

Significance of Fungicides and Antifungals for Agriculture and Medicine

1.1 Terminology

Antimycotics are active ingredients which are used for the prevention and treatment of mycoses.

Mycoses are diseases of humans, animals, and plants that are caused by infestations with parasitic fungal pathogens. Examples of mycoses are downy mildew, powdery mildew, rust, and leaf spot diseases of plants as well as athlete's foot, ringworm, candidiasis, and aspergillosis of humans. Fungi, which are neither plants nor animals, are a large group of organisms that range in size from simple yeast cells of less than 5 μm in diameter up to complex fruiting bodies which can reach 1 m in size and to diffuse colonial organizations that are reported to exist over areas of more than 800 Ha [1]. The kingdom of true fungi, also called Eumycota, contains five different phyla that are Ascomycota, Basidiomycota, Chytridiomycota, Glomeromycota, and Zygomycota that are all eukaryotic, nonvascular, nonmotile, heterotrophic, and chitin-containing, but differ in their mode of sexual reproduction and their molecular biology relationship. The ending “-mycota” is mainly used to designate a phylum, while the commonly – also in this book – used ending “-mycetes” formally denotes a class or is used informally to refer to the members of the phylum. Amongst the 6 million known and expected fungal species, ca. 8,000 of them are crop-damaging plant pathogens and ca. 625 of them are infecting humans and animals [2]. Most of these human- and plant-pathogenic fungi belong to the Ascomycetes and Basidiomycetes, but also to Deuteromycetes (also called fungi imperfecti), a group of fungi most of which belong to the Ascomycetes and which have lost the ability to reproduce sexually. However, some important plant and animal pathogens also fall into the fungus-like phylum Oomycota from the kingdom of Chromista. Fungi invade plant tissue and human skin by either gaining entry through natural openings (e.g. stomata of plants or respiratory tracts of humans) or wounds; or by direct penetration of tissue and skin, where they rapidly multiply.

Antifungals are pharmaceuticals for the treatment of mycoses in humans and animals. Human mycoses are usually divided into three different types: superficial (on the skin), subcutaneous (in and beneath the skin), and systemic

(internally, e.g. in the lung). Antifungal medications can be administered intrathecally in case of an infection of the central nervous system, ocularly in case of an infection of the eye, vaginally in case of an infection of the vaginal region, topically in case of an infection of the skin, and intravenously or orally in case of different types of infections if the antimycotic has systemic properties, means if it is taken up by and distributed within the body. Antifungals are usually divided into fungicidal agents, which kill the fungal pathogen directly (e.g. the allylamines dealt with in Chapter 2) and fungistatic agents, which inhibit fungal growth and reproduction without immediate killing, thereby preventing the infection from worsening (e.g. most azoles found in Chapter 5).

Fungicides are agrochemicals for the prevention and treatment of mycoses in plants. They can be used either foliar or as a seed treatment, which are the two most frequent application methods, but also by soil application and trunk injection. Foliar fungicides are sprayed on the leaves and other parts of the plant and are usually divided into the three different types protective (also called preventative or contact), curative, and eradivative. The majority of fungicides show their best effect if applied before any infection occurs. When present on the plant surface prior to infestation by fungal spores, such protective fungicides act as an exterior shield as they cannot move into the plant. Curative fungicides are also effective after a fungal infestation occurred but usually only in the incubation period until disease symptoms are visible. In contrast to protective fungicides, curative fungicides have systemic properties that allow their uptake and distribution within the plant. This movement can be either translaminar (through the leaf from one side to the other), acropetal (also called apoplastic, upward and outward through the xylem to the new growth), or basipetal (downward through the phloem to the roots). Finally, the rare examples of eradivative fungicides are able to stop the disease progress even after the appearance of symptoms. An alternative to the foliar spray of plants with fungicides is coating crop seeds with them, which is called seed treatment. Hereby, the seed and the resulting seedling are protected in the early growth process from damaging diseases caused by seedborne pathogens, which are carried by the seed, and soilborne pathogens, which attack from the soil.

In conclusion, the typical control of fungal plant diseases works as prevention of an infection and not as a treatment. In such way, the use of fungicides in agriculture differs significantly from the use of antifungals in medicine.

1.2 History

1.2.1 History of Fungicides

Since the dawn of agriculture, fungal pathogens have posed a persistent threat to the human food supply. Unlike the clearly visible competition between crops and weeds or the obvious damage caused by insect pests, the role of fungi in plant diseases remained poorly understood for a long time. It was not until the 19th century that most plant diseases were correctly attributed to fungal agents. Although the causes

of disease outbreaks remained largely unknown for a long time, chemical treatments have been used for over 30 centuries. The history of agrochemical fungicides [3–7] is closely associated with elemental sulfur, likely the oldest known crop protection agent [8]. Its antifungal properties were already recognized in ancient Greece, where Homer referred to “pest-averting sulfur” nearly 3,000 years ago [9]. Much of this knowledge was lost over time until it was rediscovered by Forsyth in 1802, when he recommended sulfur for controlling plant diseases [10]. To combat powdery mildew on fruit trees, he proposed spraying a mixture of quicklime, sulfur, elderberry bud, and tobacco. From 1824 onward, powdered sulfur was widely used to treat diseases of fruit trees and grapevines, such as peach powdery mildew [11]. The second half of the 19th century then saw the introduction of several pioneering sulfur-based fungicides: Eau Grisson (calcium polysulfide, $\text{CaS} \cdot \text{S}_x$, also known as lime sulfur), introduced by Grison in 1852 [12]; Bordeaux mixture ($\text{CuSO}_4 + \text{Ca}(\text{OH})_2$ that reacts to $\text{Cu}(\text{OH})_2 + \text{CaSO}_4$), developed by Millardet in 1885 [13]; and Burgundy mixture ($\text{CuSO}_4 + \text{Na}_2\text{CO}_3$), introduced by Masson in 1887 [14]. Continued experimentation with copper compounds eventually led to the development of colloidal copper hydroxide, first described as a foliar fungicide in 1923 [15]. Two decades later, in 1943, the introduction of ferbam (**1**) – an iron-containing compound and one of the earliest dithiocarbamates – marked the emergence of the first widely used foliar broad-spectrum protective fungicide, effective against rusts, molds, scabs, and other plant diseases [5]. A further important milestone was achieved in 1968 with the launch of the first broad-spectrum foliar curative fungicide, the tubulin polymerization inhibitor benomyl (**3**) (Figure 1.1) [5]. The other possibility to prevent fungal plant diseases, the treatment of seeds with appropriate fungicides, has been applied in the case of cereals for almost 400 years. Historic sources mention the use of brine in 1637, arsenic in 1755, copper sulfate in 1760, and finally phenylmercury chloride in 1914 [6, 7]. A big breakthrough was the introduction of the first fully systemic seed treatment agent in 1966, which was the succinate dehydrogenase inhibitor carboxin (**2**) (see Chapter 7) [5]. Although the early beginnings of agrochemical disease control were linked to multisite inhibitors, which block non-specifically several different biochemical pathways, today’s typical foliar and seed treatment fungicides are purely organic compounds which, in most cases, selectively block one single enzyme in a fungal biosynthesis pathway (Figure 1.1).

1.2.2 History of Antifungals

The development of pharmaceutical antifungal agents [16–19] started considerably later than that of agrochemical fungicides. During the 1940s, treatment options for fungal infections were still limited and mainly comprised potassium iodide, undecylenic acid, and phenolic dyes. A significant advance was achieved with the discovery of griseofulvin (**4**), a natural product isolated from *Penicillium griseofulvum* that disrupts intracellular tubulin polymerization. Since the late 1940s, griseofulvin has been widely used for topical fungal infections and, from the early 1960s onward, also as an orally active antifungal [20]. Two major classes of antifungal compounds that still shape the current market emerged during the 1950s. Nystatin (**5**),

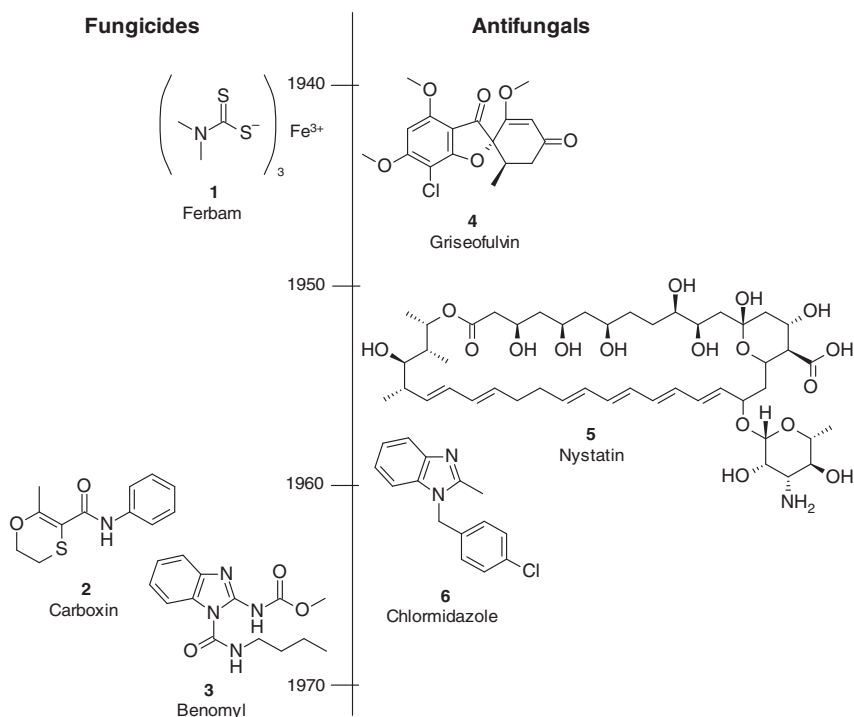


Figure 1.1 Important fungicide and antifungal milestones introduced between 1940 and 1970.

a macrolactone produced by *Streptomyces noursei*, became the first clinically used polyene antifungal in 1955. Only three years later, amphotericin B, a substantially more potent representative of this class, was discovered and remains one of the gold-standard antifungal therapies to this day (see Chapter 3) [21]. Chlormidazole (**6**), the very first azole derivative reaching the pharmaceutical market, was introduced in 1958 [16], followed 11 years later by the more typical azole antifungal miconazole which is because of its systemic action also highly useful against deep mycoses (see Chapter 5) (Figure 1.1) [22]. Interestingly, with the fungicide benomyl (**3**) and the antifungal chlormidazole (**6**), two benzimidazole derivatives are important milestones in the early history of antimycotics, although this bicyclic scaffold does not play a big role anymore in today's modern antimycotic active ingredients.

1.3 Demand

1.3.1 Fungicide Market Overview

Ensuring food security for a steadily growing human population remains one of the biggest challenges of our time. Currently, 8.1 billion people are living on Earth, a population that is forecasted to reach 9.7 billion in 2050 and the 10 billion mark before the end of this century [23]. Every evening around 828 million people go to

bed hungry, as they don't have adequate access to food and therefore face acute levels of starvation. Nine million people die from hunger every year; these are 25,000 people lost to hunger every day [24]. At the same time, the size of available arable land is shrinking, leading to the fact that the number of people fed per hectare of planted land is constantly rising, it has doubled from three in the 1970s to almost six these days [25, 26]. Not surprisingly, the global demand for grains, such as maize, rice, and wheat, also doubled within the same time frame, from 1,208 million metric tons in 1974 to almost 2,500 million metric tons in 2020 (Table 1.1) [26, 27].

This situation is further aggravated by the fact that, although the application of agrochemicals triples the native yield of the major crop plants rice and cotton and doubles the yield of maize, soybean, and potato (always compared to the yield without any crop protection), even with modern crop protection methods, each of these crops reaches only 60–75% of their maximum potential (Table 1.2) [26, 28–33].

Among the major causes of this unrealized harvest potential are fungal pathogens that cannot be adequately controlled with the currently available fungicide arsenal or that have developed resistance to widely used fungicides belonging to established single-site mode-of-action classes. Consequently, the demand for agrochemical fungicides remains very high. In 2023, global fungicide sales reached USD 19.9 billion, accounting for slightly more than one quarter of the total agrochemical market value of USD 74.8 billion. More than half of these sales were generated by sterol biosynthesis inhibitors (14 α -demethylase inhibitors, referred to as DMIs in crop protection; see Chapter 5) and respiration inhibitors, primarily inhibitors of respiratory chain Complex II (succinate dehydrogenase inhibitors [SDHIs]; see Chapter 7) and Complex III (strobilurins; see Chapter 6) (Figure 1.2). The principal crops treated with fungicides include fruits and vegetables, soybeans, cereals, and rice [34].

Table 1.1 Increasing challenges for the global agriculture.

	1974	1997	2020
Number of people fed per hectare of planted land	3.0	4.3	5.6
Global grain demand (million metric tons)	1,208	1,843	2,497

Table 1.2 Estimated harvest losses of six major crops.

	Rice	Wheat	Maize	Soybean	Cotton	Potato
Native yield without crop protection (%)	23	50	32	40	18	25
Extra yield due to crop protection (%)	40	22	37	34	53	35
Remaining potential, lost to weeds, pests, and pathogens (%)	37	28	31	26	29	40

1.3.2 Antifungal Market Overview

In comparison to agrochemical fungicides, the pharmaceutical antifungal market is considerably smaller, reaching global sales of USD 15.4 billion in 2023. This market is strongly dominated by inhibitors of 14α -demethylase in the ergosterol biosynthesis pathway – referred to as azoles in medical applications (see Chapter 5) – which accounted for nearly half of total sales (USD 7.4 billion). The azoles were followed by echinocandins (USD 4.6 billion, see Chapter 4), polyenes (USD 1.6 billion, see Chapter 3), and allylamines (USD 1.1 billion, see Chapter 2), representing the second-, third-, and fourth-largest antifungal classes, respectively [35]. Together, these four classes comprise approximately 95% of the antifungal market, indicating a substantially lower degree of market fragmentation compared to the fungicide sector, which encompasses several additional modes of action (Figure 1.2). Despite the smaller market size, the impact of fungal diseases on human health is severe. Invasive fungal infections are estimated to cause 1.5–1.7 million deaths annually, exceeding the mortality associated with diseases such as malaria or tuberculosis [36–40]. More than 90% of those deaths are attributed to *Aspergillus*, *Candida*, and *Cryptococcus* species. Especially at risk are immunocompromised patients, e.g. as a result of aggressive therapies such as anticancer chemotherapy, long-term corticosteroid treatment, and organ transplant, or as a result of an immunosuppressive infection, such as HIV/AIDS. *Aspergillus fumigatus* is the major cause of invasive aspergillosis in immunocompromised patients, which has mortality rates between 30 and 95% [36, 41]. *Candida* spp., especially *Candida albicans*, are responsible for most invasive fungal infections and are ranked as the fourth leading cause of nosocomial bloodstream infections in modern hospitals with approximately 40% mortality [37, 42]. *Cryptococcus neoformans* is an opportunistic pathogen that

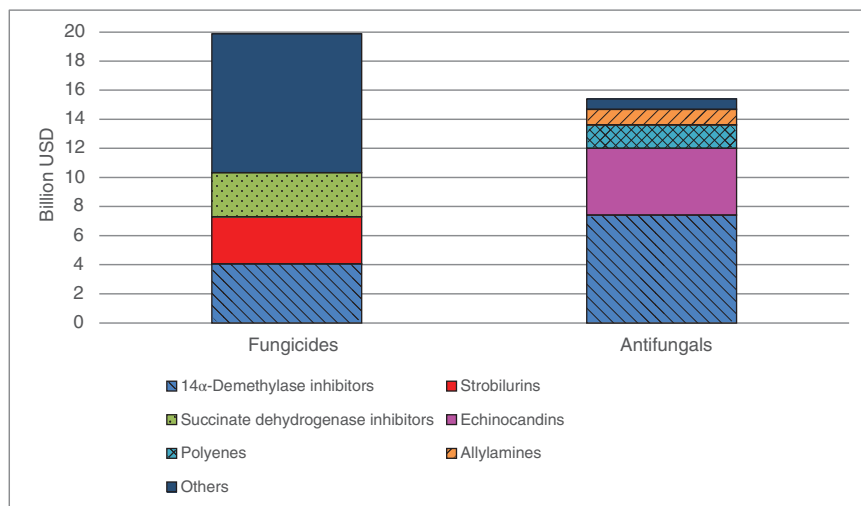


Figure 1.2 Fungicide and antifungal market size in 2023.

causes meningitis globally, particularly in HIV-infected patients, thereby killing presumably 600,000 people per year [37, 43].

As we have seen, fungal pathogens are not only a threat to global food security of mankind, but also directly to their health [2, 44, 45]. Even more worrying is that climate change seems to further increase the risk of fungal infestations for humans, animals, and plants. Not only do some fungal pathogens adapt to higher temperature and become more thermotolerant [46], but others are also moving poleward at around 7km per year [47]. All of the facts mentioned in this section demonstrate the tremendous need for antimycotics.

1.4 Cross-Industry

The fact that antimycotics are the only overlapping field between both agrochemical and pharmaceutical markets (herbicides and insecticides not existing amongst pharmaceuticals, anticancer and cardiovascular agents, etc., not needed in crop protection) is both chance as well as burden.

1.4.1 Chance: Learning Across Industries

On the one hand, the possibility to learn from each other across industries in antimycotics research regarding important questions, such as from where to obtain the most promising hits and how to best identify them, how to successfully progress as many as possible of them through hit-to-lead, lead optimization, and candidate selection stages into development, how to keep the attrition rate in late research and in development as low as possible, how to discover antimycotics with novel modes of action and how to study their mode of resistance, how to establish and run most efficiently in vitro and in vivo screening platforms, among others, is not available in other indications that exist only in pharmaceuticals or only in crop protection. This huge chance is unfortunately so far relatively unexploited as there is not much of an exchange between industries, neither amongst scientists working on antimycotics in medicinal and crop protection research nor with compound libraries. Several papers have been published on the question of whether agricultural fungicides are so far a missed opportunity for drug discovery and may accelerate the identification of novel pharmaceutical antifungals [3, 48–51]. This is a valid question as the number of successful modes of action in crop protection is much higher than in medicine, the Fungicide Resistance Action Committee has listed 52 different fungal targets on its most recent mode of action poster [52, 53], which is in sharp contrast to the currently very limited number of antifungal modes of action. Interestingly, the author could not retrieve a single paper that advocates that agrochemistry can profit from learnings of pharmaceutical antimycotics. However, considering the huge challenges described in Section 1.3, a better collaboration of the research-based agrochemical and pharmaceutical industries is advisable in the future.

1.4.2 Risk: Resistance Across Industries

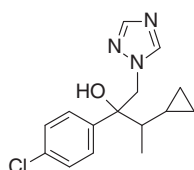
When faced with antimycotics, fungal pathogens have in principle the capacity to overcome their inhibitory action through specific resistance mechanisms. Prior to 1960, nearly all fungicides used for the control of plant pathogens were multisite inhibitors with purely protective activity, blocking nonspecifically several different biochemical pathways, for instance, by building complexes with metal-containing enzymes such as oxidases and dehydrogenases. Despite their widespread use, resistance to these compounds was a rare event and only occurred, if ever, many years after market introduction. With the triumphant march of single-site (site-specific) fungicides and antifungals, the incidence of fungicide resistance problems greatly increased, and the time interval between commercial introduction and emergence of resistance became often significantly shorter. Major drivers for fast resistance evolution of these specifically acting fungicides and antifungals are the increased selection pressure caused by their much higher potency and the relative ease in acquiring resistance by single-point mutations in the gene encoding the target. These target mutations modify the amino acid sequence of the protein, often leading to a structural change of the binding pocket. Because the amino acid sequence of a target protein can vary across species, the initial potency of the antimycotic as well as the sensitivity shift conferred by resistance mutations differ for different pathogens. As also the molecular structure of related active ingredients differs even with the size and exit vectors of pharmacophore and sidechains, different compounds from the same mode of action class are not impacted in the same manner. Antifungal resistance is a heritable fungal characteristic that develops through natural selection of fungi. The selective pressure exerted on fungi by exposure to an antimycotic favors one or more strains that are not impacted by the fungicide or antifungal because they exhibit resistance to it. Such strains can survive and reproduce in the presence of this antimycotic. Their short life cycle enables the spread of a resistant fungal population. In addition, development of antimycotic resistance depends on how the active ingredient is used, meaning in which doses and time intervals it is applied, and if any alteration with antimycotics from different modes of action classes takes place. There are five major mechanisms of fungal resistance development against antifungals [54–57] and fungicides [58–61]:

1. Alteration in the protein structure of the target site by point mutations.
2. Upregulation of the target protein.
3. Switch to alternative metabolic pathways.
4. Decrease in drug effective concentration in fungal cells by efflux processes.
5. Detoxification via degradation of the antimycotic by metabolic enzymes.

Based on the above-described ability of fungal species to become resistant to certain antimycotics, there is a huge concern that the abundant use of fungicides in agriculture which, as explained in Section 1.1, are mainly applied protectively and therefore sprayed constantly before any infestation happens, fosters the resistance development in human-pathogenic fungi [62–66]. Especially of significance and already visible is this problem amongst the 14α -demethylase inhibitors, which are not only the only major mode of action class applied in both medicine

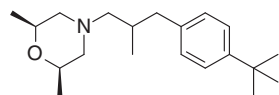
(here called azoles) and agriculture (here called DMIs), but also the biggest-selling antimycotics family in both industries (see Chapter 5). This dual use of sterol 14 α -demethylase inhibitors in the field and in the clinic has been a major driver for azole-resistant *Aspergillus fumigatus* infections in humans. As azoles are still the first line of defense and only oral option against aspergillosis, it is a big problem that *Aspergillus fumigatus* is already intrinsically resistant to the older azoles ketoconazole and fluconazole [64]. Also, modern azoles, such as voriconazole and isavuconazole, struggle with this life-threatening disease, as the excess mortality rate over a 90-day period in patients with voriconazole-resistant invasive aspergillosis and treated with voriconazole is 25% [63]. The cross-resistance of pharmaceutical and agrochemical sterol 14 α -demethylase inhibitors, which belong to the family of “conazoles,” is not by surprise, as many azoles and DMIs are closely related by structure (see similarity of cyproconazole [7] and voriconazole [8]). Two other sterol biosynthesis-inhibiting antimycotics with almost identical molecular structures are the Δ^8 – Δ^7 -isomerase and Δ^{14} -reductase blocking fungicide fenpropimorph (9) [67] and antifungal amorolfine (10) (Figure 1.3) [68].

Fungicides



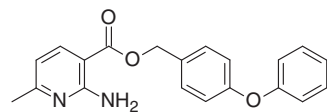
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Cyproconazole



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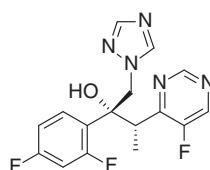
Fenpropimorph



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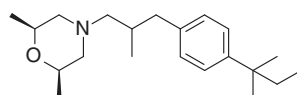
Aminopyrifen

Antifungals



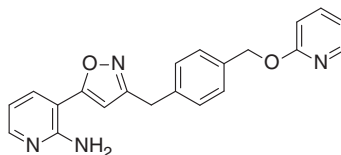
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Voriconazole



10

Amorolfine



12

Manogepix

Figure 1.3 Structural similarity of antifungals and fungicides from the conazole family of 14 α -demethylase inhibitors (cyproconazole [7] and voriconazole [8]), the Δ^8 – Δ^7 -isomerase inhibitors (fenpropimorph [9] and amorolfine [10]) and from the Gwt1 inhibitors (aminopyrifen [11] and manogepix [12]).

On the contrary, also, the widespread use of antifungal azoles in medicine is seen as a risk for agriculture. It has been recently shown that wastewater contaminated with pharmaceutical azoles can reduce the mycorrhizal nutrient transfer from the soil into the roots of wheat [69].

Also in the future, fungicides and antifungals will be needed to guarantee food and health for the human population; it will never be possible to go without one of them to avoid the occurrence of cross-resistance between both industries. However, if pharmaceuticals and agrochemicals work with the same antimycotic mode of action, then careful monitoring of any potential resistance spreading from the field to the clinics or vice versa is advisable. With inhibitors of dihydroorotate dehydrogenase (DHODH, olorofirm as pharmaceutical [70] and ipfluenoquin and quinofumelin as agrochemicals [71]) and Gwt1, an enzyme responsible for a step in the glycosylphosphatidylinositol (GPI) biosynthesis (manogepix [12] and fosmanogepix as pharmaceuticals [72], aminopyrifin [11] and aminotipyr as agrochemicals [73]), the next two modes of action classes with dual use as antifungals and fungicides are in the starting blocks (see Chapter 9). Looking at the close structural similarity of the two Gwt1 inhibitors aminopyrifin (11) and manogepix (12), cross-industry resistance problems seem inevitable also for this new mode of action (Figure 1.3).

1.5 Innovation

From all what has been written above, it is apparent that there is a constant need for new antimycotics. Because the spread of resistant isolates in fungal populations is impacting the performance of principally all major active ingredient classes, it would be favorable if the next generation of antifungals and fungicides possessed novel, so far unexploited modes of action or at least resistance-breaking properties. But where to obtain the antimycotics of the future from is an important question [74, 75]. Research groups at universities, institutes, and in the pharmaceutical and agrochemical industries address this task with cutting-edge tools, such as structure-based design [76], target-based design [77], inverse design [78], multiparameter optimization [79], and scaffold hopping [80] of leads stemming from compound libraries which are prepared in-house by combinatorial chemistry [81], exchanged with other companies, or purchased by vendors. Other sources for lead compounds are natural products [82], intermediates, and target compounds of projects in other indications [83]. Using all these tools, novel antimycotics are obtained within the following four approaches.

1.5.1 Novel Antimycotic Modes of Action Through Designing/ Screening of Completely Novel Compounds

The whole arsenal of fungicides currently available to farmers worldwide as a tool to protect their crops can be divided into altogether 52 different modes of action [52, 53]. These molecular targets affect all major physiological processes in fungi,

such as nucleic acid metabolism, cytoskeleton and motor proteins, respiration, amino acid and protein synthesis, signal transduction, lipid synthesis, transport and membrane integrity, melanin biosynthesis in cell walls, sterol biosynthesis in membranes, and cell wall biosynthesis. Two of the three biggest-selling compound classes, the Complex III-inhibiting strobilurins (see Chapter 6) and the Complex II-inhibiting SDHIs (see Chapter 7), block the fungal respiration. The third and most important fungicide class, the DMIs (see Chapter 5), inhibits one specific enzyme in the biosynthesis of ergosterol. Several further commercialized fungicides act on a whole variety of additional molecular targets. The antifungal toolkit seems a bit more limited regarding the number of available modes of action. Two of the four dominating active ingredient classes, the azoles (see Chapter 5) and the allylamines (see Chapter 2), inhibit different enzymes in the ergosterol biosynthesis pathway as well, as also the fungicidal DMIs. Ergosterol is also involved in the mode of action of the polyenes (see Chapter 3), they bind to this sterol, thereby causing rupturing or leakage of cell membranes. The echinocandins (see Chapter 4) inhibit 1,3- β -glucan synthase and therefore also act on the fungal cell wall. Besides these four major antifungal classes, there have been until recently not many alternatives. Flucytosine, an antifungal that enters the fungal cell via cytosine permease and blocks the synthesis of both DNA and RNA, is still frequently used against certain forms of candidiasis and cryptococcal meningitis [84].

Fortunately, there has been some movement regarding the discovery of novel antifungal [85–87] and fungicidal [3] modes of action recently. Two completely novel modes of action, the DHODH inhibitors (antifungal: olorofim; fungicides: ipflufenquin and quinofumelin) and the inhibitors of Gwt1, an inositol transferase in the GPI anchor biosynthesis (antifungal: manogepix [12] and fosmanogepix; fungicides: aminopyrifin [11] and aminotipyr) will enter both pharmaceutical and crop protection markets (see Chapter 9). Further novel antifungals with a new mode of action are the leucyl-tRNA synthetase inhibitor tavaborole (see Chapter 9) [88] and the chitin synthase inhibitor nikkomycin Z [89]. New fungicides with a novel mode of action are the oxysterol binding protein inhibitors oxathiapirolin and fluoxapirolin (see Chapter 8) [90], the histone deacetylase inhibitors flufenoxadiazam and cyprometoxazam (see Chapter 9) [91], and the tubulin dynamics modulator pyridachlometyl [92].

The invention pathways of the new fungicide oxathiapirolin (**16**) [3, 80, 93] and the novel antifungal manogepix (**12**) [37, 94, 95] demonstrate how important the access to appropriate compound libraries and their meaningful screening are, but also the significance of scaffold hopping in early and middle research stages. The phenylacetic acid amide derivative **13** from a diverse bis-amide library with a piperidinylthiazole core showed some modest protective activity against *Phytophthora infestans* and *Pseudoperonospora cubensis*. Three classical scaffold hopping manipulations, the isosteric ring exchange from a phenyl ring to a pyrazole delivering **14**, the ring closure of an α -methylbenzyl moiety to a tetralin leading to **15**, and an exchange of a carboxylic amide by a cyclic isoxazoline mimic afforded oxathiapirolin (**16**) which is 10,000 times more active than the original hit **13** (see Chapter 8) [3, 80, 93]. A similar success story was achieved in medicinal chemistry starting from

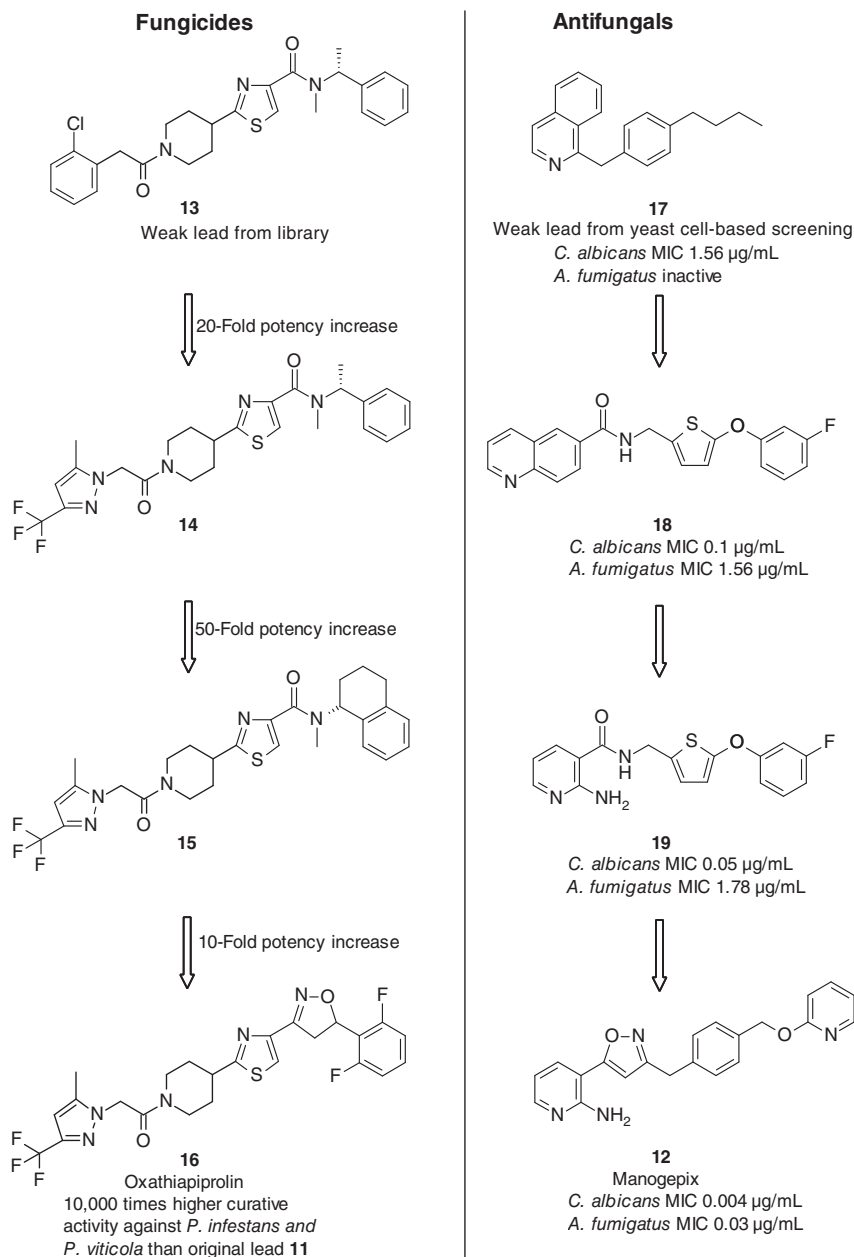
1-(4-butylbenzyl)isoquinoline (**17**), which had been identified in a yeast cell-based assay to possess moderate activity against *Candida albicans*. An optimization of the biheterocycle with concurrent sidechain optimization led to **18**, the activity of which could be further enhanced by replacement of the quinoline by a 2-aminopyridine, delivering **19**. As was the case also for the last scaffold hopping move in the invention pathway of oxathiapiprolin, also here an exchange of a carboxylic acid amide by a cyclic isoxazole mimic with simultaneous sidechain optimization delivers manogepix (**12**), which is highly active against both *Candida albicans* and *Aspergillus fumigatus* (see Chapter 9; Scheme 1.1) [37, 94, 95].

1.5.2 Novel Antimycotic Modes of Action Through Repurposing of Active Ingredients from other Indications

A second possibility to obtain novel modes of action amongst antimycotics is the application of established active ingredients from other indications, which have been shown to possess additional activity against fungal pathogens. This approach, which is called repurposing, is mainly known within pharmaceutical antifungals [94, 96, 97]. Two successful examples are tamoxifen (**19**) and sertraline (**20**) (Figure 1.4). Tamoxifen (**19**), originally an estrogen receptor modulator used in the treatment of breast cancer, has been reported as a new treatment against *Cryptococcus neoformans* [98]. The selective serotonin reuptake inhibiting antidepressant sertraline (**20**) has been shown to potentiate the anti-cryptococcal and anti-candida potency of azoles if applied as adjunctive therapy [99].

1.5.3 Design of Resistance-breaking Compounds in Known, Resistance-affected Mode of Action Classes

The most obvious method to win the constant race against the spread of new resistant mutants among fungal pathogens is the introduction of novel antimycotics with a new mode of action (Sections 1.5.1 and 1.5.2). However, a valid alternative is the design of resistance-breaking active ingredients within a mode of action class that suffers from resistance problems. A recent success story of this approach is the discovery of metyltetraprole (**23**), a novel Complex III inhibitor binding to the Qo site of cytochrome bc₁. It has been intentionally designed to control fungal populations with a G143A mutation, which is currently the major occurring strain of several leaf spot pathogens in Europe. After 25 years of strobilurin usage, a good portion of the European field population of especially the economically important pathogen *Septoria tritici*, causal agent of wheat leaf blotch, developed resistance toward this fungicide class. These sensitivity issues are mainly caused by a point mutation in the active site of cytochrome bc₁, during which a glycine is replaced by an alanine at amino acid position 143 (G143A). Although still binding to the Qo site of Complex III, metyltetraprole (**23**) is able to overcome these resistance problems, because its tetrazolinone pharmacophore is not impacted by a steric clash with the alanine of the mutated binding site like the methoxyacrylate and oximinoester or “-amide” pharmacophores of classical strobilurins such as azoxystrobin (**22**) (see Chapter 6; Figure 1.5) [100–103].



Scheme 1.1 Invention pathways of oxathiapirolin (**16**) and manogepix (**12**).

Recently, with bifemetstrobilin and metcyclofenstrobilin two further resistance-breaking Complex III inhibitors have been announced, which are highly active against resistant *Phakopsora pachyrhizi* strains with an F129L mutation, against which traditional strobilurin fungicides lost most of their potency.

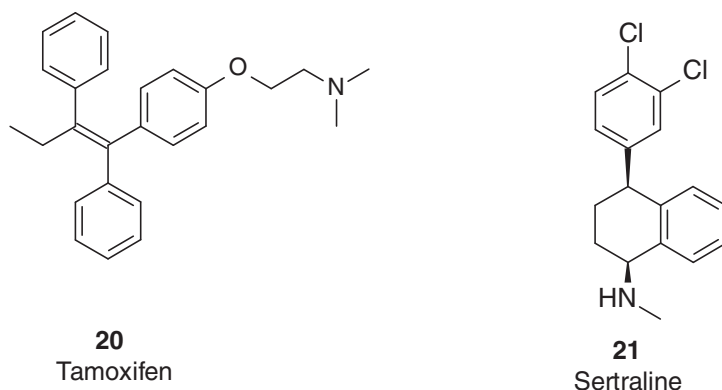


Figure 1.4 The repurposed antifungals tamoxifen (**20**) and sertraline (**21**).

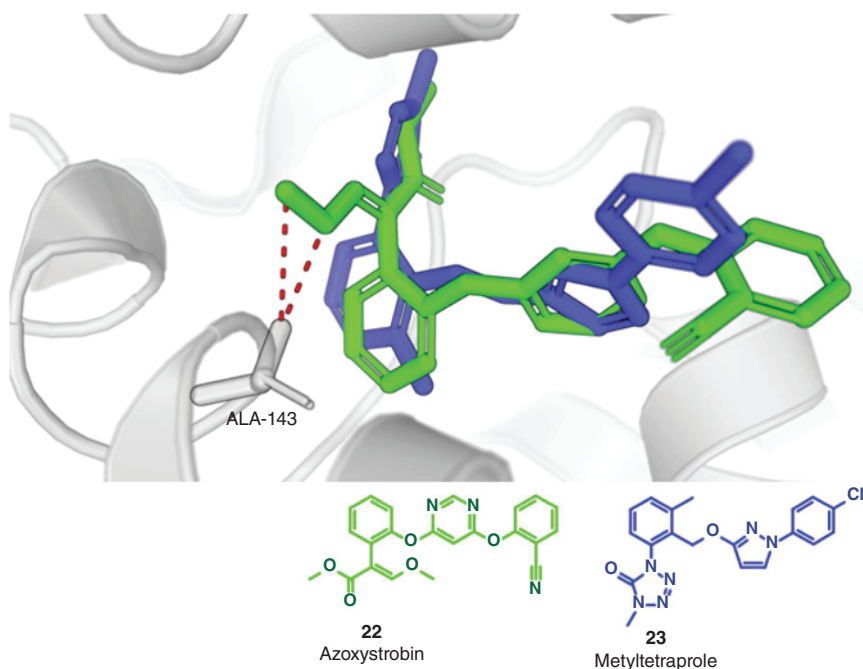


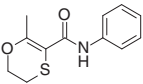
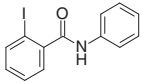
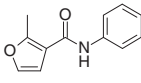
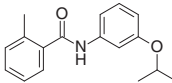
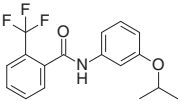
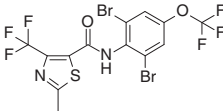
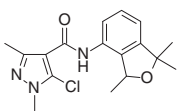
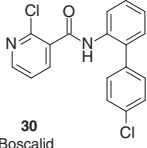
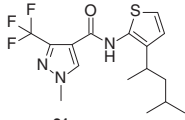
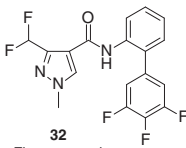
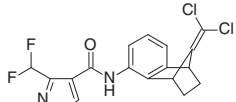
Figure 1.5 Metyltetraprole (**23**) avoiding the steric clash of azoxystrobin's (**22**) methoxy group with the mutated alanine in the Q_o site of G143A cytochrome bc₁.

1.5.4 Expanding the Scope and Application of Formerly Less Significant Mode of Action Classes

Another possibility to reach somehow a novel mode of action is to take an existing one that was formerly limited to only a few target pathogens or to a specific application method and broaden its scope to a much wider use. If successful, a

new mode of action is reached against those fungal species, which could not be treated so far with antimycotics from this class. A textbook example of how a neglected niche mode of action can become one of the most important fungicide classes with blockbuster products applied against a broad range of plant-pathogenic fungal species is the SDHIs, which block Complex II in the fungal respiratory chain. Carboxin (**2**), the first member of the SDHI class, was introduced in 1966 as a seed treatment to control smuts and bunts in cereal crops such as barley, wheat, and oats; however, it never achieved major commercial significance. In the 1970s, the structurally related anilides benodanil (**24**) and fenfuram (**25**) entered the market. In these compounds, the oxathiine carboxylic acid moiety of carboxin was replaced by benzoic acid and furan carboxylic acid, respectively. Similar to carboxin, their effectiveness in seed treatment applications remained limited. A new generation of SDHIs emerged in the 1980s with mepronil (**26**) and flutolanil (**27**), which introduced substitution in the aniline moiety as a key structural feature. These compounds are still used today, not only for seed treatment but also as foliar fungicides targeting Basidiomycetes such as *Rhizoctonia solani*, the pathogen responsible for damping-off disease in various crops. This development significantly broadened the application scope of SDHIs. In the 1990s, thifluzamide (**28**) and furametpyr (**29**) were introduced to the fungicide market. Both belong to the first SDHIs featuring an *ortho*-substituent on the aniline ring, a structural modification that proved critical for achieving optimal activity. Although these compounds exhibited improved fungicidal performance compared to earlier SDHIs, their spectrum of activity remained relatively narrow and was still largely confined to the control of *Rhizoctonia* species. It was not until the 2000s that this previously underutilized mode of action achieved a major breakthrough. Boscalid (**30**) and penthiopyrad (**31**), both featuring bulkier substituents in the *ortho*-position of the aniline or aminothiophene moiety, revealed that SDHIs could unexpectedly provide effective control against a wide range of fungal diseases, including those caused by Ascomycetes. These include molds, scab diseases, leaf spots, powdery mildew, brown rot, and early blight. The introduction of a trifluoromethyl-substituted pyrazole carboxylic acid moiety in penthiopyrad marked an important step toward further optimization of SDHIs in the 2010s. This development culminated in the difluoromethylated pyrazole carboxamides fluxapyroxad (**32**) and benzovindiflupyr (**33**), which exhibit high efficacy as foliar fungicides and provide broad-spectrum control of plant pathogens, demonstrating clear blockbuster potential. Considering the limited activity spectrum of early compounds such as carboxin (**2**), benodanil (**24**), and fenfuram (**25**) in the 1960s and 1970s, the eventual success and versatility of this mode of action would have been difficult to anticipate. The research departments of at least 10 different agrochemical companies contributed over several decades to this success story and delivered a novel mode of action for the treatment of a variety of plant diseases (see Chapter 7; Table 1.3) [3, 104–108].

Table 1.3 Evolution of SDHIs from a small niche product to broad-spectrum fungicides.

Decade	Characteristic SDHIs launched to the market	Comment
1960s	 2 Carboxin	Small seed treatment product
1970s	 24 Benodanil	Me-too products with same limited seed care potential
	 25 Fenfuram	
1980s	 26 Mepronil	Seed care still major focus, but first foliar applications
	 27 Flutolanil	
1990s	 28 Thifluzamide	More potent than previous products, but same narrow spectrum
	 29 Furametpyr	
2000s	 30 Boscalid	Step change to highly active broad-spectrum fungicides
	 31 Penthiopyrad	
2010s	 32 Fluxapyroxad	Broadly acting block-buster products
	 33 Benzovindiflupyr	

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