GREEN APPROACH TO SHYNTHESIZE 1H-PYRIDAZINO[3,4-B]INDOLE DERIVATIVES

Area 03/C1 – Chemistry, CHIM/06 – Organic chemistry

THE AIM OF THE RESEARCH

Following our interest in the construction of polycyclic N-heterocycles[1] and aware of the privileged role of the indole nucleus in natural products and medicinal science, this project is focused on synthesizing 1H-pyridazino[3,4-b]indole derivatives from indoles and 1,2-Diaza-1,3-dienes.
The proposed method is based on a first known step to obtain indolyl-hydrazone products and a second one that consists of an oxidation which allows for the creation of a C-N bond.

INTRODUCTION

Among heterocyclic compounds, those bearing an indole ring are the most recurring in nature; moreover, polycyclic indoles-based molecules have considerable medicinal importance[2-4]: they exhibit different biological properties, including anti-inflammatory, antiviral, antibacterial, antidepressant, anticancer, antihypertensive and antidiabetic activities (Figure **1**).

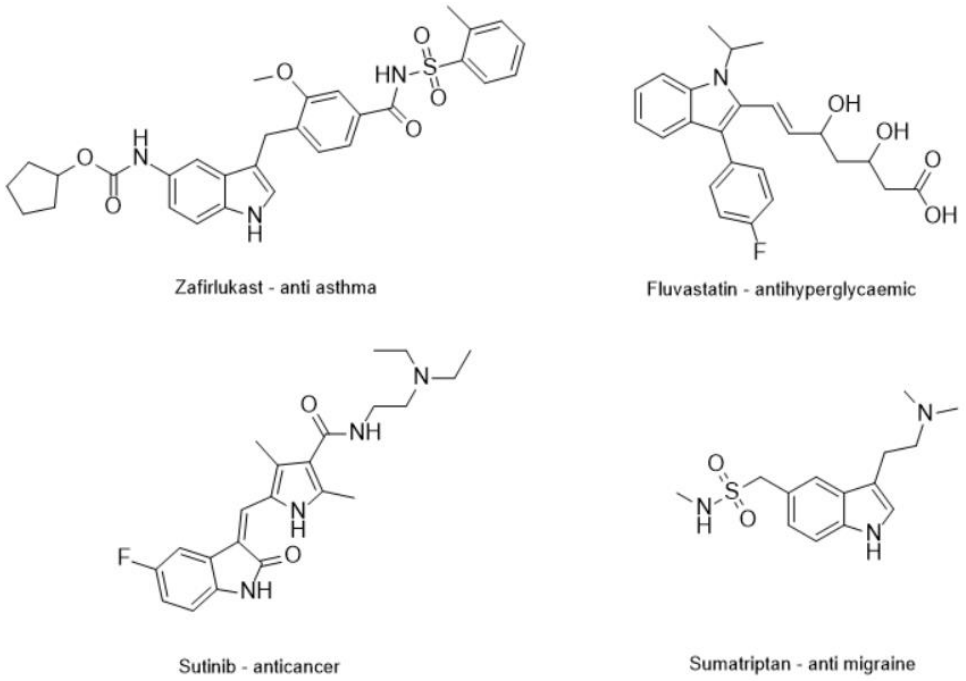
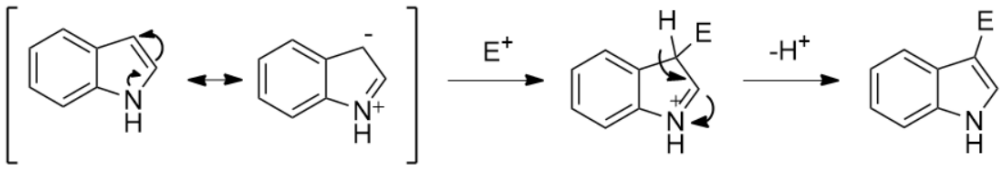


Figure 1

With regards to reactivity, the indole ring is an electron-rich system, owing to the nitrogen electron pair participating to the aromaticity of this heterocycle. Consequently, the most common reactivity of indole is towards electrophiles, which are preferably attacked by the C3 (Scheme **1**).



Scheme 1

Another reactive position is the C2, especially when the 3-position is substituted. In this case, it is possible to consider electrophiles as activators of the 2-position.
An interesting field of exploration consists in the reactivity of indole towards 1,2-Diaza-1,3-dienes (DDs), that are characterized by a carbon-carbon, nitrogen-nitrogen conjugate double bond system. Those compounds are extremely versatile: in fact, they were used as building blocks for the synthesis of several five-, six- and seven-membered heteroring systems. The chemical properties of DD are strictly related to the electron-withdrawing effect of the azo group in the heterodiene system, that make these compounds good Michael acceptors.
In a paper published in 2019, the Michael-type addition of indoles as C-3 carbon nucleophiles to various azoalkenes was reported and indolyl-hydrazone products (Figure**2**) were obtained.[5]
These compounds can undergo different reactions, as cyclization ones, by forming a C-N bond. Many reports dedicated to the synthesis of these appealing frameworks and studies on their pharmacological properties appear in the literature.[6]

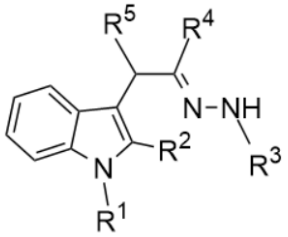
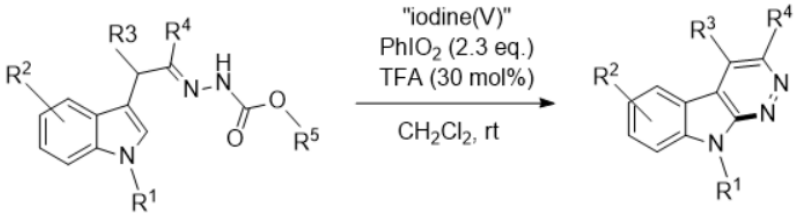


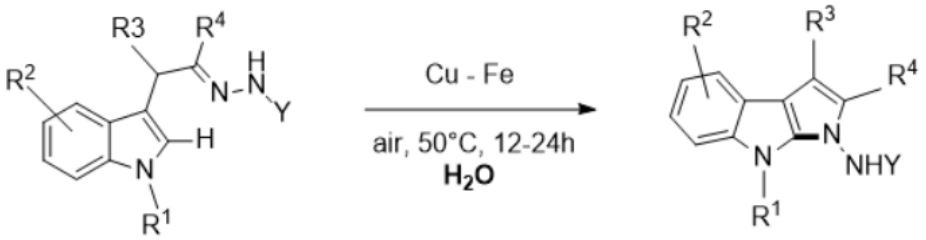
Figure2

The reactivity of unsubstituted indoles in C2 has already been studied by Favi's group; as a matter of fact, a synthesis of polysubstituted indolefused pyridazines (azacarbolines) from α-indolylhydrazones under oxidative conditions using a combination of iodylbenzene (PhIO2) and trifluoroacetic acid (TFA) has been developed. This approach allows to obtain azacarbolines via dehydrogenative C(sp^2)-N bond formation, using hypervalent iodine(V) reagent. This reaction is conducted without transition metals and harsh conditions (Scheme **2**).[7]



Scheme 2

Another example of C-N bond formation is reported from the same group: a synthesis of pyrrolo[2,3-b]indoles via direct intramolecular C–H bond amination of α-indolylhydrazones has been achieved.[8] It consists on a base and oxidant-free chemoselective transformation and it is based on a Cu/Fe co-catalyst system that operates at 50 °C in air with water as the only reaction medium. The easy product isolation together with the recyclable catalyst aqueous system can provide an effective environmentally benign approach to fused N-heterocycles of remarkable interest in pharmaceutical and medicinal chemistry. The ability of the hydrazone residue to act as a chelating/directing group as well as an aminating agent guarantees the success of this C–H functionalization (Scheme **3**).



Scheme 3

HYPOTHESIS AND DISCUSSION

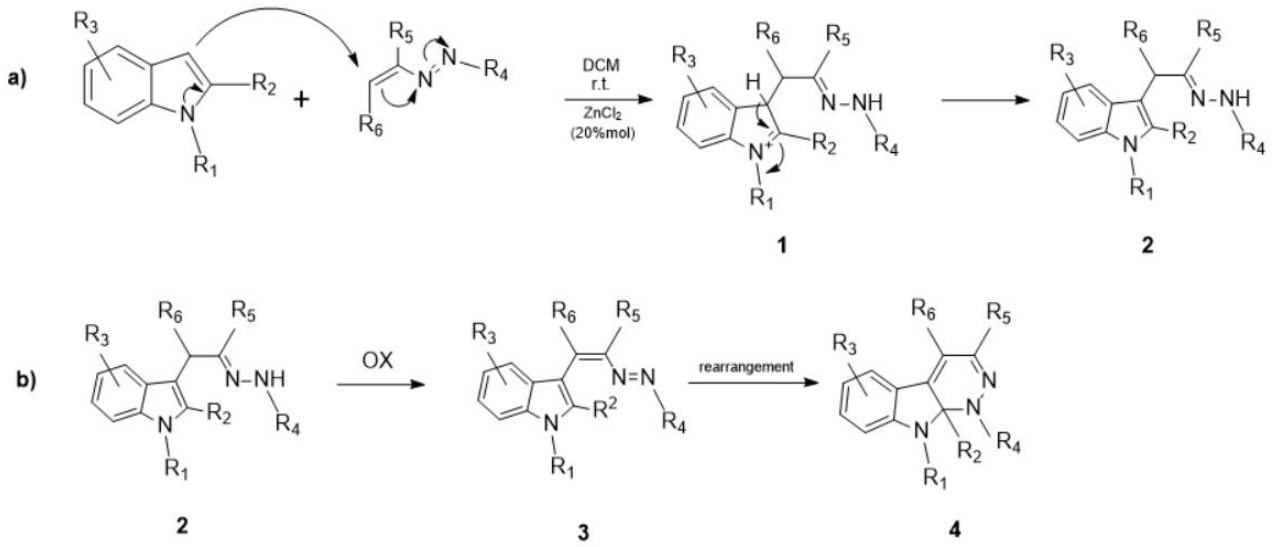
In my research project I want to study the reactivity of C2 substituted indoles, using them to obtain 1H-pyridazino[3,4-b]indole derivatives with a green approach; for this reason, I'm going to take advantage of the cited above synthetic method "on water" already used.

As stated previously, the first step of the 1H-pyridazino[3,4-b]indole derivatives synthesis is based on a known reaction that has been set up to obtain the α-Indolylhydrazones (Scheme **4a**). Given the stability of these products, it is possible to isolate and use them as substrates for the second step, that is based on an oxidation reaction (Scheme **4b**).

The reaction proceeds with Michael-type attack on the azoalkene's C4 by indole's C3 and the intermediate **1** is formed; the aromatic functionality of the indole system is restored, due to the loss of the acidic proton in its C3 and the compound **2** is obtained.

The assumed oxidation reaction should lead to the intermediate **3** with the formation of the new double bond C-C and N-N and the restoration of the diene function.

following a rearrangement, the final derivative **4** could be achieved.



Scheme 4

Green chemistry applied to the reaction

Since the proposed mechanism is based on an oxidation reaction, I'm going to follow several approaches to synthetize the final product, preferring those more sustainable; first of all, I'm going to privilege the aerobic oxidation.

Alternatively, I could use organic oxidant agents, as PIFA or PIDA; avoid metal oxidants represents a clear advantage in terms of costs, environmental impact and waste reduction. A very useful class

of reagents, broadly exploited for the synthesis of a plethora of nitrogen-containing heterocycles, is represented by hypervalent iodine reagents.
If I must use metal oxidant agents, I will test non-noble transition metals (TMs) as catalysts since they are attractive for several reasons; first row TMs (copper, iron, zinc, …) are considerably less expensive when compared to other widely employed transition metals, such as palladium, rhodium, ruthenium or iridium. Furthermore, being common in Earth's crust, their extraction is much less invasive and impactful, and this translates in a benefit from the environmental point of view. Moreover, they are usually less pollutant and less toxic, also because they have important biological roles and are naturally occurring in water and in the environment. Because of this reasons, novel methods based on the use of abundant metals rather than noble ones are of extremely high value.
As an oxidative method, a catalytic cycle will be studied, where the catalyst will be used in a non-stoichiometric way.
Many traditional solvents employed in organic and medicinal chemistry have associated issues such as toxicity, environmental, sustainability, and safety concerns; in fact, one of the most challenging goals in green chemistry is the development of reactions that run-in water as the sole solvent. This is particularly intriguing, since water is one of the cleanest substances that chemists can find on their benches, and it is the solvent of choice in nature. In addition of this, water is extremely cheap, totally safe and readily available.
The synthesis of N-heterocycles using water as the sole solvent has seen great advances in recent years; as an example, Chen and colleagues developed a protocol for the synthesis of quinolizines by simply using refluxing water with no need for catalysts or additives.[9] Moreover, Favi's work previously described shows the cyclization reaction of the hydrazone indole moiety carried out in water.[8]
On the other hand, the collaboration with the research group of Prof. Alonso represents an excellent opportunity to develop an alternative green approach. During the time abroad, the research will be devoted to the use of the innovative Deep Eutectic Solvents (DES) as reaction media.
Deep Eutectic Solvents (DESs) field[10] will be a valid support in the design and development of targeted "green" solvents capable of optimally promoting the reactions under study. This will increase the value of the procedures performed in terms of the reducing of the amounts of reactants, also considering the recycle possibility of these liquids. For these reasons the substitution of commonly used volatile organic solvents (VOCs) with DESs in the synthetic methodologies proposed could represent a green step ahead for the project and it could represent a well-integrated research topic in the project itself.
Other important points are temperature and pressure: I will prefer ambient pressure and temperature; in this way, the environmental and economic impact is minimized.
Finally, the reaction fully respects the Atom Economy, incorporating all the atoms of the final products.

EXPECTED RESULTS

The final product should be obtained easily and with a green synthetic strategy; it represents a scaffold with a remarkable chemical variability, as there are many positions that can be changed with different chemical groups. For this reason, the scaffold offers multiple possibilities of derivatizations and, therefore, of reactivity studies. Given the importance of the indole scaffold, it would be interesting, through bibliographic studies, to know research groups working with similar compounds, with the aim of planning future collaborations to investigate any pharmacokinetic and pharmacodynamic properties.

METHODOLOGY AND DESCRIPTION OF THE RESEARCH IN THE THREE-YEAR PERIOD

I strongly believe in the importance of bibliographic research with the aim of staying updated on new discoveries; for this reason, the study of literature will feature in all three years.

In the first year, I will focus on optimizing the oxidation reaction, trying to be as sustainable as possible, as clearly explained before.
In the second year, I'm going to focus on the modifications that can be made on the indole nucleus, studying its different reactivity, while in the third one I'm going to concentrate on the pyridazine nucleus. I will functionalize the scaffold with chemical groups with different electronic properties and steric hindrance with the aim of being able to examine how they can influence the reactivity of the same scaffold.
Moreover, during the second year I' m going to spend a period abroad where I will have the opportunity to further study Deep Eutectic Solvents and apply them to my project.
The thesis's writing will be dealt with during the third year, while the characterization phases of the compounds that are analysed during the project are distributed over the 3 years (Figure**3**).

	1st year	2nd year	3rdyear
bibliography study			
characterization			
oxidant reaction optimization			
substituents of the indole nucleus			
substituents of the pyrydazine nucleus			
work with DESs			
thesis writing			

Figure 3: Gantt chart

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