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PROGRAMA DE PÓS-GRADUAÇÃO EM QUÍMICA
DOUTORADO EM QUÍMICA

TESE DE DOUTORADO

The use of arylseleninic acids in the synthesis of 4-selanylanilines, 3-selanylindoles, and 2-substituted oxazole-5-carbaldehydes

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Pelotas, RS, Brasil
27 de janeiro de 2023

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The use of arylseleninic acids in the synthesis of 4-selanylanilines, 3-selanylindoles, and 2-substituted oxazole-5-carbaldehydes

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Orientador: Prof. Dr. Eder João Lenardão
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RESUMO

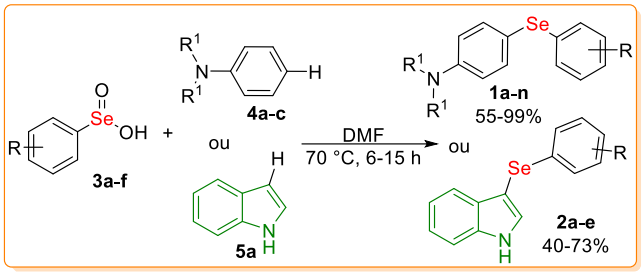
Título: O uso de ácidos arilselenínicos na síntese de 4-selanilanilinas, 3-selanilindóis e oxazol-5-carbaldeídos-2-substituídos

Autor: Laura Abenante

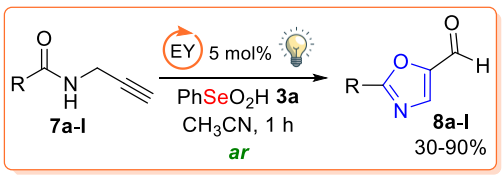
Orientador: Prof. Dr. Eder João Lenardão

Coorientador: Dr. André Ricardo Fajardo

Nesta tese são apresentados os resultados de duas novas metodologias usando ácidos arilselenínicos como agente selenilante. O primeiro trabalho descreve o uso de ácidos arilselenínicos como fonte de selênio eletrofílico, na reação com diferentes *N*,*N*-dialquilanilinas e com o indol. Os produtos desejados 4-selanilanilinas **1a**-**n** e 3-selanilindóis **2a**-**e** foram obtidos com rendimentos de bons a excelentes após 6-15 horas de reação, a 70 °C em DMF como solvente.



No segundo trabalho é relatada a ciclização de *N*-propargilamidas mediada por luz visível e promovida por ácido benzenosselenínico. Doze oxazol-5-carbaldeídos-2-substituídos **8a**-**l** foram formados com rendimentos de 30-90%, e seis deles eram inéditos na época em que foram sintetizados. O método é isento de metais, oxidantes e aquecimento, e água e disseleneto de difenila, que pode ser recuperado e reutilizado, são os únicos produtos residuais.



UNIVERSIDADE FEDERAL DE PELOTAS

PROGRAMA DE PÓS-GRADUAÇÃO EM QUÍMICA

Tese de Doutorado - Doutorado em Ciências

Pelotas, 27 de janeiro de 2023.

ABSTRACT

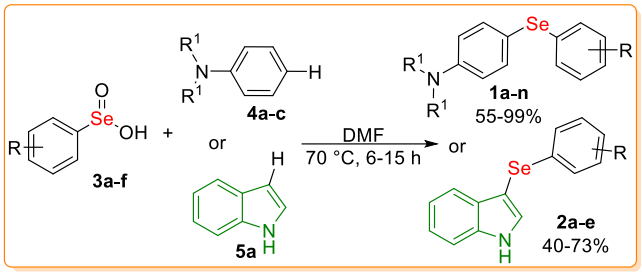
Title: *The use of arylseleninic acids in the synthesis of 4-selanylanilines, 3-selanylindoles, and 2-substituted oxazole-5-carbaldehydes*

Author: Laura Abenante

Academic Advisor: Prof. Dr. Eder João Lenardão

Academic Co-advisor: Dr. André Ricardo Fajardo

In this thesis, are presented the results of two new methodologies using arylseleninic acids as a selenylating agent. The first work describes the use of arylseleninic acids as electrophilic selenium source, in the reaction with different *N*,*N*-dialkyl-anilines and with indole. The desired products 4-selanylanilines **1a**-**n** and 3-selanylindoles **2a**-**e** were achieved in good to excellent yields after 6-15 hours of reaction, at 70 °C in DMF as solvent.



In the second work it is reported the cyclization of *N*-propargylamides mediated by visible light and promoted by benzeneseleninic acid. Twelve 2-substituted oxazole-5-carbaldehydes **8a**-**l** were formed in 30-90% yield, and six of them were unprecedented at the time they were synthesized. This method is metal-, oxidant- and heating-free, and water and diphenyl diselenide, which can be recovered and reused, are the only waste products.

UNIVERSIDADE FEDERAL DE PELOTAS

PROGRAMA DE PÓS-GRADUAÇÃO EM QUÍMICA

PhD Thesis

Pelotas, January 27th, 2023.

Summary

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List of abbreviations

δ	chemical shift (ppm)
AchE	acetylcholinesterase
BSA	benzeneseleninic acid
DCM	dichloromethane
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
EG	ethylene glycol
EY	eosin Y
GC-MS	gas chromatography coupled to mass spectrometry
HAT	hydrogen atom transfer
HRMS	high resolution mass spectrometry
J	coupling constant (Hz)
LED	*light emitting diode*
MW	microwave
Mp	melting point
m/z	mass/charge ratio
NMR	nuclear magnetic resonance
PC/s	photocatalyst/s
Py	pyridine
Rf	retention factor
r.t.	room temperature
SET	single electron transfer
TBHP	*tert*-Butyl hydrogen peroxide
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
TFAM	mitochondrial transcription factor A
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
US	ultrasound

1. Introduction and objectives

1. Introduction and objectives

N-substituted aryl compounds and their derivatives are a relevant class of organic compounds known for their biological activities (Figure 1), such as antibacterial (Ciprofloxacin),[1] antitumor (compound **A**),[2] antioxidant (compound **B**), and antituberculosis (compound **C**).[3]

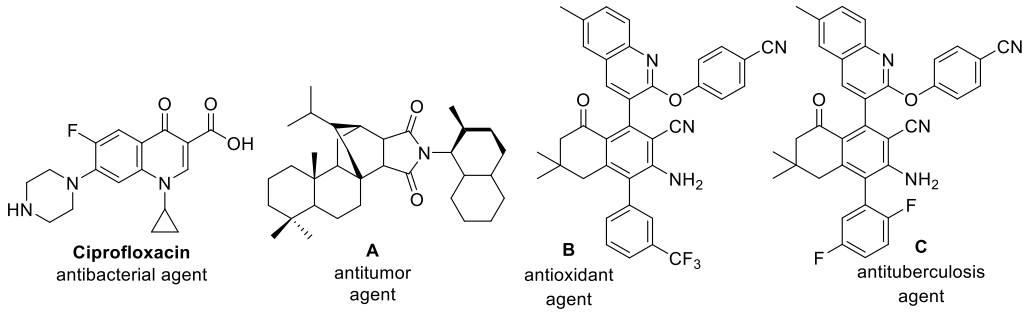


Figure 1. Examples of biologically active *N*-substituted aryl compounds.

In this context, the indole nucleus stands out due to its ability to bind many receptors,[4] and also it is a part of many drugs (Figure 2), possessing various properties, suchs as anti-headache (Naratriptan),[5] for treatment of osteoporosis (Bazedoxifene),[6] and anti-inflammatory (Indomethacin).[7] Furthermore, it is a part of the structure of the neurotransmitter serotonin, responsible for many biological functions, such as synchronization of the sleep-wake cycle, appetite control, regulation of motility and intestinal secretions, blood pressure control artery, in addition to being involved in the control of social relationships (Figure 2).[8] Thus, the indole is known as “privileged structure”[9] and the synthesis of its derivatives is a target of many research groups.[10]

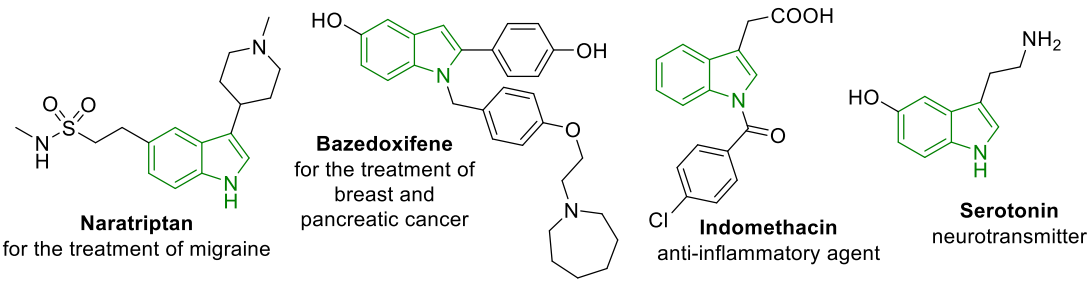


Figure 2. Examples of biologically active indoles.

On the other hand, the importance of the selenium-containing compounds is widely recognized due to their many properties, either in the chemical field or biological and pharmaceutical ones. They are useful intermediates in organic synthesis, and can act as catalysts and ligands.[11] Moreover, the selenium

compounds have shown important activities (Figure 3), such as anticarcinogenic (compound **D**),[12] antinociceptive (compound **E**),[13] anti-inflammatory (compound **F**),[14] and antioxidant (compound **G**).[15] It is important to highlight **Ebselen**, the most significant selenium compound, which demonstrated to have protective effect against oxidative stress, and also against the brain ischemia and stroke, besides preventing the noise-induced hearing loss (Figure 3).[16] Furthermore, it has shown a potent antiviral activity against the new coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), through the inhibition of a key enzyme essential for the replication and transcription of the virus.[16e]

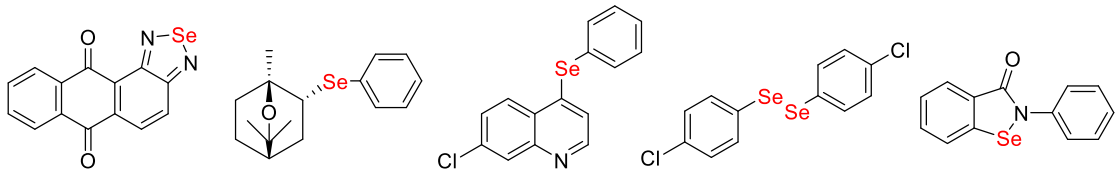


Figure 3. Examples of bioactive selenium-containing compounds.

Additionally, organoselenium compounds bearing nitrogen-containing arenes have demonstrated pharmacological activities (Figure 4).[17] Thus, several methodologies are reported in the literature to obtain molecular hybrids between organoselenium and *N*-arylsubstituted heterocyclic compounds.[18]

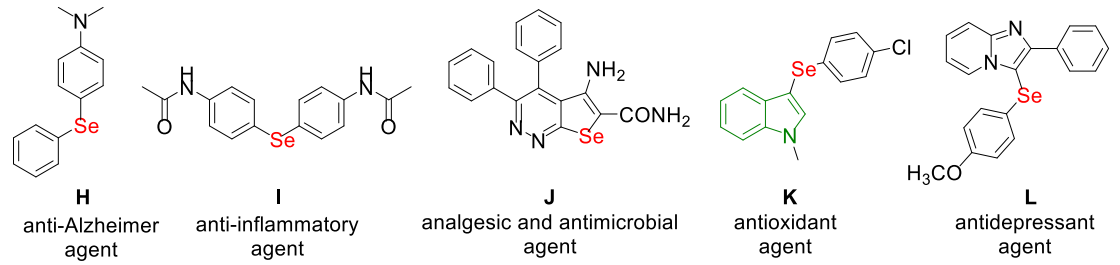
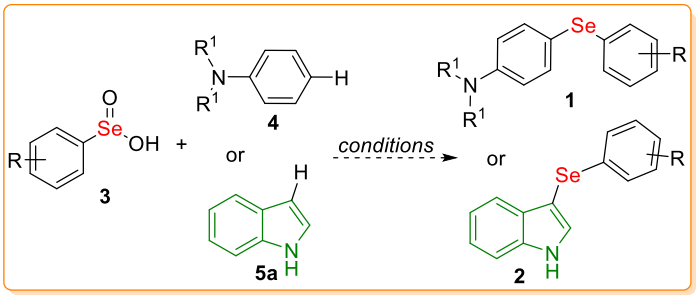


Figure 4. Selenium- and nitrogen-containing active hybrids.

However, the protocols so far developed to prepare these hybrids have some limitations, such as long reaction time, use of metal catalysis, ligands, or volative solvents. Additionally, in these procedures the electrophilic species of selenium is generated either from diorganyl diselenides *in situ* through an oxidation reaction promoted by halogen, persulfate/peroxides, or through an interaction with transition metal, or using commercially available PhSeCl or

PhSeBr as selenylating agent. These last have some limitations, because they are unstable under air, and the chloride and bromide counterions can be responsible of side reactions due to their high nucleophilicity. An alternative way to obtain selenium electrophilic species is using seleninic acids, selenium reagents already known as oxidants,[19] but still not so explored as selenium source.[20]

In this panorama, the first target of this PhD project was to develop a methodology to obtain 4-selanylanilines **1** and 3-selanylindoles **2** using arylseleninic acids **3** as a bench-stable and easy to handle electrophilic selenium source, without additive or auxiliaries, transition metal catalysis, strong acids or strong oxidant agents (Scheme 1).



Scheme 1. Our proposal to use arylseleninic acids as selenylating agent.

The photocatalysis is an alternative energy source in organic synthesis and responds to the principles of green chemistry,[21] because visible light is cheap, non-polluting, abundant, and infinite. It has been known for many years and for this many research group have turned their studies on protocols which investigated photochemical processes. The photocatalysis employes substance which are able to absorve visible light (λ ~ 400-700 nm), and when it happens, these substances are excited. In this state, they trigger a single electron transfer process (SET) and in this way organic reactions are promoted. At the end, these substances are regenerated by a redox process. Nowadays, organic molecules are used as photocatalysts (PCs), avoiding metal compounds, such as Eosin Y (EY), Rose Bengal and Rodhamine B, which have low cost, high availability and efficiency (Figura 5).

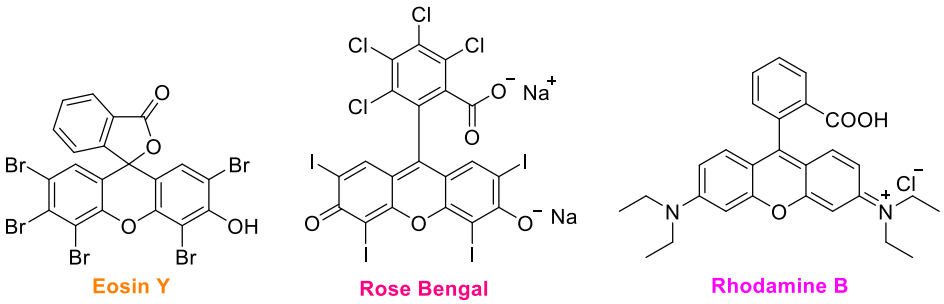
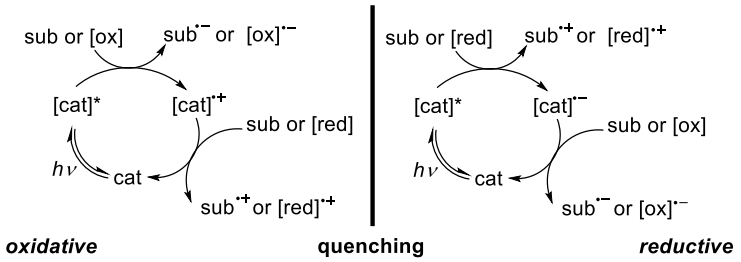


Figure 5. Dye-based photocatalysts.

They can act through two possible pathways how is depicted in the **Scheme 2**.[21c] In the oxidative quenching the excited state of PC is quenching by reducing a substrate or an oxidant, on the other hand, in the reductive one it is quenching by oxidizing a substrate or an oxidant. Then the PC is regenerating through a reduction or an oxidation process in the oxidative and reductive quenching, respectively.



Scheme 2. Oxidative and reductive quenching cycles of photocatalysts.[21c]

Considering all, another objective of this PhD was to prepare the vinyl selenide **6**, derived from 4,5- dihydroxazole, thorugh a reaction between N-propargylamide **7a** and benzeneseleninic acid **3a**, mediated by visible light (Scheme 3).

Scheme 3. Our proposal to use benzeneseleninic acid to obtain vinyl selenide **6**.

Unfortunately, it was not possible to obtain the desired product **6**, because it was formed the 2-substituted oxazole-5-carbaldehydes **8a**. The oxazole core has a wide synthetic applicability, for example in the formation of polymers and in the construction of new molecules.[22] Moreover, it is found in the structure of important classes of diverse biological active compounds (Figure 6), such as anti-

inflammatory (Oxaprozin),[23] antifungal (compound **M**),[24] antidiabetic (compound **N**),[25] and antitubercular ones (compound **O**).[26]

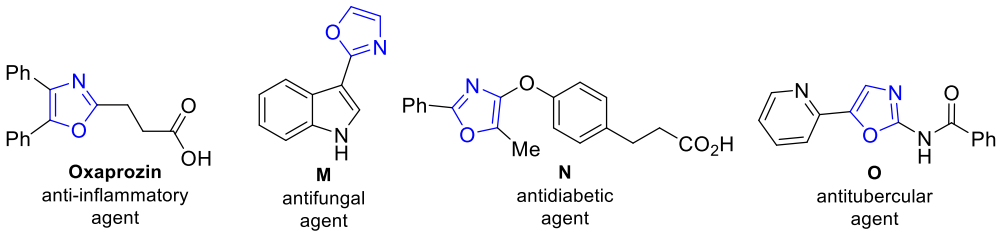


Figure 6. Biologically active oxazole derivatives.

An effective approach to acess oxazole ring is the cyclization of *N*-propargylamides. However, the methods described so far present some negative aspects, such as the use of gold and iron catalysis, strong oxidants, high temperatures and long reaction times.[27] Therefore, cleaner, more sustainable and environmentally friendly protocols are needed, according to the principles of the green chemistry.[21a,b]

Based on this, the second target of this PhD project was to synthesize 2-substituted oxazole-5-carbaldehydes **8** starting from *N*-propargylamides **7** and benzeneseleninic acid (BSA) **3a**, through a photocatalytic process (Scheme 4).

Scheme 4. Our proposal to use benzeneseleninic acid to obtain the oxazole core.

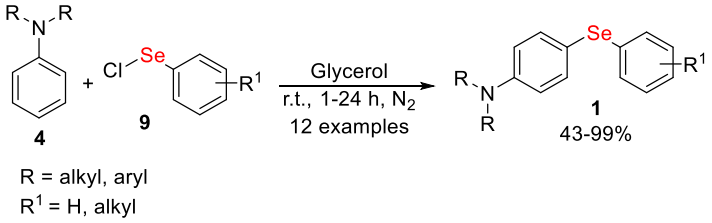
2. Literature review

2. Literature Review

In this chapter it will be discussed the literature's panorama regarding the methods available to obtain 4-selanylanilines, 3-selanylindoles and functionalized oxazoles. Moreover, it will be addressed the importance of the benzeneseleninic acid (BSA) in organic chemistry.

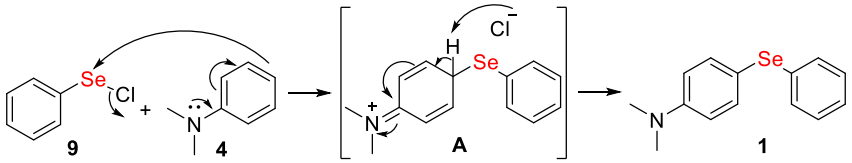
2.1 Synthesis of 4-selanylaniline and 3-selanylindole derivatives

Lenardão and co-workers[18a] in 2014 developed a protocol metal- and base-free to obtain 4-arylselanylanilines **1** from anilines **4** and arylselanyl chloride **9**. The compounds were reached in up to 99% yield at room temperature under nitrogen atmosphere using glycerol as a green solvent (Scheme 5).



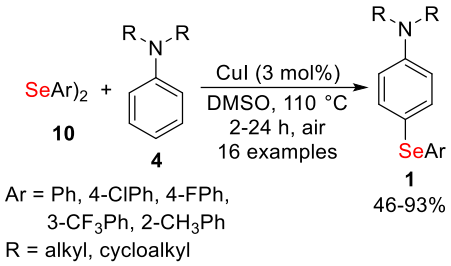
Scheme 5. Synthesis of 4-arylselanylanilines described by Lenardão.[18b]

In the proposed mechanism, the species **9** is attacked by the substrate **4** and through the proton elimination from the intermediate **A**, which could be stabilized by glycerol by hydrogen bonds, the desired product **1** is formed (Scheme 6).



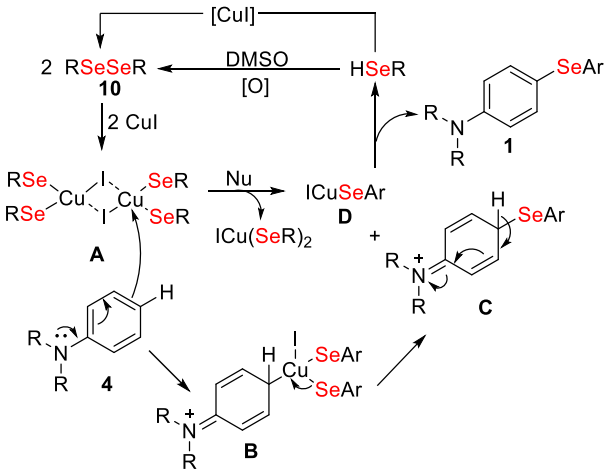
Scheme 6. Mechanism proposed by Lenardão.[18a]

In 2015,[18b] Alves and his group reported a regioselective synthesis catalyzed by copper of 4-selanylaniniles **1** from anilines **4** and diarylselenides **10**. The products were obtained in good yield, after 2-24 hours at 110 °C in DMSO (Scheme 7).



Scheme 7. Arylselenylation of anilines proposed by Alves.[18b]

The authors proposed a probable mechanism for the reaction, where firstly is formed the tetracoordinate intermediate **A**, which reacts with the aniline **4** to reach the species **B** (Scheme 8). At this point a reductive elimination achieves the intermediate **C**. From this last, a proton is eliminated and the product **1** is obtained together with arylselenol, from which the diphenyl diselenide **10** and CuI are regenerated.

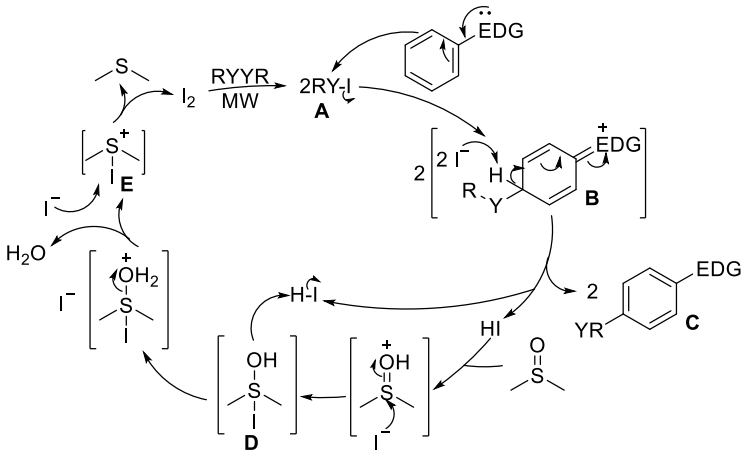


Scheme 8. Mechanism proposed by Alves.[18a]

Later, Braga and co-workers[18c] described a regioselective methodology to obtain unsymmetrical chalcogenides **1** and **11** in good to excellent yields without transition metal and solvent. The reaction was carried out between arenes containing nitrogen **4** or oxygen **12** (electron donating group) in 10 min, at 110 °C under microwave irradiation, using DMSO/I_2 as the catalysis system (Scheme 9).

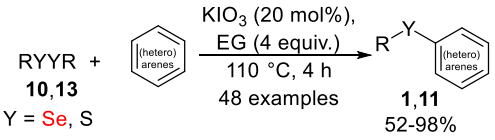
Scheme 9. Synthesis of unsymmetrical chalcogenides developed by Braga.[18c]

A possible mechanism was suggested; initially, is formed the intermediate **A**, which undergoes an attack from electron-rich arenes to give the species **B** (Scheme 10). This last suffers a proton elimination achieving **C** and HI. Then, HI reacts with DMSO to afford the intermediate **D**, which is transformed into **E**. Finally, **E** is converted into DMS, regenerating I_2.



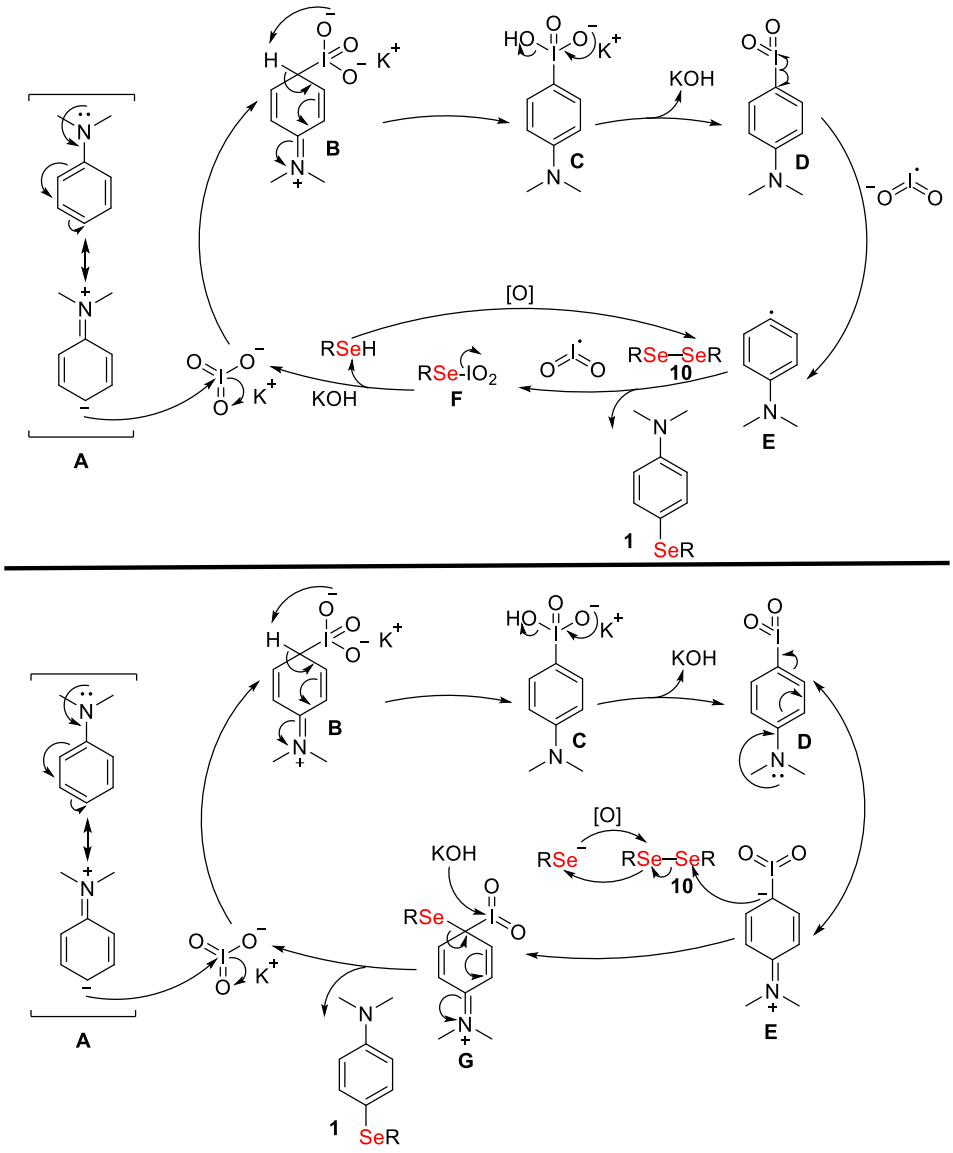
Scheme 10. Reaction mechanism proposed by Braga.[18c]

The same research group[17a] in 2018 published a regioselective chalcogenation of heteroarenes catalyzed by KIO_3, in the presence of ethylene glycol (EG) at 110 °C for 4 hours (Scheme 11). The products were reached in good to excellent yields, and they were evaluated for their anti-Alzheimer activity, inhibiting the AChE enzyme.



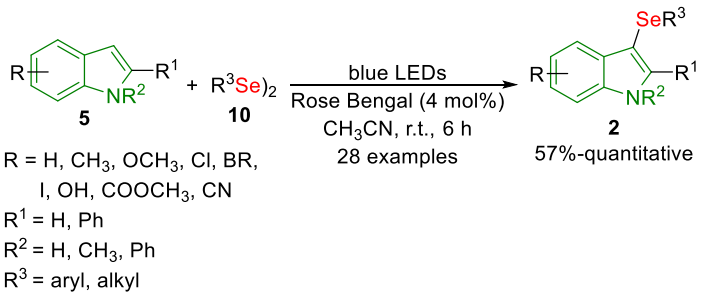
Scheme 11. Chalcogenation of heteroarenes developed by Braga.[17a]

The authors proposed two probable mechanisms; in the first, the intermediate **B** is formed from species **A** and KIO_3, and it suffers a proton transfer to reach **C** (Scheme 12). By the loss of KOH, is achieved the species **D**, which undergoes a homolytic cleavage to reach radicals **E** and IO_2. Then, diselenide **10** reacts with **E** to afford the product **1** and the intermediate **F**. This last, together with KOH, regenerates KIO_3 and selenol, which is oxidized into diselenide **10**. In the second hypothesis, after the reaction between **D** and diselenide **10**, is formed the intermediate **G**, that reacts with KOH to give the product **1** and KIO_3.



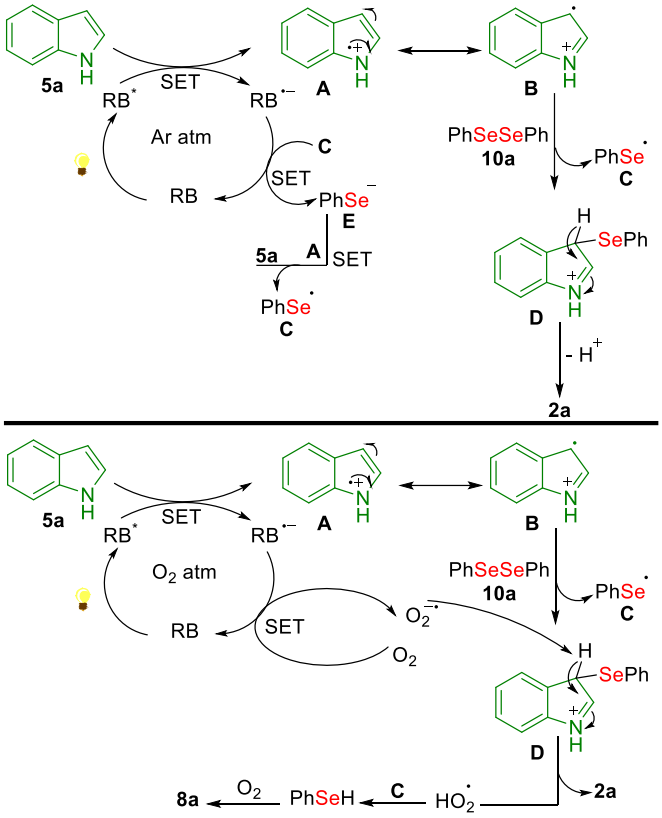
Scheme 12. Reaction mechanism proposed by Braga.[17a]

Concerning the synthesis of 3-selanylindoles **2**, one of the latest progresses achieved is the protocol reported by Braga and co-workers[18d] with the synthesis catalyzed by Rose Bengal (RB), a dye-based photocatalyst (Scheme 13). The products were achieved in good to excellent yields under irradiation with blue LEDs, without using metals at room temperature after 6 hours of reaction.



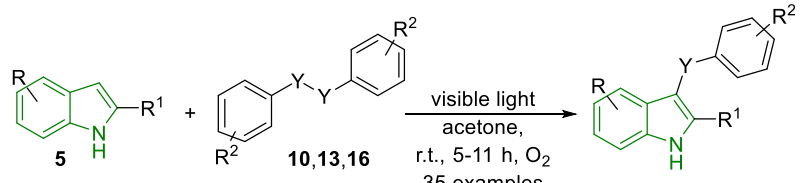
Scheme 13. Preparation of selanylindols proposed by Braga.[18d]

In the first plausible mechanism, under argon atmosphere, the photo-excited RB reacts with substrate **5a**, forming the species **A** and **B** (Scheme 14). This last reacts with diselenide **10a** to give the radical **C** and the intermediate **D**, which suffers a deprotonation affording the product **2**. In the other hypothesis, under oxygen atmosphere, a proton abstraction from **D** by O_2 anion radical leads to the product **2**.



Scheme 14. Reaction mechanism proposed by Braga.[18d]

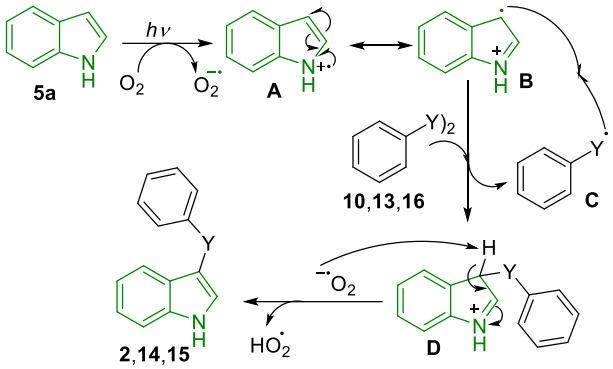
In 2018, Kumar and Rathore[18e] synthesized 3-arylselenylindoles **2**, 3-arylthioindoles **14**, and also 3-aryltelluroindoles **15** using a visible light-induced methodology, in acetone at room temperature, without base, catalyst or photocatalyst (Scheme 15). The compounds were obtained in good to excellent yields in 5-11 hours under oxygen atmosphere.



R = H, CH_3, OCH_3, F, Cl, Br, I
R^1 = H, CH_3,
R^2 = H, CH_3OCH_3, CF_3, Br, Cl, F, Ph
Y = Se, S, Te

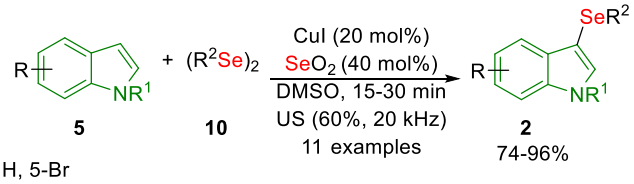
Scheme 15. Synthesis of selanylindoles by Kumar and Rathore.[18e]

A possible mechanism was supposed in which firstly the visible light excites the indol **5a** and generates the species **A**, that is in resonance with **B** (Scheme 16). This reacts with the dichalcogenide leading to the respective intermediate **D**, which undergoes a proton abstraction to give the respective product.



Scheme 16. Reaction mechanism proposed by Kumar and Rathore.[18e]

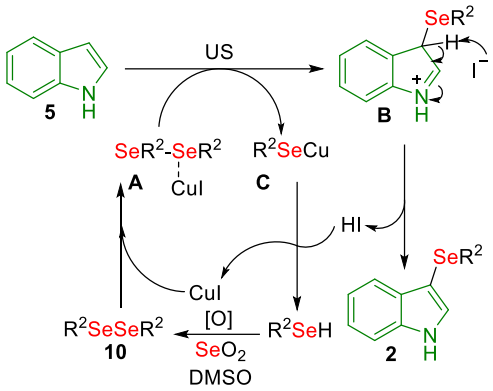
Lenardão and co-workers[18f] explored an ultrasound-assisted synthesis of 3-(organylselanyl)-1*H*-indoles **2** under catalysis of CuI/SeO_2 (Scheme 17). The reaction was carried out in DMSO, and after 15-30 minutes the products were formed in good to excellent yields. The antioxidant activity of the prepared 3-selanilindoles was evaluated *in vitro*, with good results.



R = H, 5-Br
R^1 = H, CH_3
R^2 = H, Bu, C_6H_5,4-$OCH_3C_6H_5$, 4-ClC_6H_5, 4-FC_6H_5, 3-$CF_3C_6H_5$, 2-$CH_3C_6H_5$

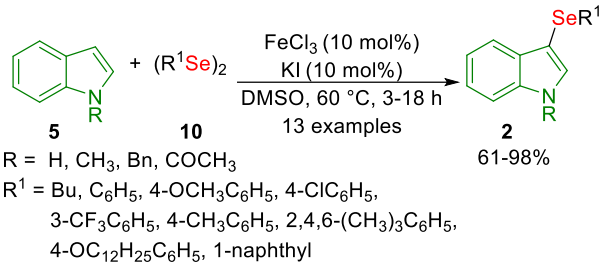
Scheme 17. Synthesis of selanylindoles by Lenardão.[18f]

The authors speculated a probable reaction mechanism in which, firstly, CuI coordinates with **10** and forms the intermediate **A**, which suffers a nucleophilic attack by the indole to reach the species **B** (Scheme 18). From this last, by a loss of proton, are obtained the product **2**, CuI and selenol. Selenol is oxidized to diselenide **10** and can restart a new cycle.



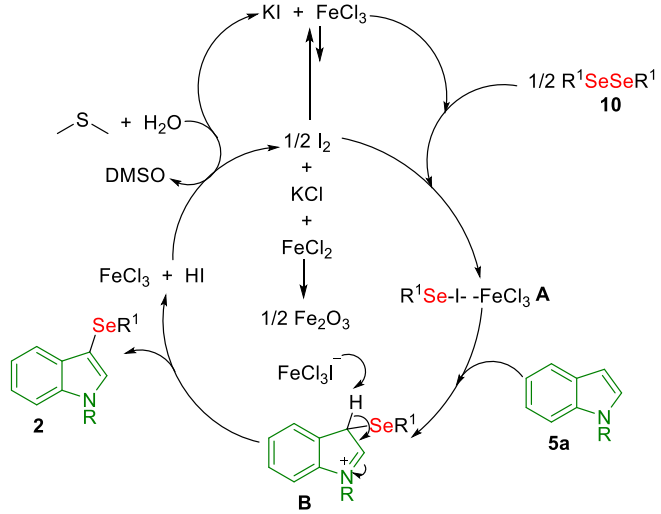
Scheme 18. Reaction mechanism proposed by Lenardão.[18f]

In 2019, Rampon and co-workers[18g] investigated the chalcogenation, selanylation, and thiolation of indoles **5** catalyzed by iron and KI (Scheme 19). Thirteen examples were reached in yields from 61% to 98% after 3-18 hours of reaction in DMSO.



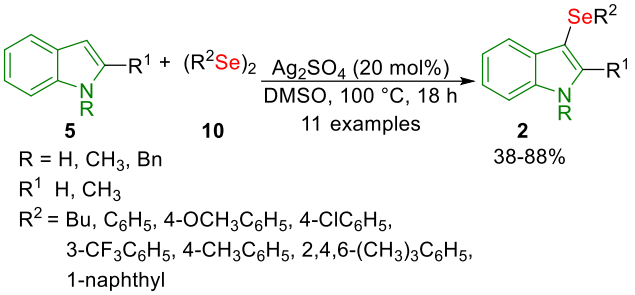
Scheme 19. Synthesis of selanylindoles by Rampon.[18g]

A plausible mechanism was hyphothesized; initially, Fe(II) and I_2 were formed, and, after the reaction with **10**, is achieved the electrophilic species **A** (Scheme 20). This reacts with substrate **5** and affords the product **2** and HI, which can be oxidized into I_2 by DMSO.



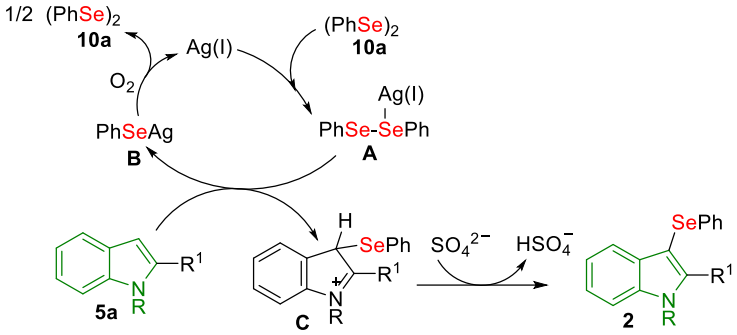
Scheme 20. Reaction mechanism proposed by Rampon.[18g]

The same research group[18h] reported the selenylation of indoles **5** with diorganoyl diselenides **10** catalyzed by Ag(I) (Scheme 21). Eleven of 3-selanylindoles **2** were obtained in 38-88% yield, after 18 hours at 100 °C in DMSO.



Scheme 21. Synthesis of 3-selanylindoles by Rampon.[18h]

In the mechanism proposed by the authors, initially an interaction between Ag(I) and diselenide **10a** forms the Lewis adduct **A** (Scheme 22). This attacks the indol **5a** releasing the species **B** and **C**. Then, the intermediate **B** is oxidized into **10a**, and **C** undergoes a deprotonation achieving the product **2**.

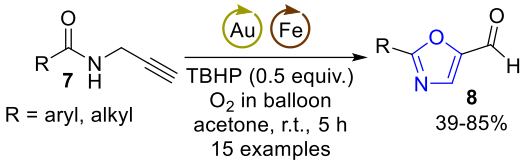


Scheme 22. Reaction mechanism proposed by Rampon.[18h]

2.2 Synthesis of functionalized oxazoles

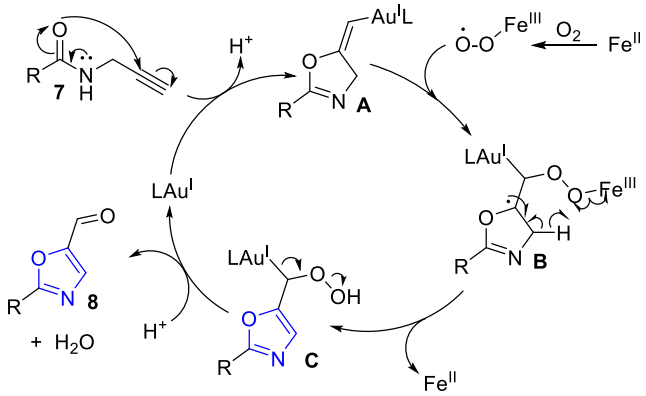
As mentioned above, a strategy to prepare the oxazole core is the cyclization of *N*-propargylamides, and it has proven to be an efficient approach.

In 2015, Shi, Jiao and co-workers[27a] published the oxidative annulation of *N*-propargylamides **7** using a dual, gold and iron, catalytic system (Scheme 23). The 2-substituted oxazole-5-carbaldehydes **8** were afforded in 39-85% yield at room temperature after 5 hours of reaction, in the presence of a strong oxidant (TBHP) and O_2.



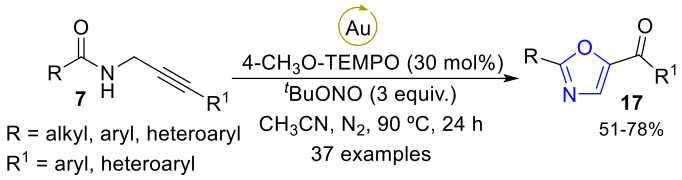
Scheme 23. Synthesis of 2-substituted oxazole-5-carbaldehydes **8** by Shi and Jiao.[27a]

The authors suggested a mechanism with the formation of the vinyl-Au-intermediate **A**, which reacts with the iron peroxide radical giving the species **B** (Scheme 24). This last quickly aromatises to **C** and regenerates the Fe catalyst. Then, the product **8** is achieved by an oxydeauration of **C**, regenerating the Au catalyst.



Scheme 24. Reaction mechanism proposed by Jiao and Shi.[27a]

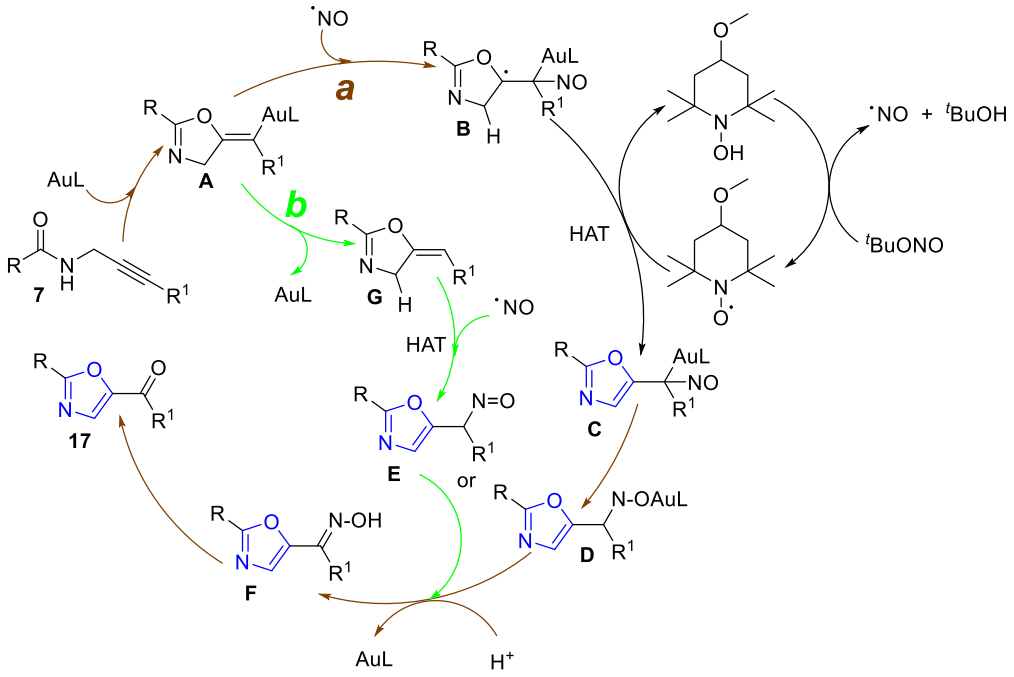
Another protocol employing gold catalysis was recently developed by Song and his group[27b] to prepare 5-oxazole ketones **17** (Scheme 25). The reaction was carried out at 90 °C for 24 hours under nitrogen atmosphere using 30 mol% of 4-CH_3O-TEMPO and 3 equiv. of ^{t}BuONO as oxidant.



Scheme 25. Synthesis of 5-oxazole ketones **17** by Song.[27b]

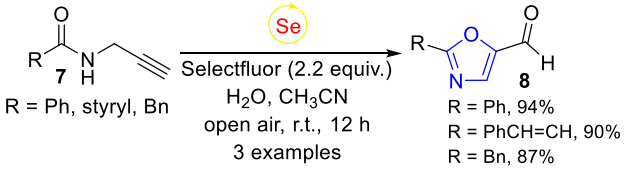
Two possible mechanisms were proposed. In the pathway *a* (brown lines), from the interaction between gold and *N*-propargylamide **7** is formed the species **A**, which reacts with NO$^\bullet$ radical to form the intermediate **B** (Scheme 26). This suffers a hydrogen atom transfer (HAT) and gives the species **C**, which undergoes an isomerization to give **D**/**E**. At this point, occurs a protodeauration, and the species **F** is formed, and from that, by hydrolization, the product **17** is

obtained. In the proposal *b* (green lines), instead, the intermediate **A** suffers a protodeauration to form **G**, which undergoes a HAT and gives the species **E**/**D**.



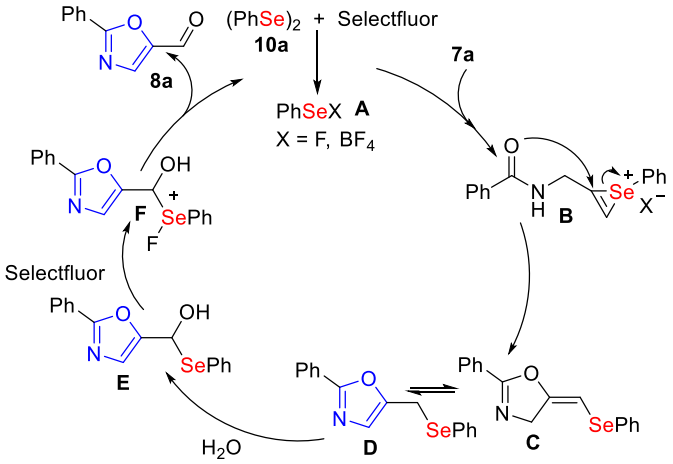
Scheme 26. Reaction mechanism proposed by Song.[27b]

In 2018, Zhao and co-workers[27c] described a cyclization of *N*-propargylamides **7** catalyzed by diphenyl diselenide **10a** in the presence of Selectfluor as oxidant (Scheme 27). Using this protocol, three 2-substituted oxazole-5-carbaldehydes **8** were formed in excellent yields.



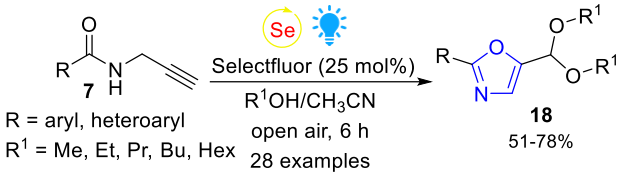
Scheme 27. Synthesis of 2-substituted oxazole-5-carbaldehydes **8** by Zhao.[27c]

In the mechanism hypothesized by the authors, initially the species **A** is formed (Scheme 28). Then, it reacts with substrate **7a** to give the seleniranium **B**. This undergoes an *intra* cyclization to give **C**, which suffers aromatization to lead to the species **D**. This last reacts with water, and in turn with the oxidant, to achieve the product **8** and regenerate the intermediate **A**.



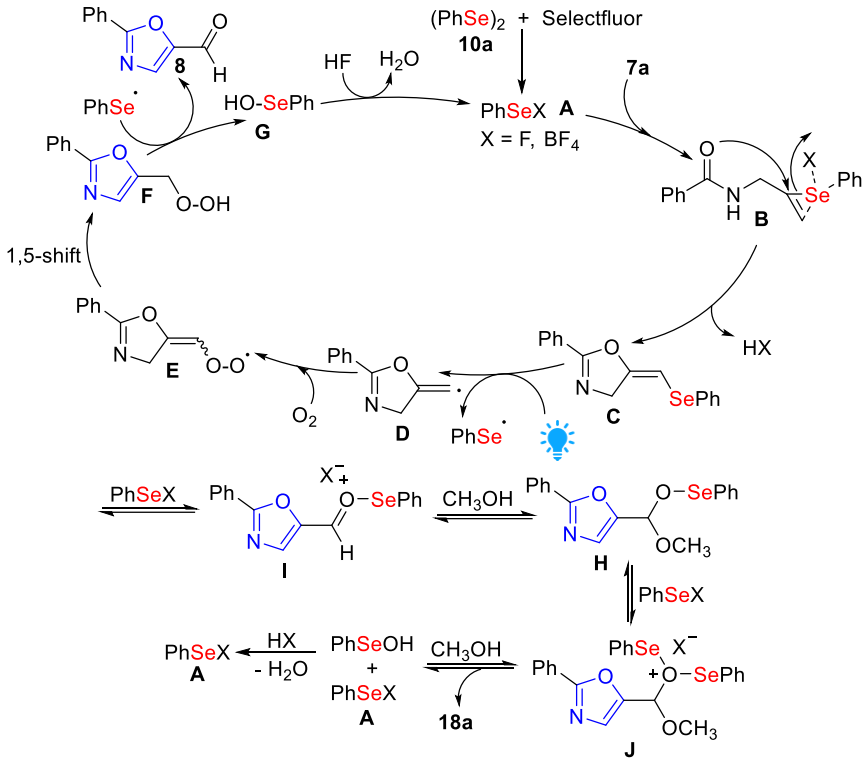
Scheme 28. Reaction mechanism proposed by Zhao.[27c]

More recently, Liu and co-workers[27d] synthesized 2-substituted oxazole-5-acetals **18** through a one-pot reaction between *N*-propargylamides **7** and alcohols promoted by visible light (Scheme 29). The products were reached in yields from 51% to 78% after 6 hours of reaction in the presence of catalytic amount of diselenides and Selectfluor.



Scheme 29. Synthesis of 2-substituted oxazole-5-acetals **18** by Liu.[27d]

A plausible mechanism was described. Firstly, the intermediate **A** is formed, and it reacts with substrate **7a**, giving the vinyl selenide **C** and PhSe• radical (Scheme 30). Then, intermediate **C** suffers a homolytic cleavage, promoted by visible light, affording the radical **D**, which reacts with oxygen to form the species **E**. Once formed, **E** undergoes a 1,5-hydrogen-shift to reach the intermediate **F**, which reacts with PhSe• radical to afford the oxazole aldehyde **8** and the intermediate **G**. This last reacts with HF or HBF_4 and regenerates the species **A**. Then, an interaction between **8** and **A** occurs, forming the species **I**, which in turn reacts with alcohol to give the intermediate **H**. The species **H** is finally converted into product **18** by the alcohol in the presence of intermediate **A** as catalyst.

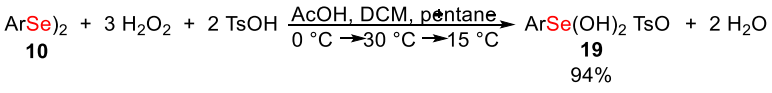


Scheme 30. Reaction mechanism proposed by Liu.[27d]

2.3 The use of seleninic acid in organic synthesis

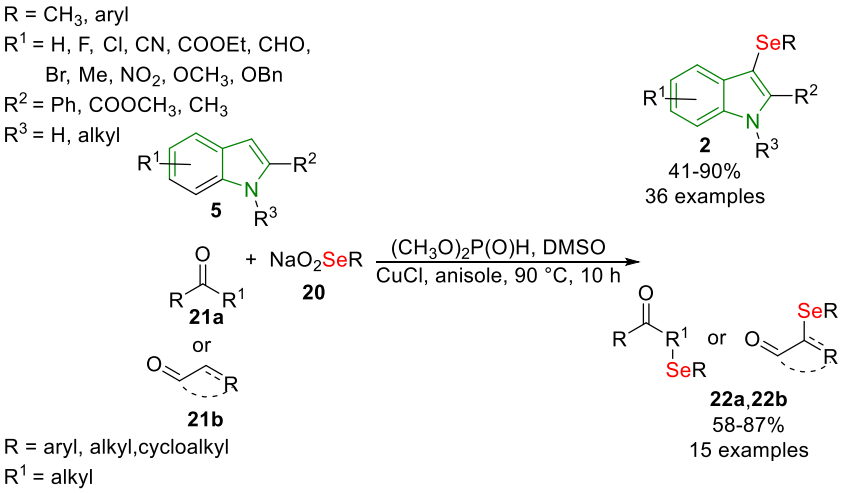
Seleninic acids are organic reagents easy to handle and to prepare, accorging to the literature, from the corresponding diselenides using ozone, TBHP or H_2O_2 as oxidants.[28]

Seleninic acid was used to prepare an alternative selenium electrophilic species by Henriksen and Stuhr-Hansen in 1996.[29] In their work they explored the preparation of *p*-toluenesulfonate, $ArSe(OH)_2^+TsO^-$, from seleninic acid, formed *in situ*, and *p*-TsOH (Scheme 31). Unfortunately, the authors dind't describe the reaction mechanism.



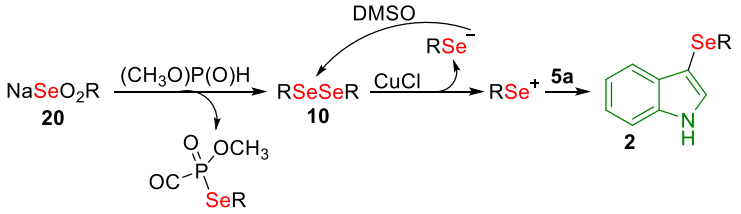
Scheme 31. Selenium electrophilic species prepared by Henriksen and Stuhr-Hansen.[29]

In 2019, Yi and his group[30] investigated a protocol in which they used for the first time sodium selenite, NaO_2SeR **20**, as direct selenylating agent, with dimethylphosphite as a reducing agent and CuCl as a catalyst (Scheme 32). The NaO_2SeR **20** was prepared through and acid-base reaction from seleninic acid, $NaHCO_3$ and methanol.



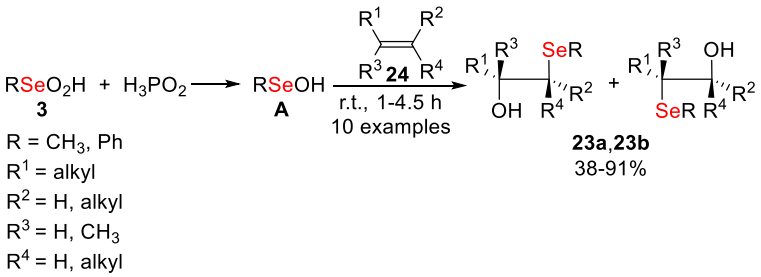
Scheme 32. Synthesis described by Yi.[30]

In the proposed mechanism, initially the diselenide **10** is formed *in situ*, and then it is converted into anion and cation species (Scheme 33). The cation reacts with indole and gives the product **2**. On the other hand, the anion is oxidized by DMSO to regenarate diselenide **10**.



Scheme 33. Reaction mechanism proposed by Yi.[30]

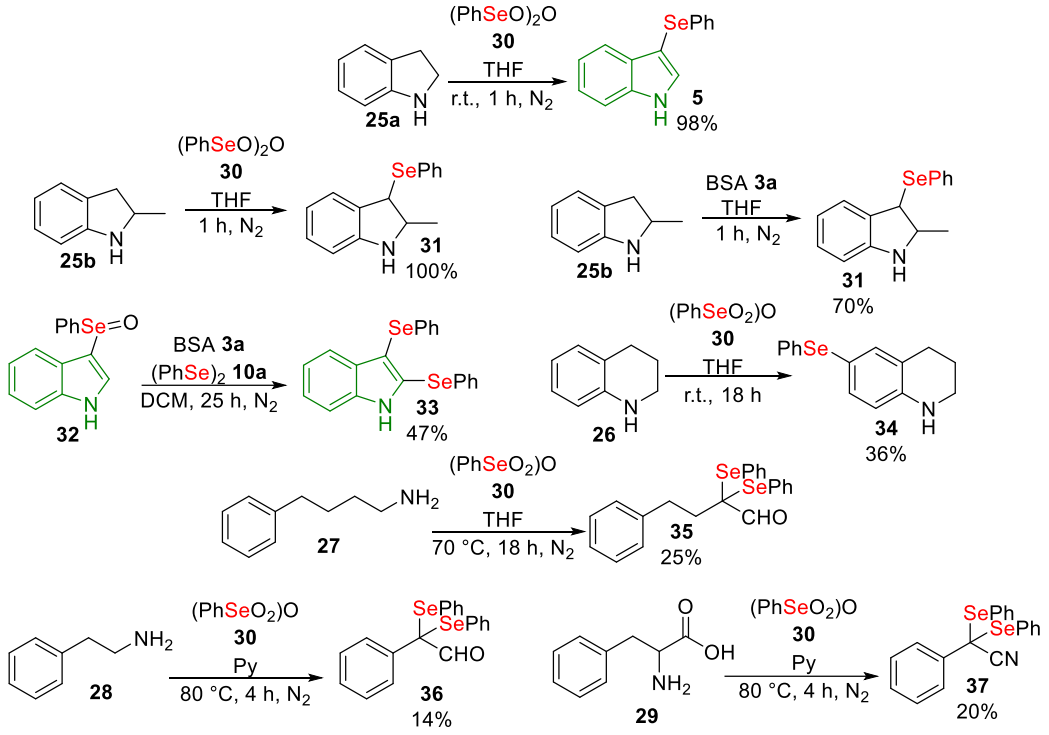
In the work of Hevesi and collaborators,[20a] methyl- or benzeneseleninic acids **3** were employed in the synthesis of β-hydroxyselenides **23**, from olefins **24**, at room temperature in 1 to 4.5 hours (Scheme 34). Unfortunately, the authors dind't describe the reaction mechanism.



Scheme 34. Synthesis proposed by Hevesi.[20a]

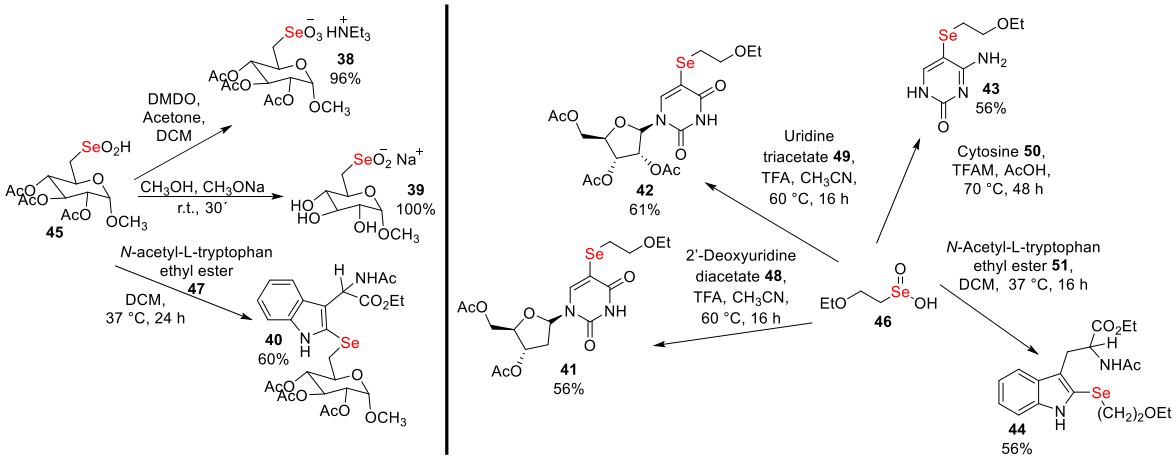
Milliet and co-workers[20b] reported the reaction of indolines **25**, tetrahydroquinoline **26**, and primary amines **27**-**29** with BSA **3a** and

benzeneseleninic anhydride **30** (Scheme 35). Unfortunately, the authors dind't describe the reaction mechanism.



Scheme 35. Study developed by Milliet.[20b]

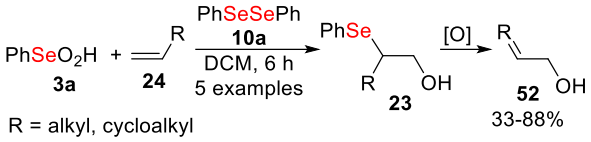
In two works, Knapp and his group[20c,d] developed the synthesis of different selenium derivatives of amino acids and of nucleosides **38-44** using aliphatic seleninic gluco-pyranoside-based acid **45**, and 2-ethoxyethaneseleninic acid **46** as selenium species (Scheme 36). Unfortunately, the authors dind't describe the reaction mechanism.



Scheme 36. Examples of seleninic acid derivatives synthesized by Knapp.[20c,d]

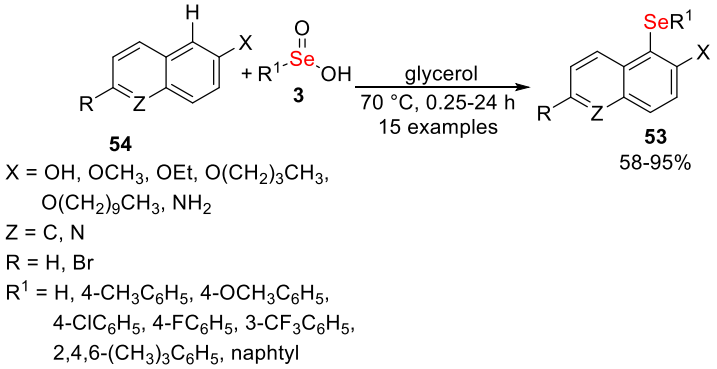
In 1978, Sharpless and Hori[20e] described the use of arylseleninic acids **3** as epoxidation catalysts, and, also, the use of BSA **3a** in the conversion of olefins

24 into allylic alcohols **52** (Scheme 37). Unfortunately, the authors dind't describe the reaction mechanism.



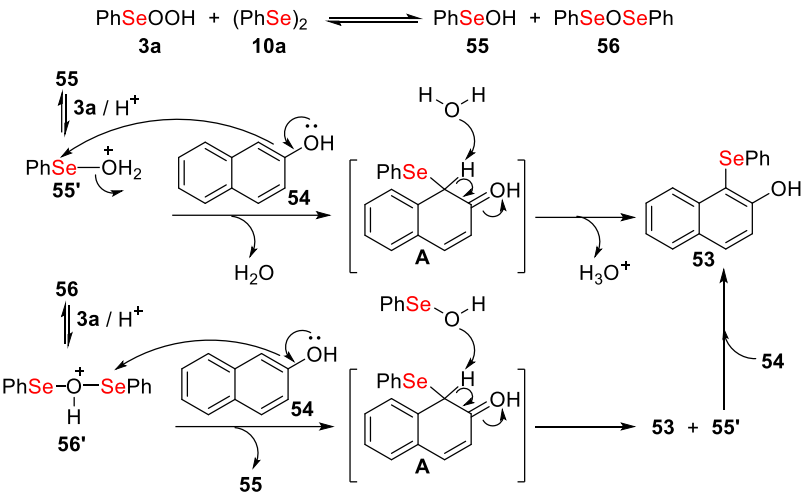
Scheme 37. Use of benzeneseleninic acid described by Sharpless and Hori.[20e]

Perin and co-workers[20f] described the use of benzeneseleninic acids as selenium source in the synthesis of 1-organoselanylnaphthalen-2-ols **53**, under mild conditions (Scheme 38). The products **53** were obtained in moderate to excellent yields in glycerol at 70 °C. The antioxidant activity of the prepared 1-organoselanylnaphthalen-2-ols was evaluated *in vitro*, with good results.



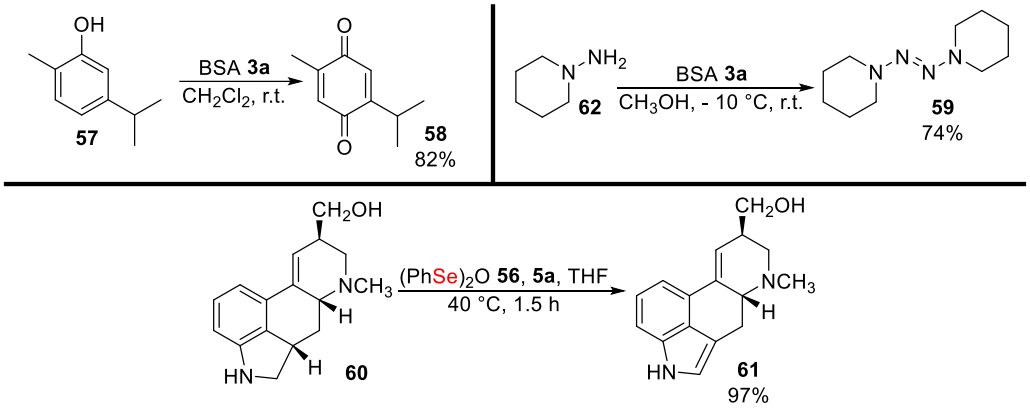
Scheme 38. Synthesis of 1-organoselanylnaphthalen-2-ols **53** by Perin.[20f]

In the mechanism proposed, firstly the comproportionation between BSA **3a** and diphenyl diselenide **10a**, present in the reaction medium, occurs, giving the electrophilic selenium species **55** and **56** (Scheme 39). These intermediates are protonated into more reactive species **55'** and **56'**, respectively. The two protonated species react with substrate **54** forming the product **53**, together with water.



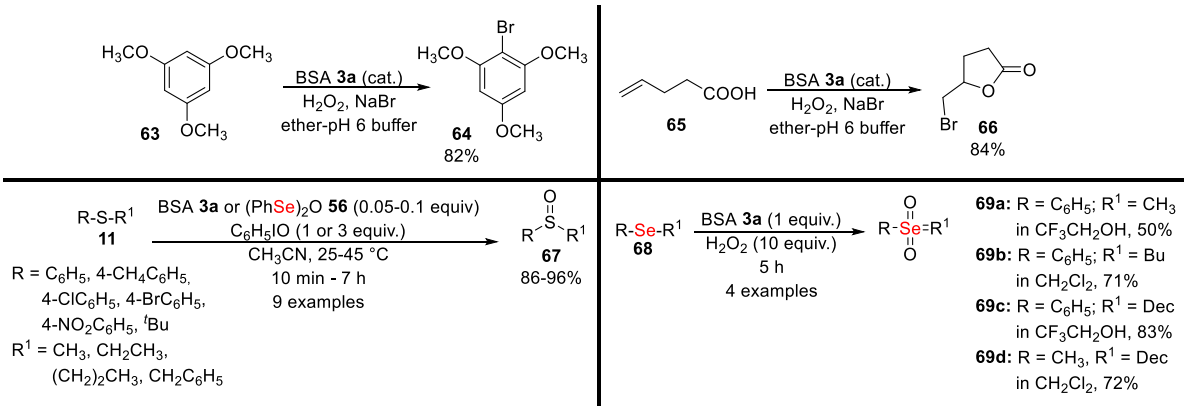
Scheme 39. Proposed mechanism by Perin.[20f]

On the other hand, BSA is used as an oxidant or catalyst in organic reactions. Such as, BSA **3a** was employed in the oxidation of phenols **57** to form 1,4-quinones **58**, and to prepare azo compounds, for example tetrazenes **59** (Scheme 40).[19a,b] Moreover, its anhydride **56** oxidized the indoline present in the alkaloid **60** to the corresponding indole (±)-lysergol **61** (Scheme 40).[19a]



Scheme 40. Use of benzeneseleninic acid as oxidant.[19a,b]

BSA can also act as catalyst in the bromination of electron-rich arenes or in the cyclization of carboxylic acids, in the presence of H_2O_2. Additionally, the oxidation of sulfides to sulfoxides, and of selenides to selenones can be promoted by BSA **3a** or anhydride **56**, in the presence of H_2O_2 or PhIO (Scheme 41).[19c,d]



Scheme 41. Use of benzeneseleninic acid as oxidant.[19c,d]

3. Results and discussion

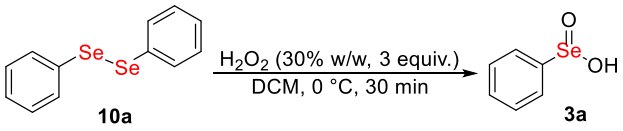
3. Results and discussion

In this chapter, we discuss the results obtained concerning the synthesis of 4-selanylanilines **1** and 3-selanylindoles **2** using arylseleninic acids as green and bench-stable selenylating agents. In the sequence, it will be addressed the results of the visibile light-promoted synthesis of 2-substituted oxazole 5-carbaldheydes **8** from *N*-propargylamides **7** in the presence of benzeneseleninic acid **3a**. Both topics will cover from the optimization stage to the scope of the reactions, besides the presentation of a probable mechanism involved. Finally, will be presented parallel works developed during the entire PhD period.

3.1 The use of arylseleninic acids in the synthesis of 4-selanylanilines (1a-n) and 3-selanylindoles (2a-e)

As mentioned in the objectives of this thesis, our first efforts were dedicated to explore the synthesis of 4-selanylanilines and 3-selanylindoles, using arylseleninic acids as bench stable and easy to handle electrophilic selenium source. With the aim to improve the literature's panorama available to access this class of compounds, since the methods described so far present some negative aspects, such as long reaction time, use of metal catalysis, ligands, or volative solvents. Besides, in these procedures the electrophilic species of selenium is generated either *in situ*, using oxidants or metals, or using unstable agents (PhSeCl/PhSeBr).

In order to find the best reaction condition, several tests were carried out. Benzeneseleninic acid **3a** and *N*,*N*-dimethylaniline **4a** were chosen as starting materials to obtain *N*,*N*-dimethyl-4-(phenylselanyl)aniline **1a**. Firstly, were synthesized benzenseleninic acid according to the literature,[28] from dipheynil diselenide **10a**, in DCM with 3 equiv. of H_2O_2 (30%) at 0 °C (Scheme 42)



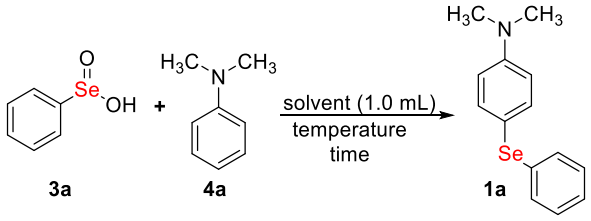
10a **3a**

Scheme 42. Preparation of BSA.[28]

Then an equimolar mixture of **3a** and **4a** (0.25 mmol) was reacted for 24 hours at room temperature in DMF, and the desired product was not reached (Table 1, entry 1). Also, with a small excess of aniline **4a** (20%) the product did not form

(Table 1, entry 2). Consequently, a temperature of 70 °C was tested using an equimolar quantity (0.25 mmol) of **3a** and **4a** for 24 hours and the desired **1a** was afforded in 42% yield (Table 1, entry 3). Then, 0.3 mmol of **4a** was used, and **1a** was achieved in 91% yield (Table 1, entry 4). At 100 °C, the title compound was obtained in 80% yield (Table 1, entry 5). In entry 6, an excess of acid **3a** was used and **1a** was generated in 91% yield (Table 1, entry 6). Since the aniline **4a** and the product **1a** have similar *Rf*, it was chosen the ratio of entry 6 to facilitate the purification process. After, various solvents were investigated (EtOH, glycerol, PEG-400, DMSO), but none of them was better than DMF (Table 1, entries 7-10). Finally, the reaction time was studied, and in 12 hours of reaction, **1a** was formed in 95% yield; instead, in 6 hours, in 94% yield (Table 1, 11 and 12). When the reaction was carried out in 3 hours the substrate **4a** was still present. Thus, entry 12 is the best reaction condition: 0.3 mmol of **3a**, 0.25 mmol of **4a**, 6 hours, 70 °C and DMF as solvent.

Table 1. Optimization of the reaction conditions to obtain **1a**.[a]



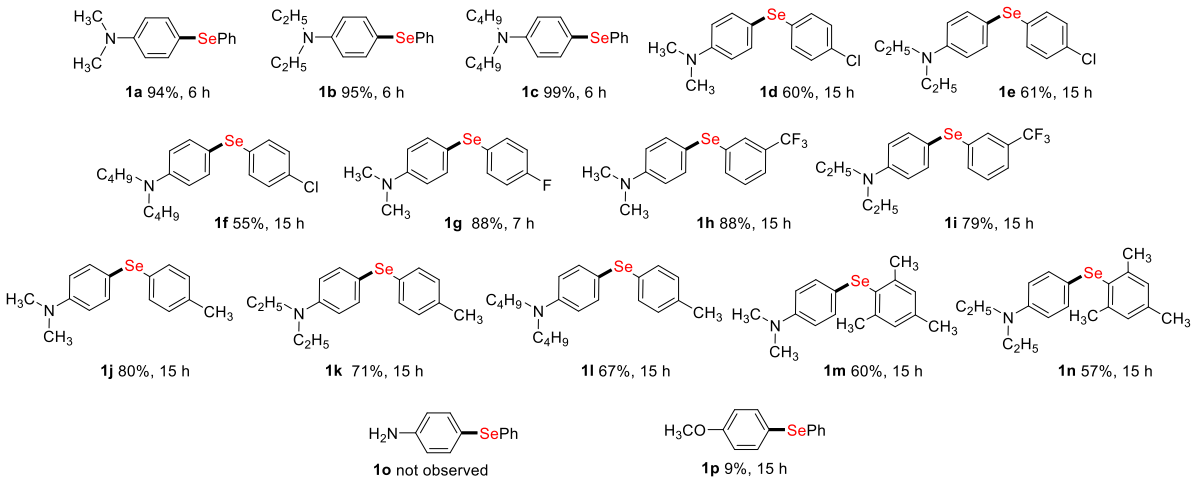
3a **4a** **1a**

Entry	3a (mmol)	4a (mmol)	Solvent	Temp (°C)	Time (h)	Yield 1a (%)[b]
1	0.25	0.25	DMF	25	24	NR
2	0.25	0.3	DMF	25	24	NR
3	0.25	0.25	DMF	70	24	42
4	0.25	0.3	DMF	70	24	91
5	0.25	0.3	DMF	100	24	80
6	0.3	0.25	DMF	70	24	91
7	0.3	0.25	EtOH	70	24	52
8	0.3	0.25	Glycerol	70	24	37
9	0.3	0.25	PEG-400	70	24	42
10	0.3	0.25	DMSO	70	24	41
11	0.3	0.25	DMF	70	12	95
12	**0.3**	**0.25**	**DMF**	**70**	**6**	**94**

[a] In a round-bottomed flask were added benzeneseleninic acid **3a**, *N*,*N*-dimethylaniline **4a** and the solvent (1.0 mL), in open air atmosphere. [b] Isolated yield obtained by preparative thin layer chromatography (hexanes/AcOEt = 97:3).

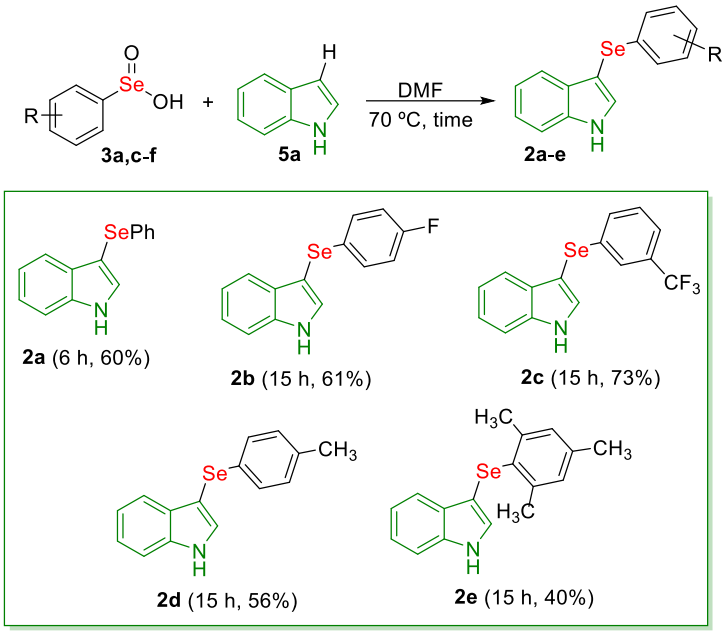
With the best condition in hand, the reaction scope was evaluated and a series of 4-selanylanilines **1** was prepared (Scheme 43). *N*,*N*-diethyl and *N*,*N*-dibutyl anilines **4b** and **4c** were employed and the products **1b** and **1c** were

obtained in 95% and 99% yield, respectively. With 4-chlorobenzeneseleninic acid **3b**, bearing an electron-withdrawing group, the products **1d**-**f** were reached in 60%, 61% and 55% yield, after 15 hours. 4-fluorbenzeneseleninic acid **3c** and aniline **4a** formed the product **1g** after 7 hours in 88% yield. When the same acid was used with *N*,*N*-diethyl and *N*,*N*-dibutyl anilines **4b** and **4c** it was not possible to purify the corresponding products. The 3-trifluoromethylbenzeneseleninic acid **3d** reacted with **4a** and **4b** satisfactorily, and the corresponding products **1h** and **1i** were obtained in 88% and 79% yield after 15 hours. When the 3-trifluoromethyl- benzeneseleninic acid **3d** was used with *N*,*N*-dibutyl **4c** the product was not achieved. Then, 4-methylbenzeneseleninic acid **3e** was tested with anilines **4a**-**c**, and the products **1j**-**l** were afforded after 15 hours in 80%, 71% and 67% yield, respectively. Also, 2,4,6-trimethylbenzeneseleninic acid **3f**, sterically hindered, reacted with **4a** and **4b** and the products **1m** and **1n** were reached in 60% and 57% yield, respectively, after 15 hours. When the 4-methyl benzeneseleninic acid **3e** was used with *N*,*N*-dibutyl **4c** the product was not achieved. All the substituted acids **3b**-**f** (4-chlorobenzeneseleninic **3b**, 4-fluorbenzene seleninic **3c**, 3-trifluoromethylbenzeneseleninic **3d**, 4-methylbenzeneseleninic **3e**, 2,4,6-trimethyl- benzeneseleninic **3f** acids) were less reactive compared to BSA, and they afforded the products **1b**-**n** in lower yields and in a longer reaction time. Among them, the acids bearing electron-withdrawing and -donating groups **3c**-**e** (4-chlorobenzeneseleninic **3b**, 4-fluorbenzene seleninic **3c**, 3-trifluoromethylbenzeneseleninic **3d**, 4-methylbenzeneseleninic **3e**) reacted well, and furnished the products **1h**-**l** in good yields, and they were more reactive than the acid bearing chloro group **3b**. Surprisingly, the acid with the fluor group **3c** furnished the product **1g** in a better yield, and in a shorter time, compared to the acid **3b**, probably due to the fact that the fluorine group, as halogen, is an attractor by electronegativity and a donor by resonance, and due to its size the retiradore effect prevails. Finally, with aniline **4o** the product did not form, even after 24 hours, maybe due to a decomposition of aniline, in *N*-oxide; and in the case of anisole **11a**, the corresponding product was achieved only in 9% of conversion (by GC-MS and ^{1}H NMR), after 15 hours, probably due to the higher electronegativity of oxygen compared to nitrogen.



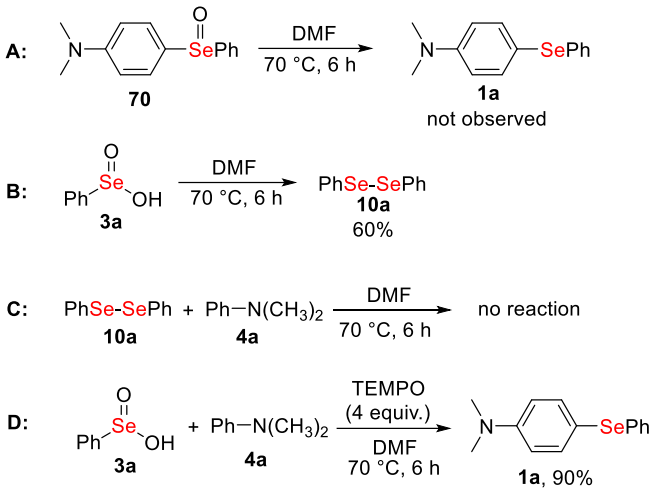
Scheme 43. Scope of the reaction in the synthesis of 4-selanylanilines (**1a**-**n**) Isolated yields after purification on preparative thin layer chromatography.

The same reaction condition was applied to the synthesis of 3-selanylindoles **2** (Scheme 44). When BSA **3a** was employed in the reaction with indole **5a**, the product **2a** was formed after 6 hours in 60% yield. With electron-deficient acid **3c** and **3d** (4-fluorbenzeneseleninic **3c** and 3-trifluoromethylbenzeneseleninic **3d**) the respective compounds **2b** and **2c** were obtained after 15 hours in 61% and 73% yield, respectively. Finally, electron-rich acids **3e** and **3f** (4-methylbenzeneseleninic **3e**, 2,4,6-trimethylbenzeneseleninic **3f**) afforded the products **2d** and **2e** in 56% and 40% yield, respectively, after 15 hours. The reactivity of the acids was the same demonstrated with the *N*,*N*-dialkyl-anilines, and on the other hand the substrate indol **5a** was less reactive than *N*,*N*-dimethylaniline **4a**. The acid with electron-withdrawing group, 3-trifluoromethylbenzeneseleninic, **3d** reacted better than that with electron-donating one, 4-methylbenzeneseleninic, **3e**, in the same reaction time. Instead, 4-fluorbenzeneseleninic acid **3c** reacted as expected with the indole **5a**.



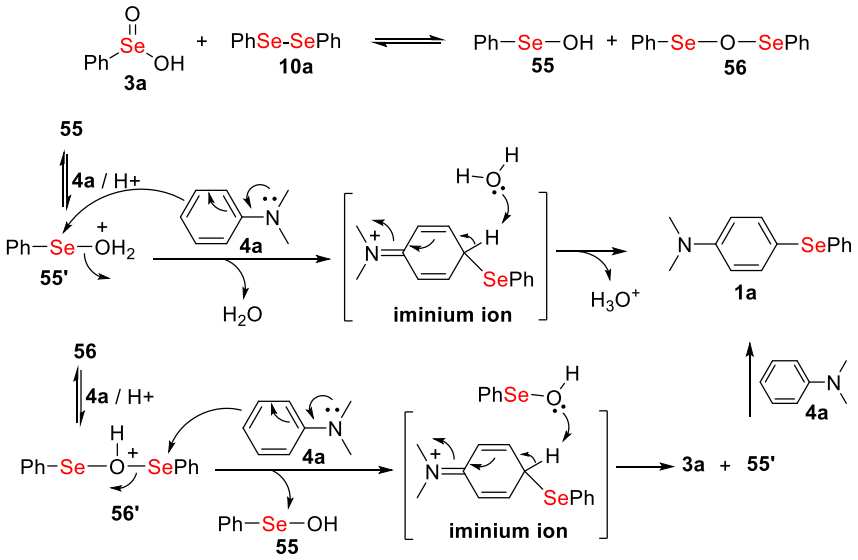
Scheme 44. Scope of the reaction in the synthesis of 3-selanylindoles (**2a**-**e**). Isolated yields after purification on preparative thin layer chromatography.

To elucidate the reaction mechanism, were carried out some control experiments (Scheme 45). Initially, the selenoxide **70** was prepared by the reaction of **1a** with *m*-CPBA[31] and used in the reaction. After 6 hours, the product **1a** was not formed, demonstrating that the species **70** is not an intermediate (Scheme 45, A). Then, the acid **3a** was stirred in DMF at 70 °C for 6 hours, and it was observed that the solution became yellow, meaning the formation of diphenyl diselenide **10a**, isolated in 60% yield (Scheme 45, B). In the experiment C, diphenyl diselenide **10a** was used as electrophilic species of selenium, but the product did not form. Finally, in the presence of radical scavenger TEMPO, the product **1a** was reached in 90% yield, signifying that a radical process is not involved (Scheme 45, D).



Scheme 45. Control experiments.

Thus, based on the literature[20a,e,30] and on the results of the control experiments, a reasonable mechanism was hypothesized (Scheme 44). Initially, the comproportionation[20b,e,32] of benzeneseleninic acid **3a** and diphenyl diselenide **10a** forms benzeneselenenic acid **55** and the anhydride **56**. Diselenide **10a** is formed in the reaction medium (Scheme 44, B), but its amount could not be enough to convert all BSA to the species **55** and **56**. Hence, it is not possible to exclude the reducing role of DMF[33] in the formation of **55**. The intermediates **55** and **56** are protonated by the acidic medium affording the more reactive species **55'** and **56'**. Then, **55'** and **56'** suffer a nucleophilic attack from aniline **4a** to form the iminium intermediate. Finally, the desired compound **1a**, together with water and **55'**, is formed. Thus, water and diphenyl diselenide **10a**, which is recovered to produce more BSA, are the only waste in the reaction.



Scheme 44. Proposed reaction mechanism.

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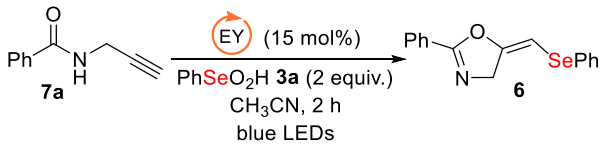
3.2 The use of arylseleninic acids in the synthesis of 2-substituted oxazole-5-carbaldehydes (8a-l)

A second objective of our work was to extend the use of benzeneseleninic acid in electrophilic cyclizations. Thus, the reaction of *N*-propargylamide with BSA was explored, in the presence of visible light, aiminig to form vinyl selenides.

Firstly, *N*-(propargyl)benzamide **7a** was prepared according to the literature[34] from benzoyl chloride and propargylammine, in DCM for 1 hour (Scheme 45).

Scheme 45. Synthesis of *N*-proparylammide **7a**.[34]

Then, the substrate **7a** was reacted with BSA **3a** (2 equiv.), in the presence of 15 mol% of the photocatalyst eosin Y (EY), under irradiation of visible light (blue LEDs) for 2 hours to obtain the vinyl selenide **6** (Scheme 46).



Scheme 46. Synthesis of vinyl selenide **6**.

The product obtained was analyzed by ^{1}H, ^{13}C, ^{77}Se NMR and CGMS analysis. Surprisingly, it was possible to observe in the ^{1}H and ^{13}C NMR spectra (Figures 7 and 8) the absence of the characteristic signals of the hydrogens H1 of the CH_2 (in 4-5 ppm) and the vinyl hydrogen H2 (in 6-7 ppm), and, also, of the carbons C1 (in 60 ppm) and C2 (in 80 ppm). Moreover, in the ^{77}Se NMR spectrum did not appear any selenium signal (Figure 9). Finally, through the CGMS analysis it was possible to find the molecular ion of 173 g/mol, which proved that the compound **6** was not formed.

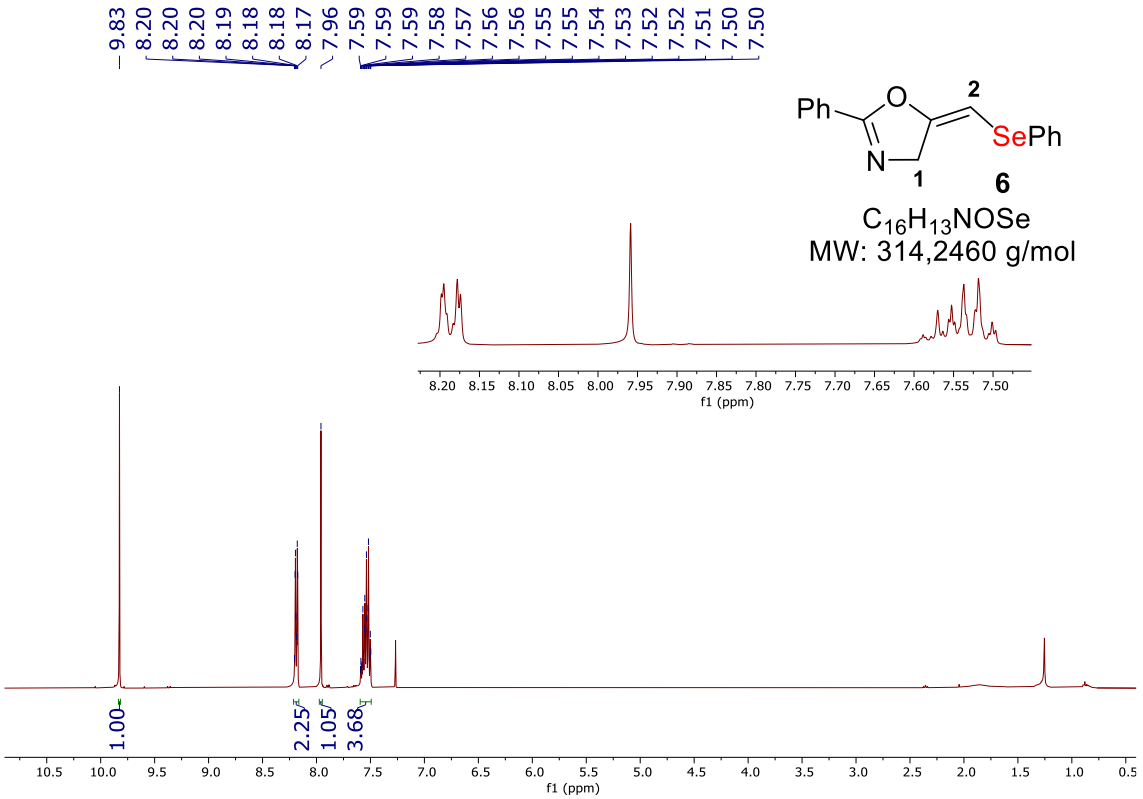


Figure 7. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound obtained from the reaction between **7a** and **3a**.

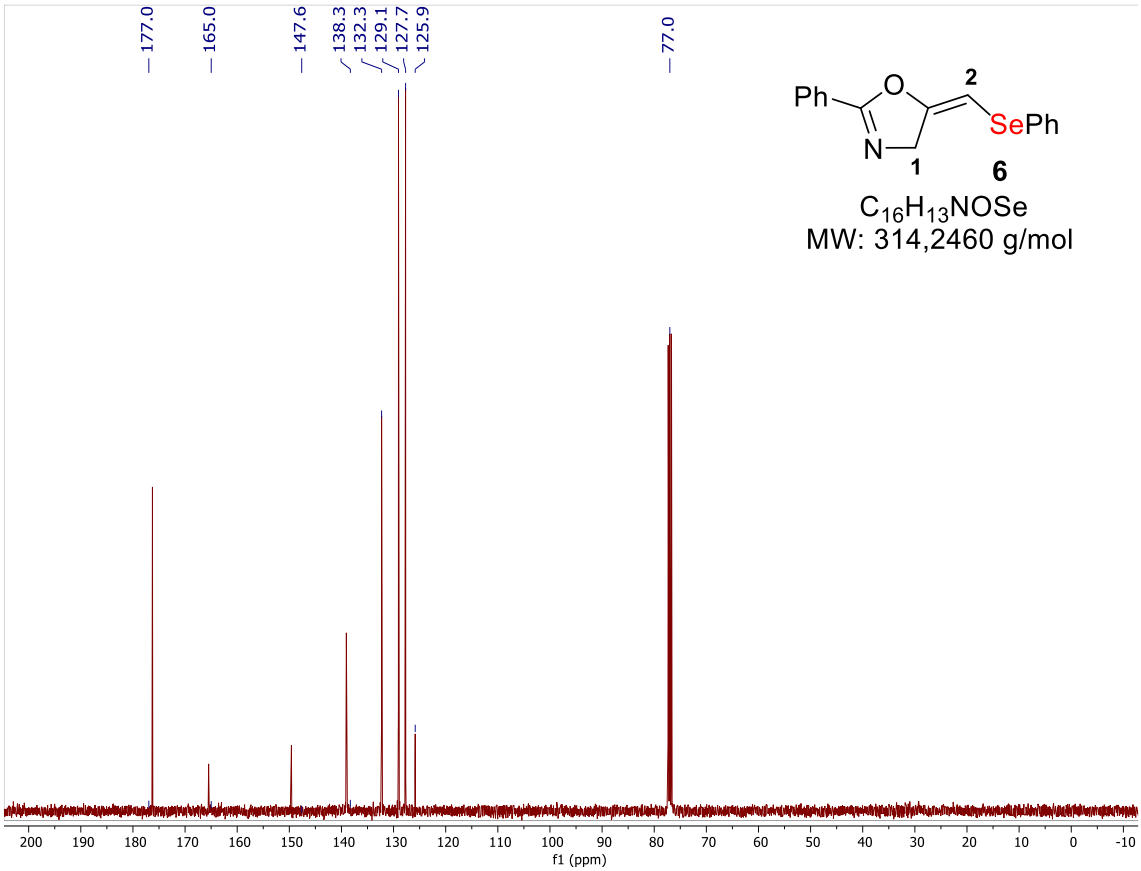
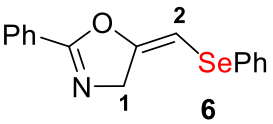


Figure 8. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound obtained from the reaction between **7a** and **3a**.



$C_{16}H_{13}NOSe$
MW: 314,2460 g/mol

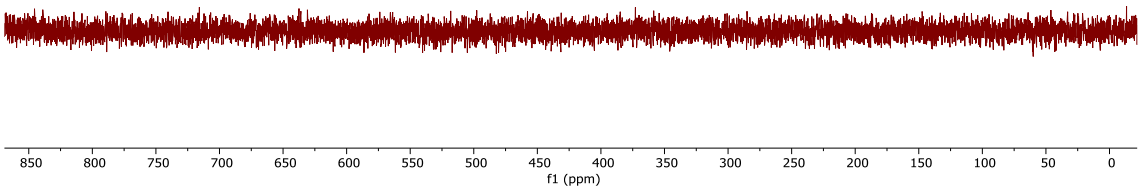


Figure 9. ^{77}Se NMR ($CDCl_3$, 76 MHz) of the compound obtained from the reaction between **7a** and **3a**.

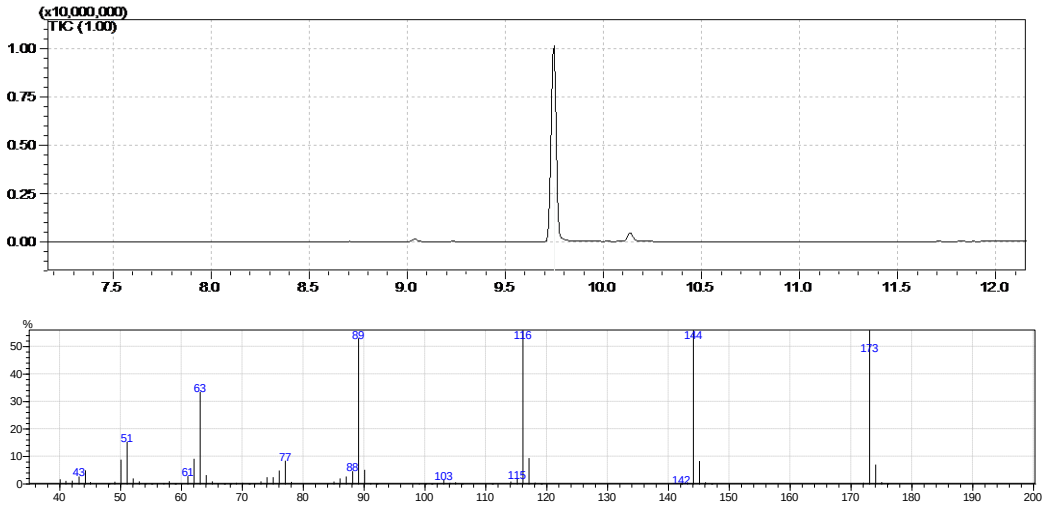


Figure 10. CGMS analysis of the compound obtained from the reaction between **7a** and **3a**.

Based on these results, it was possible to understand that the product formed was the 2-phenyloxazole-5-carbaldehyde **8a**, in 60% yield. Thus, to find the best reaction condition to obtain this compound, the optimization study began.

Table 2. Optimization of the reaction conditions to obtain **8a**.[a]

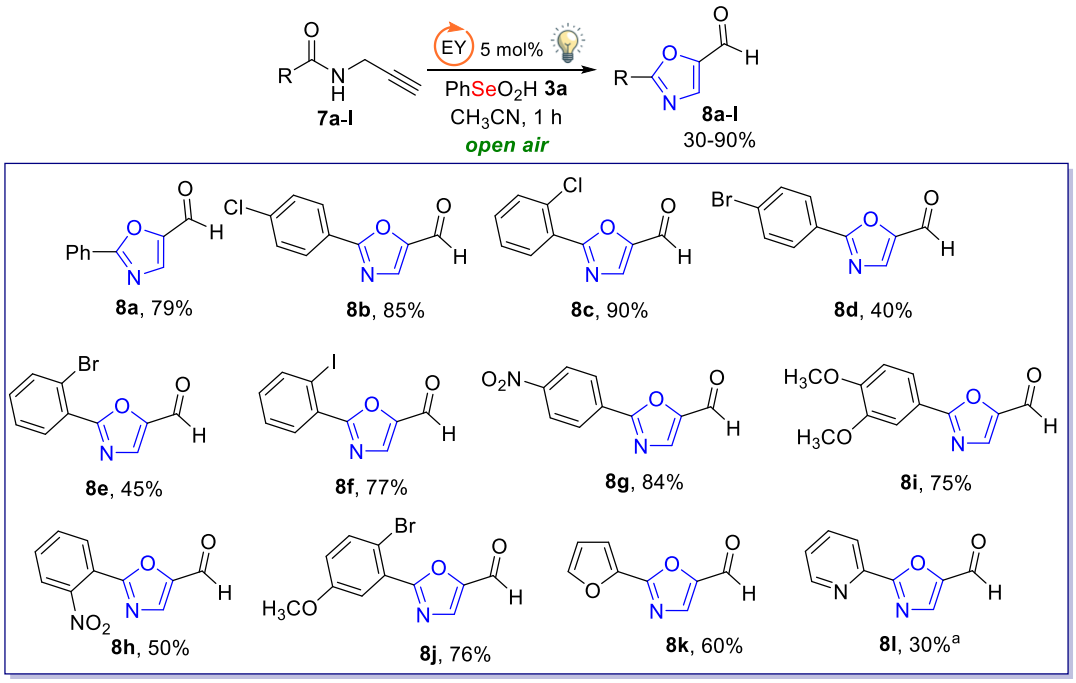
Entry	3a (equiv.)	PC (mol%)	Solvent	LED (50 W)	Time (h)	Yield 8a (%)[b]
1	2	EY (15)	CH_3CN	blue	2	60
2	2	EY (15)	CH_3CN	green	2	58
3	2	EY (15)	CH_3CN	white	2	70
4	2	EY (5)	CH_3CN	white	2	70
5	1.5	EY (5)	CH_3CN	white	2	77
6	1.0	EY (5)	CH_3CN	white	2	52
7	**1.5**	**EY (5)**	**CH_3CN**	white	**1**	**79**
8	1.5	EY (5)	CH_3CN	white	4	39
9	1.5	EY (5)	CH_3CN	white	0.5	64
10	1.5	EY (5)	EtOH	white	1	4
11	1.5	EY (5)	AcOEt	white	1	3
12	1.5	EY (5)	THF	white	1	30
13	1.5	EY (5)	DMSO	white	1	50
14	1.5	Rhodamine B (5)	CH_3CN	white	1	75
15	1.5	Methylene blue (5)	CH_3CN	white	1	72
16	1.5	Rose bengal (5)	CH_3CN	white	1	43
17	1.5	Coomassie blue (5)	CH_3CN	white	1	71
18	1.5	EY (3)	CH_3CN	white	1	68
19	1.5	EY (10)	CH_3CN	white	1	55
20	1.5	–	CH_3CN	white	2	NR

[a] In a reaction flask were added 0.3 mmol of *N*-(propargyl)benzamide **7a**, $PhSeO_2H$ **3a**, the photocatalyst, and solvent (1.0 mL). The resulting mixture was irradiated under stirring with visible light for the tabled time, under open air. [b] Isolated yield obtained after purification by column chromatography (hexanes/AcOEt = 90:10).

After the first test (Table 2, entry 1), were employed green and white LEDs, and the product **8a** was formed in 50% and 70% yield, respectively (Table 2, entries 2 and 3). Then, using white LEDs, the amount of EY was decreased to 5 mol%, and the product **8a** was obtained again in 70% (Table 2, entry 4). After, with 5 mol% of EY, were used 1.5 and 1 equiv. of BSA, and the product **8a** was achieved in 77% and 52% yield, respectively (Table 2, entries 5 and 6). Then, with 1.5 equiv. of BSA, the reaction time was investigated, and in 1 h, 4 h, and 30 min of reaction, the product **8a** was formed in 79%, 39%, and 64% yield, respectively (Table 2, entries 7-9). Different solvents were tested, when EtOH and AcOEt were used, the product **8a** was formed in 4% and 3% respectively; instead, with THF it was reached in 30% yield, and with DMSO in 50% yield (Table 2, entries 10-13). Other dye-based photocatalysts, such as Rhodamine B, Methylene blue, Rose bengal and Coomassie blue, were evaluated. However no significant improvements were observed (Table 2, entries 14-17). Then, EY was

employed in 3 and 10 mol%, reaching the product **8a** in 68% and 55% yield, respectively (Table 2, entries 18 and 19). Finally, the reaction was carried out without PC, and no product was formed, even after 2 h (Table 2, entry 20). Hence, in the entry 7 is the best reaction condition: 5 mol% of EY, 1.5 equiv. of benzeneseleninic acid **3a**, CH_3CN as solvent, under 1 h with white LEDs (50 W) irradiation.

With the best condition in hand, a series of 2-substituted oxazole-5-carbaldehydes **8** was synthesized (Scheme 47). Various *N*-propargylamides **7** were employed in the reaction with **3a**. Firstly, amides bearing halogens, such as chloro in *ortho*- and *para*-positions **7b** and **7c** were used, and they afforded the products **8b** and **8c** in 85% and 90% yield, respectively. When was studied the presence of bromine substituent in the amides **7d** and **7e**, and the yields of the products **8d** and **8e** decreased to 40% and 45%, respectively. The *ortho*-iodo-substituted *N*-(propargyl)benzamide **7f** afforded the corresponding oxazole **8f** in 77% yield. *Para*- and *ortho*-NO_2-substituted *N*-(propargyl)benzamides **7g** and **7h**, with strongly electron-withdrawing group, generated the products **8g** and **8h** in 84% and 50% yield, respectively. On the other hand, with strongly electron-donating group (2-OCH_3), amides **7i** cyclized to the product **8i** in 75% yield. Amide bearing both bromine and methoxy groups **7j** led to the oxazole **8j** in 76% yield. Additionally, *N*-(propargyl)furan-2-carboxamide **7k** was tested, and the product **8k** was generated in 60% yield. Finally, was used *N*-(prop-2-yn-1-yl)nicotinamide **7l**, and the respective oxazole **8l** was afforded in 30%, after 2 h of reaction.



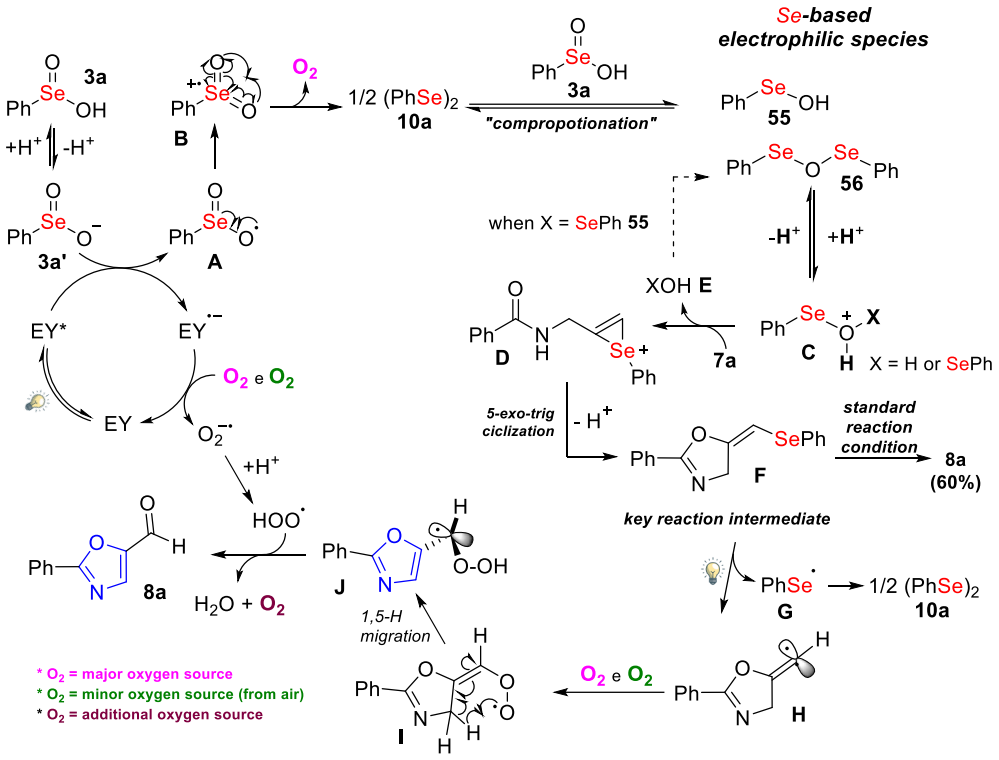
Scheme 47. Scope of the reaction in the synthesis of 2-substituted oxazole-5-carbaldehydes (**8a-l**). In a reaction tube were added 0.3 mmol of amide **7**, 1.5 equiv. of $PhSeO_2H$ **3a**, EY (5 mol%) and CH_3CN (1 mL). The resulting mixture was irradiated with white LEDs (50 W) for 1 hour, under open air. Isolated yield obtained after purification by column chromatography (hexane/AcOEt = 90:10). [a] Were used 0.19 mmol of amide **7l** and the reaction was carried out in 2 h.

Trying to clarify the mechanism of the reaction, some control experiments were conducted (Table 2). Initially, the reaction was carried out in the dark, and the product was formed only in 5% yield (Table 3, entry A). Under argon and oxygen atmospheres the product **8a** was achieved in 54% and 35% yield, respectively, demonstrating that the oxygen from the air is not essential, and maybe it is formed in the reaction (Table 3, entries B and C). In the presence of radical scavangers, TEMPO and hydroquinone, the yield of the product **8a** decreased to 30% and 28%, respectively, meaning the involvement of a radical pathway (Table 3, entries D and E). In entry F, it was employed diphenyl diselenide **10a** instead of BSA **3a** and the product did not form, confirming the crucial role of the acid. Moreover, two different acids were investigated, an electron-rich (**3d**) and electron-deficient (**3g**), and the product **8a** was reached in 72% and 69%, respectively (Table 3, entries G and H). Finally, the acid **3a** was used in catalytic amount in the presence of 2 equiv. of H_2O_2, but the product did not form (Table 3, entry I).

Table 3. Control experiments.

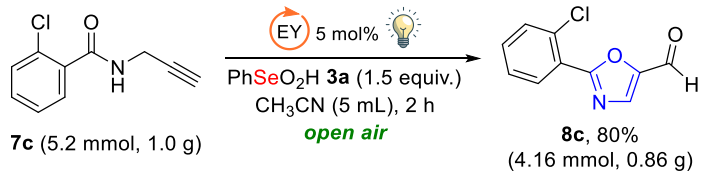
	Condition	Yield **6a** (%)
A	in the dark	5
B	under N_2	54
C	under O_2	35
D	with 4 equiv. of TEMPO	30
E	with 4 equiv. of hydroquinone	28
F	PhSeSePh **10a** was used instead of **3a**	0
G	with 3-CF_3-benzeneseleninic acid **3d** instead of **3a**	72
H	with 2-CH_3-benzeneseleninic acid **3g** instead of **3a**	69
I	with 10 mol% of **3a** and 2 equiv. of H_2O_2	0

Hence, based on the literature[27a,d,35,36] and on the control experiments, a plausible mechanism was suggested (Scheme 48). Firstly, EY is excited by visible light to EY* and it reacts with **3a'** forming $EY^{\bullet -}$ and the species **A**. This last is converted into the intermediate **B**, which decomposes in O_2 and diphenyl diselenide **10a**. At this point, the comproportionation process between **10a** and **3a** leads to the selenium electrophilic species **55** and **56**, which are both protonated into **C**.[20b,e,35,37] The substrate **7a**, in the presence of **C**, generates the intermediate **D**, which undergoes a 5-*exo*-trig cyclization reaching the vinyl selenide **F**. This last is the key reaction intermediate, and when it was prepared[26d] and used under optimal condition, the product **8a** was formed in 60%. Then, **F** suffers a homolytic cleavage to give **G**, which is converted in **10a**, and **H**. Once formed, the species **H** is oxidized into **I**, which undergoes a 1,5-*H* shift forming **J**. Finally, the intermediate **J** is oxidized by hydroperoxyl radical, affording the product **8a**, together with water and O_2.



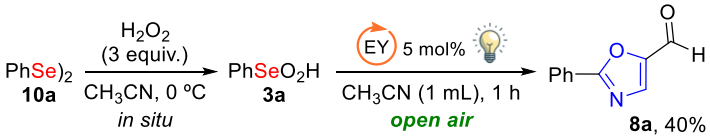
Scheme 48. Proposed reaction mechanism.

Additionally, in this work a gram scale reaction was carried out using 5.2 mmol of amide **7c**, and after 2 h of reaction, the corresponding oxazole **8c** was obtained in 80% yield (Scheme 49).



Scheme 49. Gram-scale reaction.

Moreover, it was investigated the *in situ* formation of the benzeneseleninic acid **3a** in a one-pot reaction. Initially, diphenyl diselenide **10a** was treated with H_2O_2 for 15 min., and then susbtrate **7a** and EY were added. The mixture was irradiated with white LEDs for 1 h, and the product **8a** was achieved in 40% yield (Scheme 50). This result suggests the possibility to create a flow system in which H_2O_2 and amide are constantly added.



Scheme 50. One-pot reaction.

This work was published in: *European Journal of Organic Chemistry*, 2022, 2022, e202200641, DOI: 10.1002/ejoc.202200641.

3.3 Presentation and discussion of the NMR spectral data

In this section, it will be discussed the nuclear magnetic resonance (NMR) analyses. Initially, we will present the NMR analysis conducted to clarify the mechanism of the reaction of benzeneseleninic acid **3a** with anilines **4** and indole **5a**. Then, we will present the NMR spectra of some of the prepared compounds.

In order to clarify the reaction mechanism ^{77}Se NMR analysis were carried out. In the ^{77}Se NMR spectrum of a solution of BSA **3a** in DMF, freshly prepared, appears two signals, one intense in δ = 1183 ppm (due to **3a**), and a peak of low intensity at δ = 1020 ppm. This last probably belongs to benzeneselenenic acid PhSeOH **55** and/or to the anhydride PhSeOSePh **56**, once it is not possible to detect such equilibrium at the working temperature (Figure 11). Additionally, after 24 hours, the intensity of the signal at δ = 1020 ppm increases, and another peak, (due to PhSeSePh **10a**), at δ = 455 ppm appears (Figure 12).

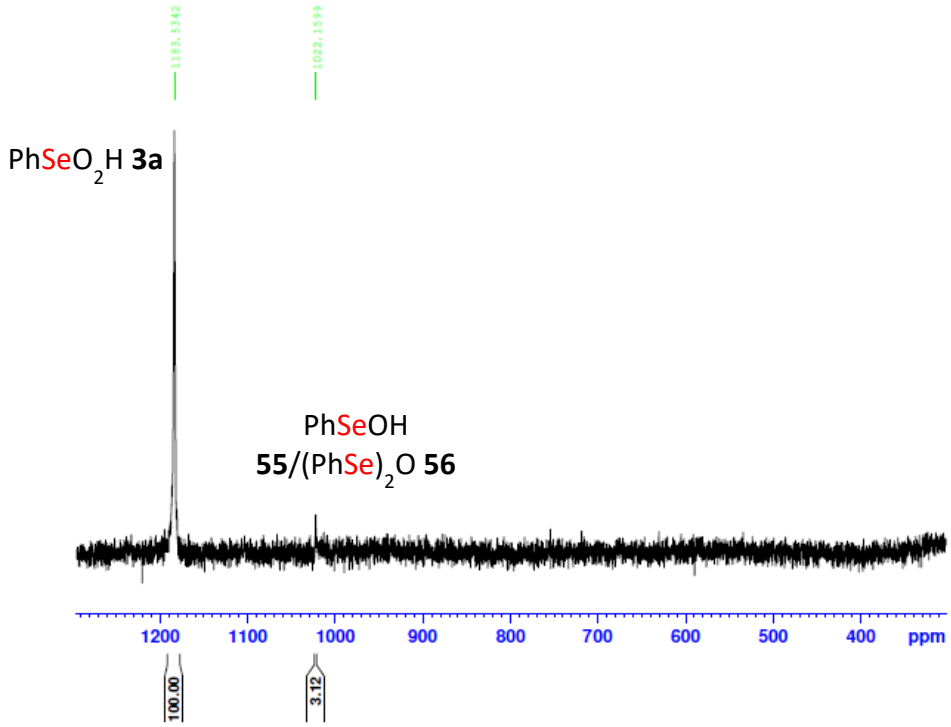


Figure 11. ^{77}Se NMR (CD_3CN, 76 MHz) spectrum of a solution in DMF of BSA **3a**, freshly prepared, at 25 °C.

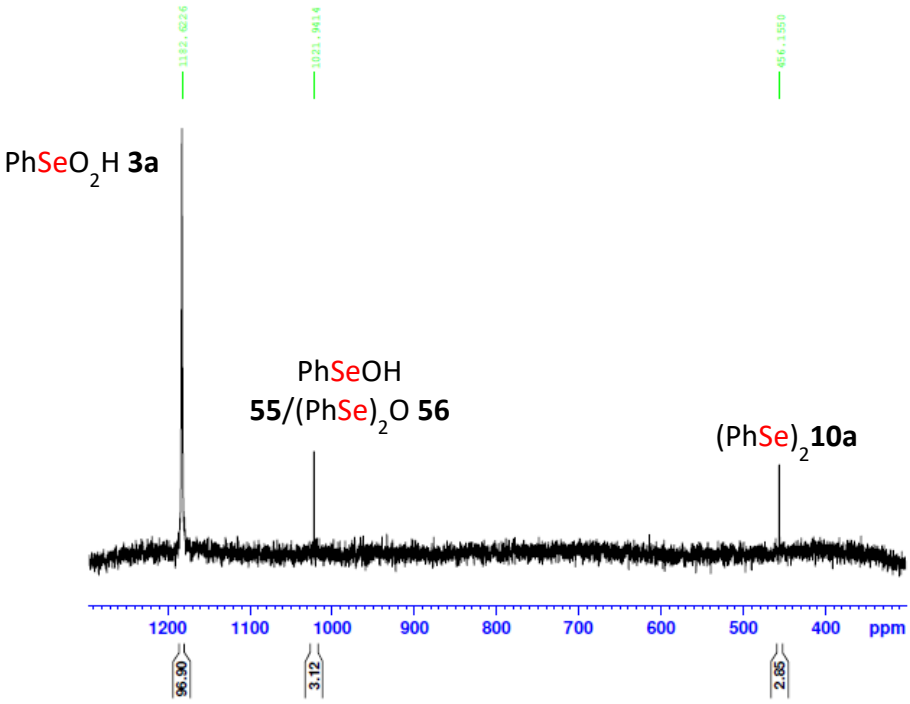


Figure 12. ^{77}Se NMR (CD_3CN, 76 MHz) spectrum of a solution in DMF of BSA **3a** after 24 h at 25 °C.

Then, the ^{77}Se NMR spectrum of an equimolar mixture of **3a** and **10a** in DMF was collected at 50 °C, a temperature similar to the reaction temperature, in which it is possible to observe three peaks: in δ = 455 ppm (diselenide **10a**); in δ = 1020 ppm (probably of the species **55** or **56)**, and in δ = 1180 ppm (BSA **3a**) (Figure 13). After 24 hours, the peak intensity of **55** or **56** increases, while decreases the peak of **3a**, as observed in the ^{77}Se NMR of the mixture between **3a** and **10a** (Figure 14). These experiments demonstrate that our mechanism proposal is plausible, once PhSeSePh **10a** is formed in the NMR tube, together with electrophilic selenium species.

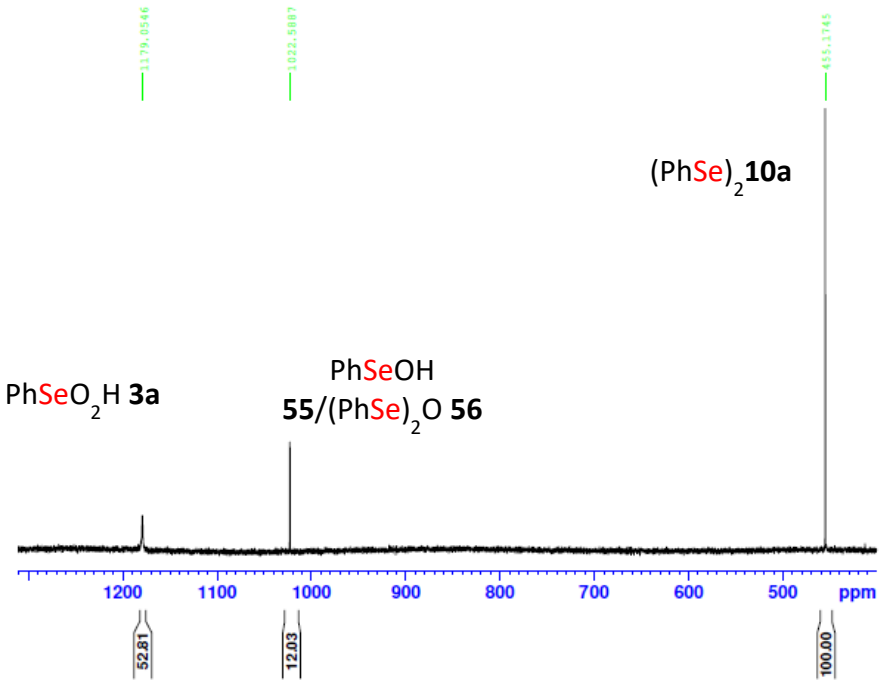


Figure 13. ^{77}Se NMR (CD_3CN, 76 MHz) spectrum of a solution in DMF of a freshly prepared mixture of BSA **3a** (0.1 mmol) and PhSeSePh **10a** (0.1 mmol) at 50 °C.

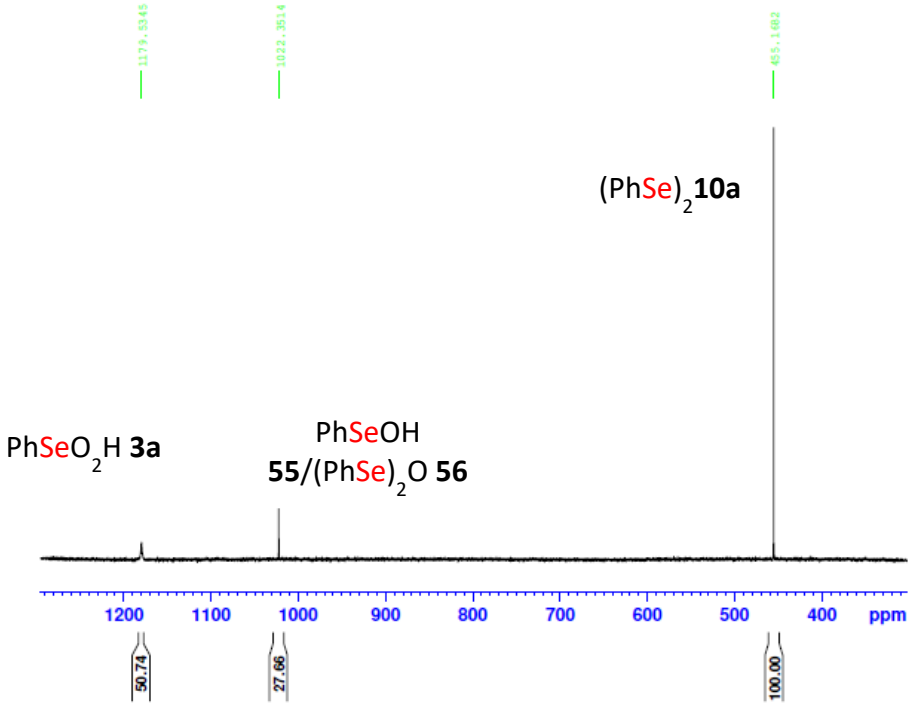
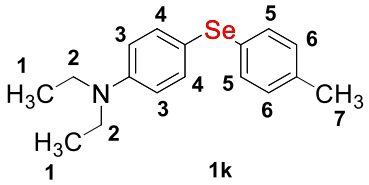


Figure 14. ^{77}Se NMR (CD_3CN, 76 MHz) spectrum of a solution in DMF of a mixture of BSA **3a** (0.1 mmol) and PhSeSePh **10a** (0.1 mmol) after 24 h at 50 °C.

To a discussion on the characterization of the selanylanilines **1** prepared in this work, were chosen the spectra of hydrogen and carbon-13 of *N*,*N*-diethyl-

4-(p-tolylselanyl)aniline **1k** (Figure 15). In the ^{1}H NMR spectrum of the compound **1k** it is possible to see all the characteristic peaks. In 1.16 ppm there is a triplet (J = 7.0 Hz) corresponding to the six hydrogen atoms H1 of the two ethyl groups. In 2.27 ppm there is a singlet belonging to the three hydrogen atoms H7 of the methyl group linked to the phenyl. In 3.35 ppm there is a quartet (J = 7.0 Hz) corresponding to the four hydrogen atoms H2 of the two CH_2 linked to the nitrogen. In 6.60 ppm there is a doublet (J = 8.9 Hz), corresponding to the two hydrogen atoms H3. In 7.01 there is a doublet (J = 7.8 Hz) belonging to the two hyrogen atoms H6. In 7.22 there is a doublet (J = 7.8 Hz) corresponding to the two hydrogen atoms H5. Finally, in 7.42 ppm there is a doublet (J = 8.9 Hz), belonging to the two hydrogen atoms H4.



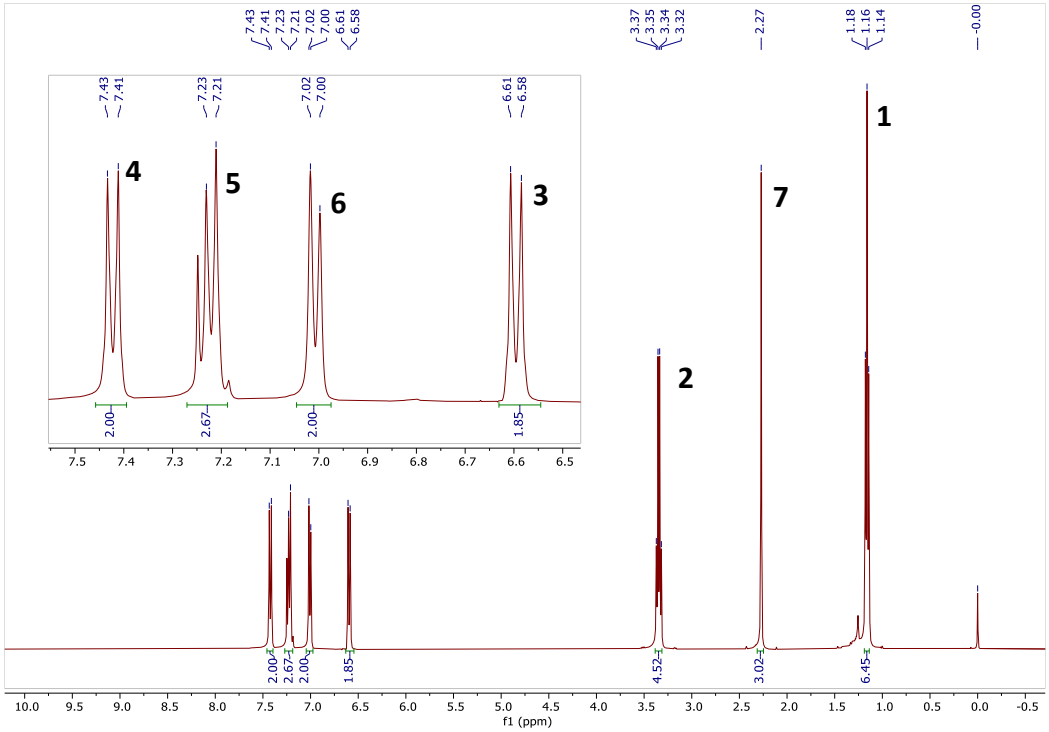


Figure 15. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1k**.

In Figure 16 is presented the ^{13}C NMR spectrum of the compound **1k**, and it is possible to see all the characteristic peaks. In 12.5 ppm there is a signal corresponding to the two carbon atoms C1 of the two ethyl groups. In 21.0 ppm there is a signal belonging to the carbon atom C11. In 44.3 ppm there is a signal

corresponding to the two carbon atoms C2 of the two CH_2 groups. In 112.4 ppm there is a signal belonging to the two carbon atoms C4. In 113.0 ppm there is a signal probably corresponding to the carbon C6. In 129.2 there is a signal possibly belonging to the carbon atom C7. In 129.8 there is a signal maybe corresponding to the two carbon atoms C8, and in 130.4 ppm there is a signal probably belonging to the two carbon atoms C5. In 135.7 ppm there is a signal possibly corresponding to the carbon atom C10. In 136.9 ppm there is a signal maybe belonging to the two carbon atoms C9. Finally, in 147.8 ppm there is a signal probably corresponding to the carbon atom C3.

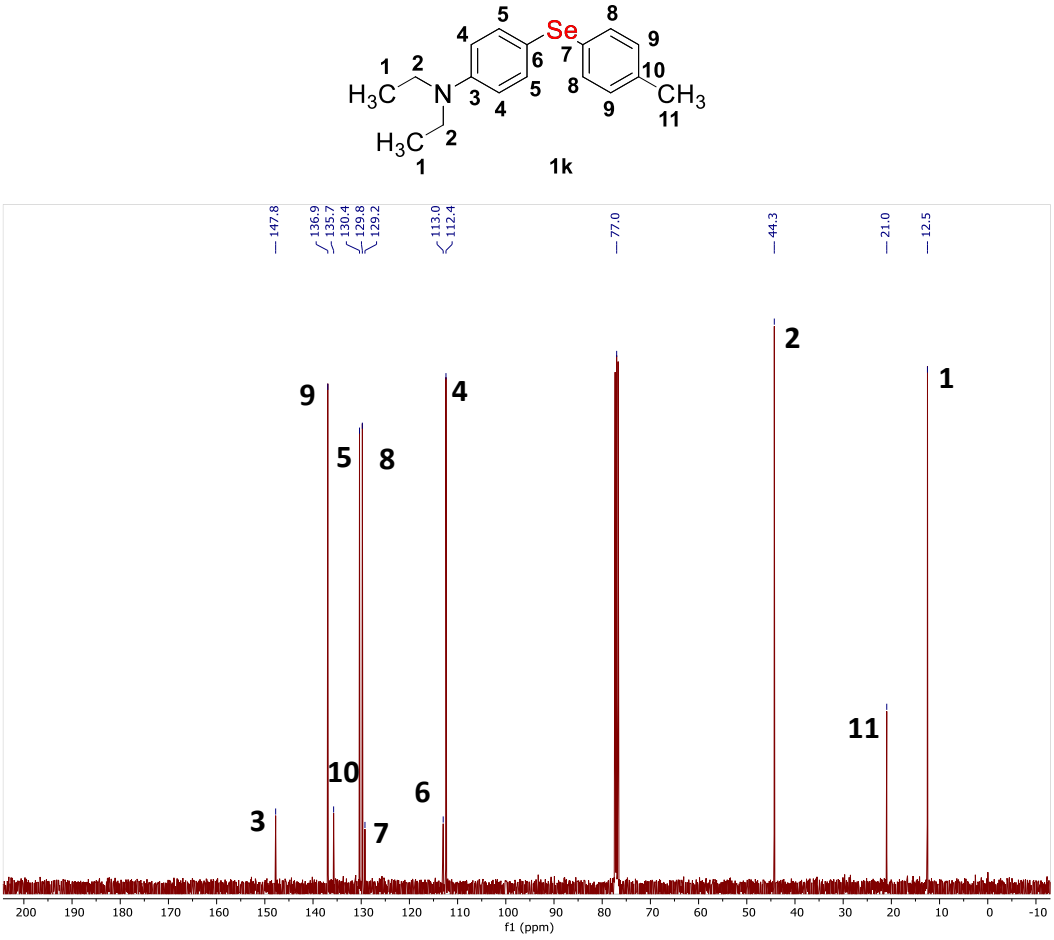


Figure 16. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1k**.

Concerning the selanylindoles **2**, the NMR spectra of hydrogen and carbon-13 of compound 3-((4-fluorophenyl)selanyl)-1*H*-indole **2b** were chosen to be discussed. In Figure 17 is presented the ^1H NMR spectrum of the compound **2b**, and it is possible to see all the characteristic peaks. In the region from 6.79 to 6.87 ppm there is a multiplet probably corresponding to the two hydrogen atoms H8. In the region from 7.14 to 7.29 ppm there is a multiplet maybe belonging to

the four hydrogen atoms H3, H4 and H7. In 7.42 ppm there is s doublet (J = 8.0 Hz) possibly corresponding to the hydrogen atom H2. In 7.45 ppm there is a doublet (J = 2.5 Hz) probably corresponding to the hydrogen atom H6. In 7.62 ppm there is a doublet (J = 7.9 Hz) maybe belonging to the hydrogen atom H5. Finally, in 8.40 ppm there is a broad signal corresponding to hydrogen atom H1, directly linked to the nitrogen.

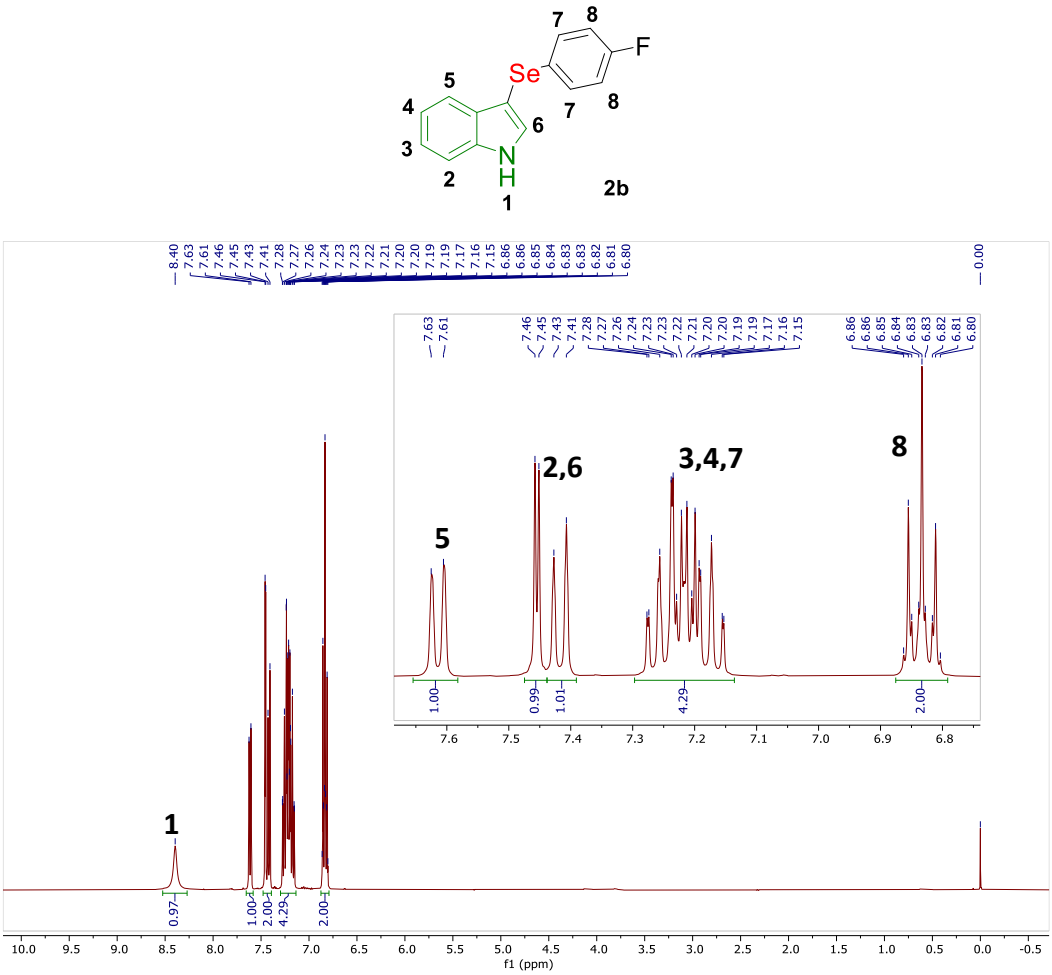


Figure 17. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **2b**.

In the Figure 18 is presented the ^{13}C NMR spectrum of the compound **2b**, and it is possible to see all the characteristic peaks. In 98.6 ppm there is a signal maybe corresponding to the carbon atom C6. In the 111.4 ppm there is a signal propably belonging to the carbon atom C1. In 116.0 there is a doublet ($^{2}J_{C\text{-}F}$ = 21.5 Hz) corresponding to the two carbon atoms C11. In 120.2 there is a signal possibly belonging to the carbon atom C4. In 120.9 there is a signal maybe corresponding to the carbon atom C3. In 123.0 ppm there is a signal probably belonging to the carbon atom C2. In 127.9 there is a doublet ($^{4}J_{C\text{-}F}$ = 3.1 Hz)

corresponding to the carbon atom C9. In 129.7 ppm there is a signal possibly belonging to the carbon atom C5. In 130.7 there is a doublet ($^{3}J_{C\text{-}F}$ = 7.6 Hz) corresponding to two carbon atoms C10. In 131.0 there is a signal maybe belonging to the carbon atom C7. In 136.4 ppm there is a signal probably corresponding to the carbon atom C8. Finally, in 161.5 ppm there is a doublet ($^{1}J_{C\text{-}F}$ = 244.6 Hz) belonging the carbon atom C12.

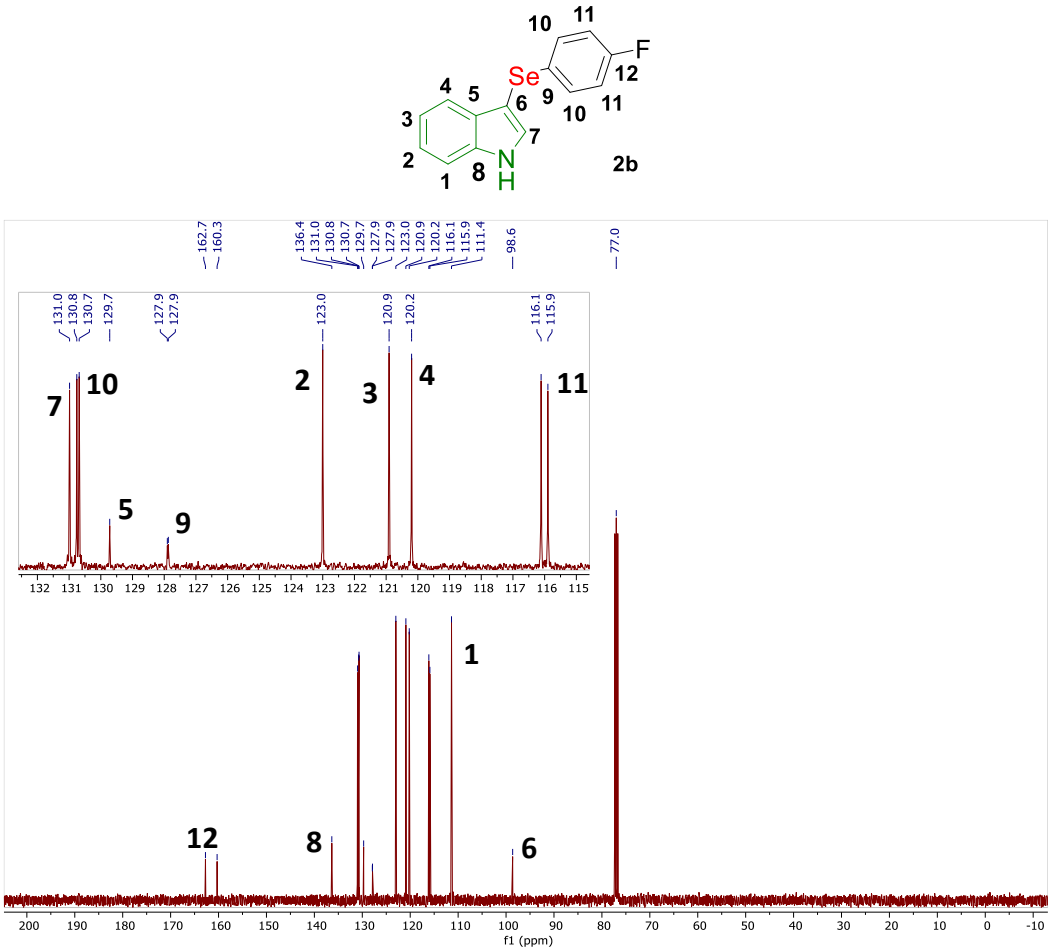


Figure 18. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **2b**.

Regarding the 2-substituted oxazole-5-carbaldehydes **8**, the NMR spectra of hydrogen and carbon-13 of compound (3-(phenylselanyl)-1*H*-indole) **8j** were chosen to be discussed. In Figure 19 is presented the ^{1}H NMR spectrum of the compound **8j**, and it is possible to see all the characteristic peaks. In 3.87 ppm there is a singlet corresponding to the three hydrogen atoms H6 of the methoxy group. In 6.95 ppm there is a double doublet (*J* = 8.8 and 3.3 Hz) probably belonging to the hydrogen atom H2. In 7.58 ppm there is a doublet (*J* = 3.3 Hz) maybe corresponding to the hydrogen atom H3. In the region from 7.60 to 7.67 there is a multiplet possibly belonging to the hydrogen atom H1. In 8.02 ppm there

is a singlet corresponding to the hdyrogen atom H4. Finally, in 9.88 ppm there is a singlet belonging to the hydrogen atom H5.

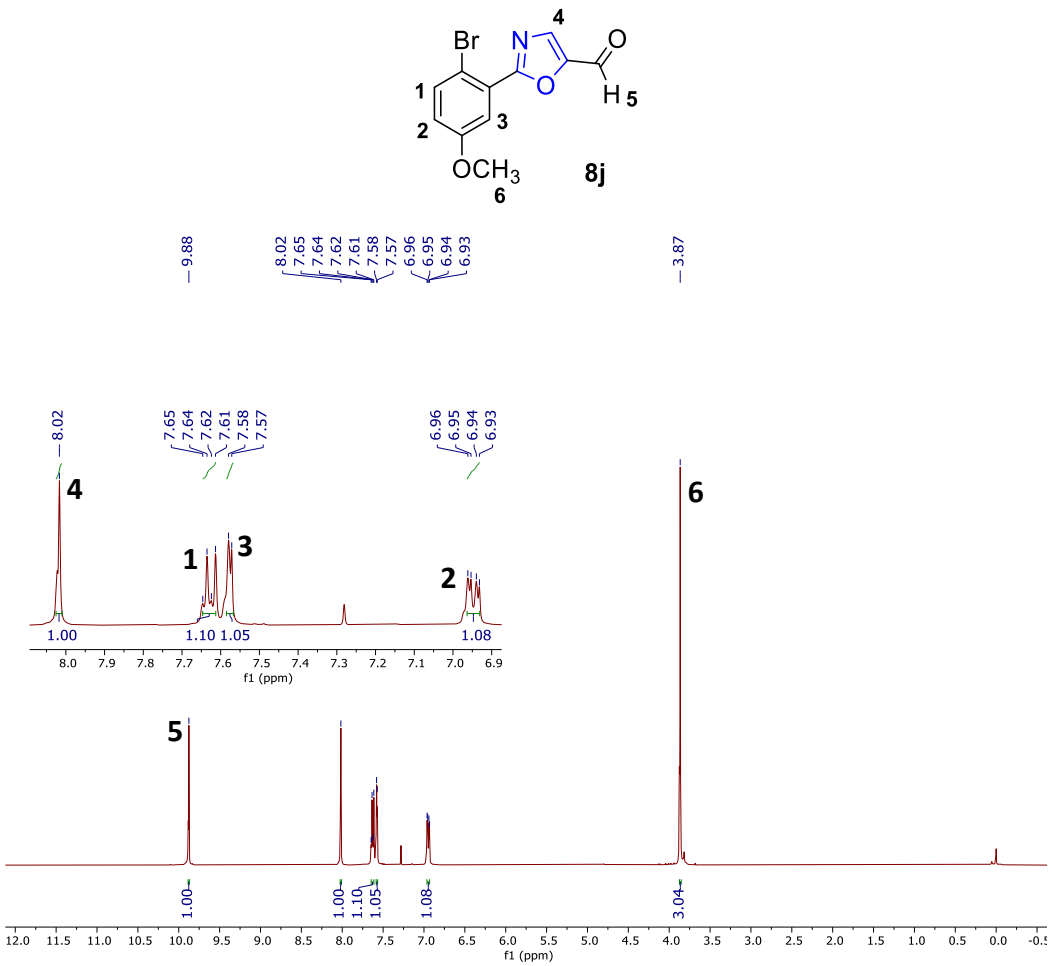


Figure 19. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **8j**.

In Figure 20 is presented the ^{13}C NMR spectrum of the compound **8j**, and it is possible to see all the characteristic peaks. In 55.7 there is a signal corresponding to the carbon atom C7. In 112.1 ppm there is a signal belonging to the carbon atom C6. In 116.3 there is a signal probably corresponding to the carbon atom C4. In 119.5 ppm there is a signal maybe belonging to the carbon atom C2. In 127.2 there is a signal possibly corresponding to the carbon atom C10. In 135.7 there is as signal probably belonging to the carbon atom C1. In 137.2 ppm there is a signal maybe corresponding to the carbon atom C9. In the 149.6 ppm there is a signal possibly belonging to the carbon atom C5. In the 158.8 there is a signal probably corresponding to the carbon atom C8. In the 163.5 ppm there is a signal maybe belonging to the carbon atom C3. In the 176.6 there is a signal corresponding to the carbon atom C11.

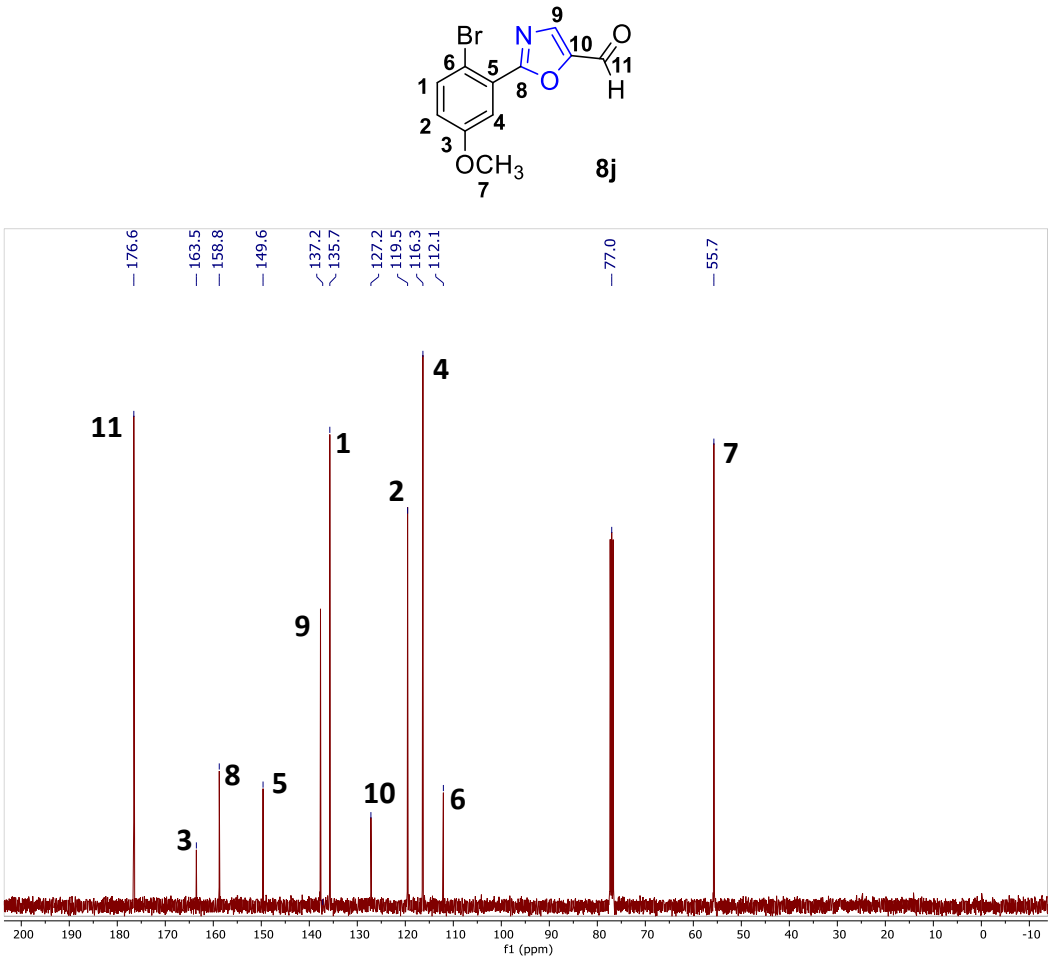


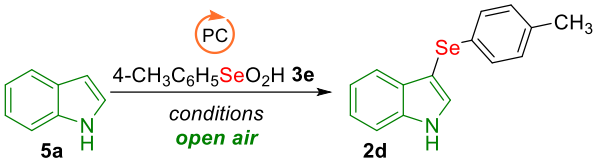
Figure 20. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **8j**.

3.4 Other parallel works

Additionally, a new green synthesis of 3-selanylindoles through the reaction between indole and arylseleninic acids under photocatalytic conditions, without using transition metal catalysis, strong acids or high temperatures is being developing. An optimization study was carried out, and indol **5a** and 4-methylbenzeneseleninc acid **3e** were chosen as starting material. Firstly, **5a** and **3e** were reacted together with 5 mol% of EY, in DMSO under irradiation of blue LED for 1 hour, forming the product **2d** in 70% yield (Table 4, entry 1). Then, amounts of 3% and 10% mol of EY were evaluated and the product **2d** was obtained in 40% and 26% yield, respectively (Table 4, entries 2 and 3). Reaction time was studied, carrying out the reaction in 30 minutes and 1 hour and the product **2d** was formed in 37% and 63%, respectively (Table 4, entries 4 and 5). Under irradiation of green and white LEDs the product **2d** was obtained in 27% and 41%, respectively (Table 4, entries 6 and 7). Then different solvents were

used, such as DMF, THF and CH_3CN, but none of them was better than DMSO (Table 4, entries 8-10). With 2 equiv. of 4-methylbenzeneseleninic acid **3e** the produc **2d** was obtained in 45% yield (Table 4, entry 11). Without photocatalyst the product **2d** was obtained in 50% yield (Table 4, entry 12). Other photocatalyst were tested, rhodamine B and methylene blue, but none of them was better than EY (Table 4, entries 13 and 14). Thus, in the entry 1 is the best reaction condition: 0.3 mmol of **5a**, 1.5 equiv. of 4-methylbenzeneseleninic acid **3e**, 5 mol% of EY, under irradiation of visible light (blue LED), for 1 hour.

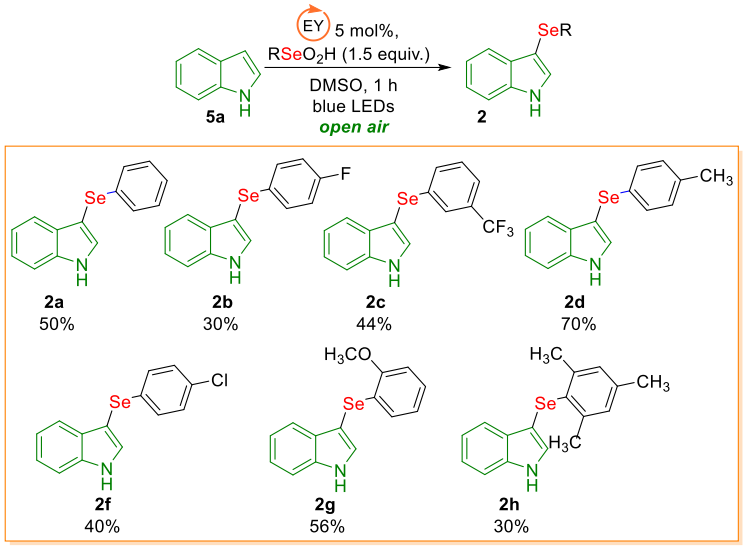
Table 4. Optimization of the reaction conditions to obtain **2a**.[a]



Entry	3e (equiv.)	PC (mol%)	Solvent	t (h)	LED (50 W)	Yield 2d (%)[a]
1	**1.5**	**EY (5)**	**DMSO**	**1**	**blue**	**70**
2	1.5	EY (3)	DMSO	1	blue	40
3	1.5	EY (10)	DMSO	1	blue	26
4	1.5	EY (5)	DMSO	0.5	blue	37
5	1.5	EY (5)	DMSO	1.5	blue	63
6	1.5	EY (5)	DMSO	1	green	27
7	1.5	EY (5)	DMSO	1	white	41
8	1.5	EY (5)	DMF	1	blue	21
9	1.5	EY (5)	THF	1	blue	23
10	1.5	EY (5)	CH_3CN	1	blue	40
11	2	EY (5)	DMSO	1	blue	45
12	1.5	/	DMSO	1	blue	50
13	1.5	Rhod.B (5)	DMSO	1	blue	32
14	1.5	Meth.Blue (5)	DMSO	1	blue	36

[a] In a reaction flask were added 0.2 mmol of indol **5a**, $PhSeO_2H$ **3a**, the photocatalyst, and solvent (1.0 mL). The resulting mixture was irradiated under stirring with visible light for the tabled time, under open air. Isolated yield obtained after purification by column chromatography (hexanes/AcOEt = 90:10).

This new protocol was used to prepare seven 3-selanylindoles **2** from the reaction between indole **5a** and different arylseleninic acids **3**, in 30-70% yield (Scheme 51). The work is still under progress.



Scheme 51. Scope of the reaction in the synthesis of 3-selanylindoles (**2a**-**d**,**f**-**h**). In a reaction tube were added 0.2 mmol of indole **5a**, 1.5 equiv. of acid **3**, EY (5 mol%) and DMSO (1 mL). The resulting mixture was irradiated with blue LEDs (50 W) for 1 hour, under open air. Isolated yield obtained after purification by column chromatography (hexane/AcOEt = 90:10).

I also was involved in the synthesis of α-phenylselenocitronellal and β-phenylthiocitronellal, according to the literature,[38] that were employed by a partner group (LaCoPol-UFPel) to prepare a polimeric material with chitosan. The films with β-phenylthiocitral-modified chitosan and poly(vinyl alcohol) demonstrated to attenuate atopic dermatitis-like symptoms in mice**.** This work was published in the journal *Carbohydrate Polymers*, 2019, 219, 240-250 (DOI: 10.1016/j.carbpol.2019.05.040).

Moreover, the β-phenylthiocitronellal prepared is, actually, being used by LaCoPol group to obtain antimicrobial curative material through the coating treatment of gauze. The resulting biomaterial will be tested in skin wounds.

Another project with LaCoPol was to synthesize the terminal ethynyl selenide[39] (Figure 16) in order to react it with acrylic polyacid, according to the literature,[40] but unfortunately the final material did not form.

Furthermore, diphenyl diselenide, bisvinyl selenide and vinyl selenide were prepared[41] (Figure 16), and they were reacted by LaCoPol group with glycidyl methacrylate-modified poly(vinyl alcohol), however the reaction was unsuccessful.

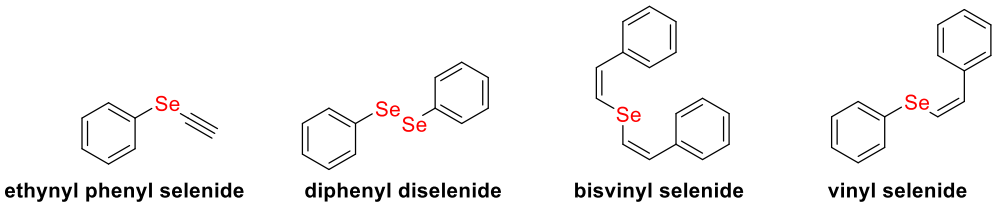


Figure 21. Selenium compounds used to prepare polymers.[39-41]

Finally, together with LaCoPol group, the benzeneseleninic acid is being used directly with the gauzes to obtain a material to be tested against skin wounds, and this work is still ongoing.

I was also a coauthor in three book chapters: 1) “Synthesis of organoselenium compounds using nonconventional reaction media” which was published in *Organoselenium Chemistry*, 2020, 1ed. Berlin: De Gruyter, 1, 193-276 (DOI: 10.1515/9783110625110-006), in which are described the methods available to obtained various classes of organoselenium compounds (diorganyl diselenides, selenoethers, β-seleno amines, β-oxy selenides, seleno ketones, selenoesters, vinyl selenides, bis-organoselanyl alkenes, selenoalkynes), according to the principles of green chemistry (using safe solvents or solvent-free, or alternative energy source); 2) "Multicomponent reactions in the synthesis of organochalcogen compounds" which was published in *Organochalcogen Compounds*, Synthesis, Catalysis and New Protocols with Greener Perspectives, 2022, 3-30 (DOI: 10.1016/B978-0-12-819449-2.00002-1), in which are discussed the multicomponents reactions-based protocols, strategies with high atom-efficiency and low time-consuming, available to prepare organochalcogen compounds (chalcogen-functionalized heterocycles, heterocycles with chalcogen embedded in the ring, selenoethers, vinyl chalcogenides, phosphorus derivatives); and 3) “Semisynthetic bioactive organoselenium and organotellurium compounds” which was published in *Organochalcogen Compounds*, Synthesis, Catalysis and New Protocols with Greener Perspectives, 2022, 253-289 (DOI: 10.1016/B978-0-12-819449-2.00003-3), in which are addressed bioactive organoselenium and organotellurium compounds (terpenes and essential oils, phenolic compounds, carbohydrates, nitrogen-containing heterocycles) synthesized from natural products.

Moreover, I took part in writing three reviews: 1) “Selenium as a Versatile Reagent in Organic Synthesis: More than Allylic Oxidation” which was published

in *Current Organic Synthesis*, 2022, 19, 331-365 (DOI: 10.2174/1570179418666210525152001), which describes classical and new selenium reagents (selenium dioxide, potassium selenocyanate, perfluoroalkylselenylating agents, selenyl halides, elemental selenium) employed in allylic oxidation; 2) “Neuropharmacology of Organoselenium Compounds in Mental Disorders and Degenerative Diseases” which was published in *Current Medicinal Chemistry* (DOI: 10.2174/0929867329666220615124412), in which is discussed the use of organoselenium compounds (e.g.: diaryl diselenides, Ebselen-derivatives, Se-containing heterocycles) in the treatment of neurodegenerative diseases (Alzheimer, Parkinson, amyotrophic lateral sclerosis, multiple sclerosis), and mental disorders (depression, anxiety, bipolar disorder, schizophrenia); and 3) “Synthesis of vinyl selenides and tellurides: an updated review” which was published in *Russian Chemical Reviews*, 2022, 91, RCR5054 (DOI: 10.57634/RCR5054), in which are addressed the transition metal-free and transition metal-catalyzed methods available to obtain vinyl selenides and vinyl tellurides.

4. Conclusions

4. Conclusions and perspectives

In this thesis work was discussed the use of arylseleninic acids as bench-stable and easy to handle electrophilic selenium source in the aromatic substitution with *N*,*N*-dialkyl-anilines and 1*H*-indole as nucleophiles, without additive or auxiliares. In this protocol the only waste of the reaction are water and diphenyl diselenide which can be recovered and reused, and this is a green aspect to be considered. It was possible to prepare fourteen 4-selanylanilines and five 3-selanylindoles in good to excellent yields under the reaction conditions, DMF as solvent at 70 °C after 6 to 15 hours. Moreover, benzenzeseleninic acid was employed in the cyclization of various *N*-propargylamides through a photocatalytic process, without metal catalysis or strong oxidants. Under irradiation with visible light (white LEDs), were synthesized twelve 2-substituted oxazole-5-carbaldehydes in 30-90% yield in only 1 hour at room temperature, and six of them were unprecedent at that time. The co-products of the procedure were water and diphenyl diselenide, which can be completely recovered and reused. It is important to mention that all the arylseleninic acids, together with the *N*-propargylamides were prepared by us according to the literature,[29,34] and both works are already published.

5. Experimental

5. Experimental

5.1 Materials and general methods

The reactions were monitored by TLC carried out on pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV_{254} by using UV light as visualization agent and the mixture of 5% vanillin in 10% H_2SO_4 under heating conditions as developing agent. Merck silica gel (particle size 63-200 μm) was used to flash chromatography, and PTLC Glass Plates L × W 20 cm × 20 cm, silica gel 60 F_{254}, 1 mm, was used in the preparative thin layer chromatography. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz on A Bruker Ascend 400 spectrometer. The spectra were recorded in $CDCl_3$ solutions. The chemical shifts are reported in ppm, referenced to tetramethysilane (TMS) as the external reference. Hydrogen coupling patterns are described as singlet (s), doublet (d), triplet (t), doublet of doublets (dd), doublet of doublet of doublets (ddd), multiplet (m) and broad (b). Coupling constants (*J*) are reported in Hertz. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz on Bruker Nuclear Ascend 400 spectrometer. The chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Selenium-77 nuclear magnetic resonance spectra (^{77}Se NMR) were obtained at 76 MHz on Bruker Nuclear Ascend 400 spectrometer. The chemical shifts are reported in ppm, referenced to diphenyl diselenide as the external reference. The HRMS analyses were performed in a Bruker micrOTOF-QII spectrometer equipped with an APCI source operating in positive mode. The samples were solubilized in acetonitrile and analyzed by direct infusion at a constant flow rate of 180 μL/min. The acquisition parameters were capillary: 4000 V, end plate offset: -500 V, nebulizer: 1.5 bar, dry gas: 1.5 L min^{-1}, and dry heater: 180 °C. The collision cell energy was set to 5.0 eV. The mass-to-charge ratio (m/z) data were processed and analyzed using Bruker Daltonics softwares: Compass Data Analysis and Isotope Pattern.

5.2 Synthesis of arylseleninic acids (3a-f)[29]

In a round-bottomed flask were added diselenide, previously prepared (0.5 mmol), and DCM (3 mL). The resulting mixture was cooled with an ice bath (0 °C). Then, H_2O_2 (30% w/w, 3.0 equiv.) was added dropwise. The resulting mixture

was stirred at 0 °C until the formation of a white suspension, and the disappearance of the yellow solution. After, the solvent was evaporated, removing DCM and residual water, being the precipitate washed several times with hexanes and dried at the vacuum pump. The freshly dried white solid was directly employed in the next reaction step as substrate.

5.3 Synthesis of 4-selanylanilines (1a-n)

In a round-bottomed flask were added phenylseleninc acid **3** (0.3 mmol), aniline **4** (0.25 mmol), DMF (2 mL) and the mixture was stirred at 70 °C for the time indicated in Table 2. After this time, the reaction was received in water (20 mL), and was extracted with ethyl acetate (3 x 10 mL), dried over $MgSO_4$ and concentrated under vacuum. Then, the crude was purified by preparative thin layer chromatography using a mixture of hexane/ethyl acetate (97:3) as the eluent.

5.4 Synthesis of 3-selanylindoles (2a-e)

In a round-bottomed flask were added arylseleninc acid **3** (0.3 mmol), indole **5** (0.25 mmol), and DMF (2 mL). The resulting mixture was stirred at 70 °C for the time indicated in Table 3. After this time, the reaction was received in water (20 mL), and was extracted with ethyl acetate (3 x 10 mL), dried over $MgSO_4$, and concentrated under vacuum. Then, the crude was purified by preparative thin layer chromatography using a mixture of hexane/ethyl acetate (90:10) as the eluent.

5.5 Synthesis of *N*-(propargyl)amide derivatives (7a-l)[34]

In a round-bottomed flask were added the benzoyl chloride derivatives (0.5 mmol) and DCM (3.0 mL), followed by the addition of propargylamine (0.55 mmol) and triethylamine (0.65 mmol), being the resulting mixture cooled with an ice bath (0 °C). The reaction progress was monitored by TLC. After the consumption of the starting material, the reaction was quenched with a saturated NH_4Cl solution (10 mL), and with brine (10 mL), being extracted with ethyl acetate (3 x 10 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude mixture was purified by column chromatography using a mixture of hexane/ethyl acetate (50:50) as the eluent.

5.6 Synthesis of 2-substituted oxazoles-5-carbaldheydes (8a-l)

In a glass tube were added the amide derivatives **7** (0.3 mmol), arylseleninic acids **3** (0.45 mmol), eosin Y (5 mol%) and MeCN (1.0 mL). The resulting mixture was stirred at room temperature under white light irradiation (white LEDs 50 W) for 1 hour. After this time, the reaction was received in water (20 mL), extracted with ethyl acetate (3 x 10 mL), washed with brine (2 x 15 mL), dried over $MgSO_4$, and concentrated under vacuum. Then, the crude was purified by column chromatography using a mixture of hexane/ethyl acetate (90:10) as the eluent. To obtain the product **6l** was used 0.19 mmol of corresponding amide **7l** and 1.5 equiv. of BSA.

5.7 Physical and spectral data

N,N-dimethyl-4-(phenylselanyl)aniline (1a).[18b] Yield: 0.065 g (94%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.51 – 7.45 (m, 2H), 7.30 – 7.24 (m, 2H), 7.22 – 7.09 (m, 3H), 6.69 – 6.64 (m, 2H), 2.97 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 150.5, 137.1, 134.6, 129.8, 129.0, 125.8, 113.7, 113.2, 40.3.

N,N-diethyl-4-(phenylselanyl)aniline (1b).[18b] Yield: 0.087 g (95%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.48 – 7.42 (m, 2H), 7.31 – 7.26 (m, 2H), 7.21 – 7.09 (m, 3H), 3.36 (q, *J* = 7.0 Hz, 4H), 1.17 (t, *J* = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 147.9, 137.5, 134.8, 129.6, 128.9, 125.7, 112.4, 112.1, 44.3, 12.5.

N,N-dibutyl-4-(phenylselanyl)aniline (1c).[18b] Yield: 0.107 g (99%); brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.43 (d, *J* = 8.9 Hz, 2H), 7.32 – 7.25 (m, 2H), 7.21 – 7.08 (m, 3H), 6.57 (d, *J* = 8.9 Hz, 2H), 3.26 (t, *J* = 7.7 Hz, 4H), 1.62 – 1.51 (m, 4H), 1.35 (h, *J* = 7.4 Hz, 4H), 0.96 (t, *J* = 7.3 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 148.3, 137.4, 134.8, 129.6, 128.9, 125.7, 112.4, 111.9, 50.7, 29.3, 20.3, 14.0.

4-((4-chlorophenyl)selanyl)-N,N-dimethylaniline (1d).[18b] Yield: 0.056 g (60%); white solid, mp: 111 – 113 ºC (Lit.:[18b] 111 – 116 ºC). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.46 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz,

2H), 6.67 (d, *J* = 8.8 Hz, 2H), 2.98 (s, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 150.6, 137.1, 133.0, 131.8, 131.0, 129.0, 113.2, 40.2.

4-((4-chlorophenyl)selanyl)-N,N-diethylaniline (1e). Yield: 0.062 g (61%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.42 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 3.35 (q, *J* = 7.0 Hz, 4H), 1.17 (t, *J* = 7.0 Hz, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 148.1, 137.5, 133.2, 131.6, 130.8, 129.0, 112.4, 111.7, 44.3, 12.5. HRMS (APCI-QTOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{19}ClNSe$, 340.0364; found, 340.0352.

N,N-dibutyl-4-((4-chlorophenyl)selanyl)aniline (1f). Yield: 0.054 g (55%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.41 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 6.57 (d, *J* = 8.4 Hz, 2H), 3.26 (t, *J* = 7.7 Hz, 4H), 1.63 – 1.51 (m, 4H), 1.35 (sex, *J* = 7.4 Hz, 4H), 0.96 (t, *J* = 7.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 148.5, 137.4, 133.2, 131.6, 130.9, 129.0, 112.4, 111.5, 50.7, 29.3, 20.3, 14.0. HRMS (APCI-QTOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{27}ClNSe$, 396.0990; found, 396.0998.

4-((4-fluorophenyl)selanyl)-N,N-dimethylaniline (1g).[18b] Yield: 0.064 g (88%); white solid, mp: 50 – 55 ºC (Lit.:[18b] 49 – 52 ºC). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.45 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.23 (m, 2H), 6.93 – 6.86 (m, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 2.96 (s, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 161.7 (d, *J* = 245,1 Hz), 150.5, 136.6, 132.1 (d, *J* = 7.5 Hz,), 128.6 (d, *J* = 3.2 Hz), 116.1 (d, *J* = 21.5 Hz), 114.3, 113.2, 40.3.

N,N-dimethyl-4-((3-(trifluoromethyl)phenyl)selanyl)aniline (1h).[18b] Yield: 0.076 g (88%); light yellow solid, mp: 45 – 47 ºC (Lit.:[18b] 48 – 52 ºC). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.52 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.40 – 7.32 (m, 2H), 7.28 – 7.21 (m, 1H), 6.67 (d, *J* = 8.8 Hz, 2H), 2.98 (s, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 150.8, 137.5, 136.3, 132.5, 131.1 (q, $J_{C\text{-}F}$ = 32.2 Hz), 129.1, 125.8 (q, $J_{C\text{-}F}$ = 3.9 Hz), 123.8 (q, $J_{C\text{-}F}$ = 270,5 Hz), 122.4 (q, $J_{C\text{-}F}$ = 3.9 Hz), 119.8, 113.2, 112.2, 39.4.

N,N-diethyl-4-((3-(trifluoromethyl)phenyl)selanyl)aniline (1i). Yield: 0.075 g (79%); yellow solid, mp: 47 – 50 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.53 (s, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.40 – 7.33 (m, 2H), 7.29 – 7.22 (m, 1H), 6.63 (d, *J*

= 8.7 Hz, 2H), 3.37 (q, *J* = 7.1 Hz, 4H), 1.18 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 148.3, 137.8, 136.5, 132.4, 131.1 (q, J_{C-F} = 32.0 Hz), 129.1, 125.7 (q, J_{C-F} = 3.8 Hz), 123.8 (q, J_{C-F} = 270.9 Hz), 122.3 (q, J_{C-F} = 3.7 Hz), 112.5, 110.7, 44.3, 12.5. HRMS (APCI-QTOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{19}F_3NSe$, 374.0630; found, 374.0627.

N,N-dimethyl-4-(p-tolylselanyl)aniline (1j).[18c] Yield: 0.058 g (80%); brown solid, mp: 60 – 65 ºC (Lit.:[18c] 67 – 69 ºC). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.45 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 2.95 (s, 6H), 2.27 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 150.3, 136.5, 135.8, 130.5, 130.3, 129.8, 114.6, 113.1, 40.3, 20.9.

N,N-diethyl-4-(p-tolylselanyl)aniline (1k). Yield: 0.056 g (71%); green oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.42 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 3.35 (q, *J* = 7.0 Hz, 4H), 2.27 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 147.8, 136.9, 135.7, 130.4, 129.8, 129.2, 113.0, 112.4, 44.3, 21.0, 12.5. HRMS (APCI-QTOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{22}NSe$, 320.0823; found, 320.0828.

N,N-dibutyl-4-(p-tolylselanyl)aniline (1l). Yield: 0.062 g (67%); brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.42 (d, *J* = 8.9 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 8.9 Hz, 2H), 3.29 – 3.21 (m, 4H), 2.27 (s, 3H), 1.61 – 1.50 (m, 6H), 1.40 – 1.29 (m, 4H), 0.95 (t, *J* = 7.3 Hz, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 148.2, 136.8, 135.7, 130.4, 129.8, 112.8, 112.4, 50.7, 29.3, 21.0, 20.3, 14.0. HRMS (APCI-QTOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{30}NSe$, 376.1469; found, 376.1472.

4-(mesitylselanyl)-N,N-dimethylaniline (1m).[18b] Yield: 0.049 g (60%); brown solid, mp: 57-60 °C (Lit.:[18b] 56 – 59 ºC). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.06 (d, *J* = 8.8 Hz, 2H), 6.94 (s, 2H), 6.57 (d, *J* = 8.8 Hz, 2H), 2.88 (s, 6H), 2.46 (s, 6H), 2.27 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 149.1, 143.1, 138.3, 131.2, 128.6, 118.1, 113.6, 40.5, 24.4, 21.0.

N,N-diethyl-4-(mesitylselanyl)aniline (1n). Yield: 0.049 g (57%); green oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.05 (d, *J* = 8.8 Hz, 2H), 6.93 (s, 2H), 6.50 (d, *J* = 8.8 Hz, 2H), 3.26 (q, *J* = 7.1 Hz, 4H), 2.47 (s, 6H), 2.26 (s, 3H), 1.10 (t, *J* = 7.1

Hz, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 146.4, 143.1, 138.2, 131.8, 128.6, 116.4, 112.9, 44.3, 24.4, 21.0, 12.5. HRMS (APCI-QTOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{26}NSe$, 348.1156; found, 348.1160.

3-(phenylselanyl)-1H-indole (2a).[18f] Yield: 0.041 g (60%); white solid, mp: 149 – 151 °C (Lit.:[18f] 150 – 151 ºC). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.42 (br, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.30 – 7.04 (m, 7H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 136.4, 133.8, 131.2, 130.0, 128.9, 128.6, 125.6, 122.9, 120.8, 120.4, 111.3, 98.2.

3-((4-fluorophenyl)selanyl)-1H-indole (2b).[18f] Yield: 0.044 g (61%); white solid, mp: 130-132 °C (Lit.:[18f] 134 – 137 ºC). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.40 (br, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.29 – 7.14 (m, 4H), 6.87 – 6.79 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 161.5 (d, $J_{C\text{-}F}$ = 244.6 Hz), 136.4, 131.0, 130.7 (d, $J_{C\text{-}F}$ = 7.6 Hz), 129.7, 127.9 (d, $J_{C\text{-}F}$ = 3.1 Hz), 123.0, 120.9, 120.2, 116.0 (d, $J_{C\text{-}F}$ = 21.5 Hz), 111.4, 98.6.

3-((3-(trifluoromethyl)phenyl)selanyl)-1H-indole (2c).[18f] Yield: 0.062 g (73%), white solid, mp: 75 – 80 °C (Lit.:[18f] 70-71 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.46 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.53 (s, 1H), 7.48 (d, *J* = 2.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.14 (m, 5H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 136.4, 135.2, 131.7, 131.5, 131.1 (q, $J_{C\text{-}F}$ = 32.2 Hz) 129.6, 129.2, 125.1 (q, $J_{C\text{-}F}$ = 4.0 Hz), 123.2, 124.4 (q, $J_{C\text{-}F}$ = 4.0 Hz), 121.1, 120.1, 111.5, 97.2.

3-(p-tolylselanyl)-1H-indole (2d).[18g] Yield: 0.040 g (56%); white solid, mp: 122 – 126 °C (Lit.:[18g] 124 – 126 ºC). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.32 (br, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.27 – 7.20 (m, 1H), 7.19 – 7.12 (m, 3H), 6.94 (d, *J* = 7.9 Hz, 2H), 2.22 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 136.3, 135.5, 130.9, 129.9, 129.7, 129.0, 122.8, 120.7, 120.3, 111.3, 98.6, 20.9.

3-(mesitylselanyl)-1H-indole (2e).[18g] Yield: 0.031 g (40%); white solid, mp: 135 – 140 °C (Lit.:[18g] 135-137 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.17 (br, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.20 – 7.14 (m, 2H), 7.13 – 7.07 (m, 1H), 6.87 (s, 2H), 2.56 (s, 6H), 2.22 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz)

δ (ppm) 142.5, 137.8, 136.1, 129.6, 128.7, 128.6, 127.9, 122.4, 120.2, 120.2, 111.1, 101.1, 24.5, 20.9.

2-phenyloxazole-5-carbaldehyde (8a).[42] Yield: 0.041 g (79%); pale white solid; mp: 57–62 °C (Lit.:[42] 71–73 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.83 (s, 1H), 8.22–8.16 (m, 2H), 7.96 (s, 1H), 7.60–7.48 (m, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ (ppm) 177.0, 165.0, 147.6, 138.3, 132.3, 129.1, 127.7, 125.9.

2-(4-chlorophenyl)oxazole-5-carbaldehyde (8b).[42] Yield: 0.053 g (85%); pale white solid; mp: 136–138 °C (Lit.:[42] 136–138 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.83 (s, 1H), 8.12 (d, J = 8.6 Hz, 2H), 7.94 (s, 1H), 7.50 (d, J = 8.6 Hz, 2H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ (ppm) 174.7, 163.0, 150.4, 139.0, 138.7, 129.5, 127.9, 124.3.

2-(2-chlorophenyl)oxazole-5-carbaldehyde (8c).[42] Yield: 0.056 g (90%); pale yellow solid; mp: 58–61 °C (Lit.:[42] 75–77 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.88 (s, 1H), 8.13 (dd, J = 7.7, 1.8 Hz, 1H), 8.02 (s, 1H), 7.60–7.37 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ (ppm) 177.0, 163.2, 152.2, 138.7, 133.5, 132.6, 131.6, 131.6, 127.0, 124.1.

2-(4-bromophenyl)oxazole-5-carbaldehyde (8d).[42] Yield: 0.030 g (40%); white solid; mp: 148–151 °C (Lit.:[42] 140–142 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.83 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.95 (s, 1H), 7.66 (d, J = 8.6 Hz, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ (ppm) 176.2, 164.5, 149.7, 139.0, 132.4, 129.0, 127.2, 124.7.

2-(2-bromophenyl)oxazole-5-carbaldehyde (8e). Yield: 0.034 g (45%); pale yellow solid; mp: 62–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.88 (s, 1H), 8.07 (dd, J = 7.8, 1.8 Hz, 1H), 8.02 (s, 1H), 7.77 (dd, J = 8.0, 1.3 Hz, 1H), 7.50–7.43 (m, 1H), 7.42–7.35 (m, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ (ppm) 176.5, 163.6, 149.6, 137.7, 134.9, 132.6, 132.0, 127.6, 126.8, 121.7. HRMS (APCIQTOF) m/z: [M+H]+ calcd for $C10H_6BrNO_2$, 251.9654; found, 251.9651. FTIR (KBr) $\bar{\nu}$ (cm^{-1}): 3445, 3320, 2925, 2871, 1760, 1678, 1580, 1517, 1464, 1329, 1150.

2-(2-iodophenyl)oxazole-5-carbaldehyde (8f). Yield: 0.068 g (77%); pale white solid; mp: 72–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.88 (s, 1H), 8.09 (dd,

J = 8.0, 1.2 Hz, 1H), 8.03 (s, 1H), 7.99 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.53–7.46 (m, 1H), 7.24–7.16 (m, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) *δ* (ppm) 176.5, 164.3, 149.6, 141.9, 137.6, 132.5, 131.6, 130.3, 128.2, 94.0. HRMS (APCIQTOF) m/z: [M+H]+ calcd for $C_{10}H_6INO_2$, 299.9516; found, 299.9511. FTIR (KBr) $\bar{\nu}$ (cm^{-1}): 3455, 2915, 2853, 1677, 1571, 1515, 1462, 1337, 1223, 1146, 1008.

2-(4-nitrophenyl)oxazole-5-carbaldehyde (8g).[43] Yield: 0.055 g (84%); orange solid; mp: 118–122 °C (Lit.:[43] 119–121 ºC). ^1H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 9.89 (s, 1H), 8.41–8.35 (m, 4H), 8.03 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) *δ* (ppm) 177.5, 162.9, 150.2, 149.8, 138.6, 131.2, 128.5, 124.3.

2-(2-nitrophenyl)oxazole-5-carbaldehyde (8h). Yield: 0.033 g (50%); pale yellow solid; mp: 98–103 °C. ^1H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 9.85 (s, 1H), 8.07–8.02 (m, 1H), 7.98 (s, 1H), 7.92–7.87 (m, 1H), 7.79–7.69 (m, 2H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) *δ* (ppm) 176.5, 160.8, 150.2, 137.7, 132.6, 132.5, 131.0, 124.3, 120.0. HRMS (APCIQTOF) m/z: [M+H]+ calcd for $C_{10}H_6N_2O_4$, 219.0400; found, 219.0397. FTIR (KBr) $\bar{\nu}$ (cm^{-1}): 3437, 3108, 3135, 2920, 2848, 1737, 1683, 1522, 1351, 1244, 1145, 1100.

2-(3,4-dimethoxyphenyl)oxazole-5-carbaldehyde (8i). Yield: 0.053 g (75%); pale white solid; mp: 158–163 °C. ^1H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 9.78 (s, 1H), 7.93 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 4.05–3.89 (m, 6H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) *δ* (ppm) 175.9, 165.6, 152.6, 149.3, 149.2, 139.6, 121.6, 118.4, 111.1, 109.9, 56.1, 56.0. HRMS (APCIQTOF) m/z: [M+H]+ calcd for $C_{12}H_{11}NO_4$, 234.0760; found, 234.0755. FTIR (KBr) $\bar{\nu}$ (cm^{-1}): 3431, 3126 3090, 2928, 2848, 1682, 1593, 1557, 1485, 1333, 1144, 1073, 1019.

2-(2-bromo-5-methoxyphenyl)oxazole-5-carbaldehyde (8j). Yield: 0.064 g (76%); orange solid; mp: 93–98 °C. ^1H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 9.88 (s, 1H), 8.02 (s, 1H), 7.67–7.60 (m, 1H), 7.58 (d, *J* = 3.3 Hz, 1H), 6.95 (dd, *J* = 8.8, 3.3 Hz, 1H), 3.87 (s, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) *δ* (ppm) 176.6, 163.5, 158.8, 149.6, 137.2, 135.7, 127.2, 119.5, 116.3, 112.1, 55.7. HRMS (APCIQTOF) m/z: [M+H]+ calcd for $C_{11}H_8BrNO_3$, 281.9760; found, 281.9755. FTIR (KBr) $\bar{\nu}$ (cm^{-1}): 3443, 2923, 2851, 1748, 1668, 1551, 1336, 1148, 1094, 1031.

2-(furan-2-yl)oxazole-5-carbaldehyde (8k).[43] Yield: 0.030 g (60%); dark orange solid; mp: 137–140 °C (Lit.:[43] 138–140 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.81 (s, 1H), 7.94 (s, 1H), 7.68 (d, *J* = 1.0 Hz, 1H), 7.31 (dd, *J* = 0.4, 3.5 Hz, 1H), 6.63 (dd, *J* = 1.8, 3,5 Hz, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ (ppm) 176.0, 157.5, 148.9, 146.5, 141.5, 138.8, 115.6, 112.6.

2-(pyridin-3-yl)oxazole-5-carbaldehyde (8l). Yield: 0.010 g (30%); pale white solid; mp: 130-133°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.94 (s, 1H), 8.82 (d, *J* = 6.4 Hz, 1H), 8.27 (d, *J* = 7.9 Hz, 1H), 8.02 (s, 1H), 7.90 (td, *J* = 7.8, 2.0 Hz, 1H), 7.49 (dd, *J* = 7.8, 4.7 Hz, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ (ppm) 177.1, 163.2, 150.6, 150.2, 144.8, 137.7, 126.1, 123.6. FTIR (KBr) $\bar{\nu}$ (cm^{-1}): 3440, 3117, 3072, 2920, 2857, 1727, 1691, 1557, 1530, 1440, 1261, 1189, 1082, 1028 .

6. References

6. References

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7. Selected spectra

7. Selected spectra

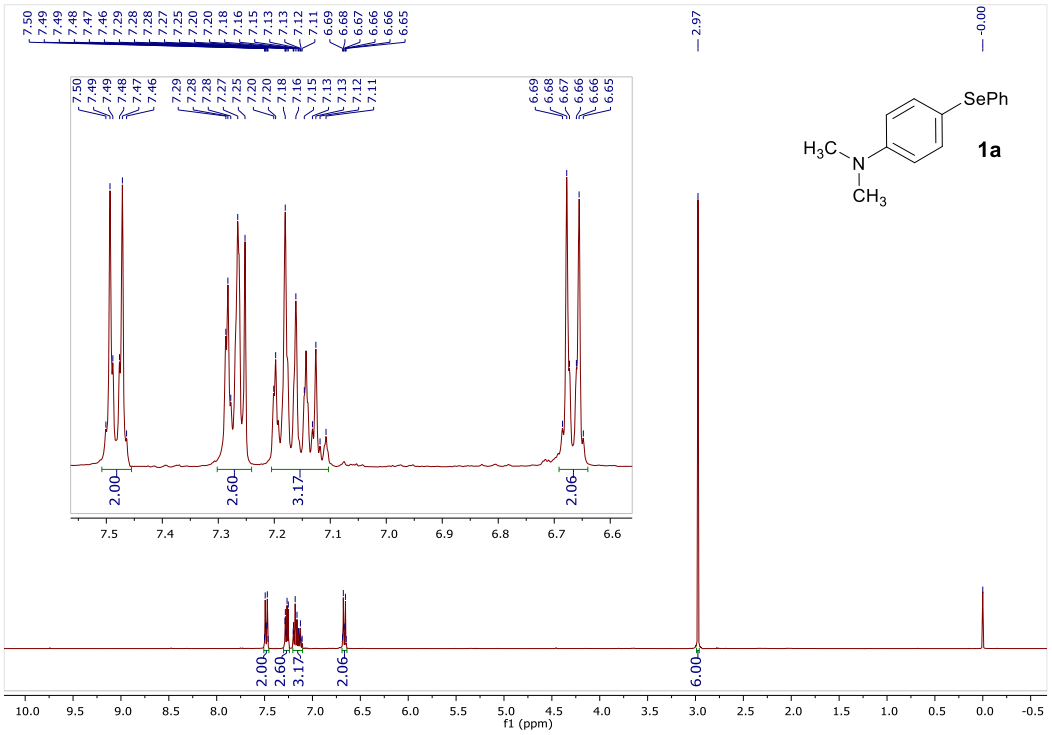

Figure 22. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1a**.

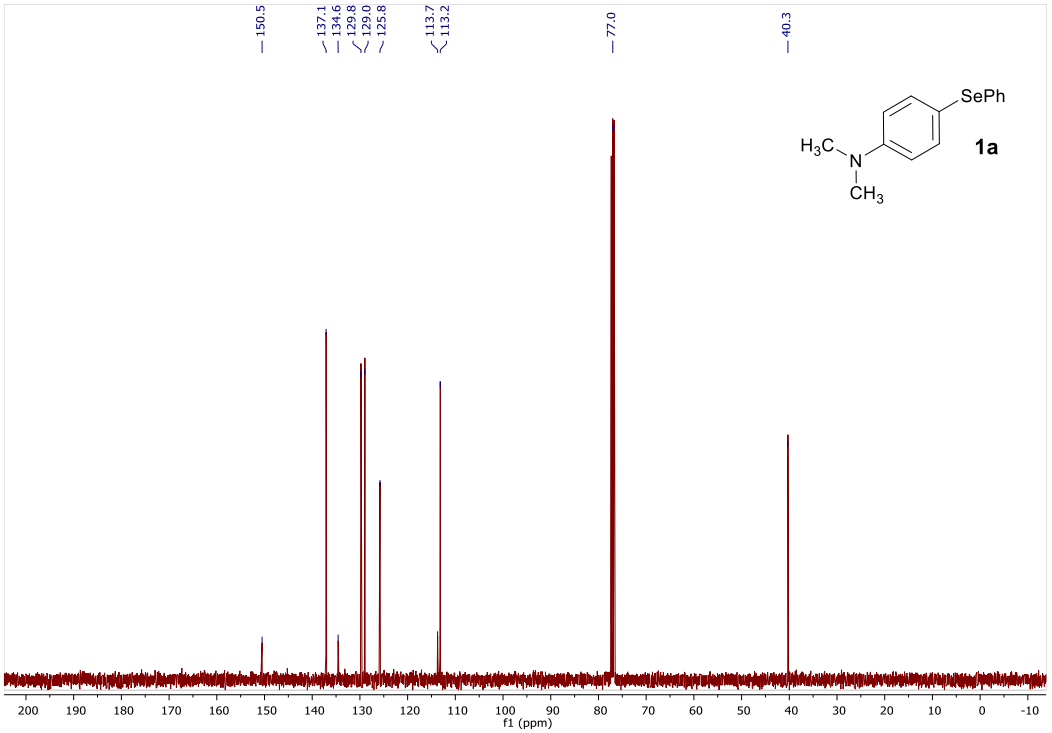

Figure 23. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1a**.

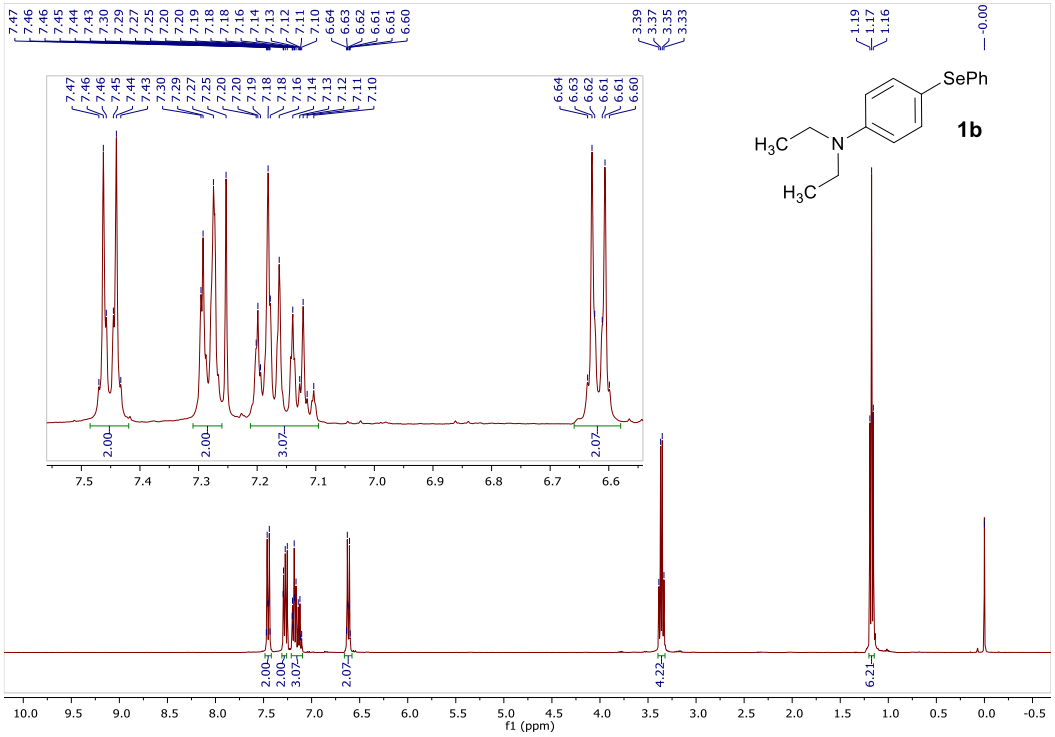

Figure 24. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1b**.

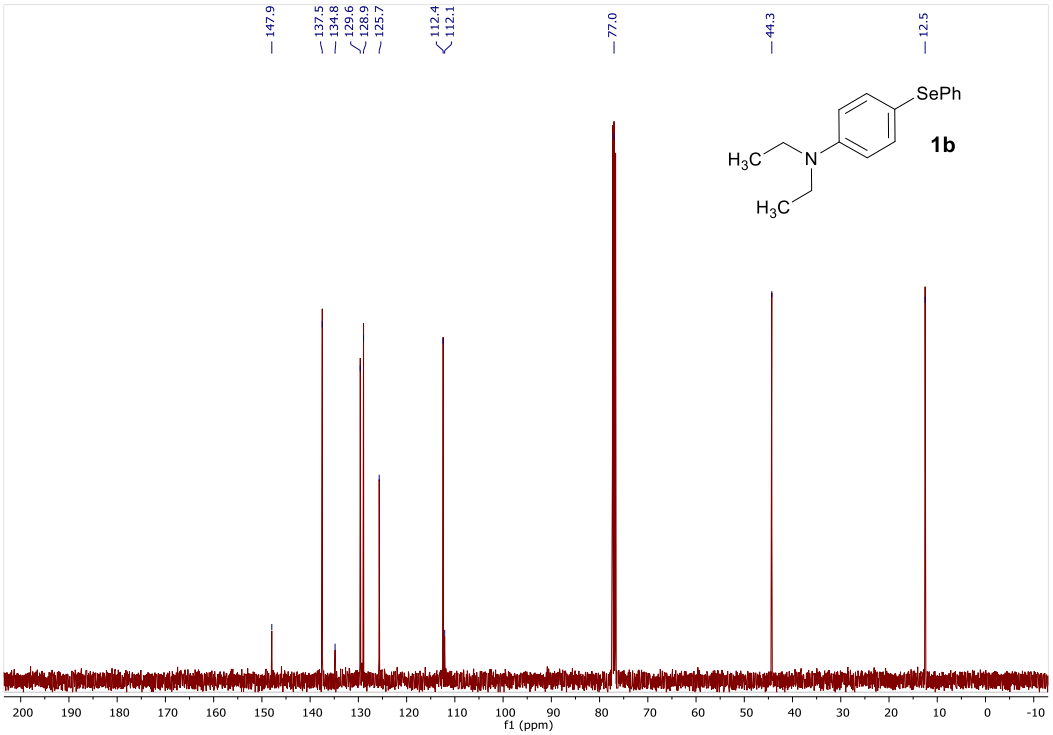

Figure 25. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1b**.

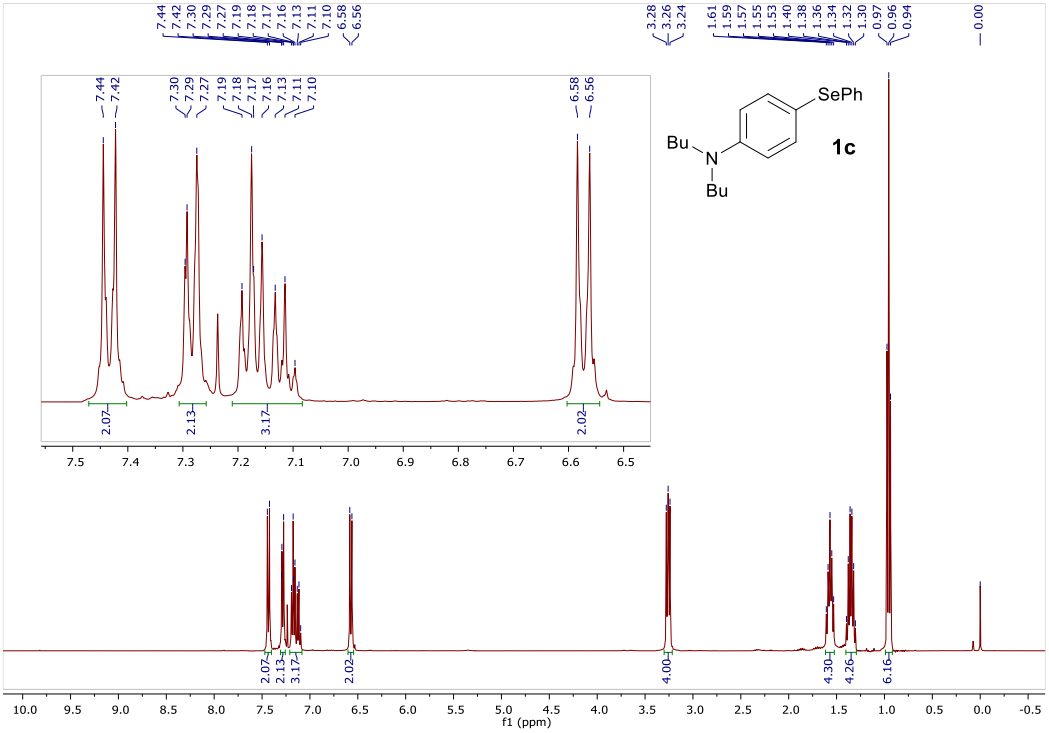

Figure 26. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1c**.

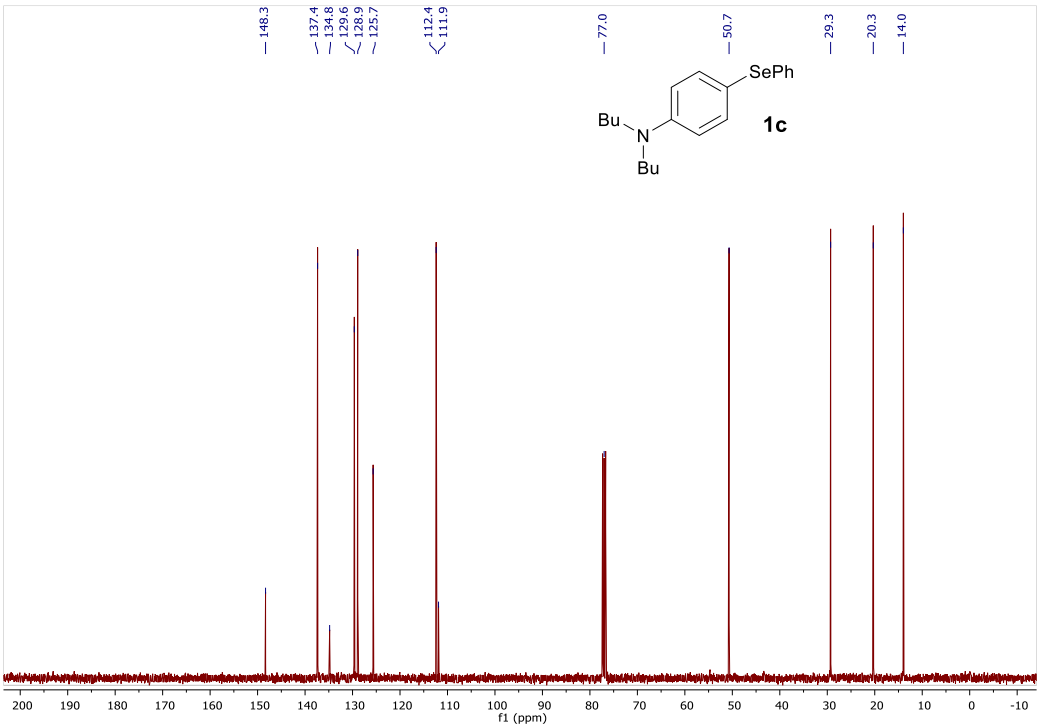

Figure 27. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1c**.

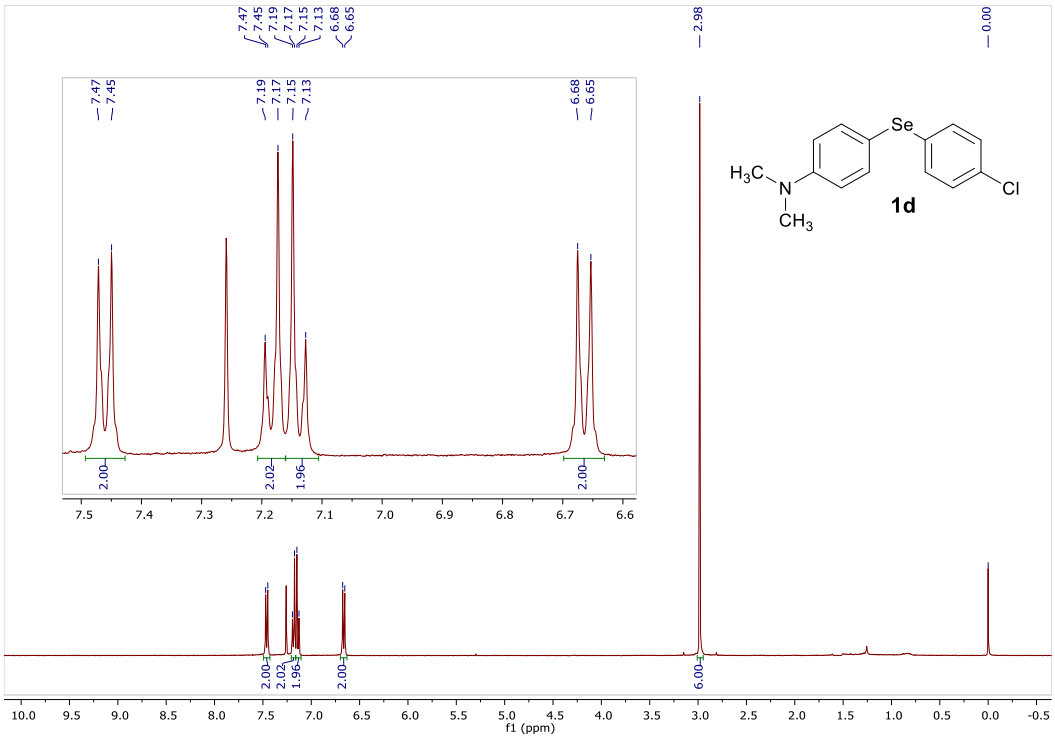

Figure 28. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1d**.

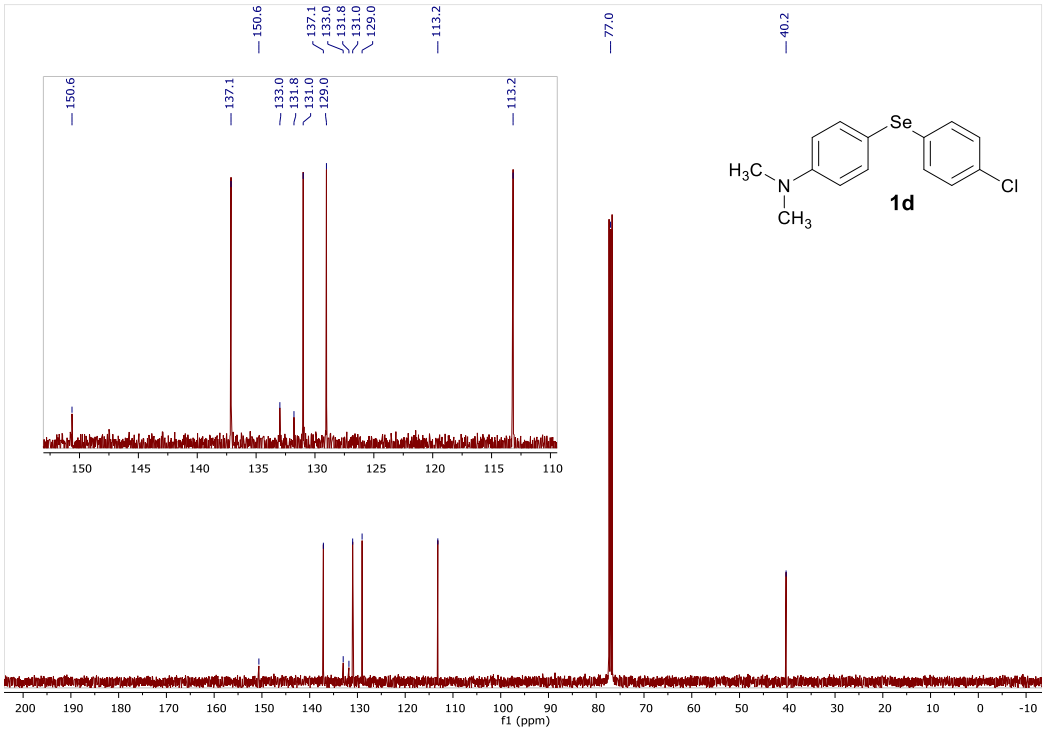

Figure 29. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1d**.

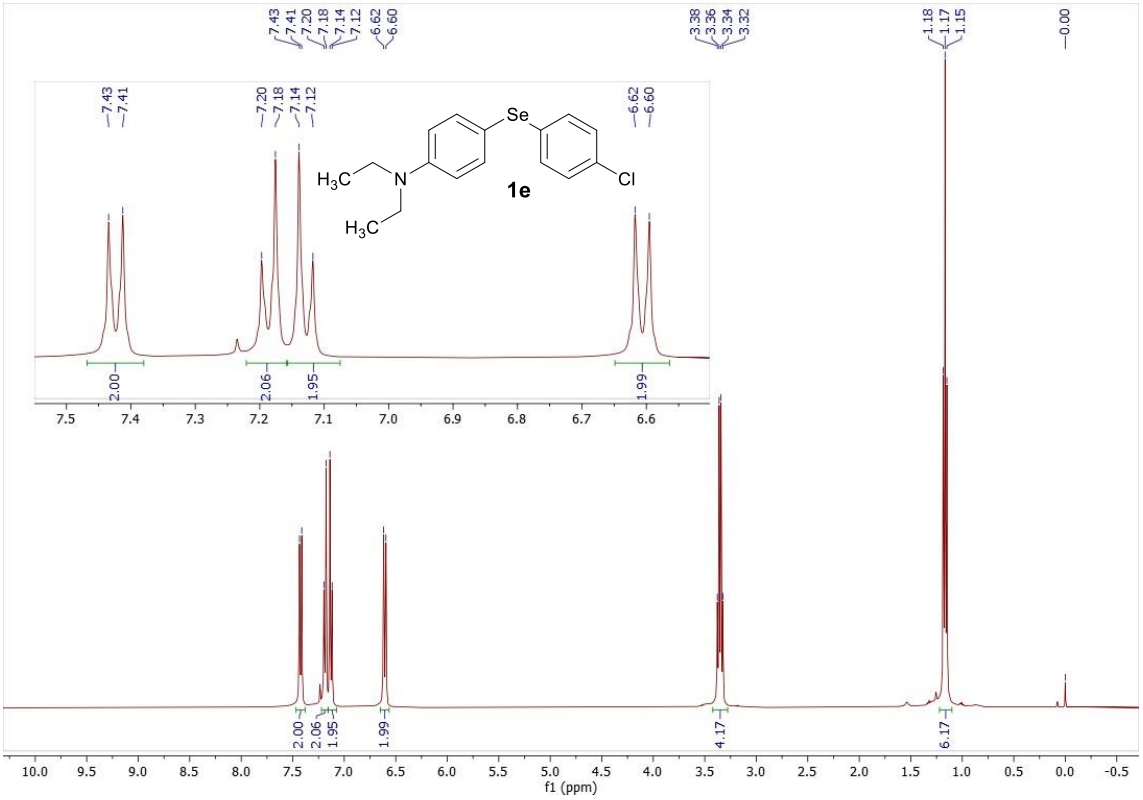

Figure 30. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1e**.

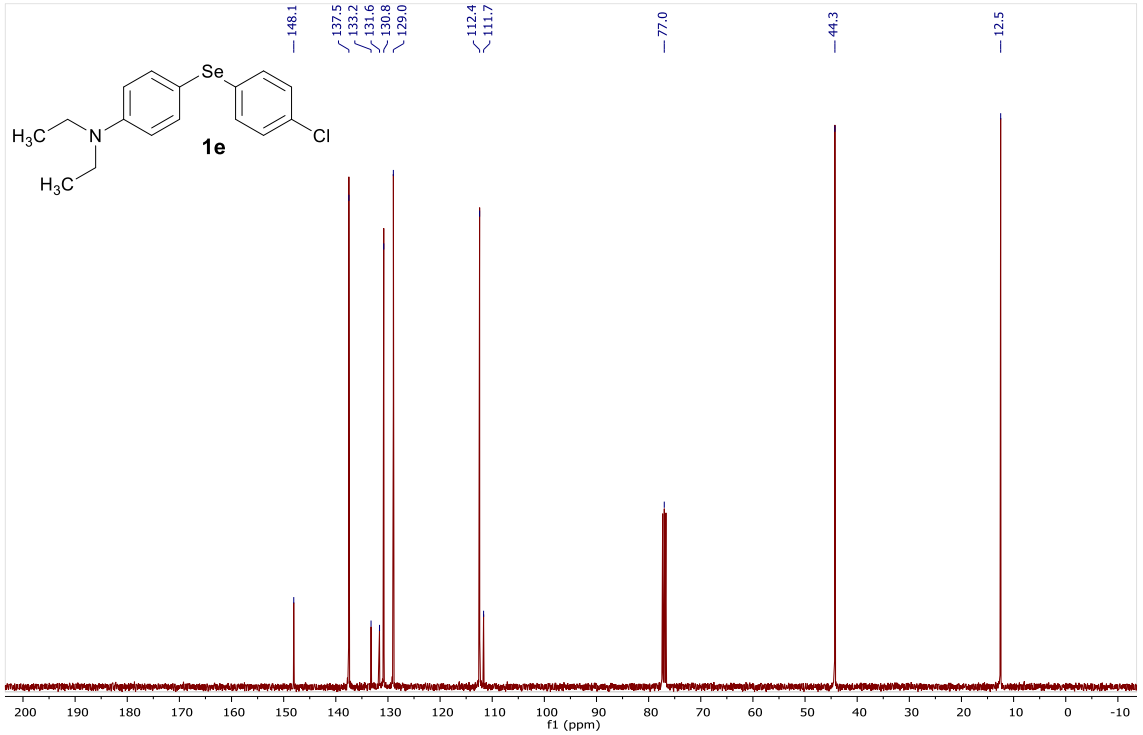

Figure 31. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1e**.

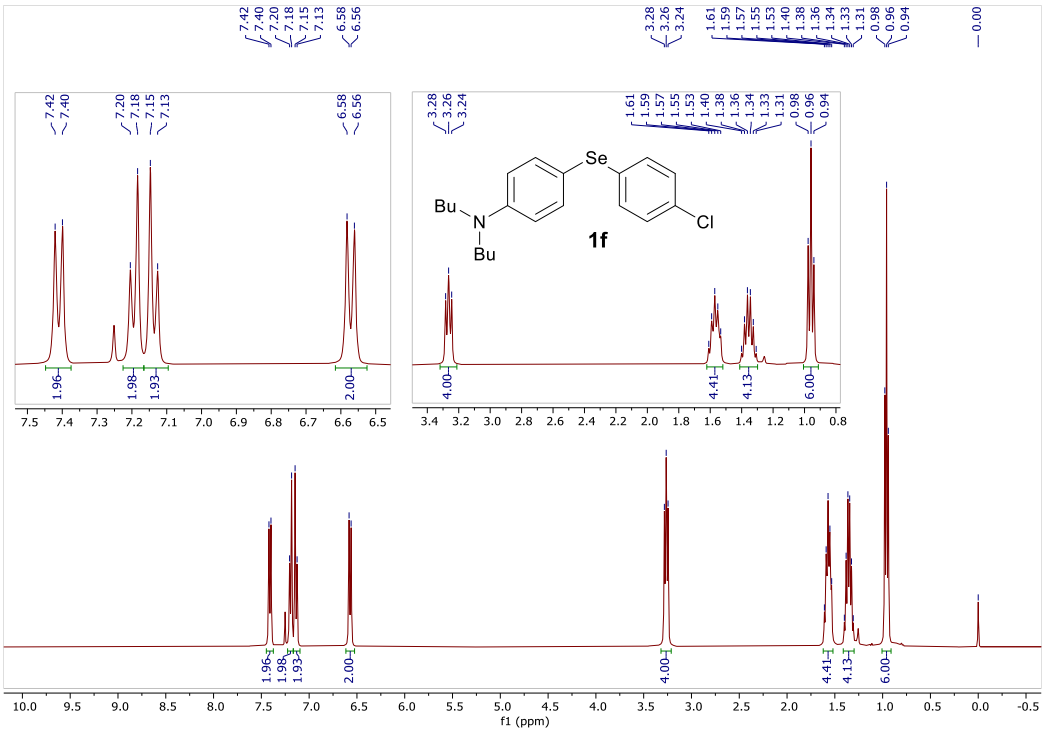

Figure 32. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1f**.

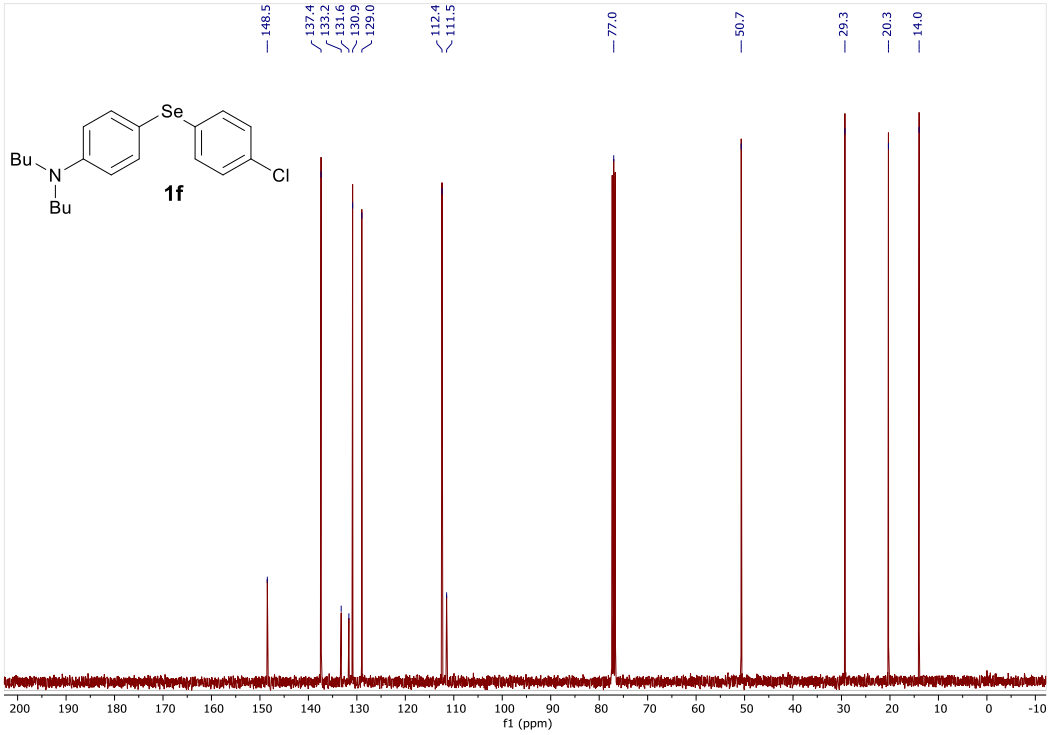

Figure 33. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1f**.

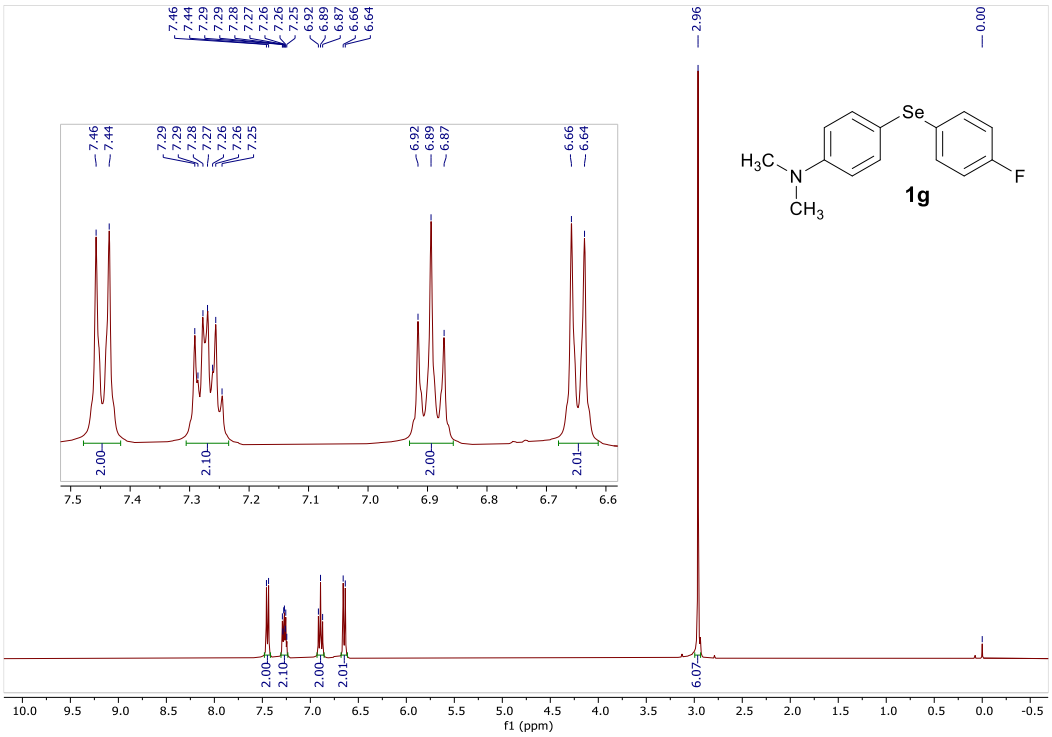

Figure 34. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1g**.

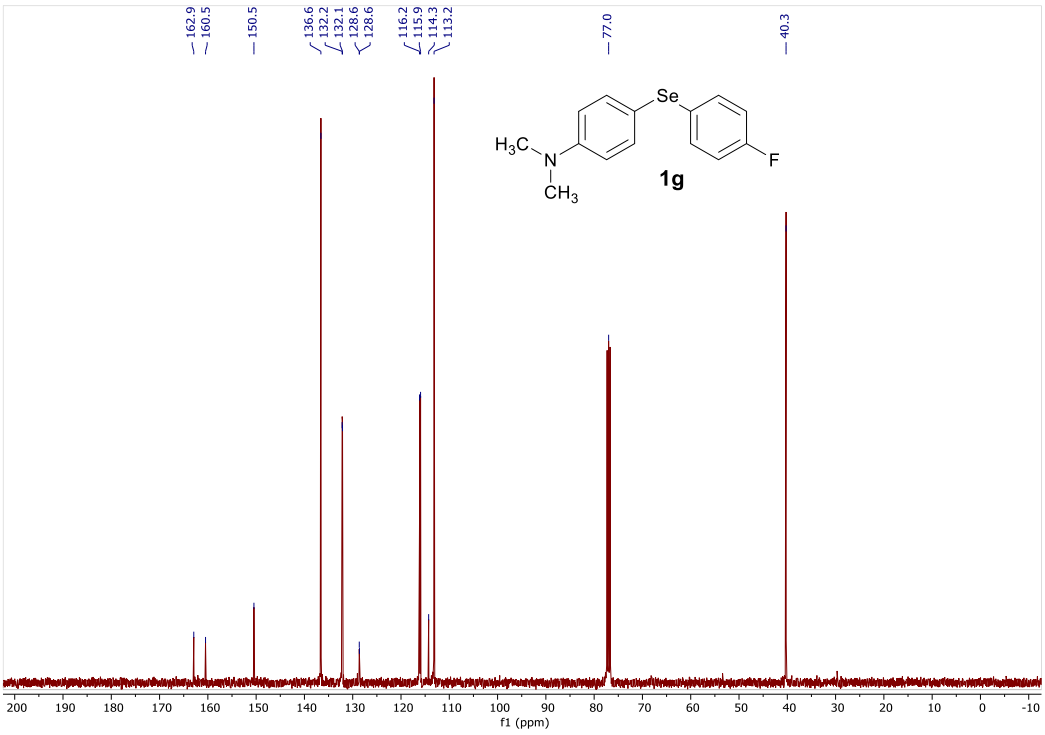

Figure 35. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1g**.

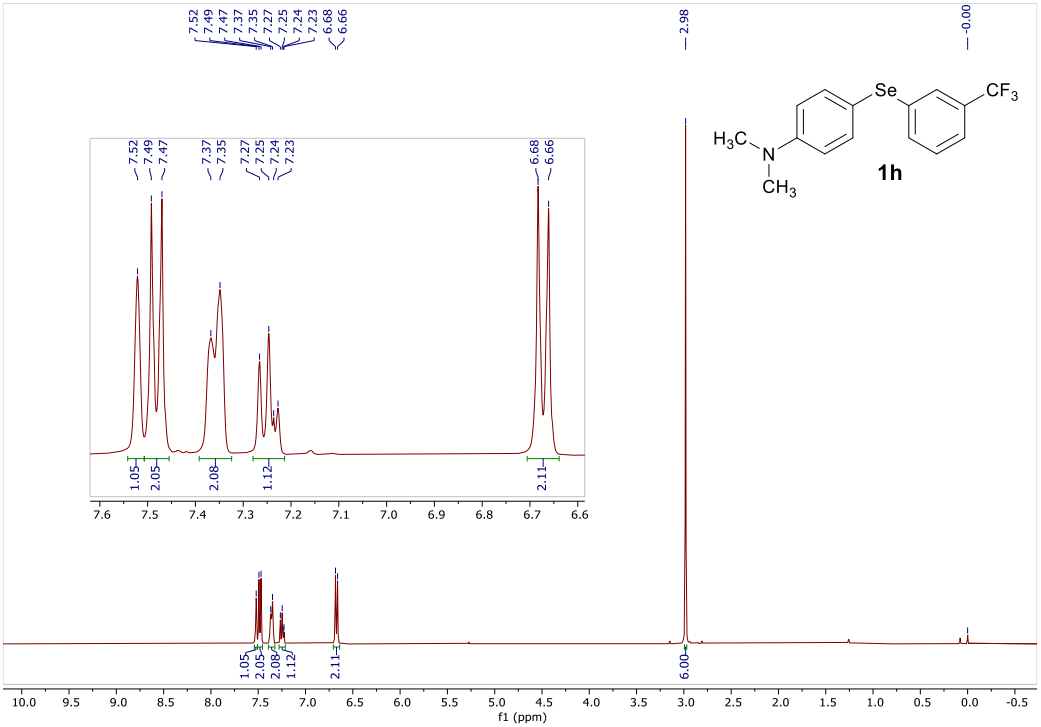

Figure 36. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1h**.

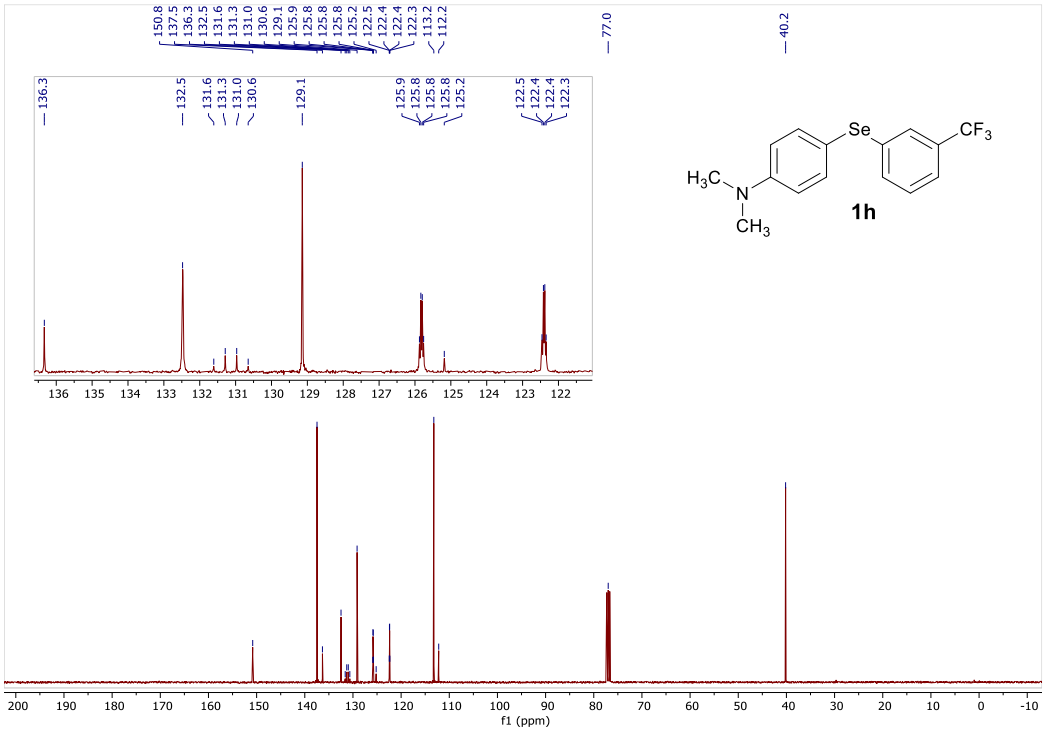

Figure 37. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1h**.

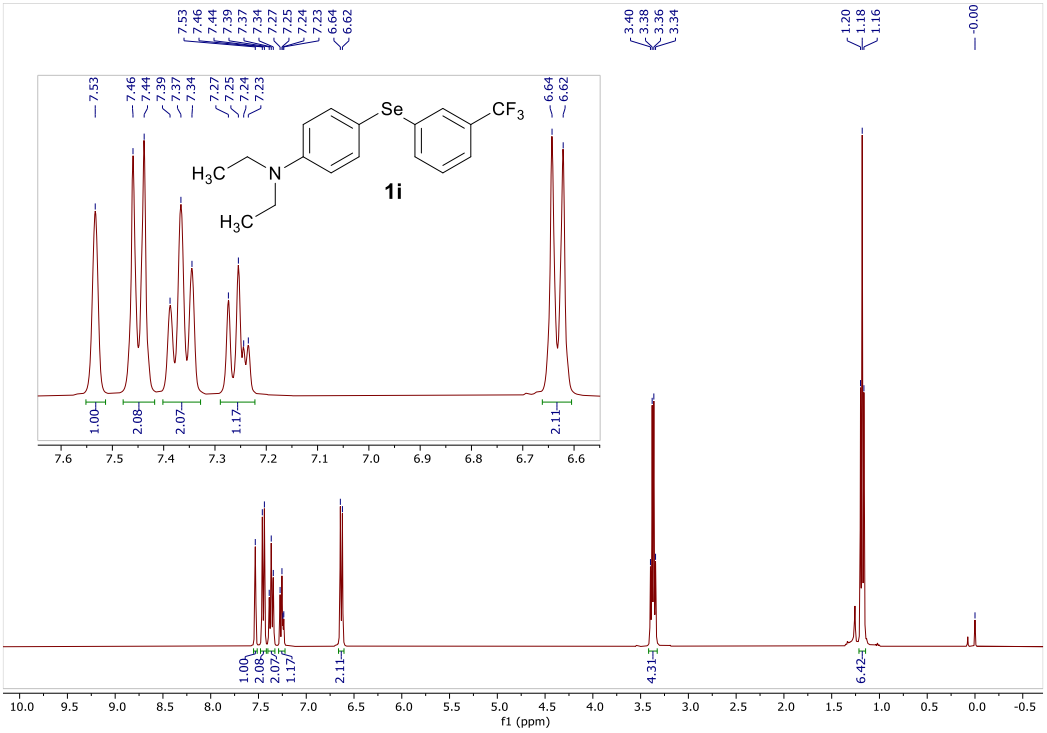

Figure 38. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1i**.

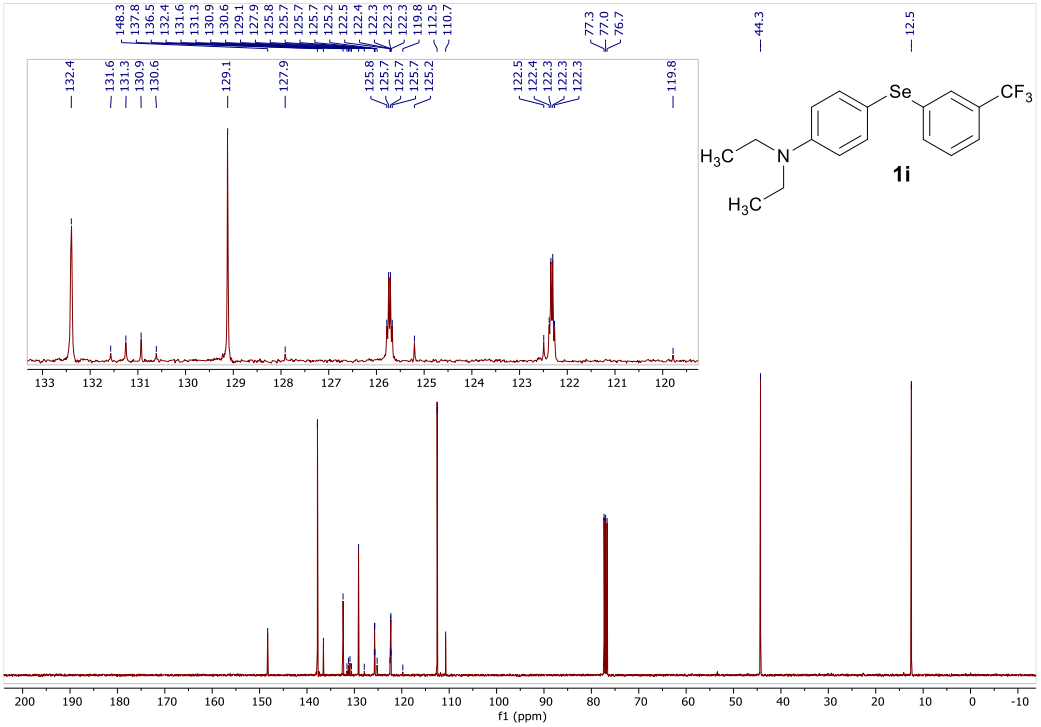

Figure 39. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1i**.

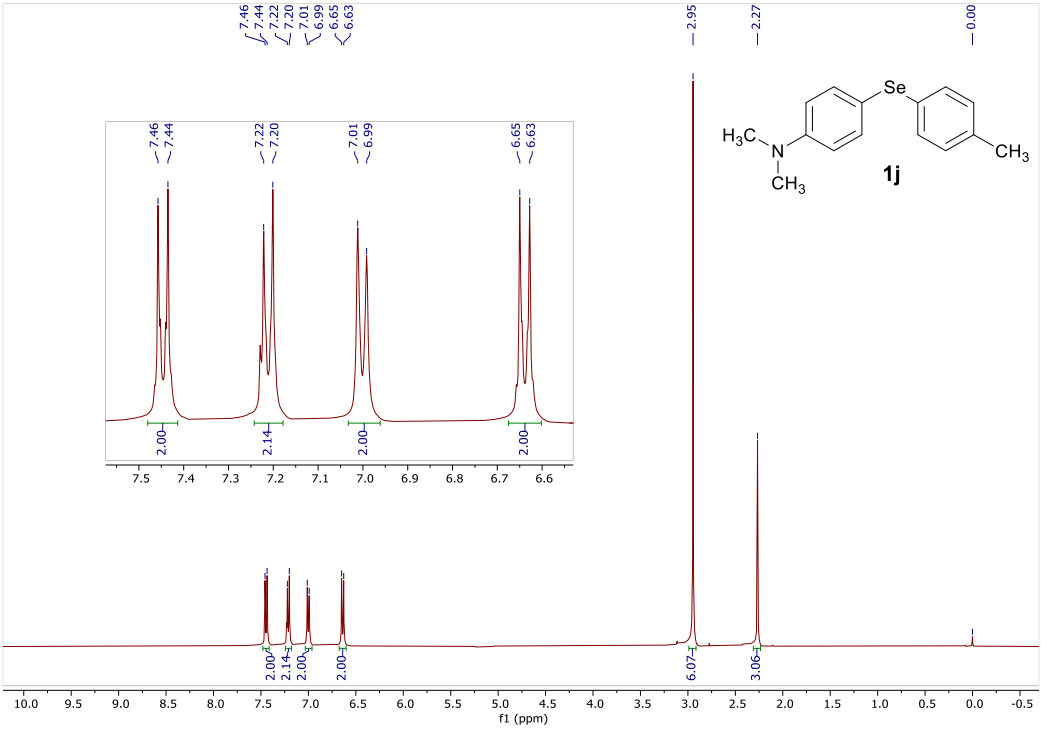

Figure 40. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1j**.

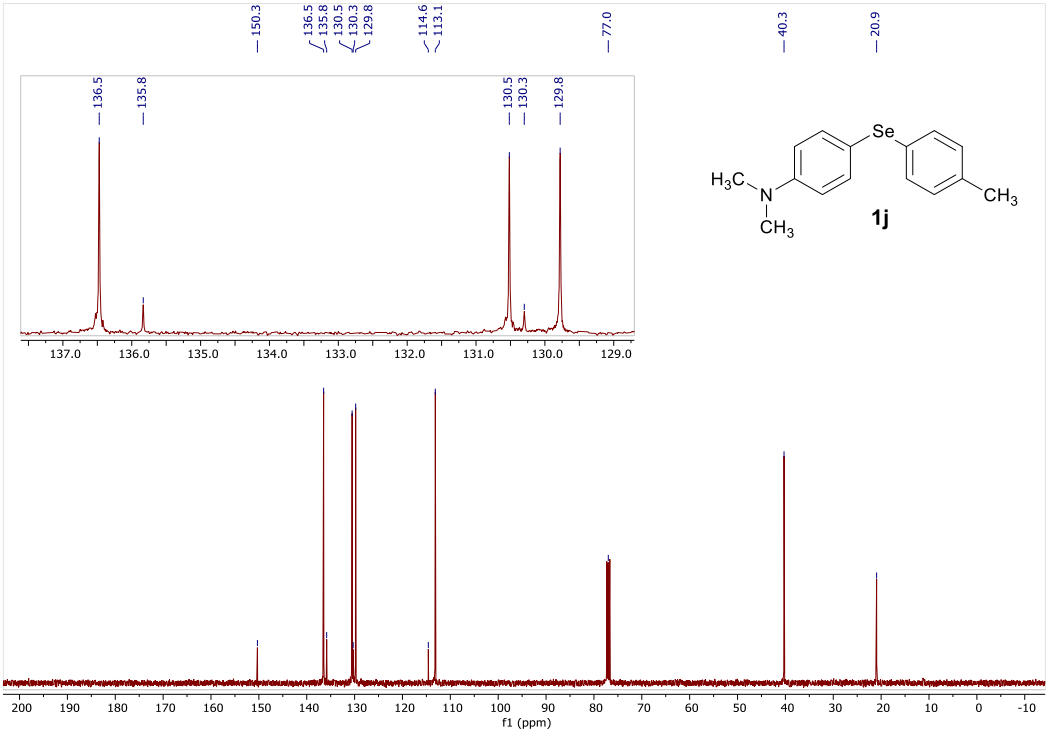

Figure 41. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1j**.

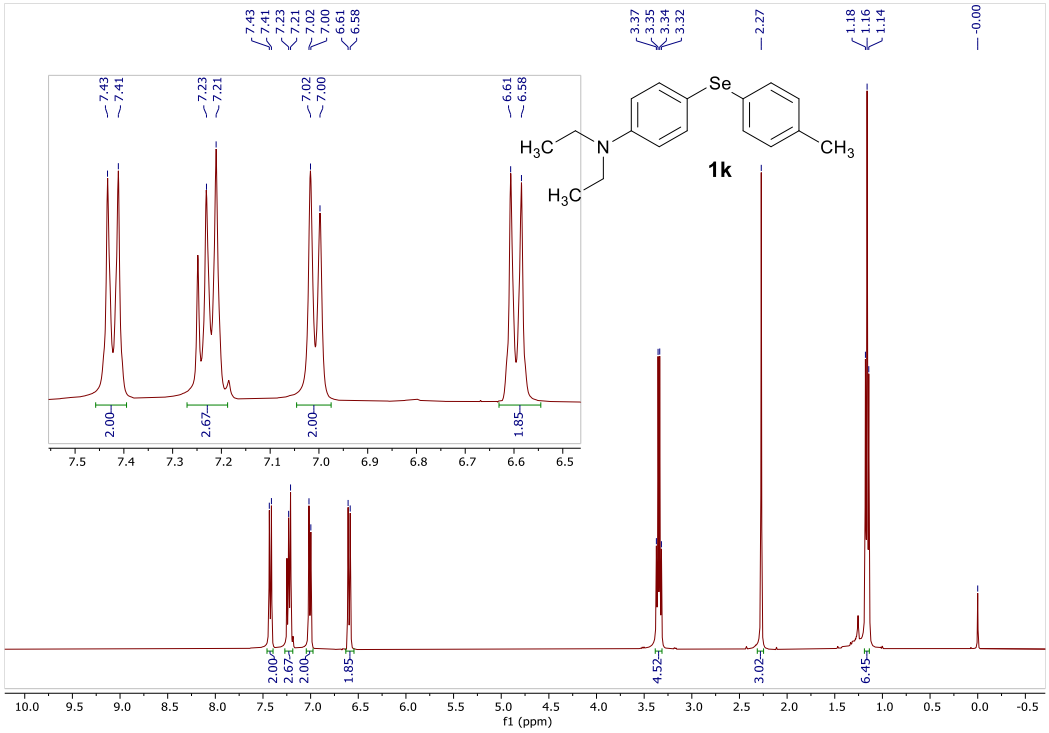

Figure 42. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1k**.

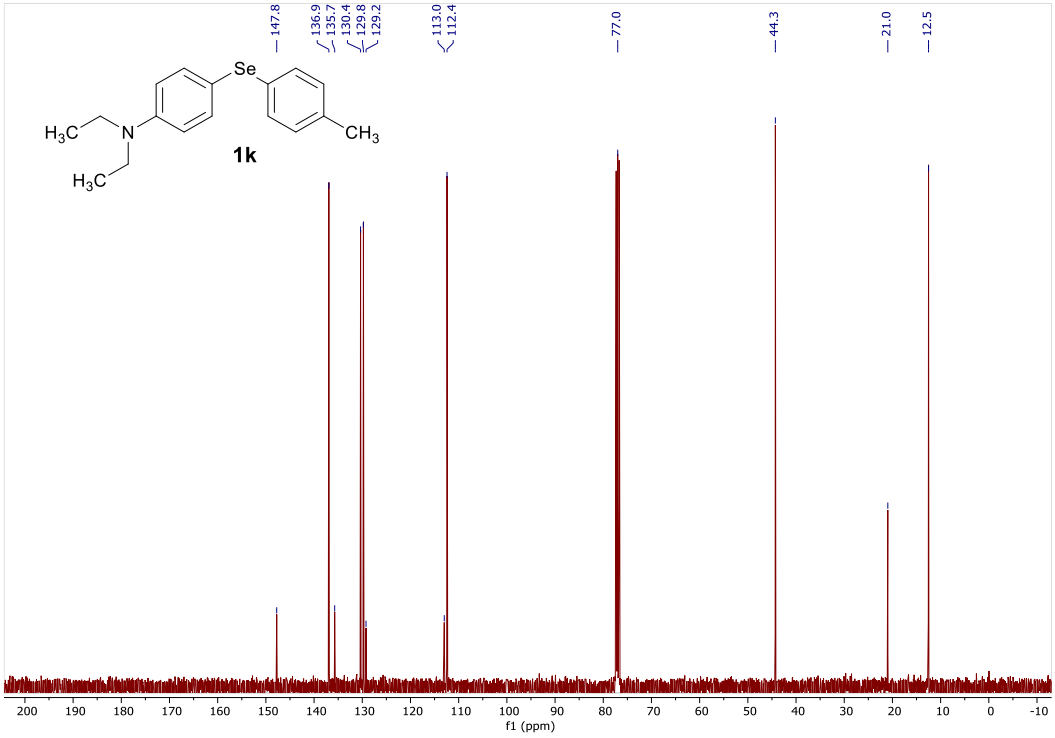

Figure 43. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1k**.

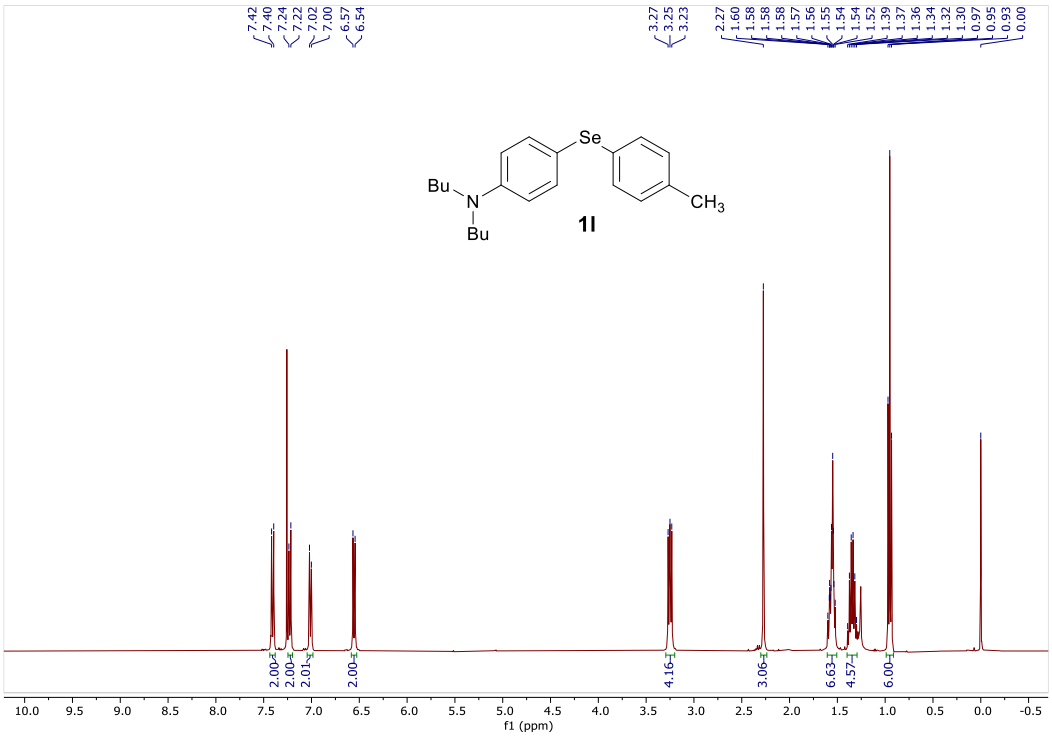

Figure 44. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1l**.

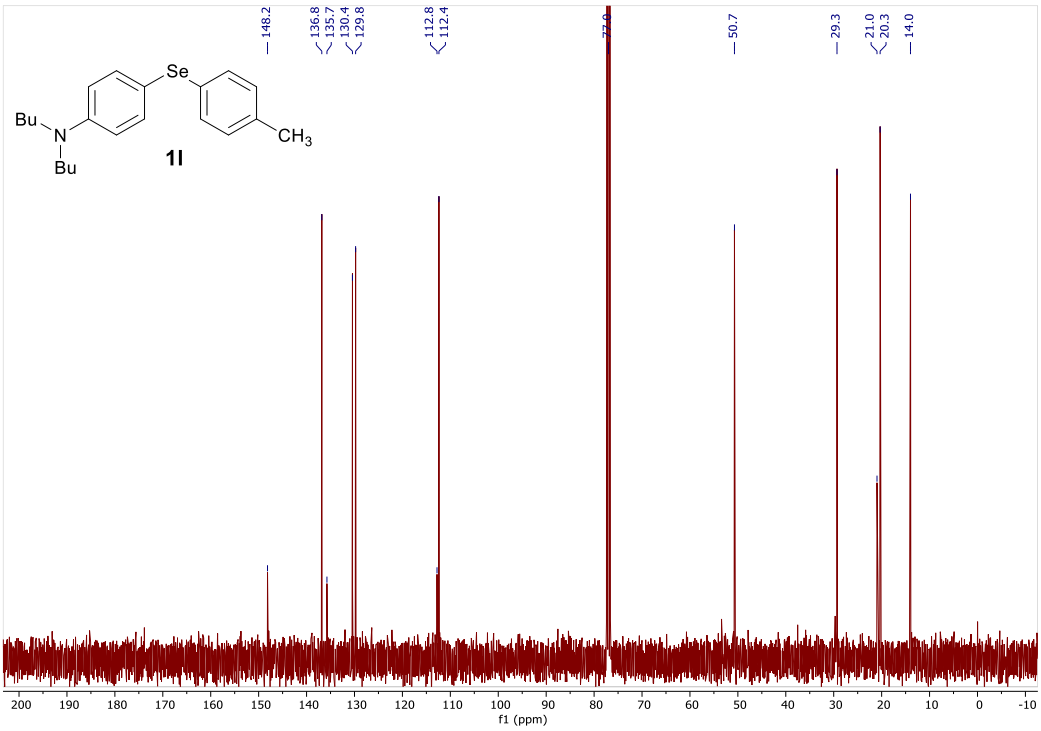

Figure 45. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1l**.

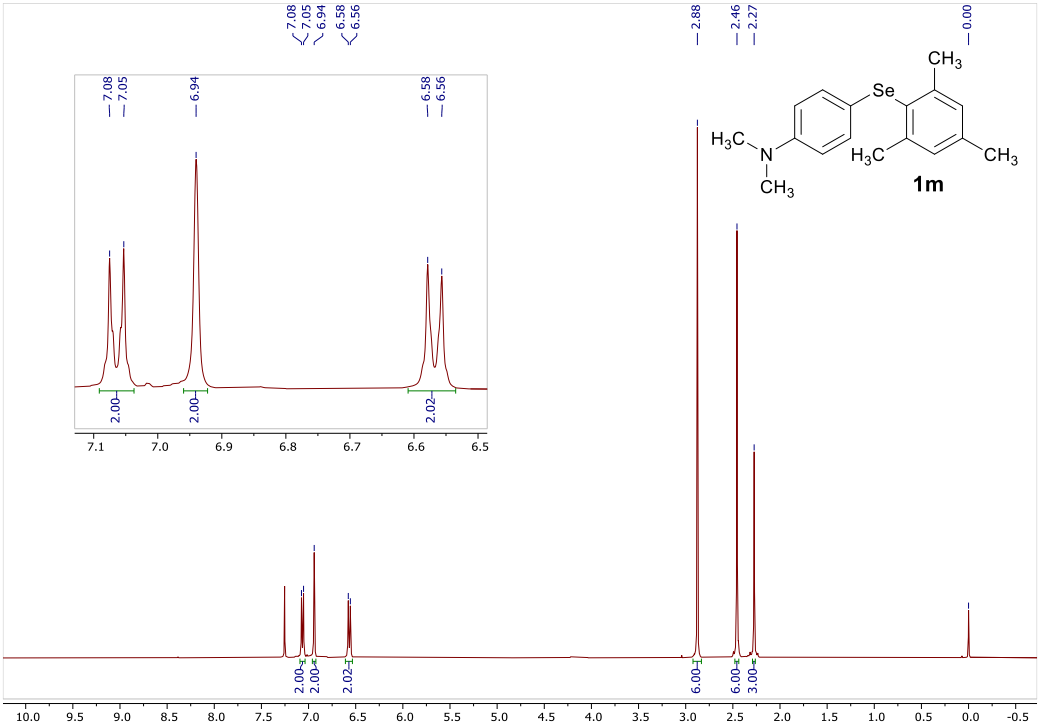

Figure 46. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1m**.

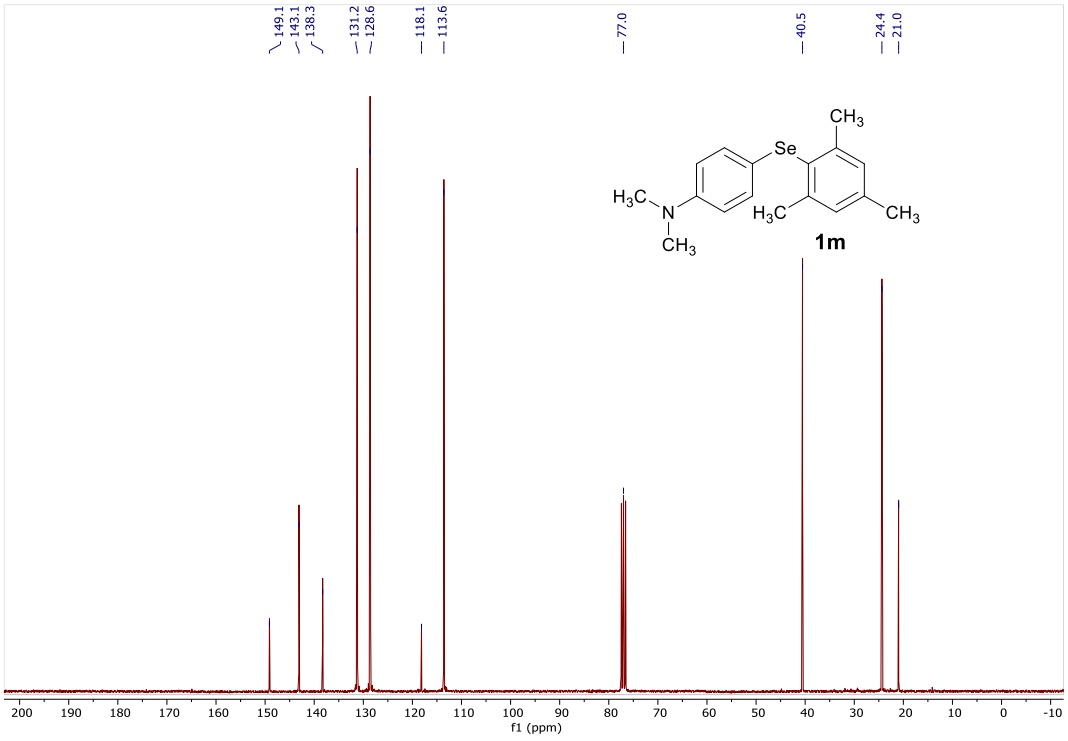

Figure 47. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1m**.

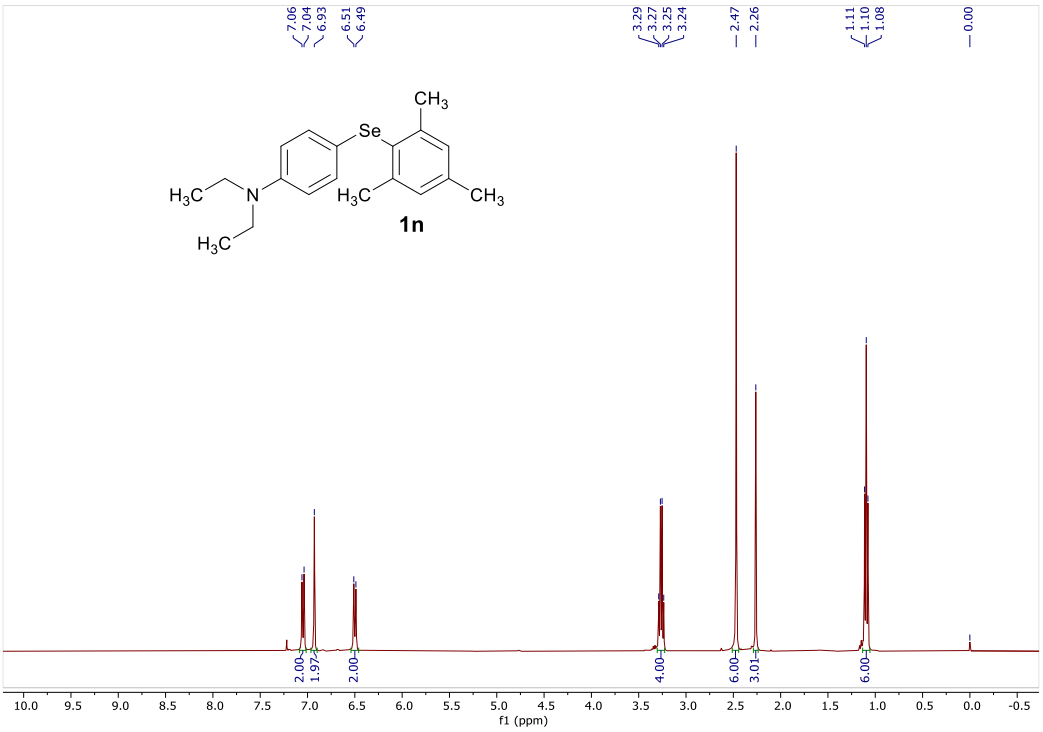

Figure 48. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **1n**.

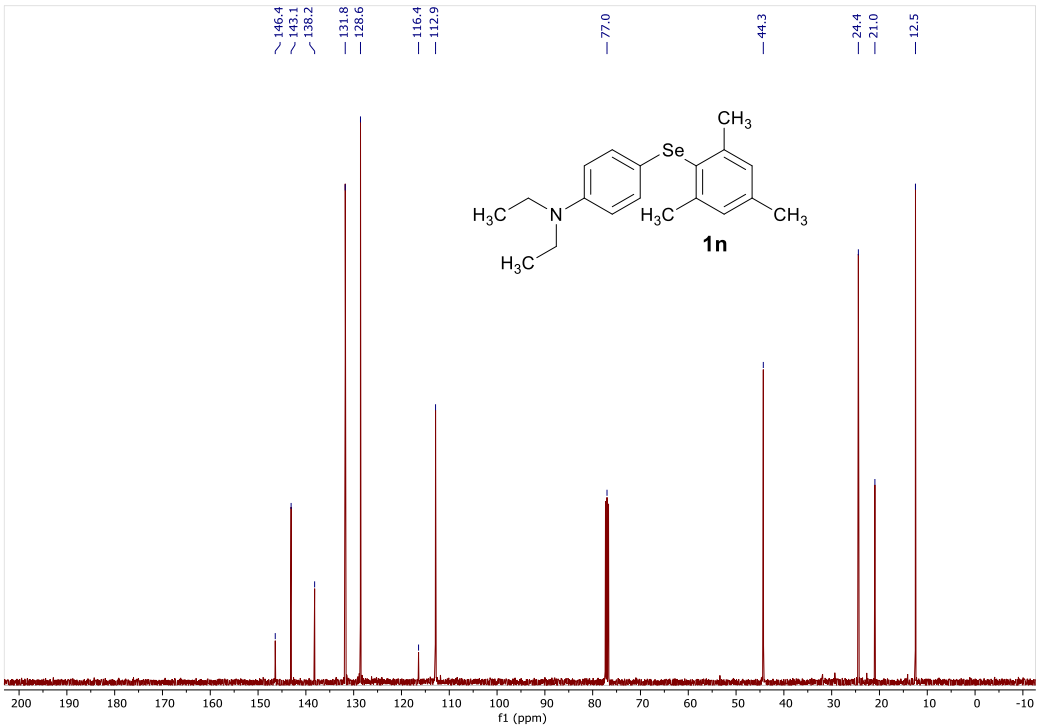

Figure 49. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **1n**.

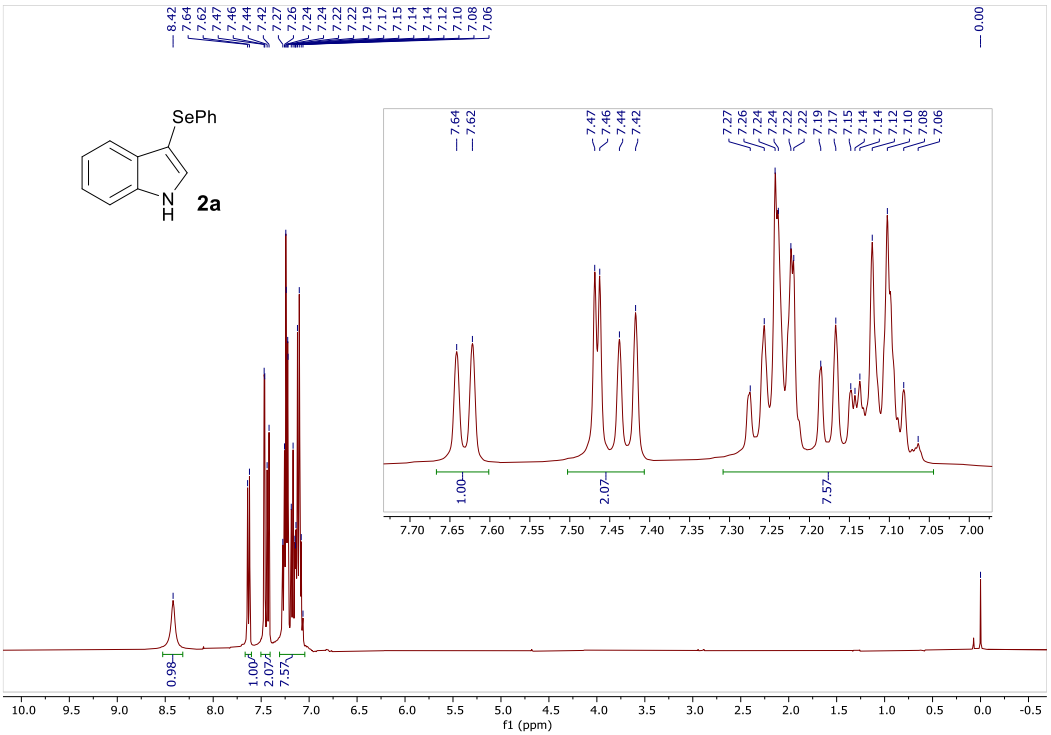

Figure 50. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **2a**.

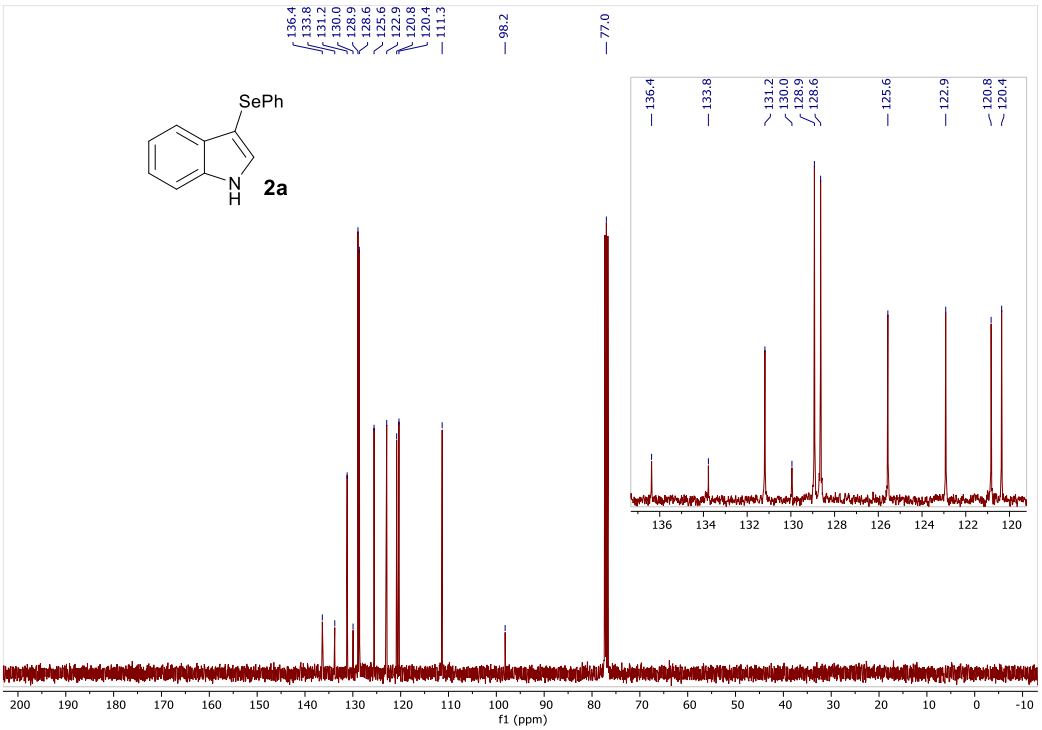

Figure 51. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **2a**.

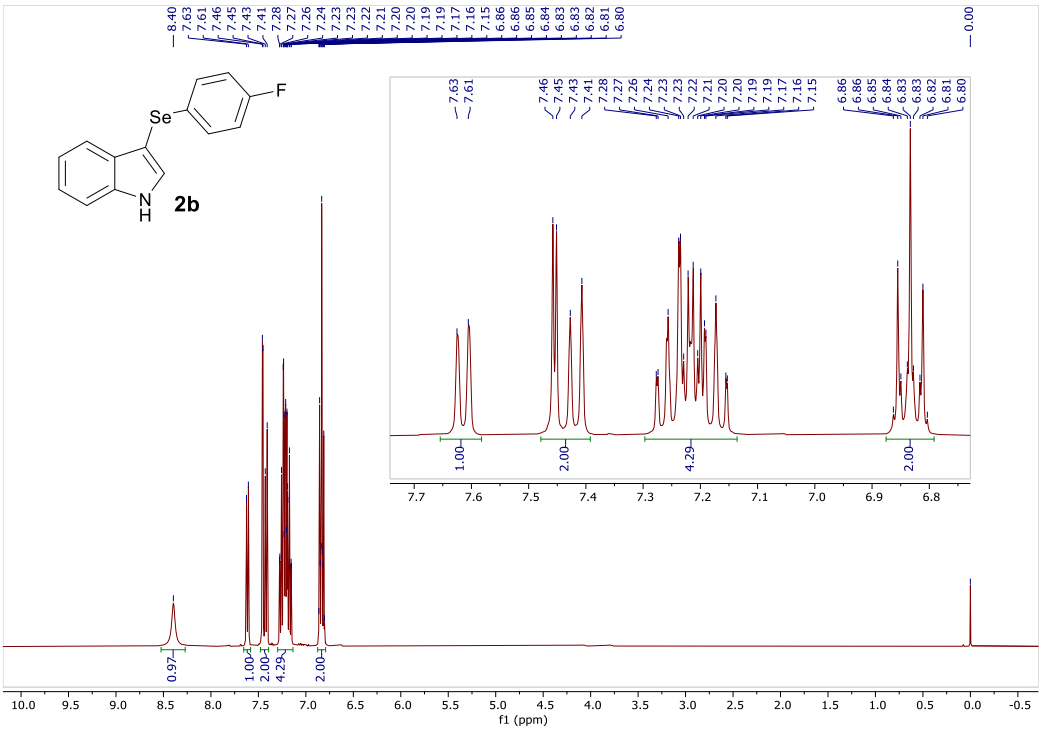

Figure 52. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **2b**.

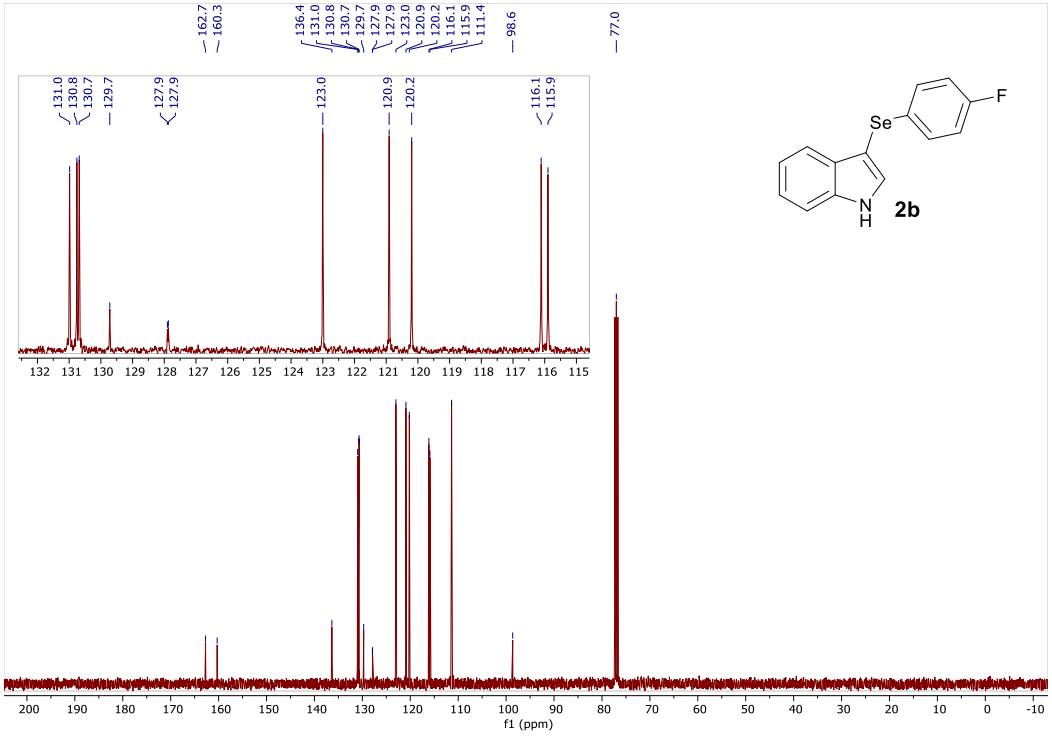

Figure 53. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **2b**.

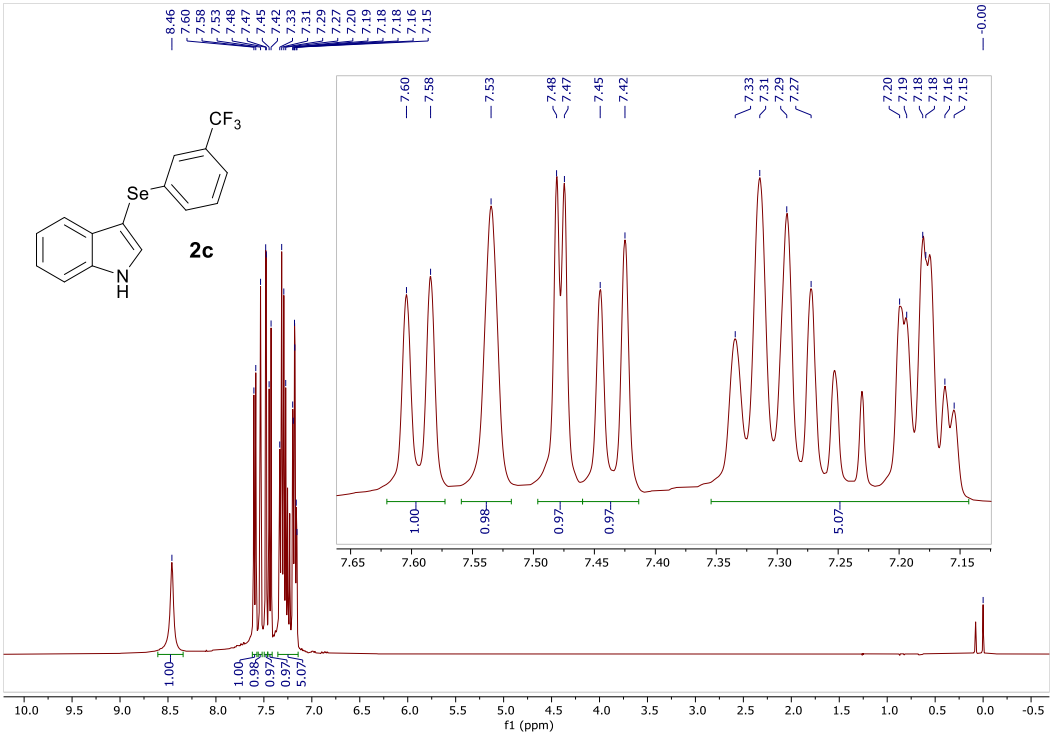

Figure 54. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **2c**.

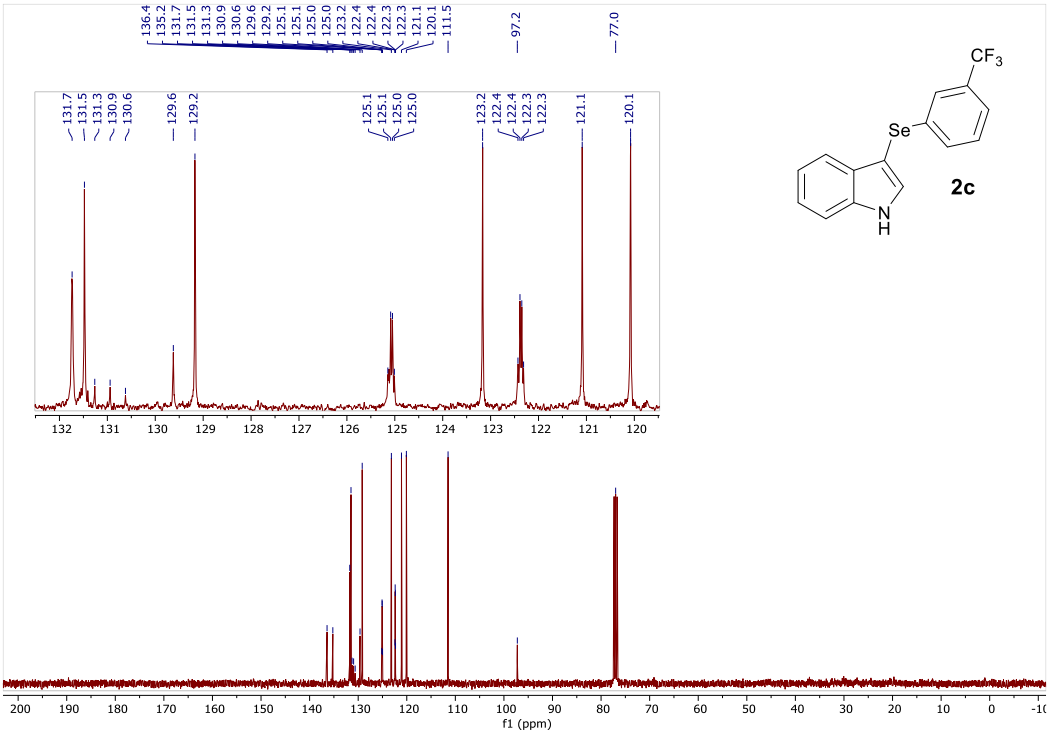

Figure 55. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **2c**.

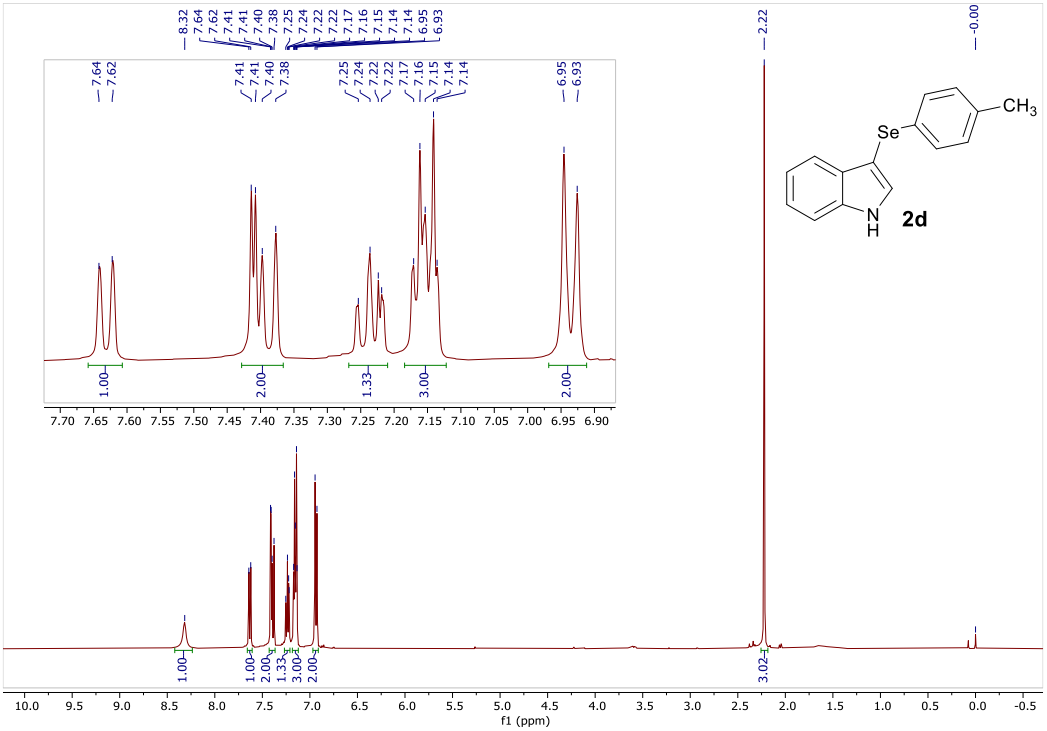

Figure 56. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **2d**.

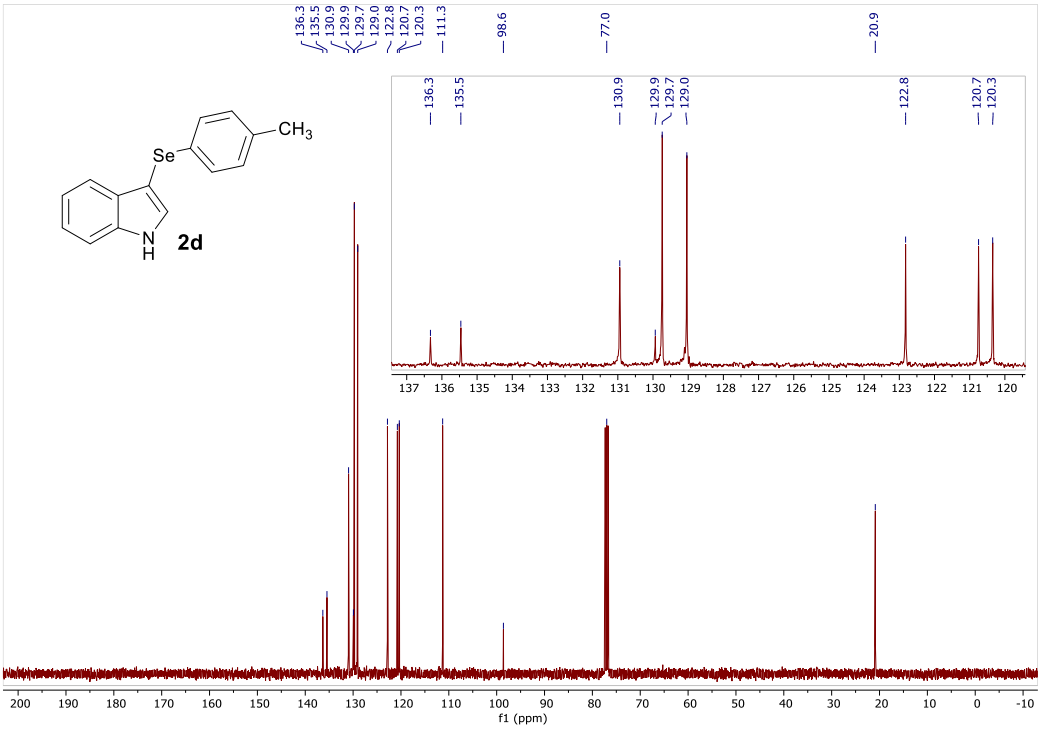

Figure 57. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **2d**.

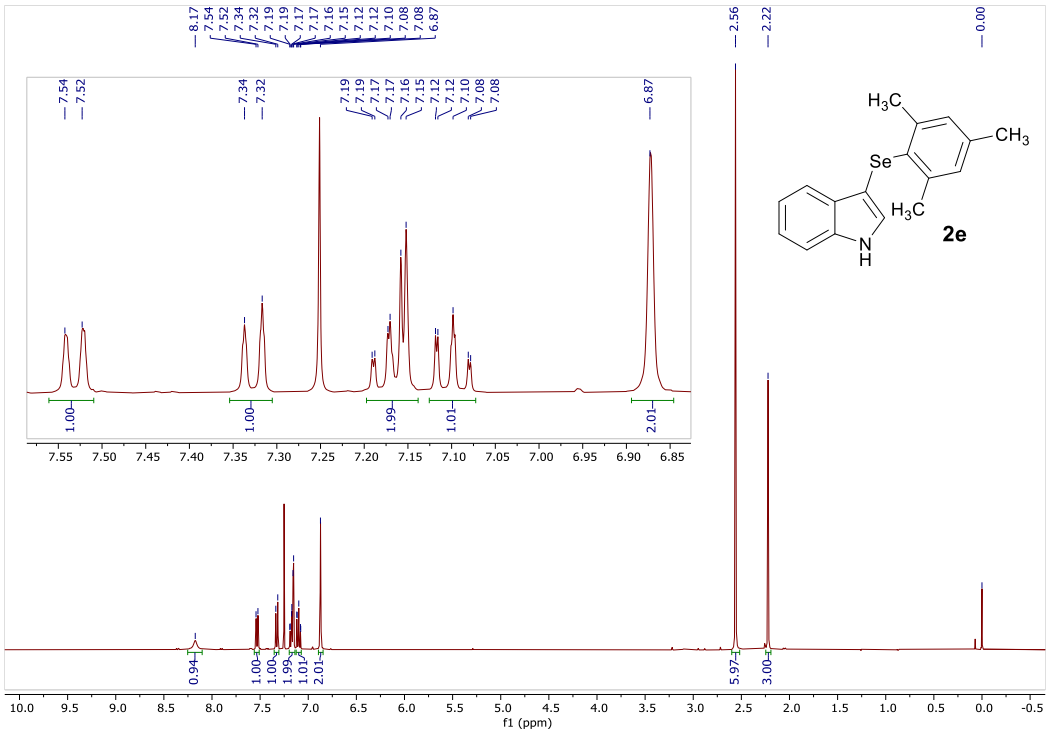

Figure 58. ^{1}H NMR ($CDCl_3$, 400 MHz) of the compound **2e**.

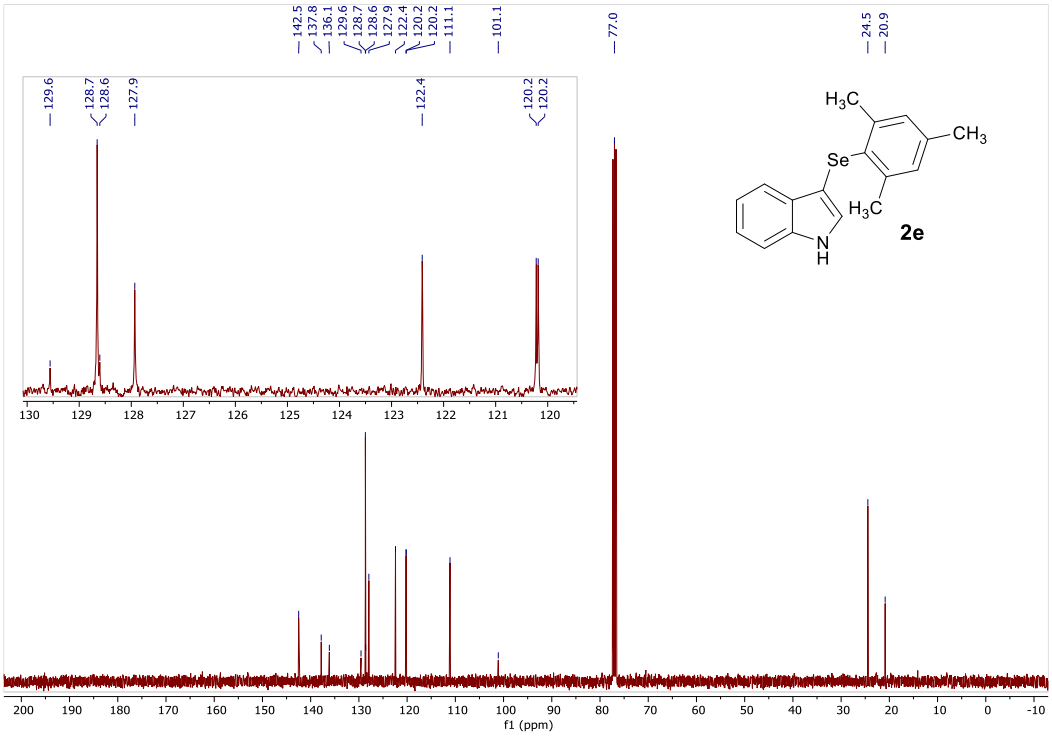

Figure 59. ^{13}C NMR ($CDCl_3$, 100 MHz) of the compound **2e**.

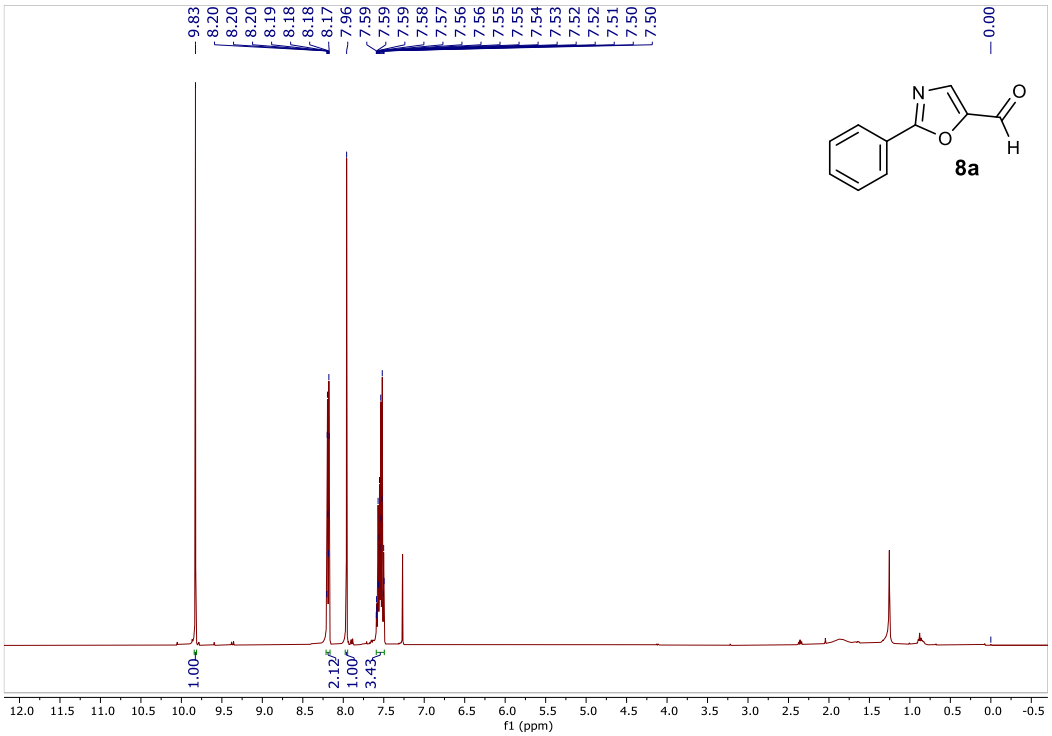

Figure 60. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8a**.

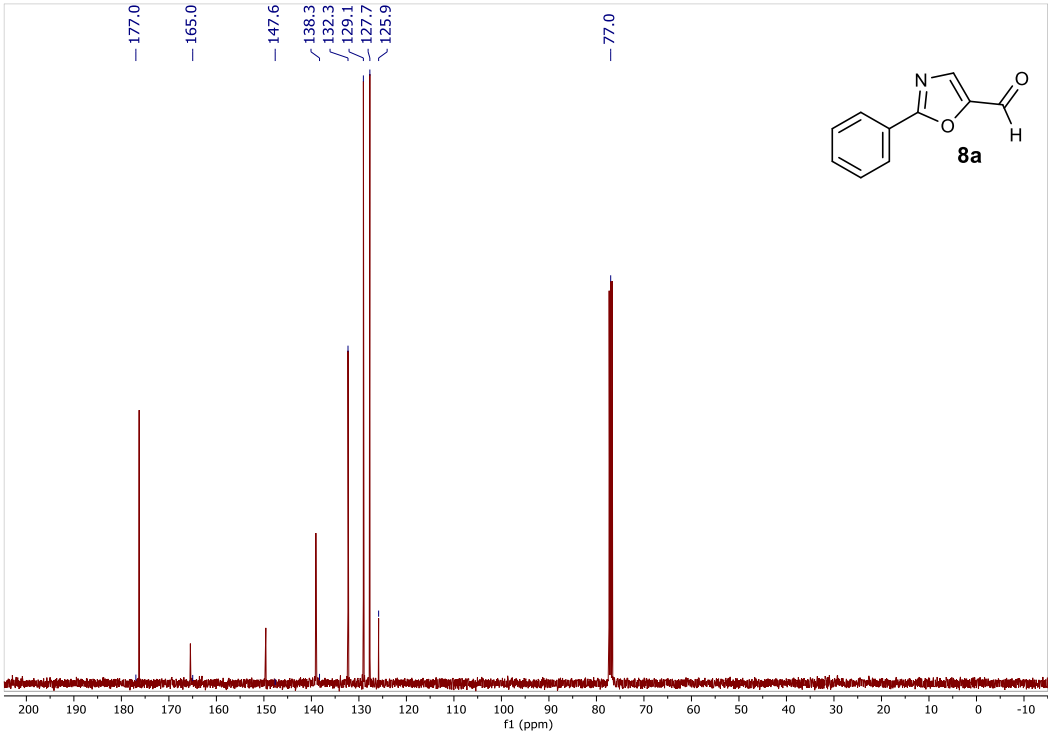

Figure 61. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8a**.

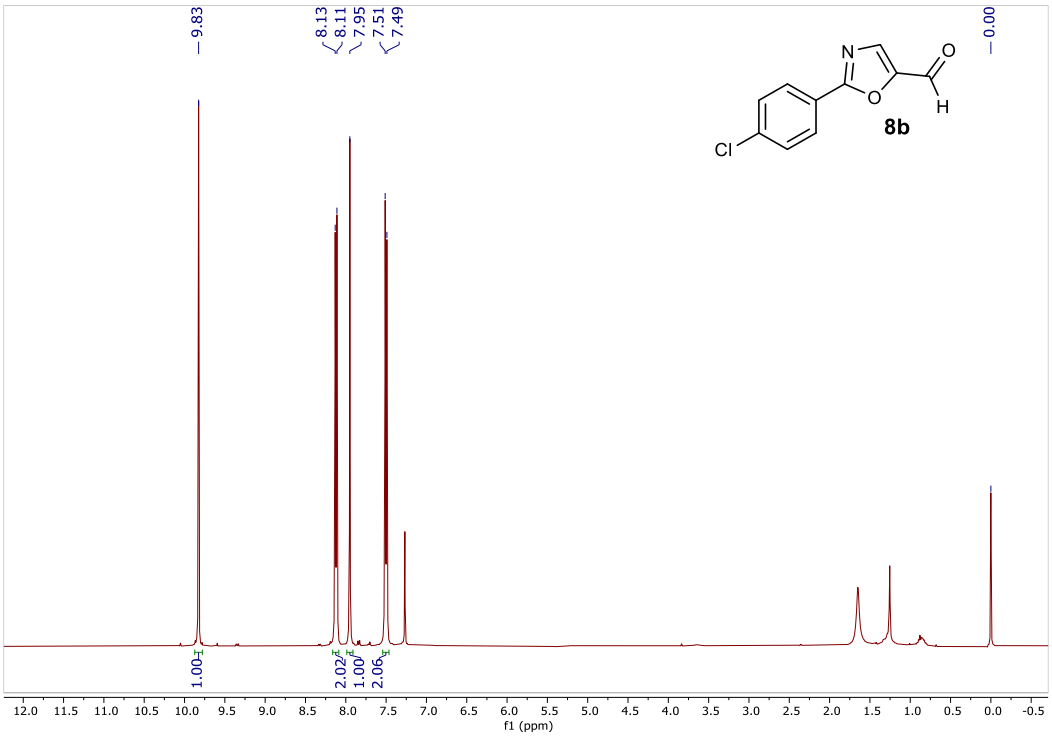

Figure 62. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8b**.

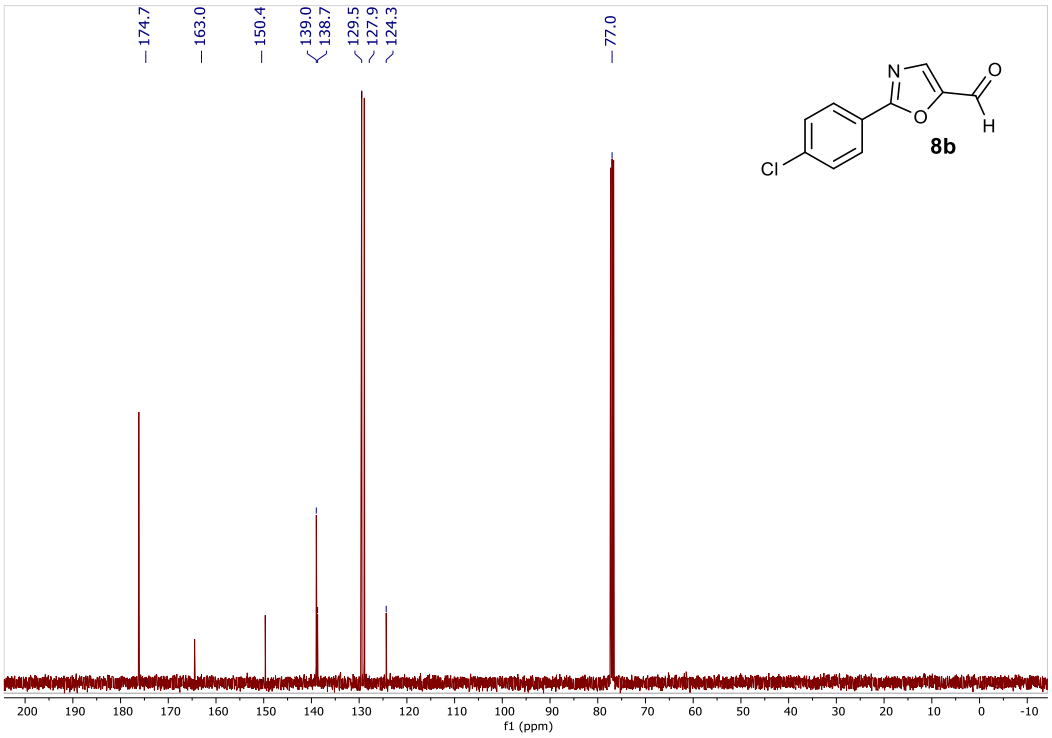

Figure 63. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8b**.

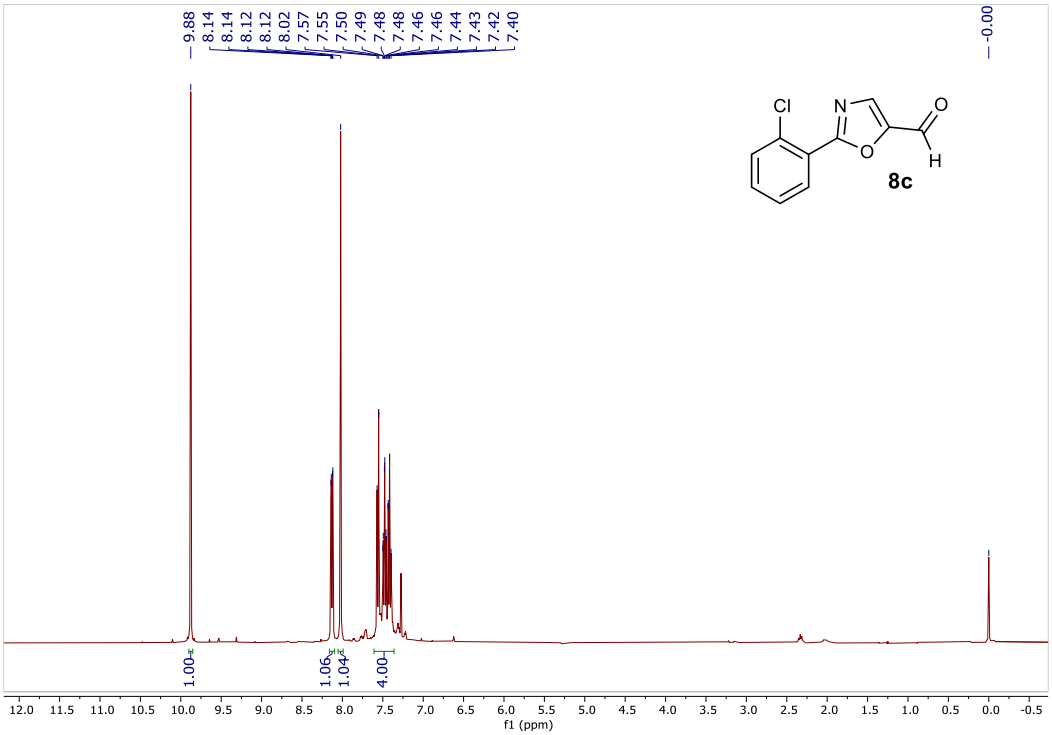

Figure 64. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8c**.

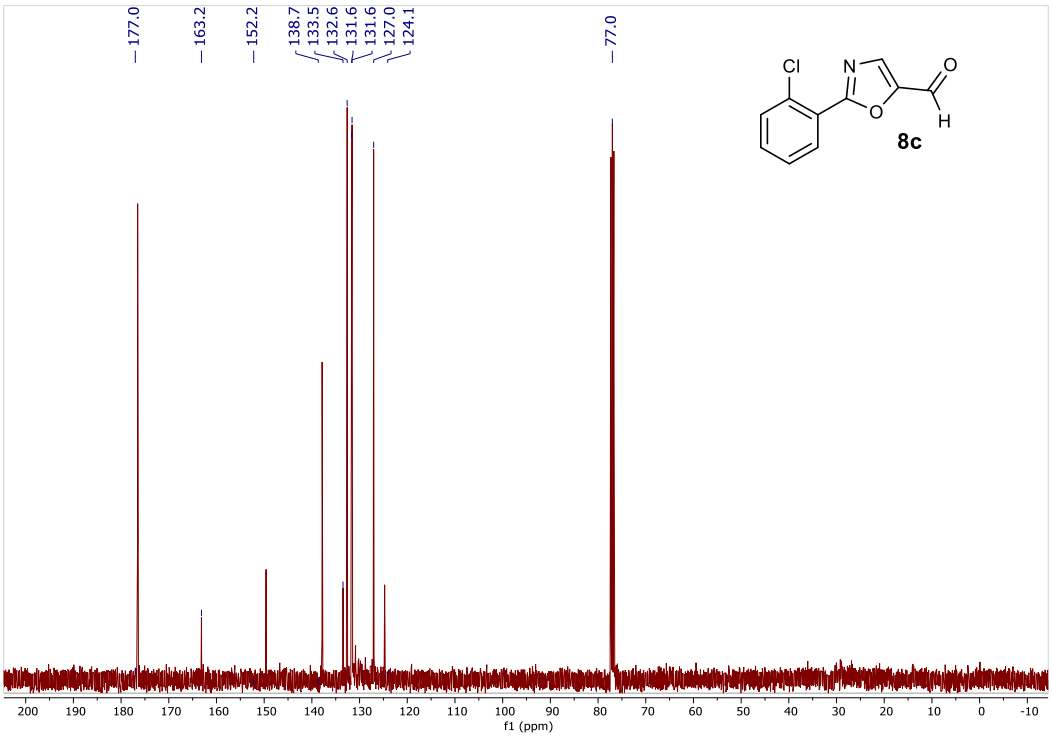

Figure 65. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8c**.

Figure 66. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8d**.

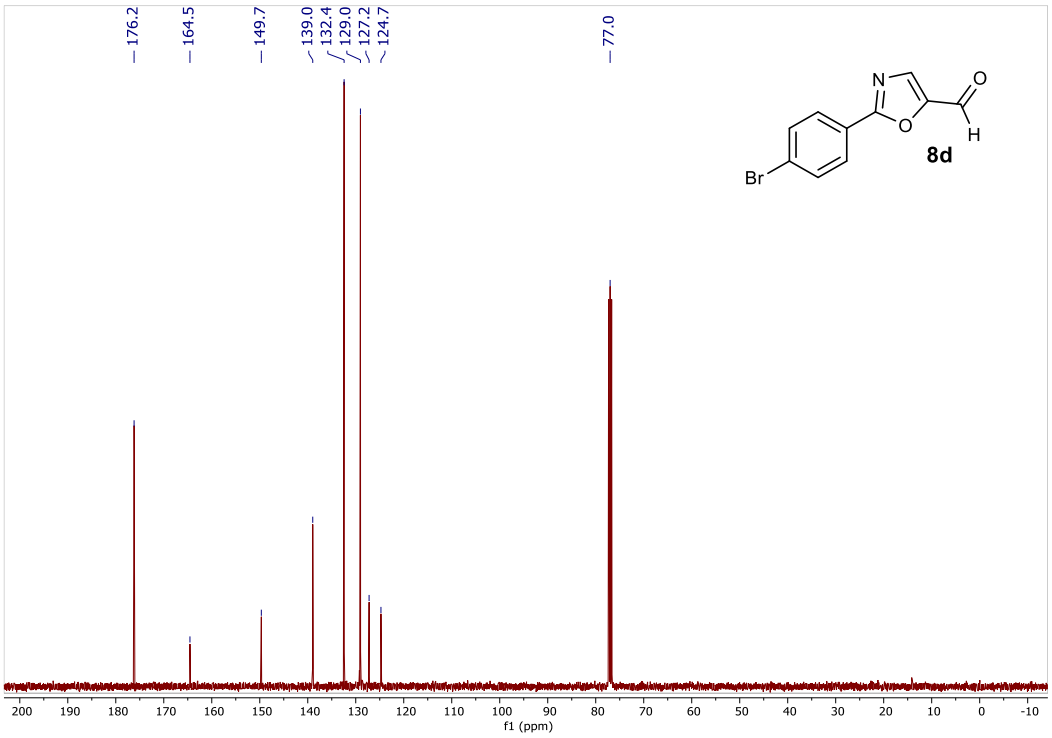

Figure 67. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8d**.

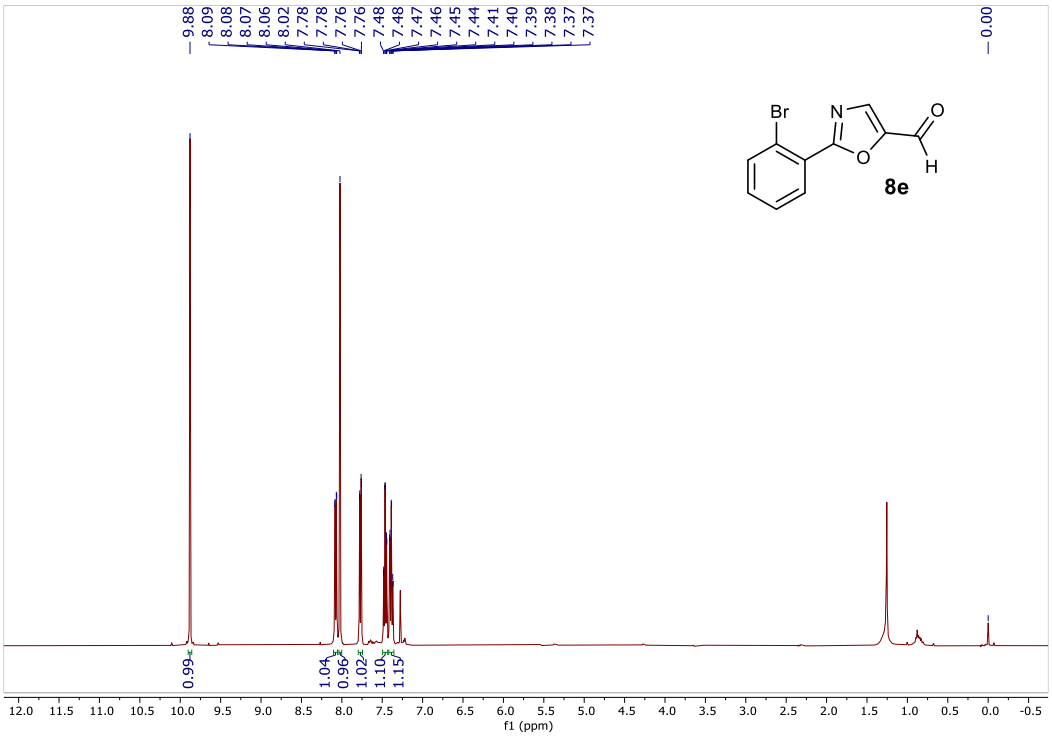

Figure 68. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8e**.

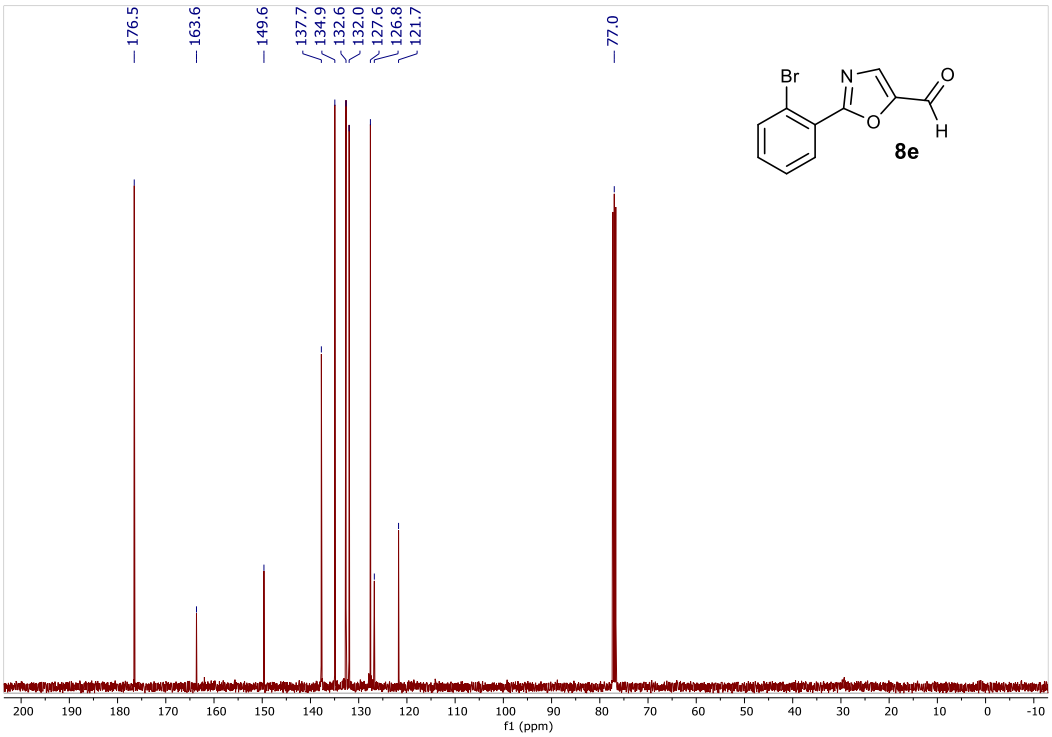

Figure 69. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8e**.

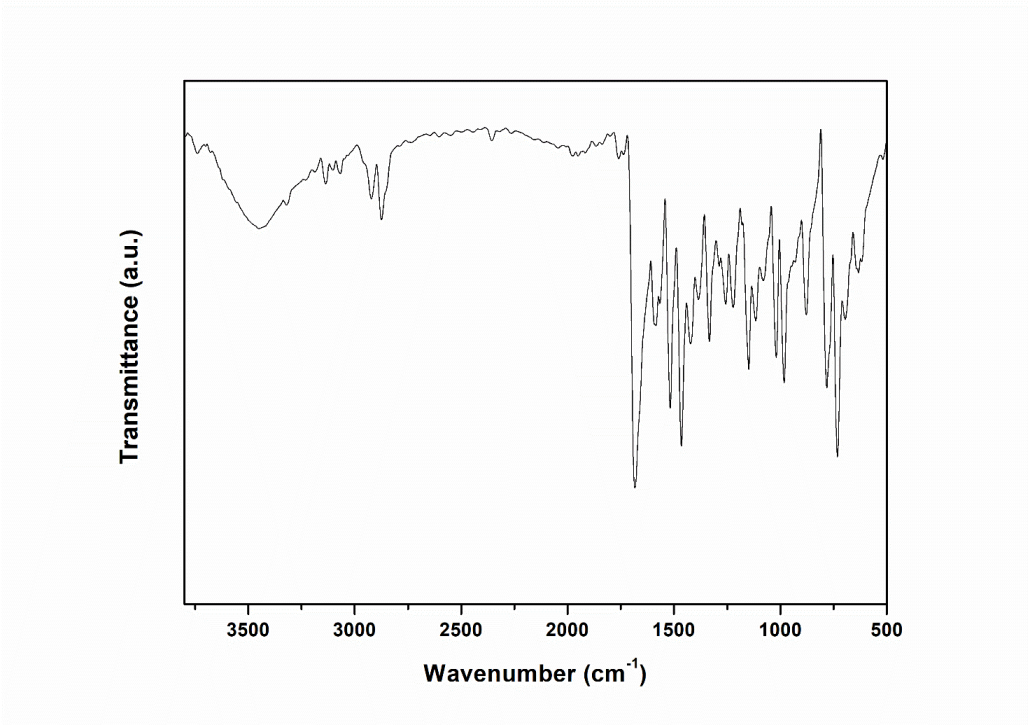

Figure 70. FTIR (KBr) spectrum of the compound **8e**.

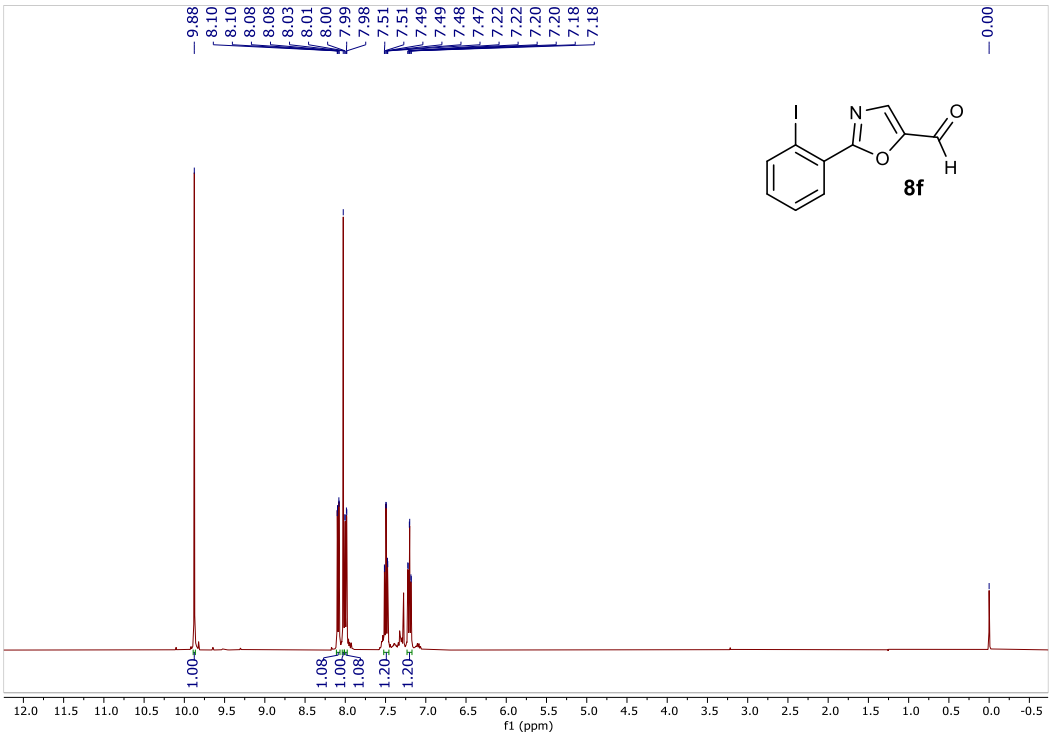

Figure 71. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8f**.

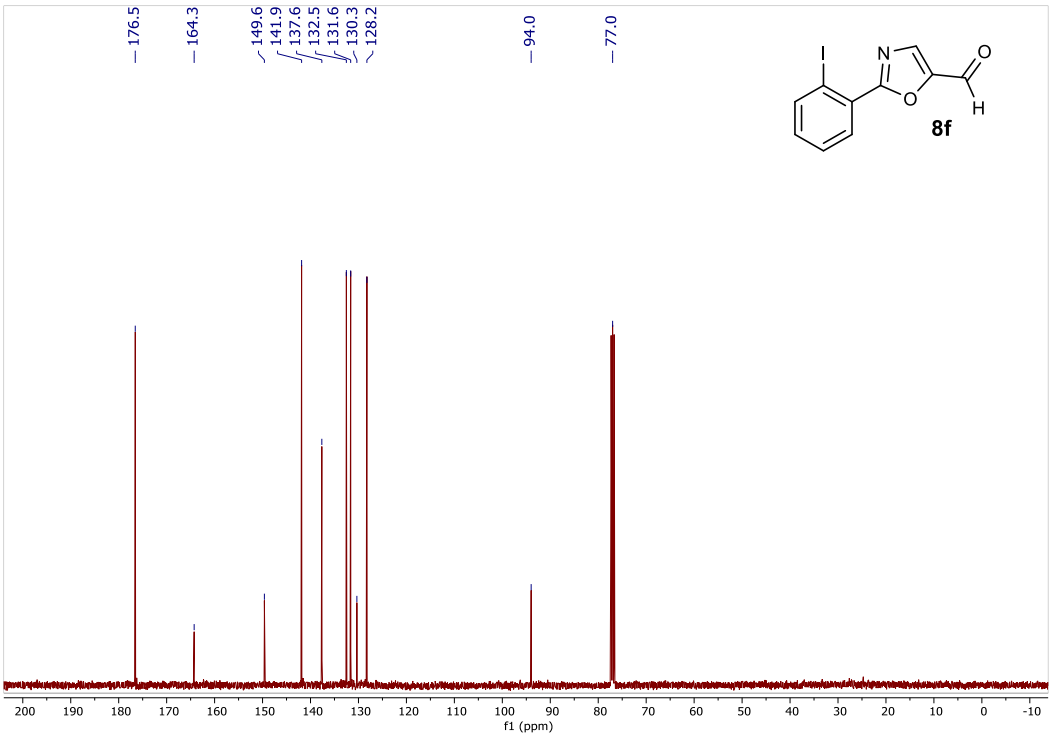

Figure 72. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8f**.

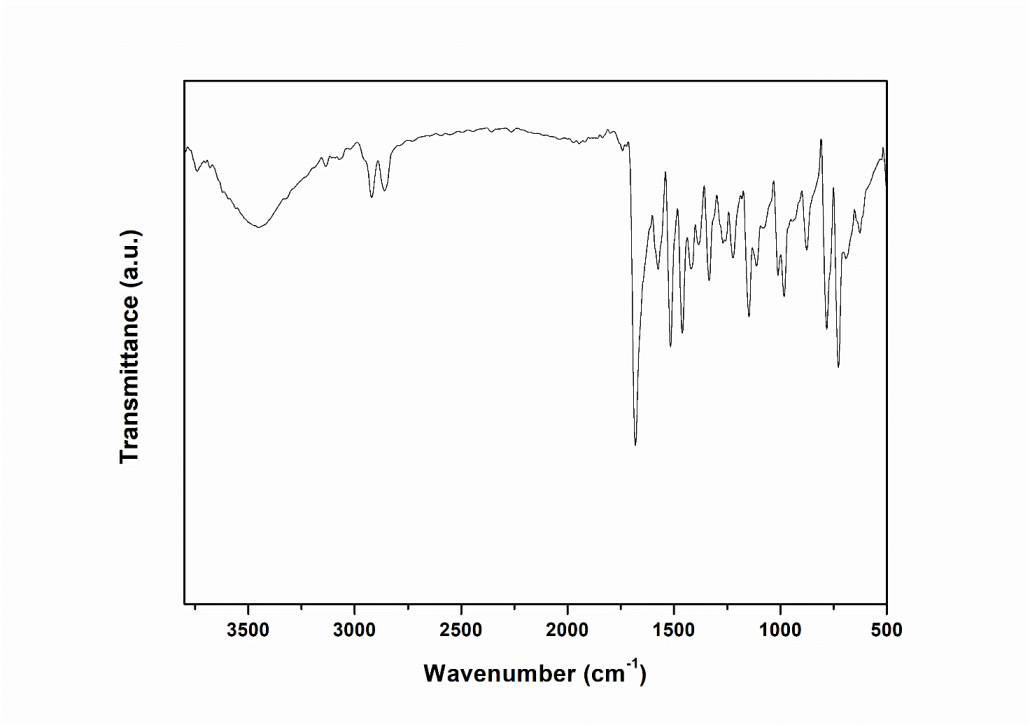

Figure 73. FTIR (KBr) spectrum of the compound **8f**.

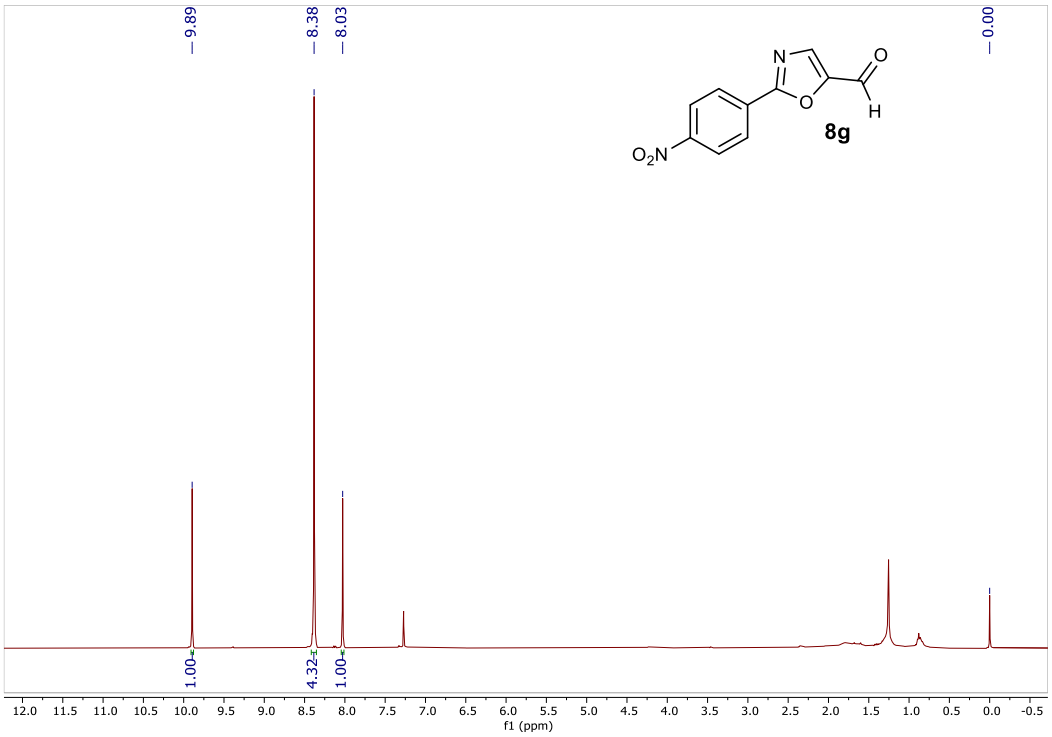

Figure 74. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8g**.

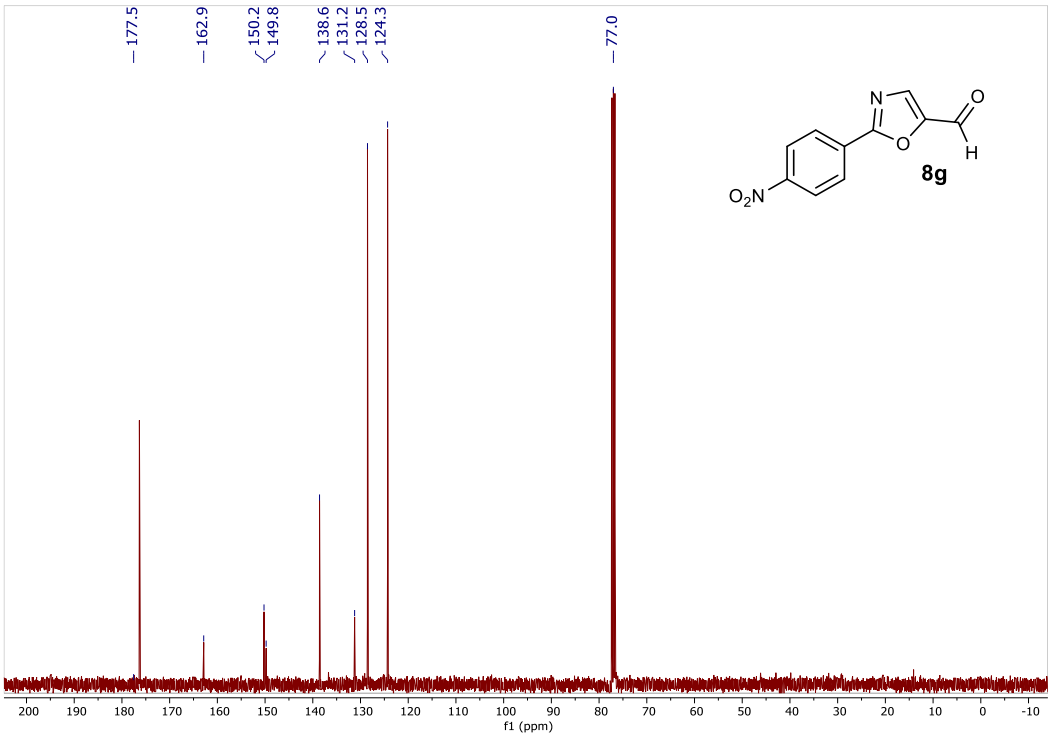

Figure 75. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8g**.

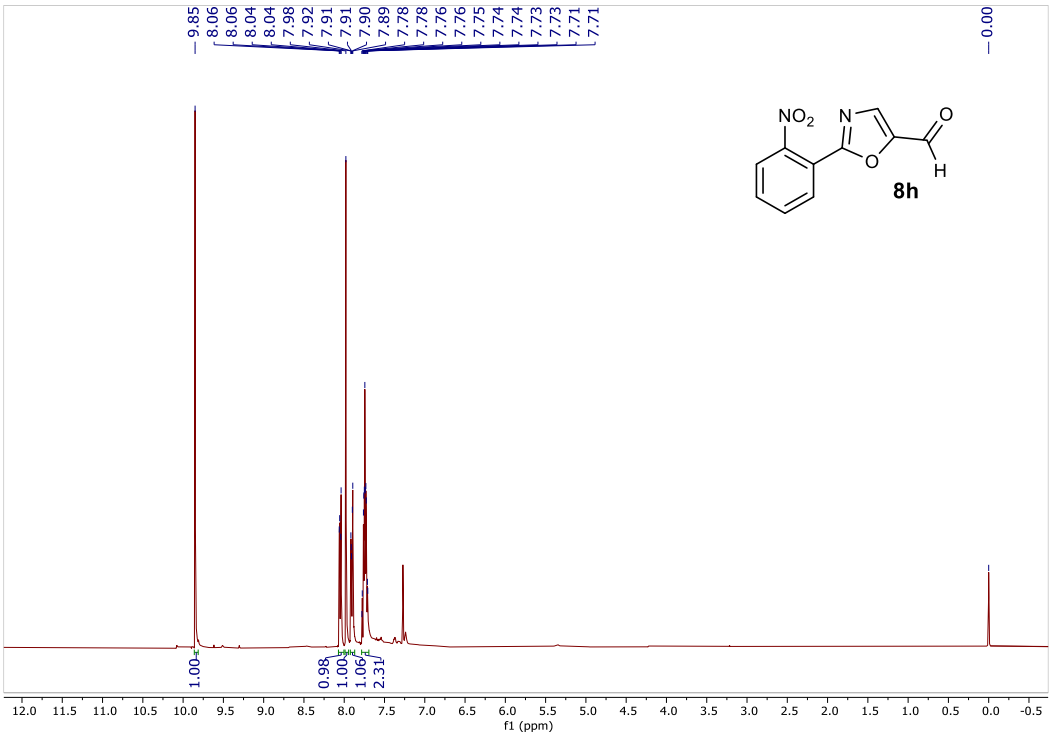

Figure 76. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8h**.

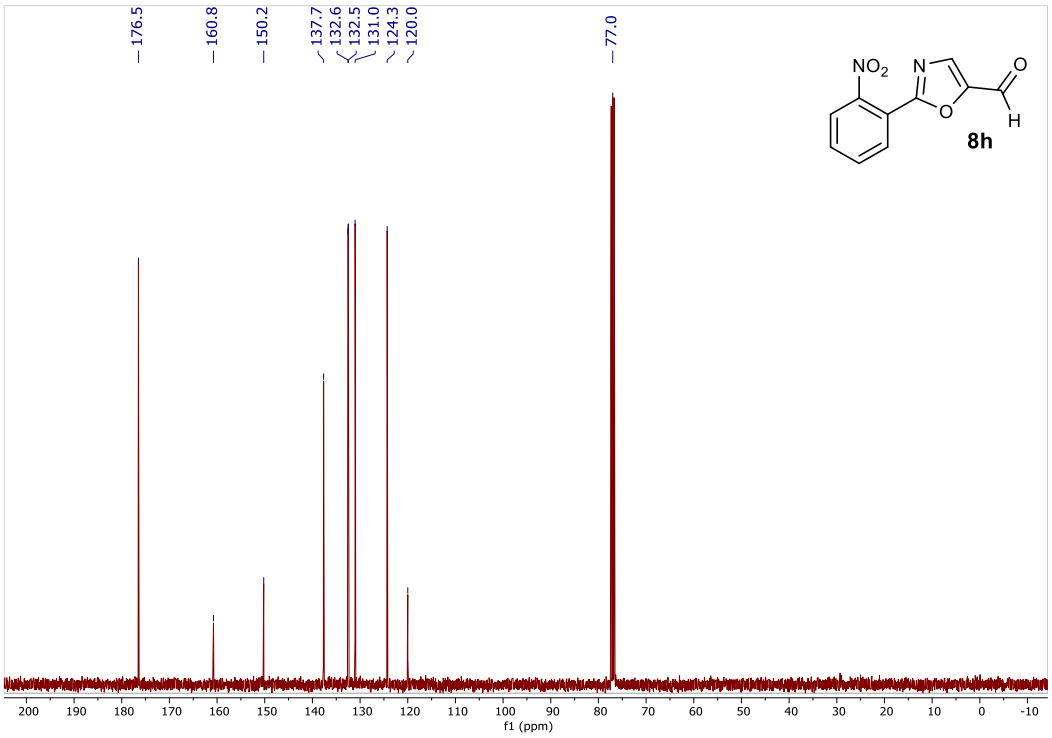

Figure 77. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8h**.

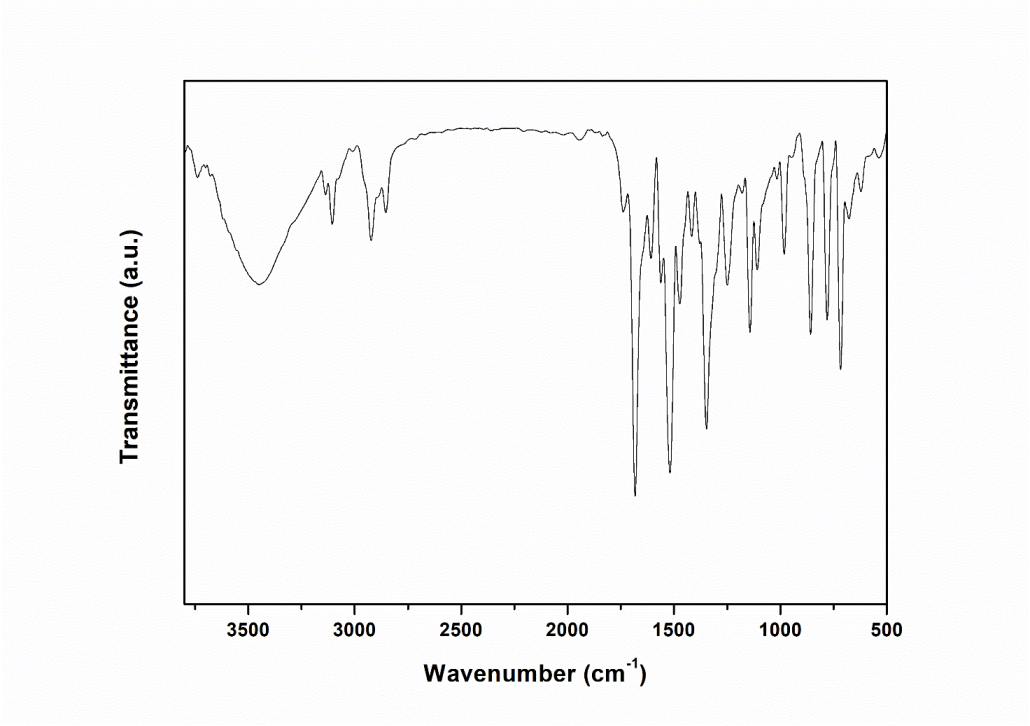

Figure 78. FTIR (KBr) spectrum of the compound **8h**.

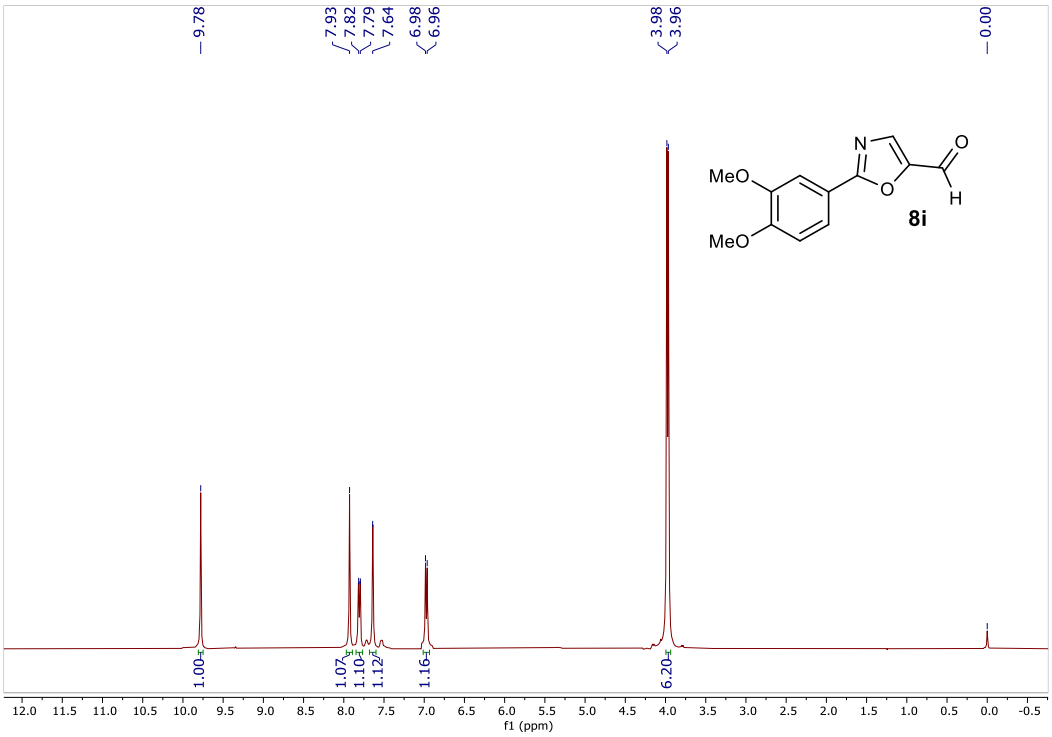

Figure 79. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8i**.

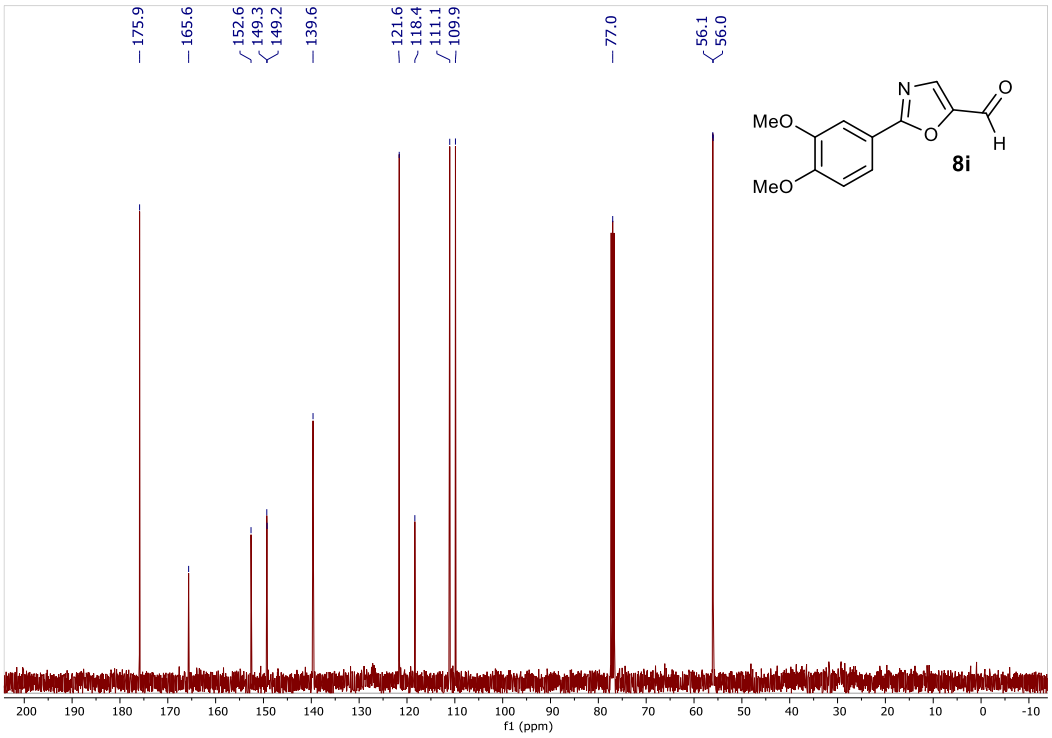

Figure 80. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8i**.

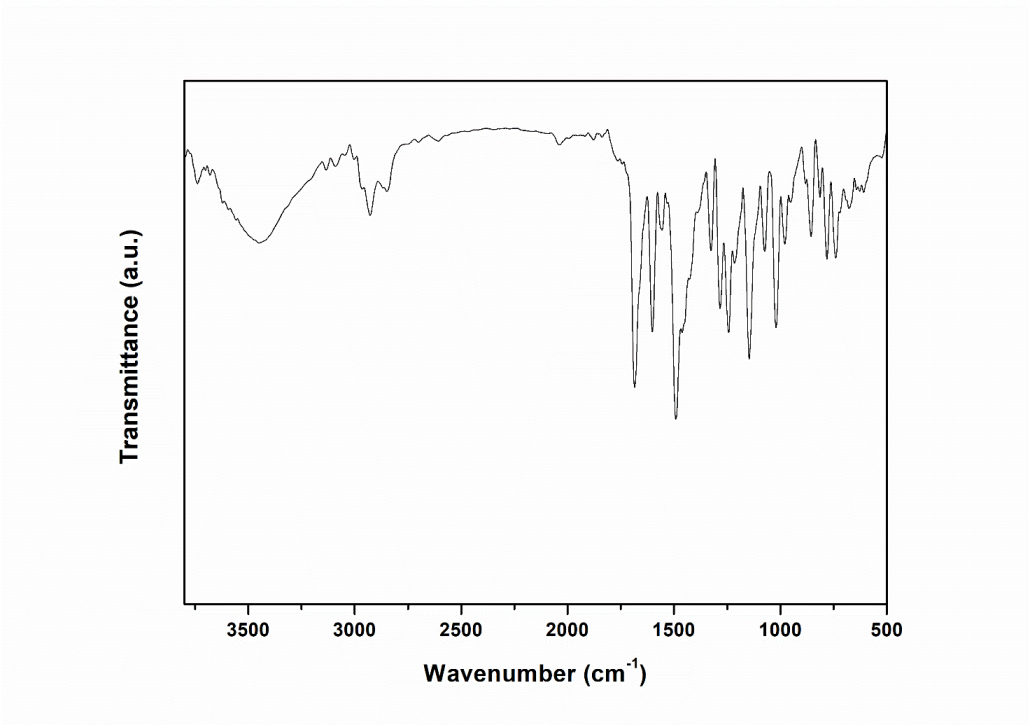

Figure 81. FTIR (KBr) spectrum of the compound **8i**.

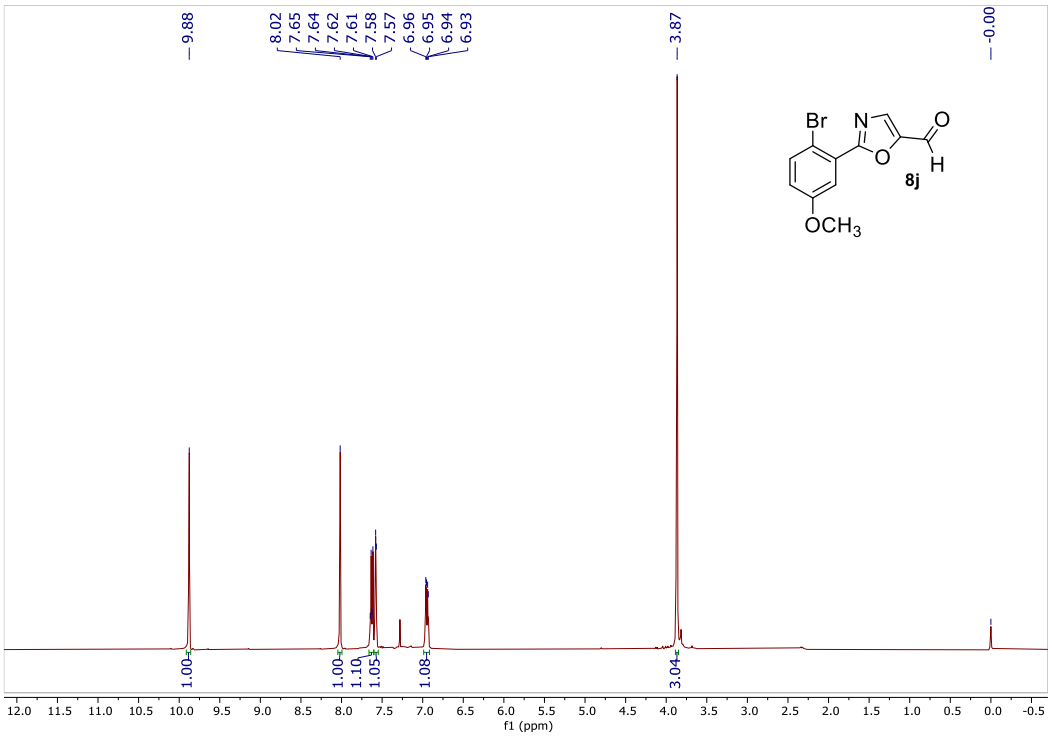

Figure 82. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8j**.

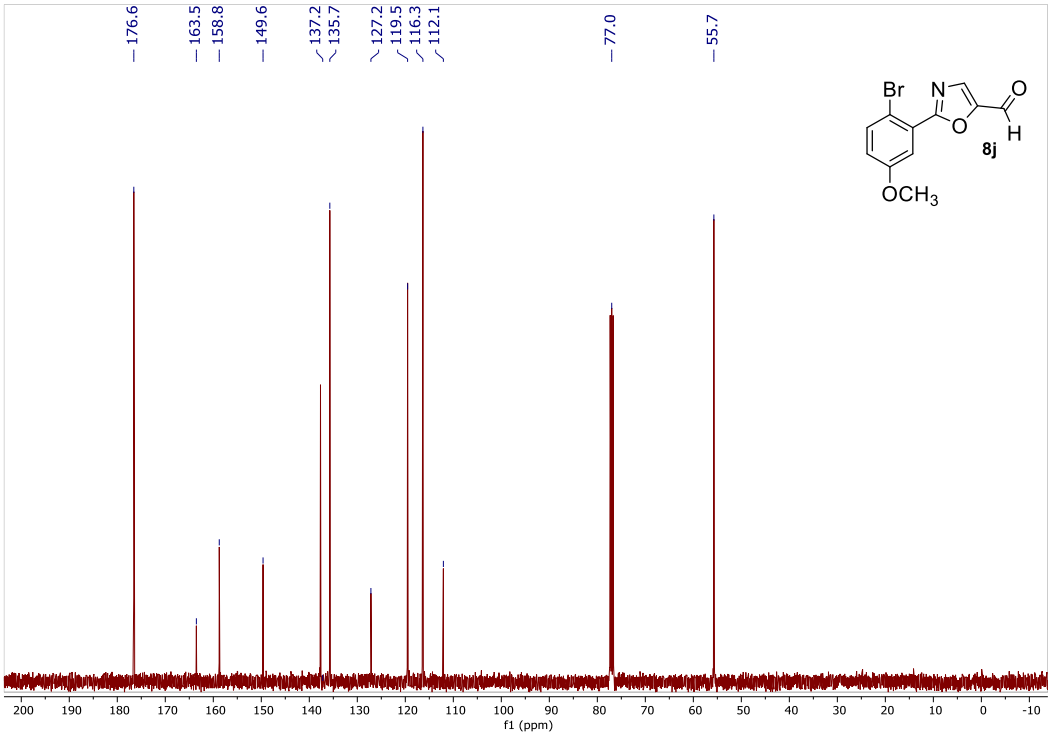

Figure 83. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8j**.

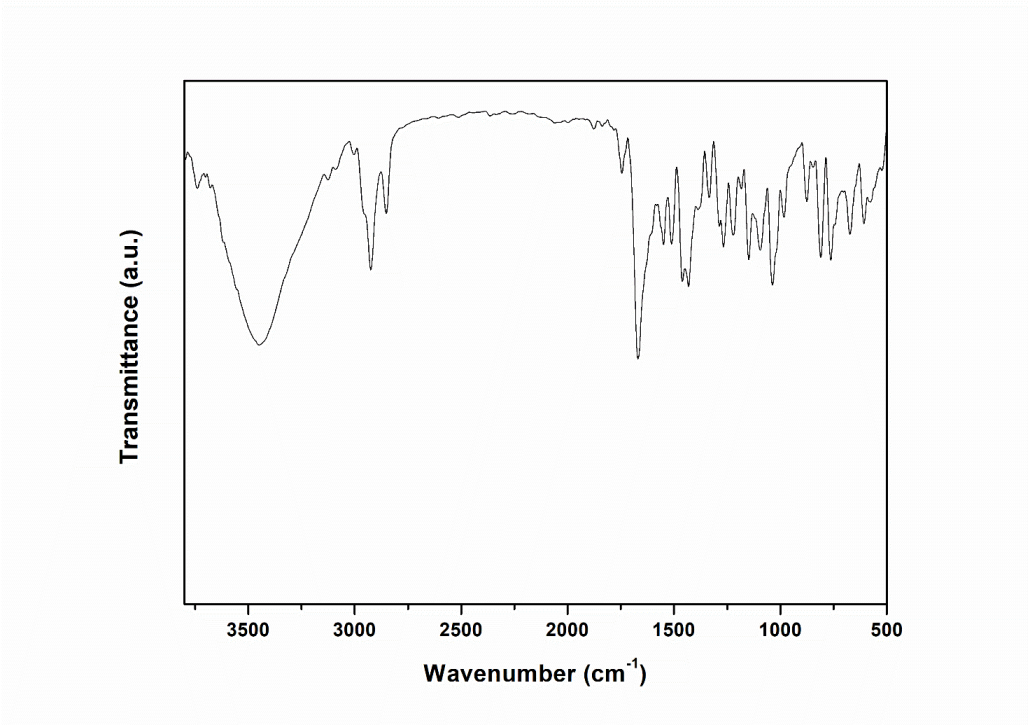

Figure 84. FTIR (KBr) spectrum of the compound **8j**.

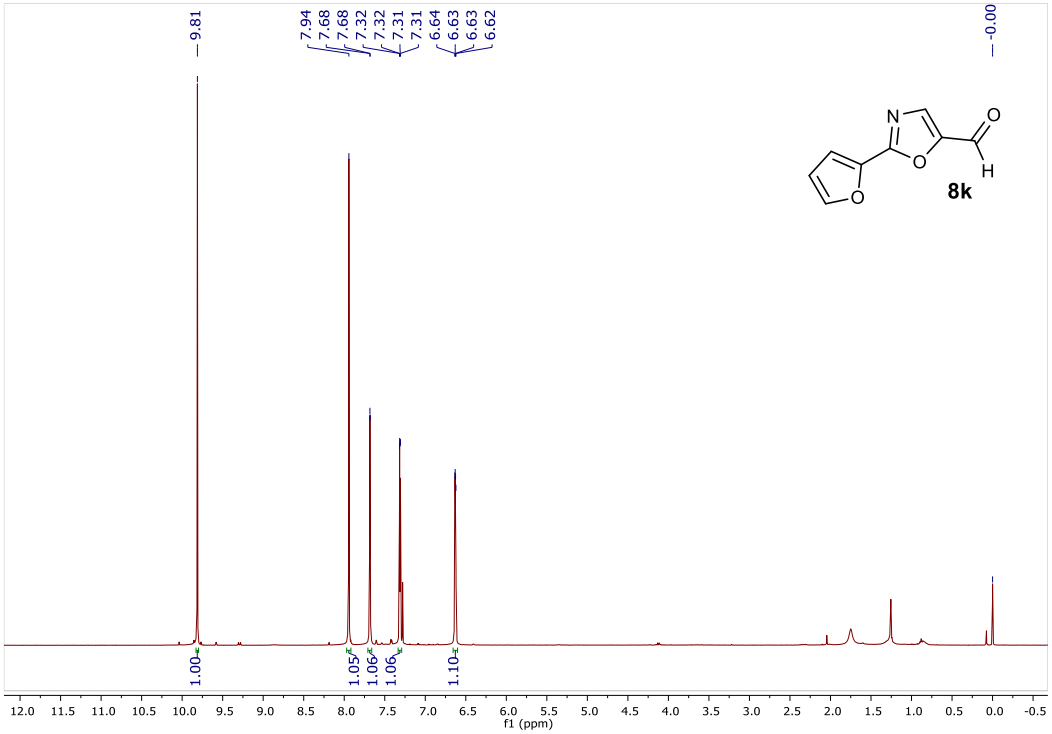

Figure 85. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8k**.

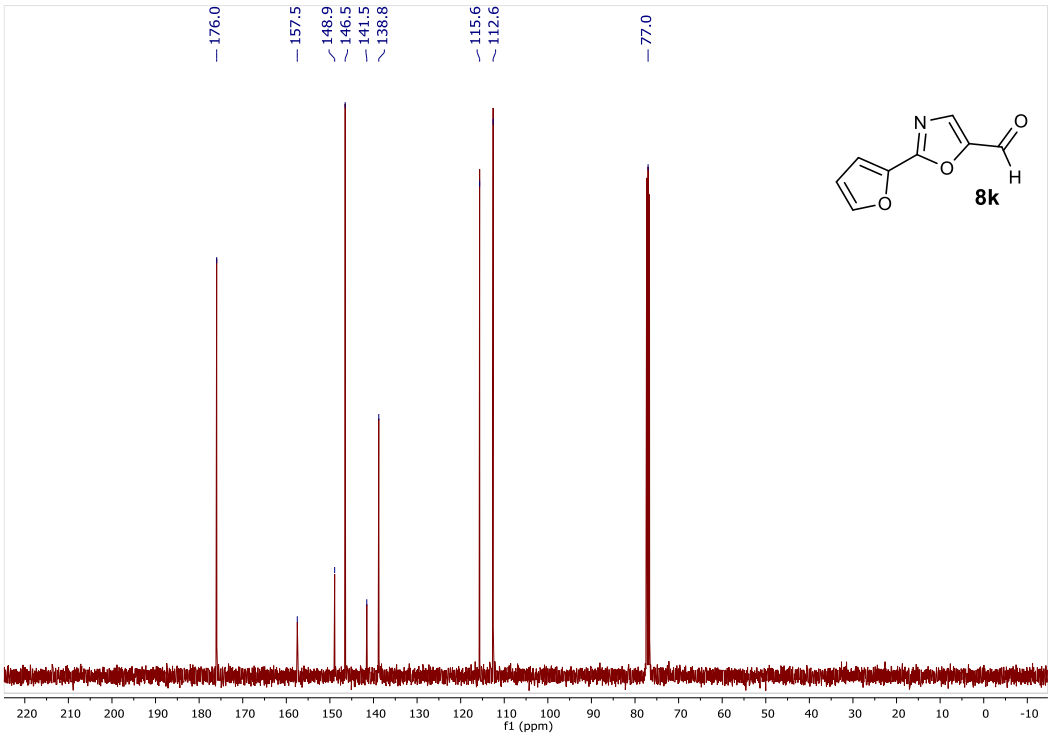

Figure 86. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8k**.

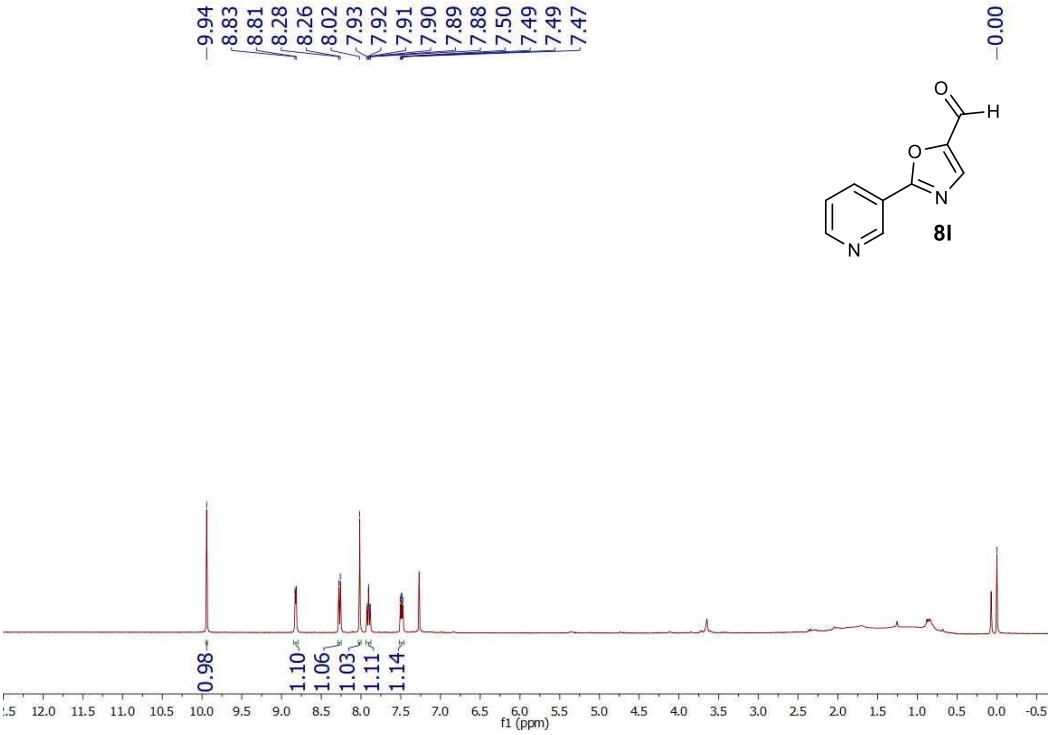

Figure 87. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the compound **8l**.

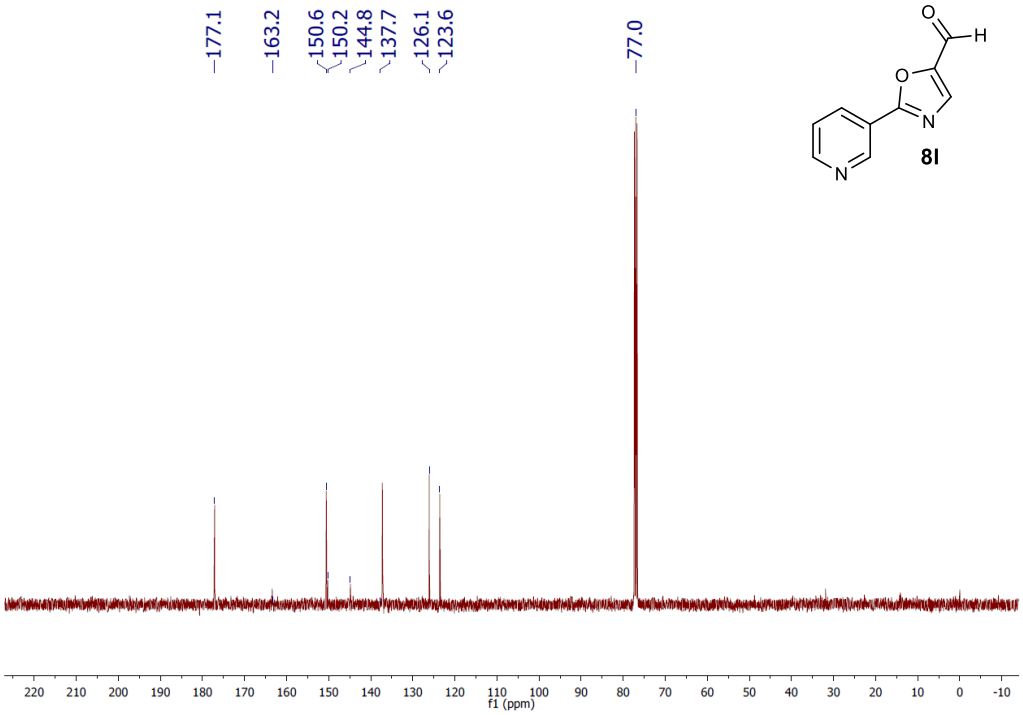

Figure 88. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the compound **8l**.

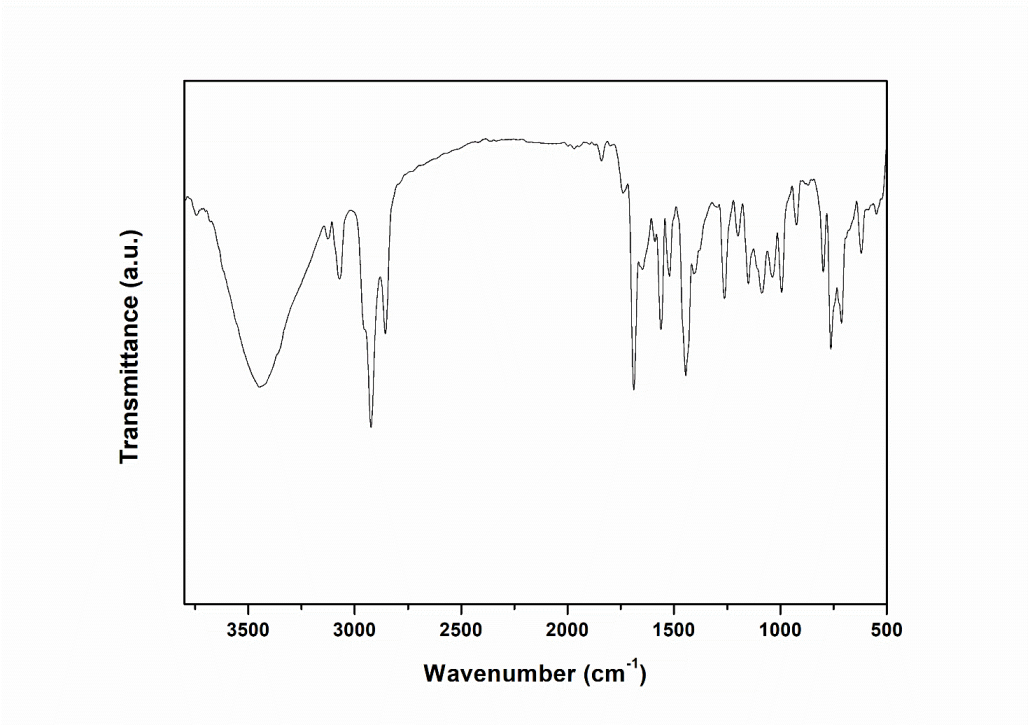

Figure 89. FTIR (KBr) spectrum of the compound **8l**.