyanate to afford the alkoxymethyl thiazole-2-yl urea derivatives **2.6**.[6][7] DIPEA or Et_3N was used as a base to neutralize the HCl-salt of the alkoxymethyl thiazol-2-amine derivatives **2.5**.
The formation of the urea-linkage involves a *N*-hydro-*C*-alkylamino-addition. A possible mechanism is depicted in Scheme 2.10.



Scheme 2.10 *Mechanism of the formation of the urea linkage*

The lone pair of the nitrogen of the alkoxymethyl thiazol-2-amine **2.5** attacks the carbonyl functionality of the 3,4-dichlorobenzylisocyanate. This is followed by a proton shift and subsequently, the alkoxymethyl thiazol-2-yl urea derivatives **2.6** are formed.

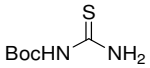
2.4 Discussion and conclusions

The alkoxymethyl thiazol-2-yl urea derivatives **2.6** were synthesized in five steps in an overall yield of <1 – 4 % from thiourea (see Scheme 2.4, 2.5, 2.7 and 2.9). For a five step synthesis the yield is fairly low.
Some of the *N*-Boc-4-(alkoxymethyl)thiazol-2-amine derivatives **2.4** and all the alkoxymethyl thiazol-2-yl urea derivatives **2.6** were purified by preparative-HPLC. Unfortunately, there was a low recovery of the compounds after purification.
Literature described the protecting of the thiourea **2.1** with a Boc-group in 90% yield. The coupling of the benzylisocyanate with the alkoxymethyl thiazol-2-amine derivatives **2.5** is described in good yields, but no exact yields were given. In this study, the products were isolated in moderate yield, possibly these reactions can be optimized.
However, the goal of this project was to synthesize a library of thiazol-2-yl urea derivatives for Replidyne Inc. which could be tested for their antibacterial activity. Therefore, the intent was to synthesize a lot of derivatives and not to optimize the yield of the synthetic route. When Replidyne Inc. would have found a derivative with an excellent antibacterial activity, the next step would be to optimize the synthetic route.
Via this five step strategy the following alkoxymethyl thiazole-2-yl urea derivatives **2.6a-i** were prepared. The details of the synthesis and the structure of **2.4a**-**i** and **2.6a-i** are described in Appendix A and B, respectively.
The synthetic route described in Scheme 2.4, 2.5, 2.7 and 2.9 has two major disadvantages. First, the purification of the alkoxymethyl thiazol-2-yl urea derivatives was problematic and often after the purification by column chromatography further purification by preparative HPLC was needed. This is the major cause of the poor yields. The second disadvantage of this route is that there is almost no flexibility for the introduction of the side chains.
For each derivative three of the five steps of the synthesis route had to be performed. It would be more efficient to synthesize a common intermediate and introduce the side chains in the last step. This new approach is described in Chapter 3.

2.5 Experimental section

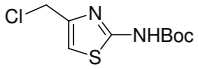
General remarks.
All the chemicals were purchased from Acros, Fluka or Aldrich and used without purification. ^{1}H-NMR spectra were recorded on a Varian 300 MHz spectrometer at room temperature. Chemical shifts are reported in ppm referenced to the residual solvent signal. Silica gel 60 was used for flash column chromatography and silica gel 60F_{254} plates (0.25 mm, Merck) were used for TLC.

***N*-Bocthiourea (2.2)**



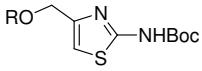
To a solution of thiourea **2.1** (5.5 g, 72.3 mmol) in tetrahydrofuran (500 mL) at 0 °C was added 60% dispersion of NaH (2.3 eq, 168.8 mmol, 6.75 g) in portions. The mixture was stirred at 0 °C for 10 minutes and subsequently treated drop wise with a solution of Boc_2O (1.06 eq, 77.1 mmol, 16.5 g) in tetrahydrofuran (100 mL). The resulting thick suspension was thoroughly stirred for 1 additional hour. The reaction mixture was poured into dichloromethane (500 mL) and was washed with aqueous saturated $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4 and the volatiles were evaporated *in vacuo*. The residue was washed with heptane (2 x 100 mL) and pentane (100 mL) to afford 9.3 g of a white solid as a mixture of mono and bis-Bocthiourea 3:1 (corresponds with 6.1 g of *N*-Bocthiourea, 48% yield) which was used as such in the next step. ^{1}H-NMR (ppm, $CDCl_3$): 1.4 (s, 9H), 2.0 (s, 2H), 8.0 (s, 1H)

***N*-Boc-4-(chloromethyl)thiazol-2-amine (2.3)**



To a solution of *N*-Bocthiourea **2.2** (3.0 g, 17 mmol) in acetone (75 mL) was added 1,3-dichloroacteone (1.1 eq, 18.7 mmol, 2.4 g) at once. The mixture was stirred at room temperature for 72 hours. The reaction mixture was treated with 3 g of $NaHCO_3$ and stirred for 15 minutes. The solids were removed by filtration and the filtrate was concentrated *in vacuo*. Purification by column chromatography (EtOAc/heptane 4/1) afforded *N*-Boc-4-(chloromethyl)thiazol-2-amine **2.3** (2.9 g, 11.6 mmol, 68%) as a white solid. ^{1}H-NMR (ppm, $CDCl_3$): 1.4 (s, 9H), 4.64 (s, 2H), 6.11 (s, 1H), 8.0 (s, 1H)

General procedure for the synthesis of the *N*-Boc-4-(alkoxymethyl)thiazol-2-amine derivatives (2.4)

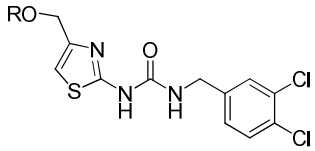


Method A: To a suspension of NaH (3 eq) in tetrahydrofuran at 0 °C was added the alcohol (3 eq) and 15-crown-5 (2 drops). The mixture was stirred at 0 °C for 30 minutes and *N*-Boc-4-(chloromethyl)thiazol-2-amine **2.3** (1 eq) was added at once. The mixture was allowed to warm to room temperature and stirred overnight at this temperature. The reaction was quenched upon addition of water. The product was extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification

by column chromatography (EtOAc/heptane 2/1) afforded the *N*-Boc-4-(alkoxymethyl)thiazol-2-amine derivatives **2.4**.

Method B: To a solution of *N*-Boc-4-(chloromethyl)thiazol-2-amine **2.3** in the corresponding alcohol was added K_2CO_3. Subsequently the mixture was stirred at 70 °C – 80 °C for 2 hours. The reaction mixture was allowed to cool to room temperature and the solids were removed by filtration. The filtrate was concentrated *in vacuo* and the crude material was purified by column chromatography (EtOAc/heptane 2/1).

General procedure for the synthesis of the alkoxymethyl thiazol-2-yl urea derivatives (2.6)



The *N*-Boc-4-(alkoxymethyl)thiazol-2-amine derivative **2.4** was dissolved in 1,4-dioxane and treated with HCl (4 N HCl in 1,4-dioxane) at room temperature overnight. The resulting mixture was concentrated *in vacuo* and stripped with toluene (2 x) to afford the corresponding alkoxymethyl thiazol-2-amine derivative **2.5**. This material was suspended in dichloromethane (or tetrahydrofuran) and triethylamine (or DIPEA) (2.2 eq) was added. To this mixture was added the 3,4-dichlorobenzylisocyanate. The mixture was stirred for 16-72 hours at room temperature and the volatiles were removed *in vacuo*. The alkoxymethyl thiazol-2-yl urea derivative **2.6** was purified by column chromatography (dichloromethane/ 2-5 % methanol) and, if needed, by an additional preparative HPLC run (RP).

2.6 Notes and references

[1] Hantzch, A. *Justus Liebigs Ann. Chem* . **1889**, *250*, 265

[2] Schiavi, B.; Ahond, A.; Poupat, C.; Potier, P. *Synthetic Communications* **2002**, *32*, 11, 1671-1674

[3] Sprague, J.M.; Land, A.H.; Ziegler, C. *J. Am. Chem. Soc.* **1946**, *68*, 2155

[4] US Patent 2006/154975

[5] US Patent 2002/86996

[6] Closier, M.D.; Islip, P.J. *J. Med. Chem.* **1970**, *13*, 638

[7] US Patent 2002/45615

[8] March, J. In *Advanced Organic Chemistry, reactions, mechanisms and structure*, third edition, Ed.; Wiley & Sons: New York, **1985**. This book was used for reaction mechanisms throughout the whole graduation assignment.

[9] Wikipedia was used for general information.

[10] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. In *Organic chemistry*, Ed.; Oxford University Press Inc.: New York, **2001**. This book was used for reaction mechanisms throughout the whole graduation assignment.

[11] Vollhardt, K.P.C., Schore, N.E. In *Organic chemistry*, fourth edition, Ed.; W.H. Freeman and Company: New York, **2002**. This book was used for reaction mechanisms throughout the whole graduation assignment.

[12] Wuts, P.G.M., Greene, T.W. In *Green's protective groups in organic synthesis*, fourth edition, Ed.; Wiley & Sons: New York, **2007**. This book was used for reaction mechanisms, throughout the whole graduation assignment.

Chapter 3 Second strategy for the synthesis of the thiazol-2-yl urea derivatives

3.1 Introduction

Initially the alkoxymethyl thiazol-2-yl urea derivatives were prepared as described in Chapter 2. However, this route had two major drawbacks. The first is that the purification of the final products was problematic and often needed preparative HPLC for complete purification. The second drawback is that three of the five steps had to be performed after the various side chains had been introduced. In this strategy no common intermediate was used.
The routes depicted in Scheme 3.3 offer more flexibility for the introduction of the side chains, since a common intermediate is used as a central starting point. A second advantage is that this strategy affords the products with less laborious purification procedures compared to the first strategy (Chapter 2) and is thus the method of choice.
In this chapter the synthesis of the thiazol-2-yl urea derivatives that fit the general structure shown in Figure 3.1 will be described.

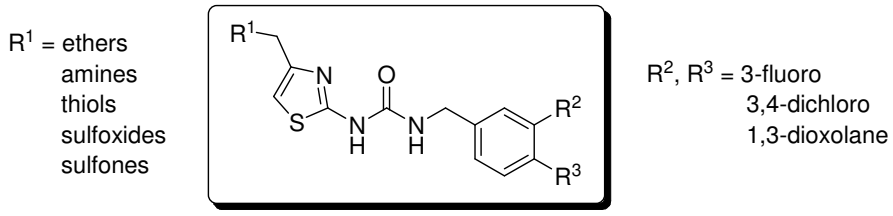
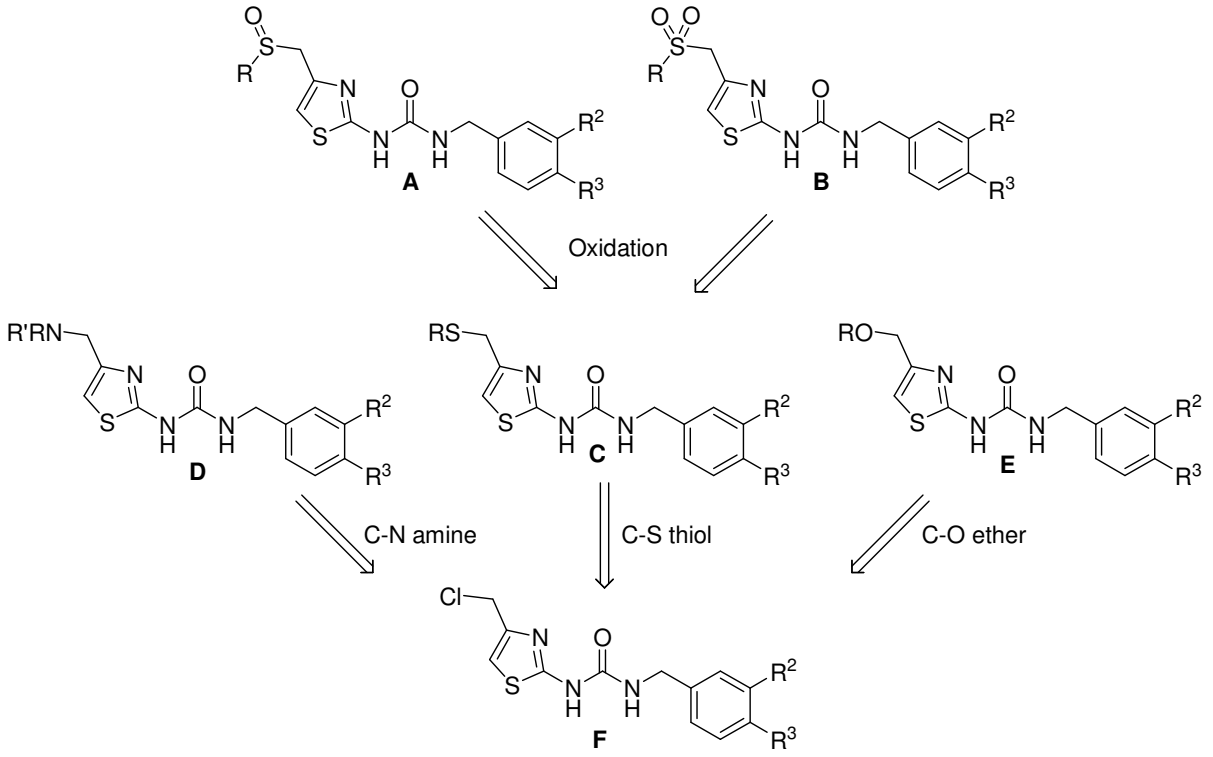


Figure 3.1 *General structure of the thiazol-2-yl urea derivatives*

This includes alkoxymethyl-, aminomethyl-, thiomethyl-, sulfoxymethyl- and sulfonylmethyl thiazol-2-yl urea derivatives, with an 3-fluorobenzyl-, 3,4-dichlorobenzyl- and 1,3-dioxolane urea linkage.
First, the retrosynthetic analysis will be described followed by the developed synthetic route and finally the experimental part.

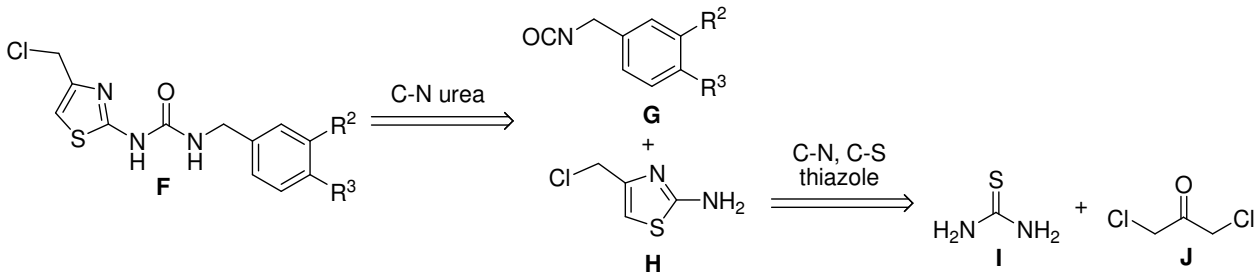
3.2 Retrosynthetic analysis and strategy

The thiazol-2-yl urea derivatives were analyzed retrosynthetically and divided in two parts (Scheme 3.1 and 3.2), and a possible synthetic route was developed (Scheme 3.3). The first part of the retrosynthetic analysis is depicted in Scheme 3.1. This part includes the synthetic analysis of the desired thiazol-2-yl urea derivatives **A**-**E**.



Scheme 3.1 *Retrosynthetic analysis of the thiazol-2-yl urea derivatives, Part I*

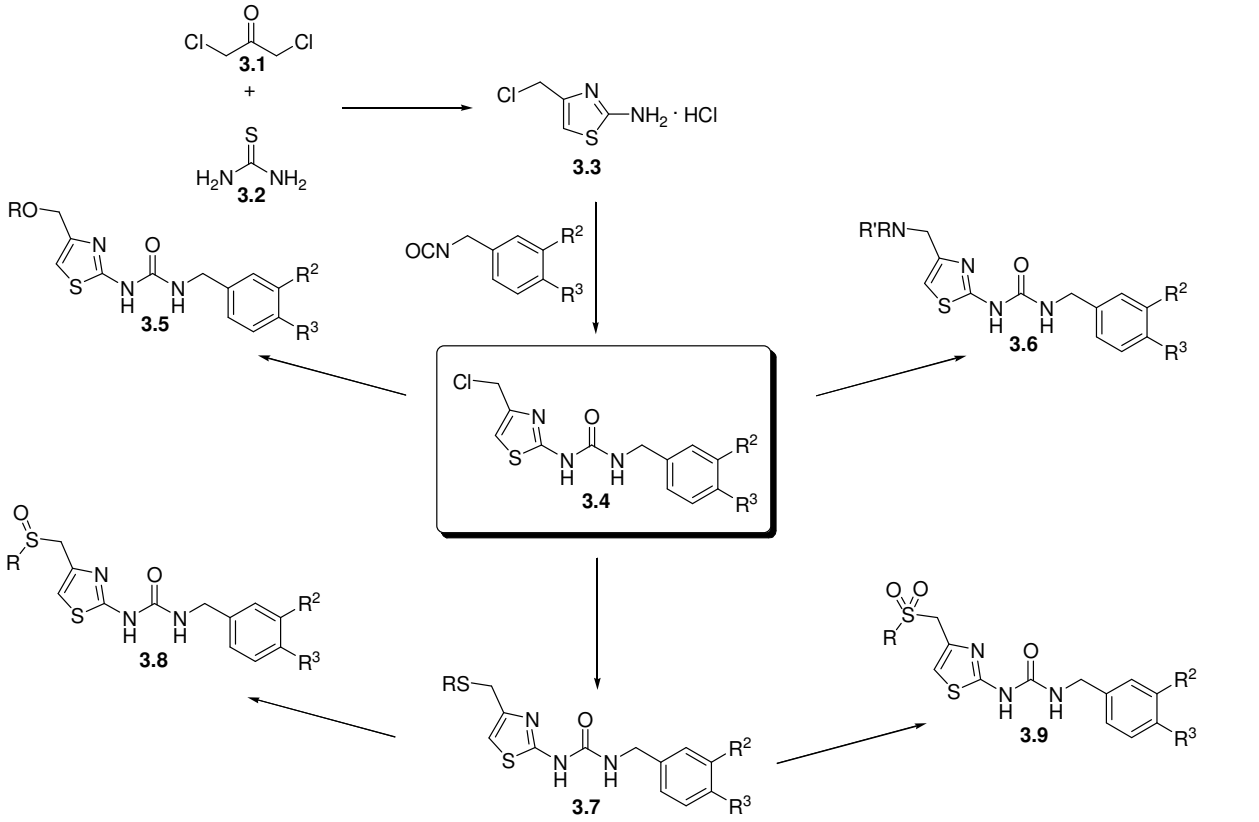
The retrosynthetic analysis shows that the sulfoxymethyl- **A** and the sulfonylmethyl thiazol-2-yl urea derivatives **B** can be prepared from the thiomethyl thiazol-2-yl urea derivatives **C** by an oxidation step. The thiomethyl thiazol-2-yl urea derivatives **C** can be prepared from the corresponding thiol and the chloromethyl thiazol-2-yl urea derivatives **F**, the common intermediate. The aminomethyl thiazol-2-yl urea derivatives **D** can also be prepared from the common intermediate **F** and the corresponding amine. The same is true for the alkoxymethyl thiazol-2-yl urea derivative **E**, which can be prepared from the common intermediate **F** and the corresponding alcohol.
The second part of the retrosynthetic analysis is depicted in Scheme 3.2. This part includes the synthetic analysis for the synthesis of the common intermediate **F**.



Scheme 3.2 *Retrosynthetic analysis of the thiazol-2-yl urea derivatives, Part II*

The retrosynthetic analysis for the chloromethyl thiazol-2-yl urea derivative **F**, translated into accessible starting materials, reveals two synthetic fragments, benzylisocyanate **G** and 4-(chloromethyl)thiazol-2-amine **H**. The benzylisocyanates **G** are commericailly available and the 4-(chloromethyl)thiazol-2-amine **H** has to be prepared from thiourea **I** and 1,3-dichloroacetone **J.**

The synthetic route that was developed after the retrosynthetic analysis is depicted in Scheme 3.3. The synthesis of the common intermediate consists of two steps; a Hantzsch thiazole synthesis[1] and the formation of an urea linkage. The thiazol-2-yl urea derivatives can be prepared in one or two steps.



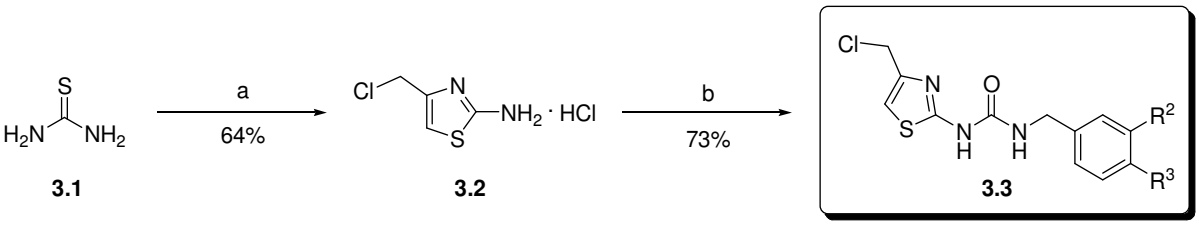
Scheme 3.3 *Standard procedures for the synthesis of the thiazol-2-yl urea derivatives.*

In the following subchapters the synthesis of the thiazol-2-yl urea derivatives will be thoroughly described. First to be discussed is the synthesis of 4-(chloromethyl)thiazol-2-amine, the common intermediate, followed by the synthesis of alkoxymethyl-, aminomethyl-, thiomethyl-, sulfoxymethyl- and sulfonylmethyl urea derivatives.

3.3 Synthesis

3.3.1 Preparation of the common intermediate

The common intermediate, chloromethyl thiazol-2-yl urea derivative **3.3**, could be prepared in two steps starting from thiourea **3.1** in an overall yield of 47%.



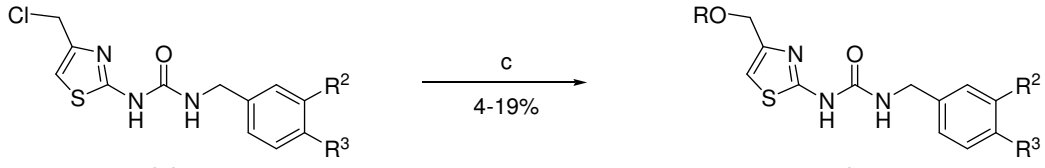
3.1 **3.2** **3.3**

Scheme 3.4 *Reagents and conditions: (a) 1,3-dichloroacetone, acetone, RT, 18 hours; (b) benzylisocyanate, DIPEA, CH_2Cl_2, RT, 18 hours. The physical form and the ^{1}H-NMR spectra of the products with various R^2, R^3 are given in the Appendix.*

The first step is a Hantzsch thiazole synthesis[1], this the reaction between 1,3-dichloroacetone and thiourea **3.1** in acetone.[2] The mechanism was described in Chapter 2 and depicted in Scheme 2.6. The second step is the formation of an urea bond from reaction of the 4-(chloromethyl)thiazol-2-amine hydrochloride **3.2** and a benzylisocyanate in dichloromethane as the solvent.[3][4] DIPEA was added to 4-(chloromethyl)thiazol-2-amine hydrochloride **3.2** to liberated the HCl-salt. The formation of the urea-linkage is an *N*-hydro-*C*-alkylamino-addition[2], which has been described in Chapter 2 and depicted in Scheme 2.10.

3.3.2 Preparation of the alkoxymethyl thiazol-2-yl urea derivatives

The alkoxymethyl thiazole-2-yl urea derivatives **3.4** are prepared from the chloromethyl thiazol-2-yl urea derivative, common intermediate **3.3**, and the corresponding alcohol in an average yield of 4-19%. No attempts were made to optimize this reaction.

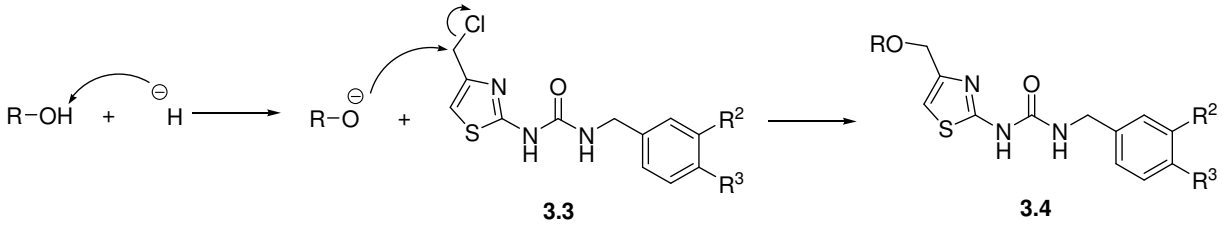


3.3 **3.4**

Scheme 3.5 *Reagents and conditions: (c) NaH, 15-crown-5, ROH, THF, RT, 2-16 hours.*

The chloromethyl thiazol-2-yl urea derivative **3.3** was coupled with the corresponding alcohol in THF to form the alkoxymethyl thiazol-2-yl urea derivatives **3.4**.[5] In this case method A was used, as described in Chapter 2. This involves the use of NaH, as a base and the alcohol as the reagent. 15-Crown-5 ether was added for a better solubility of NaH in THF.

The formation of the alkoxymethyl thiazol-2-yl urea derivatives **3.4** is an aliphatic S_N2 nucleophilic substitution, also called the Williamson ether synthesis. The mechanism of the Williamson ether synthesis is depicted in Scheme 3.6.

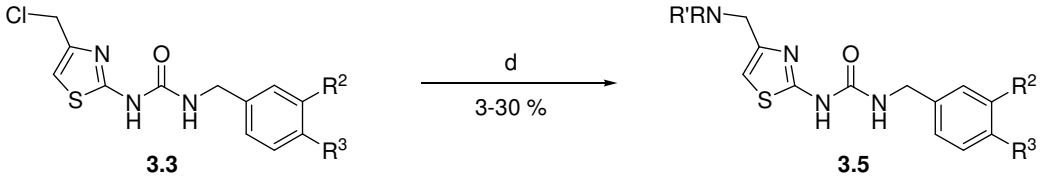


Scheme 3.6 *Mechanism of the Williamson ether synthesis*

First the alcohol is deprotonated by the base, in this case NaH, forming the alkoxide anion. The second and last step involves the attack of the anion on the carbon of the chloromethyl-functionality, followed by the release of the chloride.

3.3.3 Preparation of the aminomethyl thiazol-2-yl urea derivatives

The aminomethyl thiazole-2-yl urea derivatives **3.5** are prepared from the common intermediate **3.3** and the corresponding amine in an average yield of 3-30%.



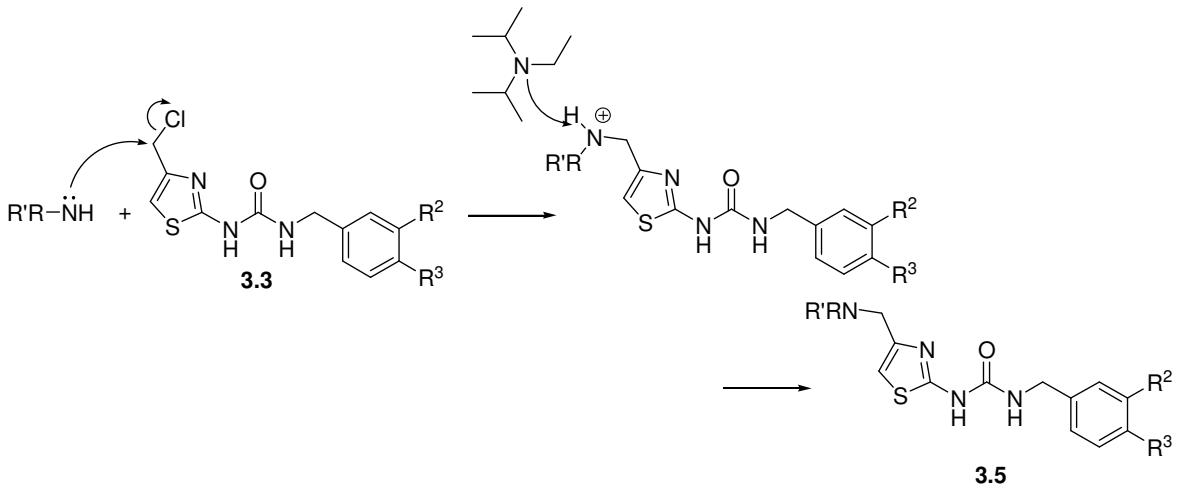
Scheme 3.7 *Reagents and conditions: (d) NaH, R^1RNH, 15-crown-5, THF, RT, 2-16 hours or DIPEA, R^1RNH, THF, 150 °C, 30 min, microwave.*

The chloromethyl thiazol-2-yl urea derivative **3.3** was coupled with the corresponding amine in THF to form the aminomethyl thiazol-2-yl urea derivatives **3.5** using two different methods.[6][7] The first method makes use of NaH as a base and the corresponding amine as the reagent. Again 15-crown-5 ether was added for better solubility of NaH in THF. A disadvantage of this method is the use of an excess (3 equivalents) of the amine. The second method makes use of 1 equivalent of DIPEA as a base and uses only 1 equivalent of the amine, which is an advantage. The method has also two other advantages. The first is the short reaction time of only 30 minutes in the microwave. The second is the facile work-up procedure, only the removal of the volatiles followed by purification using column chromatography.

The mechanism of the formation of the aminomethyl thiazol-2-yl urea derivatives **3.5**, using NaH as the base, is the same as for the formation of the alkoxymethyl thiazol-2-yl urea derivatives **3.4**, see Scheme 3.6. The NaH deprotonates the amine, forming the anion of the amine. The anion of the amine will attack on the carbon of the chloromethyl-functionality of the common intermediate **3.3**, followed by the elimination of the chloride.

When DIPEA was used as a base the reaction follows probably another mechanism as was depicted in Scheme 3.6. DIPEA is not strong enough as a base to deprotonate the

corresponding amine. The proposed mechanism for these conditions is depicted in Scheme 3.8.

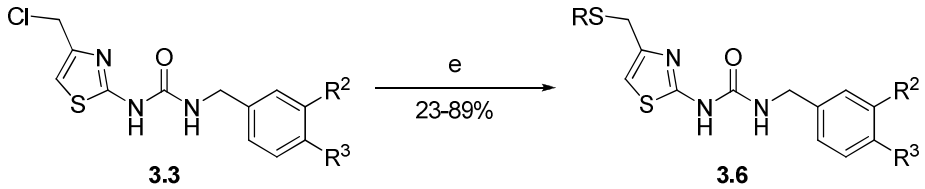


Scheme 3.8 *Mechanism of the synthesis of the aminomethyl thiazol-2-yl urea derivatives using DIPEA*

First, the lone pair of the amine attacks the carbon of the chloromethyl-functionality and the chloride is released, forming the intermediate. In the second step the DIPEA deprotonates the intermediate and forms the aminomethyl thiazol-2-yl urea derivative.

3.3.4 Preparation of the thiomethyl thiazol-2-yl urea derivatives

The thiomethyl thiazol-2-yl urea derivatives **3.6** are prepared from the common intermediate **3.3** and the corresponding thiol in an average yield of 23-89%.



Scheme 3.9 *Reagents and conditions: (e) RSH, Cs_2CO_3, NaI, THF, reflux, 2-16 hours.*

The chloromethyl thiazol-2-yl urea derivative **3.3** was coupled with the corresponding alkylthiol, thiophenol or benzylthiol in THF to form the thiomethyl thiazol-2-yl urea derivatives **3.6**.[8][9]

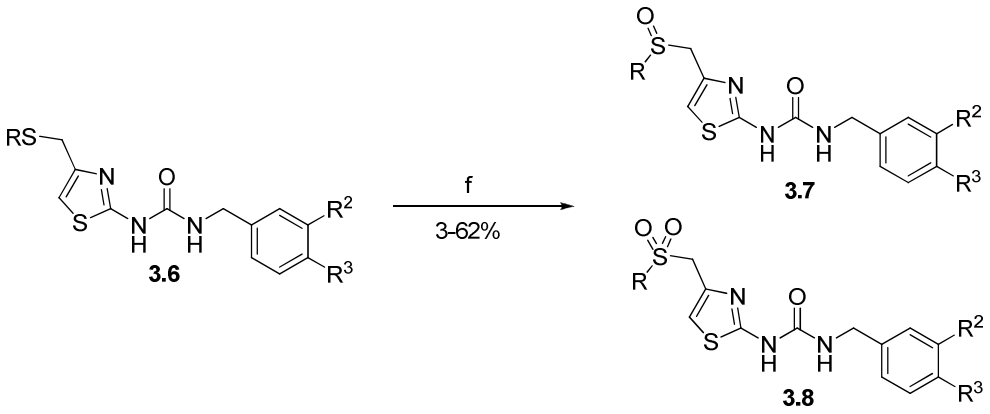
The formation of the thiomethyl thiazol-2-yl urea derivatives **3.6** is a nucleophilic substitution, also called a thio-de-halogenation. The mechanism of the formation of the thiomethyl thiazol-2-yl urea derivatives **3.6** is the same as for the formation of the alkoxymethyl thiazol-2-yl urea derivatives **3.4** and the aminomethyl thiazol-2-yl urea derivatives **3.5**, see Scheme 3.6. In this case the base, Cs_2CO_3, deprotonates the thiophenol or benzylthiol. The anion of the thiol will attack on the carbon of the chloromethyl-functionality of the common intermediate **3.3**, followed by the elimination of the chloride.

NaI was added to catalyze the reaction. In situ the chloromethyl thiazol-2-yl urea derivative **3.3** is converted to the iodomethyl thiazol-2-yl urea derivative. This is called the Finkelstein reaction[10], the reaction and mechanism is further explained in Chapter 4. The iodomethyl

thiazol-2-yl urea derivative is more reactive compared to the chloromethyl thiazol-2-yl urea derivative.

3.3.5 Preparation of the sulfoxymethyl and sulfonylmethyl thiazol-2-yl urea derivatives

The sulfoxymethyl- **3.7** and sulfonylmethyl thiazol-2-yl urea derivatives **3.8** were prepared from the thiomethyl thiazol-2-yl urea **3.6** in an average yield of 3-62%.
The large dispersion in the yield is probably be caused by incomplete conversion of the oxidation of the sulfide moiety.



Scheme 3.10 *Reagents and conditions: Oxone, EtOH, H_2O, RT, 1 hour or m-CPBA, EtOAc, RT, 18 hours*

The thiomethyl thiazol-2-yl urea derivatives **3.6** were oxidized with Oxone or *m*-CPBA (see Figure 3.2) to the corresponding sulfoxymethyl- **3.7** and sulfonylmethyl thiazol-2-yl urea derivatives **3.8**.[8][11]

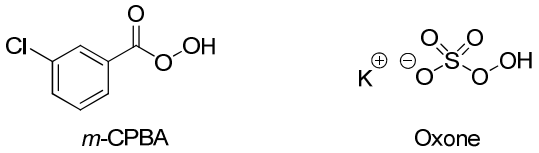
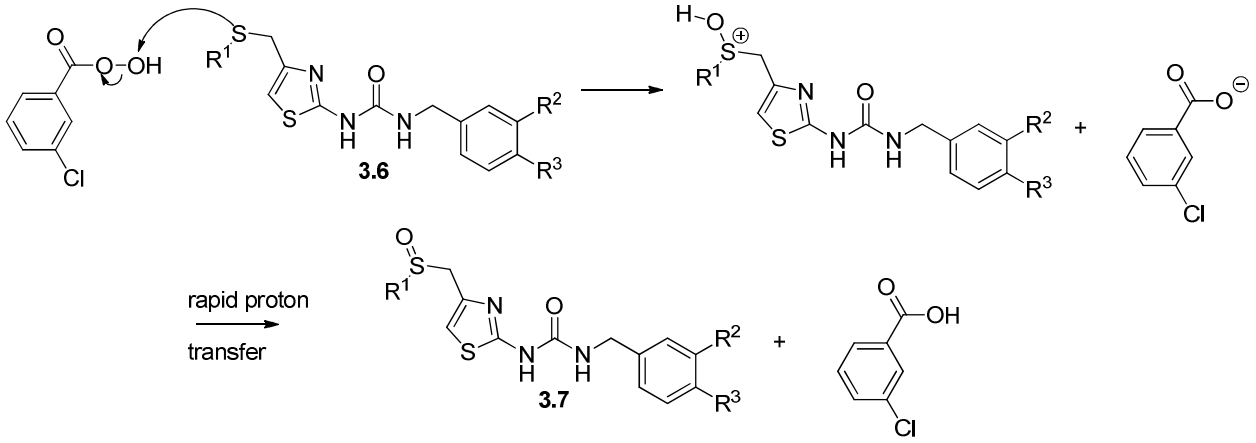


Figure 3.2 *Oxidizing agents*

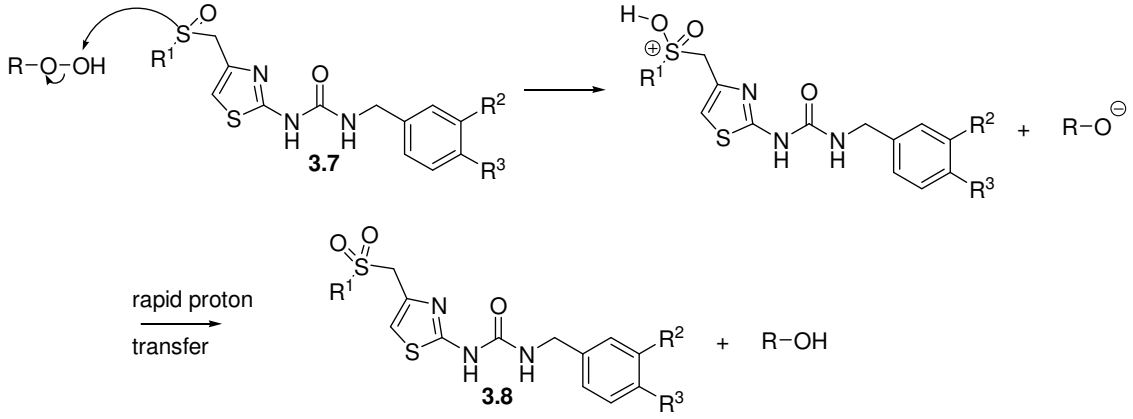
The mechanism of the oxidation of thiomethyl thiazol-2-yl urea derivatives **3.6** with *m*-CPBA or Oxone towards the sulfoxymethyl thiazol-2-yl urea derivatives **3.7** is depicted in Scheme 3.11.[12]



Scheme 3.11 *Mechanism of the oxidation to form the sulfoxides*

The lone pair of the sulfur of the sulfide attacks the hydroxyl oxygen of the peroxy compound with release of 2-chlorobenzoate. After a rapid proton transfer the sulfoxide and 2-chlorobenzoic acid was formed.

The mechanism of the oxidation of thiomethyl thiazol-2-yl urea derivatives **3.6** with *m*-CPBA or Oxone towards the sulfonylmethyl thiazol-2-yl urea derivatives **3.8** is depicted in Scheme 3.11 and 3.12.



Scheme 3.12 *Mechanism of oxidation to form the sulfones*

The first step is the formation of the sulfoxymethyl thiazol-2-yl urea derivative **3.7** (see Scheme 3.11) which was further oxidized towards the sulfonylmethyl thiazol-2-yl urea derivative **3.8**, shown in Scheme 3.12. The second oxidation step follows the same mechanistical pathway as the formation of the sulfoxymethyl thiazol-2-yl urea derivatives **3.7**.

The oxidation of the sulfide towards the sulfoxide is faster compared to the oxidation of the sulfoxide towards the sulfone. Because of this it is easy to prepare and isolate the sulfoxide using one equivalent of the oxidizing agent.

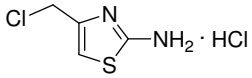
3.4 Discussion and conclusions

The common intermediate **3.3** was prepared in two steps from thiourea **3.1** in 47% overall yield. From this common intermediate several thiazol-2-yl urea derivatives could be prepared in one other step.
The alkoxymethyl thiazol-2-yl urea derivatives **3.4** were synthesized in an overall yield of 2-9% from thiourea (see Scheme 3.4 and 3.5). *Via* this three step strategy the alkoxymethyl thiazole-2-yl urea derivatives **3.4a-k** were prepared, the details of the synthesis are described in Appendix C.
The aminomethyl thiazole-2-yl urea derivatives **3.5** were synthesized in an overall yield of 1.4 – 14% from thiourea (see Scheme 3.9). *Via* this three step strategy the aminomethyl thiazole-2-yl urea derivatives **3.5a-e** were prepared, the details of the synthesis are described in Appendix D.
The thiomethyl thiazol-2-yl urea derivatives **3.6** were synthesized in an overall yield of 11-42% from thiourea (see Scheme 3.4 and 3.7). *Via* this three step strategy the thiomethyl thiazole-2-yl urea derivatives **3.6a-ab** were prepared, the details of the synthesis are described in Appendix E.
The sulfoxymethyl- **3.7** and sulfonylmethyl thiazol-2-yl urea derivatives **3.8** were synthesized in one step from thiomethyl thiazole-2-yl urea derivatives **3.6** in an overall yield of >1-24% from thiourea (see Scheme 3.4, 3.7 and 3.9). *Via* this four-step strategy the sulfoxymethyl-**3.7a-c** and sulfonylmethyl thiazol-2-yl urea derivatives **3.8a-t** were prepared, the details of the synthesis are described in Appendix F.
The synthetic strategy described in this chapter to prepare the alkoxymethyl thiazol-2-yl urea derivatives using a common intermediate **3.3** was in two ways more efficient compared to the synthetic strategy described in Chapter 2. The alkoxymethyl thiazol-2-yl urea derivatives could now be prepared in three steps instead of five steps. Also the overall yield of the strategy described in this Chapter (2-9% overall yield) is higher compared to the strategy described in Chapter 2 (>1-4% overall yield). Another big advantage of this synthetic strategy is the ease of variation of the substituents on the left-side of the thiazol-2-yl urea derivatives.
As also explained in Chaper 2 (section 2.4), the goal of this project was to synthesize a library of thiazol-2-yl urea derivatives for Replidyne Inc. which could be tested for their antibacterial activity. Therefore, the intent was to synthesize a lot of derivatives and not to optimize the yield of the synthetic route. When Replidyne Inc. would have found a derivative with an excellent antibacterial activity, the next step would be to optimize the synthetic route.
In this study, the products were isolated in moderate yield, possibly these reactions can be optimized. For example, the coupling of the common intermediate **3.3** with the corresponding alcohols, amines and sulfides leaves a lot of possibilities for improvement. Also the oxidation of the thiomethyl thiazol-2-yl urea derivatives **3.6** towards the sulfoxymethyl- **3.7** and sulfonylmethyl thiazol-2-yl urea derivatives **3.8** can be improved.

3.5 Experimental section

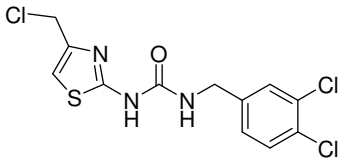
General remarks.
All the chemicals were purchased from Acros, Fluka or Aldrich and used without purification. ^{1}H-NMR spectra were recorded on a Varian 300 MHz spectrometer at room temperature. Chemical shifts are reported in ppm referenced to the residual solvent signal. Silica gel 60 was used for flash column chromatography and silica gel 60F_{254} plates (0.25 mm, Merck) were used for TLC.

4-(Chloromethyl)thiazol-2-amine hydrochloride (3.2)



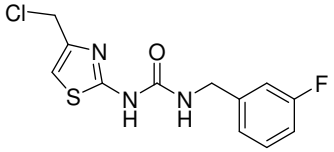
To a solution of 1,3-dichloroacetone (150 g, 1.18 mol) in acetone (600 mL) was added a solution of thiourea **3.1** (1.04 eq, 1.23 mol, 91.7 g) in acetone (3 L). The mixture was stirred overnight at room temperature. The resulting suspension was concentrated to dryness *in vacuo*. Ethanol (1.2 L) was added and the mixture was stirred for 3 hours. The insolubles were removed by filtration and the filtrate was concentrated to 500 mL. Heptane (1.5 L) was slowly added, resulting in the formation of a white precipitate. This was isolated by filtration, washed with heptanes and dried *in vacuo* to afford 4-(chloromethyl)thiazol-2-amine hydrochloride **3.2** as a white solid (141.3 g, 0.76 mol, 64%). ^{1}H-NMR (ppm, DMSO-d_6): 9.50 (bs, 2H), 7.00 (s, 1H), 4,68 (s, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-(chloromethyl)thiazol-2-yl)urea (3.3)



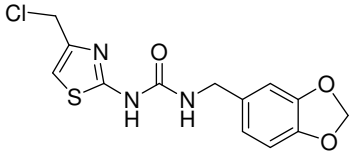
To a suspension of 4-(chloromethyl)thiazol-2-amine hydrochloride **3.2** (7.55 g, 41 mmol) in dichloromethane (150 mL) at 0 °C was added 3,4-dichlorobenzyl isocyanate (1 eq, 41 mmol, 8.27 g). A solution of DIPEA (eq, mmol, mL) in dichloromethane (30 mL) was added over a period of 30 minutes and the mixture was stirred overnight at room temperature. Water was added, the layers were separated and the 1-(3,4-dichlorobenzyl)-3-(4-(chloromethyl)thiazol-2-yl)urea **3.3** crystallized as a white solid. The mother liquor was purified by column chromatography (EtOAc/heptane 1/1). Total yield (10.5 g, 30 mmol, 73%). ^{1}H-NMR (ppm, DMSO-d_6): 10.80 (bs, 1H), 7.60 (d, 1H), 7.55 (s, 1H), 7.11 (t, 1H), 7.05 (s, 1H), 4.63 (s, 2H), 4.30 (d, 2H)

1-(3-Fluorobenzyl)-3-(4-(chloromethyl)thiazol-2-yl)urea (3.3)



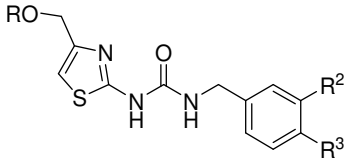
Prepared in a similar manner as 1-(3,4-dichlorobenzyl)-3-(4-(chloromethyl)thiazol-2-yl)urea. ^{1}H-NMR (ppm, DMSO-d_6): 10.70 (bs, 1H), 7.36 (dd, 1H), 7.07 (m, 4H), 4.63 (s, 2H), 4.34 (d, 2H)

1-(benzo[d][1,3]dioxol-5-ylmethyl)-3-(4-(chloromethyl)thiazol-2-yl)urea (3.3)



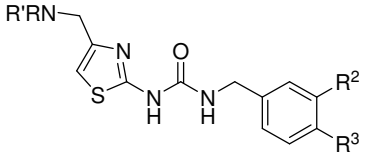
To cooled (0°C) phosgene (1.93 M solution in toluene, eq, 27.9 ml) was added THF (10 ml). Subsequently, a mixture of piperonylamine (27.0 mmol, 4.0 g) and DIPEA (eq, 56.7 mmol, 7.3 g) in THF (20 ml) was added drop wise at 0°C. After complete addition the mixture was stirred for another 40 minutes at 0°C. The reaction mixture was then concentrated. To the crude material THF (40 ml) and DIPEA (4.4 ml) were added, followed by a slurry of 4-(chloromethyl)thiazol-2-amine hydrochloride **3.2** (24.3 mmol, 4.5 g) in THF (50 ml). After stirring for 72 hours at room temperature, the reaction mixture was filtered over Celite. The Celite was washed with EtOAc. The combined filtrate was concentrated and the crude material was directly applied to column chromatography providing **3.3** (2.6 g, 32%). ^{1}H-NMR (ppm, CD_3OD): 4.32 (s, 2H), 4.55 (s, 2H), 5.91 (s, 2H), 6.79 (m, 3H), 6.96 (s, 1H)

General procedure for the synthesis of alkoxymethyl thiazol-2-yl urea derivatives (3.4)



To a suspension of NaH (3 eq) in tetrahydrofuran at 0 °C was added the alcohol (3 eq) drop wise. 15-Crown-5 (2 drops) was added and the mixture was stirred for 30 minutes at 0 °C. Subsequently, **3.3** (1 eq) was added at once and the mixture was allowed to reach room temperature and was stirred at this temperature for 2-16 hours. The conversion was checked by TLC. The reaction mixture was quenched with water and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude products **3.4** were purified by column chromatography (CH_2Cl_2/ 1-5 % methanol).

General procedure for the synthesis of the methyl thiazol-2-yl urea derivatives (3.5)

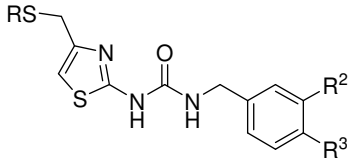


Method C: To a suspension of NaH (2.5-6 eq) in tetrahydrofuran at 0 °C was added the alcohol (3 eq) drop wise. 15-Crown-5 (2 drops) was added and the mixture was stirred for 30 minutes at 0 °C. Subsequently, **3.3** (1 eq) was added at once and the mixture was allowed to reach room temperature and was stirred at this temperature for 2-16 hours. The conversion was checked by TLC. The reaction mixture was quenched with water and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude products **3.5** were purified by column chromatography (CH_2Cl_2/ 1-5 % methanol).

Method D: To a solution of the common intermediate **3.3** (1 eq) and the corresponding amine (1 eq) in tetrahydrofuran was added DIPEA (1 eq). Subsequently, the mixture was

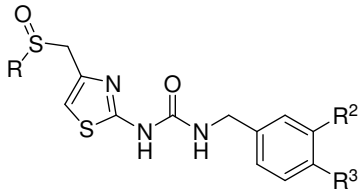
stirred for 30 minutes at 150 °C under microwave irradiation. The volatiles were removed *in vacuo* and the crude products **3.5** were purified by column chromatography (CH_2Cl_2/ 1-5 % methanol or EtOAc/heptane 1/2).

General procedure for the synthesis of the thiolmethyl thiazol-2-yl urea derivatives (3.6)

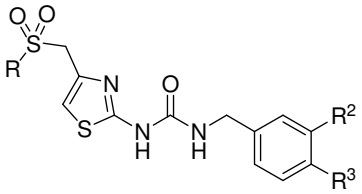


A mixture of **3.3** (1 eq), the corresponding thiophenol or benzyl thiole (2 eq), Cs_2CO_3 (2.2 eq) and NaI (0.2 eq) was stirred at reflux temperature for 2-16 hours. The reaction mixture was filtered through Celite and the crude products **3.6** were purified by column chromatography (CH_2Cl_2/methanol or EtOAc/heptane).

General procedures for the oxidation towards the sulfoxymethyl thiazol-2-yl urea derivatives (3.7) and sulfonylmethyl thiazol-2-yl urea derivatives (3.8).



3.7



3.8

Method E: *m-CPBA*

To a mixture of the thiomethyl thiazol-2-yl urea derivatives **3.6** (1 eq) in EtOAc at 0 °C was added *m*-CPBA (3 eq). The mixture was stirred overnight at room temperature. Saturated aqueous $NaHCO_3$ was added and the layers were separated. The organic layer was washed with brine and dried over Na_2SO_4. Removal of the volatiles *in vacuo* afforded the crude products **3.7** or **3.8** which were purified by column chromatography (CH_2Cl_2/ 1-10 % 7N NH_3 in methanol).

Method F: *Oxone*

A solution of the thiomethyl thiazol-2-yl urea derivatives **3.6** (1 eq) in ethanol (ca. 0.05 M) was treated with a solution of oxone (2.2 eq) in water (ca. 0.25 M). The mixture was stirred for 1 hour at room temperature. Water was added and the mixture was extracted with EtOAc/tetrahydrofuran (1/1). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude products **3.7** or **3.8** were purified by column chromatography (CH_2Cl_2/ 1-10 % 7N NH_3 in methanol).

3.6 Notes and references

[1] Hantzch, A. *Justus Liebigs Ann. Chem* . **1889**, *250*, 265

[2] Sprague, J.M.; Land, A.H.; Ziegler, C. *J. Am. Chem. Soc.* **1946**, *68*, 2155

[3] US Patent 2002/45615

[4] Closier, M.D.; Islip, P.J. *J. Med. Chem.* **1970**, *13*, 638

[5] US Patent 2006/154975

[6] WO Patent 2008/73461

[7] WO Patent 2007/87427

[8] US Patent 1993/5256675

[9] Rozman, E.; Galcerán, M.T.; Anglada, L.; Albet, C. *Journal of Pharmaceutical Sciences* **1994**, *83*, 2, 252

[10] Yoshida, Y.; Barrett, D.; Azami, H.; Morinaga, C.; Matsumoto, S.; Matsumoto, Y.; Takasugi, H. *Bioorg. and Med. Chem.* **1999**, *7*, 11, 2647

[11] WO Patent 2007/6760

[12] March, J. In *Advanced Organic Chemistry, reactions, mechanisms and structure*, third edition, Ed.; Wiley & Sons: New York, **1985**, p 1089-1090

[13] March, J. In *Advanced Organic Chemistry, reactions, mechanisms and structure*, third edition, Ed.; Wiley & Sons: New York, **1985**. This book was used for reaction mechanisms throughout the whole graduation assignment.

[14] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. In *Organic chemistry*, Ed.; Oxford University Press Inc.: New York, **2001**. This book was used for reaction mechanisms throughout the whole graduation assignment.

[15] Vollhardt, K.P.C., Schore, N.E. In *Organic chemistry*, fourth edition, Ed.; W.H. Freeman and Company: New York, **2002**. This book was used for reaction mechanisms throughout the whole graduation assignment.

[16] Wuts, P.G.M., Greene, T.W. In *Green's protective groups in organic synthesis*, fourth edition, Ed.; Wiley & Sons: New York, **2007**. This book was used for reaction mechanisms, throughout the whole graduation assignment.

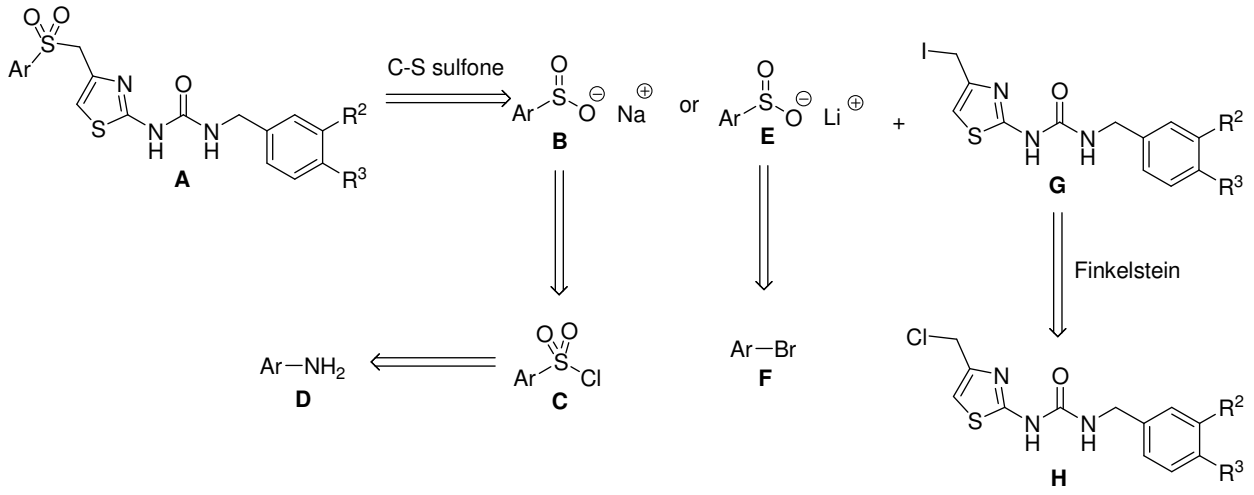
Chapter 4 Alternative strategy for the synthesis of the sulfonylmethyl thiazol-2-yl urea derivatives

4.1 Introduction

Initially, the sulfonylmethyl thiazol-2-yl urea derivatives were prepared *via* an alternative route as described in Chapter 3. The sulfonylmethyl thaizol-2-yl urea derivative was prepared by oxidation of the sulfide in the corresponding thiomethyl thiazol-2-yl urea derivative. However, this route has a major drawback. In some cases the reaction stops at the sulfoxymethyl thiazol-2-yl urea derivative stage. In other cases purification by column chromatography was needed to separate the sulfoxymethyl from the sulfonylmethyl thiazol-2-yl urea derivative.
The route depicted in Scheme 4.2 affords the sulfonylmethyl thiazol-2-yl urea derivative exclusively.

4.2 Retrosynthetic analysis and strategy

The sulfonylmethyl thiazol-2-yl urea derivatives were analyzed retrosynthetically, and a possible synthetic route was developed. The retrosynthetic analysis and the synthetic route are depicted in Scheme 4.1 and 4.2 respectively.
The retrosynthetic analysis of the sulfonylmethyl thiazol-2-yl urea derivative **A**, translated into accessible starting materials, reveals two synthetic fragments, iodomethyl thiazol-2-yl urea derivative **G** and the corresponding sodium or lithium aryl sulfinates **B** and **E**. The iodomethyl thiazol-2-yl urea derivative **G** can be prepared from the chloromethyl thiazol-2-yl urea derivative **H**. The synthesis of the chloromethyl thiazol-2-yl urea derivatives is described in Chapter 3 Scheme 3.4. The lithium aryl sulfinates **E** or sodium aryl sulfinates **B** have to be prepared.

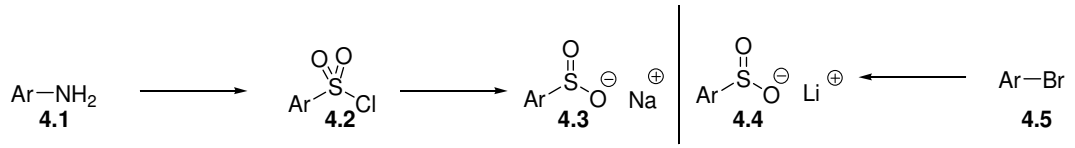


Scheme 4.1 *Retrosynthetic analysis of the sulfonylmethyl thiazol-2-yl urea derivatives*

The lithium aryl sulfinate **E** can be prepared from the corresponding bromide **F** *via* a bromo-lithium exchange and a sulfination.

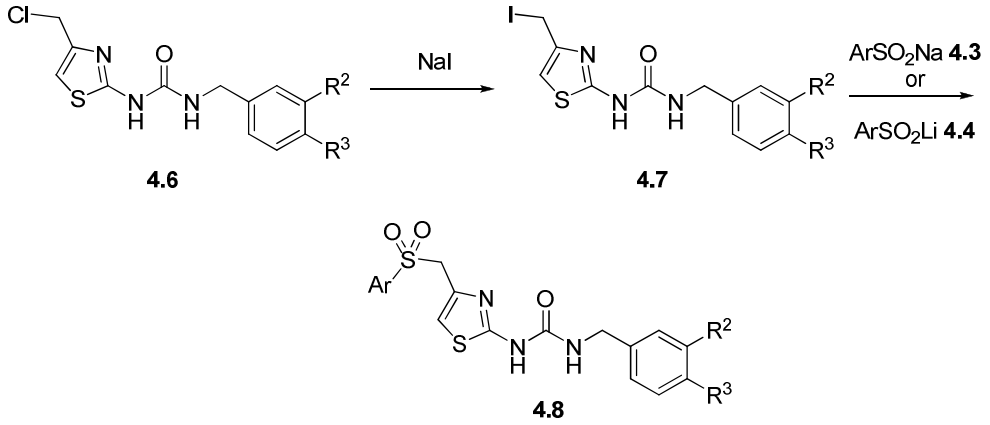
The sodium aryl sulfinate **B** can be prepared from the corresponding amine **D** after two functional group inversion steps. First, the aryl sulfinate **B** can be synthesized from the corresponding sulfonyl chloride **C**. The sulfonyl chloride **C** can be produced from the corresponding amine **D**.

The synthetic route that was developed after the retrosynthetic analysis is depicted in Scheme 4.2. The sodium aryl sulfinates can be synthesized in two steps from the corresponding amines. The lithium aryl sulfinates can be prepared in one step from the corresponding bromides.



Scheme 4.2 *Synthesis of the sodium or lithium aryl sulfinates*

The synthetic route that was developed after the retrosynthetic analysis is depicted in Scheme 4.3. The synthesis of the sulfonylmethyl thiazol-2-yl urea derivatives consists of two steps.



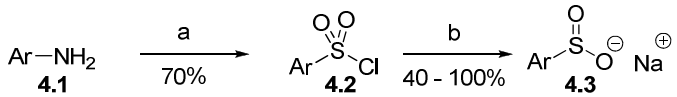
Scheme 4.3 *Second route towards the sulfonylmethyl thiazol-2-yl urea derivatives*

In the next subchapter the synthesis of the sulfonylmethyl thiazol-2-yl urea derivatives **4.8** will be thoroughly described. First, the synthesis of the iodomethyl thiazol-2-yl urea derivatives **4.7** will be discussed, followed by the synthesis of the sodium or lithium aryl sulfinates **4.3** or **4.4**. Finally, the synthesis of the sulfonylmethyl thiazol-2-yl urea derivatives **4.8** is described.

4.3 Synthesis

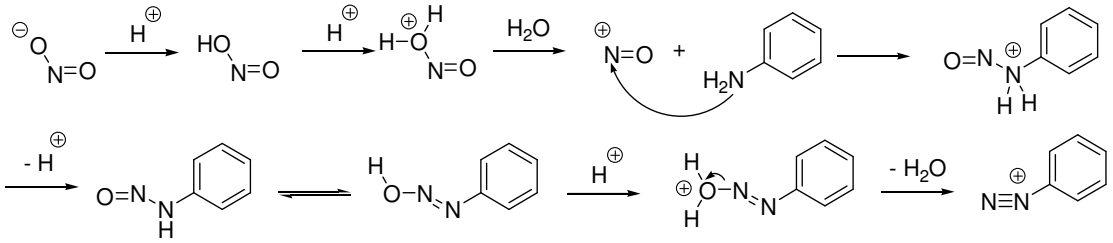
4.3.1 Preparation of the sodium or lithium aryl sulfinates

The sodium aryl sulfinates **4.3** were prepared from the corresponding amines **4.1** in two steps in an average overall yield of 28-70%.



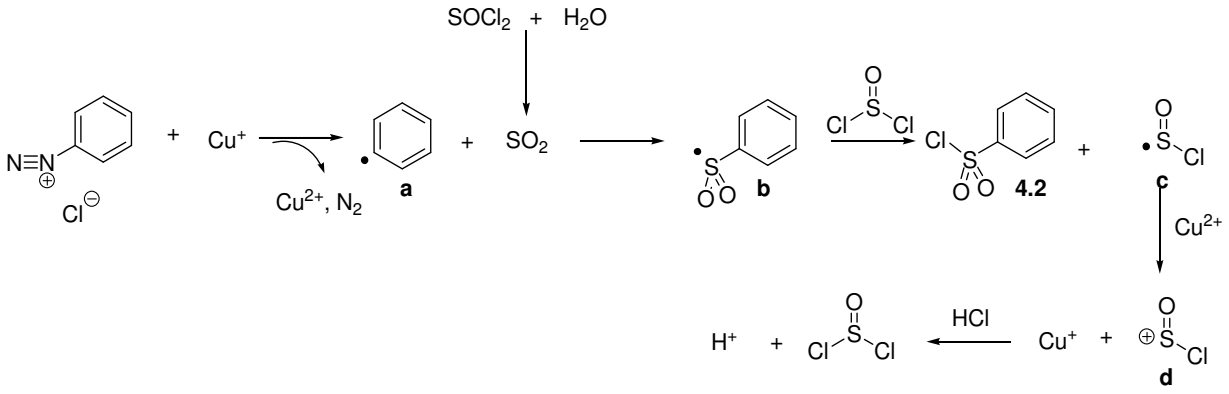
Scheme 4.3 *Reagents and conditions: (a) $NaNO_2$, HCl, H_2O, -5°C; $SOCl_2$, CuCl, H_2O, RT, 1 hour; (b) Na_2SO_3, Na_2CO_3, H_2O, reflux temperature, 18 hours.*

The first step is the treatment of the amines **4.1** with $NaNO_2$, $SOCl_2$ and CuCl to form the corresponding sulfonyl chloride **4.2**. This first step actually consist of two reactions: a diazotization[1] and a Sandmeyer-type[2] reaction. The mechanisms of the diazotization reaction is depicted in Scheme 4.4.



Scheme 4.4 *Mechanism of the diazotization reaction*

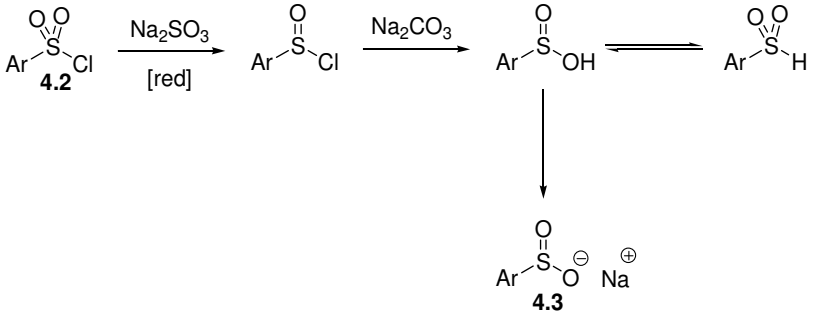
The nitrite anion is protonated by hydrochloric acid and after the elimination of water affords the NO^+ particle. The lone pair of the nitrogen from the aryl amine attacks the nitrogen of the NO^+ particle. After deprotonation, a proton-shift, protonation and the elimination of water the diazonium salt was formed.
The mechanism of the Sandmeyer-type reaction is depicted in Scheme 4.5. Thionyl chloride is the sulfur dioxide source in this reaction.



Scheme 4.5 *Mechanism of the Sandmeyer-type reaction*

Under influence of copper(I) nitrogen eliminates and forms the aryl-radical **a** and copper(II).[3] This is a Single Electron Transfer reaction. The aryl-radical **a** reacts with the sulfur dioxide, affording the aryl sulfonyl radical **b** which abstracts a chloride from thionyl chloride and forming the radical **c**. Copper(II) oxidizes the radical **c** to the sulfonyl anion **d** and forms copper(I). Finally, HCl reacts with the sulfonyl anion **d** and affords thionyl chloride.

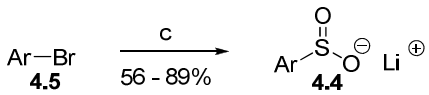
A proposed mechanism of the last step, the formation of the sodium aryl sulfinate **4.3**, is depicted in Scheme 4.6.



Scheme 4.6 *Mechanism of the formation of the sodium aryl sulfinates*

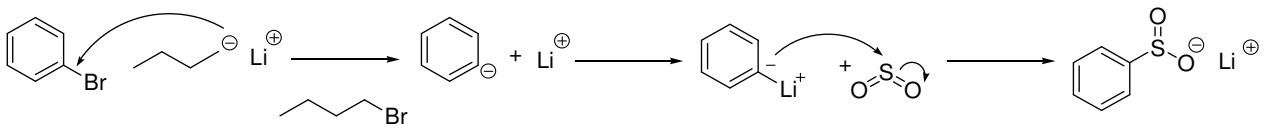
First, the sulfonyl chloride was reduced by sodiumsulfite and hydrolyzed after the addition of sodium carbonate. The sulfinic acid is in equilibrium with the tetra-valent sulfur form and hexa-valent sulfur form.[4] Finally, the sodium salt was fromed.

The lithium aryl sulfinates **4.4** were prepared in one step from the corresponding bromides **4.5** in an average yield of 56-89%.



Scheme 4.7 *Reagents and conditions: (c) n-BuLi, SO_2, THF, -78°C - RT*

The first step is a bromo-lithium exchange using *n*-BuLi, forming the aryl-lithium compounds.[5] The second step is the reaction between the aryl-lithium compound and gaseous sulfur dioxide to afford the lithium aryl sulfinate.
The mechanism of the bromo-lithium exchange and the SO_2-insertion is depicted in Scheme 4.8.

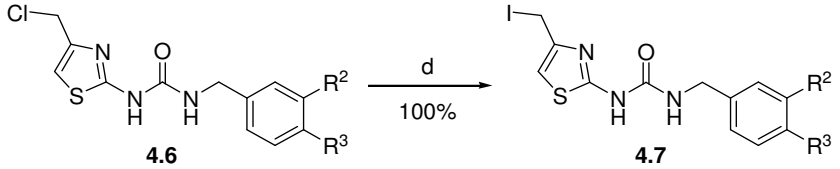


Scheme 4.8 *Mechanism of the bromo-lithium exchange and the SO_2-insertion*

The *n*-butyl carbanion exchange with the bromide on the aryl ring, forming the anion. An SO_2-insertion takes place by an attack of the carbon on the sulfur, forming the lithium aryl sulfinate.

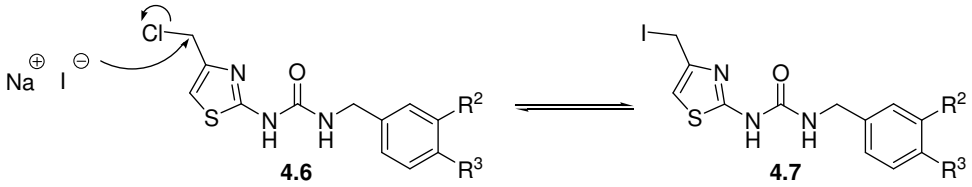
4.3.2 Preparation of the iodomethyl thiazol-2-yl urea derivatives

The iodomethyl thiazol-2-yl urea derivatives **4.7** could be prepared in one step from the common intermediate, chloromethyl thiazol-2-yl urea derivatives **4.6**, in quantitative yield. The preparation of the chloromethyl thiazol-2yl urea derivatives has been described in the previous chapter in two steps from thiourea in an overall yield of 47%.



Scheme 4.8 *Reagents and conditions: (d) NaI, acetone, RT, 2 hours*

The chloromethyl thiazol-2-yl urea derivatives **4.6** were allowed to react with NaI in acetone. This reaction is called a Finkelstein reaction.[6] The mechanism of the reaction is depicted in Scheme 4.9.

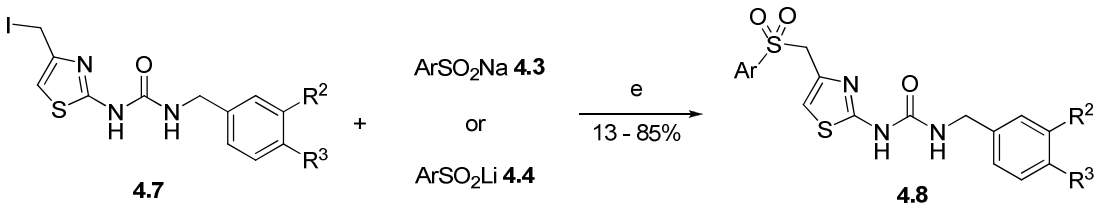


Scheme 4.9 *Mechanism of the Finkelstein reaction*

The Finkelstein reaction is a S_N2 reaction that involves the exchange of one halogen atom for another and is actually an equilibrium. However, the reaction can be driven to completion by taking the advantage of the solubility of the halide salts, or by using a large excess of the halide salt.
The iodide attacks the carbon of the chloromethyl-functionality and the chloride eliminates. In this case, 10 equivalents of NaI were used. Sodium iodide is soluble in acetone and the formed sodium chloride is not. The equilibrium is shifted to the right by excess NaI and by the precipitation of the insoluble salt.

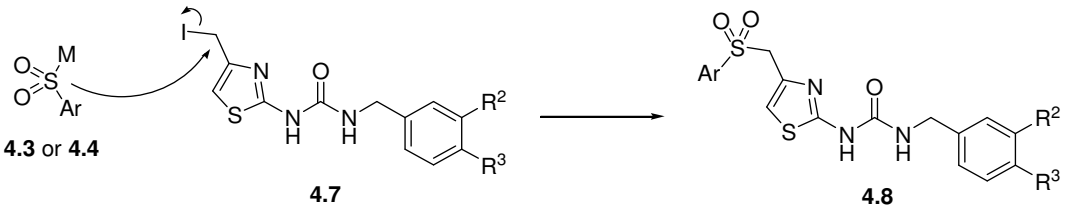
4.3.3 Preparation of the sulfonylmethyl thiazol-2-yl urea derivatives

The sulfonylmethyl thiazol-2-yl urea derivatives **4.8** can be prepared the iodomethyl thiazol-2-yl urea derivatives **4.7** in an average yield of 13-85%.



Scheme 4.10 *Reagents and conditions: (e) DMF, RT, 1-18 hours*

The iodomethyl thiazol-2-yl urea derivatives **4.7** were coupled with the corresponding sodium aryl sulfinates **4.3** or lithium aryl sulfinates **4.4** in DMF.[7]
The mechanism of the coupling is depicted in Scheme 4.11.



Scheme 4.11 *Mechanism of the coupling iodomethyl thiazol-2-yl urea derivatives*

The aryl sulfinates react with the iodomethyl thiazol-2-yl urea derivatives in the hexa-valent sulfur form. The electronegative sulfur of the aryl sulfinate attacks the carbon of the iodomethyl-functionality. The iodide eliminates and the sulfonylmethyl thiazol-2-yl urea derivative is formed.

4.4 Discussion and conclusions

The sulfonylmethyl thiazol-2-yl urea derivatives **4.8** could be prepared in four steps from thiourea in 6-40% overall yield.
The sodium aryl sulfinates could be prepared in one or two steps from the corresponding amine or sulfonyl chlorides in 40-100% overall yield depending on the commercial availability of the sulfonyl chlorides.
The details of the synthesis of the aryl sulfinates (**4.3a-e** and **4.4a-c**) and the sulfonylmethyl thiazol-2-yl urea derivatives **4.8a-g** are described in Appendix G and H, respectively.
The synthetic strategy described in this chapter to prepare the sulfonylmethyl thiazol-2-yl urea derivatives **4.8** by coupling the iodomethyl thiazol-2-yl urea derivatives with the sodium or lithium aryl sulfinates has an advantage and a disadvantage compared to the synthetic strategy described in Chapter 3. Both strategies consist of four steps. However, the overall yield is higher (Chapter 3; overall yield is <1-24%). The sodium and lithium aryl sulfinates are not commercially available and need to be prepared, which is a drawback of this strategy. Then the strategy using the sodium or lithium aryl sulfinates consists of one or two more steps and the overall yield will decrease.
As also described in Chapter 2 and 3 (section 2.4 and 3.4), the goal of this project was to synthesize a library of thiazol-2-yl urea derivative for Replidyne Inc. which could be tested for their antibacterial activity. Therefore, the intent was to synthesize a lot of derivatives and not to optimize the yield of the synthetic route. When Replidyne Inc. would have found a derivative with an excellent antibacterial activity, the next step would be to optimize the synthetic route.
In this study, the products were isolated in moderate yield, possibly these reactions can be optimized. For example, the coupling of the iodomethyl thiazol-2-yl urea derivatives **4.7** with the corresponding sodium- **4.3** or lithium aryl sulfinates **4.4** leaves a lot of possibilities for improvement.

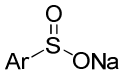
4.5 Experimental section

General remarks.
All the chemicals were purchased from Acros, Fluka or Aldrich and used without purification. ^{1}H-NMR spectra were recorded on a Varian 300 MHz spectrometer at room temperature. Chemical shifts are reported in ppm referenced to the residual solvent signal. Silica gel 60 was used for flash column chromatography and silica gel 60F_{254} plates (0.25 mm, Merck) were used for TLC.

General procedure for the synthesis of the sulfonyl chlorides (4.2)

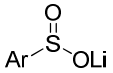
$SOCl_2$ (3.7 eq) was slowly added to cooled (<5°C) H_2O, while keeping the temperature below 5°C. The mixture was allowed to warm to room temperature, subsequently CuCl (6 mol%) was added and cooled to -5°C. A solution of $NaNO_2$ (1.1 eq) in H_2O was slowly added to a cooled (-5°C) solution of the amine **4.1** in concentrated HCl, keeping the temperature below 0°C. This mixture was added at once to the mixture of $SOCl_2$/H_2O/CuCl. The resulting mixture was stirred for 1 hour at room temperature, after 30 minutes a precipitate formed. The solids were collected by filtration, dissolved in EtOAc and washed with brine. The organic layer was dried over $MgSO_4$ and the removal of the volatiles *in vacuo* afforded the sulfonyl chlorides **4.2**.

General procedure for the synthesis of the sodium aryl sulfinates (4.3)



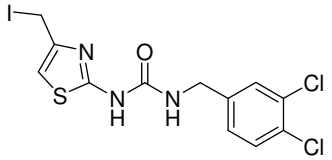
To a solution of **4.2** in acetone was added a solution of Na_2SO_3 (2 eq) in H_2O. The reaction mixture was heated to 80°C and a solution of Na_2CO_3 (1.5 eq) in H_2O was added drop-wise. Subsequently, the mixture was stirred for 18 hours at reflux temperature. The volatiles were removed *in vacuo* and the residue was stirred at reflux in EtOH. Subsequently, the inorganics were removed by filtration and the removal of the volatiles afforded the sodium sulfinates **4.3**.

General procedure for the synthesis of the lithium aryl sulfinates (4.4)



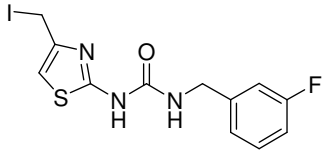
To a cooled (-78°C) solution of **4.5** in THF was added drop wise a 2.5N solution of *n*-BuLi (0.95 eq). The mixture was stirred for 15 minutes at -78°C. Subsquently, gaseous SO_2 was bubbled through the solution, resulting in the formation of a (gel-like) precipitate. The precipitate was isolated by filtration under N_2 and was washed with Et_2O and dried *in vacuo*. This afforded the lithium aryl sulfinates **4.4**.

1-(3,4-Dichlorobenzyl)-3-(4-(iodomethyl)thiazol-2-yl)urea (4.7)



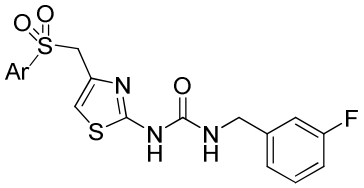
To a solution of 1-(3,4-dichlorobenzyl)-3-(4-(chloromethyl)thiazol-2-yl)urea **3.3** (1 eq) in acetone was added NaI (10 eq) at once. The mixture was stirred for 2 hours at room temperature. The volatiles were removed *in vacuo* and the mixture was taken up in water and EtOAc. The layers were separated and the organic phase was washed with water, brine and dried over Na_2SO_4. Removal of the volatiles *in vacuo* afforded 1-(3,4-dichlorobenzyl)-3-(4-(iodomethyl)thiazol-2-yl)urea **3.9** as a tan colored solid in near quantitative yield. ^{1}H-NMR (ppm, $CDCl_3$): 4.36 (s, 2H), 4.48 (d, 2H), 6.76 (s, 1H), 7.18 (dd, 1H), 7.41 (m, 2H), 9.56 (bs, 1H)

1-(3-Fluorobenzyl)-3-(4-(iodomethyl)thiazol-2-yl)urea (4.7)



Prepared in a similar manner as 1-(3,4-dichlorobenzyl)-3-(4-(iodomethyl)thiazol-2-yl)urea. ^{1}H-NMR (ppm, $CDCl_3$): 7.27 (m, 1H), 7.10 (m, 2H), 6.95 (t, 1H), 6.75 (s, 1H), 4.50 (d, 2H), 4.35 s, 2H)

General procedure for the synthesis of the sulfonylmethyl thiazol-2-yl urea derivatives (4.8)



To a solution of 1-(3-fluorobenzyl)-3-(4-(iodomethyl)thiazol-2-yl)urea **4.7** in DMF was added the sodium or lithium aryl sulfinate **4.3** or **4.4** and the mixture was stirred for 1-18 hours at room temperature. The mixture was diluted with H_2O and extracted with EtOAc. The organic layer was was with brine and dried over $MgSO_4$. The crude material was purified by crystallization from methanol or by column chromatography, affording **4.8**.

4.6 Notes and references

[1] Fahmy, S.M.; Mohared, R.M. *Tetrahedron* **1986**, *42*, 2, 687

[2] Hogan, P.J.; Cox, B.G. *Org. Process Res. Dev.*, **2009**, *13*, 5, 875

[3] Hanson, P.; Jones, J.R.; Taylor, A.B.; Walton, P.H.; Timms, A.W. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1135

[4] Gilman, H.; Fothergill, R.E. *J. Am. Chem. Soc.*, **1928**, *50*, 802

[5] Dodge, J.A.; Chamberlin, A.R. *Tetrahedron Letters* **1988**, *29*, 38, 4827

[6] Yoshida, Y.; Barrett, D.; Azami, H.; Morinaga, C.; Matsumoto, S.; Matsumoto, Y.; Takasugi, H. *Bioorg. and Med. Chem.* **1999**, *7*, 11, 2647

[7] March, J. In *Advanced Organic Chemistry, reactions, mechanisms and structure*, third edition, Ed.; Wiley & Sons: New York, **1985**. This book was used for reaction mechanisms throughout the whole graduation assignment.

[8] Wikipedia was used for general information

[9] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. In *Organic chemistry*, Ed.; Oxford University Press Inc.: New York, **2001**. This book was used for reaction mechanisms throughout the whole graduation assignment.

[10] Vollhardt, K.P.C., Schore, N.E. In *Organic chemistry*, fourth edition, Ed.; W.H. Freeman and Company: New York, **2002**. This book was used for reaction mechanisms throughout the whole graduation assignment.

[11] Wuts, P.G.M., Greene, T.W. In *Green's protective groups in organic synthesis*, fourth edition, Ed.; Wiley & Sons: New York, **2007**. This book was used for reaction mechanisms, throughout the whole graduation assignment.

Conclusions

In this research project the synthesis of a library of thiazol-2-yl urea derivatives (alkoxymethyl-, aminomethyl-, thiomethyl-, sulfoxymethyl and sulfonylmethyl thiazol-2-yl urea derivatives) has been described.

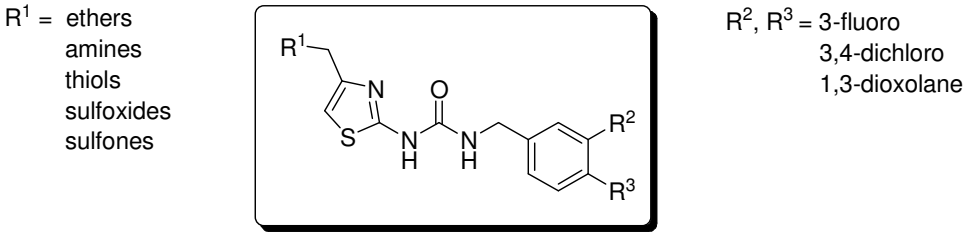
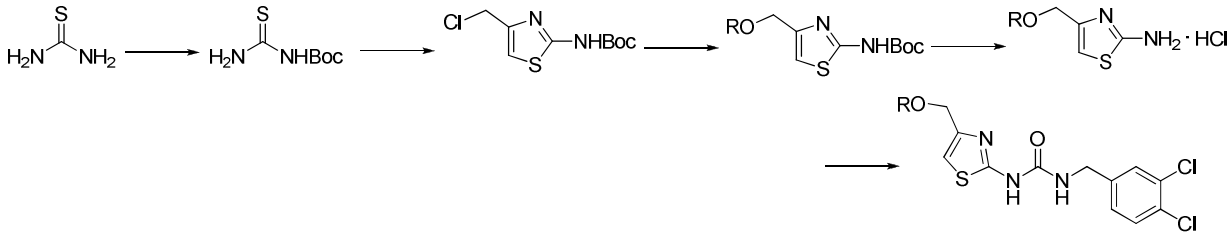
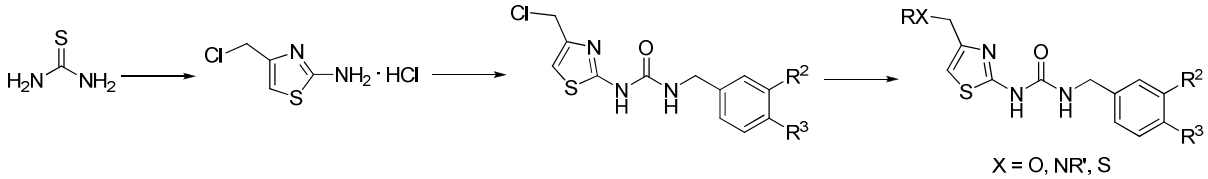


Figure 1 *Common structure of the thiazol-2-yl urea derivatives*

The synthesis of a variety of different 2-aminothiazole urea derivatives is known in the literature[1,2,3] and several synthetic pathways have been described. Also the antibacterial activity of these derivatives is described in literature[1,4].
Two different synthetic strategies, a five-step and a three-step strategy, were developed for the synthesis of the alkoxymethyl thiazol-2-yl urea derivatives.



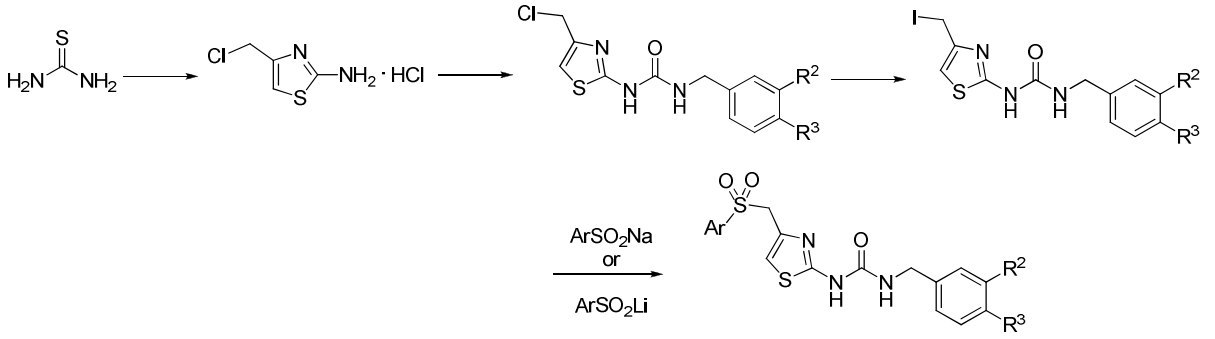
Scheme 1. *First synthetic strategy for the alkoxymethyl thiazol-2yl urea derivatives*



Scheme 2. *Second synthetic strategy for the alkoxymethyl thiazol-2-yl urea derivatives*

In contrast to the first strategy the second strategy uses a common intermediate from which the derivatives were prepared. The second strategy is preferred because the strategy is two steps shorter and the overall yield is higher. Another larger advantage is the ease of variation of the side chains compared to the first synthetic strategy.
The aminomethyl thiazol-2-yl urea derivatives and the thiomethyl thiazol-2-yl urea derivatives were prepared *via* the second synthetic strategy. The sulfoxymethyl thiazol-2-yl urea derivatives were synthesized by oxidation of the thiomethyl thiazol-2-yl urea derivatives.
The sulfonylmethyl thiazol-2-yl urea derivatives were prepared *via* the second synthetic strategy, coupling of the thiol to the common intermediate and subsequent oxidation of the

thiomethyl thiazol-2-yl urea derivatives. Also a variation to the second synthetic strategy to prepare to sulfonylmethyl thiazol-2-yl urea derivatives has been developed. This alternative strategy involves direct coupling of the common intermediate with the corresponding aryl sulfinate salts to form the sulfonylmethyl thiazol-2-yl urea derivatives.



Scheme 3. *A variation of the second synthetic strategy*

This alternative strategy has advantages and a disadvantage. In the same number of steps the sulfonylmethyl thiazol-2-yl urea derivatives were prepared in higher yields compared to the second synthetic strategy. The alternative strategy also allows the facile variation of the side chains. The aryl sulfinates used are not always commercially available and need to be synthesized in one or two steps. This increases the number of steps needed to prepare the sulfonylmethyl thiazol-2-yl urea, which is a disadvantage.

In this study, all strategies afforded the products in moderate yield, possibly the reactions can be optimized. However, it was not the goal of the research project for Replidyne Inc. to optimize the synthetic route. The goal was to synthesize easily a library of thiazol-2-yl urea derivatives.

The second synthetic strategy which was used to prepare all the different thizaol-2-yl urea derivatives is believed to be the best strategy. The strategy contains the least number of steps and makes use of commercially available reagents.

The thiazol-2-yl urea derivatives which were prepared during this research project, fitting the common structure as depicted in Figure 1, were tested at Replidyne Inc. The derivatives showed antibacterial activity against clinically relevant Gram-positive pathogens, including *S. pyogenes*, *S. aureus*, *S. pneumoniae* and *E. feacalis* [5].

Notes and references

[1] Kane, J.L.; Hirth, B.H.; Liang, B.; Gourlie, B.B.; Nahill, S.; Barsomian, G. *Bioorg. and Med. Chem. Letters.* **2003**, *13*, 4463

[2] Yonova, P.A.; Stoilkova, G.M. *J. Plant Growth Regul.* **2005**, *23*, 280-291

[3] Wiley, R.H; England, D.C.; Behr, L.C. In *Organic Reactions*; Adams, R., Ed.; Wiley & sons: New York, 1951; p 367

[4] Francisco, G.D.; Li, Z.; Albright, D.; Eudy, N.H.; Katz, A.H.; Petersen, P.J.; Labthavikul, P.; Singh, G.; Yang, Y.; Rasmussen, B.A.; Lin, Y.; Mansour, T.S. *Bioorg. and Med. Chem. Letters.* **2004**, *14*, 235

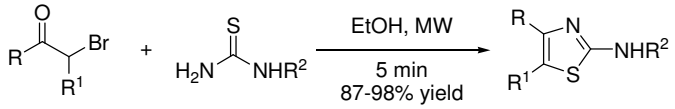
[5] Guiles, J.; Jarvis, T.; Strong, S.; Sun, X., U.S. Patent 2008/0207703 A1

Novel chemistry towards 2-aminothiazoles

After this research project a few novel synthetic approaches towards functionalized 2-aminothiazoles were described in literature. This chapter will briefly described these novel approaches. Maybe in the future, one of these new approaches could be a possible alternative for the method used in this research project. They all show good yields and different substituents could be introduced.

Microwave promoted synthesis of functionalized 2-aminothiazoles

Recently, the use of microwaves in organic chemistry gained in importance.[1] Under the influence of microwave irradiation α-bromoketones condensate with thiourea to afford functionalized 2-aminothiazoles within 5 minutes in excellent yield.[2]

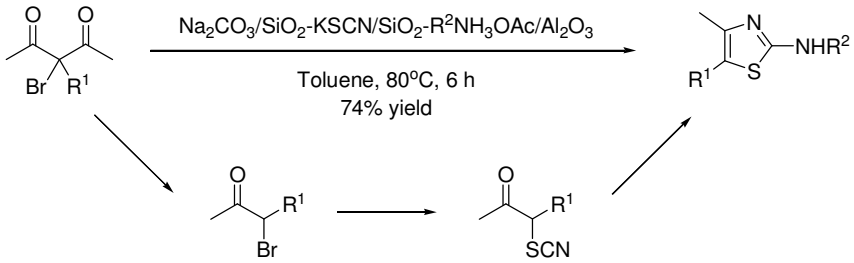


Scheme 1. *Synthesis of 2-(N-substituted)aminothiazoles*

The condensation of α-bromoketones with thiourea under influence of microwave irradiation provides an excellent route towards highly functionalized 2-aminothiazoles.

One-pot three-step reaction for the synthesis of 2-aminothiazoles

One-pot synthesis is very attractive in organic chemistry. It can carry out multi-step reaction or multiple reactions in one-pot. One-pot synthesis using inorganic solid-supported reagents is unique because, the different reaction stages are able to take places in the same vessel.[3] 3-Benzyl-3-bromopentane-2,4-dione was converted in three steps into 2-aminothiazoles derivatives.[4]



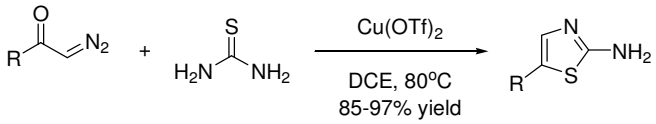
Scheme 2. *Synthesis of 2-(N-substituted)amino-4-methylthiazoles*

The first step is the deacetylation of 2-bromo-1,3-diketones affording α-bromoketones. Then the product was converted into α-thiocyanato ketones. The last step is the cyclization-amination to afford the 2-aminothiazole.

This approach using inorganic supported reagents systems affords highly efficient synthesis of 2-aminothiazles compaired to the step-wise method. All three reagents could be removed from the crude product by simple filtration.

Coupling of α-diazoketones with thiourea

The α-diazocarbonyl compounds are useful intermediates in organic synthesis due to their relative stability, facile decomposition under thermal, acid, base and transition metal catalysis conditions and ready availability.[5] The α-diazoketones were coupled with thiourea under mild conditions in the presence of 10 mol% $Cu(OTf)_2$ in dichloroethane.[6]



Scheme 3. *Synthesis of 2-aminothiazoles*

This method provides direct access to a wide range of 2-aminothiazoles from readily available diazoketones and thiourea. The method has also other advantages; mild reaction conditions, high conversions, short reaction times, high selectivity and cleaner reactions.

Notes and references

[1] Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9925

[2] Kabalka, G.W.; Mereddy, A.R. *Tetrahedron Letters* **2006**, *47*, 5171

[3] Aoyama, T.; Takido, T.; Kodomari, M. *Tetrahedron Letters* **2004**, 45, 1873

[4] Aoyama, T.; Murata, S.; Takido, T.; Kodomari, M. *Tetrahedron* **2007**, *63*, 11933

[5] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds from Cyclopropanes to Ylides*, Ed.; Wiley Inter-Science: New York, **1998**

[6] Yadav, J.S.; Subba Reddy, B.V.; Gopala Rao, Y.; Narsaiak, A.V. *Tetrahedron Letters* **2008**, *49*, 2381

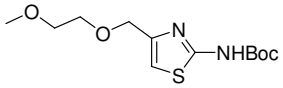
Acknowledgement

At the close of this research project, I would like to express my thanks to all of those who have provided help and support during the last 4 years.
First of all, I would like to thank Replidyne, Syncom and the Univerisity of Groningen for giving me the opportunity. I'm especially grateful to Professor Kellogg and Martijn Slagt for patiently reading and correcting my paper.
I would like to thank all my colleagues at Syncom, especially the co-workers on lab 4 and the members of the PV, for the great working atmosphere.
I also would like to send my sincere thanks to my parents, Johannes and Jacquelien, and brother, Henk, for all the support and just 'being there'.
Finally, I deeply thank Luck. You were always there to listen to me. Even when you didn't had a clue what I was talking about, you were there. Luck thanks for your endless love and for standing by me.

Angélique

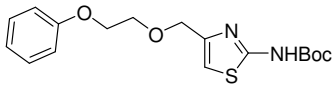
Appendix A *N*-Boc-4-(alkoxymethyl)thiazol-2-amine derivatives

tert-Butyl 4-((2-methoxyethoxy)methyl)thiazol-2-ylcarbamate 2.4a



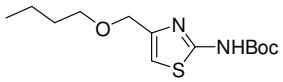
The product was prepared by applying method B and was isolated in 46% yield as a pale yellow oil. ^{1}H-NMR (ppm, $CDCl_3$): 1.56 (s, 9H), 3.39 (s, 3H), 3.54-3.58 (m, 2H), 3.64-3.69 (m, 2H), 4.58 (s, 2H), 6.82 (s, 1H)

tert-Butyl 4-((2-phenoxyethoxy)methyl)thiazol-2-ylcarbamate 2.4b



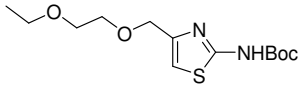
The product was prepared by applying method A and was isolated in 23% yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.40 (s, 9H), 3.68 (m, 2H), 3.95 (m, 2H), 6.78 (s, 1H), 6.93 (d, 2H), 6.98 (t, 1H), 7.30 (m, 2H)

tert-Butyl 4-(butoxymethyl)thiazol-2-ylcarbamate 2.4c



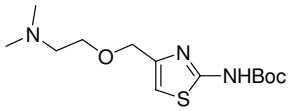
The product was prepared by applying method B and was isolated in quantitative yield. ^{1}H-NMR (ppm, $CDCl_3$): 0.80 (t, 3H), 1.40 (s, 9H), 1.10-1.50 (m, 4H), 3.24 (t, 2H), 4.28 (s, 2H), 6.55 (s, 1H)

tert-Butyl 4-((2-ethoxyethoxy)methyl)thiazol-2-ylcarbamate 2.4d



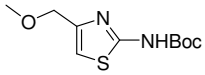
The product was prepared by applying method B and was isolated in 13% yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.20 (t, 3H), 1.50 (s, 9H), 3.45-3.58 (q, 2H), 4.58 (s, 2H), 6.80 (s, 1H)

tert-Butyl 4-((2-(dimethylamino)ethoxy)methyl)thiazol-2-ylcarbamate 2.4e



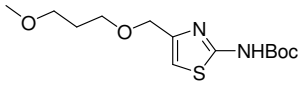
The product was prepared by applying method A and was isolated in 33% yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.55 (s, 9H), 2.25 (s, 6H), 2.58 (t, 2H), 3.61 (t, 2H), 4.50 (s, 2H), 6.80 (s, 1H)

tert-Butyl 4-(methoxymethyl)thiazol-2-ylcarbamate 2.4f



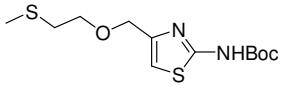
The product was prepared by applying method B and was isolated in 54% yield as a yellow oil. ^{1}H-NMR (ppm, $CDCl_3$): 1.54 (s, 9H), 3.43 (s, 3H), 4.46 (s, 2H), 6.79 (s, 1H)

tert-Butyl 4-((3-methoxypropoxy)methyl)thiazol-2-ylcarbamate 2.4g



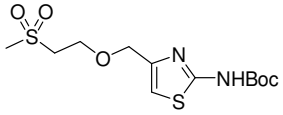
The product was prepared by applying method B and was isolated in quantitative yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.40 (s, 9H), 1.82 (m, 2H), 3.28 (s, 3H), 3.43 (m, 2H), 3.55 (m, 2H), 4.40 (s, 2H), 6.70 (s, 1H)

tert-Butyl 4-((2-(methylthio)ethoxy)methyl)thiazol-2-ylcarbamate 2.4h



The product was prepared by applying method A and was isolated in 49% yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.55 (s, 9H), 2.12 (s, 3H), 2.70 (t, 3H), 3.70 (t, 2H), 4.58 (s, 2H), 6.80 (s, 1H)

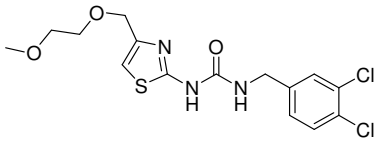
tert-Butyl 4-((2-(methylsulfonyl)ethoxy)methyl)thiazol-2-ylcarbamate 2.4i



To a solution of *tert*-Butyl 4-((2-(methylthio)ethoxy)methyl)thiazol-2-ylcarbamate (270 mg, 0.89 mmol) in dichloromethane (15 mL) was added *m*CPBA (2.0 eq, 1.82 mmol, 418 mg) and the mixture was stirred at room temperature for 1.5 hours. Aqueous saturated $NaHCO_3$ (20 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (10 mL) and the organic layer was dried over Na_2SO_4. Evaporation of the volatiles *in vacuo* afforded the crude material. This was purified by column chromatography (EtOAc/heptane 2/1), affording *tert*-butyl 4-((2-(methylsulfonyl)ethoxy)methyl)thiazol-2-ylcarbamate (270 mg, 0.80 mmol, 66%). ^{1}H-NMR (ppm, $CDCl_3$): 1.58 (s, 9H), 2.98 (s, 3H), 3.22 (t, 2H), 3.95 (t, 2H), 4.55 (s, 2H), 6.80 (s, 1H), 9.4 (bs, 1H)

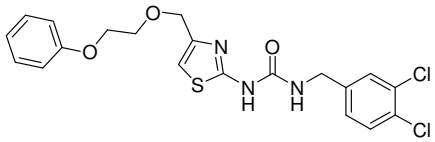
Appendix B Alkoxymethyl thiazol-2-yl urea derivatives

1-(3,4-Dichlorobenzyl)-3-(4-((2-methoxyethoxy)methyl)thiazol-2-yl)urea 2.6a



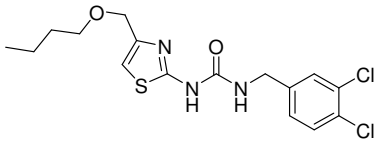
The product was isolated in 20% yield as a white solid. ^{1}H-NMR (ppm, $CDCl_3$): 3.21 (s, 3H), 3.36-3.40 (m, 2H), 3.47-3.50 (m, 2H), 4.41 (d, 2H), 4.47 (s, 2H), 6.74 (s, 1H), 7.20 (dd, 1H), 7.38 (d, 1H), 7.45 (d, 1H), 7.67 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-phenoxyethoxy)methyl)thiazol-2-yl)urea 2.6b



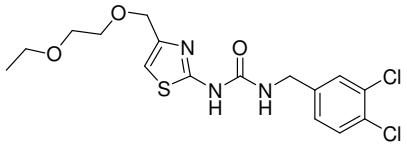
The product was also purified by preparative HPLC and isolated in 6% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.69 (m, 2H), 3.95 (m, 2H), 4.35 (d, 2H), 4.53 (s, 2H), 6.75 (m, 3H), 6.92 (t, 1H), 7.05 (d, 1H), 7.24 (m, 2H), 7.37 (s, 1H), 7.70 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-(butoxymethyl)thiazol-2-yl)urea 2.6c



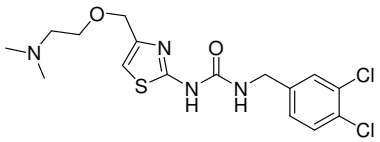
The product was also purified by preparative HPLC and isolated in 8% yield. ^{1}H-NMR (ppm, $CDCl_3$): 0.78 (t, 3H), 1.10-1.40 (m, 4H), 3.30 (t, 2H), 4.39 (s, 2H), 4.43 (s, 2H), 6.75 (s, 1H), 7.37 (s, 1H), 7.40 (d, 1H), 7.95 (bs, 1H), 11.50 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-ethoxyethoxy)methyl)thiazol-2-yl)urea 2.6d



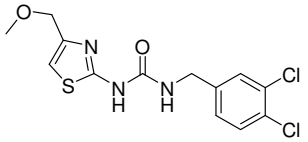
The product was also purified by preparative HPLC and isolated in 6% yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.12 (t, 3H), 3.32-3.54 (m, 6H), 4.45 (m, 4H), 6.75 (s, 1H), 7.20 (dd, 1H), 7.38 (d, 1H), 7.45 (d, 1H), 7.75 (bs, 1H), 11.30 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-(dimethylamino)ethoxy)methyl)thiazol-2-yl)urea 2.6e



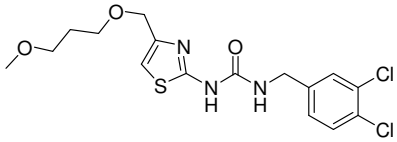
The product was also purified by preparative HPLC and isolated in 19% yield. ^{1}H-NMR (ppm, $CDCl_3$): 2.12 (s, 6H), 2.32 (t, 2H), 3.42 (t, 2H), 4.40 (m, 4H), 7.16 (dd, 1H), 7.35 (d, 1H), 7.42 (d, 1H), 7.78 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-(methoxymethyl)thiazol-2-yl)urea 2.6f



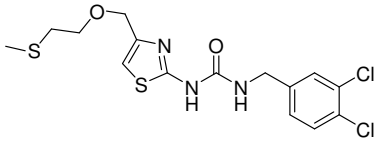
The product was also purified by preparative HPLC and isolated in 20% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.15 (s, 3H), 4.38-4.42 (m, 4H), 6.77 (s, 1H), 7.35-7.40 (m, 2H), 7.45 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((3-methoxypropoxy)methyl)thiazol-2-yl)urea 2.6g



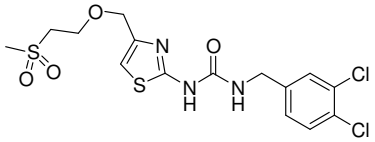
The product was also purified by preparative HPLC and isolated in 5% yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.67 (dt, 2H), 3.25 (s, 3H), 3.30 (t, 2H). 3.42 (s, 2H), 4.40 (s, 2H), 4.42 (s, 2H), 6.72 (s, 1H), 7.15 (d, 1H), 7.37 (s, 1H), 7.40 (d, 1H), 7.65 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-(methylthio)ethoxy)methyl)thiazol-2-yl)urea 2.6h



The product was also purified by preparative HPLC and isolated in 7% yield. ^{1}H-NMR (ppm, $CDCl_3$): 2.00 (s, 3H), 2.50 (t, 2H), 3.50 (t, 2H), 4.45 (s, 4H), 6.78 (s, 1H), 7.18 (dd, 1H), 7.40 (d, 1H), 7.45 (d, 1H), 7.62 (bs, 1H), 11.32 (bs, 1H)

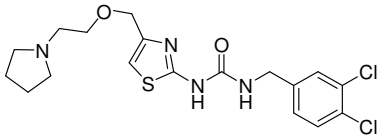
1-(3,4-dichlorobenzyl)-3-(4-((2-(methylsulfonyl)ethoxy)methyl)thiazol-2-yl)urea 2.6i



The product was purified by RP column chromatography (gradient water/methanol) and isolated in 18% yield. ^{1}H-NMR (ppm, $CDCl_3$): 2.95 (s, 3H), 3.22 (t, 2H), 3.95 (t, 2H), 4.42 (d, 2H), 4.50 (s, 2H), 6.75 (s, 1H), 7.15 (dd, 1H), 7.32-7.42 (m, 2H), 10.12 (bs, 1H)

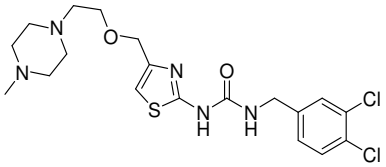
Appendix C Alkoxymethyl thiazol-2-yl urea derivatives

1-(3,4-Dichlorobenzyl)-3-(4-((2-(pyrrolidin-1-yl)ethoxy)methyl)thiazol-2-yl)urea 3.4a



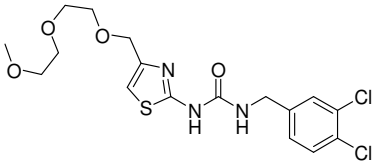
The product was further purified by preparative HPLC and isolated in 3% yield. ^{1}H-NMR (ppm, CD_3OD): 2.01 (bd, 4H), 3.07 (bs, 2H), 3.39 (t, H), 3.54 (bs, 2H), 3.77 (t, H), 4.40 (s, 2H), 4.52 (s, 2H), 6.96 (s, 1H), 7.26 (dd, 1H), 7.48 (dd, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-(4-methylpiperazin-1-yl)ethoxy)methyl)thiazol-2-yl)urea 3.4b



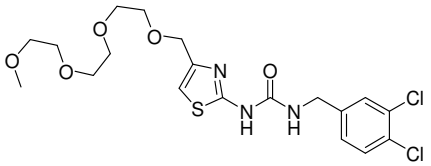
The product was isolated in 5% yield. ^{1}H-NMR (ppm, $CDCl_3$): 2.19 (s, 3H), 2.33 (bs, 4H), 2.37 (t, 2H), 3.42 (t, 2H), 4.40 (s, 2H), 4.41 (d, 2H), 6.72 (s, 1H), 7.17 (dd, 1H), 7.36 (d, 1H), 7.43 (d, 1H), 7.79 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-(2-methoxyethoxy)ethoxy)methyl)thiazol-2-yl)urea 3.4c



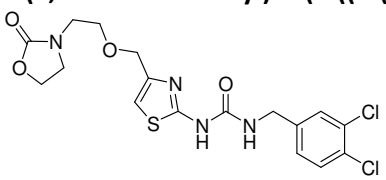
The product was isolated in 12% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.31 (s, 3H), 3.40 (m, 8H), 4.41 (d, 2H), 4.45 (s, 2H), 6.75 (s, 1H), 7.26 (dd, 1H), 7.37 (d, 1H), 7.44 (d, 1H), 7.68 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-(2-(2-methoxyethoxy)ethoxy)ethoxy)methyl)thiazol-2-yl)urea 3.4d



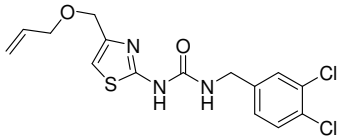
The product was further purified by preparative HPLC and isolated in 2% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.31 (s, 3H), 3.50 (m, 12H), 4.41 (d, 2H), 4.45 (s, 2H), 6.75 (s, 1H), 7.26 (dd, 1H), 7.37 (d, 1H), 7.44 (d, 1H), 7.68 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-(2-oxooxazolidin-3-yl)ethoxy)methyl)thiazol-2-yl)urea 3.4e



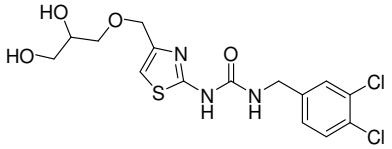
The product was isolated in 4% yield. ^{1}H-NMR (ppm, CD_3OD): 3.43 (t, 2H), 3.66 (m, 4H), 4.30 (dd, 2H), 4.40 (s, 2H), 4.46 (s, 2H), 6.88 (s, 1H), 7.25 (dd, 1H), 7.48 (d, 1H), 7.49 (s, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-(allyloxymethyl)thiazol-2-yl)urea 3.4f



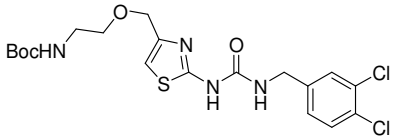
The product was isolated in 19% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.83 (d, 2H), 4.38 (d, 2H), 4.43 (s, 2H), 5.19 (m, 2H), 5.71 (m, 1H), 6.75 (s, 1H), 7.14 (dd, 1H), 7.37 (s, 1H), 7.38 (d, 1H), 7.57 (bs, 1H), 11.5 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2,3-dihydroxypropoxy)methyl)thiazol-2-yl)urea 3.4g



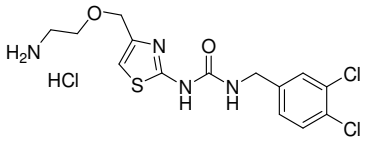
To a solution of **3.6f** (100 mg, 0.27 mmol) in a mixture of acetone/water 10/1 was added TMANO (1.5 eq, 0.40 mmol, 45 mg) and a OsO_4 solution (4% in water, 5.4 µmol, 0.34 ml). The mixture was stirred at room temperature for 3 hours and a saturated aqueous $NaHCO_3$ solution was added. The solution was extracted with EtOAc (2x) and the combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude product. The product was isolated as a white solid after purification in 23% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.50-3.62 (m, 4H), 3.86 (t, 1H), 4.33 (d, 2H), 4.38 (s, 2H), 6.62 (s, 1H), 7.05 (bs, 1H), 7.08 (d, 1H), 7.33 (d, 1H), 7.34 (s, 1H)

***tert*-Butyl 2-((2-(3-(3,4-dichlorobenzyl)ureido)thiazol-4-yl)methoxy)ethylcarbamate 3.4h**



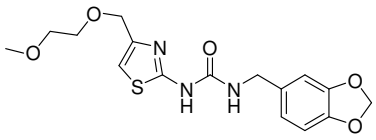
The product was isolated in 17% yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.40 (s, 9H), 3.20 (m, 2H), 3.43 (m, 2H), 4.42 (s, 2H), 4.45 (s, 2H), 4.60 (bs, 1H), 6.73 (s, 1H), 7.17 (d, 1H), 7.37 (s, 1H), 7.42 (d, 1H), 7.50 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-aminoethoxy)methyl)thiazol-2-yl)urea hydrochloride 3.4i



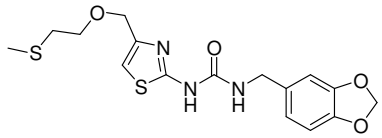
To a solution of **3.6h** (350 mg, mmol) in 1,4-dioxane (3 ml) was added 4N HCl in 1,4-dioxane (4 ml). The mixture was stirred at room temperature overnight and diethyl ether (5 ml) was added. The resulting solids were isolated by filtration and dried *in vacuo*, affording the product in 69% yield. ^{1}H-NMR (ppm, DMSO-d_6): 2.98 (m, 2H), 3.60 (m, 2H), 4.30 (d, 2H), 4.43 (s, 2H), 6.97 (s, 1H), 7.27 (d, 1H), 7.50 (s, 1H), 7.60 (d, 1H), 7.90 (bs, 2H), 10.85 (bs, 1H)

1-(Benzo[d][1,3]dioxol-5-ylmethyl)-3-(4-((2-methoxyethoxy)methyl)thiazol-2-yl)urea 3.4j



The product was further purified by preparative HPLC and isolated as a white solid in 13% yield. ^{1}H-NMR (ppm, CD_3OD): 3.30 (s, 3H), 3.51 (t, 2H), 3.54 (t, 2H), 4.11 (s, 2H), 4.25 (d, 2H), 6.07 (s, 2H), 6.48 (s, 1H), 6.76 (d, 1H), 6.81 (dd, 1H), 7.03 (s, 1H)

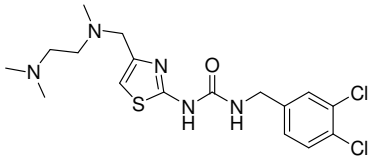
1-(Benzo[d][1,3]dioxol-5-ylmethyl)-3-(4-((2-(methylthio)ethoxy)methyl)thiazol-2-yl)urea 3.4k



The product isolated as an oil in 57% yield. ^{1}H-NMR (ppm, CD_3OD): 2.10 (s, 3H), 2.66 (t, 2H), 3.67 (t, 2H), 4.32 (s, 2H), 4.45 (s, 2H), 6.79 (m, 3H), 6.87 (s, 1H)

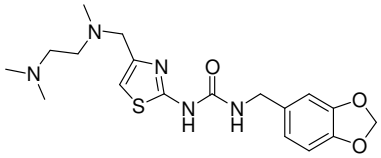
Appendix D Aminomethyl thiazol-2-yl urea derivatives

1-(3,4-Dichlorobenzyl)-3-(4-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)thiazol-2-yl)urea 3.5a



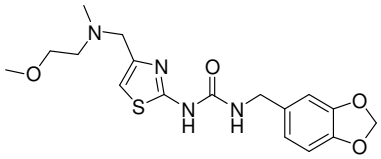
The product was prepared by applying method C and was isolated in 10% yield after further purification by making the HCl-salt. ^{1}H-NMR (ppm, CD_3OD): 2.94 (s, 3H), 2.99 (s, 6H), 3.67 (m, 4H), 4.40 (s, 2H), 4.42 (s, 2H), 7.26 (d, 2H), 7.27 (s, 1H), 7.48 (d, 2H), 7.50 (d, 1H)

1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(4-(((2-(dimethylamino)ethyl)(methyl)amino) methyl)thiazol-2-yl)urea 3.5b



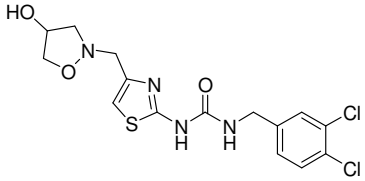
The product was prepared by applying method C and was further purified by preparative HPLC and was isolated in 5% yield. ^{1}H-NMR (ppm, CD_3OD): 2.21 (s, 6H), 2.27 (s, 3H), 2.50 (m, 2H), 2.52 (m, 2H), 3.52 (s, 2H), 4.32 (s, 2H), 5.91 (s, 2H), 6.77 (m, 3H), 6.82 (s, 1H)

1-(Benzo[d][1,3]dioxol-5-ylmethyl)-3-(4-(((2-methoxyethyl)(methyl)amino)methyl)thiazol-2-yl)urea 3.5c



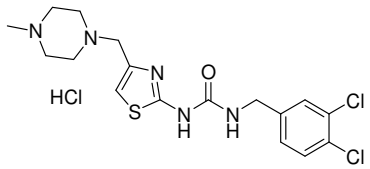
The product was prepared by applying method D and was further purified by preparative HPLC and was isolated in 3% yield. ^{1}H-NMR (ppm, CD_3OD): 3.34 (s, 3H), 3.50 (m, 2H), 3.63 (m, 2H), 4.32 (s, 2H), 4.46 (s, 2H), 5.91 (s, 2H), 6.78 (m, 3H), 6.81 (s, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-hydroxyisoxazolidin-2-yl)methyl)thiazol-2-yl)urea 3.5d



The product was prepared by applying method C and was further purified by preparative HPLC and was isolated in 1% yield. ^{1}H-NMR (ppm, CD_3OD): 2.72 (m, 2H), 3.68 (m, 3H), 3.81 (s, 2H), 4.25 (d, 2H), 6.48 (s, 1H), 7.20 (dd, 1H), 7.37 (s, 1H), 7.61 (d, 1H)

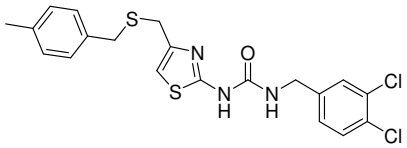
1-(3,4-Dichlorobenzyl)-3-(4-((4-methylpiperazin-1-yl)methyl)thiazol-2-yl)urea hydrochloride 3.5e



The product was prepared by applying method D and was further purified by preparing the HCl-salt (using 4N HCl in 1,4-dioxane) and was isolated in 30% yield. ^{1}H-NMR (ppm, DMSO-d_6): 2.80 (s, 3H), 3.35 (m, 4H), 3.60 (m, 4H), 4.28 (bs, 2H), 4.37 (d, 2H), 7.24 (s, 1H), 7.26 (d, 1H), 7.53 (s, 1H), 7.60 (d, 1H), 7.90 (bs, 1H), 10.90 (bs, 1H)

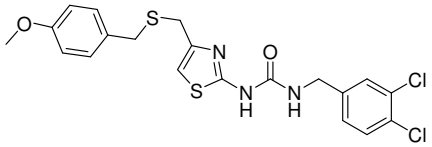
Appendix E Thiolmethyl thiazol-2-yl urea derivatives

1-(3,4-Dichlorobenzyl)-3-(4-((4-methylbenzyl)thiomethyl)thiazol-2-yl)urea 3.6a



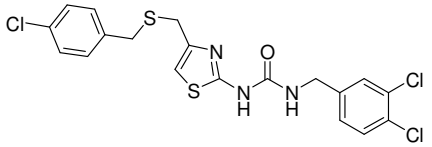
The product was isolated as an off-white solid in 37% yield. ^{1}H-NMR (ppm, CD_3OD): 2.29 (s, 3H), 3.54 (s, 2H), 3.65 (s, 2H), 4.41 (s, 2H), 6.68 (s, 1H), 7.11 (m, 4H), 7.27 (dd, 1H), 7.48 (s, 1H), 7.49 (d, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-methoxybenzylthio)methyl)thiazol-2-yl)urea 3.6b



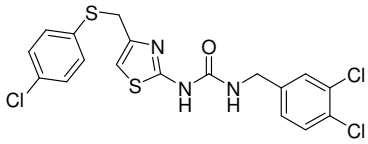
The product was isolated as a white solid in 23% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.56 (s, 2H), 3.59 (s, 2H), 3.78 (s, 3H), 4.42 (d, 2H), 6.53 (s, 1H), 6.80-6.83 (m, 2H), 7.10-7.18 (m, 3H), 7.33-7.39 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-chlorobenzylthio)methyl)thiazol-2-yl)urea 3.6c



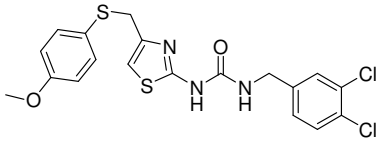
The product was isolated in a white solid in 33% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.56 (s, 2H), 3.59 (s, 2H), 4.44 (d, 2H), 6.52 (s, 1H), 7.11-7.20 (m, 3H), 7.23 (m, 2H), 7.34-7.40 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-chlorophenylthio)methyl)thiazol-2-yl)urea 3.6d



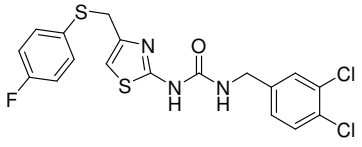
The product was isolated as a pale yellow solid in 59% yield. ^{1}H-NMR (ppm, $CDCl_3$): 4.02 (s, 2H), 4.40 (d, 2H), 6.46 (s, 1H), 7.10-7.13 (m, 1H), 7.19 (m, 4H), 7.35 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-methoxyphenylthio)methyl)thiazol-2-yl)urea 3.6e



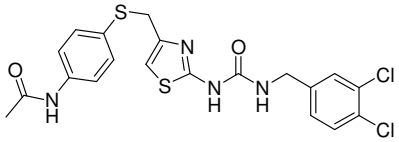
The product was isolated as a tan colored solid in 74% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.76 (s, 1H), 3.91 (s, 2H), 4.39 (d, 2H), 6.29 (s, 1H), 6.75-6.78 (m, 2H), 7.09-7.14 (m, 1H), 7.16-7.19 (m, 2H), 7.31-7.34 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-fluorophenylthio)methyl)thiazol-2-yl)urea 3.6f



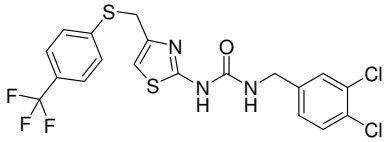
The product was isolated as a tan colored solid in 63% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.98 (s, 2H), 4.42 (s, 2H), 6.38 (s, 1H), 6.90-6.96 (m, 2H), 7.10-7.14 (m, 1H), 7.21-7.26 (m, 2H), 7.34-7.37 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-acetamidophenylthio)methyl)thiazol-2-yl)urea 3.6g



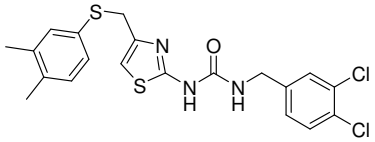
The product was isolated as a white solid in 74% yield. ^{1}H-NMR (ppm, CD_3OD): 2.09 (s, 3H), 4.02 (s, 2H), 4.39 (s, 2H), 6.57 (s, 1H), 7.23 (m, 2H), 7.47 (m, 3H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-(trifluoromethyl)phenylthio)methyl)thiazol-2-yl)urea 3.6h



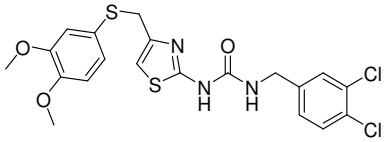
The product was isolated as an off-white solid in 89% yield. ^{1}H-NMR (ppm, CD_3OD): 4.19 (s, 2H), 4.37 (s, 2H), 6.77 (s, 1H), 7.21 (dd, 1H), 7.50 (m, 6H)

1-(3,4-Dichlorobenzyl)-3-(4-((3,4-dimethylphenylthio)methyl)thiazol-2-yl)urea 3.6i



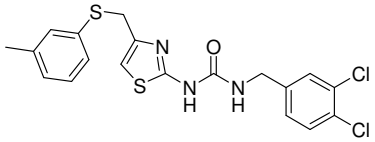
The product was isolated as a white solid in 82% yield. ^{1}H-NMR (ppm, CD_3OD): 2.17 (s, 3H), 2.19 (s, 3H), 4.00 (s, 2H), 4.37 (d, 2H), 6.42 (s, 1H), 6.99-7.04 (m, 1H), 7.07-7.10 (m, 1H), 7.31-7.34 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((3,4-dimethoxyphenylthio)methyl)thiazol-2-yl)urea 3.6j



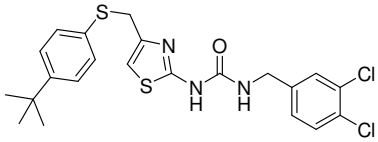
The product was isolated as a tan colored solid in 77% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.77 (s, 3H), 3.84 (s, 3H), 3.94 (s, 2H), 4.40 (d, 2H), 6.33 (s, 1H), 6.77-6.85 (m, 3H), 7.09 (m, 1H), 7.32-7.35 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-(*m*-tolylthiomethyl)thiazol-2-yl)urea 3.6k



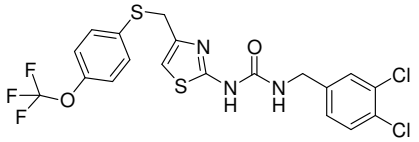
The product was isolated as a white solid in 67% yield. ^{1}H-NMR (ppm, $CDCl_3$): 2.27 (s, 3H), 4.05 (s, 2H), 4.37 (d, 2H), 6.47 (s, 1H), 6.99 (m, 1H), 7.08-7.24 (m, 4H), 7.32-7.35 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-tert-butylphenylthio)methyl)thiazol-2-yl)urea 3.6l



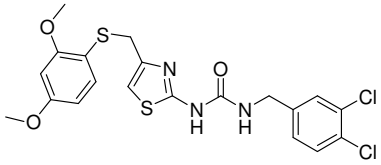
The product was isolated as a tan colored solid in 75% yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.28 (s, 9H), 4.03 (s, 2H), 4.38 (d, 2H), 6.46 (s, 1H), 7.08-7.12 (m, 1H), 7.18-7.26 (m, 2H), 7.27 (m, 2H), 7.32-7.35 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-(trifluoromethoxy)phenylthio)methyl)thiazol-2-yl)urea 3.6m



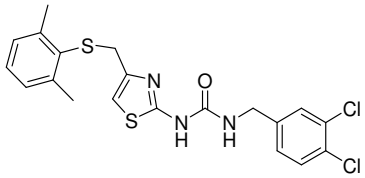
The product was isolated as a yellow semi-solid in 84% yield. ^{1}H-NMR (ppm, CD_3OD): 4.10 (s, 2H), 4.40 (s, 2H), 6.60 (s, 1H), 7.15 (d, 1H), 7.25 (d, 1H), 7.40 (m, 4H)

1-(3,4-Dichlorobenzyl)-3-(4-((2,4-dimethoxyphenylthio)methyl)thiazol-2-yl)urea 3.6n



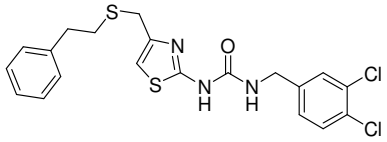
The product was isolated as a white solid in 72% yield. ^{1}H-NMR (ppm, CD_3OD): 3.61 (s, 1H), 3.81 (s, 3H), 3.86 (s, 2H), 4.37 (s, 2H), 6.15 (s, 1H), 6.35 (s, 1H), 6.41 (d, 1H), 7.04 (d, 1H), 7.18 (d, 1H), 7.25 (m, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2,6-dimethylphenylthio)methyl)thiazol-2-yl)urea 3.6o



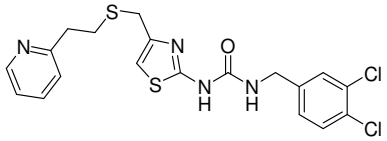
The product was isolated as a white solid in 79% yield. ^{1}H-NMR (ppm, CD_3OD): 2.40 (s, 6H), 3.80 (s, 2H), 4.40 (s, 2H), 6.20 (s, 1H), 7.05 (m, 3H), 7.25 (d, 1H), 7.50 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-(phenethylthiomethyl)thiazol-2-yl)urea 3.6p



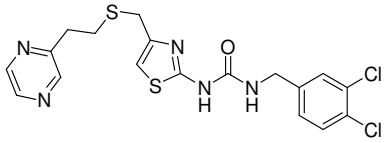
The product was isolated as a light yellow solid in 25% yield. ^{1}H-NMR (ppm, CD_3OD): 2.75 (m, 4H), 3.65 (s, 2H), 4.39 (s, 2H), 6.72 (s, 1H), 7.20 (m, 6H), 7.43 (s, 1H), 7.46 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-(pyridin-2-yl)ethylthio)methyl)thiazol-2-yl)urea 3.6q



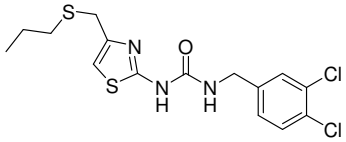
The product was isolated as a yellow oil in 28% yield. ^{1}H-NMR (ppm, CD_3OD): 2.80 (t, 2H), 3.00 (t, 2H), 3.60 (s, 2H), 4.40 (s, 2H), 6.80 (s, 1H), 7.20 (m, 4H), 7.40 (s, 1H), 7.50 (s, 1H), 7.70 (t, 1H), 8.40 (d, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-(pyrazin-2-yl)ethylthio)methyl)thiazol-2-yl)urea 3.6r



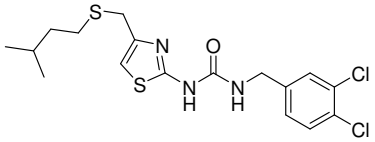
The product was isolated as an off-white solid in 30% yield. ^{1}H-NMR (ppm, CD_3OD): 2.89 (t, 2H), 3.04 (t, 2H), 3.68 (s, 2H), 4.40 (s, 2H), 6.76 (s, 1H), 7.24 (dd, 1H), 7.44 (s, 1H), 7.47 (s, 1H), 8.40 (d, 1H), 8.49 (s, 1H), 8.50 (d, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-(propylthiomethyl)thiazol-2-yl)urea 3.6s



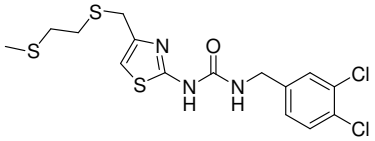
The product was isolated as an off-white solid in 67% yield. ^{1}H-NMR (ppm, CD_3OD): 0.95 (t, 3H), 1.57 (m, 2H), 2.45 (t, 2H), 3.65 (s, 2H), 4.41 (s, 2H), 6.73 (s, 1H), 7.26 (d, 1H), 7.48 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-(isopentylthiomethyl)thiazol-2-yl)urea 3.6t



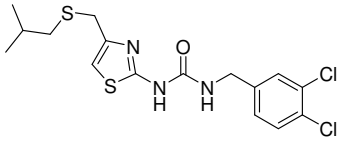
The product was isolated as a yellow solid in 38% yield. ^{1}H-NMR (ppm, CD_3OD): 0.87 (d, 6H), 1.42 (m, 2H), 1.63 (m, 1H), 2.48 (t, 2H), 3.65 (s, 2H), 4.41 (s, 2H), 6.74 (s, 1H), 7.25 (dd, 1H), 7.46 (s, 1H), 7.49 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-(methylthio)ethylthio)methyl)thiazol-2-yl)urea 3.6u



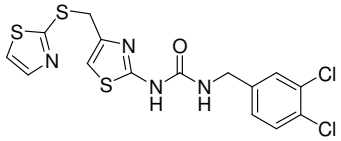
The product was isolated as a white solid in 63%. ^{1}H-NMR (ppm, CD_3OD): 2.09 (s, 3H), 2.65 (m, 4H), 3.71 (s, 2H), 4.47 (d, 2H), 6.61 (s, 1H), 7.19 (d, 1H), 7.43 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-(isobutylthiomethyl)thiazol-2-yl)urea 3.6v



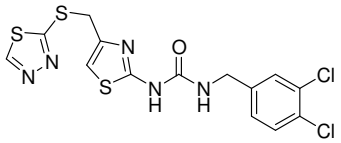
The product was isolated as a yellow oil in 31% yield. ^{1}H-NMR (ppm, CD_3OD): 0.90 (d, 6H), 1.70 (m, 1H), 2.40 (d, 2H), 3.60 (s, 2H), 4.40 (s, 2H), 6.70 (s, 1H), 7.00 (t, 1H), 7.05 (d, 1H), 7.15 (d, 1H), 7.35 (q, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((thiazol-2-ylthio)methyl)thiazol-2-yl)urea 3.6w



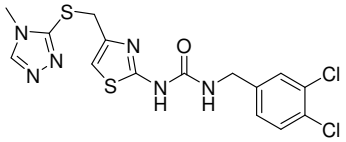
The product was isolated as a white solid in 40% yield. ^{1}H-NMR (ppm, $CDCl_3$): 2.40 (bs, 1H), 3.36 (s, 1H), 4.38 (d, 2H), 6.62 (s, 1H), 7.07 (d, 1H), 7.20 (d, 1H), 7.33 (m, 2H), 7.62 (d, 1H), 10.60 (bs, 1H)

1-(4-((1,3,4-Thiadiazol-2-ylthio)methyl)thiazol-2-yl)-3-(3,4-dichlorobenzyl)urea 3.6x



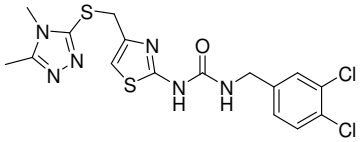
The product was isolated as a white solid in 34% yield. ^{1}H-NMR (ppm, CD_3OD): 4.30 (s, 2H), 4.40 (s, 2H), 6.70 (s, 1H), 7.10 (d, 1H), 7.35 (m, 2H), 9.00 (s, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-methyl-4H-1,2,4-triazol-3-ylthio)methyl)thiazol-2-yl)urea 3.6y



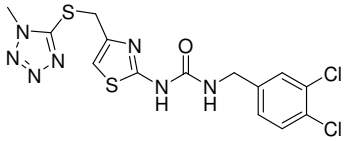
The product was isolated as a white solid in 61% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.40 (s, 3H), 4.20 (s, 2H), 4.40 (s, 2H), 6.60 (s, 1H), 7.10 (d, 1H), 7.35 (m, 2H), 8.10 (s, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((4,5-dimethyl-4H-1,2,4-triazol-3-ylthio)methyl)thiazol-2-yl)urea 3.6z



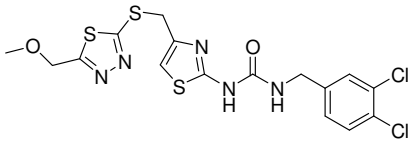
The product was isolated as a white solid in 42% yield. ^{1}H-NMR (ppm, CD_3OD): 2.39 (s, 3H), 3.41 (s, 3H), 4.17 (s, 2H), 4.88 (s, 2H), 6.65 (s, 1H), 7.25 (d, 1H), 7.48 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((1-methyl-1H-tetrazol-5-ylthio)methyl)thiazol-2-yl)urea 3.6aa



The product was isolated as a white solid in 53% yield. ^{1}H-NMR (ppm, DMSO-d_6): 3.86 (s, 3H), 4.29 (d, 2H), 4.41 (s, 2H), 6.87 (s, 1H), 7.20 (bt, 1H), 7.26 (d, 1H), 7.51 (s, 1H), 7.57 (d, 1H)

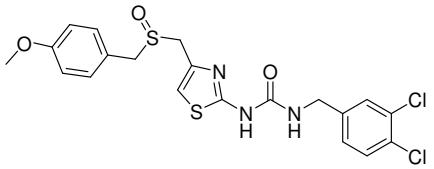
1-(3,4-Dichlorobenzyl)-3-(4-((5-(methoxymethyl)-1,3,4-thiadiazol-2-ylthio)methyl)thiazol-2-yl)urea 3.6ab



The product was isolated as a white solid in 47% yield. ^{1}H-NMR (ppm, CD_3OD): 3.42 (s, 3H), 4.40 (s, 2H), 4.47 (s, 2H), 4.76 (s, 2H), 6.90 (s, 1H), 7.25 (d, 1H), 7.48 (m, 2H)

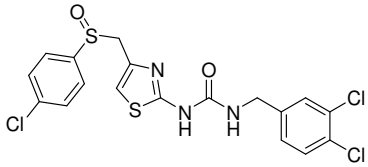
Appendix F Sulfoxymethyl thiazol-2-yl urea derivatives

1-(3,4-Dichlorobenzyl)-3-(4-((4-methoxybenzylsulfoxy)methyl)thiazol-2-yl)urea 3.7a



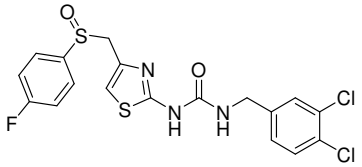
The product was prepared by applying method E and was isolated as an off-white solid in 40% yield. ^{1}H-NMR (ppm, DMSO-d_6): 3.73 (s, 3H), 3.80-4.16 (m, 6H), 4.30-4.32 (d, 2H), 6.90-6.92 (m, 3H), 7.18 (t, 1H), 7.24-7.27 (d, 2H), 7.52-7.58 (m, 2H), 10.81 (s, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-chlorophenylsulfoxy)methyl)thiazol-2-yl)urea 3.7b



The product was prepared by applying method E and was isolated as a yellow solid in 31% yield. ^{1}H-NMR (ppm, DMSO-d_6): 4.11 (s, 2H), 4.30 (d, 2H), 6.74 (s, 1H), 7.13 (t, 1H), 7.23-7.26 (d, 1H), 7.49-7.62 (m, 6H), 10.77 (s, 1H)

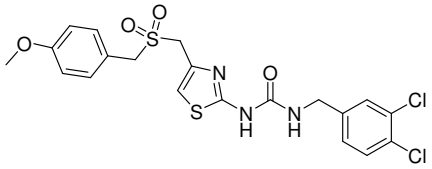
1-(3,4-Dichlorobenzyl)-3-(4-((4-fluorophenylsulfoxy)methyl)thiazol-2-yl)urea 3.7c



The product was prepared by applying method E and was isolated as a yellow solid in 42% yield. ^{1}H-NMR (ppm, $CDCl_3$): 4.10 (s, 2H), 4.41 (d, 2H), 6.27 (s, 1H), 7.14-7.19 (m, 4H), 7.37 (d, 1H), 7.41-7.45 (m, 3H), 10.17 (s, 1H)

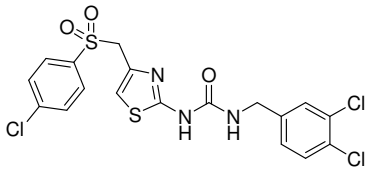
Appendix G Sulfonylmethyl thiazol-2-yl urea derivatives

1-(3,4-Dichlorobenzyl)-3-(4-((4-methoxybenzylsulfonyl)methyl)thiazol-2-yl)urea 3.8a



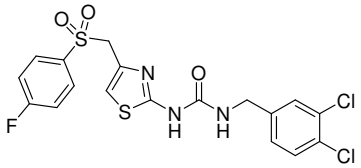
The product was prepared by applying method E and was isolated as a yellow solid in 21% yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.57 (s, 3H), 3.80 (s, 2H), 4.11 (s, 1H), 4.36 (d, 2H), 6.68 (s, 1H), 6.83-6.86 (d, 2H), 7.15-7.21 (m, 1H), 7.30-7.34 (m, 3H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-chlorophenylsulfonyl)methyl)thiazol-2-yl)urea 3.8b



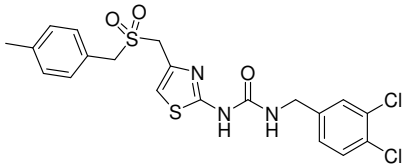
The product was prepared by applying method E and was isolated as a yellow solid in 35% yield. ^{1}H-NMR (ppm, $CDCl_3$): 4.38 (s, 2H), 4.40 (d, 2H), 6.47 (s, 1H), 7.15-7.18 (m, 1H), 7.35 (s, 1H), 7.38 (d, 1H), 7.46-7.49 (d, 2H), 7.61-7.64 (d, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-fluorophenylsulfonyl)methyl)thiazol-2-yl)urea 3.8c



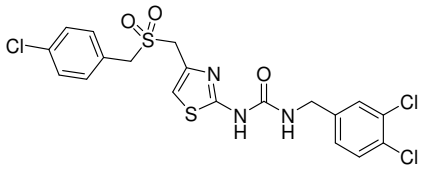
The product was prepared by applying method E and was isolated as a yellow solid in 11% yield. ^{1}H-NMR (ppm, $CDCl_3$): 4.36 (s, 2H), 4.42 (d, 2H), 6.44 (d, 2H), 7.14-7.18 (t, 3H), 7.36 (t, 2H), 7.67-7.71 (m, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-methylbenzyl)sulfonylmethyl)thiazol-2-yl)urea 3.8d



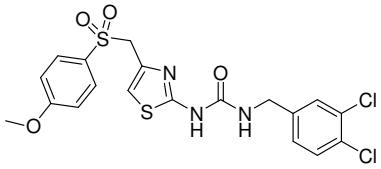
The product was prepared by applying method E and was isolated as an off-white solid in 13% yield. ^{1}H-NMR (ppm, $CDCl_3$): 2.29 (s, 3H), 3.30 (bs, 2H), 4.09 (s, 2H), 4.19 (s, 2H), 4.34 (s, 2H), 6.81 (s, 1H), 7.10 (m, 3H), 7.30 (m, 4H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-chlorobenzylsulfonyl)methyl)thiazol-2-yl)urea 3.8e



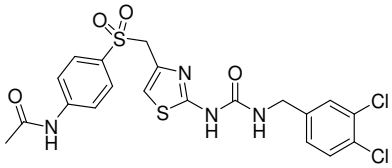
The product was prepared by applying method E and was isolated as a light yellow solid in 27% yield. ^{1}H-NMR (ppm, DMSO-d_6): 4.32 (s, 2H), 4.47 (s, 2H), 4.47 (d, 2H), 7.05 (s, 1H), 7.25-7.28 (d, 1H), 7.37-7.39 (d, 2H), 7.45-7.50 (m, 3H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-methoxyphenylsulfonyl)methyl)thiazol-2-yl)urea 3.8f



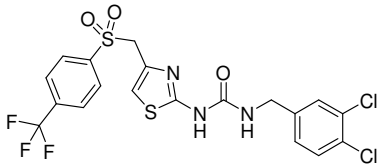
The product was prepared by applying method F and was isolated as a light brown foam in 49% yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.59 (s, 3H), 3.87 (s, 2H), 4.35 (s, 2H), 4.41-4.43 (d, 2H), 6.36 (s, 1H), 6.93-6.96 (d, 2H), 7.16 (d, 1H), 7.32-7.35 (d, 1H), 7.38 (s, 1H), 7.58-7.61 (d, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-acetamidophenylsulfonyl)methyl)thiazol-2-yl)urea 3.8g



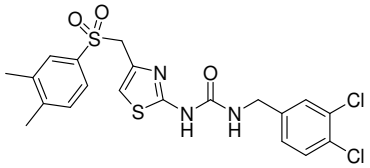
The product was prepared by applying method E and was isolated as a yellowish solid in 45% yield. ^{1}H-NMR (ppm, DMSO-d_6): 2.07 (s, 3H), 4.28 (d, 2H), 4.53 (s, 2H), 6.74 (s, 1H), 7.05 (bt, 1H), 7.25 (d, 1H), 7.51 (s, 1H), 7.56 (s, 1H), 7.60 (d, 2H), 7.73 (d, 2H), 10.30 (s, 1H), 10.75 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-(trifluoromethyl)phenylsulfonyl)methyl)thiazol-2-yl)urea 3.8h



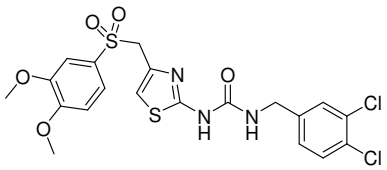
The product was prepared by applying method E and was isolated as a yellow foam in 29% yield. ^{1}H-NMR (ppm, CD_3OD): 4.37 (s, 2H), 4.59 (s, 2H), 6.84 (s, 1H), 7.23 (dd, 1H), 7.46 (m, 2H), 7.90 (m, 4H)

1-(3,4-Dichlorobenzyl)-3-(4-((3,4-dimethylphenylsulfonyl)methyl)thiazol-2-yl)urea 3.8i



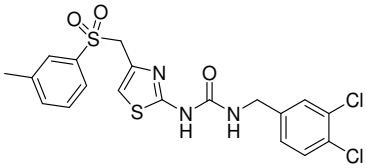
The product was prepared by applying method E and was isolated as a white solid in 45% yield. ^{1}H-NMR (ppm, CD_3OD): 2.29 (s, 3H), 2.32 (s, 3H), 4.38 (s, 1H), 4.47 (s, 2H), 6.76 (s, 1H), 7.25 (m, 2H), 7.45 (m, 4H)

1-(3,4-Dichlorobenzyl)-3-(4-((3,4-dimethoxyphenylsulfonyl)methyl)thiazol-2-yl)urea 3.8j



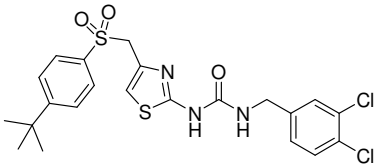
The product was prepared by applying method E and was isolated as a white solid in 56% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.85 (s, 3H), 3.95 (s, 2H), 4.37 (s, 2H), 4.44 (s, 2H), 6.40 (s, 1H). 6.91 (d, 1H), 7.11 (s, 1H), 7.19 (d, 1H), 7.27 (d, 1H), 7.36 (d, 1H), 7.43 (s, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-(*m*-tolylsulfonylmethyl)thiazol-2-yl)urea 3.8k



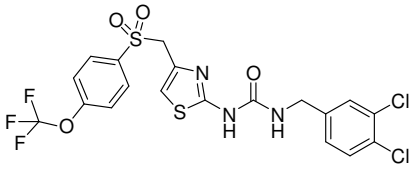
The product was prepared by applying method E and was isolated as a white solid in 37% yield. ^{1}H-NMR (ppm, $CDCl_3$): 2.39 (s, 3H), 4.36 (s, 2H), 4.41 (s, 2H), 6.41 (s, 1H), 7.17 (d, 1H), 7.26-7.52 (m, 6H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-tert-butylphenylsulfonyl)methyl)thiazol-2-yl)urea 3.8l



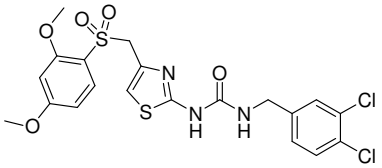
The product was prepared by applying method E and was isolated as a light yellow solid in 24% yield. ^{1}H-NMR (ppm, $CDCl_3$): 1.35 (s, 9H), 4.36 (s, 2H), 4.40 (d, 2H), 6.38 (s, 1H), 7.17 (d, 1H), 7.33 (d, 1H), 7.41 (s, 1H), 7.52 (d, 2H), 7.62 (s, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-((4-(trifluoromethoxy)phenylsulfonyl)methyl)thiazol-2-yl)urea 3.8m



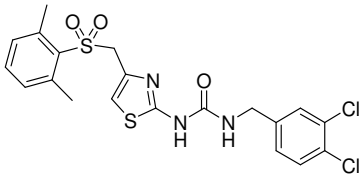
The product was prepared by applying method F and was isolated as a light yellow foam in 62% yield. ^{1}H-NMR (ppm, $CDCl_3$): 4.40 (s, 2H), 4.42 (d, 2H), 6.50 (s, 1H), 7.20 (dd, 1H), 7.40 (m, 4H), 7.81 (d, 2H), 10.50 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2,4-dimethoxyphenylsulfonyl)methyl)thiazol-2-yl)urea 3.8n



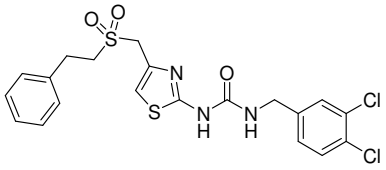
The product was prepared by applying method F and was isolated as a white solid in 53% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.87 (s, 3H), 3.89 (s, 3H), 4.38 (d, 2H), 4.58 (s, 2H), 6.47 (s, 1H), 6.48 (m, 2H), 7.15 (d, 1H), 7.30 (d, 1H), 7.42 (s, 1H), 7.58 (d, 1H), 10.60 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2,6-dimethylphenylsulfonyl)methyl)thiazol-2-yl)urea 3.8o



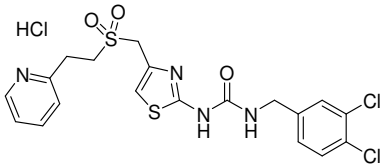
The product was prepared by applying method F, was further purified by preparative HPLC and was isolated as an off-white solid in 12% yield. ^{1}H-NMR (ppm, $CDCl_3$): 2.50 (s, 6H), 4.40 (s, 2H), 4.45 (d, 2H), 6.20 (bs, 1H), 7.10 (d, 2H), 7.25 (d, 1H), 7.40 (m, 2H), 7.48 (s, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-(phenethylsulfonylmethyl)thiazol-2-yl)urea 3.8p



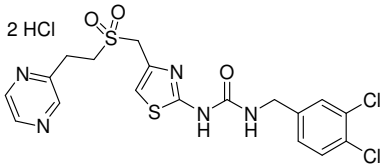
The product was prepared by applying method E and was isolated as an off-white solid in 39% yield. ^{1}H-NMR (ppm, CD_3OD): 3.08 (m, 2H), 3.40 (m, 2H), 4.39 (d, 4H), 7.04 (s, 1H), 7.23 (m, 6H), 7.44 (s, 1H), 7.47 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-(pyridin-2-yl)ethylsulfonyl)methyl)thiazol-2-yl)urea hydrochloride 3.8q



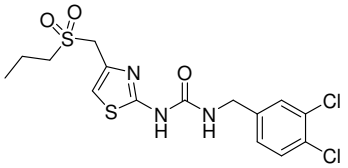
The product was prepared by applying method F, was further purified by preparative HPLC and by preparing the HCl-salt with 4N HCl in 1,4-dioxane and was isolated as a yellow solid in 3% yield. ^{1}H-NMR (ppm, CD_3OD): 3.65 (t, 2H), 3.80 (t, 2H), 4.40 (s, 2H), 4.55 (s, 2H), 7.15 (s, 1H), 7.30 (d, 1H), 7.45 (s, 1H), 7.50 (s, 1H), 8.00 (t, 1H), 8.15 (d, 1H), 8.40 (bs, 1H), 8.60 (t, 1H), 8.80 (d, 1H), 8.90 (bs, 1H)

1-(3,4-Dichlorobenzyl)-3-(4-((2-(pyrazin-2-yl)ethylsulfonyl)methyl)thiazol-2-yl)urea bis-hydrochloric salt 3.8r



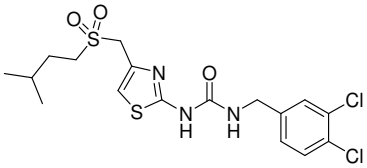
The product was prepared by applying method E and was isolated as a tan solid in 17% yield. ^{1}H-NMR (ppm, CD_3OD): 3.40 (t, 2H), 3.70 (t, 2H), 4.42 (s, 2H), 4.58 (s, 2H), 7.25 (s, 1H), 7.28 (d, 1H), 7.49 (s, 1H), 7.50 (d, 1H), 8.52 (bs, 1H), 8.66 (bs, 2H)

1-(3,4-Dichlorobenzyl)-3-(4-(propylsulfonylmethyl)thiazol-2-yl)urea 3.8s



The product was prepared by applying method E and was isolated as an off-white solid in 52% yield. ^{1}H-NMR (ppm, $CDCl_3$): 0.98 (t, 3H), 1.79 (m, 2H), 2.88 (t, 2H), 4.18 (s, 2H), 4.34 (s, 2H), 6.85 (s, 1H), 7.09 (d, 1H), 7.35 (m, 2H)

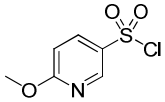
1-(3,4-Dichlorobenzyl)-3-(4-(isopentylsulfonylmethyl)thiazol-2-yl)urea 3.8t



The product was prepared by applying method E and was isolated as an off-white solid in 16% yield. ^{1}H-NMR (ppm, CD_3OD): 0.94 (d, 6H), 1.67 (m, 3H), 3.10 (t, 2H), 4.38 (s, 2H), 4.40 (s, 2H), 7.05 (s, 1H), 7.25 (dd, 1H), 7.46 (s, 1H), 7.49 (bs, 1H)

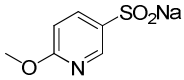
Appendix H Sodium and lithium aryl sulfinates

6-Methoxypyridine-3-sulfonyl chloride 4.2a



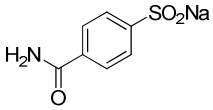
The product was isolated as an orange-brown solid in 70% yield. ^{1}H-NMR (ppm, $CDCl_3$): 4.11 (s, 3H), 6.95 (d, 1H), 8.18 (dd, 1H), 8.85 (s, 1H)

Sodium 6-methoxypyridine-3-sulfinate 4.3a



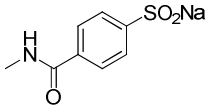
The product was isolated as a white solid in 85% yield. ^{1}H-NMR (ppm, DMSO-d_6): 3.85 (s, 3H), 6.75 (d, 1H), 7.75 (dd, 1H), 8.08 (s, 1H)

Sodium 4-carbamoylbenzenesulfinate 4.3b



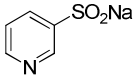
The product was isolated as a white solid in 40% yield. ^{1}H-NMR (ppm, DMSO-d_6): 7.49 (d, 2H), 7.81 (d, 2H)

Sodium 4-(methylcarbamoyl)benzenesulfinate 4.3c



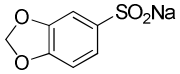
The product was isolated as a white solid in 91% yield. ^{1}H-NMR (ppm, DMSO-d_6): 2.78 (s, 3H), 7.49 (d, 1H), 7.64 (d, 1H), 7.76 (m, 2H)

Sodium pyridine-3-sulfinate 4.3d



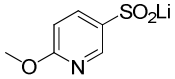
The product was isolated as a brown solid in 100% yield. ^{1}H-NMR (ppm, DMSO-d_6): 7.56 (m, 1H), 8.14 (d, 1H), 8.45 (d, 1H), 8.63 (s, 1H)

Sodium benzo[*d*][1,3]dioxole-5-sulfinate 4.3e



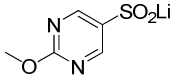
The product was isolated as a white solid in 81% yield. ^{1}H-NMR (ppm, DMSO-d_6): 6.07 (s, 2H), 7.03 (d, 1H), 7.10 (d, 1H), 7.17 (s, 1H)

Lithium 6-methoxypyridine-3-sulfinate 4.4a



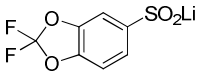
The product was isolated as a light yellow solid in 89% yield. ^{1}H-NMR (ppm, DMSO-d_6): 3.85 (s, 3H), 6.75 (d, 1H), 7.75 (dd, 1H), 8.08 (s, 1H)

Lithium 2-methoxypyrimidine-5-sulfinate 4.4b



The product was isolated as a yellow solid in 66% yield. ^{1}H-NMR (ppm, DMSO-d_6): 3.96 (s, 3H), 8.55 (s, 1H), 9.92 (s, 1H)

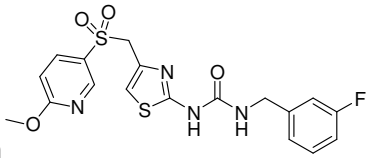
Lithium 2,2-difluorobenzo[*d*][1,3]dioxole-5-sulfinate 4.4c



The product was isolated as a white solid in 56% yield. ^{1}H-NMR (ppm, DMSO-d_6): 7.34 (s, 2H), 7.41 (s, 1H)

Appendix I Sulfonylmethyl thiazol-2-yl urea derivatives

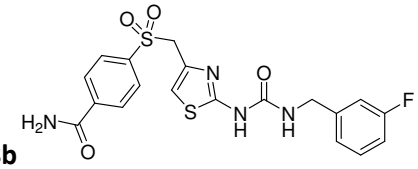
1-(3Fluorobenzyl)-3-(4-((6-methoxypyridin-3-ylsulfonayl)methyl)thiazol-2-yl)urea



4.8a

The product was isolated as an off-white solid in 39% yield by using the sodium sulfinate. The product was isolated in 75% yield by using the lithium sulfinate. ^{1}H-NMR (ppm, CD_3OD): 3.99 (s, 2H), 4.51 (d, 2H), 6.93 (m, 2H), 7.02 (m, 3H), 7.39 (m, 1H), 7.84 (d, 1H), 8.41 (s, 1H)

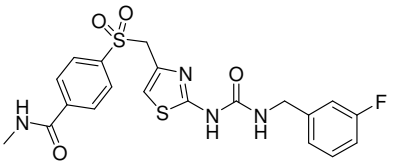
1-(3-Fluorobenzyl)-3-(4-((4-carbamoylphenylsulfonyl)methyl)thiazol-2-yl)urea



4.8b

The product was isolated as an off-white solid in 45% yield. ^{1}H-NMR (ppm, DMSO-d_6): 4.37 (d, 2H), 4.73 (s, 2H), 6.82 (s, 1H), 7.05 (m, 3H), 7.39 (m, 1H), 7.82 (d, 2H), 8.02 (d, 2H)

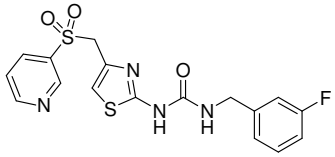
1-(3-Fluorobenzyl)-3-(4-((4-methylcarbamoylphenylsulfonyl)methyl)thiazol-2-yl)urea



4.8c

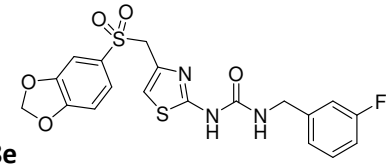
The product was isolated as an off-white solid in 40% yield. ^{1}H-NMR (ppm, DMSO-d_6): 2.82 (s, 3H), 4.37 (d, 2H), 4.64 (s, 2H), 6.81 (s, 1H), 7.05 (m, 3H), 7.41 (m, 1H), 7.82 (d, 2H), 8.02 (d, 2H)

1-(3-Fluorobenzyl)-3-(4-((pyridin-3-ylsulfonyl)methyl)thiazol-2-yl)urea 4.8d



The product was isolated as a brown solid in 85% yield. ^{1}H-NMR (ppm, DMSO-d_6): 4.25 (d, 2H), 4.67 (s, 2H), 7.02 (m, 3H), 7.31 (m, 1H), 7.62 (m, 1H), 8.43 (m, 2H), 8.91 (s, 1H)

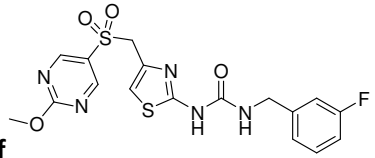
1-(3-Fluorobenzyl)-3-(4-((benzo[*d*][1,3]dioxol-5-ylsulfonyl)methyl)thiazol-2-yl)urea



4.8e

The product was isolated as a yellow solid in 72% yield. ^{1}H-NMR (ppm, CD_3OD): 4.41 (s, 2H), 4.45 (d, 2H), 6.07 (s, 2H), 6.63 (s, 1H), 7.05 (m, 4H), 7.29 (m, 1H), 7.51 (m, 2H)

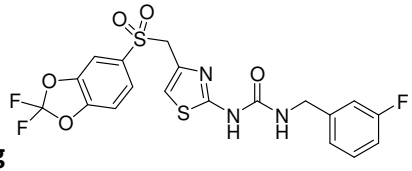
1-(3-Fluorobenzyl)-3-(4-((2-methoxypyrimidin-5-ylsulfonyl)methyl)thiazol-2-yl)urea



4.8f

The product was isolated as a white solid in 18% yield. ^{1}H-NMR (ppm, $CDCl_3$): 3.61 (s, 3H), 4.01 (s, 2H), 4.38 (d, 2H), 6.71 (s, 1H), 6.97 (m, 3H), 7.22 (m, 1H), 8.62 (s, 2H)

1-(3-Fluorobenzyl)-3-(4-((2,2-difluorobenzo[*d*][1,3]dioxol-5-ylsulfonyl)methyl)thiazol-2-yl)urea



4.8g

The product was isolated as a white solid in 25% yield. ^{1}H-NMR (ppm, $CDCl_3$): 4.41 (s, 2H), 4.45 (d, 2H), 6.63 (s, 1H), 7.05 (m, 4H), 7.29 (m, 1H), 7.51 (m, 2H)