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Synthesis of phorbazoles and breitfussins analogues

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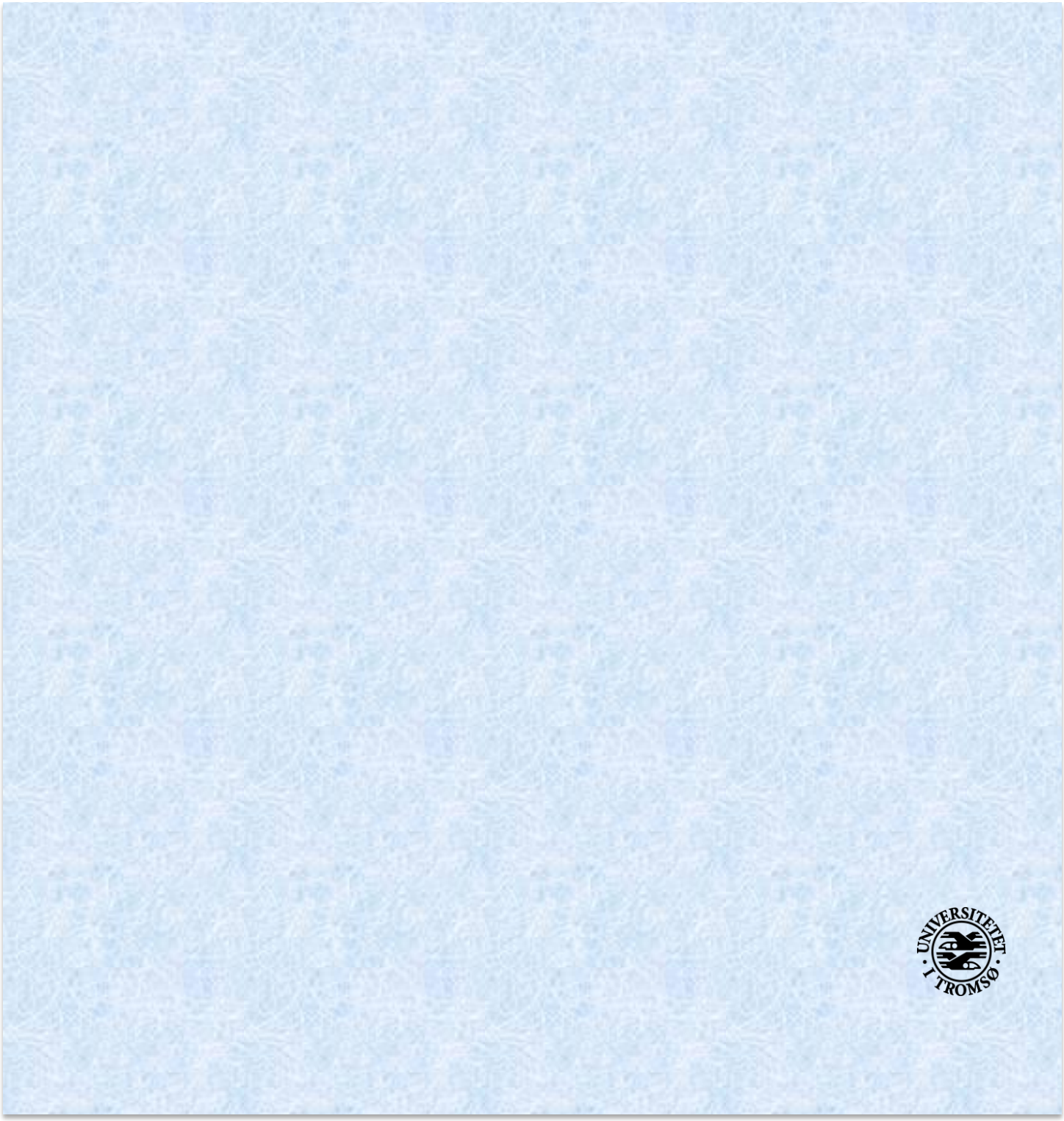
KJE-3900 Master thesis in Chemistry – May 2016



I ABSTRACT

Breitfussins are a group of a closely related heterocyclic compounds. They consist of a tetracyclic structure with an indole, an oxazole and a pyrrole. The breitfussins exhibit interesting biological activity and analogues synthesis and biological evaluation is ongoing. Phorbazoles have a structural similarity with breitfussins in which a phenol replaces the indole. As a part of this, synthesis of phorbazoles, breitfussins and analogues is underway in the Bayer group.

This thesis contains a description for the work done to synthesis a small library of a small group of phorbazoles analogues and one breitfussins analogue.

During the synthesis of the phorbazoles analogues, an isocyanide based oxazole synthesis was performed using TosMIC. Iodination of the oxazole was tested with different approaches to obtain 2,4-diiodinated and 2-iodinated oxazole derivatives. For introducing a Pyrrole on the oxazole, a Suzuki-Miyaura cross coupling reaction was performed. As a final step, selective de-protections were performed to obtain the diversity of the analogues.

The breitfussins analogue was formed in 2 steps from the commercially available starting material, methyl-1H-indole-3-carboxylate **13.**

II ACKNOWLEDGEMENTS

I am using this opportunity to thank everyone who supported me during my master's.

Firstly, I would like to express my sincere gratitude to my supervisor, Ass. Prof. Annette Bayer for giving me the opportunity to work on this project. I am so grateful for your guidance and help from the first day in my master's. Your door was always open, thank you for your support and patience.

I would like to thank my co-supervisor Ass. Prof. Jørn Hansen for all the help and support, thank you for everything I have learned from you, I always enjoyed your lectures.

I would like to express my extreme appreciation to my co-supervisor, Yngve Guttormsen. I am so thankful for patiently answering all my questions and for all the advices and support during my thesis writing and in the lab, I owe you all my lab experience.

I am also very thankful to Dr Muhammad zeeshan and Dr Magnus Engqvist for all the constructive conversations we had and for all the help and support.

I would like to thank Truls Ingebrigesten and Arnfinn Kvarsnes, you were always there when I needed your help. I am also thankful to Jostein Johansen for helping me with the HRMS.

Another thank goes to my colleagues in the department of chemistry in Tromsø, Marianne Paulsen, Sundus Akhter and Fati Shouli.

I want to thank all my friends in Tromsø and in Egypt, Arkan Murat, Mohsen Askar, Chadi Elserafi, Hatem Eldebsy, Khaled srour, Ahmed saad, ahmed elzayat and Mohamed fadel for all the support and advices.

I want to especially thank Aya Ismail for all the support and help since my first day in Tromsø.

A very special thank goes to my mother, father and little sisters, Hend and Sara, I am so blessed to have you in my life.

III ABBREVIATIONS

NP	Natural product
NMR	Nuclear Magnetic Resonance
TLC	Thin layer chromatography
HRMS	High-resolution mass spectroscopy
DCM	Dichloromethane
THF	Tetrahydrofuran
EA	Ethylacetate
DMSO	Dimethylsulphoxide
DME	Dimethoxy ethane
LiHMDS	Lithium hexamethyldisilazane
Boc	*tert*-butyloxycarboxyl
^{1}H NMR	Proton Nuclear Magnetic Resonance
^{13}C NMR	C-13 nuclear magnetic resonance
DBU	1,8-diazabicyclo[5.4. 0]undec-7-ene
TFA	Trifluoroacetic acid
TosMIC	Tosylmethylisocianide
EE	Ethoxy ethyl
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DMP	Dess–Martin periodinane
DCC	N,N'-dicyclohexylcarbodiimide
TIPS	Triisopropylsilyl ether
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
TMP	2,2,6,6-Tetramethylpiperidine
MEK	Mitogen-activated protein kinase
rt	Room temperature
eq.	equivalent

IV LIST OF FIGURES, TABLES AND SCHEMES

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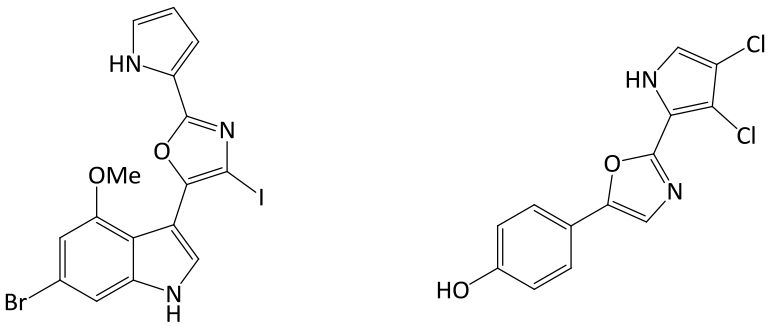
1 INTRODUCTION AND AIM OF THE THESIS

Natural products are primary and secondary metabolites produced by living organisms through metabolic pathways. Primary metabolites are required for life as they are involved in essential cellular functions including cellular structure, energy production, growth, etc. Secondary metabolites are not essential for life. However, they have a wide range of functions and give the organism a competitive function and an evolutionary advantage[1,2].

Many NPs have medicinal activities. NPs are often used as a starting point for developing new drugs. The NP can be used itself as a medicine, like penicillin, which was the first antibiotic drug, isolated from the mold, *Penicillium notatum*. Synthetic analogues of the NP with structural variations are usually prepared to improve the pharmacodynamics and pharmacokinetics of drug candidates[3,4].

Our research group has been interested in a NP class called the breitfussins, which exhibit interesting bioactivity. Breitfussin A (Figure 1) and B are NPs that were isolated from the Arctic hydrozoan *Thuiaria breitfussi* [5]. They are members of a group of a closely related heterocyclic compounds. Breitfussins consist of a tetracyclic structure with an indole, an oxazole and a pyrrole. The oxazole-pyrrole moiety is rare in natural products[6].

In addition, one other group of NPs having the oxazole-pyrrole ring system is described in the literature, the phorbazoles[7]. Phorbazoles are a family of four compounds, first isolated by Kashman et al. [8] from the sponge *phorbas clathrata* collected in south Africa in 1994 (Figure 1).



Breitfussin A Phorbazole C

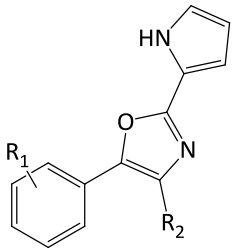
Figure 1. Breitfussin A and Phorbazole C

Due to the interesting bioactivities of the breitfussins, our group is interested in the synthesis of analogues. The aim of the thesis was:

- To synthesize analogues related to the phorbazole structure and an analogue related to the breitfussins structure.

The target phorbazoles analogues have a structural variation represented in the R_2 and R_1 groups. The R_1 being a hydroxyl, Tosyloxy or a methoxy group on different positions, the ortho and the meta positions on the phenyl ring (Figure2).

R_2=I, R_1= 3-OH (**10a**)
R_1= 2-OH (**10b**)
R_1= 3-OTs (**8a**)
R_1= 2-OTs (**8b**)
R_1= 3-OMe (**8c**)
R_1= 2-OMe (**8d**)



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R_2=H, R_1= 3-OH (**11a**)
R_1= 2-OH (**11b**)
R_1= 3-OTs (**9a**)
R_1= 2-OTs (**9b**)
R_1= 3-OMe (**9c**)
R_1= 2-OMe (**9d**)

Figure 2. Structure of target analogues of phorbazoles

The target breitfussins analogue consists of an un-substituted tetracyclic structure of an indole, an oxadiazole and a pyrrole (Figure 3).

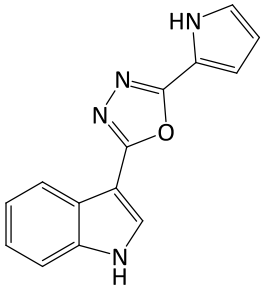

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Figure 3. Structure of target analogue of breitfussins

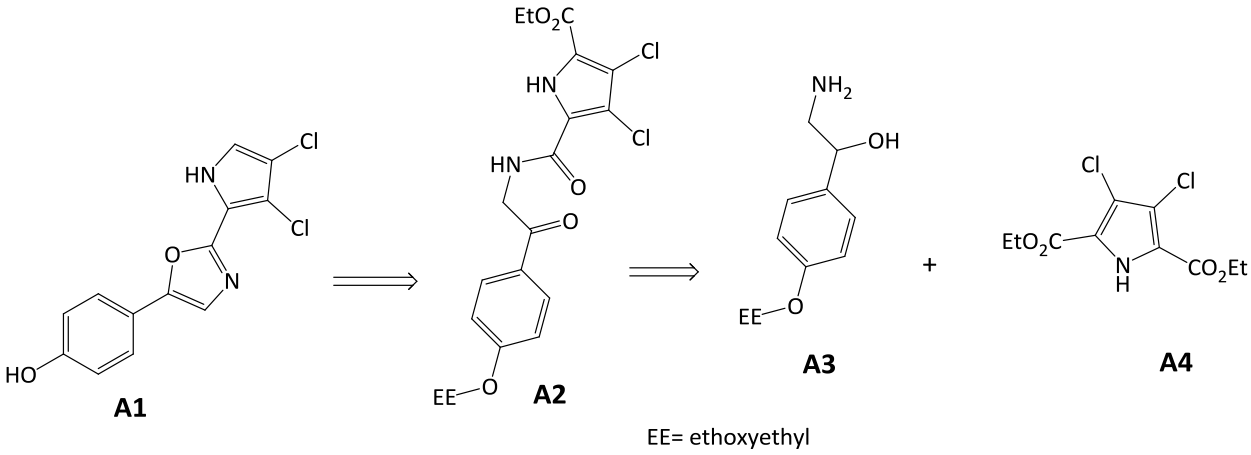
2 CHEMICAL BACKGROUND

2.1 Previous synthesis of phorbazoles and breitfussins

2.1.1 Total synthesis of phorbazole C

Leibscher and co-workers reported the first total synthesis of the marine NP, Phorbazole C[8].

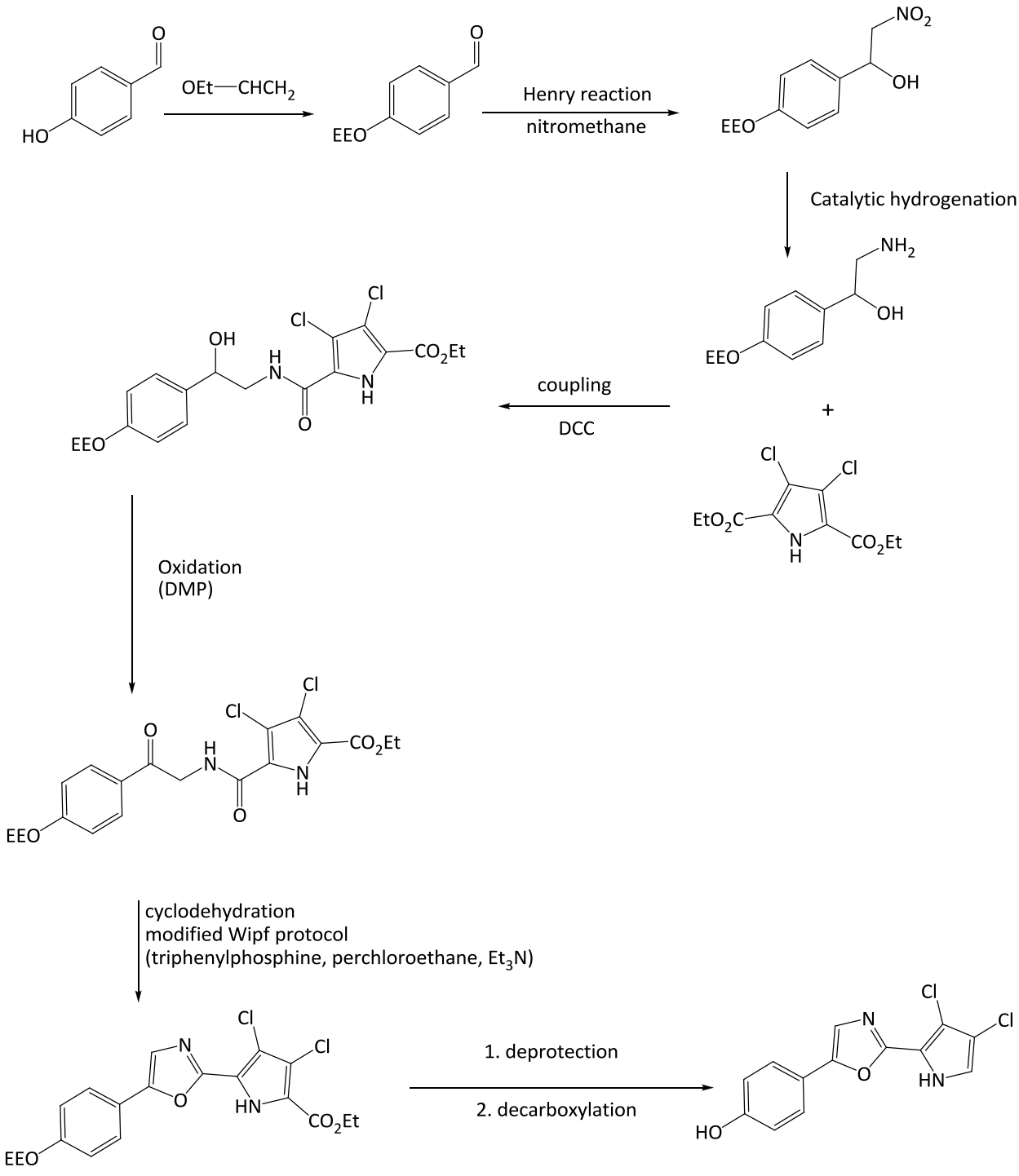
The synthetic strategy was based on the retrosynthesis shown in Scheme 1.



Scheme 1. Phorbazole C retrosynthesis

Two key steps were involved in this strategy, the first one was the formation of an amide **A2** starting from the aminoethanol **A3** and the dichloropyrrole-carboxylic acid **A4** and the second step was cyclodehydration based oxazole ring formation from acylaminoketone **A2**.

The corresponding forward synthesis starting from 4-hydroxybenzaldehyde is shown in scheme 2. The central oxazole was achieved by a cyclodehydration late in the synthesis.



Scheme 2. Total synthesis of phorbazole C

2.1.2 Total synthesis of breitfussin A and B

The first total synthesis of breitfussins, A and B (Figure 4) was described by Pandey et al. in the Bayer group[6].

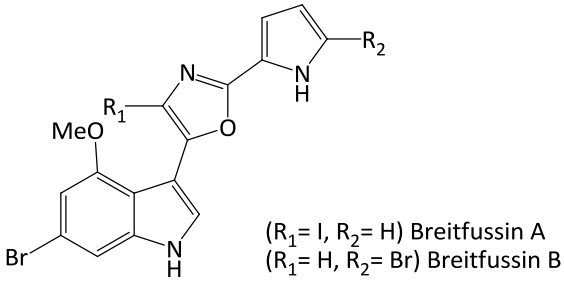
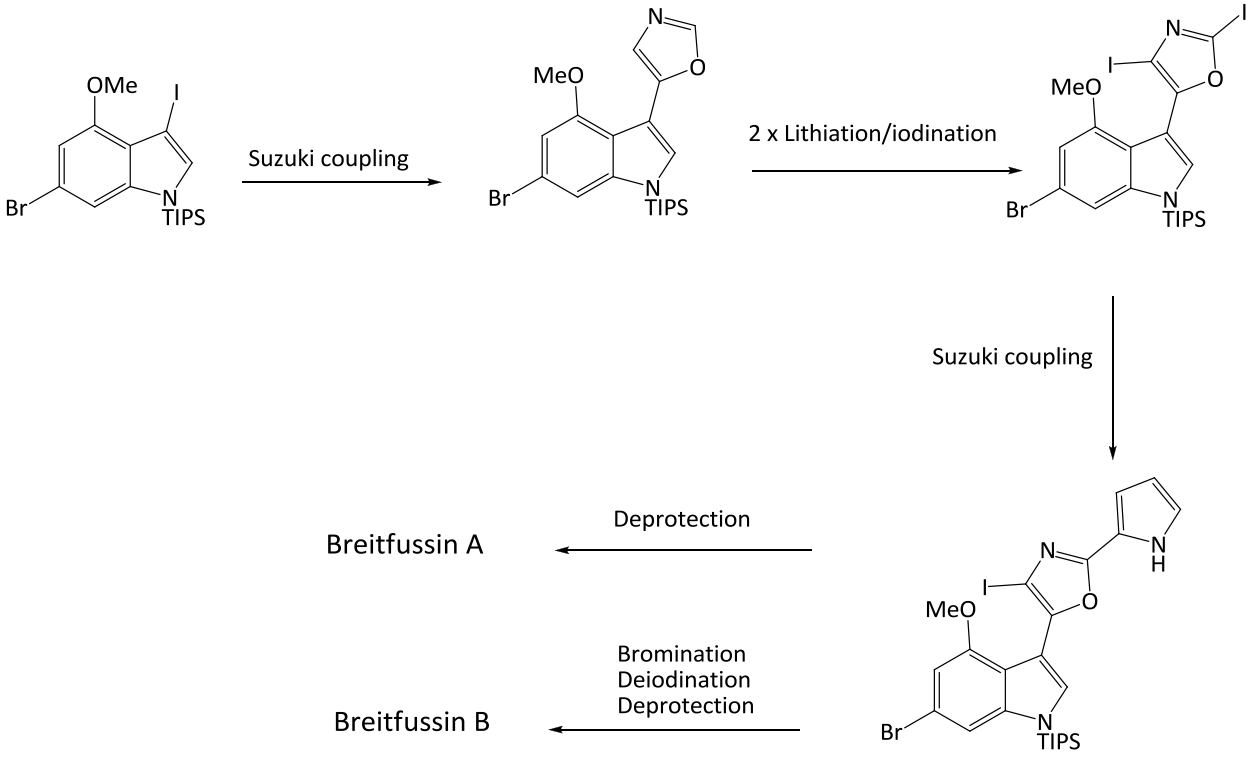


Figure 4. Breitfussins, A and B

Based on modification of a functionalized oxazole, two palladium-catalyzed cross-couplings were applied to introduce an indole and a pyrrole onto an oxazole core. Selective lithiation/iodination was carried on a common indole-oxazole derivative. 2,4-diiodinated or 2-iodinated oxazoles were obtained and used as precursors for synthesis of breitfussin A and B, respectively[6].

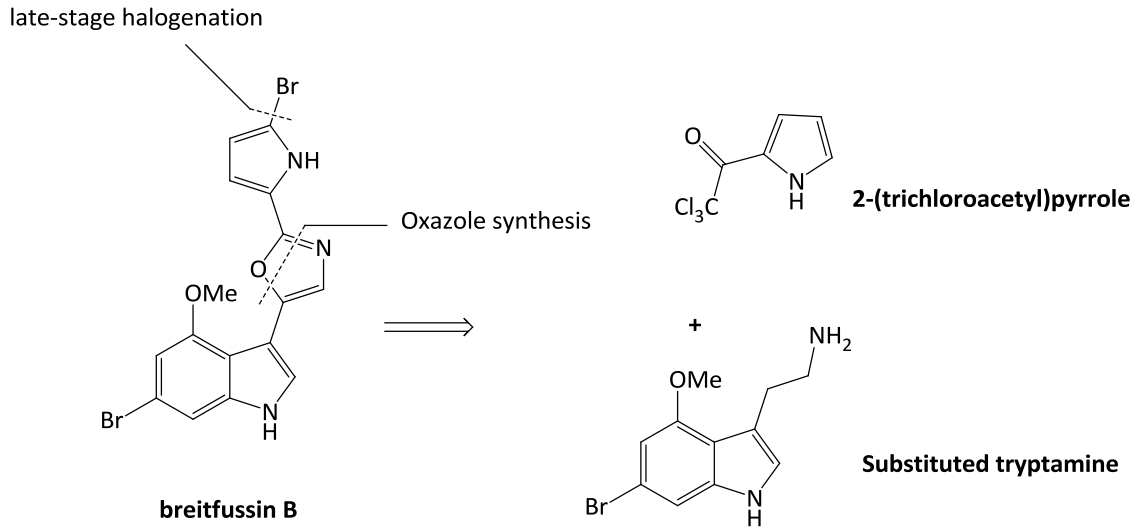
They were able to synthesize breitfussin A and B as shown in scheme 3.



Scheme 3. Total synthesis of Breitfussins, A and B

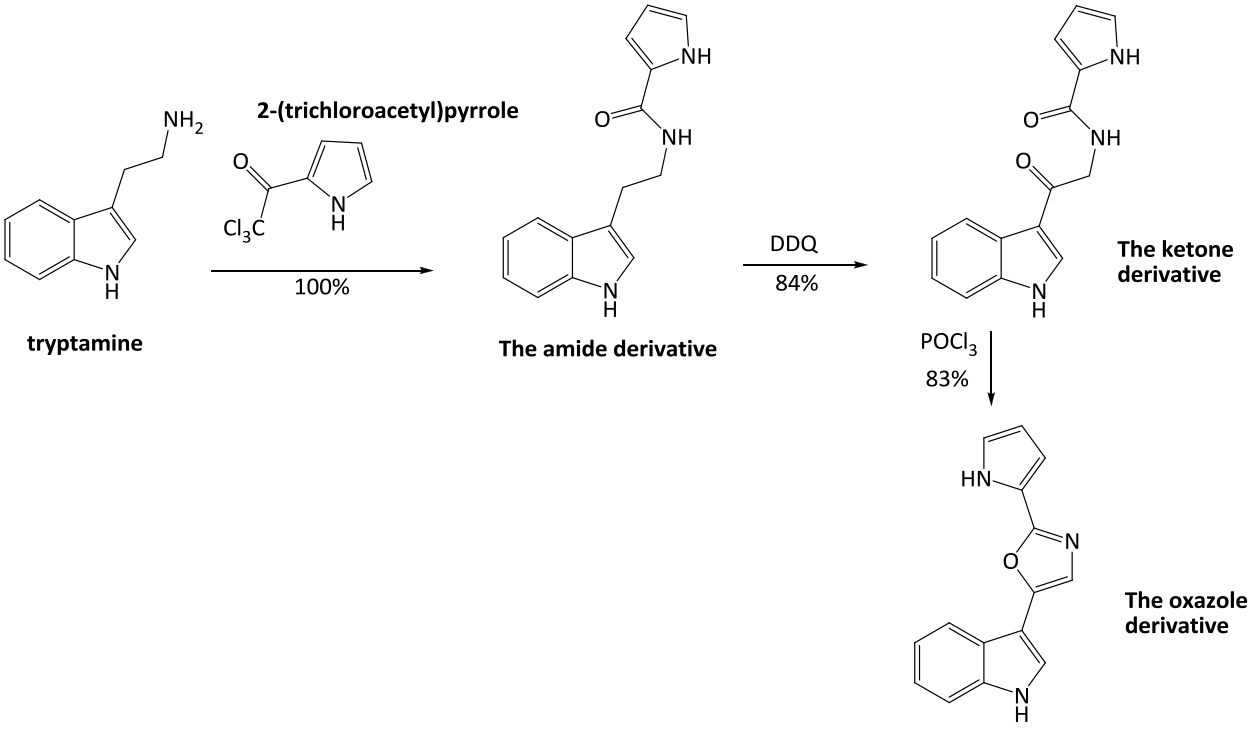
2.1.3 Synthesis of breitfussin B by late stage bromination

Jason and co-workers[9] proposed the formation of breitfussins A and B through selective late stage halogenation of a breitfussin precursor. Synthesis of the oxazole core in the breitfussin model was based on the retrosynthesis shown in scheme 4.



Scheme 4. Retrosynthesis of the breitfussins precursor described in the formation of breitfussin B by late stage halogenation

The Synthesis of a simplified model of the breitfussins was performed. Tryptamine was reacted with 2-(trichloroacetyl)pyrrole to form an amide. The amide was subjected to a DDQ-promoted oxidation to afford the ketone, which was used to form the oxazole through a subsequent Robinson-Gabriel reaction (Scheme 5).



Scheme 5. Synthesis of a simplified model of the breitfussins from tryptamine

2.2 Oxazoles synthesis

Oxazole is a heterocyclic aromatic five-membered ring with two hetero-atoms, a nitrogen and an oxygen and both are separated by one carbon atom.

Many NPs contain one or more oxazole rings as a part of their structure and many of them have an interesting biological activity. The total synthesis of some NPs containing oxazole has been described in the literature for example, Bengazole A which is a bisoxazole containing NP with antifungal activity and Muscoride A which is also an NP that contains a bisoxazole as a part of its structure and has a weak antibiotic activity (Figure 5)[10,11].

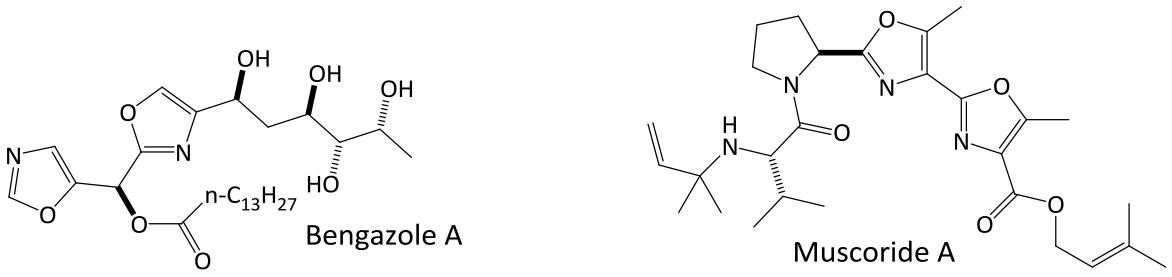


Figure 5. Oxazole containing natural products

There are various methods described in the literature for the synthesis of oxazoles and some of them are highlighted in the following sections.

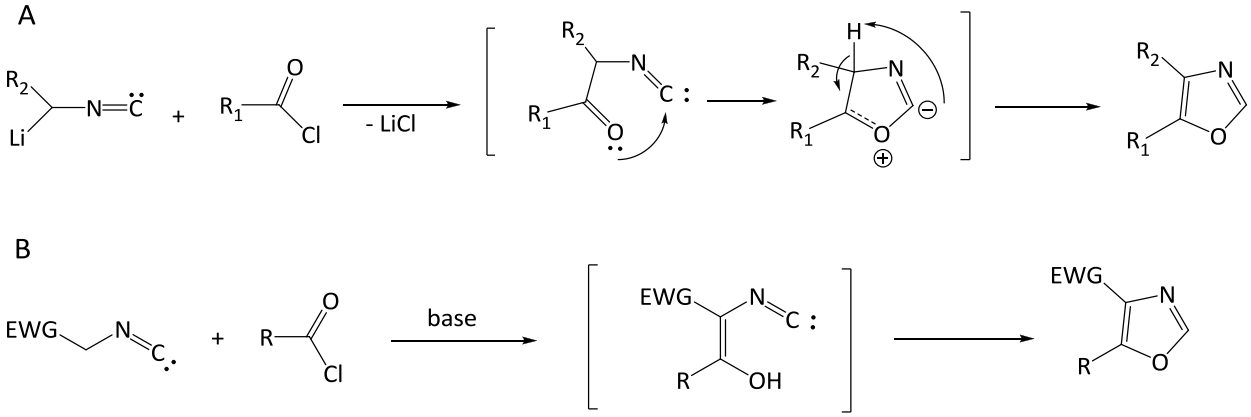
2.2.1 Isocyanide based oxazole synthesis

This section includes a description for two isocyanide dependent methods for the synthesis of 5-substituted oxazoles, Schöllkopf and Van Leusen.

Schöllkopf oxazole synthesis

Schöllkopf oxazole synthesis involves the reaction of α-metalated isocyanide with acyl chlorides or esters to give 5-substituted oxazole derivative[12].

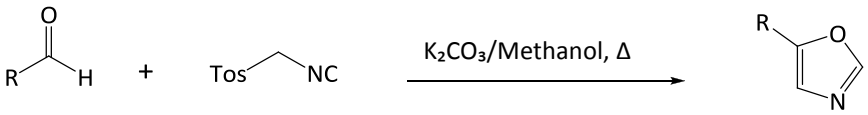
The proposed mechanism suggests that the oxazole is formed by acylation of the α-metalated isocyanide followed by an oxygen lone pair attack on the isocyanide in a cyclization step and a proton migration from C-4 to C-2 (Scheme 6 A). Another developed synthesis method based on Schöllkopf synthesis in which, an EWG-substituted isocyanides is used instead of the metalated isocyanide and reacted with acid chlorides in presence of immobilized base to give 4,5 disubstituted oxazoles directly[12] (Scheme 6 B).



Scheme 6. Mechanism of Schöllkopf oxazole synthesis

Van Leusen oxazole synthesis

In the Van Leusen oxazole synthesis, the non-toxic isocyanide derivative, tosylmethylisocyanide (TosMIC) is used as a precursor in the synthesis of 5-substituted oxazoles from the corresponding aldehydes or acyl chlorides (Scheme 7)[11].



Scheme 7. Van leusen reaction

TosMIC structure involves an isocyano group, which can undergo nucleophilic addition reactions at the terminal carbon, an acidic α-carbon atom and a sulfinyl group which serves as a good leaving group and it also enhances the acidity of the α-carbon (Figure 6)[13,14].

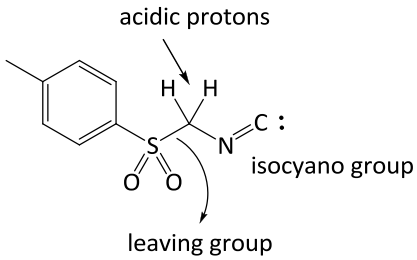
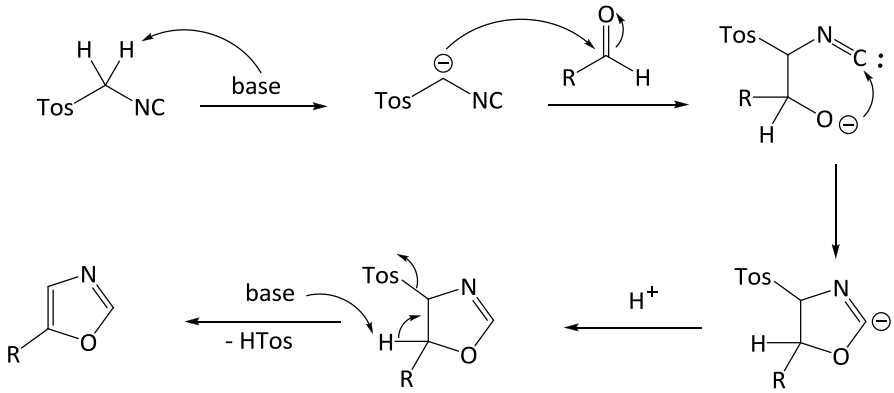


Figure 6. TosMIC structure

The mechanism of the reaction involves first, a deprotonation of the α-carbon of the TosMIC by a base. The formed carbanion attacks the aldehyde carbonyl group creating a negative charge on the oxygen which in part cyclizes through a nucleophilic addition on the terminal carbon of the isocyano group. Presence of a proton in the β-position to the sulfinyl group then allows the base to eliminate the sulfinyl group and a double bond is formed between carbons number 4 and 5, giving the oxazole as shown in scheme 8[15].



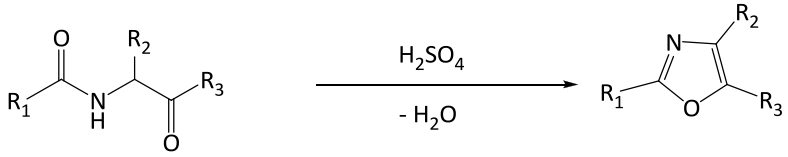
Scheme 8. Mechanism of Van leusen oxazole synthesis

2.2.2 Oxazole synthesis by Cyclodehydration

This is the most common method for oxazoles synthesis and it occurs through a dehydration process, also an oxidation process may be required16. In this section a common cyclodehydration based method for 2,4,5-substituted oxazole synthesis is described, Robinson-Gabriel oxazole synthesis.

Robinson-Gabriel oxazole synthesis

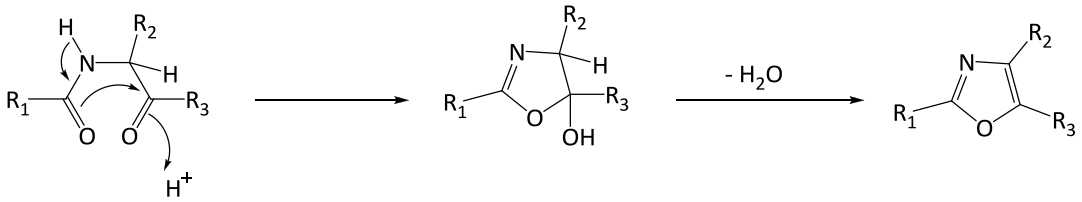
The Robinson-Gabriel synthesis forms an oxazole by the cyclodehydration of 2-acylamino-ketone in presence of dehydrating agent (Scheme 9) [17].



Scheme 9. Robinson-Gabriel oxazole synthesis reaction

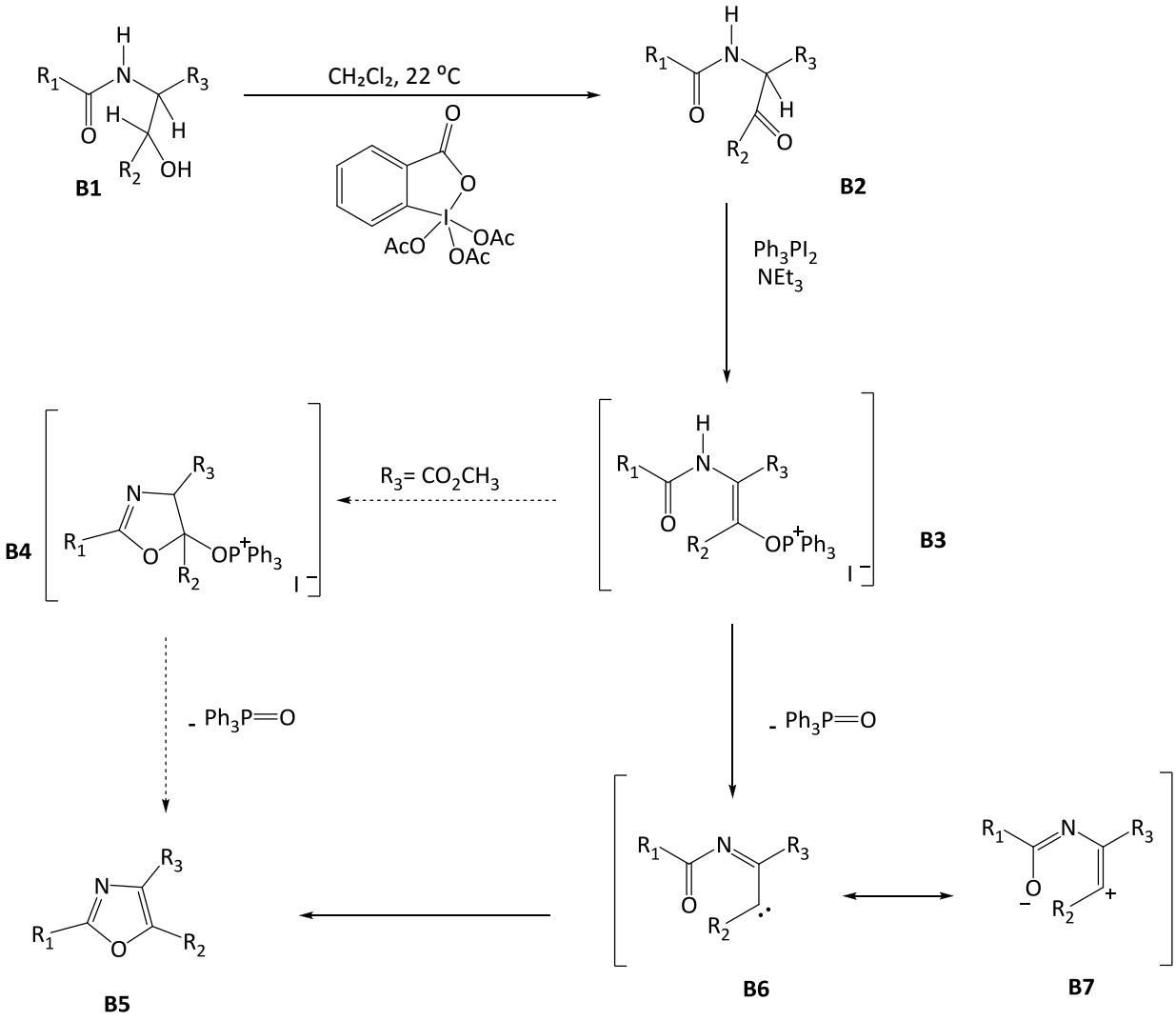
Concentrated sulfuric acid is a classical dehydrating agent but there is also several other dehydrating agents can be used including thionyl chloride, polyphosphoric acid, anhydrous hydrogen fluoride and many others[18].

The reaction mechanism involves firstly, intramolecular cyclization of the 2-acylamidoketone where the oxygen of the carbonyl group from the amide side forms a bond with the carbon of the other carbonyl group and therefore it is the one included in the oxazole ring as it has been determined to be more lewis basic by labeling studies. At the end dehydration occurs to give the oxazole derivative (Scheme 10)[19].



Scheme 10. Mechanism of Robinson-Gabriel oxazole synthesis

There have been some modification described for the Robinson-Gabriel oxazole synthesis by different research groups, for example Wipf et al. [20] reported the synthesis of substituated oxazoles using Dess-Martin reagent [21] to oxidize the side chain of β-hydroxy amides to β-keto amide from readily available amino acid derivatives. The intermediate β-keto amide was then cyclohydrated with triphenylphosphine/iodine in presence of Et_3N. Several mechanisms for the ring closure and formation of the oxazole can be envisioned. Since the reaction only occurs in presence of the base Et_3N, they proposed an enolization of the ketone and formation of the phosphonium salt **B3**. From the phosphonium salt, 2 pathways were proposed for ring closure. The first pathway by intramolecular addition of the amide onto the vinylphosphonium to form **B4**, especially when R_3 is EWG. The second pathway through the formation of acylimino carbene **B6** (Scheme 11).



Scheme 11. Synthesis of substituted oxazoles reported by Wipf

2.3 Functionalization of the oxazole ring

The target scaffolds for the project is an oxazole with and without an iodine at the 4-position. This section discusses some of the previous studies performed to introduce 2- and 4-substitutions on the oxazole.

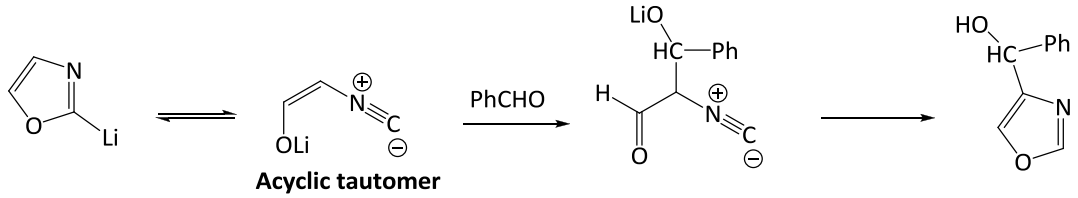
2.3.1 Lithiations of the oxazole

The usual lithiation site on oxazoles is the 2-position where the most acidic proton is carried. The 2-lithiation will lead to that the subsequent addition of the electrophile takes place on C2. However, many efforts have been done to get regioselective substitutions on the oxazole ring at other positions and some of them are highlighted in this section.

Lithiation by Vedejs and Luchetta

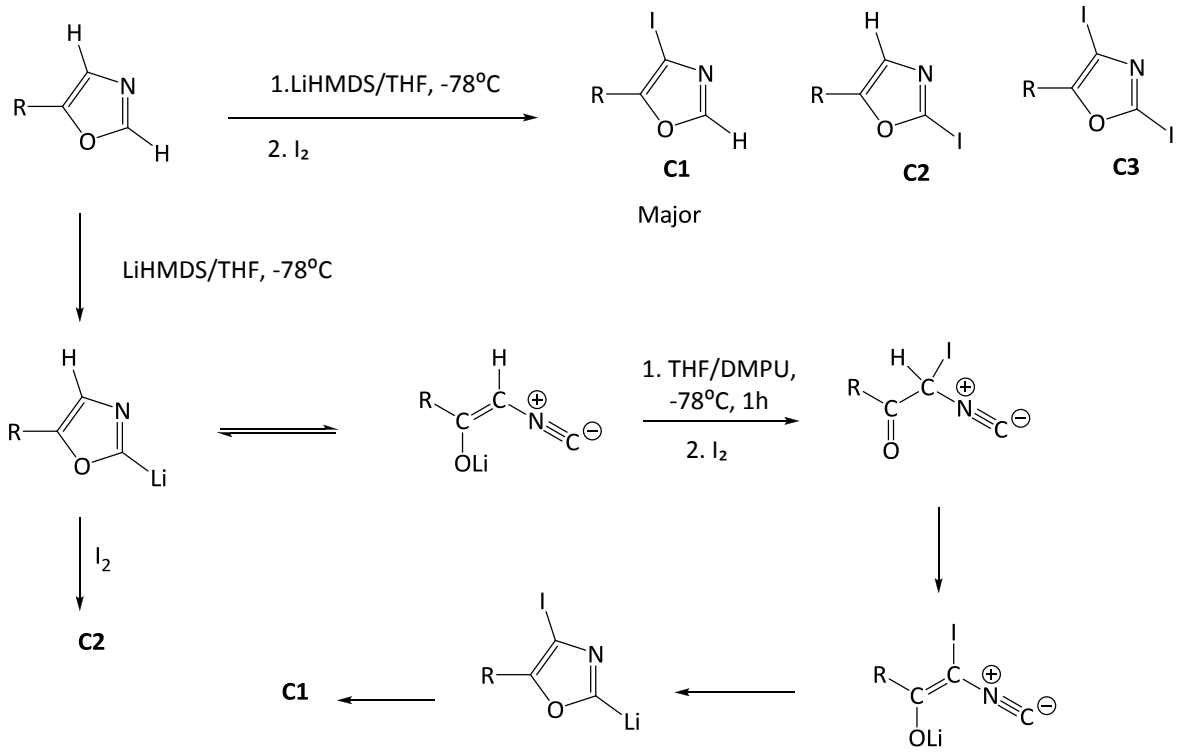
Vedejs and Luchetta[22] reported the synthesis of a 4-halogenated oxazole with no substitution at 2-position as they were interested in performing a palladium-mediated cross coupling at 4-position of the oxazole. In a previous study, Hodges et al. [23] found that the major product of reaction between lithiated oxazole at 2-position and some aldehydes is the

C4-substituted oxazole. After that, they investigated the reaction using different aldehydes in different temperatures. The resulting product ratios were dependent on the temperature and the electrophile. It was proposed that the C4 substitution occurs through the reaction of the dominant acyclic tautomer followed by proton transfer and cyclization (Scheme 12)[22].



Scheme 12. Mechanism of reaction of the acyclic tautomer of lithiated oxazole

On this basis, Vedejs and Luchetta suggested that direct halogenation at C4 is possible if the reaction conditions were selected for the acyclic tautomer. They used LiHMDS in THF and reported the synthesis of the 4-iodinated compound as a major product. Also they got a mixture of 2- iodinated and 2,4-diiodinated compounds(Scheme 13)[22,24].

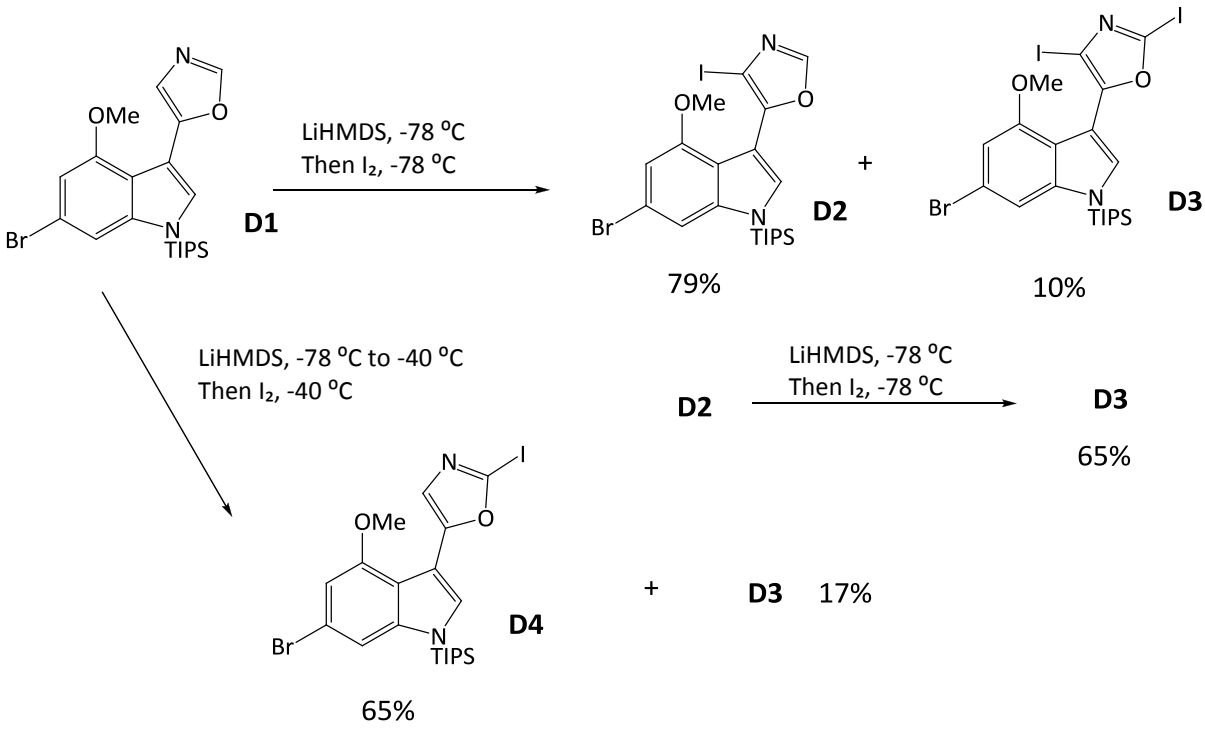


Scheme 13. Lithiation/iodinations by Vedejs and Luchetta

They reported that the experiments were difficult to reproduce but they obtained a larger ratio of the 4-iodinated to the 2-iodinated derivative when they made a modification in the procedure and added 40-50 volume % of DMPU before the addition of the base (LiHMDS).

Lithiation by Pandey et al.

Pandey et al.[6] investigated the introduction of iodo-substituents on C2 and C4 of the oxazole using metalation/iodination strategy. After screening of different bases (LiHMDS, NaHMDS) and electrophiles (1,2-diiodoethane,iodine), they found that iodination position is highly dependent on the temperature of the iodination step. Using LiHMDS (3 eq.) as a base at −78 °C followed by iodination using iodine at the same temperature, the 4-iodo derivative **D2** was obtained as the major product with 79% yield and 2,4-diiodo derivative **D3** as a minor product. By subsequent lithiation/iodination of the 4-iodo oxazole **D2** the 2,4-diiodo derivative **D3** was obtained in 65% yield. When they added the iodine at −40 °C, the 2-iodo derivative **D4** was obtained as a major product in 65% yield and also the 2,4-diiodinated derivative **D3** was obtained as a minor product (Scheme 14).



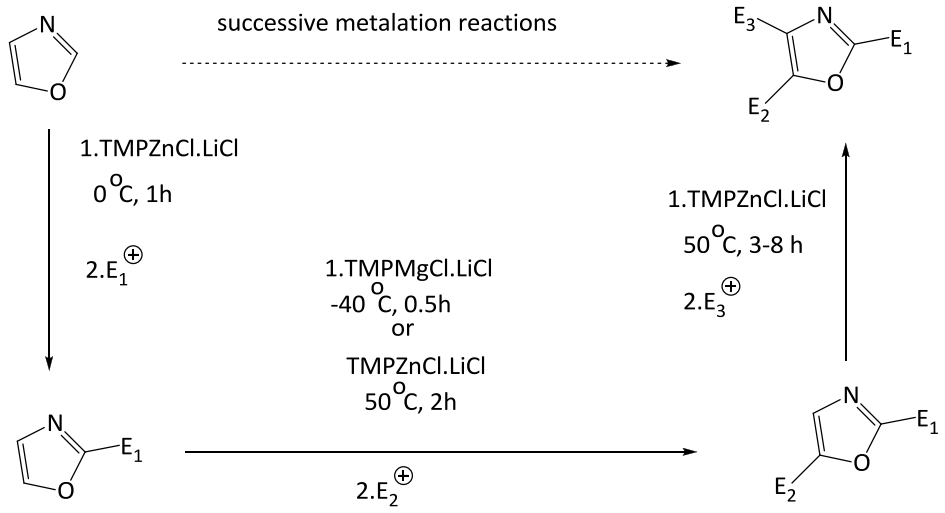
Scheme 14. Lithiation/iodinations by Pandey and et al.

2.3.2 Metalation by TMP bases of Mg and Zn

There have been always some difficulties and limitations for the lithiation of heterocyclic compounds including ring fragmentation[25] . To overcome such problems, Knochel and co-workers[26] developed a general synthesis method to form a highly functionalized 2,4,5-substituted oxazoles starting from the oxazole. A set of new sterically hindered TMP-bases complexed by LiCl was reported.

They have been able to step-wisely magnesiate or zincate the oxazole and react it with different electrophiles in 2,4,5-positions. The regioselectivity order for the metalation was

C2 first then C5 then C4 (Scheme 15). The formed zincated or magnesiated oxazole species were stable towards fragmentation and readily reactive towards various electrophiles.



Scheme 15. Successive metalations of the oxazole using TMP metal bases

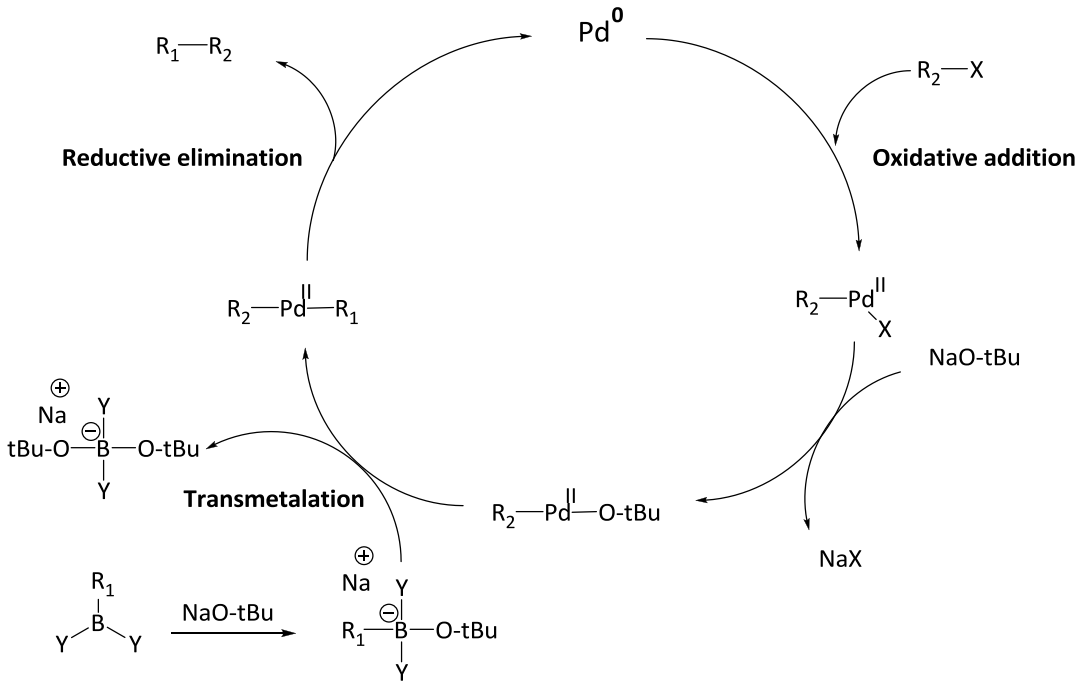
2.3.3 Carbon-carbon coupling of the oxazoles

The synthetic strategy suggests the introduction of a 2-pyrrole ring through a carbon-carbon bond with C2 of the oxazole. Different cross couplings can be applied on the oxazole including Suzuki-Miyaura, Negishi, Sonogashira and Stille[16] .This Section describes the Suzuki-Miyaura coupling approach.

Suzuki-Miyaura coupling reaction

The Suzuki-Miyaura coupling reaction is a palladium catalyzed cross coupling where a boronic acid interacts with an alkylhalide in presense of a base using palladium(0) complex as a catalyst[27-29].

The catalytic cycle for the palladium catalyzed reaction is shown in scheme 16.



Scheme 16. The palladium catalytic cycle

The first step is an oxidative addition in which, the palladium is added to the alkylhalide forming an organopalladium species. Then the base replaces the halide forming an organopalladium base complex. Simultaneously, the base forms a borate complex with the boronic acid. The two complexes undergo transmetalation where the base group from the organopalldium complex is exchanged with the R group from the borate complex. The final step is reductive elimination restoring the palladium catalyst[30 31].

2.4 Protection and de-protection

A good protecting agent is the one, which can be easily inserted, easily removed and inert to conditions of the reaction. The following sections focus on protecting and de-protecting of a phenolic OH group, also the possible ways of Boc group de-protection.

2.4.1 Protecting and deprotection a phenolic OH group

Several alternatives can be used as a protecting agent for protecting a phenolic oxygen including:

- Silylethers (Triisopropylsilyl ether (TIPS) [32] and tert-Butyldimethylsilyl ether(TBDMS) [33]).

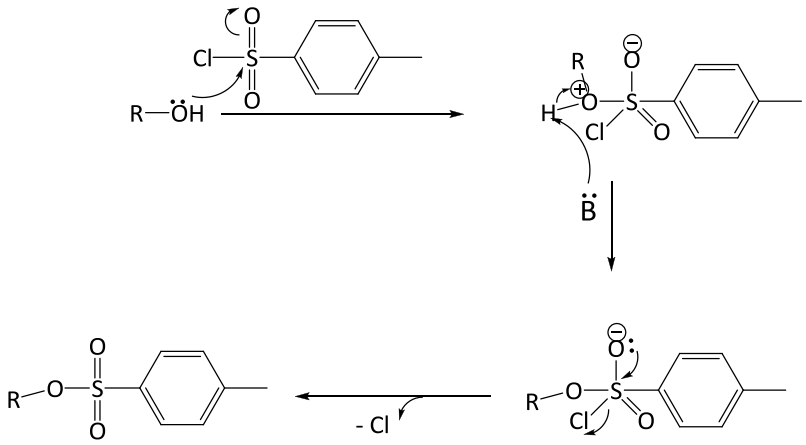
- Ethers (Methyl ether [34] and Benzyl ether [35])

- Acetals (Methoxymethyl acetal (MOM) [36] and [2-(Trimethylsilyl)ethoxy]methyl acetal (SEM) [37])

-Sulphonates (p-toluenesulfonylchloride (TsCl) [38] and methanesulfonylchloride (MsCl) [39])

Protection and deprotection of the p-toluenesulphonylchlroride(TsCl)

A general mechanism for the reaction of the Tosyl group with a hydroxyl group is shown in scheme 17.



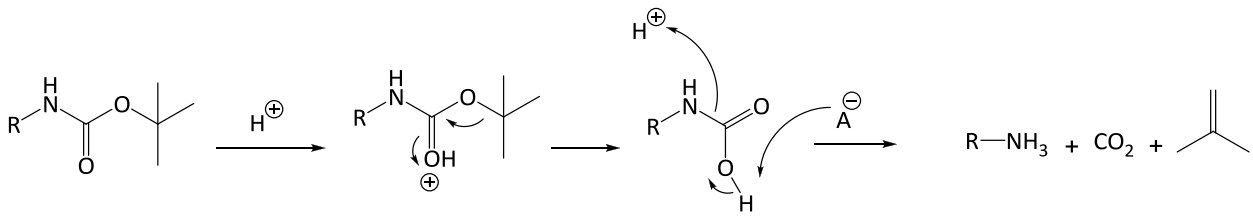
Scheme 17. Mechanism of tosylation of the hydroxyl group

The reaction mechanism is an addition elimination. In presence of a weak base, like pyridine to neutralize the formed HCl during the reaction, the lone pair on the oxygen of the hydroxyl groups attacks the Sulfur atom of the sulphonyl group creating a negative charge on one of the oxygens. The oxygen lone pair in turn attacks the sulfur atom leading to the chloride ion to leave[40].

De-protection of the tosyl group can be achieved by using a nucleophilic base like hydroxide or alkoxide ions[41].

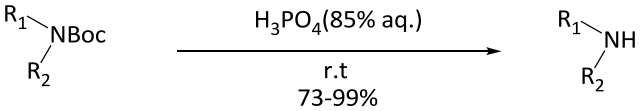
2.4.2 De-protection of the Boc group

Tert-butyloxycarbonyl (Boc group) is a protecting group used mainly to protect amines. It is easily removed in presence of strong acids (Scheme 18)[16].



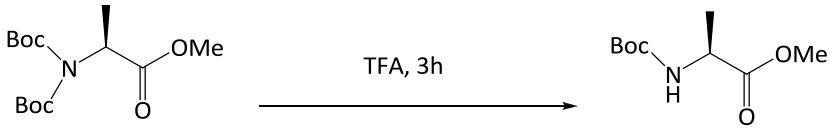
Scheme 18. mechanism of acid aided removal of the Boc group

Several alternatives can be used in that concern. Aqueous phosphoric acid is a good choice for de-protection of the Boc group (Scheme 19) and many other protecting groups with high yields. It is environmentally benign and the reaction conditions are mild and has good selectivity in the presence of other acid sensitive groups[42].

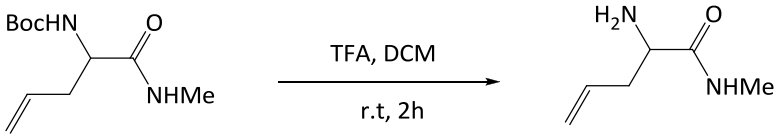


Scheme 19. Removal of the Boc group using phosphoric acid

Other alternative could be trifluoroacetic acid either neat (Scheme 20)[43] or with DCM in 1:1 ratio (Scheme 21)[44].



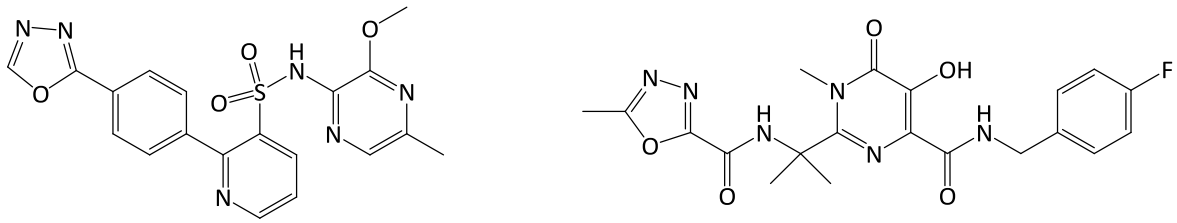
Scheme 20. Removal of the Boc group using neat TFA



Scheme 21. Removal of the Boc group using TFA/DCM (1:1)

2.5 Oxadiazoles

Oxadiazole is a heterocyclic aromatic five-membered ring with two nitrogen atoms, one oxygen atom and two carbon atoms. Oxadiazoles have four different regioisomeric forms; three of them are stable, 1,3,4-oxadiazole, 1,2,4-Oxadiazole and 1,2,5-oxadiazole, and the last one, 1,2,3-oxadiazole, is unstable. Stable oxadiazoles rings exist in many pharmacologically active compounds including the market launched antiretroviral drug, raltegravir. Also some oxadiazole containing drugs in late stage of clinical trial like zibotentan has anti-cancer activity.[45,46]



zibotentan **raltegravir**

Figure 7. Oxadiazole containing drugs

In drug design, oxadiazole can be used as a bioisoster for esters and amides to improve certain property. Warmus and co-workers[47] reported bioisisteric replacement of hydroxamate moiety with an oxadiazole in a previously reported potent and efficient MEK inhibitor, PD-184352 (CI-1040) leading to more metabolic stability and efficiency (Scheme 22).

CI-1040

Scheme 22. Bioisosteric replacement of hydroxymate with oxadiazole

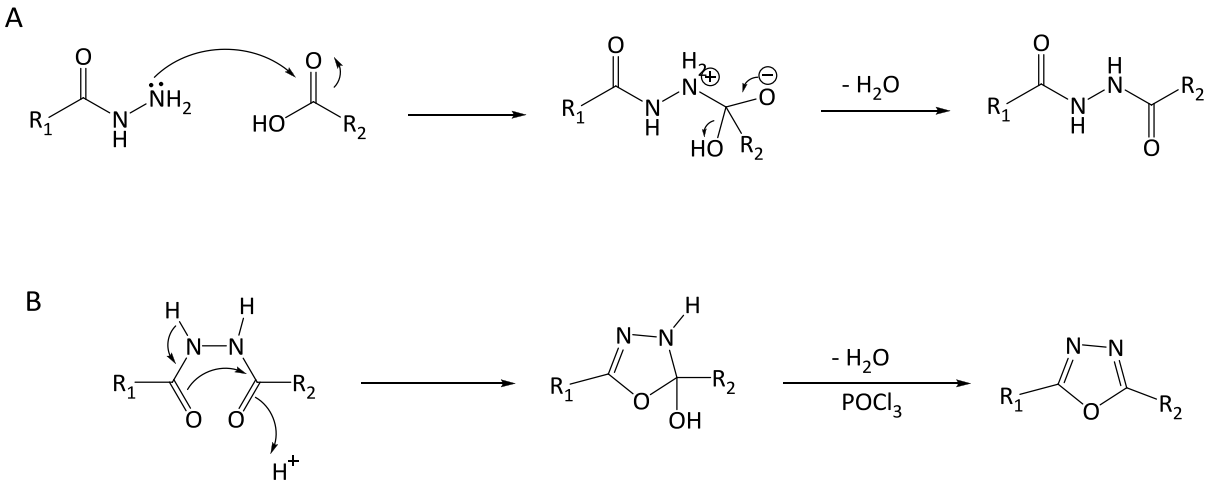
2.5.1 1,3,4-oxadiazole

1,3,4-oxadiazole is an important moiety both; chemically and biologically and is widely used in drug development. Several methods for the synthesis of 2,5-substituted 1,3,4-oxadiazole are described in the literature. One common synthesis method is highlighted in this section.

Reaction of acylhydrazide with carboxylic acid in presence of $POCl_3$

Zhang et al. [48] synthesized three series of indole-based 1,3,4-oxadiazole derivative through the reaction of 1H-indole-3-carbohydrazide with carboxylic acid in presence of Phosphorous oxychloride $POCl_3$. In a similar way Amir and co-workers [49] reported using $POCl_3$ in the synthesis of 2,5-disubstituted 1,3,4-oxadiazole. $POCl_3$ is widely used as dehydrating agent and it works mainly with alcohols.

The reaction mechanism can be envisioned to be consisting of two parts. The first part as an amide formation through a nucleophilic attack on the carboxylic acid by the hydrazide and elimination of a water molecule (Scheme 23 A). The second part is quite similar to Robinson-Gabriel oxazole synthesis, but with a small difference represented in the α-C to the nitrogen which is a nitrogen in the oxadiazole case (Scheme 23 B).

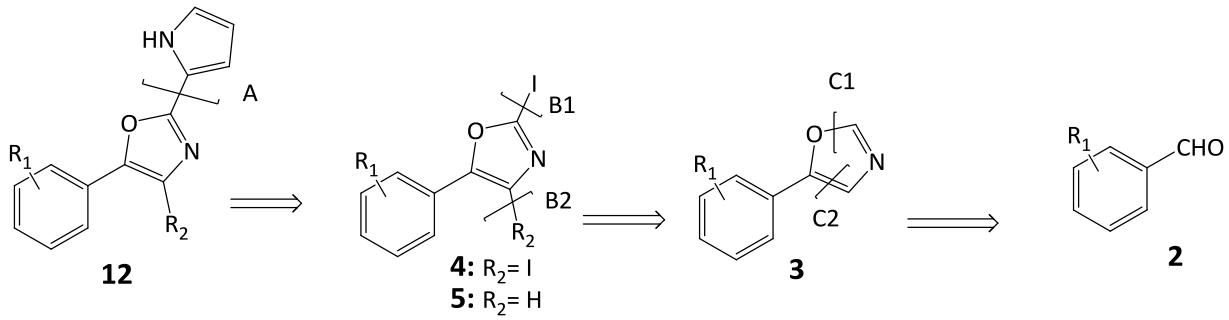


Scheme 23. Oxadiazole synthesis from carbohydrazide and carboxylic acid using $POCl_3$

3 RETROSYNTHESIS AND SYNTHETIC STRATEGY

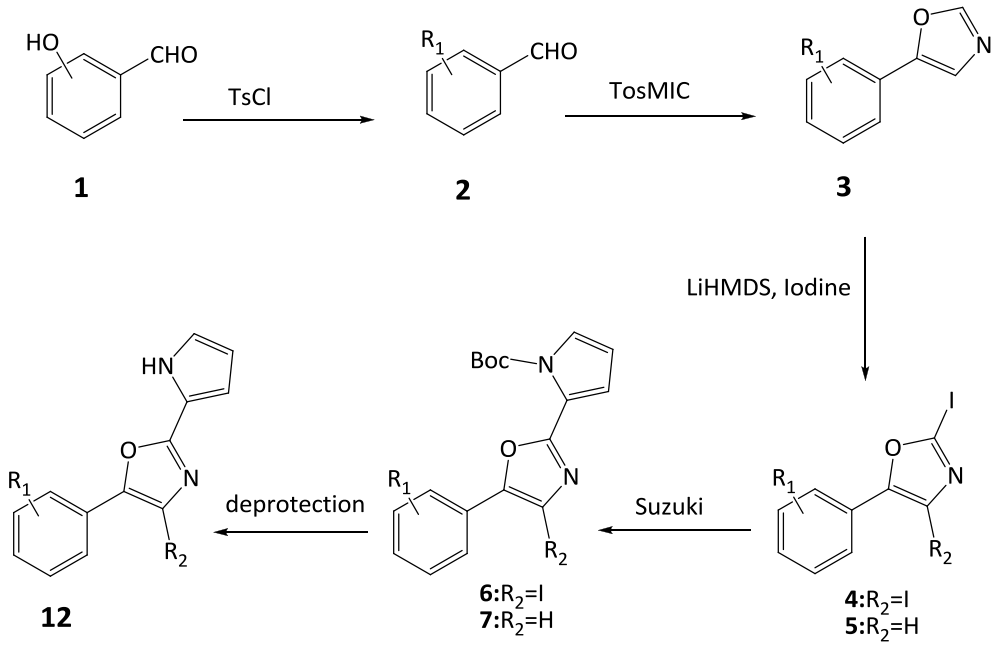
3.1 Phorbazoles analogues

The structure of target analogues **12** consist of a common core of 2,5-substituted oxazole. The 2- substituent on the oxazole is a pyrrole ring and the 5- substituent is a phenyl ring. The analogues diversity arises from the variation of the R_1 and R_2 groups. The first part of the retrosynthesis is based on the total synthesis of breitfussins A and B[6] in which, The first disconnection removes the pyrrole ring, revealing compound **4** or **5** which are the 2,4-diiodinated and the 2-iodinated oxazole derivatives, respectively. The second disconnection removes the iodides revealing the 5-substituted oxazole **3.** Based on different approach for the oxazole synthesis, the final disconnection removes the oxazole revealing **2**, the 2 or 3-substituted benzaldehyde (Scheme 24).



Scheme 24. The proposed retrosynthesis for phorbazoles analogues

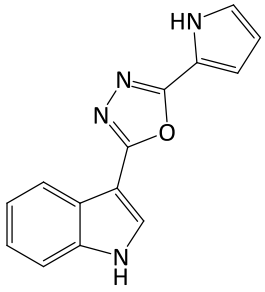
Based on the retrosynthesis, the forward synthetic plan was designed as follows; the starting material is a benzaldehyde substituted at meta or ortho positions. For the hydroxyl substituted benzaldehyde, the first step is protection of the hydroxyl with a tosyl group. After this the two groups of compounds follow the same procedure towards the targeted analogues. The oxazole is formed through a TosMIC reaction. The third step is iodination of the oxazole in which 2 approaches were considered, 2,4-diiodination and iodination on position number 2 only. The final building step is introducing the pyrrol ring by the formation of a C-C bond between 2-pyrrole and the oxazole moiety through a Suzuki-Miyaura coupling reaction (Scheme 25).



Scheme 25. The general reaction scheme for phorbazoles analogues

3.2 Breitfussins analogue

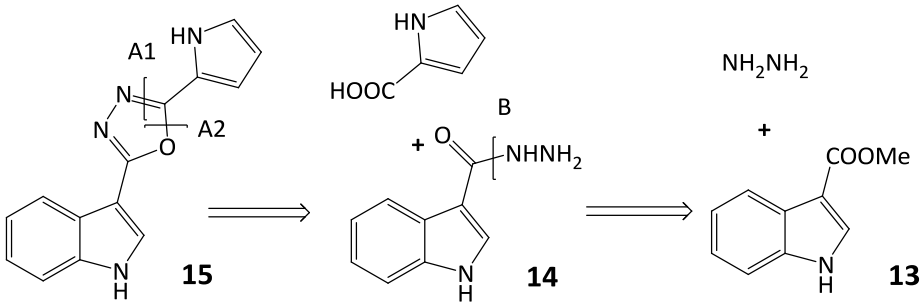
The structure of the targeted breitfussin analogue consists of the unsubsituted breitfussin skeleton with a modification in the core oxazole, in which the C-H at the 4-position is substituted with a nitrogen to form a 1,3,4-oxadiazole (Figure 8)



15

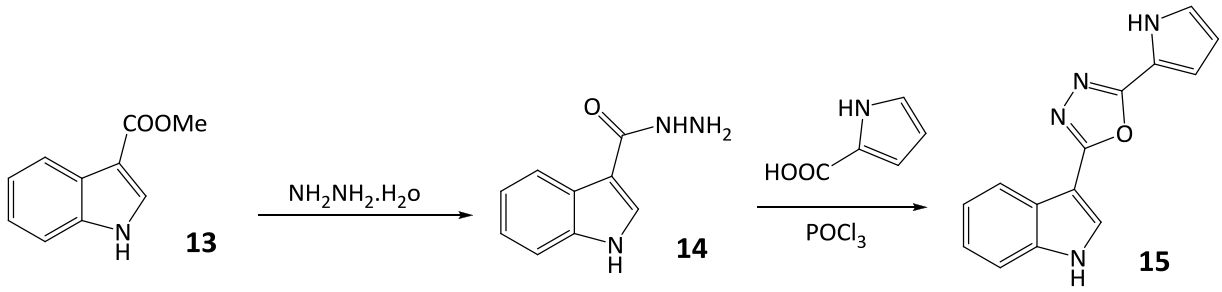
Figure 8. The structure of the target breitfussins analogue

First disconnection reveals a pyrrole with carbonyl substitution at the 2-position.The remaining part is a carbohydrazide derivative of the indole **14**. Further disconnection removes the hydrazine revealing the indole carboxylate **13** , which is commercially available and used as a starting material for the synthesis (Scheme 26).



Scheme 26. The proposed retrosynthesis for the Breitfussin analogue

The first step is a nucleophilic substitution on the carboxylate group of the starting material Methyl-1H-indole-3-carboxylate **13** with hydrazine to form the carbohydrazide of the indole **14**. This is then used in the second step where it is condensed with pyrrole-2-carboxylic acid to form an asymetric dicarbohydrazide. This is dehydratively cyclized to form the central 1,3,4-oxadiazole ring in the same reaction vessel **15** (Scheme 27).

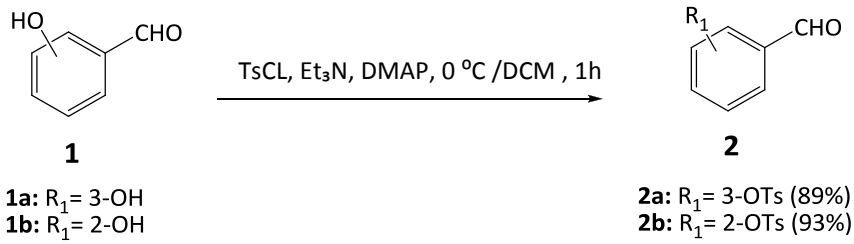


Scheme 27. The general synthetic procedure for the Breitfussin analogue

4 RESULTS AND DISCUSSION

4.1 Phorbazoles analogues

4.1.1 Tosyl protection of the hydroxybenzaldehyde



1

1a: R_1= 3-OH
1b: R_1= 2-OH

2

2a: R_1= 3-OTs (89%)
2b: R_1= 2-OTs (93%)

Scheme 28. Tosylation reaction

The phenolic oxygen carries an acidic proton, which needs to be protected to avoid problems in the Lithiation step. Tosyl group was used as a protecting group. A modified literature synthesis was performed [50] using Et_3N in DCM, and DMAP as a nucleophilic catalyst (Scheme 28). DMAP is a highly basic catalyst and it is employed in nucleophilic catalysis of a variety of reactions[51].

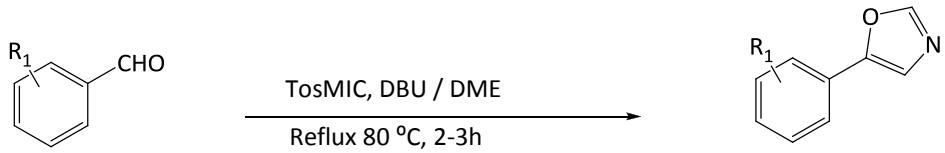
The reaction was performed on the commercially available 3-hydroxy and 2-hydroxy benzaldehydes **1a** and **1b**, respectively. No starting material was observed on TLC after 1 hour of stirring at 0 °C. The products were easily crystallized out using 15% water/ethanol. The corresponding tosylated benzaldehydes, **2a** and **2b** were obtained in 88 % and 93 % yields, respectively.

4.1.2 Oxazole synthesis

A van Luesen oxazole synthesis was used to synthesis the oxazole moiety in which TosMIC was used as a precursor. Two groups of compounds were subjected to the reaction with different conditions.

Oxazole formation with tosyloxy substituted benzaldehyde

The standard procedure uses TosMIC in presence of K_2CO_3 as a base and methanol as a refluxing solvent [52], which are the same conditions used for removing the tosyl group [41] [16]. A modification has been done on the standard procedure in which, DBU is used as a base and DME as a solvent (Scheme 29). DBU is a non-nucleophilic base [53]. DME was chosen as a solvent over methanol to avoid nucleophilic attack on the Tosyl group.



2

2a: R_1= 3-OTs
2b: R_1= 2-OTs

3

3a: R_1= 3-OTs (61%)
3b: R_1= 2-OTs (40%)

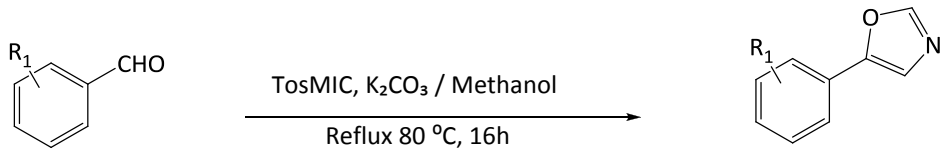
Scheme 29. Modified TosMIC procedure for oxazoles synthesis

3-tosylated benzaldehyde **2a** was refluxed with TosMIC and K_2CO_3 in DME for 3 hours and no starting material was observed on TLC. The corresponding oxazole derivative **3a** was isolated in 61% yield after column chromatography purification.

With the 2-tosylated benzaldehyde **2b**, the reaction was performed 2 times under the same conditions. In the first attempt, the reaction was run for 3 hours and the crude showed a minute amount of starting material on TLC. In the second attempt, the reaction was left to run for overnight and no starting material was observed on the TLC afterwards. The corresponding oxazole derivative **3b** was isolated after column chromatography purification. The yield from the first batch was 33% and the second one was 40 %.

Oxazole formation with methoxy substituted benzaldehyde

The methoxy benzaldehydes **2c** and **2d** were also subjected to the van Leusen oxazole synthesis using the standard procedure [52] ,with potassium carbonate as a base and methanol as refluxing solvent (Scheme 30).



2

2c: R_1= 3-OMe
2d: R_1= 2-OMe

3

3c: R_1= 3-OMe (44%)
3d: R_1= 2-OMe (30%)

Scheme 30. Standard TosMIC procedure for oxazoles synthesis

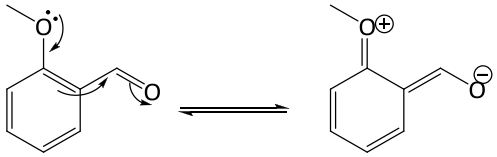
After running the reaction for16 hours using the commercially available 2-methoxy benzaldehyde **2c**, no starting material was observed on TLC from the crude. The corresponding oxazole derivative **3c** was isolated after column chromatography purification in 44 % yield.

The reaction was run for 3 hours on 2-methoxybenzaldehyde **2d**. The TLC showed a plenty of the starting material so more TosMIC was added (0.1 eq.) and the reaction was left to run for overnight. After that the reaction was complete. The corresponding oxazole derivative **3d** was isolated in 30% yield after column chromatography purification.

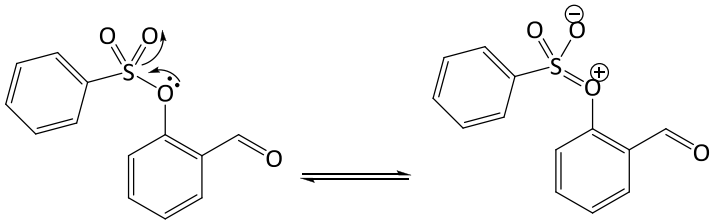
Discussion

It was observed from the previous set of reactions that a better yield is obtained from the meta substituted starting material than the ortho substituted ones. This may be rationalized if we take the steric hindrance effect into account.

It was also observed that the tosyloxy substituted starting materials give better yields than the methoxy substituted ones. This can be explained by the electronic effects, as the more electrophilic carbonyl group is more reactive to nucleophilic attack. Since the oxygen of methoxy group is more electron donating than the oxygen of the Tosyloxy group, the tosyl protected compound will react better (Scheme 31 and 32).



Scheme 31. Electron donation of the methoxy group



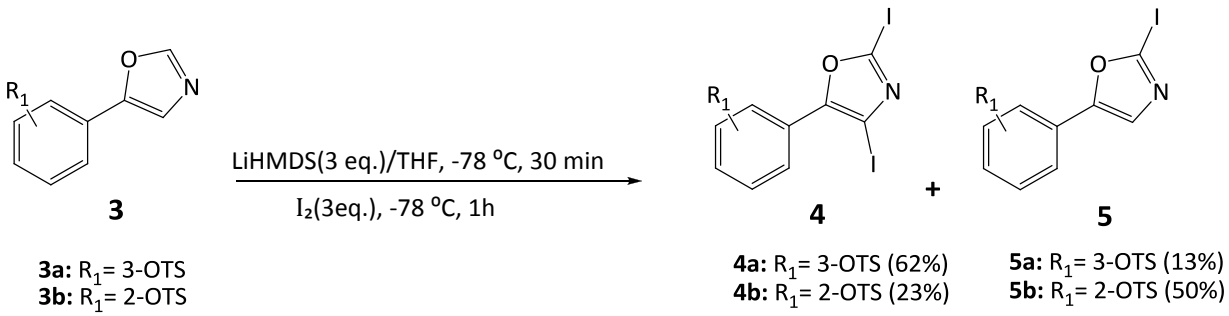
Scheme 32. Electron withdrawal of the tosyloxy group

4.1.3 Iodination of the oxazole

The four previously synthesized oxazoles were subjected to iodinations with the aim to achieve both selective 2,4-diiodination and 2-iodination. Two approaches were applied, iodination by lithiation and TMPMgCl•LiCl based iodination.

4.1.3.1 2,4-Diiodination of the oxazole by lithiation

As a previous work by our research group showed that dominant 2,4-diiodination of the oxazole can be achieved by using 3 eq. of the base at -78 °C and adding 3 eq. of iodine at the same temperature (Scheme 33). The reaction was performed on the tosylated oxazole derivatives **3a** and **3b**.



Scheme 33. Attempted Synthesis of 2,4-iodinated oxazole derivatives by Lithiation

The 3-tosylated oxazole derivative **3a** was stirred with 3 eq. of LiHMDS for 30 minutes at -78 ^{o}C. 3 eq. of the iodine as an electrophilic source for the iodide substitution was added at the same temperature as a solution in dry THF. The TLC was checked after 1h of stirring with iodine and it showed 2 closely packed spots of new compounds and traces of the starting material. After flash column purification, two fractions were collected. The first fraction was the 2,4-diiodo oxazole derivative **4a** and the second fraction was a mixture of **4a** and the 2-iodinated oxazole derivative **5a** in 3.3:1 ratio, respectively. The ratio was calculated according to the integration of the ^{1}H NMR peaks of the mixture. The calculated yield for **4a** and **5a** is 62% and 13%, respectively.

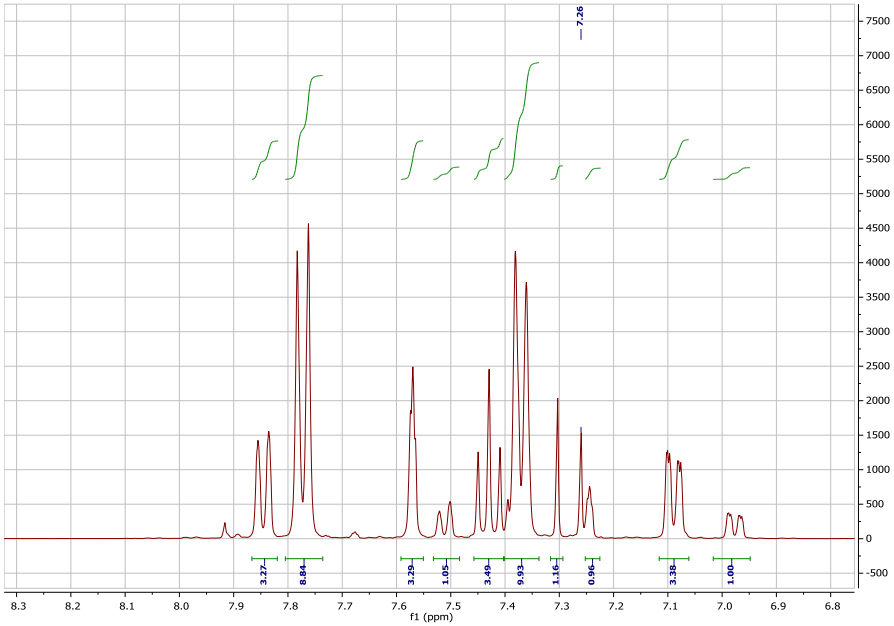


Figure 9. The ^{1}H NMR peaks integration of the di and mono-iodinated derivatives mixture, **4a** and **5a**, respectively

The 2-tosylated oxazole derivative **3b** was reacted under the same conditions as **3a** (see above). After 1h of stirring with iodine the TLC showed no starting material and one new clear spot appeared. After column chromatography purification the NMR showed that the product was a mixture of 2-iodo and 2,4-diiodo oxazole derivatives with ratio 2.2:1, respectively. The ratio was estimated based on the integration of the two CH_3 peaks of the tosyl group in the NMR spectra (Figure 8). The total protons count also supports the estimated ratio (Figure 9). According to the estimated ratio, the calculated yield of the mono-iodinated derivative is 50 % and that of the 2,4-iodnated is 23%.

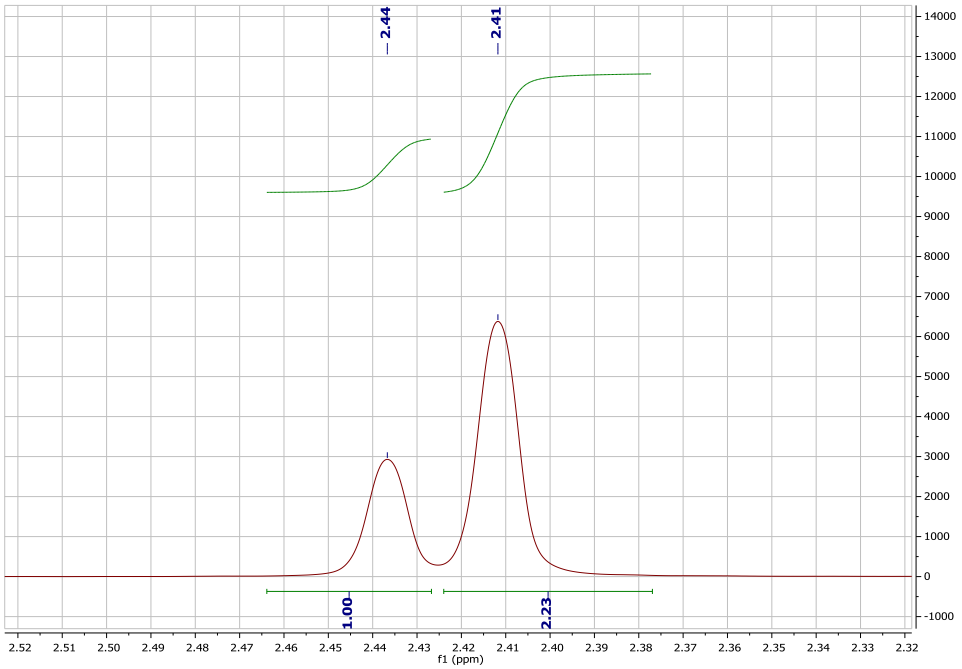


Figure 10. The integration of the two CH_3 peaks of the tosyl group for the mono and di-iodo oxazoles products obtained from 2,4-diiodination of the 2-tosylated oxazole derivative **3b**

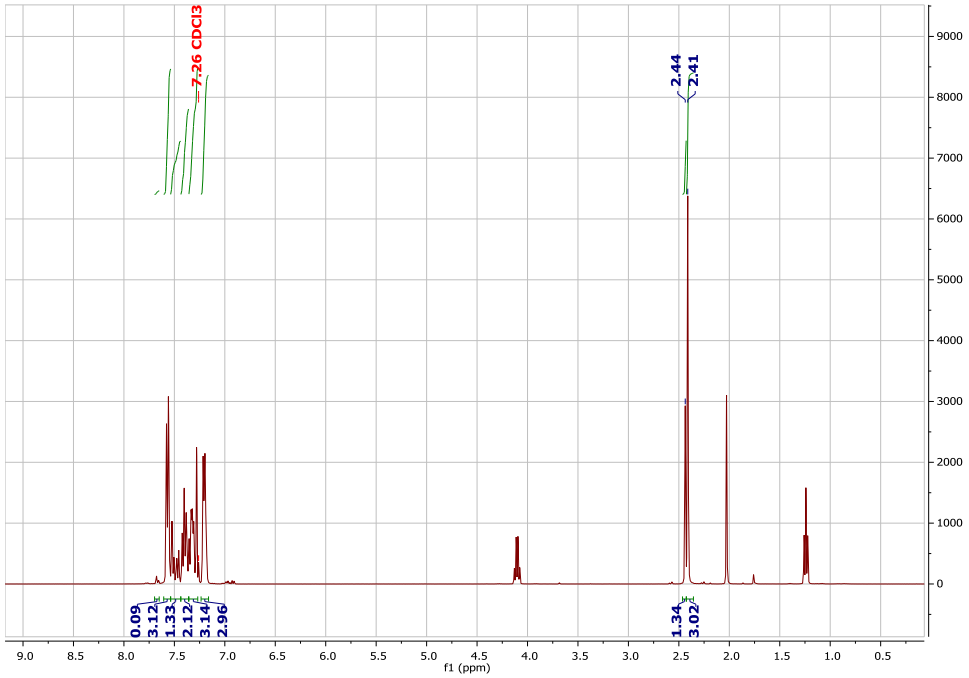
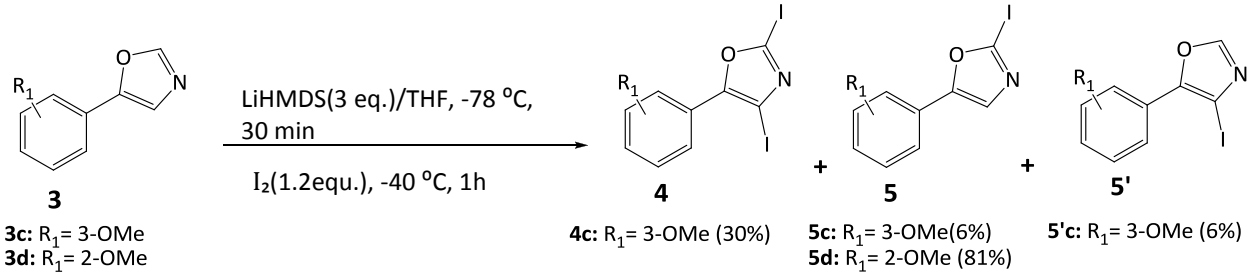


Figure 11. The total protons count for products obtained from 2,4-diiodination of the 2-tosylated oxazole derivative **3b**

4.1.3.2 2-Iodination of the oxazole

Regioselective 2-iodination of the oxazole through lithiation was reported by Pandey et. al. [6] during the total synthesis of breitfussins A and B. The same procedure was used with the methoxy oxazole derivatives **3c** and **3d** (Scheme 34).



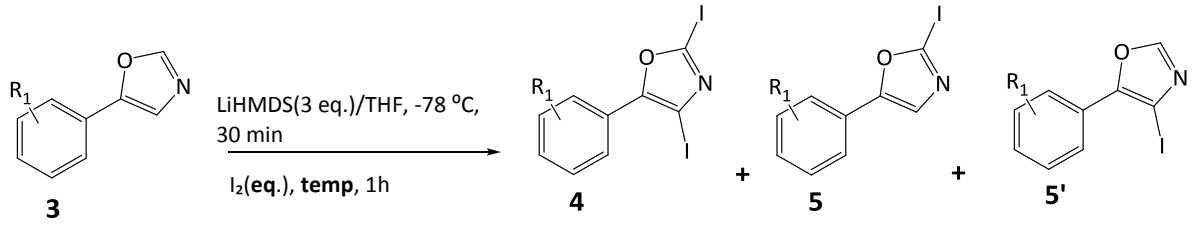
Scheme 34. Attempted Synthesis of 2-iodinated oxazole derivatives by lithiation

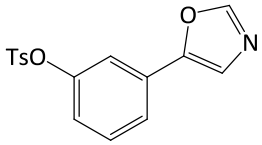
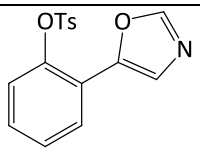
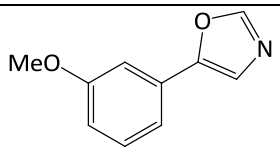
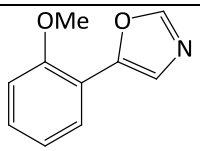
The procedure is similar to the one used for the 2,4-iodination of oxazole but the difference is that the iodine is added with less equivalents and at a higher temperature, around -40 °C.

The reaction was performed on 0.5 g scale of the 3-methoxy oxazole derivative **3c**. The TLC showed a considerable amount of the starting material in addition to 2 new spots, which were believed to belong to the mono and diiodinated compounds. Separation was attempted by column chromatography and 4 fractions were collected. The first fraction was the 2,4-diiodinated derivative **4c**. The second fraction was a mixture of 2 co-eluted compounds, presumably according to the ^{1}H NMR data the 2 and 4-iodinated derivatives **5c** and **5'c**, respectively. The third fraction was a mixture of **4c**, **5c** and **5'c**. The last fraction was the starting material in 22% recovered. Based on the NMR data, the calculated yields of the 2,4-diiodinated **4c**, 2-iodinated **5c** and 4-iodinated **5'c** are 30%, 6% and 6%, respectively.

The reaction was carried on 250 mg scale of the 2-methoxy oxazole derivative **3d**. The TLC showed traces of the starting material and one new spot. After column chromatography purification the corresponding 2-iodo oxazole derivative **5d** was separated in 81% yield.

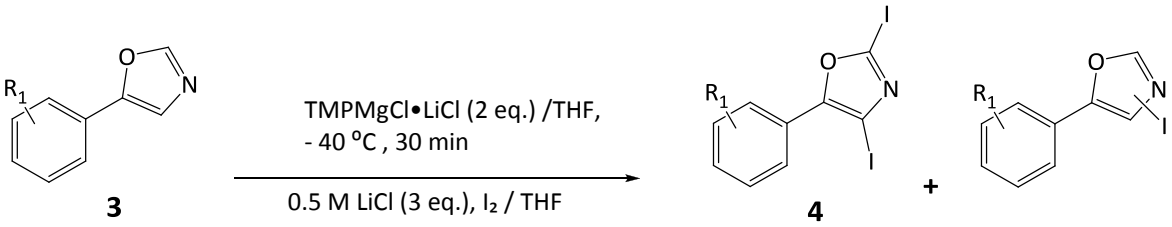
Table 1. Summary of the performed iodinations on the oxazole



entry	Starting material	I_2 eq.	Temp. of I_2 addition	The products yield		
				2,4-diiodinated	2-iodinated	4-iodinated
a	 **3a**	3	- 78 °C	**4a** 62%	**5a** 13%	-
b	 **3b**	3	- 78 °C	**4b** 23%	**5b** 50%	-
c	 **3c**	1.2	- 40 °C	**4c** 30%	**5c** 6%	**5'c** 6%
d	 **3d**	1.2	- 40 °C	-	**5d** 81%	-

4.1.3.3 Iodination of the oxazole using TMPMgCl•LiCl as a base

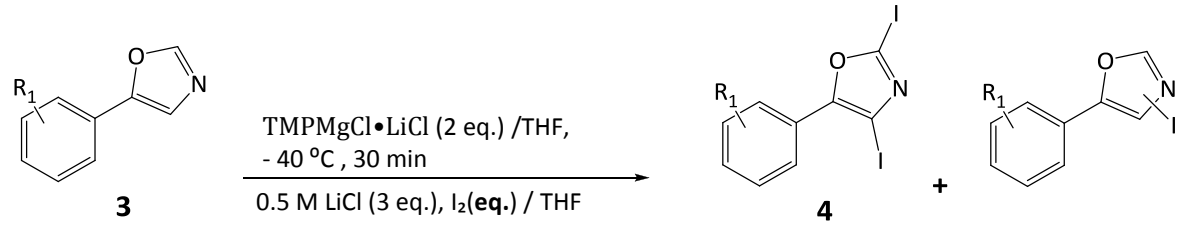
The original regioselective oxazole functionalization using TMP metal bases was proposed by Knochel and co-workers [26]. A modification on the procedures was carried by members of our research group. It was found that the reaction works faster upon addition of 0.5 M Licl in THF prior to the addition of the iodine (Scheme 35).

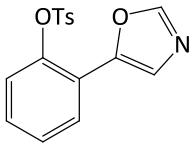
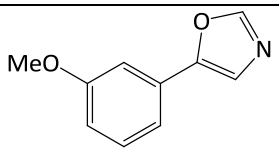
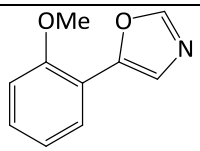


Scheme 35. Synthesis of 2-iodinated oxazole derivatives using $TMPMgCl_2$.LiCl base

The reaction was tested using different equivalents of iodine on a small scale of the oxazole derivatives, **3b**, **3c** and **3d.** TMPMgCl•LiCl was used as a base at - 40 °C. From the ^{1}H NMR data of each reaction the product ratios were estimated (table 2).

Table 2. Attempts of iodination using $TMPMgCl_2.LiCl$ base

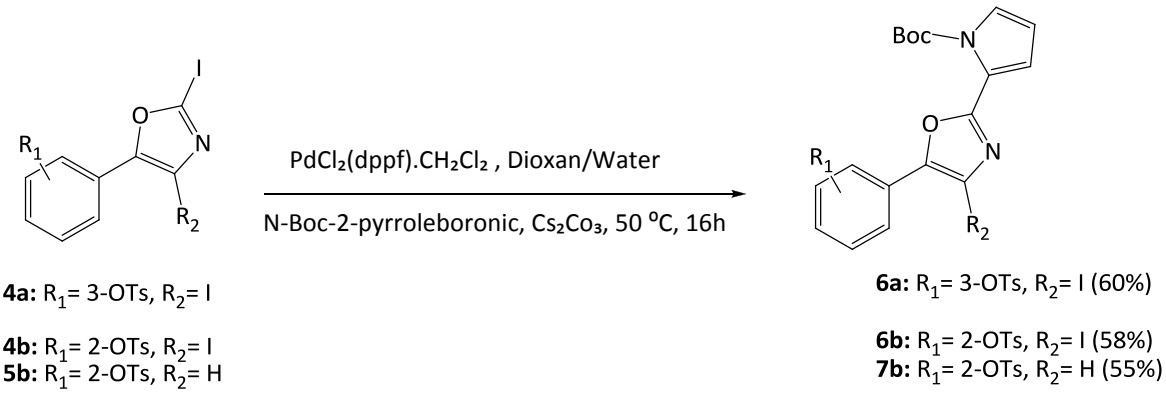


entry	Starting material	I_2 equivalents	Products ratio		
			di-iodo	Mono-iodo	Starting material
a	 **3b**	2	1	6	1.5
		1.5	1	7	7
		1.1	1	5	3.5
b	 **3c**	2	-	-	-
c	 **3d**	2	-	-	-

For the methoxy substituted oxazoles **3c** and **3d**, there was a close ratios between the starting material, the mono and the diiodinated derivatives. It was hard to assign the ^1H NMR peaks from the crude to the corresponding compounds.

4.1.4 Introduction of 2-pyrrole through Suzuki coupling reaction

Pandey et al. [6] reported a Suzuki coupling on a di-iodo oxazole derivative during the total synthesis of breitfussins A and B. The same procedure was applied on a set of previously synthesized compounds in order to introduce the 2-pyrrole ring on C2 of the oxazole (Scheme 36).



4a: R_1= 3-OTs, R_2= I

4b: R_1= 2-OTs, R_2= I
5b: R_1= 2-OTs, R_2= H

6a: R_1= 3-OTs, R_2= I (60%)

6b: R_1= 2-OTs, R_2= I (58%)
7b: R_1= 2-OTs, R_2= H (55%)

Scheme 36. The performed Suzuki-Miyaura coupling reaction

Suzuki coupling occurs between two partners, a halogenated one, which undergoes oxidative addition with palladium and the other one which is carried on the boronic acid. In our strategy, the oxazole was the halogenated partner.

Coupling of the diiodinated oxazole with 3-tosyloxy substitution 4a

The reaction was performed on the 2,4-iodo oxazole derivative **4a** and stirred for 2 hours at 50 °C but the reaction was not complete. After the mixture was left to be stirred for overnight at rt, no starting material was observed on TLC. The corresponding oxazole-pyrrole derivative **6a** was isolated in 60 % yield after column chromatography purification.

Coupling of a mixture of di- and monoiodinated oxazole with 2-tosyl substitution 4b and 5b

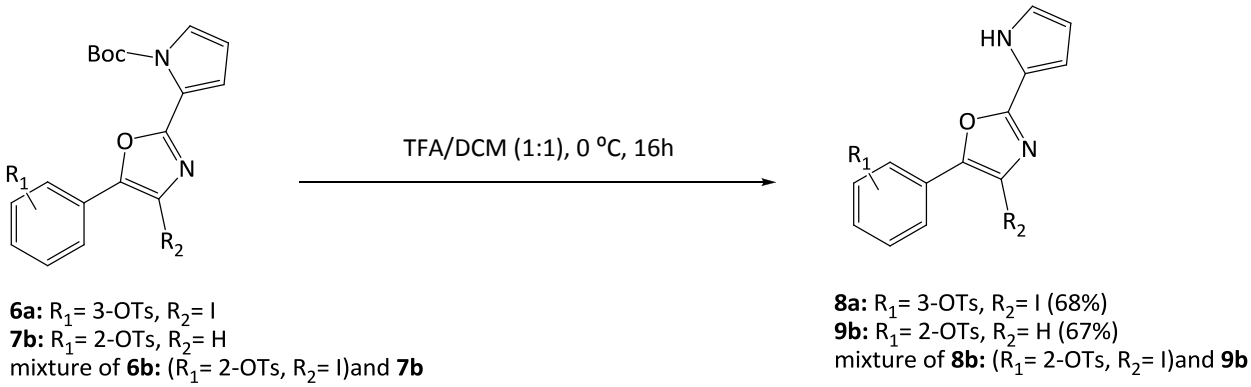
The coupling was also performed on un-separated mixture of 2,4-diiodo oxazole **4b** and 2-iodo oxazole **5b** of 1:2.2 ratio, respectively. After the reaction was run for overnight at 50 °C, only a minute amount of the starting material was observed on the TLC. The two coupled products, **6b** and **7b,** were separated after column purification**.** The separation was hard and not complete, as the two products were closely eluted, so a mixture of both was also obtained. The yields were calculated to be 58% and 55% of **6b** and **7b**, respectively

Discussion

In a previous work by our research group, they were not able to couple the mono-2-iodinated oxazole with indole substitution. The performed coupling reactions in this thesis indicate that, for ary-substituted oxazole, the 2-mono-iodinated as well as the diiodinated oxazole are feasible substrates in the coupling.

4.1.5 Boc group deprotection

Removal of Boc group using equal volumes of TFA acid and DCM was performed (Scheme 37). The same procedure was used by Johnson [54] for Boc group deprotection from an indole and a piprazine.



6a: R_1= 3-OTs, R_2= I
7b: R_1= 2-OTs, R_2= H
mixture of **6b:** (R_1= 2-OTs, R_2= I)and **7b**

8a: R_1= 3-OTs, R_2= I (68%)
9b: R_1= 2-OTs, R_2= H (67%)
mixture of **8b:** (R_1= 2-OTs, R_2= I)and **9b**

Scheme 37. Boc group deprotection

The previously coupled 4-iodooxazole with 3-tosyloxy substitution **6a** was Boc-deprotected using equal volumes of TFA and DCM. After 2 hours of stirring the starting material was observed on the TLC. The reaction was left to stir for overnight and after that no starting material was left. In turn a new spot very closely eluted to the starting material was noticed which gave a different color upon staining. The corresponding phorbazoles analogue **8a** was isolated after column chromatography purification in 68 % yield.

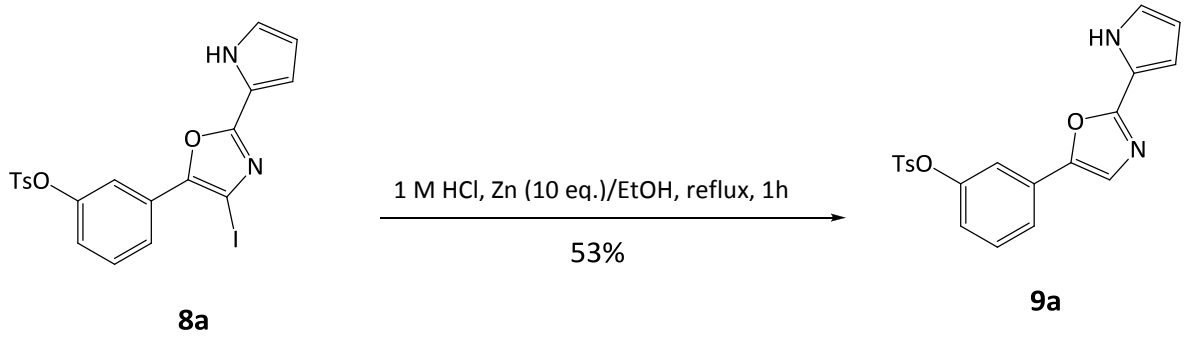
The pyrrole-oxazole with 2-tosyloxy substitution **7b** was stirred with TFA/DCM mixture for 16 hours. After this, no starting material was seen on the TLC. The corresponding phorbazoles analogue **9b** was obtained in 67 % yield.

The reaction was performed on a mixture of the 2-tosylated pyrrole-oxazole derivatives **6b** and **7b**. After 16 hours of stirring the 2 spots of the starting material disappeared and 2 new spots were noticed which were believed to belong to corresponding Boc-deprotected species **8b** and **9b**. The crude was not purified and further used in deiodination and detosylation reaction.

4.1.6 Analogue diversity by selective de-protection and de-iodination

4.1.6.1 De-iodination

Alkyl or arylhalides can be reduced by different methods. Metallic zinc is excellent for replacing a halogen with a hydrogen in acidic medium. Usually the zinc reductions takes place in a hot or a refluxing solvent[55].

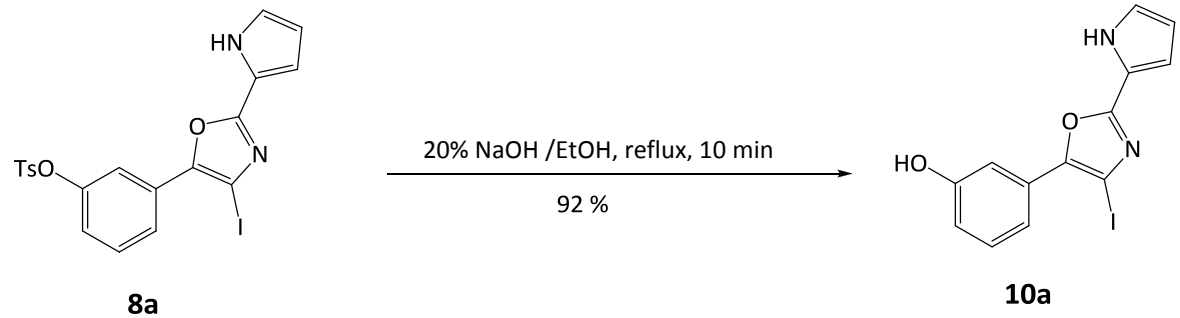


8a **9a**

Scheme 38. De-iodination reaction

The 3-tosylated iodinated analogue **8a** was heated at reflux with Zinc and hydrochloric acid in ethanol (Scheme 38). After short time, a white fluffy powder appeared in the solution which turned into yellowish precipitate after 30 minutes of stirring. EA was added but the solid did not dissolve. After that, acetone was added and the solid dissolved. No starting material was seen on the TLC and a new spot was observed. Upon addition of water the product crystallized out as grey crystals which was isolated revealing the corresponding de-iodinated analogue **9a** in 53% yield.

4.1.6.2 De-tosylation



8a **10a**

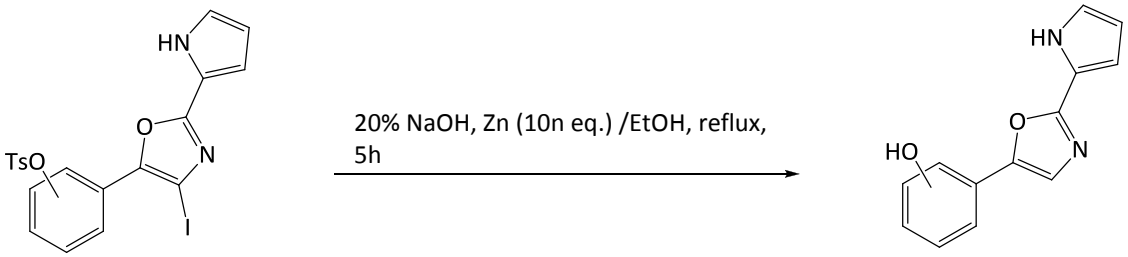
Scheme 39. De-tosylation reaction

The tosyl group is easily removed by refluxing with nucleophilic base. Mostly no purification is needed since the aqueous work up is enough to get rid of de-protected tosyl group which goes to the water phase.

The reaction was performed on the 3-tosylated derivative **8a**. It was refluxed in ethanol with the base. The product had very minor impurities after the aqueous workup. The phorbazoles analogue **10a** was obtained in 92 % yield (Scheme 39).

4.1.6.3 De-ioination and de-tosylation

It is the same reaction used for the de-tosylation but in addition, 10 eq. of zinc were added for reduction and replacing the iodine with a hydrogen (Scheme 40)



3-OTs (**8a**)
2-OTs (**8b**)

3-OH (**11a**)
2-OH (**11b**)

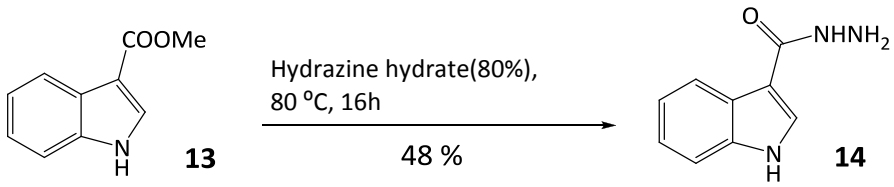
Scheme 40. De-tosylation and de-iodination reaction

The reaction was performed on the 3-tosylated iodinated analogue **8a**. The TLC checked after 1 and 3 hours, both showed the starting material in a considerable amount. After 5 hours only traces of the starting material was left. During the reaction a large amount of white crystals was formed which was filtered off before the aqueous workup. The crude was not purified. The NMR and MS data showed that the 3-hydroxy substituted analogue **11a** was obtained with some minor impurities.

In the same way, a crude mixture of the un-separated analogues, **8b** and **9b** was refluxed in ethanol with sodium hydroxide and zinc for 5 hours. The TLC showed no starting material. After aqueous workup, a grayish crude was obtained. The 2-hydroxy substituted analogue was precipitated out of an EA solution of the crude, when it was left for some time.

4.2 Breitfussins analogue

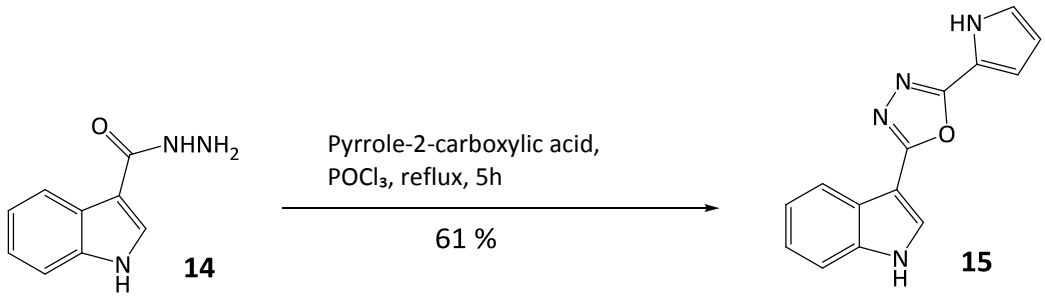
4.2.1 Synthesis of the carbohydrazide derivative



Scheme 41. Synthesis of the carbohydrazide derivative

Zhang[48] reported the synthesis of the target compound **14** in 95% yield by refluxing the starting material with hydrazine hydrate (95%) in ethanol. The reaction was performed for two times. First attempt by refluxing **13** in ethanol with the hydrazine hydrate 80% but it did not work. In the Second attempt, the starting material was stirred at 80 °C with excess of neat hydrazine hydrate 80% for 16 hours. The TLC did not show any starting material. Upon addition of a small amount of ethanol and cooling down, a white solid precipitated out of the solution, which was filtered and washed with ethanol revealing **14** in 48% yield.

4.2.2 1,3,4-Oxadiazole synthesis



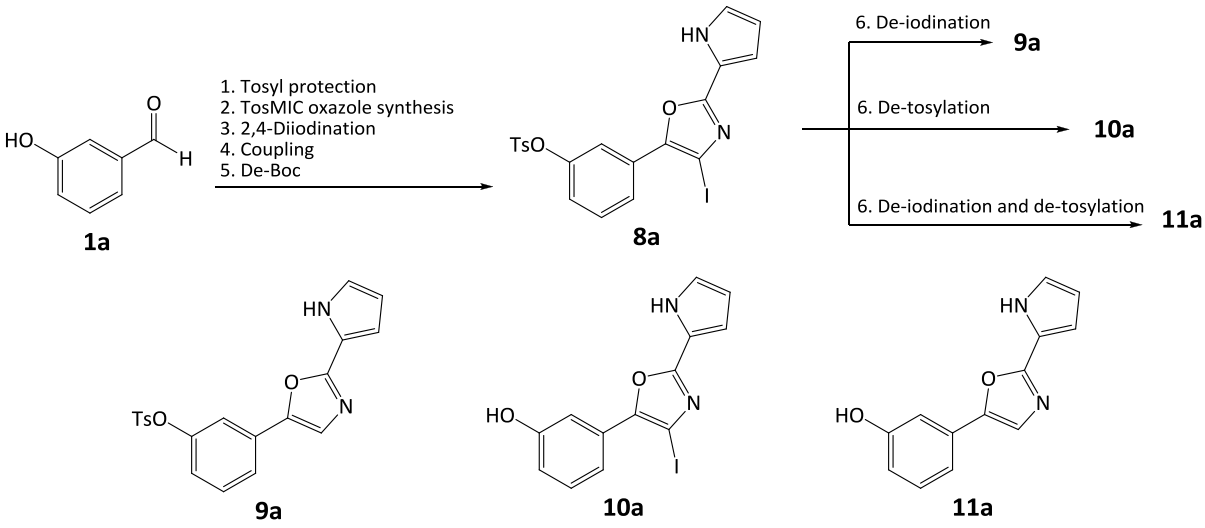
Scheme 42. Synthesis of the 1,3,4-oxadiazole derivative from the carbohydrazide

According to the procedure by Zhang[48], the carbohydrazide **14** was dissolved in $POCl_3$ and refluxed with the commercially available pyrrole-2-carboxylic acid for 5 hours and then stirred under vacuum to remove the $POCl_3$. A deep red colored solid was left after evaporation of the $POCl_3$. The crude was purified by column chromatography and the corresponding oxadiazole derivative **15** was obtained in 61% yield (Scheme 42).

5 CONCLUSION

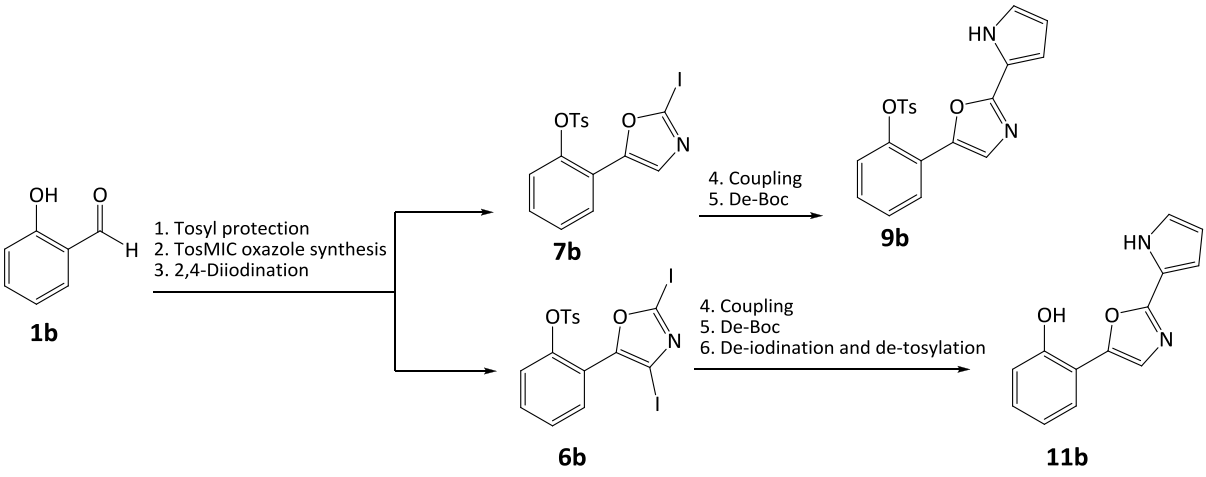
This thesis describes my efforts to synthesis a small library of phorbazoles and breitfussins analogues. The synthesis of 6 phorbazoles analogues was successful from the commercially available starting materials, 3-hydroxybenzaldehyde **1a** and 2-hydroxybenzaldehyde **1b**.

4 analogues were prepared from **1a**: **8a**, **9a**, **10a** and **11a** (scheme 43)



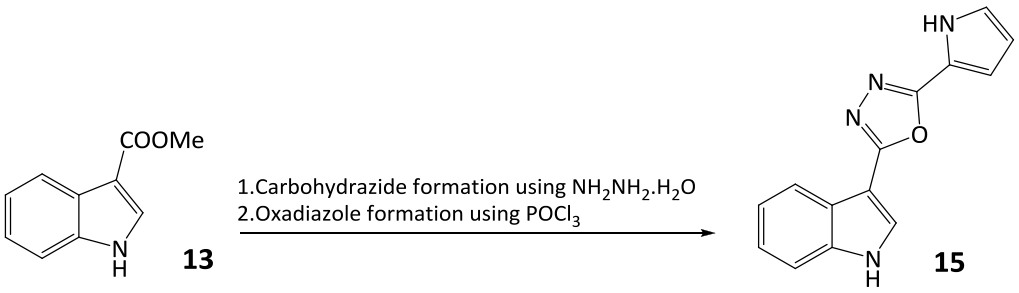
Scheme 43. The analogues obtained from the starting material, 3-hydroxybenzaldehyde **1a**

2 analogues were prepared from **1b**: **9b** and **11b** (Scheme 44)



Scheme 44. The analogues obtained from the starting material, 2-hydroxybenzaldehyde **1b**

The synthesis of one breitfussins analogue **15** in two steps was successful using methyl-1H-indole-3-carboxylate **13** as a starting material (Scheme 45).



Scheme 45. The total synthesis of the breitsussins analogue **15**

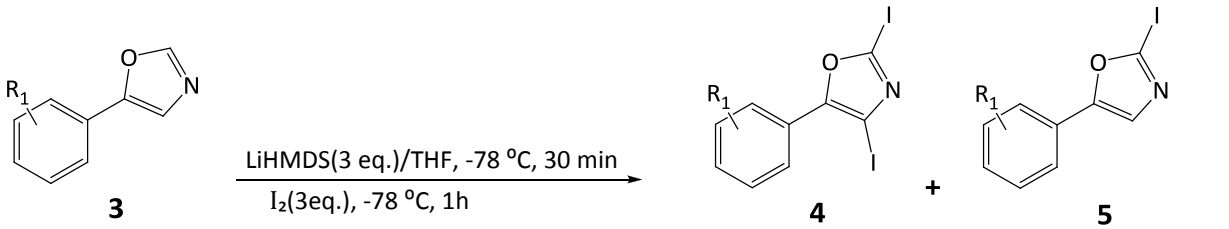
A van Leusen based oxazole synthesis was followed to form the oxazole core in the phorbazoles analogues. The reaction was performed on 4 compounds, the **3-** and **2-** tosyloxybenzaldehydes **2a** and **2b**, respectively and the 3- and 2-methoxybenzaldehydes, **2c** and **2d**, respectively. The tosyloxy substituted starting materials give better yields than the methoxy substituted ones and the 3-substitution is more favored in both cases (Scheme 46).

2a: R_1= 3-OTs
2b: R_1= 2-OTs
2c: R_1= 3-OMe
2d: R_1= 2-OMe

3a: R_1= 3-OTs (61%)
3b: R_1= 2-OTs (40%)
3c: R_1= 3-OMe (44%)
3d: R_1= 2-OMe (30)

Scheme 46. Summary of the performed oxazoles synthesis

Iodination by lithiation was performed with aim to obtain selective 2,4-diiodination and 2-iodination on the oxazole. The 2,4-iodination approach was performed on 3- and 2-tosylated oxazole derivatives, **3a** and **3b**, respectively. The 2,4-iodinated derivative was obtained as a major product from **3a** but the 2-iodinated derivative was the major product with **3b** (Scheme 47).



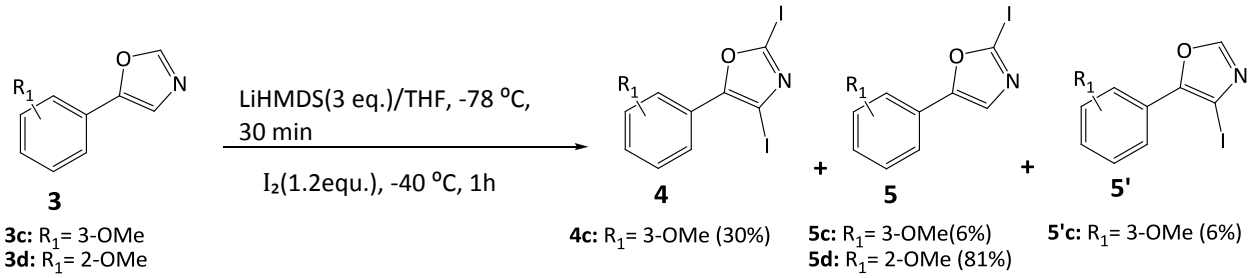
3a: R_1= 3-OTS
3b: R_1= 2-OTS

4a: R_1= 3-OTS (62%)
4b: R_1= 2-OTS (23%)

5a: R_1= 3-OTS (13%)
5b: R_1= 2-OTS (50%)

Scheme 47. The attempted 2,4-diiodination

The 2-iodination approach was performed on the 3- and 2-methoxy oxazole derivatives, **3c** and **3d**, respectively. The 2-iodinated derivative was the only product obtained from **3c**, while the 2,4-diiodinated was the major product with **3d** (Scheme 48).



3

3c: R_1= 3-OMe
3d: R_1= 2-OMe

4

4c: R_1= 3-OMe (30%)

5

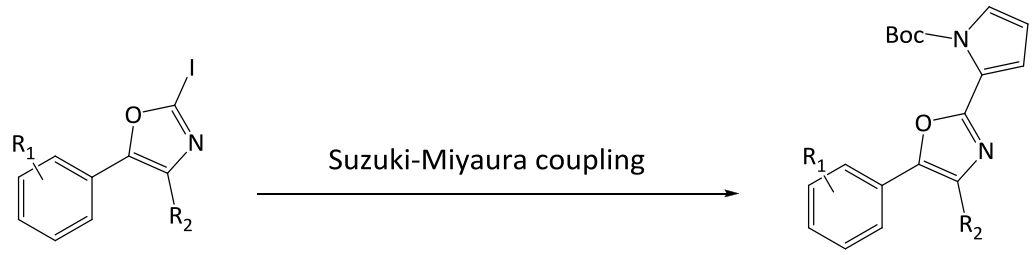
5c: R_1= 3-OMe(6%)
5d: R_1= 2-OMe (81%)

5'

5'c: R_1= 3-OMe (6%)

Scheme 48. The attempted 2-iodination

Coupling was performed on 2-iodinated and 2,4-diiodinated oxazole species with tosylated phenyl substitution on C5 and both are feasible substrates for the coupling in contrast to what was observed before with the C5 indole substitution (Scheme 49).



4a: R_1= 3-OTs, R_2= I

4b: R_1= 2-OTs, R_2= I
5b: R_1= 2-OTs, R_2= H

6a: R_1= 3-OTs, R_2= I (60%)

6b: R_1= 2-OTs, R_2= I (58%)
7b: R_1= 2-OTs, R_2= H (55%)

Scheme 49. Summary of the performed Suzuki-Miyaura coupling

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7 EXPERIMENTAL PROCEDURES

All reagents were purchased from Sigma Aldrich Co. and used as received. Dry THF was obtained from a sodium/benzophenone still. Column chromatography was performed using silica gel 35-70 micron from DAVISIL. Reactions were monitored by TLC using Merck KGaA, 60 F254 silica gel plates and visualized by UV and stains.

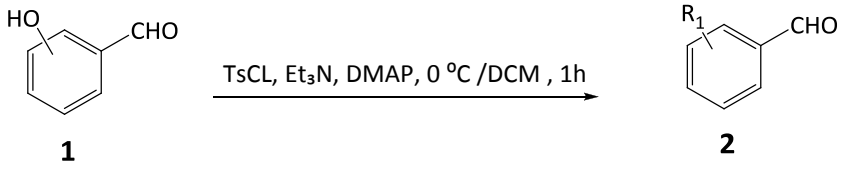
NMR spectra were recorded on 400 MHz Bruker Advance III equipped with a 5 mm SmartProbe BB/1H using $CDCl_3$, DMSO-d6 or Acetone-d6 as a solvent. The reference values for $CDCl_3$ were 7.26 and 77.02 for ^{1}H and ^{13}C-NMR spectra respectively. DMSO-d6 reference values were 2.50 and 40.23 for ^{1}H and ^{13}C-NMR spectra respectively. Acetone-d6 reference values were 2.05 and 29.98 for ^{1}H and ^{13}C-NMR spectra respectively. Some NMR spectra may contain peaks from residual solvents, mainly EA and acetone. All the NMR spectra were processed with MestReNova-10.0.2.

HRMS spectra were recorded on a Thermo scientific electron LTQ Orbitrap XL +Electrospray ion source using methanol as a solvent.

Evaporation of volatile solvents was performed by a Buchi rotavapor evaporator with an integrated vacuum pump.

7.1 Synthesis of phorbazoles analogues

7.1.1 General procedure for protection of the hydroxybenzaldehyde with tosyl group



1

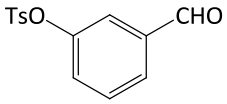
1a: R_1= 3-OH
1b: R_1= 2-OH

2

2a: R_1= 3-OTs (89%)
2b: R_1= 2-OTs (93%)

Compound **1** and 0.4 mol % of DMAP were dissolved in DCM (10 mL per 1 g of compound **1**). Et_3N (4.5 mL per 1 g of **1**) was added and the solution was cooled with stirring to 0 °C. Tosylchloride was suspended in DCM (2 mL per 1 g tosylchloride) and added dropwise to the solution. The mixture was stirred for 1 hour. A proper amount of water was added. The organic layer was separated, washed 2 times with 1 M HCl and 2 times with brine solution, dried over $MgSO_4$, filtered and the solvent evaporated. The crude was purified by recrystallization using 15 % ethanol/water and dried.

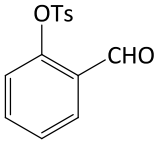
7.1.1.1 3-Formylphenyl-4-methylbenzenesulfonate (2a)



2a

3-Formylphenyl-4-methylbenzenesulfonate **2a** (20.3 g, 73 mmol, 89 %) was prepared from 3-hydroxybenzaldehyde **1a** (83 mmol) as pale yellow crystals. **TLC**; R_f=0.33 (30% EA/heptane). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 9.93 (S,1H) , 7.78 (d, J = 7.6 Hz ,1H) , 7.72 (d, J = 7.6 Hz, 2H), 7.49 (t, J= 8 Hz, 1H) , 7.47 (s, 1H), 7.33 (d, J= 8 Hz , 2H) , 7.30 (m, 1H), 2.46 (s, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 190.6, 150.2, 145.8, 137.9, 132.0, 130.4, 129.9, 128.5, 128.4, 128.2, 123.0, 21.7. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{11}O_4S$ $[M+H]^+$ 275.0378, found 275.0383.

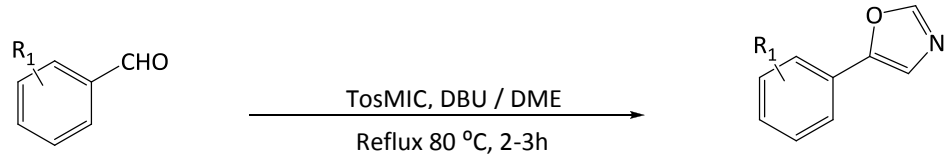
7.1.1.2 2-Formylphenyl-4-methylbenzenesulfonate (2b)



2b

2-Formylphenyl-4-methylbenzenesulfonate **2b** (21 g, 76 mmol, 93 %) was prepared from 2-hydroxybenzaldehyde **1b** (83 mmol) as pale yellow crystals. **TLC**; R_f =0.33 (30% EA/heptane). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 9.99 (S,1H), 7.87 (dd, J = 2,8 Hz, 1H) , 7.71 (d, J = 8 Hz, 2H), 7.59 (m, 1H) , 7.40 (t, j=8 Hz, 1H), 7.34 (d, J = 8 Hz, 2H) , 7.22 (d, j = 8 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 187.3, 151.2, 146.3, 135.3, 131.4, 130.1, 129.3, 128.6, 128.5, 127.5, 123.8, 21.8. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{11}O_4S$ 275.0378, found 275.0384.

7.1.2 Modified procedure for oxazole synthesis by TosMIC.



2

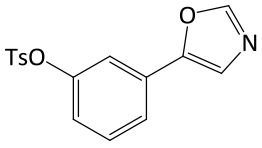
2a: R_1= 3-OTs
2b: R_1= 2-OTs

3

3a: R_1= 3-OMe (61%)
3b: R_1= 2-OMe (40%)

Compound **2** and 1.1 eq. of TosMIC were dissolved in DME (5 mL per 1 g of **2**). 1.1 eq. of DBU was added and the mixture was refluxed for 2-3 hours. Water was added and the organic layer was separated and washed 3 times with brine solution, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by column chromatography using EA/pentane as eluent in an appropriate ratio to yield the corresponding oxazole derivatives.

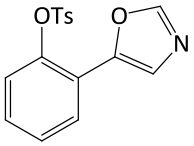
7.1.2.1 3-(Oxazol-5-yl)phenyl-4-methylbenzenesulfonate (3a)



3a

3-(Oxazol-5-yl)phenyl 4-methylbenzenesulfonate **3a** (13.9 g, 44 mmol, 61%) was prepared from 3-formylphenyl-4-methylbenzenesulfonate **2a** (72 mmol) as a yellow solid**. TLC**; R_f =0.2 (30% EA/ heptane).**^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 7.90 (S,1H), 7.74 (d, J = 8 Hz, 2H) , 7.53 (d, J = 8 Hz, 1H), 7.32 (m, 5H) , 6.94 (d, j=8 Hz, 1H), 2.45 (s, 3H)**. ^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 150.8, 150.1, 150.0, 145.6, 132.2, 130.3, 129.8, 129.4, 128.5, 122.9, 122.5, 122.3, 118.4, 21.7. **HRMS** calculated for $C_{16}H_{14}O_4NS$ $[M+H]^+$ 316.0643, found 316.0639.

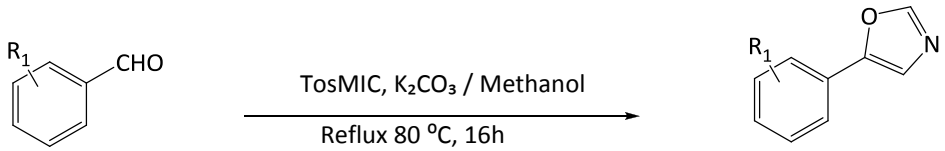
7.1.2.2 2-(Oxazol-5-yl)phenyl-4-methylbenzenesulfonate (3b)



3b

2-(Oxazol-5-yl)phenyl-4-methylbenzenesulfonate **3b** (2.3 g, 7.3 mmol, 40 %) was prepared from 2-formylphenyl-4-methylbenzenesulfonate **2b** (18 mmol) as a brown solid. **TLC**; R_f =0.2 (30% EA/heptane).**^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 7.82 (S, 1H), 7.65 (m, 1H) , 7.62 (d, J = 8 Hz, 2H), 7.43 (s, 1H), 7.36 (m, 1H) 7.31 (m, 2H), 7,20 (d, j = 8, 2H), 2.38 (s, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 150.1, 146.3, 145.7, 145.6, 132.2, 129.5, 129.3, 128.3, 127.2, 127.0, 126.0 122.6, 121.5, 21.6. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{16}H_{14}O_4NS$ 316.0643, found 316.0647.

7.1.3 Standard procedure for oxazole synthesis by TosMIC



2

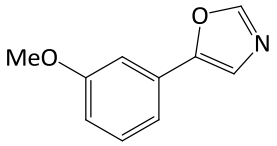
2c: R_1= 3-OMe
2d: R_1= 2-OMe

3

3c: R_1= 3-OMe (44%)
3d: R_1= 2-OMe (30%)

Compound **2** and 1.1 eq. of TosMIC were dissolved in anhydrous methanol (8 mL per 1 g of **2**). 1.1 eq. of k_2CO_3 was added and the mixture was refluxed for 16 hours. Water was added and the organic layer was separated, washed 3 times with brine solution, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified using column chromatography to yield the corresponding oxazole derivatives.

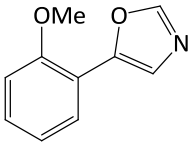
7.1.3.1 5-(3-Methoxyphenyl)oxazole (3c)



3c

5-(3-Methoxyphenyl)oxazole **3c** (2.26 g, 13 mmol, 44 %) was prepared from 3-methoxybenzaldehyde **2c** (29 mmol) as a brown solid. **TLC**; R_f =0.34 (35% EA/heptane). **^{1}H NMR** ($CDCl_3$, 400 MHz δ = 7.89 (S, 1H), 7.33 (s, 1H), 7.31 (d, J = 8 Hz, 1H), 7.23 (d, J = 8 Hz, 1H), 7.17 (t, J = 2.6 Hz, 1H) , 6.87 (dd, j = 2.6, 8 Hz, 1H), 3.84 (s, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz δ = 159.9, 151.3, 150.3, 130.0, 128.9, 121.7, 116.8, 114.2, 109.7, 55.2. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{10}H_{10}O_2N$ 176.0711, found 176.704.

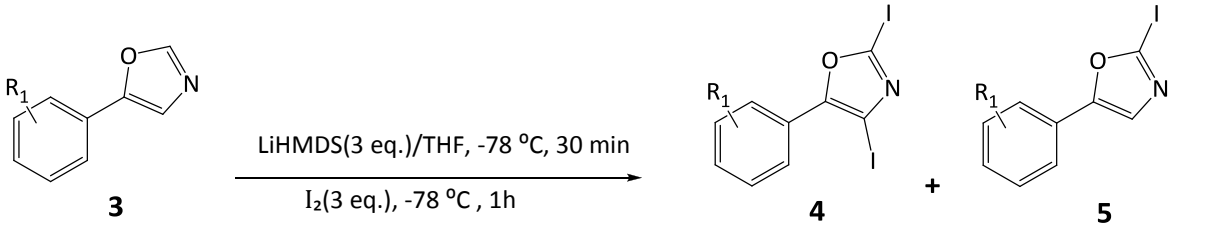
7.1.3.1 5-(2-Methoxyphenyl)oxazole (3d)



3d

5-(2-Methoxyphenyl)oxazole **3d** (1 g, 5.7 mmol, 30 %) was prepared from 2-methoxybenzaldehyde **2d** (19 mmol) as a brown oil. **TLC**; R_f =0.37 (35% EA/heptane).**^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 7.89 (S,1H), 7.78 (d, J = 8 Hz, 1H) , 7.56 (s, 1H), 7.30 (t, J = 8 Hz, 1H), 7.04 (t, J = 8 Hz, 1H) , 6.97 (d, j = 8 Hz, 1H), 3.95 (s, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 155.6, 149.4, 147.9, 129.2, 126.0, 125.4, 120.7, 116.9, 110.8, 55.4. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{10}H_{10}O_2N$ 176.0711, found 176.704.

7.1.4 General procedure for 2,4-iodination of the oxazole by lithiation



3

3a: R_1= 3-OTS
3b: R_1= 2-OTS

4

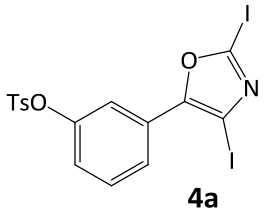
4a: R_1= 3-OTS (62%)
4b: R_1= 2-OTS (23%)

5

5b: R_1= 2-OTS (50%)

Compound **3** was dissolved in dry THF (1 mL per 1 mmol of **3**) and cooled to -78 °C. 3 eq. of freshly prepared LiHMDS (1 M in THF) were added dropwise to the solution followed by stirring for 30 minutes. 3 eq. of Iodine were dissolved in dry THF (2 mL per 1 g Iodine) and added slowly to the reaction mixture at -78 °C. The mixture was stirred for 1 hour and then left to be heated to rt. After that it was quenched with 10 % $Na_2S_2O_3$ solution and extracted with EA. The organic layer was separated, washed 3 times with brine solution, dried over $MgSO_4$, filtered and the solvent evaporated. The crude was purified by column chromatography using EA/pentane as eluent in an appropriate ratio to yield the corresponding iodinated derivatives.

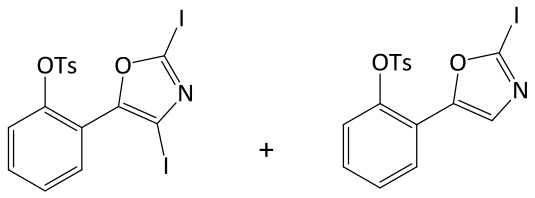
7.1.4.1 3-(2,4-Diiodooxazol-5-yl)phenyl-4-methylbenzenesulfonate (4a)



4a

3-(2,4-Diiodooxazol-5-yl)phenyl-4-methylbenzenesulfonate **4a** (3.46 g, 6.1 mmol, 62%) was prepared from 3-(oxazol-5-yl)phenyl 4-methylbenzenesulfonate **3a** (9.84 mmol) as a yellow solid. **TLC**; R_f =0.22 (30% EA/heptane). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 7.82 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 8 Hz, 2H), 7.54 (s, 1H), 7.40 (t, J = 8 Hz, 1H), 7.34 (d, J = 8 Hz, 2H), 7.06 (d, j = 8 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 155.4, 149.7, 145.6, 132.2, 130.1, 129.9, 128.6, 127.7, 124.3, 123.5, 119.7, 101.5, 80.3, 21.8. **HRMS** (ESI) m/z: $[M+K]^+$ calculated for $C_{16}H_{11}O_4NI_2KS$ 605.8135, found 605.8129.

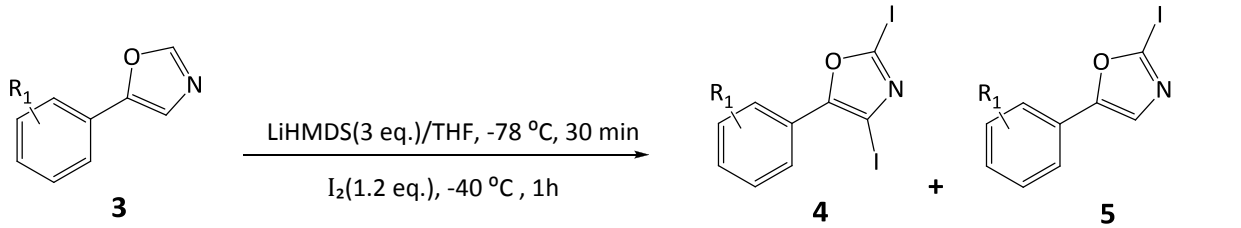
7.1.4.2 2-(2,4-Diiodooxazol-5-yl)phenyl-4-methylbenzenesulfonate 4b and 2-(2-iodooxazol-5-yl)phenyl-4-methylbenzenesulfonate (5b)



4b **5b**

A mixture (2.7 g) of 2-(2,4-diiodooxazol-5-yl)phenyl-4-methylbenzenesulfonate **4b** (1 g, 1.7 mmol, 23%) and 2-(2-iodooxazol-5-yl)phenyl-4-methylbenzenesulfonate **5b** (1.7 g, 4 mmol, 50%) was prepared as a pale yellow solid from 2-(oxazol-5-yl)phenyl-4-methylbenzenesulfonate **3b** (8 mmol). **TLC**; R_f =0.44 (30% EA/pentane).

7.1.5 General procedure for 2-iodination of the oxazole by lithiation



3

3c: R_1= 3-OMe
3d: R_1= 2-OMe

4 **5**

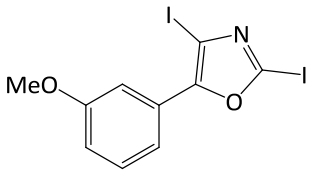
4c: R_1= 3-OMe (30%)

5c: R_1= 3-OMe
5d: R_1= 2-OMe (81%)

1 eq. of **3** was dissolved in dry THF (1 mL per 1 mmol of **3**) and cooled to -78 °C. 3 eq. of freshly prepared LiHMDS (1 M in THF) were added dropwise to the solution followed by stirring for 30 minutes. 1.2 eq. of Iodine were dissolved in dry THF (2 mL per 1 g Iodine) and added slowly to the reaction mixture at -40 °C. The mixture was stirred for 1 hour and then left to be heated to rt. After that it was quenched with 10 % $Na_2S_2O_3$ solution and extracted with EA. the organic layer was separated, washed 3 times with brine solution, dried over $MgSO_4$, filtered and the

solvent evaporated. The crude was purified by column chromatography using EA/pentane as eluent in an appropriate ratio to yield the corresponding iodinated derivatives.

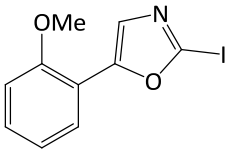
7.1.5.1 2,4-Diiodo-5-(3-methoxyphenyl)oxazole (4c)



4c

2,4-Diiodo-5-(3-methoxyphenyl)oxazole **4c** (376 mg, 0.86 mmol, 30 %) was prepared from 5-(3-methoxyphenyl)oxazole **3c** (2.8 mmol) as a yellowish crystalline solid. **TLC**; R_f =0.56 (35% EA/heptane).**^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 7.50 (d, j=8 Hz, 1H), 7.45 (s, 1H), 7.37 (t, J = 8 Hz, 1H), 6.96 (d, j = 8 Hz, 1H), 3.87 (s, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 159.6, 156.9, 129.9, 127.3, 118.4, 115.6, 111.2, 100.8, 79.5, 55.4. **HRMS** (ESI) m/z: $[M+K]^+$ calculated for $C_{10}H_7O_2NI_2K$ 465.8203, found 465.8190.

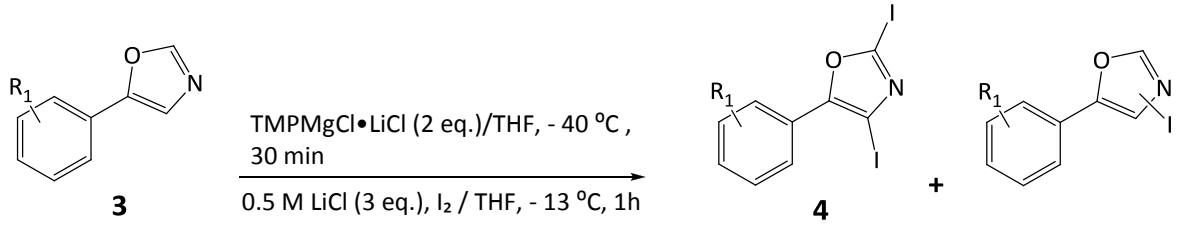
7.1.5.2 2-Iodo-5-(2-methoxyphenyl)oxazole (5d)



5d

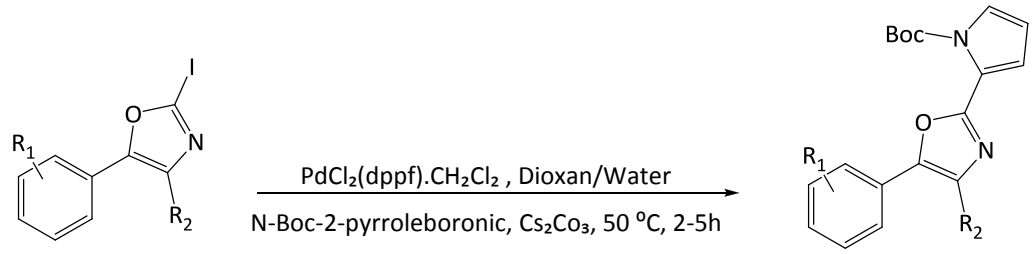
2-Iodo-5-(2-methoxyphenyl)oxazole **4h** (350 mg, 1.16 mmol, 81%) was prepared from 5-(2-methoxyphenyl)oxazole **3d** (1.4 mmol) as a yellowish crystalline solid. **TLC**; R_f =0.42 (35% EA/heptane). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 7.73 (d, j=8 Hz, 1H), 7.46 (s, 1H), 7.31 (t, J = 8 Hz, 1H), 7.04 (t, J = 8 Hz, 1H), 6.97 (d, j = 8 Hz, 1H), 3.95 (s, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 155.3, 154.2, 129.6, 129.2, 126.0, 120.8, 116.1, 110.8, 99.1, 55.4. **HRMS** (ESI) m/z: $[M+K]^+$ calculated for $C_{10}H_8O_2NIK$ 339.9236, found 339.9230.

7.1.6 General procedure for TMPMgCl•LiCl based oxazole synthesis



Compound **3** was dissolved in dry THF and cooled to -40 °C approximately. Two equivalents of TMPMgCl•LiCl were added and the mixture stirred for 30 minutes before addition of three equivalents of 0.5 M LiCl solition in THF followed by dropwise addition of the iodine in appropriate eq., dissolved in THF (2 mL THF per 1 g iodine).

7.1.7 General procedure for the Suzuki coupling on the oxazole



4a: R_1= 3-OTs, R_2= I

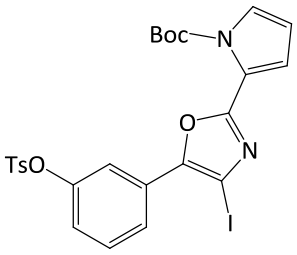
4b: R_1= 2-OTs, R_2= I
5b: R_1= 2-OTs, R_2= H

6a: R_1= 3-OTs, R_2= I (60%)

6b: R_1= 2-OTs, R_2= I (58%)
7b: R_1= 2-OTs, R_2= H (55%)

compound **4** was dissolved in degassed dioxane. Then 1.4 eq. of N-Boc-2-pyrroleboronic acid, 3 eq. of Cesium carbonate and degassed water were added, respectively. 0.1 eq. of the catalyst, $PdCl_2(dppf).CH_2Cl_2$ was last added and the mixture was degassed again and heated with stirring on oil bath for 2-5 hours at 50 ^oC. Water and EA were then added and the organic layer separated, washed 3 times with brine solution, dried over $MgSO_4$, filtered and the solvent was evaporated. Column chromatography was carried to purify the crude using EA/pentane in an appropriate ratio to give the corresponding product.

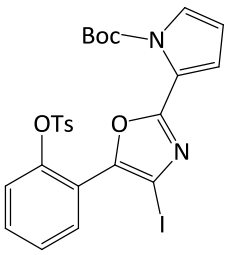
7.1.7.1 *tert*-butyl-2-(4-iodo-5-(3-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate (6a)



6a

tert-butyl-2-(4-iodo-5-(3-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate **6a** (280 mg, 0.46 mmol, 60 %) was prepared from 3-(2,4-diiodooxazol-5-yl)phenyl-4-methylbenzenesulfonate **4a** (0.76 mmol) as a yellowish oil. **TLC**; R_f =0.37 (30% EA/heptane). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 7.89 (d, J = 8 Hz, 1H), 7.74 (d, J = 8 Hz, 2H), 7.63 (s, 1H), 7.45 (m, 1H), 7.39 (t, J = 8 Hz, 1H), 7.32 (d, J = 8 Hz, 2H), 7.04 (d, j = 8 Hz, 1H), 6.76 (q, J = 2.6 Hz, 1H), 6.30 (t, J = 4 Hz, 1H), 2.42 (s, 3H), 1.45 (s, 9H). **^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 155.7, 150.1, 149.8, 148.2, 145.6, 132.3, 130.3, 129.8, 129.6, 128.5, 124.7, 123.6, 122.5, 122.1, 120.6, 119.0, 118.1, 111.0, 84.6, 27.7, 21.7.

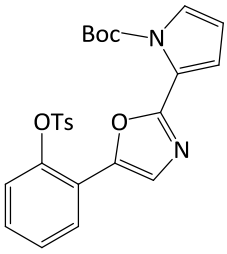
7.1.7.2 *tert*-butyl-2-(4-iodo-5-(2-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate (6b)



6b

tert-butyl-2-(4-iodo-5-(2-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate **6b** (230 mg, 0.4 mmol, 58 %)) was prepared from 2-(2,4-diiodooxazol-5-yl)phenyl-4-methylbenzenesulfonate **4b** (0.65 mmol). **TLC**; R_f =0.38 (35% EA/heptane). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 7.61 (d, J = 8 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 7.48 (t, J = 8 Hz, 1H), 7.42 (d, J = 8 Hz, 3H), 7.35 (t, J = 8 Hz, 1H), 7.09 (d, j = 8 Hz, 2H), 6.77 (q, J = 2 Hz, 1H), 6.31 (t, J = 4 Hz, 1H), 2.32 (s, 3H), 1.44 (s, 9H)**. ^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 156.7, 148.0, 147.4, 146.4, 145.4, 131.9, 131.0, 130.7, 129.7, 127.9, 127.0, 125.3, 124.5, 121.0, 119.8, 119.3, 111.0, 85.0, 83.0, 27.6, 21.7. **HRMS** (ESI) m/z: $[M+K]^+$ calculated for $C_{25}H_{23}O_6N_2IKS$ 644.9958, found 644.9953.

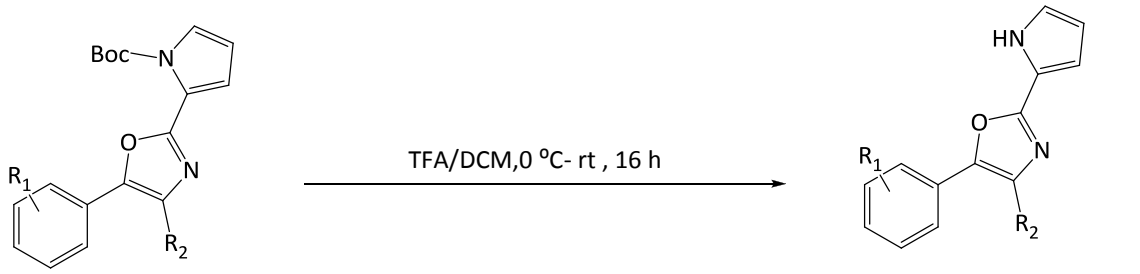
7.1.7.3 *tert*-butyl 2-(5-(2-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate (7b)



7b

tert-butyl-2-(5-(2-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate **7b** (75 mg, 0.15 mmol) was prepared from a 1 g mixture of 2-(2,4-diiodooxazol-5-yl)phenyl-4-methylbenzenesulfonate **4b** and 2-(2-iodooxazol-5-yl)phenyl-4-methylbenzenesulfonate **5b**. TLC; R_f =0.33 (35% EA/heptane). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 7.68 (m, 3H), 7.49 (s, 1H), 7.43 (m, 1H), 7.40 (m, 1H), 7.30 (m, 2H), 7.23 (d, j = 8 Hz, 2H), 6.70 (q, J = 2 Hz, 1H), 6.28 (t, J = 4 Hz, 1H), 2.37 (s, 3H), 1.40 (s, 9H). **^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 155.0, 148.2, 146.1, 145.6, 145.5, 132.5, 129.7, 129.0, 128.4, 127.4, 127.1, 126.6, 124.7, 122.5, 121.7, 120.7, 119.0, 111.0, 84.6, 27.6, 21.7. **HRMS** (ESI) m/z: $[M+K]^+$ calculated for $C_{25}H_{24}O_6N_2KS$ 519.0992, found 519.0986

7.1.8 Boc group de-protection

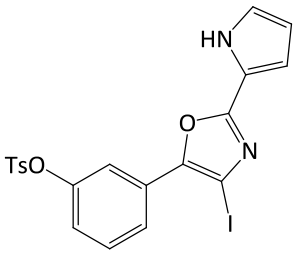


6a: R_1= 3-OTs, R_2= I
7b: R_1= 2-OTs, R_2= H

8a: R_1= 3-OTs, R_2= I (68%)
9b: R_1= 2-OTs, R_2= H (67%)

6a or **7b** was dissolved in DCM (5 mL per 1 g of **6a**) and cooled to 0 °C. TFA (5 mL per 1 g of **6a**) was added dropwise then 50 microliters of water were added and the reaction mixture was stirred for 16 hours. The mixture was quenched with aqueous solution of $NHCO_3$. The organic layer was separated and washed 3 times with brine solution, dried over $MgSO_4$, filtered and the solvent evaporated. Column chromatography was carried to purify the crude using EA/pentane in appropriate ratio to yield the corresponding product.

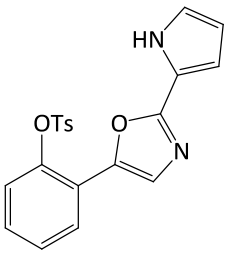
7.1.8.1 3-(4-Iodo-2-(1H-pyrrol-2-yl)oxazol-5-yl)phenyl-4-methylbenzenesulfonate (8a)



8a

3-(4-Iodo-2-(1H-pyrrol-2-yl)oxazol-5-yl)phenyl-4-methylbenzenesulfonate **8a** (198 mg, 0.4 mmol, 67.7 %) was prepared from tert-butyl-2-(4-iodo-5-(3-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate **6a** (0.57 mmol). TLC; R_f =0.45 (30% EA/heptane). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 9.17 (s, 1H), 7.90 (d, J = 8 Hz, 1H), 7.76 (d, J = 8 Hz, 2H), 7.60 (s, 1H), 7.39 (t, J = 8 Hz, 1H), 7.34 (d, J = 8 Hz, 2H), 7.03 (d, j = 8 Hz, 1H), 6.98 (s, 1H), 6.88 (s, 1H), 2.45 (s, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 157.3, 149.8, 146.8, 145.6, 137.1, 132.3, 130.0, 129.9, 128.8, 128.6, 124.0, 122.5, 122.2, 119.4, 119.0, 111.6, 110.8, 21.8. **HRMS** (ESI) m/z: $[M+K]^+$ calculated for $C_{20}H_{15}O_4N_2IKS$ 544.9434, found 544.9426.

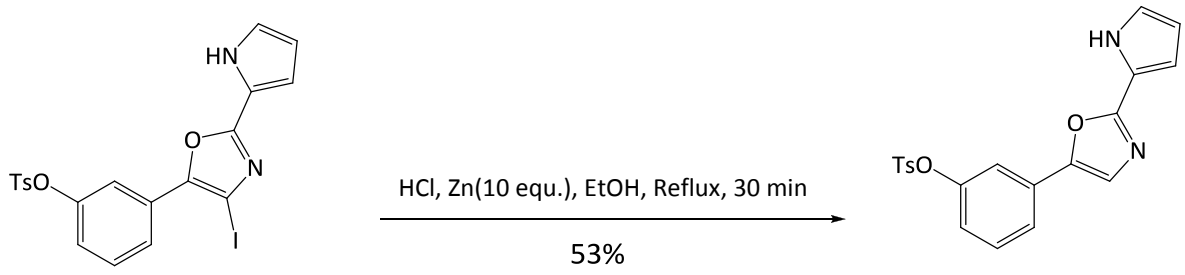
7.1.8.2 2-(2-(1H-pyrrol-2-yl)oxazol-5-yl)phenyl 4-methylbenzenesulfonate (9b)



9b

2-(2-(1H-pyrrol-2-yl)oxazol-5-yl)phenyl 4-methylbenzenesulfonate **9b** (40 mg, 0.1 mmol, 67%) was prepared as a grey solid from **7b** (75 mg, 0.15 mmol) TLC; R_f =0.44 (3% EA/heptane). **^{1}H NMR** (DMSO-d6, 400 MHz) δ = 11.96 (s, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 2H), 7.42 (m, 5H), 7.23 (d, j = 7.6 Hz, 1H), 7.04 (s, 1H), 6.79 (s, 1H), 6.24 (s, 1H), 2.31 (s, 3H). **^{13}C NMR** (DMSO-d6, 400 MHz) δ = 156.7, 146.8, 145.3, 144.4, 132.1, 130.7, 130.0, 128.8, 128.5, 127.8, 127.5, 123.3, 123.0, 122.1, 119.9, 111.4, 110.4, 21.8. **HRMS** (ESI) m/z: $[M+K]^+$ calculated for $C_{20}H_{16}O_4N_2KS$ 419.0467, found 419.0456.

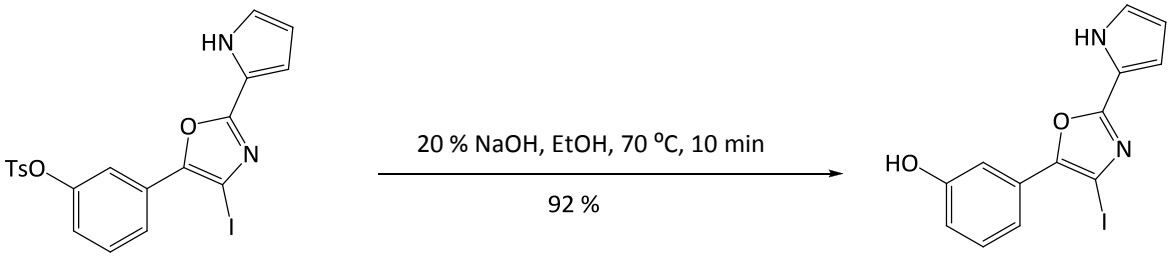
7.1.9 De-iodination



8a **9a**

3-(4-Iodo-2-(1H-pyrrol-2-yl)oxazol-5-yl)phenyl-4-methylbenzenesulfonate **8a** (0.1 mmol) was dissolved in 4.5 mL of EtOH. 0.25 mL HCL and 10 eq. of Zn were added, respectively. The mixture was heated at reflux for 30 minutes. Water and acetone were added and the product crystallized out of the solution. 3-(2-(1H-pyrrol-2-yl)oxazol-5-yl)phenyl-4-methylbenzenesulfonate **9a** (20 mg, 0.05 mmol, 53 %) was obtained as a grey solid. **TLC**; R_f =0.12 (30% EA/heptane). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 9.55 (s, 1H), 7.76 (d, J = 8 Hz, 2H), 7.54 (d, J = 8 Hz, 1H), 7.35 (m, 3H), 7.28 (d, j = 7.6 Hz, 2H), 7.01 (s, 1H), 6.93 (d, J = 8 Hz, H), 6.25 (s, 1H), 2.46 (s, 3H). **^{13}C NMR** ($CDCl_3$, 400 MHz) δ = 156.7, 148.4, 145.6, 144.4, 132.3, 130.2, 129.8, 129.6, 128.6, 123.5, 122.4, 121.8, 120.1, 117.9, 110.8, 110.6, 100.0, 21.7. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{20}H_{15}O_4N_2S$ 379.0752, found 379.0751.

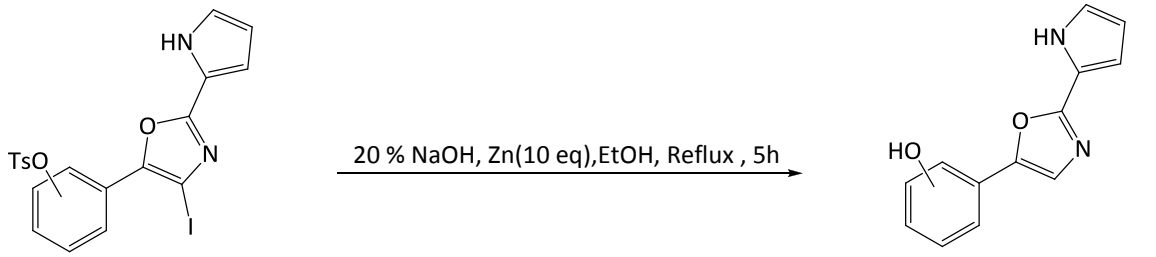
7.1.10 De-tosylation



8a **10a**

3-(4-Iodo-2-(1H-pyrrol-2-yl)oxazol-5-yl)phenyl-4-methylbenzenesulfonate **8a** (0.1 mmol) was dissolved in 4.5 mL of EtOH. 0.5 mL 20% NaOH solution was added. The mixture was stirred for 10 minutes at 70 °C. Water and Ethyl acetate were added and the organic layer was separated and washed 2 times with 20 mL brine solution, dried over $MgSO_4$, filtered and the solvent evaporated. 3-(4-iodo-2-(1H-pyrrol-2-yl)oxazol-5-yl)phenol **10a** (32 mg, 0.09 mmol, 92%) was obtained as a grey solid. TLC; R_f =0.37 (30% EA/pentane). **^{1}H NMR** (acetone-d6, 400 MHz) δ = 11.12 (s, 1H), 8.69 (s, 1H), 7.54 (d, J = 8 Hz, 2H), 7.35 (t, J = 8 Hz, 1H), 7.10 (s, 1H), 6.91 (d, j = 8 Hz, 1H), 6.88 (s, 1H), 6.29 (s, 1H). **^{13}C NMR** (acetone-d6, 400 MHz) δ = 158.6, 148.9, 130.9, 129.7, 123.5, 123.3, 120.2, 118.0, 116.8, 113.3, 112.0, 111.0, 80.7. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_8O_2N_2I$ 350.9630, found 350.9633.

7.1.11 De-iodination and de-tosylation

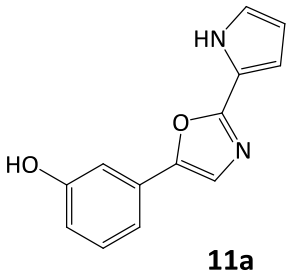


8a: 3-OTs
8b: 2-OTs

11a: 3-OH (40%)
11b: 2-OH

8a or **8b** was dissolved in EtOH (90 mL per 1 g of **8a** or **8b**). 20% NaOH solution (10 mL per 1 g of **8a** or **8b**) was added. The mixture was stirred and 10 eq. of Zn was added and the mixture was stirred at reflux for 5 hours.

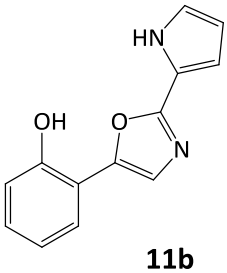
7.1.11.1 3-(2-(1H-pyrrol-2-yl)oxazol-5-yl)phenol (11a)



11a

3-(2-(1H-pyrrol-2-yl)oxazol-5-yl)phenol **11a** (10 mg, 0.04 mmol, 40 %) was prepared as a grey solid from 3-(4-iodo-2-(1H-pyrrol-2-yl)oxazol-5-yl)phenyl-4-methylbenzenesulfonate **8a** (0.1 mmol, 50 mg) **TLC**; R_f=0.15 (30% EA/pentane). **^{1}H NMR** (DMSO-d6, 400 MHz) δ = 11.92 (s, 1H), 9.65 (s, 1H), 7.62 (s, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.15 (s, 1H), 7.00 (s, 1H), 6.76 (d, J = 7.6 Hz, 2H), 6.22 (s, 1H). **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_9O_2N_2$ 225.0664, found 225.0669.

7.1.11.2 2-(2-(1H-pyrrol-2-yl)oxazol-5-yl)phenol (11b)

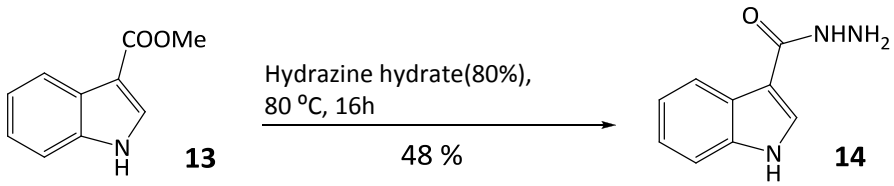


11b

2-(2-(1H-pyrrol-2-yl)oxazol-5-yl)phenol **11b** (80 mg, 0.3 mmol) was prepared as a dark grey solid from a crude mixture of **8b** and **9b**. **TLC**; R_f=0.25 (35% EA/pentane).**^{1}H NMR** (DMSO-d6, 400 MHz) δ = 11.91 (s, 1H), 10.38 (s, 1H), 7.78 (d, J = 8 Hz, 1H), 7.52 (s, 1H), 7.17 (t, J = 8 Hz, 1H), 6.96 (m, 3H), 6.78 (s, 1H), 6.22 (q, j = 2 Hz, 1H). **^{13}C NMR** (DMSO-d6, 400 MHz) δ = 155.4, 154.3, 146.7, 129.3, 126.6, 125.7, 122.7, 120.4, 120.0, 116.4, 115.7, 110.6, 110.2. **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_9O_2N_2$ 225.0664, found 225.0670.

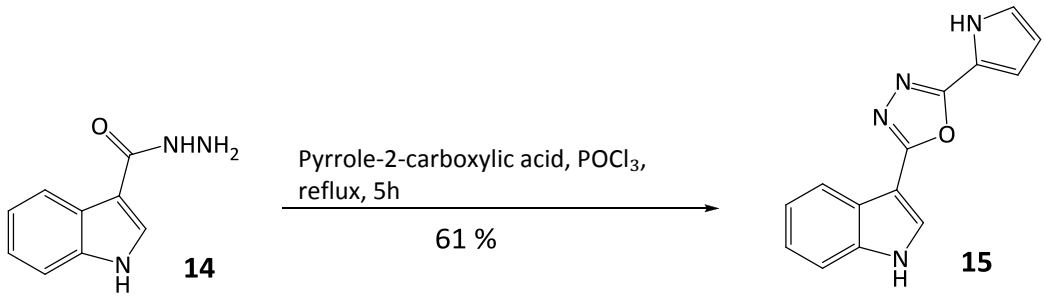
7.2 Synthesis of the breitfussins analogue

7.2.1 Synthesis of 1H-indole-3-carbohydrazide (14)



(500 mg, 3 mmol) of methyl-1H-indole-3-carboxylate **13** were added to a small excess of hydrazine hydrate(50 mmol) and heated at 80 °C for 16 hours. A small amount of ethanol were added and the solution left to cool down. The product crystallized out as a white solid which was then filtered and washed with ethanol to give (240 mg, 1.45 mmol, 48 %) of 1H-indole-3-carbohydrazide **14** as white solid**.** TLC; R_f=0.55 (acetone).**^{1}H NMR** (DMSO-d6, 400 MHz) δ = 11.50 (S,1H), 9.13 (s, 1H), 8.13 (d, J =7.6 Hz, 1H), 7.95 (s, 1H), 7.41 (d, j = 7.6 Hz, 1H), 7.10 (m, 2H), 4.30 (s, 2H). **HRMS** (ESI) m/z: $[M+H]^+$ calculated for $C_9H_8ON_3$ 174.0667, found 174.0671.

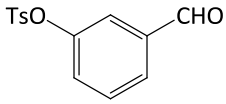
7.2.2 Synthesis of 2-(1H-indol-3-yl)-5-(1H-pyrrol-2-yl)-1,3,4-oxadiazole (15)



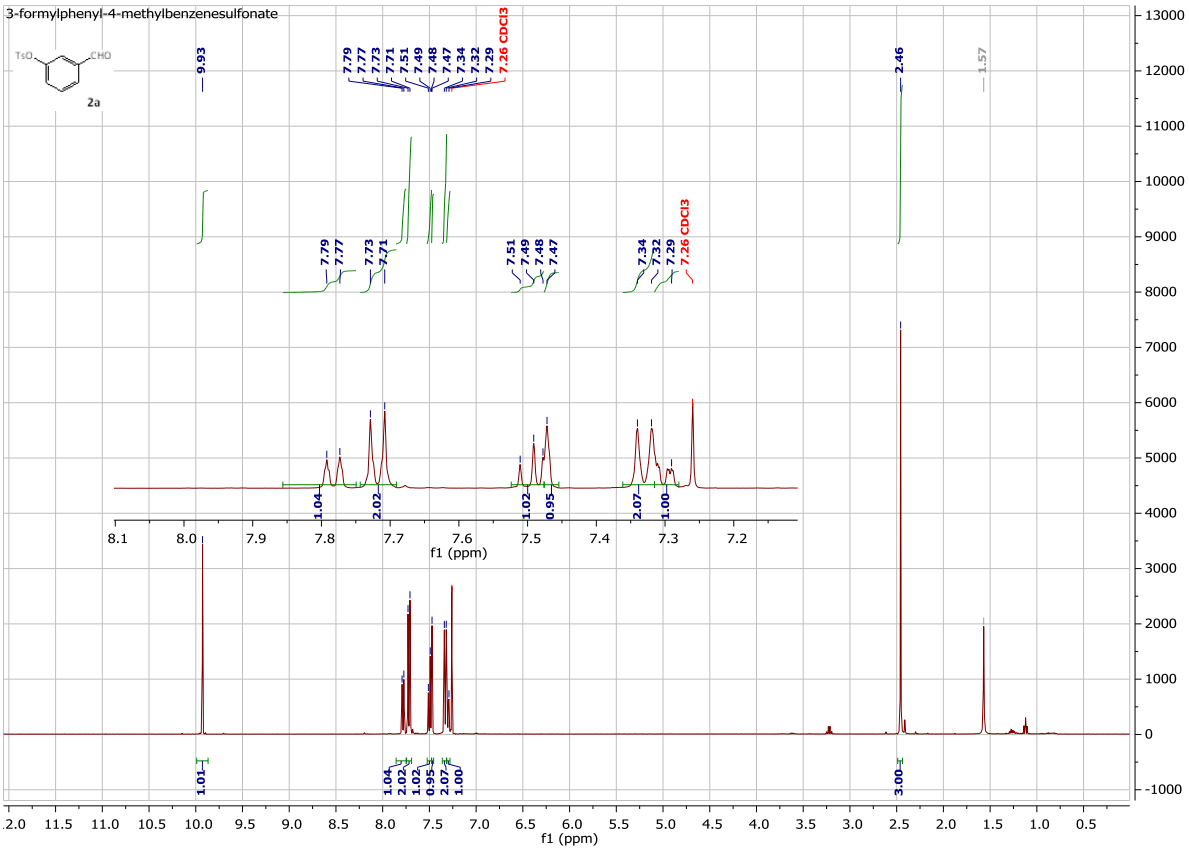
(230 mg, 1.3 mmol) of 1H-indole-3-carbohydrazide **8** and 1.3 mmol of Pyrrole-2-carboxylic acid were dissolved in $POCl_3$ (6 mL) and heated at reflux for 5 hours. After that, the mixture was stirred under vacuum to evaporate $POCl_3$. The residue was dissolved in EA and extracted with saturated $NaHCO_3$ solution. The resulting solution was washed 3 times with brine solution, dried over $MgSO_4$, filtered and the solvent was evaporated. Column chromatography was carried to purify the crude using (20-60 % acetone/pentane) to give 2-(1H-indol-3-yl)-5-(1H-pyrrol-2-yl)-1,3,4-oxadiazole **9** (200 mg, 0.8 mmol, 61%) as a pale red solid. TLC; R_f=0.88 (acetone). **^{1}H NMR** (DMSO-d6, 400 MHz) δ = 12.17 (S,1H), 12.00 (S,1H), 8.17 (d, j = 8 HZ, 2H), 7.54 (d, j = 8 Hz, 1H) 7.27 (p, j = 8 Hz, 2H), 7.10 (s, 1H), 6.88 (s, 1H), 6.29 (s, 1H). **^{13}C NMR** (DMSO-d6, 400 MHz) δ = 160.9, 157.9, 137.1, 128.6, 124.8, 123.9, 123.5, 121.8, 121.0, 116.4, 113.1, 112.2, 110.5, 100.2. **HRMS** (ESI) m/z: $[M+Na]^+$ calculated for $C_{14}H_{10}ON_4Na$ 273.0752, found 273.0743.

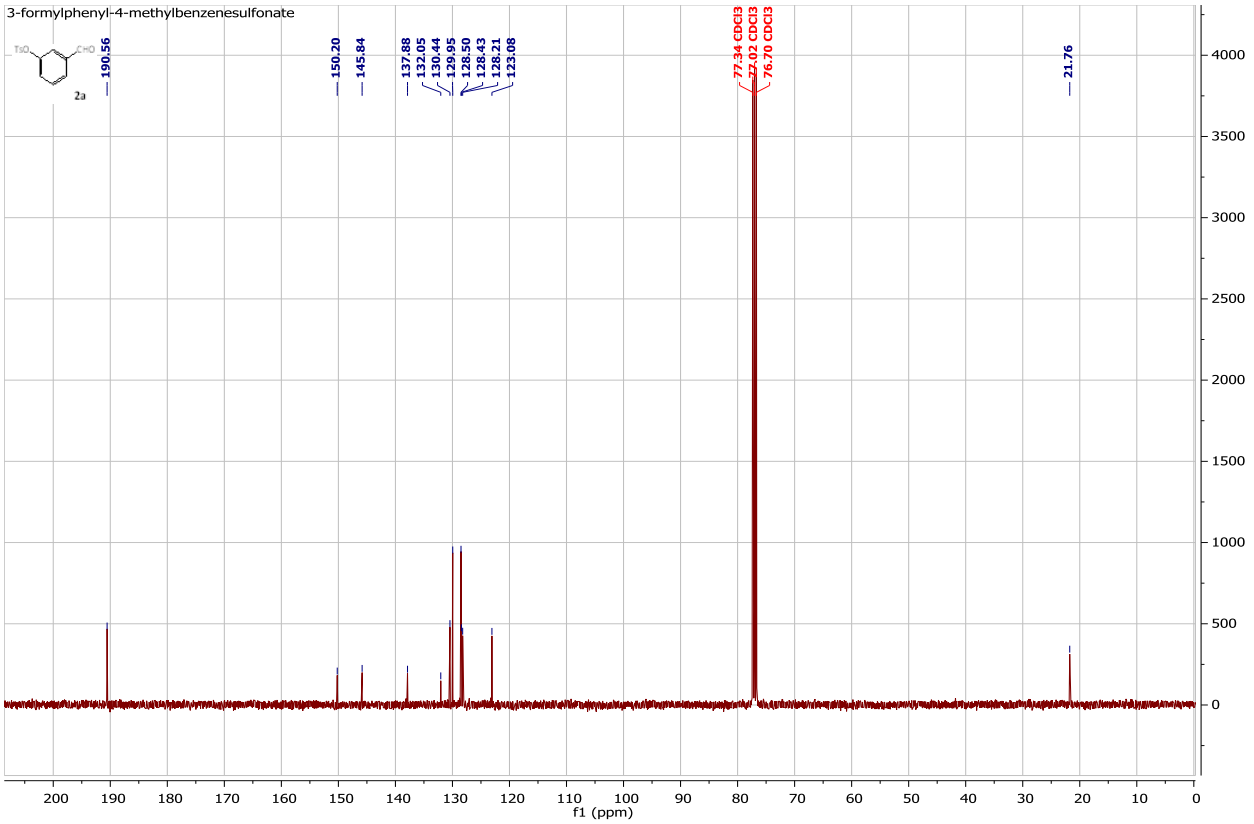
8 APPENDICES

Appendix 1: 3-formylphenyl-4-methylbenzenesulfonate (2a)



2a





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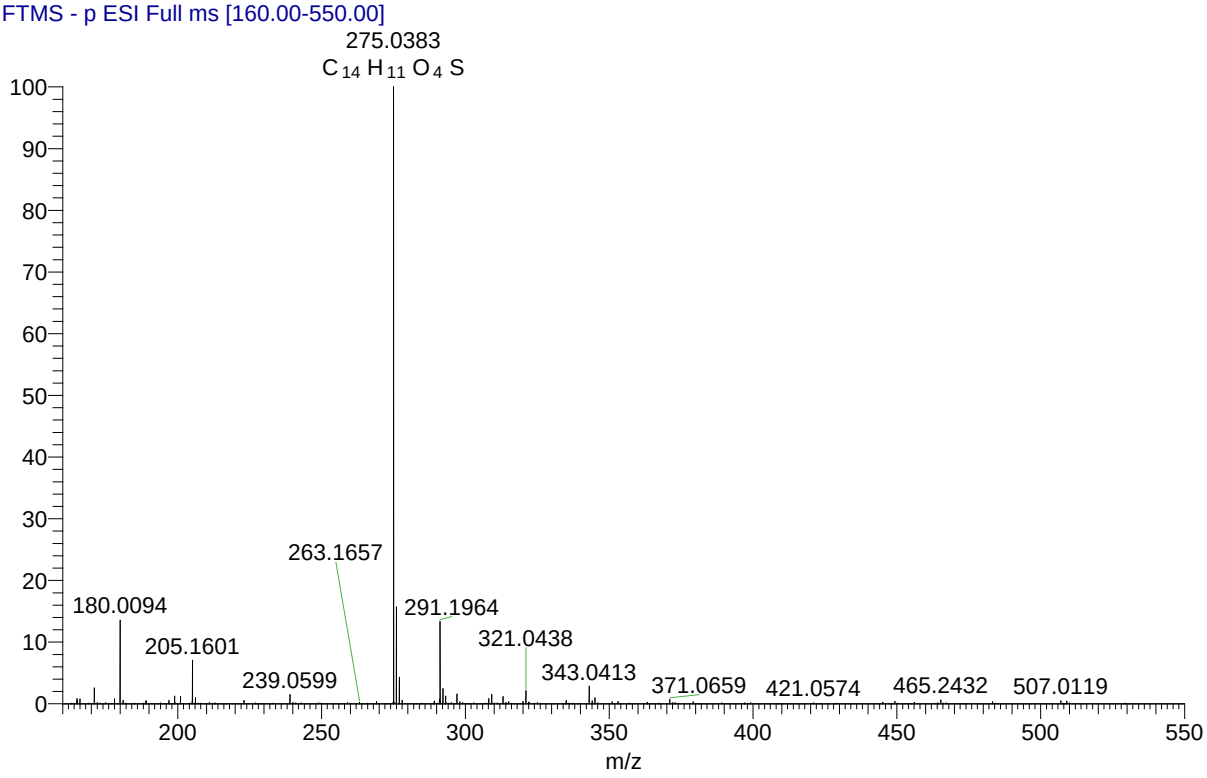
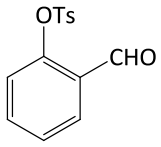
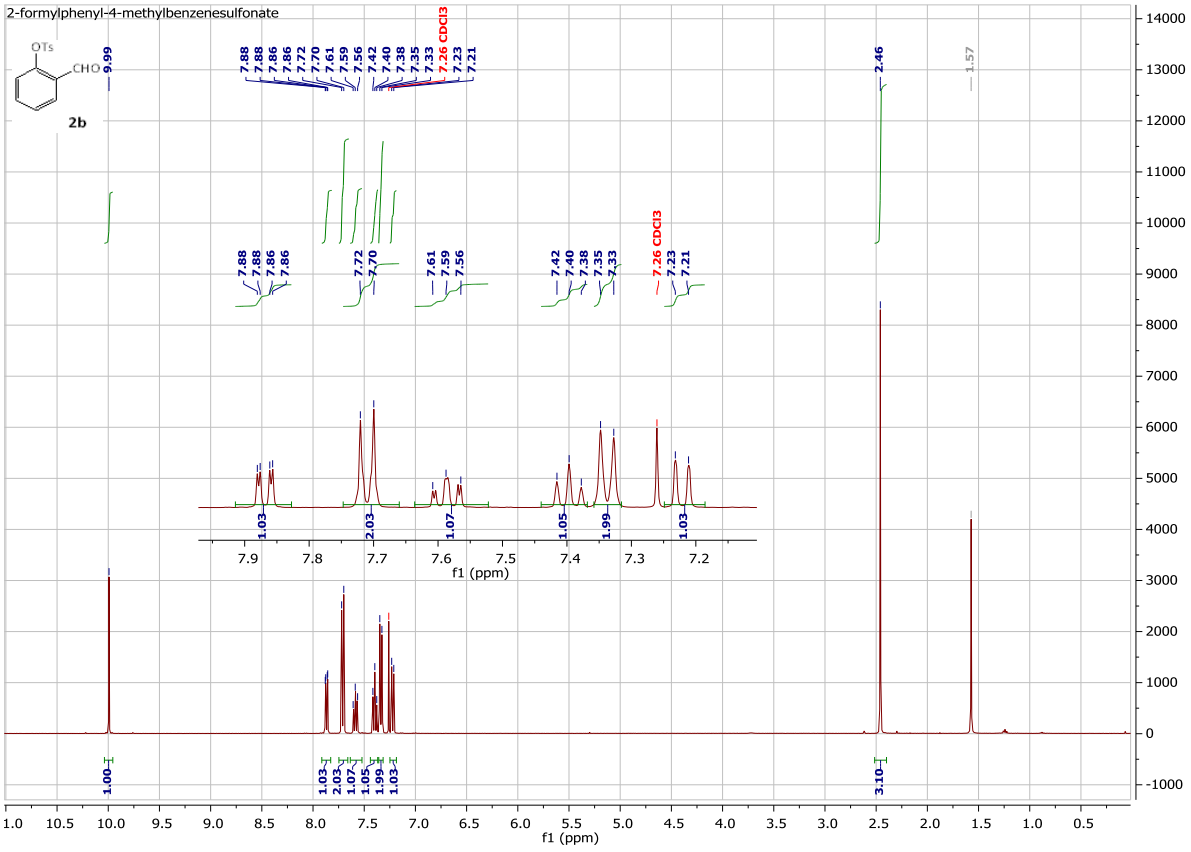
T: FTMS - p ESI Full ms [160.00-550.00]

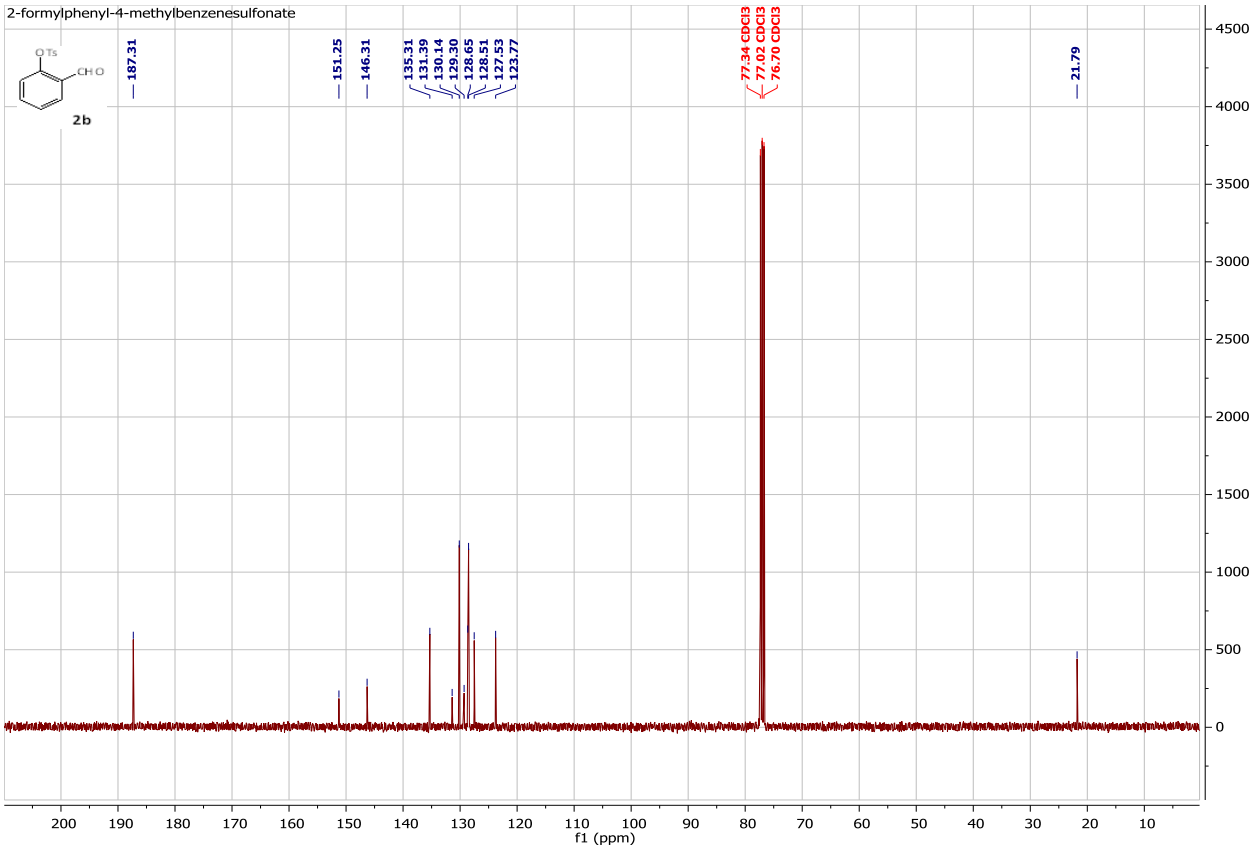


Appendix 2: 2-formylphenyl-4-methylbenzenesulfonate (2b)

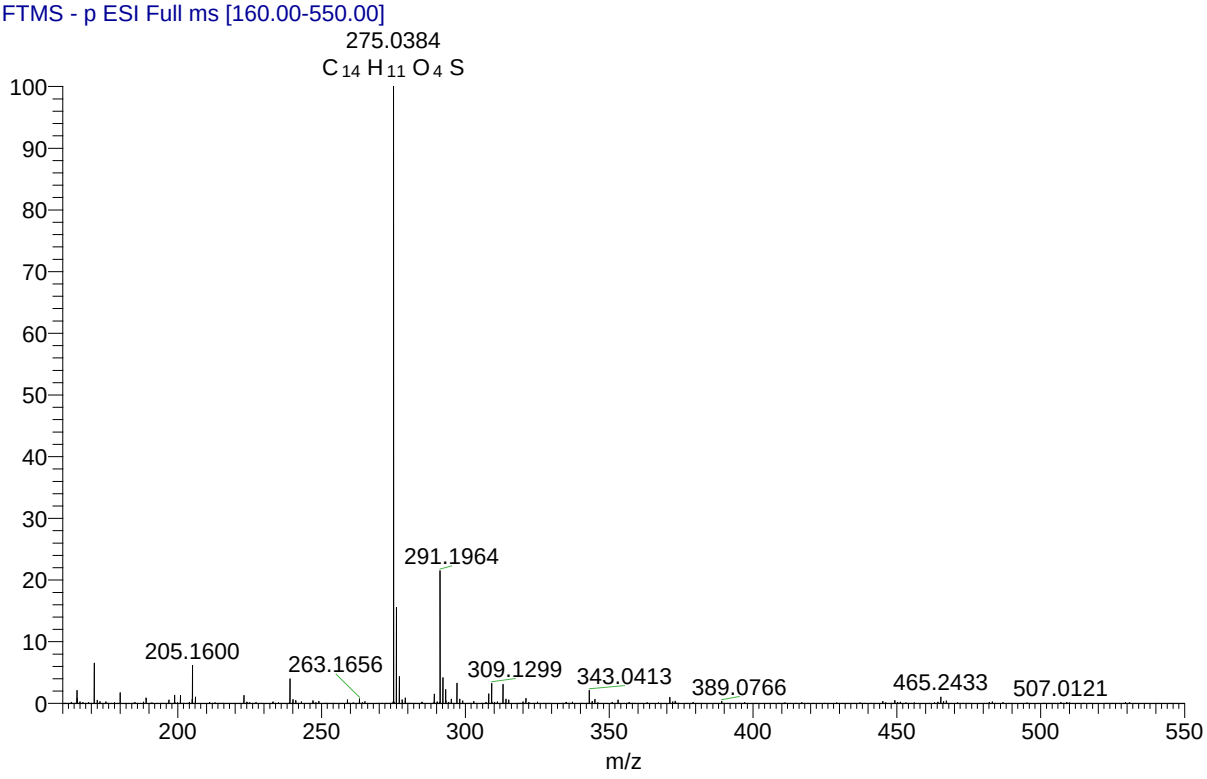


2b

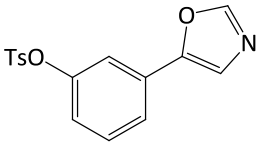




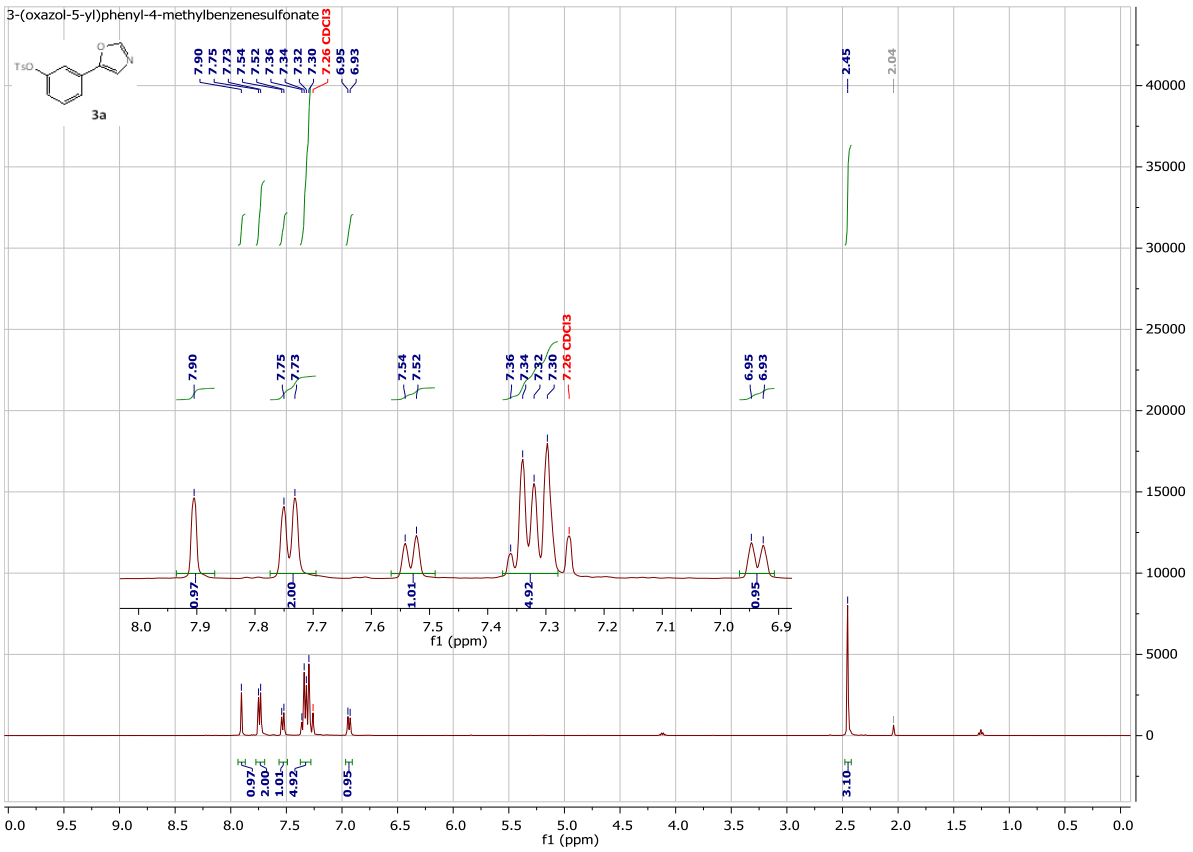
2b_neg #5 RT: 0.13 AV: 1 NL: 2.12E8
T: FTMS - p ESI Full ms [160.00-550.00]

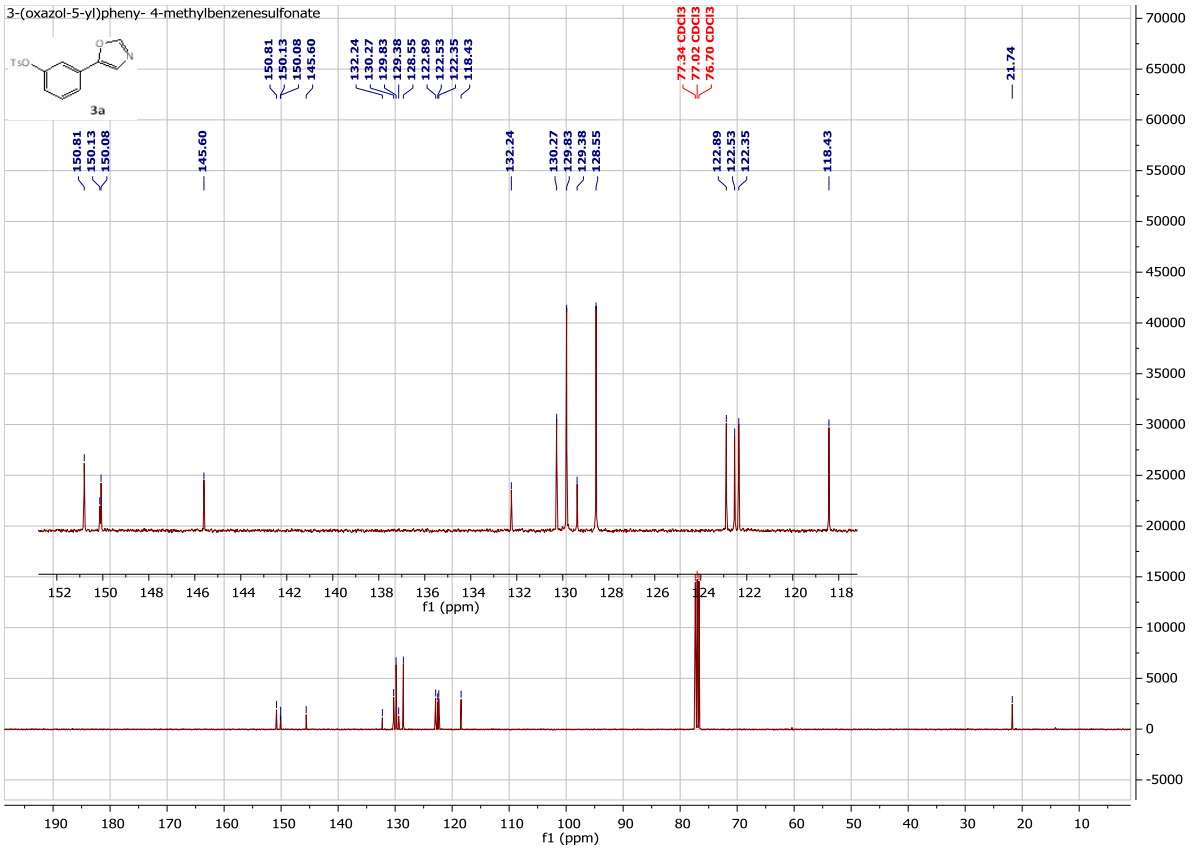


Appendix 3: 3-(oxazol-5-yl)phenyl-4-methylbenzenesulfonate (3a)

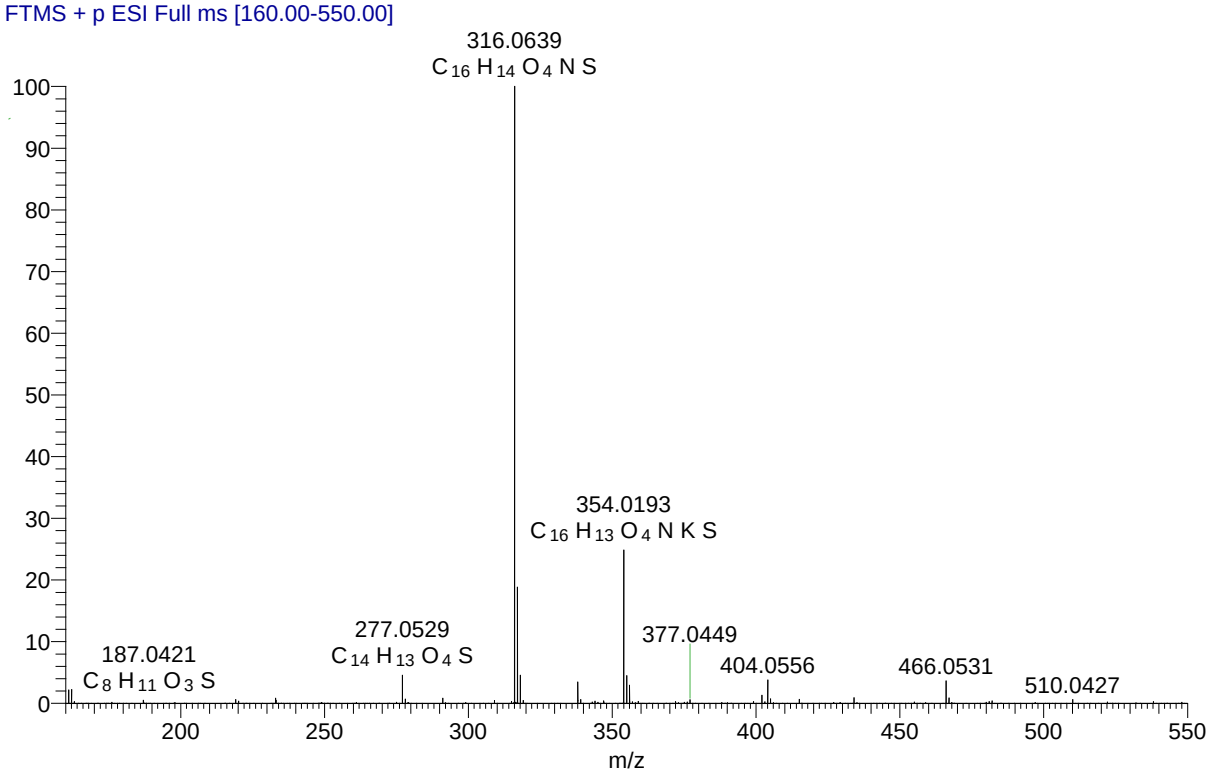


3a

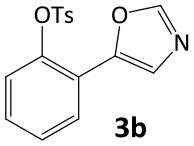




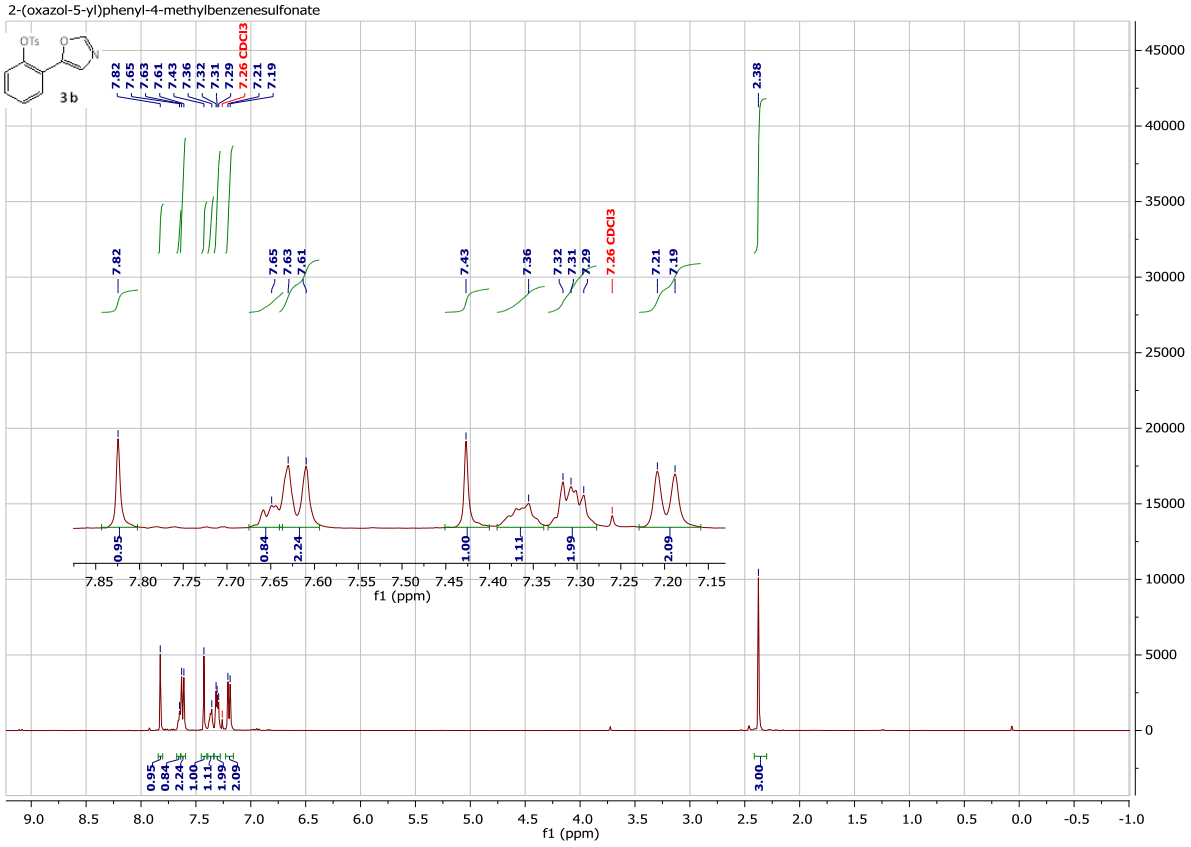
3a_posc #5 RT: 0.14 AV: 1 NL: 2.11E8
T: FTMS + p ESI Full ms [160.00-550.00]

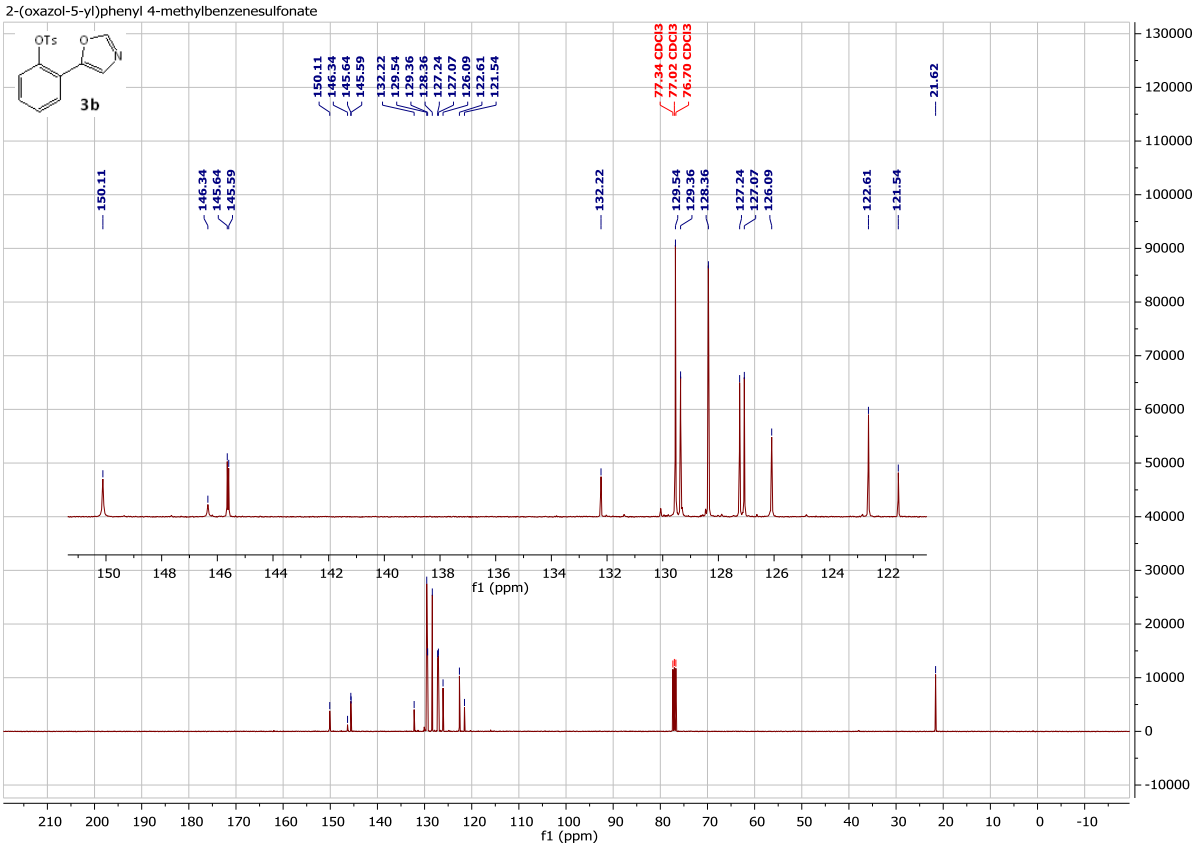


Appendix 4: 2-(oxazol-5-yl)phenyl-4-methylbenzenesulfonate (3b)

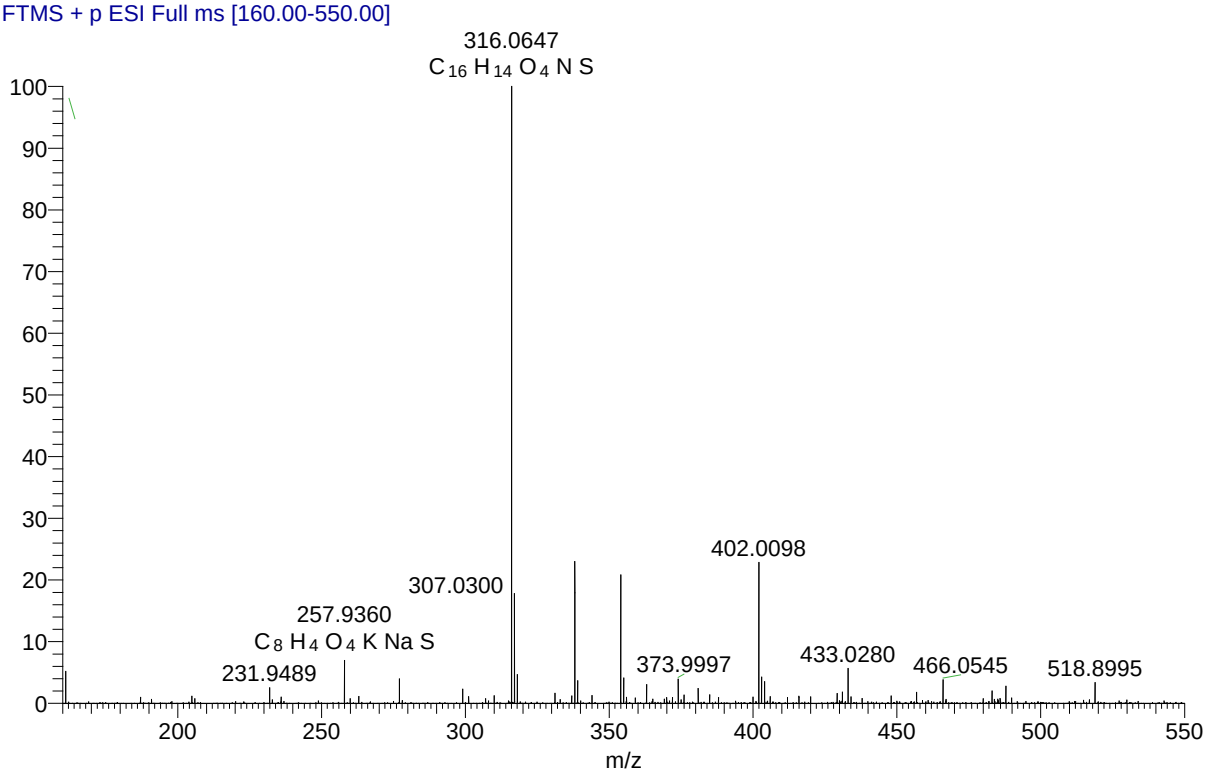


3b

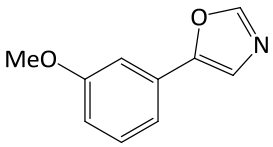




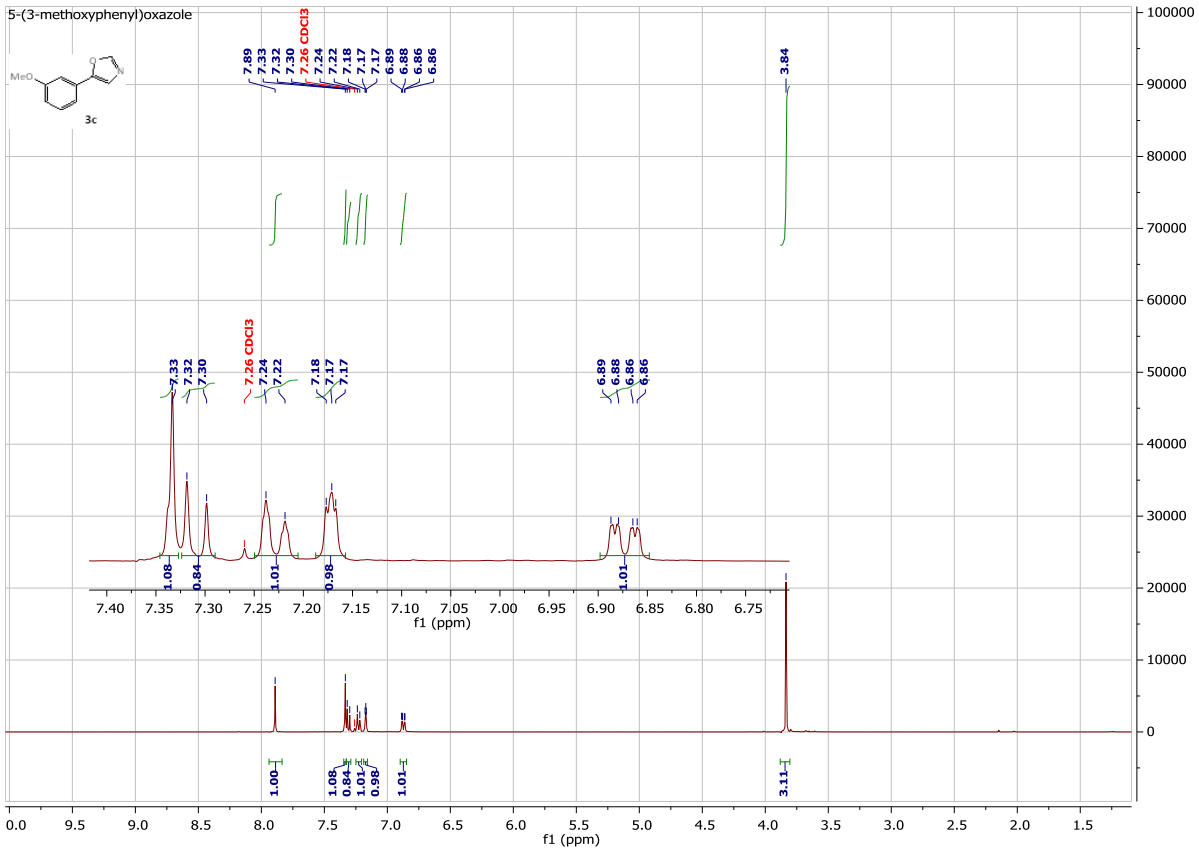
3b_pos #5 RT: 0.12 AV: 1 NL: 1.57E7
T: FTMS + p ESI Full ms [160.00-550.00]

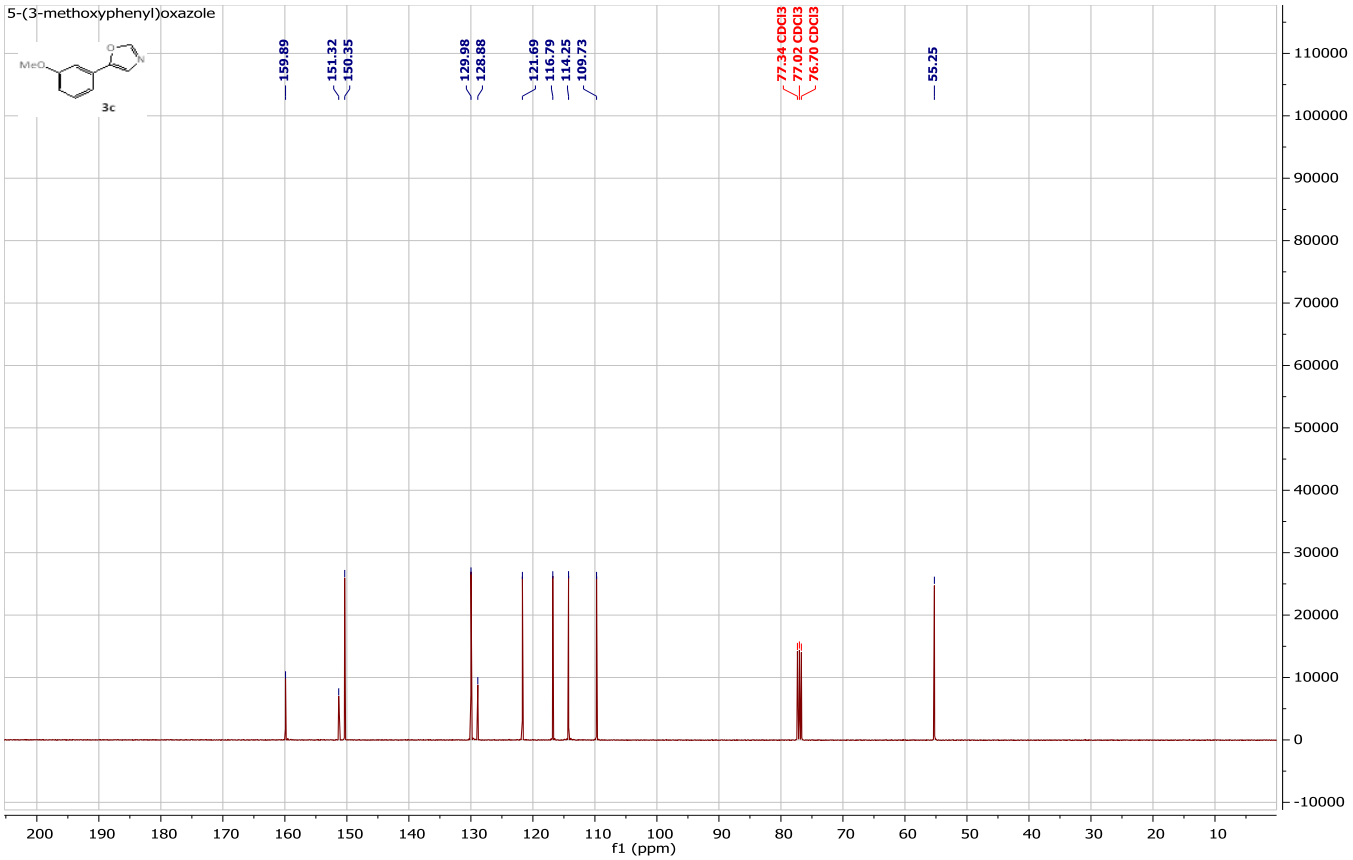


Appendix 5: 5-(3-methoxyphenyl)oxazole (3c)

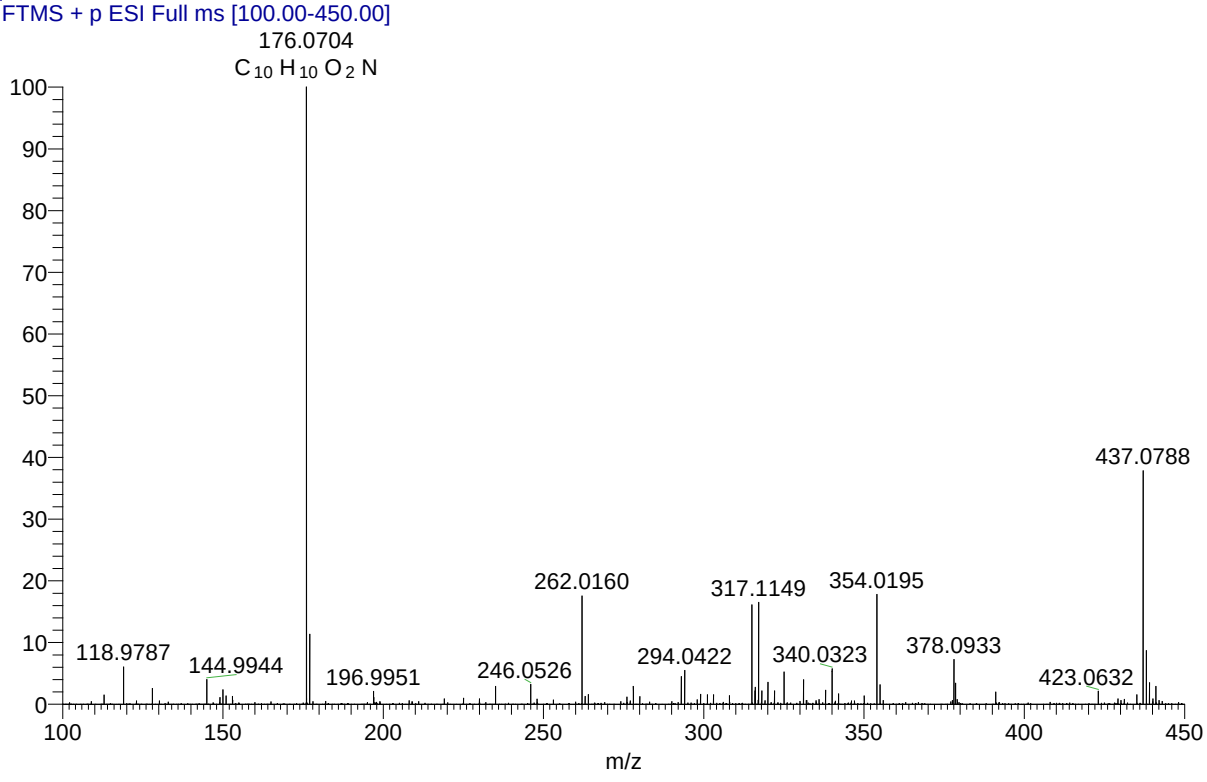


3c

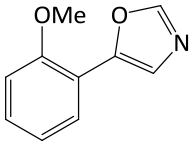




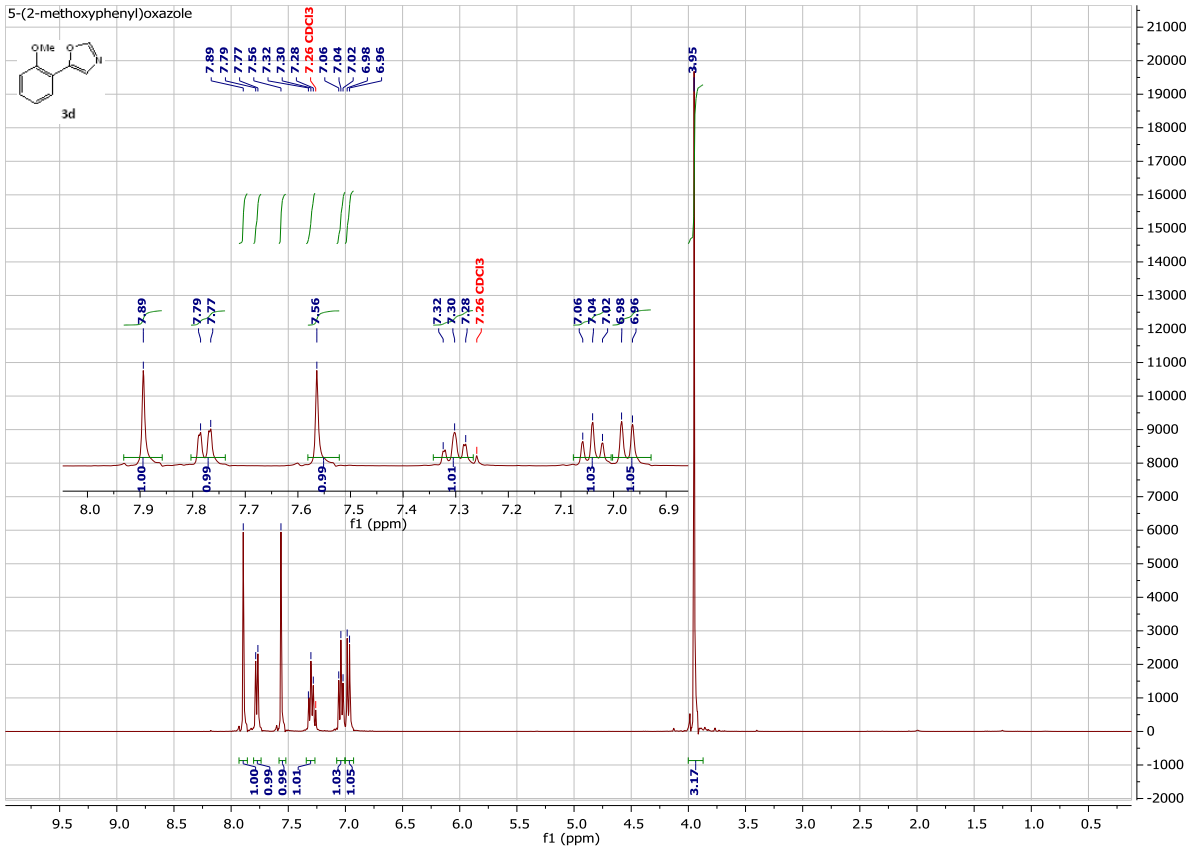
3c_pos #5 RT: 0.13 AV: 1 NL: 3.94E7
T: FTMS + p ESI Full ms [100.00-450.00]

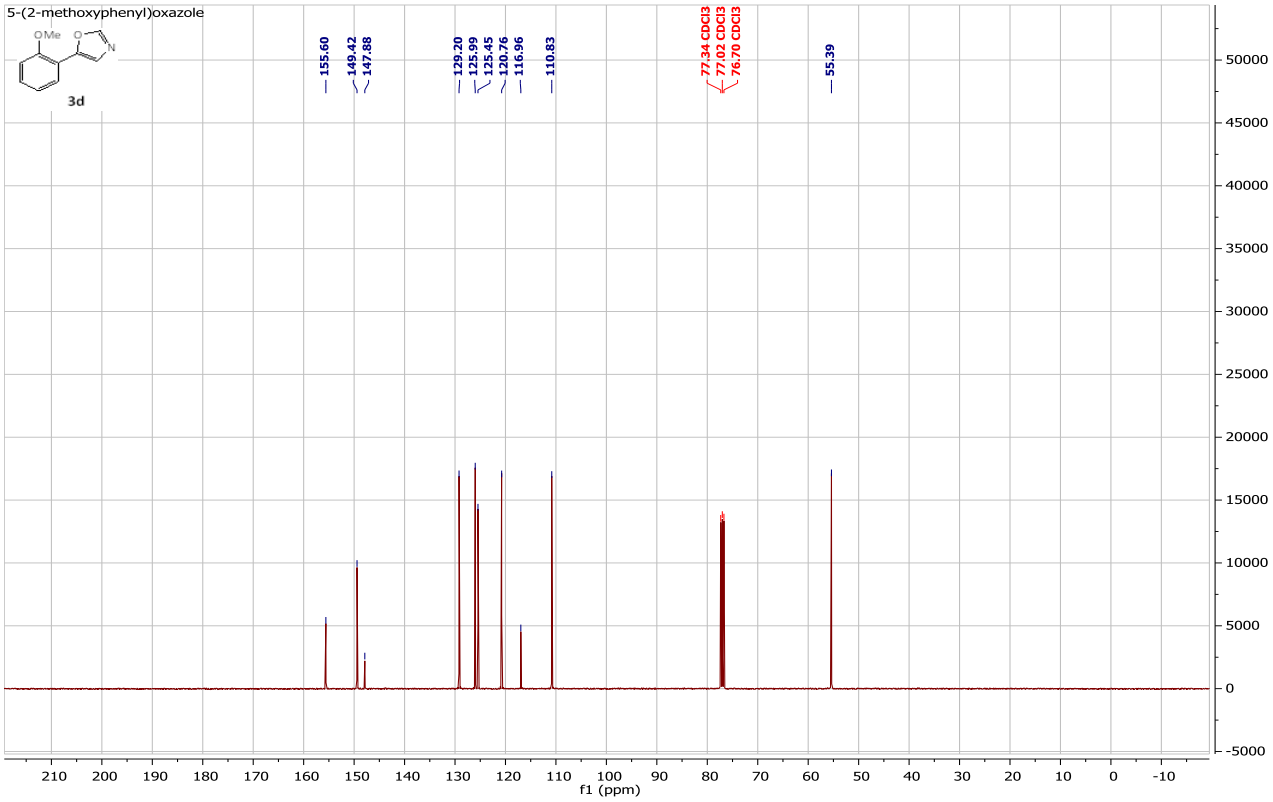


Appendix 6: 5-(2-methoxyphenyl)oxazole (3d)

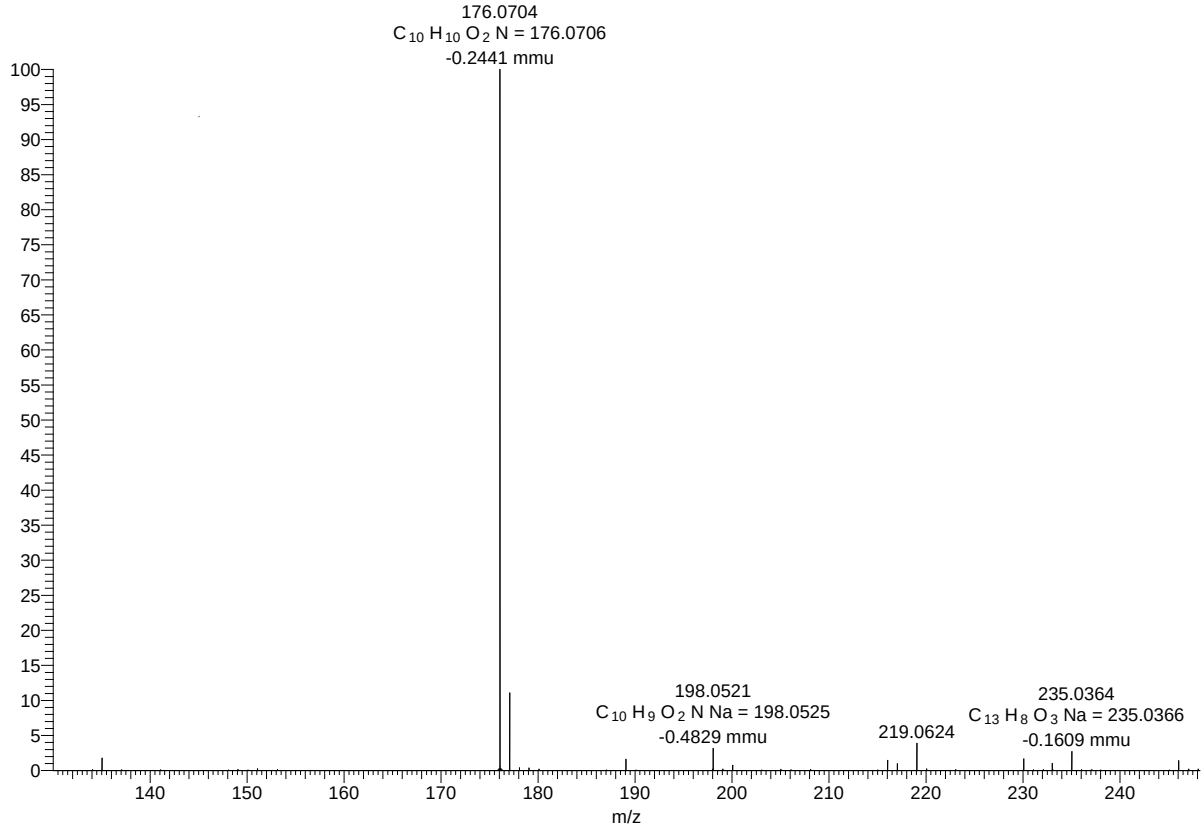


3d

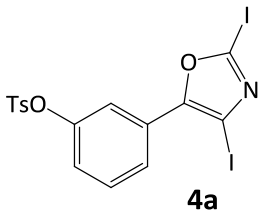




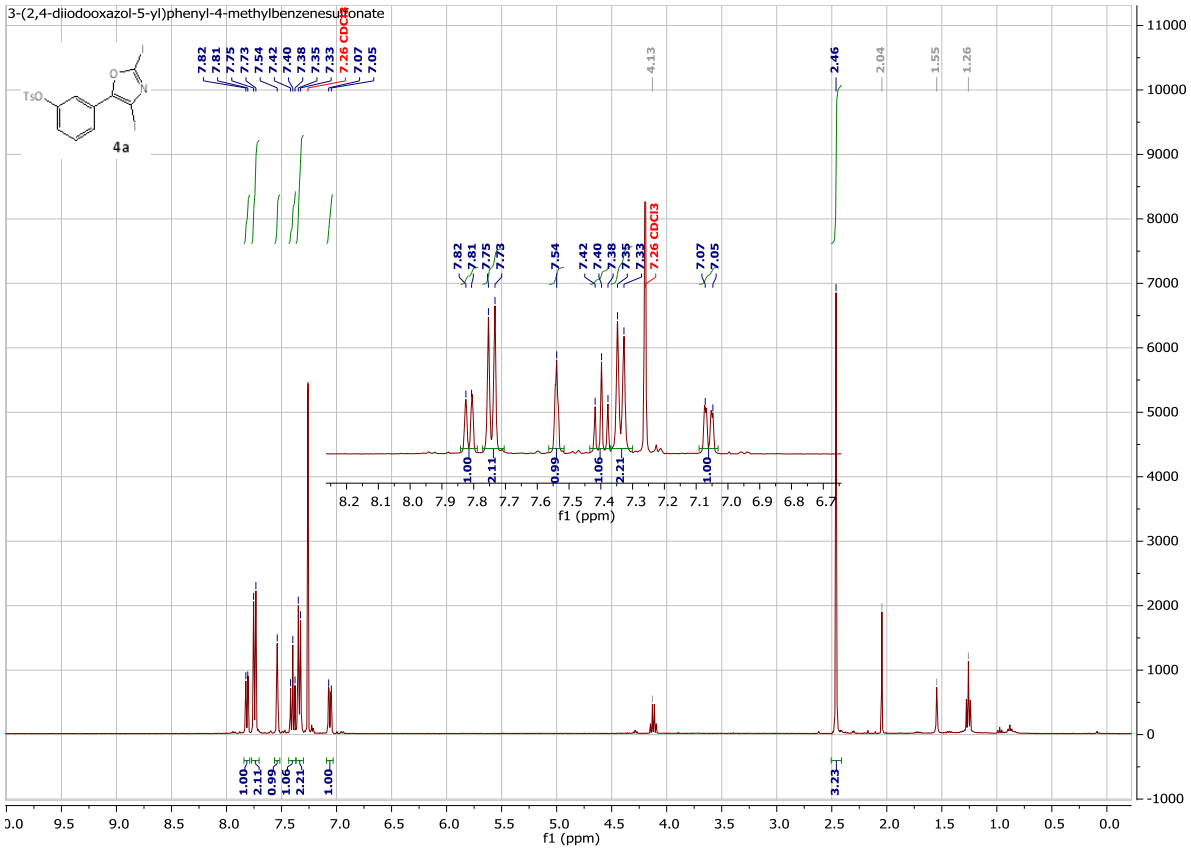
3d_160513120900 #1-5 RT: 0.01-0.13 AV: 5 NL: 3.85E7
T: FTMS + p ESI Full ms [130.00-450.00]

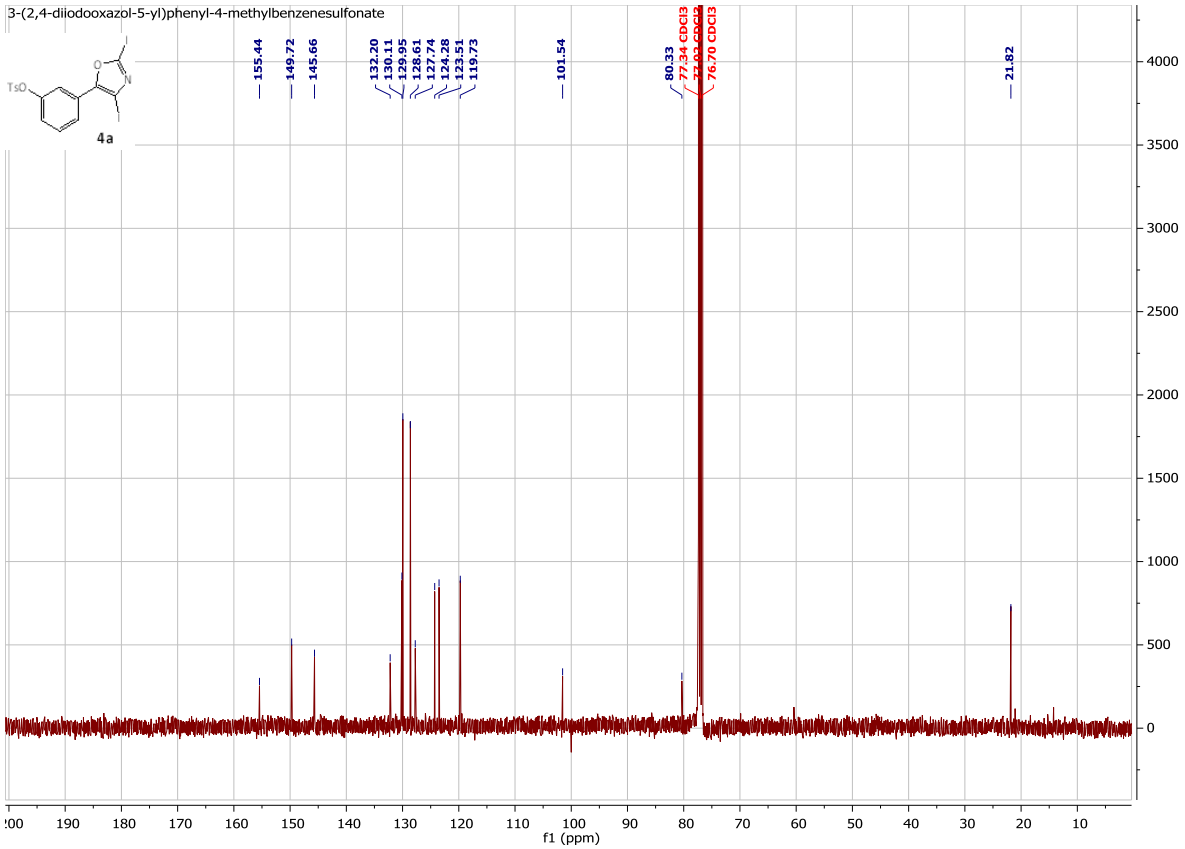


Appendix 7: 3-(2,4-diiodooxazol-5-yl)phenyl-4-methylbenzenesulfonate (4a)

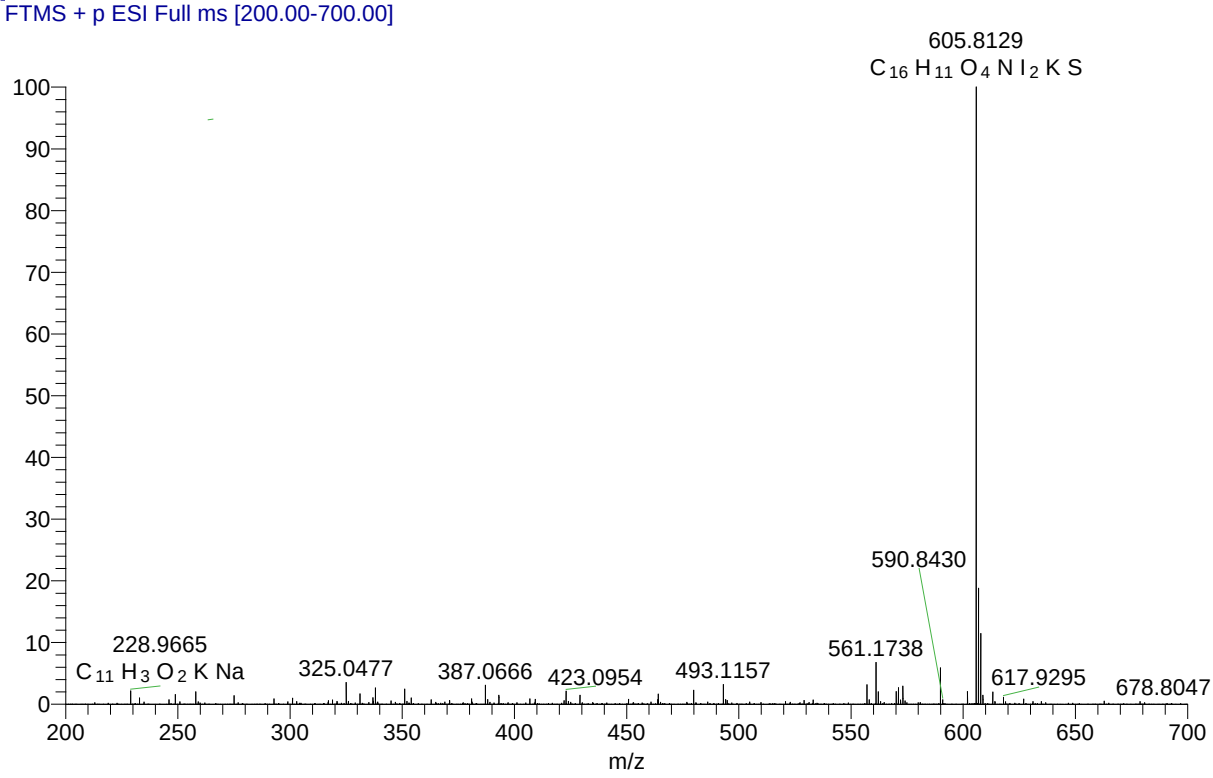


4a

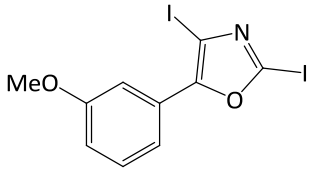




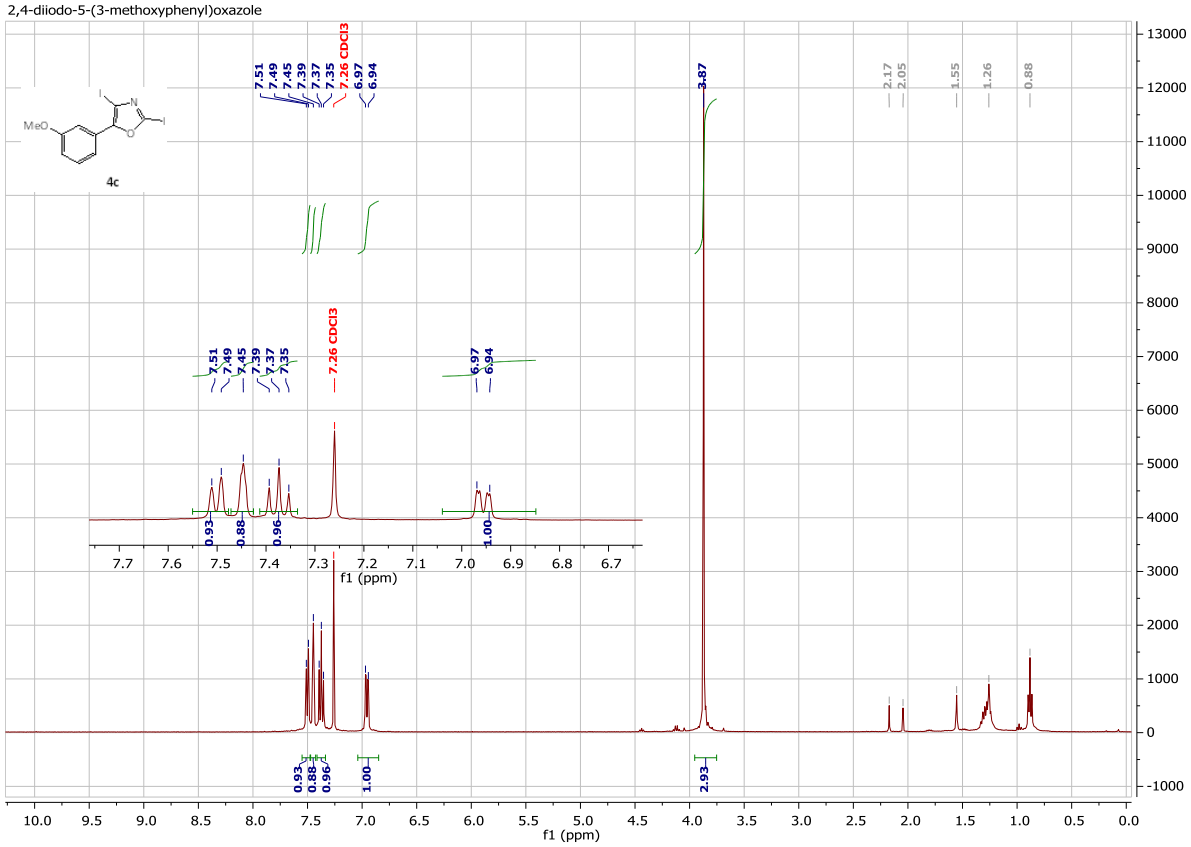
4a_pos #5 RT: 0.12 AV: 1 NL: 3.00E7
T: FTMS + p ESI Full ms [200.00-700.00]

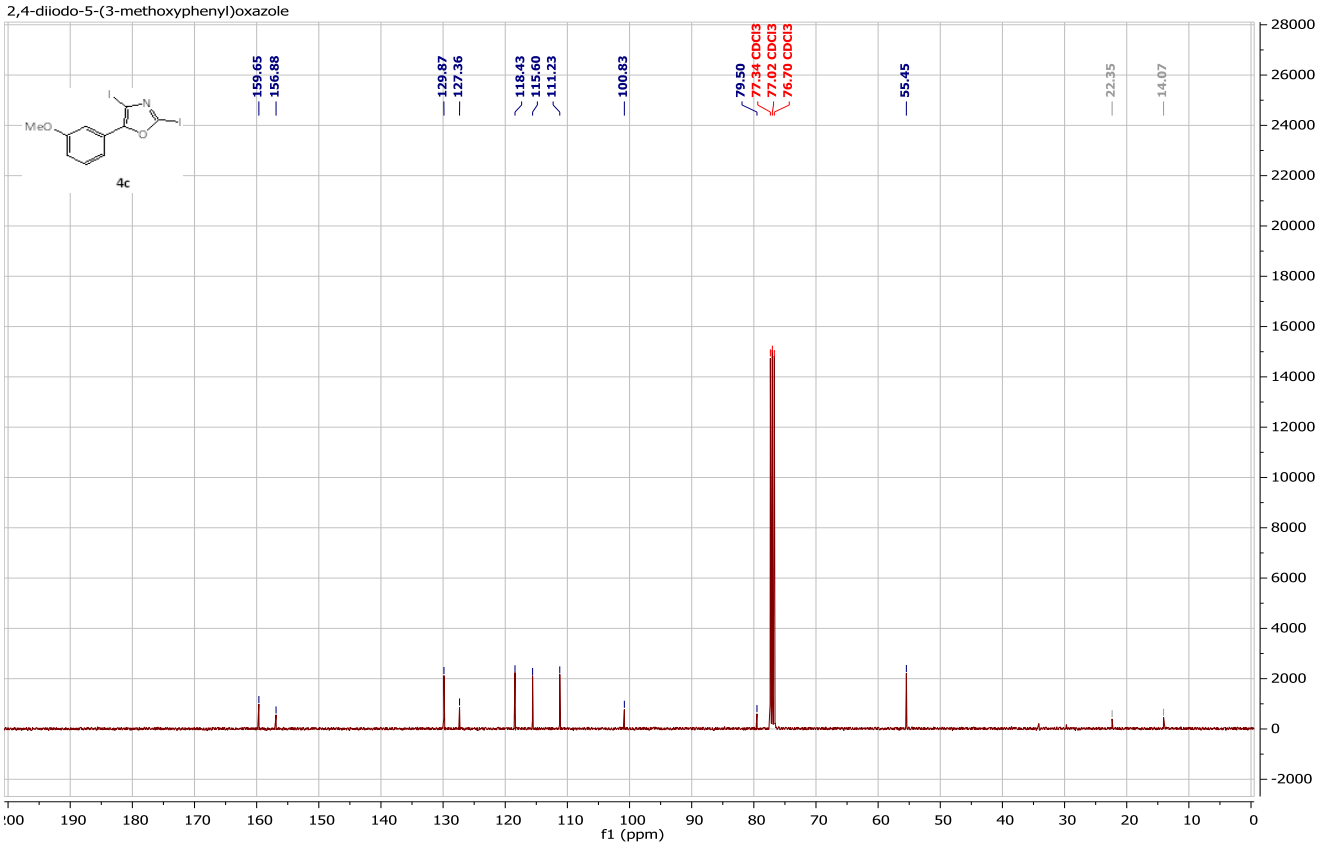


Appendix 8: 2,4-diiodo-5-(3-methoxyphenyl)oxazole (4c)

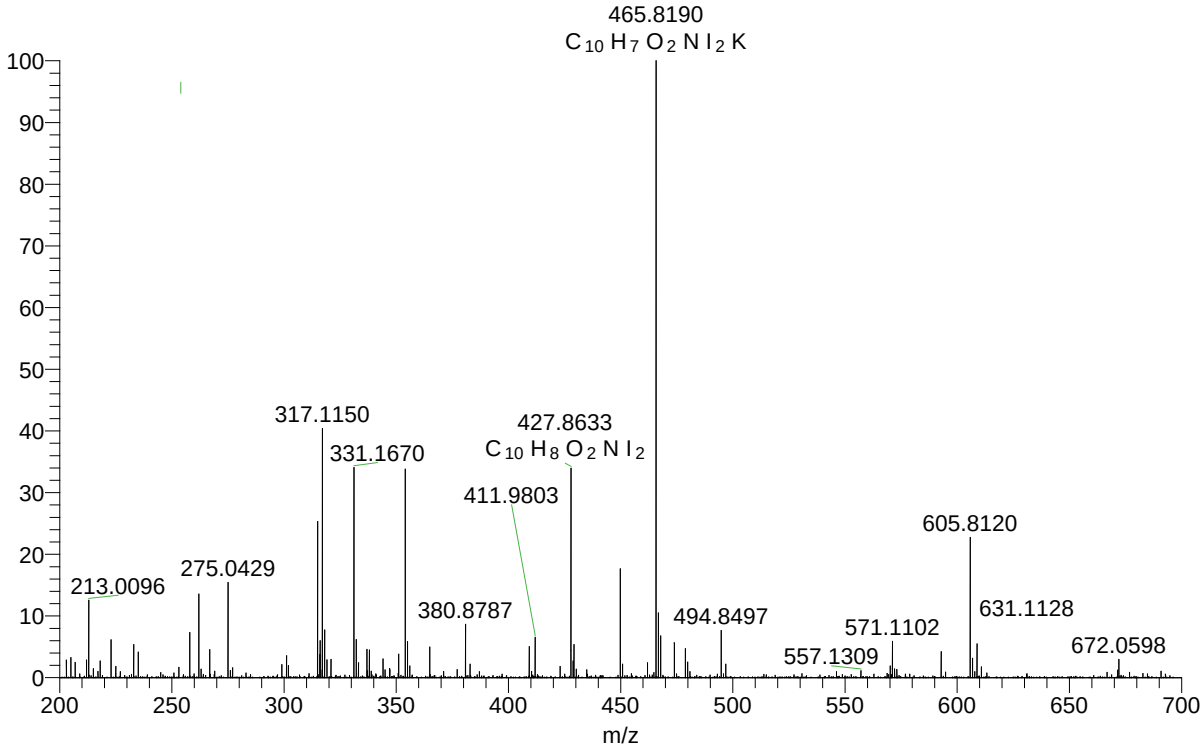


4c

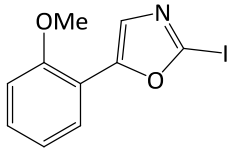




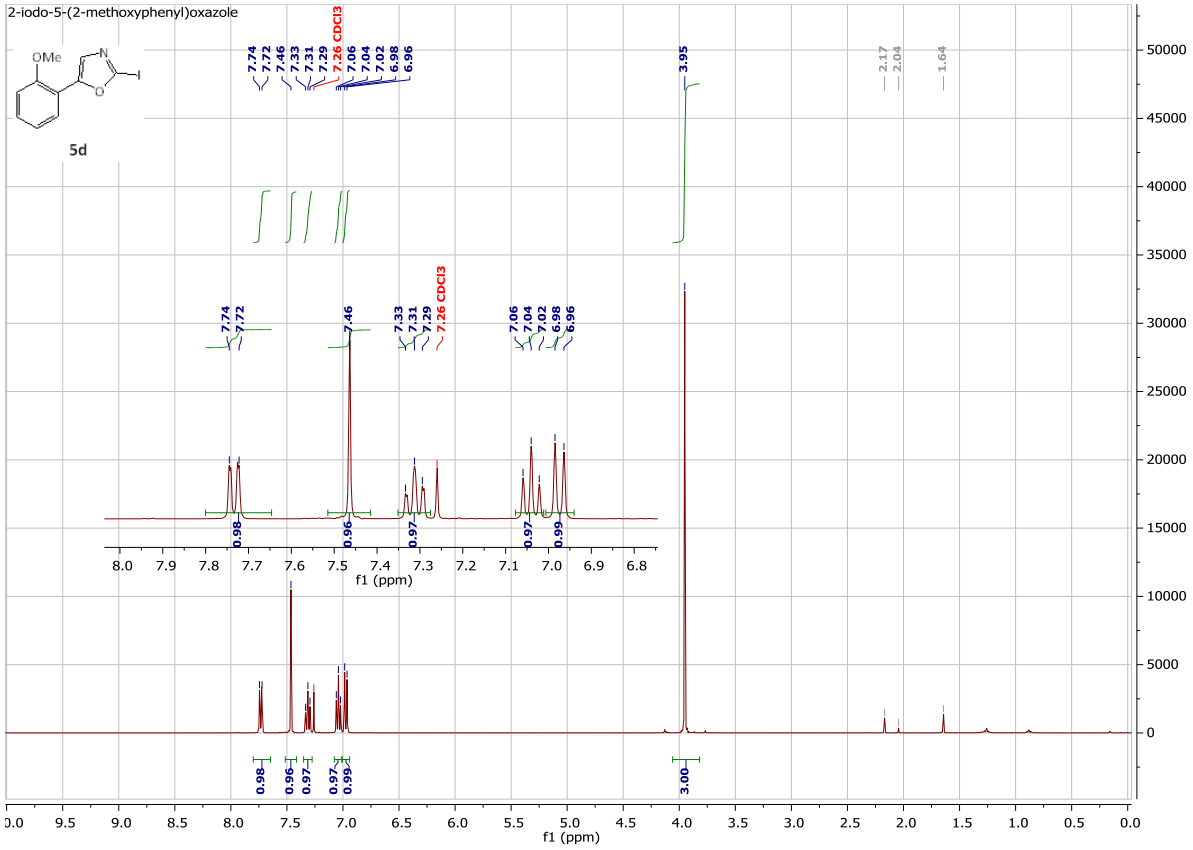
4c_pos #2 RT: 0.05 AV: 1 NL: 6.64E6
T: FTMS + p ESI Full ms [200.00-700.00]

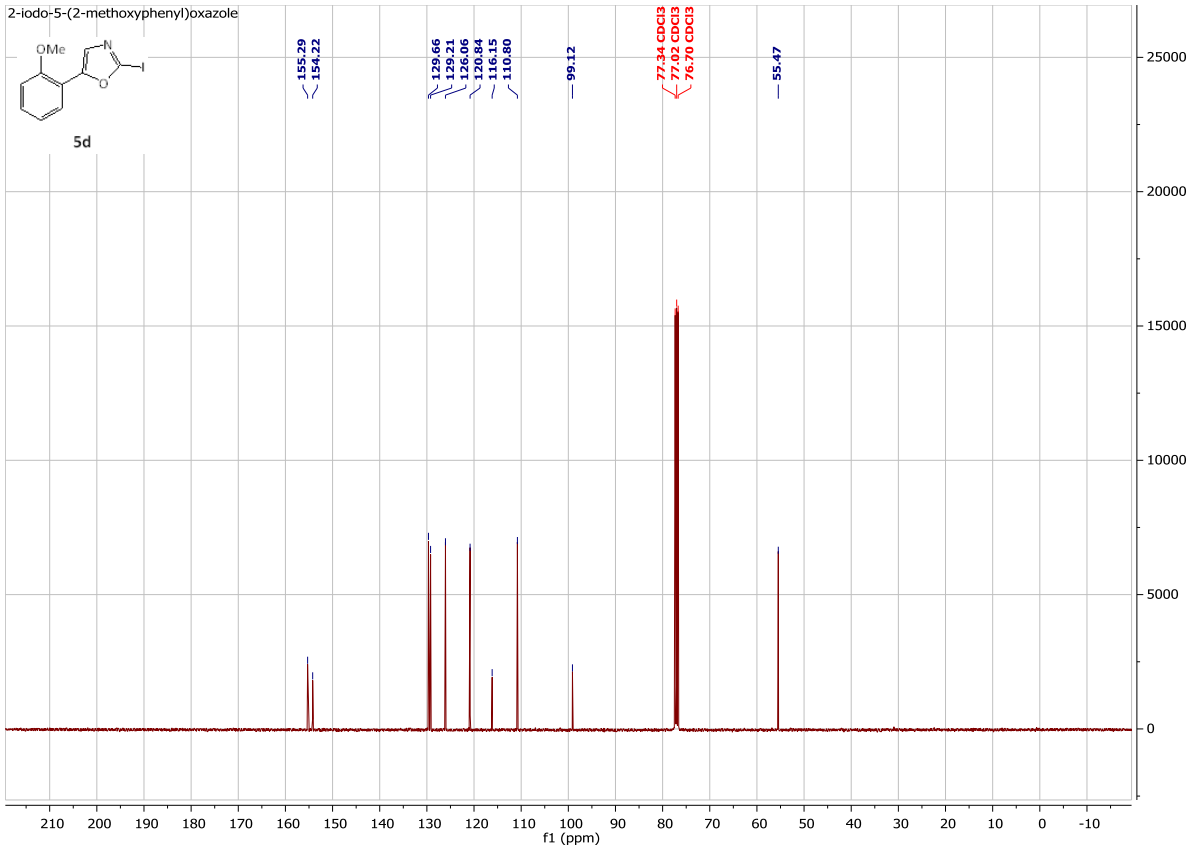


Appendix 9: 2-iodo-5-(2-methoxyphenyl)oxazole (5d)

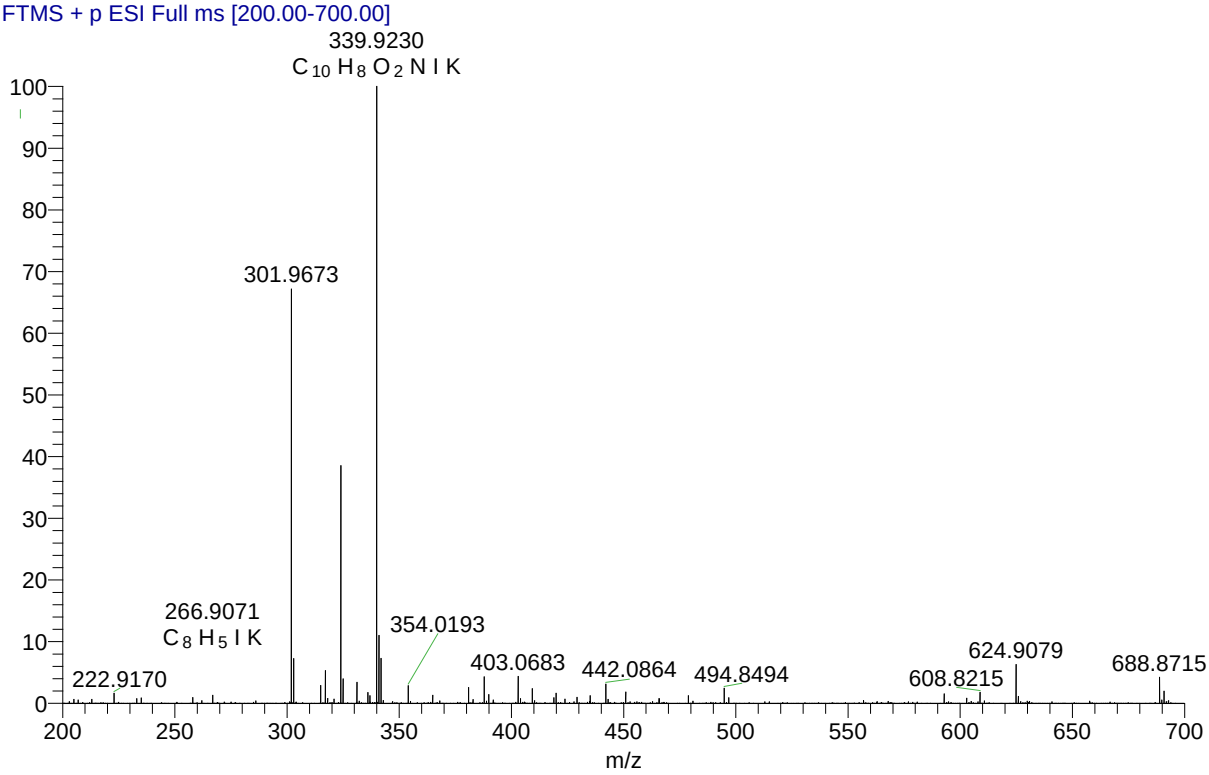


5d

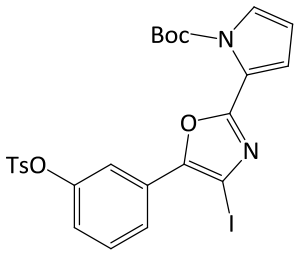




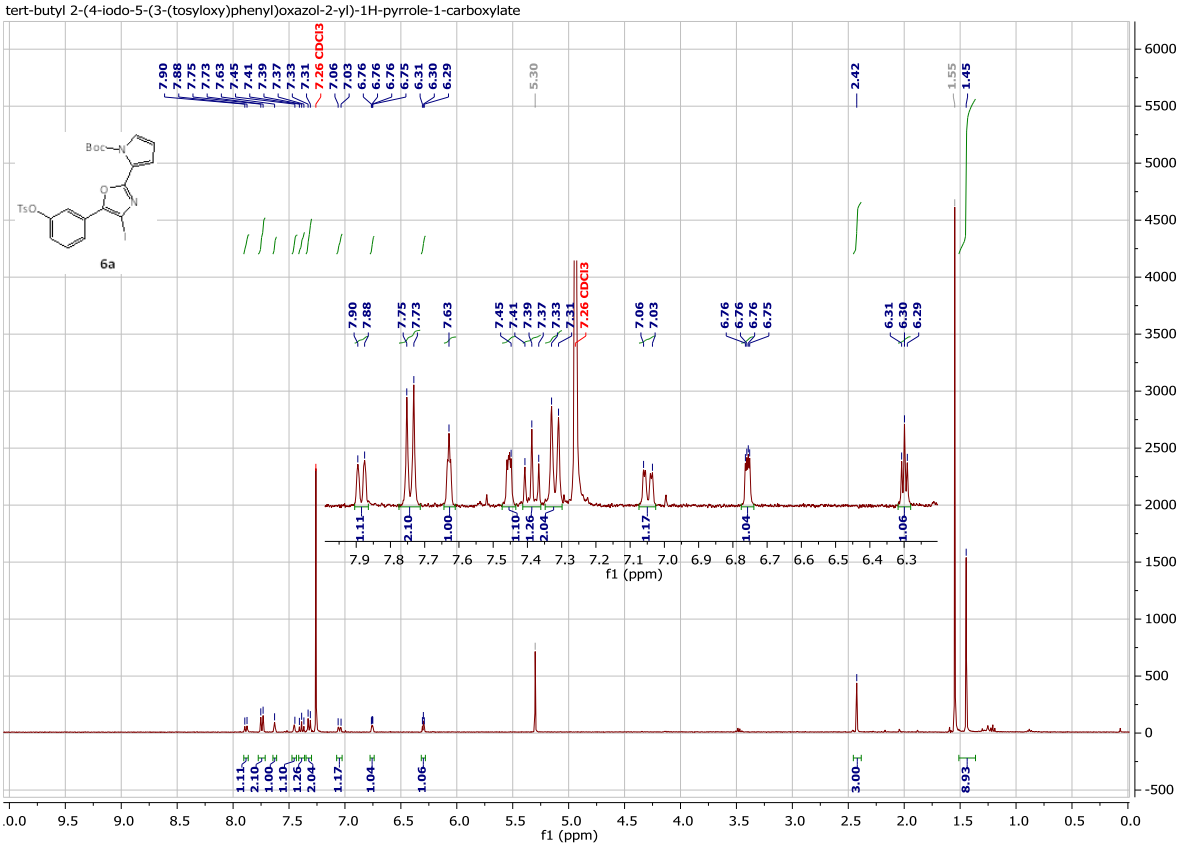
5d_pos #6 RT: 0.14 AV: 1 NL: 3.14E7
T: FTMS + p ESI Full ms [200.00-700.00]



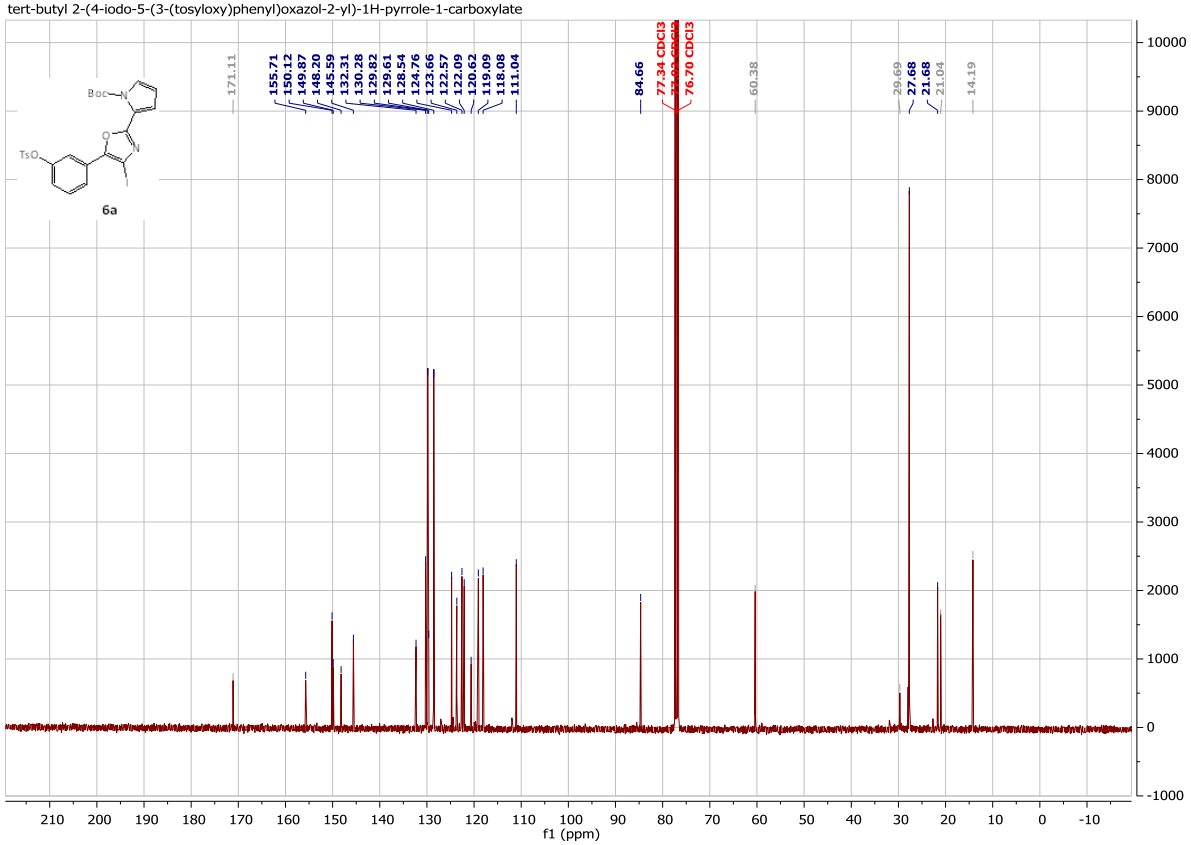
Appendix 10: tert-butyl 2-(4-iodo-5-(3-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate (6a)



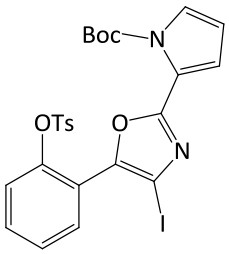
6a



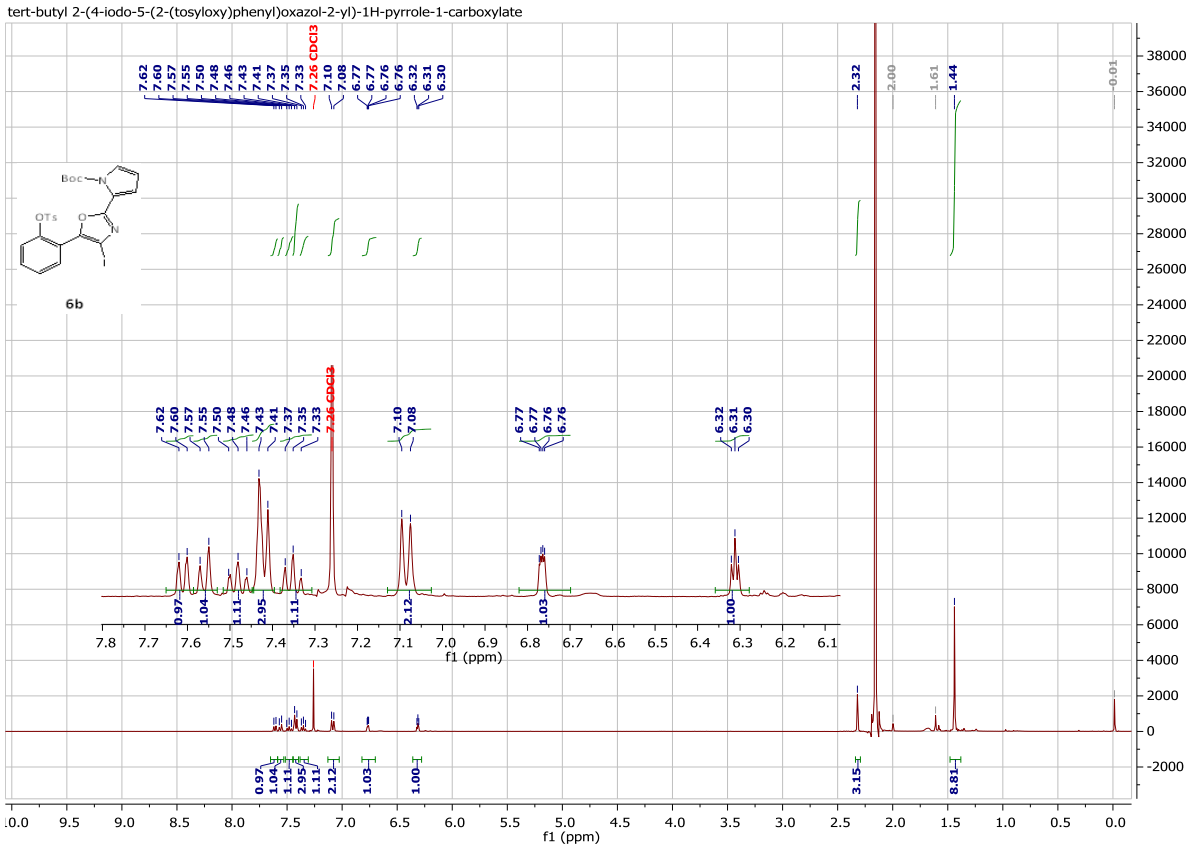
tert-butyl 2-(4-iodo-5-(3-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate



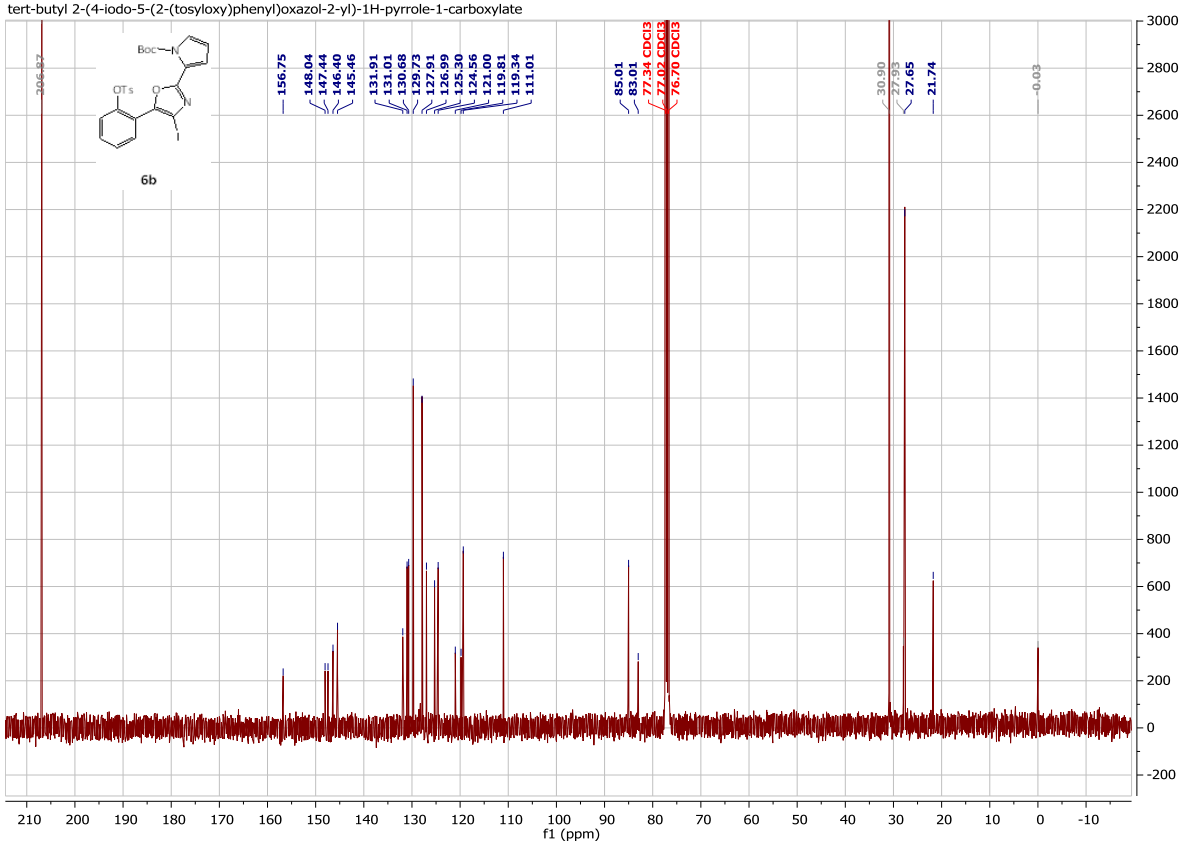
Appendix 11: tert-butyl 2-(4-iodo-5-(2-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate (6b)



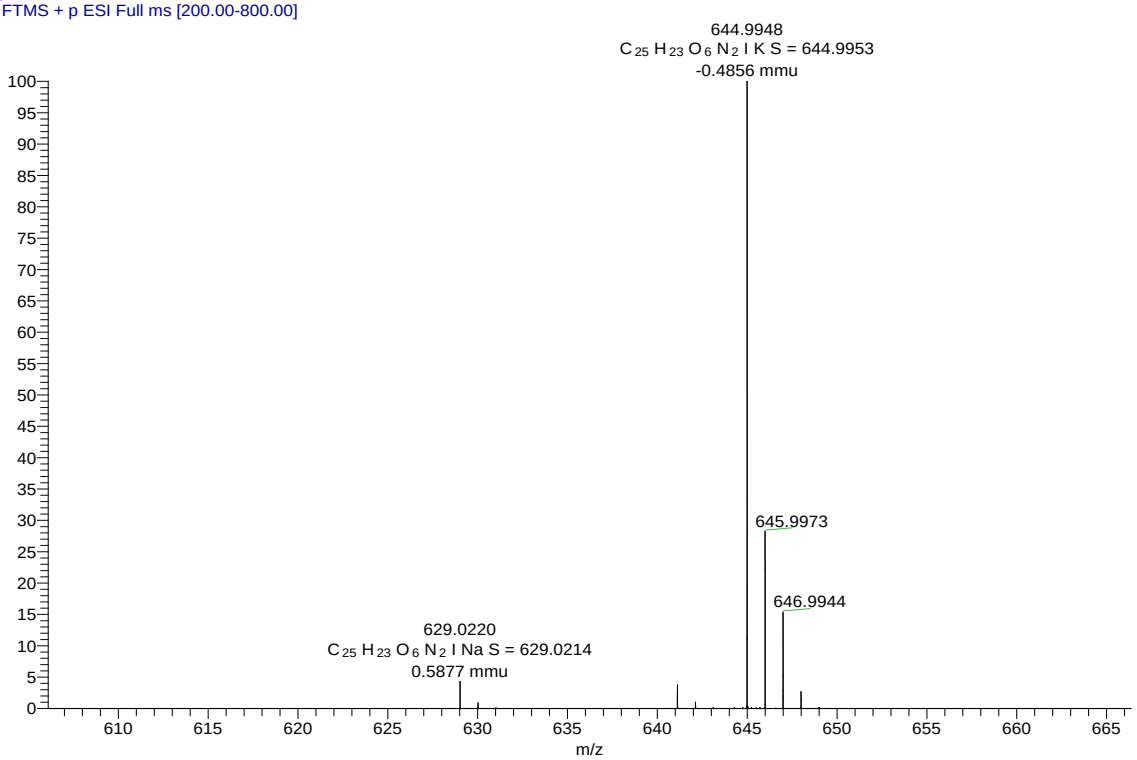
6b



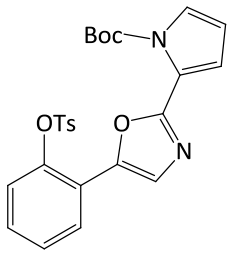
tert-butyl 2-(4-iodo-5-(2-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate



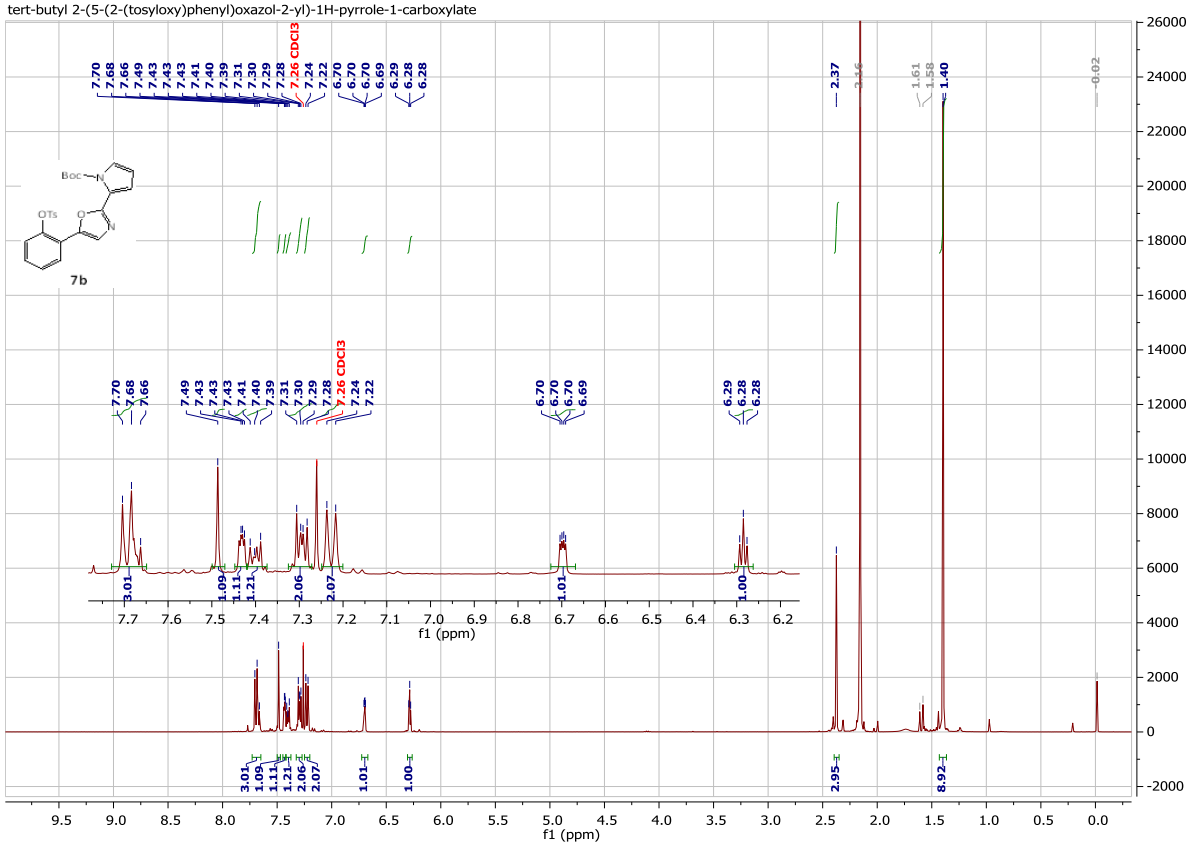
6B_pos #1-5 RT: 0.01-0.11 AV: 5 NL: 9.87E7
T: FTMS + p ESI Full ms [200.00-800.00]

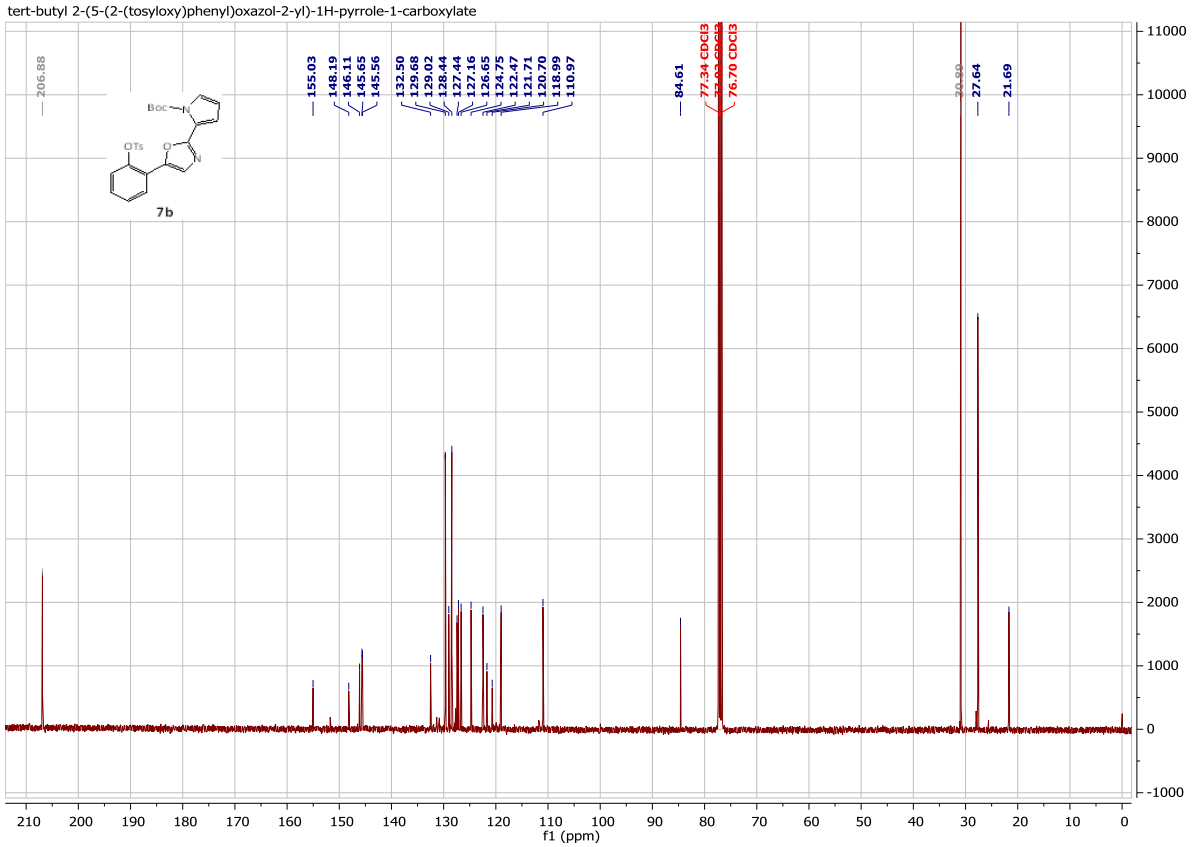


Appendix 12: tert-butyl 2-(5-(2-(tosyloxy)phenyl)oxazol-2-yl)-1H-pyrrole-1-carboxylate (7b)

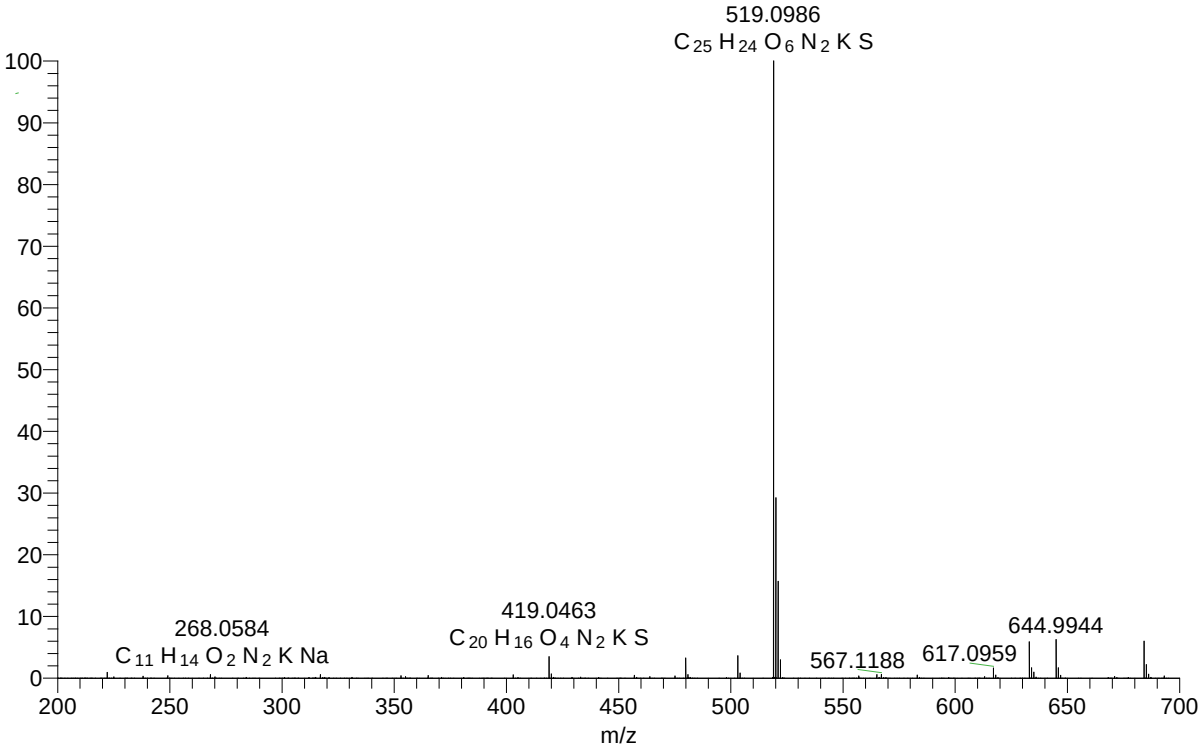


7b

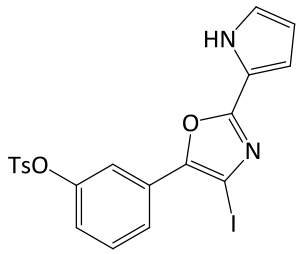




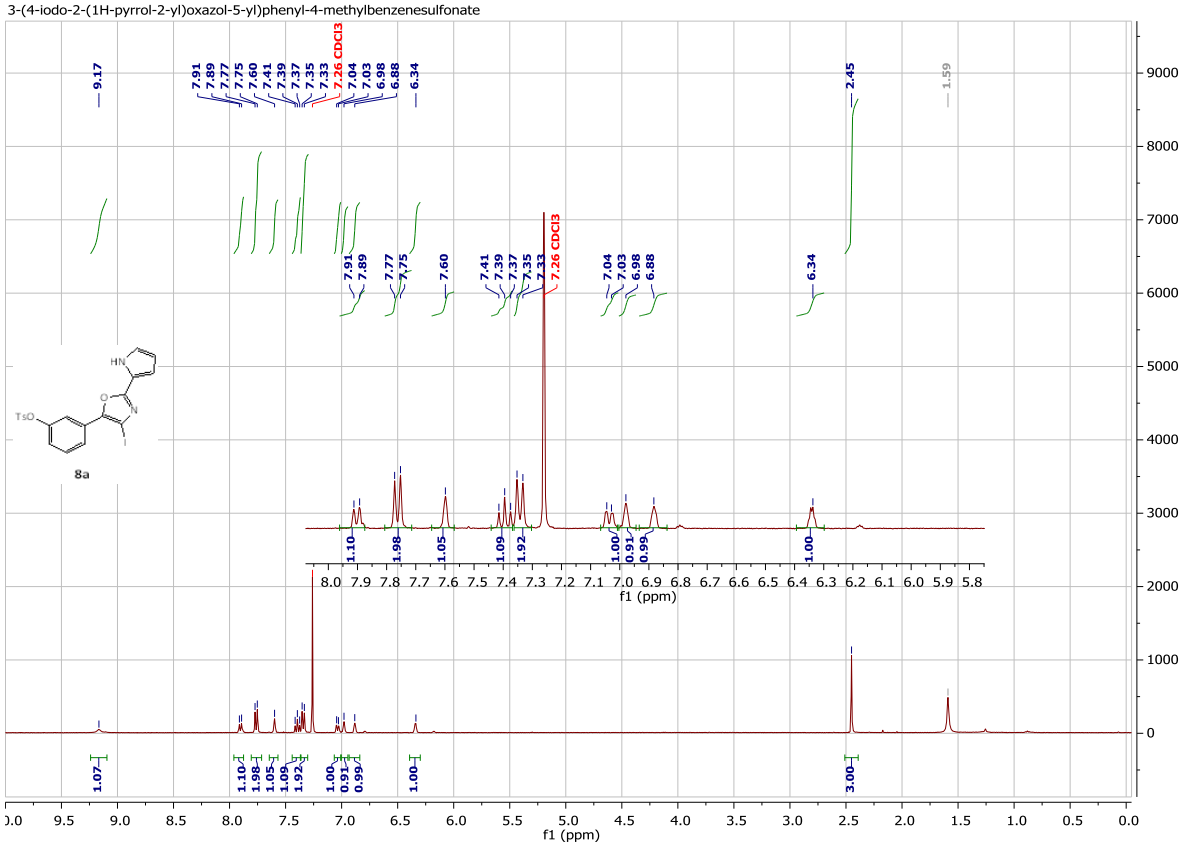
7B_pos #5 RT: 0.14 AV: 1 NL: 1.02E8
T: FTMS + p ESI Full ms [200.00-700.00]

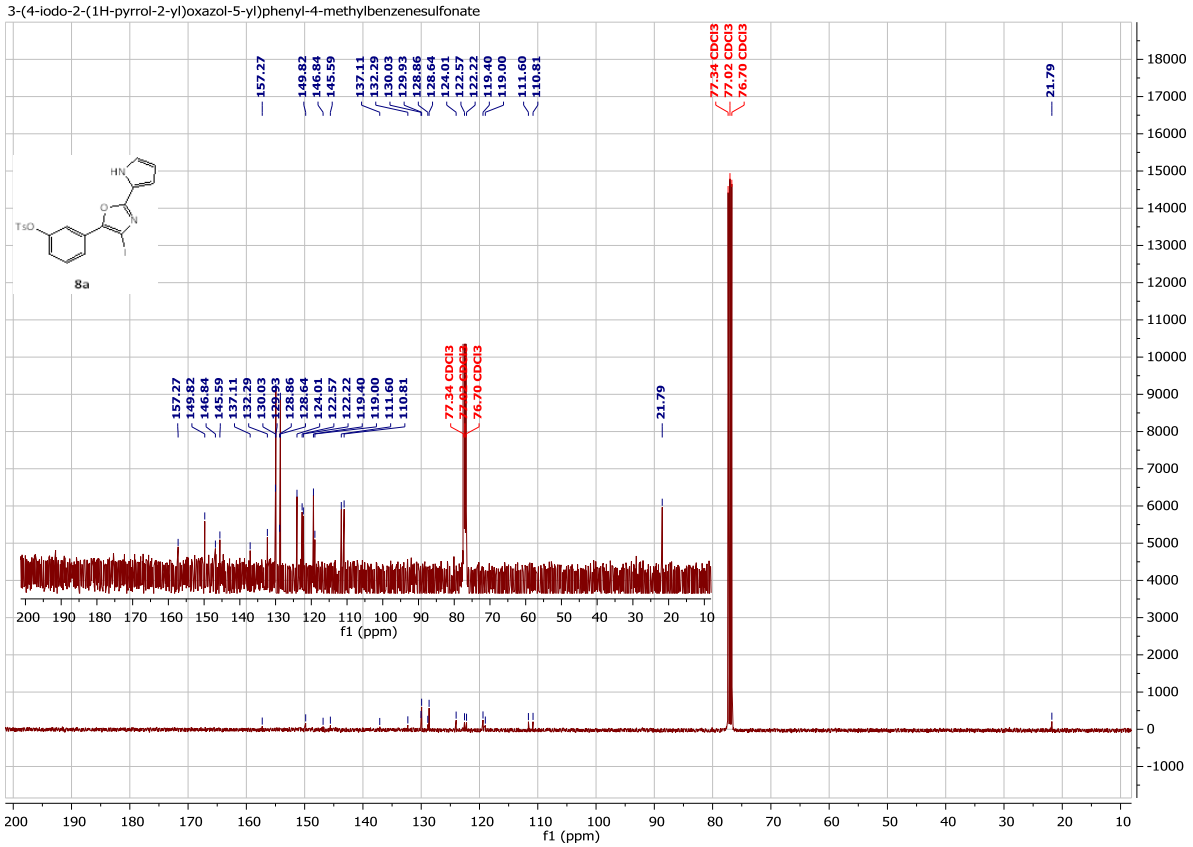


Appendix 13: 3-(4-iodo-2-(1H-pyrrol-2-yl)oxazol-5-yl)phenyl-4-methylbenzenesulfonate (8a)

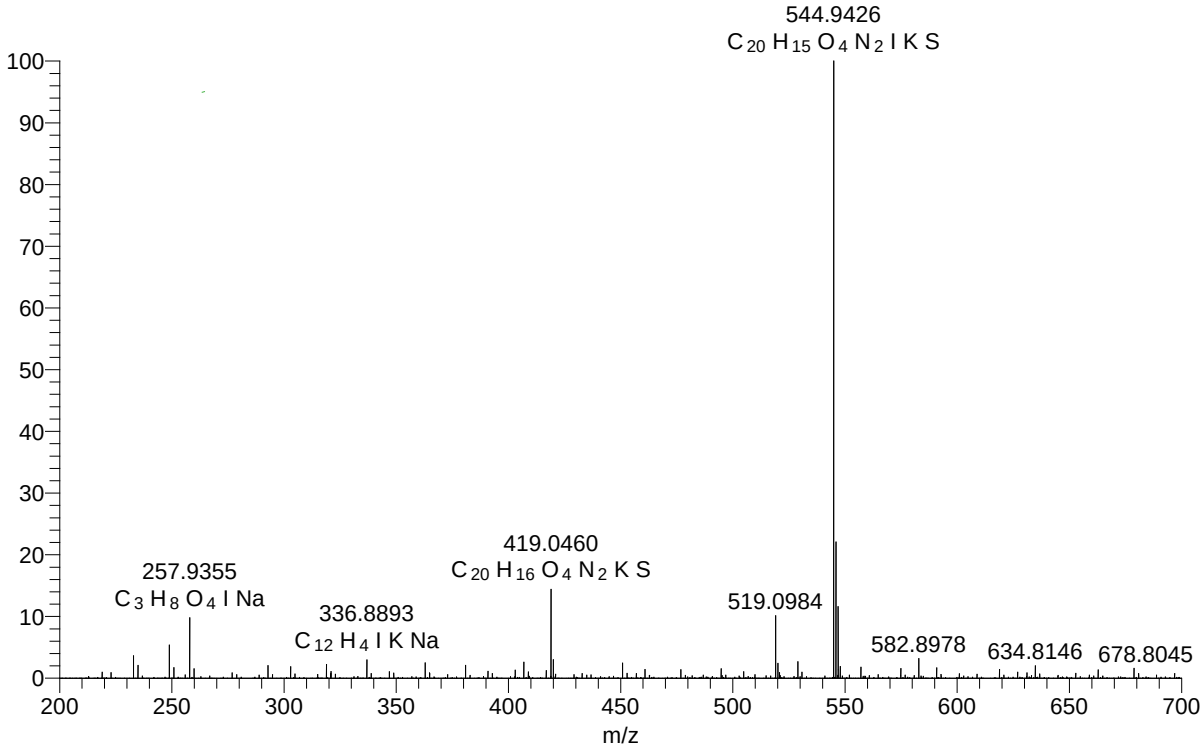


8a

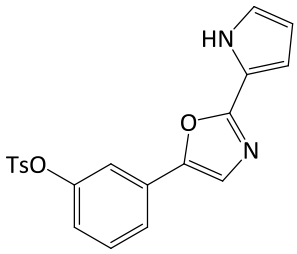




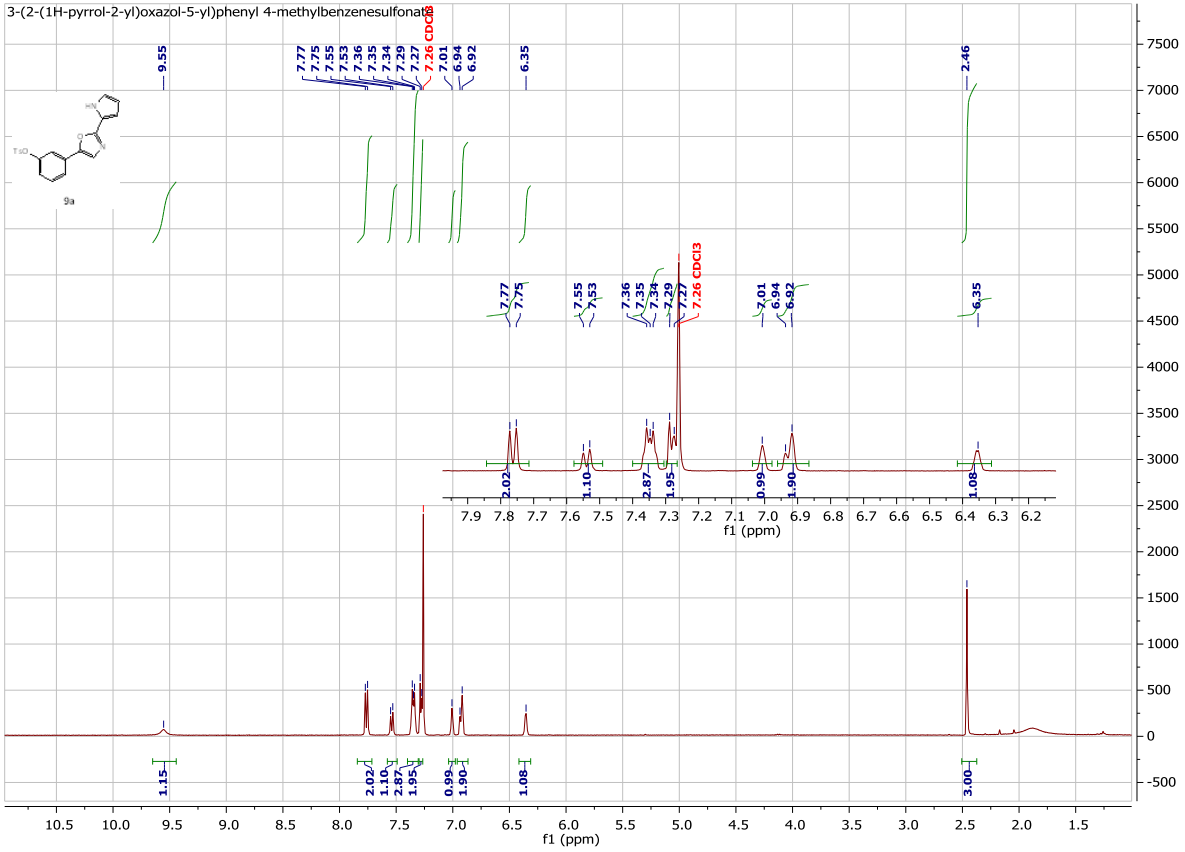
8a_posb #5 RT: 0.13 AV: 1 NL: 1.48E7
T: FTMS + p ESI Full ms [200.00-700.00]

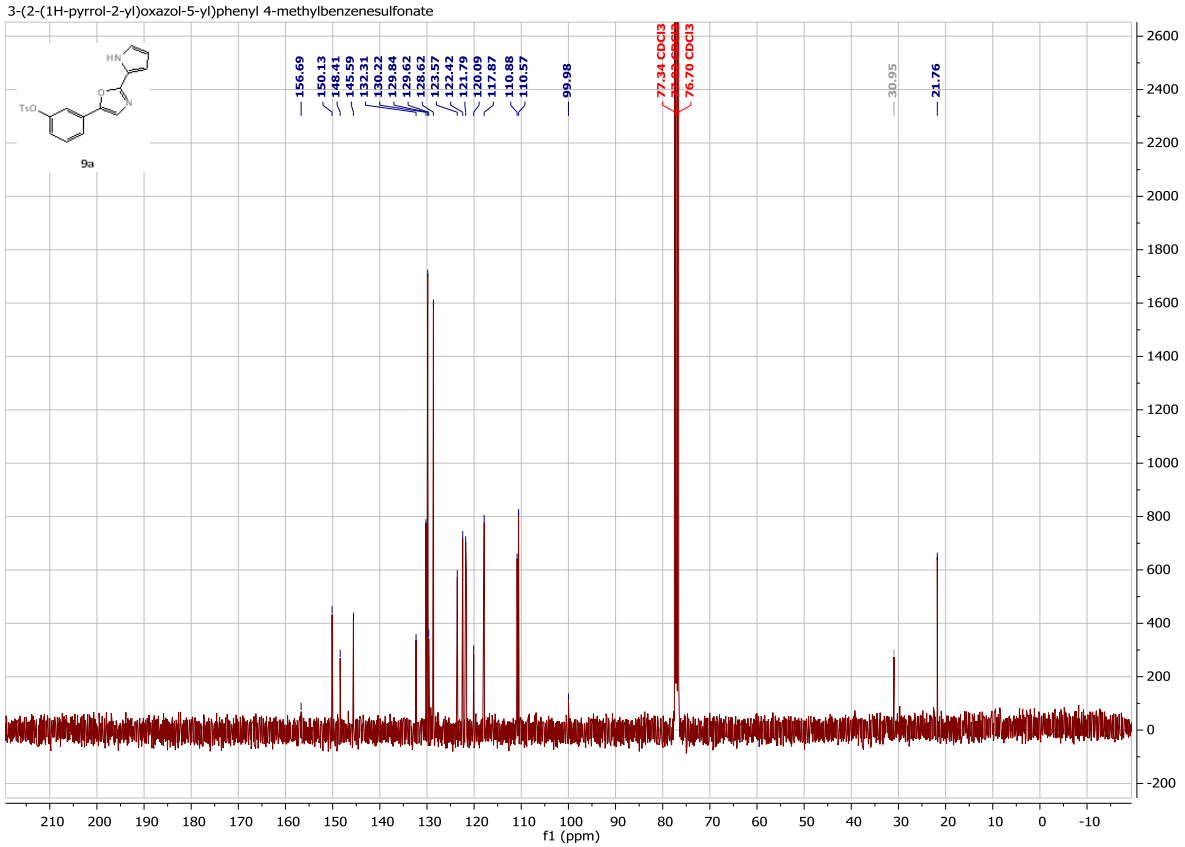


Appendix 14: 3-(2-(1H-pyrrol-2-yl)oxazol-5-yl)phenyl 4-methylbenzenesulfonate (9a)

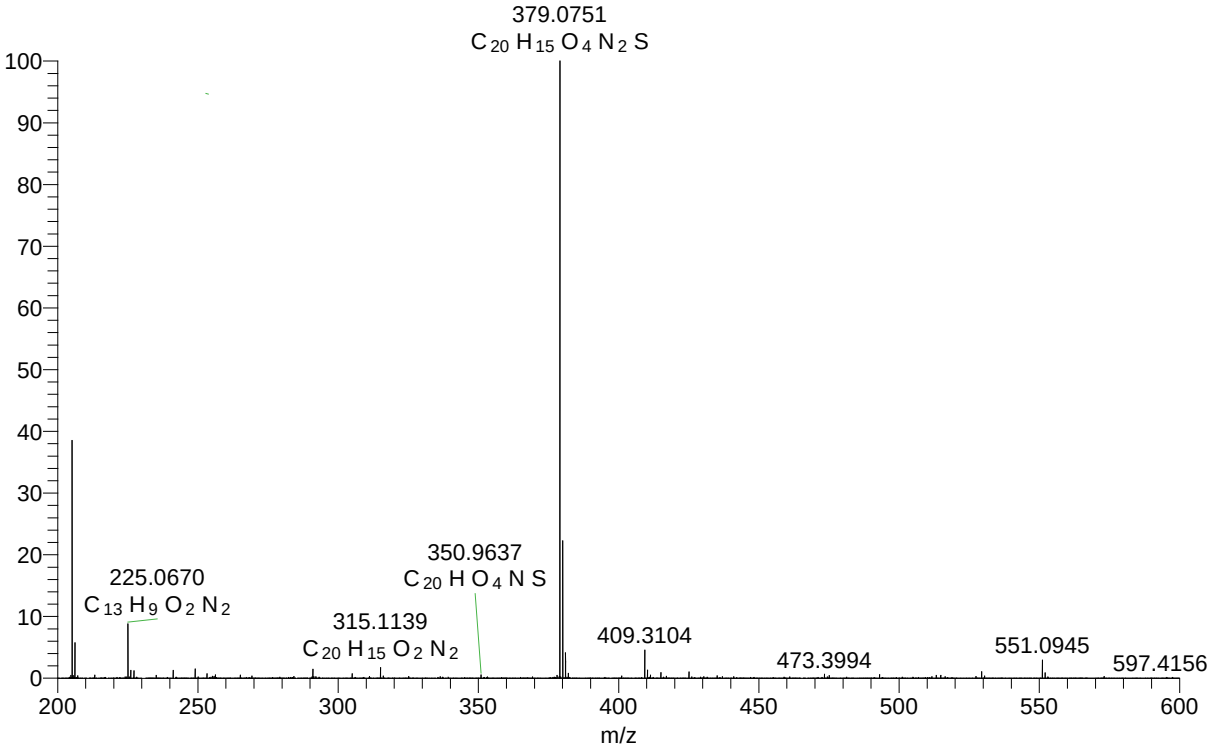


9a

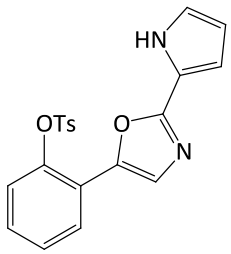




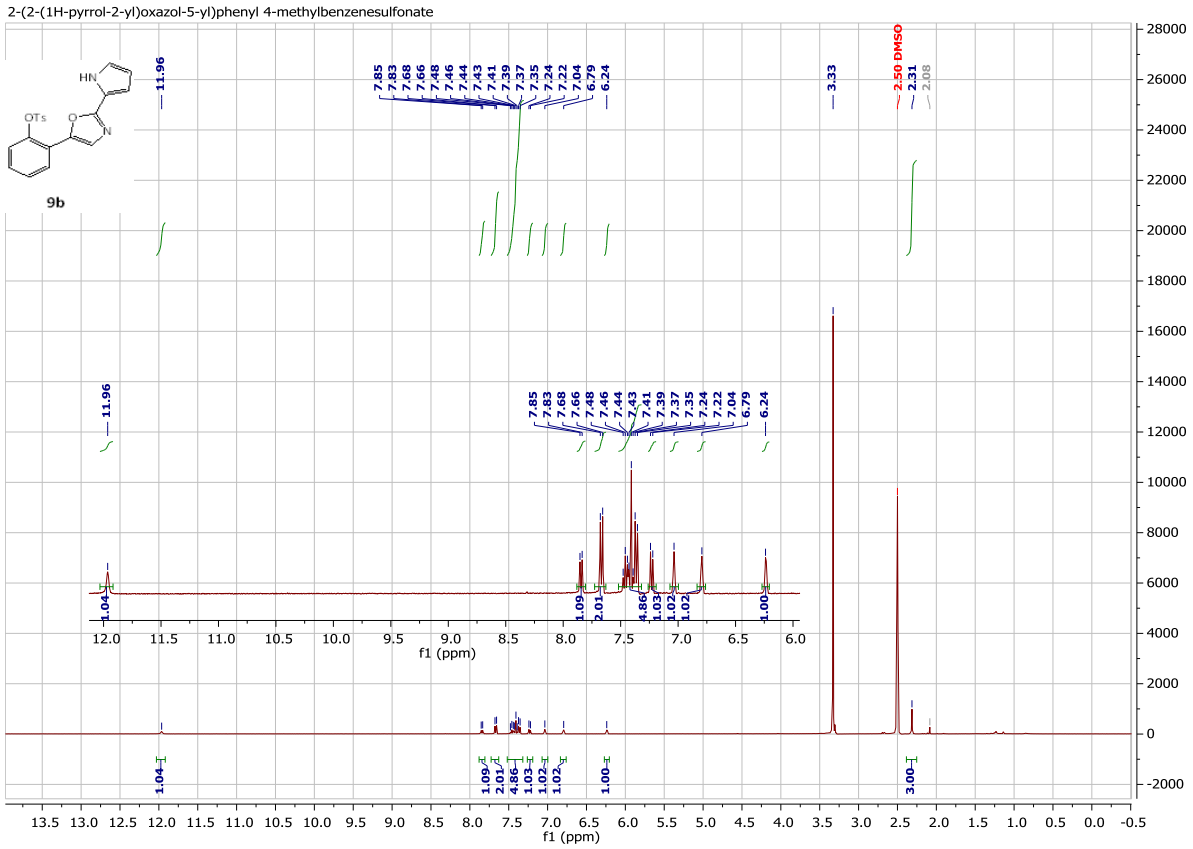
ABAM_044_neg #5 RT: 0.15 AV: 1 NL: 7.26E6
T: FTMS - p ESI Full ms [200.00-600.00]

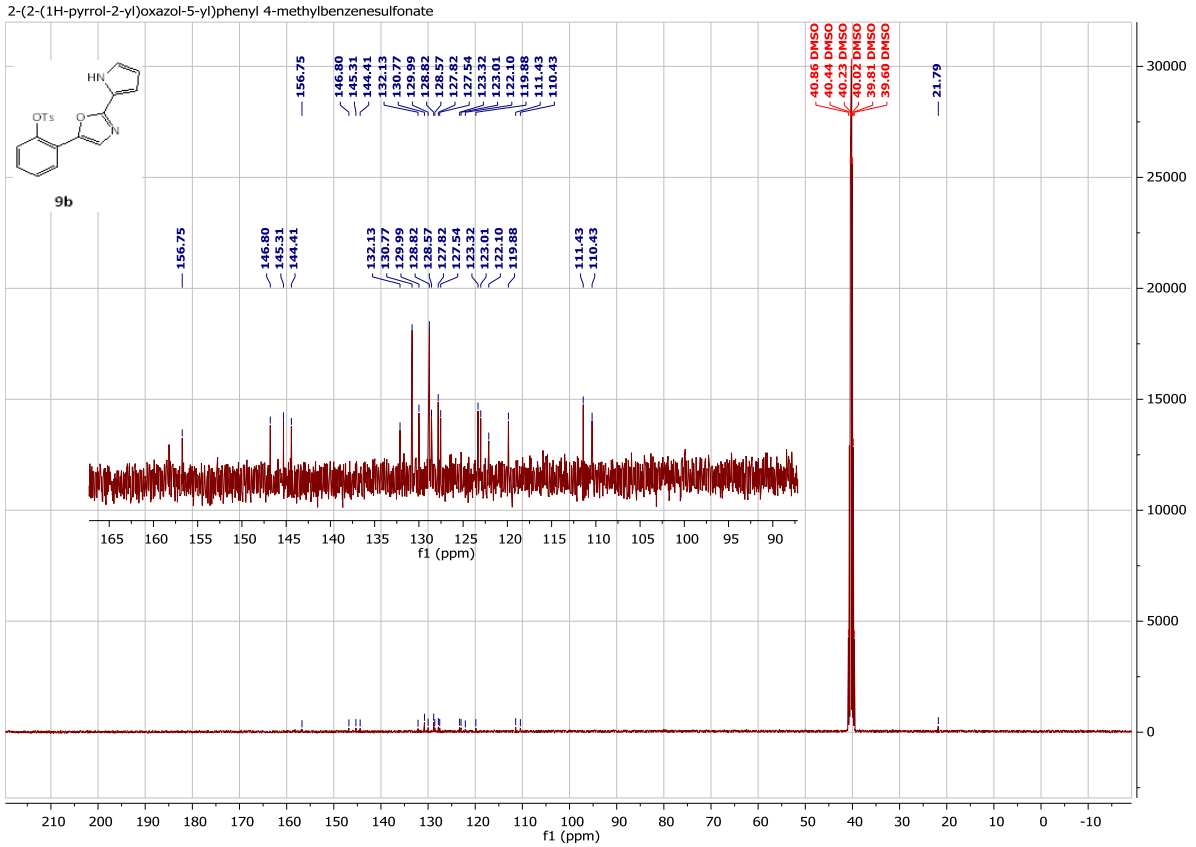


Appendix 15: 2-(2-(1H-pyrrol-2-yl)oxazol-5-yl)phenyl 4-methylbenzenesulfonate (9b)

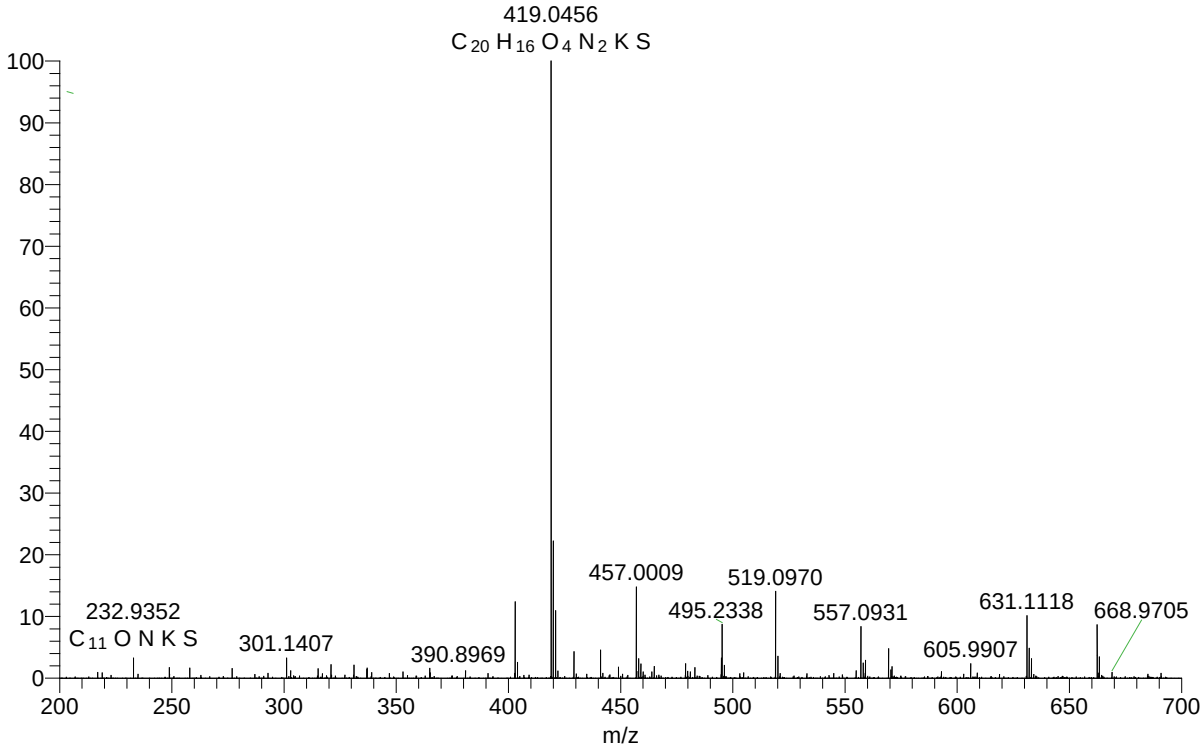


9b

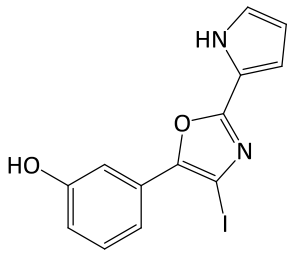




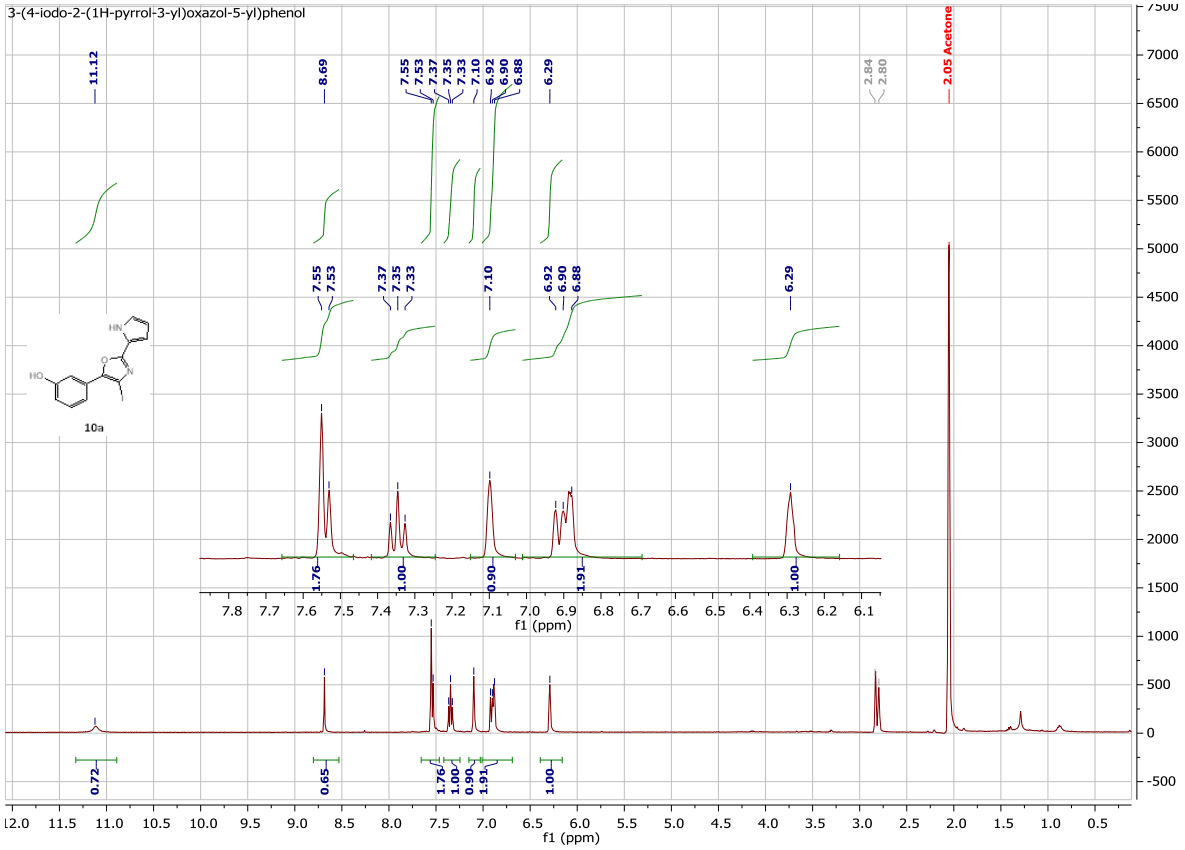
9b_pos #5 RT: 0.11 AV: 1 NL: 1.12E7
T: FTMS + p ESI Full ms [200.00-700.00]

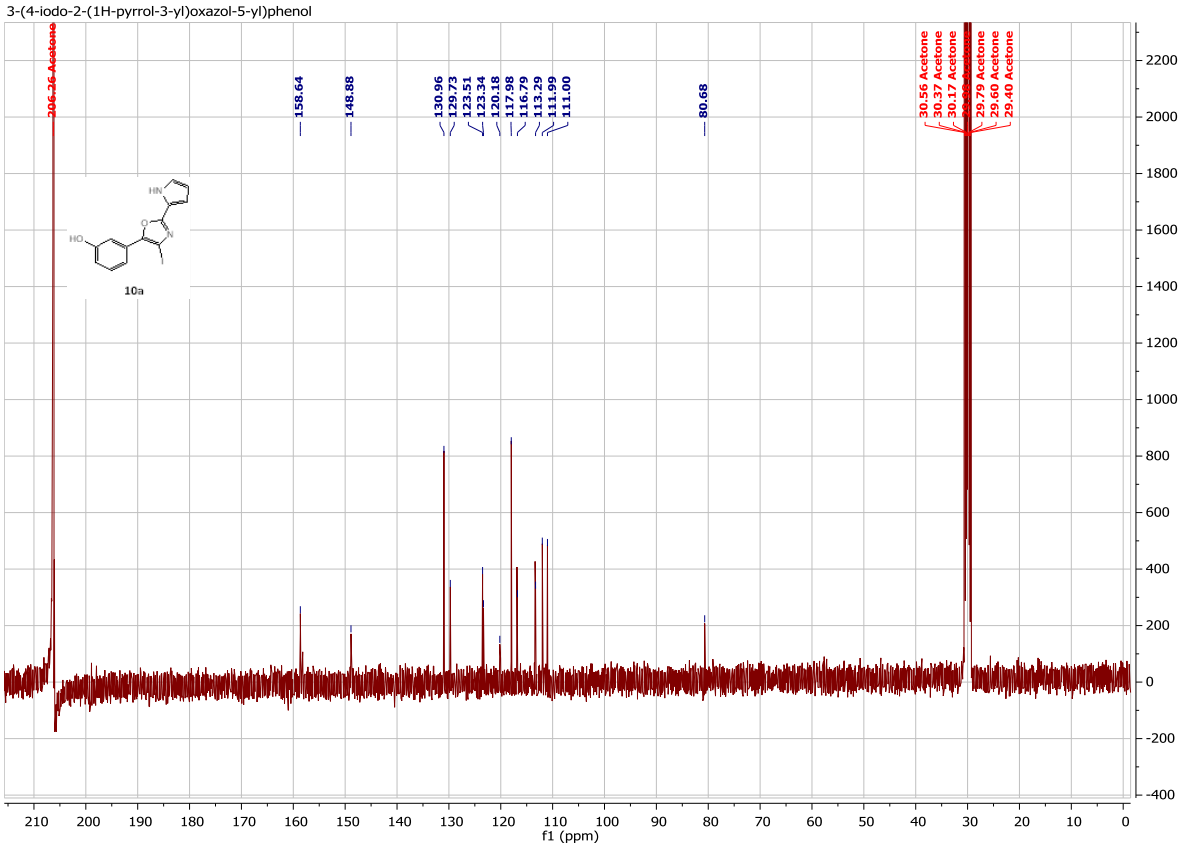


Appendix 16: 3-(4-iodo-2-(1H-pyrrol-2-yl)oxazol-5-yl)phenol (10a)

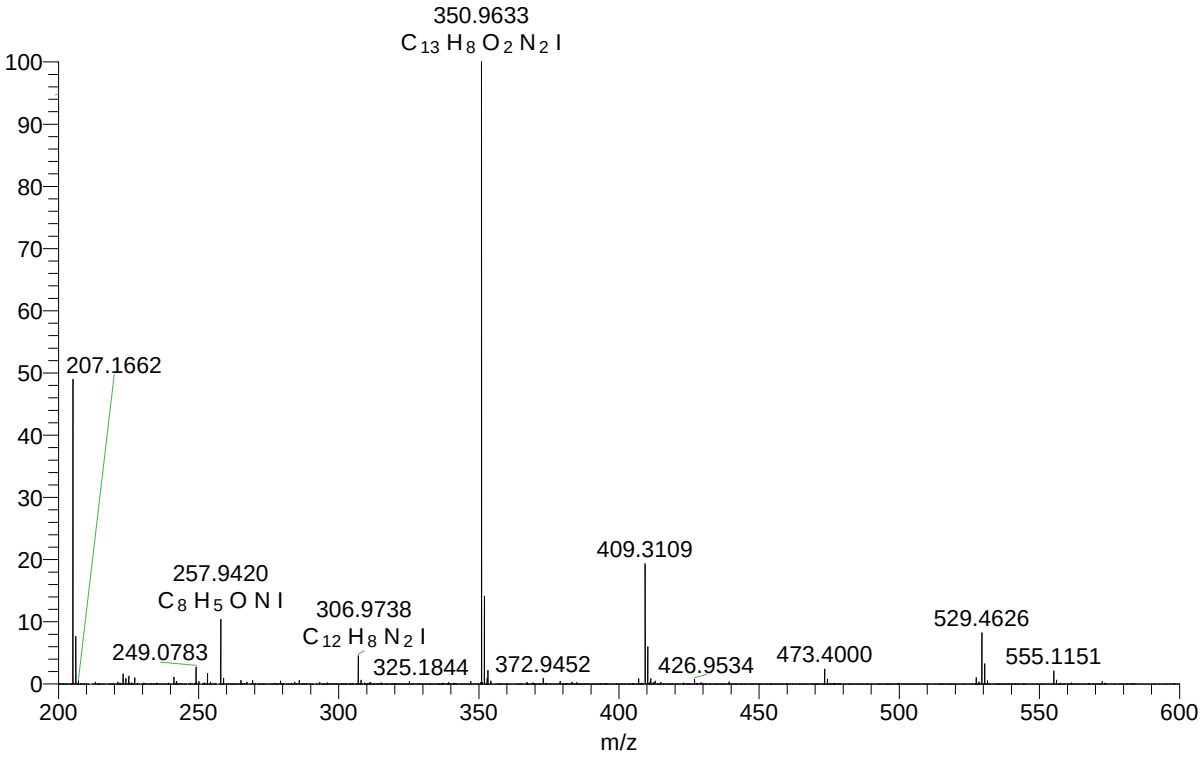


10a

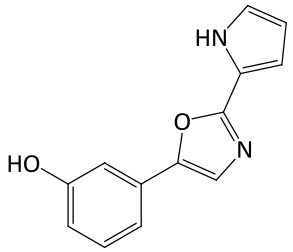




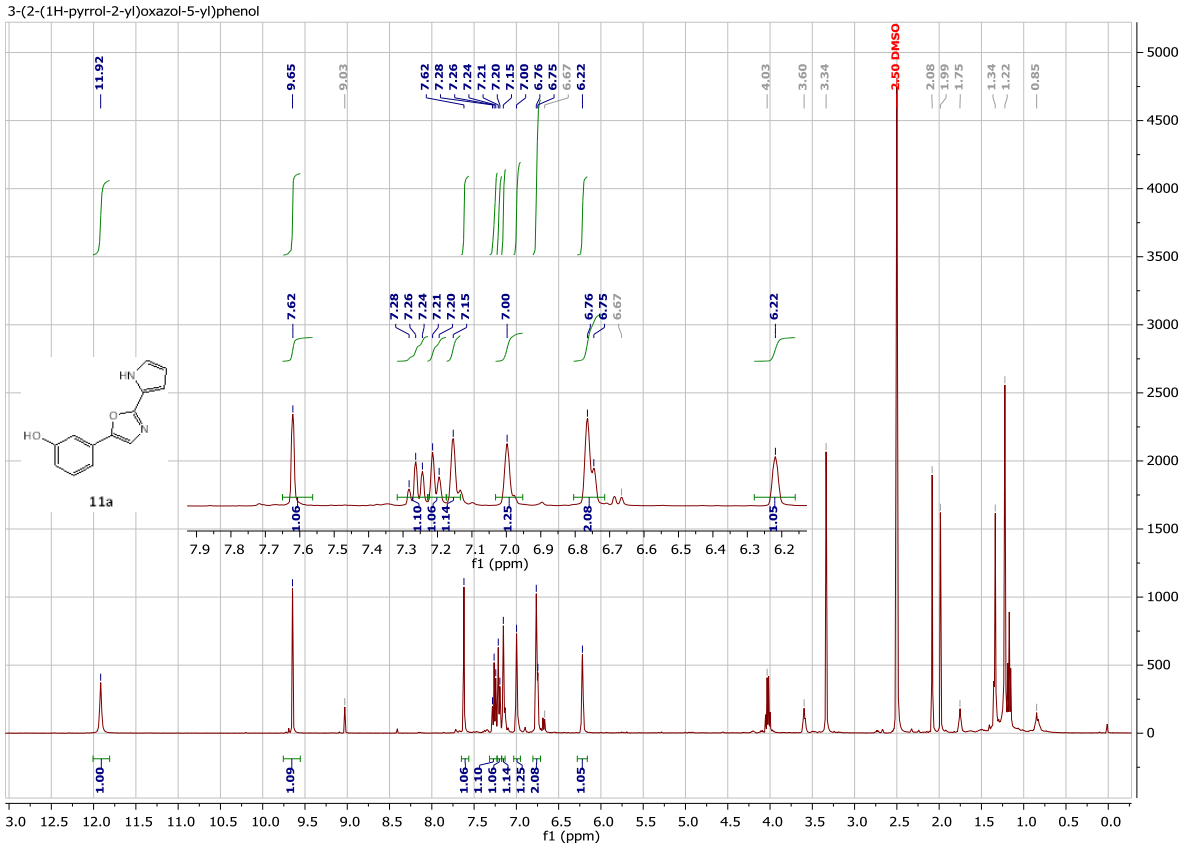
ABAM_042_neg #5 RT: 0.17 AV: 1 NL: 6.14E6
T: FTMS - p ESI Full ms [200.00-600.00]

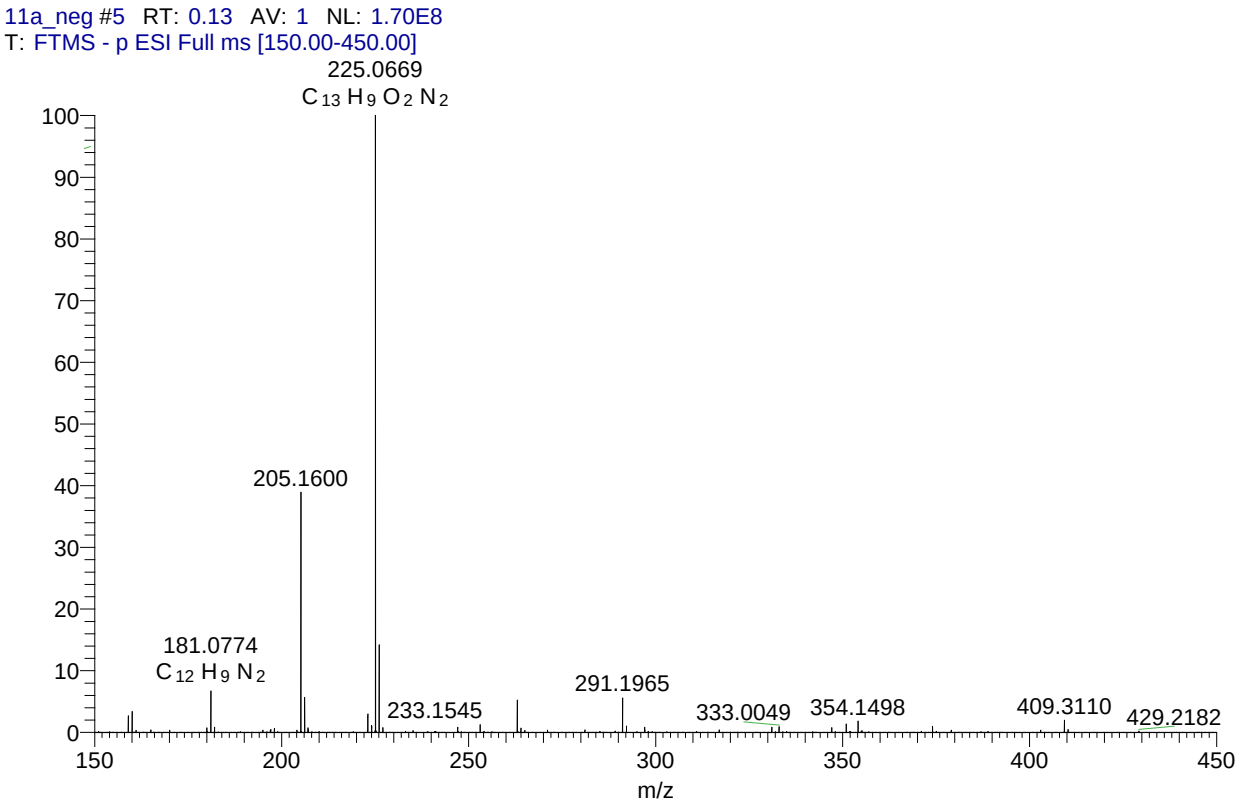


Appendix 17: 3-(2-(1H-pyrrol-2-yl)oxazol-5-yl)phenol (11a)

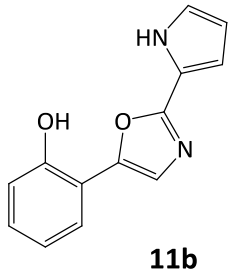


11a

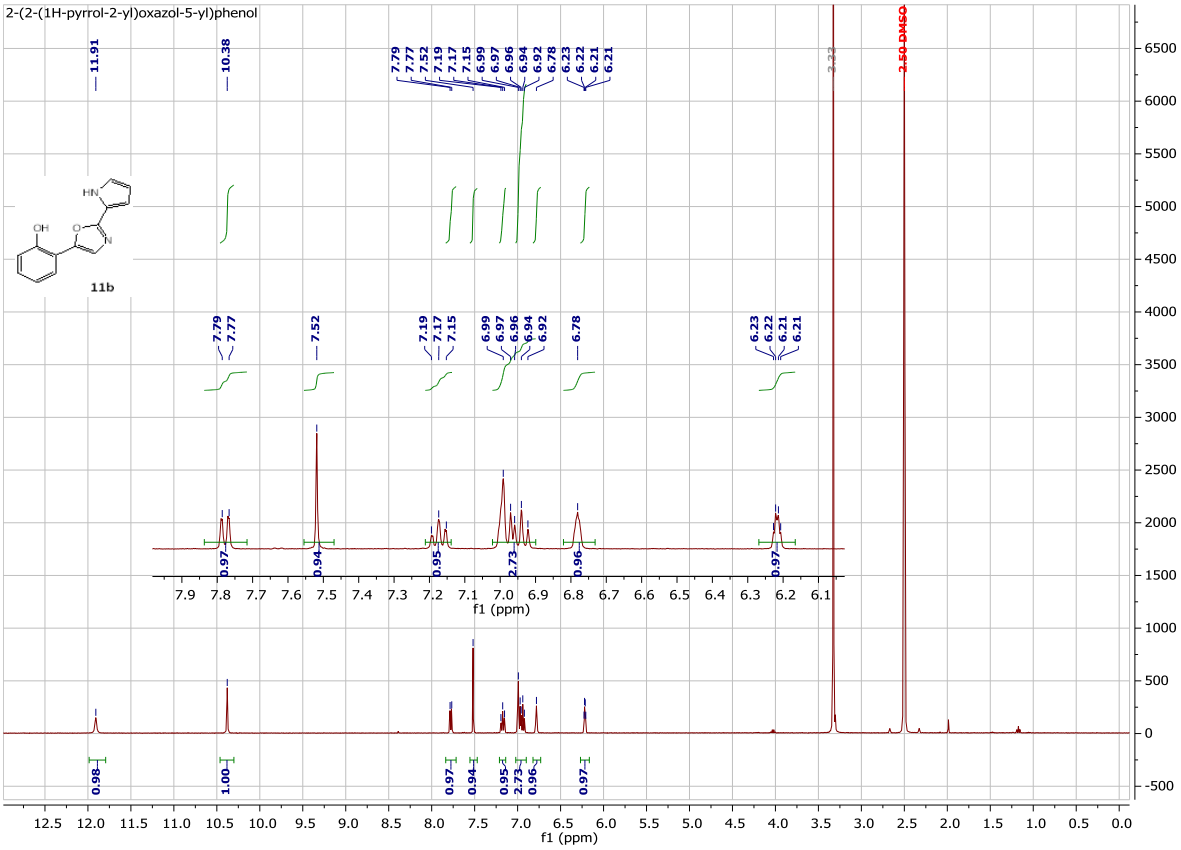


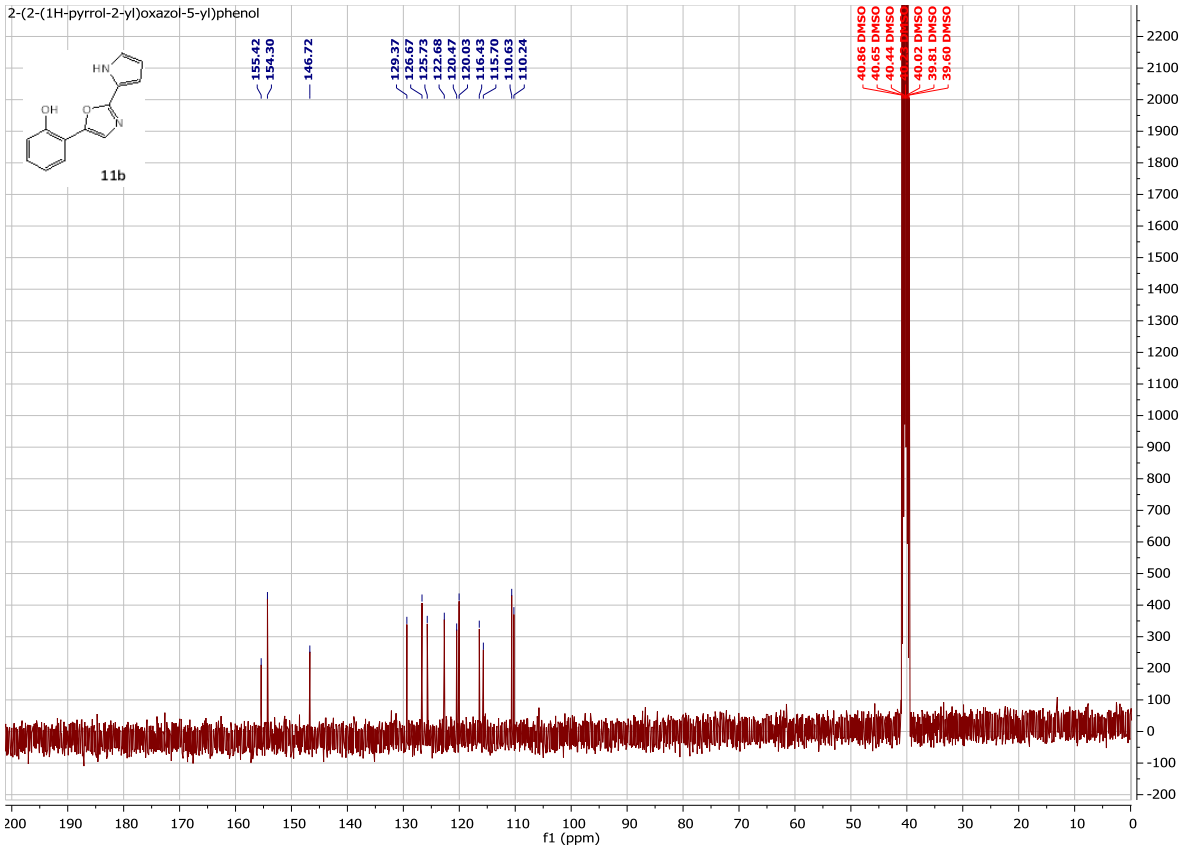

11a_neg #5 RT: 0.13 AV: 1 NL: 1.70E8
T: FTMS - p ESI Full ms [150.00-450.00]
225.0669
C 13 H 9 O 2 N 2
205.1600
181.0774
C 12 H 9 N 2
233.1545
291.1965
333.0049
354.1498
409.3110
429.2182
100
90
80
70
60
50
40
30
20
10
0
150
200
250
300
350
400
450
m/z

Appendix 18: 2-(2-(1H-pyrrol-2-yl)oxazol-5-yl)phenol

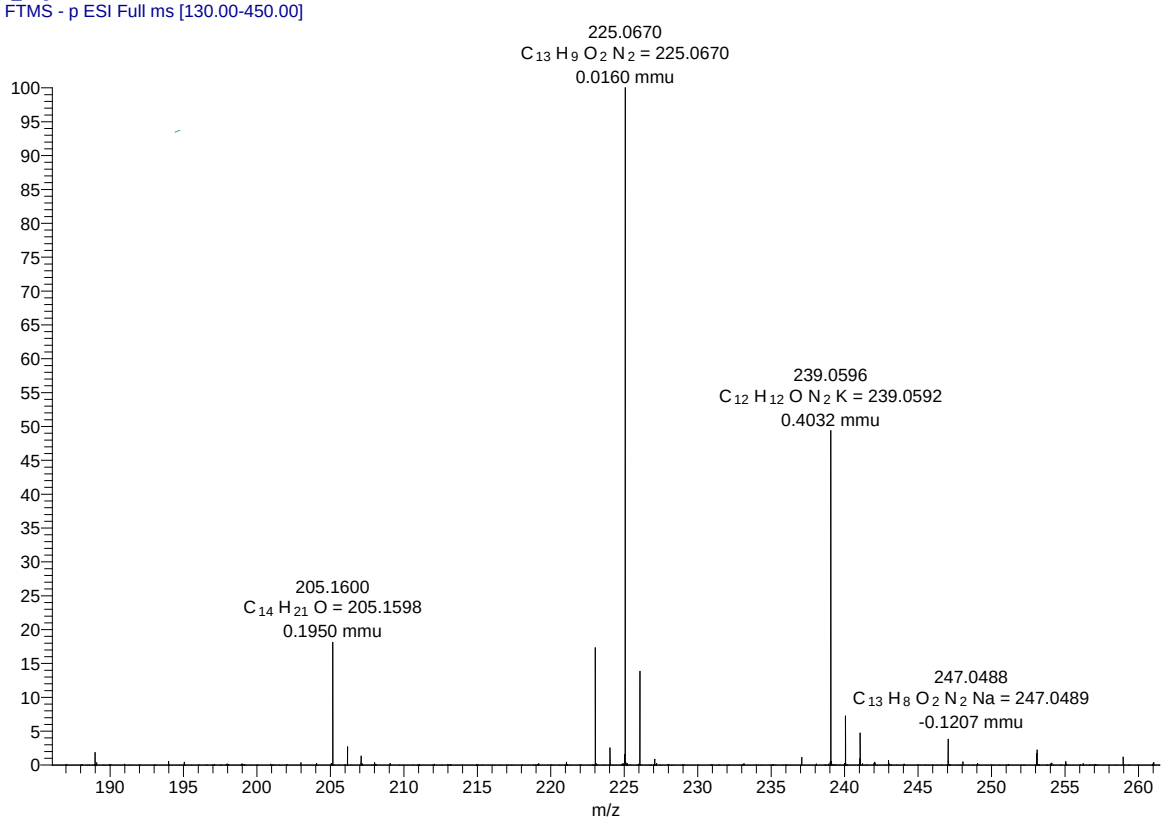


11b

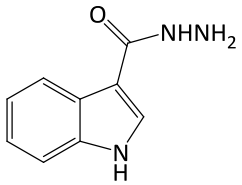




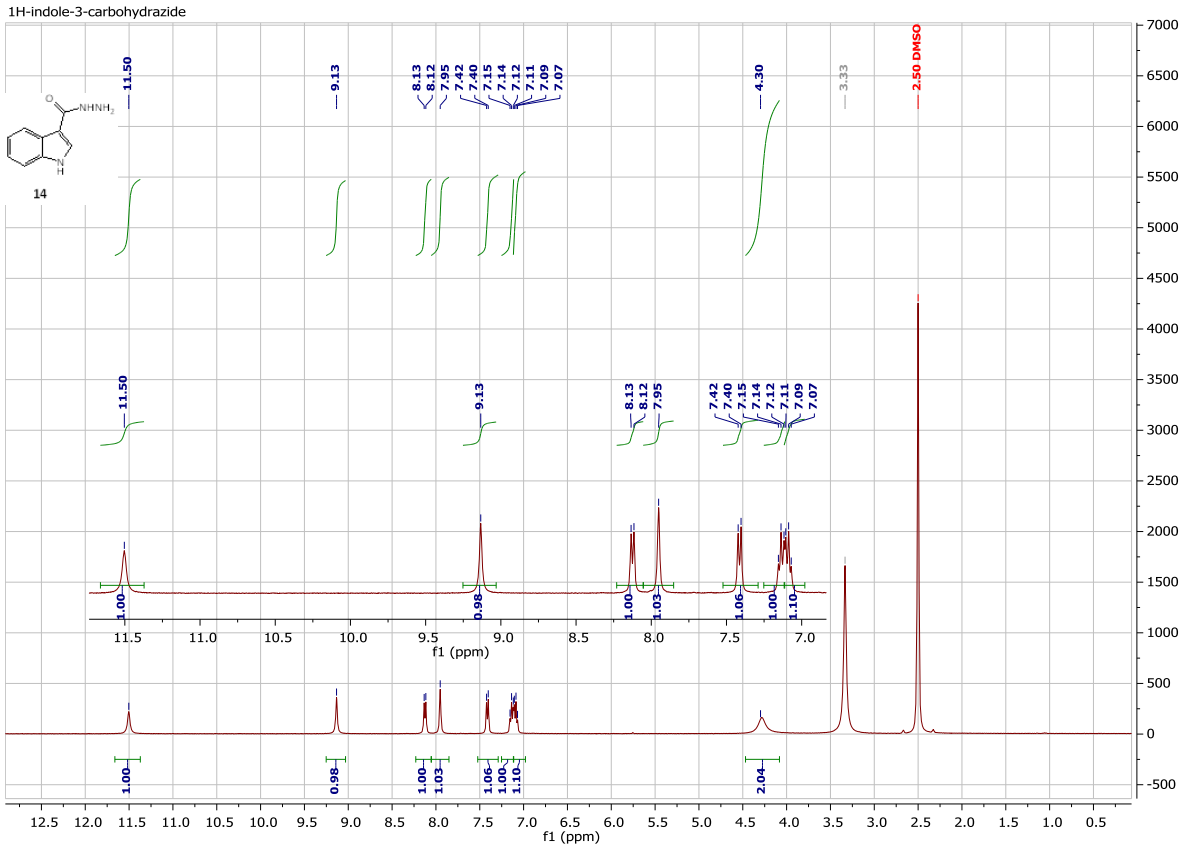
11b_neg #1-5 RT: 0.00-0.11 AV: 5 NL: 4.61E7
T: FTMS - p ESI Full ms [130.00-450.00]

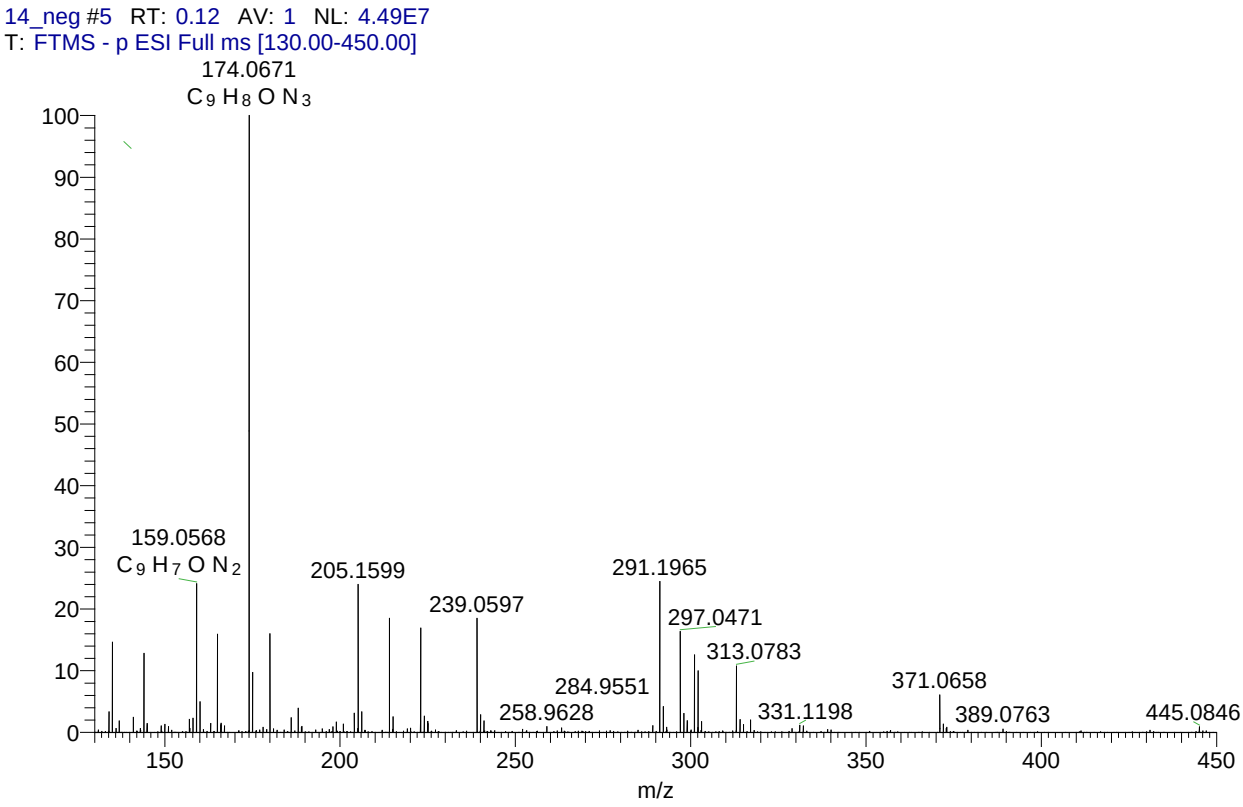


Appendix 19: 1H-indole-3-carbohydrazide

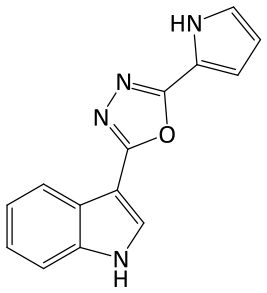


14

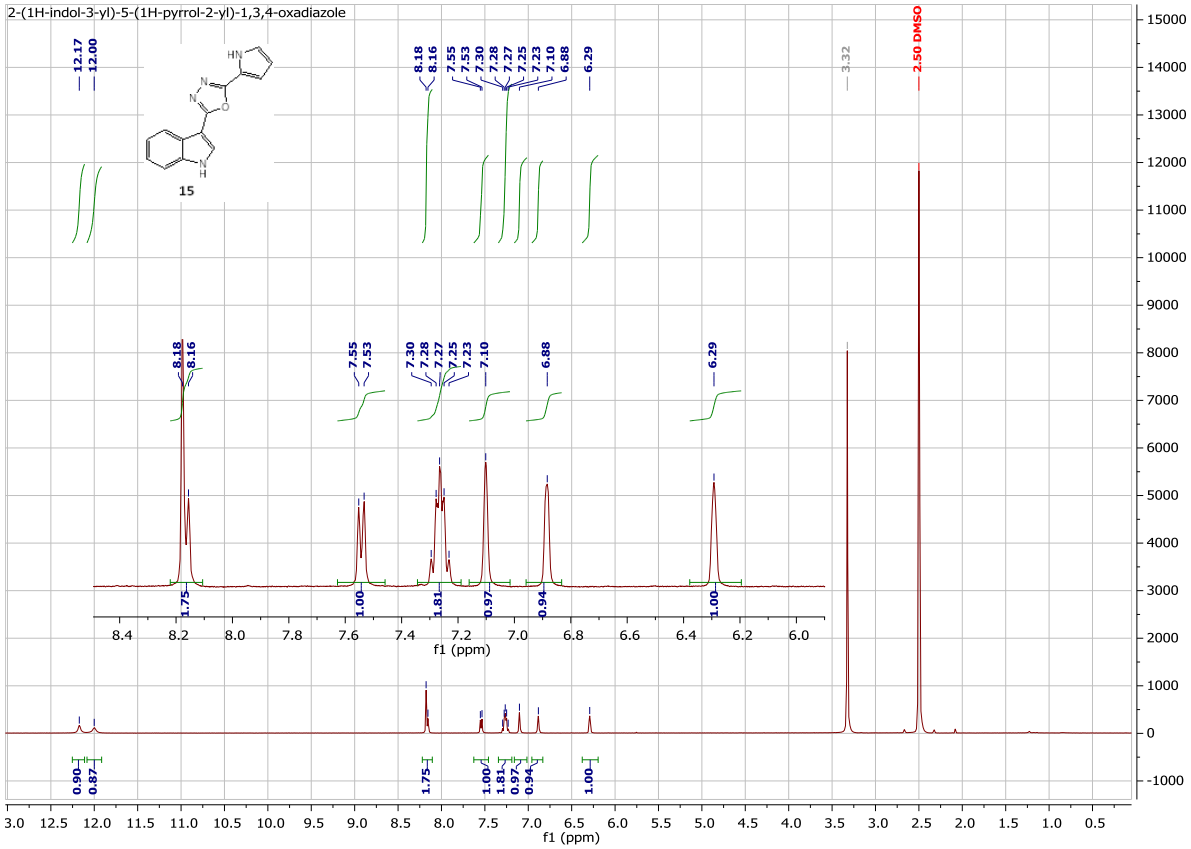


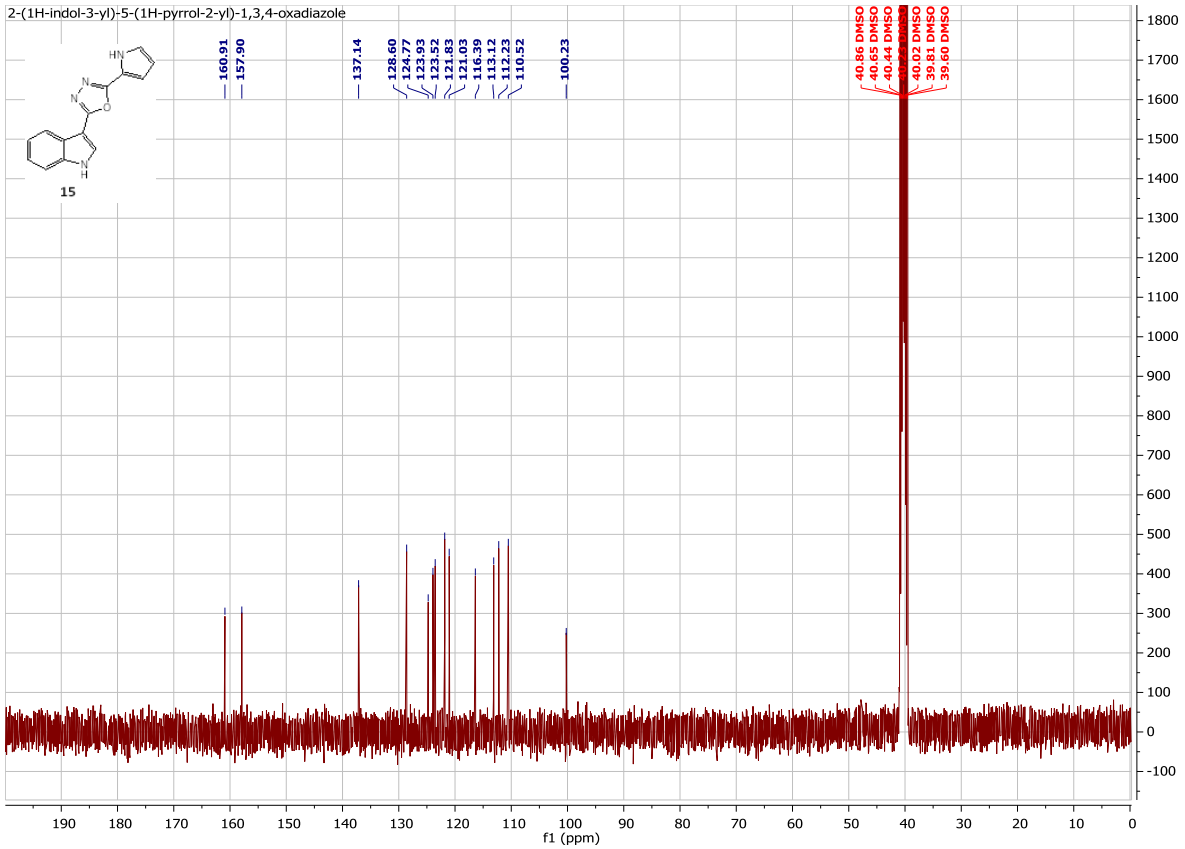

14_neg #5 RT: 0.12 AV: 1 NL: 4.49E7
T: FTMS - p ESI Full ms [130.00-450.00]
174.0671
C9 H8 O N3
159.0568
C9 H7 O N2
205.1599
239.0597
291.1965
297.0471
313.0783
284.9551
258.9628
331.1198
371.0658
389.0763
445.0846
m/z

Appendix 20: 2-(1H-indol-3-yl)-5-(1H-pyrrol-2-yl)-1,3,4-oxadiazole (15)



15





ABAM_040_b #5 RT: 0.13 AV: 1 NL: 2.18E7
T: FTMS + p ESI Full ms [200.00-600.00]