CHARLES UNIVERSITY IN PRAGUE

FACULTY OF PHARMACY

IN HRADEC KRÁLOVÉ

DEPARTMENT OF INORGANIC AND ORGANIC CHEMISTRY

DIPLOMA THESIS

Synthesis of New Seleninic Acid Compounds as Potential Antileishmanial Agents

PAMPLONA 2015 MARCELA PECHOVÁ

I would like to thank the Department of Organic and Pharmaceutical Chemistry of University of Navarra, especially Carmen Sanmartín, Ph.D., for letting me become part of her research group. Significant thanks belong to my consultant, Ylenia Baquedano Pérez, Ph.D., for all her help, guidance and patience.

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I hereby declare that this thesis is a presentation of my original research work. Wherever contributions of others are involved, every effort is made to indicate this clearly, with due reference to the literature. This work has not been used to acquire a different or the same degree.

Marcela Pechová

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ABSTRACT:

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Title of Diploma Thesis: Synthesis of New Seleninic Acid Compounds as Potential Antileishmanial Agents

Selenium containing organic compounds possess promising *in vitro* antiparasitic activity against *Leishmania* infection. Various selenocyanate and diselenide derivatives with different functional groups in the aryl ring and in the aliphatic chain, displaying promising leishmanicidal activity and higher selectivity indexes than those obtained for the reference drugs, miltefosine and edelfosine, have recently been synthesized.

Within this thesis, the synthesis of new seleninic acid derivatives from selenocyanates and diselenides is described.

Four new seleninic acids have been prepared.

ABSTRAKT:

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Název diplomové práce: Syntéza nových derivátů seleninové kyseliny jako potenciálních antileishmaniálních přípravků

Organické sloučeniny obsahující selen jsou známy pro svou slibnou *in vitro* aktivitu proti infekcím způsobenými prvoky rodu *Leishmania*. Nedávno bylo syntetizováno několik sloučenin typu selenokyanátů a diselenidů, s různě substituovaným aromátem a alifatickým řetězcem, vykazujících slibnou leishmanicidní aktivitu a vyšší indexy selektivity než referenční léčiva miltefosin a edelfosin.

V této diplomové práci popisuji syntézu nových organických kyselin selenu ze selenokyanátů a diselenidů.

Byly připraveny čtyři nové seleninové kyseliny.

LIST OF ABBREVIATIONS

CHN	Carbon-Hydrogen-Nitrogen
CL	Cutaneous Leishmaniasis
DCM	Dichlormethane
DMDO	Dimethyldioxirane
DMSO	Dimethylsulfoxide
EA	Elemental Analysis
FT-IR	Fourier Transform Infrared
IC_{50}	Half Maximal Inhibitory Concentration
IR	Infrared Spectrometry
MCL	Mucocutaneous Leishmaniasis
MSD/DS	Mass Selective Detector/Data System
MS-DIP	Mass Spectrometry – Direct Insertion Probe
NMR	Nuclear Magnetic Resonance
SD	Standard Deviation
SI	Selectivity Index
SIL-G/UV_{254}	Silicagel/Ultra Violet Light 254nm
THP-1	Tamm-Horsfall Protein
TLC	Thin Layer Chromatography
TMS	Tetramethylsilan
TSD	Triselenium Dicyanide
VL	Visceral Leishmaniasis

1. INTRODUCTION

1.1. Leishmaniases

Leishmaniases are defined as a cluster of vector-borne diseases caused by protozoan parasites of the *Leishmania* genus, transmitted through bites of infected female sandflies (*Phlebotomus*, *Psychodopygus*, *Lutzomyia*). There are more than 20 species of *Leishmania* with an estimated annual incidence of 2 million cases across 98 countries worldwide.[1]

1.1.1. Clinical Manifestation

There are diverse clinical manifestations of leishmaniases (Fig. 1) which can be divided into three main forms occurring in humans: cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL) and visceral leishmaniasis (VL, also known as kala-azar). The clinical outcome of each is defined by the species of infecting parasite and the genetic and immune susceptibility of the host.[1]

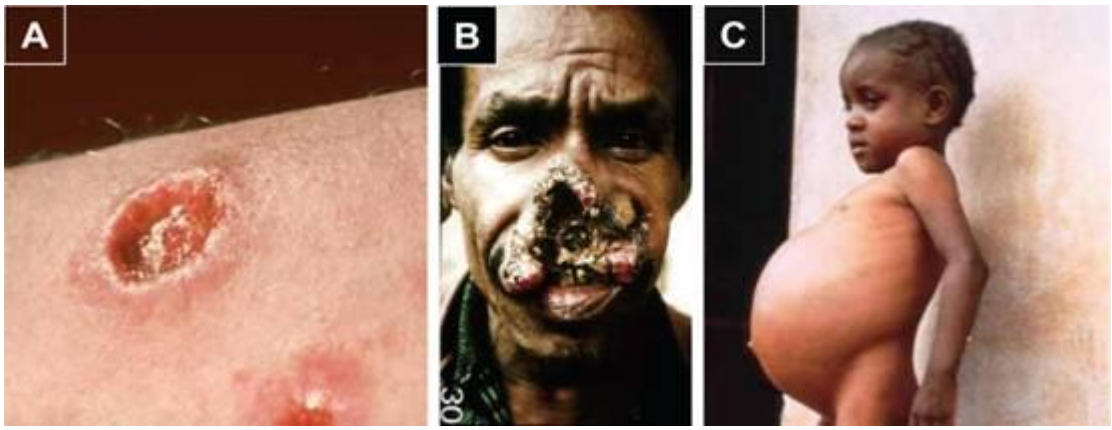


Figure 1: Clinical Manifestation of Leishmaniases – A: Skin lesion of cutaneous leishmaniasis, **B**: Mucocutaneous leishmaniasis, **C**: Visceral leishmaniasis.[2]

Cutaneous leishmaniasis (**A**) is considered the least severe of the three. It is caused by several species of *Leishmania* such as *L. major* and *L. tropica* causing singular ulcerative or nodular lesions at or near the area of insect exposure. They are mostly found at exposed areas such as face, forearms or lower legs and persist for weeks or months. Most of simple CL lesions are self-healing but in some cases, a mucocutaneous tissue can evolve.[1,3]

Mucocutaneous leishmaniasis (**B**), also known as espundia, is caused by *L. brasiliensis.* ML is a more complicated version of CL which can appear months to years after the first resolution of lesions. Its manifestation can lead to the destruction of nose, oro-, nasopharynx and eye-lid tissues, and can affect the function of the respiratory system.[1,3]

Visceral leishmaniasis (**C**), also known as kala-azar, black fever or Dumdum fever, mostly caused by *L. Donovani* and *L. infantum*, is considered the most severe of the three clinical manifestations of leishmaniases. If left untreated, the fatality is as high as 100% within two years. It is defined by irregular bouts of fever, substantial weight loss, swelling of spleen and liver, and anemia.[1,4,5]

1.1.2. Life Cycle of *Leishmania* (Fig. 2)

The female sandfly injects promastigotes, the infect stage, in the vector's (i.e. human, dog) body during blood meals by its proboscis (**1**), and the promastigotes are being phagocytized by macrophages and other types of mononuclear cells (**2**). There they transform into the tissue stage of the parasite called amastigotes (**3**), and further multiply by simple division and infect other macrophages (**4**). Non-infected sandflies become infected by ingesting infected cells during blood meals (**5**, **6**). The amastigotes transform into the promastigote forms in the gut (**7**), divide and migrate back to the proboscis (**8**). The exact type of parasite and host are the factors which influence whether the infection becomes symptomatic and whether cutaneous or visceral form occurs.[6]

Infected humans and other mammals such as dogs, foxes or small rodents are often defined as reservoirs of the disease. Treatment for animals could be a significant help in lowering the incidence of leishmaniases.[1,7]

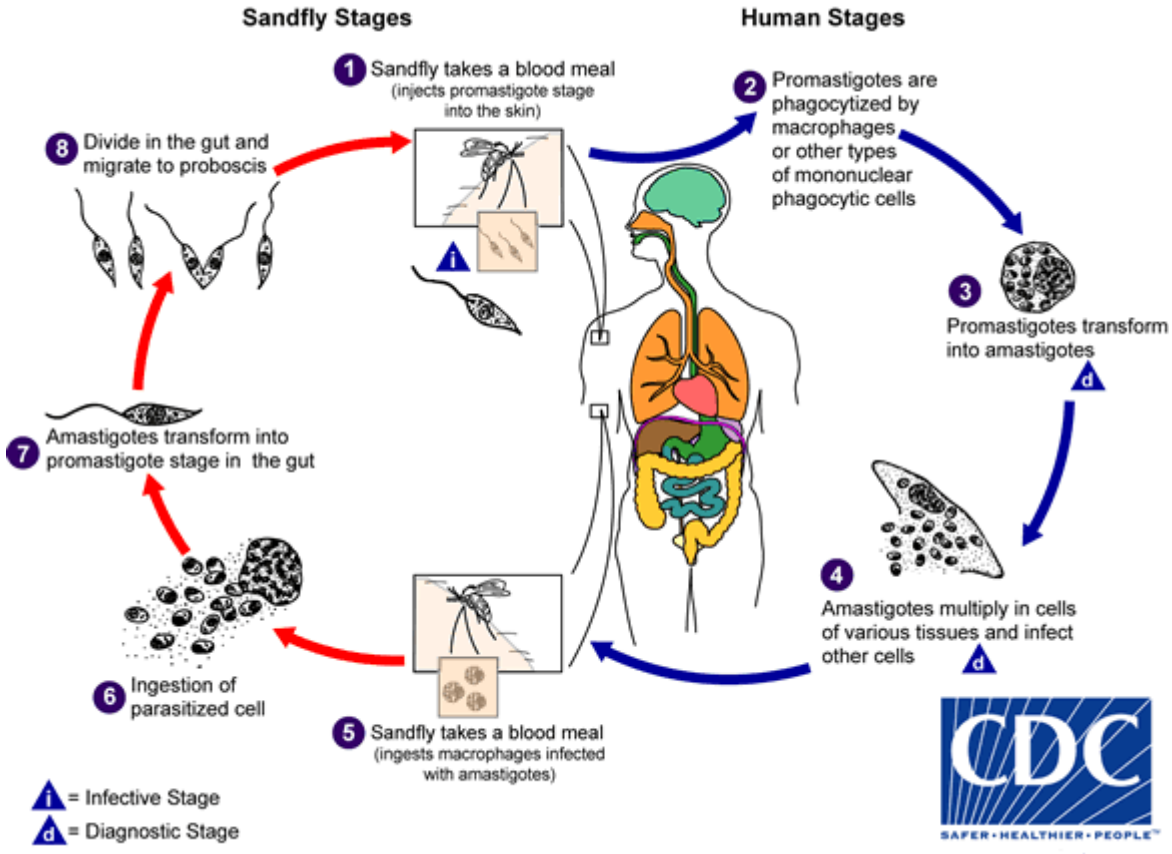
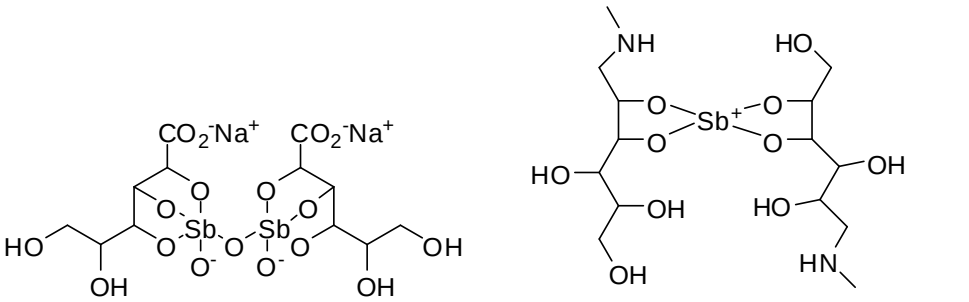


Figure 2: Life Cycle of *Leishmania*.[6]

1.2. Current Treatment

There are a number of therapies for various forms of leishmaniases and the first-line preferences depend on the regional practice and type of disease.[1]

I. Pentavalent Antimonials



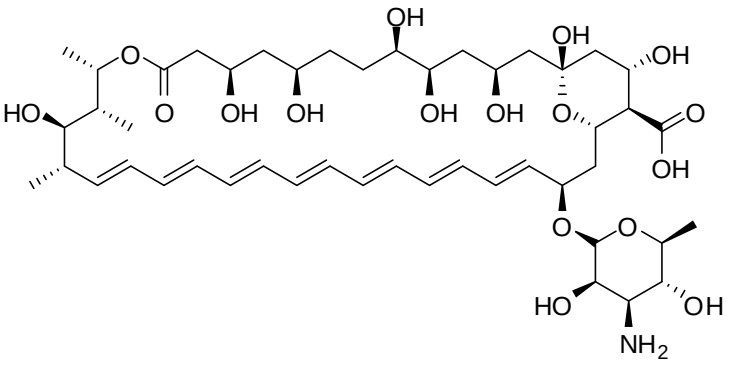
sodium stibogluconate - Pentostam meglumine antimoniate - Glucantime

Figure 3: Structure of Sodium Stiboglucanate and Meglumine Antimoniate

Meglumine antimoniate and sodium stibogluconate are two currently available pentavalent antimonials used in the treatment. The injection may be given intramuscularly or intravenously through a slow infusion or administered intralesionally for the treatment of the cutaneous form. These drugs constitute the first-line treatment although there is a significant increase in clinical resistance.[1,8]

When antimonials fail, amphotericin B and pentamidine are the second-line antiparasitics.

II. Amphotericin B



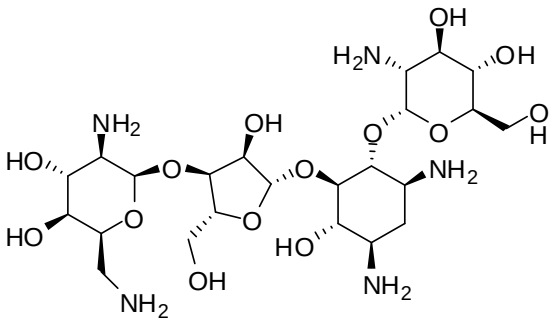
amphotericin B

Figure 4: Structure of Amphotericin B

Two forms of this polyene antibiotic are known to be effective for the treatment of leishmaniases – deoxycholate and liposomal, both administered intravenously. Although the liposomal form is known to be more efficient, to have less adverse effects and shorter time of treatment than the deoxycholate one, its clinical use is limited due to high cost.[1,3]

Lower doses of the liposomal form in combination with miltefosine or paromomycine have been shown to be effective with shorter treatment time.[9]

III. Paromomycine

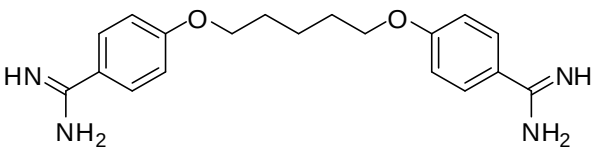


paromomycine

Figure 5: Structure of Paromomycine

Paromomycine is an aminoglycoside antibiotic used systemically for visceral and mucocutaneous form, and topically in the treatment of cutaneous leishmaniasis. Its systemic use needs to be monitored because its therapeutic index is very low. The drug can easily manifest oto-, nephro- and neurotoxic effects. It is often used in combination with liposomal amphotericin B.[1,3]

IV. Pentamidine



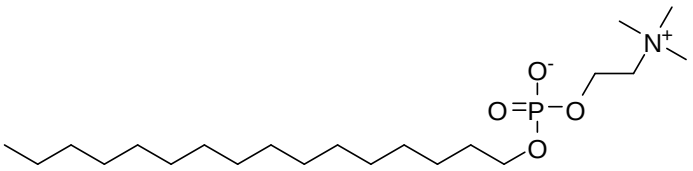
pentamidine

Figure 6: Structure of Pentamidine

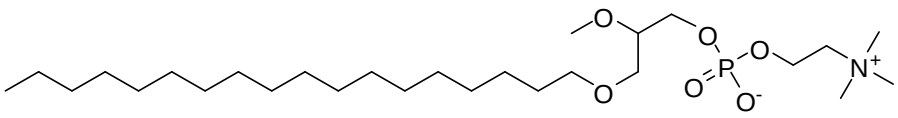
Pentamidine is a symmetric molecule containing etheric and carboamidine functional groups.

Pentamidine isethionate injection can be given intramuscularly or, preferably, by intravenous infusion. Use of this drug is highly limited by its severe adverse effects such as hypoglycemia, worsening or developing diabetes mellitus, myocardial and renal toxicity, liver enzyme abnormalities and its undesired influence on the bone marrow. Patients treated with this drug require careful monitoring.[1,3]

V. Miltefosine and Edelfosine



miltefosine - Impavido, Miltex



edelfosine

Figure 7: Structure of Miltefosine and Edelfosine

These alkylphosphocholine drugs were originally investigated as oral anticancer drugs.[1,10]

Miltefosine is the only oral drug used in the treatment of visceral leishmaniasis in both children and adults. It can also be used in combination with pentamidine. This drug is well tolerated and does not have any severe adverse effects, except its potent teratogenicity. For this reason, its prescription to pregnant women is prohibited.[3]

VI. Azoles

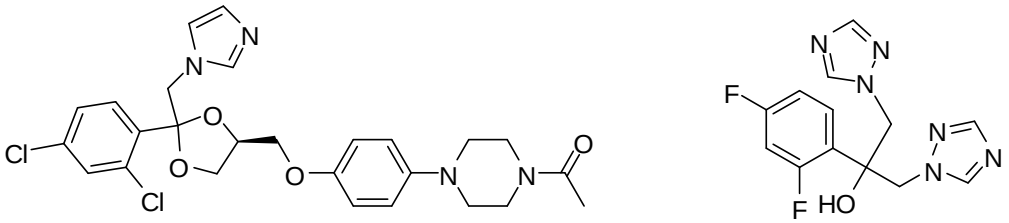
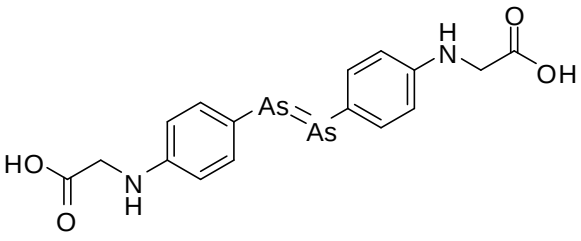


Figure 8: Structure of Ketoconazole and Fluconazole

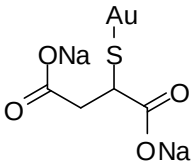
Azoles have also displayed very high *in vitro* antileishmanial activity, but have not been proven as efficient as other antileishmanial drugs in clinical practice. Ketoconazole and fluconazole administered orally have shown certain effect in the treatment of the cutaneous lesions.[1,3]

1.3. Selenium Containing Compounds in Treatment of Leishmaniases

Metal-based drugs have been used to fight against parasitic diseases for many years from the beginning of the 20th century when arsenophenylglycine (Fig. 9) was employed in the treatment of the sleeping sickness, also known as the Trypanosoma disease. Following this discovery, a wide spectrum of metal-based drugs has been synthesized and used in the treatment of parasitic and other diseases.[8] In 1987, 10 patients with visceral leishmaniasis were treated with sodium aurothiomalate (Fig. 9) with excellent clinical response.[11]



arsenophenylglycine



sodium aurothiomalate

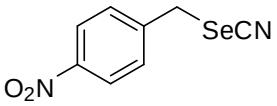
Figure 9: Structure of Arsenophenylglycine and Sodium Aurothiomalate

Recently, the development and use of metal complexes as potent antileishmanial agents is being thoroughly explored, and some organometallic and coordination complexes of palladium, gold, iridium, rhodium, platinum and zinc were tested against *Leishmania*.[12] In addition, chemotherapeutics based on platinum, copper and silver used as DNA intercalators were also examined and showed significant leishmanicidal activity.[13]

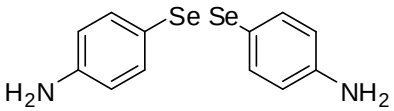
Based on the study of the relationship between plasma levels of trace elements such as copper, selenium and zinc and immunological response of studied subjects, increased concentration of selenium in the plasma has been identified as a new defensive strategy against *Leishmania* infection.[14]

Due to the persistent need for innovative drugs for the treatment of leishmaniases and success in the previous investigation of the activity of selenium containing compounds, new analogues such as selenocyanates, diselenides and selenosulfonamides have been investigated. The most potent compounds of each type are displayed in Figure 10. Their activities against amastigotes expressed as $IC_{50} \pm SD$ (μM), cytotoxic activity in THP-1 cells and selectivity

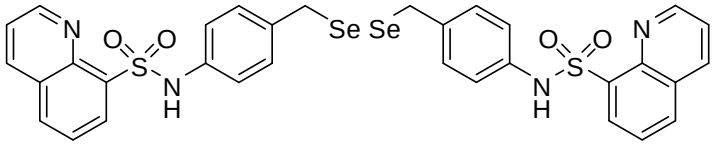
indexes (SI) in comparison with the reference drugs miltefosine and edelfosine are shown in Table 1.[10,15]



4-nitrobenzylselenocyanate **SeCN**



bis(4-aminophenyl)diselenide **Se-Se**



N,*N*'-(4,4'-diselanediylbis(methylene)bis(4,1-phenylene))diquinoline-8-sulfonamide **SA**

Figure 10: Most Potent Selenocyanate, Diselenide and Selenosulfonamide Compounds

Table 1. Biological Activity of Selected Se Derivatives Against *L. infantum* intracellular Amastigotes

Compound	**IC_{50} ± SD[a]**	**THP-1 ± SD[b]**	**SI[c]**
SeCN	0.68 ± 0.08	16.8 ± 1.8	25
Se-Se	0.65 ± 0.02	15.3 ± 0.8	24
SA	0.84 ± 0.04	>25	> 30
Edelfosine	0.82 ± 0.13	4.96 ± 0.2	6
Miltefosine	2.84 ± 0.10	18.5 ± 0.6	7

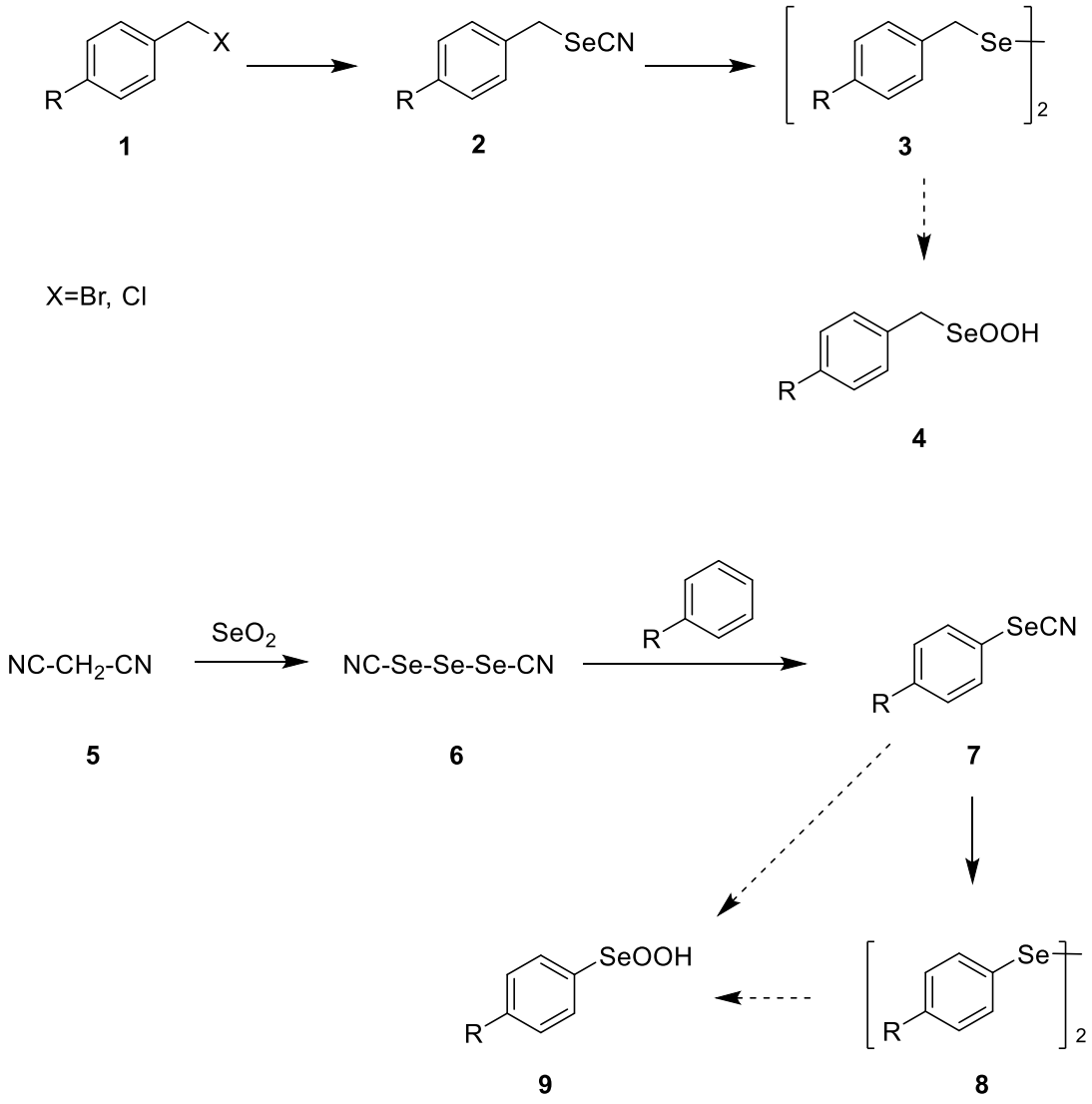
a - Half maximal inhibitory concentration of compounds against *L. infantum* intracellular amastigotes
b - Half maximal inhibitory concentration of compounds against THP-1 cells
c – Ratio of IC_{50} against L. infantum (a) and IC_{50} against THP-1 cells (b)

In vitro activities of these compounds against amastigotes are comparable to those of the reference drugs. However, their selectivity index values (ratio of IC_{50} values of the compounds against THP-1 cell relative to those against *L. infantum* amastigotes) are 4 to 5 times and 3.4 to 4.3 times higher than those obtained for the reference drugs edelfosine and miltefosine, respectively. These potent compounds are nowadays in different phases of clinical trials and their selectivity, toxicity and mechanism of action studies are being investigated.[10,15]

Consequently, novel selenium analogues, seleninic acids, are being designed and synthesized.

2. AIM OF WORK

The aim of this work was to synthesize seleninic acid analogues of the previously synthesized and biologically evaluated selenocyanates (**2, 7**) and diselenides (**3, 8**) with various substituents. These seleninic acid (**4, 9**) derivatives were also expected to possess high activity against *Leishmania infantum*.



Scheme 1 - Aim of Work

Another goal was to evaluate biological activity and toxicity of the products obtained.

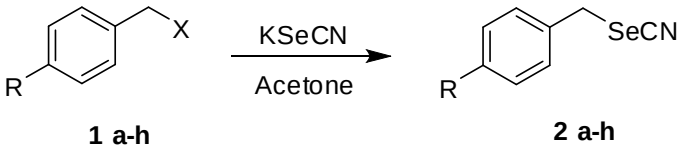
3. RESULTS AND DISCUSSION

3.1. Synthesis of Selenocyanates

3.1.1. Aliphatic Selenocyanates

General procedure for the synthesis of aliphatic selenocyanates is shown in Scheme 2. Direct nucleophilic selenocyanation using benzyl halide **1** and potassium selenocyanate as the reactants is the most common way of incorporating selenium into organic compounds.[16]

Nucleophilic substitution of the halogen atom by the selenocyanate group proceeds upon heating the reaction mixture under reflux for three hours. This method, employing acetone as the solvent, afforded significant yields for all derivatives shown in Table 2. [10]



1 a-h **2 a-h**

X=Br, Cl

Scheme 2 - Synthesis of Aliphatic Selenocyanates

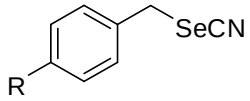


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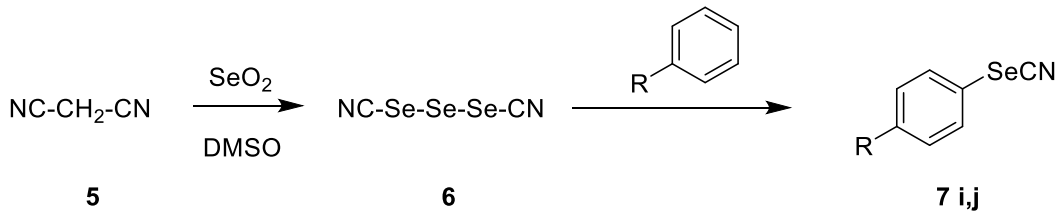
Table 2. Aliphatic Selenocyanates

Compound	–R	–X	Yield
2a	–H	–Br	66 %
2b	$-CH_3$	–Br	73 %
2c	$-O-CH_3$	–Cl	81%
2d	$-S-CH_3$	–Br	83 %
2e	–C≡N	–Br	85 %
2f	$-NO_2$	–Br	94 %
2g	$-CF_3$	–Br	85 %
2h	–Br	–Br	83 %

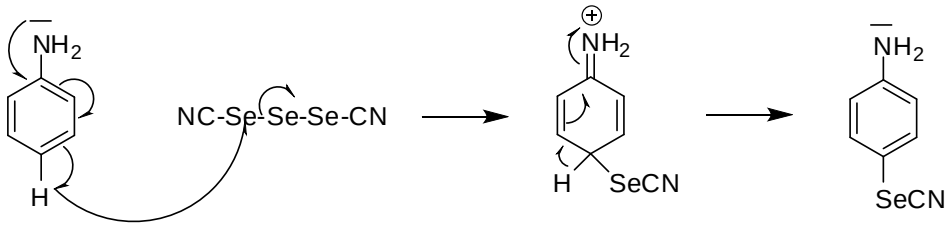
3.1.2. Aromatic Selenocyanates

Selenocyanation with triselenium dicyanate (TSD) **6** is used for direct incorporation of selenocyanide group in activated aryl compounds with free *para* position. The most common way of TSD synthesis is oxidative coupling of malononitrile **5** with selenium dioxide (Scheme 3). This reaction is exothermic with evolution of CO_2 and N_2. TSD can be isolated from the mixture by dilution with water in about 36% yields. However, it was discovered that its isolation is not necessary for further oxidative coupling of TSD with the reactant. Moreover, the presence of water rapidly decreases the yield. [17]



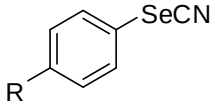
Scheme 3 - Synthesis of Aromatic Selenocyanates

The mechanism of oxidative coupling is described in Scheme 4 on compound **7i**. It is a typical example of *para*-directed electrophilic aromatic substitution.



Scheme 4 - Electrophilic Aromatic Substitution

Aromatic selenocyanates obtained via this reaction are shown in Table 3.



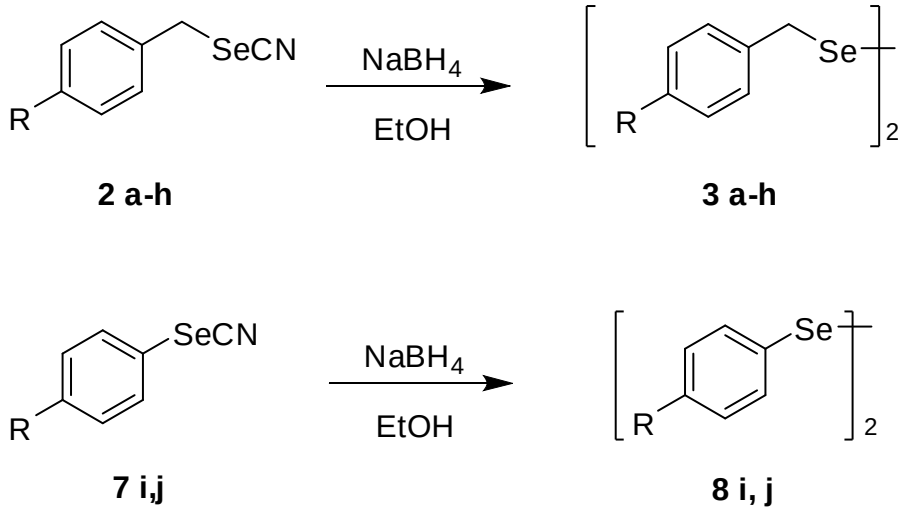
7

Table 3. Aromatic Selenocyanates

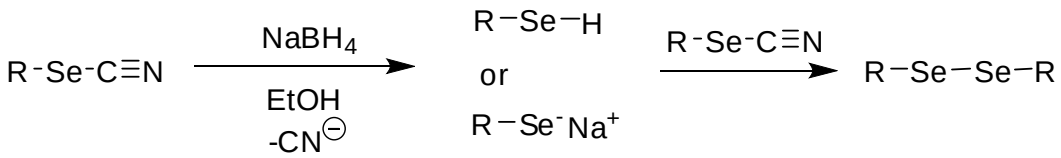
Compound	–R	Yield
7i	$-NH_2$	78 %
7j	$-N(CH_3)_2$	83 %

3.2. Synthesis of Diselenides

Reaction of selenocyanate derivatives with sodium borohydride leads to the corresponding symmetric diselenide compounds (Scheme 5). Sodium borohydride reduces selenocyanate group which leads to the formation of selenol or sodium selenide intermediate which attacks another selenocyanate molecule (Scheme 6). [10,18]

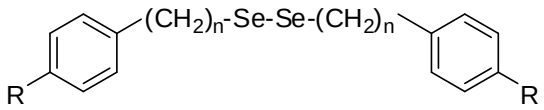


Scheme 5 - Synthesis of Diselenides



Scheme 6 - Selective Reduction of Selenocyanates to Diselenides

Diselenide compounds obtained from this reaction are displayed in Table 4.



3, 8

Table 4. Diselenides

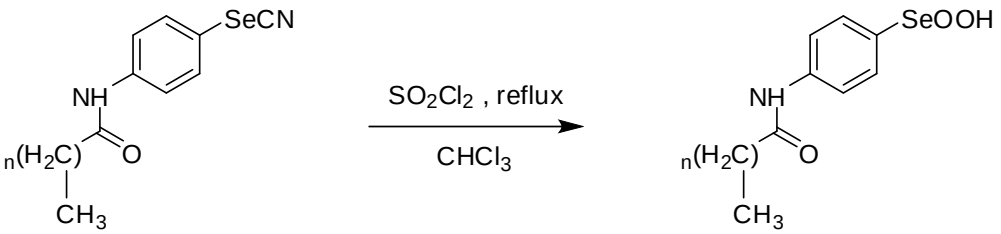
Compound	–R	n	Yield
3a	–H	1	69 %
3b	$-CH_3$	1	85 %
3c	$-O-CH_3$	1	68 %
3d	$-S-CH_3$	1	58 %
3e	–C≡N	1	84 %
3f	$-NO_2$	1	75 %
3g	$-CF_3$	1	77 %
3h	–Br	1	67 %
8i	$-NH_2$	0	80 %
8j	$-N(CH_3)_2$	0	91 %

3.3. Synthesis of Seleninic Acids

We assumed that oxidation of selenocyanates and diselenides would furnish the corresponding seleninic acid derivatives, which tend to be reactive and unstable.

The most common way to prepare seleninic acids is by oxidization of diselenides using aqueous hydrogen peroxide. This protocol, however, is not applicable for the synthesis of all seleninic acids. [16,19] This synthetic way employed 1,4-dioxane or dichloromethane as the most appropriate solvents, and the reaction time ranged from 10 minutes to 72 hours. [19–22]

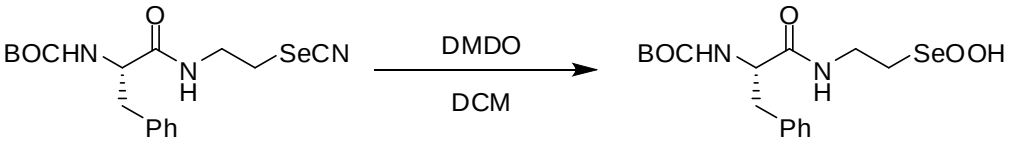
Other methods recently described in the literature involve the use of sulfuryl chloride as an oxidative agent and the corresponding phenyl selenocyanate in chloroform (Scheme 7). This method led to the synthesis of amphiphilic aromatic seleninic acids. [16,23]



n = 6, 8, 10, 12, 14

Scheme 7 - Synthesis of Amphiphilic Seleninic Acids

The third reported way of seleninic acid synthesis used oxidation by dimethyl dioxirane (DMDO) in dichloromethane. Oxidation of aliphatic selenocyanates gave up to 70% yields (Scheme 8). Unfortunately, this oxidative agent is not commercially available due to its high instability. Its preparation is highly inefficient, resulting in very low yields (less than 3%) of diluted solution of DMDO in acetone. For this reason, we did not consider using this reagent. [16,24,25]

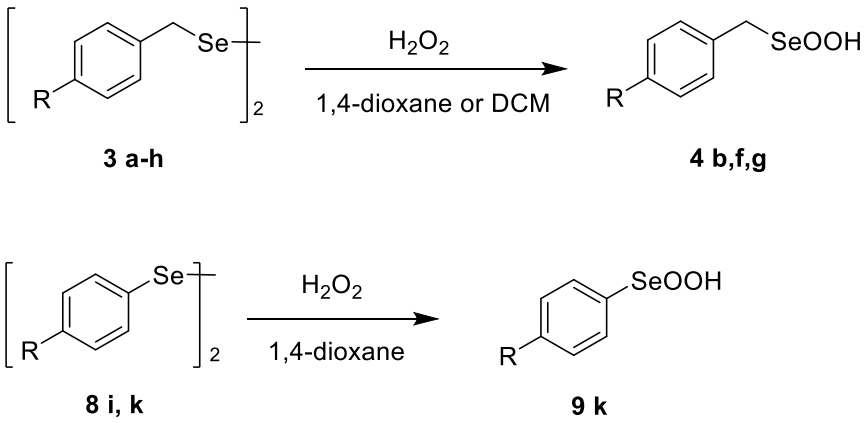


Scheme 8 - Oxidation of Selenocyanates by DMDO

3.3.1. Oxidation with Hydrogen Peroxide

Nine of the diselenide compounds **3a-h** and **8i** were treated with hydrogen peroxide in 1,4-dioxane or DCM. We succeeded in the preparation of four seleninic acid compounds (**4b**, **4f**, **4g** and **9k**). Compound **9k** was synthesized from a commercially available diphenyl diselenide **8k**.

The reaction was run in 1,4-dioxane, and excess H_2O_2 was slowly added to the solution. The solution was cooled to 0°C in order to lower the chances of any undesirable processes or decomposition of reagents or products. When the addition was complete, ice was added and the mixture was allowed to warm up to room temperature. The resultant precipitates of **4b**, **4f**, **8k** were washed with ice cold water.



Scheme 9 - Oxidation of Diselenides with H_2O_2

As regards unsuccessful attempts, we switched solvent to DCM and increased reaction time to 24 hours. In this way, we have been successful in preparing compound **4g**.

No other changes including further prolongation of the reaction time, temperature increase or application of another oxidative agent (SO_2Cl_2) with aromatic selenocyanates as substrates led to isolation of the desired products.

Table 5. Oxidation of substrates 3 and 8 with H_2O_2

Compound	–R	Solvent	n	Yield
4a	–H	1,4-dioxane or DCM	1	0 %
4b	$-CH_3$	1,4-dioxane	1	32 %
4c	$-O-CH_3$	1,4-dioxane or DCM	1	0 %
4d	$-S-CH_3$	1,4-dioxane or DCM	1	0 %
4e	–C≡N	1,4-dioxane or DCM	1	0 %
4f	$-NO_2$	1,4-dioxane	1	72 %
4g	$-CF_3$	DCM	1	15 %
4h	–Br	1,4-dioxane or DCM	1	0 %
9i	$-NH_2$	1,4-dioxane or DCM	0	0 %
9k	–H	1,4-dioxane	0	19 %

3.4. Antileishmanial Activity Evaluation

Due to the promising antileishmanial activities of the previously synthesized selenium compounds such as selenocyanates, diselenides and selenosulfonamides,[10,15] these seleninic acid compounds were to be evaluated for their activity against *Leishmania infantum* intracellular amastigotes at the Department of Microbiology and Parasitology of the University of Navarra.

As there were only four compounds synthesized and they were susceptible to decomposition, no screening has been performed.

4. CONCLUSIONS

In summary, four seleninic acid compounds (**4b**, **4f**, **4g**, **9k**) have been synthesized through different methodologies.

The first one, using hydrogen peroxide as the reagent and aliphatic (**3a-h**) or aromatic (**8i, 8j**) diselenides as substrates led to the synthesis of four desired products (**4b**, **4f**, **9k** and **4g**). The reason why the methodology was not applicable to other compounds remains unclear.

The second, using sulfuryl chloride and aromatic selenocyanate derivatives (**7i, 7j**) as substrates was not successful. There are a number of factors that contributed to the failure: contamination/decomposition of the reagent, insufficient reaction time, decomposition of substrate during the reaction, equipment or solvent contamination or a poor solvent selection.

The relative instability of seleninic acid derivatives has also been well established.

Three of the final products (**4b**, **4f** and **4g**) have not yet been reported in the literature.

All four final products were to be assayed for their activity against *Leishmania infantum* intracellular amastigotes, but no screening has been performed.

5. EXPERIMENTAL SECTION

5.1. General Methods

5.2. Chemistry

Melting points were determined with a Mettler FP82 + FP80 apparatus and are not corrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 Ultrashield™ spectrometer using TMS as the internal standard. The IR spectra were obtained on Thermo Nicolet FT-IR Nexus spectrophotometer with KBr pellets. Mass spectrometry was carried out on a MS-DIP, system Agilent MSD/DS 5973N (G2577A). Elemental microanalyses were carried out on vacuum-dried samples using a LECO CHN-900 Elemental Analyzer. Silica gel 60 (0.040-0.063 mm, Merck) was used for column chromatography and Alugram® SIL G/UV_{254} (Layer: 0.2 mm, Machereye-Nagel GmbH & Co) was used for thin-layer chromatography. Chemicals were purchased from E. Merck, Scharlau, Panreac Química, Sigma-Aldrich Química, Acros Organics and Lancaster.

5.2.1. General Procedure for Synthesis of Selenocyanates

5.2.1.1. Aliphatic Selenocyanates

To a stirred solution of corresponding halogenide derivative **1 a-h** (4.0 mmol) solved in acetone (50 mL), equimolar amount of KSeCN (4 mmol) was added and white precipitate (KBr) was formed immediately. The mixture was left stirring under reflux. After 3 hours, the precipitate was filtered off and the filtrate was evaporated until receiving a solid form of the corresponding selenocyanate **2 a-h**.

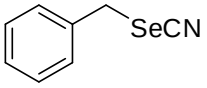
The solid was washed with water (50 mL), recrystalized from ethanol and dried under vacuum.

All selenocyanate compounds were used as reactives for further reactions.

Benzylselenocyanate (**2a**)

Molecular formula: C_8H_7NSe

Molecular weight: 196 g/mol



Melting point: 68-70°C

Appearance: white solid

Experimental procedure: From benzyl bromide **1a** and potassium selenocyanate according to the general procedure described in section 5.2.1.1. The synthesis of this compound has been previously reported by Krief et al..[18] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 2146 (s, C≡N);

NMR-^{1}H (DMSO-d_6) ppm: 4.31 (s, 2H); 7.37-7.39 (m, 5H);

NMR-^{13}C (DMSO-d_6) ppm: 33 (1C); 105 (1C); 129 (5C); 139 (1C);

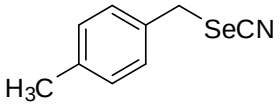
Elemental analysis, Calcd/Found (%): *C:* 48.98/48.90; *H:* 3.57/3.80; *N:* 7.14/6.68;

MS (70 eV) (m/z): 91 (100); 65 (22); 51 (9).

4-Methylbenzylselenocyanate (**2b**)

Molecular formula: C_9H_9NSe

Molecular weight: 210 g/mol



Melting point: 51-52°C

Appearance: yellow solid

Experimental procedure: From 4-methylbenzyl bromide **1b** and potassium selenocyanate according to the general procedure described in section 5.2.1.1. The synthesis of this compound has been previously reported by Jacob et al.[26] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 2148 (m, C≡N);

NMR-^{1}H (DMSO-d_6) ppm: 2.30 (s, 3H); 4.29 (s, 2H); 7.17 (d, 2H, *J* = 8 Hz), 7.26 (d, 2H, *J* = 8 Hz);

NMR-^{13}C (DMSO-d_6) ppm: 21 (1C); 33 (1C); 105 (1C); 129 (2C); 130 (2C); 136 (1C); 138 (1C);

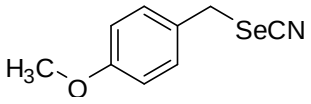
Elemental analysis, Calcd/Found (%): *C:* 51.43/51.54; *H:* 4.29/4.42; *N:* 6.67/6.42;

MS (70 eV) (m/z): 177 (5); 105 (100); 77 (11).

4-Methoxybenzylselenocyanate (**2c**)

Molecular formula: C_9H_9ONSe

Molecular weight: 226 g/mol



Melting point: 52-53°C

Appearance: light brown-yellow solid

Experimental procedure: From 4-methoxybenzyl chloride **1c** and potassium selenocyanate according to the general procedure described in section 5.2.1.1.

IR (KBr) cm^{-1}: 2146 (s, C≡N);

NMR-^{1}H (DMSO-d_6) ppm: 3.76 (s, 3H); 4.31 (s, 2H); 6.93 (d, 2H, *J* = 8.7 Hz); 7.31 (d, 2H, *J* = 8.7 Hz);

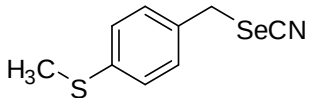
NMR-^{13}C (DMSO-d_6) ppm: 34 (1C); 56 (1C); 106 (1C); 115 (2C); 131 (3C); 160 (1C);

Elemental analysis, Calcd/Found (%): *C:* 47.79/47.69; *H:* 3.98/4.30; *N:* 6.20/5.92.

4-Methylthiobenzylselenocyanate (**2d**)

Molecular formula: C_9H_9NSSe

Molecular weight: 242 g/mol



Melting point: 81-83°C

Appearance: clear brown solid

Experimental procedure: From 1-brommethyl-4-methylthiobenzene **1d** and potassium selenocyanate according to the general procedure described in section 5.2.1.1. The synthesis of this compound has been previously reported by Plano et al.[10] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 2143 (s, C≡N); 1490 (s, S-CH_3);

NMR-^1H (DMSO-d_6) ppm: 2.47 (s, 3H); 4.29 (s, 2H); 7.24 (d, 2H, *J* = 8 Hz); 7.31 (d, 2H, *J* = 8 Hz);

NMR-^{13}C (DMSO-d_6) ppm: 15 (1C); 33 (1C); 105 (1C); 126 (2C); 130 (2C); 135 (1C); 138 (1C);

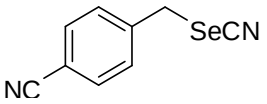
Elemental analysis, Calcd/Found (%): *C:* 44.62/44.63; *H:* 3.71/3.80; *N:* 5.78/5.55;

MS (70 eV) (m/z): 243 ($M^{+\cdot}$, 4); 137 (100); 122 (27); 78 (6).

4-Cyanobenzylselenocyanate (**2e**)

Molecular formula: $C_9H_6N_2Se$

Molecular weight: 221 g/mol



Melting point: 129-131°C

Appearance: yellow solid

Experimental procedure: From 4-(bromomethyl)benzonitrile **1e** and potassium selenocyanate according to the general procedure described in section 5.2.1.1. The synthesis of this compound has been previously reported by Prabhu et al.[27] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 2229 (s, C≡N); 2144 (s, C≡N);

NMR-^{1}H (DMSO-d_6) ppm: 4.36 (s, 2H); 7.56 (d, 2H, *J* = 8 Hz); 7.85 (d, 2H, *J* = 8 Hz);

NMR-^{13}C (DMSO-d_6) ppm: 32 (1C); 105 (1C); 111 (1C); 119 (1C); 130 (2C); 133 (2C); 145 (1C);

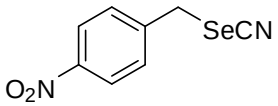
Elemental analysis, Calcd/Found (%): *C:* 49.05/48.95; *H:* 2.76/2.69; *N:* 12.47/12.33;

MS (70 eV) (m/z): 222 ($M^{+\cdot}$, 4); 116 (100); 89 (24); 63 (7).

4-Nitrobenzylselenocyanate (**2f**)

Molecular formula: $C_8H_6O_2N_2Se$

Molecular weight: 241 g/mol



Melting point: 120-122°C

Appearance: orange solid

Experimental procedure: From 4-nitrobenzyl bromide **1f** and potassium selenocyanate according to the general procedure described in section 5.2.1.1. The synthesis of this compound has been previously reported by Maartmann-Moe et al.[28] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 2147 (m, C≡N); 1518 (s, C-NO_2);

NMR-^{1}H (DMSO-d_6) ppm: 4.41 (s, 2H); 7.64 (d, *J* = 8 Hz); 8.25 (d, 2H, *J* = 8 Hz);

NMR-^{13}C (DMSO-d_6) ppm: 32 (1C); 105 (1C); 124 (2C); 130 (2C); 147 (2C); 147 (1C);

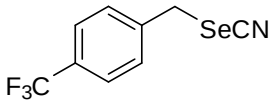
Elemental analysis, Calcd/Found (%): *C:* 39.83/39.96; *H:* 2.49/2.50; *N:* 11.62/11.56;

MS (70 eV) (m/z): 242 ($M^{+\cdot}$, 6); 169 (4); 136 (100); 106 (29); 89 (41); 78 (46); 63 (15); 51 (5).

4-(Trifluoromethyl)benzylselenocyanate (**2g**)

Molecular formula: $C_9H_6F_3NSe$

Molecular weight: 264 g/mol



Melting point: 54-55°C

Appearance: white solid

Experimental procedure: From 4-(trifluoromethyl)benzyl bromide **1g** and potassium selenocyanate according to the general procedure described in section 5.2.1.1. The synthesis of this compound has been previously reported by Plano et al.[10] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 2155 (s, C≡N); 1326 (s, C-F_3);

NMR-^{1}H (DMSO-d_6) ppm: 4.37 (s, 2H); 7.59 (d, 2H, *J* = 8 Hz); 7.75 (d, 2H, *J* = 8 Hz);

NMR-^{13}C (DMSO-d_6) ppm: 32 (1C); 105 (1C); 124 (1C); 126 (2C); 129 (1C); 130 (2C); 144 (1C);

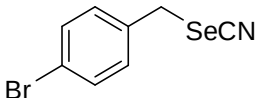
Elemental analysis, Calcd/Found (%): C: 40.90/41.10; H: 2.27/2.27; N: 5.30/4.94;

MS (70 eV) (m/z): 215 (10); 159 (100); 140 (7); 109 (16).

4-Bromobenzylselenocyanate (**2h**)

Molecular formula: C_8H_6BrNSe

Molecular weight: 275 g/mol



Melting point: 60-62°C

Appearance: brownish yellow solid

Experimental procedure: From 4-bromobenzyl bromide **1h** and potassium selenocyanate according to the general procedure described in section 5.2.1.1. The synthesis of this compound has been previously reported by Plano et al.[10] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 2149 (s, C≡N); 1000 (s, C-Br);

NMR-^{1}H (DMSO-d_6) ppm: 4.29 (s, 2H, CH_2-Se); 7.33 (d, 2H, *J* = 8 Hz); 7.57 (d, 2H, *J* = 8 Hz);

NMR-^{13}C (DMSO-d_6) ppm: 32 (1C); 105 (1C); 121 (1C); 132 (4C); 138 (1C);

Elemental analysis, Calcd/Found (%): *C:* 34.92/35.42; *H:* 2.18/2.49; *N:* 5.09/4.74;

MS (70 eV) (m/z): 183 (12); 169 (100); 90 (32); 63 (10).

5.2.1.2. Aromatic Selenocyanates

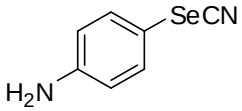
To a stirred solution of malononitrile **5** (3.0 mmol) in DMSO (15 mL), selenium dioxide (6.0 mmol) was added and the mixture was stirred for 15 minutes at room temperature in order to obtain triselenium dicyanate **6**. When the reaction stopped developing gas a corresponding aromatic amine (5.0 mmol) was added. The mixture was stirred for 2 hours at room temperature. Cold water (100 mL) was added to the solution and the resulting precipitate **7 i,j** was filtered off and continuously washed with water until the water became clear. The product was left to dry under reduced pressure.

All selenocyanate compounds were used as reactives for further reactions.

Anilin-4-ylselenocyanate (**7i**)

Moecular formula: $C_7H_6N_2Se$

Molecular weight: 197 g/mol



Melting point: 82-84°C

Appearance: yellow-green solid

Experimental procedure: From aniline according to the general procedure described in section 5.2.1.2. The synthesis of this compound has been previously reported by Kachanov et al.[17] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 3240 (s, NH_2); 2143 (m, C≡N);

NMR-^{1}H ($CDCl_3$) ppm: 6.67 (d, 2H, *J* = 8.7 Hz); 7.48 (d, 2H, *J* = 8.7 Hz);

NMR-^{13}C ($CDCl_3$) ppm: 103 (1C); 108 (1C); 117 (2C); 137 (2C); 149 (1C);

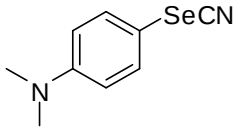
Elemental analysis, Calcd/Found (%): *C:* 42.64/42.49; *H:* 3.04/2.94; *N:* 14.21/14.42;

MS (70 eV) (m/z): 198 ($M^{+\cdot}$, 18); 184 (50); 172 (15); 118 (100); 91 (18); 80 (13); 65 (18).

4-(N,N-dimethylamino)phenylselenocyanate (**7j**)

Molecular formula: $C_9H_{10}N_2Se$

Molecular weight: 225 g/mol



Melting point: 100-101°C

Appearance: brown solid

Experimental procedure: From N,N-dimethylaniline according to the general procedure described in section 5.2.1.2. The synthesis of this compound has been previously reported by Kachanov et al.[17] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 2141 (m, C≡N);

NMR-^{1}H ($CDCl_3$) ppm: 3.02 (s, 6H, $2CH_3$); 6.67 (d, 2H, *J* = 9.1 Hz); 7.54 (d, 2H, *J* = 9.1 Hz);

Elemental analysis, Calcd/Found (%): *C:* 48.00/48.33; *H:* 4.44/4.54; *N:* 12.44/12.54;

MS (70 eV) (m/z): 226 ($M^{+\cdot}$, 38); 200 (20); 184 (8); 146 (100); 129 (6); 119 (17); 104 (10); 91 (7); 77 (10); 63 (6).

5.2.2. General Procedure for Synthesis of Diselenides

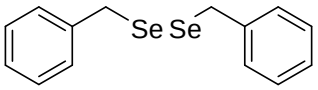
To a stirred solution of appropriate selenocyanate derivative **2 a-h** and **7 i,j** (3.0 mmol) in absolute ethanol (40 mL), $NaBH_4$ (0.75 mmol) was added in small portions with caution. The mixture was stirred for 1 hour at room temperature. The solvents were removed by rotary evaporation under reduced pressure and the residue **3 a-h** and **8 i,j** was washed with water (3 x 50 mL) and filtered off. The product was recrystallized from ethanol.

All diselenide compounds were used as reagents for further reactions.

Bisbenzyldiselenide (**3a**)

Molecular formula: $C_{14}H_{14}Se_2$

Molecular weight: 340 g/mol



Melting point: 83-85°C

Appearance: dark yellow solid

Experimental procedure: From benzylselenocyanate (**2a**) according to the general procedure described in section 5.2.2. The synthesis of this compound has been previously reported by Tian et al.[29] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 754 (s, Se-Se);

NMR-^{1}H (DMSO-d_6) ppm: 3.90 (s, 4H); 7.23-7.27 (m, 6H); 7.28-7.33 (m, 4H);

NMR-^{13}C (DMSO-d_6) ppm: 32 (2C); 128 (2C); 129 (4C); 130 (4C); 139 (2C);

Elemental analysis, Calcd/Found (%): *C:* 49.41/49.43; *H:* 4.12/4.24;

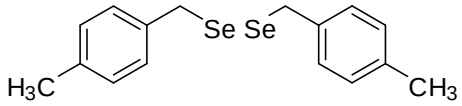
MS (70 eV) (m/z): 181 (11); 91 (100); 65 (12); 51 (2).

Bis(4-methylbenzyl)diselenide (**3b**)

Molecular formula: $C_{16}H_{18}Se_2$

Molecular weight: 368 g/mol

Melting point: 56-58°C



Appearance: yellow solid

Experimental procedure: From 4-methylbenzylselenocyanate (**2b**) according to the general procedure described in section 5.2.2. The synthesis of this compound has been previously reported by Tian et al.[29] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 714 (w, Se-Se);

NMR-^{1}H (DMSO-d_6) ppm: 2.26 (s, 6H); 3.89 (s, 4H); 7.12 (s, 8H);

NMR-^{13}C (DMSO-d_6) ppm: 21 (2C); 32 (2C); 129 (4C); 130 (4C); 136 (2C); 137 (2C);

Elemental analysis, Calcd/Found (%): *C:* 52.17/52.13; *H:* 4.89/4.77;

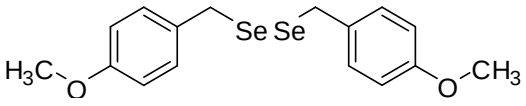
MS (70 eV) (m/z): 288 (9); 264 (9); 105 (100); 77 (8).

Bis(4-methoxybenzyl)diselenide (**3c**)

Molecular formula: $C_{16}H_{18}O_2Se_2$

Molecular weight: 400 g/mol

Melting point: 76°C



Appearance: yellow solid

Experimental procedure: From 4-methoxybenzylselenocyanate (**2c**) according to the general procedure described in section 5.2.2.

IR (KBr) cm^{-1}: 614 (Se-Se);

NMR-^{1}H (DMSO-d_6) ppm: 3.74 (s, 6H); 3.90 (s, 4H); 6.90 (d, 4H, *J* = 8 Hz); 7.19 (d, 4H, *J* =8 Hz);

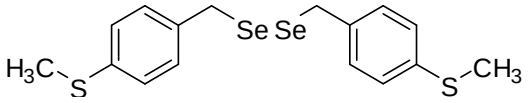
NMR-^{13}C (DMSO-d_6) ppm: 32 (2C); 56 (2C); 114 (4C); 131 (4C); 132 (2C); 159 (2C);

Elemental analysis, Calcd/Found (%): C:48.00/48.31; H: 4.50/4.83.

Bis(4-methythiobenzyl)diselenide (**3d**)

Molecular formula: $C_{16}H_{18}S_2Se_2$

Molecular weight: 432 g/mol



Melting point: 99-100°C

Appearance: clear brown solid

Experimental procedure: From 4-methylthiobenzylselenocyanate (**2d**) according to the general procedure described in section 5.2.2. The synthesis of this compound has been previously reported by Plano et al.[10] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 1491 (s, S-CH_3); 718 (w, Se-Se);

NMR-^{1}H (DMSO-d_6) ppm: 2.45 (s, 6H); 3.90 (s, 4H); 7.19 (s, 8H);

NMR-^{13}C (DMSO-d_6) ppm: 15 (2C); 32 (2C); 126 (4C); 130 (4C); 136 (2C); 137 (2C);

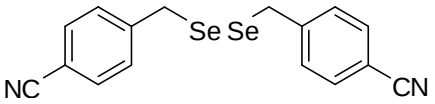
Elemental analysis, Calcd/Found (%): *C:* 44.44/44.12; *H:* 4.16/4.20;

MS (70 eV) (m/z): 137 (100); 122 (17); 91 (6); 78 (5).

Bis(4-cyanobenzyl)diselenide (**3e**)

M*olecular formula:* $C_{16}H_{12}N_2Se_2$

Molecular weight: 390 g/mol



Melting point: 136-137°C

Appearance: yellow solid

Experimental procedure: From 4-cyanobenzylselenocyanate (**2e**) according to the general procedure described in section 5.2.2. The synthesis of this compound has been previously reported by Prabhu et al.[27] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 2229 (s, C≡N); 729 (w, Se-Se);

NMR-^{1}H (DMSO-d_6) ppm: 4.02 (s, 4H, CH_2-Se, $CH_{2'}$-Se); 7.40 (d, 4H, *J* =8 Hz); 7.77 (d, 4H, *J* = 8 Hz);

NMR-^{13}C (DMSO-d_6) ppm: 31 (2C); 110 (2C); 119 (2C); 130 (4C); 133 (4C); 146 (2C);

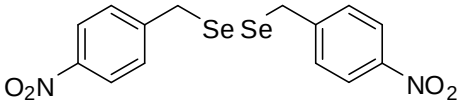
Elemental analysis, Calcd/Found (%): *C:* 49.23/49.04; *H:* 3.07/3.11; *N:* 7.18/7.07;

MS (70 eV) (m/z): 232 (33); 116 (100); 89 (21); 63 (5).

Bis(4-nitrobenzyl)diselenide (**3f**)

Molecular formula: $C_{14}H_{12}O_4N_2Se_2$

Molecular weight: 430 g/mol



Melting point: 99-100°C

Appearance: yellow solid

Experimental procedure: From 4-nitrobenzylselenocyanate (**2f**) according to the general procedure described in section 5.2.2. The synthesis of this compound has been previously reported by Prabhu et al.[27] and Degrand et al.[30] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 1516 (s, C-NO_2); 741 (m, Se-Se);

NMR-^{1}H (DMSO-d_6) ppm: 4.12 (s, 4H); 7.47 (d, 4H, *J* =9 Hz); 8.17 (d, 4H, *J* = 9 Hz);

NMR-^{13}C (DMSO-d_6) ppm: 30 (2C); 124 (4C); 130 (4C); 147 (2C); 148 (2C);

Elemental analysis, Calcd/Found (%): *C:* 39.07/39.09; *H:* 2.79/2.78; *N:* 6.51/6.37;

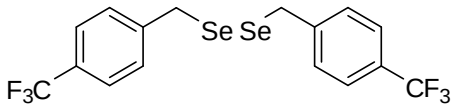
MS (70 eV) (m/z): 352 (20); 272 (10); 169 (11); 136 (100); 120 (12); 106 (30); 90 (39); 78 (52); 63 (15).

Bis(4-trifluoromethylbenzyl)diselenide (**3g**)

Molecular formula: $C_{16}H_{12}F_6Se_2$

Molecular weight: 476 g/mol

Melting point: 64-66°C



Appearance: yellow solid

Experimental procedure: From 4-trifluoromethylbenzylselenocyanate (**2g**) according to the general procedure described in section 5.2.2. The synthesis of this compound has been previously reported by Plano et al.[10] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 1325 (s, C-F_3); 825 (Se-Se);

NMR-1H (DMSO-d6) ppm: 4.04 (s, 4H); 7.43 (d, 4H, *J* =8 Hz); 7.67 (d, 4H, *J* = 8 Hz);

NMR-13C (DMSO-d6) ppm: 31 (2C); 123 (2C); 126 (4C); 128 (2C); 130 (4C); 145 (2C);

Elemental analysis, Calcd/Found (%): *C:* 40.34/40.79; *H:* 2.52/2.53;

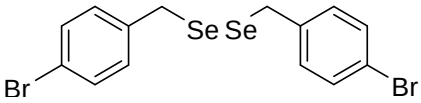
MS (70 eV) (m/z): 397 (7); 159 (100); 140 (6); 109 (15).

Bis(4-bromobenzyl)diselenide (**3h**)

Molecular formula: $C_{14}H_{12}Br_2Se_2$

Molecular weight: 498 g/mol

Melting point: 102-103°C



Appearance: yellow solid

Experimental procedure: From 4-bromobenzylselenocyanate (**2h**) according to the general procedure described in section 5.2.2. The synthesis of this compound has been previously reported by Wang et al.[31] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 1008 (s, C-Br); 710 (m, Se-Se);

NMR-^{1}H (DMSO-d_6) ppm: 3.93 (s, 4H); 7.19 (d, 4H, *J* =8 Hz); 7.51 (d, 4H, *J* = 8 Hz);

NMR-^{13}C (DMSO-d_6) ppm: 31 (2C); 120 (2C); 131 (4C); 132 (4C); 139 (2C);

Elemental analysis, Calcd/Found (%): *C:* 33.73/33.37; *H:* 2.41/2.31;

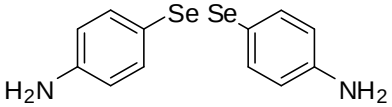
MS (70 eV) (m/z): 169 (100); 90 (27); 63 (8).

Bis(anilin-4-yl)diselenide (**8i**)

Moecular formula: $C_{12}H_{12}N_2Se_2$

Molecular weight: 342 g/mol

Melting point: 77-78°C



Appearance: bright yellow solid

Experimental procedure: From anilin-4-ylselenocyanate (**7i**) according to the general procedure described in section 5.2..2. The synthesis of this compound has been previously reported by Banks et al.[32] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 3414, 3328 (m, NH_2); 814 (m, Se-Se);

NMR-^1H ($CDCl_3$) ppm: 6.59 (d, 4H, *J* = 8.6 Hz); 7.39 (d, 4H, *J* = 8.6 Hz);

Elemental analysis, Calcd/Found (%): *C:* 42.10/42.00; *H:* 3.51/3.43; *N:* 8.19/8.13;

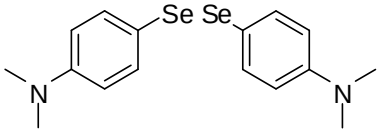
MS (70 eV) (m/z): 344 ($M^{+\cdot}$, 30); 264 (5); 184 (29); 172 (100); 145 (6); 121 (15); 91 (17); 80 (30); 65 (11).

Bis[4-(N,N-dimethylamino)phenyl]diselenide (**8j**)

Molecular formula: $C_{16}H_{20}N_2Se_2$

Molecular weight: 398 g/mol

Melting point: 114-115°C



Appearance: bright yellow solid

Experimental procedure: From 4-(N,N-dimethylamino)phenylselenocyanate (**7j**) according to the general procedure described in section 5.2.2. The synthesis of this compound has been previously reported by Pinto et al.[33] The spectral data of the compound were in agreement with published data.

IR (KBr) cm^{-1}: 802 (m, Se-Se);

NMR-^1H ($CDCl_3$) ppm: 3.00 (s, 12H); 6.62 (d, 4H, *J* = 9 Hz); 7.48 (d, 4H, *J* = 9 Hz);

Elemental analysis, Calcd/Found (%): *C:* 48.24/48.51; *H:* 5.02/5.05; *N:* 7.03/7.09;

MS (70 eV) (m/z): 400 ($M^{+\cdot}$, 22); 200 (100); 184 (11); 156 (2); 120 (5); 105 (4); 91 (2); 77 (3); 63 (1); 51 (1).

5.2.3. General Procedure for Synthesis of Seleninic Acids

5.2.3.1. Oxidation with Aqueous Hydrogen Peroxide

30% Aqueous hydrogen peroxide (1.5 mmol) was slowly added to a stirred, ice-cold solution of appropriate diselenide derivative **3 a-h**, **8i** and **8k** (0.5 mmol) in 1,4-dioxane or DCM (2 mL).

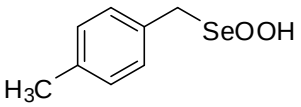
When using the 1,4-dioxane as solvent, ice (10 g) was added to the mixture and left stirring until melted. Resulting precipitate **4b**, **4f** and **9k** was filtered off and washed with water (20 mL) and ether (20 mL) until the filtrate became clear.

When using DCM as solvent, the mixture was left stirring for 2 hours at room temperature. 8 mL of DCM were added and left stirring for another 22 hours. The resulting precipitate **4g** was filtered off and washed with ether (20 mL).

p-Tolylmethaneseleninic acid (**4b**)

Molecular formula: $C_8H_{10}O_2Se \cdot ¼H_2O$

Molecular weight: 221,5 g/mol



Melting point: 58°C

Appearance: clear white solid

Experimental procedure: From bis(4-methylbenzyl)diselenide (**3b**) in 1,4-dioxane according to the general procedure described in section 5.2.3.1.

IR (KBr) cm^{-1}: 3405 (m, -OH); 1124 (w, Se=O);

NMR-^1H (DMSO-d_6) ppm: 4.03 (s, 2H); 7.15 (d, 2H, *J* = 7.3 Hz); 7.24 (d, 2H, *J* = 7.3 Hz);

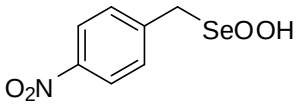
NMR-^{13}C (DMSO-d_6) ppm: 63 (1C); 129 (5C); 130 (1C);

Elemental analysis for $C_8H_{10}O_2Se \cdot ¼H_2O$, Calcd/Found (%): *C:* 43.34/43.55; *H:* 4.51/4.72;

MS (70 eV) (m/z): 105 (100); 77 (59); 91 (48).

(4-Nitrophenyl)methaneseleninic acid (**4f**)

Molecular formula: $C_7H_7O_4NSe \cdot H_2O$



Molecular weight: 266 g/mol

Melting point: 101-103°C

Appearance: light orange-yellow solid

Experimental procedure: From bis(4-nitrobenzyl)diselenide (**3f**) in 1,4-dioxane according to the general procedure described in section 5.2.3.1.

IR (KBr) cm^{-1}*:* 3398 (m, -OH); 1541 (s, $-NO_2$); 1351 (s, $-NO_2$); 1124 (m, Se=O);

NMR-^{1}*H (DMSO-*d_6*) ppm:* 4.21 (s, 2H); 7.57 (d, 2H, J = 8.7 Hz); 8.21 (d, 2H, J = 8.7 Hz);

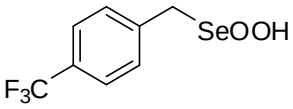
NMR-^{13}*C (DMSO-*d_6*) ppm:* 66 (1C); 123 (2C); 132 (2C); 144 (1C); 147 (1C);

Elemental analysis for $C_7H_7O_4NSe \cdot H_2O$, Calcd/Found (%): *C:* 31.58/31.85; *H:* 3.38/3.48; N: 5.26/5.37;

MS (70 eV) (m/z): 136 (100); 77 (67); 89 (49); 106 (44); 51 (42); 112 (33).

[4-(Trifluoromethyl)phenyl]methaneseleninic acid (**4g**)

Molecular formula: $C_8H_7O_2F_3Se \cdot H_2O$



Molecular weight: 289 g/mol

Melting point: 101-103°C

Appearance: white solid

Experimental procedure: From bis(4-trifluoromethylbenzyl)diselenide (**3g**) in DCM according to the general procedure described in section 5.2.3.1.

IR (KBr) cm^{-1}: 3409 (m, -OH); 1323 (s, -CF_3); 1123 (s, Se=O);

NMR-^{1}H (DMSO-d_6) ppm: 4.15 (s, 2H); 7.54 (d, 2H, *J* = 8.1 Hz); 7.71 (d, 2H, *J* = 8.1 Hz);

NMR-^{13}C (DMSO-d_6) ppm: 62 (1C); 126 (1C); 129 (3C); 132 (2C); 136 (1C);

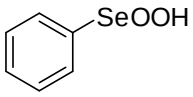
Elemental analysis for $C_8H_7O_2F_3Se \cdot H_2O$, Calcd/Found (%): *C:* 33.22/33.00; *H:* 3.11/ 3.07;

MS (70 eV) (m/z): 159 (100); 112 (76); 96 (51).

Benzeneseleninic acid (**9k**)

Molecular formula: $C_6H_6O_2Se$

Molecular weight: 189 g/mol



Melting point: 108-109°C

Appearance: white solid

Experimental procedure: From diphenyl diselenide **8k** in 1,4-dioxane according to the general procedure described in section 5.2.3.1

IR (KBr) cm^{-1}: 3448 (m, -OH); 1152 (w, Se=O);

Elemental analysis for $C_6H_6O_2Se$, Calcd/Found (%): *C:* 38.10/37.83; *H:* 3.17/3.60.

5.2.3.2. Oxidation with Sulfuryl Chloride

To a stirred solution of corresponding selenocyanate derivative **7i** and **7j** (2.5 mmol) in chloroform or DCM (25 mL), sulfuryl chloride (4.125 mmol) was added slowly. Reaction mixture was heated under reflux for 2 hours, the solvent was evaporated under vacuum and water (30 mL) was slowly (20 minutes) added to the residue and left stirring for another 20 minutes.

The purification of the product (only in first attempts):

The suspension formed in the previous step was washed with ethyl acetate (3 x 30 mL), organic phase was washed with 5M hydrochloric acid (3 x 30 mL) and subsequently dried with sodium sulfate. Sodium sulfate was filtered off and the solvent was evaporated under reduced pressure. When there was only an oily liquid left, hexane (20 mL) was added.

This procedure as described did not lead to any desired products.

6. REFERENCES

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