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Synthesis of antivirals applying Green Chemistry principles.
Síntesi d'antivirals aplicant els principis de Química Verda.

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The future will be either green or not at all.

Bob Brown

En primer lloc, vull agrair al Dr. Jordi Robles Brau per la constant ajuda i suport al llarg de tot el projecte. També a tots els amics que m'han acompanyat aquests anys de carrera i que m'han ajudat a superar-me cada dia. A les meves amigues de Moja i les meves cosines pel suport emocional que proporcionen. M'agradaria agrair els meus avis, Jordi, José, Amparo i Pepita per aconseguir que poguéssim tindre una vida justa que m'ha permès estudiar allò que volia. A la meva germana i els meus nebots i sobretot als meus pares que sense ells no hagués aconseguit res. Gràcies.

REPORT

IDENTIFICATION AND REFLECTION ON THE SUSTAINABLE DEVELOPMENT GOALS (SDG)

The Sustainable Development Goals (SDGs), adopted at the UN Sustainable Development Summit in 2015 that defined the 2030 Agenda for Sustainable Development, are universal goals to end poverty, protect the planet, and improve people's lives and prospects. These are 17 goals that address challenges such as economic inequality, innovation, climate change, sustainable consumption, peace and justice. The 2030 Agenda proposes actions in 5 broad areas called the 5Ps, which stands for People, Planet, Prosperity, Peace and Partnership.

Regarding the subject of this TFG, synthesis of antivirals based on green chemistry principles, sustainability is fully at the core of the project and touches on the areas referred to People, Planet and Prosperity. In my opinion, this TFG is mainly contributing to the following SDG:

- SDG#3 (Good Health and Good Being): Antivirals are key to ensuring good health and well-being of people because are drugs that fight against important threats to human health such as potentially epidemic and life-threating diseases (SARS-CoV2, Ebola, etc.)
- SDG#13 (Climate Action): Human beings must have the mission to protect natural resources and tackle the problems of climate change. SDG 13 is central to our project because sustainable synthesis based on green chemistry principles is important in order to meet the challenges of climate change.
- SDG#9 (Industry, Innovation and Infrastructure) and SDG#11 (Sustainable cities and communities): Prosperity must aim at sustainable economic and technological development. SDG 9 aims to build resilient infrastructures, promote sustainable industrialization, and foster innovation. Green chemistry, which is aimed at producing sustainable chemical processes by design, and antiviral drug discovery need both to

commit decisively to research and innovation. On the other hand, SDG 11 aims to build inclusive, resilient, safe, and sustainable cities. SDGs #9 and #11 seek sustainability, particularly in industry and world economy. That is why sustainable processes are so important to produce new and effective antivirals.

- SDG#12 (Responsible consumption and production): Green chemistry advocates for sustainable production of chemicals, ensures sustainable consumption of raw materials end energy, and designs production patterns that are more respectful for the environment and safer for human life.

CONTENTS

1. SUMMARY

Green chemistry aims at reducing and eliminating the use or generation of hazardous substances by designing alternative routes and choosing methodologies with environmental and safety considerations. This area was born in the 1990s motivated by concern about the effects that chemical compounds could have on human health and the environment. This is in this light that P. Anastas and J. Wagner developed a sort of guide for implementing sustainable processes summarized in the named twelve principles of green chemistry. In 2019, the Green Deal was launched in Europe, which intends to adapt EU policy in fighting climate change. Among the initiatives, the chemicals strategy for sustainability published by the European Commission supports the adoption of green chemistry principles in the European chemical industry.

The pharmaceutical sector is an economically important sector in Europe. This industry is particularly characterized by a complex and highly selective chemistry, which in turn generates a high waste/product ratio. This is why the EU proposes a strategy focused on promoting a more sustainable and affordable drug synthesis. After the experience of the COVID-19 pandemic, in coming years antivirals will probably be one of most demanded types of drugs. In fact, there is scientific evidence of the link between climate change and future pandemics, so the development of new antivirals will be strongly needed.

In this TFG project, a bibliographic search was done on examples of antiviral synthesis in which the green chemistry principles were applied, focusing on the main shortcomings of pharmaceutical chemistry. These methods include the use of more efficient catalysts, safer solvents or auxiliaries, and sustainable energies. These methodologies have been particularly analysed and compared with common procedures, and their advantages are discussed in terms of sustainability and safety.

Keywords: Green chemistry, antivirals, organic synthesis, climate change, sustainability, European Green Deal

2. RESUM

La química verda té com a objectiu la reducció i eliminació de l'ús o generació de substàncies perilloses mitjançant el disseny de rutes alternatives i l'elecció de metodologies amb consideracions mediambientals i de seguretat. Aquesta àrea va néixer a la dècada dels 90 amb motiu de la preocupació pels efectes que els compostos químics podrien tenir en la salut humana i el medi ambient. És per això que P. Anastas i J. Wagner van desenvolupar una mena de guia per implementar processos sostenibles resumits en els anomenats dotze principis de la química verda. El 2019 es va impulsar Europa el Pacte Verd, amb què adapta la política de la UE en la lluita contra el canvi climàtic. Entre les iniciatives, l'estratègia de productes químics per a la sostenibilitat publicada per la Comissió Europea recolza l'adopció dels principis de química verda en la indústria química europea.

El sector farmacèutic és un sector econòmicament important a Europa. Aquesta indústria es caracteritza particularment per una química complexa i altament selectiva, que alhora genera una elevada proporció de residus envers producte. És per això que la UE proposa una estratègia centrada en promoure una síntesi de medicaments més sostenible i assequible. Després de l'experiència de la pandèmia COVID-19, en els propers anys els antivirals probablement seran un dels tipus de medicaments més sol·licitats. De fet, hi ha evidència científica de la relació entre el canvi climàtic i les futures pandèmies, d'aquí que el desenvolupament de nous antivirals serà molt necessari.

En aquest projecte de TFG, s'ha realitzat una cerca bibliogràfica d'exemples en què s'apliquen els principis de la química verda en síntesi d'antivirals, centrant-se en les principals limitacions de la química farmacèutica. Aquests mètodes inclouen l'ús de catalitzadors més eficients, solvents o auxiliars més segurs i energies sostenibles. Concretament, s'han analitzat i comparat aquestes metodologies amb els procediments habituals, i se'n discuteixen les avantatges en termes de sostenibilitat i seguretat.

Paraules clau: Química verda, antivirals, síntesis orgànica, canvi climàtic, sostenibilitat, Pacte Verd Europeu

3. INTRODUCTION

Climate change is recognised as the greatest threat to the earth in this century. Although the last few years have seen economic slowdowns and recessions, climate change is not on pause as it is affecting all countries, ways of life, and altering national economies. The average temperature increased by 0.85°C between 1880 and 2012, but given current emissions of greenhouse gases, global temperatures are predicted to exceed 1.5 ºC by the end of the century. This is expected to cause unpredictable and rough effects on climate that might ultimately endanger human existence, as for example, rising of sea levels, scarcity of food (cereal production was shown to fall by 5%) and freshwater, among many others. In this context, governments must urgently provide long-term systemic changes that ensure a more sustainable future for citizens.[1]

3.1. GREEN CHEMISTRY

According to statistics, 84% of Europeans are concerned about the effects of chemicals on their health, and 90% about the effects on the environment, which probably explains the unfavourable vision of chemical processes in today's society.[2]

In the course of a century, chemistry has allowed life expectancy to increase from 47 years in 1900 to 75 years in 1990. This is thanks to medical advances with the creation of antibiotics which cured diseases that had devastated mankind for millennia. Chemistry enabled the expansion of food thanks to chemicals that protect crops and increase yields. It has also contributed the development of novel materials and efficient technologies. These are examples of how advances in chemistry have improved the quality of life for billions of people. But it cannot be denied that all these improvements brought about by chemicals have come at a price on human health and the environment.[3]

The effects of toxic chemicals on the environment were not considered until the years following World War II. At this point in history there were no environmental regulations in place to discuss the impacts on the environment in the process of manufacture, use or disposal. It was not until 1962 that Rachel Carson published the book "Silent Spring" in which she reported the environmental impact of DDT and other pesticides resulting in control regulations on pesticides in the USA.[4] A year earlier in Europe, human health effects were reported from the drug thalidomide, which was prescribed to relieve nausea during pregnancy. This drug caused acute birth defects

in more than 10,000 children worldwide.[5] These cases made society aware for the first time of the effects of chemicals and governments were forced to devise regulations. Over the next two decades, environmental issues began to emerge, resulting in new laws and regulations generated by governments.[6]

In his context, in the early 1990s, the US Environmental Protection Agency (EPA) coined the term Green Chemistry as a synthetic alternative route to pollution prevention towards a chemistry that is safe and sustainable by design. P. Anastas and J. Wagner developed in 1998 the Twelve Principles of Green Chemistry as a guide on the implementation of chemical processes with environmental and sustainability criteria, with five main lines of actions in the whole design, manufacture, and application steps: efficient processes, environmentally benign products, green and renewable raw materials, green solvents and use of catalysts.[3]

3.2. THE TWELVE PRINCIPLES OF GREEN CHEMISTRY

1. Waste prevention: It is better to prevent waste than to treat or clean up waste after it is formed.

In the last 30 years, importance has been given to the cost of treating the harmful substances generated. The more harmful it is, the more expensive it is to treat. It will always be more harmful to fix problems than to prevent them.

2. Atom Economy: Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

The common measure to assess the efficiency of the reaction outcome is the synthetic yield, but this ignores the generation of unwanted substances that are also produced in the reaction. Atom economy is a better indicator, as it measures how many atoms of the reactants end up in the desired final product. Atom economy is the ratio of the molecular weight of the product of a reaction to the sum of the molecular weights of all the reactants.

3. Minimization of hazardous syntheses: Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

In designing a less harmful synthesis, there are two ways to address the problem, either by minimising exposure time or by minimising harm.

4. Safer chemicals: Chemical products should be designed to preserve efficacy while reducing toxicity.

Chemists, pharmacists, and toxicologists have been working for years to develop tools that relate toxicity with molecular structure, so these can be used to diminish the toxicity of new chemicals. The goal of designing safer chemicals is to find the balance between maximising the effect of the desired product while ensuring that toxicity and hazard are kept to a minimum.

5. Safer auxiliars and solvents: The use of auxiliary substances (e.g., solvents, co-reagents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when needed.

Auxiliary substances are chemicals that are used in one reaction that do not end up as part of the desired molecule. Besides, these substances must be separated from the product and may often have toxic properties that affect human health and the environment.[3]

In the USA, 3.8 million tons of solvents are used per year in chemical manufacture, among which most are highly flammable or halogenated solvents, such as chloroform or methylene chloride, which are associated with carcinogenic effects.[7] Other solvents well known for their effect on the environment are chlorofluorocarbons (CFCs), which cause stratospheric ozone depletion. Volatile organic compounds (VOCs) are also known to generate smog, which can result in respiratory problems.[3]

6. Energy efficiency: Energy requirements of chemical processes have enormous environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

The reactivity of chemical reactions follows the laws of kinetics and thermodynamics. For transformations to take place, the activation energy of the transition state must be overcome, which requires an initial input of energy. In exothermic reactions where heat is released need to be controlled by cooling and this also entails energy consumption Additionally, after reaction completion, separation or purification processes also require energy. For all these reasons, when designing a chemical process, energy aspects must be fully considered, most specially, in the present context pf climate change.

7. Renewable feedstocks: Raw materials should be renewable rather than depleting wherever technically and economically practicable.

The chemical industry is a major consumer of petroleum-based feedstocks which has many negative effects on the environment and human health. Additionally, due to extensive consumption, raw materials could deplete.[3]

The term renewable feedstocks refer to substances that are easily regenerated in a period of time accessible to human lifetime. Plant-based and biological starting materials are some examples for renewable feedstocks.

8. Minimize derivates: Unnecessary derivatization (blocking group, protection/deprotection, and temporary modification of physical/chemical processes) should be avoided whenever possible.

The synthesis of organic chemistry is becoming increasingly complex. The use of protecting groups that temporarily block the reactivity of a functional group, and salt additives which helps to modify properties such as viscosity, water solubility or vapour pressure, are not sustainable and generate extra waste.[3]

9. Catalysis: Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

Catalysts provide advantages in transformation as they are not consumed in the course of the reaction, thus minimizing waste. They also diminish energy consumption by lowering the activation energy and being highly chemo- and stereoselective. Catalysts can be reused several times before being deactivated whereas stoichiometric reagents can only be used one time.[3]

10. Design for degradation: Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.

Persistent chemicals and bioaccumulative substances are of great concern as they can remain unaltered in the environment or even accumulate in organisms, thus triggering chronical toxicity and environmental damages.

11. Real-time analysis for pollution prevention: Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

It is necessary to monitor the reaction process in order to determine its completion and to avoid using more reagents and energy than necessary and to reduce the production of waste.

12. Inherently safer chemistry for accident prevention: Substances and forms to be used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including, leakages, explosions, and fires.

Accidents due to chemicals and chemical operations can result in the death of hundreds of human lives, and therefore the prevention of accidents is of great concern. Toxicity, flammability, and exposure must be fully considered in the process design in order to ensure complete safety.[3]

3.3. EUROPEAN GREEN DEAL

An ambitious program named as Green Deal was initiated by the European Union (EU) in December 2019, out of concern for the threat of climate change and environmental degradation. The Green Deal is named after Franklin Roosevelt's New Deal which was the social and cultural programme put in place by the US federal government to overcome the Great Depression in the 1930s.[8] The European Commission proposed to adapt EU policies on climate, transport, energy, and taxation with the aim of reducing net greenhouse gas emissions by 2030 and achieve a climate neutral and circular economy by 2050. Another objective of this pact is the protection of human health and the environment by achieving a toxic-free environment.[9]

3.4. CHEMICALS STRATEGY FOR SUSTAINABILITY TOWARDS A TOXIC-FREE ENVIRONMENT

In 2018, 3347 billion euro of chemical sales were reported worldwide, where Europe was the second largest producer of chemicals. The EU has approved approximately 40 legislative instruments aimed at the safety of products (chemicals, cosmetics, food, drugs, plant protection products, etc.) and the protection of the environment. Recently, in the context of the European Green Deal, it has also launched the Chemicals Strategy for Sustainability Towards a Toxic-Free Environment.[10]

Chemistry plays a fundamental role in everyday activities, so it is essential to increase investment and innovation to find green solutions for our economy and society. Apart from the effects of harmful chemicals on human health, the environmental impact of chemicals is leading to wider planetary crises such as climate change, biodiversity loss and ecosystem degradation. Consecutively, chemicals must be designed to be sustainable and safe at all stages of the process.

In order to achieve these objectives, several actions were proposed to protect human health and the environment and encourage innovation. For health and environmental protection, substances that could be harmful for non-essential uses must be replaced by using safe chemicals, minimising exposure to harmful substances and eliminating substances of concern from waste and restoring the environment. In order to encourage innovation, the development of greener and safer chemicals as well as processes and technologies must be promoted. Also, other aspects to promote are the production of more modern and smarter processes and new chemical recycling technologies to solve pollution. All these points are to be achieved through regulatory actions such as ensuring legislation on industrial emissions for safe chemicals or developing criteria for the design of safe and sustainable chemicals.[10]

3.4.1 Pharmaceutical strategy for Europe

Data from 2018 reports that the pharmaceutical sector in the EU has a 91 billion euro trade, being one the largest contributions to Europe's economy. Moreover, this sector is expected to continue to grow in the coming years. At the same time, there is a growing concern on the environmental impact which is leading to the development of a greener pharmacy.[11] Recently, in April 2023, the European Commission has launched a proposal for a new Directive and revision of the existing general pharmaceutical legislation, following the Pharmaceutical Strategy for Europe.[12]

Pharmaceutical substances contain biologically active substances in human, but when dispersed in the environment, can create environmental problems.[13] Besides, one of the major problems is the high ratio of waste to useful product in pharmaceutical drugs. Consequently, a greener pharmacy is becoming a matter of urgency. Similarly to Green Chemistry, Green Pharmacy can be defined as the design of pharmaceutical products and processes by eliminating or reducing harmful substances. Pharmaceutical drugs have complex structures as they are intended for healing humans in a safe and selective way. Consequently, their synthetic preparation usually involves multiple, complex and diverse stages, resulting in a high proportion of waste in comparison to overall production.[11]

In this context, the European Commission proposes a pharmaceutical strategy that covers the entire life cycle of the pharmaceutical product, from scientists to authorisation and patient access, ensuring quality, safety and efficiency in medicines and promoting the competitiveness

of the sector. This strategy is composed of legislative and non-legislative actions that can be seen summarised in figure 1.[13]

- *Ensure greater access and availability of pharmaceuticals to patients*
- *Ensure affordability of medicines for patients and health systems financial and fiscal sustainability*
- *Enable innovation including for unmet medical needs in a way that harnesses the benefits of digital and emerging science and technology and reduces the environmental footprint*
- *Support EU influence and competitiveness on the global level, reduce direct dependence on manufacturing in non-EU countries, seek a level playing field for EU operators*

Figure 1. Objectives of the EU Pharmaceutical Strategy.[13]

3.4.2 Health crisis and new antivirals

In 2020, major events and conferences were expected to be held to combat the climate emergency, but the sudden and severe health crisis caused by COVID-19 pandemic resulted in terrible socio-economic effects with over 200,000 dead and 3 million infected by the end of April.[14]

While attention was focused on the pandemic, unusual temperatures were recorded in Europe and Asia. There were also weather events in other parts of the world as a reminder that the great threat of this century is climate change. Both the health and climate crises probably have the same origin, human activity, and overexploitation of natural resources.[14] The destruction of ecosystems and habitats caused by human activity favours the spread of zoonotic diseases, animal-borne diseases transmitted to humans, which are 75% of infectious diseases in humans.[15] Deforestation, agricultural and livestock expansion, and climate change lead to environmental conditions that favour human-animal contact and the rapid spread of diseases and pandemics. An example of this correlation is the Ebola outbreak, which is associated with the destruction of tropical forests that caused bats to approach human settlements.[16]

It is difficult to predict new outbreaks and pandemics, but climatic changes and habitat alterations suggest future outbreaks and pandemics.[17] This is why the development of new antivirals are expected to be needed.

4. OBJECTIVES

This TFG intends to deal with and combine two issues of special relevance today: the fight for sustainability and against climate change in chemical processes, following the principles of green chemistry, and the development of new drugs with antiviral activity, able to deal with potentially epidemic diseases in the near future. As a result, the project aims to review new and recent contributions of green chemistry on the synthesis of antivirals.

In this light, the main objective is to search and compile new and relevant examples of the organic synthesis of antivirals using more sustainable and safe methodologies following green chemistry principles. Emphasis will be placed on the following topics: alternative energy sources, safer and non-toxic solvents or auxiliaries, high atom economy reactions, and efficient and selective catalysts. In each of these topics, the advantages of green synthesis over classical procedures will be also particularly analysed.

5. METHODS

The databases Web of Science and SciFinder, provided by CRAI-UB resources, were used for the bibliographic search. Web of Science was the main database used, as it offers access to wide bibliographic information, citations and references of scientific publications in this field. During the first week of the project, an initial search was carried out to find introductory topics on green chemistry. SciFinder was used to refine the search in the research area of pharmacology using keywords such as “green chemistry” and “sustainable chemistry”. It was noted that there has been an exponential increase in publications on this topic over the last 18 years. With respect to European Green Deal and their related programs, the official websites of the European Commission were mainly consulted.

Once introduced to the green chemistry topic, a cross search on Web of Science was carried out between the concepts of “antiviral” and “green chemistry”, obtaining 102 results. This search was refined by selecting “chemistry” and “environmental sciences ecology” topics and 74 references were found, from which the examples of green chemistry applied to antiviral synthesis were selected. To support these searches, textbooks on green chemistry, such as “Green chemistry: an introductory text”[26] and “Green chemistry: Theory and practice”[3], where to find examples of green alternatives for solvents such as ionic liquids were also consulted, and the references found were crossed with those referring to antiviral agents. The set of references that were thus collected (13 references for the introduction and 11 for the results) were submitted to a second round of selection to choose the core references that have been cited in this report (8 examples of the application of green chemistry), by either considering the advantages of the methodologies, or showing noteworthy examples of how green chemistry principles were applied.

6. RESULTS AND DISCUSSION

6.1. ALTERNATIVE ENERGY SOURCES

In Europe, the second largest producer of chemicals in the world, the chemical industry's energy consumption has been increasing. In most chemical processes, thermal energy sources are used. Most of this energy is used for heating or cooling reactors and processing of solvents and waste. Processes such as separation and purification also involve a large consumption of energy. Following on the sixth principle of Green Chemistry which states the need for achieving energy efficiency and environmental sustainability by design, efforts can be done by minimizing energy consumption at the molecular level by employing alternative sources such as photochemistry, microwaves, ultrasounds, or electrochemistry.[18]

Two examples illustrating the use of alternative energy sources in the synthesis of antivirals are explained below: first, an intramolecular Wittig reaction leading to antiviral flavones via photochemical irradiation, and second, the synthesis of isoxazoles mediated by ultrasounds.

6.1.1. Synthesis of flavones by a photochemical intramolecular Wittig reaction in water

In 2005, 3.1 million deaths were reported due to the global immunodeficiency syndrome (AIDS) epidemic caused by the human immunodeficiency virus (HIV). HIV selectively infects T4 lymphocytes and thus disables the immune system. Approximately 39 million people are currently infected with the virus.[19]

Three enzymes are essential for the replication cycle of HIV-1: reverse transcriptase, protease, and integrase. Within these enzymes, integrase (IN) is a crucial enzyme in the virus life cycle that catalyses the integration of cDNA into the human genome, facilitating stable viral replication. Since there is no cellular equivalent of IN in humans, this enzyme is of great interest for antiviral drug targeting.[19]

Among other compounds, flavones have been studied for their activity as inhibitors of HIV-1 IN.[20] Flavones (Figure 2) are compounds of the flavonoid family formed by multiply-functionalized 4*H*-chromen-4-one (1,4-benzopyrone) rings.[19] These compounds are known to have a varied and effective biological activity, resulting in different pharmacological applications.[21] Among others uses, flavones have been studied for their anti-HIV-1 action as IN inhibitor by chelating a divalent metal ion bound to the enzyme, probably followed by a radical-mediated reaction with the enzyme.[19]

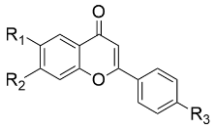
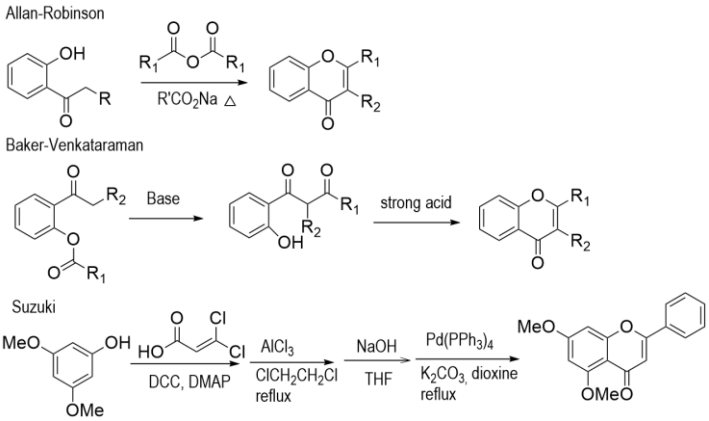


Figure 2. General structure of flavones.

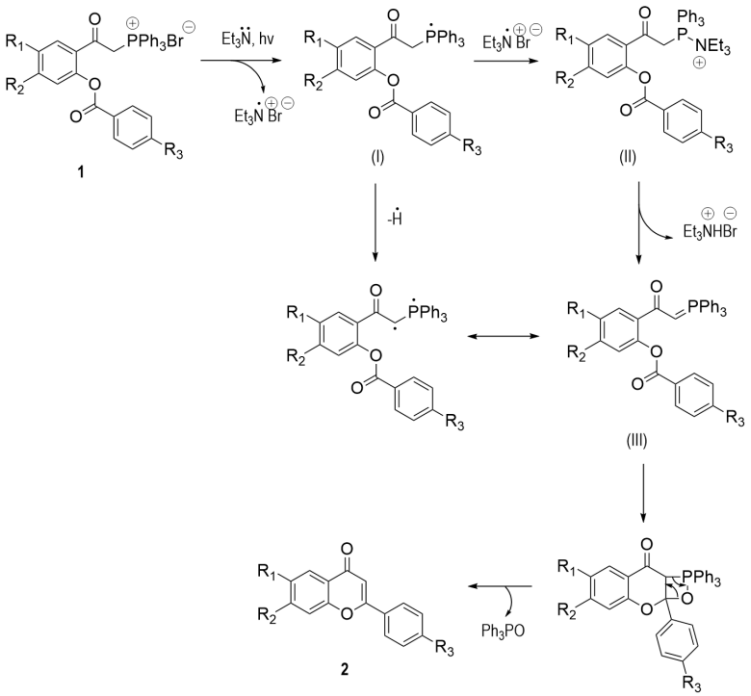
Structure and inhibitory activity have been revealed, showing the role of aromatic system as a chelating agent.[19]

Flavone synthesis can be carried out by various classical processes, such as Allan-Robinson[22] and Bayer-Venkataraman[23] reactions. More recently, intramolecular Suzuki[24] or Wittig[24] reactions have also been used. Here, an intramolecular photochemical Wittig reaction in water is highlighted as an eco-friendly alternative reaction.[20]



Scheme 1. Flavone synthesis by Allan-Robinson[22], Baker-Venkataraman[23] and Suzuki[24] reactions.

The intramolecular photochemical Wittig reaction[20] could be explained by two alternative mechanisms. Under UV irradiation (150 W tungsten lamp) the phosphonium salt **1** and triethylamine reacts to give phosphoranyl radical I. This radical transforms into phosphorus ylide (III) either by loss of atomic hydrogen or by electron transfer reaction with triethylammonium radical cation to form, a very unstable P-N+ intermediate (II), followed by elimination of triethylamine. Here, the ester carbonyl and phosphorane combine to undergo an intermolecular Wittig reaction, to yield the flavone **2** and Ph_3PO. (Scheme 2)



Scheme 2. Proposed mechanism pathways for the photochemical Wittig synthesis of flavone.[20]

This is a methodology that permits the synthesis of flavones in a clean way and high yields (63-91%).[20] Additionally, the Wittig reaction was carried out in water, a polar medium which stabilizes the ylides and the transition state of Wittig reaction, thus improving the evolution of reaction. Most importantly, from a green chemistry viewpoint, water is a harmless, non-flammable and renewable solvent.

Taking into account the source of energy, the reaction has been carried out by photochemical irradiation, which allows to photoactivate selectively a particular functional group. By having greater selectivity, unwanted by-products are obtained and therefore less waste is produced. Also, photons can be considered a clean source of energy, as they do not generate waste. Photochemical reactions also allow energy to be saved because they tend to occur at lower temperatures than non-irradiated reactions.[18]

On the other side, Wittig reactions which are a very versatile and useful way to generate alkenes entail a low atomic economy, as triphenylphosphine oxide is obtained as by-product which is difficult and expensive to process.[26]

6.1.2. Synthesis of isoxazole derivatives via ultrasounds irradiation

Isoxazole derivatives are known for their varied biological activity, such as antifungal, analgesic, anti-inflammatory, antitumor, antimicrobial, antiviral, etc.[27]

5-Isoxazol-5-yl-2'-deoxyuridines (Figure 3) have antiviral activity against the herpes simplex virus (HSV) and other RNA viruses.[27] Particularly, HSV is one of the most widespread viruses on the planet. It belongs to the *Herpesviridae* family, which are known to produce infections in humans, and has two main strains, HSV-1 and HSV-2. It is known that 50-70% of young people have antibodies against HSV-1. It causes lesions in the mouth, lips, and face in humans, starting from the skin or mucosal epithelium. Resistance to antiviral drugs against HSV is increasing, therefore, the development of new antivirals is of high importance.[28]

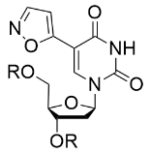
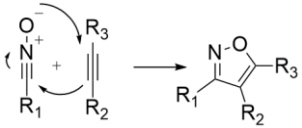


Figure 3. Structure of 5-Isoxazol-5-yl-2'-deoxyuridines.

In the course of the synthesis of 5-isoxazol-5-yl nucleosides, isoxazole intermediates are needed to be prepared. Usually, two main classical methodologies render isoxazoles[29]: i) condensation of 1,3-dicarbonyl compounds with hydroxylamine, and ii) [3+2]-cycloaddition of nitrile-oxide to alkynes. For this second synthesis, nitrile oxide was first obtained by catalysed elimination of hydrogen halide from halo-oximes (RC(Hal)=NOH). The nitrile oxide reacts subsequently with alkynes via dipolar cycloaddition to generate isoxazole, a 5-membered heterocycle. This reaction usually leads to mixtures of isomers.[29]

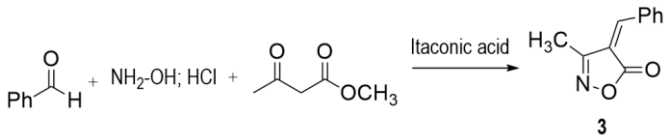


Scheme 3. Synthesis of isoxazole by a [3+2]-cycloaddition.

A green version of a condensation producing isoxazoles has been recently disclosed via ultrasound irradiation which offer advantages over the reaction carried out under conventional heating conditions.[30]

Ultrasound mediated synthesis has been a rewarding field of research for the past decades. Ultrasound is a sound wave with frequencies higher than the human ear can detect, around 18 kHz. The frequencies used in chemical reactions are normally between 20-100 kHz. In ultrasounds, a sound wave is propagated by cycles of compression and rarefaction. As it passes through a liquid, it causes the molecules to oscillate, which ultimately generates small bubbles due to the attractive forces of the molecules. When the attractive forces are great enough, they cause the bubble to collapse, generating local high temperatures, around 5000 ºC, and pressures above 1000 bar. In order to reach the collapse conditions that are optimal for the initiation of the chemical reaction, the correct frequencies and energy must be chosen. The energy produced by the collapse of bubbles is thought to initiate the chemical reaction.[26]

Sandeep B. Kasar and Shankar R. Thopate[30] carried out a preliminary study to optimize the synthesis of isoxazolone **3** by varying the temperature and the percentage of catalyst, which was itaconic acid. They found that the most efficient conditions were those summarized in Table 1. Based on these results, ultrasound irradiation achieved slightly better yield but the reaction took place 12 times faster and at half the temperature than in a conventional heated reaction.

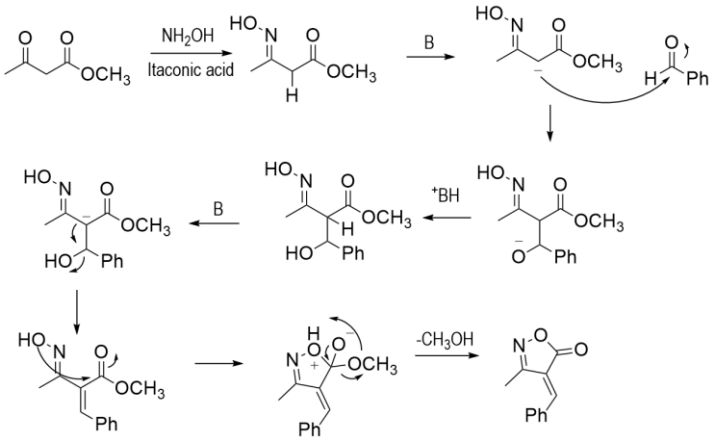


3

Scheme 4. Synthesis of (*Z*)-4-benzylidene-3-methylisoxazol-5(4*H*)-one (**3**) in water and catalysis by itaconic acid (2-methylenesuccinic acid).

Conditions	Time [min]	Yield [%]
Itaconic acid, water, 100 ºC	180	90
Itaconic acid, water, ultrasounds, 50 ºC	15	95

Table 1. Comparison of conventional heating and ultrasound irradiation method for the synthesis of (*Z*)-4-benzylidene-3-methylisoxazol-5(*4H)*-one (**3**) in the presence of 5 mol % itaconic acid as catalyst.[30]



Scheme 5. Proposed mechanism for the condensation into (*Z*)-4-benzylidene-3-methylisoxazol-5(4*H*)-one (**3**).

This reaction is a nice example of a green chemical process, since it results from the combination of a multicomponent reaction, the use of a green solvent as water and non-conventional energy sources. A multicomponent reaction simultaneously incorporates three or more reactants, so it satisfies the second principle of green chemistry on atomic economy by maximizing the incorporation of all materials used in the process into the final product.[26] Notably, the reaction was catalysed by itaconic acid, a biodegradable and non-hazardous chemical which can be obtained industrially by the fermentation of carbohydrates. Additionally, itaconic acid could be here recovered and reused without any pre-treatment with the same catalytic efficiency.[30]

6.2. SAFER SOLVENTS AND AUXILIARIES

Organic solvents, highly used in the synthesis of any drug, are the main origin of waste, as well as the cause of high energy and carbon footprints. Most organic solvents are also associated with a hazardous level of flammability. Many of them are highly volatile because of high vapour pressures at room temperature, causing environmental problems such as the greenhouse effect or ozone depletion in the stratosphere. Some solvents are also carcinogenic, such as chlorinated solvents or some aromatic compounds. For all these reasons, the fifth principle of green chemistry states the need to avoid auxiliary reagents and organic solvents whenever possible, otherwise,

to use harmless substitutes. Consecutively, safer and more sustainable solvents are key to achieve green processes[18].

Since completely removing solvents from a process is very difficult in most cases, the option is to look for alternative reaction media. If a solvent is required, the best and greenest option is undoubtedly water. It can be also chosen to minimise the amount of solvent or use a two-phase system. Other ways to comply with green principles are to use harmless and renewable solvents such as supercritical CO_2 or to carry out reactions in very low vapour pressure solvents, such as ionic liquids.[18]

Green chemistry can be also addressed to auxiliaries that are designed to fulfil specific objectives in synthesis. These substances often have properties that affect human health and the environment, so they should be avoided as possible.[3]

Two examples leading to antiviral compounds are explained below: the first on the use of ionic liquids as solvents and the next, an alternative coupling agent in the synthesis of amides.

6.2.1. Synthesis of pyrano[3,2-*c*]pyridines and pyrano[4,3-*b*]pyrans using ionic liquids

Pyridone and pyran structures are present in compounds with biological activities, such as inotropic and vasodilatory agents, and antitumor activity.[31] An example of these compounds with antiviral activity is Pyridone L-697,661 (Figure 4). This compound acts as a specific inhibitor of the reverse transcriptase (RT) in HIV-1. An important step for the virus life cycle is the reverse transcription of the RNA genome of the virus, which produces a double-stranded DNA copy.[32] The study by Goldman *et al.*[31] suggested that pyridinones inhibited RT by binding to enzyme-template-primer complexes.

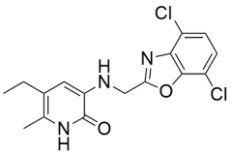
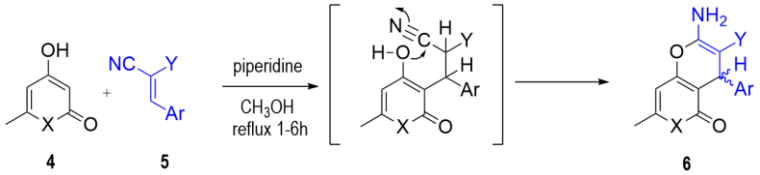


Figure 4. Pyridone L-697,661.

Pyrano[3,2-*c*]pyridine and pyrano[4,3-*b*]pyrans have been proposed as improved analogues of Pyridone L-697,661. For the synthesis of these compounds two synthetic methods were compared. The method described by Stoyanov *et al.*[33] started with the reaction of **4** and

Knoevenagel-derived reagent **5** in equimolar ratios (Scheme. 6). This reaction was carried out under methanol reflux for 1-6 hours in the presence of piperidine, leading to bicycles **6** with yields in between 56 and 95%.[33]



Scheme 6. Synthesis of pyrano[3,2-*c*]pyridine (X=N) and pyrano[4,3-*b*]pyrans (X=O) by Stoyanov *et al*.[33]

On the other hand, Xuesen *et al*.[31] carried out a study to observe the advantages of using ionic liquids instead of conventional organic solvents. Ionic liquids are salts of voluminous organic ions with a low melting temperature, due to the low degree of cation symmetry that causes the reduction of crystal energy. One of the main advantages of ionic liquids is that by varying the volume ratios of counterions, physicochemical properties such as melting temperature, viscosity, acid-base properties can be controlled.[18] Another advantage is that they can be used at high temperatures and low pressures, being stable at temperatures above 300 ºC. They can also be easily separated in liquid-liquid extractions if they are not miscible in organic solvents nor water.[26]

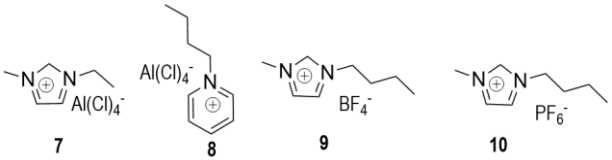
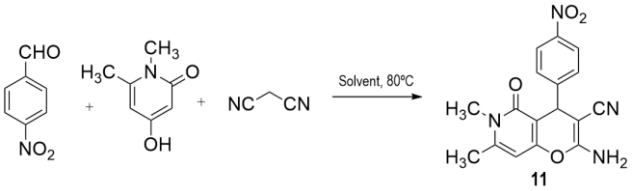


Figure 5. Some common ionic liquids at room temperature: 1-ethyl-3-methylimidazolium chloride-aluminium(III) chloride ([emim][$AlCl_4$]) (**7**), *N*-butylpyridinium-aluminium(II) chloride ([NBupy][$AlCl_4$]) (**8**), 1-butyl-3-methylimidazolium fluoride-boron trifluoride ([bmim][BF_4]) (**9**), and 1-butyl-3-methylimidazolium fluoride-hexafluorophosphate ([bmim][PF_6]) (**10**).[26]

The advantages of using an ionic liquid as solvent in the synthesis of 2-amino-5,6-dihydro-6,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (**11**) were studied and the results are shown in table 2. The ionic liquid used here was 1-butyl-3-methylimidazolium fluoride-boron trifluoride ([bmim][BF_4]) (**10**, Fig.5). The results summarised in table 2 showed the

benefits in yields and shorter reaction times when using the ionic liquid. Notably, recovering and reusing [bmim][BF_4] permitted to obtain **11** still in good yields.[31]



11

Entry	Solvent	Time [hr]	Yield [%]
1	Toluene [a]	5	75
2	[bmim][BF_4] [b]	0.1	98
3	[bmim][BF_4] [c]	1	90

[a] 10 mL of solvent
[b] 1.5 g of solvent
[c] Solvent recovered from the fourth round

Table 2. Synthesis of 2-amino-5,6-dihydro-6,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile (**11**) by using different solvents at 80 ºC.[31]

Here, a synthetic process was disclosed using an ionic liquid as a green solvent which showed higher yields and better performance. Ionic liquids are easier to recover and reuse than conventional organic solvents, can allow higher selectivity and organic compounds and enhance the rates of chemical processes by solubilizing both inorganic and organic compounds.[31]

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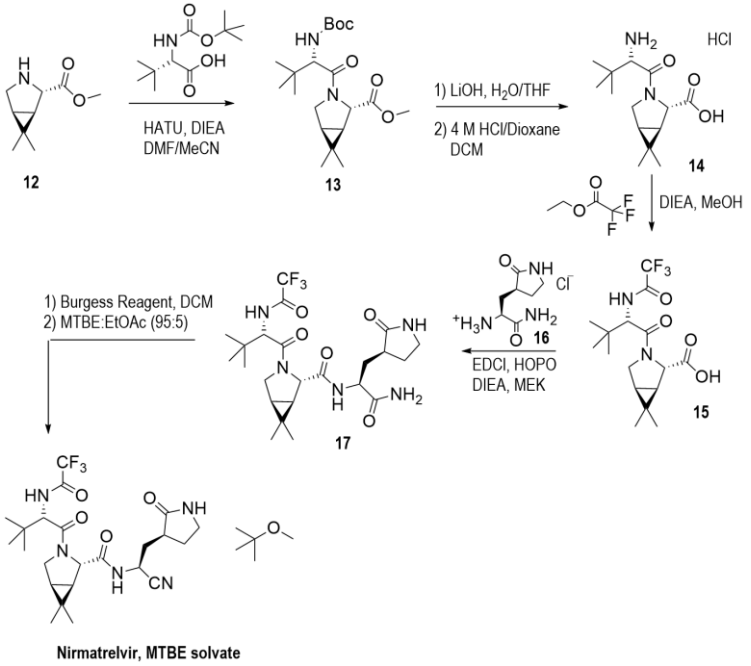
6.2.2. Synthesis of nirmatrelvir avoiding common peptide coupling reagents

An epidemic, initially identified as pneumonia, occurred in the Chinese city of Wuhan in 2019. In February 2020 the WHO described the disease as COVID-19, caused by the SARS-CoV-2 virus[34] belonging to the *Orthocoronavirinae* family. Coronaviruses genome consists in an RNA chain with 30.000 nucleotides and are known to cause severe respiratory and gastrointestinal illnesses that can even lead to death. SARS-CoV-2 virus created an urgent need for preventive measures[38] because of high transmission rates which culminated in the development of specific vaccines.

Paxlovid was one orally bioavailable antiviral developed by Pfizer, which received the emergency use authorization by the FDA (U.S. Food and Drug Administration) to fight SARS-

CoV-2 at the end of 2021, and shortly after conditional marketing authorization was also obtained by the European Commission. It is a combination of nirmatrelvir, a SARS-CoV-2 main protease inhibitor, and the commonly used HIV antiviral named ritonavir which helps to maintain the effective concentration of nirmatrelvir (Paxlovid) by being a potent inhibitor of CYP3A enzymes.[34]

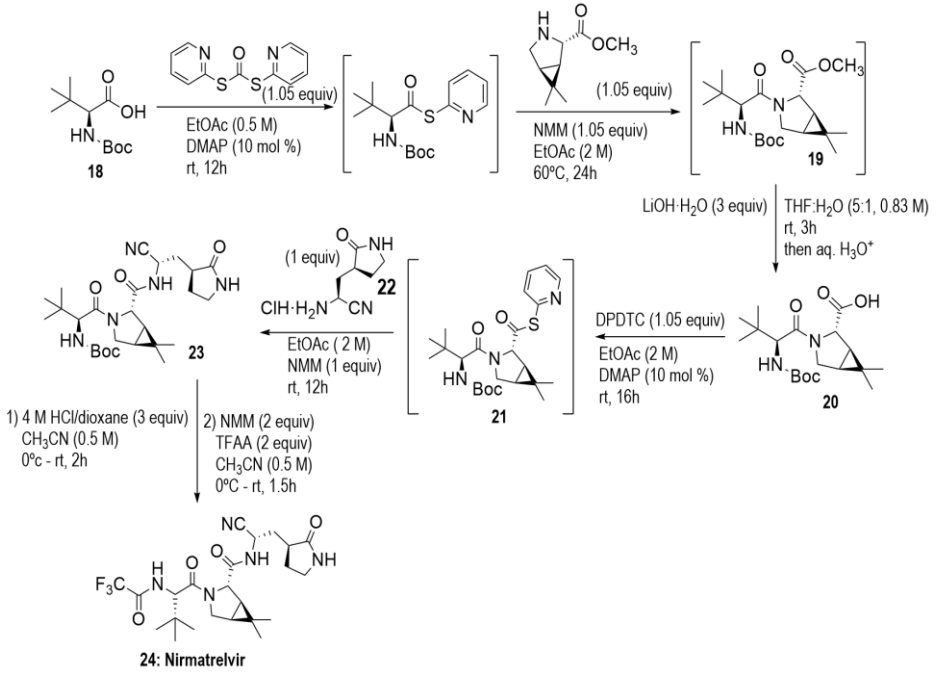
A method for the synthesis of nirmatrelvir was first proposed by Owen *et al.*[36] and further developed by Pfizer. Scheme 7 summarizes the synthesis of nirmatrelvir which starts from (1*R*,2*S*,5*S*)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate **12**. Compound **13** was synthesised by amide coupling of **12** and *N*-(tert- butoxycarbonyl)-3-methyl-*L*-valine. The ester function was further hydrolysed and the Boc protecting group was removed to form **14**. The primary amine can now react with ethyl trifluoroacetate to form trifluoroacetamide **15**. Compound **17** was synthesised by amide coupling of **16** and **15** and the primary amide further dehydrated to generate nirmatrelvir as a MTBE solvate in 49.6% yield.[36]



Scheme 7. Synthetic method for the synthesis of nirmatrelvir developed by Pfizer.[36]

This synthesis route developed by Pfizer offered room for improvement in environmental aspects. Kincaid *et al*.[37] proposed an alternative route which reduced the amount of waste generated by minimizing epimerization of chiral centres during the peptide bond-forming steps.

In this novel route (Scheme 8), compound **18**, di-2-pyridyldithiocarbonate (DPDTC) and *N*-methyl morpholine (NMM) in EtOAc was used to activate the carboxylic acid via thioesterification to form intermediate **19**. Then, **19** was consequently hydrolysed and neutralised with HCl to give carboxylic acid **20**. This was then activated with DPDTC to generate activated thioester **21** and coupled to the nitrile amine salt **22** to obtain **23**. Finally, the Boc group was removed, generating the desired product **24** with a yield of 70%.[37]



Scheme 8. Synthetic method for the synthesis of nirmatrelvir reported by Kincaid *et al*.[37]

The activation of the carboxylic acid with DPDTC rather than other common peptide coupling reagents such as HATU, DCC, COMU, etc. showed the advantage of generating 2-mercaptopyridine as by-product which could be easily removed via an in-flask extraction and further recycled. Instead, conventional peptide coupling reagents as those used in Pfizer's

synthetic route generated genotoxic by-products. Besides, the route reported by Kincaid *et al*.[37] worked through a primary amide intermediate which required the Burgess reagent for amide dehydration into nitrile. In the elimination of the Boc, HCl/dioxane in CH_3CN was optionally used which produced higher yields than when TFA was used, which generated in turn multiple side-products due to epimerisation. The table 3 shows a summary of the comparison between the two routes.[37]

Parameters	Pfizer's synthesis[38]	Kincaid *et al*. synthesis[37]
Amide bond formation	HATU, EDCI, non-recyclable solvents: DMF, MEK	DPDTC, recyclable solvent: EtOAc
Amide dehydration	Burgess reagent, solvent: CH_2Cl_2	Cat. Pd, FCH_2CN, medium: H_2O/CH_3CN
N-Boc deprotection	Solvent: CH_2Cl_2	Solvents: CH_3CN, dioxane
Global yield	48%	70%

Table 3. Comparison of the two synthetic routes of nirmatrelvir.[37]

This novel synthetic route described by Kincaid *et al.* can be considered a greener process as it achieves higher yields and uses more eco-friendly reagents for the construction of peptide bonds. It is also designed in a way that avoids expensive separation processes by paying attention to epimerisation. Consequently, it also reduces waste and environmental footprints.[37]

6.3. ATOM ECONOMY

The atom economy (AE), or percentage of the mass of all reactants incorporated into the mass of the product, is considered a measurement of how green a reaction is. Concept coined by Prof. Trost,[39] AE gives an idea of how many atoms of the reactant end up in the final product and how many in by-products or waste. Examples of quantitative atom economy reactions are additions, Diels-Alder reactions, rearrangements, etc. On the other hand, substitutions, eliminations, Wittig, or Grignard, are reactions with very low atom economies.[26]

Here below, it is explained an example of a high atom economy reaction leading to an antiviral which is further improved following a green chemistry procedure.

6.3.1. One-pot synthesis of pyrazolo[3,4-*b*]pyridinones

In 1918 there was a severe pandemic that killed 20-40 million people, but it was not until 1933 that was possible to isolate the influenza virus that caused it. Influenza virus generally infects the upper respiratory tract causing tracheobronchitis. Belonging to the family of *Orthomyxoviridae*, there are 4 types of influenza viruses, A, B, C and *Thogotovirus*. These viruses are characterized by containing six to eight segments of single-stranded negative-sense RNA.[40]

A fundamental life stage of the virus is replication. The influenza virus binds to host cell receptors through the binding of hemagglutinin (HA), an antigenic glycoprotein on the virus's surface,[41] and enters through endocytosis.[40] Liu's group[42] found that pyrazolo[3,4-b]pyridinones (Figure 6) exhibited strong HA inhibitory activity.

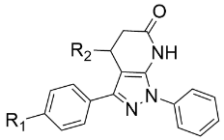
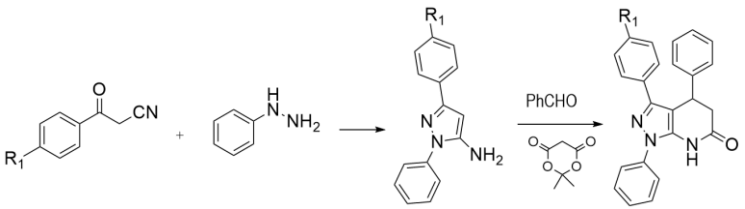


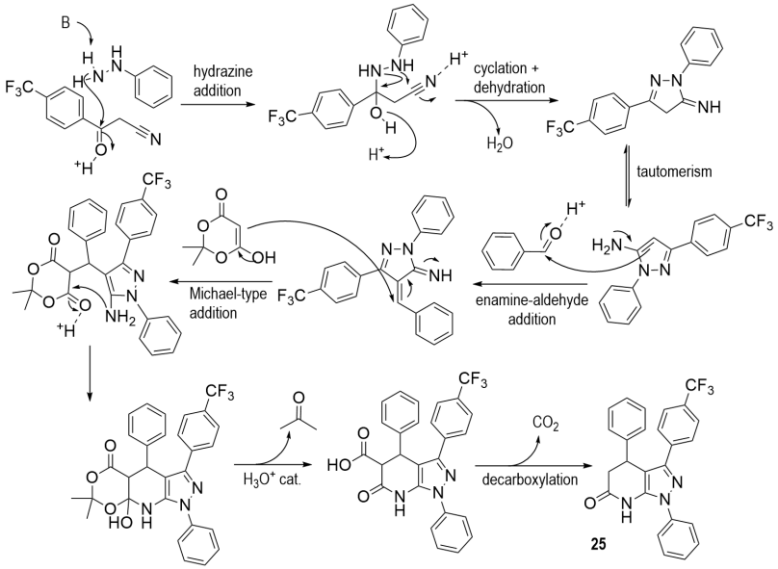
Figure 6. Structure of 4,5-Dihydro-1,2,3-triphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)- ones with antiviral activity against influenza.

Preliminary work by Liu's group helped to design an one-pot synthesis by direct construction of pyrazolo[3,4-*b*]pyridinones by condensation of benzoyl acetonitrile, phenylhydrazine, benzaldehyde and Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione). In the originally designed synthesis, EtOH was used as the solvent, and an acid catalyst was needed. An optimized and greener option was later developed by using less harmful solvents such as water and PEG (polyethylene glycol) and in which a catalyst was not needed[42] (Scheme 9). PEG is considered one of the green solvents because of reduced flammability, easily recyclability and low toxicity and environmental effects.



Scheme 9. Synthesis of 4,5-Dihydro-1,2,3-triphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-6(7*H*)-ones.[42]

Parameters such as the type of PEG and the percentage of H_2O were conveniently optimised. The best results were obtained by carrying the reaction with equimolar proportion of reagents, in a solution of 20 mg/L of PEG2000 in water and heating at 40 ºC for 1 h. Different pyrazolo[3,4-*b*]pyridinones could thus be prepared in 40-83 % yields.[42] Then, an anti-influenza virus activity test was performed and compound **25** showed the highest inhibitory activity on H5N1 pseudovirus infection. The postulated mechanism for the one-pot procedure is summarized below in scheme 10. It starts with a hydrazine addition at the carbonyl group and subsequently undergoes a cyclisation reaction. The resulting product undergoes dehydration. This intermediate tautomerizes and reacts with the aldehyde by an addition reaction. It reacts with Meldrum's acid by a Michael reaction and by catalysing with acid we obtain the carboxylic acid which decarboxylates forming **25** and CO_2.



Scheme 10. Proposed mechanism for the synthesis of 3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1,4-diphenyl-*1H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (**25**).[42]

In this procedure, the use of water as a solvent avoided the use of toxic and flammable organic solvents and provided greener separations as well as better yields. As mentioned above, PEG is a non-toxic and low flammable solvent and managed to recycle it up to five times without a noticeable decrease in yield. Furthermore, it was devised a synthesis involving four components in a one-pot and equimolar reaction, thus reducing waste and by-products and satisfying the

second principle of green chemistry that stated that sustainable procedures must show high atom economy.[42]

6.4. CATALYSIS

Catalysis is an important element in achieving sustainable chemistry. Pharmaceutical and chemical manufacturing generates waste consisting mainly of solvents and inorganic salts, which result from the stoichiometric inorganic reagents used in organic synthesis. One possible solution is to replace inorganic reagents by green catalysis methodologies.[43] Catalysts can be used to increase the selectivity of a reaction but also for energy savings. The intervention of a catalyst in the chemical process provides an alternative mechanism in which the energy barrier is lowered.[18]

Catalysts can be mainly divided into two groups, heterogeneous and homogeneous.[18] Heterogeneous catalysed reactions are those where the catalyst is insoluble in the reaction medium.[44] Heterogeneous catalysts are usually made up of derivatives of insoluble transition metals or solid acid-base substances such as zeolites, which are aluminosilicates found in nature that can be also generated artificially to confer specific pore diameter and acid-base properties. In zeolite-catalysed reactions, the surface area per unit mass is an important parameter since the reaction takes place on the surface of the catalyst.[18] Since zeolites are insoluble in the reaction medium, they are easy to separate, recycle and reuse.

Unlike heterogeneous catalysis, in homogeneous catalysis the catalyst is homogeneously distributed in the reactive medium, which favours the degree of selectivity and the resistance to poisoning.[18] However, homogeneous catalysts have the disadvantages that are difficult to recover and recycle, apart from the additional cost of separating the catalyst from the desired product.

Apart from these two main categories, there are also other possible catalytic species that can usefully be applied for green chemistry, such as biocatalysts, phase transfer catalysts, photocatalysts and asymmetric catalysts.[26] In this respect, it should be noted that the Nobel Prize 2021 in Chemistry was awarded to Benjamin List and David MacMillan "for the development of asymmetric organocatalysis".[45] This type of catalysis is called to revolutionize pharmaceutical chemistry as a method of obtaining enantiomerically pure compounds in a very efficient way and is low-wasted.[26]

Here below, three recent examples are offered of application of heterogenous, homogeneous and organo-catalysis in the preparation of useful intermediates for antivirals.

6.4.1. Synthesis of 2-aminothiophenes via heterogeneous catalysis

In medicinal chemistry, heterocyclic rings are of great use because of the varied biological properties they confer. Among many others, the 2-aminothiophenes are 5-membered *S*-heterocycles which exhibit properties in antiviral, antifungal, antiproliferative and antibacterial applications.[46] For example, the compound **26** depicted in the figure 7 showed inhibitory activity against HSV-2 protease.[47]

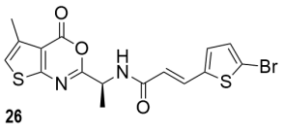


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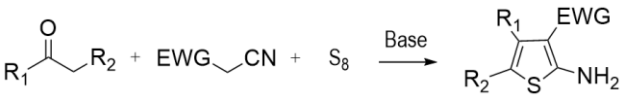
Figure 7. Structure of (*E*)-3-(5-Bromo-thiophen-2-yl)-*N*-[(S)-1-(5-methyl-4-oxo-4H-thieno[2,3-*d*][1,3]oxazin-2-yl)-ethyl]-acrylamide(**26**).[47]

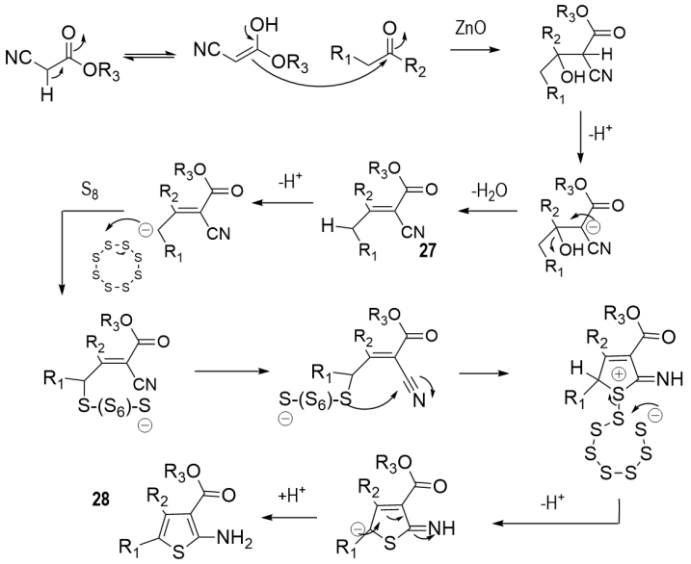
To synthesise **26**, a 2-aminothiophene (Scheme. 12) intermediate **28** was devised to be obtained by the Gewald method, a reaction of condensation of a ketone with an α-cyanoester in the presence of S_8 and a strong base catalyst.[46] The classical methodology was usually beset with several disadvantages, such as the use of expensive catalysts, long reaction times and toxic solvents.[46]



Scheme 11. General scheme of one-pot Gewald's reaction. [46]

As mentioned above, zeolites are a very useful catalytic material as they exhibit microporous and large surface areas, chemical and thermal resistance and high charge exchange capacities. These capabilities are explained by the Lewis or Bronsted acid sites that offer the solid structure and which can contribute to the reactions. Zeolites are a very cheap material and are found in abundance in nature although can contain high levels of impurities. In this context, clinoptilolite is a type of zeolite found in nature that belongs to the family of aluminosilicates with nano-sized pores and large surface areas, and active sites, and have a wide range of applications.[49]

Javadi *et al.*[48] described a Gewald-optimized process for the synthesis of **28** by using a novel nanocomposite catalyst, composed by ZnO deposited on the surface of nanoclinoptilolite (ZnO-NCP). The mechanism of reaction catalysed with ZnO-NCP was not clearly ascertained, but Scheme 12 shows a mechanism proposed by Tayebee *et al.*[50]. The α-cyanoester undergoes enolization due to the Lewis basic oxide sites of the nanocomposite,[49] to produce an aldol condensation with the ketone. Zn^{2+} probably catalysed this step by coordinating the carbonyl oxygen of the ketone and thus making it more electrophilic to the nucleophilic attack. This was followed by dehydration into compound **27**. This intermediate was then deprotonated into the enolate and reacted with S_8. The intramolecular nucleophilic attack of proximal sulphur on the cyanide group, followed by tautomerization into the aromatic ring ultimately formed the final compound **28**.[50]



Scheme 12. Proposed mechanism for the Gewald synthesis of 2-aminothiophene with ZnO-NCP as catalyst.[50]

As it shows this example, heterogeneous catalysts provide procedures compatible with green chemistry principles. The reactions can be carried out in less time and saving energy. Catalysts are also less corrosive than strong acids or bases, thus generating less waste to dispose of.

Besides, as these catalysts are solid and insoluble compounds, they are easier separated from the desired product and can be straightforwardly recycled. Notably in this above example, zeolite and ZnO were cheap and non-toxic compounds compatible with cells.[51]

6.4.2 Synthesis of Tenofovir via asymmetric transfer hydrogenation by using homogeneous catalysts

Tenofovir (Figure 8) is an acyclic nucleoside phosphonate drug that was approved in 2001 by FDA for the treatment of HIV infection, as inhibitor of viral reverse transcriptase,[52] and later in 2008 as a therapy for hepatitis B.[53]

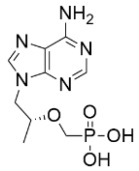
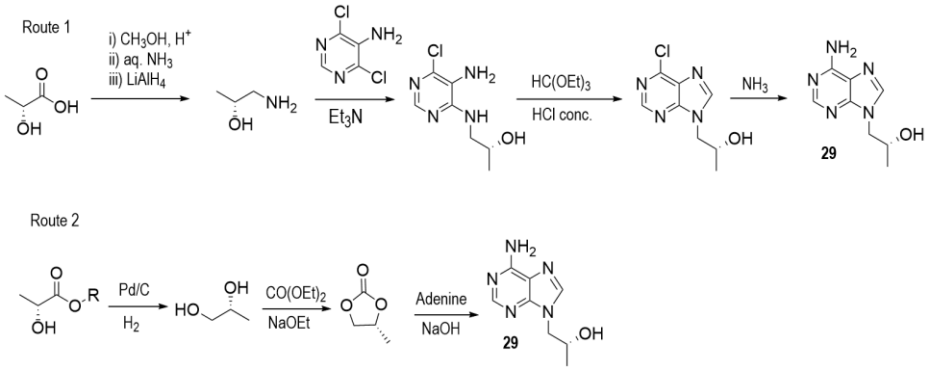


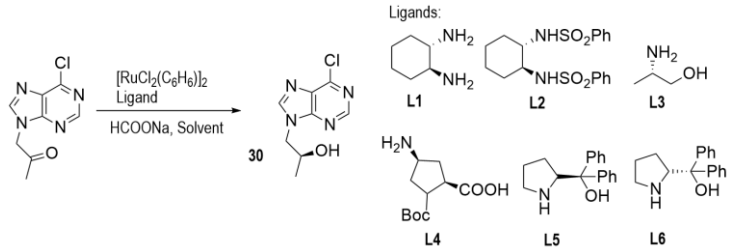
Figure 8. Structure of Tenofovir.

Most classical routes to tenofovir start by preparing chiral (*R)*-1-(6-amino-*9H*-purin-9-yl)propan-2-ol **29** from (*R*)-lactic acid. Scheme 13 depicts two common methodologies developed by Schaeffer and Vince[54] (route 1), and Holý and Masojídková[55] (route 2), respectively. Both routes are characterized for being carried out through several steps and with expensive reagents.[54,55]



Scheme 13. Synthesis of (*R*)-1-(6-Amino-9*H*-purin-9-yl)propan-2-ol (**29**) by Schaeffer and Vince[54] (Route 1), and Holý and Masojídková[55] (Route 2).

Recently, Zhang *et al*.[53] developed an alternative synthetic route for tenofovir from an achiral starting compound, which was stereoselectively transformed into **30** by an asymmetric transfer hydrogenation of ketones using a Ru (II) complex as a catalyst. They optimised the reaction by assaying 6 different ligands for metal complexation (**L1**-**L6**, see table 4). The reaction could be conveniently optimized to nearly quantitative yield and 97% ee by using **L5** ligand instead of **L1** and using acetonitrile instead of water (Table 4). The applicability and versatility of the methodology was further proved by preparing a variety of different purine derivatives, in moderate-to-high yields and >92% ee. The optical activity of the compounds proved that the methodology generated stereoselectively the *S*-isomer, the enantiomer of the intermediate needed for tenofovir.[53]



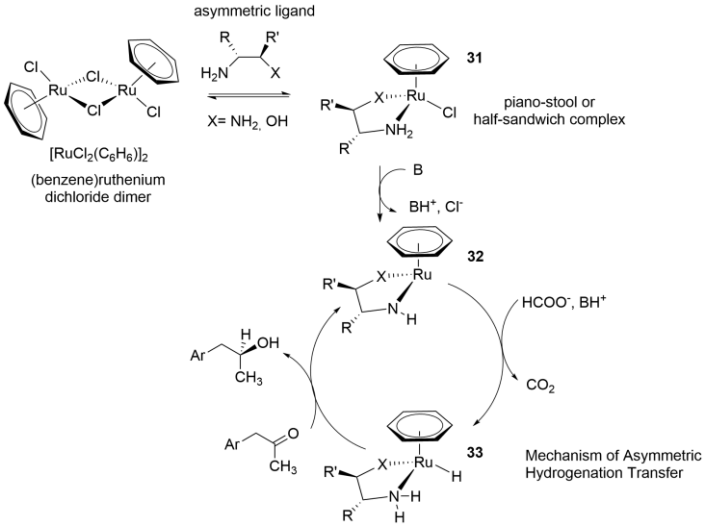
Ligand (6 mol %)	Conditions	Yield [%]	ee [%]
L1	$[RuCl_2(C_6H_6)]_2$, H_2O	70	58
L2	$[RuCl_2(C_6H_6)]_2$, H_2O	65	8
L3	$[RuCl_2(C_6H_6)]_2$, H_2O	80	15
L4	$[RuCl_2(C_6H_6)]_2$, H_2O	62	13
L5	$[RuCl_2(C_6H_6)]_2$, H_2O	40	75
L5	$[RuCl_2(C_6H_6)]_2$, CH_3CN	97	96
L6	$[RuCl_2(C_6H_6)]_2$, CH_3CN	45	97

Table 4. Optimization of the reaction conditions by Zhang *et al*.[53]

The authors further demonstrated the stereoselective nature of the catalytic mechanism by producing **29**, with an *R*-configuration, by using the ligand **L6**, which is the enantiomer of **L5**, with an enantiomeric excess of 97%.[53] (Table 4)

In the past decade, a variety of ruthenium complexes containing different combinations of mono- or bidentate ligands were developed to be used as chiral homogeneous catalysts.[56] In the

procedure of Zhang *et al.* the chiral catalyst was prepared *in situ* by reacting a ruthenium (II) complex and a chiral bidentate ligand (**L1**-**L6**, see table 4).[53] Here, the reduction of the ketone took place by asymmetric hydrogenation transfer, with formic acid acting as hydrogen donor and producing CO_2 as a by-product. In scheme 14, it is depicted a plausible mechanism for the catalytic cycle.[57]



Scheme 14. Mechanism proposed for the synthesis of (*R*)-1-(6-Amino-9*H*-purin-9-yl)propan-2-ol.

In this procedure, (benzene)ruthenium dichloride dimer, a Ru(II) species, reacted with the chiral bidentate ligand to form a piano-stool or half-sandwitch complex (**31**). The catalytic cycle started by base-mediated dehydrochlorination into complex **32** and followed with a reduction in which formate was the source of hydrogen, to produce the catalytic species **33**. The Ru(II) catalyst thus generated reduced the ketone by means of a six-membered transition state that guided the stereoselective reduction into the chiral alcohol (Scheme 14). Probably, high enantiomeric selectivity was due to the enantioface-differentiation ability of the Ru complex[58] via steric and electronic effects of the amine ligand, and edge-face C-H/π interactions. Figure 9 shows the transition states leading to the formation of the two possible enantiomers that explains why the *R* enantiomer was stereoselectively favoured (**TS1**) when **L5** ligand was used (see Table 4).[57]

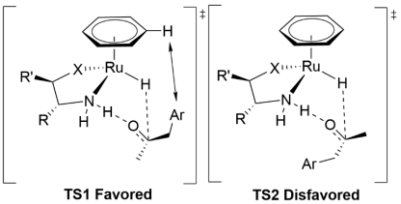


Figure 9. Transition states leading to the two enantiomers.[58]

This synthetic route here summarized provided chiral acyclonucleosides from an achiral starting compound by asymmetric transfer hydrogenation catalysed by Ru (II). It permitted a reaction to be carried out in mild conditions and few steps, and which quantitatively generated the desired product with high ee and avoided the separation of racemic mixtures.[53]

6.4.3. Synthesis of (S_P)-remdesivir by an organocatalysis reaction

The nucleoside analogue remdesivir (Figure 10) that was initially developed by Gilead Sciences to treat Ebola, was later found to have antiviral activity against other viruses. With the COVID-19 emergency, studies were carried out in the USA that showed that remdesivir had also activity against SARS-CoV-2. It acted by inhibiting RNA-dependent RNA polymerase, the viral enzyme responsible for the replication of viral RNA in infected cells.[59]

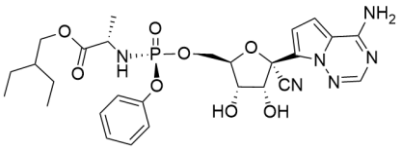


Figure 10. Structure of (S_P)-remdesivir.

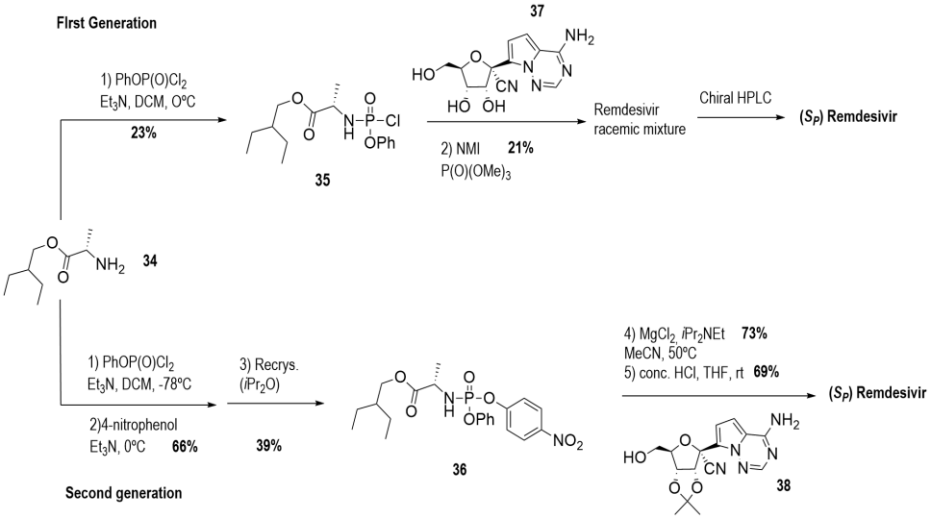
Remdesivir is a *N*-alanyl *O*-phenyl phosphoramidate prodrug derived of an α-cyano adenosine analogue in which the configuration of the stereogenic phosphorus is key to activity. The diastereomer S_P exhibited higher antiviral activity against SARS-CoV2 than the *R*p.[60] As will be seen below, the main challenge in synthesizing remdesivir was the production of the active diastereomer in the most efficient and selective way.

Siegel *et al.*[61] reported two synthetic routes for the phosphoramidate bond. The first-generation route started from *O*-2-ethylbutyl *L*-alaninate **34** which was first transformed into

chlorophosphoramidate **35**. Next, nucleoside **37** was coupled in the presence of *N*-methyl imidazole to obtain a mixture of diastereomers, which must be separated by chiral preparative HPLC to produce pure S_P isomer. (Scheme 15)

In a second-generation synthesis, amino acid **34** was first phosphorylated in two steps into a mixture of phosphoramidate diastereomers and S_P diastereomer **36** was obtained after recrystallisation. Similarly to the first route, nucleoside **38** was reacted with phosphoramidate **36** to generate (S_P)-remdesivir (Scheme 15).[61]

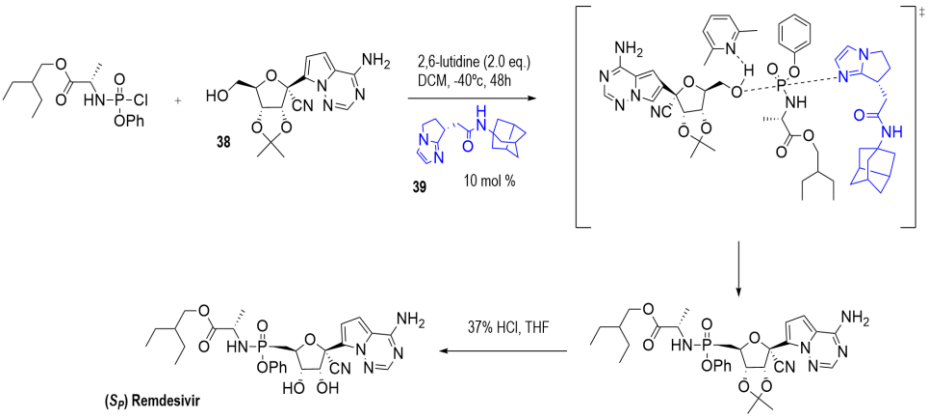
As can be seen in Scheme 15, the yields of these routes were low because of the steps of diastereomeric separation. Notably, the second route showed higher selectivity and efficiency.



Scheme 15. First and second-generation synthesis of (S_P)-remdesivir.[62]

Recently, Wang *et al*.[60] proposed a route to diastereoselectively synthesise remsdesivir via organocatalysis. They optimised the phosphorylation between chlorophosphoramidate **35** and nucleoside **38** by studying the effect of different chiral bicyclic imidazoles in order to produce the asymmetric synthesis of remdesivir. When the reaction was carried out uncatalysed, the conversion was 33%. It improved up to 62% when imidazole was present as a catalyst, although with no diastereomeric selectivity. This suggested to the authors that a nucleophilic catalyst was necessary to obtain higher yields but the chirality of both chlorophosphoramidate and nucleoside had nearly no impact on the stereochemical induction of P-stereocenter. Following this reasoning,

the group tested different chiral bicyclic imidazoles as catalysts in order to induce diasteroselectivity on phosphoramidate formation. When the sterically demanding adamantinyl catalyst **39** was used in the presence of lutidine at -40 ºC, they obtained high improvements in diastereoselectivity, with 91% de, and synthetic yield up to 73%.[60]



Scheme 16. Asymmetric synthesis of remdesivir catalysed by **39**.[62]

The unique structure of catalyst **39** used in this study allowed both good yields and excellent stereocontrol for asymmetric phosphorylation. Most probably, the steric effects between substituents make the catalyst best suited for asymmetric phosphorylation (the transition state that authors proposed for explaining diastereoselectivity is depicted in scheme 16). Using this method, the *Sp* isomer could be efficiently produced avoiding the HPLC separation or selective crystallization required in the two previous routes, with less waste and higher yields. Notably, in terms of green chemistry, this method also provided higher atom economy. Based on these benefits, it is not surprising that organocatalysis was recently applied to produce other antivirals in efficient and stereoselective way.[62]

7. CONCLUSIONS

Europe is preparing to implement programmes and regulations to achieve the reduction of the impact of human activities on the environment and human health. The pharmaceutical industry, one the greatest economic sector in Europe, is characterized by using a varied and complex chemistry, which is far from the sustainability criteria that are intended because of a high waste/product ratio and high energy expenditure.

Green chemistry offers a new approach for the development of more sustainable and effective drugs that contribute to improving people's quality of life and preserving the planet's natural resources.

The sustainable synthesis of antivirals is a promising and necessary area, especially in the current context of widespread climate change, due to the likely increase in pandemic episodes, such as the past COVID-19.

This TFG report reviews some examples of recent synthetic routes of antiviral drugs against HIV, HSV or SARS-CoV2, based on the principles of green chemistry. Namely, it is reported the use of multicomponent reactions, ultrasounds or photochemistry as energy sources, water and ionic liquids as alternative solvents, heterogeneous and homogeneous catalysts, and organocatalysis reactions. In these examples, biologically active compounds were produced efficiently, by reducing the consumption of reagents and solvents and carrying out highly atom economic reactions, thus minimising the generation of waste, increasing synthetic yields and the selectivity of the reactions.

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12. ACRONYMS

AIDS Acquired Immune Deficiency Syndrome

CFC Chlorofluorocarbons

COMU (1-(Cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethylamino-morpholino)-carbenium hexafluorophosphate

DCC *N,N*-Dicyclohexylcarbodiimide

DCM Dichloromethane

DDT DL-Dithiothreitol

DIEA *N*,*N*-Diisopropylethylamine

DMAP 4-(Dimethylamino)pyridine

DMF *N,N*-Dimethylformamide

DPDTC di-2-pyridyldithiocarbonate

EDCI 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

EPA U.S. Environmental Protection Agency

EU European Union

FDA U.S. Food and Drug Administration

HA Influenza Hemagglutinin

HATU 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate

HIV Human Immunodeficiency virus

HOPO 2-hydroxypyridine-*N*-oxide

HPLC High Performance Liquid Chromatography

HSV Herpes Simplex Virus

IN Retroviral integrase

MEK Methyl ethyl ketone

MTBE Methyl *tert*-butyl ether

NCP Nanoclinoptilolite

NMI	*N*-methylimidazole
NMM	*N*-methylmorpholine
PEG	Polyethylene glycol
RT	Reverse transcriptase
rt	Room temperature
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
UV	Ultraviolet Radiation
VOC	Volatile organic compounds
WHO	World Health Organization