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An alumina-modified glassy carbon electrode: a robust platform for accurate nimodipine detection in pharmaceutical applications†

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Nimodipine (NMP) is a calcium channel blocker known for maintaining blood perfusion, particularly in the brain. Given its importance and widespread applicability, tracking NMP during industrial processes for both pharmaceutical dosage forms and raw material samples is crucial. This article discusses the use of a glassy carbon electrode (GCE) polished with commercial alumina for NMP determination. Atomic force microscopy (AFM) confirmed the presence of residual alumina on the surface of the GCE, and electrochemically active surface area (EASA) analysis demonstrated an enhancement in the active area. The alumina-polished electrode (GCE/AP) exhibited a superior response for NMP, with voltammograms obtained *via* differential pulse voltammetry (DPV). In this investigation, we employed density functional theory (DFT) calculations to examine the electrochemical characteristics of NMP from a theoretical standpoint. The geometry was optimized by employing the Generalized Gradient Approximation (GGA) functional, BP86, in conjunction with the Def2-TZVPPPD basis set and D3BJ dispersion corrections. To identify potential sites for oxidation and reduction, Fukui indices and dual descriptors were employed. The results indicate that the nitro group is the most probable site for reduction, whereas the dihydropyridine ring displays a proclivity for electrophilic attack. Regarding electroanalysis, two calibration curves were established through consecutive additions of NMP, with linear ranges of 0.20 to 49.0 μmol L^{-1} and 2.92 to 13.5 μmol L^{-1}, respectively. The theoretical limits of detection (LOD) and quantification (LOQ) were, respectively, 0.06 μmol L^{-1} and 0.20 μmol L^{-1} for the first curve, and 4.0 μmol L^{-1} and 12.0 μmol L^{-1} for the second curve. Common constituents in pharmaceutical tablets were tested as potential interferents, and GCE/AP showed acceptable anti-interference ability. NMP was successfully quantified in tablet and raw material samples using the novel electrochemical method and High-Performance Liquid Chromatography (HPLC). Statistical analysis revealed no significant differences between the results. This confirms that the GCE/AP sensor was effectively applied to pharmaceutical samples, consistent with findings reported in the literature.

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1. Introduction

The calcium channel blocker nimodipine (NMP), see Fig. 1, is a compound broadly used to treat diseases such as

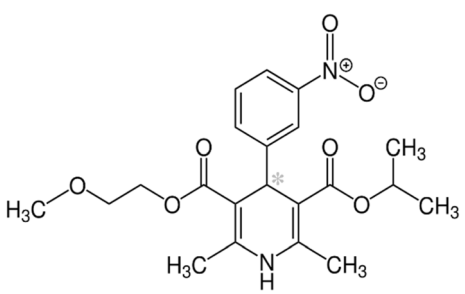

Fig. 1 NMP chemical structure.

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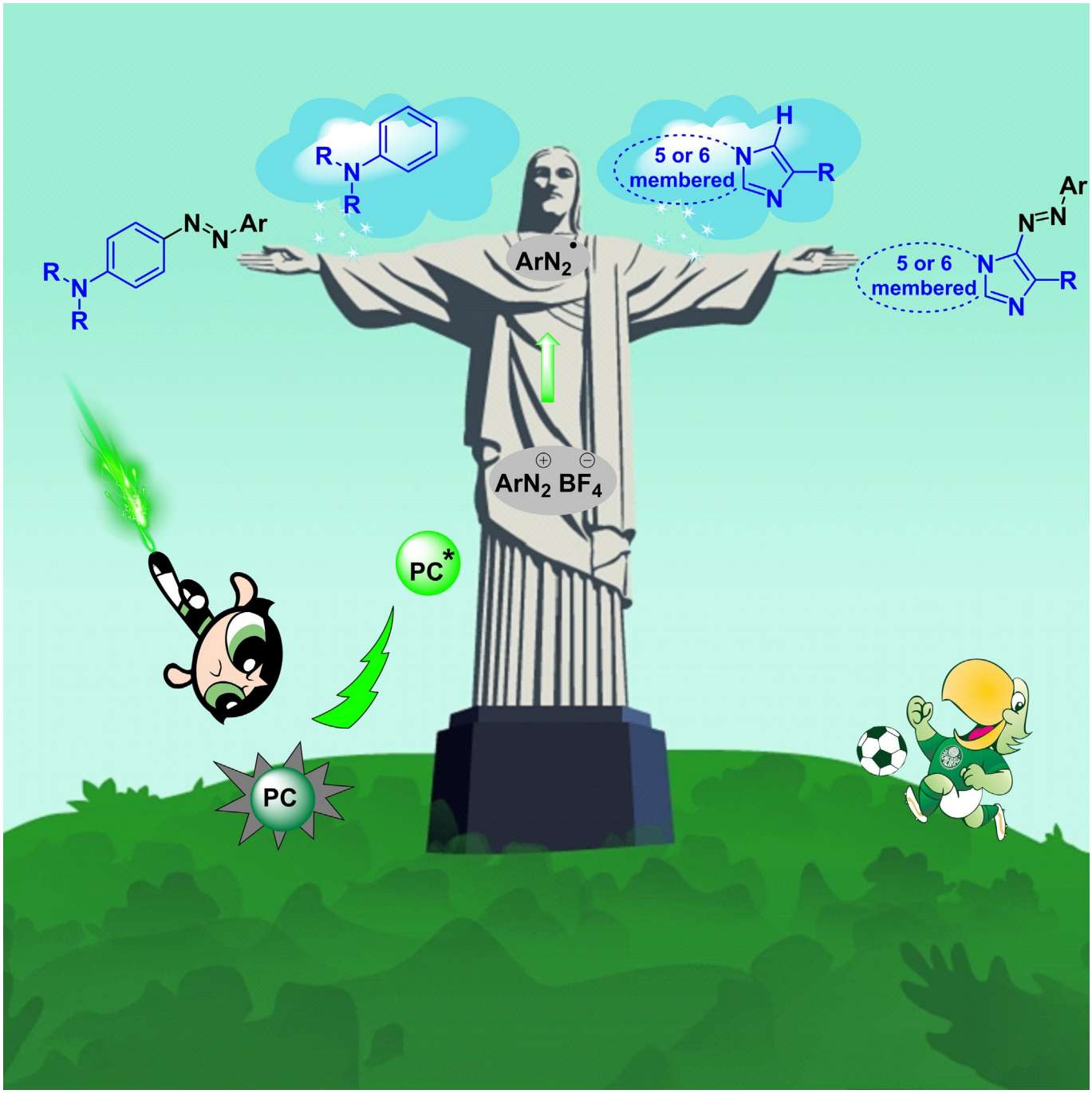
Azo Coupling

Photoinduced, Direct C(sp^2)–H Bond Azo Coupling of Imidazoheteroarenes and Imidazoanilines with Aryl Diazonium Salts Catalyzed by Eosin Y

Sumbal Saba[+],[a] Caio R. Dos Santos,[b] Bruno R. Zavarise,[b] Aline A. S. Naujorks[+],[c] Marcelo S. Franco,[b] Alex R. Schneider,[b] Marcos R. Scheide,[b] Ricardo F. Affeldt,[b] Jamal Rafique,*[c] and Antonio L. Braga*[b]



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Green Approach for the Synthesis of Chalcogenyl-2,3-dihydrobenzofuran Derivatives Through Allyl-phenols/Naphthols and Their Potential as MAO-B Inhibitors

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This work presents the design, synthesis, and MAO-B inhibitor activity of a series of chalcogenyl-2,3-dihydrobenzofurans derivatives. Using solvent- and metal-free methodology, a series of chalcogen-containing dihydrobenzofurans **7**–**9** was obtained with yields ranging from 40% to 99%, using an I_2/DMSO catalytic system. All compounds were fully structurally characterized using ^{1}H and ^{13}C NMR analysis, and the unprecedented compounds were additionally analyzed using high-resolution mass spectrometry (HRMS). In addition, the mechanistic proposal that iodide is the most likely species to act in the transfer of protons along the reaction path was studied through theoretical calculations. Finally, the compounds **7b**–**e**, **8a**–**e**, and **9a** showed great promise as inhibitors against MAO-B activity.

Introduction

Oxidative stress (OS) can be defined as the imbalance between the production of oxidants and their eradication by defense mechanisms.[1] Since this term was first coined by Helmut Sies, the field of redox biology has evolved from concepts of oxidative stress in pathology to redox signaling in physiology.[2] This biological phenomenon involves the chemistry of reactive oxygen-derived species (ROS). It is related to high levels of intracellular ROS, such as the superoxide anion ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), and non-radical molecules, such as hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$), which damage lipids, proteins, and DNA.[3]

Many studies have already demonstrated that ROS play an important role in neurodegenerative diseases that affect older populations; however, the mechanisms of action of the ROS and their damage are not fully understood by the scientific community.[4] Many authors defend this route for the treatment of these diseases, so molecules with antioxidant action seem to be an attractive approach in the prevention and/or treatment of disorders linked to ROS.[5]

The concentrations of these species need to be controlled in humans through several defense mechanisms that involve several antioxidant and detoxifying enzymes. The role of antioxidants is to lower or terminate the chain reactions caused by ROS by removing free radicals or inhibiting other oxidation reactions by being oxidized themselves.

Monoamines oxidases (MAOs) are mammalian flavoenzymes that bind to the external mitochondrial membrane.[6] MAOs contribute to cellular oxidative stress since their reactions generate some neurotoxic by-products, such as hydrogen peroxide and the corresponding aldehydes.[7] These enzymes were discovered almost a century ago and represent targets of validated drugs for neurodegenerative diseases due to their activity in the cerebral catabolism of monoamines (serotonin, norepinephrine, and dopamine) and seem to play an important role in many neurological and psychiatric disorders.[8] MAOS can be expressed as two isoenzymes, A and B. MAO-A preferentially

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Selenylated-oxadiazoles as promising DNA intercalators: Synthesis, electronic structure, DNA interaction and cleavage

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ABSTRACT

A series of selenylated-oxadiazoles were prepared and their interaction with DNA was investigated. The photophysical studies showed that all the selenylated compounds presented absorption between 270 and 329 nm, assigned to combined n→π* and π→π* transitions, and an intense blue emission (325–380 nm) with quantum yield in the range of Φ_F = 0.1–0.4. DFT and TD-DFT calculations were also performed to study the likely geometry and the excited state of these compounds. Electrochemical studies revealed the ionization potential energies (−5.13 to −6.01 eV) and electron affinity energies (−2.25 to −2.83 eV), depending directly on the electronic effect (electron-donating or electron-withdrawing) of the substituent attached to the product. Finally, the UV–Vis DNA interaction experiments indicated that the compounds can interact with the DNA molecule due to intercalation, except for **3g** (which interacted via electrostatic interaction). Plasmid cleavage assay presented positive results only for **3f** that presented the strongest interaction results. These results made the tested selenylated-oxadiazoles as suitable structures for the development of drugs and the design of structurally-related therapeutics.

1. Introduction

In the last few decades, there has been rising attention around the medicinal properties of organoselenium compounds, as these compounds exhibit fascinating biological characteristics [1,2]. In particular, the fact that certain enzymes that contain selenium can feature antioxidant properties. Several reports highlight their antioxidant, anti-inflammatory, antitumor, and antiviral activities [3–6]. Notably, some organoselenium compounds display the mimetic activity of these enzymes, making them attractive synthetic targets [7,8]. Considering the current pandemic of corona virus (COVID-19), a very interesting study just appeared in the literature where an organoselenium compound (Ebselen) presented the strongest antiviral effect at a concentration of 10 μM treatment in COVID-19 virus infected Vero cells [9]. Therefore, the construction of the C–S/Se bond seems to be a very important target in organic synthesis and has attracted considerable attention in the last years [10–15].

Similarly, the 1,3,4-oxadiazole (ODZ) scaffold is a ubiquitous

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RESEARCH ARTICLE

ELECTROANALYSIS

Exploiting the synergistic effects of combined carbon-based materials for rape drug diazepam electrochemical sensing: Application to simulated casework matrices

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Abstract

Diazepam (DZP), a long-lasting benzodiazepine and controlled substance, is prevalent on the illegal market, notably as a date rape drug. This study presents a novel electrochemical sensor (CPE/GCPE/MWCNTs) for DZP determination in lab routines. Characterized through LSV, EIS, and SEM, the sensor revealed a pH-dependent, irreversible reduction process at approximately −0.70 V (*vs.* $Ag/AgCl_{(sat)}$). Optimization with SWV and 0.1 mol L^{-1} B–R solution (pH 1.0) produced a calibration curve spanning 1.49 to 21.5 μmol L^{-1}. LOD and LOQ were 0.33 and 1.10 μmol L^{-1}, respectively. Quantification in spiked samples exhibited no significant differences compared to HPLC-DAD, endorsing the sensor for monitoring date rape drugs in forensic analysis.

KEYWORDS
diazepam, distilled beverages, forensic analysis, multi-walled carbon nanotubes, nanomaterials, voltammetry

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ORIGINAL RESEARCH
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Versatile Electrochemical Synthesis of Selenylbenzo[*b*]Furan Derivatives Through the Cyclization of 2-Alkynylphenols

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We report an electrochemical oxidative intramolecular cyclization reaction between 2-alkynylphenol derivatives and different diselenides species to generate a wide variety of substituted-benzo[*b*]furans. Driven by the galvanostatic electrolysis assembled in an undivided cell, it provided efficient transformation into oxidant-, base-, and metal-free conditions in an open system at room temperature. With satisfactory functional group compatibility, the products were obtained in good to excellent yields.

Keywords: selenylbenzo[*b*]furans, seleno-cyclization, electrosynthesis, diselenide, selenium

INTRODUCTION

The benzo[*b*]furan core is present in several derivatives of natural products, containing various types of biological activities (Heravi et al., 2017). Many drugs and candidates for clinical drugs have this nucleus (Miao et al., 2019; Radadiya et al., 2015), such as bufuralol, ailanthoidol, benziodarone, nonekenetin, and cloridarol, as shown in **Figure 1** (Asif 2016; Tang et al., 2021). The reported therapeutic activities include antitumor (Romagnoli et al., 2015; Xu et al., 2017), antidepressant (Boukharsa et al., 2016), anti-inflammatory (Xie et al., 2014), antioxidant (Chand et al., 2017), and fungicide (Liang et al., 2016) activities and may also inhibit the formation of amyloid plaques that are characteristic of Alzheimer's disease (Hiremathad et al., 2018).

Similarly, the construction of the C–Se bond is among the important transformation in organic synthesis (Rafique et al., 2016b; Rafique et al., 2021), mainly due to their properties such as synthetic intermediates in organic transformations (Shao et al., 2019; Arora et al., 2021) and material sciences (Li et al., 2020) as well as in the medicinal chemistry (Nogueria et al., 2021). In the past few decades, these compounds have gained increasing interest, mainly due to their antioxidant (Mugesh and Singh 2000; Botteselle et al., 2021), anti-Alzheimer (Rodrigues et al., 2018; Scheide et al., 2020b; Kumawat et al., 2021), anti-inflammatory (He et al., 2021), antitumor (Spengler et al., 2019; Chen et al., 2020; Dos Santos et al., 2021; Santos et al., 2022), antiviral (Ali et al., 2021), and other biological activities (Wang et al., 2016; Frizon et al., 2020; Rafique et al., 2020; Galant et al., 2021; Martín-Escolano et al., 2021; Veloso et al., 2021).

Considering the biological relevance of benzo[*b*]furans and the wide spectrum of therapeutic properties of organoselenides, there are few synthetic methods that are available to access organo-selenylbenzo[*b*]furans. The most frequent approaches are cyclization reactions using 2-

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REVIEW

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Electrohalogenation of organic compounds

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Herein, we present an overview of recent advances in the electrochemical halogenation of organic compounds. Halogen-containing compounds are essential building blocks for post-functionalization in academic research and in different industrial sectors, notably pharmaceutical companies. One of the main advantages of using electrosynthesis is its environmentally-friendly characteristics. Electrosynthesis is recognized as a methodology that can fulfill different criteria of the green chemistry concept and constitutes a promising tool in the development of new procedures in organic synthesis. In this review we target sp, sp^2 and sp^3 carbon fluorination, chlorination, bromination and iodination reactions using electrolysis as a redox medium. Mechanistic insights and substrate reactivity are also discussed.

1. Introduction

Compared to the various classes of organic compounds, halogen-containing species are the most explored, with high functionality and high versatile synthetic intermediates. However, many approaches to halogenation reactions involve the use of unstable or potentially hazardous agents, such as an excess of molecular halogen, *N*-halosuccinimides, hydrohalogenation or strongly alkaline reaction media.[1–5]

Electrochemical transformations have many benefits over traditional methodologies, allowing reactions that would otherwise require aggressive conditions, such as dangerous chemicals or expensive catalysts, to be conducted under relatively mild conditions.[6–9] Electrosynthesis can provide the desired products with high chemoselectivity, high tolerance of functional groups and easy scaling configuration, using only electrons as redox reagents.[10] Thus, the production of waste is minimized, making this one of the most sustainable approaches in modern organic chemistry.[11–13] Additionally, electrochemistry can be applied in several areas of interest, such as energy storage, the treatment of effluents, environmental monitoring and many industrial applications.[14–20]

Electrochemistry is an extremely attractive tool for organic synthesis, being a promising and simple technique, allowing

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Celso R. Nicoleti

Celso R. Nicoleti obtained his Ph.D. degree in 2015 at the Federal University of Santa Catarina (Florianópolis – Brazil) under the supervision of Prof. Vanderlei G. Machado, working on the synthesis of optical devices for the detection of anionic, neutral, and cationic analytes. At present he is working Prof. Antonio Luiz Braga's research group as a post-doctoral student. His research interests focus on the development of green methodologies involving the organic electrosynthesis of compounds with biological and pharmacological activity.

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Electrochemical synthesis of selenyl-dihydrofurans *via* anodic selenofunctionalization of allyl-naphthol/phenol derivatives and their anti-Alzheimer activity†

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Herein, we report an eco-friendly, electrosynthetic approach for the intramolecular oxyselenylation of allyl-naphthol/phenol derivatives. This reaction proceeds with 0.2 equiv. of $^{n}Bu_4NClO_4$ as an electrolyte and Pt working electrodes in an undivided cell, resulting in the selenyl-dihydrofurans in good to excellent yields. Furthermore, several of the synthesized products presented a high percentage of acetylcholinesterase (AChE) inhibition, highlighting their potential anti-Alzheimer activity.

The dihydrobenzofuran (DHB) core, found in many natural bioactive products and pharmaceuticals, represents an important "privileged scaffold".[1] Indeed, many bioactive compounds from natural sources carry a 2,3-dihydrobenzofuran core (Fig. 1), such as (+)-decursivine (**I**),[2a] (+)-lithospermic acid (**II**),[2b] (−)-linderol A (**III**),[2c] pterocarpin (**IV**),[2d] (+)-conocarpan (**V**),[2e] heliannuol G (**VI**).[2f] DHBs are well-known for their potential applications as pharmacological agents, being associated with antioxidant, antitumor, anti-platelet, anti-malarial, anti-inflammatory, anti-depressant and anti-convulsant properties.[1,2] Several of the putative entactogen drugs, *e.g.*, **5-APDB**, **5-MAPDB**, **6-APDB**, **MBPV** (Fig. 1),[3] have the DHB moiety in their core structure.

Similarly, organoselenium compounds are an important class of molecules that attract great interest, due to their biological properties.[4] In recent decades, reports of their antioxidant, anti-inflammatory, antitumor and antiviral activities have led to increased interest in these compounds.[4,5] Iwaoka has recently demonstrated the importance of organoselenium moiety in the preparation of selenoinsulin.[5f] Also, in the past few years, several authors have highlighted the importance of the organoselenyl moiety in the inhibition of AChE for anti-Alzheimer activity.[6] Furthermore, organoselenium compounds are ubiquitous in organic chemistry, acting as catalysts,[7] photosensitizers,[8] building blocks[9] and reaction intermediates.[10]

Considering the biological relevance of DHB and the wide spectrum of therapeutic properties of organoselenides, relatively few synthetic methods for the construction of organoselenyl-DHB have been reported in the literature (Scheme 1A). The addition of organoselenium cations to unsaturated compounds is the most common approach and reactive selenated species in the presence of oxidants is also frequently used.[11] These methods offer interesting features but some protocols have drawbacks, which include the use of non-green solvents, pre-functionalized coupling partners, low atom economy, unstable substrates and elaborate multi-step processes.

Furthermore, in recent years, intensive research has been carried out in the area of organic reactions using electrosynthesis.[12] Reactions promoted in an electrochemical cell can lead to a variety of *in situ* generated intermediates, which are not

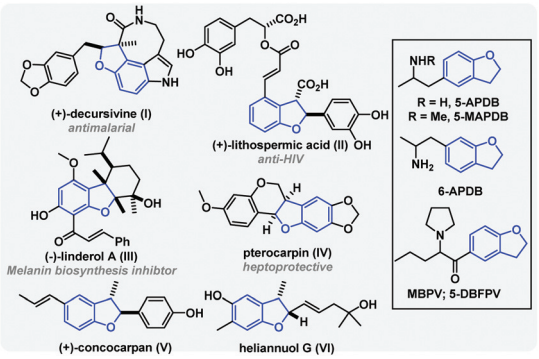

Fig. 1 Biologically-relevant DHBs.

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It takes two to tango: synthesis of cytotoxic quinones containing two redox active centers with potential antitumor activity†

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We report the synthesis of 47 new quinone-based derivatives *via* click chemistry and their subsequent evaluation against cancer cell lines and the control L929 murine fibroblast cell line. These compounds combine two redox centers, such as an *ortho*-quinone/*para*-quinone or quinones/selenium with the 1,2,3-triazole nucleus. Several of these compounds present IC_{50} values below 0.5 μM in cancer cell lines with significantly lower cytotoxicity in the control cell line L929 and good selectivity index. Hence, our study confirms the use of a complete and very diverse range of quinone compounds with potential application against certain cancer cell lines.

1. Introduction

Quinones represent a particularly exciting class of natural products. These redox-active secondary metabolites are highly abundant in nature, and also exhibit pronounced redox modulatory activity in many target cells, which frequently translates into a pronounced and often also selective cytotoxic activity, for instance, against cancer cell lines under oxidative stress (OS).[1] Not surprisingly, lapachol and its derivatives, *e.g.*, β-lapachone (β-lap), which occur naturally in the ipe tree, already present a pivotal role in cancer therapy, since studies have proven that β-lap showed significant activity against Sarcoma 180 ascite tumour cells (S-180 cells) *in vitro*, and in mice bearing S-180 tumors.[2] Antitumor activity of β-lap is based on its specialty to elevate endogenous levels of NAD(P)H: quinone oxidoreductase 1 (NQO1),[3] and whereas the clinical uses of β-lap are limited due to its high hydrophobicity, the compound and its derivatives are one focus of ongoing research in this field.

For over a decade, our research groups have dedicated efforts to the synthesis and modification of quinone-based compounds, especially 1,2- and 1,4-naphthoquinone derivatives,[4] using classical strategies such as molecular hybridization[5] and bioisosterism.[6] To achieve synthetic challenges and prepare selected molecules, robust methodologies such as C–H activation[7] and Cu(I) catalysed azide-alkyne cycloaddition (CuAAC) reaction[8] have been employed successfully, resulting in potent bioactive molecules. The triazole moiety is also considered a leading pharmacophore,[9] and the use of "click" reactions to modify the furan and pyran ring, also named as "C-ring" of most common lapachol derivatives like β-lap and nor-β-lap have been employed by us for the synthesis of powerful multifunctional redox modulators.[10,11]

Apart from the high potentiality against cancer cells, the toxicity of NQs to normal cells has also been reported.[12] Nonetheless, we recently discovered that the combination of a quinone-based compound and a selenium core could circumvent this problem, *i.e.*, the hybrid compounds inhibited the growth of cancer cells more selectively, with keeping their potency.[13] To expand our library of redox-sensitive compounds for the identification of more potent and selective antitumor agents, herein we report the synthesis and antitumour activity of novel hybrid molecules combining the quinoidal redox system of β-lap and nor-β-lap

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Borophosphate glass as an active media for CuO nanoparticle growth: an efficient catalyst for selenylation of oxadiazoles and application in redox reactions

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Herein, we report the preparation of CuO@ borophosphate nanoparticles (CuOnano@glass) and their wide catalytic applications. The glass annealing, under a controlled atmosphere, enables the growth of copper nanoparticles on the glass surface (not within) by an uncommon bottom-up process. Following the thermal annealing of metallic nanoparticles under air atmosphere, supported copper oxide nanoparticles CuONPs on the glass surface can be obtained. The approach enables the glass matrix to be explored as a precursor and a route for the synthesis of supported copper-based nanoparticles in a solvent-free process without immobilization steps or stabilizing agents. In order to demonstrate the wide synthetic utility of this CuONPs glass-based catalyst, one-pot three-component domino reactions were performed under an air atmosphere, affording the desired selenylated oxadiazoles in good to excellent yields. We also extended the application of these new materials as a glass-based catalyst in the phenol hydroxylation and the reduction of 4-nitrophenol.

Glass materials are widely used in everyday life, with a range of applications from the technological (e.g., lasers) to the ordinary, such as kitchen devices, bottles and windows in buildings. Notable characteristics are the low reactiveness and high stability of the oxide glasses, mainly silica-based glasses, upon exposure to a variety of chemicals. Due to the well-established route for the synthesis of glass, glass-based materials have gained great importance in our lives[1].

Phosphate-based (borophosphate) glasses show remarkable characteristics including low processing temperatures, simple starting materials and high capacity to dissolve metal oxides[2]. In addition, they can be easily doped with copper or silver ions[2,3]. In particular, copper-doped borophosphate glass enables the synthesis of supported nanoparticles through annealing under a hydrogen atmosphere by a bottom-up process with high Surface-Enhanced Raman Scattering (SERS) activity[4]. The growth of metallic nanoparticles on the glass surface (not within), with short annealing times, is unusual[5] and the growth of supported nanoparticles on annealing under a reductive atmosphere can be exploited for the development of a glass-based catalyst. The synthesis and immobilization in a single-step process, without organic/inorganic reducing agents (e.g., citric acid, ascorbate,

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Catalyst- and metal-free C(sp^2)–H bond selenylation of (*N*-hetero)-arenes using diselenides and trichloroisocyanuric acid at room temperature

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In this paper, we report an eco-friendly approach for the C(sp^2)–H bond selenylation of imidazopyridines and other *N*-heteroarenes as well as simple arenes at ambient temperature. This new protocol consists of the reaction between (*N*-hetero)-arenes and the diorganyl-diselenides and trichloroisocyanuric acid (TCCA)-ethanol reagent system. In a short reaction time, the desired selenylated products were obtained regioselectively in good yields, with tolerance for a wide range of functional groups.

The construction of the C–Se bond is gaining increasing interest in organic synthesis, as these compounds exhibit fascinating biological characteristics[1–4]. In this regard, diorganyl-selenides are well-known for their diverse biological properties, mainly their antioxidant, anti-inflammatory, anti-Alzheimer and anticancer activities[5–9]. These ubiquitous structures play a fundamental role in modern organic synthesis and are employed in several reactions as catalysts, ligands and synthetic intermediates in total synthesis, as well as in ionic liquids[10,11]. They are also applied in materials science[12]. Therefore, research studies have led to important discoveries regarding selective C-Se bond formation and in this context, a notable approach is direct selenylation reactions[2,3,10,13–17].

Similarly, *N*-heteroarenes, e.g., imidazo[1,2-*a*]pyridine (IP), imidazo[2,1-*b*]thiazole and indole are privileged scaffolds[18–20], given their pharmaceutical, biological and materials science applications[18,20–22]. These motifs are present in several commercially-available drugs (Fig. 1), highlighting the importance of these nuclei[19–21]. Therefore, they are considered as structures of interest in organic synthesis[23–28].

Considering the therapeutic properties of (*N*-hetero)arenes and the biological relevance of organoselenium compounds, molecular hybridization of these structures could lead to molecules with promising biological properties (Fig. 1)[29–31]. In this regard, a new synthetic methodology to the construct the C–Se bond in (*N*-hetero) arenes has become a research hotspot[2–4,36–43].

In contrast to cross-coupling reactions, the formation of *N*-heteroarene containing organoselenides via C(sp^2)–H bond functionalization provides a straightforward one-step bond formation route. This approach remains underexplored, although direct C–H functionalization is an atom-economical and greener alternative. For this type of direct C(sp^2)–H bond selenylation of (*N*-hetero)arenes with diorganyl diselenides, there are two possible pathways: (a) nucleophilic species from arenes, generated in situ[44,45] and (b) electrophilic species from diselenides, generated in-situ[46,47]. In terms of practicality, the former pathway is limited due to narrow substrate scope, while the development of a new method involving the activation of diselenides through the later pathway is highly desirable.

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