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Perspective

Harnessing the 12 Green Chemistry Principles for Sustainable Antiparasitic Drugs: Toward the One Health Approach

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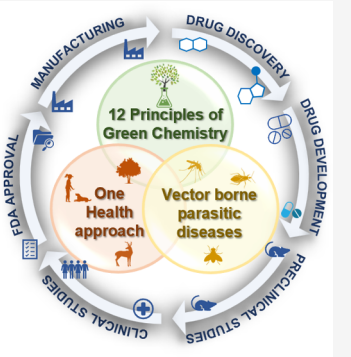
ABSTRACT: Antiparasitic drug development stands as a critical endeavor in combating infectious diseases which, by affecting the well-being of humans, animals, and the environment, pose significant global health challenges. In a scenario where conventional pharmacological interventions have proven inadequate, the One Health approach, which emphasizes interdisciplinary collaboration and holistic solutions, emerges as a vital strategy. By advocating for the integration of One Health principles into the R&D pharmaceutical pipeline, this Perspective promotes green chemistry methodologies to foster the development of environmentally friendly antiparasitic drugs for both human and animal health. Moreover, it highlights the urgent need to address vector-borne parasitic diseases (VBPDs) within the context of One Health-driven sustainable development, underscoring the pivotal role of medicinal chemists in driving transformative change. Aligned with the Sustainable Development Goals (SDGs) and the European Green Deal, this Perspective explores the application of the 12 Principles of Green Chemistry as a systematic framework to guide drug discovery and production efforts in the context of VBPD. Through interdisciplinary collaboration and a constant commitment to sustainability, the field can overcome the challenges posed by VBPD while promoting global and environmental responsibility. Serving as a call to action, scientists are urged to integrate One Health concepts and green chemistry principles into routine drug development practices, thereby paving the way for a more sustainable R&D pharmaceutical pipeline for antiparasitic drugs.



KEYWORDS: *green chemistry, antiparasitic drugs, vector-borne parasitic diseases, sustainable development goals, One Health*

Globally, about 25% of the population suffers from one or more parasitic infections, of which vector-borne parasite diseases (VBPDs) are a major concern. Among them, zoonotic diseases affecting humans and animals are drawing increased attention. These diseases are caused by parasites transmitted through the bites of vectors, such as mosquitoes, ticks, fleas, sandflies, and triatomine bugs.[1] The parasites responsible for these infections include protozoa, helminths, and endoparasites. Notorious VBPD examples are malaria, caused by *Plasmodium* parasites; leishmaniasis, caused by *Leishmania* species; Chagas disease, caused by *Trypanosoma cruzi*; human African trypanosomiasis (HAT), caused by *Trypanosoma brucei rhodesiense* and *T. b. gambiense*; and animal African trypanosomiasis (AAT), caused by related trypanosome species including *T. b. brucei*, *T. congolense*, *T. evansi*, and *T. vivax*. The geographical distribution of VBPD is linked to specific regions with favorable environmental conditions for both the vectors and the parasites they carry. Since the 2000s, some appeared in new regions and are emerging and/or re-emerging at an increasing pace. Studies emphasized that the interactions among pathogens, human and animal hosts, and the environment play a key role for the emergence or re-emergence of VBPD.[2] A suite of factors such as climate change, major catastrophic events, deforestation, urbanization, and global travel contribute to spread and resurgence, posing a significant public health threat.[3]

Despite advancements in medical research and drug development, current pharmacological treatments for these diseases continue to fall short of the need. Inadequacy stems from various factors, including the ability of parasites to develop resistance, intricate life cycles of the vectors involved, and lack of effective vaccines. As a result, the burden of VBPD persists, leading to substantial morbidity and mortality worldwide. A possible way out of the longstanding impasse of VBPD management is the One Health approach.[4] This is an integrated, unifying approach that aims to sustainably balance and optimize *the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems)*, by recognizing that they *are*

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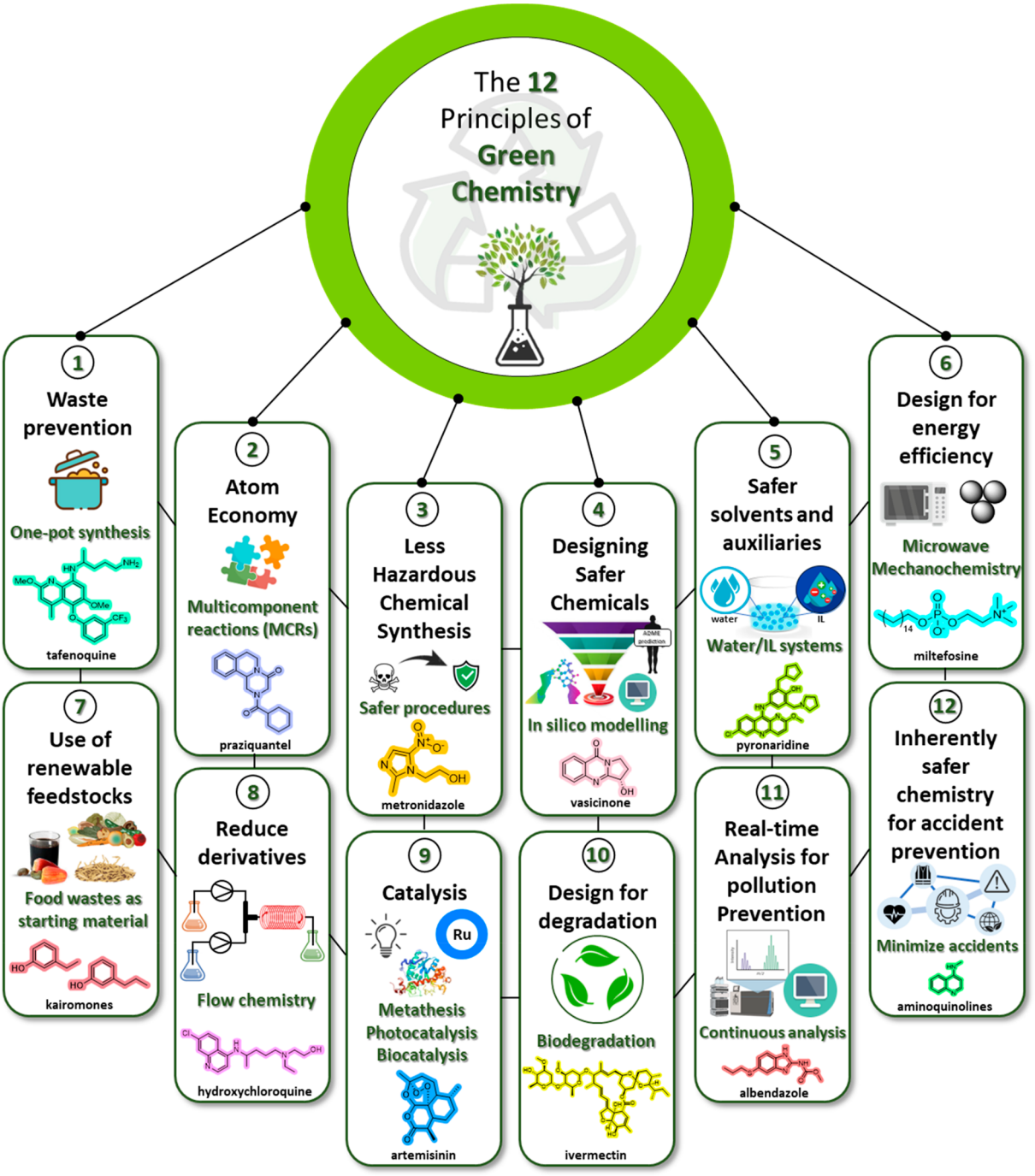

Figure 1. Cartoon representation of the 12 Principles of Green Chemistry applied to the antiparasitic research and development pharmaceutical pipeline.

closely linked and interdependent.[5] In a simplistic but effective way, experts say that there is no healthy life on a sick planet. Building on such a holistic view, One Health encourages collaboration among diverse disciplines, promoting unified efforts expected to provide more sustainable knowledge, experiences, and a better constituency in health policy. The upcoming WHO VBPD roadmap for 2021−2030 underscores the necessity of a One Health approach for achieving its ambitious control and elimination targets.[6]

One Health[6−8] is not completely novel, as already in the 19th century the famed pathologist Rudolf Virchow recognized the importance of health issues at the interface of humans, animals, and the environment.[9] However, surely novel is its use in the context of the R&D pharmaceutical pipeline. A PubMed search (February 2024) for articles containing the keywords "One Health" and "vector-borne parasitic diseases" returned 1.074 results; by limiting the scope to the terms "One Health" and "drug development", just 79 results have been retrieved. Remarkably, 51% have been issued in the last 3 years, revealing a recent increasing trend. Most of these articles deals with policy and health issues and focuses on Covid-19. When the search is further restricted to the early phase of the pipeline and PubMed interrogated as "One Health" and "medicinal chemistry", the results are just 13 (Figure S1).

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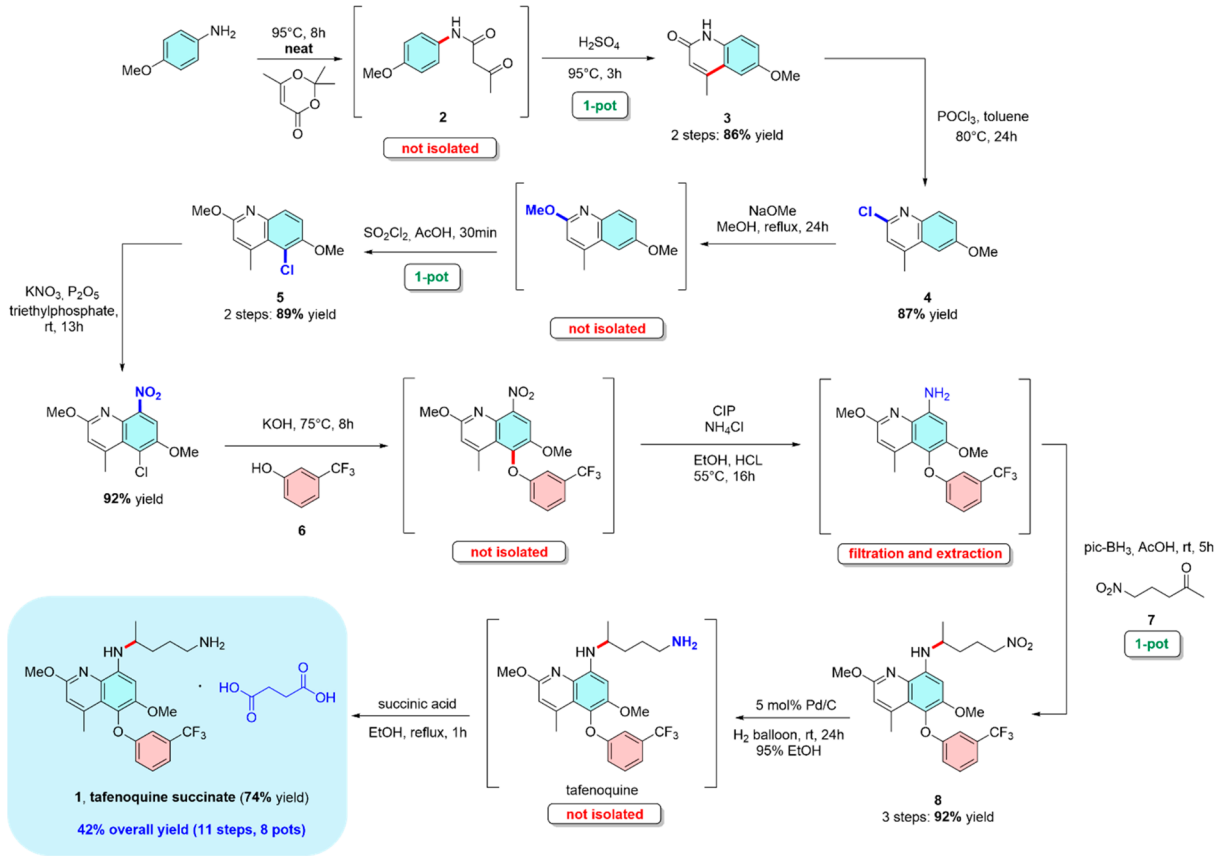
Scheme 1. 11-Step, 8-Pot Synthesis of Tafenoquine Succinate Showing a 3-Fold Decrease in Waste Creation



How can we, as medicinal chemists, implement the One Health concepts into our daily R&D efforts for new antiparasitic drugs? In our opinion, this is the best time for successful One Health approaches, due to the current context of *sustainable development*.[10,11] In fact, January 2016 marked the universal kick off toward the 15-years era of the Sustainable Development Goals (SDGs). Specifically, SDG number 3[12] aspires to ensure health and well-being for all, including a strong commitment to end the epidemics of malaria. In parallel, the Pharmaceutical Strategy for Europe, in line with the European Green Deal, advocates the development of high-quality, safe, effective, greener, and affordable medicines to ensure access and to address unmet medical needs.[13] Nowadays, *sustainability-by-design* is a key concept toward a more sustainable and responsible approach throughout the entire R&D pharmaceutical pipeline, including drug discovery, delivery, manufacturing, packaging, advertising, and marketing.[14,15]

In 2019, we realized that medicinal chemists were *challenged not only to create more effective and less toxic drugs but also to do so in a timely, green, and sustainable fashion*.[16] This is particularly pressing for those diseases disproportionately affecting low-income populations, such as the poverty-related parasitic diseases. Thus, ensuring access to medicines, which includes their availability and affordability, is a significant concern in global public health. Recently, a consortium of European Universities has been built to advocate a global, systematic approach and places the emphasis on sustainability already in early stages of the R&D pharmaceutical pipeline, such as drug discovery.[17]

To make a step further toward One Health, we believe that the emerging green and sustainable practices in medicinal chemistry[18−20] are a great opportunity for developing new drugs for animal and human VBPDs, produced by alternative and environmentally friendly methods. In other words, we want to use chemistry for curing both animals and humans but not at the expense of the environment.

Herein, to call for a systematic approach and emphasize the need of One Health-driven sustainability concepts in VBPD, we critically investigate the relative greenness of drug development efforts in the field reported in the 1990−2023 time frame. Particularly, this Perspective has been organized according to the "12 Principles of Green Chemistry"[21] by discussing examples of R&D pharmaceutical endeavors harnessing at least one of these principles (Figure 1). The examples (all dealing with molecules or marketed drugs with therapeutic potential against VBPDs) have been selected for illustrative purposes and have not been subjected to further impact assessments. We hope to lay the basis for and further inspire scientists to put into routine practice green chemistry principles toward a sustainable pipeline for VBPDs, in line with One Health.

THE 12 PRINCIPLES OF GREEN CHEMISTRY AND DRUG DEVELOPMENT FOR VBPDS

The U.S. Pollution Prevention Act of 1990 was probably the stimulus for chemists to become environmentally aware. In the late 1980s, as a result of an increasing environmental awareness, emphasis gradually switched from "*end of pipe*" waste treatment to pollution prevention at source, recognizing that chemistry is the solution rather than the problem. This awareness culminated in the introduction of the term "Green Chemistry" at the US Environmental Protection Agency (EPA) in the early 1990s. Green Chemistry is defined as the "*design of chemical products*

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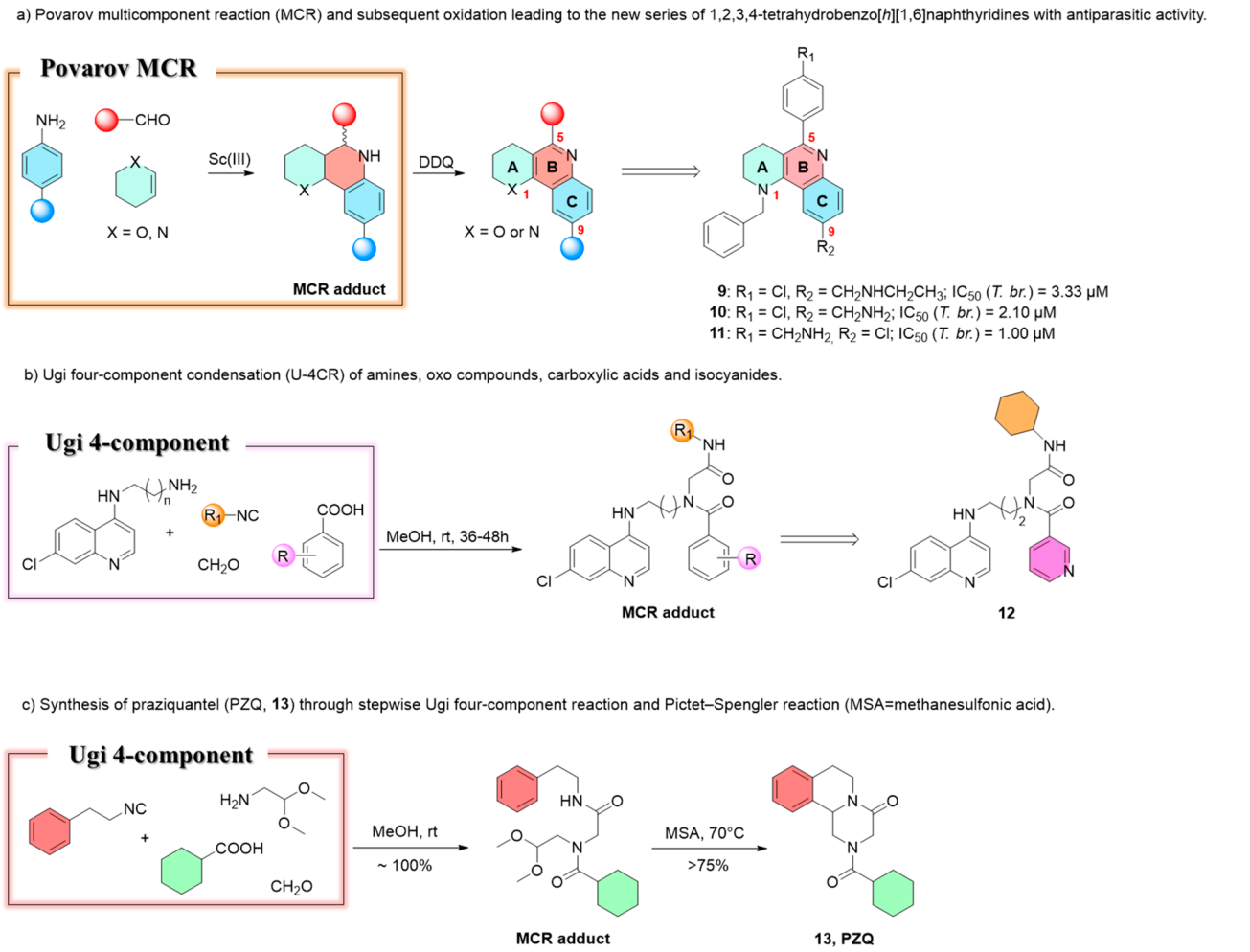

Figure 2. Multicomponent reactions (MCRs) were exploited for the synthesis of antiparasitic drugs.

using (preferably renewable) raw materials and processes to reduce or eliminate the use and generation of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products". This definition and the concept of Green Chemistry gained formal recognition with the publication of the "12 Principles of Green Chemistry" by Paul T. Anastas and John C. Warner in 1998.[21] The US Pollution Prevention Act of 1990 focused on the need of environmental pollution prevention rather than waste remediation, recognizing that waste prevention at the source not only eliminates the cost of waste treatment but actually strengthens economic competitiveness through more efficient use of raw materials.[22] In the last 25 years, such concept has become firmly entrenched in both industry and academia. Moreover, increasing pressure from governmental restrictions, such as the REACH regulation in the EU, requires chemical manufacturers to reduce their environmental footprint, providing additional motivation for the development of greener routes to active pharmaceutical ingredient (API) synthesis.[23] Although implementation remains challenging, experts from pharma see manifold opportunities in making APIs greener in different stages along the R&D process. Collaboration across pharmaceutical companies, authorities, and academia as well as financial, social, and regulatory incentives are viewed as highly promising to facilitate transition.[24]

1. Waste Prevention. *"It is better to prevent waste than to treat or clean up waste after it has been created."*[25]

At the heart of green chemistry lies the principle of waste prevention. Traditional chemical processes often generate copious amounts of byproducts, contributing to environmental pollution. A green chemist aspires to reduce the burden on ecosystems by design processes that minimize or eliminate waste or by excluding materials that will not be part of the desired final molecule. Specifically, the use of solvents, catalysts, and auxiliaries in a chemical reaction as well as handling solvents for separation and purification steps must be reconsidered. A first green metric dealing with waste prevention is the *E*-factor proposed in 1991.[26] The *E*-factor is the ratio of kg waste to kg product, whereby waste was defined as "*anything that is not the desired product*".[27] A higher *E*-factor means more waste and, consequently, greater negative environmental impact, while lower *E*-factors reflect low process materials input, cost reduction of hazardous and toxic waste disposal, improved capacity utilization, and reduced energy demand.

An important example of the effective application of waste prevention in antiparasitic drugs is the synthesis of tafenoquine, recently approved by the US Food and Drug Administration as the first new single-dose treatment for *Plasmodium vivax*. Differently from the previous synthetic routes, where many steps and toxic reagents represented big limitations, Lipshutz's team successfully managed to develop a green and economically attractive synthesis of tafenoquine succinate (**1**, Scheme 1).[28] Specifically, *N*-(4-methoxyphenyl)-3-oxobutanamide **2** has been obtained in a two-step one-pot synthesis starting from 4-

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methoxy aniline and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, following Sheldon's philosophy that "*the best solvent is no solvent*" (see principle #5).[29] Without isolation, **2** was converted to the desired 6-methoxy-4-methylquinolin-2(1*H*)-one **3** via Knorr quinoline synthesis in acidic media. Then, chlorination was performed in the presence of $POCl_3$ and toluene, which was nicely recovered, minimizing the generation of organic waste. The 2-chloroquinoline intermediate **4** served as substrate for another two-step one-pot reaction (S_NAr with an excess of anhydrous sodium methoxide and chlorination with sulfuryl chloride in acetic acid) that afforded **5**. Next, the *in situ* nitration (generation of N_2O_5 via dehydration of KNO_3 with P_2O_5) was followed by a three-step, one-pot sequence (neat S_NAr with the phenol **6**; nitro reduction to amine in the presence of carbonyl iron powder (CIP), ethanol, and conc. hydrochloric acid; reductive amination with ketone **7** in the presence of α-picoline borane as a hydride source) leading to **8**. Final nitro reduction with Pd/C under H_2 pressure and precipitation of the succinate salt released desired molecule **1**. When compared to the one previously reported by GSK, this alternative and environmentally friendly route showed a 3-fold decrease in waste creation, with a low value of the *E*-factor (E = 17 vs E = 69 of GSK).

2. Atom Economy. *"Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product."*[25]

Atom economy (AE) refers to the enhancement of the reaction efficiency by reducing the depletion of raw materials. The AE metric[26] is a useful tool for rapid evaluation of different routes, as it is calculated by dividing the molecular weight of the product by the total of the molecular weights of all substances formed in the stoichiometric equation for the reaction involved. In this context, chemical transformations like cycloadditions, molecular rearrangements, and isomerizations are intrinsically atom-economical since 100% of the atoms in the reactants remain in the desired product. Similarly, multicomponent reactions (MCRs) are atom economic, as most atoms of the reactants, if not all, are found in the product. In addition, the simultaneous association/dissociation of multiple bonds in a one-pot manner offers the opportunity to save organic solvents and chromatographic stationary phases and reduces waste generation, guaranteeing efficiency and sustainability (see principles #1 and #6). Furthermore, MCRs also offer the advantage of accessing small molecules with broad structural diversity and molecular complexity in an efficient and rapid manner.[30,31] As such, their use is increasingly growing in drug discovery programs, including those within the antiparasitic field.

In 2015, Muñoz-Torrero's group reported a multicomponent Povarov reaction to obtain three tricyclic derivatives showing antiprotozoan activities.[32] Specifically, this transformation requires a cyclic enamide as an activated olefin, resulting in ring A, an aromatic aldehyde releasing the substituent at position 5 (ring B), and an aniline, which affords the ring C with the substituent at position 9 under $Sc(OTf)_3$ catalysis in acetonitrile. Its corresponding aromatization in the presence of DDQ provides the fused aromatic system (Figure 2a). The obtained compounds (**9**−**11**) displayed similar low-micromolar IC_{50} and IC_{90} against *T. cruzi*, *T. brucei*, and *L. infantum*, although suffering of low efficacy for epi- and pro-mastigotes and low safety indexes. A widely used MCR is the Ugi four-component reaction (U-4CR): a condensation among amine, an oxo compound, carboxylic acid, and isocyanide. Chibale's group reported the synthesis and biological evaluation of a new class of Ugi adducts based on the aminoquinoline antimalarial pharmacophore, obtained via U-4CR that occurred at room temperature in anhydrous methanol in a parallel array format (Figure 2b). 4-Aminoquinoline and 2-imidazolines cores showed activity against *Plasmodium falciparum* and *T. brucei*,[33] with the best compound (**12**) showing an IC_{50} value of 73 nM against a resistant strain of *P. falciparum* (K1).[34] Another important application of U-4CR is the synthesis of the drug praziquantel (PZQ, **13**). Praziquantel is one of the 12 drugs of the WHO list of essential medicines, and it is currently the drug of choice for the treatment of both veterinary and human trematode and cestode infections, including human schistosomiasis. Dömling's group, differently from the original five-step synthesis, set out a short and convergent synthesis that affords PZQ with an overall yield of 45% in just three-step synthesis. The first two steps are the preparation of the (2-isocyanoethyl) benzene used in the classical Ugi MCR to react with paraformaldehyde, cyclohexylcarboxylic acid, and 2,2-dimethoxy ethylamine to yield the "MCR adduct" quantitatively (Figure 2c).[35] Then, a Pictet−Spengler reaction carried out at 70 °C in the presence of methanesulfonic acid (MSA) and under solvent-free conditions released the desired PZQ. This improvement positively affects not only the *cost of goods*, but also the versatile MCR chemistry allows for the synthesis of many analogues, which may serve as backup drugs in case of resistance emergence.

Other interesting examples include an A^3-MCR (Aldehyde-Amine-Alkyne condensation) affording intermediates for tetrasubstituted imidazolium salts[36] and a Reissert-type MCR[37] releasing benzimidazolium derivatives. Both approaches provided molecules with promising activity against *T. cruzi* and *T. brucei*.

3. Less Hazardous Chemical Synthesis. *"Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment."*[25]

The judicious selection of safer, less toxic chemicals and synthetic routes is central to green chemistry. By choosing substances and designing synthetic methodologies that pose minimal threats to human and animal health and the environment, chemists can mitigate potential adverse impacts associated with chemical production and use.

Metronidazole is widely used as an antibacterial and antiprotozoal agent for livestock and human beings. The conventional synthetic approach initiates with the *N*-methylation of 4-nitroimidazole, employing classical and highly toxic methylating agents such as dimethyl sulfate and methyl iodide. Against these drawbacks, a green chemistry route was developed by using methanol as the methylating reagent and *p*-toluenesulfonic acid as the catalyst.[38] The benefits of simple conditions, ease of operation, minimal pollution, and the only byproducts resulting from the three-step reactions being water and ammonia gas make the new synthesis both environmentally friendly and cost-effective.

4. Designing Safer Chemicals. *"Chemical products should be designed to affect their desired function while minimizing their toxicity."*[25]

The fourth principle advocates for a better understanding of the fundamental relationship between chemical structure and physiological response, which supports the design of chemicals that satisfy their functions while simultaneously reducing their toxicity. A "safe chemical" is a chemical having reduced toxicity

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to humans and that does not persist or bioaccumulate in the environment.[39] When the idea of a "safe chemical" was recognized nearly a century ago, it was surrounded by a clear lack of interest, while recently that interest has increased significantly.[40]

Drugs are peculiar chemicals in that respect. They are ab initio designed to be not toxic to the patients, and toxicodynamic and toxicokinetic in terms of ADME (absorption, distribution, metabolism, and excretion) are integral parts of the current pipeline. Over the last two decades, experimental tools for *in vitro* characterization of ADME-Tox profiles of compounds have been largely utilized in the initial phases of drug discovery and development. This aims to improve the success rate of discovery programs and facilitate the progression of more promising candidates into the pipeline. In the framework of the "New Medicines for Trypanosomatidic Infections" project, Gul and collaborators have successfully applied this approach, demonstrating how screening compounds based on ADME-Tox criteria contributes to identify compounds, with favorable pharmacokinetic properties and reduced toxicity, capable of integration into the trypanosomatidic drug discovery value chain.[41] By evaluating synthetic compounds and natural products against ADME-Tox profiles early in the R&D pharmaceutical pipeline, researchers enhance the likelihood of identifying antiparasitic compounds that not only exhibited therapeutic efficacy but also meet stringent safety standards. This approach underscores the commitment to green chemistry principles, advocating for the development of chemicals that fulfill their intended functions, while minimizing adverse effects on human health and the environment.

A huge push on that direction was given by computer-aided drug discovery that can today efficiently provide the researcher with predicted ADME-Tox data.[42] This not only helps in a better estimation of the human health risks but also can aid in reducing the number of necessary test animals for determining safety. In this respect, *in silico* approaches are extremely advantageous, as they are time-efficient, eco-friendly, sustainable, and adhere to principle #4 of green chemistry.

Conversely, ecotoxicity has not received similar significant attention so far. Drugs for human use are primarily introduced into the environment as unmetabolized drugs and/or their metabolites through the discharge of effluent water, while unused drugs may come from sources such as hospitals, households, and the pharmaceutical industry. These substances often find their way into wastewater treatment plants, where the extent of drug degradation varies. Equally, veterinary pharmaceuticals, serving various purposes, such as prophylaxis, treatment, and growth support in the target animal organisms, are released through feces and urine, eventually reaching aquatic environments. Consequently, pharmaceuticals, together with personal care products, currently represent a distinct group of chemicals, specifically referred to as emerging environmental contaminants, because of their intrinsic capacity to trigger biological effects.[43] Particularly, antimalarials are predicted to be among the most frequent hazardous pharmaceuticals to algae, daphnia, and fishes. Furthermore, antiparasitic drugs fenbendazole and ivermectin highly affect the survival of the soil nematode *Pristionchus maupasi*. Thus, a structured implementation of *in silico* methods for ecotoxicological assessment is highly needed for designing and synthesizing pharmaceuticals able to prevent environmental risk.[44]

A different approach that fulfills the "safety" principle is offered by prodrug strategies. Prodrugs are inactive or less active precursor forms of therapeutic agents that undergo conversion to their active forms within the body. This approach not only prioritizes patient safety by mitigating potential toxicity but also could address environmental concerns through the intentional design of pharmaceuticals that exhibit enhanced biodegradability, minimized ecological impact, and improved pharmacokinetics.[45] For example, an innovative malaria treatment proposes the use of nanosized assemblies of polymeric prodrugs, leveraging the advantages of nanomedicines for improved drug stability and water solubility. Specifically, based on the antimalarial combination of artemether (AM) and lumefantrine (LUM), recommended by the World Health Organization,[46] Fortuin and co-workers described a facile route to the synthesis of a targeted, biodegradable, and highly functional polymeric prodrug (PVP−PVL/VEBCPs) to deliver the AM/LUM combination, while addressing issues of drug stability and uptake.[47]

5. Safer Solvents and Auxiliaries. *"The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used."*[25]

Traditional solvents often contribute significantly to environmental degradation and human health risks, while green chemistry promotes the use of safer alternatives, such as water or biobased solvents, and the reduction or elimination of auxiliary substances whenever possible.[48] Water has multiple advantages, being nonflammable, nonhazardous, nontoxic, uniquely redox-stable, and an inexpensive solvent, with the additional benefit of being a nonexhaustible resource. Consequently, there is growing interest in the development of synthetically useful reactions utilizing water as the reaction medium. However, it is imperative to consider the issue of water depauperating.

Lipshutz and co-workers, in collaboration with the Bill and Melinda Gates Foundation, have developed an alternative synthesis to the antimalarial drug pyronaridine that relies on the use of water.[49] The three-step convergent route utilizes an initial neat reaction, followed by two steps performed under aqueous micellar catalysis conditions, where an appropriately engineered micelle-forming nonionic surfactant promotes the solubilization of typically water-insoluble substrates. The authors managed not only to establish a green protocol (safer solvents/no solvent, *E*-factors of 9 compared to a previous *E*-factor of 46) but also to increase the overall yield moving from 69% to 95%.

The #5 principle also takes care of the development of environmentally friendly and nonvolatile solvents. In this respect, ionic liquids (ILs) are nonvolatile, with thermal stability over 350 °C, minimize evaporation and environmental release, and are nonexplosive, easy to handle, thermally robust, and recyclable.[50] ILs are just gaining attention in the VBPD field. Zhang and co-workers reported a novel, highly efficient, simple, and benign in nature procedure for the preparation of antiparasitic pyrimidine nucleoside−thiazolinin-4-one derivatives by using ILs as recyclable promoters and reaction media. This novel protocol avoids the use of volatile and poisonous conventional organic solvents with the enormous advantage that ILs can also be easily recovered and efficiently reused. Despite the identified compounds showed moderate *in vitro* activity, the authors set an interesting procedure for a wider exploitation of ILs in VBPD drug discovery.[51]

6. Design for Energy Efficiency. *"Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic*

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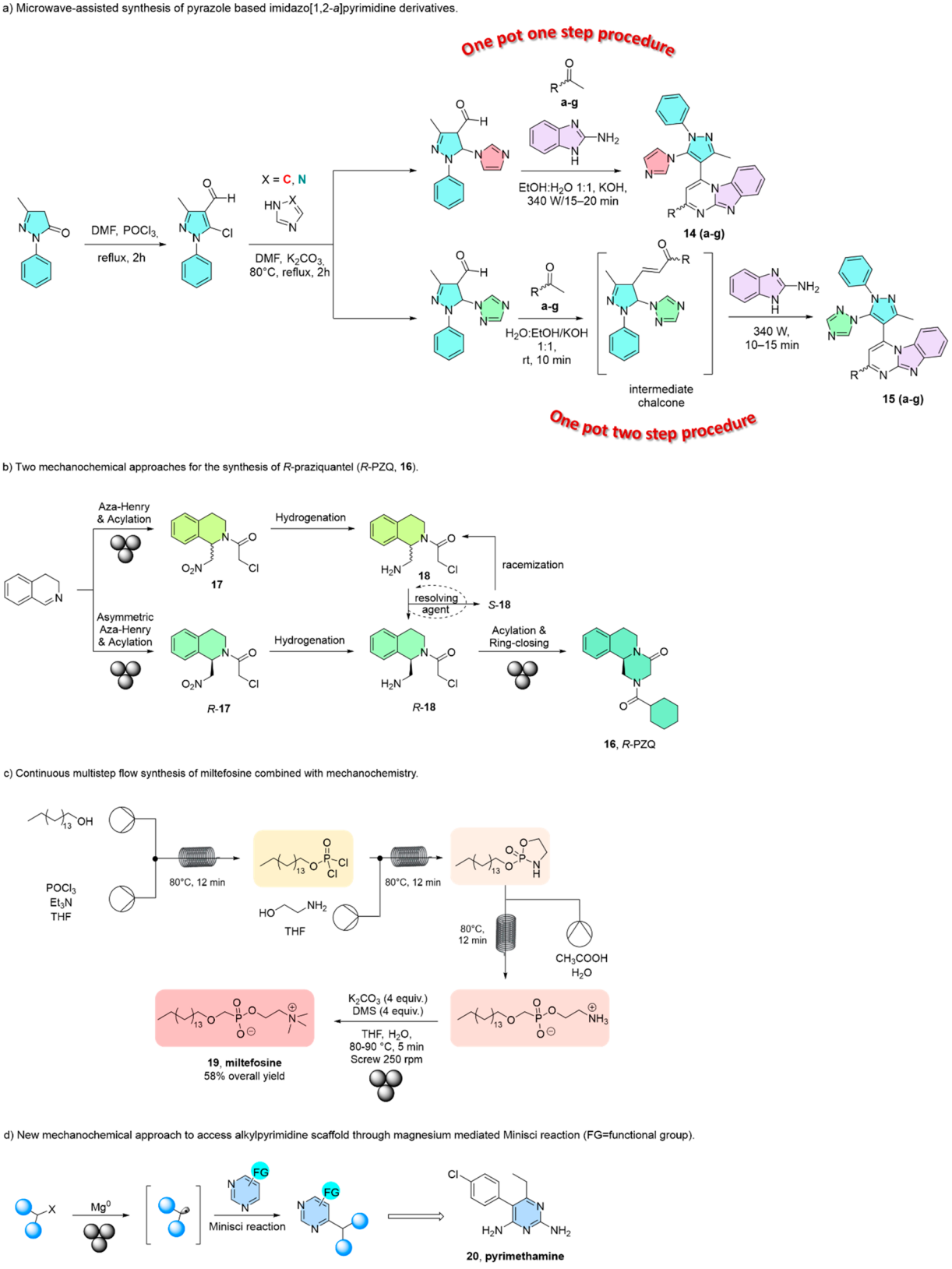

Figure 3. Microwave and mechanochemical strategies exploited for the green synthesis of antiparasitic drugs.

methods should be conducted at ambient temperature and pressure."[25]

Energy-intensive processes are considerable contributors to the environmental footprint of chemical manufacturing. Green chemistry seeks to optimize energy consumption, encouraging methods that minimize energy requirements and exploring renewable energy sources to power chemical processes. In this scenario, the design of chemical processes or systems that do not require intensive energy is highly desirable.[52]

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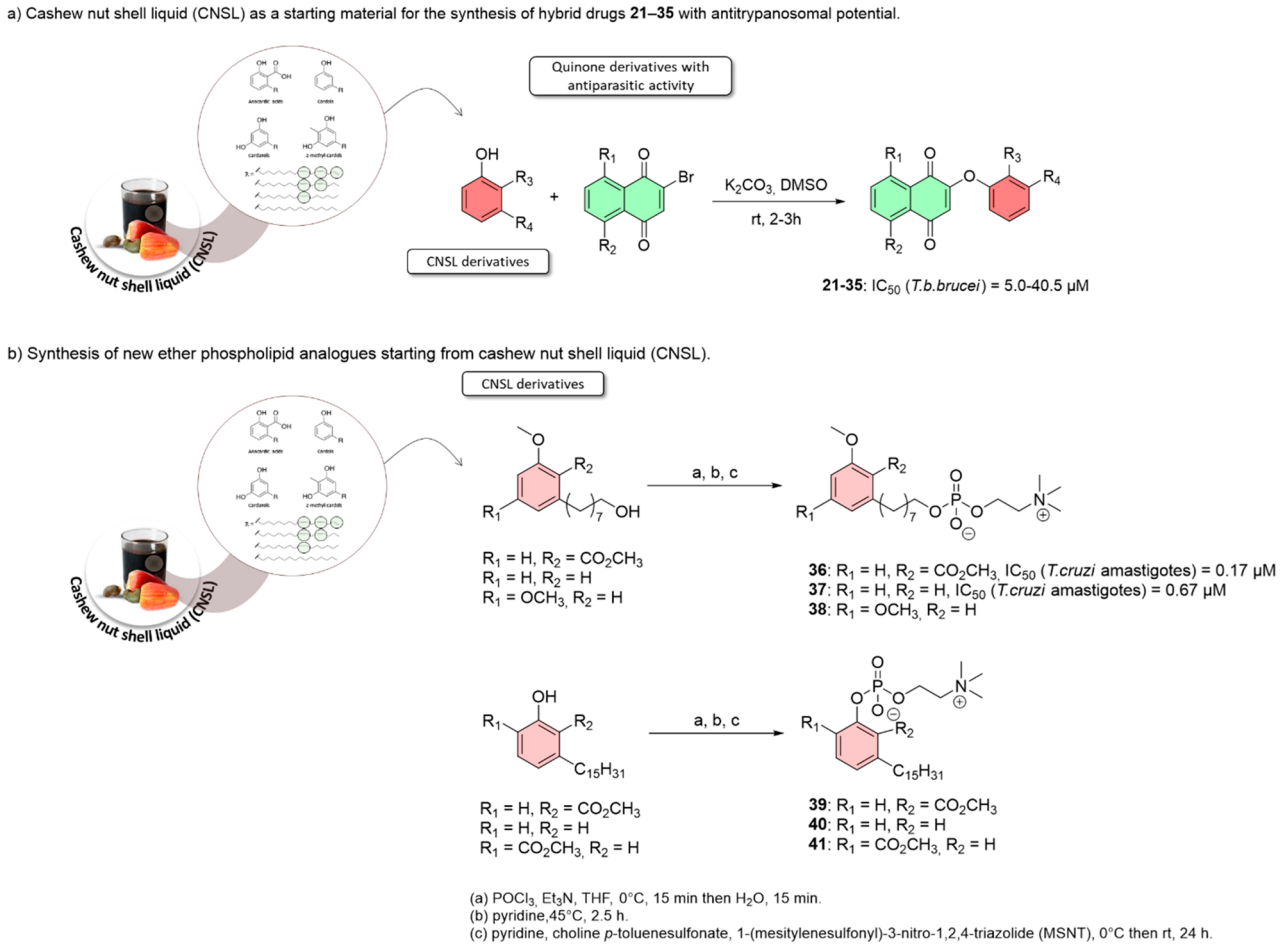

Figure 4. Use of renewable feedstocks for the green synthesis of antiparasitic drugs.

At first sight, microwave (MW)-assisted chemistry may have a direct correlation to principles 5 and 6 of Green Chemistry as it may work in solvent-free conditions and because the energy efficiency of MW dielectric heating technology might be traced back to the decrease in reaction compared to traditionally heated processes. In addition, MW radiation directly heats the reaction mixture without heating the apparatus or reaction vessels. Thus, MW methods should be regarded as being energy-efficient, although the overall greenness of the process must be evaluated case-by-case.[53] An example of MW irradiation in VBPDs is reported by Prasad and collaborators,[54] who described a facile, mild, and environmentally benign one-pot synthetic protocol (see principle #2) to obtain nitrogen-containing fused heterocycle motifs. The synthetic pathway (Figure 3a) started with a Vilsmeier−Haack reaction that released the 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde. This intermediate underwent a nucleophilic displacement of the chloro group with imidazole/1,2,4-triazole nuclei using anhydrous potassium carbonate in DMF, affording the corresponding substituted imidazo/1,2,4-triazole pyrazolyl aldehydes. Next, to obtain **14a−g** and **15a−g**, they elaborated two different ways: "the one pot, one step procedure" where all three components are added at once and "the one pot, two steps procedure". The latter protocol involved the initial *in situ* formation of Michael adducts at room temperature, followed by the addition of 2-aminobenimidazole, which resulted in quantitative yields in both steps. Importantly, in both cases, they used eco-friendly and safe solvent medium, EtOH:H_2O (1:1), as well as MW irradiation (340 W, 10−15 min), to access a series of derivatives (**14a−g** and **15a−g**) with excellent yield (71−93%) and shortened the reaction time (10−20 min) compared to the 24 h reflux conventional route. The synthesized compounds were screened for their *in vitro* antimalarial activity against chloroquine and quinine sensitive strains of *P. falciparum* in comparison to standard drugs, and some of them displayed excellent antimalarial activity with IC_{50} values of 0.030−0.079 μg/mL.[54]

Mechanochemistry, similar to MW reactions, aligns with principles 5 and 6 of green chemistry by prioritizing energy efficiency and waste reduction. Particularly, in mechanochemistry, chemical reactions are initiated by mechanical energy at room temperature and the use of solvents is minimized.[55] In essence, mechanochemistry reactions not only are predominantly solvent-free but also exhibit energy-savings, high-productivity, and room-temperature characteristics compared to conventional solution-based methods. For these reasons, the rising popularity of mechanochemical syntheses of antiparasitic drugs is evident. Because mechanochemistry is very efficient in asymmetric synthesis, it has been successfully applied by Shou et al. for the concise and environmentally friendly synthesis of the *R*-eutomer of praziquantel (*R*-PZQ, **16**). They performed a mechanochemical (asymmetric) aza-Henry/acylation reaction (to obtain intermediates **17** or *R*-**17**) and then a hydrogenation reaction (**18** or *R*-**18**), followed by a solvent-free acylation and ring closing reaction (Figure 3b).[56] PZQ is traditionally administered in its racemic form, although only the *R*-enantiomer is active, while the *S*-enantiomer is inactive and

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has poor taste. The key intermediate (*R*)-1-aminomethyl tetrahydroisoquinoline (*R*-**18**) can be obtained either by the resolution of the racemic material or by an enantioselective synthesis. A scaled-up experiment showed that the efficiency of the multimillimolar (50 mM) reaction was not significantly compromised. Notably, in a circular fashion, racemization of *S*-**18** is also achieved by using safe, cheap, and recyclable D,L-tartaric acid.[56]

Interestingly, Patil and co-workers have combined continuous flow synthesis and continuous mechanochemistry to obtain the antileishmanial drug miltefosine (**19**) with 58% overall yield. Contrary to the conventional batch protocol (15 h), the overall synthetic route (4 steps) requires a very short reaction time (34 min) avoiding isolations and purifications of intermediates. The first three steps were reported in the flow reactor with solution-based chemistry, while for the last methylation step by dimethyl sulfate (DMS) and K_2CO_3 (the reactants are in a solid/paste form), mechanochemistry using a screw reactor was the only way to make the entire process continuous and efficient (Figure 3c).[57] The authors noted that their approach facilitated continuous synthesis of **19** at a scale of 10 g/h, which is sufficient to treat 4800 patients per day.[57]

Wu et al. redescribed the synthesis of the antimalarial drug pyrimethamine (**20**) following an innovative mechanochemical protocol (Figure 3d).[58] Pyrimethamine is a drug active against the erythrocytic stages of all *Plasmodium* species by inhibiting plasmodial dihydrofolate reductase (DHFR), thus blocking the biosynthesis of purines and pyrimidines. Here, the authors presented an easy and efficient method to get access to 4-alkylpyrimidines from diverse commercially available alkyl halides via a mechanochemical regioselective Minisci reaction. The straightforward approach drawn is based on the mechanochemical interaction of alkyl halide reagents with freshly generated magnesium surfaces that, upon release of various alkyl radicals, might be caught by pyrimidines.[58] Scalabilities were preliminary assessed by scaling up the experiment from a submillimolar to a multimillimolar reaction, revealing that effectiveness was not affected.[58]

7. Use of Renewable Feedstocks. *"A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable."*[25]

Biowastes and residues, generated at a global scale in the millions of tons, require valorization. One of the primary goals of green chemistry is to produce sustainable chemical feedstocks from renewable resources.[59] While sustainable methods for producing energy (hydrogen, biogas), fuels (ethanol, biodiesel), and fine chemicals from biomass have been widely adopted, their application for drugs remains an open task.[60] However, the production of bioactive compounds from agricultural and food waste holds immense promise within the framework of a circular economy perspective, as these materials represent an almost inexhaustible source of high-value-added molecules.[16] Recently, our group has proposed the sustainable conversion of cashew nut shell liquid (CNSL)-biomass into bioactive compounds for antiparasitic applications.[61] CNSL, derived from *Anacardium occidentale*, is an inedible oil obtained as a byproduct during cashew nut processing. It is chemically composed of phenolic compounds, namely, anacardic acids, cardanols, cardols, and 2-methylcardols, all sharing a pentadecyl alkyl side chain with a variable degree of unsaturation. Although endowed with an intrinsic biological activity, CNSL components are not potent enough as drug candidates. Thus, our approach has involved linking isolated CNSL derivatives to a quinone scaffold, known for its antitrypanosomal activity (Figure 4a).[61] We have investigated CNSL as a source of novel antiparasitic agents for both HAT and AAT, the latter being particularly impactful on African agriculture and food security. The synthesis, a one-pot nucleophilic substitution reaction in DMSO and requiring no purification, fulfilled the green requirements. The resulting hybrid molecules (**21**−**35**) exhibited anti-*T. b. brucei* activity in the micromolar range (from 5.0 to 40.5 μM) and no human cytotoxicity. In a further effort, we have decorated the 8-carbon chain of CNSL derivatives with a phosphonic group and a final quaternary ammonium salt (Figure 4b), aiming to obtain food waste-derived miltefosine analogues (**36**−**41**). The target ether phospholipids (**36**−**41**) were synthesized starting from the CNSL-alcohol derivatives in a three step synthesis involving treatment with phosphorus oxychloride ($POCl_3$) and triethylamine in THF to afford the corresponding pyridinium salts after hydrolysis and treatment with pyridine. In turn, the latter ones were coupled with the choline headgroup in the presence of 1-(mesitylenesulfonyl)-3-nitro-1,2,4-triazolide (MSNT) as the condensing agent. The obtained derivatives were active on the epimastigote, trypomastigote, and amastigote life stages of *T. cruzi*, with **36** exhibiting a remarkable submicromolar activity (**36**, IC_{50} = 0.17 μM) against the clinically relevant, intracellular amastigote form of *T. cruzi*.[62]

Interestingly, purified CNSL has also been used to synthesize kairomone analogues, specifically 3-ethyl- and 3-propylphenols. These compounds serve as potent attractants for traps to control the tsetse fly population, the primary vector for both HAT and AAT.[63]

8. Reduce Derivatives. *"Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste."*[25]

Minimizing the use of unnecessary derivatization steps in chemical synthesis is crucial to green chemistry. Each additional synthetic step not only consumes resources but also contributes to waste generation. By optimizing synthetic routes, chemists can increase the overall process efficiency. To fulfill this goal, various approaches have been attempted. For instance, the solvent-free, one-pot, and multicomponent procedures depicted in Figure 2 are in line with both principles #1 and #8. Furthermore, flow chemistry enhances sustainability in pharmaceutical processes through precise control, cost efficiency, and increased safety in pharmaceutical multistep preparations, making it more efficient and cost-effective than batch processes.[64,65] Recently, Yu and co-workers presented a remarkably efficient continuous synthesis method for the antimalarial drug hydroxychloroquine (HCQ). Noteworthy, enhancements in this novel process involve the removal of protecting groups and an overall yield of 52%. This efficient process has the potential to increase the global access to this strategically important antimalarial drug, and scalability of the process is being evaluated.[66]

In the peculiar context of medicinal chemistry, "reduce derivatives" can be interpreted as reducing the number of compounds synthesized in the hit selection and hit-to-lead stages. In the pursuit of sustainable drug discovery, computational approaches play a pivotal role in reducing the number of chemical derivatives. In this respect, they can influence and triage design and execution, impacting the likelihood of rapidly generating high-value molecules in a more sustainable manner. In fact, providing the chemists with the tools to design and refine

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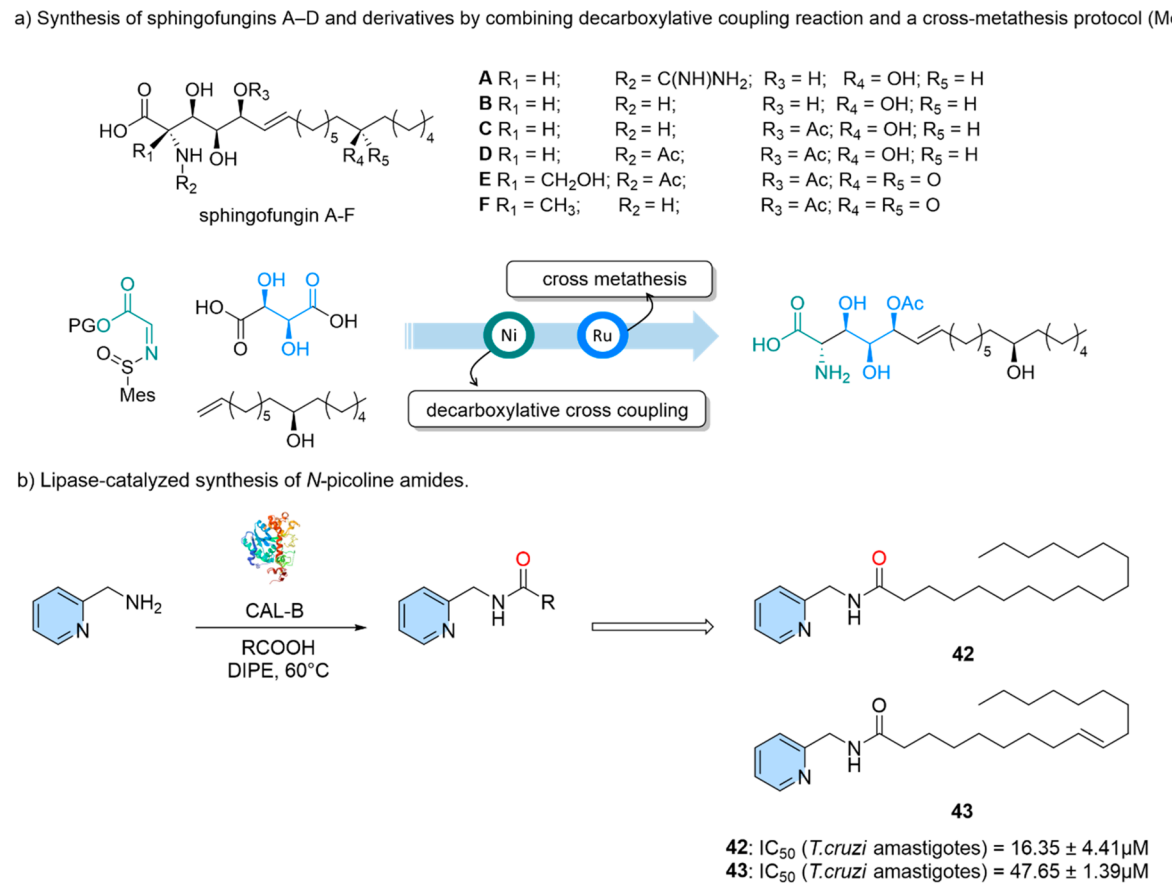

Figure 5. Examples of Grubbs ruthenium catalytic, photocatalytic, and biocatalytic strategies exploited for the green synthesis of antiparasitic drugs.

vast libraries and stressing on "druglikeness", they emerge as a *green by design* paradigm.[42] Interestingly, Duran-Frigola and Chibale's group[67] used ZairaChem, an artificial intelligence (AI) and machine learning (ML) tool designed for quantitative structure−activity/property relationship (QSAR/QSPR) modeling for malaria and tuberculosis drug discovery. Implemented at the H3D Centre in Africa and operating with minimal computational resources, ZairaChem facilitates a virtual screening cascade that comprises 15 models covering key decision-making assays from whole-cell phenotypic screening to aqueous solubility, permeability, and cytotoxicity. By computationally profiling compounds prior to synthesis and testing, the project demonstrates how AI/ML tools can inform the progression of frontrunner compounds, a groundbreaking endeavor in low-resource research settings. This deployment represents a significant advancement in leveraging computational approaches to adhere to the eighth principle of green chemistry, advocating for the reduction of chemical derivatives in drug discovery processes.

On the same vein, late-stage functionalizations (LSFs) can help medicinal chemistry meet the requirements of principle #8.[68] LSFs are synthetic methodologies capable of installing

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functional groups on already decorated scaffolds to provide different products in a single reaction, thus reducing the number of steps to produce a large, diverse library of compounds for SAR studies. However, they seem more suited for accessing focused libraries around a selected core scaffold due to the limited exploration of the chemical space.

9. Catalysis. *"Catalytic reagents (as selective as possible) are superior to stoichiometric reagents."*[25]

In the past decades, the synthetic toolbox of organic chemists has been expanded by the addition of a significant number of innovative catalytic reactions. In fact, metathesis, biocatalysis, and photocatalysis are rather new, clean, and efficient synthetic tools available. Catalysis is central to green chemistry, facilitating milder reactions, reducing energy needs, and improving the selectivity. Catalysts, often more sustainable than reagents, are crucial in synthesizing API and bioactives. Examples of metathesis, biocatalysis, and photocatalysis in VBPD are provided below.

Grubbs ruthenium catalysts allow olefin metathesis through a mechanism similar to Wittig-type reactions, avoiding the production of a large amount of waste; for this reason, Grubbs catalysts have found a vast array of applications.[69] In the VBPD field, an interesting example is furnished by Raguž and co-workers,[70] who reported a short and flexible synthetic approach to obtain antiparasitic sphingofungins by combining a versatile decarboxylative coupling reaction and a cross-metathesis protocol (Figure 5a). Several synthetic strategies have been developed for the total synthesis of sphingofungins but all featuring ten or more synthetic steps and low yields. The implementation of a decarboxylative cross-coupling reaction of chiral sulfinyl imines with a functionalized tartaric acid derivative was the key step to obtain the core scaffold of sphingofungins, bearing four consecutive stereocenters and a terminal double bond. The subsequent metathesis introduced structural diversity at a late stage, affording eight sphingofungins among which is the first total synthesis of sphingofungin C (eight steps from commercially available protected tartaric acid) and sphingofungin A (ten steps). This versatile route allowed the shortest synthesis of sphingofungin B and D yet reported. The antiparasitic activity of all sphingofungin derivatives was evaluated against *P. falciparum*, *T. cruzi*, *T. b. rhodesiense*, and *L. donovani*.[70] Noteworthy, sphingofungin B demonstrated good antiplasmodial activity (1.6 μg mL^{-1}) and no cytotoxicity.

Biocatalysis, a technique employing enzymes for organic transformations, has become a prominent tool in API synthesis, providing a platform with exceptional selectivity and efficiency.[71] Moreover, the environmentally friendly nature of biocatalysis allows one to minimize the use of hazardous reagents and reduce waste. In a sustainable R&D perspective, it not only contributes to the efficient development of more effective treatments but also underscores the commitment to environmentally conscious and socially responsible practices.[72] In 2023, García et al.[73] described the synthesis of a series of *N*-pyridinylmethyl amides (Figure 5b), through a lipase-catalyzed acylation with excellent yields. Lipase B from *Candida antarctica* (CAL B) was used to obtain a series of *N*-picolineamides from structurally different carboxylic acids and diisopropyl ether (DIPE) as solvent. The compounds were evaluated as antiproliferative agents against *T. cruzi* and revealed significant activity; for instance, derivatives **42** and **43** showed potency comparable to reference drug nifurtimox against the clinically relevant amastigote form. Notably, a strong synergy between nifurtimox and **42** was noted, nearly halting amastigote proliferation. This finding is significant, as it would enable the use of lower drug concentrations. These results, combined with the comparable (**42**) and lower cytotoxicity (**43**) in Vero cells compared to nifurtimox, position these compounds as promising leads in the development of safe antiparasitic agents.[73]

Photocatalysis is a promising technology that may overcome environmental and energy problems and offer greener, more sustainable chemical synthesis. A photocatalyzed synthesis of artemisinin (**44**) was developed by Triemer et al., starting from the discarded components of the extract of *Artemisia annua* plants (Figure 5c).[74] Specifically, the crude extract from *A. annua* leaves containing dihydroartemisinic acid (DHAA) and chlorophylls as reactants and photosensitizer is combined with pure oxygen and then fed into a continuous-flow photoreactor in the presence of trifluoroacetic acid (TFA). The photooxidation step that affords the hydroperoxide intermediate can be done for 3 min with red light (87%) or for 5 min with blue light (88%) at −20 °C. The fully continuous process, reacting a crude plant extract, oxygen, acid, and light yielded 67% of artemisinin, thus outperforming the traditional synthesis to produce **44**, a key API for VBPD. Correctly, the authors proposed this as a "*literally green chemical synthesis of artemisinin*", as it successfully combines both principles #7 and #9.[74]

10. Design for Degradation. *"Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment."*[25]

Recognizing that all chemicals may eventually become waste, green chemistry promotes the design of products that break down into innocuous substances after use. This principle, in synergy with principle 4, aims to minimize the persistence and accumulation of chemical pollutants in the environment and ultimately to reduce toxicity. However, knowledge regarding the biodegradation of human and veterinary pharmaceuticals, along with their metabolites, and their effects on ecological processes driven by microorganisms remains limited.[75] Nevertheless, the toxicity in terrestrial and aquatic environments, particularly the chronic ecotoxicological impact on invertebrates, plants, and algae, is under investigation for broad-spectrum antiparasitic agents widely used in animal husbandry and agriculture, which may pose environmental threats. One example is the class of macrocyclic lactones that includes drugs such as ivermectin and abamectin. They have been shown to be excreted into the environment in relatively high amounts as unmetabolized drug or transformation products (TPs), as they undergo relatively rapid degradation in the environment by processes such as oxidation, hydrolysis, and photolysis, which has resulted in them being considered as potential emerging contaminants of concern.[76] Hence, bioremediation could be a promising alternative tool for removing macrocyclic lactones from the environment due to its cost-effectiveness, inherent eco-friendly characteristics, and potential for complete decomposition of harmful compounds. Zheng et al. reported the biodegradation of abamectin by a macrolide-tolerant strain of bacteria isolated from soil and, more recently, the same group investigated the degradation of ivermectin by a newly isolated bacterium *Aeromonas taiwanensis*.[77,78] After being excreted by treated animals, these compounds undergo biodegradation through microbial action in soil and water, reducing their persistence and potential ecological impact.

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In the field of antiparasitic drugs for human treatments, researchers are exploring drug delivery systems that enhance the biodegradation of antiparasitic agents after they have served their therapeutic purpose. This can involve utilizing biodegradable polymers or carrier systems that facilitate controlled release of the drug while promoting degradation and clearance from the body. The discovery and synthesis of the novel biocompatible and biodegradable nanomaterials with no toxicity are relevant because most antiparasitic drugs have low bioavailability due to their insolubility and their short half-life.[79]

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."*[25]

Implementing real-time monitoring and analytical techniques during chemical processes allows for the immediate detection and correction of potential issues. This principle emphasizes the importance of proactive measures to prevent pollution rather than reactive strategies. Computational advances and continuous flow and analysis described above fulfill the requirement of this principle (see principles #4 and #8). In principle, Real-Time Analysis for Pollution Prevention (RTAP) principles can be applied to various stages of the drug discovery and production process to identify and mitigate potential sources of pollution or environmental harm. In the context of antiparasitic drugs, Martínez-Villalba et al. explored the feasibility of using Direct Analysis in Real Time (DART) coupled with high-resolution mass spectrometry (HRMS) for the analysis of antiparasitic veterinary drugs (e.g., albendazole and other benzimidazoles) in feed and food samples.[80] While the study focuses on the analytical aspects of drug detection and quantification rather than the development, it highlights the potential of real-time analysis techniques like DART-HRMS to contribute to pollution prevention efforts by enabling rapid and sensitive detection of antiparasitic drug residues in environmental samples.

12. Inherently Safer Chemistry for Accident Prevention. *"Substances and the form of a substance used in chemical processes should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires."*[25]

Green chemistry advocates for the use of inherently safer chemical processes and technologies. By minimizing the potential for accidents and the severity of their consequences, this principle contributes to a safer and more resilient chemical industry. Consequently, achieving a degree of operational simplicity that minimizes the potential for accidents is imperative in all fields.[58] A practical application in VBPD drug discovery was reported by Tiwari and co-workers, who developed a safer reduction procedure for converting amino acid amides into corresponding *N*-methylated secondary amines. Initially, the amide bond reduction was performed using lithium aluminum hydride (LAH), well-known for its high reactivity, moisture sensitivity, and pyrophoric nature. To avoid complex operation, tedious purification, and low yield, Red-Al (Vitride) was employed as an alternative reducing agent, given its mildness and operational ease. Following this optimized approach, a series of novel 4-*N*-methylaminoquinoline analogues were synthesized and evaluated for their antimalarial activity. Among the tested compounds, nine showed an IC_{50} value < 0.5 μM against both a chloroquine-sensitive and resistant strain of *P. falciparum*, with acceptable cytotoxicity. Selected compounds were also screened for their *in vivo* antimalarial activity against *Plasmodium yoelii nigeriensis* parasite in mice, showing good results.[81]

SUMMARY AND OUTLOOK

The COVID-19 pandemic has taught us a lot. One clear lesson is that we live in an increasingly interdependent world, with overlapping drivers of diseases and environmental changes and intertwined development implications. This orients toward the need for, and benefits, of "One Health", an integrated approach to human, animal, and environmental health, which should also encompass the R&D pharmaceutical pipeline. From the cases collected in this Perspective, it appears that chemists are increasingly more aware of the importance of the 12 Green Chemistry principles and have successfully applied them to tackle human and animal VBPDs and antimicrobial resistance. As these two are basic pillars of One Health, we might conclude that we are already on the right track. However, this seems to not be done in a fully conscious way but rather as a response to the increasing sustainability pressure of the field. The One Health-driven R&D pharmaceutical pipeline is more than just leveraging green chemistry for sustainable chemistry practices. It requires a truly holistic view and a common purpose among all relevant stakeholders for restructuring the entire R&D pharmaceutical pipeline.

A point where there is ample room for improvement is the appreciation of the interlink between drug development for animal and humans. Humans and animals share a lot of their biology, and according to the WHO, over 60% of all known causes of infectious disease are shared between humans and animals. For instance, if veterinary clinical trials were linked to human drug development, resources could be saved and treatments developed more quickly for both humans and animals. Synergy would also easily arise from the cooperation with agrochemical companies, who already effectively deal with the issues of biodegradability and ecotoxicity. We, as medicinal chemists, can pull our weight and rationally design and synthesize new small molecules that not only are more potent, bioavailable, and less toxic but also respect the environment and are affordable to all the "animals" in need!

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsinfecdis.4c00172.

Articles containing the keywords "One Health" and "drug development" per year (PDF)

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Notes

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