

## SEARCH FOR NEW DRUGS

### POLYENE MACROLIDE ANTIBIOTIC DERIVATIVES: PREPARATION, OVERCOMING DRUG RESISTANCE, AND PROSPECTS FOR USE IN MEDICAL PRACTICE (REVIEW)

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Translated from *Khimiko-Farmatsevticheskii Zhurnal*, Vol. 52, No. 11, pp. 14 – 26, November, 2018.

*Original article submitted September 18, 2017.*

Series of semi-synthetic polyene macrolide antibiotics (PMAs) that were prepared by chemical modification in original research by the authors are reviewed. Chemical modification, in particular phosphorylation, was shown to produce highly efficacious PMAs with low toxicities and extended spectra of biological activity. The prospects of using liposomal and nano-derivatives of these antifungal antibiotics are discussed. Crucial issues related to the resistance of pathogenic fungi and the expanding distribution of invasive mycoses are identified. Semi-synthetic PMAs are shown to be highly effective at preventing and treating invasive mycoses and opportunistic fungal infections occurring in AIDS patients. Special attention is paid to structure—activity relationships for the semi-synthetic PMAs. Possible mechanisms of action of these compounds on pathogenic fungi are discussed. An automated intellectual information system was developed for selecting the optimal conditions for development, synthesis, and application in medical practice of new PMAs.

**Keywords:** polyene macrolide antibiotics, chemical modification, semi-synthetic derivatives, nanotechnology, drug resistance, invasive mycoses, AIDS, automated intellectual information system.

Fungal infections continue to rise because of environmental pollution, increased radiation background, irrational use of broad-spectrum antibiotics, extensive use of cytostatics and immunosuppressants, and several other factors [1 – 3]. Invasive mycoses are becoming more problematical for medical practice because of the rising population of immunocompromised patient populations [4 – 6]. The number of available and approved systemic antifungal antibiotics is known to be inadequate today [7 – 9]. However, progress in the design of new antifungal drugs is not keeping pace with the increase of mycological diseases, in particular, invasive fungal infections that are an existential and growing problem for modern medicine [10 – 12].

Polyene macrolide antibiotics (PMAs) such as amphotericin B, levorin, nystatin, pimarinic, candicidin, and others are widely used in medical practice to treat both surface and

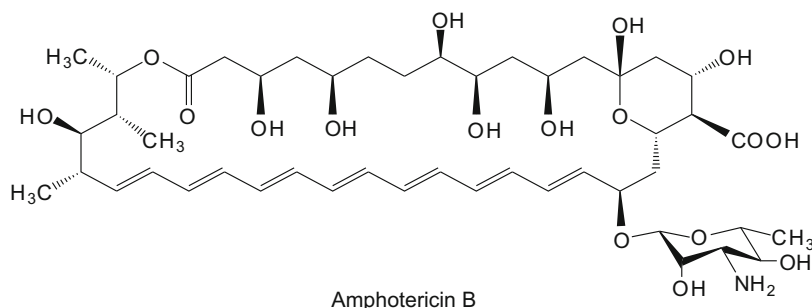
deep mycoses [4 – 6]. PMAs include a numerous group of natural compounds with over 200 drugs that are active against yeast, yeast-like, and saprophytic and pathogenic species of mycelial fungi [13 – 18]. Also, PMAs used in medical practice do not fully meet the needs of physicians and clinicians because of their limited efficacy due to their low water solubility [4 – 6], high toxicity (mainly nephrotoxicity) [7 – 9], and emergence of resistant species of pathogenic fungi [19, 20]. Therefore, the search for new PMAs with improved medical and biological properties is critical.

#### Preparation of new semi-synthetic PMAs by chemical modification

PMAs are known to be polyfunctional compounds with large lactone rings (from 26 to 33 atoms) and conjugated double bonds (from 4 to 7) [10 – 14]. PMAs are subdivided according to number of double bonds as tetraenes, pentaenes, hexaenes, and heptaenes. PMA molecules are usually separated into two parts, i.e., the rigid unsaturated part of the

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Amphotericin B

**Fig. 1.** Structural formula of heptaene macrolide antibiotic amphotericin B.

macrolactone ring with hydrophobic properties and the flexible polyol part that is responsible for the hydrophilicity. Other important structural components of PMAs are the carboxylic acid and amine in the carbohydrate moiety (Fig. 1).

Most studied PMAs contain the amino sugar mycosamine (3-amino-3,6-dideoxy-D-mannose). The overwhelming majority of PMAs are prepared by modifying these antifungal drugs at the carboxylic acid or amine.

Currently, various semi-synthetic PMA derivatives prepared by chemical modification have been reported [11, 12, 21–25]. However, information on the preparation of organophosphorus derivatives of these antifungal drugs is missing. Organophosphorus compounds are widely employed in various industrial sectors. Their industrial output is constantly expanding [26–30]. An especially valuable property of organophosphorus compounds is their biological activity that enables them to be used in medical practice [31–37]. In this respect, the use of synthetic methods developed for organophosphorus chemistry for chemical modification of biologically active compounds and especially antibiotics is a promising direction for discovering highly efficacious drugs. Hydrophosphorylation using hypophosphorous acid and aromatic aldehydes was proposed by us as a method for chemical modification of PMAs. This reaction can be considered a variation of the Kabachnik–Fields reaction [26, 38, 39]. The first reaction step consists of addition of the primary amine of the PMA carbohydrate moiety to the aromatic aldehyde carbonyl to form an azomethine intermediate. The second step involves the reaction of hypophosphorous acid with the C=N bond of the azomethine intermediate to give hydrophosphoryl PMAs. Hydrophosphoryl derivatives of levorin [40], nystatin [41], amphotericin B [42], mycoheptin [43], pimaricin [44], and lucensomycin [45] were synthesized using the proposed method. Use of various dialkylphosphites and 4-bromobenzaldehyde for chemical modification of pimaricin also under Kabachnik–Fields reaction conditions was shown by us to produce 3'-N- $\alpha$ -dialkoxy(diphenoxy)phosphonate derivatives of this tetraene macrolide antibiotic [46]. The possibility of using an Atherton–Todd reaction for chemical modification of amphotericin B and lucensomycin was studied by us [47–51]. Thus, dialkyl(aryl)amidophosphate derivatives were formed by the

reaction of these PMAs with various dialkyl(aryl)phosphites in the presence of an organic base. Pimaricin was chemically modified by diethyl chloroacetylenephosphonate with high selectivity to form its phosphorylated aldoketenimine derivative, i.e., the organophosphorus reagent reacted with the mycosamine primary amine [52, 53].

Fluorinated amphotericin B [54] and nystatin [55] derivatives were prepared via reactions with anhydrides of perfluorocarboxylic acids. Fluorinated levorin esters resulted from esterification of this heptaene macrolide antibiotic by organic fluoroalcohols [56]. Nystatin reacted with trialkylchlorosilanes to synthesize the *N*-trialkylsilyl derivatives [57, 58]. The *N*-benzyl derivatives of amphotericin B [59], pimaricin [60, 61], and lucensomycin [62] were prepared by reductive amination. Nucleophilic aromatic substitution was used to synthesize *N*-aryl-substituted pimaricin derivatives [63]. Biological tests showed that semi-synthetic PMAs exhibited pronounced antifungal activity against a large group of pathogenic fungi, primarily yeast-like fungi of the genus *Candida*. Also, they were 3–5 times less toxic than the starting antibiotics. Furthermore, chemical modification of PMAs can introduce various functional groups, e.g., hydrophosphoryl, which increased considerably the water solubility of levorin, nystatin, amphotericin B, mycoheptin, pimaricin, and lucensomycin derivatives [40–45, 64, 65]. This improved the biopharmaceutical properties of the antifungal preparations.

Chemical modification of biologically active compounds in several instances altered the spectrum of biological activity of the derivatives and reduced their toxicity [21, 22, 31, 32]. Previously, various researchers found that PMAs had nonspecific antiviral [66–70] and antitumor activity [68–70]. The mechanism of action of these antifungal antibiotics involved reorientation of the lipid (sterol) component of the virion shell surface or virus-specific receptors of cellular cytoplasmic membrane leading to inactivation of the virus or prevention of its penetration into a sensitive cell [71–76]. Chemical modification of PMAs by us changed their spectra of biological activity. Thus, additional virology testing found that several semi-synthetic derivatives of levorin [40], nystatin [41], amphotericin B [42], mycoheptin [43], and lucensomycin [45] that were prepared by us exhib-

ited high antiviral activity against DNA-containing Vaccinia virus and RNA-containing oncogenic Rous sarcoma and type A and B influenza viruses. The results obtained for hydrophosphoryl derivatives of these PMAs in the RNA-containing Rous sarcoma retrovirus model were especially interesting because this model was proposed as a retrovirus model suitable for screening and studying anti-AIDS drugs [66, 67].

### Search for liposomal and nanoscale PMAs

Biopharmaceutical approaches to reducing toxicity and improving PMA (mainly amphotericin B and nystatin) pharmacokinetics have recently become well known. Therefore, various amphotericin B derivatives were prepared as liposomal preparations (AmBisome<sup>®</sup>) [77–87], lipid complexes (Abelcet<sup>®</sup>) [88–92], colloidal dispersions (Amphocil) [93–95], and liposomal nystatin preparation (Nyostran<sup>®</sup>) [96–104]. Liposomal dosage forms of amphotericin B (AmBisome) and nystatin (Nyostran) are complete spherical vesicles formed by aqueous dispersions of certain polar lipids, e.g., phospholipids and cholesterol. Homogenization of phospholipids in aqueous solution forms single or multiple concentric bilayer membranes [105–107]. The lipophilic groups in amphotericin B enable it to be incorporated into liposome lipid bilayers. The preparation distributes as intact liposomes in tissues with fungal infections. The active ingredient is released only after touching cells of pathogenic fungi and not those of normal tissues. Other advantages of PMA liposomal preparations are lower toxicity, prolonged pharmacokinetics, and better tolerability [108, 109]. The lipid complex of amphotericin B (Abelcet) is a combination of the antibiotic and two lipids, i.e., dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol with a 1:1 ratio of drug to lipids [88–92]. Clinical trials of this preparation are currently modest although it is used for candidiasis, aspergillosis, cryptococcosis, and other serious fungal diseases [7–9]. Amphocil preparation is a colloidal suspension of amphotericin B consisting of equimolar amounts of antibiotic and cholesterol sulfate [93–95]. Use of Amphocil preparation is considered efficacious for treating serious deep mycoses, in particular lung aspergillosis. Abelcet, Amphocil, and AmBisome preparations reduced substantially the nephrotoxicity of amphotericin B.

The safety, biodegradability, and accessibility of liposomes are attractive to researchers [110–112]. Furthermore, the high variability of liposomes is a big advantage. For example, the characteristics of liposomal carriers of biologically active compounds can be changed over wide limits by changing the methods for forming lipid vesicles and including various molecules in them. The physical and chemical instability typical of phospholipid membranes is one of the problems with using liposomes as carriers because it destabilizes the lipid bilayer and destroys the liposomes [110, 112, 113]. Polymers such as polyethylene glycol and its synthetic derivatives that protect liposomes from premature

destruction are used to produce more stable liposomes and prolong their circulation in the blood pool [110, 113, 114].

Nanotechnology has recently played a significant role in the search for innovative PMAs because medical nanotechnological studies are focused on producing a new generation of preparations with more effective drug delivery methods and improved stability [115–120].

Nanoscale structures such as fullerenes and carbon nanotubes were proposed in several studies to be used as containers for medicinal preparations [121, 122]. Fullerenes have unique properties because of their high reactivity resulting from the large number of free carbon valences. Encapsulation in lipid vesicles is one method for administering them [123]. However, pure fullerenes are little suited for biomedical applications because of their insolubility in aqueous solutions. Therefore, functionalization of fullerenes was demonstrated to increase the bioavailability of these compounds and; therefore, make them more efficacious for biosystem research [124]. Carbon nanotubes have increased affinity for lipid structures. They can form stable supramolecular complexes (ensembles) with peptides and nucleic acids [125, 126] and encapsulate these molecules [127, 128]. Nanocomposite polyelectrolyte capsules were used as effective drug delivery vehicles. They were prepared by poly-ion assembly, which consisted of sequential adsorption of oppositely charged polyelectrolytes on the surface of colloidal particles followed by dissolution and removal of the starting template [105, 130]. Capsules of widely varying sizes (from 50 nm to 50  $\mu$ m) can be prepared using this method. Practically any synthetic and natural polyelectrolytes [130, 131], lipid bilayers, inorganic nanoparticles [e.g., Ag, Au, or Fe(II)-oxide nanoparticles], and multivalent metal ions can be chosen as the shell material with controlled thickness and multifunctional walls [132, 133]. The researchers emphasized that the studied capsules had controlled permeability for any low- and high-molecular-mass compounds [134]. Inorganic nanoparticles of magnetite Fe<sub>3</sub>O<sub>4</sub> with highly pronounced magnetic properties were added to the shell composition of such microcapsules during their synthesis so that their movement could be controlled by applying an external magnetic field [129]. However, reports of the application of nanostructures as containers for drug delivery to target cells are still scarce (except for liposomes). Biological safety issues are still insufficiently studied for nanomaterials [135–137]. Toxicity data for fullerenes [137–139] and carbon nanotubes [131–133, 140] from pharmacological tests in animal models are now available.

The principal research results and recommendations for the production of various nanoparticles, primarily medicines, were reported [121–140] and used further to prepare nanoscale derivatives of drugs, including PMAs. Thus, reviews have emphasized that targeted screening of PMA nanoparticles is a promising direction for producing safe derivatives with pronounced antifungal activity [141–144]. A series of nanoscale derivatives of the heptaene macrolide an-

tibiotic amphotericin B were recently prepared by modern nanotechnology methods [145 – 156]. Nanoscale amphotericin B derivatives possessed pronounced antifungal activity and were less toxic and more stable than the starting antibiotics [157 – 164]. Nanoscale nystatin and natamycin (pimaricin) derivatives were investigated [165 – 173] and also exhibited better bioavailability and less toxicity than the starting antibiotics. They were considered promising antifungal drugs for treating candidiasis of various etiologies. Nanoscale derivatives of the tetraene macrolide antibiotics pimarin (natamycin), nystatin A<sub>1</sub>, lucensomycin, and tetramycin B that were coated with the surfactant Tween-80 were prepared by us [174]. Production of the nanoscale tetraene macrolide antibiotic derivatives included two steps of 1) synthesis of the copolymer of D, L-lactide (LD) and polyethylene glycol (PEG) and 2) use of the LD—PEG copolymer to produce nanoscale tetraene macrolide antibiotic derivatives using Tween-80 surfactant. The research found that the nanoscale tetraene macrolide antibiotic derivatives prepared using the developed method could improve considerably the biopharmaceutical properties of these antifungal antibiotics.

#### **Drug resistance of pathogenic fungi and overcoming it using new PMAs**

Systemic administration of antifungal drugs, including PMAs, to treat mycoses led to the development of resistance to them in a series of pathogenic fungi [175 – 178]. Resistance of fungi is known to be natural and acquired. Natural (primary) resistance is characterized by a lack of antimycotic targets in fungal species and is encountered extremely rarely [179 – 181]. In practice, natural resistance is understood to mean that a fungus species remains vital in the presence of an antimycotic at concentrations actually achievable in humans. Acquired (secondary) resistance is understood to mean that separate fungal strains remain vital at those drug concentrations that suppress the main population of pathogenic fungi [179, 181, 182]. Acquired resistance in most instances results from the acquisition of new genetic information or a change of the expression level of autologous genes [183 – 185]. An increase of the minimal inhibitory concentration of a drug and a structural change of the target of antimycotic action as a result of spontaneous mutations in genes coding it are important parameters indicating the development of secondary resistance. This decreases (or eliminates) the ability of the target to bind to the antimycotics [186 – 188].

PMAs are known to exhibit both fungistatic and fungicidal activity due to binding of these antimycotics to ergosterol in the fungal membrane, which leads to destruction of the membrane, loss of the cytoplasm contents, and cell death [4 – 6, 13, 14]. Development of resistance could result from complicated genetic processes leading to changes in membrane component biosynthesis because fungal cell structural elements and not enzymes are the targets of PMA action

[6 – 9, 189]. The probability of such events is relatively low and related to the comparatively low incidence of resistance to PMAs in pathogenic fungi. The biochemical and genetic aspects of resistance to PMAs have been insufficiently studied. However, several researchers support the hypothesis that the ergosterol content in the cytoplasmic membrane is reduced and that of its structural analogs is increased in resistant strains [190 – 194]. Experimental results indicate that new sterols observed in cells of resistant strains are frequently intermediates from ergosterol [191]. Furthermore, new sterols can also be products of circuitous pathways to synthesize the sterol component. Biochemical tests found that lanosterol transmethylation was disturbed in resistant fungal strains. Sterols were synthesized further by a different pathway that did not require methyl transfer [190, 191]. Additional research showed that fungal resistance was a consequence of shielding or reorientation of membrane sites that interact with PMAs [195, 196]. Such changes could result from mutations or phenotypic modifications affecting not the sterols themselves but other membrane components. Some data indicate that phospholipids may be directly involved in the action of PMAs on fungal cells. The magnitude of the damage from PMAs was observed to depend on the membrane phase state, which was determined by the presence of unsaturated bonds in the phospholipid fatty acids [190, 191, 197, 198].

Several researchers noted that resistance to PMAs varied significantly as a function of medium composition and cultivation conditions for yeast and yeast-like fungi [196, 197, 199]. Resistance to PMAs increased as the culture passed from the logarithmic growth phase to steady-state.

One of the fungal resistance mechanisms to the action of PMAs was active elimination (efflux, ejection) of drugs from the fungal cell [197, 200, 201].

Our previous results on chemical transformation of PMAs and literature data from the latest research on the resistance mechanisms of pathogenic fungi to the action of PMAs [6, 10, 13, 15 – 18, 183, 187, 198, 201] showed that the obtained semi-synthetic PMA derivatives were effective against many resistant strains of pathogenic fungi and, primarily, the yeast-like genus *Candida* [45, 47, 49, 202 – 210].

The importance of the search for new antimycotics, including semi-synthetic PMAs that exhibit pronounced fungicidal activity against resistant pathogenic fungi, should be emphasized because the problem of their resistance to the arsenal of antimycotics available to physicians and clinicians has reached threatening levels. This is an important problem for treating mycoses of various etiologies in both developed and developing countries. Therefore, the World Health Organization (WHO) developed an international program called Global Strategy of WHO for Delaying Resistance to Antimicrobial Drugs that is directed at preventing the constantly growing number of pathogenic microorganisms (including fungi) exhibiting resistance to drugs used systemically for many years and those recently implemented into medical practice [211].

### Prospects for medical application of new PMAs for treating invasive mycoses

The wide availability of new medical technologies, diagnostic and therapeutic procedures, cytostatic and immunosuppressive therapies, transplantation, pandemic HIV infections, and progress in treating bacterial infections has increased the immunocompromised patient population with a high risk of invasive mycoses [7, 9, 212, 213]. Invasive mycoses form a group of infection complications due to invasion (penetration) of fungi into various human tissues. According to many researchers, the number of invasive mycoses is continuously increasing. The lethal outcomes associated with them remain very high at 40–90% [214–216]. The main etiological agents of these diseases are *Candida* spp., *Aspergillus fumigatus*, and *Cryptococcus neoformans*. The main outcomes of resistance problems are the clinical inefficacy of many antifungal preparations used to treat mycoses and a change in the fungal pathogen flora, in particular, dominance of yeast-like *Candida* spp. other than *albicans*, e.g., *C. glabrata* and *C. krusei* [1, 9, 217, 218]. Furthermore, a rise in the incidence of invasive mycoses caused by various strains of *Fusarium* spp., *Scedosporium* spp., *Rhizopus* spp., *Mucor* spp., and others was reported. These species are becoming resistant to the most widely used antifungals [7–9, 219–226].

Opportunistic fungal infections in AIDS patients are another important problem in clinical medicine. Human immunodeficiency virus (HIV) infection is a slowly progressing infectious disease resulting from infection by HIV, which affects primarily the immune system [227, 228]. HIV belongs to the family of RNA-containing retroviruses and is classified in the subfamily of lentiviruses, i.e., viruses of slow infections. HIV has selective tropism for T4-lymphocytes (T-helpers-inductors), which seriously disturbs immune reactions and results in the organism becoming highly susceptible to opportunistic infections and tumors that eventually lead to a lethal outcome [229–233]. Cases of acquired immunodeficiency syndrome (AIDS), which is the final stage of HIV-infection progression, have now been recorded globally in most countries. Illnesses and infections to an even larger extent have risen consistently over the past 20 years and reached gigantic numbers. This led to the conclusion that HIV-infection could be characterized as a pandemic. The WHO designated the battle against AIDS as a high priority problem with global significance [4–6, 10–15, 234, 235].

Multi-year studies indicated that AIDS enabled protozoal, fungal, bacterial, and viral opportunistic infections that were the main cause of lethal outcomes [7–9, 16–20]. Yeast-like *Candida* fungi should be identified first among fungal infections causing opportunistic illnesses because they are commonly distributed in HIV patients and can cause clinical forms of surface and deep mycoses (candidiasis) [4–6, 10, 11, 179]. According to the latest data, there are ~200 *Candida* species, only some of which are pathogenic. Four species dominate in humans, i.e., *C. albicans*, *C. glabrata*,

*C. krusei*, and *C. tropicalis* [236–239]. These yeast-like fungi produce several toxic substances and other aggressive factors such as endotoxins, enzymes (phospholipase, proteinase, collagenase), and cell parts [179, 237, 238]. The interactions of fungi with cells take various forms from surface candidiasis not associated with host-cell (carrier) destruction to penetration of fungi into the bloodstream with development of candidemia and formation of multiple infections in internal organs.

Other important opportunistic fungi include 1) *Cryptococcus neoformans*, which causes cryptococcosis that leads to infections of the lungs, bone marrow, lymph nodes, liver, and joints, and 2) *Aspergillus fumigatus*, which is responsible for aspergillosis of the lungs, brain, thyroid, spleen, and kidneys [240–246]. Furthermore, cases of other opportunistic fungal infections in AIDS patients such as histoplasmosis, blastomycosis, zygomycosis, and paracoccidioidomycosis have been reported [247–253].

In this respect, use of PMAs with broad spectra of antifungal activity for prevention and therapy of invasive mycoses and opportunistic fungal infections in AIDS patients is very significant. However, as already noted above, the therapeutic efficacy of PMAs used currently in mycological practice is limited for several reasons. The obtained semi-synthetic amphotericin B derivatives were shown by us to exhibit pronounced antifungal activity against several resistant strains of pathogenic fungi such as *C. albicans*, *A. fumigatus*, and *C. neoformans*, which cause opportunistic fungal infections [40–46, 49–51, 60–63, 254–259].

### Mechanism of action of semi-synthetic PMAs

PMAs are membranotropic agents according to available information because they interact with sterols localized primarily in the hydrophobic parts of cellular and model membranes to induce irreversible changes of ion and nonelectrolyte permeability [4–6, 260]. Fungal cells treated with PMAs lose ions and low-molecular-mass compounds ( $K^+$ ,  $i\text{-PO}_4^{3-}$ , carboxylic acids, amino acids, etc.), change respiration rate, and slow protein synthesis. Various research groups found that more significant changes in the membrane structure led to greater growth in the number and size of various components diffusing into the cell and out of it. The process was regulated only by their concentration gradients [1–3, 12–16, 20, 261, 262]. Nucleotides and proteins were observed leaving cells at high PMA concentrations. Molecular dynamics of the mechanism of action of PMAs (mainly using amphotericin B as an example) were studied with great interest [263–265]. The change of ion permeability of fungal cell membranes after interaction with PMAs was determined by the number and position of hydroxyls on these antifungal drugs, which were concentrated in the channel inner cavity [266, 267]. Modern approaches for studying the mechanism of action of PMAs using Langmuir–Blodgett films were reported [268, 269]. The method is based on the

formation on a hydrophilic surface of a monolayer of an amphiphilic compound (amphotericin B) and its subsequent transfer to a solid substrate. The polyol fragment was confirmed to affect the PMA mechanism of action using targeted synthesis of amphotericin B derivatives substituted in the 7-position on the hydrophilic part of the molecule [270]. The mechanism of action of amphotericin B was studied using electron transfer, auto-oxidation, oxidative stress, determination of the electron affinity of an atom, and used of reactive oxygen species [271]. A complex of amphotericin B containing  $^{19}\text{F}$  in the 14- and 32-positions and ergosterol containing  $^{13}\text{C}$  in the 4-, 26-, and 27-positions was synthesized for a more detailed study of the interaction of amphotericin B and ergosterol [272].

The following basic proposals can be made based on existing literature data on the mechanism of action of PMAs [1–3, 12–16, 20–22, 259, 261–272] and considering structural analyses of semi-synthetic PMAs synthesized by us from amphotericin B, nystatin, levorin, pimarin, and lucensomycin [40–50, 53–63]: 1) chemical modification of PMAs resulting in the formation of their semi-synthetic derivatives with a larger number of hydroxyls than the starting drugs obviously facilitates faster and more widespread formation of channels through which fungal cell structural components diffuse; 2) the presence in modified PMAs of new functional groups such as phosphate, phosphonate, and fluorinated organic and organosilicon probably leads to many interactions with fungal cell membrane sterol sensitive sites. This increases their reorientation and, as a result, the additional permeability for structural components. However, special biological studies including the use of modern methods of molecular biology, medical microbiology, and pharmacology are required to confirm these proposals.

### Structure – activity relationship for semisynthetic PMAs

Statistically significant correlations between structural features and biological properties were found for various classes of drugs, including for PMAs [3, 13, 189, 193]. Relationships between the structures of various PMAs and their antifungal activity were recently studied by several research groups [23–25, 273–275].

The structure – activity relationship of the semi-synthetic PMA antifungals prepared by us was also studied. Thus, a study of the relationship between the chemical structures of *N*-benzyl amphotericin B derivatives and their antifungal activity found that compounds with halide atoms in the phenyl *para*-position were most active [59]. Derivatives containing alkyl or no substituents in the *para*-position were least active. An analogous trend was noted for *N*-benzyl pimarin derivatives [61]. An analysis of the structure—activity relationship of antifungal hydrophosphoryl derivatives of levorin [40], nystatin [41], amphotericin B [42], mycoheptin [43], pimarin [44], and lucensomycin [45] containing various substituents in the phenyl *para*-position found the same

trend, i.e., compounds with halides on the phenyl ring, primarily Br or F, had the highest antifungal activity. Organophosphorus derivatives (phosphates or phosphonates) of PMAs [40–50] were shown by us to have the greatest antifungal activity of the functionally substituted PMAs such as fluorinated organic [54–56], organosilicon [57, 58], *N*-benzyl [59–62], and *N*-aryl derivatives [63] against both test cultures and clinical strains of various classes of pathogenic fungi and yeast-like fungi of the genus *Candida*.

### Development of an automated intellectual information system

An analysis of medical information systems and bioinformatics development pathways showed that various types of information systems are used to find new directions in highly efficient synthesis and manufacturing of drugs, including for treating various diseases including fungal infections [276–284].

The synthesis of new efficacious PMAs and the study of their medical and biological properties constitute a long and costly process requiring input from chemists, biologists, and computer modeling and experimental and theoretical data processing experts [285–290]. The architecture of an automated intellectual information system (AIIS) aimed at various users, i.e., synthetic chemists, biotechnology engineers, physicians and clinicians, and medical information experts, and systems programmers was developed by us to shorten the times for research and analysis of existing practical and theoretical data [50, 210, 291, 292]. The AIIS recommends to synthetic chemists a selected direction for chemical modification of PMAs; to the physician and clinician, a selection of PMAs and their semi-synthetic derivatives with given characteristics considering the health of the patient. The developed interfaces enable information experts and engineers to supplement the system with data about newly synthesized and modified antibiotics. The AIIS architecture is a machine software set including PMA derivative synthesis apparatuses, instruments for establishing their structures, a laboratory for conducting biological tests, and a computer client—server system loaded with applied software developed by us [293–295]. The software structure includes a subsystem for developing the documentation for laboratory regulation of PMA derivatives and a subsystem for intellectual data analysis to select highly efficacious PMAs based on neuronal networks. The information module includes a database of rules for evidence-based selection of antifungal drugs and patient and user databases. Therefore, the proposed AIIS architecture and its software enable the synthesis parameters for new PMA derivatives with improved medical and biological properties and great potential for applications in medical mycology to be rationally selected from an intellectual analysis.

Chemical modification of PMAs was used to prepare a series of semi-synthetic derivatives with improved pharma-

cological and biopharmaceutical properties and pronounced activity against various fungal infections.

An analysis of the reasons for fungal pathogen resistance led to the conclusion that studies of the structure and functions of the cellular membranes of these microorganisms are very important for developing measures to overcome the drug resistance of pathogenic fungi and for a deeper understanding of the mechanism of action of these antifungal antibiotics.

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