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GREEN CHEMISTRY STRATEGIES IN DRUG DISCOVERY AND DEVELOPMENT

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Abstract
Background: The drug discovery and development process traditionally involve the use of hazardous chemicals, high energy consumption, and generates significant waste, leading to adverse environmental impacts. To address these concerns, the integration of green chemistry principles has gained attention in the field.
Aim: The purpose of this study was to evaluate and discuss the implementation of green chemistry strategies in the field of drug discovery and development.
Method: Green chemistry strategies included the use of computational methods and high-throughput screening to prioritize compounds, the utilization of greener solvents and reaction conditions, the implementation of innovative techniques like flow chemistry to reduce waste, and the design of molecules with reduced toxicity and improved biodegradability.
Result: By adopting green chemistry strategies, drug discovery and development processes can minimize resource consumption, waste generation, and the use of hazardous chemicals. This approach also leaded to improved efficiency, safety, and sustainability.
Conclusion: The incorporation of green chemistry principles in drug discovery and development offers significant potential for the pharmaceutical industry to develop safer, more effective drugs while reducing their environmental impact. Implementing these strategies promotes a greener and more sustainable future for drug development.

Keywords: Green chemistry, Sustainability, Greener solvents, Toxicity reduction

INTRODUCTION

Green chemistry, also known as sustainable chemistry, is a scientific approach that aims to design and develop chemical products and processes that minimize the use and generation of hazardous substances. It focuses on the principles of environmental sustainability, resource efficiency, and human health protection (1). In recent years, green chemistry strategies have gained significant attention and importance in various industries, including drug discovery and development.

The field of drug discovery and development involves the identification, synthesis, and optimization of novel chemical compounds with therapeutic potential. Traditionally, this process has relied on the extensive use of organic solvents, energy-intensive reactions, and generation of large amounts of chemical waste, which pose significant environmental and health hazards (2). However, with the

growing recognition of the need for sustainable practices, researchers and pharmaceutical companies are increasingly adopting green chemistry principles to reduce the environmental impact of drug development while maintaining high standards of efficacy and safety.

Green chemistry strategies in drug discovery and development encompass a wide range of approaches, including the design of greener synthetic routes, development of environmentally friendly solvents, utilization of renewable feedstocks, and application of efficient catalytic processes (3). These strategies aim to minimize or eliminate the use of hazardous substances, reduce energy consumption, improve reaction yields, and decrease waste generation throughout the drug development process.

Environmental Benefits of Green Chemistry Strategies

The incorporation of green chemistry strategies in drug discovery and development offers numerous environmental benefits, contributing to sustainability and reducing the environmental footprint of the pharmaceutical industry (4). One significant advantage is the minimization of resource consumption. By employing computational methods and high-throughput screening techniques, researchers can prioritize and select drug candidates with higher chances of success, thus reducing the need for extensive synthesis and testing, and conserving valuable resources. Additionally, the use of greener solvents, such as water or bio-based alternatives, reduces the reliance on hazardous and environmentally damaging solvents, resulting in a decrease in both resource consumption and waste generation (5).

By adopting innovative techniques like flow chemistry, reactions can be performed continuously in a controlled flow system, minimizing the generation of unwanted byproducts and increasing process efficiency (6). Moreover, the recovery and recycling of valuable intermediates and catalysts play a crucial role in waste reduction and resource conservation. These recycling processes minimize the need for additional synthesis steps, leading to more sustainable and eco-friendly drug development.

By optimizing reaction conditions, such as temperature, pressure, and catalytic systems, energy consumption can be reduced, leading to a decrease in greenhouse gas emissions and overall environmental impact. The use of milder reaction conditions also reduces the formation of hazardous byproducts, thereby enhancing the safety and sustainability of the drug development process (7).

Challenges and Considerations of Green Chemistry

The adoption and implementation of green chemistry principles in drug discovery and development present certain challenges that need to be addressed. One key challenge is the need for education and awareness among researchers and industry professionals regarding the principles and benefits of green chemistry (8). It requires a shift in mindset and a willingness to embrace new approaches and methodologies that prioritize sustainability.

The availability and accessibility of greener alternatives, such as solvents, reagents, and catalysts, can pose a challenge. The pharmaceutical industry relies heavily on well-established and widely used chemicals and processes, making it challenging to transition to more sustainable options (9). The development and commercial availability of greener alternatives need to be encouraged and supported through research and development efforts and collaborations between academia, industry, and regulatory bodies (10).

Integrating green chemistry principles into existing drug development processes can be complex due to the intricate nature of the pharmaceutical industry. Drug discovery and development involve a multitude of interconnected stages, including synthesis, formulation, and manufacturing, each with its unique set of challenges and considerations (11). Green chemistry strategies need to be seamlessly integrated into these processes without compromising the safety, efficacy, and quality of the final

drug product.

Regulatory considerations play a vital role in the integration of green chemistry practices. Regulatory frameworks need to be updated and aligned to support the adoption of greener alternatives and encourage sustainable practices (12). Collaboration between industry stakeholders, regulatory agencies, and policymakers is crucial in establishing guidelines and incentives that promote the integration of green chemistry into drug development processes.

Problem Statement

The problem at hand is the limited knowledge and implementation of green chemistry practices in drug discovery and development. Although green chemistry offers innovative scientific solutions to environmental problems, there is a need to bridge the gap between theoretical principles and their practical application in the laboratory. This requires identifying alternative and environmentally friendly reaction conditions, optimizing reaction rates, and reducing the overall temperature of reactions while maintaining high standards of efficacy and safety.

The pharmaceutical industry faces unique challenges in adopting green chemistry strategies, including the complexity and diversity of drug molecules, the need for efficient synthesis routes, and stringent regulatory requirements. Overcoming these challenges and integrating green chemistry principles into drug discovery and development processes requires a comprehensive understanding of the potential benefits, limitations, and practical considerations involved.

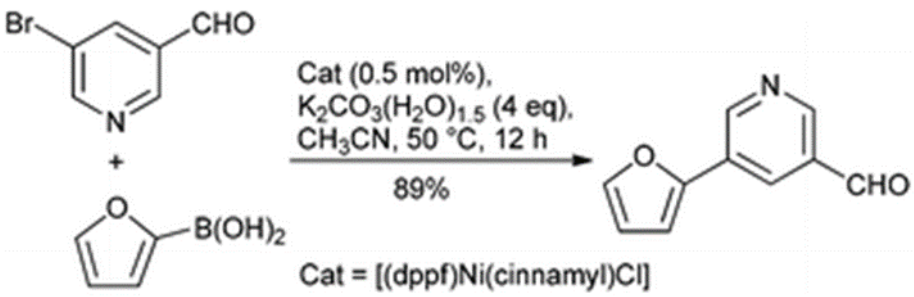
Effective methodology utilizing cheap/sustainable metals

The use of expensive and potentially toxic transition metals in catalytic processes poses challenges for sustainability. Boit is focused on exploring non-precious metals like nickel, copper, and iron as catalysts due to their lower cost, lower toxicity, and potential for broader substrate scope. These metals offer new reactivity and can enable the coupling of challenging substrates while reducing the environmental impact (13).

Green chemistry research aims to develop methods that can efficiently couple important and challenging substrates, such as heterocycles and sterically-encumbered compounds. By expanding the range of electrophilic coupling partners in C-C and C-N bond formation reactions, researchers can enable the synthesis of complex molecules in a more sustainable manner.

Cobalt is a metal of interest due to its greater earth abundance compared to precious metals like palladium. However, its current short supply, primarily due to its use in batteries, and tighter guidelines regarding its toxicity require further investigation. Developing cobalt catalysis methods with a focus on green chemistry principles could offer potential benefits for industrial applications.

Studies on utilizing nickel in cross-couplings have shown promising results. While previous couplings using nickel catalysts had high catalyst loadings and limited scope, recent advancements have addressed these issues. Ge and Green, developed a single-component catalyst system that enables couplings under mild conditions with low catalyst loadings (0.5 mol%) (14).



Scheme 1 Single component Ni

Wang et al. used commercially available Ni (Cl)2(PCy3)2 as a pre-catalyst for Suzuki coupling, examining over 30 solvents to identify greener alternatives. Tert-amyl alcohol and 2-MeTHF were selected for further studies, providing quantitative yields, developed a NiCl2/morpholine based system for coupling various aryl and heteroaryl chlorides with aryl- and alkenyl-boronic acids, although higher Ni loading (10 mol%) was required, the residual Ni in the final products was shown to be <9.7 ppm. These advancements pave the way for the use of more cost-effective nickel-based catalysts in environmentally friendly cross-coupling reactions (15).

According to Tian et al. conducted a study comparing the use of nickel (Ni) and palladium (Pd) catalysts in a Suzuki reaction to scale up the production of the Pi3K inhibitor, GDC-0941. They observed a 19% increase in yield with the Ni-catalyzed protocol compared to the optimized Pd-catalyzed method. Importantly, they also demonstrated that the Ni catalyst could be easily removed using an aqueous ammonia wash, while the Pd methodology required the use of scavenger resins. By employing the Ni-mediated reaction, they successfully obtained 54 kg of the desired material (16).

Over the past decade, significant progress has been made in developing reagents and approaches for fluorination, offering greater flexibility to medicinal and development chemists. Notably, the development of nucleophilic deoxyfluorinating reagents has shown improved stability and selectivity, replacing older reagents like SF4. However, challenges remain, such as the need for additional promoters and the use of unfavorable solvents, as well as limited availability and issues with elimination in some cases.

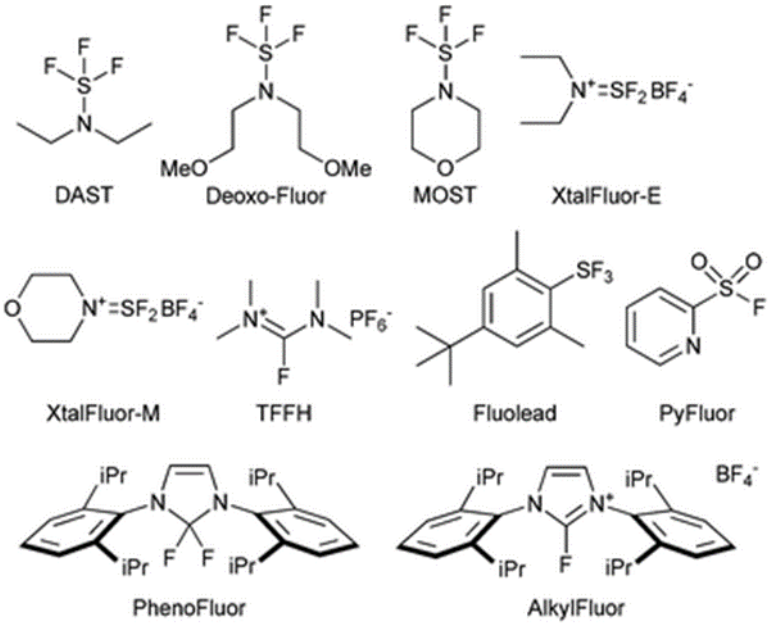


Figure. 1 The evolution of reagents for deoxyfluorination.

To address safety concerns, new reagents with improved safety profiles, such as Xtalfluor-E and -M, Fluolead, TFFH, PhenoFluor, PyFluor, and AlkylFluor, have emerged. Nevertheless, there is still room for improvement, especially in developing reagents for introducing 18F for PET-labeling. Advancements in green fluorination have provided valuable options for introducing fluorine in a more sustainable and selective manner.

Alternatives for oxidations

One promising area of research is photocatalytic oxidation, which has seen significant growth in recent years. These approaches utilize molecular oxygen or air as the oxidant, visible light or sunlight as the photochemical activator, and can be conducted in aqueous media, reducing safety concerns associated with flammable solvents. Catalysts are typically supported on solid supports, nanoparticles, or quantum dots doped with appropriate metals (17). While the preparation of these materials can be laborious, their potential for repeated recovery and reuse mitigates their impact. Although oxidations of alcohols to aldehydes, ketones, and esters have been demonstrated, further

exploration is needed to expand their application within the pharmaceutical industry.

Another noteworthy transformation is the oxidation of amines to imines. Catalytic systems involving alloxan as a co-catalyst, with synthetic Flavin or Cu(I) salt as the catalyst, have been successfully employed. Air serves as the terminal oxidant, and the reactions are typically carried out at ambient temperature and pressure in solvents like acetonitrile. While these transformations mostly yield highly symmetric imine products, the Cu(I) system has shown the potential to generate asymmetric imines, albeit with lower yield and selectivity. Adaptations would be necessary when working with more complex substrates used in the pharmaceutical industry to address solvent concerns.

To address safety issues associated with using air as a terminal oxidant in flammable solvents, alternative oxidants that produce benign by-products are sought after, with hydrogen peroxide being particularly attractive. This reagent acts as an effective oxidant, generating water as the by-product. In combination with 0.2 mol% CuSO4·5H2O and benzylic or primary alkyl amines in aqueous conditions, moderate to high yields of pseudo-symmetric imines can be obtained.

Flow reactors offer another approach to achieve viable aerobic oxidation in flammable solvents. Controlling the heat generated during aerobic oxidations is crucial due to their exothermic nature. Flow reactors provide a minimal volume for the reaction and a higher surface-to-volume ratio compared to batch processing, enabling more efficient heat management and avoiding the presence of a headspace. By controlling flow rate and channel length, product stability can be enhanced, and the potential for runaway reactions can be reduced by minimizing contact time with the harsh reaction conditions within the flow reactor.

From the research of Jordan et al. were already highlighting the need for replacing dipolar aprotic solvents, recognizing the challenges associated with their handling and disposal. However, since then, significant regulatory hurdles have arisen in Europe (18). N-Methylpyrrolidinone (NMP), N,N-dimethylacetamide (DMAc), and N,N-dimethylformamide (DMF) have been nominated as substances of very high concern (SVHC) and are under scrutiny as part of the European Union REACH regulations due to their potential reproductive toxicity. These nominations were made between 2011 and 2012. The specific restrictions or authorizations for these solvents are yet to be determined, but any of these outcomes will undoubtedly make industrial use of NMP, DMAc, or DMF more challenging in the future.

A survey conducted by Ashcroft et al. analyzed the use of these solvents in the process chemistry journal Org. Process Res. Dev. from 1997 to 2012. The survey examined the percentage of processes utilizing these solvents over time, investigated the reasons for their usage, and proposed strategies for minimizing their use. However, to make further progress in this solvent class, the development of new solvents is imperative. These alternative solvents should possess the desired polarity to dissolve polar materials while being non-toxic (19).

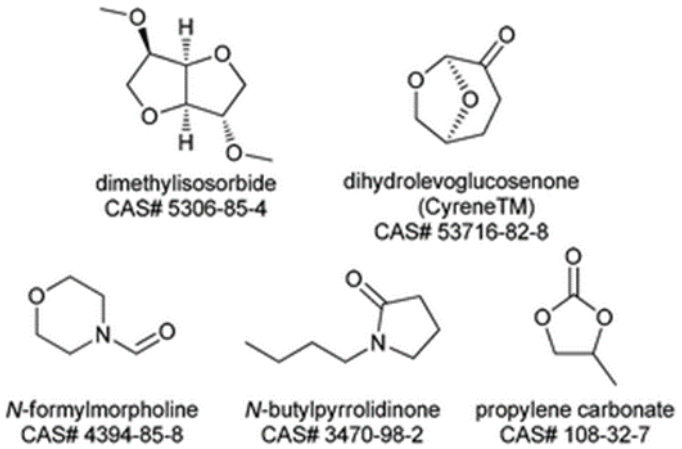


Figure. 2 Potential dipolar aprotic solvent replacements.

Due to the environmental and health risks associated with dipolar aprotic solvents such as N-methylpyrrolidin-2-one (NMP), N,N-dimethylformamide (DMF), and N,N-dimethylacetamide (DMAc), there is a growing need for suitable replacements that offer lower risks and reduced environmental impact while maintaining their utility from a chemical perspective.

Several alternatives have emerged as potential replacements for dipolar aprotic solvents. One option is the use of greener solvents, such as bio-based solvents derived from renewable resources. These solvents, including terpenes, ionic liquids, and deep eutectic solvents, offer lower toxicity profiles and reduced environmental impacts. They are derived from natural sources, making them more sustainable and biodegradable, thus addressing the concerns associated with traditional dipolar aprotic solvents.

Another approach involves utilizing polar aprotic solvents that have lower toxicity and reduced environmental impact compared to their dipolar counterparts. Examples include dimethyl sulfoxide (DMSO) and ethyl acetate, which offer similar solubilizing abilities and polarity but with improved safety profiles. These solvents have been extensively studied and are considered safer alternatives for various chemical reactions and processes.

Additionally, Zhang et al. have explored the use of water as a solvent or co-solvent in reactions that traditionally employ dipolar aprotic solvents. Water is a sustainable and readily available solvent with minimal environmental impact. By modifying reaction conditions and using appropriate catalysts or surfactants, water can be used effectively in many reactions that require high polarity and solubility (20).

Green chemistry principles have led to the development of alternative reaction strategies that minimize or eliminate the need for dipolar aprotic solvents. Examples include the use of microwave-assisted reactions, flow chemistry, and solid-phase reactions, which offer more sustainable and efficient synthetic routes with reduced reliance on traditional solvents.

Future opportunities

In the realm of green chemistry, there are exciting future opportunities for developing greener approaches to peptide and oligonucleotide syntheses in the field of drug discovery and development. Peptides and oligonucleotides are essential components of many therapeutic agents, but their synthesis often involves multiple steps, the use of hazardous reagents, and generates substantial waste (21).

One potential avenue for greener peptide synthesis is the utilization of alternative coupling strategies that eliminate or reduce the use of toxic reagents. Traditional methods, such as solid-phase peptide synthesis, commonly rely on the use of coupling agents and protecting groups that can generate hazardous waste (22). Exploring alternative coupling chemistries, such as bioorthogonal reactions or enzyme-catalyzed processes, can significantly reduce or eliminate the need for such reagents, thereby decreasing the environmental footprint of peptide synthesis.

The adoption of greener solvents and reaction conditions is a key aspect of green peptide and oligonucleotide syntheses. Traditional methods often employ organic solvents that are harmful to human health and the environment. Exploring water-based reactions and the use of bio-based solvents can significantly reduce the environmental impact while maintaining high reaction efficiency (23). Developing more sustainable separation and purification methods for peptides and oligonucleotides, such as membrane-based techniques or chromatographic approaches with reduced solvent consumption, can further contribute to greener processes.

Incorporating green chemistry principles in peptide and oligonucleotide synthesis also extends to waste reduction and recycling. Implementing strategies such as catalytic reactions or flow chemistry

can minimize the generation of unwanted byproducts, leading to cleaner and more efficient syntheses (24). Exploring methods for recycling and reusing catalysts, reagents, and solvents can significantly reduce resource consumption and waste generation, improving the overall sustainability of the synthesis process.

CONCLUSIONS

The implementation of green chemistry strategies in drug discovery and development holds great promise for promoting sustainability, minimizing environmental impact, and improving overall process efficiency. The utilization of computational methods and high-throughput screening techniques enables the prioritization of drug candidates, reducing the need for extensive synthesis and testing and conserving valuable resources. The adoption of greener solvents and reaction conditions, such as water-based or bio-based alternatives, helps minimize the use of hazardous chemicals, reduces waste generation, and enhances process efficiency.

Incorporating innovative techniques like flow chemistry and process intensification contributes to safer reactions with reduced energy consumption and waste production. By designing molecules with reduced toxicity and improved biodegradability, the pharmaceutical industry can develop safer and more environmentally friendly drug candidates. Challenges related to the adoption and implementation of green chemistry principles, as well as the integration into existing drug development processes, must be addressed through education, collaboration, and regulatory support. Through overcoming these challenges and embracing green chemistry, the pharmaceutical industry can pave the way for a more sustainable and environmentally conscious approach to drug discovery and development, benefiting both human health and the planet.

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