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Recent developments in membrane targeting antifungal agents to mitigate antifungal resistance

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Fungal infections cause severe and life-threatening complications especially in immunocompromised individuals. Antifungals targeting cellular machinery and cell membranes including azoles are used in clinical practice to manage topical to systemic fungal infections. However, continuous exposure to clinically used antifungal agents in managing the fungal infections results in the development of multi-drug resistance *via* adapting different kinds of intrinsic and extrinsic mechanisms. The unique chemical composition of fungal membranes presents attractive targets for antifungal drug discovery as it is difficult for fungal cells to modify the membrane targets for emergence of drug resistance. Here, we discussed available antifungal drugs with their detailed mechanism of action and described different antifungal resistance mechanisms. We further emphasized structure–activity relationship studies of membrane-targeting antifungal agents, and classified membrane-targeting antifungal agents on the basis of their core scaffold with detailed pharmacological properties. This review aims to pique the interest of potential researchers who could explore this interesting and intricate fungal realm.

1. Introduction

Fungal infections cause mild allergic reactions to severe, disfiguring, and potentially fatal invasive fungal diseases affecting over a billion people globally, and are responsible for ~1.6 million deaths per year around the globe.[1] Superficial fungal infections such as ringworm, mucosal, and vaginal infections account for 15% of fungal infections, thereby making them the most deadly among other communicable diseases.[2,3] Innate immunity, also called the first line of defence, caused by the body surface and epithelial surfaces of the respiratory, genitourinary, and gastrointestinal tracts, acts as a barrier against fungi.[4] Cells of innate response like neutrophils and dendritic cells can cause direct antifungal effects or can secrete microbicidal compounds to clear fungal infections.[5–7] Notably, the host immune system acts as a defence army against fungal infections. However, immunocompromised patients are always at high risk as employment of immunosuppressive drugs in clinical settings and advent of HIV patients are important factors for increased number of immunocompromised individuals.[8,9]

Fungal pathogens can be categorized into primary and opportunistic, where primary fungi are responsible for invasive fungal infections in healthy individuals, and opportunistic pathogens only affect immunodeficient individuals.[10] Five different antifungal classes, including azoles, polyenes, echinocandins, allylamines, and antimetabolites, are commonly prescribed to manage topical to systemic fungal infections. Azoles like fluconazole, ketoconazole, and itraconazole are commonly used to manage mild topical and systemic infections,[11] and polyenes like amphotericin B (AmB) are employed to tackle systemic fungal infections.[12] Apart from these, echinocandins, allylamines, and antimetabolites are the other commonly used drugs that are usually prescribed.[13] However, overprescription or misuse of these antifungal agents can lead to the development of drug-resistant fungal pathogens like *C. auris*.[14] Therefore, antimicrobial resistance (AMR), considered the next pandemic, is responsible for 0.7 million deaths annually, and around 10 million deaths are expected by 2050.[15,16] Development of multidrug-resistant microbial infections, including skin structure, nosocomial, and urinary tract infections, creates a challenge for patients undergoing chemotherapy, surgical procedures, and transplantation.[17]

Microbial cells, including bacteria and fungi, develop different intrinsic and extrinsic mechanisms to develop resistance against antimicrobial regimens.[18] Fungal cells possess several mechanisms like overexpression of drug targets and efflux pumps, alteration in drug targets, and biofilm formation to develop drug resistance. Overexpression of efflux pumps and alteration in drug targets are mainly associated with azole resistance, whereas alteration in drug targets and biofilm formation are two mechanisms commonly adapted by fungal cells to gain resistance against every antifungal drug. Individually or collectively, these

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mechanisms result in drug-resistant fungal cells,[19] and development of drug-resistant pathogens has accelerated the pursuit of novel antifungal agents like new azole-derivatives (luliconazole and albaconazole).[20,21] Apart from this, repurposing of non-antifungal drugs, biofilm inhibitors, and molecules from natural resources has emerged as a potential antifungal approach.[22–27]

The fungal cell membrane presents a unique chemical composition that differs from those of other microbial and mammalian cells due to the presence of ergosterol in the lipid bilayer, chitin as the basement layer, and glucan-based molecules, thereby making it a potential target for antifungal drug discovery.[28] Antimicrobial peptides (AMPs) play an essential role in the host defence system, and as a part of the innate system, AMPs disrupt microbial membranes, including fungal membranes, through electrostatic interactions to eradicate microbial infections.[29] However, the stability and safety profile of AMPs limit their clinical applications which inspired researchers to design and develop mimics of AMPs to target fungal membranes.[30] Here, we described different clinically used antifungal drugs with their limitations, and emphasized the emergence of antifungal resistance and its different mechanisms. We then presented recent advancements in the design and development of membrane-targeting antifungals that use fungal cell membranes as potential therapeutic targets.

2. Clinically used antifungal agents

Over the last century, several topical antimicrobial agents have been used to manage common fungal and bacterial infections. However, to target invasive mycoses that need systemic antifungal medication, five major antifungal classes, azoles, polyenes, echinocandins, antimetabolite, and allylamines are approved by the Food and Drug Administration (FDA) (Fig. 1). Azole-based drugs are commonly prescribed, and known as principal class antifungal agents to manage topical and systemic fungal infections as these agents target the lanosterol 14α-demethylase enzyme, an essential enzyme in ergosterol biosynthesis. Major advantages of azoles are that they can be taken orally and display a broad-spectrum activity against various fungal strains. On the basis of the heterocyclic ring, azole-based antifungal drugs can be further divided into three subclasses: imidazoles, triazoles, and tetrazoles (Fig. 1a–c).[31] From the mid-1970s to the 1990s, various imidazole-based azoles emerged such as miconazole, clotrimazole, econazole, ketoconazole, tioconazole, and sulconazole (Fig. 1a). Different imidazole-containing antifungals have been approved recently, including sertaconazole and luliconazole.[32] Starting in the 1990s, triazole-based azoles have become increasingly popular such as terconazole, fluconazole, itraconazole, voriconazole, posaconazole, efinaconazole, and isavuconazonium.[33] Triazole-based azoles are thought to be more specific to the fungal cytochrome P450 enzyme than their earlier imidazole-based counterparts. In addition, two more triazoles, albaconazole and PC945, are currently in clinical trials.[34] Tetrazole-based antifungal agents have shown a broad spectrum of antifungal properties against different fungal species, and also displayed good oral bioavailability as compared to other azoles (Fig. 1c). Recently, a tetrazole-based fungal cytochrome P450-inhibitor, oteseconazole (VT-1161), has completed its phase III clinical trial. Studies demonstrated that VT-1161 has greater specificity against fungal cytochrome over the human one.[35,36] VT-1129 and VT-1598 are two more tetrazole-based molecules in the pre-clinical phase.[37,38]

Apart from azoles, polyenes have also been used extensively as primary fungicidal agents against species of *Aspergillus*, *Candida*, and *Cryptococcus* since their discovery in the 1950s (Fig. 1d).[39,40] Polyenes are amphipathic natural products of *Streptomyces nodosus*, a soil actinomycete,[41] and are usually prescribed for systemic fungal infections such as cryptococcal meningitis, aspergillosis, and superficial fungal infections such as thrush. Among over 200 polyenes, six molecules have been used in clinical settings, including amphotericin B (AmB), nystatin, natamycin, trichomycin, candicidin, and methyl paricin,[42] where natamycin is used against ophthalmic infections, and nystatin is used to manage vulvovaginal and oral fungal infections (Fig. 1d).[43] AmB is the leading prototype for systemic fungal infections as it forms membrane-spanning channels during its interactions with ergosterol-containing membranes, thereby causing leakage of cellular components and cell death. A liposomal formulation of AmB has been prescribed to treat systemic mycoses.[43] However, recent in-depth structural and biophysical studies revealed that polyenes bind to ergosterol, and impair its ability to carry out its normal vital cellular functions, leading to membrane permeabilization.[44,45] As there is a close structural relationship between ergosterol and the mammalian membrane sterol cholesterol, the use of polyenes in medicine is constrained despite its potent killing activity.[46,47]

Echinocandins are antifungal drugs that treat fungal infections associated with *Candida* and *Aspergillus*, and are derived from the natural product echinocandin B, a lipopeptide produced by the fungus *Glarea lozoyensis*.[48] Echinocandins have three structural components, a cyclic hexapeptide lactone core, a fatty acid side chain, and an amide group. The cyclic hexapeptide lactone core is composed of two amino acids, a diaminobutyric acid (Dab) and either a hydroxyphenylalanine (Hyp) or a homophenylalanine (Hph).[49] A fatty acid side chain is linked to the core *via* an amide bond, and provides a hydrophobic environment that is essential for the drug's activity.[50] In order to develop potent and better echinocandins, researchers are keen to modify the lipid side chains.[51,52] Mechanistically, echinocandins act by inhibiting the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall, and therefore, these are specific in nature, as normal cells do not possess a cell wall.[53] Echinocandins like caspofungin (CFG), anidulafungin (AFG), and micafungin

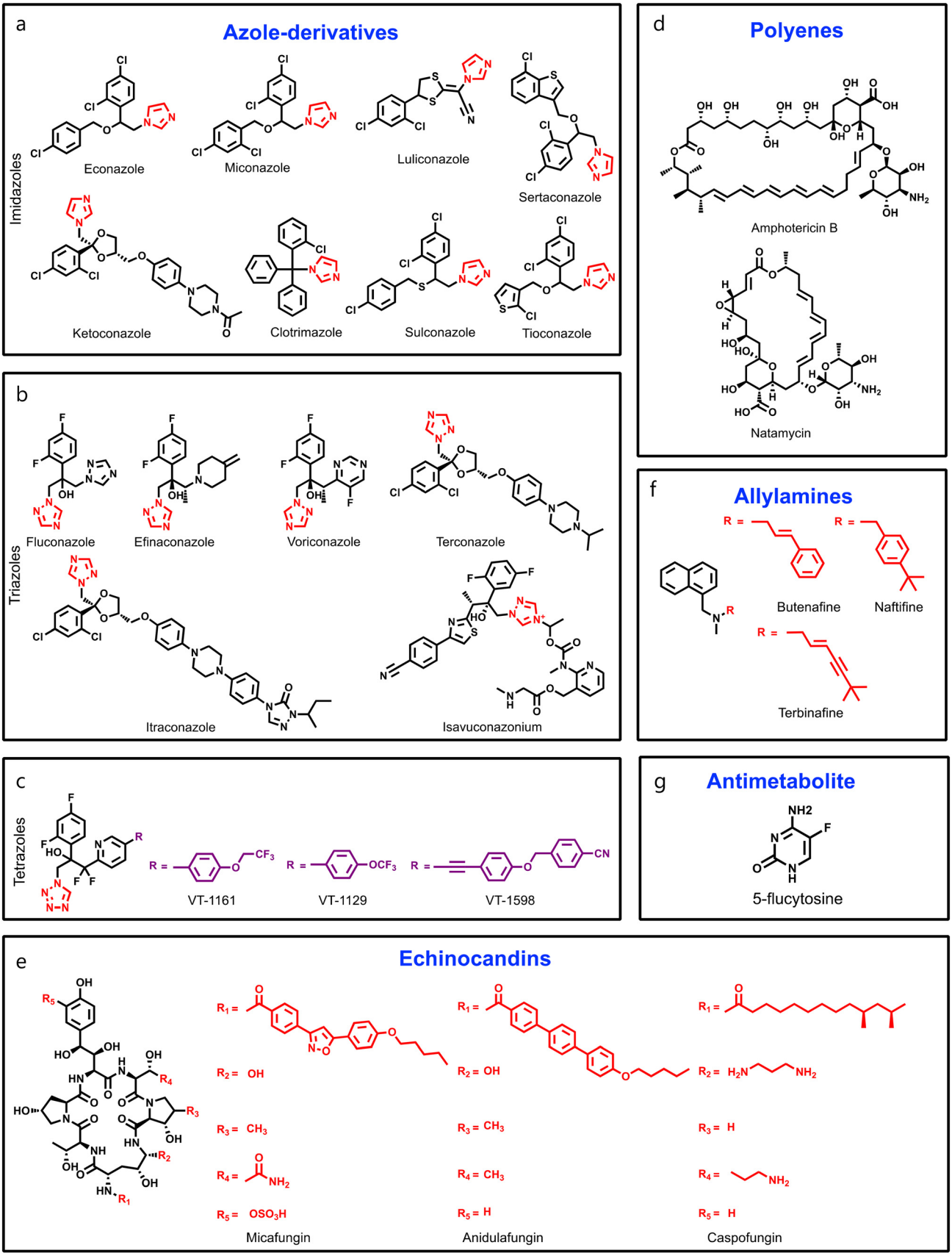
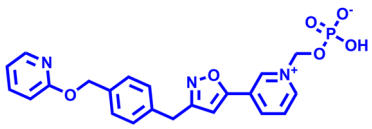
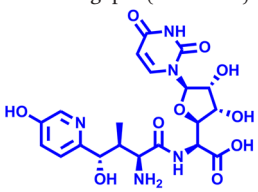
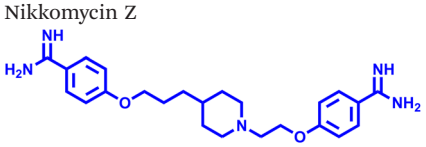
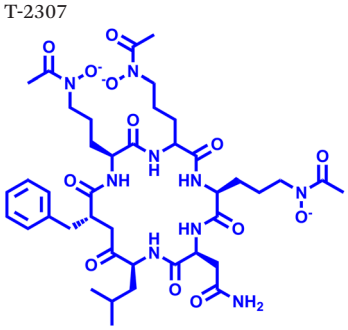
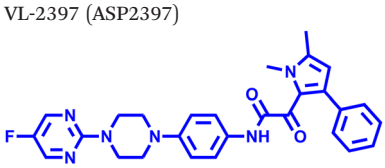
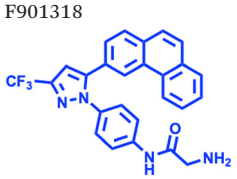


Fig. 1 (a–c) Chemical structures of FDA-approved antifungal drugs: imidazole ring containing azoles (a), triazole ring containing azoles (b), and tetrazole ring containing azoles (c). (d) Chemical structures of amphotericin B and natamycin. (e) General chemical structures of echinocandin antifungal drugs. (f) Common chemical structures of antifungal allylamines. (g) Chemical structure of 5-flucytosine (5-FU).

(MFG) are particularly useful in treating infections in immunocompromised patients,[54] and a new molecule of this class, rezafungin (CD101), is in phase III clinical studies (Fig. 1e). However, the poor oral bioavailability of echinocandins affects their usage in clinical settings, and like AmB, echinocandins are administered through an intravenous route.[55]

Allylamines and antimetabolites are two other classes of synthetic antifungals, where the allylamines have a naphthalene group as an essential pharmacophoric feature (Fig. 1f).[56] Allylamine-based drugs hinder the production of ergosterol by blocking the action of squalene epoxidase, also known as squalene monooxygenase, and this is a selective, reversible, and non-competitive inhibition.[57] Drugs like terbinafine, butenafine, and naftifine are examples of allylamines, and are generally formulated as creams or powders to target topical fungal infections, and terbinafine is only used as an oral formulation and employed to treat onychomycosis.[58] Apart from fungal cell wall targeting drugs, DNA/RNA targeting drugs like 5-flucytosine (5-FU) are used in managing fatal fungal infections (Fig. 1g). It is a pyrimidine-based prodrug of the active metabolite 5-fluorouracil, and targets DNA/RNA synthesis by inhibiting thymidylate synthase.[59] However, the toxicity profile of 5-FU, and development of fungal resistance restrict its use in clinical practice. Therefore, it is used in combination with AmB for the treatment of severe candidiasis.[60]

Table 1 List of antifungal compounds under clinical studies

Drug candidate	Molecular target	Current status
 Fosmanogepix (APX-001A)	Glycosyl phosphatidylinositol synthesis	Phase II completed (NCT04148287)
 Nikkomycin Z	Chitin synthase	Phase I completed (NCT00834184)
 T-2307	Mitochondrial membrane potential	Phase I completed (ref. 206)
 VL-2397 (ASP2397)	Aluminium chelating agent	Phase II terminated (NCT03327727)
 F901318	Dihydroorotate dehydrogenase	Phase II (NCT02856178)
 AR-12	Stimulates host immunity, and inhibits fungal acetyl CoA synthase 1	Phase I completed for oncology (NCT00978523)

Besides this, several compounds like fosmanogepix (APX-001A), nikkomycin Z, and T-2307 are in clinical trials (Table 1). Amplyx Pharmaceuticals developed APX-001 and its *N*-phosphonooxymethyl prodrug that affects the glycosylphosphatidylinositol (GPI) biosynthetic pathway by inhibiting the Gwt1 enzyme. APX-001 showed good tolerance and antifungal properties in clinical phase 1 trials. Nikkomycin Z was isolated from *Streptomyces tendae* which is a pyrimidine nucleoside and inhibits the biosynthesis of chitin. Nikkomycin Z is a specific antifungal agent, as chitin is absent in mammalian cells. T-2307 is an arylamidine-based antifungal agent that exhibits potent fungicidal properties. It mainly disrupts the mitochondrial membrane potential of fungal cells, which leads to fungal cell death, and is well tolerated in human phase 1 studies.

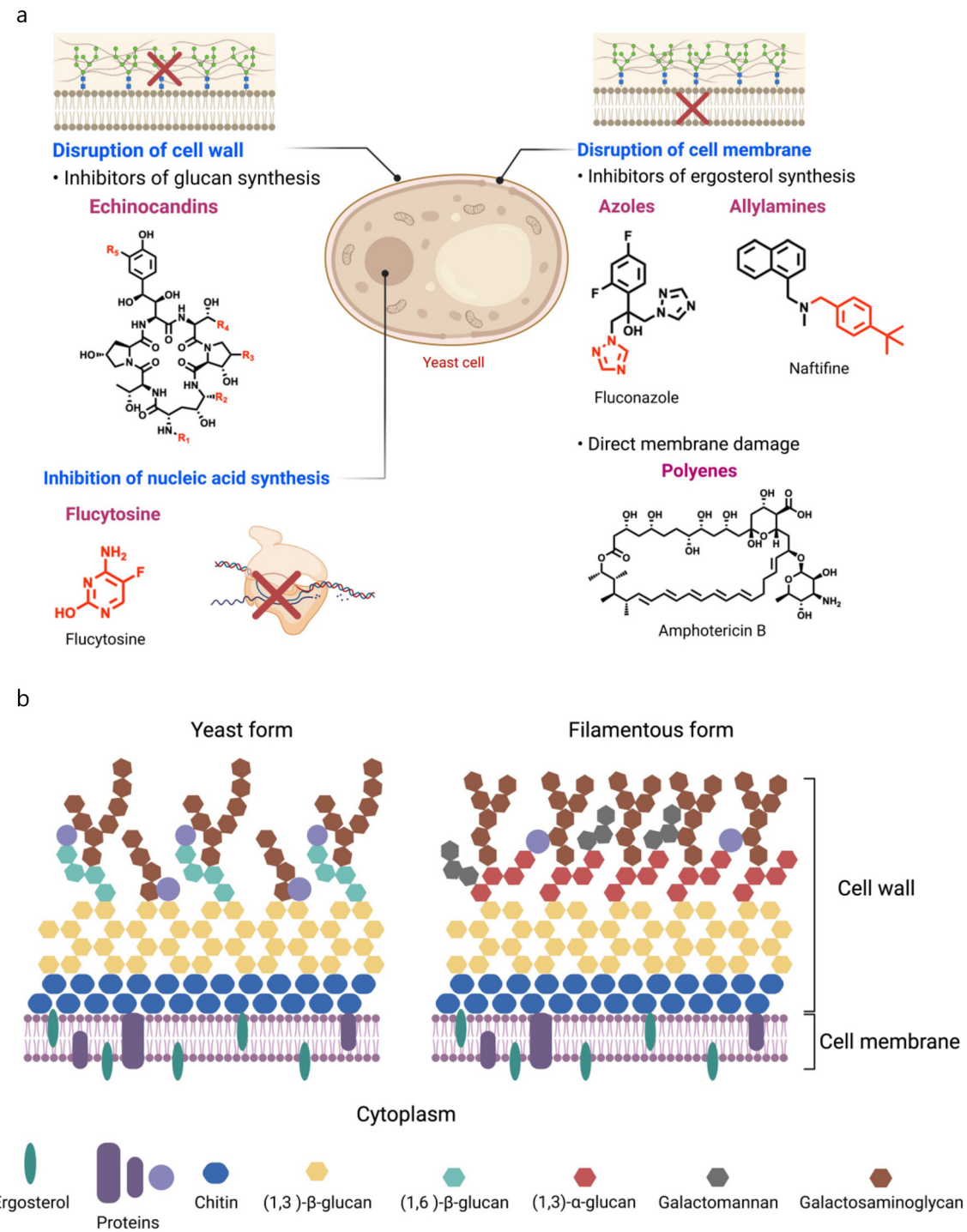


Fig. 2 (a) Mechanism of action of antifungal drugs. (b) Structural features of the fungal cell wall and cell membrane.

3. Antifungal resistance: an emerging problem

Fungal cells can adapt different mechanisms to evade antifungal drugs for their survival, like modification of drug targets, overexpression of multi-drug transporters, and stimulation of cellular stress (Fig. 2a).[61] Fungal cells employ overexpression and mutations of ERG11, and expression of efflux pumps to develop resistance against azoles. As the ERG11 gene is a critical player in the encoding of lanosterol 14α-demethylase, fungi cells increase the transcriptional levels of ERG11 mRNA leading to overexpression of lanosterol 14α-demethylase.[62] Fungi cells can also alter the azole-binding site of lanosterol 14α-demethylase as found in *C. albicans*. According to earlier research, three "hot spot" areas within ERG11p include several crucial allelic variants that reduce fluconazole sensitivity.[63] Whaley *et al.* summarized different mutations found in ERG11 of *C. albicans*. In addition, overexpression of efflux pumps, such as ATP-binding cassette transporters, can expel intracellular azoles and cause drug resistance.[64]

Even though polyenes have been utilized for many years, resistance against polyenes is still much less common than that against other antifungal drugs as polyenes target a structural component of the cell membrane instead of a vital enzyme.[65] However, mutations in ergosterol biosynthesis enzymes, including ERG2, ERG3, ERG5, and ERG11, can contribute to the reduction of AmB potency against *C. albicans*.[66] Mutations in ERG2, ERG6, and ERG11 were found in polyene-resistant *C. glabrata* clinical isolates,[67] and in ERG1, ERG2, ERG6, and ERG13 in the case of *C. auris*.[68] A recent investigation on *C. auris* emphasized the potential role of drug transporters in amphotericin B resistance, where whole-genome sequencing of polyene-resistant clinical isolates showed four non-synonymous mutations, one of which was in a potential membrane transporter.[69]

Chronologically, echinocandins are the newest antifungals with a narrow spectrum of activity, and only few reports have demonstrated resistance to echinocandins. *Candida* species develop resistance against echinocandins by mutating FKS genes.[70] Echinocandins target β-1,3-glucan synthase, which is present in fungal membranes and possesses a catalytic subunit called FKS1. Fungi also possess its homologs, the FKS2 and FKS3 proteins, with low expression, and they regulate the FKS1 expression.[71] FKS1 and FKS2 protein mutations majorly contribute to echinocandin resistance, and there are three hot spot regions in the FKS1 protein for mutations, where region I includes amino acid residues FLTLSLRDPI, region II includes PAIDWIRR, and region III includes WRNIFTRL.[72] In addition, a few reports also suggested an increase in chitin production responsible for echinocandin resistance. However, the overexpression of efflux pumps shows a minimal role in echinocandin resistance.[73]

Apart from these mechanisms, fungal cells can form biofilms that act as a barrier against antifungal drugs and the host immune system. A fungal biofilm involves a community of irreversible adherent fungal cells on a surface like inert materials, living tissue, and medical devices.[74] The biofilm life-cycle consists of four steps, initial attachment, proliferation, maturation, and dispersion, and among fungi strains, *Candida* species have the highest ability to form biofilms. Biofilm formation in terms of morphology, extracellular matrix (ECM), and ability to adapt to antifungal resistance varies from species to species, and this variability creates a hurdle in discovering an effective approach to address biofilm-associated threats.[75] Fungal biofilms show intrinsic resistance against both azoles and polyene derivatives.[76] However, some reports suggest that polyenes display potent antibiofilm properties, but a high toxicity profile limits their clinical applications.[77,78] A liposomal formulation of AmB demonstrates potent antibiofilm activity against *C. albicans* biofilms.[79] Apart from these drugs, several new approaches have emerged to avoid fungal biofilms, including the combination of DNAse with antifungal regimens, modulators of quorum sensing, AMPs, antifungal coatings, and photodynamic therapy.[80] Drug repurposing is also an emerging approach to tackle fungal biofilms,[81] and several reviews emphasized emerging new and old drug candidates against fungal biofilms.[82,83]

4. Fungal membrane as a therapeutic target

The fungal plasma membrane and cell wall work together to provide cells strength, which allows cells to sustain turgor pressure, and also offers protection against antifungal agents.[84] Fungal cells are fundamentally different from mammalian cells since their membranes are composed of different lipids, which therefore, makes them more susceptible to certain drugs, and making it possible to create therapeutic regimens that specifically target fungal cells without impacting human cells.[85] As lipids are essential components of all cells, the fungal cell membrane is also composed of different lipids such as glycerophospholipids, sphingolipids, and sterols, where glycerophospholipids constitute 55–75% of the total lipids.[86] Depending upon head groups, glycerophospholipids can be phosphatidylethanolamine (PE), phosphatidylcholine (PC), phosphatidylserine (PS), and phosphatidylinositol (PI) (Fig. 2b),[87] and are major partners of total phospholipids in *Saccharomyces cerevisiae*.[88] Apart from glycerophospholipids, sphingolipids are also essential constituents of fungal membranes, and constitute 7–16% of fungal membrane lipids.[89] Sphingolipids have a sphingosine backbone, linked with sphingoid long-chain aliphatic amino alcohols, and sphingoids such as sphingosine, dihydrosphingosine, and ceramides are biosynthesized from nonsphingolipid precursors.[90]

In addition, sterols are another lipid component constituting 30–40% of fungal membranes. Sterols are amphipathic lipids with rigid and compact ring structures, and play vital roles including regulation of membranes' fluidity and permeability, and control of membrane-bound enzymes. Like

cholesterol, fungal membranes are armed with a sterol-based biomolecule, ergosterol, which is also known as a fungal hormone, and maintains fungal membrane integrity and promotes growth and proliferation.[91] Numerous reports described the role of ergosterol in the maintenance of mitochondrial DNA and stress adaptation as well.[92,93] The biosynthetic pathway of ergosterol involves multistep biochemical reactions that occur in the endoplasmic reticulum, and numerous enzymes catalyse these biochemical conversions.[94,95] Two categories of genes involved in the initial stages of ergosterol biosynthesis include essential genes (such as ERG1, ERG7, ERG9, ERG11, ERG24, ERG25, ERG26, and ERG27) and non-essential genes. For example, ERG9 encodes squalene synthase, an enzyme that catalyzes the production of squalene, a precursor for ergosterol. In addition, ERG1 and ERG7 code for squalene epoxidase and lanosterol synthase, other essential enzymes of the ergosterol synthesis pathway. ERG11, which codes for lanosterol 14α-demethylase, is also of the fungal cytochrome P450 family.[96] Therefore, a majority of antifungal medications available for clinical use have been developed to target ergosterol biosynthesis due to its unique biosynthesis pathway, distinctive structural characteristics, and essential roles.[97] Apart from the individual class of lipids, the fungal membrane is also armed with lipid rafts composed of sterol and sphingolipids that play an important role in cell growth and development of cell polarity, formation of hyphae, and pathogenicity.[98] Besides lipids, the fungal membrane also has various proteins that serve different functions like signal transduction, and cytoskeleton and cell wall synthesis.[99,100] Therefore, the fungal membrane is composed of various biomolecules, including lipids and proteins, and collectively, these biomolecules impart a negative charge on the cell membrane. Miyake *et al.* showed that *C. albicans* cells possess a negative zeta potential at pH 7.4.[101] They treated the fungal cells with antifungal agents (AmB, miconazole, ketoconazole, azalomycin F, and aculeacin A) at sub-inhibitory concentration and observed that these agents affected the zeta potential of fungal cells. Moreover, the relationship obtained between the change in zeta potential and adherence suggests that decreased electric repulsive forces were responsible for enhanced adherence of fungal cells.[101]

C. albicans is the most common and opportunistic pathogen responsible for IFDs, and its cell wall is composed of a two-layered structure. A β-glucan–chitin skeleton is considered as the main core of *C. albicans* that provides strength and shape to it. Chitin is localized in the inner layer, and its chains can form strong anti-parallel H-bonded structures. β-1,3-glucans are present in the inner cell wall, and are connected with β-1,6-glucans that link the inner and outer cell walls.[102] The synthesis of β-1,3-glucans is catalysed by β-1,3-glucan synthase, composed of an enzyme complex with two subunits (Fksp and Rho1p). Fksp is responsible for the transfer of sugar groups from an activated donor to a specific donor through glycosidic linkage, and it is encoded by three ortholog genes, FKS1, FKS2, and FKS3, in *C. albicans*.[103] Apart from this, β-1,6-glucans have side chains with varying lengths and distributions that can form complex structures stabilized through interchain H-bonds. Notably, β-1,6-glucans serve as linker molecules connecting various cell wall proteins to the β-1,3-glucan–chitin core through glycosylphosphatidylinositol (GPI) proteins. In addition, β-1,6-glucan levels are high in the *C. albicans* cell wall compared to that in *S. cerevisiae*.[104] Mannoproteins are the major biochemical constituents of the outer layer of the *C. albicans* cell wall. Chemically, these GPI-modified molecules are cross-linked to β-1,6-glucans through *N*- or *O*-linkage *N*-linked mannans are constituted of α-1,6-mannose, that have a backbone with α-1,2-oligomannose, and sidechains armed with β-1,2-mono to tetra mannans. In contrast, *O*-linked mannans are linked to glycoproteins of the cell wall. Mannans do not affect the cell shape, as they are comparatively less rigid than β-glucans and chitin.[105] However, they have low permeability and porosity which contributes to the cell wall's resistance against antifungal agents and host defense mechanisms. In addition, they are also known as PAMP (pathogen-associated molecular pattern) ligands that affect host defense mechanisms.[106]

AMPs are part of a host's innate immune system, and bear short amino acid sequences with a net positive charge and can form α-helical and β-sheet secondary structures. These conformations provide facial amphiphilicity to AMPs, essential for their antimicrobial activity. As electrostatic differences exist, AMPs preferentially target microbial membranes over the host, and their structural features and mode of action are well documented in several reviews.[107,108] Different models, including barrel-stave, carpet, toroidal-pore, and translocation models were proposed to dictate the membrane disruption properties of AMPs.[109] Apart from membrane disruptions, AMPs can also impact intracellular targets *via* generation of ROS (reactive oxygen species), autophagy, and mitochondrial dysfunction.[110,111] Cysteine-rich antifungal peptides have been classified based on their source like insects, plants, and mammals,[112] and recently, Struyfs *et al.* summarized known peptides with antifungal properties through membrane interactions.[113,114] However, the lack of stability and poor pharmacological profile of AMPs limit their clinical applications,[115,116] and therefore, led to researchers developing various molecules targeting the fungal membranes.[117]

5. Recent fungal membrane-targeting molecules

5.1 Peptide-based molecules

Limited therapeutic applications of AMPs have inspired researchers to design and develop AMP-mimicking peptide-based molecules, as macromolecular antimicrobials like peptides and cationic polymers can target multi-drug-resistant pathogens.[118,119] In this regard, Zhou *et al.* developed synthetic copolypeptides, and investigated their antimicrobial activities against fungal and bacterial pathogens.[120] However, the presence of a hydrophobic moiety

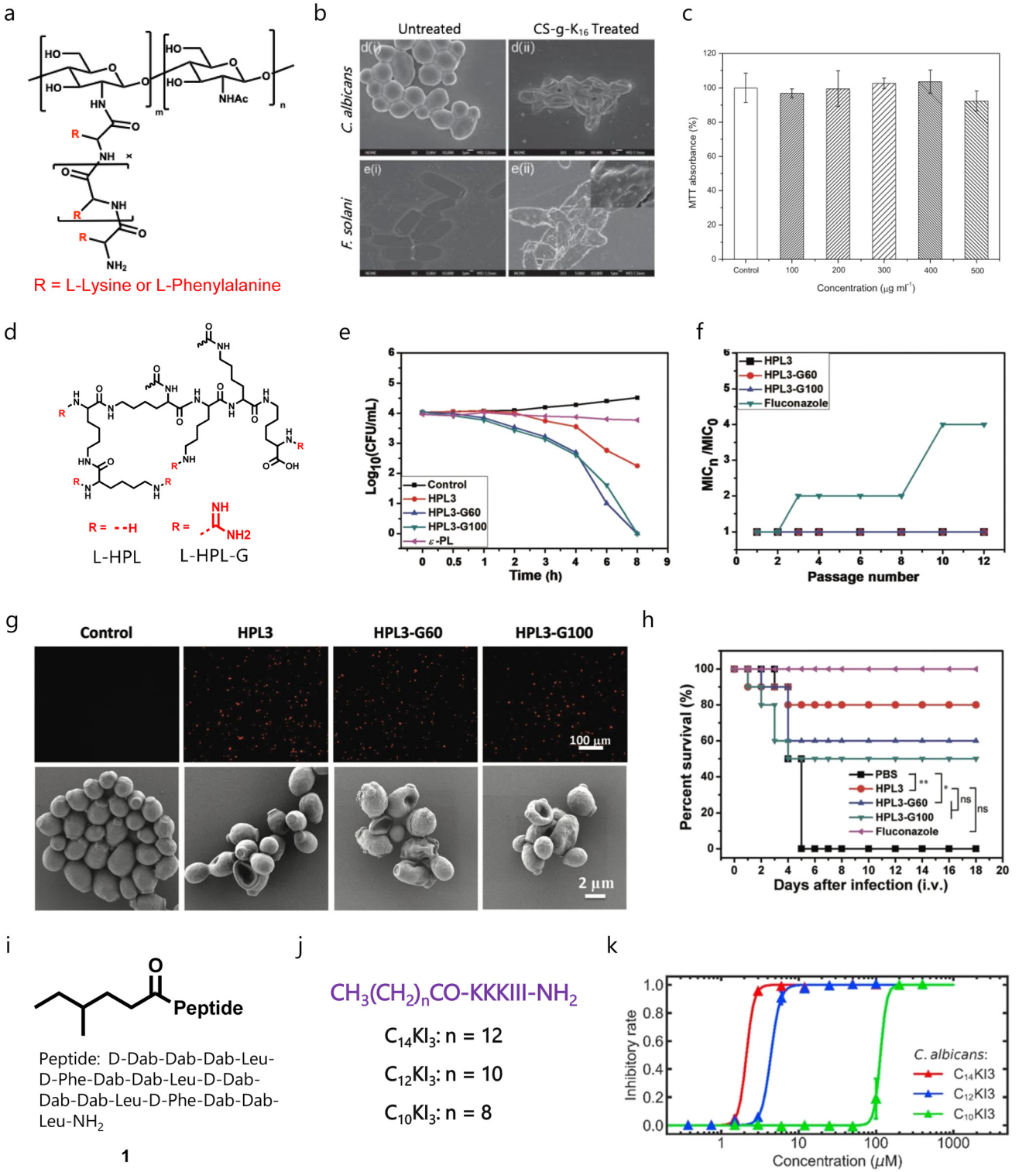


Fig. 3 Peptide-based antifungal molecules. (a) Chemical structure of peptidopolysaccharide scaffold derived molecules. (b) Membrane disruption activity of a peptidopolysaccharide derivative (CS-*g*-K_{16}). (c) Cytotoxicity profile of the peptidopolysaccharide derivative (CS-*g*-K_{16}) at different concentrations. (d) Molecular structure of hyperbranched polylysine (HPL) scaffold containing molecules. (e) Time-dependent killing studies of HPL derivatives against fungal cells. (f) Drug resistance studies of HPLs with fluconazole. (g) Membrane lysing property of HPLs. (h) Survival efficacy of HPLs against a murine fungal infection model. (i) Molecular structure of compound **1**. (j) Molecular structure with amino acid sequences of acylated short peptides. (k) Growth inhibitory rate of acylated short peptides (Fig. 3b and c reproduced from ref. 121 with permission from John Wiley and Sons, copyright 2012, Fig. 3e–h reproduced from ref. 125 with permission from John Wiley and Sons, copyright 2022, and Fig. 3k reproduced from ref. 129 with permission from Elsevier, copyright 2023).

is responsible for their higher toxicity profile. Li *et al.* developed and tested peptidopolysaccharides as broad-spectrum antimicrobials against both fungal and bacterial strains, and found that the antimicrobial properties depend on the number of tethered lysine residues.[121] A peptidopolysaccharide tethered with 16 lysine residues was found to be highly effective with membrane-disruptive properties and negligible toxicity against RBCs and human aorta smooth muscle cells (SMCs) (Fig. 3a–c). Apart from the peptidopolysaccharides, nylon-based polymers (called poly-β-peptides) also showed broad-spectrum properties against different bacterial and fungal pathogens.[122–124]

Liu *et al.* developed a series of hyperbranched polylysine (HPL) based antifungal agents (Fig. 3d).[125] They employed condensation polymerization to get six different HPL derivatives, and amine groups of HPL3 were guanylated through 1*H*-pyrazole-1-carboxamidine which yielded HPL3-G*x*. Among the guanylated HPLs, HPL3-G60 showed potent antifungal activity against different fungal pathogens, and HPL-G*x* (x = 40–80) was found to be 32-fold more active than HPL3 against *C. parapsilosis* (Fig. 3e). Interestingly, fungal pathogens could not develop resistance against these HPL-G*x* agents (Fig. 3f). In-depth mechanistic studies revealed that treatment with HPL-G*x* can damage the cell wall and membrane (Fig. 3g) with minimal toxicity against RBCs and NIH 3T3 cells. Further, they investigated these peptides against a lethal *C. albicans* murine model, and among different treatment regimens, fluconazole and HPL3 through an intravenous route showed better mice survival (Fig. 3h).[125]

Lipopolypeptide-based amphiphiles also showed pharmacological properties against bacterial and fungal infections.[126] Zoysa *et al.* designed and developed a series of sixteen battacin lipopolypeptides as putative antifungal agents.[127] Among these molecules, the 4-methylhexanoyl tethered trimeric lipopolypeptide having ten units of D-2,4-diaminobutyric acid (D-Dab) (compound **1**) exhibited potent antifungal activity against *C. albicans* with a MIC value of 6.25 μM without affecting RBCs (Fig. 3i). Importantly, the antifungal activity of compound **1** was maintained in an acidic environment, and showed synergism with AmB. Additionally, compound **1** demonstrated potent antibiofilm properties against pre-formed *C. albicans* biofilms in a dose-dependent manner. Mechanistically, compound **1** was found to disrupt the fungal membranes.[127] Lu's group reported acylated antimicrobial peptides to target bacterial pathogens where they used a $C_xG(IIKK)_yI–NH_2$ backbone with varied acyl chains.[128] In another report, they tested a series of CnKI3 lipopeptides against different microbes, and found that an increase in alkyl chain length can enhance the spectrum of antimicrobial activities and decrease the critical aggregation concentration (Fig. 3j). They also reported that the peptide bearing a C_{14} alkyl chain showed potent antifungal activity against a *C. albicans* strain (Fig. 3k).[129]

Recently, Zhang and co-workers designed and developed lipo-γ-AA peptides (oligomers of *N*-acylated-*N*-aminoethyl amino acids) having different fatty acids including palmitic acid, oleic acid, and stearic acid to target fungal infections (Fig. 4a).[130] They found that **MW5** (palmitic acid-tethered) showed potent broad-spectrum activity against fungal pathogens, and fungal cells do not gain any resistance against **MW5** up to 25 days (Fig. 4b). Mechanistically, **MW5** disrupts the fungal membrane and produces ROS (Fig. 4c), and application of **MW5** enhanced the *G. mellonella* survival against fungal infection (Fig. 4d). Interestingly, **MW5** can rejuvenate the therapeutic efficacy of fluconazole against drug-resistant *C. albicans*, and the combination of **MW5** and fluconazole exhibited promising therapeutic potential against a mucocutaneous murine model with an ~2 fold reduction in fungal burden as compared to the untreated group (Fig. 4e and f).

As the synthesis of polypeptides and their derivatives is tedious, therefore, short synthetic peptide-based cationic amphiphiles have gained more attention. Lum *et al.* employed two known AMPs, **KABT-AMP** and **uperin 3.6** as prototypes (Fig. 4g), to design and develop a series of new antifungal peptides.[131] In order to increase the therapeutic potential of **uperin 3.6**, the less hydrophobic amino acids were replaced with three lysine residues (Fig. 4h). Further, they fused **KABT** and **uperin 3.6** to develop four hybrids (**KU1**–**KU4**) (Fig. 4i). In the case of **uperin 3.6** analogues, replacement of two lysine residues led to improved antimicrobial activity, whereas substitution of a single lysine residue led to similar antimicrobial properties. In the case of **uperin** derivatives, both the parent molecule and **Upn-Lys6** showed similar killing kinetics. Among the developed hybrid peptides, **KU4** was found to be the most potent peptide in terms of killing kinetics, as **KU4** showed an ~5.55 log decrease in CFU mL^{-1} within 6 h. Among the hybrid peptides, **KU4** also showed potent antibiofilm properties against *C. albicans*. Interestingly, **Upn-lys6** showed similar antibiofilm properties to **KU4**, while the parent peptide and other uperin analogues were found to be less potent. Moreover, these peptides displayed synergism with conventional antifungal drugs and other AMPs against *C. albicans*, and displayed minimal toxicity against RBCs and human epithelial cells.[131] In a similar fashion, Lyu *et al.* developed a series of PMAP-36-based short peptides (Fig. 4j), and tested them against different fungal and bacterial pathogens.[132] SAR studies showed that a decrease in chain length enhances the antimicrobial properties and reduces the toxicity profile of the parent peptide, and **RII8** showed promising antimicrobial properties (Fig. 4j). Mechanistically, **RII8** can cause membrane disruptions and cellular damage in a dose-dependent manner (Fig. 4k and l).[132]

Recently, Sharma *et al.* designed and developed short synthetic peptide-derived amphiphiles based on the dipeptides Trp–His(1-Bn)–OMe/NHBn and tripeptides His(1-Bn)–Trp–His(1-Bn)–OMe/NHBn, and highlighted compound **2** as an effective fungicide against different fungal pathogens which did not affect mammalian cells and RBCs (Fig. 5a).[133] In-depth mechanistic studies revealed the membrane-disruptive properties of compound **2** (Fig. 5b), and it showed

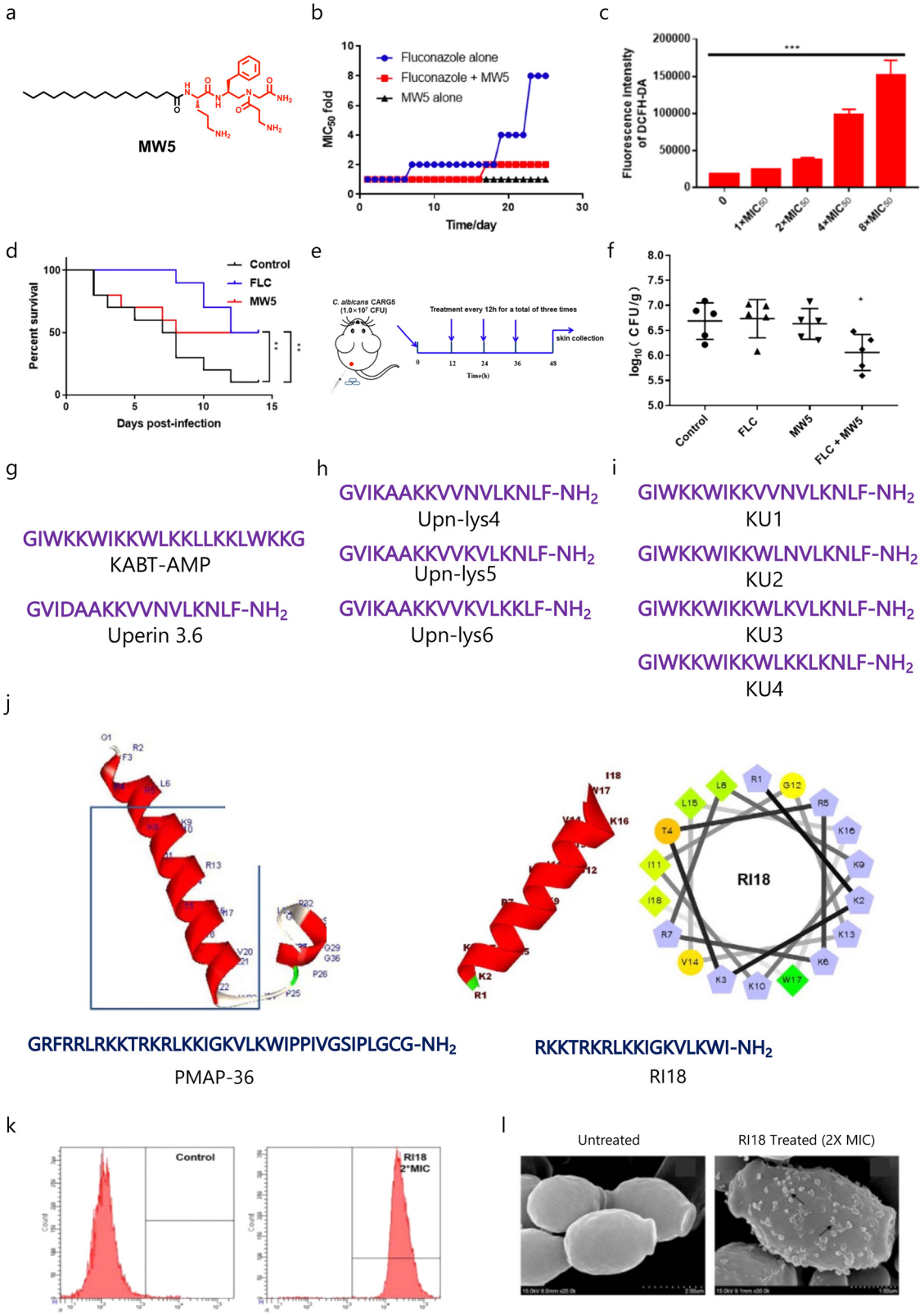


Fig. 4 (a) Chemical structure of the **MW5** molecule. (b) Drug-resistance study of the **MW5** amphiphile with and without fluconazole. (c) ROS study showing increased production of ROS with increased concentration of **MW5**. (d) Survival studies of **MW5** against a *G. mellonella* fungal infection model. (e) A schematic showing the experimental plan for a murine infection model. (f) Antifungal efficacy of **MW5** against the murine infection model. (g–i) Amino acid sequences of parent AMPs and their derivatives. (j) Three dimensional structure and amino acid sequences of the parent peptide (PMAP-36) and developed potent short peptide (RI18). (k and l) Membrane-targeting properties of RII8 (Fig. 4b–f reproduced from ref. 130 with permission from the American Chemical Society, copyright 2022, and Fig. 4j–l reproduced from ref. 132 with permission from Springer Nature, copyright 2016).

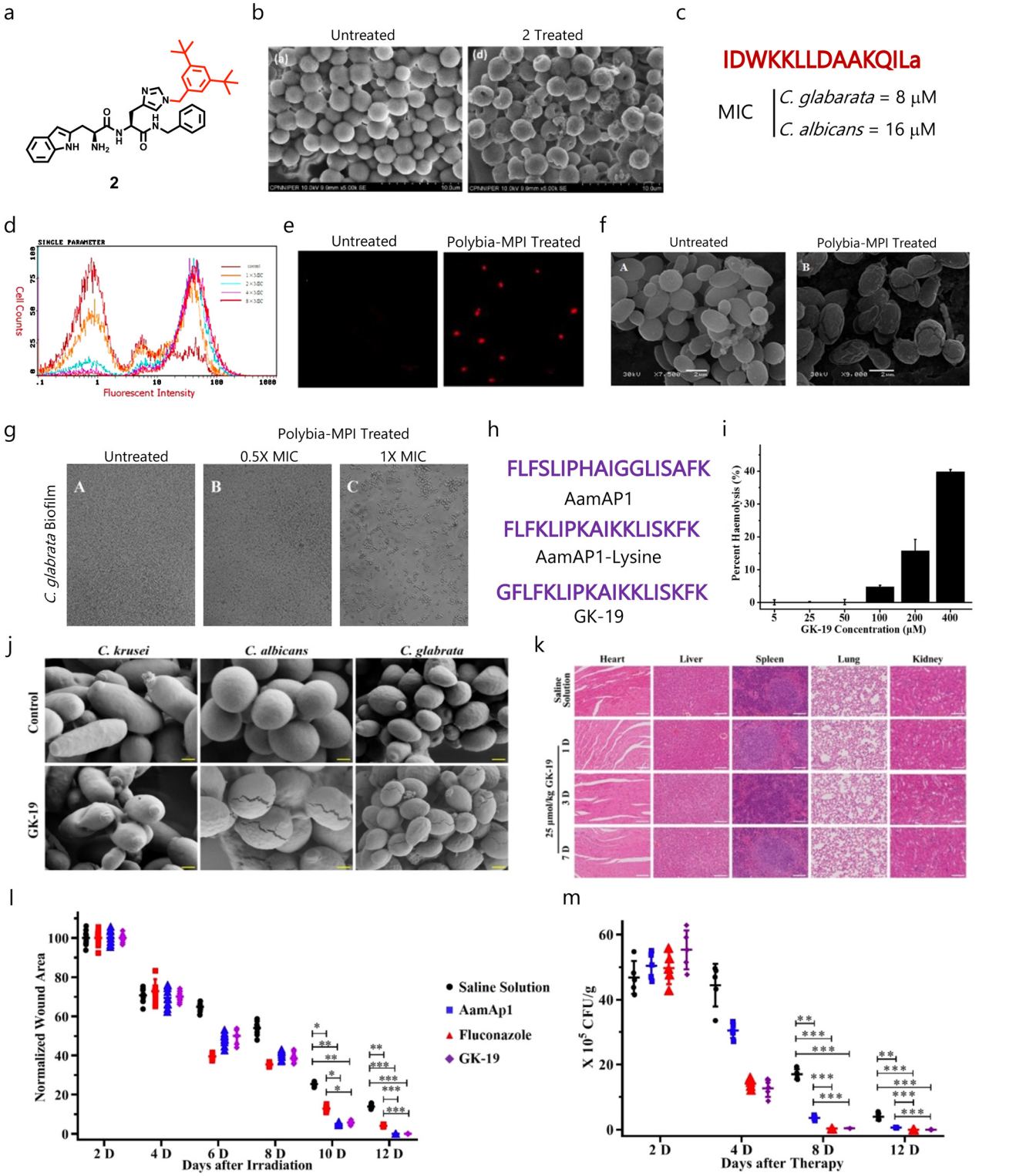


Fig. 5 (a) Chemical structure of compound **2**. (b) SEM images of untreated and treated fungal cells with compound **2** showing its membrane disruption properties. (c) Amino acid sequence and MIC of **Polybia-MPI**. (d) Flow cytometry studies showing PI-positive cells or membrane compromised cells after treatment with **Polybia-MPI**. (e) Confocal images validating the flow cytometry results. (f) SEM micrographs validating the membrane disruption mechanism of **Polybia-MPI**. (g) SEM images demonstrating the dose-dependent antibiofilm properties of **Polybia-MPI**. (h) Amino acid sequence of AamAP1, AamAP1-lysine (parent AMPs) and **GK-19**. (i) Hemolytic properties of **GK-19** against RBCs. (j) SEM micrographs displaying the membrane-targeting properties of **GK-19** against *C. albicans* and *C. glabrata*. (k) Histological analysis of major organs suggesting the non-toxic behaviour of **GK-19**. (l) Time-dependent wound healing study showing the ability of **GK-19** to heal the wound area. (m) Change in fungal load burden after giving different treatment regimens, suggesting that **GK-19** has promising antifungal therapeutic efficacy (Fig. 5b reproduced from ref. 133 with permission from Elsevier, copyright 2022, Fig. 5d–g reproduced from ref. 134 with permission from Elsevier, copyright 2014, and Fig. 5i–m reproduced from ref. 136 with permission from MDPI, copyright 2022).

synergism with AmB against *C. neoformans* fungal cells.[133] **Polybia-MPI** was initially discovered in the venom of the social wasp species *Polybia paulista*, and displayed broad-spectrum antibacterial properties. Wang's group showed the antifungal properties of **Polybia-MPI** with a MIC_{80} of 8 and 16 μM against *C. glabrata* and *C. albicans*, respectively (Fig. 5c).[134] Flow cytometry analysis showed that **Polybia-MPI** can disrupt the fungal membranes in a dose-dependent manner (Fig. 5d). They also validated these findings with confocal (Fig. 5e) and SEM imaging (Fig. 5f). In addition, they observed concentration-dependent antibiofilm properties against *C. glabrata* biofilms (Fig. 5g).

Venom obtained from scorpions contains AMPs like AamAP1 that displays broad-spectrum antimicrobial properties.[135] As their hemolytic profile is a major challenge, different derivatives were developed to enhance the safety of these AMPs. Recently, Song *et al.* designed and evaluated a venom AMP-derivative called **GK-19** as a putative antimicrobial agent by introducing a glycine group at the N-terminal end of AamAP1 to decrease the hydrophobicity and enhance helicity (Fig. 5h).[136] Studies demonstrated that the developed peptide exhibited minimal toxicity against RBCs (Fig. 5i). Further, **GK-19** showed broad-spectrum antimicrobial properties against different bacterial and fungal pathogens, and exhibited dose-dependent membrane-lysis properties (Fig. 5j). In addition, it was found to be non-toxic against major organs like the heart, liver, spleen and lungs (Fig. 5k). **GK-19** also exhibited promising antimicrobial and healing properties in a murine skin and soft tissue infection model (Fig. 5l and m).[136]

5.2 Steroid-based amphiphiles

Bile acids (BAs) are steroidal biomolecules that play a significant role in lipid metabolism. BAs are derived from cholesterol metabolism, and the presence of a steroidal backbone and hydroxyl groups is responsible for their amphipathic nature.[137] BA-derivatives have been employed in advanced drug delivery systems like hydrogels and nanoformulations.[138–141] BA-derivatives also showed potent anticancer,[142] anti-inflammatory,[143] and antimicrobial properties,[144] and can also be used as diagnostic tools.[145] BA-based antimicrobials called ceragenins were introduced by Paul B. Savage, as they can act as putative antibacterial agents by targeting bacterial membranes,[146–151] and have also been shown as potent antifungals.

Hazra *et al.* reported a series of BA–chloramphenicol derivatives by conjugating chloramphenicol at the C24 position of cholic acid (CA) and deoxycholic acid (DCA) through an amide linkage.[152] Among the series of seven molecules, the DCA derivative showed potent antifungal properties against *Cryptococcus neoformans* (Fig. 6a). In another report, they synthesized BA–fluconazole conjugates using DCA and CA through click chemistry and tested them against different fungal strains (Fig. 6b and c).[153] Among these conjugates, the DCA-based fluconazole conjugate was found to be most potent with a MIC_{80} of 3.12 μg mL^{-1} against *C. albicans* (Fig. 6b). SAR studies showed that conjugation of fluconazole at the C24 position of BA led to better antifungal properties as compared to that at the C3 position. They also conjugated different heterocyclic groups including imidazole, benzimidazole, triazole, and benzotriazole at the C24 position of DCA. However, these heterocyclic conjugates were found to be less fungicidal in nature.[153] They further installed a β-lactam moiety at the C24 position of CA and DCA through triazole linkage with varying amide linkages at the C24 position of BAs to establish SARs (Fig. 6d).[154] Studies showed that incorporation of an amide linkage with *para*-chlorobenzene can enhance the antimicrobial properties of DCA and CA-derivatives.[154] Aher *et al.* designed and synthesized BA-based amino sterol molecules by installing a terminal amine group through ethyleneamine and ethylamine at the C3 position of methyl esters of CA and DCA.[155] SAR studies showed that molecules armed with ethylenediamine bearing an extra amino moiety showed better antifungal properties over molecules having an ethylamine group.[155]

Singla *et al.* designed and synthesized a series of 16 amphipathic derivatives of CA by attaching lysine to C3-β-amino cholic acid methyl ester to maintain a suitable ratio of hydrophobic to hydrophilic groups, which is necessary for antimicrobial effects (Fig. 6e).[156] A set of synthesized conjugates that featured a fluorenyl-9-methoxycarbonyl moiety linked to CA *via* a lysine linker displayed decisive antimicrobial action against *S. aureus*, *E. coli*, and *C. albicans*. The efficacy of these compounds further increased with an increase in lysine residues. Moreover, the lead compounds exhibited good antimicrobial properties against drug-resistant bacterial and fungal clinical isolates, and also boosted the effectiveness of antifungal agents such as AmB and voriconazole. In addition, they were also found to damage microbial membranes while not causing any hemolytic activity or toxicity to normal cells or cancer cell lines.[156]

For the past decade, our group has been working on the development of CA-derived antimicrobial agents. We installed glycine groups at the C3, C7, and C12 positions of CA, and varied the C24 position with different alkyl chains (Fig. 6f).[157] Among these amphiphiles, molecules having three glycine moieties with butyl (**CAA-4**) and hexyl chains (**CAA-6**) at the C24 terminal were found to be highly potent against fungal cells. Studies revealed that both amphiphiles were fungicidal in nature (Fig. 6g and h). Notably, fungal cells did not gain resistance against both amphiphiles (Fig. 6i and j), and the amphiphiles were found to be active against pre-formed *Candida* biofilms (Fig. 6k). Moreover, amphiphile-coated catheters displayed promising therapeutic efficacy against a *C. albicans* wound infection model in mice (Fig. 6l–n).[158] Moreover, **CAA-6** also showed potent antibacterial properties against different Gram-positive and Gram-negative pathogens.[159]

We also designed and synthesized CA–peptide conjugates by installing a benzyl moiety at the C24 position of CA, and 20 natural amino acids were conjugated at the hydroxyl

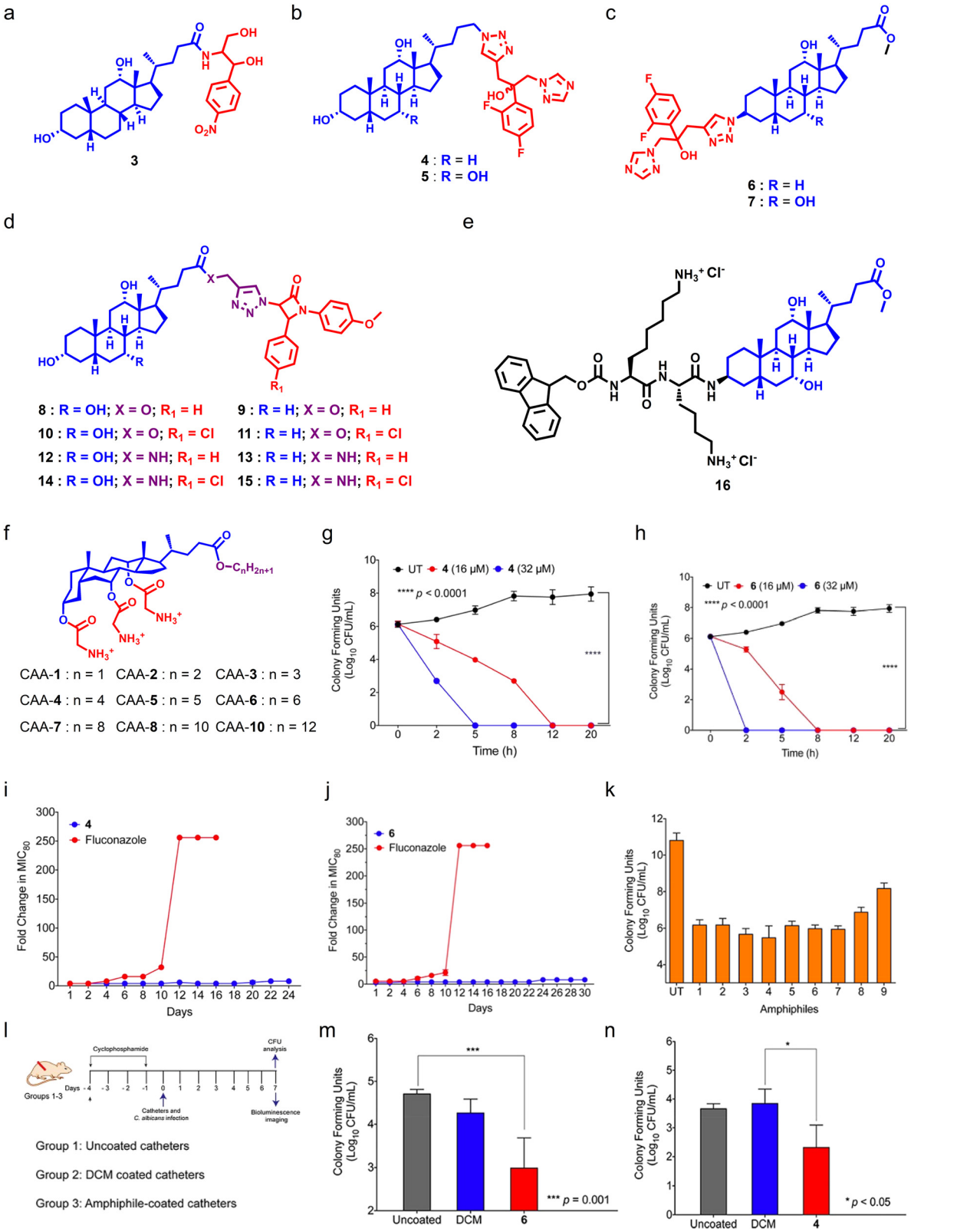


Fig. 6 (a) Chemical structure of potent chloramphenicol-tethered bile acid molecule. (b) General chemical structure of C24 tethered fluconazole bile acid molecules. (c) General chemical structure of C3 tethered fluconazole bile acid molecules. (d) General molecular structure of β-lactam conjugated bile acid molecules. (e) Chemical structure of potent cholic acid–lysine conjugate amphiphile. (f) Chemical scaffold of cholic acid-based amphiphiles. (g and h) Time-dependent killing kinetics of **CAA-4** (g) and **CAA-6** (h) against *C. albicans*. (I and j) Drug-resistant studies of **CAA-4** (i) and **CAA-6** (j) against *C. albicans*. (k) Antibiofilm properties of cholic acid-based amphiphiles with preformed *C. albicans*-mediated biofilms. (l) A schematic showing the plan for animal experiments. (m and n) Antifungal efficacy of **CAA-4** (m) and **CAA-6** (n) against a murine wound infection model (Fig. 6g–n reproduced from ref. 158 with permission from the American Chemical Society, copyright 2021).

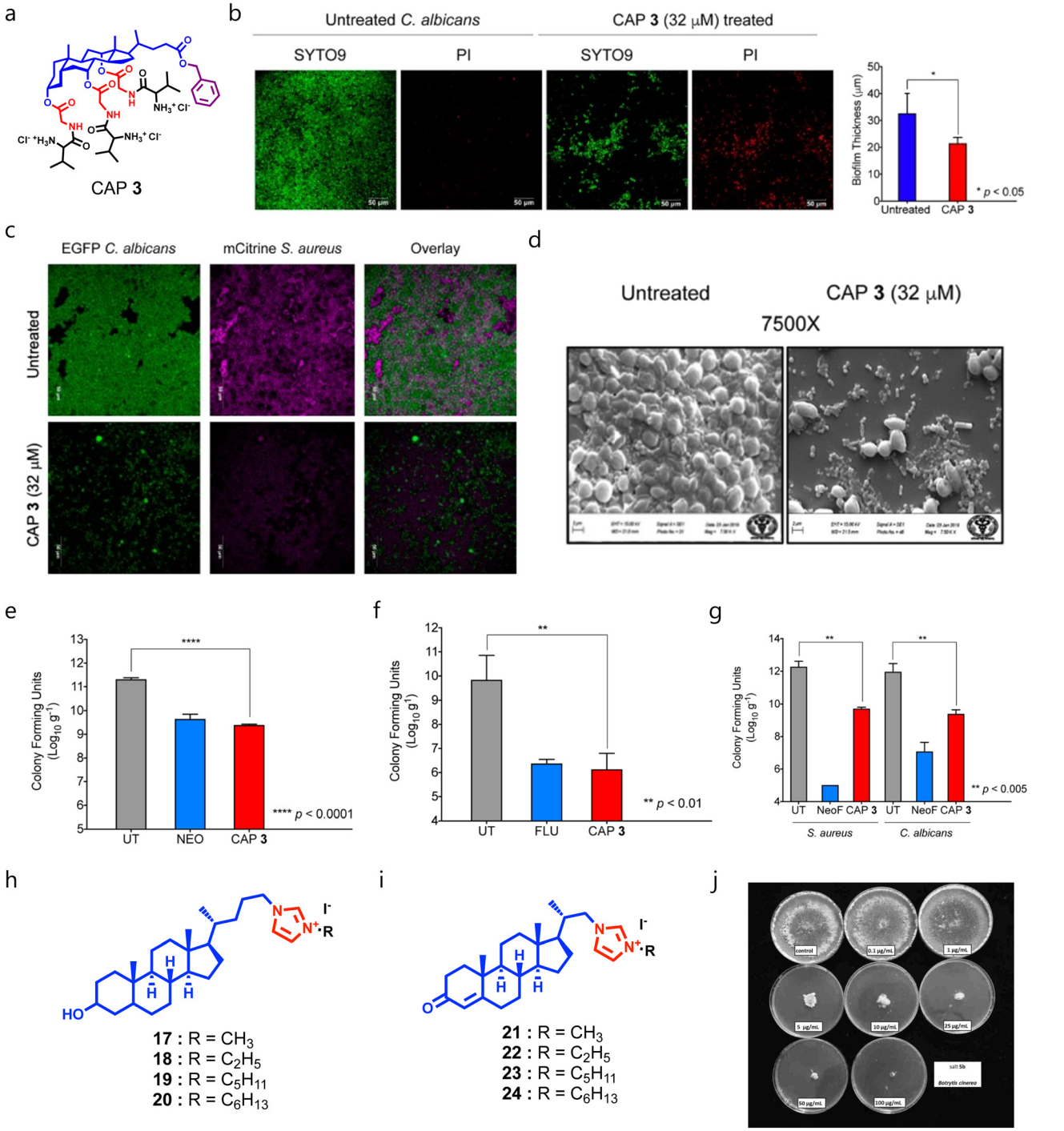


Fig. 7 (a) Chemical structure of **CAP-3**. (b) Antibiofilm studies of **CAP-3** against *C. albicans*-mediated pre-formed biofilms. (c) Antibiofilm studies of **CAP-3** against *S. aureus*, *C. albicans*, and polymicrobial (*S. aureus* + *C. albicans*) biofilms. (d) SEM images showing that **CAP-3** can eradicate the pre-formed polymicrobial biofilms. (e–g) Therapeutic efficacy of **CAP-3** against a *S. aureus* wound infection model (e), *C. albicans* wound infection model (f), and polymicrobial (*S. aureus* + *C. albicans*) murine infection model (g). (h) General chemical structure of lithocholic acid-based imidazolium salts. (i) General chemical structure of 3-oxo-23,24-dinorchol-4-en-22-al. (j) Images showing the dose-dependent antifungal activity of compound **18** (Fig. 7b–g reproduced from ref. 161 with permission from the American Society for Microbiology, copyright 2019, and Fig. 7j reproduced from ref. 162 with permission from Elsevier, copyright 2019).

position of CA through a glycine linker (Fig. 7a).[160] Among the series, the molecule armed with a glycine–valine moiety (**CAP-3**) displayed potent broad-spectrum antimicrobial properties against Gram-positive bacteria, Gram-negative bacteria, and fungal pathogens. **CAP-3** showed potent antibiofilm properties against *Candida*-mediated biofilms (Fig. 7b), and against polymicrobial biofilms (Fig. 7c and d). Mechanistically, **CAP-3** targets the microbial membranes

through electrostatic interactions, and can also degrade pre-formed polymicrobial biofilms on cover slips and medical devices like catheters. **CAP-3** showed promising therapeutic potential against *S. aureus* (Fig. 7e), *C. albicans* (Fig. 7f) and polymicrobial (Fig. 7g) murine wound infection models.[161] Recently, Hryniewicka *et al.* synthesized steroid-based imidazolium salts using lithocholic acid (LCA) and 3-oxo-23,24-dinorchol-4-en-22-al. First, the imidazole moiety was installed at the C24 position of LCA, and was treated with alkyl bromides or iodides with varying chain lengths (Fig. 7h).[162] In a similar fashion, they have synthesized imidazolium salts of 3-oxo-23,24-dinorchol-4-en-22-al (Fig. 7i). Both series were screened against *C. albicans* and other bacterial strains, and the LCA-based imidazolium salts bearing methyl (compound **17**) and ethyl (compound **18**) showed potent fungicidal properties against *C. albicans* with a MIC_{80} value of 0.25 μg mL^{-1} and 0.5 μg mL^{-1} respectively.[162]

Collectively, these reports suggest that steroid-based amphiphiles display promising therapeutic applications against different microbial infections by disrupting their cell membrane. Notably, findings also demonstrated that fungal strains were unable to gain resistance against these steroid-based amphiphiles. In addition, these amphiphiles also displayed potent antifungal activity against different murine infection models. However, their cytotoxicity and pharmacokinetic profiles still remain a quest to solve. Further fine-tuning of potent amphiphiles can be done to afford lower cytotoxicity with a better pharmacokinetic profile.

5.3 Aromatic and heterocyclic amphiphiles

Aromatic and heterocyclic cationic amphiphiles are easy to synthesize, and display a wide range of therapeutic applications.[163] Notably, aromatic and heterocyclic cationic amphiphiles, including naturally obtained plant secondary metabolites, display potent antimicrobial activity. Lin *et al.* used a xanthone scaffold and installed aliphatic amines and basic amino acids through ether linkage,[164] and found that molecules bearing formamidyl (compound **25**) and *n*-butyl (compound **26**) showed potent antifungal proprieties with a MIC_{80} of 0.78 and 3.13 μg mL^{-1} respectively (Fig. 8a). Compound **25** was found to be fungicidal in nature whereas compound **26** displayed

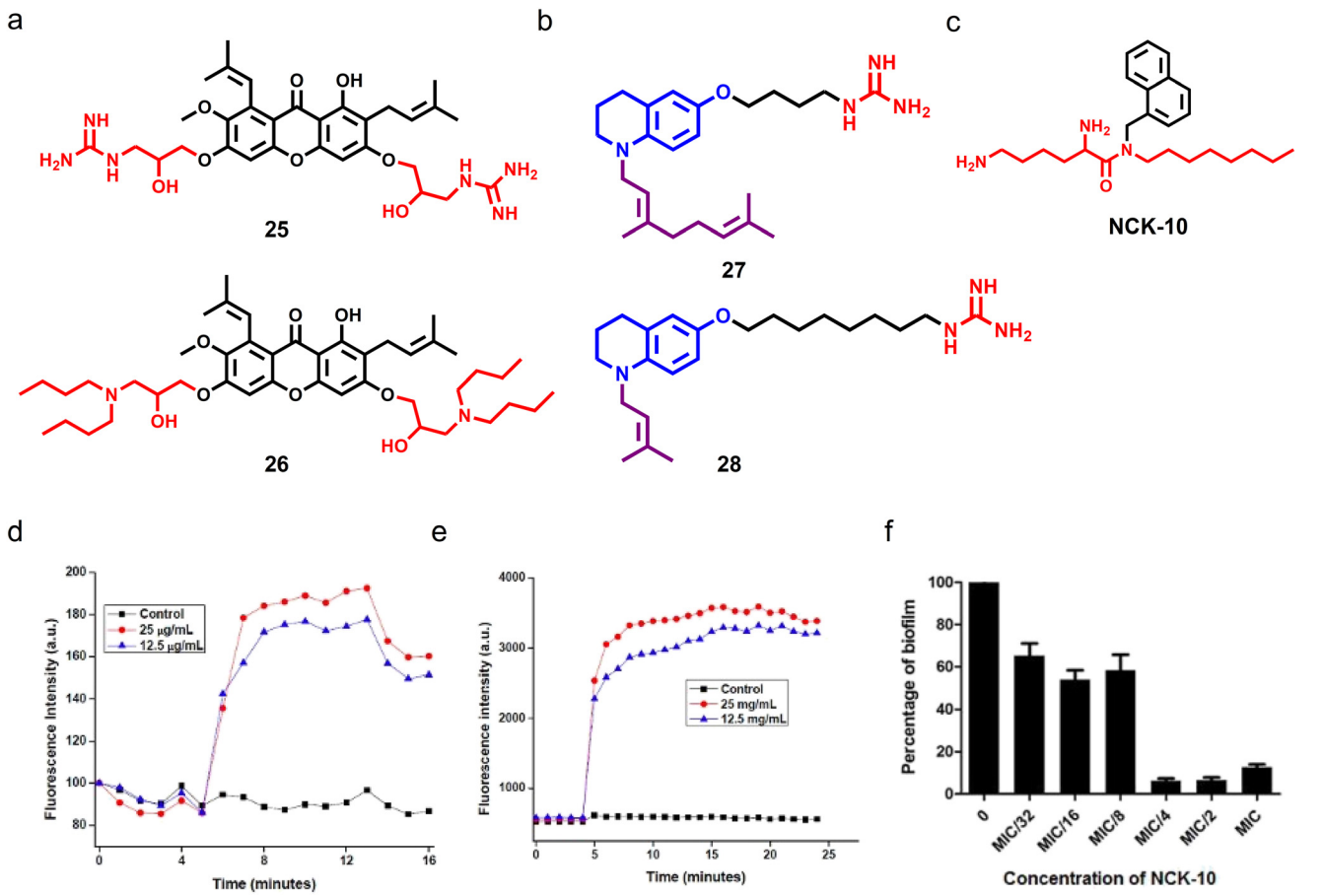


Fig. 8 (a) Chemical structures of potent xanthone-based cationic compounds **25** and **26**. (b) Molecular structures of most potent tetrahydroquinoline-based compounds **26** and **27**. (c) Molecular structure of **NCK-10**. (d) Fluorescence-based assay showing that **NCK-10** can depolarize the fungal cell membrane in a dose-dependent manner. (e) Fluorescence-based study suggesting that **NCK-10** can permeabilize the fungal membrane. (f) *In vitro* study showing that **NCK-10** can inhibit the formation of *C. albicans* biofilms. (Fig. 8d–f reproduced from ref. 166 with permission from the American Chemical Society, copyright 2017).

fungistatic properties. Interestingly, only a 2-fold change in the MIC_{80} of compound **26** was observed in multi-passage resistance studies, whereas the MIC_{80} of compound **25** decreased with passage. Additionally, compound **25** demonstrated high membrane-permeabilizing properties compared to compound **26**, and showed potent antifungal activity against drug-resistant fungal pathogens. Moreover, both the compounds exhibited additive and synergistic effects in combination with FDA approved antifungal agents against *C. albicans*. Topical application of compound **25** (0.2%) showed potent antifungal efficacy compared to natamycin with a 25-fold reduction in fungal burden.[164]

In another report, a series of tetrahydroquinoline-based amphiphiles was synthesized and explored for antimicrobial properties, and both cationic and hydrophobic groups were tethered to the scaffold.[165] Among the series, compounds having nonyl and isopropyl groups with a spacer length of 4 and 8 displayed potent broad-spectrum antimicrobial properties against fungi, Gram-positive and Gram-negative pathogens (compounds **27** and **28**) (Fig. 8b). Both the amphiphiles showed dose-dependent fungicidal behaviour, and continued exposure to both compounds did not allow fungal cells to gain any resistance against them. Mechanistic studies demonstrated that both compounds have membrane-permeabilization activities.[165] Ghosh *et al.* developed an aryl-based cationic amphiphile (**NCK-10**) by conjugating an aryl–alkyl–lysine with an alkyl chain of ten carbon atoms, which showed potent antifungal activity against *C. albicans* and *C. neoformans* with a MIC_{80} value of 12.5 μg mL^{-1} and 3.1 μg mL^{-1} respectively (Fig. 8c).[166] Different biochemical and microscopy studies revealed the dose-dependent fungal membrane-permeabilization ability of **NCK-10** (Fig. 8d and e). **NCK-10** also exhibited dose-dependent antifungal properties against pre-formed *C. albicans* biofilms (Fig. 8f).[166]

As long-chain of ionic surfactants is important for amphiphilic nature and antimicrobial properties, Kashapov and colleagues developed single-chain diatonic surfactants bearing pyridinium as a core scaffold.[167] Cationic surfactants armed with vinyl bipyridinium (**VBP-16**) and viologen (**V-16**) moieties as the head groups were tethered with a hexadecyl tail, and exhibited moderate antifungal and antibacterial properties (Fig. 9a).[167] Kuznetsova *et al.* developed imidazolium-based cationic amphiphiles (called the MPI series) with self-assembly properties, where they used a methoxyphenyl fragment linked with an imidazole group, and different alkyl chains including decyl, dodecyl, tetradecyl, and hexadecyl were installed at the imidazole group (Fig. 9b).[168] Transmission electron microscopy displayed spherical aggregates of MPI-10 (Fig. 9c). SAR studies showed that the antifungal properties were enhanced with an increase in alkyl chain length, and the amphiphile armed with a 16 carbon chain length group demonstrated potent antifungal properties with a MIC_{80} of 7.8 μg mL^{-1} and minimum fungicidal concentration of 125 μg mL^{-1}.[168] Stephen G. Pyne's group extensively worked on the design and synthesis of small peptidomimetic antimicrobial agents.[169–173] Recently, they reported the design and synthesis of a series of biphenyl positional isomers (Fig. 9d), and among these isomers, the 4,4′-isomer (compound **36**) showed potent antifungal activity against *C. albicans* with a MIC_{80} of 1 μg mL^{-1}.[174]

Apart from AMP mimicking small molecules, ionic liquids also possess promising antifungal therapeutic potential. Inspired by previously reported quaternary ammonium-based surfactants (QACs), Garcia *et al.* designed and synthesized two series of cationic liquids by employing *N*-methylimidazole and pyridine as the core scaffold, and tethered different alkyl chains, including C_6 to C_{14}, through a cleavable ester linkage (Fig. 9e).[175] In both series, the molecules having a pyridine core tethered with a C_{12} alkyl chain showed potent antifungal properties against *C. albicans* (Fig. 9e).[175] Further, ionic liquids also displayed potent antifungal properties against *Alternaria* species, known to cause a seed-borne disease that affects plant production.

Karaman *et al.* tested a series of 18 imidazolium-based ionic liquids, and all the ionic liquids showed good antifungal properties that depend on the alkyl chain.[176] As imidazolium is a key pharmacophoric feature for the development of antifungal ionic liquids and their exact mechanism is still an enigma, Reddy *et al.* investigated the antibiofilm activity of already reported alkylated imidazolium ionic liquids and performed in-depth mechanistic studies.[177] They employed three different ionic liquids bearing C_4, C_{12}, and C_{16} alkyl chains, and demonstrated that an increment in alkyl chain length can also enhance the antifungal potency of ionic liquids. The ionic liquid having C_{16} displayed potent biofilm inhibition properties (Fig. 9f and g). Interestingly, both ionic liquids with C_{12} and C_{16} chains were found to be effective against clinical strains, and the ionic liquid bearing a C_{16} alkyl chain was found to be most potent against clinical strain-mediated biofilms (Fig. 9h). Microscopy images revealed that treatment with the C_{16} ionic liquid can cause shrinkage of *C. albicans* cells and membrane permeabilization, thereby causing the release of intracellular materials (Fig. 9i and j). In addition, treatment with the C_{16} ionic liquid decreased the ergosterol content in a dose-dependent manner (Fig. 9k). Moreover, treatment with the C_{16} ionic liquid also caused ROS generation and affected the mitochondrial membrane potential.[177]

Sutar and co-workers employed FDA-approved anthelmintic drugs, including albendazole (ABZ), mebendazole (MBZ), and flubendazole (FBZ), to develop docusate-based ionic liquids (Fig. 9l).[178] The docusate-based ionic liquids were synthesized by treating these drugs with sodium docusate (Doc) in the presence of 1 M HCl and methanol. Antifungal studies showed that the developed ABZs were more potent than the parent drugs. Further, the treatment with the docusate-based ionic liquids inhibited *C. neoformans* growth by interfering with microtubule assembly (Fig. 9m–o). Notably, the docusate-based ionic liquids have greater organic solubility over the drugs, and incorporation of polymers provided a micelle-forming ability to the docusate-based ionic liquids.[178]

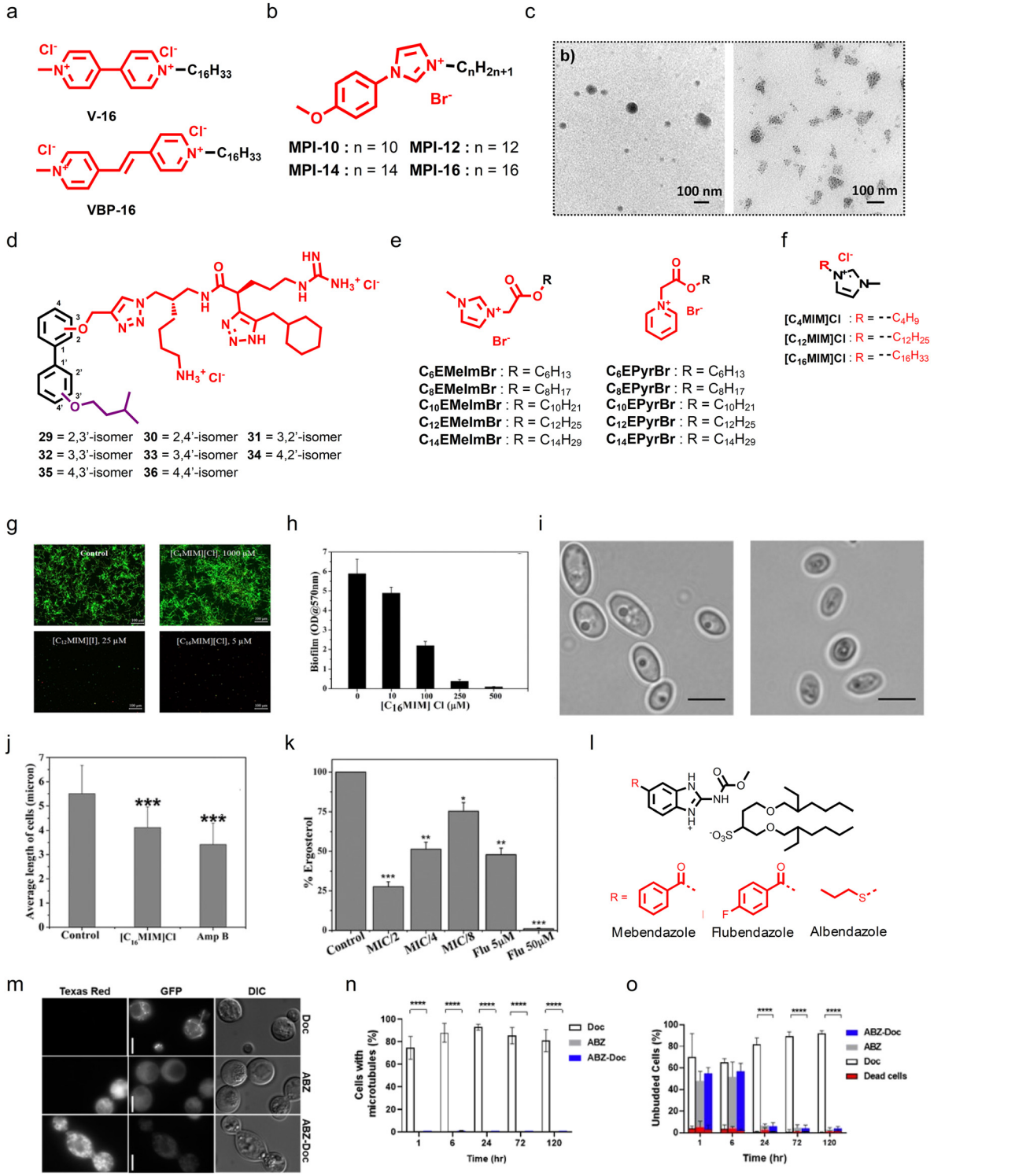


Fig. 9 (a) Chemical structures of **V-16** and **VBP-16**. (b) Chemistry of the MPI series. (c) TEM images displaying that MPI-10 can form aggregates. (d) Chemistry of biphenyl positional isomers. (e) Chemistry of imidazole and pyridine-based cationic esters. (f) Chemical structure of the potent imidazole-based cationic amphiphile [C_{16}MIM]Cl. (g) Confocal microscopy images showing the antibiofilm properties of [C_{16}MIM]Cl against pre-formed *Candida* biofilms. (h) Quantification of antibiofilm properties of [C_{16}MIM]Cl. (i) Micrographs showing healthy and [C_{16}MIM]Cl treated fungal cells, suggesting that [C_{16}MIM]Cl can affect the morphology and length of fungal cells. (j) Quantitative analysis suggesting that [C_{16}MIM]Cl can reduce the fungal cell length. (k) *In vitro* study showing that [C_{16}MIM]Cl treatment can reduce the ergosterol level in a dose-dependent manner. (l) Chemistry of docusate-based ionic liquids from anthelmintic drugs. (m) Investigation of β-tubulin dynamics during treatment with ABZ, ABZ-Doc, and Doc against *C. neoformans*. (n) Quantification of visible microtubules at different time points after treatment with ABZ, ABZ-Doc, and Doc. (o) Quantification of unbudded cells at different time points after ABZ, ABZ-Doc, and Doc treatment (Fig. 9c reproduced from ref. 168 with permission from the American Chemical Society, copyright 2022, Fig. 9g–k reproduced from ref. 177 with permission from Frontiers Media S.A., copyright 2020, and Fig. 9m and n reproduced from ref. 178 with permission from the American Chemical Society, copyright 2021).

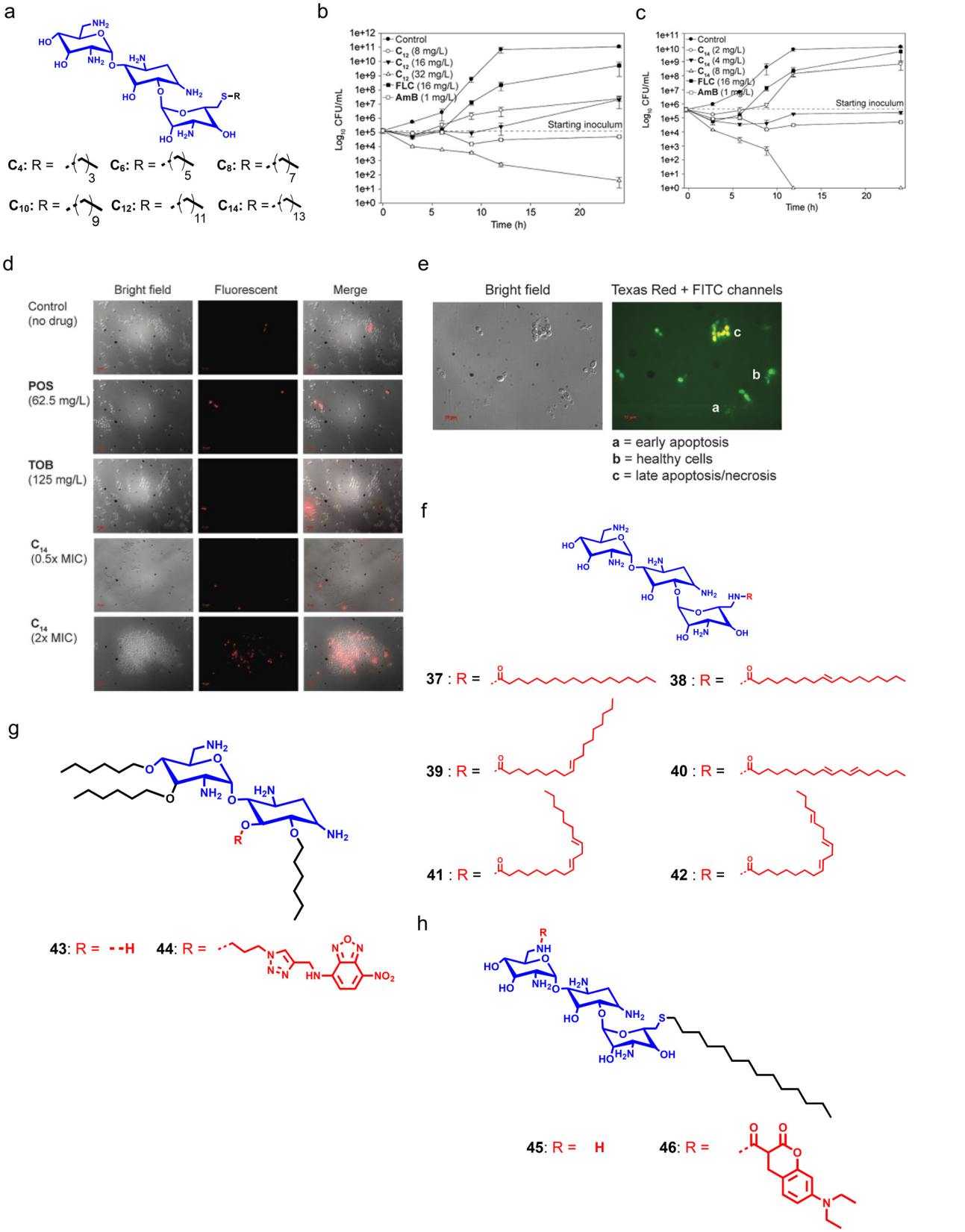


Fig. 10 (a) Molecular structure of the C_{14}-tethered derivative of tobramycin. (b and c) Time-dependent killing kinetics with different concentrations of tobramycin-derivatives. (d) Micrographs revealing the dose-dependent membrane-targeting properties of the C_{14}-tethered tobramycin. (e) Confocal images showing that the C_{14}-tethered derivative of tobramycin can induce late apoptosis or necrosis in fungal cells. (f) Chemical structure of tobramycin and its derivatives. (g) Chemical structures of neamine derivatives. (h) Chemical structures of fluorescent tobramycin derivatives (Fig. 10b–e reproduced from ref. 176 with permission from the American Society for Microbiology, copyright 2015).

5.4 Antibiotic-derivatives as antifungal agents

Aminoglycosides like kanamycin, tobramycin (TOB), and gentamicin are naturally occurring antibiotics primarily utilized as bacteria-fighting agents. The inositol–amino sugar combination having hydroxyl and amino groups in the general structural motif of these antibiotics is essential for their interactions with RNA of the 30S subunit of ribosomes, and impedes protein translation. Long-term and excessive use of traditional aminoglycosides in medicine and agriculture has allowed resistant strains to develop, thereby making these antibiotics ineffective. Therefore, to combat this resistance, development of aminoglycosides should consider the likelihood of resistance and be flexible enough to adapt to the evolution of bacteria.[179,180] Although aminoglycosides are effective antifungals at much higher concentrations, the S. Garneau-Tsodikova group designed and synthesized a series of cationic amphiphilic derivatives of TOB by conjugating different linear, branched, cyclized, and aromatic groups at the C_6' position (Fig. 10a).[181] In further studies, they added a new amphiphile with a C_{14} alkyl chain in the series and tested it against both yeast and filamentous fungi strains.[182] TOB alone showed minimal antifungal properties, while its derivatives showed moderate to high fungicidal properties (Fig. 10b and c). In contrast, the amphiphile having C_{14} showed potent antifungal efficacy through membrane disruption with a minimal cytotoxicity profile (Fig. 10d). Moreover, confocal microscopy studies demonstrated that treatment with the C_{14} TOB-derivative can induce late apoptosis or necrosis in fungal cells (Fig. 10e).[182]

Steinbuch *et al.* designed and synthesized a series of TOB-derived cationic compounds with varying degrees of unsaturation in the lipid chain to target fungal infections. Initial antifungal screening of the synthesized compounds against different fungal strains suggested that tethering of lipid chains can enhance the antifungal activity by 32-fold as compared to TOB.[183] Further, they selected two compounds having a fully saturated and unsaturated lipid group, respectively. SAR studies indicated that these compounds have poor antibacterial properties, and are specific against fungal cells. Compound **41**, having the highest degree of unsaturation, showed the lowest toxicity against RBCs (Fig. 10f). Additionally, these amphiphiles can disrupt the fungal membrane and also displayed antifungal activities against intracellular fungal infection.[183] To understand the antifungal mechanism of cationic aminoglycoside-derivatives, Jaber *et al.* designed and synthesized fluorophore–aminoglycoside conjugates (compounds **43–46**) using neamine and TOB, and installed nitrobenzoxadiazole (NBD) on neamine, and 7-diethylaminocoumarin on tobramycin (Fig. 10g and h).[184] The developed amphiphiles showed similar antifungal properties and showed the disappearance of mCherry fluorescence in Eno1–mCherry expressing *C. albicans* which demonstrated plasma membrane destruction. In addition, treatment with aminoglycoside-based cationic amphiphiles also disrupted the nuclear envelope and penetrated the nucleus where these amphiphiles strike the DNA structure.[184]

Logviniuk *et al.* synthesized and studied a series of 16 cationic amphiphiles, where they conjugated different alkyl chains with varying degrees of unsaturation at hydroxy groups of nebramine (Fig. 11a–d).[185] Amphiphiles tethered with a di-*O*-*n*-hexyl alkyl chain showed moderate to poor antifungal properties. In contrast, amphiphiles bearing di-*O*-

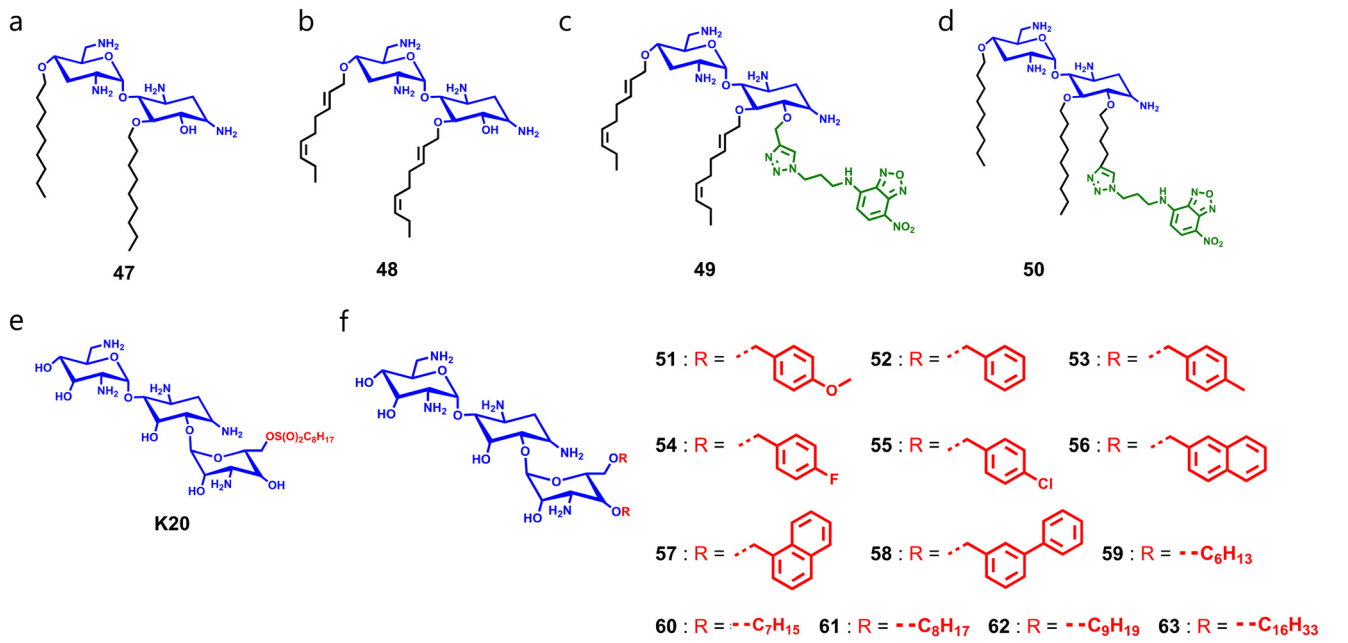


Fig. 11 (a–d) Chemical structures of nebramine-derivatives **47** (a), **48** (b), **49** (c), and **50** (d). (e) Chemical structure of kanamycin-derivative K20. (f) General chemical structure of diaryl and dialkyl substituted kanamycin-derivatives.

n-nonyl groups with varying degrees of unsaturation demonstrated better antifungal properties as they have a comparatively higher hydrophobicity than the di-*O*-*n*-hexyl group substituted molecules. SAR studies showed that the arrangement of unsaturation modestly impacted the antifungal properties of di-*O*-*n*-nonyl substituted amphiphiles, and the presence of three saturated aliphatic chains reduced the antifungal properties due to increased hydrophilicity (Fig. 11a and b). Therefore, an optimum balance of hydrophilicity and hydrophobicity should be obtained to achieve antifungal properties. To decipher membrane accumulation, they also synthesized fluorophore conjugates, compounds **47** and **48**, by installing NBD through click chemistry (Fig. 11c and d).[185] Apart from TOB, other aminoglycoside-derivatives like kanamycin also displayed potent antifungal properties.[186] Recently, Alfindee *et al.* tested earlier reported C4″,C6″-dialkyl and diaryl kanamycin derivatives against different fungal pathogens and showed the disubstituted kanamycin-derivatives as potent membrane-permeabilizers (Fig. 11e and f).[187]

Collectively, these findings suggest that incorporation of amphiphilicity in available aminoglycosides can enhance their antifungal potency. In addition, developed amphiphilic aminoglycosides can disrupt the fungal membranes and eradicate pre-formed fungal biofilms. Synthesized fluorophore-labeled molecules validated the membrane-targeting abilities of amphiphilic aminoglycosides. However, development of minimally toxic antifungal amphiphilic aminoglycosides is still a mystery which may be resolved by further fine tuning of these amphiphiles.

5.5 Polymer-based amphiphiles

Antifungal polymers are important in both medical and agricultural industries, where fungal infections can cause significant damage. In the medical sector, antifungal polymers are used in drug delivery systems and wound dressings, while in the agricultural industry, they are used as antifungal coatings for fruits and vegetables. In addition, cationic polymeric materials can also be used in paint and film coatings to restrict microbial growth. Therefore, the development of antifungal polymers has been driven by the need to find effective and safe alternatives to traditional antifungal agents. One of the most common mechanisms of antifungal polymers involves the interactions of the polymer with the fungal cell membrane resulting in membrane disruptions, causing leakage of intracellular contents and ultimately leading to fungal cell death. Another mechanism involves interactions of the polymer with the fungal cell wall which can lead to cell wall damage and subsequent cell death. The exact mechanism of action of antifungal polymers can vary depending on the specific polymer used and type of fungus being targeted.[188] Understanding the mechanisms of action of antifungal polymers is crucial for their effective application in both medical and agricultural settings. Several reviews summarized the applications of polymers to combat infectious diseases.[189,190]

Guanidine is an important pharmacophoric feature that displays potent antimicrobial properties, and Baugh summarized recently reported guanidine-containing antifungal molecules.[191] Oule and co-workers reported polyhexamethylene guanidine (PHMG) hydrochloride as a potent antimicrobial macromolecule that showed broad-spectrum antibacterial properties against drug-resistant pathogens with minimal toxicity against mammalian cells.[192] In addition, its physiochemical properties, like water solubility, and non-corrosive and odorless nature, make it a versatile antibacterial disinfectant.[192] Choi *et al.* demonstrated that treatment with the hydrochloride salt of PHMG can hamper the morphology of *C. albicans* cells, reduce the phospholipid area and disrupt the plasma membrane by altering the membrane potential without exhibiting any toxicity against human RBCs.[193] Brzezinska and co-workers developed derivatives of PHMG using polylactide (PLA), polyhydroxybutyrate (PHB), and polycaprolactone (PCL) which were found to be more fungicidal in nature as compared to native PHMG.[194] Further studies demonstrated that these derivatives can hamper the morphology of fungal cells, eradicate biofilm formation, and inhibit hydrolase activity in *C. albicans*.[194] PHMG was also used to manage plant fungal diseases, where it showed potent fungicidal properties against *P. digitatum* by disrupting the cell wall and membrane.[195] Recently, Ntow-Boahene *et al.* investigated the antifungal properties of the polyhexamethylene biguanide (PHMB) macromolecule against different fungal pathogens such as *S. cerevisiae*, *C. albicans*, *F. oxysporum* and *P. glabrum*. PHMB showed potent antifungal activity against fungal pathogens with a MIC_{90} value of 2–8 μg mL^{-1}. Further, biochemical studies revealed that PHMB can permeabilize fungal cell membranes in a time-dependent and dose-dependent manner. After permeabilizing fungal membranes, PHMB accumulates within the cytosol and hampers the nuclear membrane leading to DNA binding and fragmentation. Collectively, these findings suggest that PHMB also targets intracellular organelles.[196] Despite its antifungal properties, the aerosol form of PHMG can cause lung fibrosis by inducing epithelial–mesenchymal transition (EMT).[197]

Polyethyleneimines (PEIs) are polymeric compounds that bear an amine group and a spacer of two carbon atoms. As they have the ability to permeabilize the cell membrane, they are widely used in drug delivery and gene therapy applications.[198] In addition, PEIs display antifungal properties through depolarizing *C. albicans* membranes, and also exhibit antibiofilm activity in a dose-dependent manner.[199] Low molecular weight PEIs display minimal toxicity, and higher molecular weight PEIs are more toxic against mammalian cells.[200] Haldar and group designed and developed PEI-based antimicrobial coating materials where they prepared two series of linear and branched colorless organo-soluble PEI (of different molecular weights) coating

materials through Eschweiler–Clarke methylation, and then quaternized them with different alkyl bromides.[201] Among the linear derivatives, the polymer bearing $C_{18}H_{37}$ alkyl chains with lower molecular weight showed potent antimicrobial activity, and in the case of branched derivatives, polymers armed with $C_{12}H_{25}$ alkyl chains with higher molecular weight were found to be more active against bacterial and fungal pathogens. In-depth mechanistic studies revealed that the active polymers can disrupt the bacterial and fungal cell membranes without affecting hRBCs, and fungal pathogens were unable to gain resistance against the active polymers for up to 20 passages.[201]

Real *et al.* prepared an antifungal film coating by loading econazole nitrate in a polymeric matrix composed of chitosan, Carbopol, polyethylene glycol 400, and sorbitol which displayed better antifungal properties against *C. krusei* and *C. parapsilosis* as compared to commercial creams.[202] Nagaraja and co-workers developed a hydrophilic-antimicrobial polymer coating material functionalized with polymaliamides, and it was found to be more active against Gram-positive bacteria and *M. smegmatis*. Moreover, it displayed excellent film-forming properties and thus it can be used in the paint and food packaging industries.[203] Schaefer *et al.* designed and developed a library of antifungal polyacrylamide polymers using the PET-RAFT polymerization technique. Among these polyacrylamide polymers, 40-LP-2030, a linear polymer with a pentyl alkyl chain, was found to be a potent antifungal agent, and non-toxic against mammalian RBCs and fibroblasts.[204] Recently, Yeung *et al.* developed two polyethylene-derived water-soluble amphiphilic polymers that showed potent antifungal activities through depolarizing the fungal membrane potential.[205]

Collectively, these reports suggest that polymer-based amphiphiles can effectively target the fungal membrane, and can be used to deliver already available antifungal agents to a targeted site. Notably, antifungal polymeric materials can be used in paint and film coatings to prevent invasive fungal diseases.

6. Conclusion

Fungal infections in hospitals and clinical settings, exacerbated by drug resistance, are more challenging at the global level, and cause serious public health concern. Fungi cause diverse disease forms ranging from superficial allergic conditions to life threatening invasive diseases affecting millions of individuals annually, and ineffective detection tools hinder the timely discernment of infection. Further, overuse and misuse of antifungal drugs in clinical settings contributes to the development of AMR where fungal cells employ intrinsic and extrinsic factors to gain resistance against azoles, polyenes, echinocandins, antimetabolites, and allylamines. As the emergence of drug-resistant fungal pathogens like *C. auris* is a serious threat to mankind, the condition of antimicrobial resistance is dire, and it is imperative to take some potential steps to overcome this crisis. Therefore, knowledge at the ground level and policies focusing to improve appropriate diagnostic testing in humans would play a significant role.

Continuous pre-clinical evaluation and clinical studies with available approaches can successfully overcome the incidences of antifungal resistance. The discoveries uncovered in screening campaigns and detailed sequencing of resistant species could lay a stepping stone to starting research on new antifungal agents having improved efficacy. Although development of new antibiotics capable to target the specific mechanism is a time consuming exercise, adoption of existing antibiotics using stewardship therapy and usage of small membrane targeting agents could complement to fill in the void of antifungal pipeline in future. Recently, a few molecules like VT-II29, VT-II6I and VT-I598 (specific inhibitors of Cyp5I), CDI0I (inhibitor of glucan synthase), F90I3I8 (inhibitor of fungal pyrimidine biosynthesis) and T-2307 (fungal mitochondrial membrane inhibitor) have come up as agents to tackle the resistance of fungal species, and could have potential to act as future antifungal agents. Moreover, repurposing of old drugs and host immune cell targeted approaches can potentially eradicate existing resistant fungal species. Personalized immune therapy, translation of sequencing techniques, awareness of resistant dermatophytosis, ability to access antifungal susceptibility testing, and antifungal vaccines can have a scope in the future antifungal field.

The fungal cell membrane presents unique drug targets as its biochemical composition is different from those of other microbes, and the presence of PC, PE, sphingolipids, and lipid rafts make it anionic in nature. Therefore, AMPs which are well-defined biomolecules of the host innate immune system can disrupt the microbial membrane through strong electrostatic interactions. However, the stability and toxicity profile of AMPs restrict their employment in clinical settings. Inspired from the unique biochemical composition of fungal cell membranes and the functions of AMPs, researchers are keen to design and develop membrane-targeting amphiphilic molecules. Moreover, these amphiphiles can act as potential adjuvants that rejuvenate the antifungal properties of available drugs.

However, their toxicity against hosts creates a huge hurdle in clinical translation as most of the antifungal amphiphiles were found to be toxic against mammalian cells. Therefore, amphiphiles with a high therapeutic index can be advanced to preclinical studies. However, some cationic amphiphiles display lower toxicity against mammalian cells but they have a narrow spectrum of activity, and the poor pharmacokinetic profile of amphiphiles hampers their usage in clinical settings. Membrane-targeting agents like daptomycin are specific against Gram-positive pathogens, and is not orally bioavailable to cure lung infections. Collectively, these factors affect the clinical translation of membrane-targeting amphiphiles, and also provide an opportunity to rationally design and develop membrane targeting cationic amphiphiles. In summary, the unique biochemical composition of fungal membranes can be employed as a

therapeutic target to design and develop antifungal regimens against fungal pathogens.

Conflicts of interest

The authors declare that they have no competing interests.

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