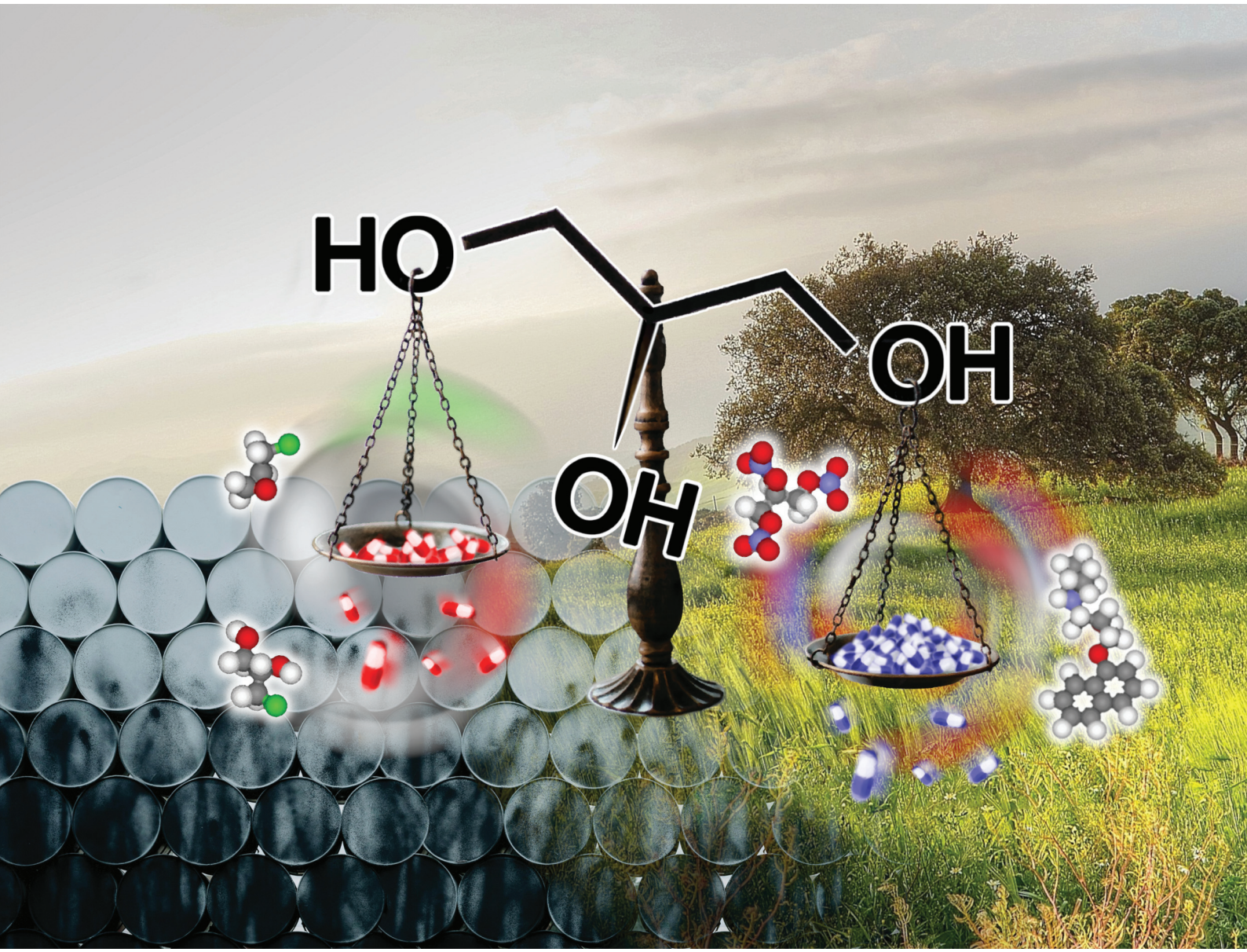
Volume 26
Number 19
7 October 2024
Pages 9927-10352

# Green Chemistry

Cutting-edge research for a greener sustainable future

rsc.li/greenchem




ISSN 1463-9262

ROYAL SOCIETY OF CHEMISTRY

**PERSPECTIVE**

Jean-Christophe M. Monbaliu *et al.*

Glycerol and its derivatives as potential C-3 bio-based building blocks for accessing active pharmaceutical ingredients

25 YEARS ANNIVERSARY

Green Chemistry

PERSPECTIVE

View Article Online
View Journal | View Issue



Cite this: *Green Chem.*, 2024, **26**, 10029

# Glycerol and its derivatives as potential C-3 bio-based building blocks for accessing active pharmaceutical ingredients

Romain Morodo,†[a] Loïc Bovy,†[a] Diana V. Silva-Brenes[a,b] and Jean-Christophe M. Monbaliu *[a,b,c]

Received 20th April 2024,
Accepted 20th June 2024

DOI: 10.1039/d4gc01957a

rsc.li/greenchem



This review discusses the underexploited potential of renewable glycerol and its derivatives for the preparation of active pharmaceutical ingredients, some of which are on the World Health Organization list of essential medicines. The regulatory challenges faced by industries regarding the replacement of petro-based building blocks with renewably sourced ones are described before diving into pharmaceutical ingredients that could potentially incorporate these bio-based atoms. The active pharmaceutical ingredients (APIs) are sorted by their therapeutical potential, including entities treating cardiovascular diseases, musculoskeletal drugs and compounds endowed with anti-infective properties. Finally, polymeric drugs and more eclectic substrates such as dietary supplements, radiosensitizers or chemotherapeutical agents are considered in the last two sub-sections. The broad spectrum of presented substrates relying on glycerol or potentially glycerol-derived reagents in their synthetic pathway emphasizes the potential contribution of bio-based substrates in already developed industrial processes. The examples in this review hint toward a future chemical development in which APIs may be constructed with increasing percentages of bio-sourced atoms.

## 1. Introduction

The concept of bio-based chemicals involves the use of biomass to replace petrol as a source of chemicals. A sector of chemists has turned to starch, cellulose, lignin, and oil, among other biomass, as raw materials to provide new chemical platforms that can fit consumer needs. To be usable, biomass must be degraded to its constitutive compounds, principally sugars, which can then be further modified to obtain chemical building blocks.[1] The development of these bio-based platforms is meant to provide an alternative to conventional petroleum-derived products,[2] decreasing the environmental impact of current chemical processes and the reliance on ever-decreasing petrol reserves. Furthermore, the adoption of widely available biomass as a source of chemicals, as opposed to geographically limited petrol sources, will have strong economic and even political implications.

A great deal of effort has gone into identifying the most promising candidates for bio-based platforms to help focus the attention of both chemists and investors to strategies that have the best chance of success. Among the building blocks that have been highlighted, glycerol stands out particularly due to its exceptionally high availability.

Glycerol, or 1,2,3-propanetriol (**1**, CAS 56-81-5), is one of the main components of triglycerides found in fats and oils (Fig. 1). Its currently abundant production is due to it being a by-product of the biodiesel, soap, and cooking oil recycling industries. Most of the glycerol on the market is currently bio-sourced, with trends suggesting it will continue to be increasingly the case. A report from 2004 estimated that 25% of the glycerol on the market was being produced synthetically,[1] whereas 2016 reports placed the amount of synthetic glycerol on the market at around 12%.[3] The production of glycerol has been significantly boosted by the biodiesel industry, which in turn has continued to increase with the support of tax incentives and legislation. Around 1 ton of biodiesel results in the formation of 100 kg of glycerol as by-product.[3,4] The cost of glycerol has continued to experience a downward trend for the past decades. In 2019, European transaction prices for glycerol (≥99.5% purity) were around 856 USD per metric ton (USD per mt),[5] whereas export prices of crude glycerol averaged 266 USD per mt.[6] As a point of comparison,

[a]*Center for Integrated Technology and Organic Synthesis, MolSys Research Unit, University of Liège, B-4000 Liège (Sart Tilman), Belgium.*
*E-mail: jc.monbaliu@uliege.be; https://www.citos.uliege.be*
[b]*FloW4all Flow Technology Resource center, University of Liège, B-4000 Liège (Sart-Tilman), Belgium*
[c]*WEL Research Institute, Avenue Pasteur 6, B-1300 Wavre, Belgium*
† Equal contributions.

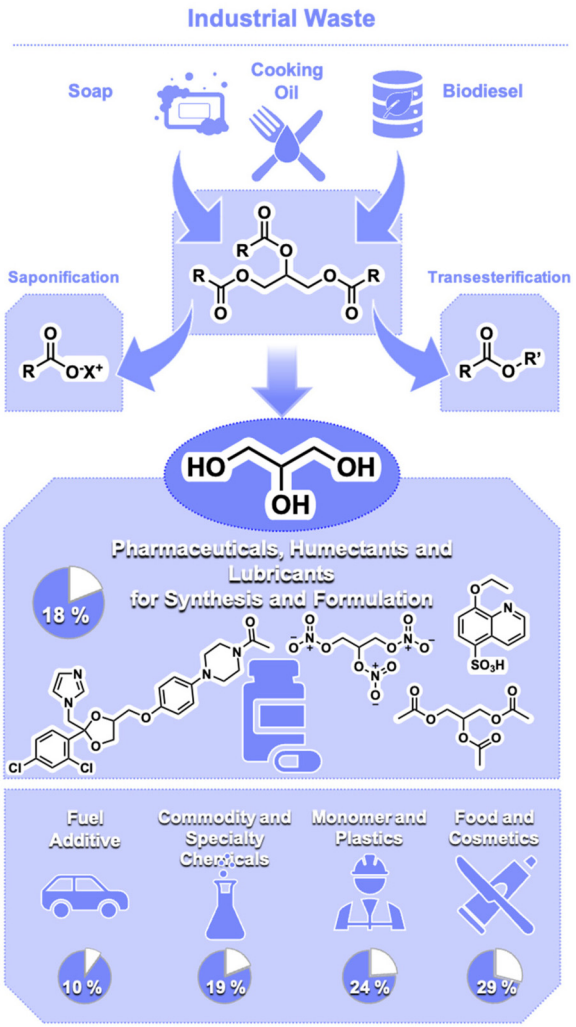



**Fig. 1** Sources to produce bio-based glycerol (**1**) and current main applications of glycerol on the market alongside estimations of its end use.

propylene (≥99.5% pure) was valued at 980 USD per mt (2019).[7]

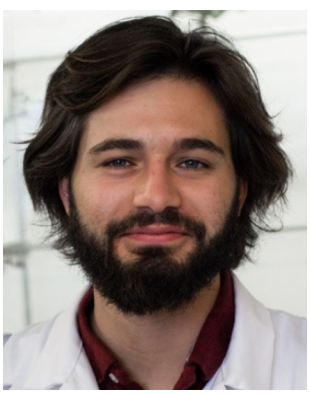
Because glycerol is obtained as a by-product of the biodiesel industries, its current cost of production is virtually negligible. The factor determining the cost of glycerol is the refinement process, with small biorefineries often finding landfilling to be more economical than refining glycerol. A 2004 estimate placed the cost of refining at around $0.23–$0.38 per kg (230–380 USD per mt) depending on the size of the facility.[3] However, even with this cost for its refinement, the large production of crude glycerol, and consequent low price, point to an extraordinary potential to develop its use to replace products that were typically obtained from petroleum.[8]

Traditional uses of glycerol include pharmaceuticals, personal care products, foams, and foods, with these sectors comprising almost 60% of its usage.[9] Due to its hygroscopicity, it is frequently used as a humectant, lubricant or to improve the softness of materials. In the food and pharmaceutical sectors, it serves as a humectant and texture-enhancing additive. Glycerol (**1**) is also used as a sweetener and to prolong the shelf-life of products in the food industry. It has also applications as a moisturizer in cosmetics and personal care products, or in the preparation of plastics to improve their flexibility. In the historical period of World War II, glycerol was in particularly high demand for the preparation of nitro-glycerine explosives (Fig. 1).[9]

Glycerol's low cost due to current overproduction has led many to propose various derivatizations of the compound, in efforts to open new ways to valorise the derivative.[10] Typical C-3 building blocks that can be synthesized from **1** encompass allyl alcohol (**2**),[11–13] which can be further oxidized to yield higher derivatives such as acrolein (**3**)[10] and acrylic acid (**4**).[10] Additionally, 1,3-dihydroxyacetone (**5**),[14,15] 1,3-propanediol (**6**),[16] lactic acid (**7**),[17] ethyl acrylate (**8**) and solketal (**9**),[18] among other derivatives, are also attainable.

**Romain Morodo**

*Romain Morodo studied chemistry at the University of Liège (Belgium) and obtained a Ph.D. degree in organic chemistry and process technologies in 2022. He went to Avon (France) for a research internship at the Corning European Technology Center working on scale-up operations in continuous flow reactors and completed a research stay at the University of Groningen (Netherlands) working on organophosphorus chemistry. He was awarded a Postdoctoral Fellowship from the Belgian American Educational Foundation and relocated to the U.S.A. at Stanford University to develop new organocatalysts and leverage automation and machine-learning tools for accelerated material discovery in collaboration with IBM.*



**Loïc Bovy**

*Loïc Bovy earned his Master's degree in chemical sciences at the University of Liège (Belgium) in 2022 before starting his Ph.D. training as a teaching assistant at the Center for Integrated Technology and Organic Synthesis (CiTOS). His research focuses on the upgrading of bio-based building blocks towards active pharmaceutical ingredients by leveraging the perks of continuous flow chemistry and automation.*

The most notable and extensively utilized C-3 building blocks potentially originating from **1**, however, are monochlorohydrins **10a,b**, dichlorohydrins **11a,b**, and the epoxides derived therefrom: epichlorohydrin (**12**) and glycidol (**13**). The Epicerol (Solvay) and the GTE (Dow) processes[19,20] are staple transformations connecting **1** with the formation of reactive C-3 oxiranes **12** and **13** (Fig. 2). The overall transformation involves a first hydrochlorination of **1** toward **10**, **11** with aqueous HCl and a simple (di)carboxylic acid catalyst. In a second stage, the dechlorination of compounds **10**, **11** under alkaline conditions opens a gateway toward oxirane derivatives **12** and **13**. Appropriate control of the reaction parameters as well as catalyst selection is particularly relevant to tune the reaction selectivity.[21] Such a process has been also intensified under continuous flow conditions.[22] These processes stand as a robust alternative to the conventional chlorination of petro-based propylene (**14**) for the obtaining these versatile building blocks (Fig. 2).

Another potentially appealing feature not shared with parent **1** resides in the presence of a stereogenic center at $C_2$ on both **12** and **13**. Enantioenriched oxiranes **12** and **13** can be accessed through a hydrolytic kinetic resolution (HKR) as introduced by Jacobsen in the late 1990s. The procedure relies on the enantioselective hydrolysis of a terminal epoxide in the presence of a Co-salen complex. It yields two distinct valuable products, namely an enantioenriched epoxide and the corresponding enantioenriched diol. To illustrate this point with *rac*-**12**, the optimized protocol utilizes (*R*,*R*)-**16** as a catalyst along with 0.55 equivalents of $H_2O$ in THF at 4 °C (24 h). This leads to (*S*)-**12** with a remarkable enantiomeric excess (ee) of >99% in 42% yield. Concurrently, monochlorohydrin (*R*)-**10b** was obtained in a 52% yield (ee of 89%) (Fig. 3a). Swapping the catalyst to its enantiomer (*S*,*S*)-**16**, (*R*)-**12** and (*S*)-**10b** can be generated. Furthermore, enantiomerically pure (*S*)-**12** can be directly synthesized from (*R*)-**10b** under alkaline conditions (88% yield, >99% ee) (Fig. 3b). HKR on *rac*-**13** leads to a lower yield due to undesired side oligomerizations. The access to enantioenriched glycerol-derived reactive oxiranes and monochlorohydrins holds significant potential for the development of chiral derivatives, as are frequently encountered, for example, in the pharmaceutical industry.

This review presents a compilation of active pharmaceutical ingredients (APIs) the synthesis of which contains **1** or some of the compounds that could potentially be derived from it. Fig. 4 gives a distribution of the number of molecules here reported by the nature of the glycerol (**1**) derivative used in their synthesis. More than half of the APIs that we have managed to identify are due to the incorporation of epichlorohydrin (**12**). The presence of two reactive electrophilic sites in the C-3 molecule makes it a versatile building block, and previous reports agree on how their distinct reactivity makes them an attractive option to incorporate potentially bio-based C-3 building blocks in the chain of value.[23,24]

The following section will discuss more in depth the advantages and the challenges of incorporating more bio-based atoms into currently existing APIs, many of which are listed as WHO essential medicines and/or frequently prescribed medications.

## 2. The case for the use of glycerol derivatives

Efforts promoting low-carbon-intensity pathways have been gaining momentum in the chemical industry in general,[25–28] including the pharmaceutical industry.[29,30] In support of these efforts, we have taken an in-depth look into the feasibility of

**Diana V. Silva-Brenes**

*Diana V. Silva-Brenes completed her PhD in organic chemistry at the University of Puerto Rico, with the support of an NSF-GRFP. Following this period of training, Diana went on to develop research in flow chemistry at the Center for Integrated Technology and Organic Synthesis (CiTOS) at the University of Liège under Dr Jean-Christophe Monbaliu. She has since become the scientific manager of the FloW4all Resource Center for Flow Chemistry Technology at the University of Liège, establishing collaborations with industrial and academic partners that wish to use flow chemistry to tackle challenges in synthesis.*

**Jean-Christophe M. Monbaliu**

*Jean-Christophe M. Monbaliu is Professor of Organic Chemistry at the University of Liège (Belgium) and Principal Investigator at the WEL Research Institute. He earned his PhD (Organic Chemistry) in 2008 from the Université catholique de Louvain, Belgium. Following several postdoctoral experiences at leading institutions (Ghent University; University of Florida; Massachusetts Institute of Technology), he created the Center for Integrated Technology and Organic Synthesis (CiTOS) at the University of Liège in 2013. Monbaliu also leads the first European Corning® Advanced-Flow™ Reactor Qualified Lab. In 2022, he founded FloW4all, a Flow Technology Platform dedicated to training, technology transfer, and industry services.*

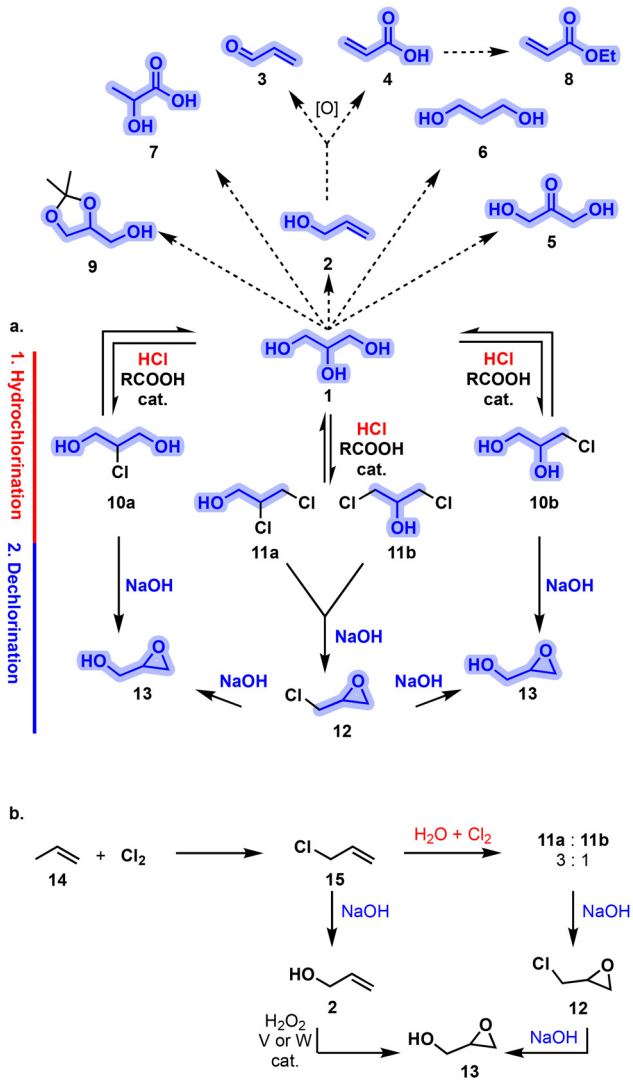



Fig. 2 Some derivatives potentially sourced from glycerol **1**. (a) Production of bio-based monochlorohydrins **10a,b**, dichlorohydrins **11a, b**, epichlorohydrin (**12**) and glycidol (**13**) from **1**. (b) Petro-based route for the synthesis of epichlorohydrin (**12**) and glycidol (**13**).

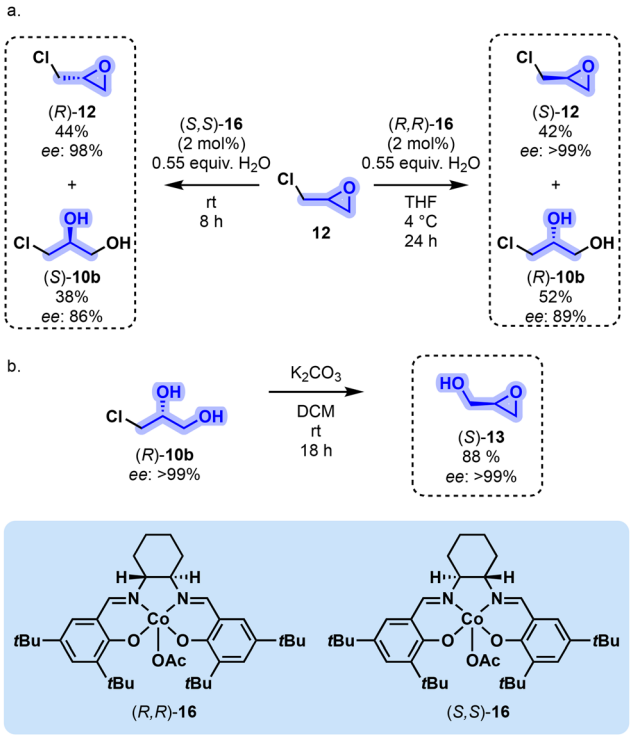



Fig. 3 Access to enantiomerically pure epoxide building blocks by (a) hydrolytic kinetic resolution (HKR) of racemic epichlorohydrin (*rac*-**12**) toward enantioenriched **12** and **10b** using Co-salen complexes and (b) further preparation of (*S*)-**13** from (*R*)-**10b** under basic conditions.

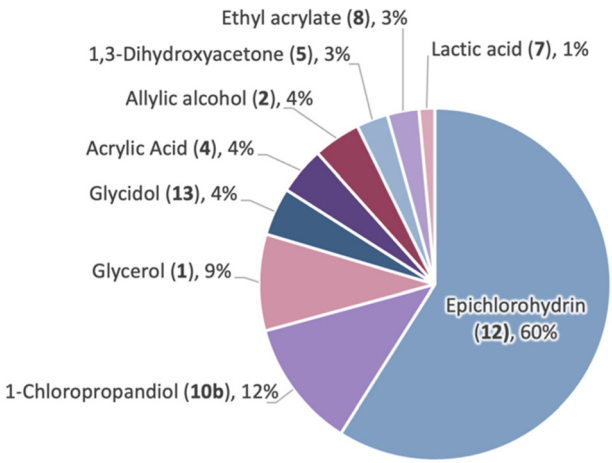



Fig. 4 Distribution of the APIs included in this review according to the potentially glycerol-derived building block incorporated as part of the synthesis.

turning to bio-sourced reagents for the pharmaceutical industry, and particularly, to the use of **1** and derivatives.

One of the main reasons that glycerol (**1**) has been identified as an important bio-based building block is because it can be used in the preparation of highly useful derivatives with established use in the chemical industry. The nova-Institute,[31] a leading thinker for the transition to climate neutrality, has outlined three categories to classify bio-based chemicals,[32] depending on how they can be integrated into current chemical pathways (Fig. 5). Drop-in platforms correspond to compounds that hold established commercial processes and markets. These platforms were initially developed using petro-based compounds; however, they can be replaced by the drop-in counterpart, obtained from biomass using alternative synthetic routes. A subcategory of these compounds, smart drop-in platforms, refers to compounds whose synthesis starting from bio-based sources is potentially more advantageous (*e.g.* shorter or with lower energy requirements) than the route used to obtain them from petro-based sources. Finally, the category of dedicated platform is assigned to bio-based molecules which do not match existing petro-based building blocks, thus paving the way to new uncharted territories. Glycerol (**1**) can be considered a smart drop-in, as it is

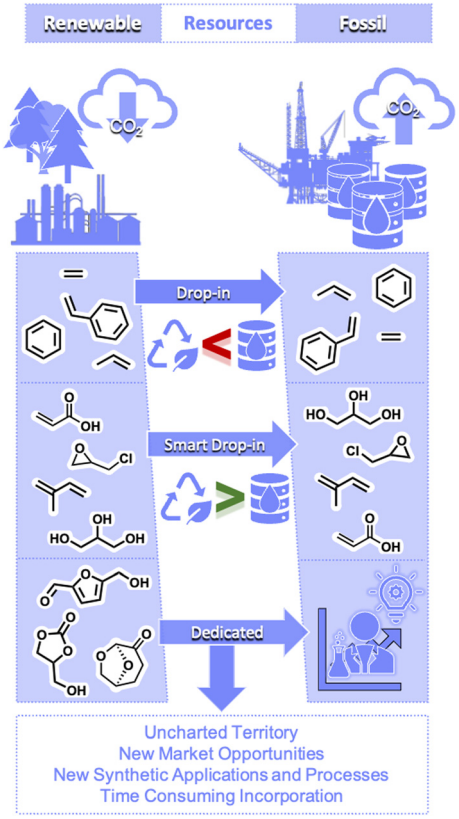



**Fig. 5** Visual summary of the drop-in, smart drop-in and dedicated bio-based platforms concept.

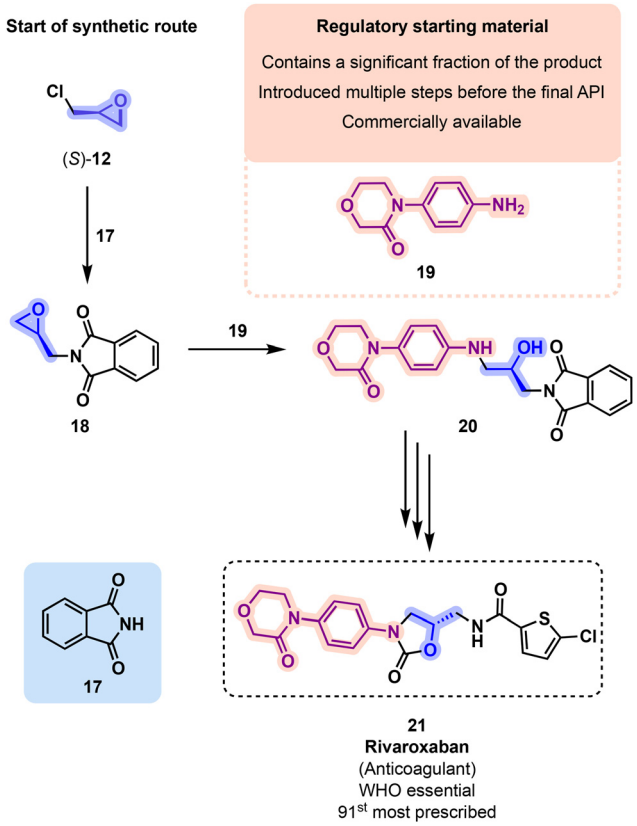



**Fig. 6** Example where potentially renewable (*S*)-**12** is integrated into the synthesis of an API (rivaroxaban, **21**) before introduction of the regulatory starting material (RSM). The administrative burden for a change of source for (*S*)-**12** under this scenario is likely less important.

directly obtained from the hydrolysis of oils. Expanding the uses of **1** is therefore one of the most efficient ways of increasing the use of bio-sourced atoms in current industrial processes, including pharmaceuticals (Fig. 5).

Epichlorohydrin (**12**) obtained from **1** is listed as another smart drop-in platform. As highlighted in Fig. 2, the process starting from propylene is much more energy intensive, relies on dangerous reagents and requires additional steps when compared with the process relying on **1**, therefore confirming the status of smart drop-in of **12**. This clear advantage in the production of bio-based epichlorohydrin (**12**), coupled with the increasing amounts of glycerol by-product from the biodiesel industry, has propelled the steady rise in production of bio-sourced **12** during recent years, specifically for the polymer industry.[33–35]

Despite these advantages, the incorporation of bio-sourced options for the pharmaceutical industries is slow to come. Bio-sourced compounds are tied to the fear of variability, one such being the change of seasons.[36] On occasions, the bio-sourced glycerol obtained does not have the necessary specifications. For example, after the flooding of biodiesel glycerol on the market prompted DOW chemicals to close its synthetic glycerol production facilities in the United States in 2005,[37] some pharmaceutical clients were unable to find bio-sourced glycerol substitutes with sufficient quality to sustain their processes.[36]

On the other hand, many pharmaceutical plants were able to switch to by-product glycerol, with the reduced price of material compensating for the research expenses tied to this change.[36] This points to one of the main challenges toward incorporating bio-based atoms into already marketed drugs. Even a seemingly straightforward switch from a petro-based building block to its structurally identical bio-based counterpart entails an administrative burden related to market authorization. Any change made to the manufacturing process of an authorized API necessitates approval from the pertinent authority. For instance, in Europe, centrally authorized medicines are handled through the European Medicines Agency (EMA), while each Member State's competent authorities (*i.e.* the Federal Agency for Medicines and Health Products, FAMPH, in Belgium)[38] manage the process for nationally authorized medicines. In the US, these matters are under the authority of the U.S. Food and Drug Administration (FDA).[39]

The EMA indicates that the extent of modifications to a given process toward a marketed pharmaceutical dictates the necessary follow-up steps to be undertaken by the Marketing Authorization Holder (MAH). The MAH must demonstrate that the change, *e.g.* in supplier, does not compromise the quality of the finished API product.[40,41] In general, variations can be categorized into minor variations (Type IA and Type IB under

the EMA) and major variations (Type II for EMA), each associated with an increasing administrative/economic burden for the MAH.[42] Briefly, for Type IA variations, the MAH has 12 months to present the documentation to the competent authority, but can implement the variation while continuing to supply the API on the market, whereas for Type IB variations, the MAH must notify the variations and wait for 30 days before implementing them. A variation is considered minor only if all of the following conditions are fulfilled: (a) it does not change the qualitative and quantitative impurity profile and/or the physico-chemical properties of the final API product, (b) no alterations to the synthetic route are introduced, (c) no new reagents, catalysts or solvents are used in the process, and all intermediates remain the same and (d) the specifications of the API product or its intermediates are unaffected. Type II Major variations require extensive documentation and reviewing, as well as an extended timeline (usually 60 days prior to a decision). This could also lead to the possibility of requiring the filing of a new Drug Master File (DMF) with a new market approval application with the necessity for extensive documentation of (im)purity profiles.[42]

Strictly speaking, bio-based and petro-based compounds are identical molecular entities, and there are no specific regulations on replacing one for the other in a process toward a marketed API product. However, the change of supplier or of manufacturing site that would likely be required to switch to bio-based does constitute a variation. Whether the impact of such a variation is considered as minor or major will depend on each case. The main aspect to consider will be the proximity of the synthetic step in which the change is introduced to the final API. To better understand this difference, some familiarity with the concept of Good Manufacturing Practices (GMP) and Regulatory Starting Materials (RSMs) is helpful. These concepts are developed in the guidelines of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).[43]

The (Regulatory) Starting Material (RSM) is a raw material, an intermediate, or an API component that bears a significant structural fragment from the final API structure (*i.e.*, it is not a solvent or reagent, Fig. 6).[44] The decision on which compound in the synthetic pathway is the RSM is made with the regulators and will impact the rigor with which a step will be monitored. The RSM is selected among the steps that impact the impurity profile of the final drug, and should have multiple steps before arriving at the API.[45] The reason is that a greater amount of steps will provide more intermediate purification procedures, which in turn provide greater chances of removing impurities.

Introduction of the RSM into the synthesis marks the step under which Good Manufacturing Practices (GMP) must begin.[44] GMP intends to provide a framework to ensure that APIs meet specific quality and purity criteria. Changing structurally identical petro-based to bio-based glycerol derivatives raises concerns regarding the impurity profiles of the corresponding APIs, and therefore, their Critical Quality Attributes (CQAs). CQAs are specific physical, chemical, biological or microbiological properties or inherent features that should be within an appropriate limit, range, or distribution to ensure the desired product quality.[46] The manufacturing process should identify key material attributes and process conditions affecting API CQAs. This includes understanding the fate and removal of impurities originating from raw materials, which is critical for ensuring the quality of the final API.[45]

The proposed RSM must meet appropriate specifications and be justified, with supporting analytical procedures suited to the detection of impurities and their fate added in subsequent steps. Changes to the specifications of RSMs are therefore type II variations, subjected to post-approval requirements. Additional purification steps may be necessary for commercially available commodities to ensure consistent quality, with specifications provided for both incoming and purified materials.[45] In general, if the synthetic pathway of a compound has been described as part of the drug filing, any modifications will entail a reglementary impact. While the ICH does not explicitly cover upstream changes, it advocates using fundamental science and risk-based concepts to assess their impact.

Aside from its use as or to produce starting materials, glycerol has been used on occasions as a solvent. Specific guidance on replacing petro-based solvents with bio-based ones is currently unavailable. Both the EMA and FDA are committed to supporting the adoption of environmentally friendly manufacturing technologies, a commitment that aligns with the European Union's "Strategic Approach to Pharmaceuticals in the Environment".[47] However, a change of solvent will be treated as a major variation by regulatory agencies, strongly disincentivizing an expansion of the use of glycerol for currently approved APIs. Furthermore, some commercially available bio-based solvents have not yet been included in FDA solvent classes[48] or CHEM21 solvent selection guides.[49]

The following sections review a variety of marketed APIs according to their primary pharmaceutical and biological activity classes, focusing notably on cardiovascular medications. Other pharmaceutical classes include antidepressants, antihistaminics, UV-B protection, alimentary supplements, contrast agents, cholerectics and antihypertensives, among others. This review fits in the overall effort to reduce the environmental burden associated with waste-extensive processes and their inherent reliance on exhaustible petro-based resources. This paves the avenue toward the incorporation of bio-based atoms within the backbone of common pharmaceuticals.

## 3. Active pharmaceutical ingredients derived from glycerol

### 3.1 Cardiovascular pharmaceuticals

Among the various classes of APIs featuring a glycerol-related backbone, numerous examples of pharmaceutical blockbusters concern cardiovascular medications (Fig. 7). Beta blocker agents (section 3.1.1.) are one of the highest selling medications in Western countries. They are aimed at reducing heart rate and contraction force, hence lowering blood pressure. They usually feature a common β-amino alcohol moiety as the

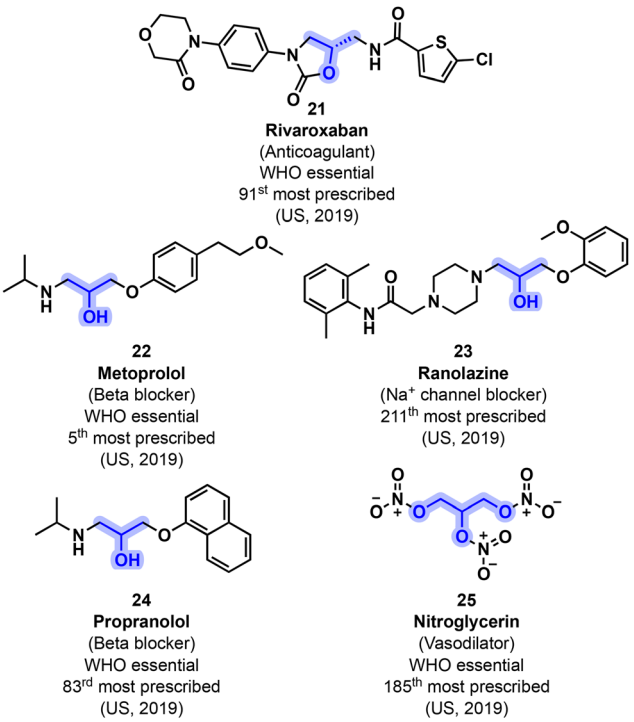



Fig. 7 Representative examples of various classes of cardiovascular medications that could potentially incorporate bio-based glycerol and its derived building blocks.

central feature. Epichlorohydrin **12** and glycidol **13** became centerpieces for the convenient preparation of such derivatives through an etherification/aminolysis sequence. It is worth mentioning that oxirane **12**, with its inherent ambivalent electrophilicity, is commonly preferred over **13**. Section 3.1.2 concerns the use of glycerol-based building blocks to access $Na^+$ channel blockers. $Na^+$ channel blockers regulate cardiac action potentials and are prescribed for the treatment of cardiac arrhythmias. Other cardiovascular medications include anticoagulants and vasodilators, which prevent blood clotting and lower the blood pressure, respectively. These medications can also be potentially accessed through glycerol-derived building blocks and are discussed in sections 3.1.3 and 3.1.4, respectively.

**3.1.1 Beta blockers.** The beta blocker group of APIs gathers drugs for the treatment of various cardiovascular conditions such as arrhythmias, angina pectoris, and hypertension or to prevent heart failure. β-Blockers typically feature a central β-amino alcohol moiety **27**, which generally originates from an oxirane derivative such as **12**. The general process is illustrated in Fig. 8 and involves a glycidyl ether synthesis (toward **26**) and a subsequent aminolysis toward **27**.[50]

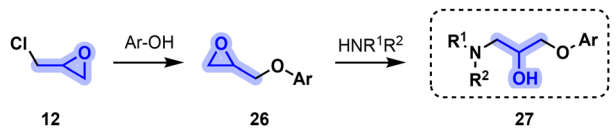



Fig. 8 Common synthetic route toward beta blockers **27** featuring a β-amino alcohol moiety starting from epichlorohydrin (**12**).

Among the various beta blockers derived from **12**, six APIs are part of the WHO list of essential medicines[51] and are amongst the most prescribed drugs in the US (Table 1).[52] On top of these, twelve additional beta blockers are listed in Table 1 alongside their structure, indications and class.

In addition to containing the familiar amino alcohol scaffold, carteolol (**41**) incorporates another glycerol-derived building block in its cyclic moiety, namely, acrylic acid (**4**). Phenol-derived intermediate **46** is obtained by reacting acrylic acid (**4**) with α-β unsaturated ketone **44** before reducing the resulting intermediate with carbon-supported palladium and hydrogen. Williamson etherification between epichlorohydrin (**12**) and **46** leads to glycidyl ether **47**, the latter then undergoing ring-opening aminolysis by *tert*-butylamine to obtain carteolol[53] (**41**, Fig. 9).

Aside from being a renewable source of valuable oxiranes, glycerol (**1**) can act as a green polar protic solvent. As such, and taking advantage of the protic nature of **1**, Hussain, Kumar and coworkers developed a procedure toward propranolol (**24**) and atenolol (**29**) from aryl glycidyl ethers (**26**) and isopropyl amine in the presence of glycerol as both solvent and catalyst (Fig. 10). Propranolol (**24**) and atenolol (**29**) were obtained with 97% and 93% yields respectively in under 3 h. Additionally, glycerol was easily recycled and retained its reactivity even after up to 4 cycles: on the 5th cycle, yields started to drop below the 90% mark.[54]

**3.1.2 $Na^+$ channel blockers.** Sodium channel blockers are typically used for treating various arrhythmias. Among $Na^+$ channel blockers, propafenone (**52**) and ranolazine (**23**) are prepared starting from oxirane **12** to install the central β-amino alcohol moiety. A subsidiary of BASF developed a process toward **52** relying on the reaction of **12** with hydroxyacetophenone **48**. The first step leads to glycidyl ether intermediate **49**, which is further reacted with propylamine to yield β-amino alcohol **50** (Fig. 11). In a subsequent step, **50** is reacted with benzaldehyde (**51**) and then reduced to give **52**.[55]

Ranolazine (**23**), another β-amino alcohol derivative with $Na^+$ channel blocking properties, was the 211th most prescribed drug in the U.S. (2.5 million) in 2019.[56] It can be obtained by reacting **12** with guaiacol (**53**), another potentially bio-based building block, leading to glycidyl ether intermediate **54** (Fig. 11). Using piperazine-derived reactant **55** in conjunction with **54** allows ranolazine (**23**) to be obtained.

**3.1.3 Anticoagulants.** Anticoagulating agents are another important class of cardiovascular medications. One of the most notorious anticoagulants is warfarin, which has been used since the 1940s; however, the emergence of deleterious interactions of warfarin with other medications triggered a demand for alternatives such as rivaroxaban (**21**, Fig. 12).

Rivaroxaban (**21**) was developed by Bayer Healthcare and patented in 2007. Its preparation starts from (*S*)-**12** and phthalimide **17** (Fig. 12). Intermediate **18** is next reacted with aniline derivative **19** to yield diamino alcohol **20**, which is next cyclized with **56** toward oxazolidinone **57**. Final deprotection followed by a reaction with thiophene **58** ultimately gives **21**.[57] Rivaroxaban is currently marketed by Bayer and by Janssen (in

**Table 1** Approved beta blocker medications presenting a central β-amino alcohol moiety constructed from epichlorohydrin **12**. The medications included in WHO essential medicines are indicated with WHO. Medications in the top 300 prescriptions in 2019 are indicated by the number (#) ranking

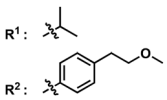
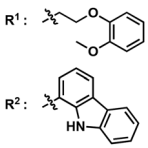
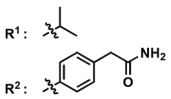
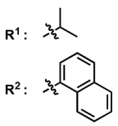
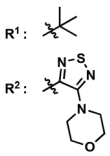
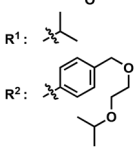
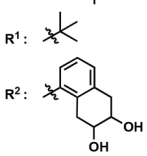
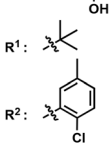
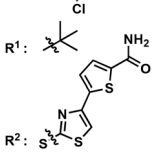
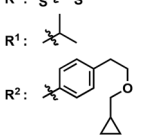
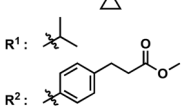
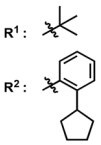
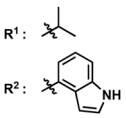
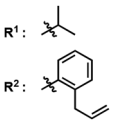
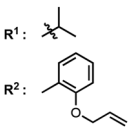
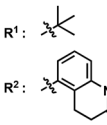
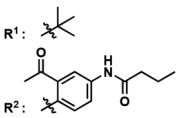
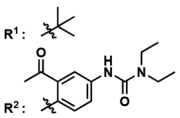
| Name | Structure | Indications |
|---|---|---|
| Metoprolol (**22**)<br>WHO #5 |  | Angina pectoris<br>Hypertension<br>Myocardial infarction<br>Tachycardia<br>Heart failure |
| Carvedilol (**28**)<br>WHO #33 |  | Hypertension<br>Heart failure |
| Atenolol (**29**)<br>WHO #39 |  | Angina pectoris<br>Hypertension<br>Myocardial infarction<br>Tachycardia<br>Hyperthyroidism |
| Propranolol (**24**)<br>WHO #83 |  | Angina pectoris<br>Hypertension<br>Myocardial infarction<br>Tachycardia<br>Migraine prophylaxis |
| Timolol (**30**)<br>WHO #160 |  | Hypertension<br>Myocardial infarction<br>Migraine prophylaxis<br>Glaucoma |
| Bisoprolol (**31**)<br>WHO |  | Angina pectoris<br>Hypertension<br>Heart failure<br>Glaucoma |
| Nadolol (**32**) |  | Angina pectoris<br>Hypertension<br>Arrhythmia |
| Bupranolol (**33**) |  | Hypertension<br>Tachycardia<br>Glaucoma |
| Arotinolol (**34**) |  | Hypertension<br>Tachycardia<br>Glaucoma |
| Betaxolol (**35**) |  | Hypertension<br>Glaucoma |
| Esmolol (**36**) |  | Hypertension<br>Tachycardia |

**Table 1** *(Contd.)*

| Name | Structure | Indications |
|---|---|---|
| Penbutolol (**37**) |  | Hypertension |
| Pindolol (**38**) |  | Hypertension |
| Alprenolol (**39**) |  | Angina pectoris |
| Oxprenolol (**40**) |  | Angina pectoris<br>Hypertension<br>Arrhythmia |
| Carteolol (**41**) |  | Hypertension<br>Glaucoma |
| Acebutolol (**42**) |  | Hypertension<br>Arrhythmia |
| Celiprolol (**43**) |  | Hypertension<br>Angina pectoris |

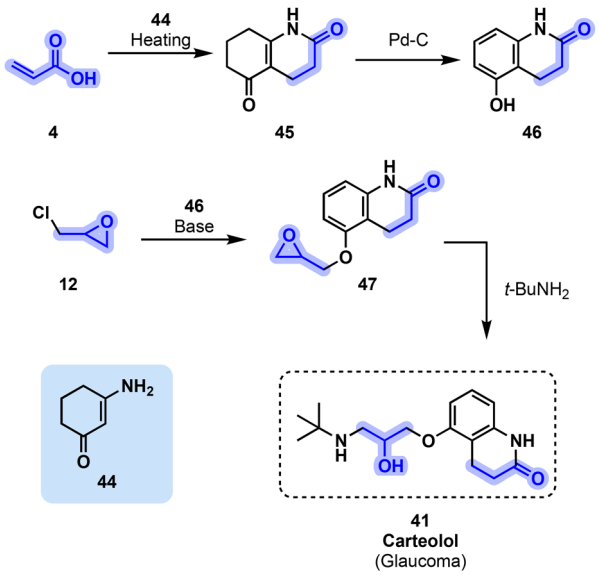



**Fig. 9** Preparation of beta-blocker **41**, highlighting the incorporation of acrylic acid (**4**) and epichlorohydrin (**12**).

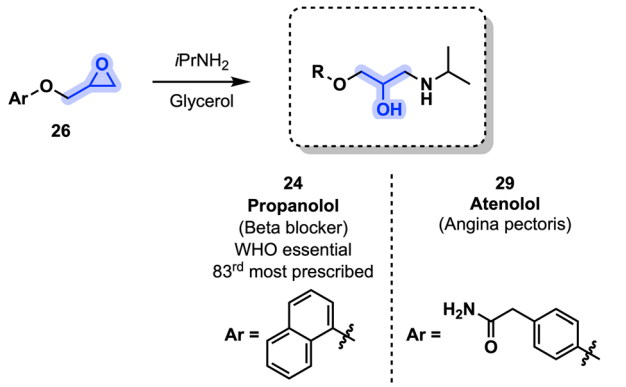



Fig. 10 Synthesis of beta-blockers **24** and **29** relying on glycerol (**1**) as solvent and catalyst for the aminolysis of glycidyl ether (**26**).

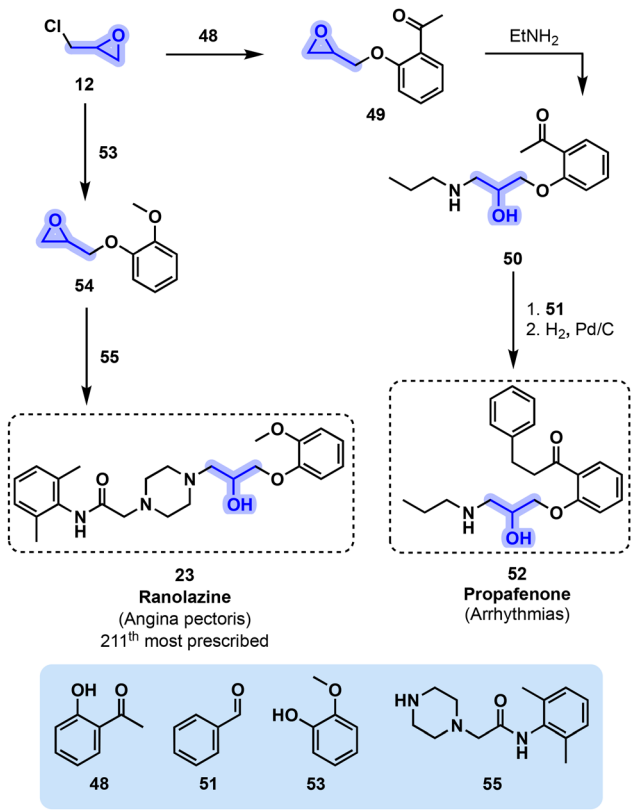



Fig. 11 Synthetic pathways toward $Na^+$ channel blockers propafenone (**52**) and ranolazine (**23**) starting from epichlorohydrin (**12**).

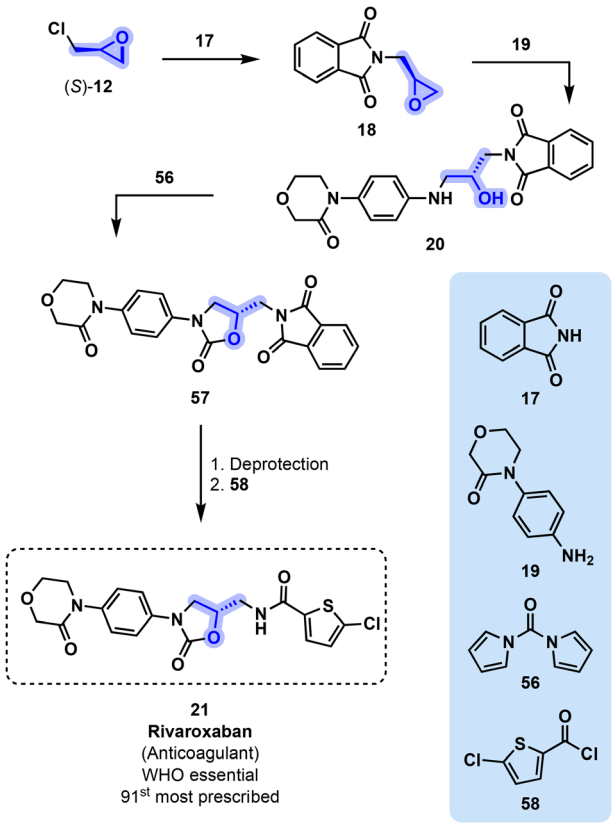



Fig. 12 Synthetic route toward rivaroxaban (**21**) starting from (*S*)-epichlorohydrin (**12**).

the U.S.) since 2011. It was prescribed 8.8 million times in the U.S. in 2019 and is present on the WHO's list of essential medicines.[51]

**3.1.4 Vasodilators.** Vasodilators directly act on vessel wall smooth muscle cells, inducing their relaxation. Vasodilation can help decrease blood pressure and is thus used in the treatment of hypertension, angina pectoris and heart failure.[58]

Among vasodilators, a subclass regroups various organic molecules featuring nitrate functional groups. Metabolism of these derivatives leads to the generation of nitric oxide (NO), a strong natural vasodilator. For instance, nitroglycerin (**25**) has been used to treat angina pectoris for more than 150 years. Compound **25** can be directly sourced from glycerol (**1**) by using a nitration mixture ($HNO_3/H_2SO_4$) (Fig. 13).[59] Nitroglycerin was prescribed more than 3.1 million times (US, 2019) and is considered a WHO essential medication.[51,52]

Xanthinol (**62**) is another vasodilator agent that can be sourced from theophylline (**59**) and oxirane **12**. Oxirane **12** reacts with **59** to yield chlorohydrin intermediate **60**, which is then further reacted with amino alcohol derivative **61** to produce xanthinol (**62**, Fig. 14). The usual formulation includes a nicotinate salt.[60]

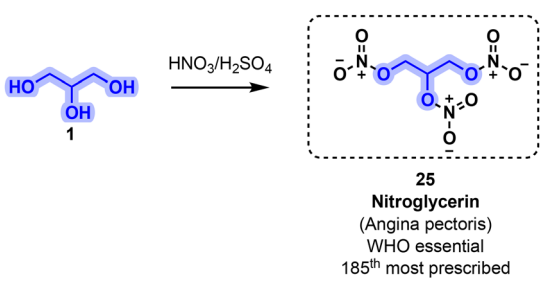



Fig. 13 Industrial process used for the manufacture of nitroglycerin (**25**) starting from glycerol (**1**).

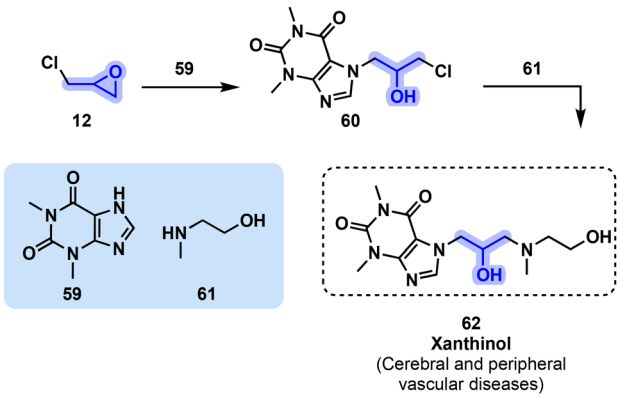



Fig. 14 Synthesis of xanthinol (**62**) starting from theophylline (**59**) and epichlorohydrin (**12**).

As opposed to beta amino alcohols described above, eprosartan (**70**) is a molecule exhibiting angiotensin II receptor blocking properties, allowing the reduction of vasoconstriction and decrease of blood pressure through a different biological mechanism. It is currently marketed by Abbot industries in the US after purchasing Kos Pharmaceuticals which was evaluating a scope of antihypertensive drugs.

Eprosartan (**70**) can be obtained following several synthetic pathways. GSK patented a procedure which relies on 1,3-dihydroxyacetone (**5**) for the synthesis of pyrazole intermediate **64**. Dihydroxyacetone (**5**), a potentially glycerol-derived molecule, is first reacted with amidine **63** in the presence of liquefied ammonia before undergoing acetylation by acetic anhydride. The cyclic intermediate is then reacted with benzyl alcohol derivative **65** in the presence of a base and trifluoroacetic anhydride to yield the corresponding diester **66**. The latter is then hydrolyzed by aqueous NaOH, and the alcohol thus obtained is oxidized into its corresponding aldehyde by $MnO_2$. The penultimate synthetic step consists in an aldol condensation of aldehyde intermediate **67** with thiophene derivative **68** in the presence of LDA. The resulting alcohol is then acetylated to yield intermediate **69**. Finally, a DBU-triggered elimination reaction results in eprosartan (**70**, Fig. 15). This route manages to incorporate all three carbon atoms of **5**.[61]

### 3.2 Musculoskeletal medications

Myorelaxants can be divided into 3 subclasses: (a) drugs used during surgery or assisted ventilation, (b) drugs for the treatment of spasms and (c) short-term pain relievers for spasms arising from musculoskeletal conditions.[62] The latter includes common over-the-counter medicines and gathers a variety of drugs that can be produced from glycerol and derivatives.

For instance, guaifenesin (**72**) was marketed in the 1930s and as of today is still used as an expectorant. Now available as a generic medication, **72** was still the 256$^{th}$ most prescribed drug in the U.S. in 2019.[52] Guaifenesin can be prepared from bio-based guaiacol (**53**) and glycerol (**1**), or one of its activated derivatives such as monochlorohydrin (**10b**) or oxiranes **12**, **13**.

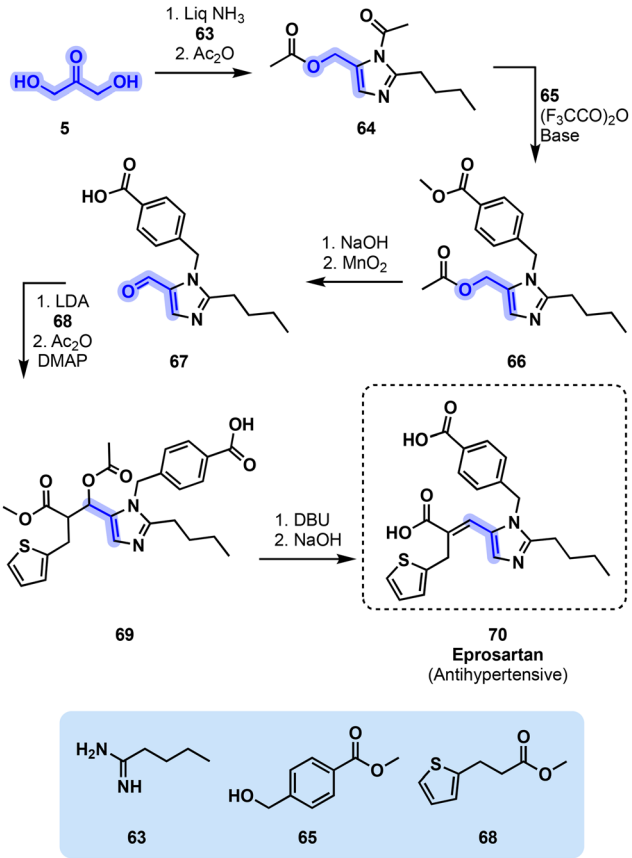



Fig. 15 Multistep synthesis of antihypertensive **70** from 1,3-dihydroxyacetone (**5**).

The most common preparation of **72** involves a straightforward Williamson ether synthesis (Fig. 16, R = OMe).[63]

Methocarbamol (**75**), a carbamate derivative of **72**, can be subsequently obtained by using diethyl carbonate (**74**) and

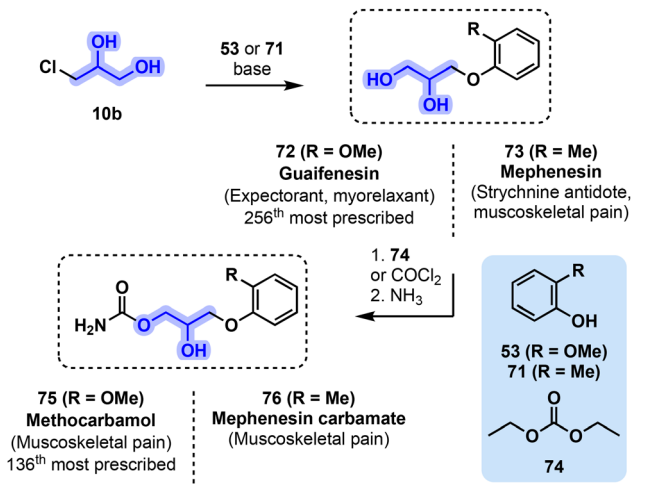



Fig. 16 Common synthetic pathways toward guaifenesin (**72**, R = OMe), mephenesin (**73**, R = Me) and their carbamate derivatives methocarbamol (**75**, R = OMe) and mephenesin carbamate (**76**, R = Me).

ammonia toward methocarbamol (**75**, Fig. 16, R = OMe).[64] Methocarbamol (**75**) was approved by the US Food and Drug Administration (FDA) in 1957 and is used for the short-term management of musculoskeletal conditions.[65] Now available as a generic prescription drug, **75** was the 136th most prescribed drug in the U.S. in 2019.[56]

Mephenesin (**73**) is structurally closely related to **72**, yet its applications have been limited to some cases of strychnine poisoning in combination with barbiturates as an antidote.[66] It was however never prescribed as a myorelaxant, owing to severe deleterious side-effects including respiratory conditions and addiction. Compound **73** is currently discontinued in the U.S. and in France, yet it still finds applications as an ingredient for ointments in various countries.[67] The preparation of **73** is similar to **72** and involves the reaction of a monochlorohydrin **10b** with phenol derivative **71** (Fig. 16, R = Me).[68]

A carbamate derivative **76** is currently used for various musculoskeletal pain conditions and can be directly obtained from **73** after a treatment with phosgene and ammonia (Fig. 16, R = Me).[69] Mephenesin carbamate (**76**) was marketed in the U.S. starting from 1954.[70]

Oxazolidinone myorelaxants can be directly derivatized from vicinal diols such as **72** and analogs. For instance, mephenoxalone (**77**) is obtained from guaifenesin (**72**) through the reaction of **72** with urea (Fig. 17a).[71] Mephenoxalone (**77**) is prescribed for the treatment of muscular spasms and as an anxiolytic. It was approved in the US since 1961.[72] Metaxalone (**79**) is another oxazalidinone myorelaxant that can also be obtained by treating **78** with urea (Fig. 17b).[73] Metaxalone was approved in 1962 and is mainly used for the management of musculoskeletal pain.[74] It was the 332nd most prescribed drug in the U.S. in 2018 and is available as a generic medication.[75]

Another 1,2-propanediol derivative related to pharmaceuticals **72** and **73** is chlorphenesin **81** (Fig. 18), but while it presents myorelaxant properties, safer alternatives are available. It is nowadays mostly used as an antibiotic and antifungal (see section 3.1.1, *vide infra*).

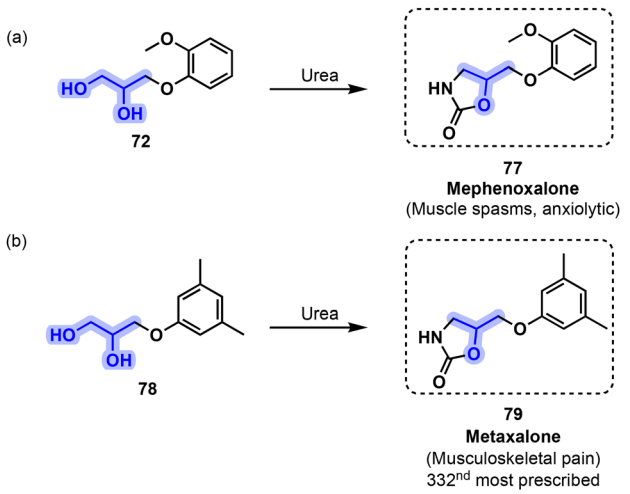



**Fig. 17** Preparation of the oxazolidinone-based muscle relaxants (a) mephenoxalone (**77**) and (b) metaxalone (**79**) from vicinal diols **72** and **78** in the presence of urea.

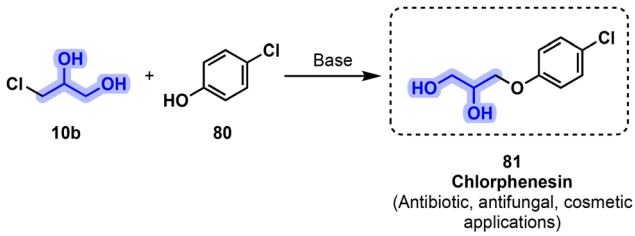



**Fig. 18** Synthesis of antibiotic and antifungal chlorphenesin (**81**) through a Williamson etherification with monochlorohydrin **10b**.

### 3.3 Antimicrobial medications

Antimicrobial drugs include all medications that kill or weaken the growth of microorganisms and are generally classified based on the type of pathogen affected, which includes antibiotics, antifungals, antiparasitics and antivirals. APIs that are efficient against multiple classes of microorganisms are defined as broad-spectrum therapeutics.[76] Nowadays, antimicrobial resistance (AMR) is considered by the WHO as one of the biggest threats to global health, food security and development.[77] In 2019, an estimated 1.27 million deaths were attributed to AMR.[78] Drug-resistant diseases could lead to 10 million deaths per year by 2050 if no proper mitigation strategy is established.[79] The development of new antimicrobial medications especially with narrow-spectrum applications in addition to other approaches such as phage therapy or vaccines is therefore of critical importance.[80–82] Antimicrobial API sourcing is highly dependent on petro-based resources similarly to other APIs, yet several examples including some essential medicines present central moieties that can be constructed from glycerol (**1**) or its derived building blocks. A (partially) bio-based synthetic pathway of key antimicrobials could secure an alternative sourcing of these important drugs against high volatility price and availability of raw materials.

**3.3.1 Antibiotic medications.** One of the main classes of antimicrobials is those used to tackle bacteria (antibiotics). Since the discovery of penicillin by Fleming in 1928, the development of substances used to fight bacterial infections has continued to be critical. Antibiotics are usually classified according to their mechanism of action or targets; however, specific pharmacophores can also gather several entities and are usually related to similar targets and mechanisms.

As discussed in section 3.2, **81** was first used for its muscle relaxant properties but is nowadays mostly used as biocide and fungicide in cosmetic applications. It is used against Gram-positive and Gram-negative bacteria as well as various fungi. In 2011 it was used in more than 1300 cosmetic preparations.[83] Its preparation is relatively similar to other 1,2-diol muscle relaxants and consists of a Williamson ether synthesis

between **10b** and an adapted phenol derivative **80** in the presence of a base (Fig. 18).

A major breakthrough in the advancement of antibiotics happened in the early 2000s with the development of linezolid, the first FDA-approved oxazolidinone used for the treatment of bacterial infection.[84] Active against a large variety of Gram-positive bacteria, linezolid (**86**, Fig. 19) is used to treat skin conditions, pneumonia and tuberculosis involving drug-resistant pathogens.[85]

This WHO essential medicine[51] is now available as a generic medication. Linezolid was developed by scientists from Pharmacia & Upjohn (now part of Pfizer) in the 1990s and approved by the FDA in 2000.[86] The original process-scale synthesis of **86** involves the use of (*S*)-**10b** in conjunction with derivative **83** (obtained from **82**) to form the central oxazolidinone cycle toward **84** under basic conditions. Next, an amine derivative **85** is obtained from **84** to finally form the amide moiety of linezolid (**86**) with acetic anhydride (Fig. 19).[84] An alternative 7-step synthesis of **86** using (*S*)-epichlorohydrin ((*S*)-**12**) was recently reported.[87]

Tedizolid (**90**, Fig. 20) is a second oxazolidinone antibiotic structurally related to **86** that was approved in 2014 by the FDA for the treatment of acute skin infections.[88] Tedizolid (**90**) is effective against Gram-positive pathogens through protein synthesis inhibition and shows a higher potency for the treatment of staphylococci- and enterococci-related infections compared to linezolid.[89] The drug was originally discovered by South Korean company Dong-A Pharmaceuticals and developed by Cubist Pharmaceuticals (USA, now part of Merck & Co.).[90]

Preparation of **90** involves a critical intermediate (*R*)-**88** that can be produced from epichlorohydrin (**12**) through an enantioselective reaction involving a Co-salen complex. (*R*)-**88** is then reacted with tetrazole derivative **89**, which itself is obtained from commercially available pyridine derivative **88** in a multistep process. Tedizolid (**90**) is finally obtained from (*R*)-**88** and **89** using LiHMDS and DMPU. The corresponding phosphate prodrug **91** is directly obtained from **90** using $POCl_3$ (Fig. 20).[91–93]

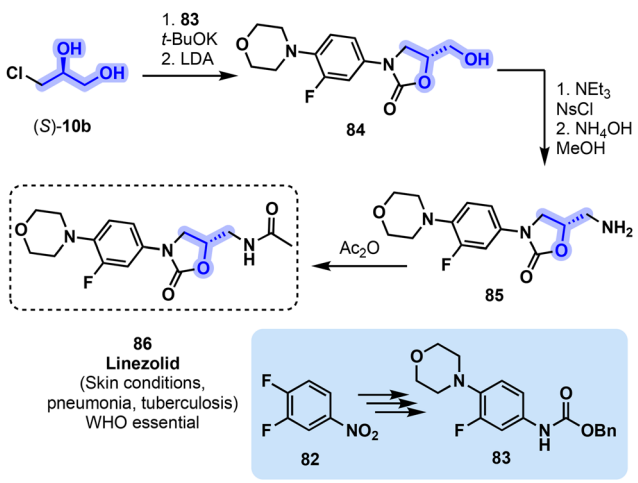



**Fig. 19** Process-scale synthesis of linezolid (**86**) involving building block (*S*)-**10b**. LDA = lithium diisopropylamide, NsCl = 4-nitrobenzenesulfonyl chloride.

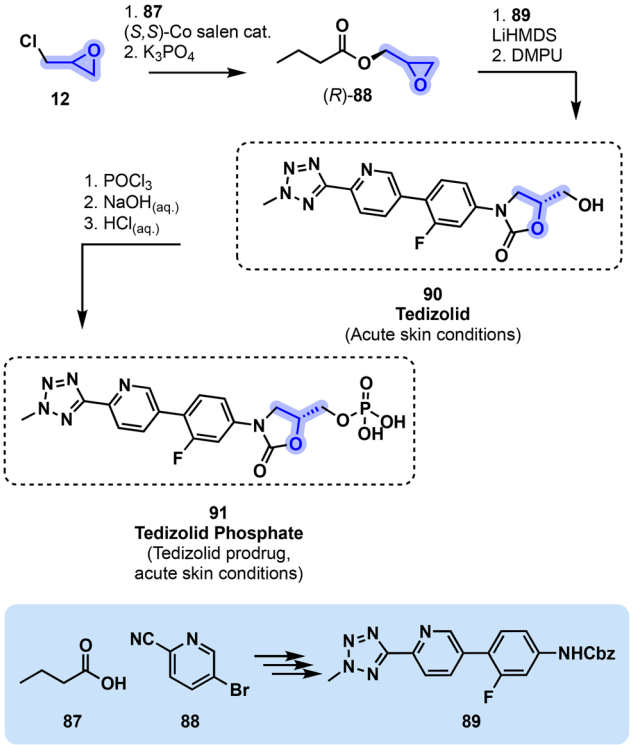



**Fig. 20** Process-scale synthesis of tedizolid (**90**) and its phosphate prodrug **91** involving epichlorohydrin (**12**). LiHMDS = lithiumbis(trimethylsilyl)amide, DMPU = *N*,*N*′-dimethylpropyleneurea.

Another common structure frequently encountered in antibiotic medications is related to nitrofurans. Nifuratel (**96**) presents a characteristic nitrofuran moiety additionally to an oxazolidinone ring. It is used as a broad-spectrum treatment for vaginitis. Nifuratel (**96**) is efficient against *Chlamydia trachomatis* and presents antifungal and antiprotozoal activity. A combination with another drug, nystatin, is frequently used to ensure the elimination of all pathogens that could cause a vaginal inflammation.[94] Nifuratel (**96**) is available and approved in various European and Asian countries. Its preparation involves epichlorohydrin (**12**) which is first converted to **92** using MeSH in the presence of a base. Next, hydrazine is used to form **93** from **92**, which is subsequently reacted with carbonate **74** to form oxazolidone **94**. Nitrofuran **95** is finally reacted with **94** toward nifuratel (Fig. 21, **96**).[95,96]

Furaltadone (**101**) is only differentiated from **96** by a morpholine ring in place of a methylthioether. Furaltadone (**101**) is a veterinary drug mostly used to treat gastrointestinal infections of livestock. Its synthesis is similar to nifuratel (**96**) and starts with epichlorohydrin (**12**) and morpholine (**97**) in the presence of a base toward a first epoxide intermediate (**98**). Treatment with hydrazine leads to **99** which is further reacted with diethyl carbonate (**74**) leading to oxazolidinone **100**. Finally, **100** and nitrofuran **95** are reacted to form furaltadone (**101**, Fig. 21).[97,98]

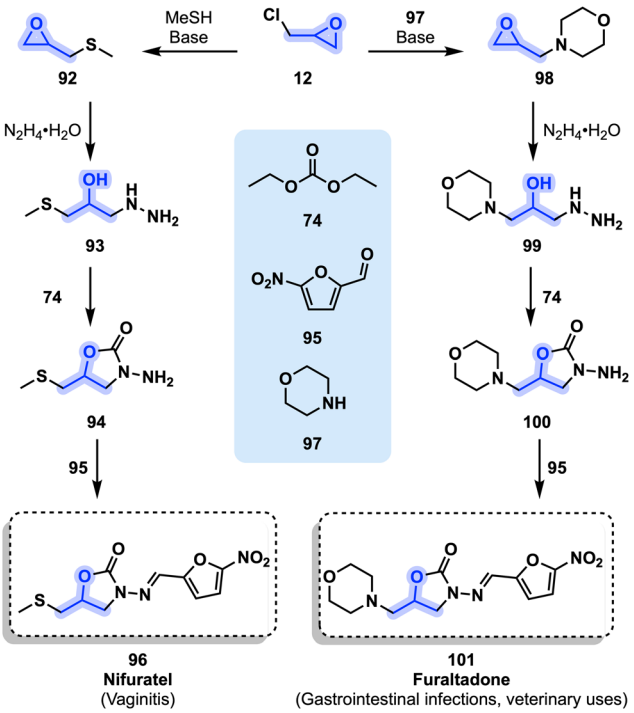



Fig. 21 Synthesis of nifuratel (**96**) and furaltadone (**101**) from epichlorohydrin (**12**) and a nitrofuran derivative **95**.

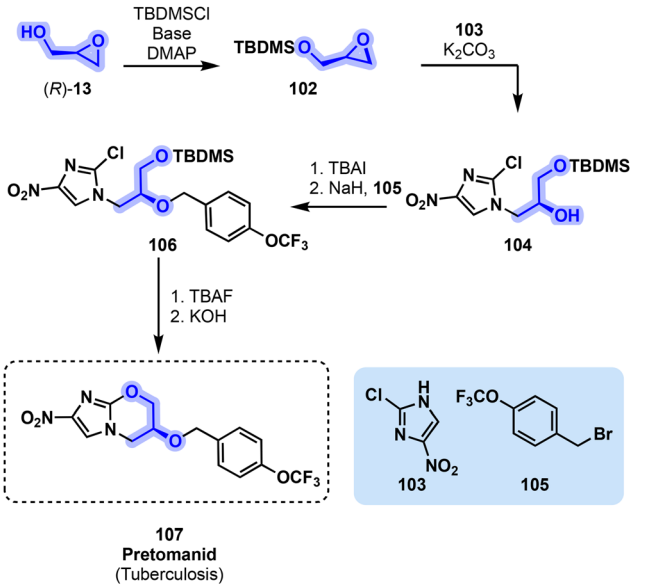



Fig. 22 Synthetic pathway toward pretomanid (**107**) involving (*R*)-glycidol ((*R*)-**13**). TBDMSCl = *tert*-butyldimethylsilyl chloride, DMAP = 4-dimethylaminopyridine, TBAI = tetra-*n*-butylammonium iodide, TBAF = tetra-*n*-butylammonium fluoride.

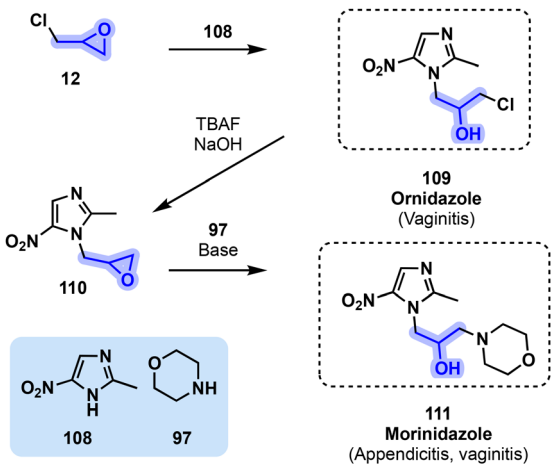



Fig. 23 Preparation of nitroimidazole APIs ornidazole (**109**) and morinidazole (**111**) from epichlorohydrin (**12**). TBAF = tetra-*n*-butylammonium fluoride.

A recently approved nitroimidazole derivative pretomanid (**107**) is another important antibiotic. It is used in the treatment of multidrug-resistant tuberculosis in combination with other antibiotics including linezolid (**86**). Pretomanid (**107**) was developed by the Global Alliance for Tuberculosis Drug Development located in South Africa and was approved by the FDA in 2019 as a first-in-class medication.[99,100] A synthetic pathway toward pretomanid (**107**) involves the use of (*R*)-glycidol ((*R*)-**13**) for the production of protected epoxide **102**. A nitroimidazole derivative **103** is next reacted with **102** in the presence of a base, leading to **104**. The unprotected alcohol of **104** is next functionalized with bromobenzyl derivative **105**, affording compound **106**. A final deprotection of the primary alcohol followed by cyclization affords pretomanid (**107**, Fig. 22).[90,101,102]

Another nitroimidazole antibiotic, ornidazole (**109**, Fig. 23), is used in the treatment of infections caused by anaerobic bacteria and is itself an intermediate for the synthesis of morinidazole (**111**). Both **109** and **111** have been found to display broad-spectrum antiparasitic properties in addition to their antibacterial applications. They are used in the treatment of various types of vaginitis including trichonomiasis.[103] Morinidazole can also be used in appendicitis events. Ornidazole (**109**) is available in various European and Asian countries while morinidazole (**111**) was approved by the China Food and Drug Administration (CFDA) in 2014.[90] Ornidazole (**109**) can be directly obtained through an acid-catalyzed reaction between epichlorohydrin (**12**) and nitroimidazole **108**. A ring closure of **109** under basic conditions affords the corresponding epoxide **110** that can be directly converted to morinidazole (**111**) through an aminolysis with morpholine derivative **97** (Fig. 23).[90,104]

**3.3.2 Antifungals.** Antifungal medications are used in the treatment of a wide variety of mycoses such as ringworm, athlete's foot, thrush and certain types of meningitis. Antifungals can be either local or systemic, mostly acting as inhibitors of the synthesis of critical sterol derivatives such as ergosterol.[105,106] Similarly to antibiotics, drug-resistance in fungi is a serious concern and the development of novel medications or treatments is urgently needed.[106,107] Additionally to

chlorphenesin (**81**) and nifuratel (**96**) discussed above, other antifungal medications can be sourced from glycerol and its derivatives.

Terbinafine (**117**) is part of the allylamine family of antifungal agents. It is considered as an essential medicine by the WHO and was the 277th most prescribed drug in the US in 2019.[51,52] It is used in the treatment of a variety of nail and skin infections. It is available since the 1990s in Europe and in the US.[108,109] A potential synthetic pathway toward **117** starts from epichlorohydrin (**12**) and secondary amine **112** to generate intermediate **113** under basic conditions. Next, **113** is reacted with organolithium derivative **114** in the presence of a Lewis acid ($BF_3{\cdot}OEt_2$) toward β-amino alcohol **115**. Terbinafine (**117**) is finally obtained through the activation of **115** with MsCl and a base followed by addition of DBU and heating (Fig. 24).[109]

Another main class of antifungals relates to azole compounds. Developed in the 1970s by Janssen Pharmaceutica, azole antifungals rapidly emerged as an important branch of medications treating various types of mycosis. Ketoconazole (**125b**, Fig. 25), an imidazole derivative, was approved by the FDA in 1981 and is still one of the most prescribed drugs in the US (171st, 2019).[52] As of today, the use of oral ketoconazole (**125b**) is strictly limited because of its hepatotoxicity and only indicated when other alternatives are not available. The topical use of **125b**, however, is still considered safe and is employed in the treatment of various conditions.[110] Terconazole (**125a**) is another antifungal azole medication developed by Janssen Pharmaceutica that is structurally related to **125b**. It was approved for medical use by the FDA in 1987 and is mainly

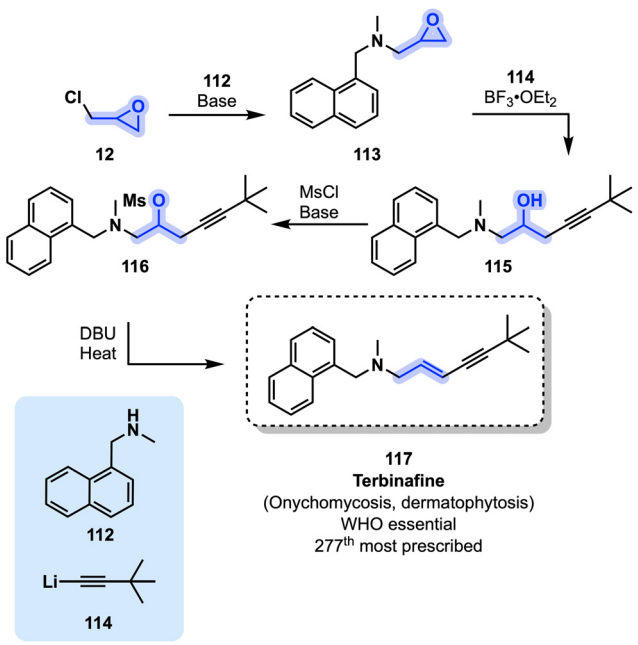



Fig. 24 Synthesis of antifungal drug terbinafine (**117**) from epichlorohydrin (**12**). MsCl = methanesulfonyl chloride, DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene.

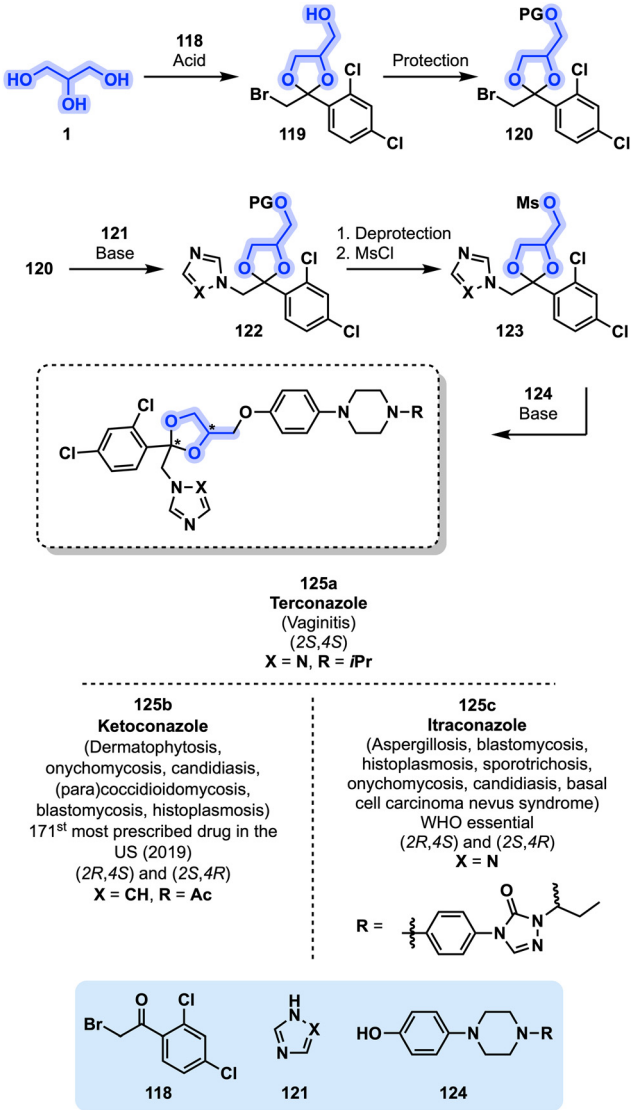



Fig. 25 General synthetic pathway toward antifungal azoles **125a–c** bearing a central dioxolane ring from glycerol (**1**). PG = protecting group, MsCl = methanesulfonyl chloride.

used in the topical treatment of vaginitis caused by *Candida* fungi.[111,112] Itraconazole (**125c**) is a critically important azole antifungal developed concomitantly with **125a** and **125b** in the 1970s. Itraconazole (**125c**) displays antifungal activity against a broader spectrum of pathogens than ketoconazole (**125a**) and is used to treat a large variety of mycoses.[105,113,114] It was approved by the FDA in 1992, is part of the list of essential medicines of the WHO and was designated as an orphan drug by both the FDA and the EMA for the treatment of basal cell carcinoma nevus syndrome and the prevention of invasive aspergillosis, respectively.[51,115,116]

A general synthetic procedure toward azole antifungals **125a–c** starting from glycerol (**1**) can be found in the original patents from Janssen.[117,118] Acetalization using **1** and arylketone **118** allows the generation of the central dioxolane core

**119** in which the primary alcohol is protected leading to **120**. Next, depending on the desired product, an imidazole or triazole derivative **121** is employed in a substitution reaction leading to **122**. A deprotection of **122** followed by functionalization using MsCl allows the generation of mesylate **123** which can be reacted with piperazine derivative **124** to finally generate antifungal azoles **125a–c** (Fig. 25).

Triacetin (**126**) is mostly used in cosmetic applications, as a food additive (E1518) and as an excipient, and finds further use as a solvent or humectant.[119] The first synthesis of triacetin dates back to the 19th century and it is generally produced through an esterification using acetic acid or acetic anhydride with an optional acid or basic catalyst (Fig. 26).[120] Antifungal properties of **126** have been observed, due to decomposition and the release of acetic acid by esterases located in fungi. It is used in the treatment of superficial dermatomycoses.[119,121]

**3.3.3 Antiparasitics.** Antiparasitics are used in the treatment of various diseases caused by organisms such as helminths, amoebae or protozoa. Among the diverse conditions caused by parasites, some neglected tropical diseases (NTDs) have been highlighted by the World Health Organization to cause significant mortality and morbidity despite negligible considerations in global health policies.[122] Occurring in sub-Saharan regions of Africa, African trypanosomiasis (sleeping sickness) is an NTD that provoked *ca.* 3500 deaths in 2015 (down from 34 000 in 1990)[123] and which is caused by some species of *Trypanosoma brucei* protozoa generally transmitted by infected tsetse fly bites. After an initial stage of fever, headaches, joint pains, and itching, a second stage ensues resulting in confusion, poor coordination and sleeping disorder symptoms leading to death without proper treatment.[124] Melarsoprol (**131**) is a first-line treatment for the second stage of African trypanosomiasis and is considered as an essential medicine by the WHO.[51] The synthesis of **131** is shown in Fig. 27.

Preparation of **131** usually involves the use of dimercaprol (**127**), which is itself part of the WHO's essential medicine list. It is employed as a chelating agent for heavy metal poisoning (*e.g.*, Hg, As, Pb). More recently, dithiol **127** was accepted by the FDA as a treatment against Wilson's disease, a condition consisting of the accumulation of copper in the brain and liver with neurological consequences.[125] Though varying methods toward dimercaprol were developed, the first one relied on allyl alcohol (**2**), which is brominated before being treated by

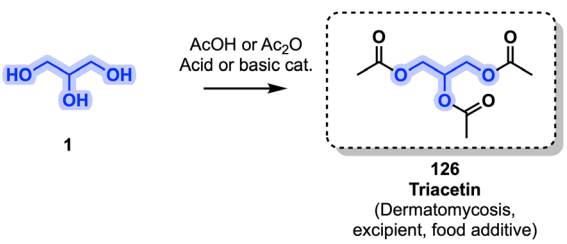



**Fig. 26** Common preparation of triacetin (**126**) from glycerol (**1**).

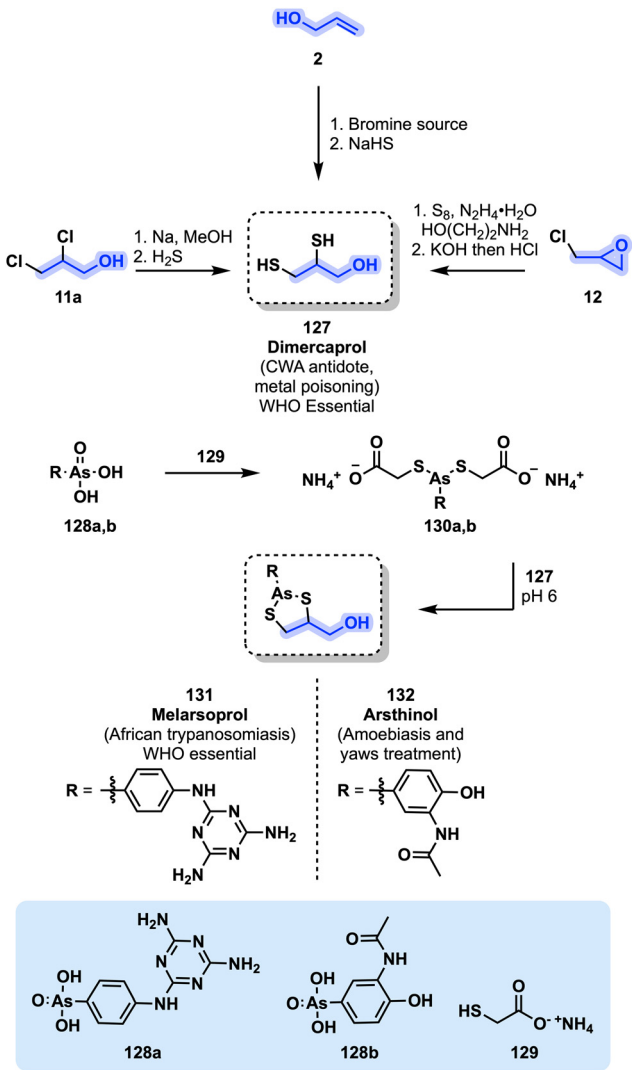



**Fig. 27** Preparation of chelating agent dimercaprol (**127**) and antiparasitic drugs melarsoprol (**131**) and arsthinol (**132**) from allylic alcohol (**2**), dichlorohydrin (**11a**) or epichlorohydrin (**12**).

NaHS.[126] Similarly, the treatment of dichlorohydrin **11a** with a solution of sodium and MeOH saturated with $H_2S$ can afford **127** (Fig. 27). Finally, dimercaprol can be obtained starting from epichlorohydrin (**12**) and sulfur with hydrazine to yield thiol oligomers. The latter are then treated by KOH and HCl to obtain the corresponding monomers.[127] Dimercaprol was originally used as an antidote for Lewisite, an organoarsenic chemical warfare agent used during World War II.[128] Arsenic acid derivative **128a** can be treated with ammonium thioglycolate (**129**) affording compound **130a**. Chelation of **130a** with dimercaprol finally leads to the formation of melarsoprol (**131**).[129] The same reactions can be applied to acetarsol **128b**, a drug initially used to treat syphilis, to prepare arsthinol **132**, a drug used to treat yaws and amoebiasis[130] (Fig. 27).

**3.3.4 Antivirals.** Similarly to the aforementioned anti-infective drug classes, antiviral medications are facing drug resistance due to the constant mutations in viruses' genomes.[131]

The critical importance of versatile tools to tackle virus infections has been recently highlighted with the COVID-19 pandemic.[132] Used to prevent cytomegalovirus infections, ganciclovir (**135**) and its L-valyl ester prodrug valganciclovir (**139**, Fig. 28) are generally employed for immunocompromised patients, *i.e.* after an organ transplant and HIV-infected individuals, while the infection usually remains unnoticed in healthy people.[133,134]

Valganciclovir (**139**) is considered as an essential medicine by the WHO.[51] Synthetic processes toward both **135** and **139** share similar patterns and can start from epichlorohydrin (**12**) (Fig. 28). Use of benzyl alcohol (BnOH) in conjunction with **12** under basic conditions enables the production of two 1,3-protected alcohols (Fig. 28). Following a chloromethylation with HCl and paraformaldehyde and acetylation with AcOK, derivative **133** is obtained. *N*,*N*′-Diacetylguanine (**134**) is next used in a condensation reaction with **133** to generate ganciclovir (**135**) after a deprotection and a deacetylation reaction. The preparation of valganciclovir (**139**) follows a similar pathway and starts with the synthesis of mono-benzylated derivative **136** from **12** (Fig. 28). Condensation between **136** and **134** leads to **137** after an acetalization followed by a deprotection in the presence of $NH_4OH$/MeOH. Installation of the L-valyl scaffold (**138**) followed by a final deprotection provides valganciclovir (**139**).[135] Valganciclovir was developed by F. Hoffmann-La Roche and approved by the FDA in 2001.[136]

Another alternative drug to deal with cytomegalovirus infections in immunocompromised hosts is cidofovir (**144**), which is particularly relevant to treat cytomegalovirus retinitis conditions. Cidofovir was developed by Gilead Sciences and was approved by the FDA in 1996.[137] A practical synthesis of **144** starting from (*R*)-glycidol (*R*)-**13** was developed by scientists from Bristol-Myers Squibb (Fig. 29).

A tritylation of (*R*)-**13** followed by a ring-opening with cytosine derivative **140** afforded intermediate **141**. Alkylation of **141** with a tosylphosphonate reactant **142** in the presence of NaH allowed the production of **143** which subsequently afforded cidofovir (**144**) after a deprotection protocol.[138]

### 3.4 Polymeric drugs

The impact of polymeric materials for the pharmaceutical industry spans a variety of applications. In most cases, polymers are used as delivery vehicles, such as in micellar formulations, or used as conjugates with proteins, aptamers or drugs.[139] A few cases exist, however, in which the polymer itself is the active component. This use of polymers as drugs is attractive due to their extraordinary multivalency.[140] A subcategory of polymeric drugs that can highly benefit from multivalency is polymeric sequesterants.[139]

The use of polymers to sequester unwanted molecules received a significant push from the work of George Whitesides and the foundation of GelTex Pharmaceuticals Inc.[141] A few years after its foundation, GelTex Pharmaceuticals obtained FDA approval for sevelamer hydro-

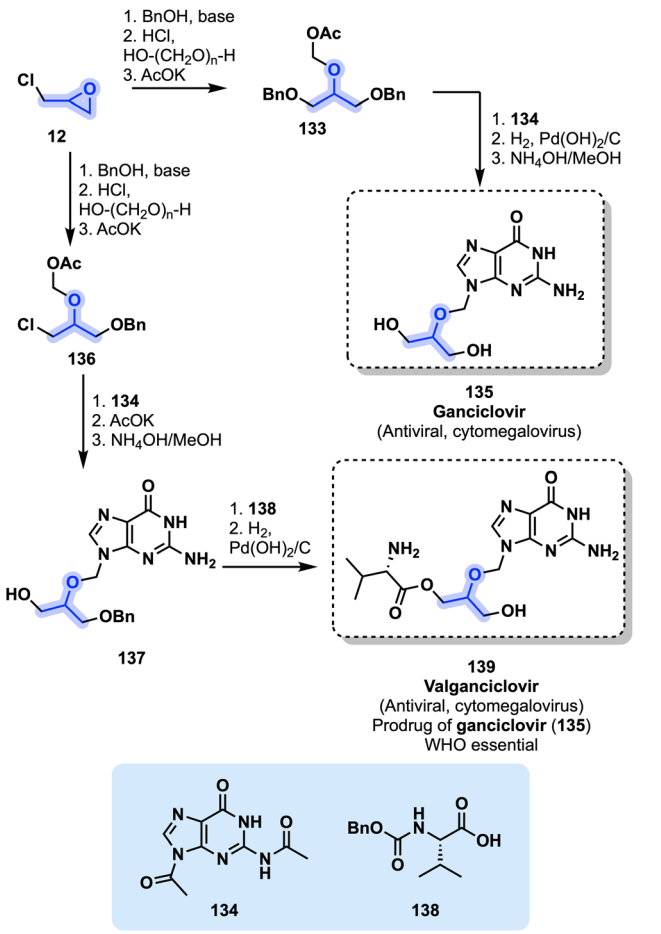



Fig. 28 Preparation of ganciclovir (**135**) and its prodrug valganciclovir (**139**) from epichlorohydrin (**12**).

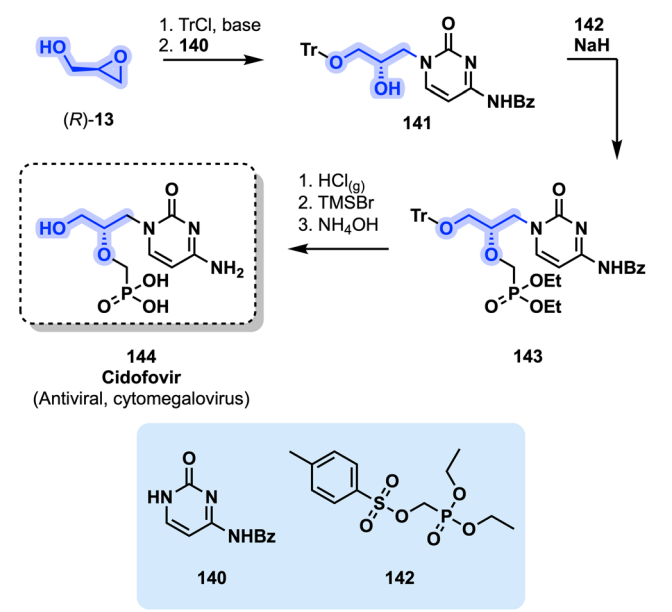



Fig. 29 Preparation of cidofovir (**144**) from (*R*)-glycidol ((*R*)-**13**). TrCl = trityl chloride, TMSBr = trimethylsilyl bromide.

chloride (RenaGel®), a polymer designed to reduce the level of serum phosphorous in patients with end-stage renal disease.[142] Sevelamer (**146**, Fig. 30) is synthesized by crosslinking a poly(allylamine) (**145**) with epichlorohydrin (**12**).[143] The polymer is designed to contain a high fraction of amine groups that, when protonated at a pH below 7, provide a polycationic matrix which binds phosphate. This in turn leads to a reduced absorption of dietary phosphorous.[144] Currently sevelamer is the recommended alternative treatment in cases when calcium-based phosphate binders cannot be used.[145] A second formulation in which the hydrochloride salt is replaced by bicarbonate (sevelamer carbonate) is also available for cases where the acidosis was experienced as a side effect.[146]

GelTex Pharmaceuticals also developed the bile acid sequestrant colesevelam hydrochloride (Welchol®), following a similar rationale as for sevelamer. Physiologically, the sequestration of bile acids decreases lipid levels by limiting their solubility and therefore their absorption. Furthermore, the depletion of bile acids triggers their replenishment through the synthesis of new bile acids which competes with that of cholesterol, decreasing its levels. Colesevelam is one of only three bile acid sequestrants approved in the United States.[148]

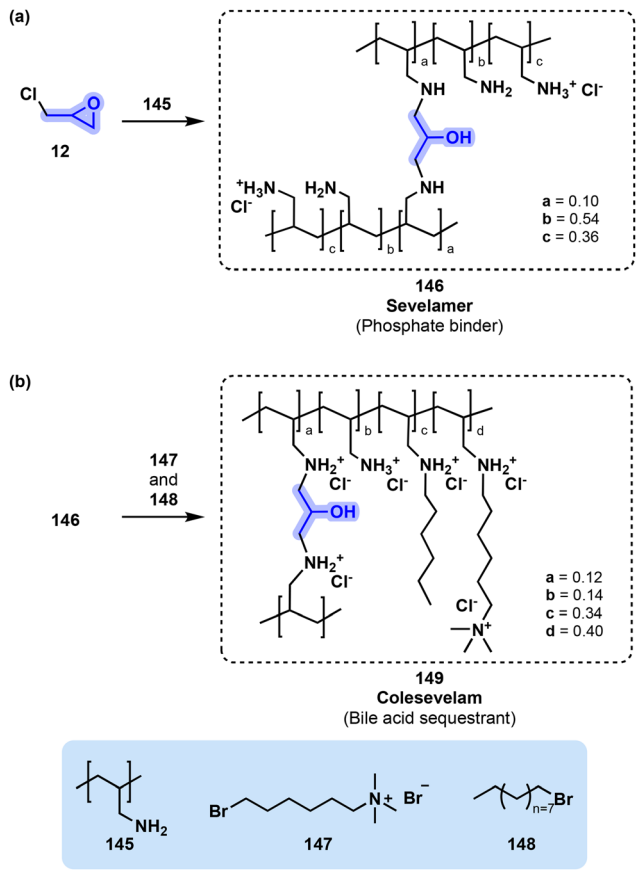



**Fig. 30** (a) Synthesis of sevelamer (**146**) through the reaction of epichlorohydrin (**12**) with poly(allylamine) (**145**). The fraction of monomeric units is reported in the FDA package insert.[112] (b) Post-polymerization modification leading to the preparation of bile sequestrant colesevelam (**149**). The ratio of monomeric units is taken from the FDA chemistry review.[147]

Like sevelamer (**146**), colesevelam (**149**, Fig. 30) is synthesized through the crosslinking of a poly(allylamine) (**145**) with epichlorohydrin (**12**). However, the drug has been engineered to increase interaction with bile acids by incorporating hydrophobic sidechains. To this end, the crosslinked poly(allylamine) is alkylated with (6-bromohexyl) trimethylammonium (**147**) and bromodecane (**148**) to obtain colesevelam (**149**, Fig. 30).[149] The length of the sidechains has been modulated to provide a complementary fit to bile acids and therefore increased affinity.[150] Colesevelam (**149**) has been demonstrated to have higher potency than the other available bile acid sequesterants.[151] Bile acid sequestering also helps regulate glucose levels.[120] Colesevelam (**149**) is the only bile acid sequestrant to receive FDA approval for the treatment of type 2 diabetes.[152,153]

In both cases (sevelemar and colesevelam), the use of epichlorohydrin (**12**) as crosslinker has been considered as advantageous due to its low molecular weight and its hydrophilicity. These properties contribute to the increased water-holding capacity of the resulting hydrogel. Its low cost and high availability further contribute to the attractiveness of this choice.[154] The interest in these polymeric drugs as sequestrants is evidenced by their commercial success, which led to the purchase of GelTex Pharmaceuticals by Genzyme (2000), and eventually by Sanofi (2011).[155]

### 3.5 Miscellaneous

**3.5.1 Febuprol (choleretic).** Bile, also called gall, is a liquid produced by the liver and stored in the gallbladder. It is excreted to promote the digestion of lipids in the small intestine and the incorporation of fat-like vitamins such as vitamins A, D, E and K.[156] Weak bile production or excretion can therefore be correlated to essential fatty acid and vitamin deficiencies. Additionally, the lack of fatty acid absorption results in their progression through the intestinal tract to reach zones unsuited for their digestion, possibly being the source of pathologies of the large intestine.[157]

Drugs stimulating hepatic bile production such as febuprol **152** are called choleretics. Despite the preparation of febuprol (**152**) being reported in 1954 by Minor *et al.*, its use was only patented in 1974 by Klinge-Pharma for its choleretic properties.[158,159] Production of febuprol (**152**) begins by a nucleophilic substitution of epichlorohydrin (**12**) by a phenol (**150**) molecule in the presence of a base to yield **151**, a glycidyl ether. This molecule then undergoes ring opening by *n*-butanol to swiftly obtain febuprol (**152**) as a solid (Fig. 31).

**3.5.2 Viloxazine (ADHD).** Viloxazine (**159**, Fig. 32) was first reported in 1972, as a potential psychotropic agent, described as having similarities with antidepressants and amphetamines, while having a lower toxicity than other known drugs.[160] It was approved by the UK as a treatment for depression in 1974 and remained on the market for more than 30 years.[161] Its retirement from the market was due to commercial reasons, and not related to safety concerns. As of 2021,

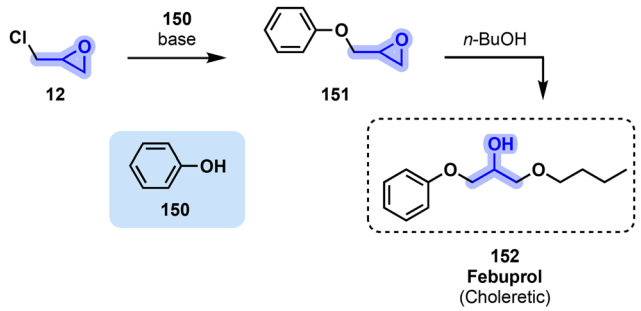



Fig. 31 Synthetic route toward choleretic februprol (**152**) starting from epichlorohydrin (**12**).

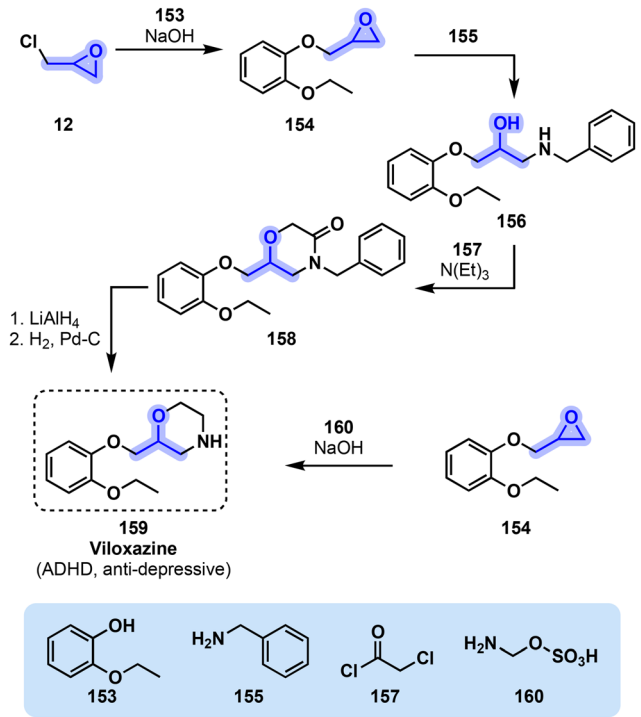



Fig. 32 Synthesis of viloxazine (**159**), starting from epichlorohydrin (**12**). The final compound can be accessed through a 4-step synthetic route, or directly from intermediate **154** using aminoethyl hydrogen sulfate **160**.

an extended release formulation of viloxazine (Qelbree™) was approved by the FDA as a treatment for attention deficit/hyperactivity disorder (ADHD).[162]

The synthetic scheme for viloxazine as originally reported is shown in Fig. 32. The synthesis begins with the reaction of *o*-ethoxyphenol (**153**) with epichlorohydrin (**12**) under basic conditions. The resulting aryloxypropylene oxide (**154**) is reacted with benzylamine (**155**), followed by chloroacetyl chloride (**157**) and cyclization, to arrive at intermediate **158.** Reduction with a metal hydride and deprotection of the amine affords the final compound.[160] A modification to this synthesis uses 2-aminoethyl hydrogen sulfate (**160**) to access the final product directly from intermediate **154.**[50,163]

**3.5.3 Setiptiline (antidepressant).** Setiptiline (**153**, Fig. 33) is an antidepressant of the tetracycline category sold under the brand name of Tecipul, developed and marketed by Japanese pharmaceutical company Mochida in 1987.

The synthesis of tetracyclic **164** incorporates glycerol-derived ethyl acrylate **8** into its preparation. The first step consists in a hydroamination reaction between ethyl acrylate (**8**) and secondary amine **161**, yielding tertiary amine intermediate **162.** Deprotonation in alpha of the ester function from **162** by sodium ethoxide leads to cyclization and intermediate **163.** Finally, an HCl-catalyzed cyclization followed by decarbonylation with polyphosphoric acid provided antidepressant setiptiline (**164**, Fig. 33).[164]

**3.5.4 Cromoglicic acid (asthma).** Cromoglicic acid (**169**, Fig. 34), also known as cromolyn, is used for the treatment of allergic bronchial asthma. It is a prophylactic agent which has enabled some patients to decrease or eliminate the use of more harmful treatments such as steroids. Although not useful in cases of asthmatic crisis, it is used as a long-term treatment for chronic asthma. Its very low toxicity and absence of significant side effects makes it an important medication.[165]

The chemical synthesis of cromolyn (**169**) uses one molecule of epichlorohydrin (**12**) to react with two molecules of 2,6-dihydroxyacetophenone (**165**) during a 48 h reflux to afford bischromone (**166**). This compound is then reacted with diethyl oxalate (**167**) to form diester derivative **168**, which is hydrolyzed with sodium hydroxide to arrive at the final product (**169**).[166,167] Alternatively, the intermediate **166** can be prepared using 1,3-dibromo-2-hydroxypropane instead of epichlorohydrin (**12**).[166,167]

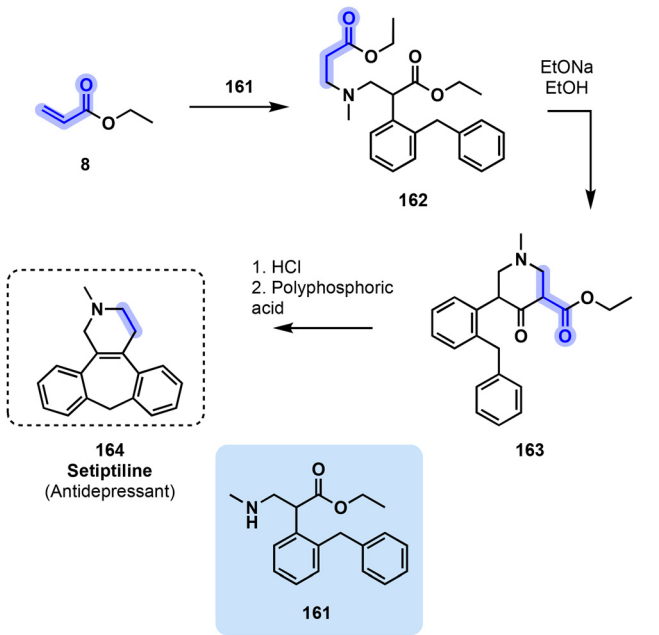



Fig. 33 3-Step synthetic process toward antidepressant **164** starting from glycerol-derived ethyl acrylate (8).

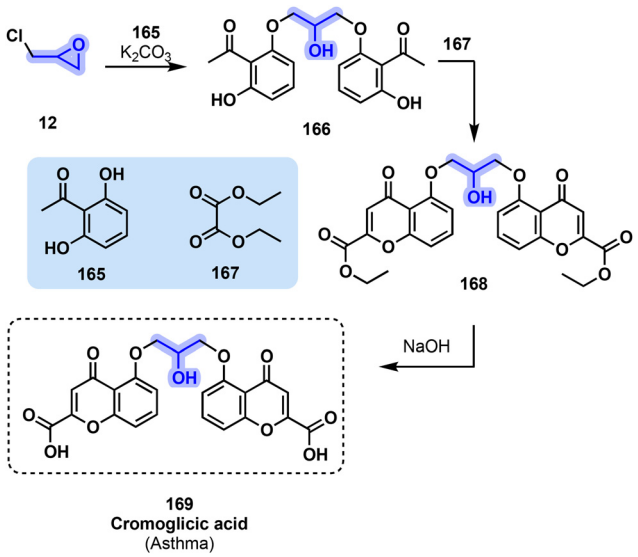



Fig. 34 Synthetic scheme for the preparation of cromoglicic acid (**169**).

**3.5.5 Dropropizine (antitussive).** Antitussive medications come in a variety of forms, from complex codeine and dextromethorphan to simpler butamirate and dropropizine (**171**, Fig. 35). These drugs are often prescribed alongside other medications such as analgesics and decongestants to treat the symptoms of the common cold. Dropropizine (**171**) was first patented in 1961 as a racemate though it has since been determined that levodropropizine is the active enantiomer, leading to its commercialization in 2000.

The synthesis of **171** was first reported in 1962 and consisted of the aminolysis of glycidol (**13**) by secondary amine **170** in the presence of a base.[168] Despite this streamlined procedure, **171** can be obtained through other pathways. In 2016, Kann and coworkers[169] reported a ruthenium-catalyzed hydrogen borrowing procedure to access beta amino alcohols from solketal (**9**) and a suitable amine. One such was phenylpiperazine (**170**) which provided the desired antitussive with an 86% yield over three synthetic steps. Five years later, Werner and coworkers[170] found an alternative method for the production of **171** starting from epichlorohydrin (**12**) and amine **170**. The two were reacted in the presence of a base to obtain the epoxide intermediate. The isolated epoxide was further used to trap $CO_2$ in the presence of phosphonium catalyst **172** to obtain the corresponding cyclic carbonate (**173**), which can be viewed as protected dropropizine. The subsequent deprotection step was then implemented in the presence of NaOH to finally obtain the antitussive API. The last two steps can be decoupled or performed as a one-pot process, the latter however leading to a drop in yield from 95 to 61%.

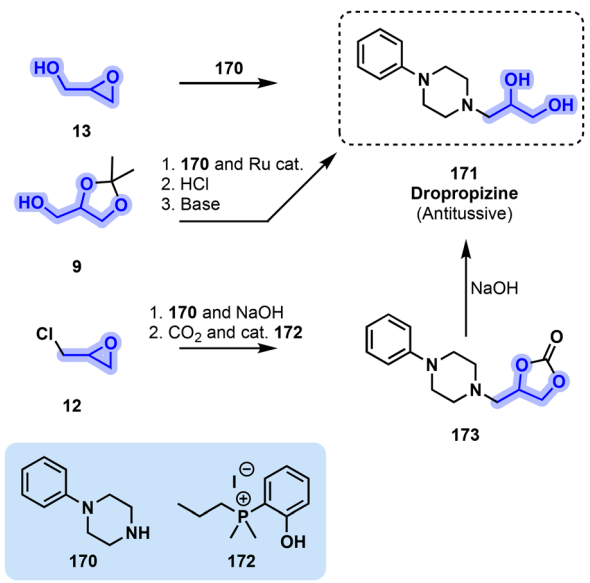



Fig. 35 Synthesis of antitussive dropropizine (**171**) from the direct aminolysis of **13** by **170**, through ruthenium-catalyzed hydrogen borrowing of solketal (**9**) and amine **170** or from cyclic carbonate **173** yielded from **12**, **170** and $CO_2$.

**3.5.6 Azelastatine (antihistaminic).** Allergies are the result of an excessive reaction of the immune system when faced with an allergen or an antigenic molecule perceived as a significantly superior threat to the organism than it actually is.[171] Taking antihistaminic medications can dampen or completely prevent the symptoms of allergic reactions. One such antihistaminic API is azelastine (**181**).

Azelastine (**181**) synthesis begins with the hydroamination of acrylic ester **8** by **174** toward **175** in the presence of EtONa. **175** is then cyclized in the presence of a base to obtain ketone intermediate **176** which is then subsequently coupled to benzhydrazide **177** and reduced by $NaBH_4$ to obtain **178**. Upon acid treatment, newly formed hydrazine **179** is released from **178**. Ketone derivative **180** finally reacts with hydrazine **179** before undergoing reduction and cyclization into azelastine (**181**, Fig. 36).

**3.5.7 Prolonium iodide (hypothyroidism).** Prolonium iodide (**183**, Fig. 37) was first patented by Jürgen Callsen for Bayer in 1925, claiming that it was an iodine source with therapeutical applications.[172] Aside from congenital iodine deficiency syndrome (CIDS), before understanding the importance of iodine in thyroidal activity, iodine deficiency (or congenital hypothyroidism) was mostly observed in isolated land such as mountains where little marine food was available or in populations relying on food grown on iodine-poor soils.[173] Individuals suffering from congenital hypothyroidism displayed mental deficiencies, deafness, stance issues and squint among others. Iodine deficiency is now considered as a preventable cause of mental deficiency.[174]

Prolonium iodide (**183**) can be obtained following a two-step synthesis, the first step consisting of aminolysis and nucleophilic substitution of epichlorohydrin (**12**) by an excess of dimethylamine to yield 1,3-bis(dimethylamino)-2-propanol **182**. This intermediate is then swiftly methylated in the presence of 2 equiv. of methyl iodide to yield the desired iodide salt **183** (Fig. 37).[172]

**3.5.8 Carnitine (supplement).** Carnitine (**186**) is a quaternary ammonium compound first isolated from meat extract in

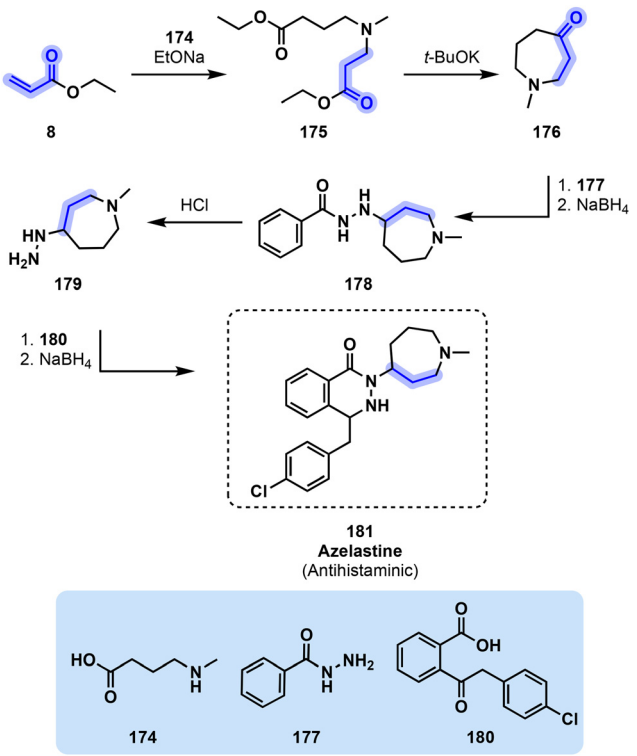



Fig. 36 Multistep preparation of azelastine (**181**) starting from ethyl acrylate (**8**).

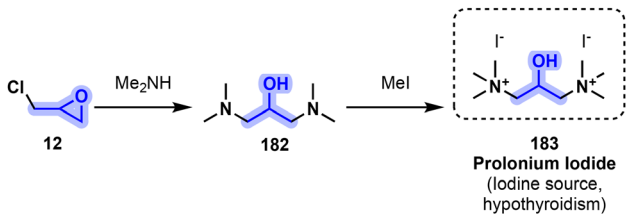



Fig. 37 Two-step preparation of prolonium iodide (**183**) from epichlorohydrin (**12**).

1905, giving it its name (from the latin word "carnis" meaning meat or flesh). It is stored in skeletal and cardiac muscles where it can metabolize fatty acids into energy. Primary alimentary sources of carnitine (**186**, Fig. 38) are red meat, milk, fish and poultry. However, enough endogenous **186** is produced by the human body regardless of alimentary sources, to the point that individuals following a strict vegetarian or vegan diet rarely suffer from carnitine deficiency. Preterm infants, people with genetic disorders, or older people sometimes require carnitine (**186**) supplements, earning it a "New Molecular Entity" title by the FDA in 1985.

While both D- and L-carnitine exist, only the latter is naturally synthesized, with D-carnitine inhibiting the effect of L-carnitine. Endogenous carnitine is synthesized from lysine, a proteogenic amino acid. In contrast to the biological pathway, the initial industrial synthesis of carnitine starts with the ring

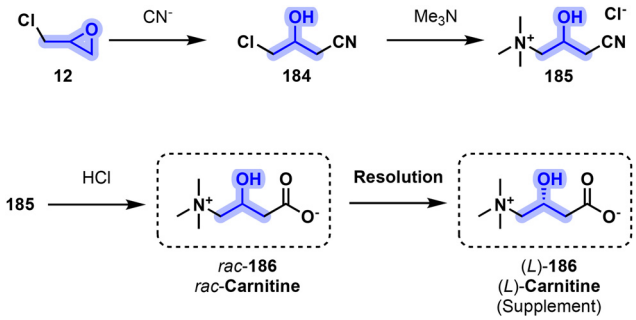



Fig. 38 Industrial synthetic method toward (L)-carnitine ((*L*)-**186**).

opening of epichlorohydrin (**12**) by a cyanide ion to obtain 4-chloro-3-hydroxybutyronitrile (**184**). The resulting chlorinated derivative is then reacted with trimethylamine to yield **185** (carnitine nitrile chloride). The nitrile moiety is then reacted with aqueous HCl to convert it into the corresponding carboxylic acid to yield racemic carnitine *rac*-**186**, which then requires chiral resolution to obtain biologically relevant L-carnitine (*L*)-**186** (Fig. 38).[175]

**3.5.9 Calcium pantothenate/pantethine (vitamin $B_5$).** As essential as vitamins may be to maintain proper metabolic function, only very small amounts can be endogenously produced. They therefore need to be assimilated through dietary intake. One of such is vitamin $B_5$, which is essential in the oxidation and metabolism of fatty acids. Vitamin $B_5$ supplements for human or animal purpose are sold, mostly under the form of calcium salts (**190**). Dietary supplements with cholesterol-lowering effects are also available under the form of pantethine (**192**), a dimer of pantothenic acid linked by cystamine (**191**). Aside from its importance in the fatty acid oxidation process, vitamin $B_5$ is greatly exploited in the cosmetic industry for its hydrating and hair strengthening properties.

Vitamin $B_5$ (**190**) production begins with the amination of acrylic acid **4** by ammonia to yield beta alanine[176] (**187**) which is then neutralized by $Ca(OH)_2$ into the corresponding salt[177] (**188**). Finally, the amino acid skeleton is lengthened by the reaction with lactone **189** to obtain calcium pantothenate (**190**, Fig. 39), the commercial form of vitamin $B_5$ supplements. A single extra step which consists in the coupling of two molecules of calcium pantothenate to one of cystamine (**191**) in the presence of HOBt and DCC as coupling agents[178] is required to go from **190** to **192**.

**3.5.10 Misonidazole and fluoromisonidazole (radiosensitizer/hypoxia PET imaging).** 2-Nitroimidazoles derivatives, such as [$^{18}$F]fluoromisonidazole **199**, were developed during the 1980s as selective hypoxia-targeting positron emission tomography (PET) radiotracers.[179] Upon entering healthy cells, the nitro group of **199** undergoes reduction followed by oxidation before exiting the cell. This excretion implies that there is no radiotracer accumulation and therefore no signal detected upon PET analysis. However, if **199** enters a tumor cell, reduction is still performed but the oxidation is undermined by the hypoxic environment of the tumor cells. This in

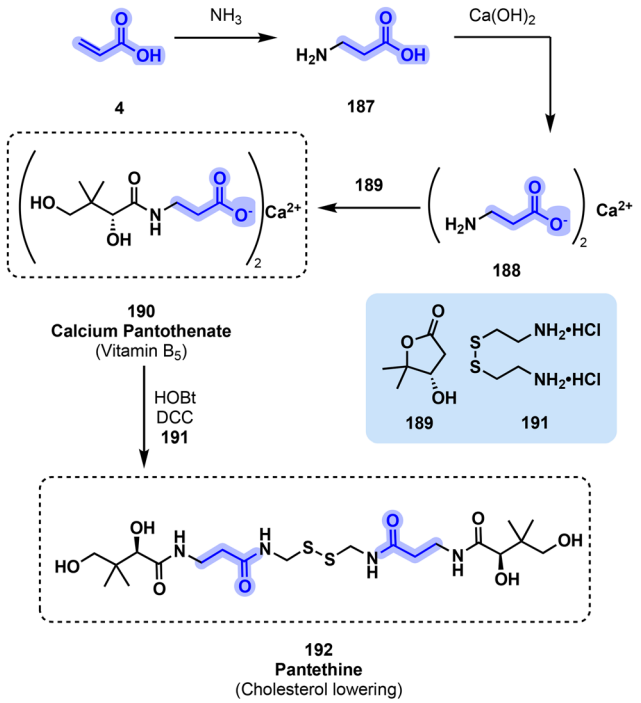



Fig. 39 Preparation of calcium pantothenate (**190**) and its dimeric form pantethine (**192**) from acrylic acid (**4**). HOBt = hydroxybenzotriazole, DCC = dicyclohexylcarbodiimide.

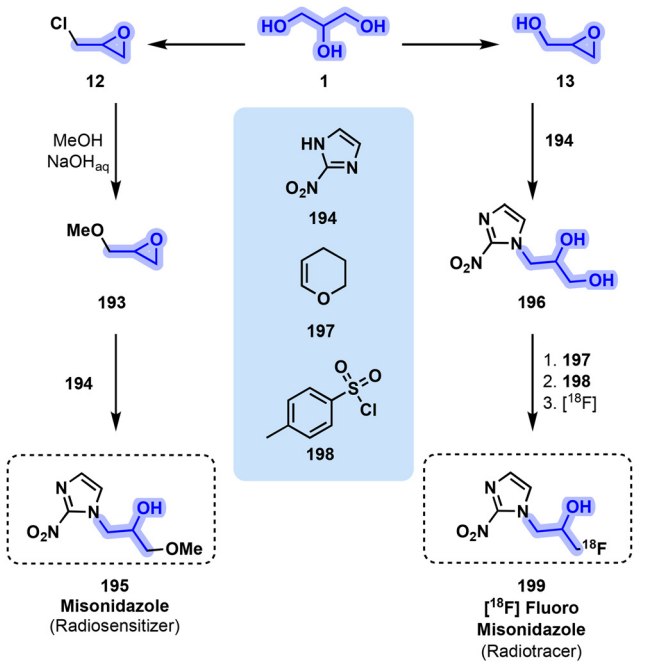



Fig. 40 Diverging pathways leading to misonidazole (**195**) and [$^{18}$F] fluoromisodinazole (**199**) from glycerol-derived epichlorohydrin (**12**) or glycidol (**13**).

turn delays the excretion of **199** leading to the accumulation of the tracer and therefore the detection of the tumorous area.[180]

While **199** and other parent molecules allow the detection of the area needing treatment, misonidazole (**195**) is a drug with radiosensitizing properties, enhancing the therapeutic impact of radiation treatment on cancerous patients. Both molecules follow similar synthetic routes, starting from **12** or **13**. In the case of **195**, methyl glycidyl ether is the first intermediate before undergoing epoxide opening in the presence of 2-nitroimidazole (**194**) to obtain **195**. When synthesizing [$^{18}$F] fluoromisonidazole, **13** ring opening by 2-nitroimidazole (**194**) is the first step, quickly followed by protection by dihydropyran (**197**) and activation by tosyl chloride (**198**) of the two alcohol moieties. The final and most important step consists of radiolabelling with $^{18}$F and deprotection to retain as much radiochemical activity as possible[95,181–183] to finally yield **199** (Fig. 40).

**3.5.11 Iopamidol (contrast agent).** Iodine-containing radiocontrast agents such as **204** (Fig. 41) attenuate the intensity of incoming X-rays, thus decreasing their detection after passing through the desired area. They are used to highlight the blood vessels or organs and their condition in the case of angiography.[184] Iopamidol **204** is one such contrast agent, which was first introduced in 1981 by Bracco Diagnostics and has remained on the market ever since.

The classic and initial method to obtain **204** integrates two different potential glycerol derivatives throughout its synthetic

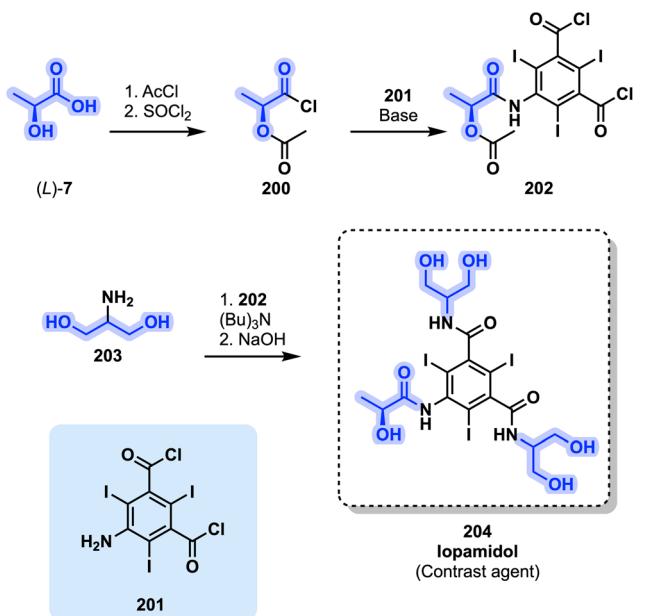



Fig. 41 Synthetic pathway leading to contrast agent iopamidol (**204**) incorporating two different glycerol derivatives: L-lactic acid ((*L*)-**7**) and 2-aminoglycerol (**203**).

pathway. Firstly, L-lactic acid ((*L*)-7) is acylated to protect its hydroxyl moiety before being activated into the corresponding acyl chloride, yielding **200**. The latter is then coupled to the iodine-bearing aromatic core **201** in the presence of a base to obtain **202**. Secondly, the two remaining acyl chloride func-

tions on the central aromatic ring react with a pair of 2-aminoglycerol (**203**) molecules in the presence of $(Bu)_3N$. Finally, the hydrolysis of the protecting acetyl group of L-lactic acid ((*L*)-**7**) completes the synthetic route toward iopamidol (**204**, Fig. 41). Alternative methods have since been developed and published with the aim of having safer and greener synthetic steps. One of such relies on mechanochemistry for the reaction between 2-aminoglycerol and intermediate **202**. Mechanochemistry uses mechanical energy transfered by rapidly moving bearings to activate the reagents in an enclosed milling reactor, instead of solely relying on thermal energy for the chemical reaction to proceed. This allows for a drastic reduction in solvent waste both during the reaction as well as the workup. Lattuada and coworkers reported in 2020 a method relying on a fivefold excess of 2-aminoglycerol (**203**) over intermediate **202** in the presence of an *N*-methylmorpholine as proton scavenger. No solvent was added and after 30 min of milling, **204** was obtained in an excellent 98% crude yield.[185]

**3.5.12 Methotrexate (chemotherapy).** The importance of folic acid in leukemia was noted at the end of the 1940s when the administration of folic acid supplements led to the condition worsening while reducing its intake had a positive impact on the condition.[186] This observation opened the doors to new research on therapeutic folic acid analogs to treat some cancers. These studies converged toward methotrexate **210**, an antimetabolite with chemotherapeutic and immune system suppressing properties, which effectively blocks the production of DNA, RNA, thymidylic acid and proteins of rapidly dividing cells, preventing the propagation of cancer cells.[187] Despite new chemotherapeutic drugs being developed since its first report, methotrexate (**210**) is on the WHO list of essential medicines and was the 113th most prescribed drug in the US in 2020.[188]

**210** can be accessed from glycerol derivative 1,3-dihydroxyacetone (**5**) by reacting it with symmetrical pyrimidine **205** before oxidizing the resulting bicyclic compound into intermediate **206** (Fig. 42). The remaining alcohol function is then replaced by bromine in the presence of triphenylphosphine to activate **207** for the following reaction with secondary amine **208**. The diester can then be hydrolyzed in the presence of aqueous NaOH followed by HCl to obtain the desired API **210** (Fig. 42).[189] It is noteworthy that reagent **208** is prepared from glutamic acid ester, a DOE Top 10 recipient of bio-based molecules with promising applications and the corresponding acyl chloride.[190]

**3.5.13 Actinoquinol (UV-B ocular protection).** Quinolines[191] and quinazolines are ubiquitous in the pharmaceutical industry, being present in more than 200 active compounds, among them 8-hydroxyquinoline derivative actinoquinol (**216**). Actinoquinol (**216**) is sold as eye drops to prevent UV-B-mediated oxidative damage to the cornea, preventing the early development of cataract troubles and macular degeneration

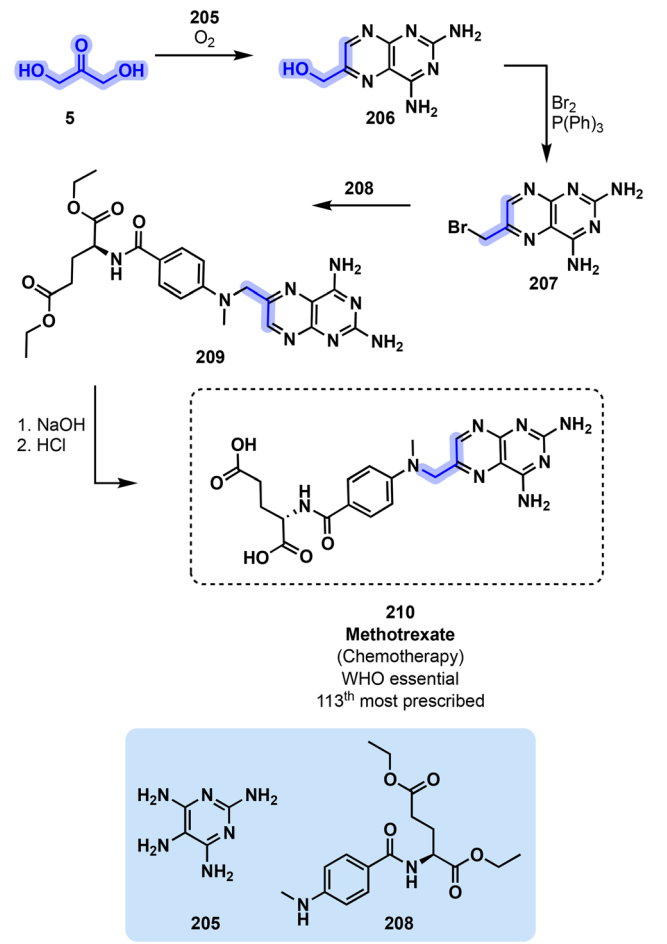



Fig. 42 Preparation of methotrexate (**210**) incorporating bio-based 1,3-dihydroxyacetone (**5**) and glutamic acid derivative (**208**).

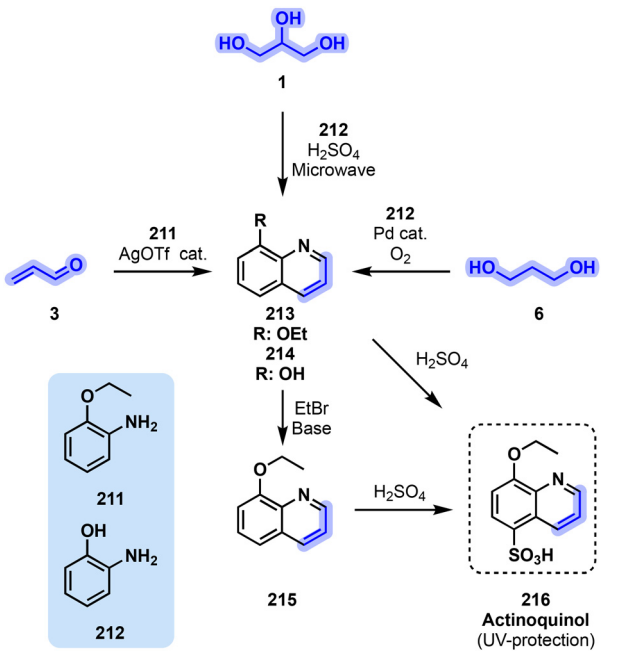



Fig. 43 Preparation of quinoline precursors of actinoquinol (**216**) from aniline derivatives (**211** and **212**) and glycerol-derived building blocks acrolein (**3**) and 1,3-propanediol (**6**) as well as glycerol (**1**).

**Table 2** Summary of all APIs covered in this review in alphabetical order, including their medical use and the glycerol derivative included in the synthesis and the steps that are remaining before arrival at the final API. In cases where an alternative route using a different glycerol derivative has been reported, the identity of that derivative is also included

| Medication name | Medication type | Glycerol derivative | Steps | Alt. route |
|---|---|---|---|---|
| Acebutolol | Beta-blocker | **12** | 2 | |
| Actinoquinol | UV-B ocular protection | **1** | 2 | **3, 6** |
| Alprenolol | Beta-blocker | **12** | 2 | |
| Arotinolol | Beta-blocker | **12** | 2 | |
| Arsthinol | Antiparasitic | **2** | 2 | **11a, 12** |
| Atenolol | Beta-blocker | **12** | 2 | |
| Azelastine | Antihistaminic | **8** | 7 | |
| Betaxolol | Beta-blocker | **12** | 2 | |
| Bisoprolol | Beta-blocker | **12** | 2 | |
| Bupranolol | Beta-blocker | **12** | 2 | |
| Calcium panothenate | Supplement | **4** | 3 | |
| Carnitine | Supplement | **12** | 3 | |
| Carteolol | Beta-blocker | **12** | 2 | **4** |
| Carvedilol | Beta-blocker | **12** | 2 | |
| Celiprolol | Beta-blocker | **12** | 2 | |
| Chlorphenesin | Antibiotic/ antifungal | **10b** | 1 | |
| Cidofovir | Antiviral | (*R*)-**13** | 6 | |
| Colesevelam | Bile acid sequestrant | **12** | 1 | |
| Cromoglicic acid | Asthma | **12** | 3 | |
| Dimercaprol | Poisoning antidote | **2** | 2 | **11a, 12** |
| Dropropizine | Antitussive | **12** | 1 | **13, 9** |
| Eprosartan | Anti-hypertensive | **5** | 9 | |
| Esmolol | Beta-blocker | **12** | 2 | |
| Febuprol | Choleretic | **12** | 2 | |
| Furaltadone | Antibiotics veterinary | **12** | 4 | |
| Ganciclovir | Antiviral | **12** | 6 | |
| Guaifenesin | Myorelaxant | **10b** | 1 | |
| Iopamidol | Contrast agent | **7** | 5 | |
| Itraconazole | Antifungal | **1** | 6 | |
| Ketoconazole | Antifungal | **1** | 6 | |
| Linezolid | Antibiotic | (*S*)-**10b** | 4 | |
| Melarsoprol | Antiparasitic | **2** | 2 | **11a, 12** |
| Mephenesin | Strychnine poisoning | **10b** | 1 | |
| Mephenesin carbamate | Myorelaxant | **10b** | 4 | |
| Mephenoxalone | Myorelaxant | **10b** | 4 | |
| Metaxalone | Myorelaxant | **10b** | 4 | |
| Methocarbamol | Myorelaxant | **10b** | 3 | |
| Methotrexate | Chemotherapy | **5** | 5 | |
| Metoprolol | Beta-blocker | **12** | 2 | |
| Misonidazole | Radiosensitizer | **12** | 2 | |
| 18F-Misonidazole | Radiotracer | **13** | 4 | |
| Morinidazole | Antibiotics | **12** | 3 | |
| Nadolol | Beta-blocker | **12** | 2 | |
| Nifuratel | Antibiotics | **12** | 4 | |
| Nitroglycerin | Vasodilator | **1** | 1 | |
| Ornidazole | Antibiotics | **12** | 1 | |
| Oxprenolol | Beta-blocker | **12** | 2 | |
| Pantethine | Supplement | **4** | 4 | |
| Penbutolol | Beta-blocker | **12** | 2 | |
| Pindolol | Beta-blocker | **12** | 2 | |
| Pretomanid | Antibiotic | (*R*)-**10** | 4 | |
| Prolonium iodide | Hypothyroidism | **12** | 2 | |
| Propafenone | $Na^+$ channel blocker | **12** | 4 | |
| Propranolol | Beta-blocker | **12** | 2 | |
| Ranolazine | $Na^+$ channel blocker | **12** | 2 | |
| Rivaroxaban | Anticoagulant | (*S*)-**12** | 5 | |
| Setiptline | Antidepressant | **8** | 4 | |
| Sevelamer | Phosphate sequestrant | **12** | 1 | |
| Tedizolid | Antibiotics | **12** | 2 | |
| Tedizolid phosphate | Antibiotics | **12** | 3 | |
| Terbinafine | Antifungal | **12** | 4 | |
| Terconazole | Antifungal | **1** | 6 | |
| Timolol | Beta-blocker | **12** | 2 | |
| Triacetin | Antifungal | **1** | 1 | |
| Valganciclovir | Antivirals | **12** | 8 | |
| Viloxazine | ADHD | **12** | 5 | |
| Xanthinol | Vasodilator | **12** | 2 | |

toward blindness.[192] The preparation of quinolines is mostly performed through a Skraup synthesis which consists in the dehydration of glycerol to generate acrolein *in situ* by sulfuric acid. The latter then reacts with the desired aniline derivative. The formed intermediate undergoes cyclization, dehydration and oxidation to finally obtain the finished product in the presence of nitrobenzene as solvent and oxidizing agent.

Two methods toward actinoquinol (**216**, Fig. 43) precursors were reported in 2014. Len and coworkers reported a greener alternative to this reaction by performing it under microwave irradiation while replacing nitrobenzene, which originally acted as solvent and oxidizer, by water.[193] This solvent switch was however accompanied by the need for more sulfuric acid for the dehydration of glycerol (**1**) and that of the final ring to compensate for the loss of the oxidizing agent. The microwave-assisted reaction took place over 10 min at 200 °C, affording 8-hydroxyquinoline (**214**) in a rather low 34% yield.

The second actinoquinol (**216**) intermediate synthesis was reported by Zhang and Xu.[194] The disclosed methodology is based on the silver-mediated condensation of ene-carbonyl or yne-carbonyl molecules with anilines to yield a broad scope of substituted quinolines. One such ene-carbonyl substrates is acrolein (**3**), which would logically be yielded from glycerol (**1**) dehydration in a standard Skraup synthesis. AgOTf and HOTf (5 mol%) in toluene sufficed to convert amine **211** and acrolein (**3**) into intermediate **213** after 4 h under reflux with a 62% yield. Interestingly, no oxidizer had to be added to the reaction medium for the final step, with dissolved air being enough for that task. Finally, Jiang *et al.*[195] developed a third general method toward quinoline derivatives, among which was **214**. This was achieved through palladium catalysis and aerobic oxidation of aniline **212** and 1,3-propanediol (**6**) as both solvent and reagent. The catalytic system, consisting of 5 mol% of Pd $(OAc)_2$, 10 mol% of 2,4,6-collidine as the ligand and 20 mol% of trifluoro acetic acid under an $O_2$ atmosphere, allowed **214** to be obtained in 55% yield after stirring the reaction medium at 150 °C for 16 h. Intermediate **214** was then reacted toward **215** which would undergo sulfonylation to finally afford UV-B-protecting **216.**

## 4. Conclusions

The accessibility of extensive building block libraries derived from the transformation of oil-derived resources at the beginning of the 20th century gave rise to the ability to synthesize complex molecules on a large scale. This in turn opened the door to the preparation of APIs capable of treating a wide variety of human ailments. With the passage of time, the drawbacks of our reliance on petrochemicals have become evident. Not only is this dependence detrimental to the environment, but it also creates inequalities since petrochemicals are finite and unequally distributed geographically. This realization has motivated the efforts to establish biomass as the source of starting materials for a new chemical industry. These efforts have led to the identification of new bio-based platforms that can be directly derived from biomass and transformed into useful building blocks. Numerous reports on clever and efficient methods to obtain useful bio-based platforms from biomass have been published. The field has developed to the point where concrete applications of these developments now exist, for example, for the preparation of bio-based polymers. Among these platforms, glycerol (**1**) stands out as highly available compound that is currently akin to waste, but that possesses great potential to be used as a source of bio-based atoms.

This review aimed at focusing chemists' attention on the application of bio-based platforms to the field of pharmaceutical synthesis. Specifically, it sheds light on how the incorporation of bio-sourced atoms is already possible using glycerol (**1**) and its derivatives. The therapeutic applications and synthesis of all relevant APIs included in this review are recapitulated in Table 2. In total, almost 70 different APIs were reported, highlighting each time how already existing synthetic pathways can provide venues to incorporate bio-based atoms. In most examples, the potential incorporation of bio-based glycerol comes in the form of its derivatization toward current common building blocks such as epichlorohydrin (**12**).

There are still significant challenges before bio-sourced APIs become a reality, especially concerning the strict regulation surrounding the preparation of APIs. However, the number of molecules that could be potentially prepared and the variety of purposes that they cover justifies the need for a careful consideration of this possibility. Some of the pharmaceuticals presented here are categorized as essential medicines by the World Health Organization, whereas several others constitute part of the list of the top 300 most prescribed drugs in the US in 2019.

The examples presented in this review are focused on replacing fragments of existing APIs with bio-sourced atoms. However, the use of biomass offers more direct access to building blocks that were less accessible under the petro-based paradigm. A more efficient use of bio-sourced atoms would benefit from taking these molecules into consideration in the early stages of the production of molecular libraries and drug discovery. This approach could allow efforts in green chemistry to go beyond the production of (smart) drop-in molecules that mimic historically relevant building blocks originating in the petrol industry. Instead, future developments should look toward the incorporation of so-called dedicated platforms, and from there, to the production of entirely bio-sourced APIs.

## Author contributions

R. M. designed the original plan of the manuscript, selected the target APIs and prepared a preliminary draft. L. B. and D. V. S. B. prepared the manuscript. J. C. M. M. revised the manuscript.

## Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

The authors acknowledge the Interreg V-A Euregio Meuse-Rhine (EMR) program (IN FLOW) for funding. IN FLOW was granted a € 2.1 M total budget from the European Regional Development Fund (ERDF). With the investment of EU funds in Interreg projects, the European Union directly invests in economic development, innovation, territorial development, social inclusion and education in the Euregio Meuse-Rhine. The authors also thank the University of Liège and the F.R.S.-FNRS (Incentive grant for scientific research MIS F453020F, J. C. M. M.). The authors also thank Dr Pierre Francotte (ULiège, Department of Pharmacy), Dr Damien Cornut (Mithra Pharmaceuticals), Dr Laurent Provins (UCB Pharma), Dr Jean Fournier (Oril Industrie), Maryse Phan (Oril Industrie) and the EMA Pharmaceutical Quality Office for their answers related to the regulatory aspects. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

## References

1 T. Werpy and G. Petersen, Top Value Added Chemicals from Biomass: Volume I – Results of Screening for Potential Candidates from Sugars and Synthesis Gas, Office of Biomass Program Report DOE/GO-102004-1992, U.S. Department of Energy, United States, 2004.

2 FACT SHEET: Overview of USDA's BioPreferred Program, **https://www.usda.gov/media/press-releases/2016/02/18/**

fact-sheet-overview-usdas-biopreferred-program, (accessed Nov 2, 2023).
3 M. J. Biddy, C. Scarlata and C. Kinchin, Chemicals from Biomass: A Market Assessment of Bioproducts with Near-Term Potential, N. R. E. L. (NREL) Report NREL/TP-5100-65509, U.S. Department of Energy, Golden, CO (USA), 2016.
4 R. Christoph, B. Schmidt, U. Steinberner, W. Dilla and R. Karinen, *Ullmann's Encyclopedia of Industrial Chemistry*, 2006.
5 Glycerol Prices | Historical and Current, https://www.intratec.us/chemical-markets/glycerol-price, (accessed April 1, 2024).
6 World - Crude Glycerol, Glycerine Waters And Lyes - Market Analysis, Forecast, Size, Trends And Insights, https://www.indexbox.io/search/crude-glycerol-market/, (accessed April 1, 2024).
7 Propylene Prices | Current and Forecast, https://www.intratec.us/chemical-markets/propylene-price, (accessed April 1, 2024).
8 https://www.biodieselmagazine.com/articles/7662/the-pure-potential-of-glycerin, (accessed April 1, 2024).
9 M. Pagliaro and M. Rossi, in *The Future of Glycerol*, The Royal Society of Chemistry, Cambridge, UK, 2nd edn., 2010, ch. 1, pp. 1–28.
10 B. Katryniok, S. Paul, V. Bellière-Baca, P. Rey and F. Dumeignil, *Green Chem.*, 2010, **12**, 2079–2098.
11 X. Li and Y. Zhang, *ACS Catal.*, 2016, **6**, 143–150.
12 N. N. Tshibalonza and J.-C. M. Monbaliu, *Green Chem.*, 2017, **19**, 3006–3013.
13 E. Arceo, P. Marsden, R. G. Bergman and J. A. Ellman, *Chem. Commun.*, 2009, 3357–3359.
14 P. M. Walgode, R. P. V. Faria and A. E. Rodrigues, *Catal. Rev.*, 2021, **63**, 422–511.
15 L. Luo, W. Chen, S.-M. Xu, J. Yang, M. Li, H. Zhou, H. Duan, *et al.*, *J. Am. Chem. Soc.*, 2022, **144**, 7720–7730.
16 M. Główka and T. Krawczyk, *ACS Sustainable Chem. Eng.*, 2023, **11**, 7274–7287.
17 N. Razali and A. Z. Abdullah, *Appl. Catal., A*, 2017, **543**, 234–246.
18 M. R. Nanda, Y. Zhang, Z. Yuan, W. Qin, H. S. Ghaziaskar and C. Xu, *Renewable Sustainable Energy Rev.*, 2016, **56**, 1022–1031.
19 B. M. Bell, J. R. Briggs, R. M. Campbell, S. M. Chambers, P. D. Gaarenstroom, J. G. Hippler, C. P. Wolfe, *et al.*, *Clean: Soil, Air, Water*, 2008, **36**, 657–661.
20 G. M. Lari, G. Pastore, C. Mondelli and J. Pérez-Ramírez, *Green Chem.*, 2018, **20**, 148–159.
21 E. Santacesaria, R. Vitiello, R. Tesser, V. Russo, R. Turco and M. Di Serio, *Ind. Eng. Chem. Res*, 2014, **53**, 8939–8962.
22 R. Morodo, R. Gérardy, G. Petit and J.-C. M. Monbaliu, *Green Chem.*, 2019, **21**, 4422–4433.
23 P. Prete, D. Cespi, F. Passarini, C. Capacchione, A. Proto and R. Cucciniello, *Curr. Opin. Green Sustainable Chem.*, 2022, **35**, 100624–100624.
24 G. S. Singh, K. Mollet, M. D'Hooghe and N. De Kimpe, *Chem. Rev.*, 2013, **113**, 1441–1498.
25 *Bold Goals for U.S. Biotechnology and Biomanufacturing*, White House Office of Science and Technology Policy, Washington D.C., USA, 2023.
26 J. Spekreijse, K. Vikla, M. Vis, K. Boysen-Urban, G. Philippidis and R. M'Barek, *Bio-based value chains for chemicals, plastics and pharmaceuticals – A comparison of bio-based and fossil-based value chains*, European Commission Joint Research Centre Publications Office, 2021.
27 T. Ronzon, T. Lammens, J. Spekreijse, M. Vis and C. Parisi, *Insights into the European market for bio-based chemicals – Analysis based on 10 key product categories*, European Commission Joint Research Centre, Publications Office, 2019.
28 L. Nattrass, C. Biggs, A. Bauen, C. Parisi, E. Rodríguez-Cerezo and M. Gómez-Barbero, *The EU bio-based industry – Results from a survey*, Joint Research Centre- Institute for Prospective Technological Studies Publications Office, 2016.
29 G. Kaisin, L. Bovy, Y. Joyard, N. Maindron, V. Tadino and J.-C. M. Monbaliu, *J. Flow Chem.*, 2023, **13**, 77–90.
30 L. Wollensack, K. Budzinski and J. Backmann, *Curr. Opin. Green Sustainable Chem.*, 2022, **33**, 100586.
31 https://nova-institute.eu, (accessed April 4, 2024).
32 M. Carus, L. Dammer, Á. Puente, A. Raschka and D. O. Arendt, Bio-based drop-in, smart drop-in and dedicated chemicals, Report Version 2017-12, nova-Institut GmbH, 2017.
33 R. Chinthapalli, P. Skoczinski, M. Carus, W. Baltus, D. de Guzman, H. Käb and J. Ravenstijn, *et al.*, *Bio-based Building Blocks and Polymers – Global Capacities, Production and Trends 2018–2023*, nova-Institut GmbH, Hürth, Germany, 2019.
34 P. Skoczinski, M. Carus, G. Tweddle, P. Ruiz, D. de Guzman, J. Ravenstijn and A. Raschka, *et al.*, *Bio-based Building Blocks and Polymers Global Capacities, Production and Trends 2022–2027*, nova-Institut GmbH, Hürth, Germany, 2023.
35 P. Skoczinski, M. Carus, G. Tweddle, P. Ruiz, N. Hark, A. Zhang and A. Raschka, *et al.*, *Bio-based Building Blocks and Polymers Global Capacities, Production and Trends 2023–2028*, nova-Institut GmbH, Hürth, Germany, 2024.
36 Synthetic glycerine is back (but never really went away)! https://www.outsourcing-pharma.com/Article/2008/10/16/Synthetic-glycerine-is-back-but-never-really-went-away, (accessed April 4, 2024).
37 Combating The Glycerin Glut, https://biodieselmagazine.com/articles/combating-the-glycerin-glut-1123, (accessed April 4, 2024).
38 FAMHP, https://www.famhp.be/en, (accessed February 29, 2024).
39 https://www.fda.gov/, (accessed February 29, 2024).
40 Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations

to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, https://data.europa.eu/eli/reg/2008/1234/2021-05-13, (accessed April 8, 2024).
41 European Medicines Agency post-authorisation procedural advice for users of the centralised procedure, Human Medicines Evaluation Division Report EMEA-H-19984/03 Rev. 107, European Medicines Agency, Amsterdam, Netherlands, 2024.
42 Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.C_.2013.223.01.0001.01.ENG&toc=OJ%3AC%3A2013%3A223%3ATOC, (accessed April 8, 2024, 56).
43 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), https://www.ich.org/, (accessed February 29, 2024).
44 International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7, ICH Harmonised Tripartite Guideline 2000.
45 International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use Development And Manufacture Of Drug Substances (Chemical Entities And Biotechnological/Biological Entities) Q11, ICH Harmonised Tripartite Guideline 2012.
46 International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use Pharmaceutical Development Q8(R2), ICH Harmonised Tripartite Guideline 2009.
47 Communication From The Commission To The European Parliament, The Council And The European Economic And Social Committee: European Union Strategic Approach to Pharmaceuticals in the Environment, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52019DC0128&qid=1605854880622, (accessed February 29, 2024).
48 Q3C—Tables and List Guidance for Industry, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3c-tables-and-list-rev-4, (accessed July 25, 2023).
49 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, *Green Chem.*, 2016, **18**, 288–296.
50 A. Kleemann, J. Engel, B. Kutscher and D. Reichert, *Pharmaceutical Substances: Syntheses, Patents and Applications of the most relevant APIs*, Georg Thieme Verlag, Stuttgart, 4th edn, 2009.
51 WHO model list of essential medicines, World Health Organization 2021.
52 The Top 300 of 2021, https://clincalc.com/DrugStats/Top300Drugs.aspx, (accessed April 5, 2024).
53 Y. Tamura, K. Nakagawa, S. Yoshizaki and N. Murakami, *US Pat*, US3910924A, 1975.
54 M. Saquib, M. F. Khan, J. Singh, B. Khan, Priti, P. Kumar and M. K. Hussain, *Sustainable Chem. Pharm.*, 2022, **30**, 100860.
55 H. Lietz, *US Pat*, US4474986A, 1984.
56 The Top 300 of 2019, https://clincalc.com/DrugStats/Top300Drugs.aspx, (accessed Dec 10, 2022).
57 E. Perzborn and T. Krahn, *International Pat*, WO2007/039134Al, 2009.
58 Y. C. Loh, C. S. Tan, Y. S. Ch'ng, M. Ahmad, M. Z. Asmawi and M. F. Yam, *Molecules*, 2016, **21**, 495.
59 P. G. Wang, M. Xian, X. Tang, X. Wu, Z. Wen, T. Cai and A. J. Janczuk, *Chem. Rev.*, 2002, **102**, 1091–1134.
60 L. Schjelderup and A. J. Aasen, *Acta Chem. Scand.*, 1986, **40**, 505–507.
61 J. A. Finkelstein, R. M. Keenan and J. Weinstock, *US Pat*, US5185351A, 1993.
62 O. Melen, Muscle Relaxants, in *Essentials of Pain Medicine and Regional Anesthesia*, ed. H. T. Benzon, S. N. Raja, R. E. Molloy, S. S. Liu and S. M. Fishman, Churchill Livingstone, Philadelphia, 2nd edn, 2005, ch. 17, pp. 159–165.
63 A. M. Truscello, C. Gambarotti, M. Lauria, S. Auricchio, G. Leonardi, S. U. Shisodia and A. Citterio, *Green Chem.*, 2013, **15**, 625–628.
64 C. Brunnengräber, *Germany Pat*, DE1249852B, 1967.
65 *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Methocarbamol, https://www.ncbi.nlm.nih.gov/books/NBK548286/, (accessed November 11, 2023).
66 B. J. Maron, J. R. Krupp and B. Tune, *J. Pediatr.*, 1971, **78**, 697–699.
67 Décontractyl (méphénésine) : retrait des autorisations de mise sur le marché à compter du 28 juin 2019, https://ansm.sante.fr/actualites/decontractyl-mephenesine-retrait-des-autorisations-de-mise-sur-le-marche-a-compter-du-28-juin-2019, (accessed Feb 19, 2023).
68 M. B. Hadimani, M. K. Purohit, C. Vanampally, R. Van der Ploeg, V. Arballo, D. Morrow, L. P. Kotra, *et al.*, *J. Med. Chem.*, 2013, **56**, 5071–5078.
69 H. L. Yale, E. J. Pribyl, W. Braker, F. H. Bergeim and W. A. Lott, *J. Am. Chem. Soc.*, 1950, **72**, 3710–3716.
70 Mephenesin, https://drugs.ncats.io/substance/7B8PIR2954, (accessed Feb 19, 2023).
71 C. D. Lunsford, R. P. Mays, J. A. Richman Jr and R. S. Murphey, *J. Am. Chem. Soc.*, 1960, **82**, 1166–1171.
72 Mephenoxalone, https://drugs.ncats.io/drug/CZ87T54W8W).
73 S. Reddy, *US Pat*, US20110306773A1, 2011.
74 Drug Approval Package: Skelexin (Metaxalone) Tablets, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/013217s044_SkelexinTOC.cfm, (accessed February 10, 2023).

75 Metaxalone, https://drugs.ncats.io/drug/1NMA9J598Y, (accessed Feb 20, 2023).
76 A. Firth and P. Prathapan, *Curr. Res. Pharmacol. Drug Discov.*, 2021, **2**, 100011.
77 https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance, (accessed Feb 20, 2023).
78 C. J. L. Murray, K. S. Ikuta, F. Sharara, L. Swetschinski, G. Robles Aguilar, A. Gray, M. Naghavi, *et al.*, *Lancet*, 2022, **399**, 629–655.
79 New report calls for urgent action to avert antimicrobial resistance crisis, https://www.who.int/news/item/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis, (accessed Feb 20, 2023).
80 J. S. Gerber, R. K. Ross, M. Bryan, A. R. Localio, J. E. Szymczak, R. Wasserman, A. G. Fiks, *et al.*, *J. Am. Med. Assoc.*, 2017, **318**, 2325–2336.
81 D. M. Lin, B. Koskella and H. C. Lin, *World J. Gastrointest. Pharmacol. Ther.*, 2017, **8**, 162–173.
82 R. P. N. Mishra, E. Oviedo-Orta, P. Prachi, R. Rappuoli and F. Bagnoli, *Curr. Opin. Microbiol.*, 2012, **15**, 596–602.
83 A. A. Bredikhin, D. V. Zakharychev, A. T. Gubaidullin, A. I. Samigullina and Z. A. Bredikhina, *Cryst. Growth Des.*, 2021, **21**, 3211–3224.
84 M. R. Barbachyn and C. W. Ford, *Angew. Chem., Int. Ed.*, 2003, **42**, 2010–2023.
85 The Selection and Use of Essential Medicines (2015), W. T. R. Series Report TRS 994, World Health Organization, 2015.
86 Linezolid (oral/injection), https://www.drugs.com/mtm/linezolid-oral-injection.html, (accessed Feb 20, 2023).
87 M. G. Russell and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2019, **58**, 7678–7681.
88 Tedizolid (oral/injection), https://www.drugs.com/mtm/tedizolid-oral-injection.html, (accessed Feb 20, 2023).
89 G. G. Zhanel, R. Love, H. Adam, A. Golden, S. Zelenitsky, F. Schweizer, J. A. Karlowsky, *et al.*, *Drugs*, 2015, **75**, 253–270.
90 A. C. Flick, H. X. Ding, C. A. Leverett, R. E. Kyne, K. K. C. Liu, S. J. Fink and C. J. O'Donnell, *Bioorg. Med. Chem.*, 2016, **24**, 1937–1980.
91 C. A. Costello, J. A. Simson, R. J. Duguid and D. Phillipson, *WIPO (PCT) Pat*, WO2010042887A2, 2010.
92 D. Phillipson, *WIPO (PCT) Pat*, WO2010091131A1, 2010.
93 W. Li, S. S. Thakur, S.-W. Chen, C.-K. Shin, R. B. Kawthekar and G.-J. Kim, *Tetrahedron Lett.*, 2006, **47**, 3453–3457.
94 W. Mendling and F. Mailland, *Arzneimittelforschung*, 2002, **52**, 8–13.
95 M. Bastrakov and A. Starosotnikov, *Pharmaceuticals*, 2022, **15**, 705.
96 刘新泉, 王平, 刘明霞 and 李晓峰, *China Pat*, CN102863434A, 2014.
97 J. Shu, L. He, H. Ding, L. Wang, H. Guo, Y. Gao, Z. Zeng, *et al.*, *Anal. Methods*, 2014, **6**, 2306–2313.
98 A. Leitner, P. Zöllner and W. Lindner, *J. Chromatogr. A*, 2001, **939**, 49–58.
99 FDA approves new drug for treatment-resistant forms of tuberculosis that affects the lungs, https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-resistant-forms-tuberculosis-affects-lungs, (accessed Feb 20, 2023).
100 *New drug therapy approvals 2019*, Center For Drug Evaluation And Research U.S. Food and Drug Administration, Silver Spring, MD, 2019.
101 M. Sato, H. Azuma, A. Daigaku, S. Sato, K. Takasu, K. Okano and H. Tokuyama, *Angew. Chem., Int. Ed.*, 2017, **56**, 1087–1091.
102 B. Parthasaradhi Reddy, K. Rathnakar Reddy, A. Venkat Narsimha Reddy and B. Vamsi Krishna, *India Pat*, IN201641030408, 2016.
103 M. H. Wilcox, in *Infectious Diseases*, ed. J. Cohen, W. G. Powderly and S. M. Opal, Elsevier, 4th edn, 2017, pp. 1261–1263.
104 Z. Junsong, Z. Guangming, J. Chunxiao and M. Duobin, *Chin. J. Pharm.*, 2004, 644–660.
105 K. Liaras and M. Soković, in *Antifungal Compounds Discovery*, Elsevier, Amsterdam, 2021, ch. 5, pp. 167–262.
106 M. Soković and K. Liaras, in *Antifungal Compounds Discovery*, ed. M. Soković and K. Liaras, Elsevier, Amsterdam, 2021, ch. 3, pp. 49–66.
107 W. W. Hope, L. McEntee, J. Livermore, S. Whalley, A. Johnson, N. Farrington, J. H. Rex, *et al.*, *mBio*, 2017, **8**, e01157–e01117.
108 S. Krishnan-Natesan, *Expert Opin. Pharmacother.*, 2009, **10**, 2723–2733.
109 K. Karimian, R. C. H. S. Leung-Toung, Y. Li and T. F. Tam, *US Pat*, US005817875A, 1998.
110 A. K. Gupta and D. C. A. Lyons, *J. Cutaneous Med. Surg.*, 2015, **19**, 352–357.
111 G. Sood, P. Nyirjesy, M. V. Weitz and A. Chatwani, *Infect. Dis. Obstet. Gynecol.*, 2000, **8**, 240–243.
112 Terconazole, https://www.drugs.com/monograph/terconazole.html, (accessed Feb 20, 2023).
113 Itraconazole, https://www.drugs.com/monograph/itraconazole.html, (accessed Feb 20, 2023).
114 D. J. Sheehan, C. A. Hitchcock and C. M. Sibley, *Clin. Microbiol. Rev.*, 1999, **12**, 40–79.
115 Search Orphan Drug Designations and Approvals: Itraconazole, https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=473715, (accessed Feb 20, 2023).
116 Orphan designation for the prevention of invasive aspergillosis, Report EU/3/18/2024, European Medicines Agency, 2018.
117 J. Heeres, L. J. J. Backx and J. H. Mostmans, *US Pat*, US4223036A, 1980.
118 J. Heeres, L. J. J. Backx and J. H. Mostmans, *US Pat*, US4144346A, 1979.
119 M. Z. Fiume and F. A. Andersen, *Int. J. Toxicol.*, 2003, **22**, 1–10.
120 M. Berthelot, *Ann. Chim. Phys.*, 1854, **41**, 216–319.

121 PubChem Annotation Record for TRIACETIN, https://pubchem.ncbi.nlm.nih.gov/source/hsdb/585, (accessed Feb 20, 2023).
122 Neglected tropical diseases, https://www.who.int/health-topics/neglected-tropical-diseases#tab=tab_2, (accessed Feb 20, 2023).
123 H. Wang, M. Naghavi, C. Allen, R. M. Barber, Z. A. Bhutta, A. Carter, C. J. L. Murray, *et al.*, *Lancet*, 2016, **388**, 1459–1544.
124 Trypanosomiasis, human African (sleeping sickness), https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness), (accessed Feb 20, 2023).
125 L. Leggio, G. Addolorato, L. Abenavoli and G. Gasbarrini, *Int. J. Immunopathol. Pharmacol.*, 2005, **18**, 7–14.
126 P. R. Albert, S. L. Arthur, T. R. H. Stewart, W. F. Neville, M. A. Frank and G. E. James, *US Pat*, US2432797A, 1947.
127 E. P. Levanova, V. A. Grabel'nykh, E. N. Sukhomazova, I. A. Zemirova, N. V. Russavskaya, A. I. Albanov, N. A. Korchevin, *et al.*, *Russ. J. Org. Chem.*, 2008, **44**, 1428–1433.
128 R. A. Peters, L. A. Stocken and R. H. S. Thompson, *Nature*, 1945, **156**, 616–619.
129 S. Gibaud, R. Alfonsi, P. Mutzenhardt, I. Fries and A. Astier, *J. Organomet. Chem.*, 2006, **691**, 1081–1084.
130 E. A. H. Friedheim, *Am. J. Trop. Med. Hyg.*, 1949, **s1–29**, 185–188.
131 G. Thébaud, J. Chadœuf, M. J. Morelli, J. W. McCauley and D. T. Haydon, *Proc. R. Soc. B*, 2010, **277**, 809–817.
132 S. J. R. da Silva, J. C. F. do Nascimento, R. P. Germano Mendes, K. M. Guarines, C. Targino Alves da Silva, P. G. da Silva, L. Pena, *et al.*, *ACS Infect. Dis.*, 2022, **8**, 1758–1814.
133 Ganciclovir, https://medlineplus.gov/druginfo/meds/a605011.html, (accessed Feb 20, 2023).
134 Valganciclovir, https://medlineplus.gov/druginfo/meds/a605021.html, (accessed Feb 20, 2023).
135 R. Vardanyan and V. Hruby, in *Synthesis of Best-Seller Drugs*, ed. R. Vardanyan and V. Hruby, Academic Press, Boston, 2016, pp. 687–736.
136 valGANciclovir https://www.drugs.com/monograph/valganciclovir.html, (accessed Feb 20, 2023).
137 Cidofovir, https://www.drugs.com/mtm/cidofovir.html, (accessed Feb 20, 2023).
138 P. R. Brodfuehrer, H. G. Howell, C. Sapino and P. Vemishetti, *Tetrahedron Lett.*, 1994, **35**, 3243–3246.
139 R. Duncan and M. J. Vicent, *Adv. Drug Delivery Rev.*, 2013, **65**, 60–70.
140 J. Li, F. Yu, Y. Chen and D. Oupicky, *J. Controlled Release*, 2015, **219**, 369–382.
141 Take My Fat Please, https://www.bloomberg.com/news/articles/1998-09-21/take-my-fat-please, (accessed March 1, 2023).
142 Drug Approval Package: Renagel (Sevelamer Hydrochloride) Capsules, https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020926.cfm, (accessed March 1, 2023).
143 S. R. Holmes-Farley, W. H. Mandeville and G. M. Whitesides, *US Pat*, US5667775A, 1995.
144 D. P. Rosenbaum, S. R. Holmes-Farley, W. H. Mandeville, M. Pitruzzello and D. I. Goldberg, *Nephrol., Dial., Transplant.*, 1997, **12**, 961–964.
145 C. R. Nolan and W. Y. Qunibi, *Kidney Int.*, 2005, **67**, S13–S20.
146 Drug Approval Package- Renvela (Sevelamer Carbonate) Tablets, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022127s000TOC.cfm, (accessed March 2, 2024).
147 Drug Approval Package Welchol (colesevelam HCL) for Oral Suspension, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022362_welchol_toc.cfm, (accessed March 27, 2023).
148 LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bile Acid Resins or Sequestrants, https://www.ncbi.nlm.nih.gov/books/NBK548342/, (accessed March 1, 2023).
149 I. W. Harry Mandeville III and S. R. Holmes-Farley, *US Pat.*, US5693675A, 1995.
150 A. Corsini, E. Windier and M. Farnier, *Eur. J. Cardiovasc. Prev. Rehabil.*, 2009, **16**, 1–9.
151 M. H. Davidson, M. A. Dillon, B. Gordon, P. Jones, J. Samuels, S. Weiss, S. K. Burke, *et al.*, *Arch. Intern. Med.*, 1999, **159**, 1893–1900.
152 V. A. Fonseca, Y. Handelsman and B. Staels, *Diabetes, Obes. Metab.*, 2010, **12**, 384–392.
153 Prescribing information - Welchol (colesevelam) https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022362s007lbl.pdf, (accessed March 1, 2024).
154 I. W. Harry Mandeville III and S. R. Holmes-Farley, *US Pat.*, 5679717A, 1997.
155 Sanofi-aventis To Acquire Genzyme For $74.00 In Cash Per Share Plus Contingent Value Right, https://www.pharmaceuticalonline.com/doc/sanofi-aventis-to-acquire-genzyme-for-7400-0001, (accessed March 1, 2023).
156 A. Hoffman, *Biochem. J.*, 1963, **89**, 57–68.
157 S. L. Gorbach, *Gastroenterology*, 1971, **60**, 1110–1129.
158 W. F. Minor, R. R. Smith and L. C. Cheney, *J. Am. Chem. Soc.*, 1954, **76**, 2993–2996.
159 H. Hoffmann, H. Grill, J. Wagner and G. Hofrichter, *US Pat*, US3839587A, 1974.
160 K. B. Mallion, A. H. Todd, R. W. Turner, J. G. Bainbridge, D. T. Greenwood, J. Madinaveitia, B. A. Whittle, *et al.*, *Nature*, 1972, **238**, 157–158.
161 R. L. Findling, S. A. Candler, A. F. Nasser, S. Schwabe, C. Yu, J. Garcia-Olivares, J. H. Newcorn, *et al.*, *CNS Drugs*, 2021, **35**, 643–653.
162 Drugs@FDA: FDA-Approved Drugs, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=211964, (accessed March 7, 2023).
163 S. Lee, *US Pat*, US3712890A, 1970.
164 W. J. V. D. Burg, *US Pat*, US4002632, 1977.
165 K. S. Gregson and J. D. Bennett, in *Pharmacology and Therapeutics for Dentistry*, ed. F. J. Dowd, B. S. Johnson

and A. J. Mariotti, Mosby, 7th edn, 2017, ch. 27, pp. 392–403.
166 C. Fitzmaurice and T. Lee, *US Pat*, US3777033A, 1973.
167 H. Cairns, C. Fitzmaurice, D. Hunter, P. B. Johnson, J. King, T. B. Lee, J. S. G. Cox, *et al.*, *J. Med. Chem.*, 1972, **15**, 583–589.
168 F. B. H. Morren, *Germany Pat*, DE1178435B, 1964.
169 A. Said Stålsmeden, J. L. Belmonte Vázquez, K. van Weerdenburg, R. Rae, P.-O. Norrby and N. Kann, *ACS Sustainable Chem. Eng.*, 2016, **4**, 5730–5736.
170 Y. Hu, Z. Wei, A. Frey, C. Kubis, C.-Y. Ren, A. Spannenberg, T. Werner, *et al.*, *ChemSusChem*, 2021, **14**, 363–372.
171 R. A. Goldsby, *Immunology*, W.H. Freeman, New York, 5th edn, 2003.
172 C. Jurgen, *US Pat*, US1526627A, 1925.
173 M. B. Zimmermann, P. L. Jooste and C. S. Pandav, *Lancet*, 2008, **372**, 1251–1262.
174 M. Ahmed, *Lancet*, 2008, **372**, 88.
175 K. Strijbis, F. M. Vaz and B. Distel, *IUBMB Life*, 2010, **62**, 357–362.
176 J. S. H. Babcock and B. R. Baker, *US Pat*, US2376334A, 1945.
177 F. Hoffmann, *Aktiengesellschaft Switerland Pat*, CH221847A, 1942.
178 E. E. Snell, E. L. Wittle and J. A. Moore, *US Pat*, US2625565A, 1953.
179 P. A. Jerabek, T. B. Patrick, M. R. Kilbourn, D. D. Dischino and M. J. Welch, *Int. J. Radiat. Appl. Instrum., Part A*, 1986, **37**, 599–605.
180 A. G. Sorace, A. A. Elkassem, S. J. Galgano, S. E. Lapi, B. M. Larimer, S. C. Partridge, A. D. Smith, *et al.*, *Semin. Nucl. Med.*, 2020, **50**, 488–504.
181 R. Matthes and H. Frey, *Biomacromolecules*, 2022, **23**, 2219–2235.
182 F. Wilde, C. Chamseddin, H. Lemmerhirt, P. J. Bednarski, T. Jira and A. Link, *Arch. Pharm.*, 2014, **347**, 153–160.
183 E. Nieto, R. Alajarín, J. Álvarez-Builla, I. Larrañaga, E. Gorospe and M. A. Pozo, *Synthesis*, 2010, 3700–3704.
184 *Concise Medical Dictionary*, ed., E. Martin, Oxford University Press, Oxford, UK, 2015.
185 A. Barge, F. Baricco, G. Cravotto, R. Fretta and L. Lattuada, *ACS Sustainable Chem. Eng.*, 2020, **8**, 12825–12830.
186 *Methotrexate*, ed. B. N. Cronstein and J. R. Bertino, Birkhäuser Verlag, Basel, Switerland, 2000.
187 P. T. Rajagopalan, Z. Zhang, L. McCourt, M. Dwyer, S. J. Benkovic and G. G. Hammes, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 13481–13486.
188 The Top 300 of 2020, **https://clincalc.com/DrugStats/Top300Drugs.aspx**, (accessed Nov 4, 2023).
189 J. A. Ellard, *US Pat*, US4080325A, 1978.
190 J. E. Holladay, J. F. White, J. J. Bozell and D. Johnson, *Top Value Added Chemicals From Biomass*, Pacific Northwest National Laboratory (PNNL) and National Renewable Energy Laboratory (NREL), Springfield, VA, 2004.
191 X.-F. Shang, S. L. Morris-Natschke, Y.-Q. Liu, X. Guo, X.-S. Xu, M. Goto, K.-H. Lee, *et al.*, *Med. Res. Rev.*, 2018, **38**, 775–828.
192 B. R. Hammond, B. A. Johnson and E. R. George, *Exp. Eye Res.*, 2014, **129**, 135–150.
193 H. Saggadi, D. Luart, N. Thiebault, I. Polaert, L. Estel and C. Len, *RSC Adv.*, 2014, **4**, 21456–21464.
194 X. Zhang and X. Xu, *Chem. – Asian J.*, 2014, **9**, 3089–3093.
195 J. Li, J. Zhang, H. Yang and G. Jiang, *J. Org. Chem.*, 2017, **82**, 3284–3290.