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Multitarget antibacterial hybrids

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Abstract

Antimicrobial resistance (AMR) constitutes one of the foremost threats to global public health in the XXI century: according to the data of the World Health Organization for 2025, one of the six laboratory-confirmed bacterial infections exhibits resistance to standard antibiotic therapy, with annual resistance rates increasing by 5–15 % across more than 40 % of pathogen–antibiotic combinations. Amid the declining efficacy of single-target antibiotics, the development of multitarget hybrid antibacterial agents – single molecules incorporating two or more pharmacophoric moieties capable of simultaneously engaging distinct bacterial targets – has gained critical relevance. This review systematically outlines the principal strategies for designing such hybrids: linked, fused, and merged pharmacophores. It also addresses key pharmacokinetic and toxicological considerations, limitations inherent to conventional combination therapy, and the advantages conferred by hybrid molecules, including a unified pharmacokinetic profile, elimination of chemical incompatibilities between components, and simplified dosing regimens. Particular emphasis is placed on the mechanisms of action of hybrid compounds. Several reviewed hybrids demonstrate low minimum inhibitory concentrations, reduced frequencies of spontaneous resistance emergence, and favourable fractional inhibitory concentration indices (FIC ≤ 0.5), underscoring the therapeutic potential of this approach. Some examples of compounds are highlighted for their potent activity against diverse resistant bacterial strains and biofilms. A number of hybrid compounds have successfully advanced through clinical trials (TNP-2092, TNP-2198, cefilavancin, DNV-3837).

Keywords: antimicrobial resistance, multitarget antibiotics, hybrid molecules, pharmacophore, antibacterial activity

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INTRODUCTION

Antibiotic resistance is one of the ten critical dangers to public health in the XXI century. According to the data of the World Health Organisation for 2025, for one in six laboratory-confirmed cases of bacterial infections, application of the standard antibiotic-based therapy turned out to be ineffective because of the resistance of infectious agents. Annual increase in resistance is 5–15 % over more than 40 % of pathogen–antibiotic combinations [1].

Modern medicine is essentially dependent on antibiotics not only to treat infections but also to prevent complications after surgical interventions, chemotherapy, organ transplantation and other invasive procedures. The loss of their efficiency brings threats to the achievements of the entire public health system: even planned surgeries or childbearing can again pose a mortal threat [2, 3].

Predictions of the consequences of the absence of effective measures against antibiotic resistance are extremely anxious: according to the study published in The Lancet in 2024 [4], infections caused by antibiotic-resistant strains can become the reason of more than 39 mln deaths during the period from 2025 to 2050. The annual number of direct lethal outcomes due to resistance to antibiotics will increase from 1 mln in 2025 to about 1.91 mln by 2050. If the cases in which resistance to antibiotics is an accompanying factor, the total number of related deaths can exceed 8 to 10 mln per year. These figures surpass the mortality from cancer and emphasise the urgent necessity to expand the range of antibacterial agents [4].

Under these conditions, development of new antibacterial agents, innovative approaches and rational strategies able to overcome the existing resistance mechanisms and provide sustainable efficiency becomes not just a research problem but also an imperative for modern medicine.

For a long time, the search and development of new antibiotics gave preference to substances that affected only one specific target. A general opinion was that molecules with a sole target are ideal antibiotics because their high specificity to the target is associated with not so many side effects. This resulted in the preferable usage of a target-based approach in the discovery of antibacterial agents, while the compounds aimed at multiple or complex targets were considered to be non-specific and unsuitable for subsequent development. However, it has been demonstrated during the recent decades that resistance to antibiotics with only one specific target develops too rapidly, and it has been recognised that agents aimed at more than one target deserve attention, and they should be used because of the lower rate of resistance development [5–7].

In response to the accelerating emergence of resistance to monotarget antibiotics, clinical practice extensively employs combined therapy, with simultaneous administration of two or more antibacterial agents. The major theoretical substantiation of this approach lies in the fact that the probability of simultaneous emergence of pathogen resistance to several agents is substantially lower than to a single one [8]. In addition, definite combinations may cause synergism, when the total antibacterial activity exceeds the additive activity [8, 9].

A typical example of the combination of two antibiotics is the co-administration of sulphanilamides and trimethoprim: the former agent inhibits dihydropteroate synthetase, while the latter one inhibits dihydrofolate reductase, thus blocking up two sequential stages of folate synthesis [10]. Another widespread combination type is antibiotic–adjuvant, where the second component possesses its own weak antibacterial activity or does not possess any at all, but it enhances the action of the main preparation. An example may be a combination of amoxicillin with clavulanic acid, which inhibits β-lactamase thus protecting the antibiotic from enzymatic hydrolysis [11].

At the same time, combined therapy is conjugated with a series of substantial pharmacological and clinical limitations.

The incompatibility of pharmacokinetic and pharmacodynamic profiles of the components often prevents synergism *in vivo*, even if it is observed *in vitro*. One of the antibiotics can be rapidly metabolised or excreted, have a different distribution over tissues, or differ in the rate of binding with the target, which causes inconsistent presence of both agents in the site of infection in therapeutic concentrations [11, 12].

Combinations may enhance toxicity. For example, a combination of aminoglycosides with cephalosporins is associated with an increased risk of renal toxicity, which limits their clinical application [13, 14].

Chemical incompatibility of agents is also possible. For instance, if certain aminoglycosides (for example, gentamycin or tobramycin) are mixed with β-lactams (for example, penicillin, ticarcillin or carbenicillin) in the same solution for infusion, inactive complexes are formed, which reduces the efficiency of both agents [15, 16].

In addition, combined therapy brings complications into the dosing regimen, reduces the patients' compliance to treatment and increases the cost of therapy [17].

Taking into account the listed limitations and shortcomings of combined therapy, increasing attention has been paid in recent years to multitarget hybrid antibacterial agents (hybrids). A hybrid is a united molecule containing two (or

more) pharmacophore fragments that can interact with different targets after penetration into cells [17, 18].

This approach allows combining the advantages of antibiotic combinations and avoiding their key disadvantages:

– provision of the united pharmacokinetic profile;

– elimination of negative interactions between components;

– reduction of the risk of chemical incompatibility;

– simplification of dosing.

In the present review, the major approaches to the design of multitarget antibacterial agents based on hybrid structures are considered, along with recent achievements in this area.

CLASSIFICATION OF ANTIBACTERIAL HYBRID AGENTS

Multitarget hybrids can be divided into several groups based on their chemical structure. Judging from the presence or absence of a linker between two pharmacophore groups, they are divided into two classes: linker-containing and linker-free. Hybrid molecules without linker groups, in turn, are divided relying on the degree of pharmacophore overlap into fused and merged structures (Fig. 1) [18, 19].

The choice of a certain strategy for the development of hybrid structures is to a high extent determined by the possibility to modify a fragment of molecular structure without the loss of antibacterial properties. Antibiotics of many classes contain reactive groups which can be modified without any loss or with only an insignificant decrease in their antibacterial activity. For instance, among antibacterial hybrids described in the literature, most of the structures have been developed on the basis of fluoroquinolone antibiotics – inhibitors of DNA-topoisomerase. It is easy to introduce substituents at the 7th position of quinoline structure without any loss of antibacterial activity, which opens broad possibilities to design hybrid molecules (Fig. 2). In addition, the antibiotics of this class are chemically stable under conditions that are typical for organic synthesis, including a broad temperature range, acidity (pH) variations, and most standard solvents, which makes it possible to carry out multistage modifications. Therefore, antibiotics containing these reactive groups in their structure are ideal precursors for the synthesis of hybrid structures using a linker group.

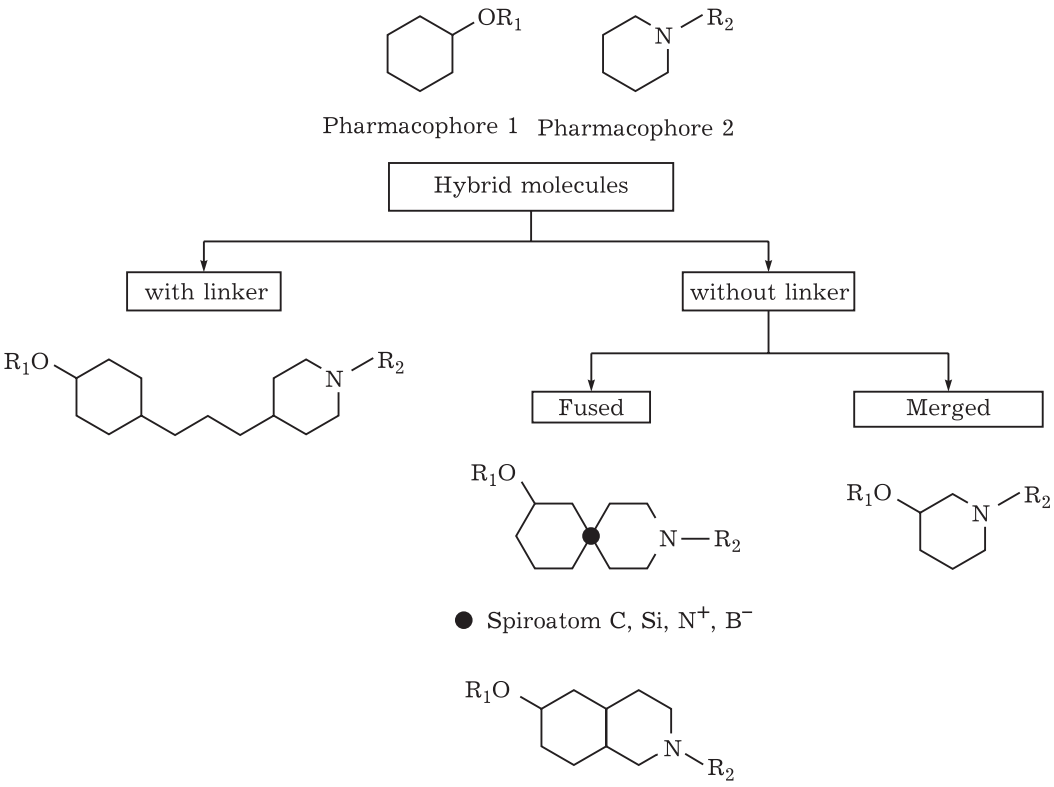


Fig. 1. Different types of pharmacophore combinations.

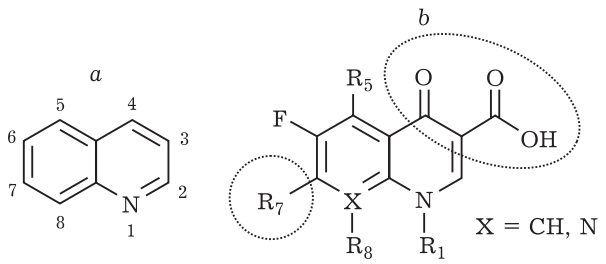


Fig. 2. Structural formula and numbering of quinoline atoms (*a*). The general structural formula of fluoroquinolones (*b*): 4-oxo-3-carboxyl fragment playing the key role in binding with DNA-topoisomerases is marked with an oval, and the substituent at position 7 is marked with a circle.

Another class of compounds possessing antibacterial activity includes synthetic analogues of antimicrobial peptides – cationic amphiphiles. The structure of cationic amphiphiles contains one or several positively charged groups and lipophilic fragments. These compounds interact first of all with bacterial cells, promoting the penetration of hybrid structures into cells. In addition, they can cause disturbance of transmembrane potential, cytoplasm leakage, and finally cell death [20]. The diverse architecture of cationic amphiphiles allows easier implementation of hybrid molecule synthesis by pharmacophore fragment fusing or merging.

LINKED HYBRID STRUCTURES

To make stable hybrids, it is necessary to use a linking group based on chemical bonds that would not be affected by enzymatic and non-enzymatic cleavage in the host organism.

Examples of compounds of this kind are hybrids based on two antibiotics – trimethoprim and various fluoroquinolones linked through alkyl groups (ethylene, propylene, and propane-1,3-diyl) [21]. Biological activity of the obtained compounds was evaluated by measuring the minimum inhibitory concentration (MIC) against two strains of gram-positive staphylococci (*Staphylococcus aureus* and *S. epidermidis*) and gram-negative *Escherichia coli*. The strains used in the work were *S. aureus* and *E. coli* sensitive both to trimethoprim and to ciprofloxacin, one strain of *S. aureus* sensitive to trimethoprime but resistant to ciprofloxacin, and one strain of *S. epidermidis* sensitive to ciprofloxacin but resistant to trimethoprime. The activities of the obtained compounds were compared with the activities of individual drugs (ciprofloxacin, trimethoprime) and their equimolar mixture. The antibacterial activity of all hybrid compounds turned out to be substantially higher than the activity of trimethoprime and comparable with the activity of ciprofloxacin, the most active compound was BP-4Q-002 (Fig. 3, *a*). It should also be noted that several hybrids remained active against strains resistant to one of the parent antibiotics, displaying superior activity compared to the corresponding equimolar mixture. There are also published data on the hybrids of fluoroquinolones with various fravonoids in which pharmacophores are also bound through the ethylene linker [22]. Flavonoids possess a broad biological activity range, there are experimental confirmations that flavonoids efficiently inhibit efflux pumps in bacterial cells. Activity of the resulting compounds was evaluated against the multi-resistant *E. coli* strain, tetracycline-resistant *Bacillus subtilis* strain, methicillin-resistant *S. aureus* strain and amphotericin B-resistant *Candida albicans* strain. The most active agent was determined to be the hybrid composed of flavonoid naringenin and ciprofloxacin (see Fig. 3, *b*), demonstrating activity levels 8, 43, 23 and 88 times higher against the listed strains, respectively, in comparison with ciprofloxacin. The activity of this hybrid against DNA-gyrase of *E. coli* is 25 times higher, and the extent of outflow from cells is about 5 times lower in comparison with ciprofloxacin. The most evident explanation of these data is that the incorporation of a flavonoid into the fluoroquinolone structure to form the hybrid compound may render inhibiting activity against efflux pumps or at least prevent the compounds themselves from becoming their substrate.

The authors of [23] describe the synthesis and biological activity of various hybrids of ciprofloxacin with isatin and its derivatives. Isatin is an endogenous compound detected in many organisms, it possesses a broad range of biological activity (antibacterial, anticancer, anti-HIV, antimalarial and antituberculous). The antibiotic was combined with isatin using a propane-1,3-diyl linker. Ciprofloxacin was modified both at the amino group of the piperazine ring and at the carboxyl group to form bis-isatin hybrids (Fig. 4). Antibacterial activity of the obtained compounds was evaluated against methicillin-sensitive and methicillin-resistant strains of gram-positive *S. epidermidis* and *S. aureus*, the strains of gram-negative *Enterococcus faecalis* and *Enterococcus faecium*, and compared with the activity of ciprofloxacin and levofloxacin. The antimycobacterial activity of the compounds was also assessed against the strain H37Rv and multiresistant strain of *Mycobacterium tuberculosis*, and compared with the

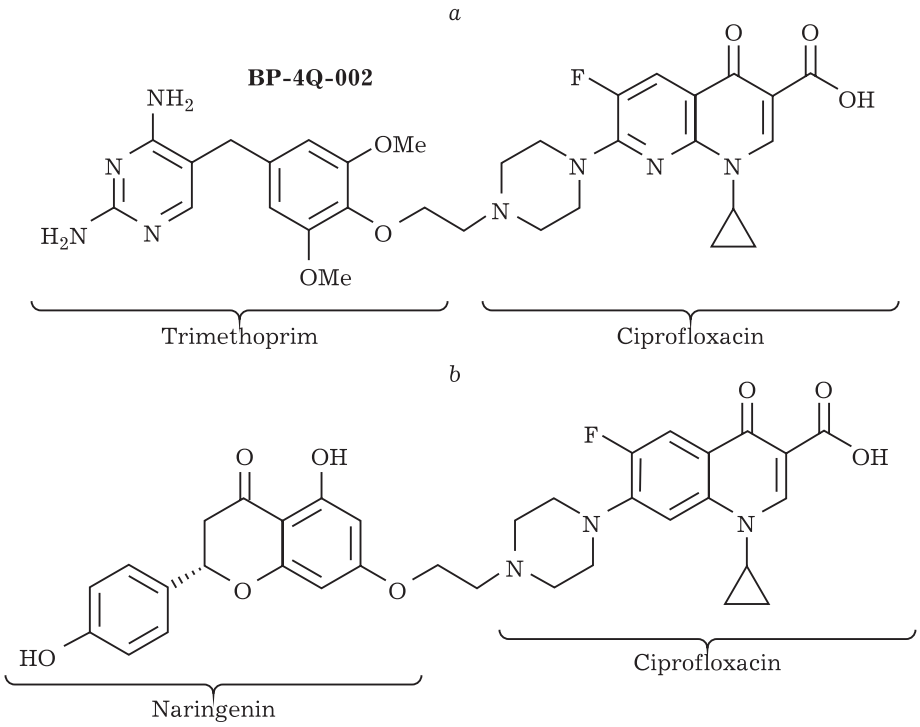


Fig. 3. Structural formulas of the hybrids with ethylene linker group: *a* – hybrid of trimethoprim and fluoroquinolone (BP-4Q-002); *b* – hybrid of naringenin and ciprofloxacin.

activity of ciprofloxacin, isoniazid and rifampicin. Finally, it has been demonstrated that bis-isatin hybrids (see Fig. 4, *c*, *d*) possess substantially lower activity in comparison with mono-isatin hybrids (see Fig. 4, *a*, *b*) and reference compounds, which is explained by the key role of non-modified 4-oxo-3-carboxylic fragment (see Fig. 2) of quinoline antibiotics for their antibacterial activity. The activity of mono-isatin hybrids against gram-positive bacteria turned out to be higher on average than against gram-negative bacteria. Among these molecules, the highest activity was demonstrated by the hybrid with the following substituents: R_1 = Me; R_2 = NOMe (see Fig. 4, *b*).

Cadazolid (Fig. 5, *a*) is a hybrid of ciprofloxacin derivative and tedizolid residue [24]. Tedizolid is a derivative of 1,3-oxazolidin-2-one, which is able to inhibit translation in bacteria by integrating into the P-site on the 50S ribosomal subunit and blocking peptidyl-tRNA transfer from A-site to P-site. Pharmacophore parts in the hybrid structure are linked through a methylene bridge. It has been determined during the studies that the frequency of spontaneous resistance to cadazolid was 1–4 orders of magnitude lower than in reference antibiotics. Thus, a powerful translation inhibitor with weakly pronounced inhibition of replication was developed. In 2018, the third phase of the clinical trial of cadazolid for the treatment of infections caused by *Clostridioides difficile* had been completed. However, in spite of the fact that cadazolid proved itself to be an efficient translation inhibitor *in vitro* (in particular against linezolid-stable strains), the level of DNA-gyrase turned out to be lower in comparison with ciprofloxacin and moxifloxacin. After analysis of the results of *in vivo* tests, further advancement was ceased because the hybrid was inferior to vancomycin in therapeutic efficiency [25].

The pair of compounds DNV-3837 / DNV-3681 (see Fig. 5, *b*), similarly to cadazolid, are hybrids based on a ciprofloxacin derivative and linezolid, a derivative of oxazolidine. DNV-3837 is a water-soluble compound, rapidly dephosphorylised after intravenous injection, with the formation of DNV-3681, which is the active form of this hybrid. Preclinical trials have shown that DNV-3837 is efficient against 114 different clinical isolates of *C. difficile*, including hypervirulent *C. difficile* NAP1 strain [26]. The efficiency of DNV-3837 exceeds the efficiency of most standard antibiotics, including vancomycin, metronidazole and fidaxomicin. Moreover, DNV-3837 was determined to be active against *C. difficile* isolates stable to both moxifloxacin and linezolid [27]. In 2022, the second phase of the clinical trial (NCT03988855)

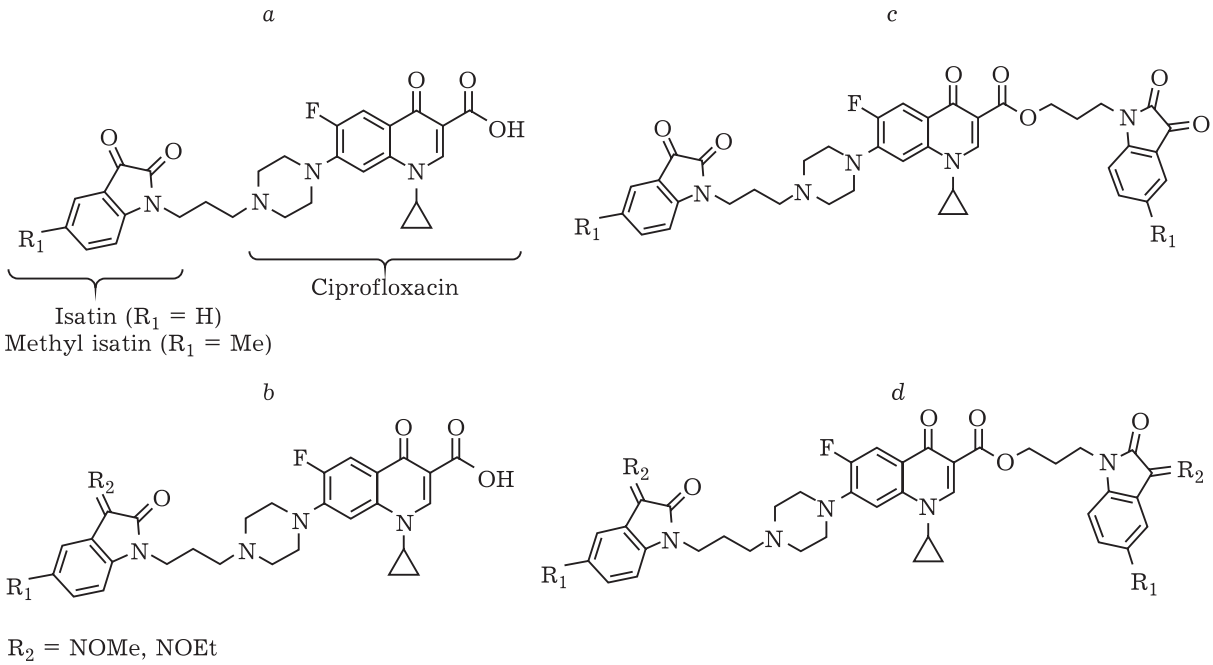


Fig. 4. Structural formulas of ciprofloxacin hybrids with isatin and its derivatives, with propane-1,3-diyl linker. Mono-isatin hybrids (*a*, *b*), bis-isatin hybrids (*c*, *d*).

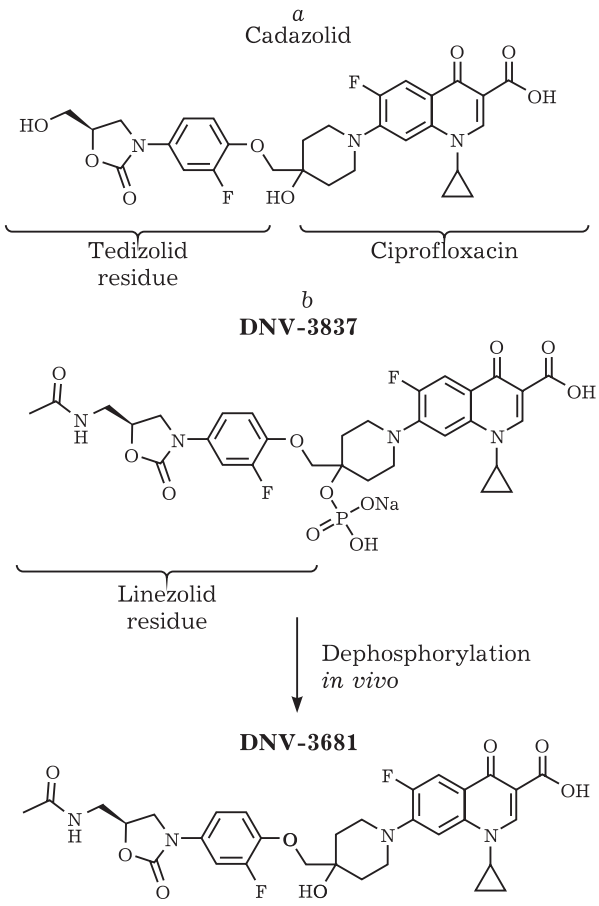


Fig. 5. Structural formulas of cadazolid (*a*) and compounds DNV-3837 / DNV-3681 (*b*).

of DNV-3837 for the treatment of infections caused by *C. difficile* was completed, however, at present there are no actual data on trial results in open sources.

Attempts to develop antibacterial hybrids based on tobramycin with fluoroquinolones connected with an extended C12 alkyl linker have been described (Fig. 6, *a*) [28, 29]. Tobramycin is an aminoglycoside antibiotic inhibiting bacterial translation by binding with the 30S ribosomal subunit. However, activity investigation showed that the synthesised compounds did not possess full-scale bifunctional action: the translation inhibiting activity of the tobramycin fragment is lost, while the replication inhibiting activity of the fluoroquinolone fragment is only partially preserved. It turned out that these hybrids possess another effect: they can cause damage to the outer membranes of gram-negative bacteria and dissipate the proton-motive force (PMF). Therefore, they can enhance the action of other antibiotics acting as adjuvants. After that, hybrids of tobramycin with various inhibitors of efflux pumps, amino acid derivatives and polymyxin were obtained (see Fig. 6, *b*–*f*), in which tobramycin acts as a vector. These hybrids have demonstrated a very promising ability to synergism with other antibiotics if used in combination (Fractional Inhibitory Concentration, FIC-index ≤ 0.5), which allowed retrieving their efficiency against resistant strains [30–34].

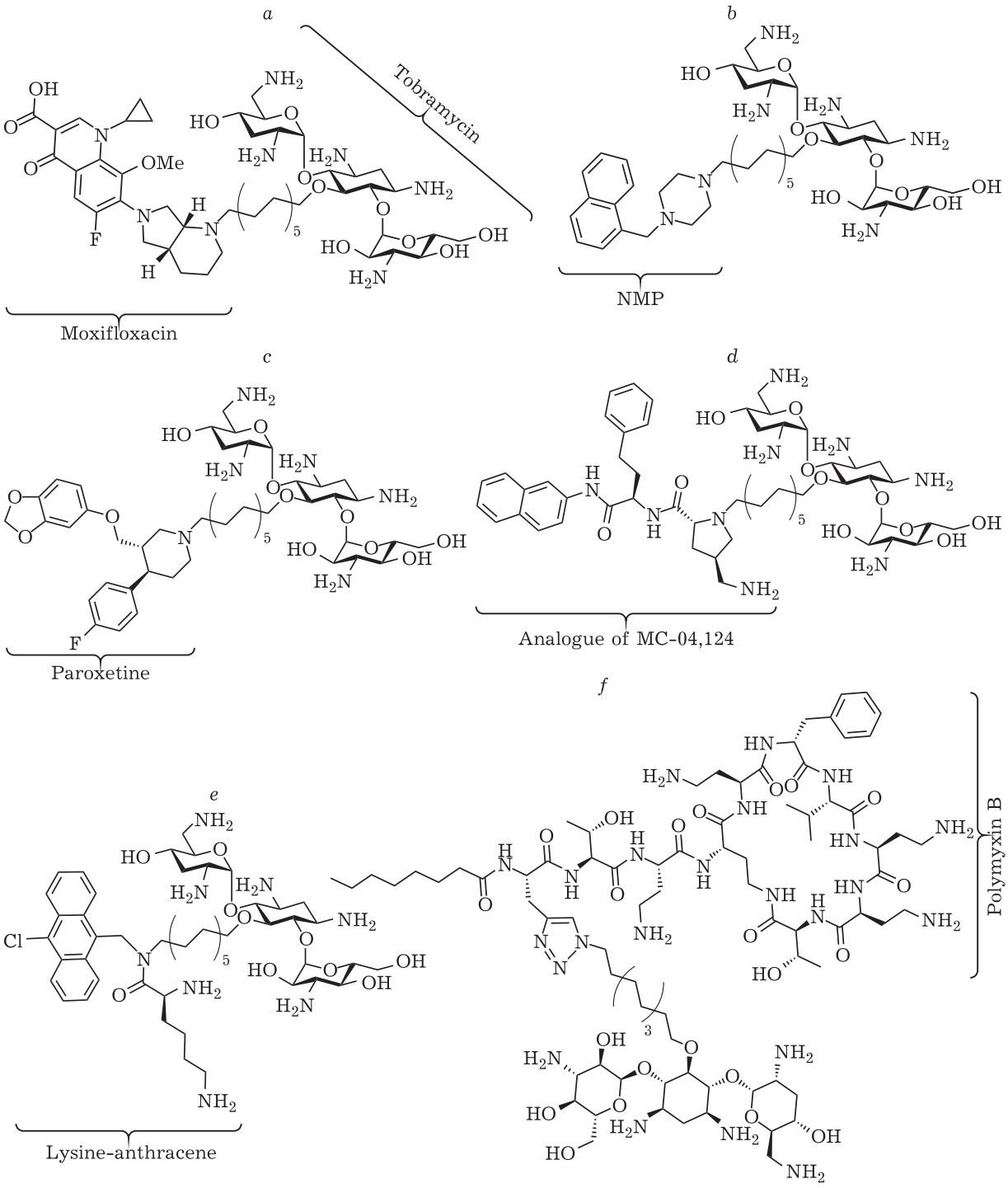


Fig. 6. Structural formulas of tobramycin: with moxifloxacin (*a*), with 1-(1-naphthylmethyl)-piperazine (NMP) (*b*), with paroxetine (*c*), with an analogue of MC-04,124 (*d*), with lysine-anthracene derivative (*e*), with polymyxin B (*f*).

Researchers from Theravance Biopharma, Inc. described the synthesis and studied antimicrobial properties of hybrids based on vancomycin and cephalosporin [35]. Vancomycin is a glycopeptide antibiotic inhibiting the synthesis of bacterial cell walls by binding to the D-Ala-D-Ala peptide moiety. This hybrid was expected to inhibit two sequential stages of cell wall synthesis at a time. Three positions to introduce modification were chosen in vancomycin molecule (Fig. 7, *a*): the amino group of vancosamine (V_V), C-end carboxyl group of the peptide chain (V_C) and the resorcinol residue (V_R). Similarly, three positions have been chosen in the cephalosporin structure to add

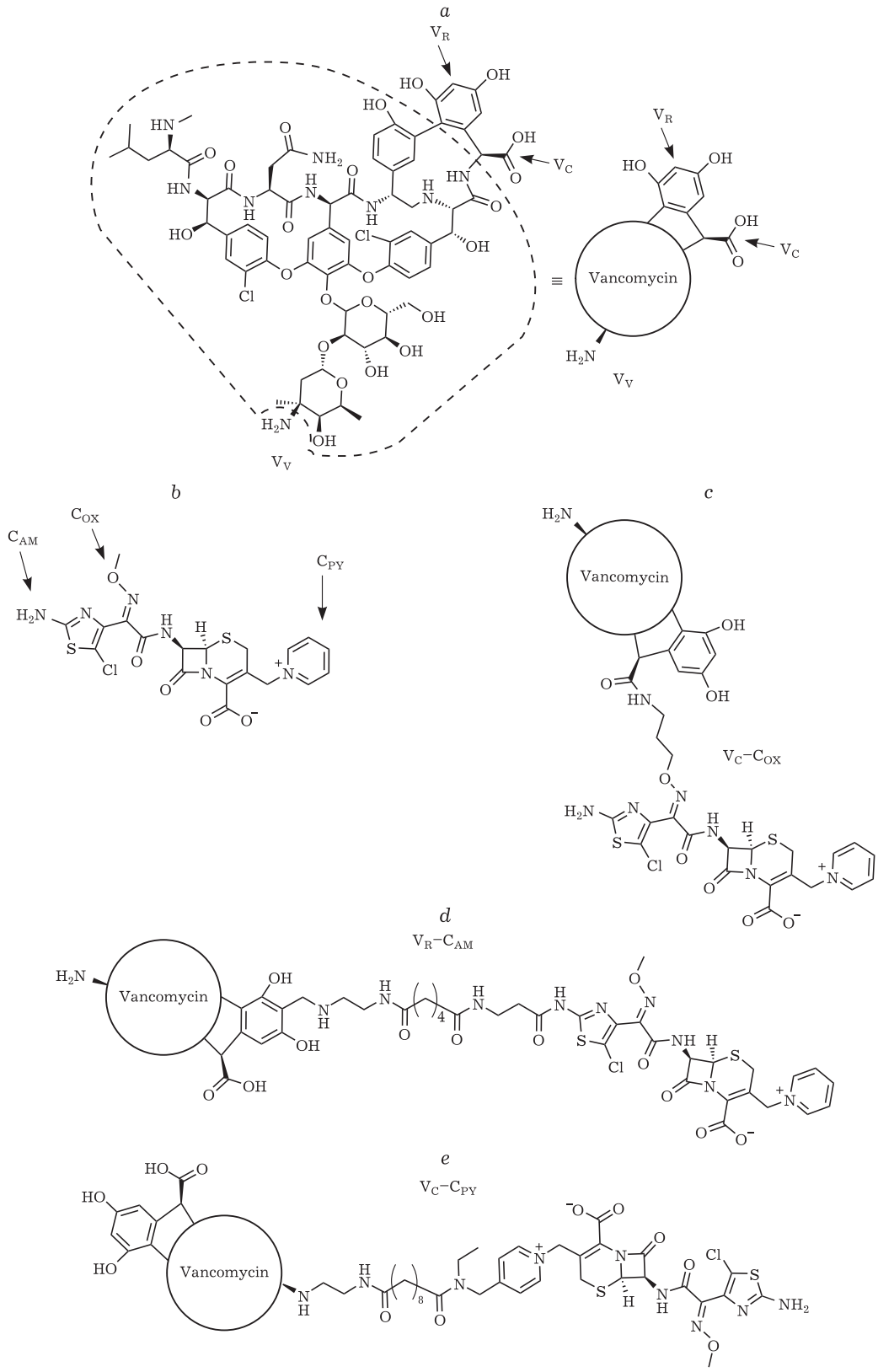


Fig. 7. Structural formulas: *a* – vancomycin (three positions to introduce modification are marked, V_V, V_R and V_{OX}); *b* – cephalosporin (three positions to introduce modifications are marked, C_{AM}, C_{OX} and C_{PY}); *c* – cefilavancin (TD-1792) – hybrid with linker at positions V_C–C_{OX}; *d* – hybrid with linker at positions V_R–C_{AM}; *e* – hybrid with linker at positions V_V–C_{PY}.

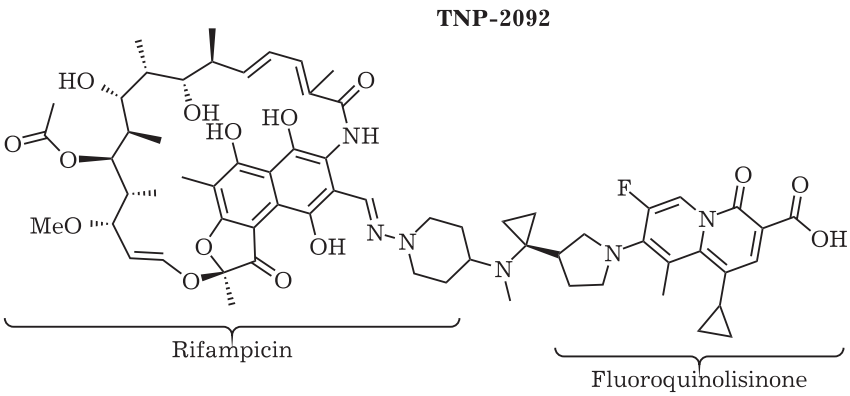


Fig. 8. Structural formula of hybrid TNP-2092.

the linker group: the amino group of amino-thiazole fragment (C_{AM}), the oxime group (C_{OX}), pyridine residue (C_{PY}) (see Fig. 7, *b*). Nine hybrids were synthesised, differing by the sites occupied by the linker group in the structure of both antibiotics. Examples of hybrids with three different methods of pharmacophore linking are shown in Fig. 7, *c*–*e*. All these compounds exhibited high activity against a broad range of gram-positive pathogens, including methicillin-resistant and vancomycin-resistant *S. aureus* strains, which indirectly confirms the bifunctional method of action. The highest antibacterial activity *in vitro* and high efficiency *in vivo* in the experiments with mice, in comparison with vancomycin, was demonstrated by the hybrid with propane-1,3-diyl linker attached at V_C–C_{OX} positions (see Fig. 7, *c*) [35–39]. At present, this hybrid, known as TD-1792 or cefilavancin, is commercially available after clinical trials.

Compound TNP-2092 (Fig. 8), developed by TenNor Therapeutics Ltd., is a hybrid of rifampicin and fluoroquinolone, developed for more efficient therapy of persistent bacterial infections [40]. Rifampicin is a broad-spectrum semi-synthetic antibiotic inhibiting DNA-dependent RNA-polymerase. A series of hybrids based on rifampicin were developed, synthesised and studied in order to discover a multitarget compound that would exhibit a high level of activity against persistent pathogens and at the same time minimise the development of resistance to rifampicin. Compound TNP-2092, with the linker group containing cyclopropyl fragment, was detected to be the most effective one. Its bactericidal activity *in vitro* against the methicillin-sensitive *S. epidermidis* strain was determined to be higher by a factor of 2 and 31, against methicillin-sensitive *S. epidermidis* strain – by a factor of 2 and 500, and against *Streptococcus pneumoniae* – 2 and 17, respectively, in comparison with rifampicin and ciprofloxacin. TNP-2092 inhibits three key bacterial enzymes: RNA-polymerase, DNA-gyrase and topoisomerase IV, which ensures the high activity of this compound even with respect to biofilms [41]. This compound retains activity against strains resistant to rifampicin and fluoroquinolones because it is not a substrate for efflux pumps, which often provide resistance to fluoroquinolones [42]. The incidence rate of resistance to TNP-2092 in the wild type of *S. aureus* is very low ($<1 \cdot 10^{-12}$), which is substantially lower than the value for rifampin ($2.9 \cdot 10^{-8}$) and ciprofloxacin ($5 \cdot 10^{-9}$) [43]. In 2020, TNP-2092 successfully completed the second phase of clinical trials for the treatment of acute bacterial infections of the skin and skin structures. At present, TNP-2092 is in the first and second phases of clinical trials to evaluate the safety and pharmacokinetic profiles, for the treatment of early or acute hematogenous infection of joints (NCT06889701).

In [44], a series of ciprofloxacin hybrids with neomycin B, an aminoglycoside antibiotic, bound by various linker groups formed by azide-alkyne cycloaddition, has been presented. Neomycins are translation inhibitors due to their ability to bind with the 30S ribosomal subunit. Activity of these hybrids was evaluated against several strains of gram-positive and gram-negative bacteria including kanamycin-resistant *E. coli* strain and methicillin-resistant *S. aureus* strain, and compared with the activity of ciprofloxacin and neomycin B. The most active hybrids are shown in Fig. 9. The hybrids demonstrated higher activity than neomycin B but lower than ciprofloxacin. At the same time, these compounds were ~18–31 times more active in inhibiting DNA-gyrase than cipro-

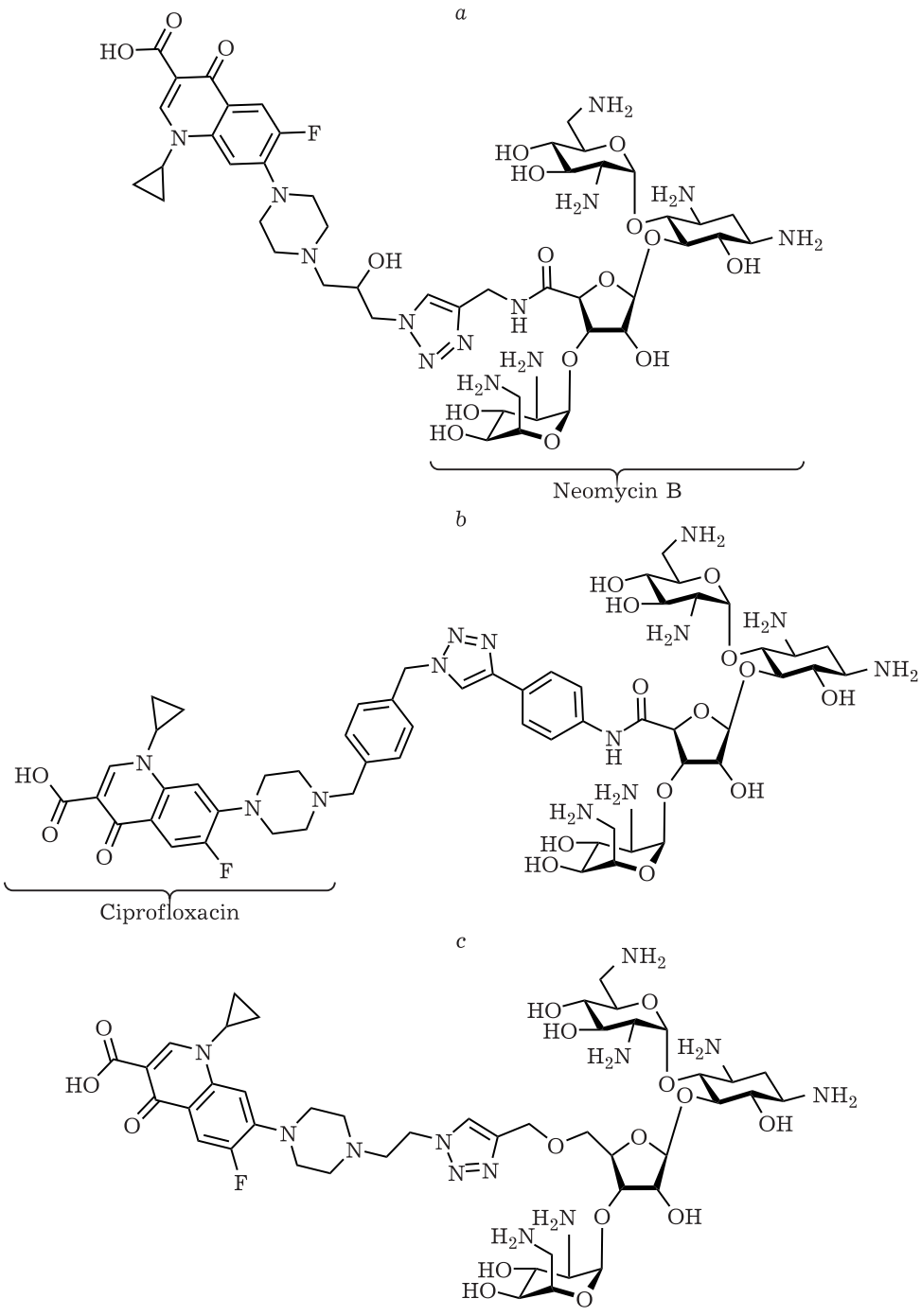


Fig. 9. Structural formulas of hybrids based on ciprofloxacin and neomycin B.

floxacin. So, the lower activity of hybrid structures in comparison with ciprofloxacin in experiments with bacteria is most probably associated with the problems arising when these hybrids penetrate the bacterial cell walls. This can be explained by the relatively high molecular mass of the compounds under investigation, 1100–1200 g/mol. Nevertheless, in an experiment with one of the hybrids (see Fig. 9, *b*) a substantial delay in the development of resistance has been observed for the strains of gram-negative *E. coli* and gram-positive *B. subtilis* in comparison with both neomycin B and ciprofloxacin, as well as with their equimolar mixture.

FUSED HYDRID STRUCTURES

Hybrids formed by fused pharmacophores are those having one common atom or bond. From

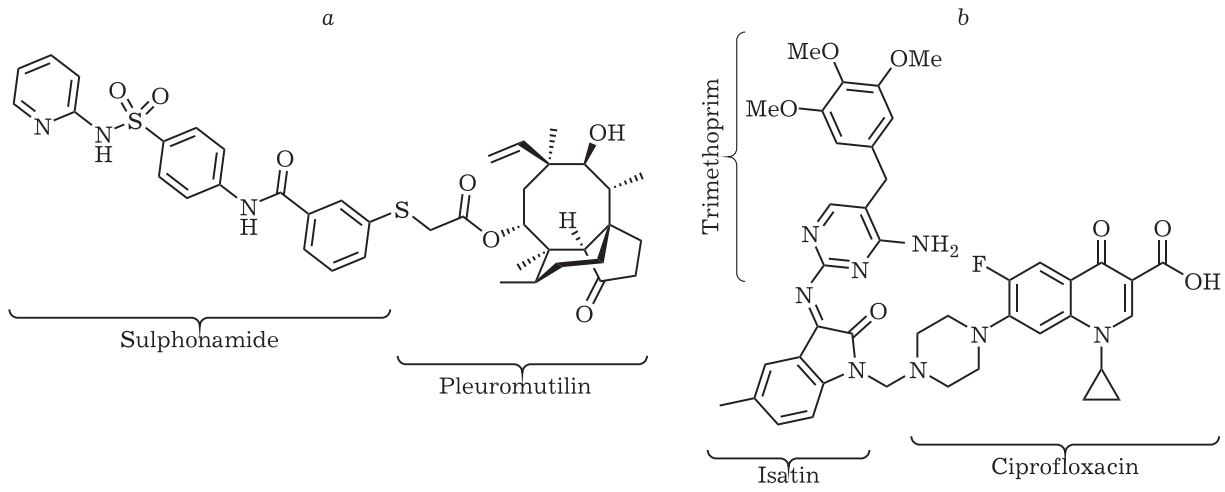


Fig. 10. Structural formulas of the hybrid of pleuromutilin with sulphonamide (*a*) and a ternary hybrid of ciprofloxacin, isatin and trimethoprim (*b*).

the viewpoint of synthesis, design and preparation of these structures is a substantially more difficult task.

It is reported in [45] that a series of hybrids were obtained on the basis of pleuromutilin (translation inhibitor due to binding with the 23S ribosomal subunit) and a sulphonamide antibiotic (an inhibitor of dihydropteroate syntase). The most active hybrid (Fig. 10, *a*) in which pharmacophores are bound through a sulphur atom, has demonstrated more active antibacterial activity against gram-positive *S. aureus* (including MRSA), *Streptococcus equi* and *Mycoplasma gallisepticum* than sulphonamide, and a comparable activity with valnemulin. The activity against MRSA was 31 times higher than that of valnemulin. No information on the studies of the mechanism of action has been published for these hybrids.

The authors of [46] proposed a series of hybrid structures combining ciprofloxacin with trimethoprim and isatin for the therapy of HIV-associated opportunistic infections. The hybrids were determined to be more active against a broad range of pathogenic bacteria in comparison with fluoroquinolones. The structure of the most active compound from the indicated series is shown in Fig. 10, *b*, here trimethoprim and isatin are linked through the nitrogen atom of the guanidine group of trimethoprim.

Another example of hybrids formed by fused pharmacophores is the structures prepared on the basis of ciprofloxacin and tetracationic amphiphilic compounds including two residues of 1,4-diazabicyclo[2.2.2]octane (DABCO) [47]. Cationic amphiphiles containing two DABCO residues, which are themselves bifunctional compounds because they can destroy bacterial membranes and provoke RNA hydrolysis, which provides their high antibacterial activity [48–52]. An example of an amphiphile of this kind is shown in Fig. 11, *a*. To expand the spectrum of bacterial targets, ciprofloxacin was included into the structure of tetracationic amphiphile. In the proposed hybrids, pharmacophores are linked through the nitrogen atom of the piperazine residue of the antibiotic and differ from each other by the length of alkyl fragments between the residues of DABCO and ciprofloxacin. The structural formula of the most active hybrid is shown in Fig. 11, *b*. The results of MIC determination revealed a similar level of activity in comparison with ciprofloxacin. Time-kill kinetics assay against *S. aureus* revealed that the hybrid achieved a bactericidal effect 6 times faster than the reference antibiotic. The multitarget effect of the hybrid compound was confirmed by studies of morphological changes in *S. aureus* under the action of the hybrid, a DABCO-containing amphiphile and ciprofloxacin separately on ultrathin sections using a transmission electron microscope [53].

MERGED HYBRID STRUCTURES

A series of ciprofloxacin hybrids with 3-arylfuran-2(5H)-one, which is a pharmacophore group able to interact with typosyl-tRNA synthetase, is presented in [54]. Both pharmacophores have similar fragments in their structure: a piperazine fragment in ciprofloxacin and a morpholine fragment in the most active derivative of arylfuranone. This fragment was used to combine these two antibacterial compounds (Fig. 12). It has been shown that the resulting hybrids possess

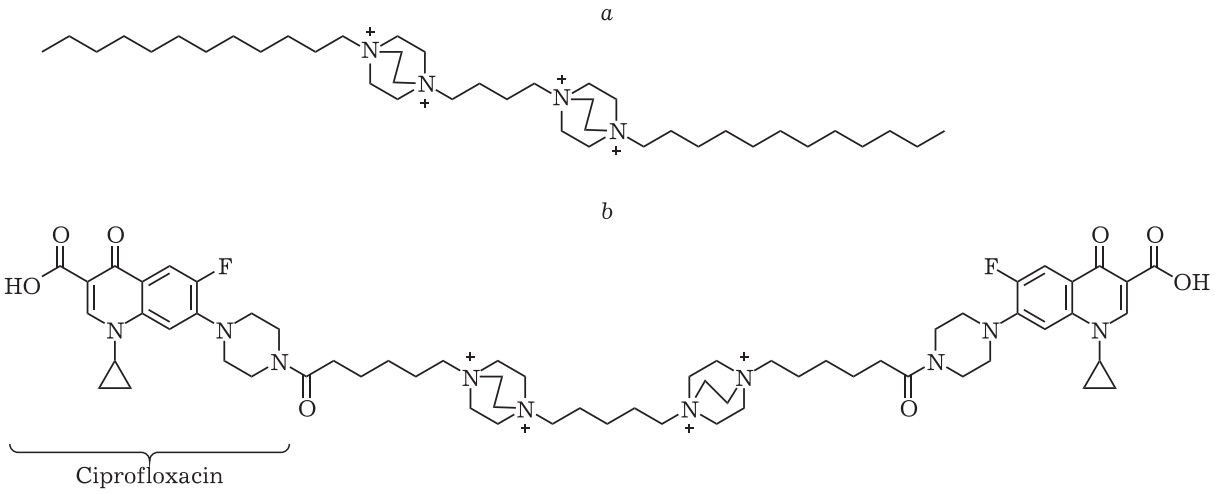


Fig. 11. Structural formulas of the tetracationic amphiphilic compound with two DABCO residues (*a*), the most active hybrid of ciprofloxacin with DABCO-containing amphiphile (*b*).

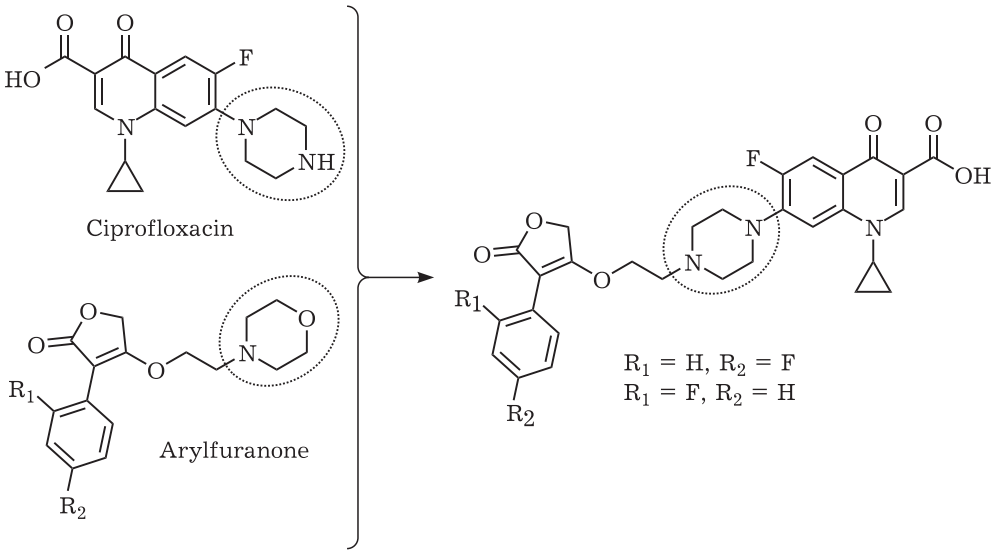


Fig. 12. Structural formulas of ciprofloxacin, arylfuranone derivative and their hybrid. Dash line marks a common similar fragment.

a broad activity range against either gram-positive or gram-negative bacteria. The compounds (based on 3-(2-fluorophenyl)furan-2(5H)-one and 3-(4-fluorophenyl)furan-2(5H)-one) were determined to be the most active ones: 24 times more active than ciprofloxacin against multiresistant *E. coli*, 31 times more active than ciprofloxacin against methicillin-resistant *S. aureus*, 22 times more active than ciprofloxacin against tetracycline-resistant *B. subtilis*. Moreover, it has been shown that these conjugates inhibit DNA-gyrase *in vitro* 3 times more actively than ciprofloxacin, and exhibit a comparable level of activity in comparison with 3-(4-hydroxyphenyl)-4-(2-morpholinoethoxy)furan-2(5H)-one against tyrosyl-tRNA synthetase.

Another example of a hybrid molecule with merged pharmacophore fragments can be TNP-2198 (rifasutenizol) [55], which is a hybrid of rifabutin and metronidazole, by analogy with the previously considered TNP-2092. A common motif of two pharmacophores is the ethylene fragment (Fig. 13). Metronidazole is a derivative of nitroimidazole, antibiotic and antiprotozoal agent able to form nitroxide radicals that damage DNA of most anaerobic bacteria and protozoa. Hybrid TNP-2198 demonstrated higher activity than an equimolar mixture of rifabutin with metronidazole, and it was also active against strains resistant to rifamycins and nitroimidazoles. According to the results of X-ray diffraction analysis, the hybrid molecule interacts through its rifabutin

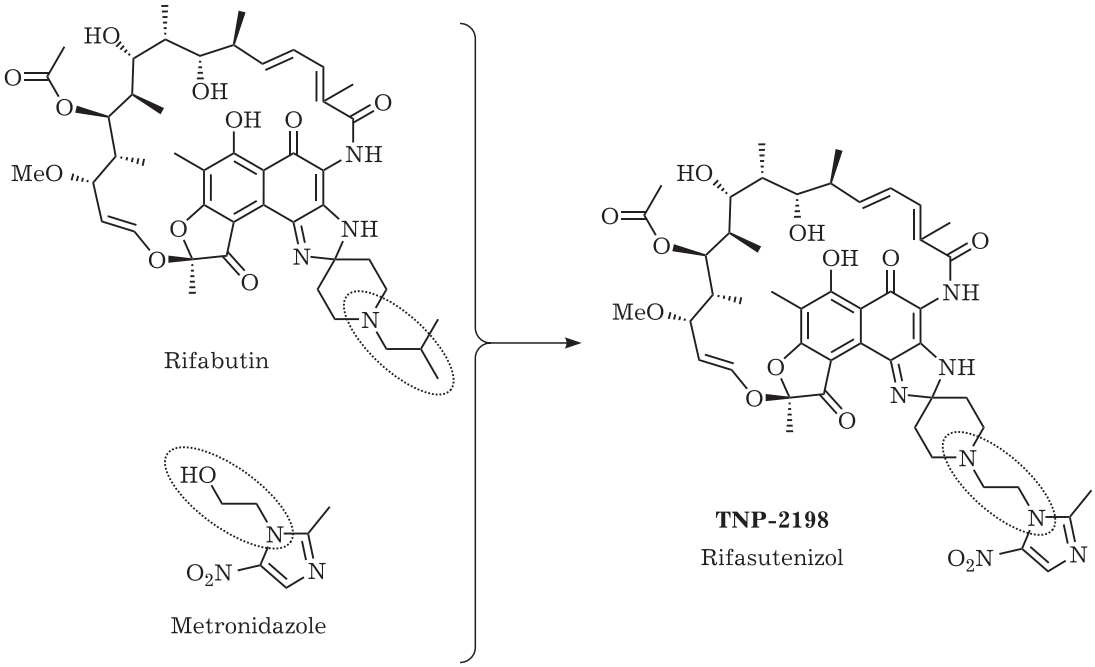


Fig. 13. Structural formulas of rifabutin, metronidazole and their hybrid TNP-2198. Dash line marks the motif belonging to both pharmacophores.

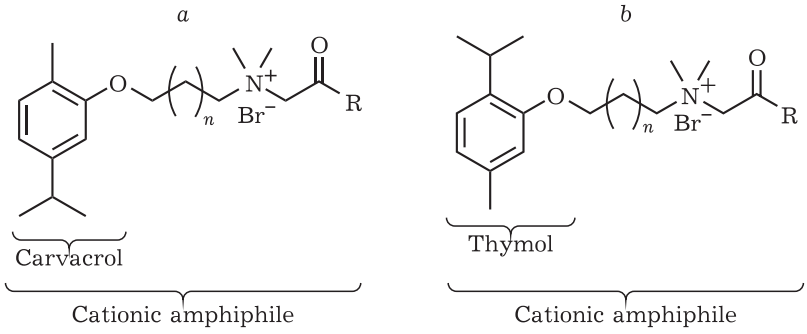
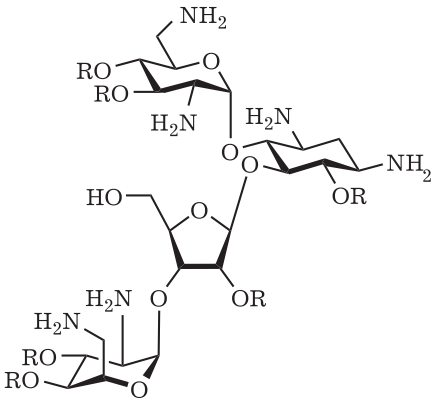


Fig. 14. General structure of hybrids based on a cationic amphiphile with carvacrol (*a*) and thymol (*b*) (n = 1–3; R = primary and secondary amino groups).

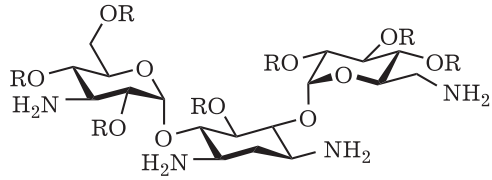
part with the rifamycin-binding site of DNA-dependent RNA-polymerase, while the nitroimdazole part interacts directly with DNA, forming hydrogen bonds with the base. In 2024, compound TNP-2198 successfully completed the third phase of clinical trials for the treatment of infection caused by *Helicobacter pylori*, in combination with rabeprazole and amoxicillin.

Some examples of the structures with merged pharmacophores based on cationic amphiphils and monoterpenes have been described. In [56], a series of compounds is presented, in which monoterpenes carvacrol and thymol form a fragment of the hydrophobic part of cationic amphiphite with common structures shown in Fig. 14. The total number of compounds obtained in the work was 72, and their antibacterial activity was investigated. Most of these compounds demonstrated antibacterial activity against gram-negative (*E. coli*, *Pseudomonas aeruginosa*) and gram-positive (*S. aureus*, *E. faecalis*) microorganisms, including their antibiotic-resistant strains. The most active hybrids demonstrated antibacterial activity within the concentration range of 2–8 μg/mL, while the initial compounds carvacrol and thymol are active in concentrations of 128 μg/mL and higher.

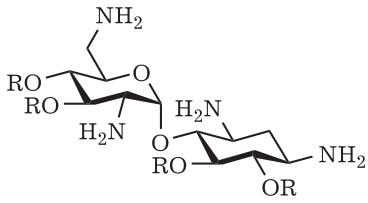
Another example of cationic amphiphils with merged pharmacophores is presented in the series of works [57–59], where aminoglycoside antibiotics neomycin, neamine, kanamycin and amikacin were used as the cationic amphiphile fragments (Fig. 15). The most active antibacterial compounds turned out to be amphiphiles based



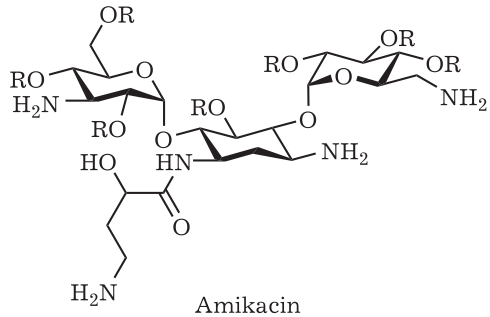
Neomycin B



Kanamycin A



Neamin



Amikacin

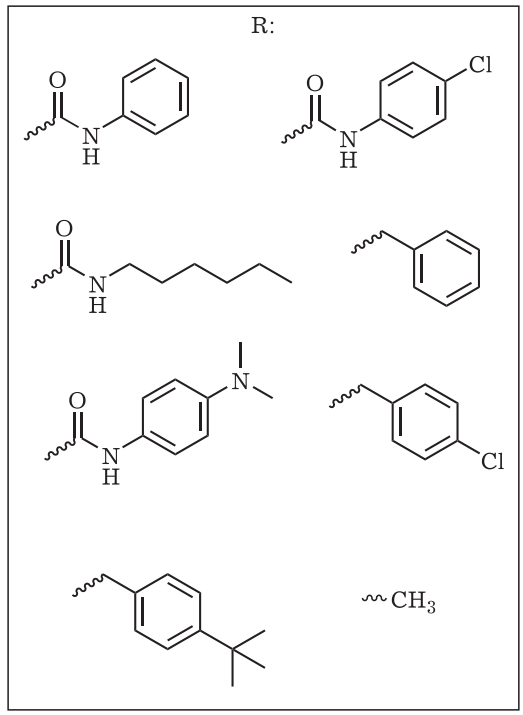


Fig. 15. Structural formulas of amphiphilic derivatives based on aminoglycosides.

on neomycin B, containing alkyl or arylalkyl hydrophobic fragments. These analogues demonstrate 256 times higher antibacterial activity against resistant strains in comparison with neomycin B.

CONCLUSION

Development of multitarget antibacterial compounds is a promising direction to combat the growing resistance of pathogenic microorganisms

to traditional antibiotics. Analysis of modern research shows that the strategy of designing hybrid molecules that combine pharmacophores of two or more classes of antibacterial compounds allows one not only to expand the range of antimicrobial activity but also to reduce the probability of resistance development.

The key issue is the ability of hybrid compounds to affect several targets in the pathogenic cell, which often provides synergism of bactericidal effect and overcomes resistance mechanisms characteristic of the initial components. In some cases, hybrid molecules demonstrate improved pharmacokinetic characteristics in comparison with the parent antibiotics: some of them can be introduced either intravenously or orally, and some can even intentionally be accumulated in certain tissues, which opens the possibilities for the therapy of localised infections.

Thus, the development of multitarget antibacterial compounds opens new frontiers in creating efficient and safe agents to treat complex bacterial infections, particularly those associated with biofilms and medicinal implants. Further studies in the area, including optimisation of the hybrid structure, investigation of toxicological profile, and clinical trials, will promote the introduction of the innovative drugs into clinical practice and cope with one of the most urgent problems of modern medicine – resistance to antibiotics.

REFERENCES

1. Global Antibiotic Resistance Surveillance Report 2025: Summary, WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS), World Health Organization, Geneva, 2025. URL: https://iris.who.int/server/api/core/bitstreams/139d068a-1086-43f7-a47d-575d0118d034/content (accessed 02.12.2025).
2. Gordillo Altamirano F. L., Barr J. J., Phage therapy in the postantibiotic era, *Clin. Microbiol. Rev.*, 2019, Vol. 32, No. 2, Art. e00066-18.
3. Tang K. W. K., Millar B. C., Moore J. E., Antimicrobial resistance (AMR), *Br. J. Biomed. Sci.*, 2023, Vol. 80, Art. 11387.
4. Naghavi M., Vollset S. E., Ikuta K. S., Swetschinski L. R., Gray A. P. et al., Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050, *Lancet*, 2024, Vol. 404, No. 10459, P. 1199–1226.
5. Gajdács M., The concept of an ideal antibiotic: implications for drug design, *Molecules*, 2019, Vol. 24, No. 5, Art. 892.
6. Brötz-Oesterhelt H., Brunner N. A., How many modes of action should an antibiotic have?, *Curr. Opin. Pharmacol.*, 2008, Vol. 8, No. 5, P. 564–573.
7. Silver L. L., Multi-targeting by monotherapeutic antibacterials, *Nat. Rev. Drug Discovery*, 2007, Vol. 6, No. 1, P. 41–55.
8. Mulani M. S., Kamble E. E., Kumkar S. N., Tawre M. S., Pardesi K. R., Emerging strategies to combat ESKAPE pathogens in the era of antimicrobial resistance: a review, *Front. Microbiol.*, 2019, Vol. 10, P. 539.
9. Theuretzbacher U., Dual-mechanism antibiotics, *Nat. Microbiol.*, 2020, Vol. 5, No. 8, P. 984–985.
10. Masters P. A., O'Bryan T. A., Zurlo J., Miller D. Q., Joshi N., Trimethoprim-sulfamethoxazole revisited, *Archives of Internal Medicine*, 2003, Vol. 163, No. 4, P. 402–410.
11. Rybak M. J., McGrath B. J., Combination antimicrobial therapy for bacterial infections. Guidelines for the clinician, *Drugs*, 1996, Vol. 52, No. 3, P. 390–405.
12. Tamma P. D., Cosgrove S. E., Maragakis L. L., Combination therapy for treatment of infections with gram-negative bacteria, *Clin. Microbiol. Rev.*, 2012, Vol. 25, No. 3, P. 450–470.
13. Mannion J. C., Bloch R., Popovich N. G., Cephalosporin-aminoglycoside synergistic nephrotoxicity: fact or fiction?, *Drug Intell. Clin. Pharm.*, 1981, Vol. 15, No. 4, P. 248–256.
14. Paul M., Benuri-Silbiger I., Soares-Weiser K., Leibovici L., â Lactam monotherapy versus â lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials, *British Medical Journal*, 2004, Vol. 328, No. 7441, P. 668–672.
15. Kradjan W. A., Burger R., *In vivo* inactivation of gentamicin by carbenicillin and ticarcillin, *Archives of Internal Medicine*, 1980, Vol. 140, No. 12, P. 1668–1670.
16. Tindula R. J., Ambrose P. J., Harralson A. F., Aminoglycoside inactivation by penicillins and cephalosporins and its impact on drug-level monitoring, *Drug Intell. Clin. Pharm.*, 1983, Vol. 17, No. 12, P. 906–908.
17. Zhou J., Jiang X., He S., Jiang H., Feng F., Liu W., Qu W., Sun H., Rational design of multitarget-directed ligands: strategies and emerging paradigms, *J. Med. Chem.*, 2019, Vol. 62, No. 20, P. 8881–8914.
18. Feng J., Zheng Y., Ma W., Ihsan A., Hao H., Cheng G., Wang X., Multitarget antibacterial drugs: an effective strategy to combat bacterial resistance, *Pharmacol. Ther.*, 2023, Vol. 252, Art. 108550.
19. Bremner J., Multiple Action-Based Design Approaches to Antibacterials, Springer, Singapore, 2021, 193 p.
20. Ghosh C., Haldar J., Membrane-active small molecules: designs inspired by antimicrobial peptides, *ChemMedChem*, 2015, Vol. 10, No. 10, P. 1606–1624.
21. Pat. WO 2010025906 A2, 2010.
22. Xiao Z.-P., Wang X.-D., Wang P.-F., Zhou Y., Zhang J.-W., Zhang L., Zhou J., Zhou S.-S., Ouyang H., Lin X.-Y., Mustapa M., Reyinbaike A., Zhu H.-L., Design, synthesis, and evaluation of novel fluoroquinolone-flavonoid hybrids as potent antibiotics against drug-resistant microorganisms, *Eur. J. Med. Chem.*, 2014, Vol. 80, P. 92–100.
23. Wang R., Yin X., Zhang Y., Yan W., Design, synthesis and antimicrobial evaluation of propylene-tethered ciprofloxacin-isatin hybrids, *Eur. J. Med. Chem.*, 2018, Vol. 156, P. 580–586.
24. Locher H. H., Seiler P., Chen X., Schroeder S., Pfaff P., Enderlin M., Klenk A., Fournier E., Hubschwerlen C., Ritz D., Kelly C. P., Keck W., *In vitro* and *in vivo* antibacterial evaluation of cadazolid, a new antibiotic for treatment of *Clostridium difficile* infections, *Antimicrob. Agents Chemother.*, 2014, Vol. 58, No. 2, P. 892–900.
25. Gerding D. N., Cornely O. A., Grill S., Kracker H., Marrast A. C., Nord C. E., Talbot G. H., Buitrago M., Diaconescu I. G., de Oliveira C. M., Preotescu L., Pullman J., Louie T. J., Wilcox M. H., Cadazolid for the treatment of *Clostridium difficile* infection: results of two double-blind,

placebo-controlled, non-inferiority, randomised phase 3 trials, *Lancet Infect. Dis.*, 2019, Vol. 19, No. 3, P. 265–274.
26. Rashid M.-U., Dalhoff A., Weintraub A., Nord C. E., *In vitro* activity of MCB3681 against *Clostridium difficile* strains, *Anaerobe*, 2014, Vol. 28, P. 216–219.
27. Freeman J., Pilling S., Vernon J., Wilcox M. H., *In vitro* activities of MCB3681 and eight comparators against *Clostridium difficile* isolates with known ribotypes and diverse geographical spread, *Antimicrob. Agents Chemother.*, 2017, Vol. 61, No. 3, Art. e02077-16.
28. Gorityala B. K., Guchhait G., Goswami S., Fernando D. M., Kumar A., Zhanel G. G., Schweizer F., Hybrid antibiotic overcomes resistance in *P. aeruginosa* by enhancing outer membrane penetration and reducing efflux, *J. Med. Chem.*, 2016, Vol. 59, No. 18, P. 8441–8455.
29. Gorityala B. K., Guchhait G., Fernando D. M., Deo S., McKenna S. A., Zhanel G. G., Kumar A., Schweizer F., Adjuvants based on hybrid antibiotics overcome resistance in *Pseudomonas aeruginosa* and enhance fluoroquinolone efficacy, *Angew. Chem. Int. Ed. Engl.*, 2016, Vol. 55, No. 2, P. 555–559.
30. Yang X., Goswami S., Gorityala B. K., Domalaon R., Lyu Y., Kumar A., Zhanel G. G., Schweizer F., A tobramycin vector enhances synergy and efficacy of efflux pump inhibitors against multidrug-resistant gram-negative bacteria, *J. Med. Chem.*, 2017, Vol. 60, No. 9, P. 3913–3932.
31. Lyu Y., Yang X., Goswami S., Gorityala B. K., Idowu T., Domalaon R., Zhanel G. G., Shan A., Schweizer F., Amphiphilic tobramycin-lysine conjugates sensitize multidrug resistant gram-negative bacteria to rifampicin and minocycline, *J. Med. Chem.*, 2017, Vol. 60, No. 9, P. 3684–3702.
32. Lyu Y., Domalaon R., Yang X., Schweizer F., Amphiphilic lysine conjugated to tobramycin synergizes legacy antibiotics against wild-type and multidrug-resistant *Pseudomonas aeruginosa*, *Pept. Sci.*, 2019, Vol. 111, No. 1, Art. e23091.
33. Domalaon R., Yang X., Lyu Y., Zhanel G. G., Schweizer F., Polymyxin B_3–tobramycin hybrids with *Pseudomonas aeruginosa*-selective antibacterial activity and strong potentiation of rifampicin, minocycline, and vancomycin, *ACS Infect. Dis.*, 2017, Vol. 3, No. 12, P. 941–954.
34. Renau T. E., Léger R., Filonova L., Flamme E. M., Wang M., Yen R., Madsen D., Griffith D., Chamberland S., Dudley M. N., Lee V. J., Lomovskaya O., Watkins W. J., Ohta T., Nakayama K., Ishida Y., Conformationally-restricted analogues of efflux pump inhibitors that potentiate the activity of levofloxacin in *Pseudomonas aeruginosa*, *Bioorg. Med. Chem. Lett.*, 2003, Vol. 13, No. 16, P. 2755–2758.
35. Long D. D., Aggen J. B., Chinn J., Choi S.-K., Christensen B. G., Fatheree P. R., Green D., Hedge S. S., Judice J. K., Kaniga K., Krause K. M., Leadbetter M., Linsell M. S., Marquess D. G., Moran E. J., Nodwell M. B., Pace J. L., Trapp S. G., Turne S. D., Exploring the positional attachment of glycopeptide/beta-lactam heterodimers, *J. Antibiot.*, 2008, Vol. 61, No. 10, P. 603–614.
36. Tyrrell K. L., Citron D. M., Warren Y. A., Goldstein E. J., *In vitro* activity of TD-1792, a multivalent glycopeptide-cephalosporin antibiotic, against 377 strains of anaerobic bacteria and 34 strains of *Corynebacterium* species, *Antimicrob. Agents Chemother.*, 2012, Vol. 56, No. 4, P. 2194–2197.
37. Stryjewski M. E., Potgieter P. D., Li Y.-P., Barriere S. L., Churukian A., Kingsley J., Corey G. R., TD-1792 versus vancomycin for treatment of complicated skin and skin structure infections, *Antimicrob. Agents Chemother.*, 2012, Vol. 56, No. 11, P. 5476–5483.
38. Blais J., Lewis S. R., Krause K. M., Benton B. M., Antistaphylococcal activity of TD-1792, a multivalent glycopeptide-cephalosporin antibiotic, *Antimicrob. Agents Chemother.*, 2012, Vol. 56, No. 3, P. 1584–1587.
39. Leuthner K. D., Vidaillac C., Cheung C. M., Rybak M. J., *In vitro* activity of the new multivalent glycopeptide-cephalosporin antibiotic TD-1792 against vancomycin-nonsusceptible *Staphylococcus* isolates, *Antimicrob. Agents Chemother.*, 2010, Vol. 54, No. 9, P. 3799–3803.
40. Ma Z., Lynch A. S., Development of a dual-acting antibacterial agent (TNP-2092) for the treatment of persistent bacterial infections, *J. Med. Chem.*, 2016, Vol. 59, No. 14, P. 6645–6657.
41. Fisher C. R., Schmidt-Malan S. M., Yuan Y., He S., Ma Z., Patel R., 691. Activity of TNP-2092 against biofilms formed by prosthetic joint infection-associated staphylococci, *Open Forum Infectious Diseases*, 2019, Vol. 6, Suppl. 2, P. S313.
42. Robertson G. T., Bonventre E. J., Doyle T. B., Du Q., Duncan L., Morris T. W., Roche E. D., Yan D., Lynch A. S., *In vitro* evaluation of CBR-2092, a novel rifamycin-quinolone hybrid antibiotic: studies of the mode of action in *Staphylococcus aureus*, *Antimicrob. Agents Chemother.*, 2008, Vol. 52, No. 7, P. 2313–2323.
43. Robertson G. T., Bonventre E. J., Doyle T. B., Du Q., Duncan L., Morris T. W., Roche E. D., Yan D., Lynch A. S., *In vitro* evaluation of CBR-2092, a novel rifamycin-quinolone hybrid antibiotic: microbiology profiling studies with staphylococci and streptococci, *Antimicrob. Agents Chemother.*, 2008, Vol. 52, No. 7, P. 2324–2334.
44. Pokrovskaya V., Belakhov V., Hainrichson M., Yaron S., Baasov T., Design, synthesis, and evaluation of novel fluoroquinolone-aminoglycoside hybrid antibiotics, *J. Med. Chem.*, 2009, Vol. 52, No. 8, P. 2243–2254.
45. Chen L., Yang D., Pan Z., Lai L., Liu J., Fang B., Shi S., Synthesis and antimicrobial activity of the hybrid molecules between sulfonamides and active antimicrobial pleuromutilin derivative, *Chem. Biol. Drug Des.*, 2015, Vol. 86, No. 2, P. 239–245.
46. Sriram D., Bal T. R., Yogeeswari P., Aminopyrimidinimino isatin analogues: design of novel non-nucleoside HIV-1 reverse transcriptase inhibitors with broad-spectrum chemotherapeutic properties, *J. Pharm. Pharm. Sci.*, 2005, Vol. 8, No. 3, P. 565–577.
47. Zadvornykh D., Zhang Z., Liu C., Serpokrylova I., Bardasheva A., Tikunova N., Silnikov V., Koroleva L., Antibacterial activity of cationic amphiphil conjugates with ciprofloxacin, *International Journal of Health Sciences*, 2022, Vol. 6, No. S7, P. 3009–3023.
48. Burakova E. A., Saranina I. V., Tikunova N. V., Silnikov V. N., Tetracationic compounds based on 1,4-diazabicyclo[2.2.2]octane: antibacterial activity and reactions with N-containing nucleophiles, *Russ. Chem. Bul.*, 2015, Vol. 64, No. 6, P. 1400–1405.
49. Yarinich L. A., Burakova E. A., Zakharov B. A., Boldyreva E. V., Babkina I. N., Tikunova N. V., Silnikov V. N., Synthesis and structure-activity relationship of novel 1,4-diazabicyclo[2.2.2]octane derivatives as potent antimicrobial agents, *Eur. J. Med. Chem.*, 2015, Vol. 95, P. 563–573.
50. Burakova E. A., Saranina I. V., Tikunova N. V., Nazarkina Z. K., Laktionov P. P., Karpinskaya L. A., Anikin V. B., Zarubaev V. V., Silnikov V. N., Biological evaluation of tetracationic compounds based on two 1,4-diazabicyclo[2.2.2]-octane moieties connected by different linkers, *Bioorg. Med. Chem.*, 2016, Vol. 24, No. 22, P. 6012–6020.
51. Baturina O., Naumova N., Tupikin A., Dmitrienko E., Silnikov V., Kabilov M., Short-term changes in fecal bacteriobiome of healthy laboratory mice after antiviral preparation administration, *Drugs and Drug Candidates*, 2024, Vol. 3, No. 4, P. 879–889.

52. Grigor'eva A. E., Tupitsyna A. V., Ryabova E. S., Bardasheva A. V., Zadvornykh D. A., Koroleva L. S., Silnikov V. N., Ryabchikova E. I., Ribosome disorganization and other effects of artificial RNAse DL412 on Salmonella enterica cells, *Appl. Biochem. Microbiol.*, 2025, Vol. 61, No. 2, P. 228–237.
53. Grigor'eva A. E., Bardasheva A. V., Ryabova E. S., Tupitsyna A. V., Zadvornykh D. A., Koroleva L. S., Silnikov V. N., Tikunova N. V., Ryabchikova E. I., Changes in the ultrastructure of *Staphylococcus aureus* cells make it possible to identify and analyze the injuring effects of ciprofloxacin, polycationic amphiphile and their hybrid, *Microorganisms*, 2023, Vol. 11, No. 9, Art. 2192.
54. Wang X.-D., Wei W., Wang P.-F., Tang Y.-T., Deng R.-C., Li B., Zhou S.-S., Zhang J.-W., Zhang L., Xiao Z.-P., Ouyang H., Zhu H.-L., Novel 3-arylfuran-2(5*H*)-one-fluoroquinolone hybrid: design, synthesis and evaluation as antibacterial agent, *Bioorg. Med. Chem.*, 2014, Vol. 22, No. 14, P. 3620–3628.
55. Ma Z., He S., Yuan Y., Zhuang Z., Liu Y., Wang H., Chen J., Xu X., Ding C., Molodtsov V., Lin W., Robertson G. T., Weiss W. J., Pulse M., Nguyen P., Duncan L., Doyle T., Ebright R. H., Lynch A. S., Design, synthesis, and characterization of TNP-2198, a dual-targeted rifamycin-nitroimidazole conjugate with potent activity against microaerophilic and anaerobic bacterial pathogens, *J. Med. Chem.*, 2022, Vol. 65, No. 6, P. 4481–4495.
56. Dong H., You Y., Wang N., Wang M., Song T., He Y., Zou Y., He Y., Peng T., Mei L., Development of amphipathic derivatives of thymol and carvacrol as potent broad-spectrum antibacterial agents, *Eur. J. Med. Chem.*, 2024, Vol. 276, Art. 116716.
57. Bera S., Zhanel G. G., Schweizer F., Antibacterial activities of aminoglycoside antibiotics-derived cationic amphiphiles. Polyol-modified neomycin B-, kanamycin A-, amikacin-, and neamine-based amphiphiles with potent broad spectrum antibacterial activity, *J. Med. Chem.*, 2010, Vol. 53, No. 9, P. 3626–3631.
58. Zimmermann L., Das I., Désiré J., Sautrey G., Vinicius Barros R. S., El Khoury M., Mingeot-Leclercq M.-P., Décout J.-L., New broad-spectrum antibacterial amphiphilic aminoglycosides active against resistant bacteria: from neamine derivatives to smaller neosamine analogues, *J. Med. Chem.*, 2016, Vol. 59, No. 20, P. 9350–9369.
59. Zimmermann L., Kempf J., Briée F., Swain J., Mingeot-Leclercq M. P., Décout J. L., Broad-spectrum antibacterial amphiphilic aminoglycosides: a new focus on the structure of the lipophilic groups extends the series of active dialkyl neamines, *Eur. J. Med. Chem.*, 2018, Vol. 157, P. 1512–1525.

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