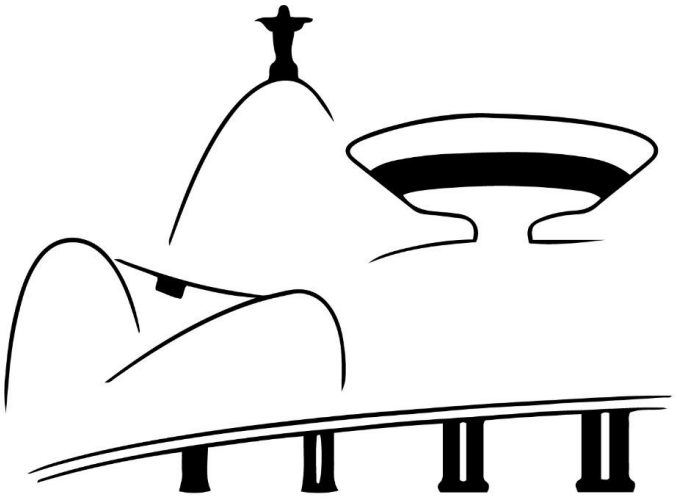

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10th Workshop of the Selenium and Sulfur Redox and Catalysis Network

BOOK OF ABSTRACTS

November 25th–26th 2022

Niterói–RJ

10th Workshop of the Selenium and Sulfur Redox and Catalysis Network

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SUMMARY

FRIDAY - November 25th 2022

- **11h00-13h30: Registration**
- **13h30-14h00: Open Ceremony**
- **14h00-14h35: Opening Conference**

"Contributions of LabSOA in the synthesis of bioactive compounds."

During the last 30 years the Organic Synthesis Laboratory at UFF has developed new synthetic methods and prepared hundreds of new molecules including nucleosides, diazo compounds, heterocycles and especially naphthoquinones. In this conference, examples of methods designed to obtain new naphthoquinones with different N, O, S and Se substituents and their biological results will be presented.

Speaker: Vitor Ferreira (UFF, Brazil)

- **14h35-15h00: Lecture**

"Heavy-Atom Hydrogen-Bond Activation of Carbon–Selenium σ–Bonds."

The regio- and stereoselective catalytic oxidative functionalization of non-polarized olefinic π-bonds constitutes an important and, thus, heavily investigated field of current chemical research. Among the panoply of oxidative transformations involving alkenes as substrates, both allylic and vinylic functionalization reactions have been focal points of numerous method-oriented investigations. Until now, however, the majority of such catalytic methods is still based on the use of certain transition metal catalysts such as palladium or copper complexes. In stark contrast, kindred processes enabled by non-metallic catalysts are not equally well developed. This circumstance is insofar remarkable and – to some extent – surprising as certain p-block element compounds such as organic sulfur- and selenium species have been previously shown to exhibit high catalytic activity in the oxidative conversion of simple alkenes. In this context, our research group has focused, inter alia, on harnessing the pronounced carbophilicity, i.e., the high chemoselectivity of selenenium ions (RSe^+) toward olefinic π-bonds, for the development of novel photoredox catalysis concepts to directly derivatize simple, non-polarized alkenes under oxidative conditions. Exemplary results of our efforts include Se-catalyzed allylic and vinylic aminations as well as C(sp^3)–H acyloxylations of alkenes. In addition, we have recently shown that alkyl(aryl)selanes can sustain hydrogen-bonding interactions, in which the selenium center serves as a heavy-atom acceptor. This feature was for the first time exploited to transiently generate Se(III) nucleofuges by photoredox catalysis to selectively initiate H-bond-

assisted substitution reactions as opposed to the traditional elimination reactions. This decisive alteration of the photoredox catalytic manifold enabled the facile formation new carbon–carbon s-bonds in the context of 1,2-migratory fragmentation reactions.

Speaker: **Alexander Breder** (UR, Germany)

- **15h00-15h25: Lecture**

"Design and Synthesis of Selenopeptides."

In living organisms, selenium (Se) is found mostly as a form of selenocysteine (Sec) or selenomethionine (Sem). These amino acids are selenium analogs of natural amino acids cysteine (Cys) and methionine (Met), respectively. Sec is incorporated into proteins according to the genetic information to make various selenoenzymes, while Met is a non-proteinogenic amino acid, which is incorporated into proteins randomly instead of S. With the development of the solid-phase peptide synthesis (SPPS) methodologies, it is now possible to chemically synthesize these selenoproteins in principle. We have recently succeeded in the synthesis of several selenium analogs of natural peptides and proteins, such as selenoglutathione and selenoinsulin, in which the sulfur (S) atoms are replaced with Se atoms. These selenium analogs indeed showed unique chemical and biological behaviors, which are different from those of the original natural products. The active site models of representative selenoenzymes, i.e., glutathione peroxidase (GPx) and thioredoxin reductase (TrxR), were also designed with Sec-containing short peptides. In this presentation, the technical aspects of the design and synthesis of selenopeptides are discussed based on our recent achievements and also the following topics.

1. Synthesis of Sec derivatives, which are useful for peptide synthesis

2. Synthesis of selenoglutathione (GSeSeG)

3. Synthesis of selenoinsulin

4. Design of the GPx active site

5. Design of the TrxR active site

Speaker: **Michio Iwaoka** (Tokai University, Japan)

- **15h25-15h40: Lecture**

"Flowing Chalcogens: Flow chemistry approaches with organoselenium and organosulfur compounds."

Organoselenium and organosulfur compounds are of attracting interest due to their peculiar properties exploited in organic synthesis, medicinal chemistry and polymer science. As a consequence, sustainability-directed methods to facilitate

their synthesis are highly demanded. Continuous flow systems offer several advantages over batch chemistry but they are poorly explored in the organochalcogens research field. Here, the flow synthesis of diselenylbisbenzoic acid (DSBA) together with a Se-catalyzed bioinspired oxidation strategy will be presented.

Speaker: **Luca Sancineto** (UNIPG, Italy)

- **15h40-15h55: Lecture**

"Organoselenium Catalytic Antioxidants - Inhibitors of Ferroptosis."

In the course of our ongoing research interest on the synthesis and antioxidant properties of heterocyclic amine-based organoselenium compounds, we developed various ebselenamines and N-thiphenyl ebselenamines as very good antioxidants. They act as glutathione peroxidase (GPx) mimics as well as lipid peroxyl radical-trapping antioxidants, and this phenomenon in combinations termed as "Multifunctional Antioxidants". All these compounds inhibit the lipid peroxidation and decompose the hydrogen peroxide more efficiently than vitamin E and ebselen (used as benchmark references), respectively. In continuation of our research, we recently synthesized various amine-based organoselenium compounds including diselenides, monoselenides and also selenocynates. Further, the newly identified organoselenium compounds were evaluated for their GPx-like activity by thiophenol assay. The GPx-activities of all newly synthesized compounds have been found higher than Ph_2Se_2, used as a reference compound. The radical-trapping antioxidant activities of synthesized compounds have been accessed by 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. Also, their antiferroptotic activities have been studied and compared with a reference compound liproxstatin in GPx conditional knockout cell lines.

Speaker: **Vijay Singh** (PU, India)

- **15h55-16h15: Coffee-Break**

- **16h15-16h25: Lecture**

"Eco-friendly Uracil Selenylation Employing I_2/DMSO as a Catalytic Oxidation System."

Speaker: **Maria Eduarda Thedy** (UFSC, Brazil)

- **16h25-16h35: Lecture**

"Design and synthesis of new chalcogen-functionalized naphthoquinones with potential antitumor activity."

Speaker: **Luana da Silva Gomes** (UFF, Brazil)

- **16h35-16h55: Lecture**

"Enantioselective Transformations from Sulfoxonium Ylides."

Sulfoxonium ylides have been employed in a plethora of new and intrinsic chemistry, especially in the last years. Bench stability and handling are also advantages of this class of organosulfur, and its use in industry as safer alternatives to diazo compounds has been evaluated during several years. Despite all that, efficiently asymmetric transformations, specifically catalytic enantioselective versions, have only emerged in the last years. This work will discuss the main results of our laboratory in the enantioselective formal N-H, S-H and C-H insertion reactions from sulfoxonium ylides, as well as fluorination reactions, employing non-covalent and covalent catalysis. These methods permited the synthesis of several α-difunctionalized carbonyl compounds, containing heteroatoms, in an enantioenriched fashion.

Speaker: **Antonio Burtoloso** (USP, Brazil)

- **16h55-17h20: Lecture**

"Selenium nucleophiles and sulfur electrophiles: An exciting synthetic combination."

The catalytic cycle proposed for GPx activity foresees an enzymatic selenol (Enz-SeH) oxidized by a peroxide to give a selenenic acid (Enz-SeOH), which reacts with glutathione (GSH) to give water and a selenenylsulfide (Enz-SeSG). In the final step, the mixed dichalcogenide reacts with a second equivalent of GSH, to reform the selenol and a disulfide i.e., oxidized glutathione GSSG. Thus, the selenenylsulfide (Enz-SeSG) represents a key intermediate in this enzymatic peroxides quencher cycle. Taking into account the importance of this process, several synthetic approaches to obtain mixed dichalcogenides have been studied. However, a limited number of methods are actually available for the preparation of different substituted selenenylsulfides. In this communication, we present a procedure for the synthesis of selenylsulfides based on the use of alkyl- and arylselenols as nucleophiles and alkyl and aryl-N-thiophthalimides as sulfur electrophiles. The role of substituents, on either the nucleophile and the electrophile, the scope and limitation of the procedure, as well as the stability of mixed dichalcogenides prepared so far, are the topics of the discussion. The opportunities emerged reacting N-thiophthalimides with bis(trimethysilyl)selenide, $(Me_3Si)_2Se$, and catalytic amounts of fluoride anion will be discussed as well.

Speaker: **Stefano Menichetti** (UniFI, Italy)

- **17h20-17h30: Lecture**

"How to Publish: Closer look into Submission"

Speaker: Elizabeth Magalhães (RSC, Brazil)

- **17h30-18h30: Poster Session**

- **18h00-20h30: Welcome Cocktail**

SATURDAY - November 26th 2022

- **09h00-09h10: Lecture**

"Synthesis of 3-chalcogenyl-indoles using Urea-hydrogen peroxide as oxidizing agent."

Speaker: **Julia Menezes** (UNIPAMPA, Brazil)

- **09h10-09h20: Lecture**

"Selenium catalyst in the oxidation of phenols. Model reactions for the development of new protocols in the treatment of biomasses."

Speaker: **Cecilia Scimmi** (UNIPG, Italy)

- **09h20-09h45: Lecture**

"Acylselenoureas: Reactivity & coordination chemistry."

Acylselenoureas [ArC(O)NHC(Se)NR_2] have been known for about 50 years and were investigated for several applications including analytical chemistry of metals, metal extraction and chromatographic metal separation. A detailed understanding of the coordination chemistry of these compounds has only emerged in the past fifteen years, with development of modern analytical tools, especially 77Se-NMR spectroscopy and X-ray diffraction. More recently, new applications for metal complexes with acylselenourea ligands have emerged including complexes as single-source precursors for metal-selenide nanomaterials and biologically active compounds. This presentation will highlight some of our contributions to this field, illustrating the structural diversity with examples from across the periodic table.

Speaker: **Fabian Mohr** (Univ. of Wuppertal, Germany)

- **09h45-10h05: Lecture**

"Selenium as a reactive atomic center in bioorganic chemosensing systems."

Molecular chemosensing requires a fluorophore(s) choice. Beyond this, there are many ways of decorating new derivatives with effective substituents which may be able to assist in "switching". One way is to use heavy atoms. Among the choices, it is often convenient to use group 16 centers, and wherever there may naturally be e.g., an ethereal O, it can be switched to S or Se, or Te. We have had luck with different systems over the years. After initiating this work, we found that M. R. Detty in 1990 published what is to be regarded as a landmark paper in this field.

Speaker: **David Churchill** (KAIST, Korea)

- **10h05-10h15: Lecture**

"Synthesis and biological evaluation of new menadione-organosulfur hybrids against Plasmodium falciparum."

Speaker: **Ruan Ribeiro** (UFF, Brazil)

- **10h15-10h25: Lecture**

"Asymmetric Aza-Wacker Reactions by Photo-Aerobic Selenium-π-Acid Catalysis."

Speaker: **Theresa Appleson** (UR, Germany)

- **10h25-10h50: Lecture**

"Carbosulfonylation of Alkenes with Visible-Light Photocatalysis."

In the last decades, the emphasis and application of sustainable chemistry principles have driven a change in behavior of both chemical industry and academy. In this context, the recognition of environmental benefits presented in photochemical reactions has motivated the scientific community to develop efficient and simple strategies for the synthesis of biologically relevant organic compounds. Sulfone is a prominent motif widely present in the chemical structure of agrochemicals, pharmaceuticals and many other highly valuable compounds. In this regard, we will present our recent findings on a conjunctive visible-light strategy for the precise installation of C- and S- functionalities onto styrenes using sodium sulfinates and CO_2 as coupling partners. The protocol allowed the preparation of carboxy-sulfonylated compounds in good yields and broad functional group tolerance. Additionally, a dual photocatalytic sulfonylation-arylation of electron-rich alkenes will also be discussed.

Speaker: **Márcio Paixão** (UFSCar, Brazil)

- **10h50-11h05: Lecture**

"Structural modifications of benzisoselenazolones to influence the specific bio-activity."

The field of biologically relevant organoselenium compounds is dominantly associated with their ability to mimic the antioxidant enzyme glutathione peroxidase (GPx). However thoroughly the topic is discussed and studied, the design of a highly active and selective Se-therapeutic still remains a challenge. Besides numerous biological activities that the N-substituted-1,2-benzisoselenazol-3(2H)-ones where proven to exhibit, the recently emerged pandemic of COVID-19 has set a new research direction as the antiviral M^{pro}-inhibitors. Since the bio-activity of GPx-mimetics has been recently reborn as the 'hot topic' in the field, new highly efficient procedures for their synthesis are required. A summary of currently known synthetic protocols for reactive Se-N bond formation, including the well-known reaction of 2-(chloroseleno)benzoyl chloride with appropriate primary amine and variously performed ortho-substitutions of N-substituted benzamides with Se-nucleophiles, will be discussed, followed by a recently developed greener approach. Finally, a series of most bio-active 1,2-benzisoselenazol-3(2H)-ones, with the results of their antioxidant and antiproliferative activity, will be presented and conclusions concerning the structure-activity correlation will be also provided.

Speaker: **Agata Pacuła-Miszewska** (NCU, Poland)

- **11h05-11h25: Coffee-Break**

- **11h25-11h40: Lecture**

"The naphthyl (O/S/Se)ether-linked 1,3,5-triazine 5-HT_6R antagonists as new pharmacological approach to Alzheimer's disease therapy."

Serotonin receptor 5-HT_6 is important target in search for new Alzheimer's disease therapy. We examine new naphthyl selenoether 1,3,5-triazine 5-HT_6R ligands in comparison to the (thio)ether ones. The new compounds have been obtained within multistep syntheses, involving the catalytic synthesis of naphthyl diselenides using Grignard reagent, the Se-ether ester synthesis with suitable bromoalkylesters, followed by cyclic condensations with the piperazine biguanide in basic conditions.

Speaker: **Jadwiga Handzlik** (UJ CM, Poland)

- **11h40-11h50: Lecture**

"Theoretical studies of selenium-functionalized Tacrine."

Speaker: **Roberto Morais** (UFPel, Brazil)

- **11h50-12h00: Lecture**

"Selenonium salts as phase-transfer catalysts in nucleophilic substitution reactions."

Speaker: **Alix Bastidas** (UFMG, Brazil)

- **12h00-12h10: Lecture**

"Human Relaxin Through Two-chains Folding Coupled with Interchain Disulfide Formation."

Speaker: **Yuri Satoh** (Tokay University, Japan)

- **12h10-14h00: Lunch**

- **14h00-14h35: Lecture**

"1,3-dimethyl-4-imidazoline-2-selone derivatives: reactivity towards di-halogens and the importance of the experimental conditions."

In this overview, an attempt is made to put together the basic knowledge concerning the reactions of dihalogens X_2 (I_2, Br_2) and inter-halogens IX (IBr, ICl) with heterocyclic pentatomic thioamides and selenoamides, and to review and rationalize variations in the structural motifs observed.

Speaker: **Vito Lippolis** (UNICA, Italy)

- **14h35-15h00: Lecture**

"The Supramolecular Chemistry of iso-Chalcogenazoles."

The current surge of interest on supramolecular interactions between electron-rich centers and electrophilic sites on atoms of heavy p-block elements, e.g., halogen bonding, has reached the chalcogens. While most studies in this area have been concerned with control of crystalline structure and solid-state properties, some of those intermolecular interactions are strong enough to form well-defined discrete aggregates. Prominent example in this regard is the iso-chalcogenazole N-oxides, which spontaneously auto-associate by Ch...O (Ch = Se, Te) chalcogen-bonding interactions. The tellurium derivatives form tetra- and hexameric annular aggregates that are persistent in solution, host small molecules, act as fullerene receptors, form macrocyclic transition-metal complexes, are resilient to tellurium halogenation and unreactive towards Lewis bases as strong as N-heterocyclic carbenes. Yet, mineral acids or boranes BR_3 (R

= Ph, F) block aggregation. The borane adducts have an enhanced affinity for Lewis bases, which enables the formation of new supramolecular structures. This presentation will highlight recent findings and the development of new supramolecular building blocks based on derivatives of these heterocycles.

Speaker: **Ignacio Vargas-Baca** (McMaster, Canada)

- **15h00-15h25: Lecture**

"Dialkyl and Diaryl Diselenides - Methods of Synthesis, Applications and Bioactivity."

Organoselenium compounds are increasingly used as useful reagents in organic synthesis. Particularly diselenides play an important role in the synthesis of organoselenium derivatives and their applications. This is mainly due to the fact that they can be easily transformed into electrophilic, nucleophilic, and free radical reagents. Chiral diselenides have found a number of applications in asymmetric syntheses, e.g., in the reactions of alkoxyselenenylation, selenocyclization, and addition of diethylzinc to aldehydes, as well as in the synthesis of natural products. Diselenides were also tested for their biological properties, e.g., as antioxidants able to mimic the antioxidant enzyme glutathione peroxidase (GPx) or anticancer antiviral and antibacterial agents. During the lecture, we will present our experiences concerning the methods of synthesis of dialkyl derivatives, mainly cyclic and bicyclic terpenes, and diaryl diselenides substituted in the ortho position with amide groups. Applications of dialkyl diselenides in asymmetric methoxyselenenylation and selenocyclization reactions, and the research on the antioxidant and anticancer properties of the obtained derivatives, including chiral derivatives, will be presented. We will show the influence of the structure of the diselenides on their biological activity.

Speaker: **Jacek Ścianowski** (NCU, Poland)

- **15h25-15h40: Lecture**

"Alkylation reactions in water catalyzed by organoselenium compounds."

Methylation of organic substrates is a highly important transformation for living organisms. Nature employs enzymes called methyltransferases to promote such reactions utilizing S-adenosyl-L-methionine (SAM) as the alkylating agent. The active site of SAM is a sulfonium center, which acts as a carrier of an electrophilic methyl group, releasing the corresponding sulfide as the leaving group. Prior state of the art indicates that under stoichiometric conditions selenonium salts are better alkylating agents than sulfonium salts. Accordingly, our research group has been interested lately in the design, synthesis, and application of organoselenium compounds to promote alkylation of several

substrates in water. Our strategy comprehends the preparation of selenonium salts employing renewable sources of methyl group and the development of catalytic reactions promoted by selenides and/or selenonium salts.

Speaker: **Eduardo Alberto** (UFMG, Brazil)

- **15h40-15h55: Lecture**

"Hypercoordinated organopnicogen (III) compounds containing Pn-E (Pn = Sb, Bi; E = O, S, Se) - structure and reactivity."

C-H bond activation and carbon dioxide fixation/activation using heavy organopnicogen(III) species are both topics of seminal interest in the modern organometallic research. Recent results in the synthesis, characterization and reactivity of organopnicogen(III) (Sb, Bi) aryloxides and related thio derivatives, $ArPn(EAr')_2$ (E = O, S), as well as oxides, cyclo-$Ar_2Pn_2O_2$ (Pn = Sb, Bi), will be presented. The organic Ar groups attached to the metal atom are aromatic ligands with one or two pendant arms of the type of 2-$(Me_2NCH_2)C_6H_4$ and 2,6-$(R_2NCH_2)_2C_6H_3$ (R = Me, iPr) or 2,6-$\{E'(CH_2CH_2)_2NCH_2\}_2C_6H_3$ (E' = NMe, O), with potential for intermolecular coordination. Significant differences, depending on the nature of the pnictogen, were revealed in solid state. The reactivity of particular $ArPn(EAr')_2$ (E = O, S) towards chalcogens (oxygen, sulfur or selenium) and iodine will be also discussed.

Speaker: **Cristian Silvestru** (UBB, Romania)

- **15h55-16h15: Coffee-Break**

- **16h15-17h15: Round Table**

"A system thinking approach for a Complex System elucidation."

Speakers: Claudio Santi (UNIPG, Italy)

Eder Lenardão (UFPel, Brazil)

- **17h15-18h00: Closing Ceremony (Awards)**

- **18h00-20h30: Dinner**

LIST OF ABSTRACTS

12. **Selenium catalyst in the oxidation of phenols. Model reactions for the development of new protocols in the treatment of biomasses**
    Cecilia Scimmi, Luca Sancineto, Francesca Marini and Claudio Santi*
13. **Synthesis of 1,2,3-triazole-thiophene hybrids that inhibit the proteolytic activity of Jararaca**
    Danielle M. da Surreição, Maria E. L. de Lima, Danielle P. Portela, Dora C. S. Costa, Brenda B. Q. Ornellas, Fernando C. da Silva, Vitor F. Ferreira, André L. Fuly and Daniel T. G. Gonzaga*
14. **Hydrogen-Bond-Modulation of Se^{III} Nucleofugality within Selenohydrins to Enable Photoredox Catalytic Semipinacol Manifolds**
    Sooyoung Park, Amit K. Dutta, Carina Allacher, Anton Abramov, Philipp Dullinger, Katerina Kuzmanoska, Daniela Fritsch, Patrick Hitzfeld, Dominik Horinek, Julia Rehbein,* Patrick Nürnberger,* Ruth M. Gschwind* and Alexander Breder.*
15. **Selenium as a reactive atomic center in bioorganic chemosensing systems**
    David G. Churchill,* Donghyeon Kim, Jongkeol An, Neha Jain, Youngsam Kim, Sandip V. Mulay, Minsuk Choi, Sangyong Jon, Sudesh T. Manjare, Mahesh B. Halle and Tesla Yudhistira.
16. **Design and synthesis of new chalcogen-functionalized naphthoquinones with potential antitumor activity**
    Érica de O. Costa,* Luana S. Gomes, Fernando C. da Silva, Vitor F. Ferreira and Vanessa Nascimento
17. **Menadione linked with chalcogens: design and synthesis of promising structures against tuberculosis**
    Luana S. Gomes,* Nathália L. B. Santos, Ruan C. B. Ribeiro, Alcione S. de Carvalho, Maria Cristina S. Lourenço, Fernando C. da Silva, Vitor F. Ferreira and Vanessa Nascimento
18. **The naphthyl (O/S/Se)ether-linked 1,3,5-triazine 5-HT_6R antagonists as new pharmacological approach to Alzheimer's disease therapy**
    Jadwiga Handzlik,* Małgorzata Więcek, Patryk Pyka, Wesam Ali, Natalia Wilczyńska-Zawal, Sylwia Sudoł-Tałaj, Magdalena Jastrzębska-Więsek, Grzegorz Satała, Ewelina Honkisz-Orzechowska, Wawrzyniec Haberek, Katarzyna Kucwaj-Brysz, Anna Partyka and Anna Wesołowska.
19. **Synthesis of 3-chalcogenyl-indoles using Urea-hydrogen peroxide as oxidizing agent**
    Julia R. Menezes,* Fabiola C. Santos, Mylena M. Goulart, Juliano A. Roehrs and Juliano B. Azeredo

20. **Application of Cyrene as bio-solvent on the seleno-cyclization of 4-penten-1-ol**
    Julia Rosa Menezes and Juliano B. Azeredo*
21. **Se-substituted thiazole derivatives as strong potentiators of antibiotic activity against Staphylococcus aureus strains**
    Karolina Witek,* Aneta Kaczor, Ewa Żesławska, Sabina Podlewska, Małgorzata Anna Marć, Wojciech Nitek, Gniewomir Latacz, Waldemar Teichman, Markus Bischoff, Claus Jacob and Jadwiga Handzlik
22. **Redox Chemistry of Cyclic Diselenide Reagents as a Tool for Manipulating Structure of Proteins**
    Kenta Arai,* Shunsuke Tsukagoshi and Rumi Mikami
23. **Flowing Chalcogens: Flow chemistry approaches with organoselenium and organosulfur compounds**
    Francesca Mangiavacchi, Francesca Marini, Francesca Begini, Dorota Krasowska, Jozef Drabowicz, Claudio Santi and Luca Sancineto
24. **Eco-friendly Uracil Selenylation Employing I_2/DMSO as a Catalytic Oxidation System**
    Maria Eduarda C. Thedy,* Juliano B. Azeredo and Antonio L. Braga
25. **Selenium compounds are potent inhibitors of oxidant damage**
    Luke Carroll, Kelly Gardiner, Marta Ignasiak, Jeppe Holmehave, Shingo Shimodaira, Thomas Breitenbach, Michio Iwaoka, Peter R. Ogilby, David I. Pattison and Michael J. Davies*
26. **Use of the Selenoxide-pillar[5]arene as a new alternative to obtaining nitriles in water**
    Pâmella Cordeiro,* Victor Menezes, Ingrid Chipoline, Alix Ángel, Eduardo Alberto and Vanessa Nascimento
27. **Synthesis of new selenotetrazoles as potent corrosion inhibitors**
    Victor H. M. Costa,* Pâmella S. Cordeiro, Vinicius M. dos Santos, Caio M. Fernandes, Joel S. Reis, Eduardo A. Ponzio and Vanessa Nascimento
28. **Synthesis of Methylated Selenonium Salts from Biorenewable Sources of Methyl Group**
    Philipe Raphael O. Campos* and Eduardo E Alberto
29. **Theoretical studies of selenium-functionalized Tacrine**
    Roberto B. Morais, Manoela Sacramento and Diego Alves*
30. **Synthesis and biological evaluation of new menadione-organosulfur hybrids against** *Plasmodium falciparum*
    Ruan Carlos B. Ribeiro,* Carolina B. G. Teles, Alcione S. de Carvalho, Fernando C. da Silva and Vitor F. Ferreira

31. **Science at the interface of chemistry and biology: Bioassay guided phytochemical studies on** *Malvastrum coromandelianum* **and** *Curcuma zedoria*
    Sheema, Salman Zafar* and Ghias Uddin
32. **Organoselenium Catalytic Antioxidants - Inhibitors of Ferroptosis**
    Babli Chillar, Thamara N. X. Da Silva, Jose P. F. Angeli and Vijay P. Singh*
33. **Facile Preparation of Type-2 Human Relaxin Through Two-chains Folding Coupled with Interchain Disulfide Formation**
    Yuri Satoh, Hidekazu Katayama, Michio Iwaoka and Kenta Arai*

H_2S scavenging capacity of acrolein explored by DFT

Leonardo C. Martins (IC)[1*], Caio A. Leal (PG)[1] and Rodolfo G. Fiorot (PQ)[1]

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Keywords: *H_2S capture, molecular modeling, oil streams.*

Background

A major problem to the oil industry is the presence of hydrogen sulfide (H_2S) in industrial effluents. Employing chemical scavengers, such as aldehydes, is a strategy to circumvent this issue.

Results and Discussion

One of the main problems that the oil industry faces is the presence of hydrogen sulfide (H_2S) in industrial effluents, an alarmingly toxic and corrosive gas. A frequent method to remove H_2S is the use of chemical scavengers most commonly triazines.[1] Recently, our group published a computational investigation showing that the H_2S capture efficiency by 1,3,5-hexahydrotriazine, one of the most used triazines, does not follow the expected 1:3 ratio (scavenger:H_2S), but 1: 2[2]. This is the only paper, to the best of our knowledge, which explores the reaction mechanism for the H_2S capture by a chemical scavenger and provide a sound thermochemical and kinetic evaluation of the process. The search for alternative and improved scavengers has been growing over the years. The computationally aided assessments are proving to be efficient, economical compared to field analysis, and safe. Experimental studies point acrolein (2-propenal) as a feasible candidate since it avoids the polymerization/incrustation problem associated to triazines[3]. However, these are outdated studies and more recent evaluations are lacking. Herein, based on the mechanism proposed in 1991 to the H_2S scavenge by acrolein (**Figure 1**), we evaluate the energy profile for this process.

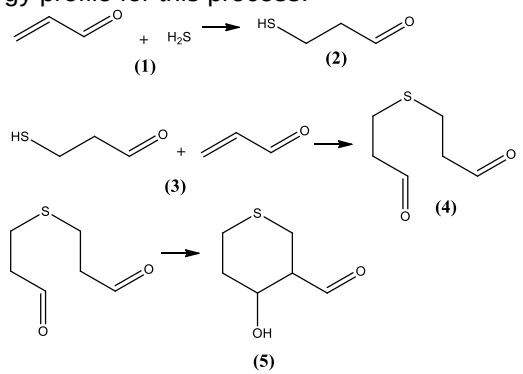

Figure 1. Proposed mechanism for the H_2S scavenge by acrolein.

Simulations were performed at the Density Functional Theory (DFT) CAM-B3LYP/aug-cc-pVDZ method, previously validated by our research group[4]. The energy change for the reaction is depicted in the **Figure 2**. Our computations suggest that all the steps are thermodynamically favorable and the global energy release to form the proposed product is ΔH^{298} = –39.1 kcal mol^{-1}. Although structure **11** was not originally proposed[3] , its formation is possible. It would be able to polymerize, causing the incrustation associated with the usage of triazines. Our results point that the **10** ⇌ **11** equilibrium would be shifted towards **10**, corroborating with the experimental observation that incrustation is not a problem associated with the usage of acrolein. The analysis of the energy barriers to evaluate the kinetic behavior of the process are under development.

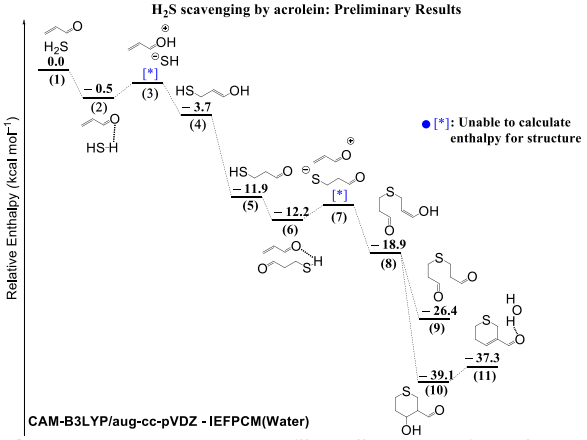

Figure 2. Energy profile diagram for the H_2S scavenging process by acrolein.

Conclusion

Based on the presented data, the reaction proved to be thermodynamic favorable for the H_2S removal by acrolein. The hypothetical equilibrium to form **11** is shifted towards **10**, which is consistent to the experimental observation that acrolein would not polymerize and cause incrustation. We are performing kinetic simulations to compare the capture rate with other aldehyde-based scavengers.

Acknowledgments

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Asymmetric *Aza*-Wacker Reactions by Photo-Aerobic Selenium-π-Acid Catalysis

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Keywords: *Photoredoxcatalysis, Selenium-π-acid catalysis, Asymmetric amination.*

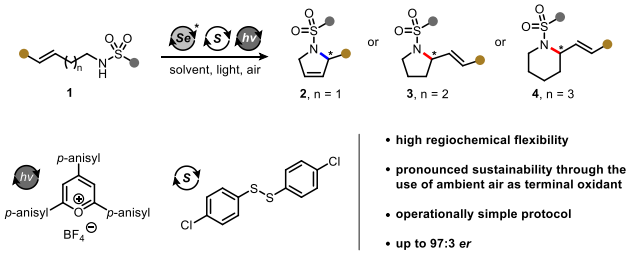
Background

An unprecedented enantioselective photo-aerobic *aza*-Wacker reaction is reported, which enables the synthesis of chiral 3-pyrrolines, pyrrolidines, and piperidines by chiral selenium-π-acid catalysts.

Results and Discussion

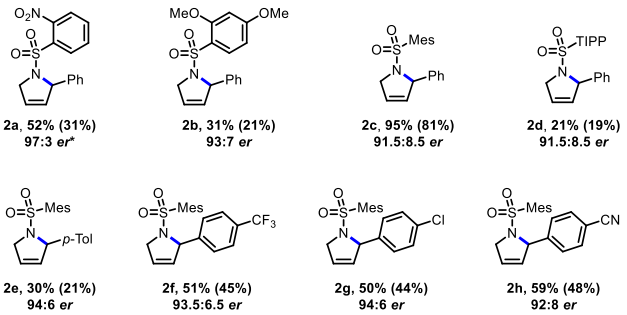
Previously, we demonstrated that photo-excited pyrylium catalysts can oxidize aryldiselanes to initiate various selenocatalytic transformations of alkenes, such as lactonizations, esterifications, etherifications and phosphatations.[1] On the basis of this multicatalysis concept, we were now successful in developing an asymmetric, photo-aerobic cyclization protocol for the conversion of unsaturated sulfonamides to furnish a broad set of chiral 3-pyrrolines, pyrrolidines, and piperidines (Figure 1).

Figure 1. Enantioselective *aza*-Wacker cyclization via selenium-π-acid catalysis.



The title protocol is operationally simple, highly carbon-efficient through the use of ambient air as the terminal oxidant, and very tolerant of functional groups (Figure 2). In addition, our procedure provides the cyclization products in reasonable to very good enantiomeric ratios (*er*) of up to 97:3. It is noteworthy that there are very few catalytic procedures known for the synthesis of chiral 3-pyrrolines by 5-*exo*-trig cyclizations and that the title protocol represents the first enantioselective, photo-aerobic variant.
Mechanistically, the reaction is suspected to proceed through a sequence of two radical-polar-crossover events.[2,3]

Figure 2. Selected examples of the product scope.



*Yields were determined by ^{1}H-NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parenthesis and *er* values were determined by chiral HPLC. TIPP = 2,4,6-triisopropylphenyl.

Conclusion

In summary, we have disclosed the first enantioselective selenium-π-acid based photo-aerobic *aza*-Wacker cyclization protocol, which provides an expedient entryway toward diversely decorated *N*-heterocycles in reasonable to good yields and high *er* values.

Acknowledgments

This work was financially supported by the German Research Foundation, (DFG, BR 4907/1-1; BR 4907/3-1), and the European Research Council (ERC Starting Grant ELDORADO; grant agreement No. 803426).

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Design and synthesis of pyrazolyl benzenosulfonamide derivatives as potential antibacterial activity

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Keywords: *Synthesis, Pyrazole, Sulfonamides, Antibacterial.*

Background

The process of bacterial resistance to available antibiotics has been considered a serious threat to public health worldwide. The World Health Organization (WHO) considers combating bacterial resistance as a high priority, therefore it encourages research and development of new substances that have antibacterial activity.[1,2] The synthesis of derivatives that have the benzenesulfonamide moiety is of great interest, since this nucleus has a wide range of pharmacological properties, including antimicrobial. As example, we can mention the antibacterial sulfadimidine (**1**) and sulfamethoxazole (**2**). It is also important to highlight the use of anti-inflammatory drugs in bacterial infections, such as celecoxib (**3**), Figure 1.[3]

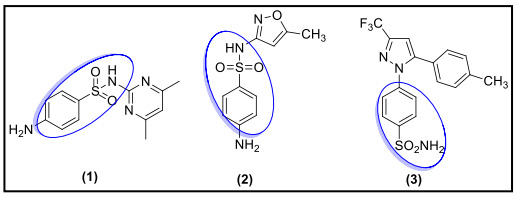

Figure 1: Examples of sulfonamides with antibacterial activity and anti-inflammatory activity.

Results and Discussion

This project involves design, synthesis, and spectroscopic characterization of new pyrazolyl benzenesulfonamide derivatives **(Ia-h)**, with prospection for antibacterial activity. The synthetic route used to obtain the new **Ia-h** derivatives is shown in Figure 2. The preparation of this series of derivatives has as first step the cyclization reaction between substituted phenylhydrazines **(IIa-c)** and ethyl ethoxymethylene cyanoacetate to obtain ethyl 5-amino-1-aryl-1*H*-pyrazol-4-carboxylate derivatives **(IIIa-c)**. The 5-amino-1-aryl-1*H*-pyrazoles **(IVa-c)** can be readily made via hydrolysis and decarboxylation of corresponding pyrazoles **IIIa-c**. The preparation of new pyrazolyl benzenesulfonamide derivatives **(Ia-h)** was performed through a sulfonation reaction between intermediates **IVa-c** and excess of corresponding benzene sulfonyl chlorides.[4]

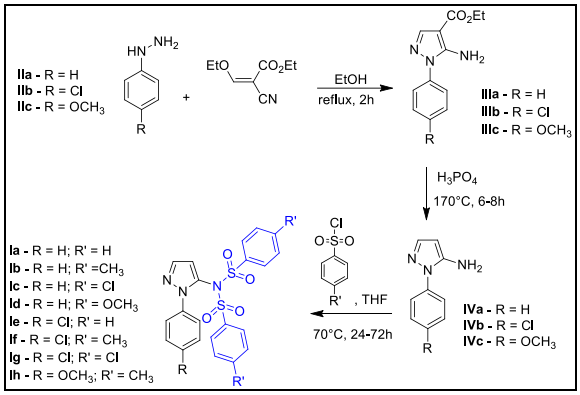

Figure 2: Preparation of pyrazolyl benzenesulfon-amide derivatives **Ia-h**.

The heterocyclic compounds **Ia-h** were purified and obtained with yields ranging from 30% to 65%. They also were characterized by spectroscopic methods such as IR, ^{1}H, ^{13}C NMR and, in particular, the structure of **Ib** was solved by X-ray diffraction analysis. The synthesized substances will be properly evaluated against different strains of Gram-negative and Gram-positive bacterial.

Conclusion

The derivatives were successfully synthesized and their structures elucidated by the techniques applied. Furthermore, it was possible to confirm the disulfonylation of the substances with the final products analysis in special with the X-ray diffraction analysis. Concerning the biological activity, the synthesized substances will be properly evaluated against different strains of Gram-negative and Gram-positive bacterial.

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Selenonium salts as phase-transfer catalysts in nucleophilic substitution reactions

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Keywords: *Organocatalysis, phase-transfer catalyst, Chalcogen bond, organochalcogenocyanates.*

Background

Organochalcogenium compounds have been the focus of study in recent years due to their pharmacological importance, their anticancer properties and their use as building blocks in different transformations.

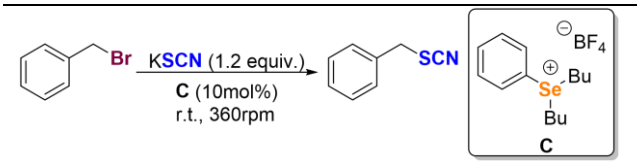
Selenonium salts can be efficiently used as phase transfer catalysts in nucleophilic substitution reactions between benzyl bromide and KSCN, using water and dimethylcarbonate (20:1) as solvents.

Results and Discussion

Herein we present a methodology for the transformation of benzyl bromides into thiocyanates, in a heterogeneous reaction system through nucleophilic substitution reactions in aqueous media assisted by phase transfer catalysts.

Table 1 shows the optimization of the reaction. The best condition was observed when 10 mol% of selenonium salt and a water/dimethylcarbonate (20:1) mixture was used as solvent, resulting in 86% isolated yield .

Table 1. Optimization of the reaction.

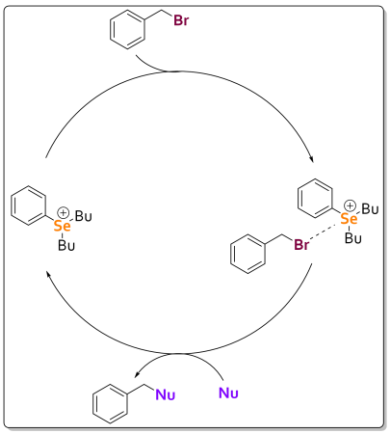


Exp.	Catalyst (10 mol%)	Solvent (2 mL)[a]	Time (min)	Yield[b] (%)
1	-	H_2O	10	3
2	**C**	H_2O	10	**60±6**
3	**C**	H_2O/DMC 20:1	10	41
4[c]	**-**	H_2O/DMC 20:1	10	5
5[c]	**C**	H_2O/DMC 20:1	10	**86±2**
6[c]	**C**	H_2O/DMC 20:1	60	**88**

[a] DMC = dimethylcarbonate; [b] Isolated yield. [c] 2 equiv. of KSCN

Due to the results obtained so far, we suggest that the reaction occurs by interaction between selenonium salt (Lewis acid) and bromide trough a chalcogen bond (**Figure 1**). This interaction allows the carbon bound to bromine to be more electrophilic and thus more susceptible to nucleophilic attack.

Figure 1. Proposed catalytic cycle



Conclusion

A methodology for nucleophilic substitution of bromide for thiocyanate was efficiently developed in a heterogeneous reaction system using selenonium salts as a phase-transfer catalyst and a mixture of water and dimethylcarbonate 20:1 in 10 min of reaction.

Acknowledgments

This study was financed in part by CNPq and CAPES. The authors are grateful to FAPEMIG (grant APQ-00349-22) for financial support of this research.

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Green synthesis of calcogenyl-2,3-dihydrobenzofurans derivatives through allyl-phenols/naphthols and their MAO-B inhibitory activities

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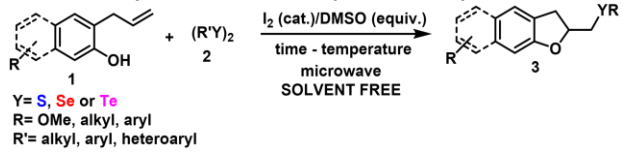
Keywords: *Green Chemistry, Chalcogenofunctionalization, antioxidant*

Background

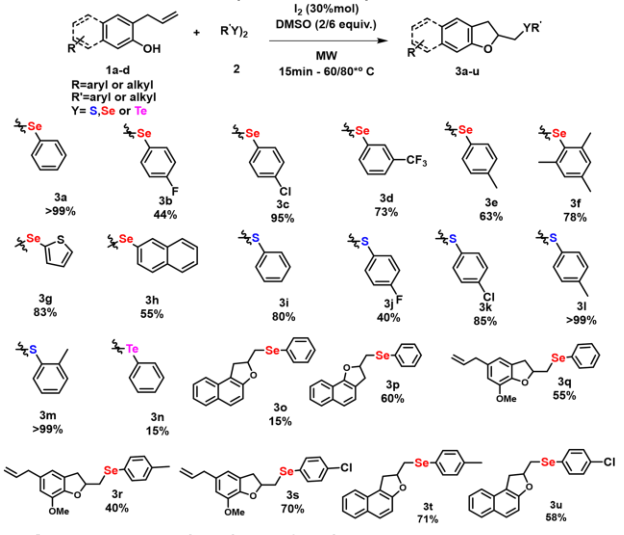
Organochalcogenides and the 2,3-dihydrobenzofuran scaffold have been the subject of great synthetic interest due to their biological potential.[1,2] These compounds are known for their pharmacological activities as antioxidant, antitumor, antiplatelet, antimalarial, anti-inflammatory, antidepressant and described anticonvulsant properties.[3] The present work was focused on the sustainable synthesis of a product containing two of pharmacological interest cores: organochalcogens and 2,3-dihydrobenzofuran (**Scheme 1**).



Scheme 1: General scheme.

Results and Discussion

Chemistry: Initially, the reaction conditions were evaluated through the amount of oxidant, reagents **1** and **2**, amount of catalyst, time and temperature. The best reactional condiction was obtained after 11 sets of different tests. The desired product was isolated in quantitative yield. With the optimized conditions in hands, a large scope was explored and are summarized below (**Scheme 2**).



Scheme 2: Evaluation of substrates.

Biochemistry: The compounds **3b**, **3c**, **3d** and **3e** were effective in inhibiting the cerebral MAO B activity (**Figure 1**). MAO B inhibitors are used in the treatment of neurodegenerative conditions such as Parkinson's and Alzheimer's diseases.[4] Therefore, calcogenyl-2,3-dihydrobenzofurans derivatives are potential drugs to be tested *in vivo* aiming regulate the brain monoamine levels (*e.g.* dopamine) and reduce the oxidative stress, given that MAO are major producers of mitochondrial ROS.

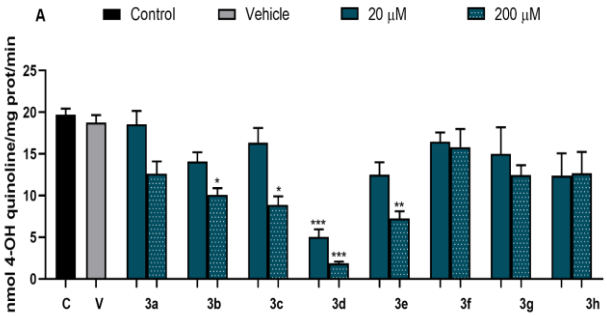


Figure 1: Effect of the compounds on cerebral MAO-B activity in vitro. (*) $p < 0.05$ and (***) $p < 0.0001$ compared with the vehicle (V) group. One-way ANOVA followed of the Tukey's test.

Conclusion

In conclusion, the synthesis of 21 chalcogenyl-2,3-dihydrobenzofuran derivatives was successfully completed. Finally, compared to traditional methods, the methodology developed is a simple and practical tool free of solvents and metals, following the principles of green chemistry for the oxychalcogenation of 2-allyl-phenols/naphthols core derivatives, in addition to presenting their MAO-B inhibitory activities.

Acknowledgments

UFF, CNPq, CAPES, FAPERJ, PPGQ-UFF, LaReMN.

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Fight against tuberculosis: Synthesis of new seleno-functionalized pillar[n]arenes

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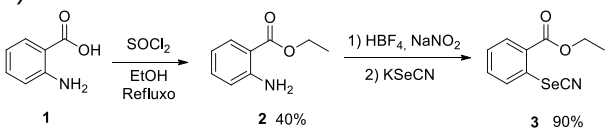
Keywords: *isoniazid, seleno-pillar[n]arene, supramolecular.*

Background

Tuberculosis is a highly contagious disease, considered the leading cause of death worldwide from a single infectious agent. The World Health Organization (WHO) estimates that 1/4 of the world's population is infected.[1] The great challenge faced in combating the disease is the increase in resistant strains. In this situation, isoniazid is one of the primary medications used to treat the illness. Its metabolism involves a terminal nitrogen acetylation step that, when performed early, inactivates the drug, a fact associated with the phenomena of strain resistance. Thus, the control of N-acetylation can be considered an important alternative to prevent this problem.[2] In this context, we can highlight the application of macrocycles as drug nanocarriers, which can control isoniazid acetylation reactions.[3] Another valuable strategy that has been highlighted is the use of selenium compounds, which have recognized activity against tuberculosis.[4] Thus, the objective of this work is the synthesis of a potential nanocarrier of isoniazid, which is seleno-pillar[n]arene, aiming to guarantee its resistance to acetylation, and consequently, an improvement of the antituberculosis activity.

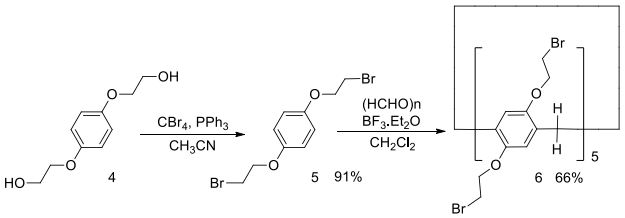
Results and Discussion

For the development of this project, a 2-step methodology was first established for the synthesis of the selenocyanate **3**. In this way, the esterification was carried out, which led to the formation of derivative **2** in 40% of yield. Subsequently, diazotization was performed followed by nucleophilic substitution, obtaining selenocyanate **3** with excellent yield (90%, Scheme 1).[5]



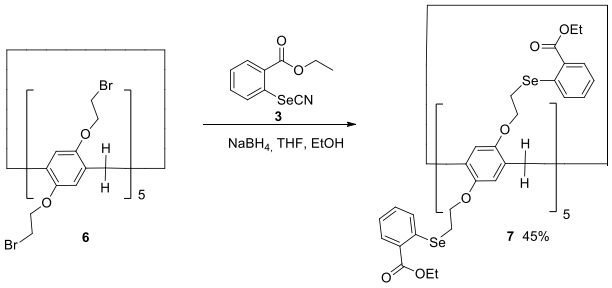
Scheme 1. Syntetic route of selenocyanate **3**.

In parallel, a bromination was carried out to produce the brominated monomer **5** with a yield of 91%. The cyclization for obtention of the pillar[n]arene **6** was conducted with 66% of yield (Scheme 2).[6]



Scheme 2. Syntetic route of pillar[n]arene **6**.

The proposed methodology for the achievement of the target macrocycle is based on a nucleophilic substitution reaction between selenocyanate **3** and pillar[n]arene **6** (Scheme 3).[7] With the proposed methodology for obtaining the macromolecule, seleno-pilar[n]arene 7 was obtained with a yield of 45%.



Scheme 3. Syntetic route seleno-pillar[n]arene **7**.

Conclusion

It was possible to obtain selenocyanate **3** and pillar[n]arene **6** with good yields. The last synthetic step, to obtain the seleno-pillar[n]arene **7** and it's respective salt is under the final evaluation. With these macrocycle in hands we intend to load them with INH and evaluate the efficiency of the system against early N-acetylation and also tuberculosis.

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Aldehydes as H_2S scavengers: A DFT study

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Keywords: *Molecular modeling, Hydrogen sulfide, Reaction mechanism.*

Background

Simulation of the reaction mechanism for the H_2S activity of aldehydes employed by petroleum industry; Comparison of the thermodynamic and kinetic efficiency of the different scavenging aldehydes.

Results and Discussion

Computational chemistry is an efficient and safe strategy to evaluate H_2S scavenging processes, since hydrogen sulfide is a toxic, corrosive and inflammable gas that requires sophisticated lab installations and rigorous security regulations. Literature lacks information on the understanding, at molecular level, of the H_2S capture performance of chemical absorbents and their respective reaction mechanisms. To the best of our knowledge, our research group published the only paper reporting the energy profile for the H_2S capture by the most employed non-regenerative scavenger (1,3,5-triazine)[1] by the oil industry. Aiming to expand the knowledge on the field, herein we evaluated the H_2S scavenging (thermochemical and kinetic) efficiency by this emergent class scavenger: aldehydes[2].

We started by validating the computational method. After comparing different combinations of functionals and basis sets, CAM-B3LYP/aug-cc-pVDZ provided the lowest absolute deviation value compared to the reference thermochemical and kinetic experimental values[3]. Then, we evaluated the energy change for the H_2S removal steps by formaldehyde and acetaldehyde, according to the proposed mechanism[4]. We identified that water plays a pivotal role to the process' viability, decreasing the energy barrier by *ca.* $\Delta H^{\ddagger}$ = 15 kcal mol^{-1}, and the global enthalpy variation from 2.2 to –1.2 kcal mol^{-1}. The Gibbs free energy also follows the same tendency, pointing to a spontaneous reaction in the presence of water. The simulated energy barriers in terms of enthalpy for both formaldehyde and acetaldehyde throughout the process lies within the interval 15.5–19.9 kcal mol^{-1} and 17.4–19.3 kcal mol^{-1} respectively.

Glyoxal is another appealing dialdehyde employed by industry as H_2S scavenger. No data on the inspection of the mechanism is found in literature. The only relevant information we located was the product characterization for the reaction between H_2S and glyoxal in a work from 1992[4], that reveals an stoichiometric ratio of 3:2 (glyoxal:aldehyde). Based on this and on the finding regarding the importance of the water molecule to the reaction course, we proposed a reaction mechanism (**Figure 1**) and evaluated the energy change throughout the process. The simulated energy barriers (12.5–17.5 kcal mol^{-1}) suggest that III is the rate-determining step. Noticeably, these values are lower than the barriers computed for formaldehyde, agreeing to experimental observation that the reaction with glyoxal is faster[5].

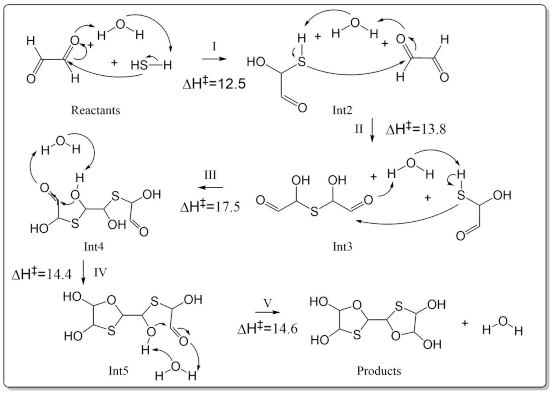

Figure 1. Proposed mechanism for H_2S capture by glyoxal and energy barriers (kcal mol^{-1}).

Conclusion

In light of these results, we can highlight the important role of water in the scavenging process, making it viable in thermodynamic and kinetic aspects. Moreover, the analysis of glyoxal as H_2S scavenger and the proposed mechanism explained, based on energy values, why it reacts faster than the other aldehydes, being an appealing alternative to substitute triazine-based scavengers. In addition, considering the high toxicity of hydrogen sulfide[5], computational studies related to its scavenging present a large advantage by the absence of direct contact with this substance, ensuring safety and health of researchers.

Acknowledgments

FAPERJ, CNPq and LoboC (project ID 22006).

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Synthesis of 1,3-Dioxan-2-ones by Photo-Aerobic Selenium-π-Acid Multicatalysis

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Keywords: *Cyclic Carbonates, Selenium-π-Acid Multicatalysis, Allylic Oxidation*

Background

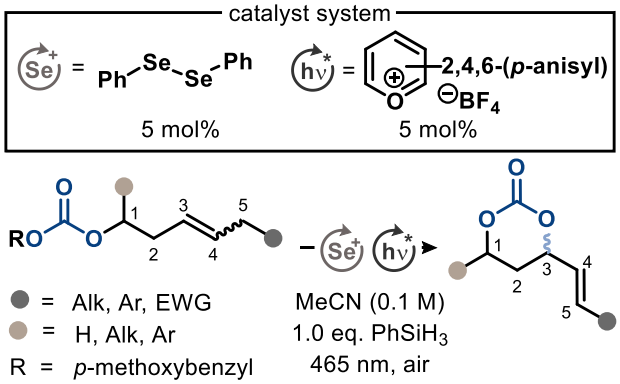
1,3-Dioxan-2-ones are synthesized from homoallylic carbonic acid esters through the multicatalytic interplay of organic photoredox catalysts and selenium-π-acids using ambient air and visible light.

Results and Discussion

Based on our previous investigations toward selenium-π-acid catalyzed redox functionalizations of simple alkenes and alkynes,[1,2] we became interested in the question of whether non-protic nucleophiles such as homoallylic carbonic acid esters may undergo an intramolecular oxidative coupling reaction to furnish the corresponding 1,3-dioxan-2-ones.

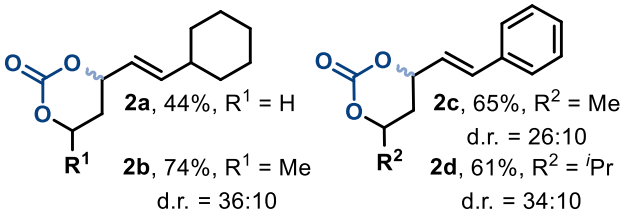
After extensive screening, the optimized reaction conditions (Figure **1**) were applied to a series of branched and unbranched homoallylic carbonates.

Figure 1. Optimized photo-aerobic allylic functionalization of alkenes.



Various functional groups such as halides, esters and ethers were well tolerated. As expected, branched substrates performed noticeably better compared to their unbranched analogs (Figure 2, compd. **2b** vs. **2a**). Interestingly, the addition of a substituent to the carbinol C-atom (C1) resulted in diastereoselectivities ranging from 19:10 to 36:10. 2D NMR spectroscopic analysis of **2c** revealed that the cyclization preferentially occurs with *cis*-diastereoselectivity with regard to the substituents at C1 and C3. In addition, the C4/C5 double bond was formed with high *E*-selectivity. We also noticed that the diastereoinduction increased – and thus correlated – with rising steric demand of the respective terminal group R^2 (Figure 2, compd. **2c** vs. **2d**), albeit only to a moderate extent.

Figure 2. Selected examples of the substrate scope. Caption: NMR yields, d.r. = diastereomeric ratio.



Conclusion

In summary, we have developed a new protocol for the synthesis of 4-mono- and 4,6-disubstituted 1,3-dioxan-2-ones from branched and unbranched carbonic acid esters, respectively, by photo-aerobic selenium-π-acid multicatalysis. The carbonate products were formed in yields of up to 74% and, in the case of 4,6-disubstituted dioxanones, with a pronounced *cis*-diastereoselectivity. Key advantages of the title protocol are the carbon-efficient use of ambient air as the terminal oxidant and visible light as a gratuitous energy source, which circumvents the use of sensitive or even corrosive oxidants such as elemental iodine or hypervalent iodanes.

Acknowledgments

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Synthesis and biological evaluation of 1,2,3-triazole selenides against *Trypanossoma Cruzi*

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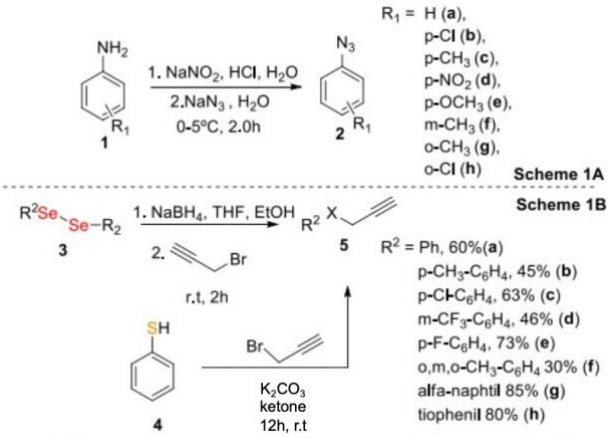
Keywords: *Antiprotozoan, hybridization, organoselenium*

Background

The WHO recognizes 20 neglected tropical diseases, on which Chagas Disease (CD) is one of the most prevalent and causes more than 50,000 deaths a year. It is caused by the protozoan *Trypanosoma cruzi* and there've been only two viable treatments in the clinic since the 1940s[1]. Therefore, there is a gap in the development of a new therapy for CD considering its relevance to public health. In this work, using a hybridization strategy linking two classes of compounds that previously showed several biological activities,[2,3] we report the synthesis and biological evaluation of novel triazole-1,2,3-selenides against *T. cruzi*.

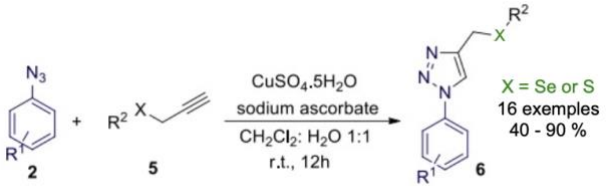
Results and Discussion

For the synthesis of the 1,2,3-triazole-selenides, a convergent route methodology was used, using aromatic azides (**2**) which were obtained from commercial anilines (Scheme 1A), and the propargylic chalcogenides (**5**) wich were obtained with propargyl bromide (Scheme 1B).



Sch. 1. Synthesis of aromatic azides **2** and propargylic chalcogenides **5**

Finally, the 1,2,3-triazole selenides (**6a-p**) were obtained by a 1,3-dipolar cyclo-addition with the copper and ascorbate as catalytic system (Scheme 2). A series of 16 new compounds were obtained with yields ranging from 40 to 90% and confirmed by ^{1}H NMR.



Sch. 2. Synthesis of chalcogenide-triazole hybrids

The potential of these compounds to inhibit the protozoan *T. cruzi* was demonstrated through IC50 values described in Table 1.

Tab 1. Yields and structure of **6a-p** and their antiprotozoan activity

	R¹	R²	Yields	IC₅₀ (μM)		R¹	R²	Yields	IC₅₀ (μM)
6a	4-CH_3	Ph	75%	9,3	**6i**	H	4-Cl-C_6H_4	60%	16,8
6b	4-Cl	Ph	90%	11,5	**6j**	H	4-CH_3-C_6H_4	70%	7,4
6c	H	Ph	52%	8,2	**6k**	H	4-F-C_6H_4	76%	11,6
6d	4-NO_2	Ph	42%	>64	**6l**	H	2,4,6-CH_3-C_6H_2	50%	39,2
6e	4-OCH_3	Ph	84%	12,7	**6m**	H	3-CF_3-C_6H_4	63%	**5,4**
6f	2-Cl	Ph	56%	15,2	**6n**	H	Naphtyl	80%	**3,1**
6g	2-CH_3	Ph	85%	9,8	**6o**	H	Thiofenyl	50%	21,2
6h	3-CH_3	Ph	82%	9,2	**6p***	H	H	40%	15,6

* X = S; Benzniadazole [positive control] = 2,1 μM

Thus, seven of them were considered active, with derivatives **6m** and **6n** being the best in the serie. Since the effectiveness of a drug is related to biodisponibility -which include the ability to penetrate biological barriers, reach the pharmacological target and induce its activity- the oral bioavailability of these compounds was predicted by Swissadme Web Tool. In this way a moderate outcome was predicted for all compounds. In addition, other tests are being made, mainly to determine the mechanism of action of the **6m-n** compounds considering cytotoxicity results showed high selectivity of these hybrids.

Conclusion

In conclusion, in this work we reported the successful obtainment of a novel series of 16 1,2,3-triazole selenides hybrids . These derivatives were tested against CD and presented excellent results as possible new drugs .

Acknowledgments

FAPERJ CNPq Universidade Federal Fluminense

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Seleno-pillar[n]arenes for tuberculosis chemotherapy

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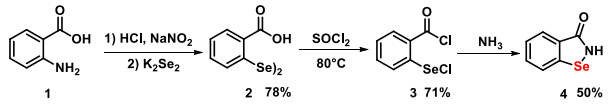
Keywords: *isoniazid, mycobacterium tuberculosis, macrocicles, ebselen.*

Background

Tuberculosis (TB) is a highly contageous disease that affects, principally, the lungs. The biggest challenge against this disease is the increase in drug-resistance that occurs, generally, because of the abandonment of the long treatment.[1] In this context, isoniazid (INH) is one of the main agents used for the treatment of TB. The metabolism of this drug involves a terminal nitrogen acetylation step that, when carried out earlier, inactivates the drug and it is associated to bacterias resistance to INH.[2] Therefore, controlling this reaction is highly important, in which a promising alternative could be the application of macromolecules as capsules for the drug.[3] Thus, the aim of this project consists in developing a potential nanocarrier of INH, assuring its resistance to N-acetylation. For this, we propose the synthesis of a new seleno-pillar[n]arene, as a result of the combination of two structures (ebselen + pillararene) which, separately, proved to be potent antibacterial agents.[4]

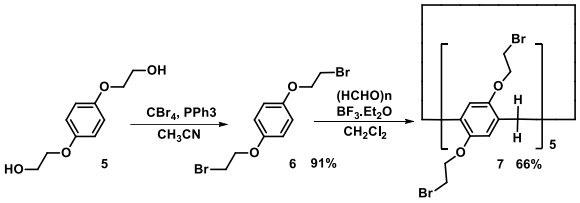
Results and Discussion

For the development of this project a 3 steps methodology was established for the synthesis of the ebselen analogue compound **4**. First, a diazotization followed by a nucleophilic substitution was performed, obtaining the diselenide **2** with 78% of yield. Then, the diselenide was put under a reaction with thionyl chloride, resulting in the intermediary **3** (71%). Finally, a cyclization using ammonia was performed, resulting in the final product, ebselen analogue **4**, with a yield of 50% (Scheme 1).[5]



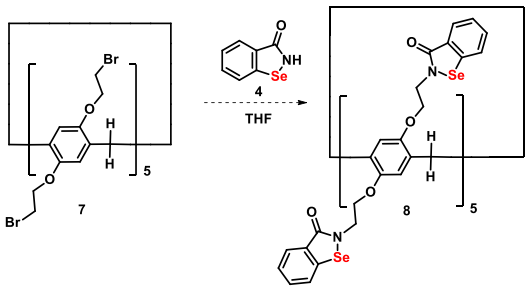
Scheme 1. Synthetic route of ebselen analogue compound **4**.

For the synthesis of pillar[n]arene **7**, firstly, a bromination reaction was performed, obtaining the brominated monomer with a yield of 91% and, next, a cyclization with a yield of 66% (Scheme 2).[6]



Scheme 2. Synthetic route of pillar[n]arene **7**.

Considering the importance of the desired macromolecule in the objective of ensuring the resistance to early acetylation of the drug INH, a methodology was proposed for the synthetic route of seleno-pillar[n]arene **8** through a nucleophilic substitution reaction using the compound **4** (Scheme 3).[7] The effectiveness of this reaction is still being evaluated, as well as its purification step.



Scheme 3. Synthetic route for seleno-pillar[n]arene **8**.

Conclusion

The compound **4** was obtained in a good yield. Furthermore, pillar[n]arene **7** was also obtained in a good yield, which can be put under reaction with different substituents, besides ebselen analogue **4**, with the purpose of forming drug carriers with distinct properties. As perspectives, it is intended to obtain the seleno-pillar[n]arene **8**, as well as load it with INH to evaluate the efficiency against early N-acetylation.

Acknowledgments

UFF, CNPq and FAPERJ.

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Application of the Chalcogen-pillar[n]arenes as catalysts for nucleophilic substitution in aqueous media

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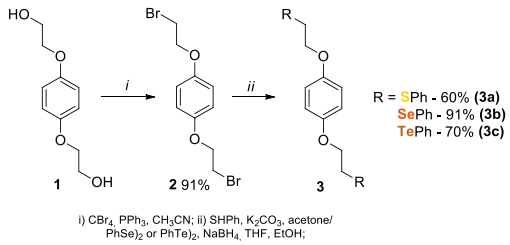
Keywords: *catalysis, macrocycle, selenium, tellurium.*

Background

The ability of enzymes to catalyze reactions in the biological environment arouses the interest of organic chemists, and this is not a new. In this sense, organochalcogens are a class of compounds that stand out at mimicking enzymes, for example, they were established as catalysts of redox reactions, mimicking glutathione peroxidase enzyme.[1] More recently, salts of chalcogens have demonstrated the ability to transfer an electrophilic moiety to a given nucleophile, mimicking SAM - an enzyme of the methyl transferase class.[2] Pillar[n]arenes, macrocycles formed by hydroquinone units, also have showed catalytic ability and selectivity, due to its cavity with the potential to host small molecules through supramolecular interactions.[3] Therefore, the objective of this work is to combine chalcogens and pillararenes, chalcogen-pillararene hybrids, and evaluate their catalytic potentials in organic transformations using water as a solvent.

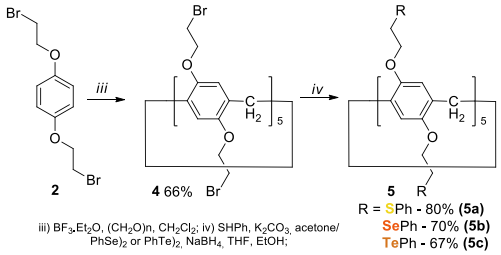
Results and Discussion

For the synthesis of the desired catalysts, starting with commercial compound **1**, which gave rise to **2** in 91% yield. This compound was functionalized to obtain monomers containing chalcogens (**3a-c**) (Scheme 1).



Scheme 1. Syntetic route of monomers **3**.

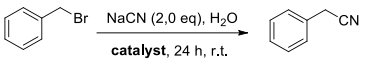
Then, **2** was cyclized with Lewis acid and paraformaldehyde, yielding the pillar[5]arene **(4)**. Finally, this macrocycle was also functionalized to obtain the chalcogen-pillararenes **(5a-c)** (Scheme 2).



Scheme 2. Syntesis of chalcogen-pillar[5]arenes **5**.

Molecules **3** and **5** were tested as catalysts in the reaction, having water as solvent, to obtain 2-phenylacetonitrile and the results can be seen in the Table 1. It's observed that without catalyst the reaction isn't completed. Using **5c**, the best catalyst, the reaction achieved a yield of 96%.

Table 1. Nitrile formation reaction and catalysis results



	Catalyst	Yields (%)
1	-	15
2	MSPh (**3a**) – 5% mol	16
3	MSePh (**3b**) – 5% mol	29
4	MTePh (**3c**) – 5% mol	45
5	P[5]SPh (**5a**) – 1% mol	22
6	P[5]SePh (**5b**) – 1% mol	55
7	P[5]TePh (**5c**) – 1% mol	96

Conclusion

The synthesis and unprecedented application of chalcogen-pyrenes was a success. The best result was presented by P[5]TePh (**5c**) which was an excellent catalyst in a heterogeneous medium, showing both the potential of tellurium chalcogen and the supramolecular cavity of the macrocycle. From this, new tests are underway, such as catalyst recovery, reaction scope, scale-up.

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Selenium catalyst in the oxidation of phenols. Model reactions for the development of new protocols in the treatment of biomasses.

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Keywords: *Biomasses, Oxidation, Selenium*

Background

Biomass are known as renewable source of energy and fine chemicals. Lignin (LI) and Olive mill wastewater (OMW) are two examples of biomasses and different procedures were developed to treat both.

Results and Discussion

Oxidative protocols catalyzed by organoselenium compounds are known as effective methods to perform a number of different reactions under mild and sustainable conditions[1]. In this communication we report the application of some procedures recently developed in our group to the treatment of the abovementioned biomasses. In particular, the aim of the project is to optimize condition for the depolymerization of LI and the detoxification of OMW. In the first case it will be possible to envision LI as a renewable source of fine chemicals while in the second case the procedure focus on the possibility to reuse OMW for the fields irrigation. As an example it is reported the use of LI to produce vanillin[2] and several methods were proposed to remove from OMW the polyphenols that are responsible of the phytotoxicity and, as antioxidant, the resistance to biodegradation[3]. In this project a new green oxidative protocol (Figure 1) was developed using as oxidant hydrogen peroxide and as catalyst organoselenium compounds as well as elemental selenium. The reactions were firstly performed on model compounds (phenol, catechol and some of its derivatives) able to mimic the main organic scaffolds present in both biomasses. As results of the oxidation the corresponding muconic acids and butyrolactones were obtained.

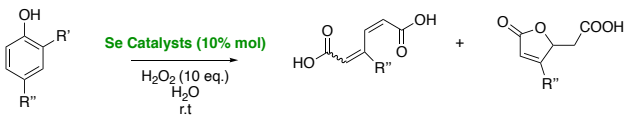
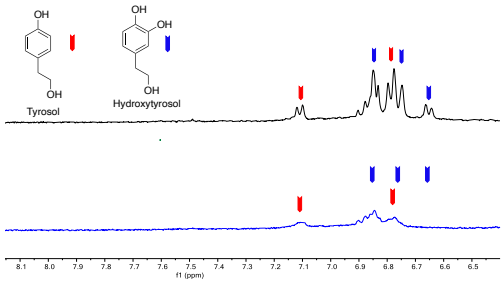


Figure 1. Oxidative protocol.

Different catalysts showed not only different catalytic activity, but we demonstrated that a proper selection allows the chemoselective obtainment of the *cis-cis* muconic acid or the *trans-trans* muconic acid while the nature of the substrate drives the reaction toward the formation of a butenolide.

Moreover, the same protocol was applied directly on native OMW. ^{1}H-NMR analysis demonstrated that, in accordance with the results obtained on model compounds, the oxidation removes completely the hydroxytirosol that is one of the most abundant polyphenols identified into the OMW.



Conclusion

A new eco-friendly oxidative protocol able to oxidize phenols derivatives was developed obtaining as product the corresponding muconic acids and the butyrolactones. With this results in hands, the protocol was also applied on the OMW, and it resulted into the elimination of a part of polyphenols.

Acknowledgments

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Synthesis of 1,2,3-triazole-thiophene hybrids that inhibit the proteolytic activity of Jararaca

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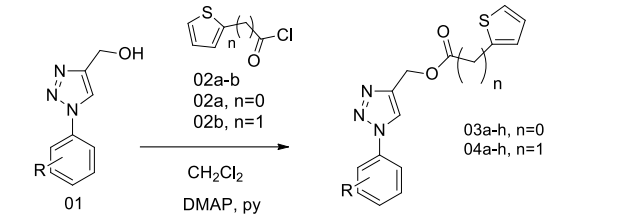
Keywords: *1,2,3-triazole, thiophene, proteolytic activity*

Background

The jararaca is one of the most common snakes in southeastern Brazil. The main symptoms of the bite are pain, swelling, bleeding in the wound and mucous membranes, necrosis and renal failure.[1]

Results and Discussion

From 1,2,3-triazole alcohols (a-g) esterification reactions were carried out with both 2-thiophenecarbonyl chloride and 2-thiophenylacetyl chloride.



01a, R= H
01b, R= 2,5-diCl
01c, R= 3,4-diCl
01d, R= 4-NO_2
01e, R= 4-OCH_3
01f, R= 4-F
01g, R= 4-CH_3

03a, R=H ; 80%
03b, R=2,5-diCl ; 85%
03c, R=3,4-diCl ; 60%
03d, R=4-NO_2 ; 73%
03e. R=4-OCH_3 ; 85%
03f, R=4-F ; 98%
03g, R=4-CH_3 78%

04a, R=3,4-diCl ; 54%
04b, R=4-NO_2 ; 55%
04c, R=4-F ; 50%
04d, R=4-OCH_3 ; 35%
04e, R= 2,5-diCl ; 35%
04f, R= H ; 35%
04g, R= 4-CH_3 ; 42%

Figure 1. Synthesis of esters hybrids 1,2,3-triazole-thiophene

The compounds synthesized were evaluated against the inhibition of jararaca´s poison proteolysis.The compounds 4d and 4e presented the best results with inhibition of proteolysis about 40%.

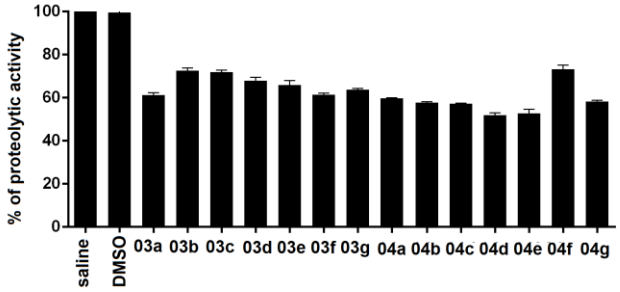


Table 1. Effect of 1,2,3-triazole-thiophene hybrid esters on the proteolytic activity of jararaca venom

Conclusion

The esterification methodology using 2-thiophenecarbonyl chloride proved to be efficient and reproducible. However, the methodology employing 2-thiopheneacetyl chloride needs improvement.

Acknowledgments

The authors thank UFF, UERJ, FAPERJ and CNPq

[1] Uma jararaca nada comum: conheça a maior causadora de acidentes com cobras do Brasil - Instituto Butantan

Hydrogen-Bond-Modulation of Se^{III} Nucleofugality within Selenohydrins to Enable Photoredox Catalytic Semipinacol Manifolds

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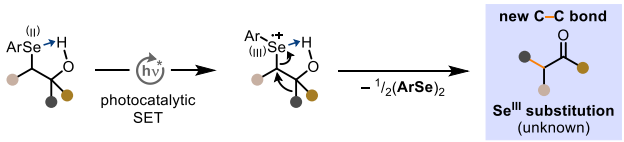
Keywords: *photoredox catalysis, semipinacol rearrangements, O–H···Se^{III} hydrogen bond interactions*

Background

A photoredox catalytic 1,2-carbon-shift manifold is enabled by an unprecedented O–H···Se^{III} hydrogen bond co-activation of C–Se σ-bonds, which has significant implications for synthetic use of H-bond interactions with heavy atoms.

Results and Discussion

Traditionally, the activation of C–Se σ-bonds proceeds through Se^{IV} intermediates *via* oxidative activation with external electrophiles and bases, which have the disadvantage that these intermediates often result in rapid elimination of the Se^{IV} residue.[2,3] Therefore, we commenced our investigations to find suitable conditions to trigger the rearrangement of selenohydrins *via* a photo-catalytic activation to form new C–C σ-bonds.



Scheme 1. Noncovalent Se–C co-activation *via* OH···Se^{III} H-bond interactions.[1]

The photo-aerobic rearrangement proved effective for the synthesis of a wide array of cyclic and acyclic ketones **2a-u** tolerating common functional groups, such as halogens, amines and heterocycles (see Figure 1).

Magnetization transfer by scalar coupling confirmed the strong and stable O–H···Se H-bond by an intense cross peak between OH and Se in the NMR spectra. Additional molecular dynamic simulations indisputably show that the OH···Se H-bond is by far stronger and more covalent. This suggests that a designed activation of Se moieties *via* H-bonds is feasible. The nucleofuge released upon photo-oxidation of selenohydrins in HFIP was identified by transient absorption spectroscopy as the $PhSeH^{\bullet+}$ radical cation. Further DFT calculations confirmed the mesolytic nature of the bond cleavage.

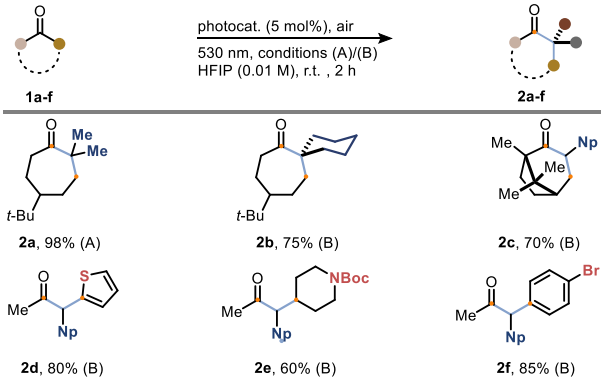


Figure 1. Reaction scope – a selection; conditions: (A) rose bengal, (B) rose bengal + cinnamic acid (50 mol%);

Conclusion

We have shown for the first time that the nucleofugality of selenium residues can be modulated by the combination of single electron oxidation and OH···Se H-bond interactions. This Se–C bond activation principle has been implemented in a photoredox catalytic type I semipinacol rearrangement of selenohydrins **1a-z´** to provide ketones **2a-u** in good to excellent yields. Our findings are expected to have significant implications for the synthetic exploitation of H-bond interactions involving heavy, less electronegative acceptor atoms such as selenium.

Acknowledgments

We thank R. J. Kutta, E. Harrer, D. Grenda for technical and operational support. We thank the European Research Council (ERC Starting Grant "ELDORADO", grant agreement No. 803426), the German Research Foundation (DFG, RTG 2620) and the Studienstiftung des deutschen Volkes for financial support. Furthermore, the project was funded by the German Research Foundation (DFG, TRR 325 – 44632635).

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Selenium as a reactive atomic center in bioorganic chemosensing systems

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Keywords: *Selenium, "crowdoxidation", M. R. Detty.*

Background

Molecular chemosensing requires a fluorophore(s) choice. Beyond this, there are many ways of decorating new derivatives with effective substituents which may be able to assist in "switching". One way is to use heavy atoms. Among the choices, it is often convenient to use group 16 centers, and wherever there may naturally be e.g. an ethereal O, it can be switched to S or Se, or Te. We have had luck with different systems over the years. After initiating this work, we found that M. R. Detty in 1990 published what is to be regarded as a landmark paper in this field.

Results and Discussion

We use rigid chemical platforms which are fluorogenic and stem back to "turn-on" fluorescence findings by Detty[1], and our own "crowdoxidation" probes. The molecular skeletons have involved BODIPY, coumarin, phthalimide and others.[2-11] We have also reviewed the literature[2,4]. The presence of one Se atom often imports a "red shift" and "turn-off" state to the molecular system. The discovered organoselenium systems can fall into two categories with regard to analyte reactivity: ones that become Se oxidized and retain C-Se bonding, and those that allow for C-Se bond cleavage and leaving group departure.

Conclusion

Various systems have been synthesized and characterized. We have discussed findings from recent publications that contain different types of molecular probe systems. Neuroscience, as with any scientific endeavor needs new modalities of probing; we hope that our findings with regard to ROS and selenium-containing systems serve to create starting points for future neurodegenerative disease related research efforts.

Acknowledgments

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Design and synthesis of new chalcogen-functionalized naphthoquinones with potential antitumor activity

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Keywords: *organoselenium, cancer, molecular hybridization.*

Background

Cancer is a major public health problem worldwide totaling about 9,6 million deaths.[1] The main treatments for this disease, such as chemotherapy, radiotherapy and surgery, can have several side effects and are not effective in advanced stages when there are great chances of metastasis.[2] In this sense, the development of new, more effective and safer substances for the cancer treatment is extremely necessary.[3] Chalcogen-derived molecules, as well as naphthoquinones, are two classes of compounds that have aroused the interest of researchers because of their wide range of biological applications, mainly against different types of tumors.[3] As part of our interest in organochalcogen compounds, we report in this work the synthesis of new chalcogenenaphthoquinones aiming the development of a more selective and active pharmaceutical option for the cancer treatment (Figure 1).

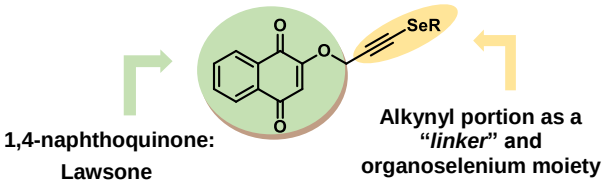

Figure 1. Rational design for 1,4-naphthoquinone and alkynyl selenide hybrids.

Results and Discussion

Initially, the optimization aimed at the variation of parameters such as temperature, followed by the equivalent with and without the presence of base. In addition, the catalyst, with CuO and CuCl, and the solvents were varied. The best condition found was with 0.9 equivalents of **3a**, without bases and at room temperature. By this way, the desired product **4a** was obtained in 85% yield (Scheme 1).

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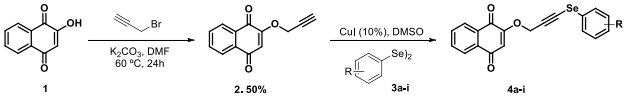

Scheme 1. General synthetic route.

After, the scope and limitations of the proposed methodology were investigated. Thus, a variety of diorganoyl diselenides were tested and the desired new products, **4a-4i** were obtained in moderate to excellent yields, ranging from 40-85% (Figure 2).

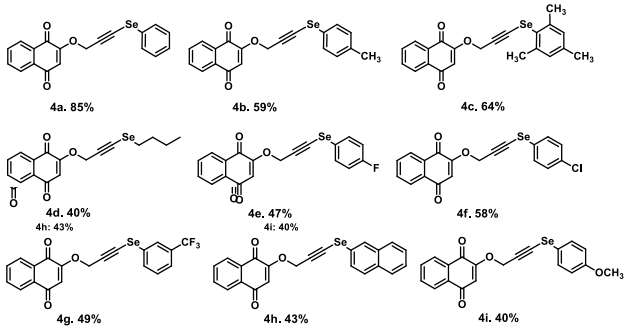

Figure 2. Scope variation of diorganoyl diselenides.

The developed protocol was also tested against different diorganoyl dichalcogenides (Te and S). To our delight, four new derivatives could be obtained with good yields for the class **(5a-5d)** with yields of 24-60%.

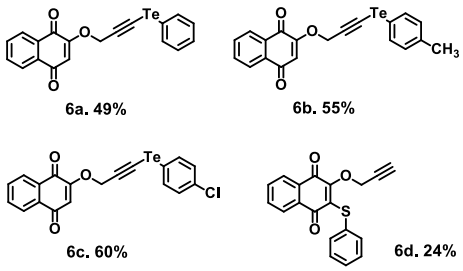

Figure 3. Scope variation of diorganoyl dichalcogenides.

Conclusions

It is possible to conclude that in this work the synthesis of a 13 new chalcogenonaphthoquinone hybrids with good to excellent yields was developed. With this in hand, we intend to verify its antitumor activity with partner research groups.

Acknowledgments

UFF, CAPES, FAPERJ, CNPq.

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Menadione linked with chalcogens: design and synthesis of promising structures against tuberculosis

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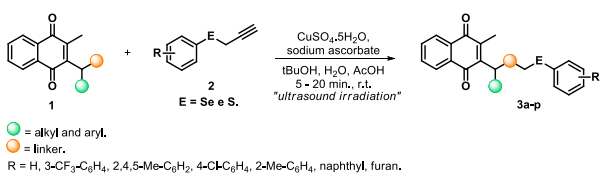
Keywords: *selenium; naphtoquinones; organochalcogens.*

Background

Tuberculosis (TB) remains a global public health challenge. The emergence of the COVID-19 pandemic culminated in the reorganization of actions, services and health systems around the world, which, according to the World Health Organization (WHO), reversed years of progress in TB control. In Brazil, in 2021, 68,271 new cases of TB were reported, which is equivalent to an incidence rate of 32.0 cases per 100,000 inhabitants.[1] The first-choice anti-TB treatment was developed over 40 years ago. This, together with the development of *Mycobacterium tuberculosis* strains resistant to multiple drugs and the co-infection with the AIDS virus, has worsened the picture of this disease worldwide. The urgent need for more effective treatments against multidrug-resistant strains has stimulated industries, governments and non-governmental organizations to search for new drugs.[2] In this sense, organochalcogen compounds have been of great interest to synthetic and medicinal chemists due to their remarkable biological properties.[3] Quinones, in particular naphthoquinones have wide therapeutic applicability.[4] Considering the importance of organochalcogen compounds and 1,4-naphthoquinones mainly from a biological point of view, the objective of this project is the planning and synthesis of an unprecedented series of new chalcogenonaphthoquinones with potential application against tuberculosis.

Results and Discussion

The target compounds were obtained through the reaction between menadione derivatives and alkynes containing chalcogen atoms (Se and S). The formation of chalcogenonaphthoquinones with an important linker was provided by the cycloaddition reaction Cu(I)-catalyzed 1,3-dipolar (**Scheme 1**).



Scheme 1. Synthetic route to obtain products **3a-p**.

With this methodology it has been possible achieve 16 new molecules with good to excellent yields and variations both in the quinone portion and organochalcogen moiety. The molecules and their respective yields can be seen in Figure 1.

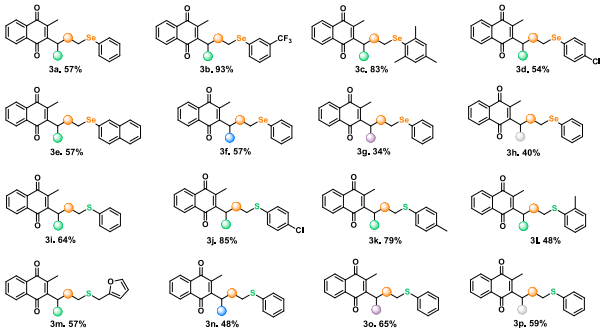


Figure 1. Structure of the products obtained **3a-p**.

The synthesized molecules were screened against the *Mycobacterium tuberculosis* H37Rv ATCC 27294. The best results were found for compounds **3b**, **3d**, **3f**, **3g** and **3h**, with the best MIC values (Table 1).

Table 1. Results of screening trials.

Compound	MIC (µg/ml)
3b	≤ 50
3d	≤ 3,2
3f	≤ 6,25
3g	≤ 12,5
3h	≤ 25
Rifampicin	1,0

A complementary microbiological assay was also performed for the above molecules in order to detect sensitivity/resistance against the wild-type strain of *M. tuberculosis* T 113 (resistant to rifampicin and isoniazid). Optimal results were obtained with MIC values ≤ 3,12 µg/ml for compounds **3d**, **3g** and **3h**.

Conclusion

In conclusion, a total of 16 new hybrid chalcogenonaphthoquinones were synthesized, with promising results against *M. tuberculosis*.

Acknowledgments

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The naphthyl (O/S/Se)ether-linked 1,3,5-triazine 5-HT$_6$R antagonists as new pharmacological approach to Alzheimer's disease therapy

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Keywords: *Selenoether, 5-HT$_6$ receptor, Alzheimer's disease.*

Background

Serotonin receptor 5-HT$_6$ is important target in search for new Alzheimer's disease therapy. We examine new naphthyl selenoether 1,3,5-triazine 5-HT$_6$R ligands in comparison to the (thio)ether ones [1-3].

Results and Discussion

The new compounds have been obtained within multistep syntheses, involving the catalytic synthesis of naphthyl diselenides using Grignard reagent, the Se-ether ester synthesis with suitable bromoalkylesters, followed by cyclic condensations with the piperazine biguanide in basic conditions. The compounds were evaluated on their 5-HT$_6$R affinity in the radioligand binding assay. The intrinsic activity and neuroprotective effects *in vitro* for selected compounds were examined, too. Two most active compounds (**WA-22** and **PPK-32**, Fig.1) were tested in behavioral studies in rats *in vivo*. The Se-ethers tested showed significant nanomolar affinities and antagonistic action for 5-HT$_6$R. **WA-22** and **PPK-32** were able to reverse memory disturbances in rats at the dose such low as 0.3 mg/kg. Their neuroprotective effects in the neuroblastoma model *in vitro* have been confirmed.

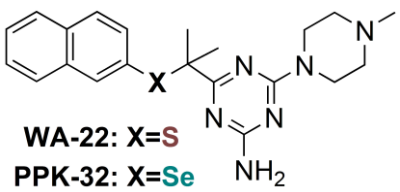

Figure 1. Compounds **WA-22** and **PPK-32**.

Conclusion

Qualitative structure-activity relationship analysis indicates that Se-ether-containing β-naphthyl compounds are especially beneficial for 5-HT$_6$R activity, and the activity, with respect to chalcogen, increases in order O<<S<Se.

Results of the behavioral studies *in vivo* demonstrated the high potency of diMe-branched Se- and thioether derivatives (**WA-22** and **PPK-32**) to reverse memory disturbances, thus giving a hope for an elaboration of innovative therapies of AD, based on the presented triazine compounds.

Acknowledgments

Partly supported by the National Science Centre, Poland (grant UMO-2018/31/B/NZ7/02160) and Jagiellonian University Medical College N42/DBS/000196. Part of the studies was performed within Student Medicinal Chemistry Club (SKN Chemii Medycznej UJ CM, Kraków).

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Synthesis of 3-chalcogenyl-indoles using Urea-hydrogen peroxide as oxidizing agent.

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Keywords: *3- chalcogenyl -indoles, Urea-hydrogen peroxide and green chemistry.*

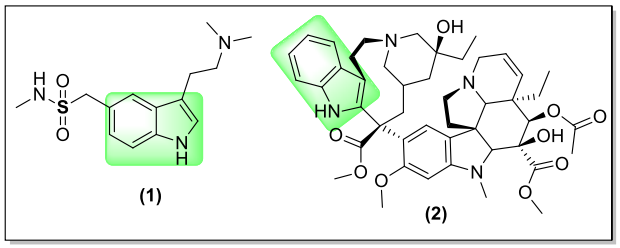
Background

Green methodology for the synthesis of 3-chalcogenyl-indoles and their derivatives. Urea-hydrogen peroxide as a safe oxidant. Carbon-chalogen bond formation in arylic systems.

Results and Discussion

The search for methodologies that have a lower environmental impact in the synthesis of molecules of biological interest is a promising area. In this context, the development of methodologies for carbon-chalcogen bond formation has been highlighting due to biological properties attributed tho these compounds. On the other hand, the indole nucleus is present in several commercial drugs, such as sumatriptan **(1)** and vinblastine **(2)** (Figure 1).[1]

Figure 1. Structure of sumatriptan and vinblastine.



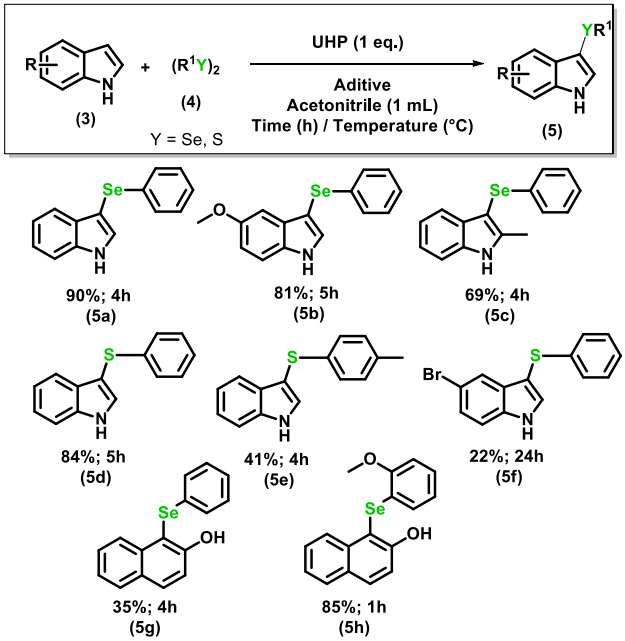
The Urea-hydrogen peroxide (UHP) is well recognized a safer oxidizing agent, due to the fact that it is solid, anhydrous, compatible with a range of functional groups and its handling reduces the risk of explosions when compared to oxidants in aqueous solution (Scheme 1).[2]

The present work aims to develop a new methodology for the synthesis of 3-chalcogenyl-indoles and their derivatives and to evaluate the potential of UHP in the oxidative cleavage of the diorganoyl dichlogenides bond. Indoles (0,5 mmol) **(3)** and diorganoyl dichalcogenides (0,25 mmol) **(4)** were used as starting materials, in the presence of 1 equivalent of UHP, molecular iodine or potassium iodide amd acetonitrile as solvent. The seleno-compounds were obtained in 80 ºC while the sulfenil-indoles were prepared at room temperature. With optimized condition, it was possible to perform the structural variations of the starting materials and the results are presented in the Scheme 2.

Scheme 1. General reaction scheme

- ✓Solid
- ✓Anhydrous;
- ✓Compatible with a range of functional groups;
- ✓Provides safety to the manipulator

Scheme 2. Scope of structural variation.



Conclusion

Therefore, it was possible developed a new method for the synthesis of 3-chalcogenyl-indoles, using UHP as the oxidizing agent. This work allowed the safe preparation of several compounds with good yields.

Acknowledgments

UNIPAMPA, IFFSUL, CAPES

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Application of Cyrene as bio-solvent on the seleno-cyclization of 4-penten-1-ol

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Keywords: *Cyrene, bio-solvent, seleno-cyclization.*

Background

The use of eco-friendly solvents has been gaining more and more space in the development of organic synthesis methodologies. In this context, the increasing number of solvents derived from biomass used for this purpose in the last years is remarkable, since they are obtained from abundant raw materials or they are by-products of industrial processes. In this context, cyrene (di-hydrolevoglucosenone) is a substance obtained from the pyrolysis of cellulose in the energy generation from biomass. Because it is a polar aprotic compound, it has potential to be used in replacement for traditional aprotic polar solvents, such as DMF or HMPA. Moreover, it can be easily removed from the reaction medium by washing with water.[1]

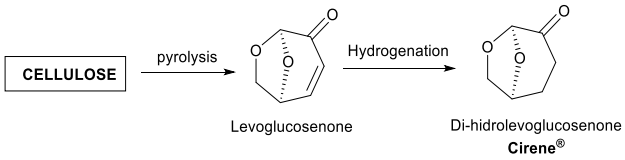


Figure 1. Process to obtain cyrene from cellulose

On the other hand, eletrophilic seleno-cyclization of alkenes is an important method to prepare 5 or 6-member rings containing an organoselenium moiety, which are important building blocks in organic synthesis.[2] Therefore, the objective of this work is to apply cyrene as a sustainable solvent in the seleno-cyclization of alkenes, through the formation *in situ* of electrophilic selenium species (Figure 2).

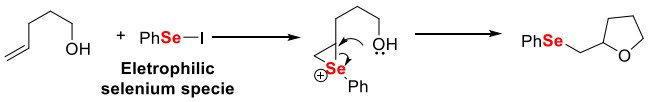
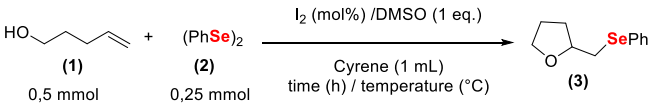


Figure 2. Seleno-cyclization of 4-penten-1-ol

Results and Discussion

For the optimization of the reaction parameters, it was used 4-penten-1-ol **(1)** and diphenyl diselenide **(2)** as standard reagents in the presence of iodine as catalyst and dimethyl sulfoxide as oxidant. All the tests were carried out in the presence of 1 mL of cyrene. In this way, it was evaluated the ideal time, temperature and the catalyst amount for this process (Table 1). Within the parameters studied, the best condition was found using 20 mol% of I_2, 1 equivalent of DMSO, in 90 minutes at 50 ºC of temperature, where the product 5-exo-trig **(3)** were prepared in 97% yield (Entry 3).

Table 1. Seleno-cyclization of 4-penten-1-ol **(1)**, in cyrene.



Entry	Time (min)	T (ºC)	Catalyst (mol%)	Yield (%)
1	15	50	I_2 (20)	13
2	60	50	I_2 (20)	77
3	**90**	**50**	**I_2 (20)**	**97**
4	120	50	I_2 (20)	93
5	90	25	I_2 (20)	39
6	90	50	KI (20)	-
7	90	50	I_2 (15)	77
8	90	50	I_2 (10)	71

Conclusion

In conclusion, it was possible to apply the cyrene, a substance obtained as a by-product of biomass energy generation, as a solvent in seleno-cyclization reactions of alkenes. Additional studies are still in progress.

Acknowledgments

CAPES, PPGCF-UNIPAMPA

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Se-substituted thiazole derivatives as strong potentiators of antibiotic activity against *Staphylococcus aureus* strains.

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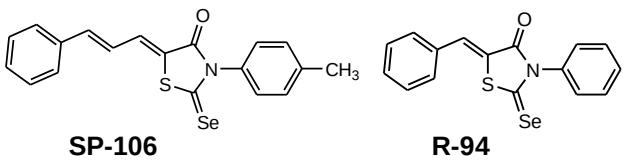
Keywords: *Se-substituted thiazoles, Staphylococcus aureus,* MRSA, bacterial resistance, antibiotic adjuvants.

Background

S. aureus infections pose a severe threat as the bacteria acquire resistance to most available antibacterials. We assess new Se-substituted thiazoles for antibiotic adjuvant action in *S. aureus* [1,2].

Results and Discussion

New selenium-containing thiazole derivatives were examined for the ability to enhance the antibacterial activity of different antibiotics against a set of *S. aureus* clinical isolates. Results of susceptibility testing show that compounds exert weak anti-staphylococcal activity. However, it has been found that derivatives **SP-106** and **R-94** at sublethal concentrations restore the efficacy of β-lactam antibiotic oxacillin against methicillin-resistant S. aureus (MRSA). No influence on oxacillin activity against methicillin-susceptible *S. aureus* (MSSA) suggests an impact of compounds on MRSA resistance mechanism to β-lactams associated with PBP2a. Interestingly, derivatives **SP-106** and **R-94** were also able to restore the activity of erythromycin but were devoid of adjuvant action in combination with ciprofloxacin and vancomycin against resistant, to these antibiotics, bacterial strains.



SP-106 **R-94**

Figure 1. Compounds **SP-106** and **R-94**.

Conclusion

The SAR analysis performed indicates that the type of chalcogen substituent attached to the aromatic ring of thiazole plays a crucial role in the cooperative action of compounds with oxacillin. It has been found that the introduction of the selenium atom at position 2 of the thiazole nucleus determines the adjuvant properties of the hit compounds **SP-106** and **R-94.** Another structural feature influencing the capacity of molecules to enhance oxacillin efficacy seem to include the presence of oxygen atom at position C4 and aromatic moieties at position N3 and C5 of the thiazole core. Promising antibiotic adjuvant properties of Se-substituted thiazole derivatives make them good candidates for further development as anti-MDR agents able to reverse the activity of antimicrobial drugs against MRSA.

Acknowledgments

The study was partly supported by the Jagiellonian University Medical College grant N42/DBS/000196 and N42/DBS/000296.

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Redox Chemistry of Cyclic Diselenide Reagents as a Tool for Manipulating Structure of Proteins

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Keywords: *Protein folding, Disulfide, Proteostasis*

Background

Quality of proteins in the endoplasmic reticulum (ER), where nascent polypeptides gain a unique 3D structure, is maintained by various ER-resident enzymes, such as protein disulfide isomerase (PDI). PDI not only catalyzes disulfide (SS)-formation and SS-isomerization between cysteine residues by its oxidoreductase activity but also suppress protein aggregation by its molecular chaperon activity during oxidative protein folding (**Figure 1**). Because dysfunction of PDI under ER stress leads to protein misfolding, development of a chemical tool to control the protein quality possesses clinical values from the viewpoint of the treatment of human misfolding diseases such as neurodegenerative disorders.

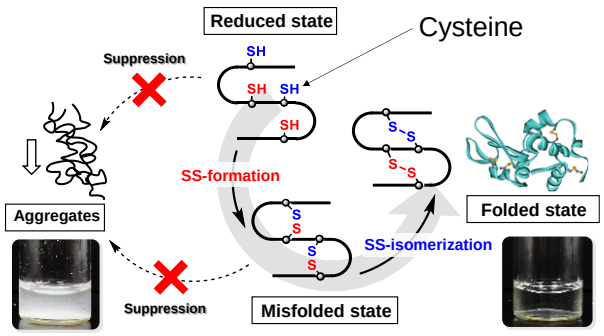

Figure 1. Cysteinyl SS-related reactions and protein aggregation controlled by PDI during oxidative folding.

Results and Discussion

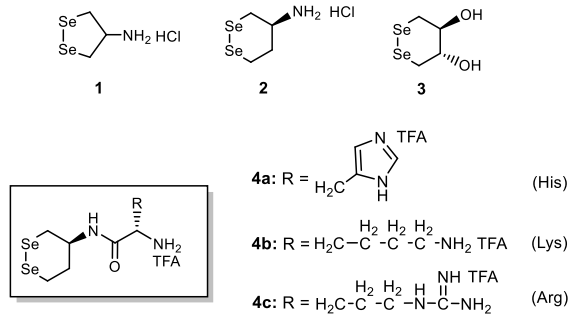

Figure 2. Water-soluble cyclic diselenide compounds as a PDI mimic synthesized in this study.

In this study, we synthesized cyclic diselenide-based compounds (**1**–**3**) as candidates of alternative molecules of PDI (**Figure 2**). When the oxidative folding of reduced ribonuclease A (R^{RNase}) having no SS bonds as a model substrate protein was performed in a redox buffer solution containing glutathione (GSSG/GSH [0.2 mM/1.0 mM]) with a catalytic amount of compounds **1**–**3**, the folding rates were obviously faster than that observed in the absence of the compounds.[1] Subsequently, we designed basic amino acid conjugates (**4a**–**c**, **Figure 2**) of compound **2**, which were inspired by the redox active center of PDI (i.e. CGHC sequence), and applied those as the oxidative folding catalyst. Interestingly, application of the compounds to the oxidative folding of hen egg-white lysozyme revealed that conjugation of the basic amino acids, especially histidine (His), to **2** improves the capability as the PDI-like redox catalyst. Surprisingly, furthermore, these compounds also showed remarkable suppression capacity against protein aggregation. In this presentation, the detailed catalytic mechanisms will also be explained.

Conclusion

The results obtained in this study suggest that cyclic diselenide compounds would be promising in applications to artificial control of *proteostasis*. We are now evaluating the use of these compounds as folding additives by using different substrate proteins and investigating their possible use for medicinal applications.[2,3]

Acknowledgments

This work was financially supported by JSPS KAKENHI [Grant Number 17K18123 (to K.A.)] and the Research and Study Project of Tokai University, Educational System General Research Organization. This author thanks his students for their hard work for this study.

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Flowing Chalcogens: Flow chemistry approaches with organoselenium and organosulfur compounds

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Keywords: *Organoselenium; sulfur, flow chemistry.*

Background

Organoselenium and organosulfur compounds are of attracting interest due to their peculiar properties exploited in organic synthesis, medicinal chemistry and polymer science.[1] As a consequence, sustainability-directed methods to facilitate their synthesis are highly demanded.
Continuous flow systems offer several advantages over batch chemistry but they are poorly explored in the organochalcogens research field.[2] Here, the flow synthesis of diselenylbisbenzoic acid (DSBA, **3a**) [3] together with a Se-catalyzed bioinspired oxidation strategy[4] will be presented.

Results and Discussion

For the DSBA synthesis, a freshly prepared solution of alkali metal diselenide and diazonium salt were fluxed in a tubular flow reactor. Synthetic aspects of the reaction and the unexpected formation of the unusual byproduct (**4a**) will be here discussed (Figure 1).

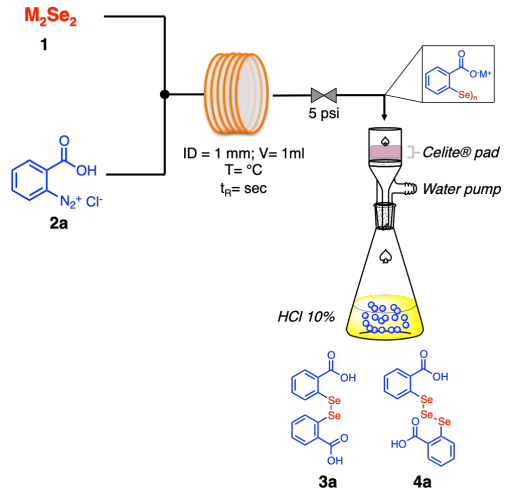

Figure 1. Synthesis of **3a** and **4a**.

A glutathione peroxidase-inspired oxidation methodology for the chemoselective conversion of sulfides into sulfoxides and sulfones is also presented (Figure 2).

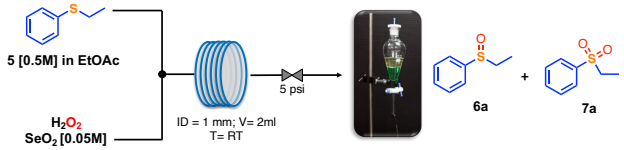

Figure 2. Synthesis of **6a** and **7a**.

A similar approach for the preparation of oxaziridines will be also briefly detailed.

Conclusion

Flow chemistry is highlighted as a valuable tool suitable for focused as well as flexible synthetic procedures.

Acknowledgments

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Eco-friendly Uracil Selenylation Employing I_2/DMSO as a Catalytic Oxidation System

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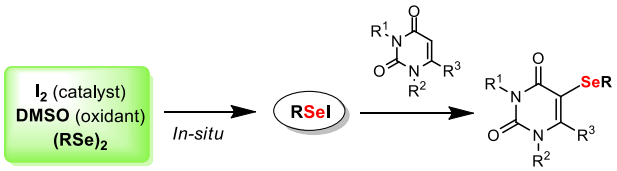
Keywords: *selenium, catalysis, uracil.*

Background

In this work, we are developing a new greener synthetic protocol for C5 uracil selenylation employing I_2 as catalyst in DMSO and diorganoyl diselenides in order to obtain the corresponding 5-organylselenyl uracils.[1]

Results and Discussion

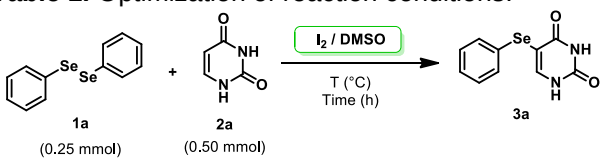
As demonstrated in the general reaction scheme below, we used the I_2/DMSO oxidative catalytic system to perform the uracil functionalization with an organoselenium moiety (Scheme 1).



Scheme 1. General reaction scheme.

The I_2/DMSO association has proved to be a simple, effective, metal-free and eco-friendly oxidative system with a wide range of applications in organic synthesis.[2] Initially, uracil (**1a)** and diphenyl diselenide (**2a**) were selected as the model substrates in order to identify the optimal experimental conditions for the synthesis of 5-phenylselanyluracil (**3a**), as described in Table 1.

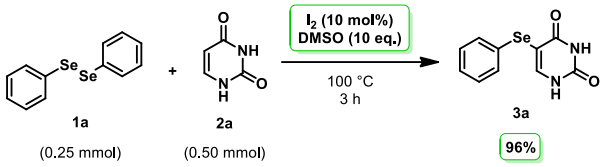
Table 1. Optimization of reaction conditions.



#	I_2 (mol%)	DMSO (equiv.)	T (°C)	t (h)	Yield[a] (%)
1	10	10	100	3	96
2	7.5	10	100	3	71
3	10	8	100	3	73
4	10	10	90	3	37
5	10	10	80	3	33
6	10	10	100	2	83
7	10	10	110	2	74

[a]Isolated yield.

After several optimization tests, we reached the best reaction condition (Scheme 2) using I_2 in the catalytic amount of 10 mol% and 10 equivalents of DMSO at 100 °C for 3h, obtaining the desired product (**3a**) in 96% yield.

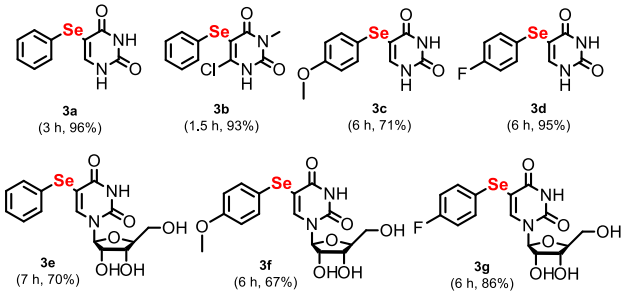


Scheme 2. Optimized reaction condition.

Conclusion

Currently, other examples of uracil and derivatives are being tested under the best reaction conditions, including uracil-containing nucleosides. In all cases, good to excellent yields were obtained showing that this transformation has potential to become a new environmentally sustainable methodology for selenylation of this class of substances.

Some examples:



Acknowledgments

We thank the funding agencies: CAPES, CNPq, FAPESC, and both universities UFSC and UNIPAMPA.

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Selenium compounds are potent inhibitors of oxidant damage

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Keywords: *Oxidants, selenium, inflammation*

Background

The formation of oxidants at sites of inflammation by activated leukocytes is critical for the killing of invading pathogens (e.g. bacteria). Oxidant generation is however associated with damage to host cells, and has been linked to multiple human diseases including cardiovascular disease, some cancers, rheumatoid arthritis, asthma, cystic fibrosis and multiple neurodegenerative conditions.

Leukocytes generate multiple oxidants including hypohalous acids (HOX, X = Cl, Br, SCN, via the heme enzyme myeloperoxidase), and peroxynitrous acid (ONOOH, from reaction of $O_2^{\cdot-}$ with $NO^{\cdot}$).

Sulphur-containing amino acids (cysteine, cystine and methionine) are targets for these oxidants in biological systems, with rate constants, k, for reaction of HOCl with Cys and glutathione being ~3 x 10^8 and ~1 x 10^8 $M^{-1}.s^{-1}$, respectively. Reaction with Met and *N*-Ac-methionine occurs with k ~3 x 10^7 M^{-} and ~ 2 x 10^8 $M^{-1}.s^{-1}$, respectively. In the light of these data we have investigated the kinetics of reaction of these oxidants with selenium-containing species to determine whether these can act as competitive scavengers.

Results and Discussion

Previous kinetic data for reaction of oxidants (e.g. HOCl, ONOOH) with selenium species are limited. Here we provide apparent second order rate constants for reaction of selenols (RSeH), selenides (RSeR′) and diselenides (RSeSeR') with biologically-relevant oxidants (HOCl, H_2O_2, other peroxides) as well as overall consumption data for the excited state species singlet oxygen ($^1O_2$). Selenols show very high reactivity with HOCl and O_2 with rate constants >10^8 $M^{-1}.s^{-1}$ whilst selenides and iselenides typically react with rate constants one (selenides) or two- (diselenides) orders of magnitude slower. Rate constants for reaction of diselenides with H_2O_2 and other hydroperoxides are much slower, with k for H_2O_2 being <1 $M^{-1}.s^{-1}$, and for amino acid and peptide hydroperoxides ~10^2 $M^{-1}.s^{-1}$. The rate constants determined for HOCl and $^1O_2$ with these selenium species are greater than, or similar to, rate constants for amino acid side chains on proteins, including Cys and Met, suggesting that selenium-containing compounds may be effective oxidant scavengers. Some of these reactions may be catalytic in nature due to ready recycling of the oxidized selenium species. Thus, the major oxidation product generated from the selenoethers is the corresponding selenoxide, which can be readily reduced (recycled) to the parent by thiols (e.g. GSH) and also some enzyme systems. These compounds can therefore act in a catalytic manner. Some of these materials have shown positive effects in cell and animal models.

Conclusion

These kinetic data indicate that a number of organoselenium compounds can act as efficient, and in some cases catalytic, scavengers of oxidants.

Acknowledgments

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Use of the Selenoxide-pillar[5]arene as a new alternative to obtaining nitriles in water

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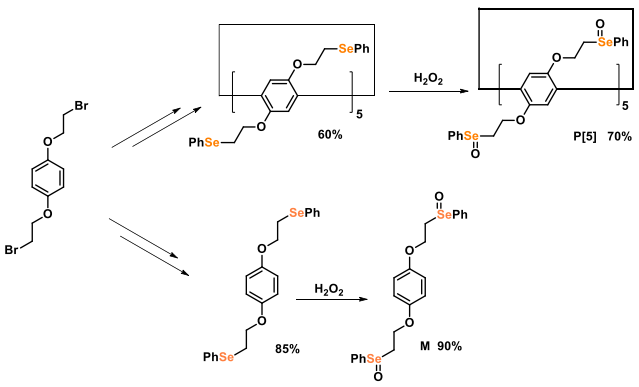
Keywords: *Selenium, pillararene, catalyst.*

Background

Because of the singular electron-rich cavity and easy functionalization, pillar[n]arenes have been extensively studied for several applications.[1] Besides, selenium compounds are highlighted in different fields, including catalytic potential in promoted organic reactions.[2] Therefore, the objective of this work is to promote the synthesis of C-C bond, in a greener reactional media through the use of pillar[5]arenes combined with organochalcogens as catalysts.

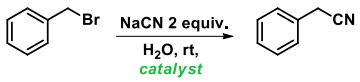
Results and Discussion

For the development of this project, it was first established a methodology for the synthesis of selenocatalysts. Thus, a selenoxide-pillar[5]arene **P[5]** and its monomer **M** were obtained. Both structures are derived from selenoxides, which gives them better solubility in the aqueous reaction medium (Scheme 1). Finally, these compounds were tested as catalyst in the obtention of nitriles in water – which are excellent synthetic precursors (Table 1). Noticeably, the best reactional condition is found in entry 3, which provided the product with 75% yield, using **P[5]** 1 mol%, NaCN (2eq.) during 16 hours. Also, through the higher yield of the **P[5]** comparatively to **M**, indicates that macromolecule cavity acts positively during the course of reaction.



Scheme1: Synthesis of catalysts **M** and **P[5]**.

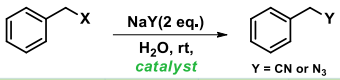
Table 1. Reaction optimization.



	Catalyst	Time (h)	Yeld (%)
1	--------	24	17
2	**M**(5 mol%)	16	41
3	**P[5] (1 mol%)**	**16**	**75**
4	**P[5]** (1 mol%)	6	30
5	**P[5]** (1 mol%)	12	22
6	**P[5]** (1 mol%)	24	55
7	**P[5]** (0,75 mol%)	16	60
8	**P[5]** (2 mol%)	16	70

From these promising results, further studies were carried out to explore the reactional applicability. For this, the variation of both leaving and nucleophilic groups of the reaction was evaluated. As we can see in table 2, the catalyst P[5] again proved to be highly efficient, because it allowed obtaining the products of interest in significant yields when compared to the absence of the catalyst.

Table 2: Scope of other leaving and nucleophilic groups.



	Substrate	Nucleophile	Catalyst	Yeld (%)
9		NaCN	1 mol%	15
10		NaCN	-----	5
11		NaCN	1 mol%	30
12		NaCN	-----	15
13		NaN_3	1 mol%	65
14		NaN_3	-----	5

Conclusion

In conclusion, the catalysts were obtained in excellent yields and proved to be efficient in promoting the nucleophilic reaction. Further studies continue to be carried to explore the scope of the reaction, its scalability and catalyst recovery.

Acknowledgments

FAPERJ, CAPES, UFF, UFMG

[1]Yang et al.; Pillararene-based molecular-scale porous materials, *Chem. Commun.*, **2021**,57, 13429-13447. [2]Alberto, E. et al.; From Stoichiometric Reagents to Catalytic Partners:, *Adv. Synth. Catal*. **2021**, 364,87-93.

Synthesis of new selenotetrazoles as potent corrosion inhibitors

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Keywords: *Heterocyclic, Corrosion, Selenium*

Background

Corrosion is a spontaneous behavior of metallic materials, which consists of their degradation due to interaction with their environment. One of the main methods of metal corrosion protection is the application of organic compounds containing heteroatoms such as N, O and S. Their presence and also π-electrons increase the adsorbent properties of the metal surface because of the ability to donate electron pairs for empty d orbitals of the surface atoms[1]. Tetrazole is a heterocyclic structure containing four nitrogen atoms and has great range of applications. In addition, organoselenium compounds are found in the literature linked to pharmacological activities and anti-oxidative stress action, however, despite their great potential, much less is reported about their applications in material sciences.[2] Based on this, the objective of this work is to explore the anticorrosive potential of the combination of antioxidative properties of selenium and the heterocyclic structure of tetrazole with nitrogen atoms and π-electrons.

Results and Discussion

Initially, the obtation of the compounds was performed. The synthesis started with the alkyl esters **1a-b**, obtained by a Fischer-Speier esterification reaction. Subsequently, the selenocyanate portion was added to the structure to obtain **2a-b**. Finally, tetrazole was formed with a reaction using sodium azide giving the new compound **3a-b** in a 50 and 70% of yield, respectively[3]

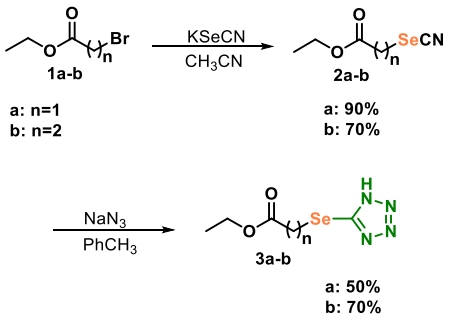

Figure 1. Synthetic route to alkyl derivatives **3a-b.**

In order to provide greater anticorrosive capacity, anthranilic acid was chosen as the aromatic structure for insertion of SeCN and eventually selenotetrazole. Therefore, variations in the position of the selenocyanate were performed. The way to obtain these molecules began with the obtention of the starting material **4a-c** through a esterification. Subsequently, the addition of SeCN in the structure was achieved through the formation of a diazonium salt, generating the products **5a-c.** The synthesis of the desired products **6a-c** with tetrazole followed the methodology previously established. It is also important to note that an attempt was made to hydrolyze the ester group of these compounds to obtain free acid structures, but this was not possible so far.

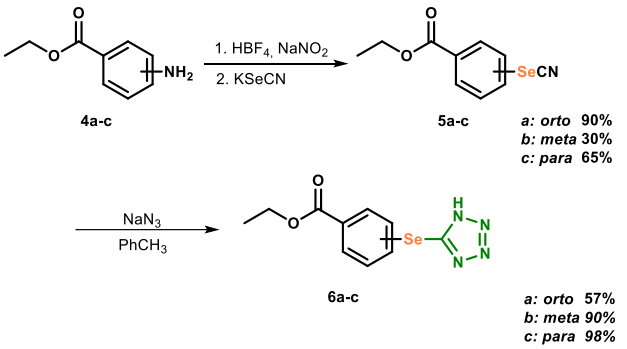

Figure 2. Synthetic route for aromatic derivatives **6a-c.**

Conclusion

From the results obtained, it can be concluded that the synthesis established to obtain the series of derivatives containing the selenocyanate and selenotetrazole it was a success, allowing the formation of 10 new molecules, with good yield values. In addition, due to the number of heteroatoms and π electrons in the structures, the series will be tested as possible corrosion inhibitors by Laboratory of the Federal University of Rio de Janeiro (LAMUFF).

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Synthesis of Methylated Selenonium Salts from Biorenewable Sources of Methyl Group

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Keywords: *Selenonium salts, methylating agents, 'magic' methyl effect, organochalcogenonium compounds.*

Background

Methylation reactions happens all the time in our Nature and a great example is the use of S-adenosyl-methionine (SAM) in living organisms. This organochalcogenonium salts has the ability to donate a methyl group to biomolecules and can change their properties through the well-known 'magic' effect of methylation. This effect is well explored in the pharmaceutical industry.

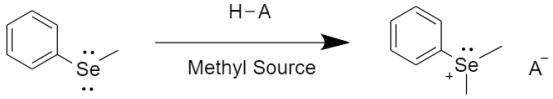
Other organochalcogenonium salts have been increasingly explored, mainly for their use as alkylating agents. Most of the studies found include sulfonium salts, while selenonium salts are still poorly studied. Due to its larger size, we believe that selenium has a greater ability to donate an alkyl group compared to sulfur.

We have developed methodologies for methylation of selenides through the use of environmentally safer solvents (or green solvents) to obtain selenonium salts. In addition to producing possible alkylating agents, we aim to reduce the use of alkyl halides by using other sources of alkyl donors. This action aims to the use of less toxic solvents for those who handle it and also that their source would be biorenewable.

Results and Discussion

We have developed 4 methodologies, so far, for the preparation of selenonium salts without the use of alkyl halides. Sulfuric acid or methanesulfonic acid was used together with methyl sources such as methanol or dimethylcarbonate (DMC). The reaction (figure 1) uses acid to activate the electrophilicity of the methyl group in the sources presented. In this way, we can obtain a methyl group through an acid and base reaction.

Figure 1. Methodology of selenides methylation.



The four methodologies created use the combination of one of the acids and one of the methyl sources presented.

We found out that the greatest methodology tested so far is the use of a mixture of methanesulfonic acid and dimethylcarbonate with a yield of 80%. When methanol was used, yields were about 70% with both acids. Methanol and methanesulfonic acid showed only 32% yield. All reactions were carried out under reflux, 70°C, 16 hours and were used 1 mmol of starting material. Table 1 below specifies the reaction conditions.

Table 1 – Optimization conditions

Exp.	DMC (mL)	MeOH (mL)	$MeSO_3H$ (mmol)	H_2SO_4 (mmol)	Yield[a] (%)
1	1.0	-	1.2	-	80
2	-	1.0	1.2	-	32
3	-	1.0	-	1.2	70
4	0.5	-	-	1.2	67

[a] Estimated yield based on how much starting material were consumed.

Conclusion

So far, we have been able to produce methodologies for the preparation of selenonium salts with satisfactory yields. These two developed salts are not found in the literature, which indicates that they are new molecules.

Acknowledgments

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Theoretical studies of selenium-functionalized Tacrine

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Keywords: *Organoselenium compounds, Alzheimer's disease, Molecular docking.*

Background

Alzheimer's disease (AD), the most common cause of age-dependent dementia, is one of the most significant healthcare problems worldwide and to develop effective therapies for AD patients is of critical urgency. Currently, acethylcholinesterase (AChE) inhibitors as Tacrine are prescribed to minimize Alzheimer's symptoms. Additionally, studies have indicated that abnormal accumulation of β-amyloid peptides (generated by action of β-secretase 1, BACE1) is also a likely culprit in AD pathogenesis.[1] However, drugs like Tacrine presents side effects caused by continuous use, such as nausea, hepatotoxicity, among others.[2] In this sense, our research group synthetized a series of Tacrine derivatives containing organoselanyl groups and performed molecular docking analysis, one of the most basic and important strategy for drug discovery.

Results and Discussion

In this study, a series of sixteen Tacrine derivatives containing organoselanyl groups were analyzed by means of the molecular docking tool using AutoDock Vina software (version 1.1.1) in relation to their binding affinity with AChE and BACE1, in that the three best score data are presented in Table 1.
The best results were observed to compounds **2** and **3** (Figure 1). Their interactions are shown in the Figure 2.

Table 1. Result generated by the software AutoDock Vina (version 1.1.1).

AChE	Compound	Tacrine	1	2
	ΔG (-kcal/mol)	-9,3	-12,4	-12,7
BACE1	**Compound**	**CFA**	**2**	**3**
	ΔG (-kcal/mol)	-8,8	-10	-10,2

Figure 1. Series of molecules with the best results.

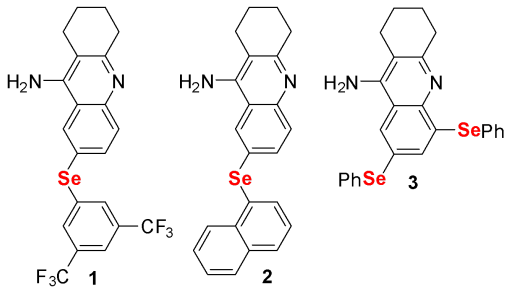
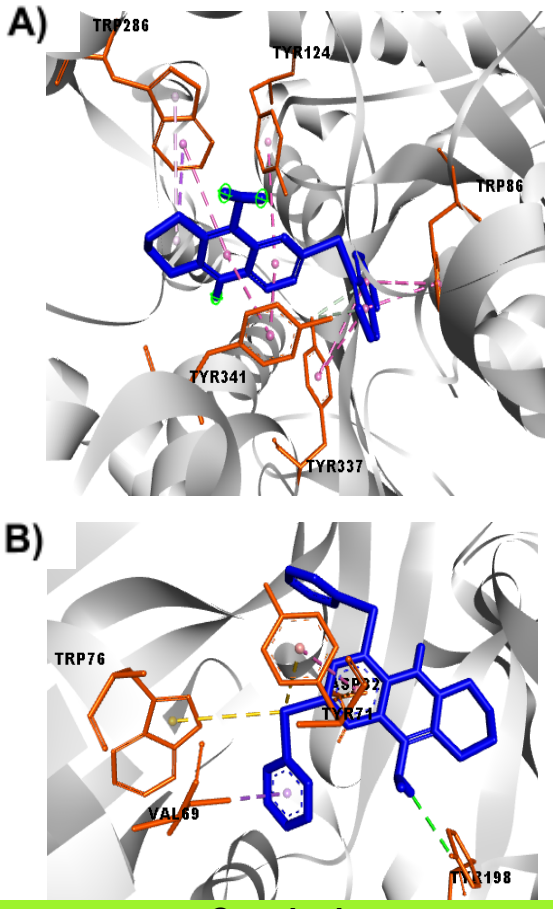


Figure 2.A) Interaction of the compound **2** with acetylcholinesterase (AChE) and B) interaction of the compound **3** with β-secretase 1 (BACE1).



Conclusion

In conclusion, the Tacrine derivatives **2** and **3** analyzed by molecular docking in relation to their binding affinity with the enzyme acetylcholinesterase (AChE) and BACE1 showed higher score values than Tacrine and CFA, respectively.

Acknowledgments

CAPES, CNPq, FAPERGS and FINEP.

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Synthesis and biological evaluation of new menadione-organosulfur hybrids against *Plasmodium falciparum*

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Keywords: *Malaria, Naphthoquinones, Organosulfur compounds.*

Background

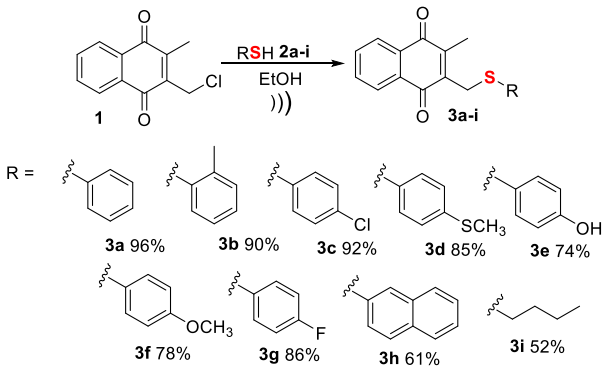
Considering the biological activity of naphthoquinones and organosulfur compounds, in this work we report the synthesis of new menadione-organosulfur hybrids and the evaluation of their *in vitro* anti-*P. falciparum* activity.

Results and Discussion

According to the World Health Organization (WHO), neglected diseases affect about one billion people in the world.[1] Among those, malaria stands out as an acute, febrile, infectious disease transmitted to humans through the bite of female *Anopheles* mosquitoes infected with plasmodium. There are five species of plasmodia responsible for transmission in humans: *P. falciparum*, *P. vivax*. *P. ovale*, *P. malariae* and *P. knowlesi*. However, *P. falciparum* is the most aggressive one, being responsible for 90% of deaths in the world.[2]

In that way, the search for new therapeutical options to treat such condition is of the utmost importance. In this context, naphthoquinones are a characteristic group of quinones widely distributed in nature with importance in different areas of chemistry and biochemistry.[3]

Broadly, the design of the scaffold was based on two fragments: one being menadione (naphthoquinone) and the other, the sulfur-functionalized moiety. The desired products were obtained in good to excellent yields (52-96%).



Scheme 1. Synthesis of menadione-organosulfur hybrids **3a-i**.

The biological evaluation was carried out at the Department of Malaria and Leishmaniasis Bioassays, at Fundação Oswaldo Cruz, Rondônia. The compounds were evaluated against the W2 strain, using fluorescence detectors technique at initial concentrations of 200 to 1.56 µM, and the medium was incubated for 48 hours.

Among the nine tested compounds, four were active, presenting IC_{50} values between 1.94 – 10.84 µM. Compounds with IC_{50} >15 µM were considered inactive. It worth to highlight that compound **3f** was the most potent against the parasite.

Table 1. IC_{50} values for the most active hybrids against the W2 strain of *P. falciparum*.

Compound	IC_{50}(µM)
3f	**1.94**
3a	**3.72**
3i	**6.22**
3h	**10.84**

Conclusion

The preliminary results of the biological evaluation have shown that the new menadione-organosulfur hybrids displayed promising activity against *P. falciparum*. Next, we intent to study the activity of such molecules against other strains, as well as their toxicity profile.

Acknowledgments

CAPES, CNPq, FAPERJ and FIOCRUZ-RO.

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Science at the interface of chemistry and biology: Bioassay guided phytochemical studies on *Malvastrum coromandelianum* and *Curcuma zedoria*

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Keywords *Malvastrum coromandelianum, Curcuma zedoria, GC-MS, anti-microbial.*

Background

Medicinal plants are a source of bioactive molecules. The underground parts of *Malvastrum coromandelianum* and whole plant of *Curcuma zedoria* were selected for phytochemical and biological analysis.

Results and Discussion

GC-MS analysis *Curcuma edoaria* was carried out, indicating the presence of 24 compounds, selected on the basis of high SI and RSI values. Some of these compounds have been reported to have potent biological activities. Chromatographic separation has led to the isolation of some molecules, structure elucidation of which is in progress. Later these compounds will be subjected to biological evaluation.

GC-MS analysis of *Malvastrum coromandelianum* (L.) Garcke has led to the identification of about 20 compounds, few of which have been earlier identified as bioactive molecules. Phytoconstituents categorized as sterols, terpenes, phenols, vitamins, fatty acids have been recognized. Biological evaluation of the crude extract has revealed that the extract is a good anti-bacterial agent, active against *Escherichia coli, Staphylococcus aureus, Klesbiella pneumoniae, Proteus mirabilis, Bacillus subtilis*. *Bacillus subitlis* was the most inhibited strain with 11, 13, and 17 mm at 30, 50,100 µg/ml concentration. It was observed that crude ethyl acetate fraction of *M. coromandelianum* exhibited good activity as compared to other fractions of plant.

Table.1: Shows Anti-bacterial activity o of *M. coromandelianum*

Zone of Inhibition in mm				Ofloxacin (5 µg/mL)
Name of Bacteria	30 µg/mL	50 µg/mL	100 µg/mL	Positive Control
Klesbiella pneumoniae	10 mm	12 mm	15 mm	30 mm
Escherichia coli	10 mm	18 mm	20 mm	26 mm
Staphylococcus aureus	12 mm	15 mm	25 mm	21 mm
Proteus mirabilis	10 mm	13 mm	15 mm	32 mm
Bacillus subitlis	11 mm	13 mm	17 mm	31 mm

Table.2: Shows Anti-bacterial activity o of *Curcuma Zedoria*

Zone of Inhibition in mm				Ampicillin (5 µg/mL)
Name of Bacteria	30 µg/mL	50 µg/mL	100 µg/mL	Positive Control
Staphylococcus aureus	24 mm	26 mm	28 mm	30 mm
Pseudomonas aeruginosa	25 mm	23 mm	27 mm	31 mm

Conclusion

The findings of our research provide a platform for pharmacological studies on these plants at molecular level. Moreover, these findings will attract natural product chemists and pharmacologists to probe these medicinal plants for discovery of lead molecules.

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Organoselenium Catalytic Antioxidants – Inhibitors of Ferroptosis

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Keywords: *Selenium, Antioxidant, Ferroptosis.*

Background

Ferroptosis is a form of programmed cell death which is iron-dependent non-apoptotic cell death.[1] Biochemically and genetically, ferroptosis is different from other well-known entries of classical cell death like apoptosis, necrosis and autophagy.[2] Glutathione peroxidase 4 (GPx4) is one of seven selenoproteins in mammalians, appears to play an important role. The low reduced glutathione (GSH) level results to inactivation of phospholipid glutathione peroxidase 4 (GPx4) enzymes which prevents accumulation of phospholipid hydroperoxide (LOOH) in biological membranes.

Results and Discussion

In the course of our ongoing research interest on the synthesis and antioxidant properties of heterocyclic amine-based organoselenium compounds, we developed various ebselenamines and *N*-thiophenyl ebselenamines as very good antioxidants.[3-5]

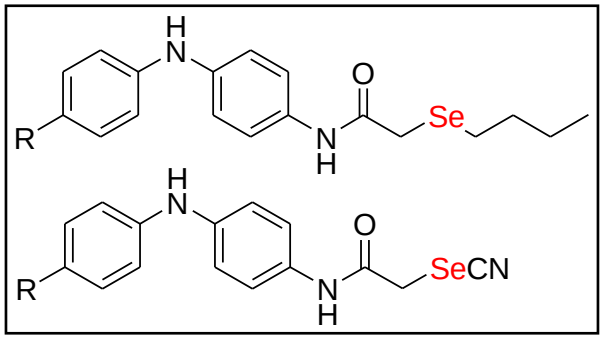

Figure 1. Aminic Organoselenium Compounds.

In continuation of our research, we recently synthesized various amine-based organoselenium compounds including diselenides, monoselenides and also selenocynates.[6] Further, the newly identified organoselenium compounds were evaluated for their GPx-like activity by thiophenol assay. The GPx-activities of all newly synthesized compounds have been found higher than Ph_2Se_2, used as a reference compound. The radical-trapping antioxidant (RTA) activities of synthesized compounds have been accessed by 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. Also their antiferroptotic activities have been studied and compared with a reference compound liproxstatin in GPx4 conditional knockout cell. The effect of the organoselenium compounds in rescuing cells from cell death induced by loss of GPx4 was evaluated.

Conclusion

All these compounds inhibit the lipid peroxidation and decompose the hydrogen peroxide more efficiently than vitamin E and ebselen (used as benchmark references), respectively. Furthermore, all the synthesized compounds are found to quench DPPH radical, however the diselenides possess maximum RTA properties among all the tested compounds and the reference compound vitamin E. Noticeably, the compounds that showed the best antiferroptotic activity were the same that presented a higher RTA capacity.

Acknowledgments

The Council of Scientific and Industrial Research (CSIR), New Delhi is acknowledged for the financial support with grant no. 01(3074)/21/EMR-II. We gratefully acknowledge the Department of Chemistry & Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh.

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Facile Preparation of Type-2 Human Relaxin Through Two-chains Folding Coupled with Interchain Disulfide Formation

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Background

Type 2-human relaxin (hRlx2) has been found to exhibit tissue antifibrotic and anti-inflammatory effects as well as its original function as a pregnancy hormone that dilates the birth canal in pregnant women. Therefore, it is expected to have pharmacological effects of hRlx2 on various diseases such as cardiac disease, renal failure, and endometriosis. hRlx2, a super family of insulin, comprises two peptides, the A-chain and B-chain. The native structure (N) is stabilized by two interchain disulfide (SS) bridges, Cys^{A11}–Cys^{B11} and Cys^{A24}–Cys^{B23}, in addition to one intrachain SS linkage, Cys^{A10}–Cys^{A15} (Figure 1). Consequently, artificial preparation of relaxins is challenging, and relaxins sold as a reagent is extremely expensive (3,000 USD/mg). This study aimed to develop a simple synthetic method for hRlx2 via Native Chain Assembly (NCA),[1] by which the A- and B-chains are directly coupled to generate folded insulin family in a solution.

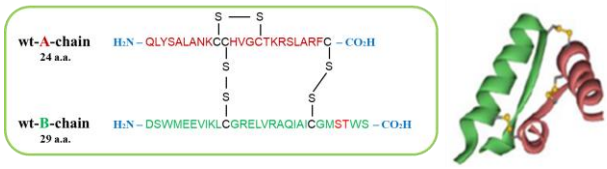

Figure 1. Primary sequence (left) and three-dimensional (right) structure of type 2-human relaxin (hRlx2).

Results and Discussion

Using a general solid phase peptide synthesis method, the A-chain and B-chain were obtained with high purities. When the synthetic peptides were mixed under appropriate conditions in the presence of glutathione, the interchain coupling between the chains progressed, and N was gradually generated, and final folding yield estimated from HPLC was 47% (Figure 2a). The HPLC retention time of N was the same as those of commercially available hRlx2 as a standard. In addition, the result of mass spectroscopic analysis of obtained hRlx2 (m/z: 5982.2) was reasonably in agreement with the expected mass (m/z: $[M+H]^+$, 5981.1) (Figure 2b). Furthermore, CD spectral analysis of the product showed that synthetic hRlx2 has almost same secondary structure as that of commercial hRlx2 (Figure 3a). Thus, these results suggested that hRlx2 prepared via NCA has the exactly folded structure and biological activity as the hormone. Indeed, synthetic hRlx2 was found to have receptor binding capability that is comparable to that of commercial hRlx2 (Figure 2b).

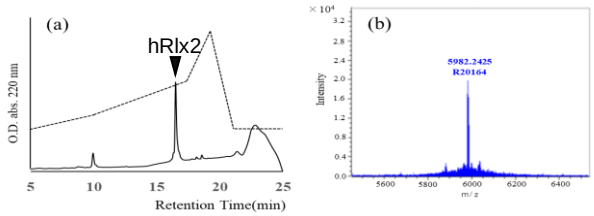

Figure 2. Preparation of hRlx2 via NCA (a) HPLC chart obtained from NCA of the A-chain and B-chain. (b) Mass spectrum obtained from MALDI-TOF-MS analysis of synthetic hRlx2.

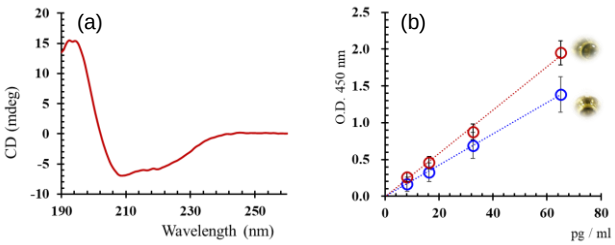

Figure 3. Characterization of synthetic hRlx2. (a) Synthesis of hRlx2. CD spectra of synthetic and commercial hRlx2. (c) Investigation of receptor binding capacities of synthetic and commercial hRlx2 by ELISA.

Conclusion

Taking advantage of NCA method, hRlx2 was successfully synthesized. In the presentation, the synthesis and structure of a hRlx2 analogue that substituted a part of SS bond in the wild-type by diselenide bond, will also be demonstrated.

Acknowledgments

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