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Green Chemistry for Tropical Disease

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26.1 Introduction

Despite huge advancements in the treatment of infectious diseases since 1900, many thousands of people die every day of treatable infectious diseases in the Developing World [1]. While the price of drugs to treat infectious diseases may not be the only barrier to treatment, costs do limit access to medicines in less-developed countries (LDCs) where the average daily income may be less than US$2 per day [2].

An example of where lowering drug costs can increase access to medicines for treatment is in HIV/AIDS. Great progress has been made over the past decade at increasing access to HIV/AIDS treatment in lowest- to middle-income countries. The number of patients on treatment in LDCs has increased from fewer than 200 000 in 2002 to 6.6 million by the end of 2010 [3]. As the international community makes life-long commitments to maintaining patients on treatment, and continues to scale up the number of patients who access HIV/AIDS drugs, budgetary pressures require a strong focus on maximizing the value-for-money in delivering effective treatment to patients.

The Clinton Health Access Initiative (CHAI) is a global health organization committed to strengthening integrated health systems in the developing world and expanding access to care and treatment for HIV/AIDS, malaria and tuberculosis. CHAI's solution-oriented approach focuses on improving market dynamics for medicines and diagnostics; lowering prices for treatment; accelerating access to life-saving technologies; introducing new, innovative combination products that are specifically targeted for the needs of lower- and middle-income countries, and helping governments build the capacity required for high-quality care and treatment programs.

Established in 2002 by President Clinton as the Clinton HIV/AIDS Initiative, CHAI initially focused on addressing the limited access to HIV/AIDS treatment faced by LDCs, where more than 90% of individuals

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living with HIV/AIDS reside. By working in collaboration with governments and non-governmental organization (NGO) partners, CHAI has been able to expand treatment access and save the lives of people with HIV/AIDS, malaria, and other infectious diseases that disproportionately affect low-income populations. Since its inception, CHAI has helped millions of people access the medicines needed for treatment, representing nearly half of all the people living with HIV and on treatment in developing countries.

The principles of green chemistry overlap with the need for more affordable medicines, but this is not always readily apparent. What could appear to be a conflict—the desire to reduce the volume of waste produced and released to the environment during medicines production, versus a desire to greatly increase the amount of pharmaceutically active drugs that are made and used every year—can also be looked at as a synergy. Lower prices for drugs can be achieved by discovering and using more efficient processes to make and deliver these products.

By examining the costs contributing to the price of pharmaceutical products, one can identify ways to reduce both the cost of those products and the environmental footprint associated with their use. In order to consider approaches to reducing the cost of antiretroviral (ARV) or other drugs, it is important to first consider the relationship between the underlying cost of the product and the market price. For a highly commoditized product with a dose of 100 mg or more, the product cost typically breaks down as follows [4]:

- Active pharmaceutical ingredient (API): 65–75% of market price
- Formulation and packaging cost: 10–20% of market price
- Profit: 5–15% of market price.

This distribution of cost contributions leads to multiple possibilities for interventions that can lower cost; these can be divided into two categories:

- Interventions that reduce the cost of the API
- Interventions that reduce the amount of API dosed for maximum efficacy.

This chapter will primarily focus on the first category: improvements which reduce the cost of APIs, especially those that reduce the cost of APIs by increasing the efficiency of the manufacturing process. CHAI has supported and conducted its own process research since 2006. The purpose of these efforts is to lower the cost of essential medicines in low- to middle-income markets. The results of some of these efforts are discussed. Before focusing on those interventions—the green process chemistry—let us first briefly discuss interventions that can change the amount of drug needed to provide an efficacious dose of a drug product.

26.2 Interventions in Drug Dosing

26.2.1 Dose reduction through innovative drug formulation

Frequently in the clinical development of an experimental new product, the simplest formulation that conveniently and reliably delivers a clinically effective exposure of drug in blood plasma is selected for development in order to save time, cost, and complexity in the drug development process. The measurement of the amount of drug present in blood plasma over time, after intravenous dosing, in human subjects is defined as 100% bioavailability for any given drug. The measurement of the amount of drug present in blood plasma over time, after exposure to a specific dosage form, is a measure of the relative bioavailability of that drug delivery form. Many drugs demonstrate relatively low bioavailability after oral dosing, and most essential

medicines for LDCs are delivered orally. The remainder of the drug is excreted (either as unchanged "parent" drug or as metabolites) and never interacts with the molecular target to provide a positive therapeutic effect. The excretion of APIs has, of course, an environmental impact as well. Any change of a dosage form that is safe, convenient, and yet also increases the bioavailability of the drug can be seen as a positive enhancement in human dosing; and can also be viewed as having a green impact.

The case for pursuing dose optimizations that increase the bioavailability of essential medicines can be illustrated by considering a drug that has a relative bioavailability of 25%. For this product, 75% of the administered drug that would otherwise be present in blood plasma (upon intravenous dosing) is excreted into the environment. If a new formulation were available that increases the bioavailability to 50%, the amount of waste produced from the manufacture of that product would drop by half, thus providing the same effect as if the manufacturing process were improved to double its efficiency. The new formulation would also have the advantage of halving the amount of active drug (and associated metabolites) excreted to the environment.

This type of intervention is not commonly pursued as a post-marketing product enhancement, partly because of a limited ability to market a product that is designed to be exactly like the originally approved product. Precedents for this approach do exist, however, including dose reduction for the cholesterol-regulating drug fenofibrate. A reduction in the dose required to achieve efficacy is achieved via improved bioavailability of fenofibrate in some modified dosage forms. These modified dosage forms incorporate API that has been micronized to provide drug of very small particle size, resulting in enhanced absorption [5] and an increase in bioavailability. A number of protease inhibitor (PI) drugs also have blood levels that are "boosted" by co-dosing in combination with the PI drug ritonavir. This effect of "pharmacokinetic enhancement" is achieved by the inhibition of the cytochrome enzyme CYP 450 isoform 3A4. Cytochrome P450 enzymes are a super-family of enzymes that bind iron; CYP enzymes commonly act to oxidatively metabolize drugs [6]. The binding of ritonavir to CYP 3A4 results in a down-regulation of its activity that slows down the metabolism of other protease inhibitors. This increases the bioavailability of several PI drugs that are primarily metabolized by this enzyme.

Extended release technology also could allow for more efficient dosing. In the treatment of infectious diseases, the most important dosing consideration involves determining the minimum inhibitory concentration (MIC) required for effective drug action, then establishing a dose (quantity and frequency) that yields drug exposures in systemic circulation that exceed the MIC. With an immediate release formulation, an excessive peak concentration (C_{max}) often results shortly after dosing. This unattractive feature of immediate-release delivery forms is necessary in order to maintain blood levels of drug above the MIC for a long enough period of time so that the frequency of dosing is not excessive. In this case it is well-known that anti-infective drugs are often preferred by patients when delivered once or twice daily, rather than three or four times per day. The use of extended release formulations (Figure 26.1) can result in multiple benefits: lowering the peak concentration (C_{max}) and "smoothing" the curve that describes blood concentrations of the drug with time; this is often seen to result in a lowered incidence of adverse side effects, in addition to decreased dosing frequency and reduced release of metabolized drug into the environment.

Advances in formulation technology allow increasingly selective delivery of drugs to tissues, organs, or cell types in the body that need it most, allowing for lower doses overall and reducing side effects for patients [7].

26.2.2 Dose optimization: green dose setting

The clinical studies used to set the dose of an investigative new drug candidate are time-consuming and expensive. Dose selection is frequently accomplished on the basis of a few Phase II clinical studies that may span a wide range of dosages. The design and interpretation of these studies is often driven by the

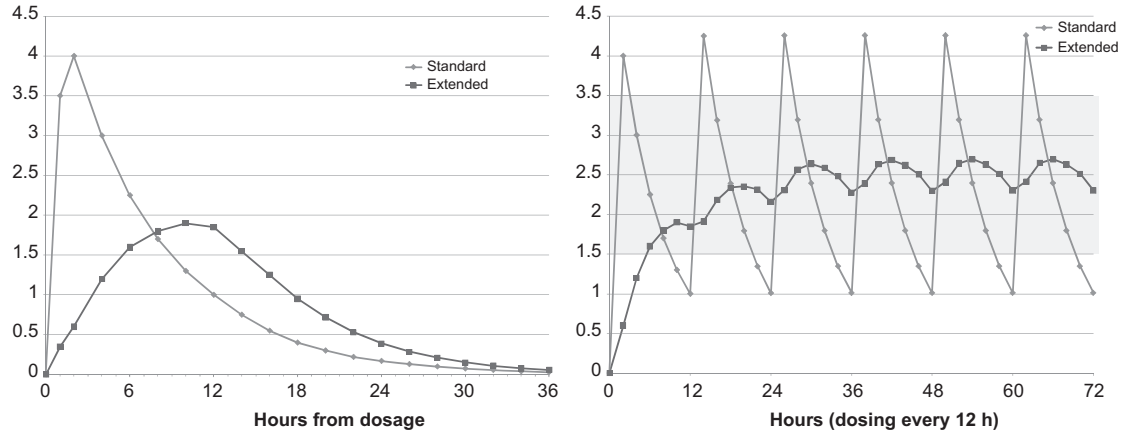


Figure 26.1 *Theoretical dosing curves for standard and extended release dose forms.*

identified maximum tolerated dose and the minimum efficacious dose. For a new drug, demonstrating efficacy that is equivalent or superior to existing drugs in the market frequently outweighs the need to select a dose that minimizes non-severe side effects. This is particularly true for drugs intended to treat infectious diseases, where a significant consideration in early clinical trials may be to dose patients to the maximum-tolerated dose in order to achieve maximum inhibition of the infectious agent. What may be sacrificed or overlooked is the connection between a drug's tolerability and a patient's adherence to the drug in real-world settings, with poor adherence being a major driver of treatment failure and drug resistance [8].

Although they may be costly and time-consuming, additional clinical studies to better select the truly optimal doses of certain drugs, when supported by existing data, can be an effective means of improving patient outcomes. Dose optimization studies can result in improved drug tolerability and reduced adverse clinical events. This also, however, reduces the amount of drug required per dose and, eventually, the amount of drug excreted into the environment. Such studies can clearly be in the patient's best interest and the reduced environmental impact of drug excretion is aligned with this purpose.

In the area of HIV, there are a number of precedents for a dose-optimization strategy, including the results of dose reduction studies on stavudine (d4T) [9], where dosing was reduced from 40 to 30 mg BID (twice daily). Dose optimization trials resulted in reduced side effects and improved tolerability. With the drug zidovudine (AZT), dosing was reduced from the originally approved dose of 400 mg every 4 h (six times daily) to the current recommended dose of 300 mg BID. A number of other opportunities have been identified for dose optimization. These opportunities include reformulation to reduce the dose of efavirenz (EFV), tenofovir, and multiple protease inhibitors. In some cases clinical trials are now underway [10].

26.3 Active Pharmaceutical Ingredient Cost Reduction with Green Chemistry

26.3.1 Revision of the original manufacturing process

The most straightforward interventions for medicines cost reduction (from a conceptual but not necessarily an execution perspective) are those that reduce the cost of the most expensive component of drugs: the API. At its most basic, the process for making APIs involves converting raw materials, which are simpler, more readily available chemicals, into the API in a series of chemical reactions. The cost of this process will be dependent on the cost of the raw materials and the efficiency with which the process converts those

materials into the API. These same factors—choice of raw materials, number of synthetic steps, and the efficiency of the process for API production—also drive the amount of waste produced in the manufacture of the drug.

The original manufacturing process for an API is generally fixed (that is, firmly defined) at a point in time prior to manufacturing the supplies for Phase III clinical trials, well in advance of drug approval and initial marketing. The starting materials, synthetic operations, catalysts, solvents, reaction and isolation conditions, and so on, are selected and defined, so that the profile of related substances present, residual solvent levels, and physico-chemical characteristics of the API are defined within the specifications prior to process validation in the context of the regulatory filing. Because of the time pressures present in getting a drug through the clinical trial and approval process, these manufacturing processes are often fixed before peak efficiency can be achieved through process research. At or after approval, there is a significant disincentive to changing the manufacturing process described in the regulatory filing for market approval, because of the risk, expense, and time involved. Significant changes to a manufacturing process may require additional toxicology studies or a bioequivalence study in order to obtain regulatory approval; such changes must deliver substantial advantages to justify switching the process.

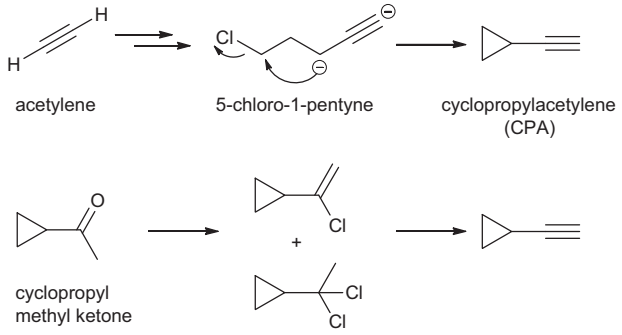
However, the originator pharmaceutical company or a new supplier of the drug (generic manufacturer) can often improve the chemical process used to manufacture the API, increasing the efficiency with which the raw materials are converted into the API (process optimization). With implementation (and regulatory approval) of the improvement, the process costs and/or environmental impact of making the API are reduced.

In some cases, a more dramatic ground-up reworking of the process can be considered, in the form of introducing a wholly or substantially new process. Here, the raw materials may be the same or may be different (with the potential for significant savings using simpler raw materials), fewer steps may be required to convert to make the product, the process may be more efficient at converting the raw materials into API, and other benefits may be realized.

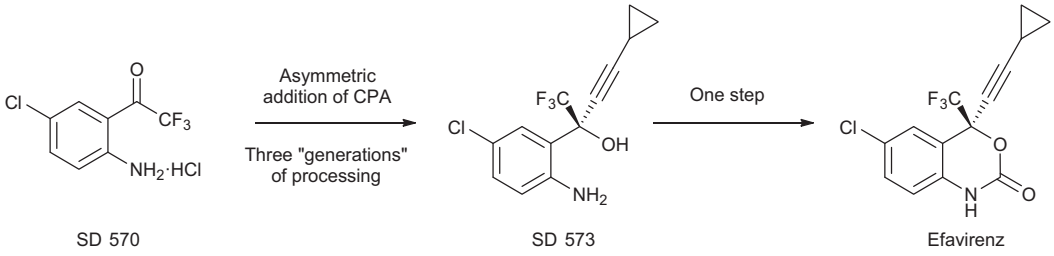
26.3.2 Case studies: manufacture of drugs for AntiRetroviral therapy

EFV is a non-nucleoside inhibitor of HIV-1 reverse transcriptase first approved by the US FDA (Dupont Pharmacueticals) in September 1998. EFV is part of the ARV cocktails efavirenz/lamivudine/tenofovir disoproxil fumarate (EFV/LMV/TDF) and efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) that are highly recommended for the first-line management of HIV/AIDS in many countries, including the USA. The global demand for EFV in developing countries (including Brazil and the Republic of South Africa) in 2011 was estimated at roughly 500 metric tons. EFV is generally delivered to adults as a once-daily, 600 mg dose. Several Indian companies have been approved by the US FDA for generic production to supply less-developed countries under the PEPFAR program. EFV API is, therefore, synthesized by several different processes derived from a common route of synthesis. Efavirenz was launched at a per-kilo manufacturing cost of roughly US$1600/kg. Today, however, EFV API can be purchased (2011) on a 5 MT scale for as little as US$130/kg from companies that are FDA-approved and/or WHO-Prequalified. The reduction in cost of EFV mirrors the increasing "greenness" of synthesis. Two critical sets of improvements have very substantially increased the "greenness" of EFV manufacturing over time. The first of these is changes to the production of cyclopropylacetylene (CPA; Scheme 26.1); while the second is the implementation of at least three successive generations of improvements in the asymmetric addition of CPA to the trifluoromethylketone SD570 to generate SD573 (Scheme 26.2).

Multiple producers have prepared 5-chloro-1-pentyne via reaction of sodium acetylide with 1-bromo-3-chloropropane in liquid ammonia. The laboratory scale conversion of 5-chloro-1-pentyne to CPA via its dianion using more than 2 equiv. of n-butyllithium as base was published by Zhao *et al.* [11]. This



Scheme 26.1 *Preparation of cyclopropylacetylene.*



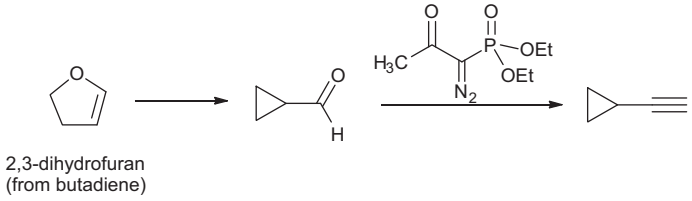
Scheme 26.2 *Preparation of efavirenz.*

procedure generates large amounts of butane via off-gassing, and the CPA produced in this way must be purified by fractional distillation (at least 30–40 plates of separating power) to provide material of adequate purity for use in the asymmetric addition step. This procedure was completely redesigned in a later patent [12] but this approach still suffers from the use of 2 mol equiv. of a very strong alkyllithium base.

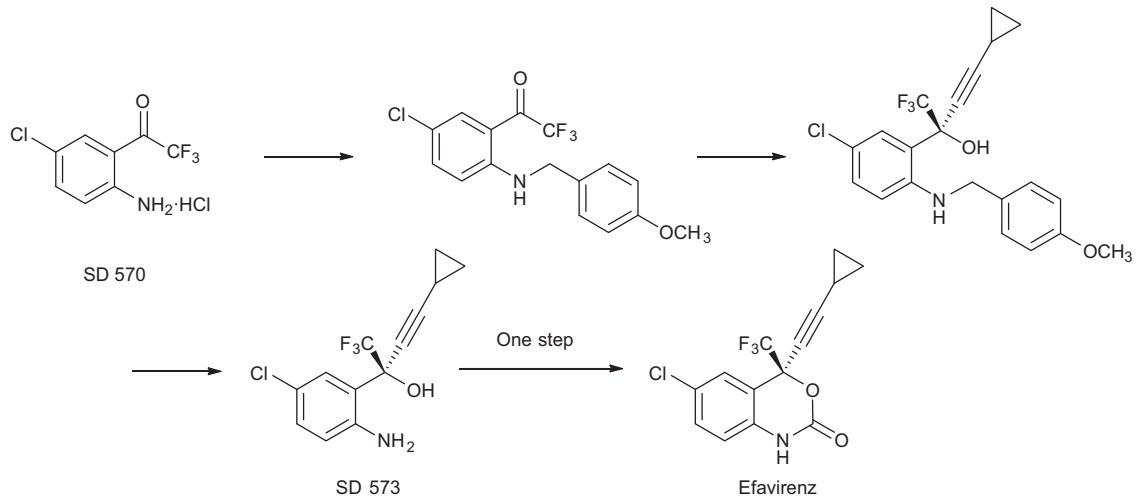
As an alternative, cyclopropyl methyl ketone reacts with phosphorous(V) pentachloride in quinoline to prepare a mixture of vinyl chloride and geminal dichloride [13]. Elimination of the chlorides to CPA followed by distillation gives a reasonable synthesis from inexpensive starting materials.

The commercial synthesis of CPA from cyclopropane carboxaldehyde has since proven to be at least 70% more efficient to either of these approaches in terms of E-factor (Scheme 26.3).

An early variant of this process has been described [14]. The actual conversion of aldehyde to acetylene does not take place with a high E-factor, but the utilization of the aldehyde as a starting material for a one-pot reaction sequence provides a significant green chemistry component to the overall process. Cyclopropanecarboxaldehyde is produced commercially from 2,3-dihydrofuran (2,3-DHF) by a thermal rearrangement;



Scheme 26.3 *Preparation of cyclopropylacetylene from dihydrofuran.*

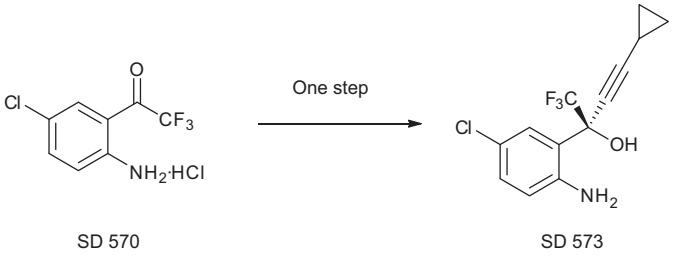


Scheme 26.4 *First-generation synthesis of efavirenz.*

2,3-DHF is prepared from butadiene by way of butadiene monoxide. Butadiene and the butadiene monoxide are used in thousands of ton scale for many commercial products, including the production of synthetic rubber and making tetrahydrofuran; this amounts to a one-pot synthesis of CPA from a very high E-factor starting material.

The first-generation synthesis of EFV (Scheme 26.4) required protection of the aniline nitrogen with a *p*-methoxybenzyl (PMB) group in order to achieve high enantioselectivity in the addition of lithium CPA to the aryl trifluoromethyl ketone. There are several publications relating to this asymmetric addition; an interesting study by Professor David Collum at Cornell provided spectroscopic evidence for the likely structure of the solution-state aggregate of lithium cyclopropylacetylide and the chiral ligand pyrrolidinyl(norephedrine). The solution aggregate results in high enantioselectivity of addition of LiCPA [15]. Removal of the PMB group was effectively a two-step procedure [16]. Conversion of SD573 to EFV was found to be best carried out with phosgene for reasons of volume efficiency, impurity profile, and easy control of crystallization of the correct polymorph. Many companies are not equipped to use phosgene in pharmaceutical production; the best of many alternatives to phosgene has been disclosed by Bristol-Myers Squibb [17].

Subsequent generations of this synthesis have focused on the direct conversion of SD570 to SD573 without the protection of the aniline moiety (Scheme 26.5). One-step conversion to SD573 was first published by Tan *et al.* [18], using stoichiometric dialkylzinc reagents and the chloromagnesium Grignard reagent of CPA. This process is clearly more efficient than the first-generation synthesis by virtue of its brevity, and



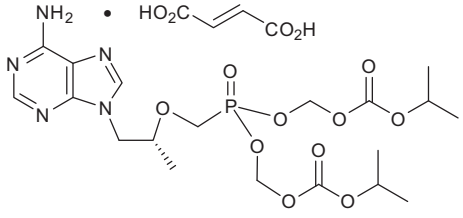
Scheme 26.5 *Second-generation synthesis of efavirenz.*

has been used in different forms—and significantly further improved—by multiple Indian producers of generic EFV. Substantial improvements were also made to this conversion by Lonza Corp., the producer of API for high-income countries. Processes utilizing stoichiometric dialkylzinc reagents still, however, suffer not only from the inefficiency of generating 2 mol of gaseous hydrocarbon (methane or ethane) per mol of zinc reagent, but also from the manufacture, transportation, and handling problems of working with highly pyrophoric reagents. A full mol equivalent of zinc(II) hydroxide is also produced as solid waste in this step. Very recently a revision of this asymmetric addition has been described which uses asymmetric autocatalysis and substoichiometric dialkylzinc reagent [19]; the authors on this paper are from both Lonza and Eric Carreira's research group. Carreira's earlier work in utilizing inorganic zinc(II) salts for asymmetric alkynylation reactions has also been utilized in this regard [20,21].

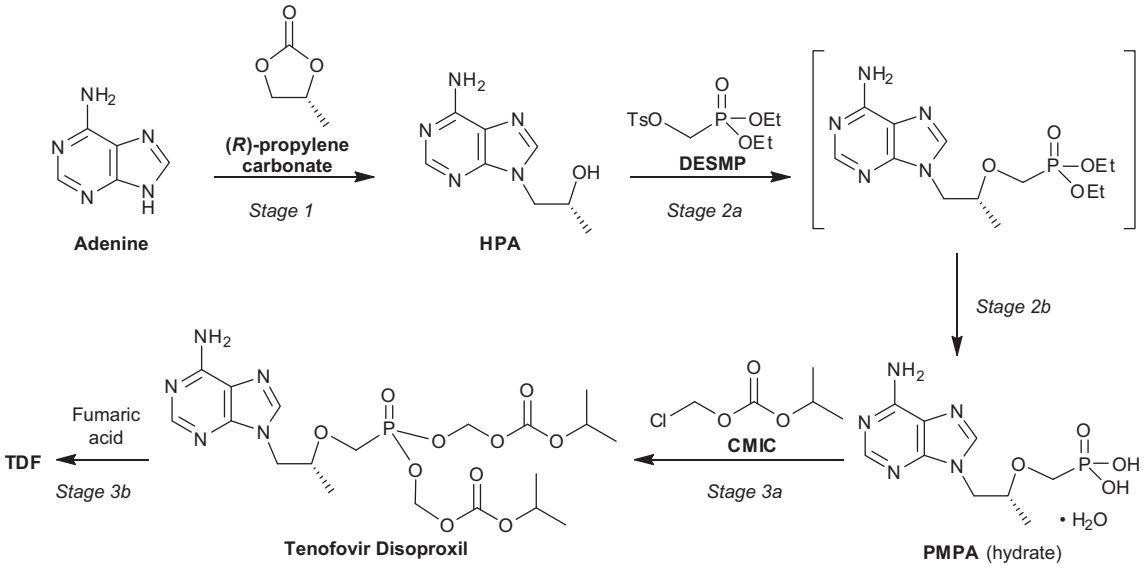
The next generation of improvement avoids these dialkylzinc reagents. Jiang and Si have reported the use of zinc chloride/triethylamine for the addition of CPA to provide racemic SD570 [22]. This publication was followed by one describing use of zinc(II) triflate and zinc(II) diflate to effect this addition with high enatiomeric control, giving commercially useful degrees of enantioselectivity [23]. These processes potentially eliminate over 90% of the waste generated in the first-generation conversion of SD570 to SD573. The use of inorganic zinc(II) salts also eliminates the use of pyrophoric dialkylzinc reagents, can be run at closer to room temperature than other additions, and does not generate volatile organic gases. The inorganic zinc(II) approach has a significantly improved E-factor (roughly 40%) over the use of dialkylzinc reagents. It is also notable that the replacement of zinc(II) triflate with the corresponding zinc(II) diflate allows for the use of an easily obtained, much less expensive reagent. We refer those interested in the specific conditions for carrying out these reactions to the patent literature referenced above.

The phase diagram for SD573 as a free base is such that a very high chiral purity (roughly 97% *ee*) is required in order for crystallization to upgrade the enantiomeric purity. Enantioselectivities for addition of CPA-lithium to the trifluoromethyl ketone SD570 using the chiral ligand (pyrrolidinyl)norephedrine [24] are generally in the range of 96–99%. The first-generation synthesis of EFV consistently produced API with less than 0.1% of the wrong enantiomer present, due to the tendency to shed the wrong enantiomer through crystallization at intermediate stages. The second generation of this synthesis (dialkylzinc reagents) also utilized the same chiral ligand. The methanesulfonate salt of SD573 is often utilized as a means of upgrading the chiral purity of this intermediate, with minimal losses of desired product in the mother liquors. The third generation of this synthesis, however, clearly provides small but definite improvements in enantioselectivity by utilizing a diamino-alcohol chiral ligand derived from a chloramphenicol precursor [12].

Another component of recommended ARV cocktails is TDF (Scheme 26.6), developed by Gilead Laboratories and approved by the US FDA in 2001. TDF is generally administered to adults as a once daily 300 mg dose. With approximately 2.4 million patients taking TDF in generic-accessible countries, the



Scheme 26.6 *Tenofovir disoproxil fumarate.*



Scheme 26.7 *Synthesis of TDF.*

current demand is over 250 metric tons. Based on CHAI projections, this demand may triple in the developing world over the next 4 years, as more and more patients in LDCs initiate or transition to a therapy which includes TDF. As with EFV, much of this TDF production is taking place in Indian generic pharmaceutical manufacturing facilities.

TDF serves as a pro-drug of the molecule tenofovir, 9-[9(*R*)-2-(phosphonomethoxy)propyl]-adenine, or PMPA. The poorly soluble PMPA is absorbed into the bloodstream as the prodrug ester; the isopropyl methoxy carbonate (isoproxil) groups are rapidly hydrolyzed by intracellular enzymes. The limited stability of these isoproxil groups (even in aqueous solution) is ideal for use in a pro-drug, but this hydrolytic instability makes manufacture and isolation of the molecule particularly challenging. Notable for TDF manufacture, these challenges become more difficult on scale-up, where extended processing times required for larger batches resulted in decreased process yields.

When generic production of TDF began in 2006, the cost of treatment per patient per year (pppy) was US$207 for the TDF drug component (API) alone. Reducing this cost would be essential to placing this drug on the preferred first-line regimen in the developing world.

Based on the initially patented process [25], the overall yield for the three-stage synthesis was about 15% (Scheme 26.7). While the first stage proceeds in good yield (approximately 80%), the subsequent stages were found to be particularly challenging. Researchers set to improve the efficiency of manufacture of these stages, culminating in a publication of work which improves the overall yield to approximately 25% [26].

For Stage 2a, 9-[9(*R*)-2-hydroxyprop-1-yl]adenine (HPA) is treated with a base and the diethyl ester of tosyloxymethylphosphonic acid (DESMP), and the intermediate diethyl ester is hydrolyzed under acidic conditions to provide PMPA. The patented procedure used lithium *tert*-butoxide as the base, but subsequent research showed that magnesium *tert*-butoxide was superior [27]. The procedure for hydrolysis called for a significant molar excess of trimethylsilyl bromide, a costly material which is also difficult to handle. Alternatively one may use aqueous HBr [28], but such conditions require exhaustive distillation of organic solvents used in Stage 2a, resulting in long processing times. In a significant improvement, it was discovered that a combination *in situ* of sodium bromide and trimethylsilyl chloride was equally effective [29].

The improved process provides PMPA in 77% yield, a significant improvement over the 50% yield typical for the original, more costly, process.

Further process improvements were possible in the final stage of chemistry, conversion of PMPA to the prodrug tenofovir disoproxil. In a polar aprotic solvent, PMPA is reacted with chloromethyl isopropyl carbonate (CMIC) in the presence of an amine base such as triethylamine. The procedure as originally reported rarely provided as much as 35% yield of isolated TDF salt; monitoring the reaction progress by high-performance liquid chromatography (HPLC) gives a maximum of about 50% product along with starting material, intermediate monoester, and various degradants. Two pathways exist for degradation: the amine function on the purine ring may react to form acylated or alkylated by-products, and the isoproxil functions may be (a) incompletely incorporated or (b) partially cleaved, likely due to participation of the chloride ion released in the reaction.

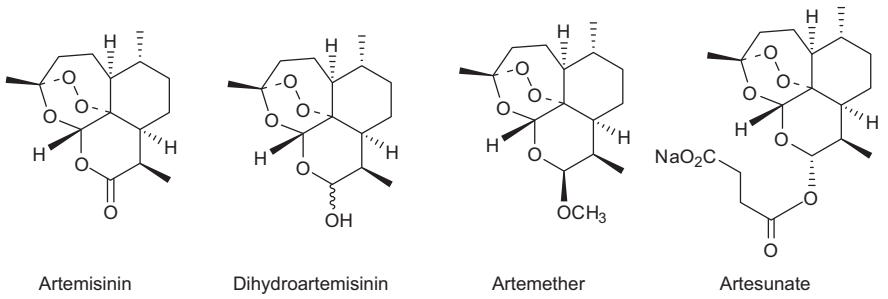
A first improvement was made by converting PMPA hydrate starting material to an anhydrous state, either through rigorous solid-state drying under high heat and vacuum or by heating a suspension of the solid with distillation of a water azeotrope using a solvent such as cyclohexane. By ensuring a low water content in the reaction mixture, reactions at the purine amine are minimized, and reaction conversions may reach 65 area% with isolated yields improving accordingly to 50–55%. It was still difficult, however, to drive the reaction to further completion, as experiments showed that the tenofovir disoproxil would slowly hydrolyze to the monoester under the reaction conditions. The goal was then to reach maximum reaction conversion in a short time in order to maximize product recovery.

As noted above, the PMPA solid is poorly soluble, even in the reaction solvent of choice, the polar aprotic solvent *N*-methylpyrrolidinone (NMP). We considered then, in our laboratories, whether the addition of a phase transfer reagent such as a quaternary ammonium salt might improve the reaction rate. Indeed, addition of a full equivalent of tetrabutylammonium bromide increased the reaction rate, so that the reaction reached maximum completion in about 4 h rather than about 10 h. Conversion also reaches 75%. Fortunately, the presence of the phase transfer reagent does not complicate the usual reaction workup, and isolated yields improve to 60–65%.

A further refinement of these two improvements is to eliminate water and improve solubility through a single procedure: conversion of the PMPA hydrate to an anhydrous amine salt with improved solubility in the reaction medium [30]. In the simplest way, PMPA is reacted with 1 equiv. of triethylamine to provide the corresponding salt in high yield. While this salt is not stable at high humidity, this can be easily handled in a manufacturing environment. Other salts might prove to be more stable, but we note that triethylamine occupies a privileged position in the range of amine bases available to conduct this reaction. Although (for instance) diisopropylethylamine (DIPEA) overcomes the solubility problems of the PMPA triethylamine salt in NMP, two new impurities are generated in the Stage 3 process by switching from triethylamine to this base. Use of the triethylammonium salt in the subsequent reaction provides good conversion and good yields, even while reducing the amount of phase transfer reagent.

While we have not strictly applied core principles of green chemistry to this process—solvent consumption and process stream volumes are still rather high—it is clear that a doubling of the yield for two steps of chemistry provides a significant environmental benefit in production of this needed medicine.

In addition to applying the intervention of improving the chemical route to TDF, CHAI also worked to establish new suppliers of the drug, providing them with the best available chemical processes, and to establish new suppliers of the key starting materials. Notably, a new supplier of magnesium *tert*-butoxide in India allowed manufacturers to quickly reach production scale. Largely as a result of these interventions, the price for TDF has dropped from the US$207 noted above in 2006 to about US$80 today. Approximately 20% of this cost reduction can be attributed directly to the improved chemical process being used. As the further refinements discussed above are implemented, further price drops are expected. TDF is now priced to allow its widespread use as a first-line treatment for HIV/AIDS.

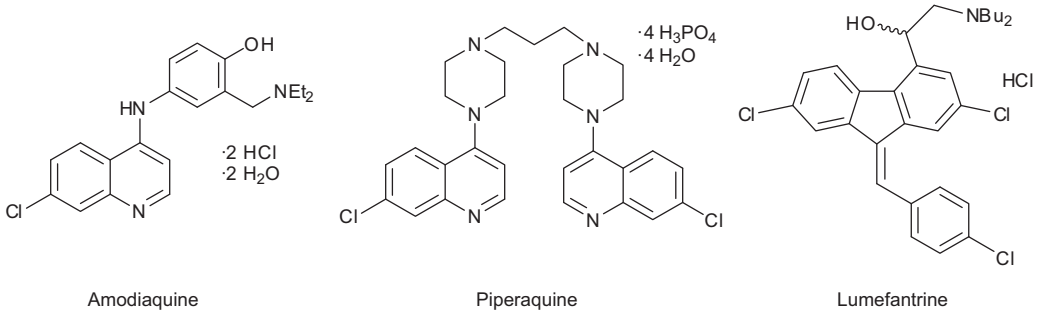


Scheme 26.8 *Artemisinin and artemisinin-derived antimalarial compounds.*

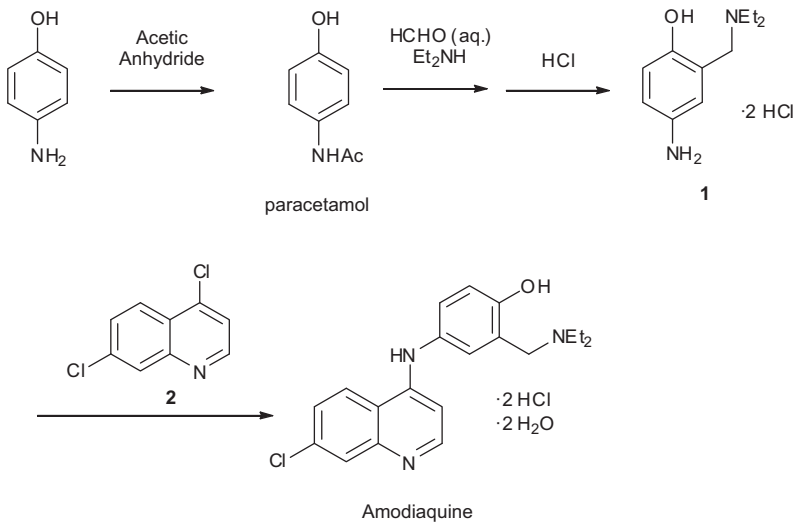
26.3.3 Case studies: Artemisinin combination therapies for malaria treatment

Artemisinin is extracted and purified from the herb *Artemisia annua* by a number of different processes including using petroleum distillates (hexanes or even gasoline), supercritical fluids, or ionic liquids [31]. While artemisinin itself is an antimalarial drug of long standing, clinical efficacy is improved by conversion to one of several semi-synthetic derivatives of the natural product (Scheme 26.8). Artemisinin is reduced to dihydroatemisinin (DHA) with sodium or potassium borohydride [32]; both artemether (DHA methyl ether) and artesunate (DHA succinate ester) are derived through one additional synthetic step [33]. The artemisinin-derived ACT components have a cost that is largely driven by the price of artemisinin. At the time of writing, the costs of artemether and artesunate are about US$600/kg.

Artemisinin combination therapies (ACTs) are recommended by the World Health Organization (WHO) for the treatment of uncomplicated malaria for all patients who can tolerate artemisinin therapy. The artemisinin-derived component of an ACT rapidly and effectively clears circulating blood schizonts, but has a short half-life of only a few hours. The synthetic component of an ACT has a long half-life (usually several days) and is significantly distributed into tissues because of its high lipophilicity. The synthetic component of an ACT thereby provides for a long-lasting antiparasitic effect, thus preventing recrudescence. The main ACT combinations used in LDCs are: (1) artemether/lumefantrine; (2) artesunate/amodiaquine; and, more recently, (3) dihydroartemisinin/piperaquine (Scheme 26.9) . Because the synthetic component of an ACT is dosed at 2.7–6 times the amount of the artemisinin-derived component, the "green factor" of synthesizing ACTs is largely driven by the process for making the synthetic ACT component.



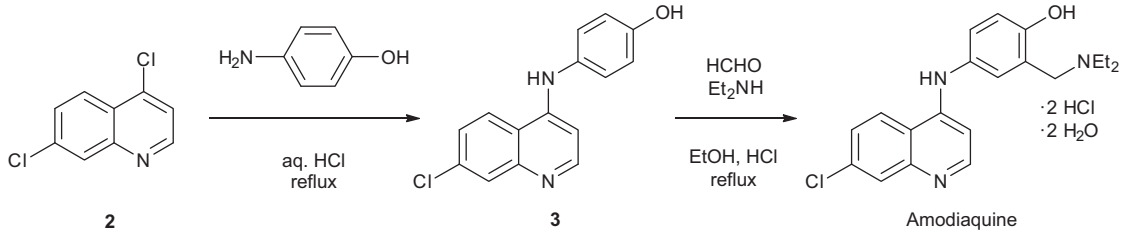
Scheme 26.9 *Synthetic antimalarial compounds for ACT.*



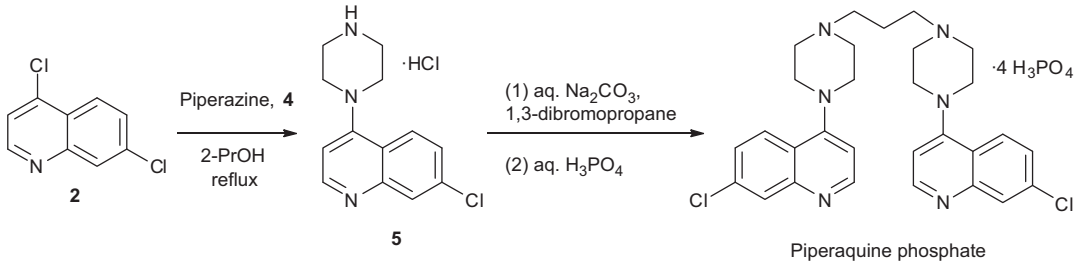
Scheme 26.10 *Commercial synthesis of amodiaquine.*

Although amodiaquine was first reported as an antimalarial compound over 60 years ago by Burckhalter *et al.* [34], its use as component in artesunate:amodiaquine has greatly revived interest in this molecule. Amodiaquine has been commercially synthesized in a four-step process from 4-aminophenol and 4,7-dichloroquinoline (Scheme 26.10). Treatment of 4-aminophenol with acetic anhydride yields paracetamol, which is very inexpensive by virtue of its use as an analgesic with an annual global volume of roughly 60 000 tons. Paracetamol undergoes a Mannich reaction (formaldehyde, diethylamine) followed by hydrolytic removal of the acetyl group to give the substituted 4-aminophenol **1**, which is then reacted with 4,7-dichloroquinoline **2** to give amodiaquine.

This is actually a rather reasonable synthesis of amodiaquine, with published yields of approximately 60–65% based on 4,7-dichloroquinoline; API can be purchased for prices in the range of US$20–30/kg on metric ton scale. One of us (Fortunak) has developed a synthesis of amodiaquine, however, that avoids two of these steps, and eliminates over 80% of the waste generated in the commercial synthesis. Reaction of 4,7-dichloroquinoline **2** with 4-aminophenol in aqueous hydrochloric acid (reflux) gives nearly quantitative conversion to **3** (Scheme 26.11). Mannich reaction of **3** (ethanolic HCl, aqueous formaldehyde, diethylamine) yields amodiaquine in overall yields of 90–92% from 4,7-dichloroquinoline. The overall E-factor for this synthesis is roughly 7.



Scheme 26.11 *Two-step synthesis of amodiaquine.*

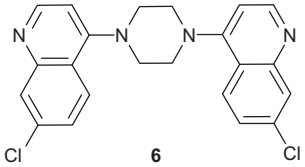


Scheme 26.12 *Green Synthesis of piperaquine.*

Several related commercial processes for the synthesis of piperaquine API have been described [35,36]. These processes differ largely in the solvents used for Step 2, the isolation method for intermediate **3**, and the choice of base used in each step (Scheme 26.12).

The general procedure for Step 1 is fairly consistent; piperazine (**4**; 3 mol equiv.) and 4,7-dichloroquinoline **2** are refluxed in 2-propanol (7–10 vol.; w/v) with potassium carbonate as base. An excess of piperazine is used in this reaction to minimize the formation of the dimeric impurity shown as **6** (Scheme 26.13). After the reaction is complete, the 2-propanol is distilled away and exchanged to dichloromethane (10 vol.). Water is added to extract excess piperazine, and a second aqueous extraction with hydrochloric acid is used to prepare the salt of intermediate **5**. The solid product is isolated by concentration of the aqueous layer and crystallization from acetonitrile (10 vol.). This process is clearly inefficient with respect to solvent usage, with several energy- and time-consuming solvent exchanges. The isolated intermediate is carried forward to piperaquine in an additional two operations. Heating 1-bromo-3-chloropropane with intermediate **5** in aqueous sodium carbonate yields piperaquine free base. The free base is converted into piperaquine phosphate (the API) by addition of 4 equiv. of phosphoric acid in an aqueous suspension.

We have found that the Step 1 reaction for synthesizing piperaquine works best by refluxing dichloroquinoline and piperazine in 2-propanol in the absence of any additional base, giving approximately 97% yield of material that is >99.8% pure by HPLC analysis. Addition of ethyl acetate (5 vol.) causes much of the excess piperazine to crystallize (largely as its hydrochloride salt), which is removed by filtration. Water washing (5 vol.) to remove remaining piperazine is followed by concentration and solvent exchange to water (6 vol.). This mixture is carried directly to piperaquine free base by heating to reflux with 1 mol equiv. of sodium carbonate and 0.5 mol equiv. of 1,3-dibromopropane. The isolated yield of material that is >99% pure by HPLC is 92–93% over two steps. It must be noted that the free base of piperaquine has very limited aqueous solubility. Conversion to the tetraphosphate salt is also carried out in water (10 vol.). This improved process for producing piperaquine utilizes roughly 5 vol. of 2-propanol, 5 vol. of ethyl acetate and 21 vol. of water. The overall E-factor for this synthesis is roughly 33, with aqueous streams accounting for roughly two-thirds of this material.



Scheme 26.13 *Piperaquine dimeric impurity.*

26.4 Conclusions

The United Nations Millennium Development Program includes Goal 6 [37] as: "combat HIV/AIDS, malaria, and other diseases." In mid-2005 the Progress Report towards these goals indicated that the richest 15% of the world's population consumed 91% of medicines. The number of low-to-middle income people worldwide with access to medicines for the treatment of HIV/AIDS, malaria and other infectious diseases has increased enormously since 2001. The global figures for mortality from these diseases have also decreased in absolute terms over the last decade. Chemistry to reduce the cost of APIs for treatment of these diseases has played a very significant role in increasing access to needed medicines; some of this work has been highlighted in this chapter. Much still remains to be done, although it can be optimistically concluded that much more progress towards increased access to medicines is achievable through the application of new chemistry, reformulation, and dose optimization studies.

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