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REVIEW ARTICLE

Hybrids/Conjugates/Chimera Drugs-Antimicrobial Hybrids: Antibiotics, Antifungals, Antituberculars, Antimalarials

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Abstract: Antimicrobial hybrids are compounds that can inhibit, stop the growth of, or kill microorganisms, including bacteria, fungi, and parasites. Antibiotics, a subset of antimicrobial agents, specifically target bacteria and include well-established classes such as β-lactams, macrolides, quinolones, and oxazolidinones. Other antimicrobial hybrids are designed for treating a wide range of diseases, including fungal infections, leishmaniasis, parasitic diseases (such as trypanosomiasis and malaria), leprosy, and tuberculosis. Some hybrids are designed to treat a variety of diseases. This review highlights studies primarily published between 2000 and 2023, with a few from 2024, underscoring the dynamic and rapidly evolving nature of antimicrobial hybrid research.

Keywords: Hybrids, antimicrobial, antibiotic ,fungal infections, leishmaniasis, parasitic infections, trypanosomiasis, malaria, leprosy.

1. INTRODUCTION

The first comprehensive review on hybrid compounds focused on chimera molecules developed for the treatment of central nervous system disorders [1]. In contrast, this review centers on the application of hybrid drugs as antimicrobial agents, as discussed in recent literature.

Relevant publications were identified through targeted searches in *SciFinder* and in leading medicinal chemistry and related biological journals, including those from the American Chemical Society, *Bioorganic & Medicinal Chemistry*, *Bioorganic & Medicinal Chemistry Letters*, *Current Medicinal Chemistry*, *European Journal of Medicinal Chemistry*, *Antimicrobial Agents and Chemotherapy*, *Bioorganic Chemistry*, and *MedChemComm*. The primary search terms used were *hybrids*, *conjugates*, and *chimeras*.

The selected abstracts highlight compounds exhibiting significant or promising antimicrobial activity against bacterial, fungal, tuberculosis, and malaria-related pathogens. These studies emphasize the chemical structures of the most active molecules. A common structural feature among many of these hybrids is the incorporation of heterocyclic "azole" moieties-such as triazoles [2], tetrazoles, carbazoles, pyrazoles, oxadiazoles, isoxazoles, and imidazoles-as well as other bioactive scaffolds like quinolines, triazines, and chalcones.

2. SELECTED REVIEWS OF ANTIMICROBIALS

Fedorowicz and Saczewski published a comprehensive survey on hybrid quinolones and fluoroquinolones, highlighting artificial nucleases capable of cleaving DNA, as well as quinolone-peptide hybrids, NO-donor quinolone hybrids, fluoroquinolone-bisphosphonate hybrids, and various other antimicrobial quinolone hybrids [3]. Reviews by Shi *et al*. and Gao *et al*. focused on hybrids designed to combat resistance in ESKAPE bacteria (*E. coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) [4-6]. Xu *et al*. presented a dedicated review on fluoroquinolone-isatin conjugates [7], while Huang *et al*. summarized the antibacterial activities of tetrazole-derived hybrids [8]. Klahn and Brönstrup proposed a novel hypothesis for designing dual-action hybrid antibiotics effective against Gram-negative (G-) pathogens, particularly *Pseudomonas aeruginosa*, which have developed various resistance mechanisms. They discussed hybrids

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created by linking an antibiotic to a second functional unit, often another antibiotic [9]. Bremner *et al*. and Domalaon *et al*. reviewed hybrids composed of two bridged antibiotics in several extensive publications [10-12]. Henriquez-Figuereo, Sanmartín, and Plano *et al*. reviewed hybrids containing sulfur, selenium, and tellurium, and their potential in treating tropical diseases [13]. Saadeh and Mubarak examined the role of hybrids in combating microbial drug resistance [14].

3. BIOFILM INHIBITORS, EFFLUX PUMP INHIBITORS, MRSA, QUORUM SENSING INHIBITORS

When evaluating the activity of antimicrobial agents, it is essential to assess their effectiveness against Gram-positive (G+) methicillin-resistant *Staphylococcus aureus* (MRSA). Over time, many bacteria have developed resistance to commonly used antibiotics, creating a global health threat as infections become increasingly difficult to treat. A significant mechanism contributing to antibiotic resistance is the emergence of efflux pumps, which actively remove antibiotics from bacterial cells, rendering them less susceptible to treatment. Another key factor in microbial virulence is quorum sensing, a process by which bacteria regulate their population density through gene expression. This regulation is critical for biofilm formation, and when bacterial populations reach a certain density, biofilms can form and shield bacteria from the host immune response, enabling them to resist phagocytosis and cause persistent infections. As a result, strategies aimed at inhibiting biofilm formation or disrupting established biofilms are considered promising antibacterial approaches. More detailed descriptions of quorum sensing and bacterial biofilms can be found on Wikipedia [15, 16].

3.1. Biofilm Inhibitors

Hybrids of ciprofloxacin linked to 3-hydroxypyridin-4(1*H*)-ones were evaluated as dual antibacterial and antibiofilm agents against *Pseudomonas aeruginosa*. The most active compound, **1**, exhibited minimum inhibitory concentrations (MICs) of 0.86 and 0.43 μM against *P. aeruginosa* strains 27853 and PAO1, respectively, and reduced biofilm formation by 78.3%. The mechanism of action was linked to the interference with iron uptake, which resulted in inhibited bacterial motility and reduced virulence [17]. Additionally, the non-toxic ciprofloxacin-nitroxide hybrid, **2**, achieved complete destruction of established *P. aeruginosa* biofilms [18]. Linking 1,3,5-triazines to pyrazoles *via* a thioamidic bridge resulted in hybrids with potent antibacterial activity. Compound **3** exhibited MICs ranging from 3.91 to 15.62 μM/mL and demonstrated antibiofilm activity at 15.62 μM/mL [19]. Quaternary ammonium salts (compound **4**), obtained by intensive methylation of the nitrogen atoms in fluoroquinolone antibiotics (ciprofloxacin, enoxacin, gatifloxacin, lomefloxacin, and norfloxacin), exhibited strong antibacterial activity against both G+ and G- bacteria (MICs as low as 6.25 μM). These compounds also reduced biofilm mass in *Pseudomonas aeruginosa* ATCC 15442 and were found to be of low toxicity [20]. Additional antibiofilm agents against *P. aeruginosa* include hybrids of 3-benzimidazoles linked to hydroxypyridin-4-(2*H*)-ones, such as compound **5** [21]. The pyrazolopyrimido[4,5-*d*]pyrimidine hybrid **6** also inhibited *Micrococcus luteus* and *S. aureus*, with MICs of 3.9 and 7.8 μg/mL, respectively [22]. Biofilm formation inhibitors **7a** and **7b** showed approximately 50% efficacy against the pathogenic yeast *Candida albicans* at concentrations of 2-4 μg/mL [23]. Additionally, hybrids like compound **8** (IC_{50} 0.5 μg/mL), derived from curcumin and aminophosphonates, effectively eradicated *S. aureus* biofilms and expanded the antibacterial spectrum when combined with norfloxacin. This mechanism involved disruption of bacterial cell membrane integrity (Fig. **1**) [24].

3.2. Efflux Pump Inhibitors

Hybrid drugs, such as compound **9**, inhibit the NorA efflux pump and enhance the photodynamic inactivation of G- *Escherichia coli* and *Acinetobacter baumannii* bacteria [25, 26]. Antibiotic hybrids **10** and **11**, which combine carbazole derivatives with efflux pump inhibitors like gallic acid or 3-indoleacetic acid, exhibited remarkable potency at a concentration of 0.05 μg/mL against several bacterial strains, including *E. coli*, *Staphylococcus aureus*, *Pasteurella multocida*, and *Bacillus subtilis* [27]. Hybrid drugs **12**, which combine the calcium channel blocker verapamil and certain antipsychotic phenothiazines-both known efflux pump inhibitors-were found to be non-toxic and enhanced antitubercular activity, with an MIC_{90} of approximately 3.17 μg/mL, due to efflux pump inhibition [28]. Additionally, conjugating 5-nitro-2-phenyl-1*H*-indole (which lacks intrinsic antibacterial activity) with the natural product berberine resulted in a reduced MIC for berberine by inhibiting the NorA efflux pump. Ester prodrugs of indole and berberine, as well as hybrids like compound **13**, demonstrated high antibacterial potency against G+ bacteria *S. aureus* 8325-4, *E. faecalis* V-583, and *Bacillus cereus* T, with MIC values of 3.1, 6.3, and 3.1 μM, respectively (Fig. **2**) [29, 30].

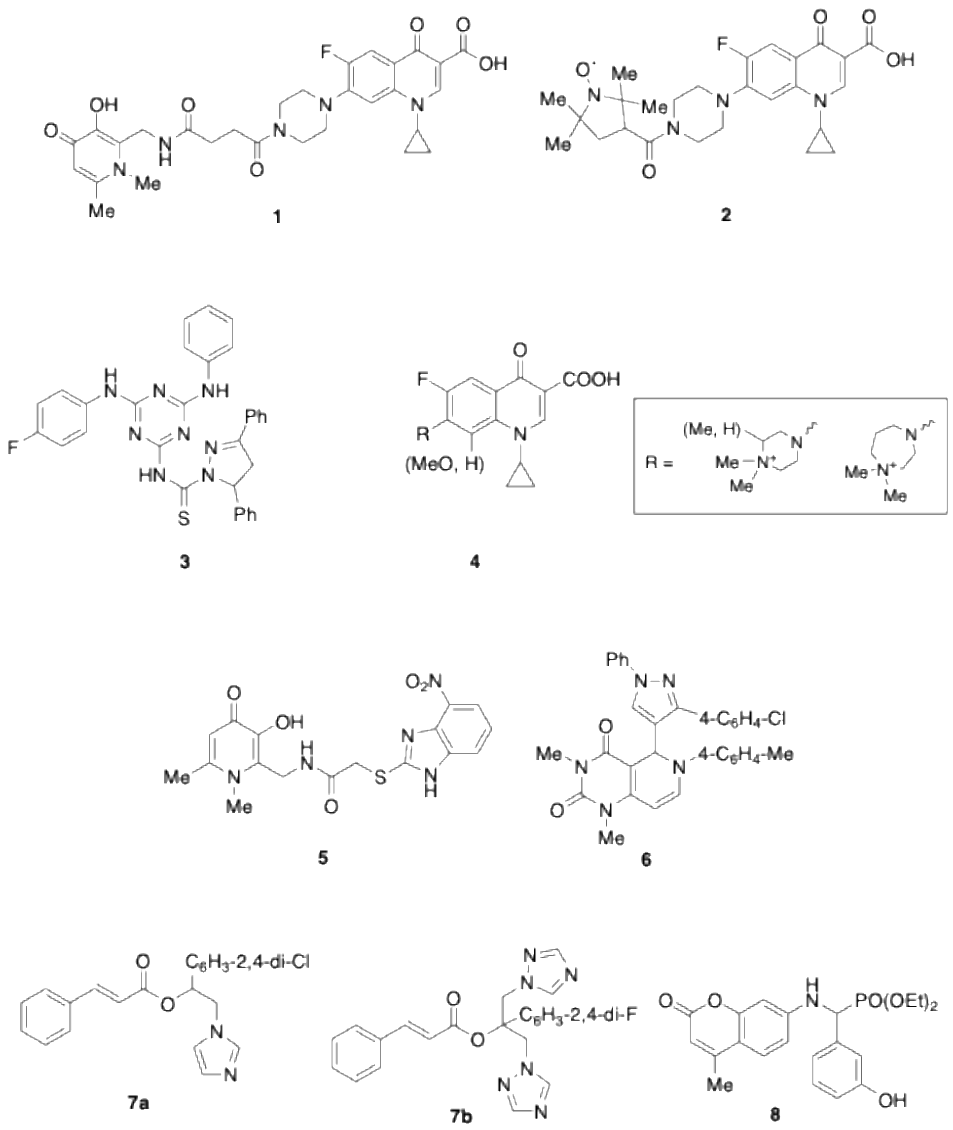


Fig. (1). Biofilm formation inhibitors.

3.3. *MRSA*

Reviews by Qiao, Zhu, Verma, Kumar, and Rangappa explored MRSA inhibitors derived from thiazoles and oxadiazoles as potential antibiotics against MRSA [31, 32]. Researchers conjugated amphiphilic aminoglycosides, such as neomycin B and kanamycin A, with cationic peptide antibacterial agents through 1,2,3-triazole linkages, creating aminoglycoside-peptide triazole conjugates, including hybrid **14**. These conjugates exhibited enhanced antibacterial potency against MRSA and gentamicin-resistant *Pseudomonas aeruginosa*, though they were less effective against susceptible strains [33]. The indole-carbazole hybrid **15** showed notable antibacterial activity, with an MIC of 1 μg/mL against MRSA, comparable to vancomycin, and resulted in 75% survival in a mouse model [34]. Novel hybrids derived from the terpene pleuromutilin, conjugated with pyridinium entities, such as compound **16**, displayed a broad antibacterial spectrum, with MICs as low as 0.0625 μg/mL against *Staphylococcus aureus*, MRSA, and *Escherichia coli* [35]. The coumarin-thiazole hybrid **17** exhibited six times greater inhibitory activity against MRSA (MIC = 4 μM) compared to norfloxacin, functioning as a disruptor of the bacterial membrane while binding to DNA gyrase through stable hydrogen bonds, thereby impeding cell replication [36]. Benzothiazole-urea hybrids like compound **18** demonstrated similar antibacterial efficacy against MRSA in a mouse model of abdominal infection [37]. Non-cardiotoxic amide-containing hybrids, such as compound **19**, were designed as bacterial topoisomerase inhibitors (NBTIs) to minimize hERG channel inhibition. These hybrids showed potent antibacterial activity against G+ bacteria, including methicillin-resistant

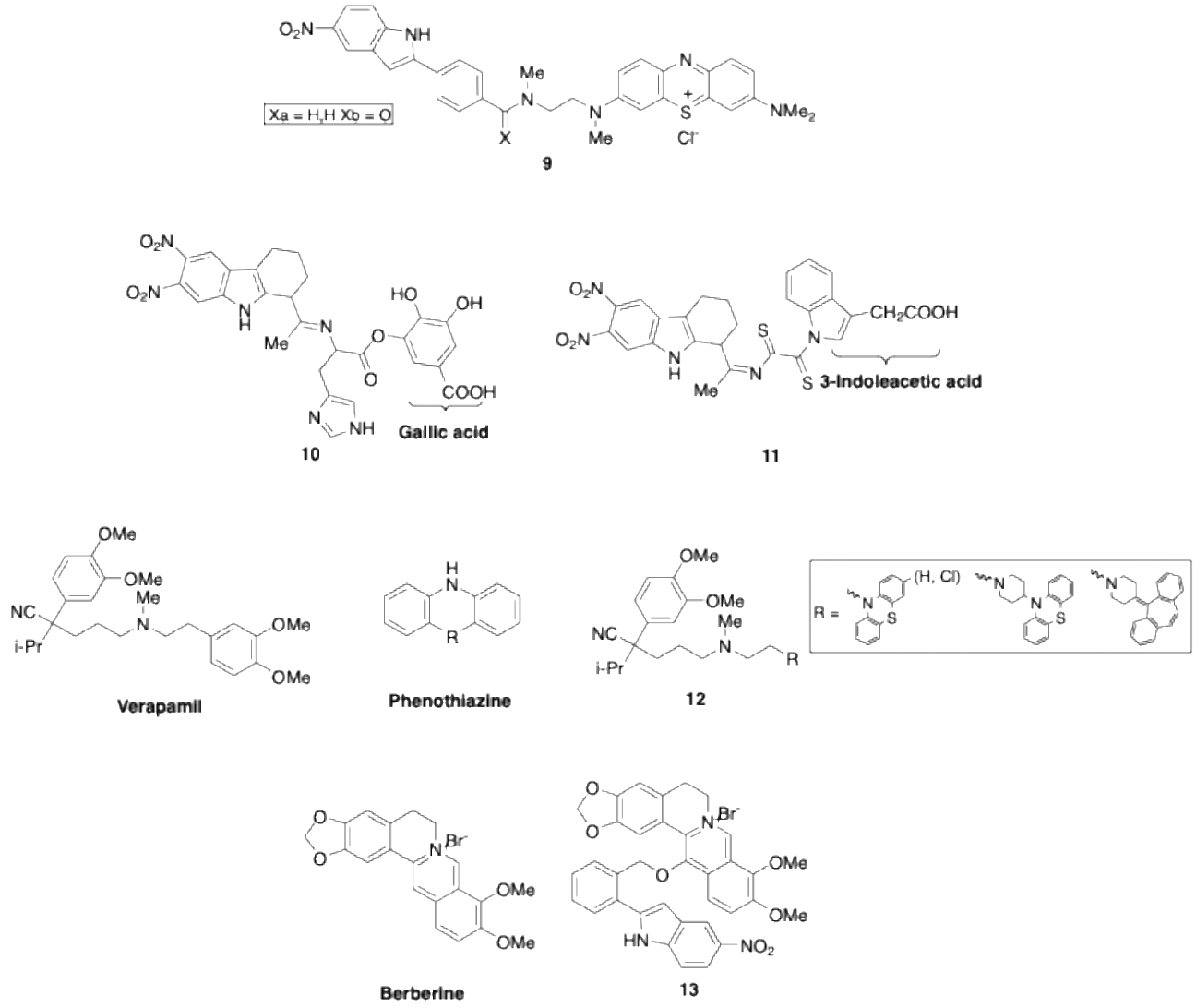


Fig. (2). Efflux pump inhibitors.

MRSA, in murine models [38]. Additionally, quinolinium stilbene benzenesulfonates, such as compound **20**, exhibited broad-spectrum activity against both G+ MRSA (including *S. aureus*, *Bacillus subtilis*, and vancomycin-resistant *Enterococcus faecalis*) and G- bacteria (*Shigella sonnei*) (Fig. **3**) [39].

3.4. Quorum Sensing Inhibitors

Coumarin-derived hybrids, such as compound **21**, exhibit dual activities of iron chelation and quorum sensing inhibition, effectively disrupting biofilm formation in *Pseudomonas aeruginosa* infections. These compounds also demonstrate synergistic antibacterial effects when combined with ciprofloxacin and tobramycin [40]. Research on chromene-hydrazone hybrids revealed that these compounds possess anti-ferroptosis (a form of iron-dependent programmed cell death), antibacterial, and anti-quorum-sensing properties. Among these, semicarbazone **22a** and benzenesulfonyl hydrazone derivatives **22b** showed moderate quorum sensing inhibition [41]. An antimicrobial peptide, CP7-FP13-2, specifically inhibited quorum sensing and exhibited antibacterial activity against *S. aureus* by disrupting bacterial cell integrity [42]. Benzoxazole hybrids, such as compound 23, were found to combine quorum sensing inhibition with potent antibiofilm activity (Fig. **4**) [43].

4. ANTIBIOTICS

4.1. β-Lactams

Hybrid **24**, synthesized by linking the β-lactam antibiotic Δ-2-cephamycins to tetramic acid, demonstrated potent antibacterial activity against clinical strains of both G+ and G- bacteria, including *Klebsiella pneumoniae* and *E. coli* [44]. Hybrid **25**, which combines a β-lactam with an isatin unit through a 1,2,3-triazole

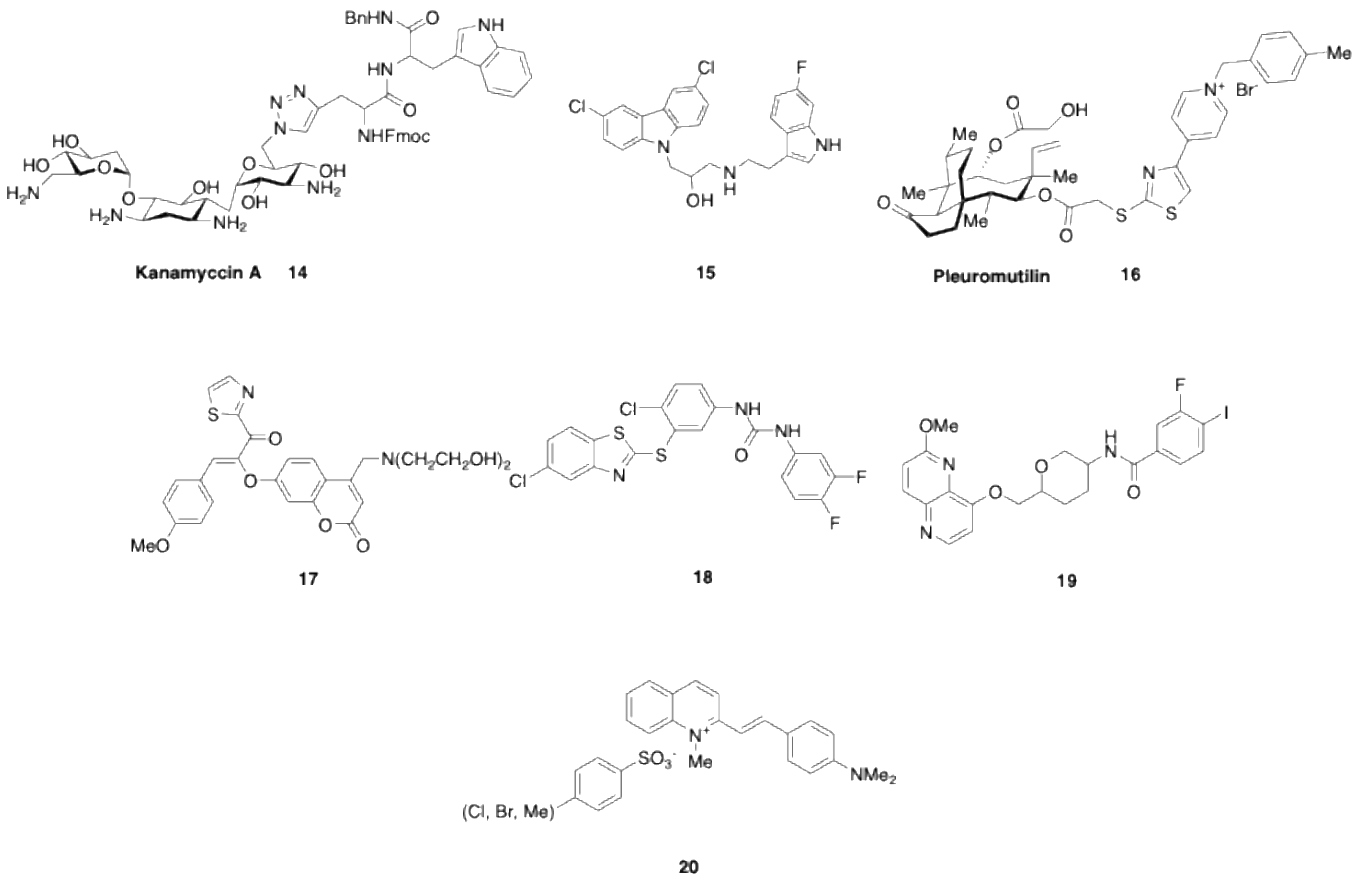


Fig. (3). MRSA inhibitors.

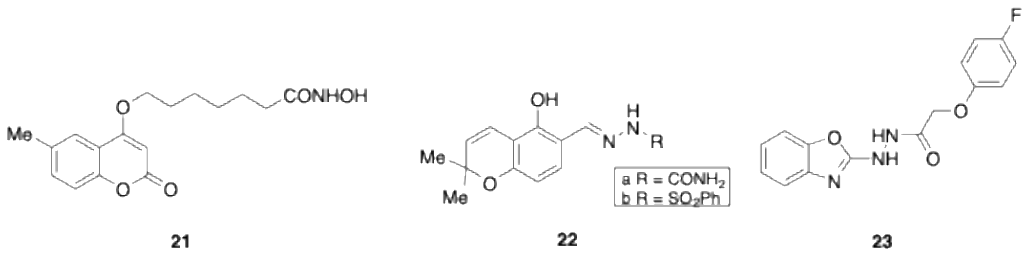


Fig. (4). Quorum sensing inhibitors.

bridge obtained *via* click chemistry, effectively inhibited the growth of *D. vaginalis* at a concentration of 100 μM [45]. Conjugate **26**, created by linking ampicillin with phosphine-gold units, proved to be a highly effective antibiotic against G+ bacteria, exhibiting 120 times greater potency than ampicillin against *S. aureus*, *S. epidermidis*, and *Enterococcus faecium* [46]. The cephalosporin-catechol hybrid **27** displayed broad-spectrum antibacterial activity *in vitro*, particularly against *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, and showed significant *in vivo* efficacy against *A. baumannii* compared to other catechol-derived antibiotics (Fig. **5**) [47].

4.2. Mycin Antibiotics

The extensive family of antimicrobial agents known as "mycins" includes both natural and synthetic compounds. Some of these drugs have been in use for decades and remain first-line antibiotics, while others have fallen out of favor due to bacterial resistance or unacceptable toxicity. This diverse group encompasses aminoglycosides (*e.g.*, erythromycin, tobramycin, azithromycin, neomycin), glycopeptides (*e.g.*, vancomycin), ketolides (*e.g.*, solithromycin), lincosamides (*e.g.*, lincomycin), polymyxins, rifamycins (both natural and synthetic), and others. To enhance their biological activity, improve water solubility, combat resistant bacterial strains, and/or reduce toxicity, many of these antibiotics have been modified into hybrid compounds. These hybrids are often created by linking a "mycin" to a second antibiotic, frequently from the quinolone family. This approach is favored due to the presence of carboxylic acid and secondary amino functionalities in quinolones, which facilitate the formation of linking bridges.

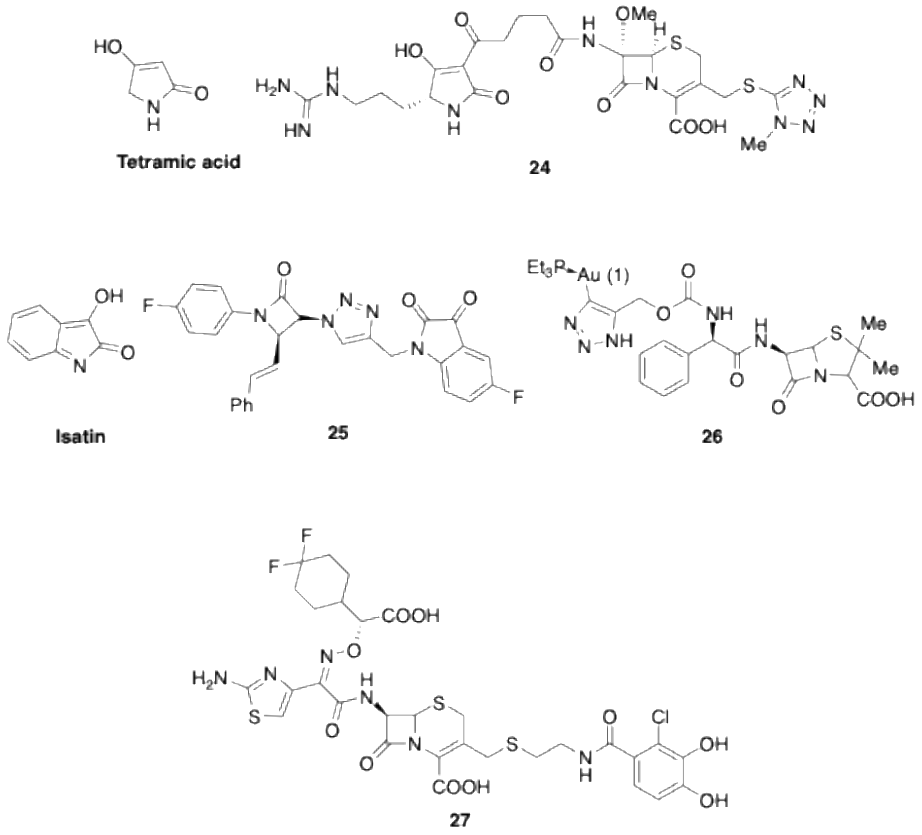


Fig. (5). β-Lactam antibiotics.

Mutak *et al*. reported that hybrids **28a** and **28b**, which combine the macrolide erythromycin with a ciprofloxacin unit, exhibited potent activity against resistant bacteria [48]. Conjugate **29** demonstrated high efficacy against resistant strains of *Streptococcus pneumoniae* and *Streptococcus pyogenes*, and was particularly effective against resistant *Staphylococcus aureus*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The azithromycin-quinolone hybrid **30** also displayed significant antibacterial activity (Fig. **6a**) [49].

Additionally, erythromycin analogs, such as the solithromycin oxime derivatives **31** and dehydrosolithromycin congeners **32**, showed enhanced activity against various resistant bacterial strains [50, 51]. Tobramycin, an aminoglycoside antibiotic primarily used for treating G- infections-particularly *Pseudomonas* strains-was combined with polymyxin B3 in hybrid **33**. This conjugate was highly effective against carbapenem-resistant and MDR *P. aeruginosa* clinical isolates. Similar effectiveness was observed with tobramycin-ciprofloxacin hybrids, which restored antibiotic activity against *P. aeruginosa* [52, 53]. Other hybrids, such as those combining tobramycin with proline-rich peptides, also demonstrated activity against resistant pathogens [54]. Tobramycin-ciprofloxacin conjugates, with ciprofloxacin attached at two different positions on tobramycin (compounds **34a** and 3**4b**), exhibited notable adjuvant effects (Fig. **6b**) [55].

Arbekacin analogs of tobramycin, *e.g*. **35**, were effective against both susceptible and MRSA strains of *P. aeruginosa* [56]. Nebramine-quinolone hybrids, including nebramine-moxifloxacin **36**, displayed adjuvant potency by reducing the MIC of moxifloxacin to below 1 μg/mL against multidrug resistance (MDR) *P. aeruginosa* [57]. Hybridization of polymyxin and vancomycin, as in compound **37**, improved activity against G- bacteria (Fig. **6c**) [58].

The rifamycin-nitroimidazole hybrid, compound **38**, exhibited potent activity against microaerophilic and anaerobic bacteria resistant to both rifamycins and nitroimidazoles. This compound is currently undergoing Phase 2 clinical trials for the treatment of *Helicobacter pylori*, *Clostridioides difficile*, and bacterial vaginosis infections [59]. The rifamycin-quinolone derivative **39a**, known as CBR-2092, demonstrated superior bactericidal activity compared to moxifloxacin, rifampin, and a combination of both [60]. Kanglemycin, a close analog of rifamycin, was hybridized with garenoxacin in compound **39b** to overcome resistance mutations. The design of the linking bridge was critical for achieving effective anti-*Staphylococcus aureus* activity [61].

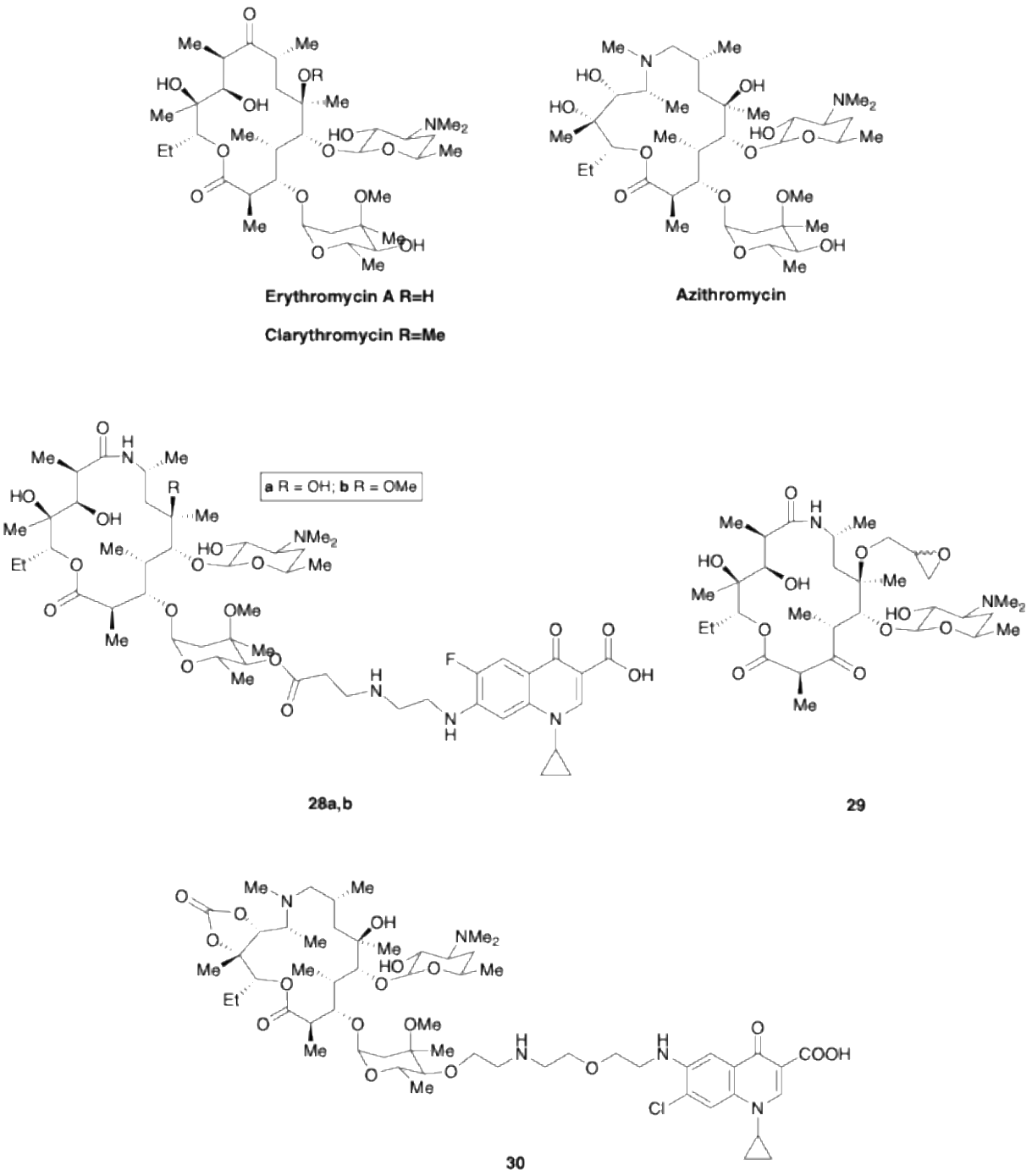


Fig. (6a). Mycin antibiotics.

Other mycin hybrids include a neomycin-ciprofloxacin derivative **40**, which exhibited higher potency than neomycin B against G- bacteria and MRSA, inhibited bacterial protein synthesis as effectively as or better than neomycin B, and was up to 32 times more potent as an inhibitor of DNA gyrase and topoisomerase IV than ciprofloxacin [62]. Another conjugate, compound **41**, involved linking neomycin to phenolic units *via* a 1,2,3-triazole-containing bridge (Fig. **6d**) [63, 64].

The glycosylated macrocyclic fidaxomicin, used for treating *Clostridium difficile* infections, was initially coupled with biphenolic dichlorohomoorsellinic acid and later with ciprofloxacin. The resulting product, compound **42**, was found to improve aqueous solubility and enhanced antibiotic activity compared to fidaxomicin [65]. Kanamycin, used for severe bacterial infections and hydatidosis, was hybridized with ciprofloxacin to form compound **43**, which significantly

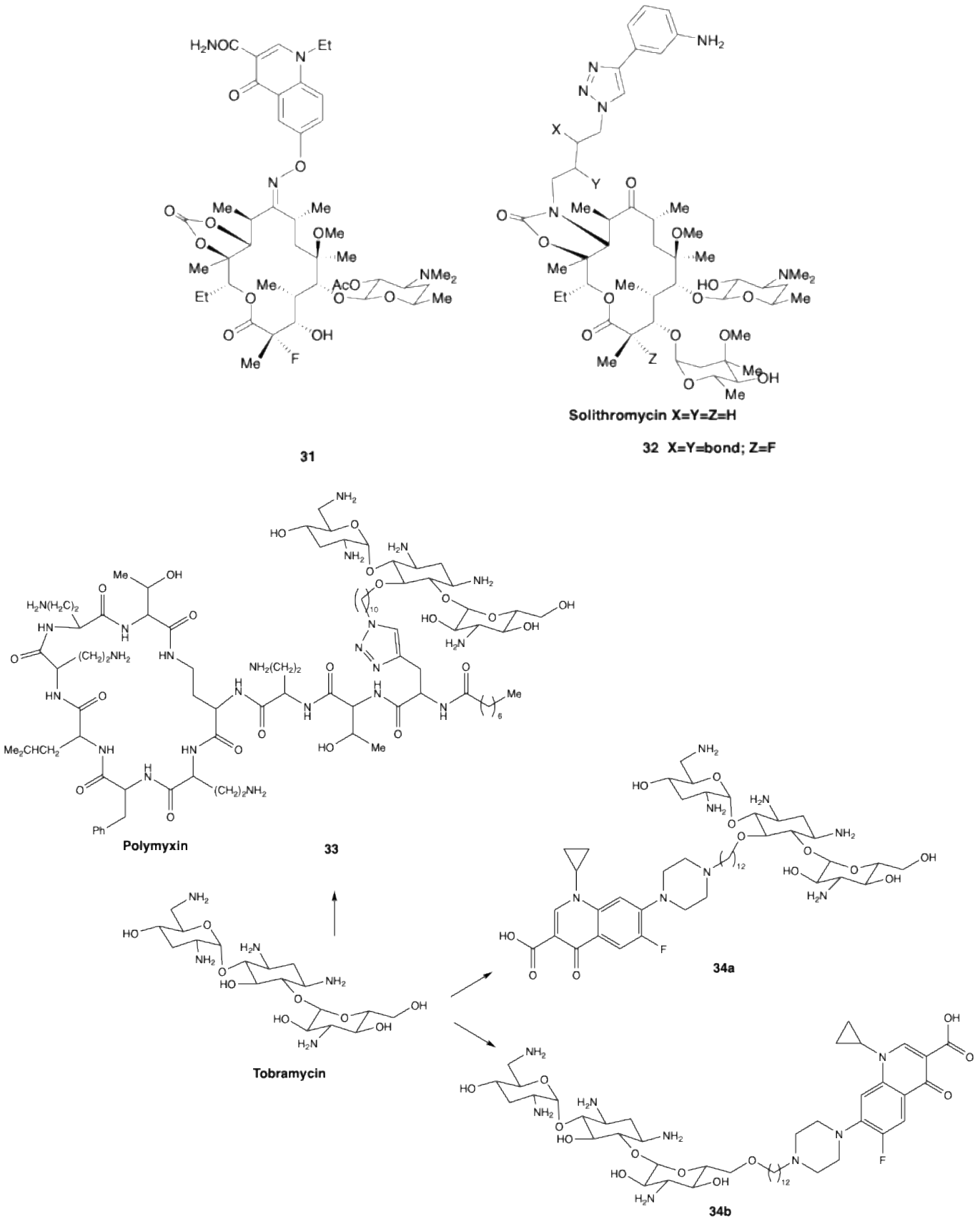
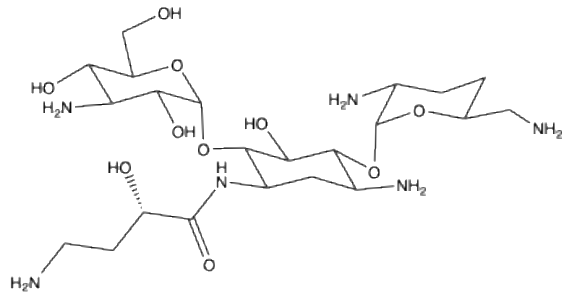
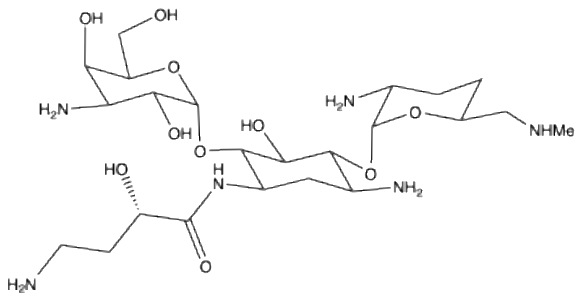


Fig. (6b). Mycin antibiotics.



Arbekacin



5,4''-Diepi-6'-*N*-methyl-arbikacin

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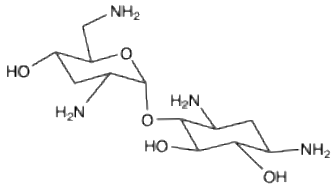
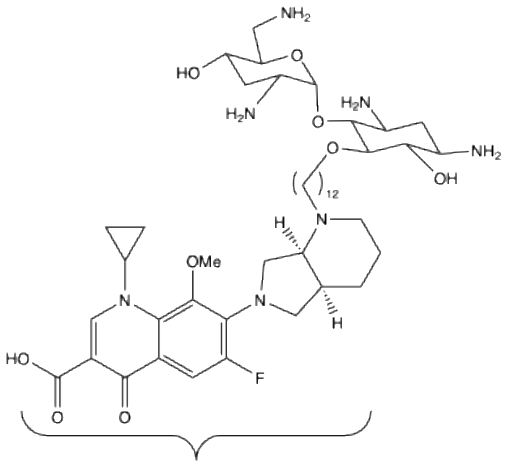


Nebramine



Moxifloxacin

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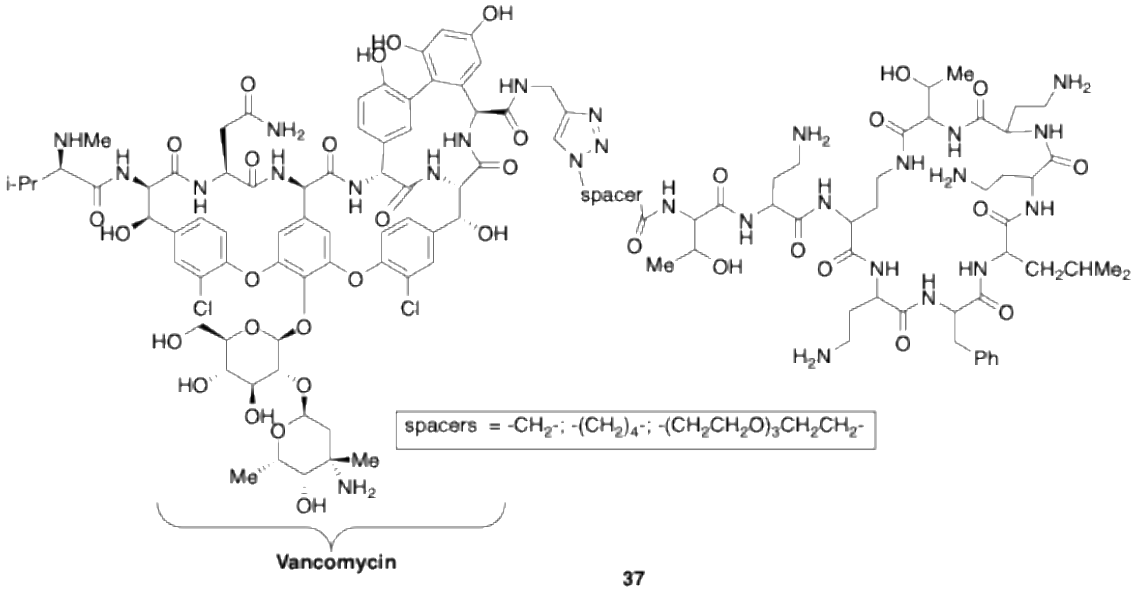

Vancomycin

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Fig. (6c). Mycin antibiotics.

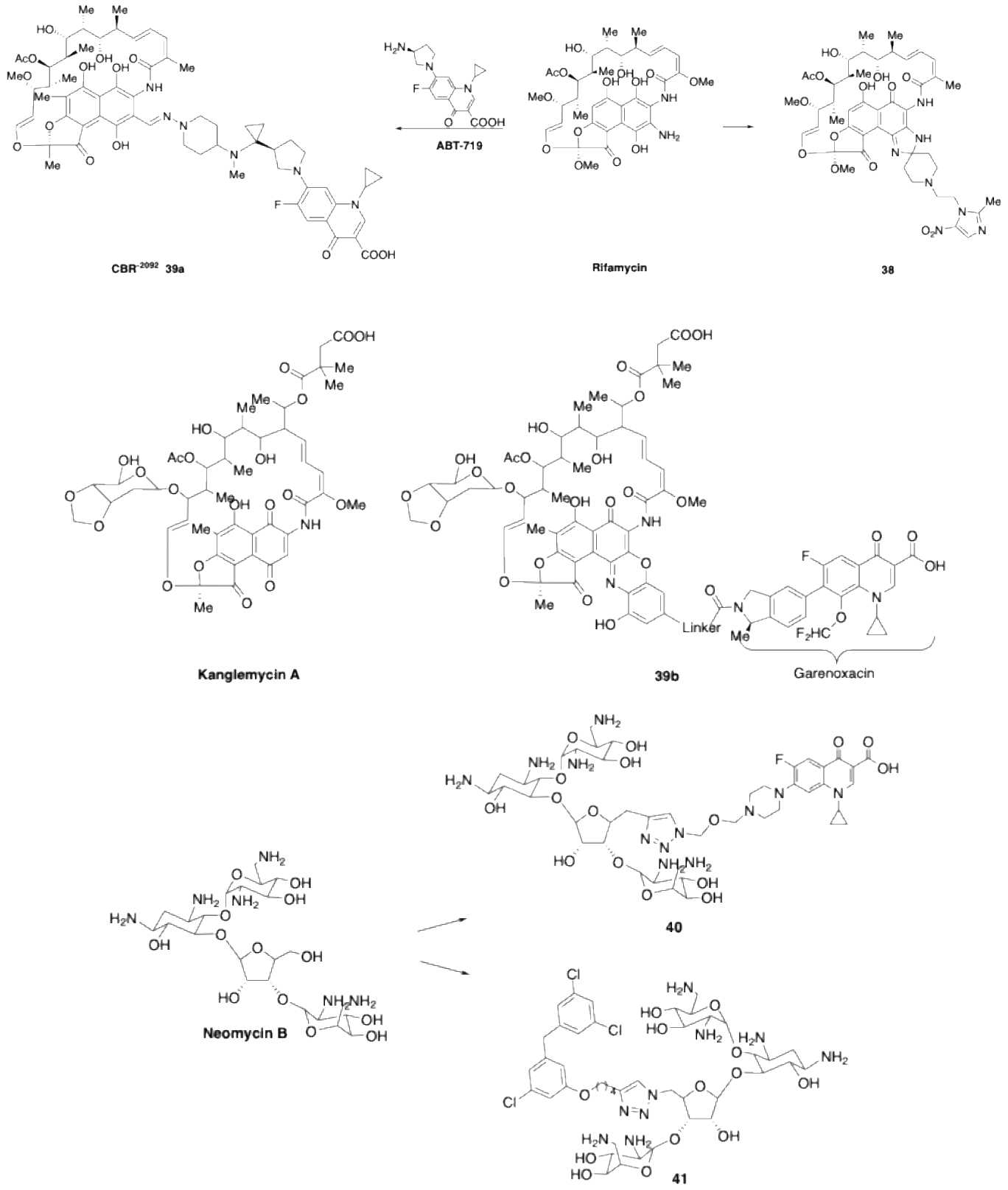


Fig. (6d). Mycin antibiotics.

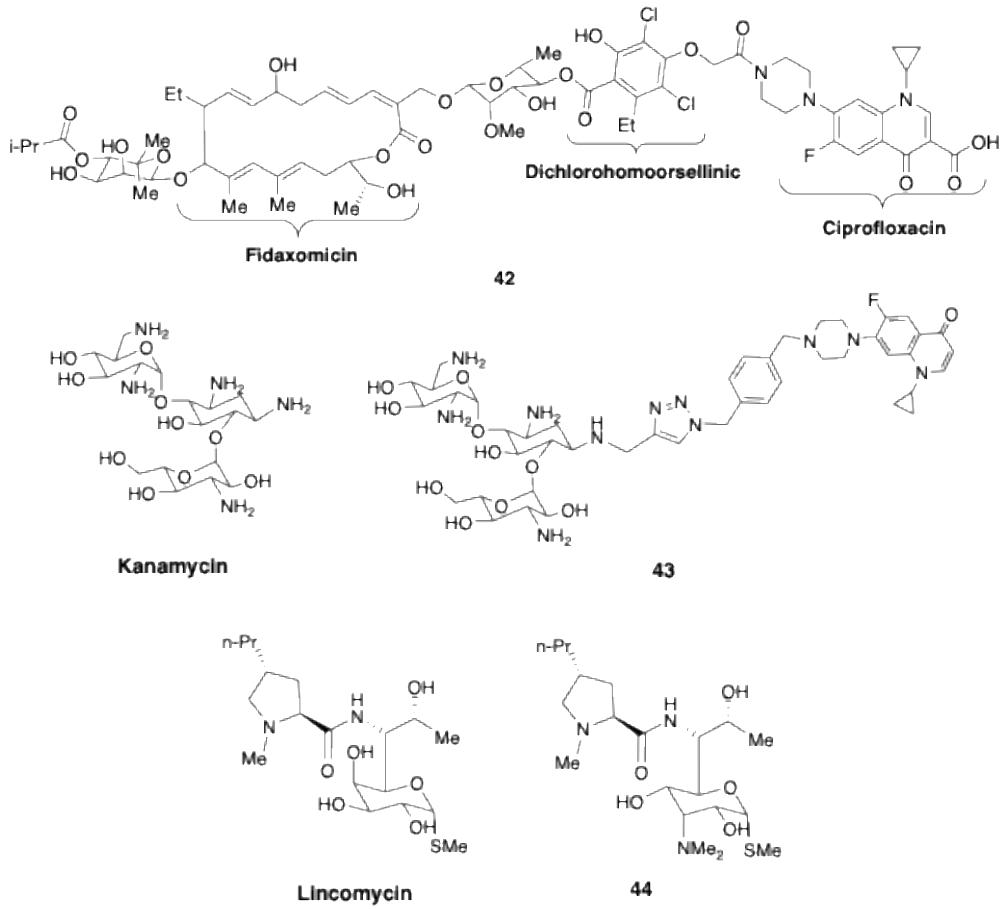


Fig. (6e). Mycin antibiotics.

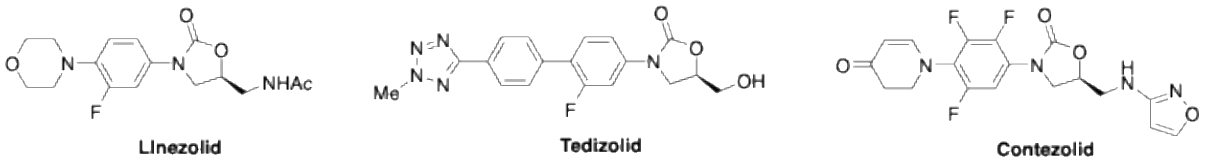


Fig. (7). Clinically approved oxazolidone antibiotics.

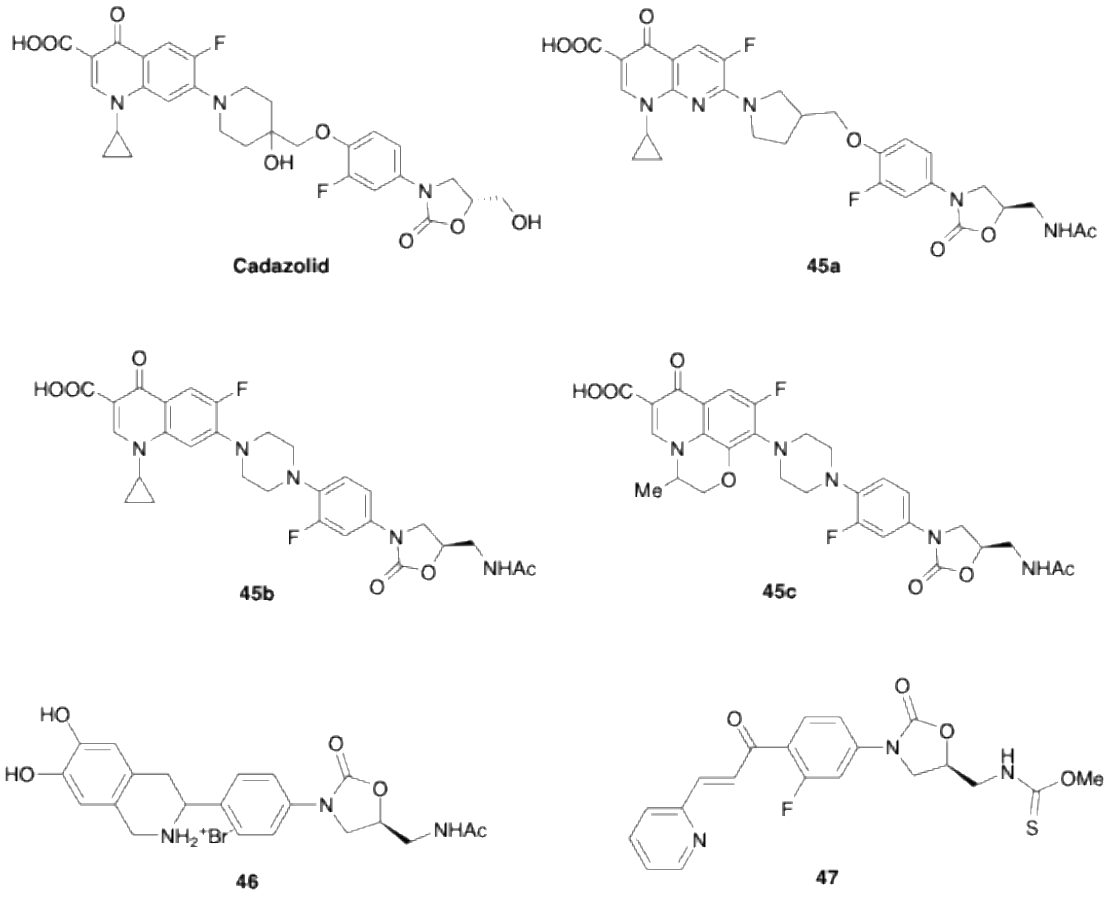
delayed the development of resistance in *E. coli* and *Bacillus subtilis* [66]. However, compound **44**, derived from a substituted 3-deoxy lincomycin bridged to the desosamine unit of erythromycin, showed limited antimicrobial activity, which was attributed to poor cell penetration or efflux [67]. Extensive studies suggest that the most effective antibiotics for treating *Clostridium difficile* infections remain vancomycin, fidaxomicin, and metronidazole (Fig. **6e**) [68].

4.3. Oxazolidinones - Thiazolidinones - Imidazolidinones

Clinically approved oxazolidinone antibiotics, including linezolid, tedizolid phosphate, and contezolid, are effective against G+ bacteria. Reviews on the development of new oxazolidinones have been extensively published by Renslo *et al*., Michalska *et al*., and Yuan, Wang, and Liu *et al* [69-71]. A perspective review specifically focused on oxazolidinone antibacterial agents was also published by Luo, Wang, and Tang *et al.* [72]. Furthermore, Aggen *et al*. provided guidelines for overcoming efflux and permeation barriers in *Escherichia coli* (Fig. **7**) [73].

Hybrids **45a-c**, created by combining two antibiotics, were derived from the clinically approved cadazolid, which is effective against *Clostridium difficile* infections [74-78]. Another promising antibacterial agent, hybrid **46**, was developed by replacing the morpholino group of linezolid with a tetrahydroisoquinoline-6,7-diol [79]. Further modification of linezolid in hybrid **47** involved replacing the acetamide group with a thiocarbamate and substituting the morpholine ring

with a 3-pyridin-2-yl-acryloyl group. This hybrid was reported to show an *in vitro* antimicrobial MIC range from 0.25 to 2 μg/mL [80]. Subsequent modifications led to the development of isoxazolinyl oxazolidinone hybrids **48**, which were 2-10 times more potent than linezolid against *Staphylococcus aureus*, *Bacillus cereus*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *Streptococcus pyogenes* [81]. Further optimization produced hybrid **49**, which exhibited even greater antibacterial activity, with an MIC ranging from 0.006 to 195 μg/mL [82]. Benzo[*d*]thiazole-based thiazolidinone hybrids were evaluated against a broad range of bacteria, including *Salmonella typhimurium*, *Staphylococcus aureus*, *Escherichia coli*, and *Listeria monocytogenes*, as well as resistant strains like *Pseudomonas aeruginosa*, *E. coli*, and MRSA. These hybrids showed minimal bactericidal concentrations (MBCs) and minimal inhibitory concentrations (MICs) in the ranges of 0.15-3 mg/mL and 0.1-2 mg/mL, respectively. Among them, conjugate **50** proved to be the most potent [83]. Additionally, novel pyrrole-thiazolidone hybrids were designed and tested against ESKAP (Enterococcus faecium, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) bacteria. Hybrid **51** demonstrated significant activity against *Mycobacterium tuberculosis* H37Rv, multiple MRSA strains, and reduced *S. aureus* biofilm formation [84]. In the pursuit of new antibiotics for various infections, several stable lactam analogs, such as hybrid **52**, derived from the marine depsipeptide solonamides, exhibited comparable activity against the *Staphylococcus aureus* AgrC receptor [85]. Furthermore, hybrid **53**, which combines fragments of sparsomycin and linezolid, showed strong interaction with the 50S ribosome. This led to the development of diaryl analogs **54**, which displayed potent activity against both linezolid-susceptible and -resistant G+ bacteria, as well as common G- bacteria like *Haemophilus influenzae* and *Moraxella catarrhalis* (Fig. **8**) [86].



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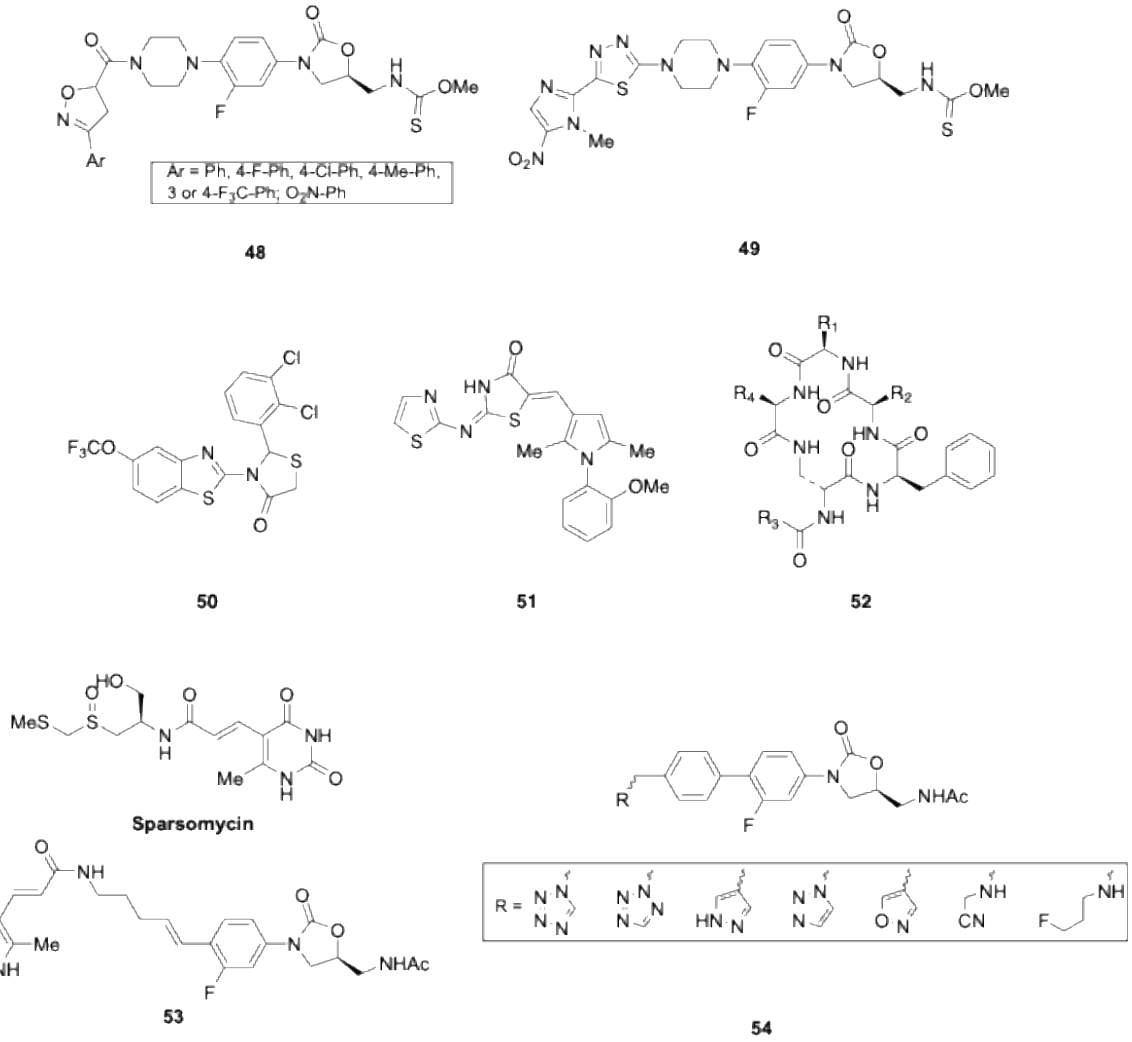


Fig. (8). Oxazolidinones, thiazolidinones and imidazolidinones.

4.4. Quinolines and Quinolones

Quinolone antibiotics represent a diverse class of compounds characterized by their amino and carboxylic functionalities, which facilitate the creation of hybrids with other biologically active drugs. Among these, ciprofloxacin is the most commonly used quinolone for forming such conjugates. This section explores various quinolone hybrids, specifically those combined with other antimicrobial agents, often referred to as "mycins."

4.4.1. Reviews on Quinolone Hybrids

Extensive reviews on the advancements in synthetic quinolones and their hybrids have been published by Monga *et al.*, as well as Blaskovich *et al.*, Feng and Liu, and Zhao and Ji. These reviews offer in-depth insights into the development and applications of quinolone-based hybrids [87-90].

4.4.2. Key Quinolone Hybrids and Their Activities

- **Miconazole-Ciprofloxacin Hybrid (55):** A fluorinated analog of the antifungal miconazole, tethered to ciprofloxacin, exhibited exceptional antibacterial activity [91].
- **Fluconazole-Clinafloxacin Hybrid (56):** This hybrid showed significant antibacterial efficacy [92].
- **Fluoroquinolone-3-Arylfuran-2(5H)-one Hybrid (57):** The combination of fluoroquinolones with novel 3-arylfuran-2(5*H*)-ones resulted in broad-spectrum antibacterial activity against MDR strains of both G+ and G- bacteria. Compound **57**, with an MIC_{50} of 0.11 mg/mL against MDR *E. coli*, was approximately 50 times more potent than ciprofloxacin. It also inhibited DN832-A gyrase and tyrosyl-RNA synthase, further enhancing its therapeutic potential [93].

- **Metronidazole-Quinolone Hybrids (58, 59):** The linkage of metronidazole fragments to quinolones produced hybrids such as **58** and **59**, which showed promising antibacterial activity. Hybrid **59** intercalates into the DNA of *Pseudomonas aeruginosa* through a Cu^{2+} bridge, forming a stable ternary complex [94, 95].
- **Trimethoprim-Quinolone Hybrids (60, 61):** These hybrids, created by connecting fluoroquinolones to the pyrimidine fragment of trimethoprim using click chemistry, exhibited broad-spectrum activity against both drug-resistant and drug-sensitive G+ and G- bacteria. Notably, they were non-toxic, adding to their therapeutic potential [96].
- **Ciprofloxacin-Naringenin Hybrid (62):** The combination of ciprofloxacin with the flavonoid efflux pump inhibitor naringenin led to hybrid **62** that exhibited strong antibacterial activity. Its MIC_{50} values ranged from 0.062 to 0.71 mg/mL against MDR *Escherichia coli* ATCC 35218, tetracycline-resistant *Bacillus subtilis* ATCC 6633, MRSA ATCC 25923, and amphotericin B-resistant *Candida albicans* ATCC 90873 [97].
- **Ciprofloxacin-Sulfonamide Hybrids (63, 64):** Hybridization of ciprofloxacin with sulfonamides led to compounds that showed significant improvements in antibacterial activity against both G+ and G- pathogens, such as *S. aureus Newman* and *E. coli* ATCC 8739, compared to ciprofloxacin alone [98].
- **Piperazinyl Quinolone Derivatives (65):** These derivatives, including compound **65**, demonstrated enhanced potency against G+ bacteria, such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, outperforming both norfloxacin and ciprofloxacin. The nature of the thio group (S *vs*. SO_2) played a crucial role in determining the compound's activity [99].
- **Fluoroquinolone Hybrids (66-68):** Additional optimization of antibacterial activity was achieved with hybrids of quinolones and fluoroquinolones. Compounds **66-68** displayed strong activity against *Salmonella typhi*, *Staphylococcus aureus*, and *Streptococcus pyogenes*, respectively (Fig. **9**) [100].

4.4.3. Addressing Antibiotic Resistance through Quinolone Hybrids

As bacterial resistance to numerous antibiotics, including quinolones, continues to rise, there has been an intensified focus on developing a wide range of hybrid compounds. The primary objective is to combat or delay the development of resistance. To achieve this, quinolone antibiotics are being linked with biologically active molecules or fragments, with the expectation that these hybrid compounds may offer enhanced efficacy compared to their individual components. Additionally, the hope is that hybridization will slow the emergence of bacterial resistance. Below are selected examples of quinolone-based hybrids, compounds **69-81**:

- **Compound 69:** A hybrid of ciprofloxacin and 2-fluoroaniline, demonstrating promising antibacterial activity [101].
- **Compound 70:** Norfloxacin linked to a pyrimidine, showing activity against both G+ and G- bacteria [102].
- **Compound 71:** A combination of ciprofloxacin and pyrazine, exhibiting effective antimicrobial properties [103].
- **Compound 72:** A ciprofloxacin-thiadiazole hybrid, which exhibited enhanced antibacterial activity [104].
- **Compound 73:** Combining ciprofloxacin with 1,2,4-triazole gave a hybrid that showed significant antibacterial efficacy [105-106].
- **Compound 74:** Ciprofloxacin hybridized with the natural product isatin *via* a propylene bridge, displayed strong antibacterial activity [107].
- **Compound 75:** A quinolone-7-thiazoxime hybrid mitigated bacterial resistance by binding to DNA gyrase [108].
- **Compound 76:** A ciprofloxacin-benzopyrone conjugate, demonstrated effective bactericidal activity, with MICs ranging from 0.5-2 μM [109].
- **Compound 77:** A quaternary ammonium salt derived from gatifloxacin was active against *E. coli* gyrase supercoiling [110].
- **Compound 78:** A hybrid of fluoroquinolone and a triazolyl ethanol fragment, exhibiting both antimicrobial and antifungal activity, superior to chloramphenicol, norfloxacin, and fluconazole [111].
- **Compound 79:** By combining DAPT and cis-1,3-diamino-piperidine-triazines, this hybrid shows activity against *Pseudomonas aeruginosa*, even in the presence of serum [112].

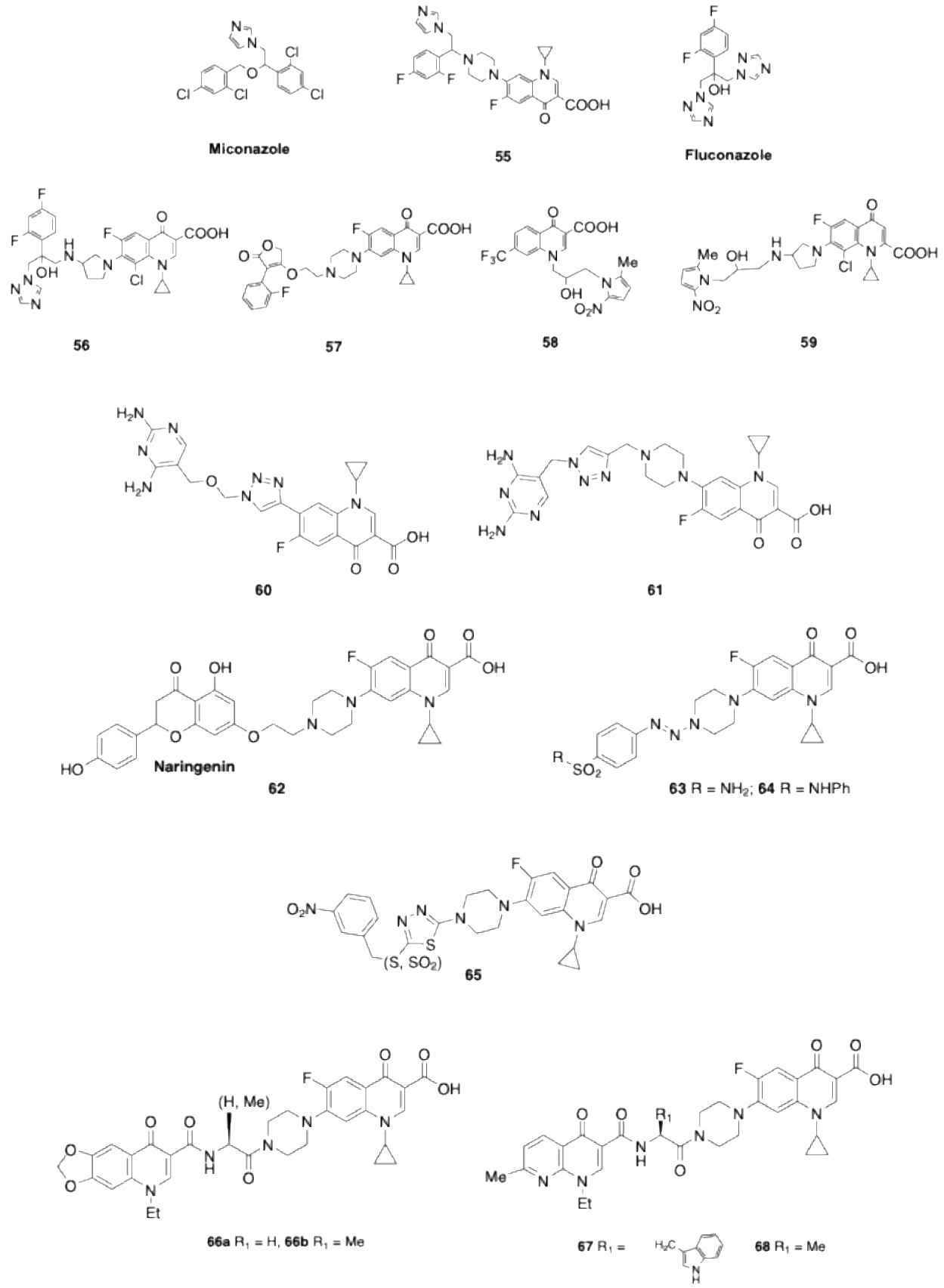


Fig. (9). Quinolone antibacterials.

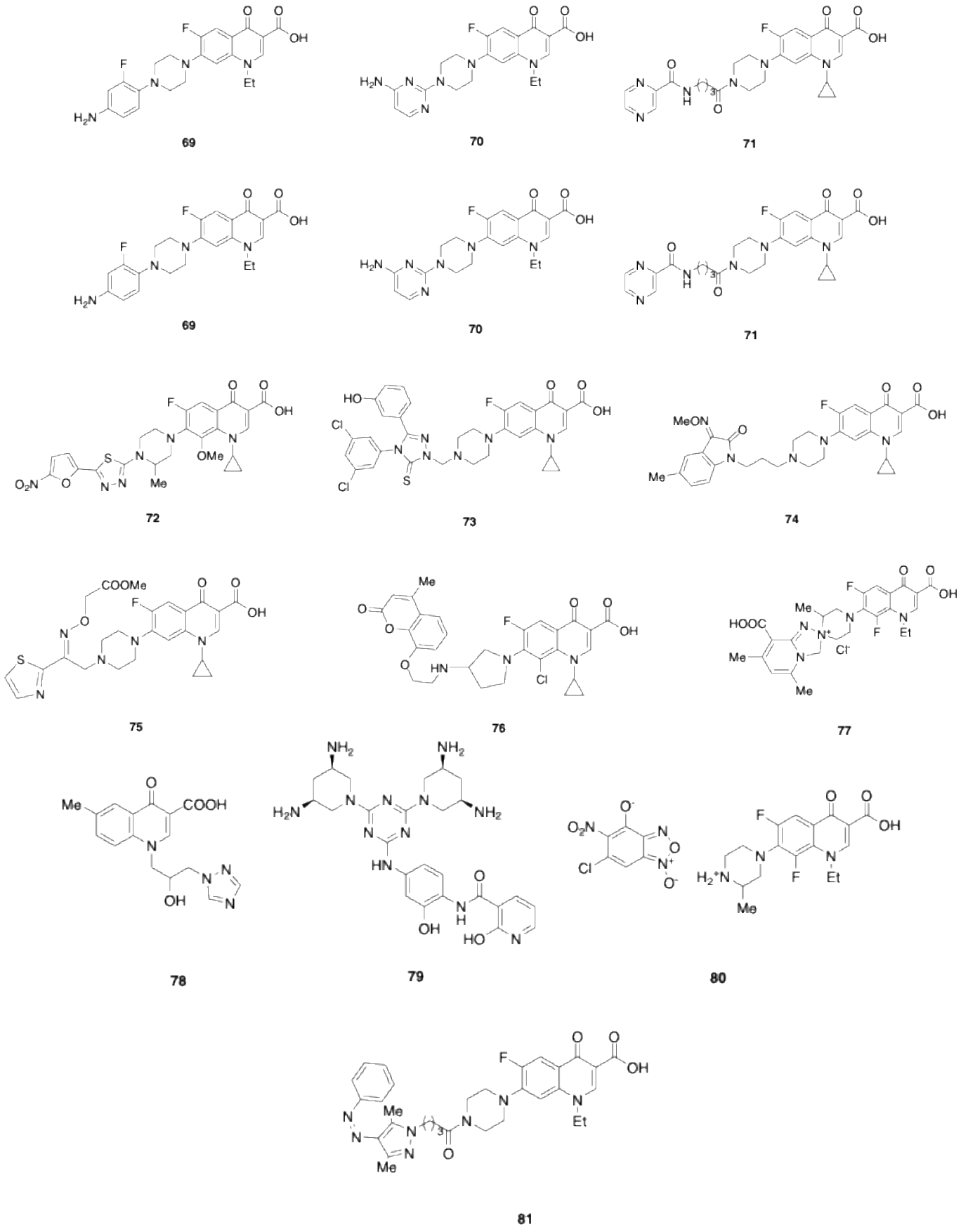


Fig. (10). Miscellaneous quinolone antibiotic hybrids.

- **Compound 80:** A hydrolyzed benzofuroxan-fluoroquinolone hybrid that forms salts with improved antibacterial activity against *Bacillus cereus* 8035 compared to the parent compound lomefloxacin [113].
- **Compound 81:** A photoswitchable antibiotic combining a quinolone with azopyrazole, which demonstrates bidirectional photoisomerization and enhances antibacterial activity upon irradiation, particularly against G+ bacteria (Fig. **10**) [114].

These quinolone hybrids represent a promising avenue for developing more potent antibiotics and overcoming the challenge of bacterial resistance.

4.5. Assorted Antibacterial Hybrids

Recent studies on antibacterial hybrids featuring oxadiazole derivatives have identified compounds such as **82-84**, which typically demonstrate activity against both G+ bacteria (*e.g.*, *Staphylococcus aureus*, *Bacillus subtilis*) and G- bacteria (*e.g.*, *Escherichia coli*, *Pseudomonas aeruginosa*) [115-117]. Other hybrids incorporating sulfonamido groups, such as compound **85**, have shown promising potency against *E. coli* K2, while hybrid **86** exhibited inhibitory effects against resistant *Enterococcus faecalis* [118, 119].

The metronidazole-iminotetrahydroberberine hybrid **87** displayed broad-spectrum antibacterial activity, with an MIC of 0.024 mM against *P. aeruginosa*, outperforming berberine, metronidazole, and norfloxacin in terms of potency [120]. Dihydrotriazine hybrids, represented by compound **88**, exhibited effective inhibitory effects with an MIC of 0.5 μg/mL against various bacterial strains, including G+ (*S. aureus* 4220 and QRSA CCARM 3505) and G- (*E. coli* 1924) pathogens [121].

New triazole-fused imidazo[2,1-*b*]thiazole hybrids, such as compound **89**, showed robust inhibition of both G+ and G- bacteria, with MICs ranging from 1.9 to 3.9 μg/mL [122]. Xanthone-muchimangin hybrids, represented by compound **90**, exhibited significant antibacterial activity against *S. aureus*, *B. subtilis*, *Klebsiella pneumoniae*, and *E. coli* [123].

Compounds like **91**, which act as potent low-nanomolar inhibitors of bacterial DNA gyrase and topoisomerase IV, demonstrated strong antibacterial effects against ESKAPE pathogens. These hybrids were non-toxic *in vitro* and showed impressive potency against both G+ (MICs ranging from 0.0078 to 0.0625 μg/mL) and G- pathogens (MICs ranging from 1 to 2 μg/mL). The dual enzyme inhibition mechanism of these compounds suggests a reduced risk of bacterial resistance development (Fig. **11**) [124].

5. ANTIFUNGAL HYBRIDS

Fungi, intricate architects of the microbial world, encompass over 300 known human pathogens, many of which are responsible for severe and difficult-to-treat diseases. These include aspergillosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mycetomas, and paracoccidioidomycosis. Individuals with compromised immune systems, such as those with HIV/AIDS, cancer, or organ transplants, are especially vulnerable to infections caused by genera like *Aspergillus*, *Candida*, *Cryptococcus*, *Histoplasma*, and *Pneumocystis*. In addition to internal infections, fungi can affect the skin, nails, hair, and eyes, causing conditions like ringworm and athlete's foot. Fungal spores also play a role in triggering allergic reactions, which can result in a range of immune responses.

The arsenal of antifungal agents available for treatment includes a diverse range of compounds. Key classes include polyenes, such as amphotericin B, fluorocytosine, and azoles (both imidazoles and triazoles). Other important agents include allylamines like terbinafine and naftifine, as well as griseofulvin and tolnaftate. These antifungals have been further optimized into hybrid forms to enhance efficacy and broaden their therapeutic potential in treating fungal infections.

In parallel, pulmonary tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a major global health threat, claiming over two million lives annually. Although antibiotics are the primary treatment for TB, there has been a growing focus on hybrid compounds that target both fungal infections and TB. This review explores these hybrid compounds, which often share structural similarities aimed at increasing effectiveness against both types of pathogens.

5.1. Selected Antifungal Hybrid Reviews

Several comprehensive reviews have discussed antifungal hybrids in detail:

- Marzi *et al*. provided an extensive review of biologically active 1,2,3-triazole derivatives, including clinically approved antifungal hybrids [125].
- Ghani reviewed various azole derivatives as antifungals [126].
- Wang *et al*. explored antifungal tetrazole hybrids [127].

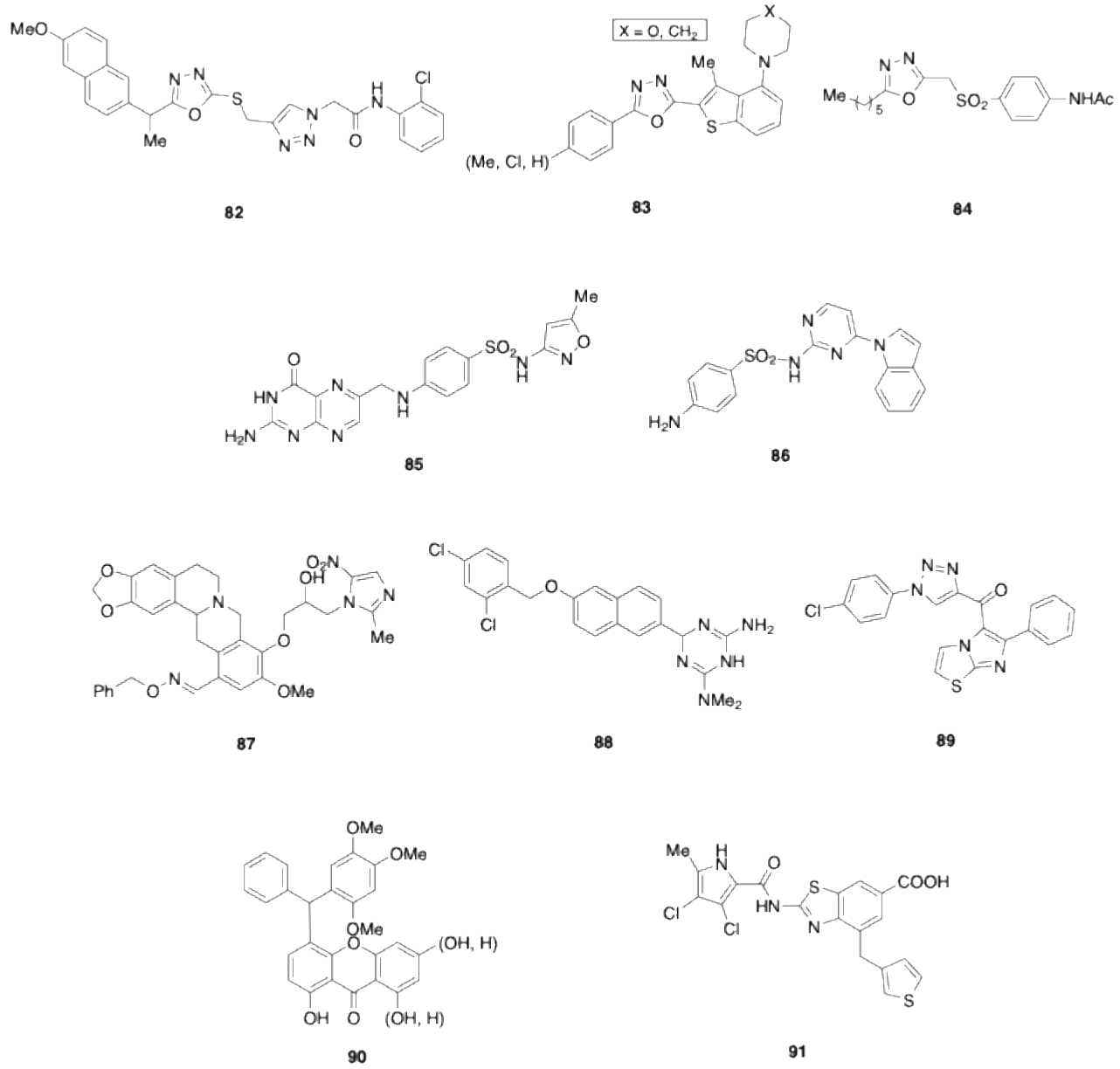


Fig. (11). Diverse antibacterial hybrids.

- Sharma and Chandrika presented a minireview on promising antifungal conjugates [128].
- Jin summarized antifungal flavonoids [129].
- Wan *et al.* examined β-carboline as a basis for antifungal compounds [130].
- Karpoormath *et al.* reviewed the piperazine platform for drug development, including antifungal agents, covering literature from 1971 to 2019 [131].
- Emami *et al*. discussed the structures and properties of voriconazole analogs [132].
- Muszalska-Kolos *et al*. published a perspective on the antifungal effects of azole and amphotericin B conjugates with fatty acids, polysaccharides, proteins, and synthetic polymers [133].

5.2. 1,2,3- and 1,2,4-Triazole-Derived Hybrids

Several reviews have also examined hybrids with antitubercular properties:

- Elsman *et al*. presented a synopsis of 5-nitrofuran derivatives as potential antitubercular agents [134].
- Antitubercular hybrids based on thiazolidin-4-ones were reviewed by Trotsko [135].
- Sharma and Tiwari discussed antitubercular triazole derivatives [136].

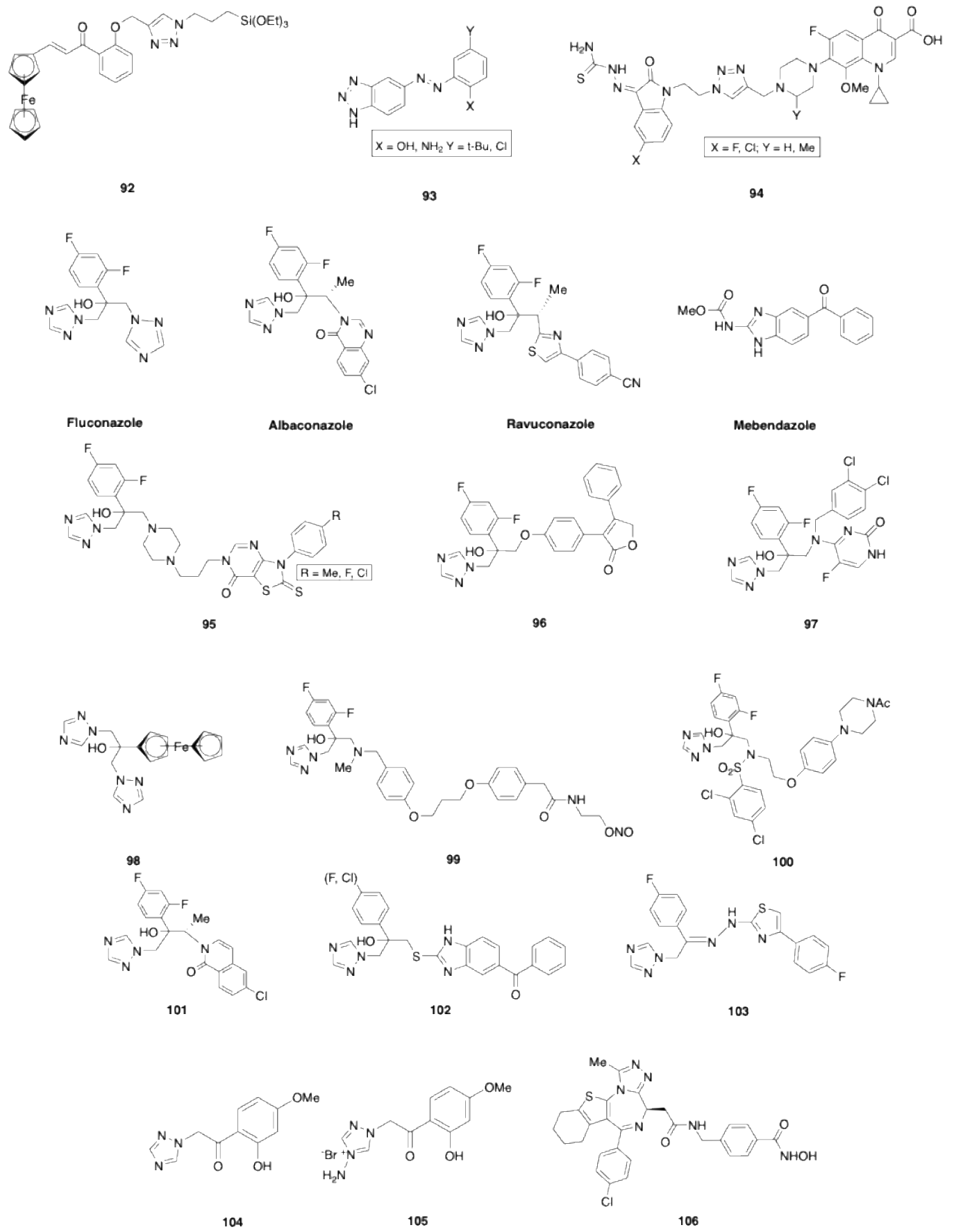


Fig. (12). Antifungal triazole hybrids.

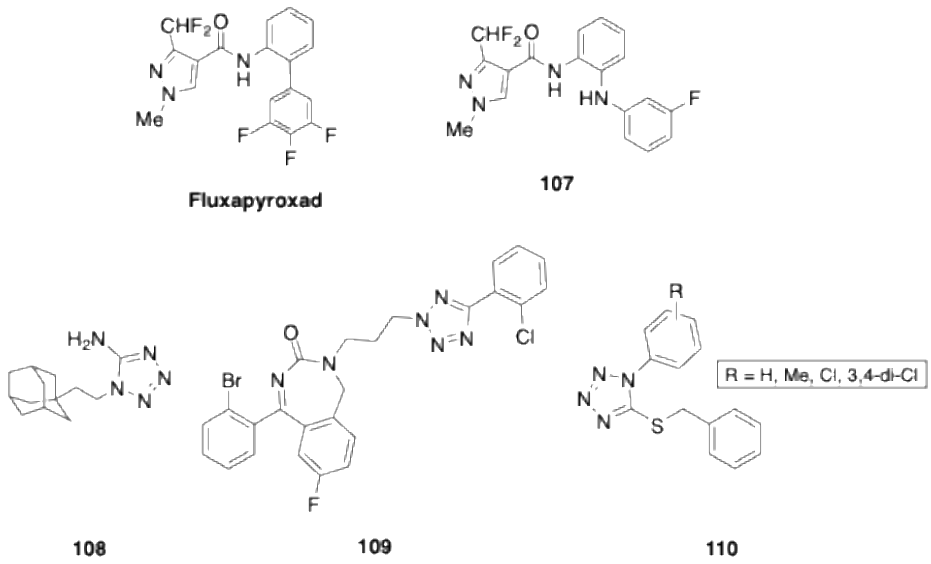


Fig. (13). Antifungal pyrazole and tetrazole hybrids.

- In 2022, Dhameliya *et al*. published a five-year review of anti-tubercular compounds [137].

Notable antifungal hybrids include:

- Ferrocene-chalcones linked *via* a 1,2,3-triazole ring to trialkoxysilane groups (compound **92**), which exhibited excellent efficacy against *Giardia lamblia* [138].
- Benzotriazoles (compound **93**) demonstrating a broad spectrum of antifungal activity [139].
- Fluoroquinolones linked to indolones *via* a 1,2,3-triazole-carrying bridge (compound **94**) showing significant anti-mycobacterial activity [140].
- Several anti-mycobacterial hybrids (compounds **95-100**) incorporating fluconazole and its analogs, including ravuconazole [141-146].
- Albaconazole-based hybrids (compound **101**), which exhibited potent *in vitro* antifungal activity against *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*, with MIC values ranging from <0.008 to 2 μg/mL. These hybrids also showed effectiveness against fluconazole-resistant *C. auris* and improved survival in mice infected with *C. albicans* [147].
- Similar promising activities were observed for compounds **102** and **103** [148-149].
- Azole (compound **104**) and azolium (compound **105**) fragments linked to phenols are non-toxic antifungals [150].

Hybrids effective against resistant *C. albicans* include dual inhibitors of the bromodomain protein BRD4, linked to an HDAC inhibitor, such as compound **106** (Fig. **12**) [151].

5.3. Pyrazole and Tetrazole-Derived Antifungal Hybrids

The pyrazole carboxamide hybrid **107** exhibits significant antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum*, *Phytophthora infestans*, and *Fusarium graminearum*. It outperforms the fungicide fluxapyroxad and targets succinate dehydrogenase as its mechanism of action [152]. The 5-aminotetrazole hybrid **108** shows promising potential for treating candidal infections, with potent activity at concentrations as low as 1.3 μM. It is effective both as a standalone treatment and in combination with polyene antifungals, particularly nystatin [153]. Furthermore, hybrids incorporating tetrazole units linked to benzodiazepines, such as compound **109**, inhibit *Candida* without inducing toxicity [154]. Other hybrids, like compound **110**, synthesized from various precursors, have demonstrated a broad spectrum of antiparasitic activities, including antibacterial, antimycobacterial, antifungal, and antiproliferative effects (Fig. **13**) [155].

5.4. Benzimidazole, Imidazole, and Imidazoline-Derived Antifungal Hybrids

Two studies by Sun *et al*. investigated hybrids combining classical NSAIDs (*e.g*., ketoprofen, naproxen, flurbiprofen) with diazole and triazole moieties, leading to compounds like **111**. These hybrids effectively inhibited the CYP51 enzyme, resulting in the accumulation of reactive oxygen species (ROS) and subse-

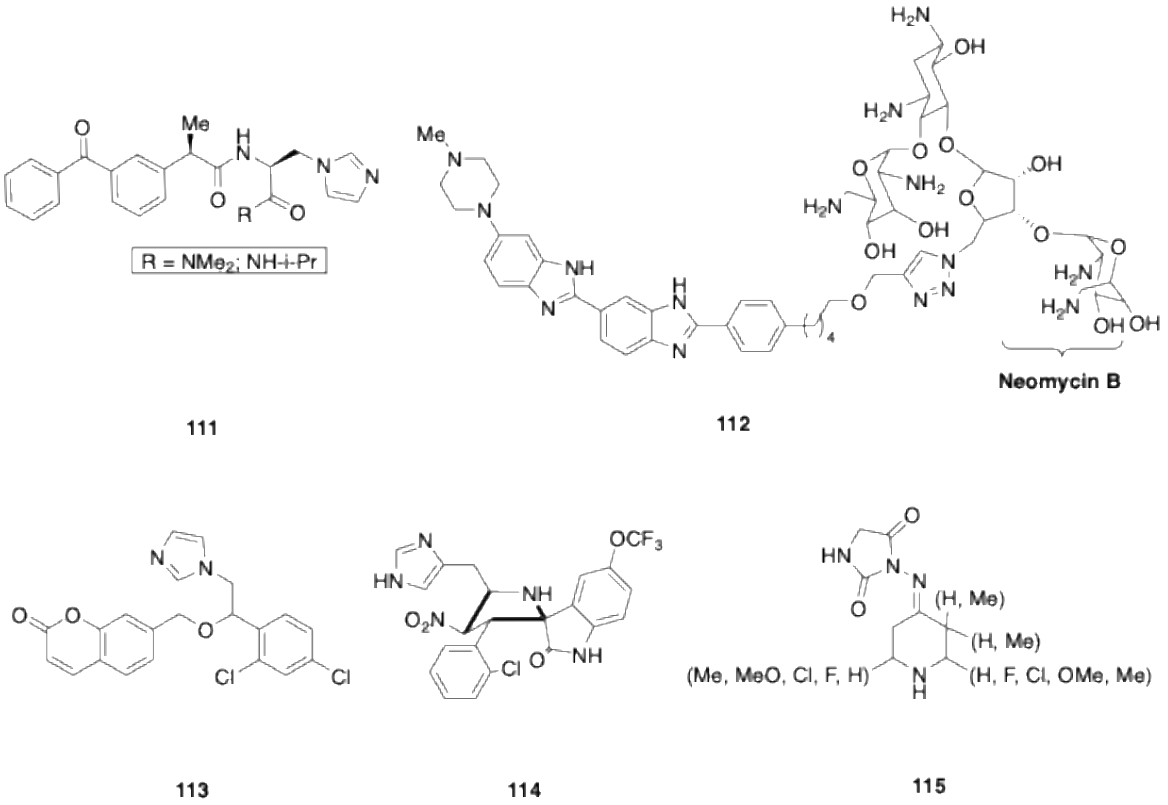


Fig. (14). Benzimidazole, imidazole and imidazoline-derived hybrids.

quent fungal apoptosis. Additionally, they inhibited COX-2, an enzyme involved in inflammatory processes [156, 157]. Benzimidazole-based hybrids, such as **112**, demonstrated antifungal activity against *Candida* spp. and *Cryptococcus neoformans*, with MICs ranging from <0.063 to 1 μg/mL. These compounds also exhibited favorable ADMET (absorption, distribution, metabolism, excretion, toxicity) properties compared to the standard antifungal fluconazole. Docking studies revealed that the benzimidazol-2-ylthio fragment played a key role in their antifungal efficacy [158].

Coumarin-imidazole hybrids, exemplified by **113**, exhibited notable antibiofilm activity and were effective against drug-resistant fungi, including fluconazole-resistant *C. albicans*, by inhibiting ergosterol biosynthesis [159]. The spirooxindolo-pyrrolidine hybrid **114** showed antifungal activity and inhibited biofilm formation, with no observed toxicity to mammalian cells [160]. A series of novel 2-thioxoimidazolidin-4-one analogs, such as **115**, displayed broad antifungal and antimicrobial activity against a variety of pathogens, including several *Candida albicans* strains, *Staphylococcus aureus*, β-hemolytic *streptococcus*, *Vibrio cholerae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Aspergillus flavus* (Fig. **14**) [161].

5.5. Thiazole and Hydrazine-Derived Antifungal Hybrids

The hybrid **116**, with an MIC of 1.56 mg/mL, effectively inhibited 99% of the growth of the *M. tuberculosis* H37Rv strain [162]. Methylidenebenzenesulfonohydrazones, when linked to heterocycles, were tested for antifungal activity against phytopathogenic fungi such as *Fusarium graminearum*, *Alternaria solani*, *Valsa mali*, *Phytophthora capsici*, *Fusarium solani*, *Botrytis cinerea*, and *Glomerella cingulata*. Among these, compound **117** showed significant activity at concentrations of 100 μg/mL [163]. The selenochroman hybrid **118** demonstrated substantial antifungal potency, with MICs ranging from 0.5 to 2 μg/mL against fluconazole-resistant strains of *Candida albicans*, *Cryptococcus neoformans*, *Candida zeylanoides*, and *Aspergillus fumigatus* [164]. Pyrimido[4,5-*d*]pyridazinone-N-acylhydrazone hybrids, tested against *Paracoccidioides brasiliensis* (Pb18), the causative agent of paracoccidioidomycosis, showed promising results. Compound **119** exhibited superior activity compared to amphotericin B [165].

The phenolic natural product dihydrozingerone, known for its antioxidant and antibacterial properties, when combined with thiazole hydrazine, resulted in

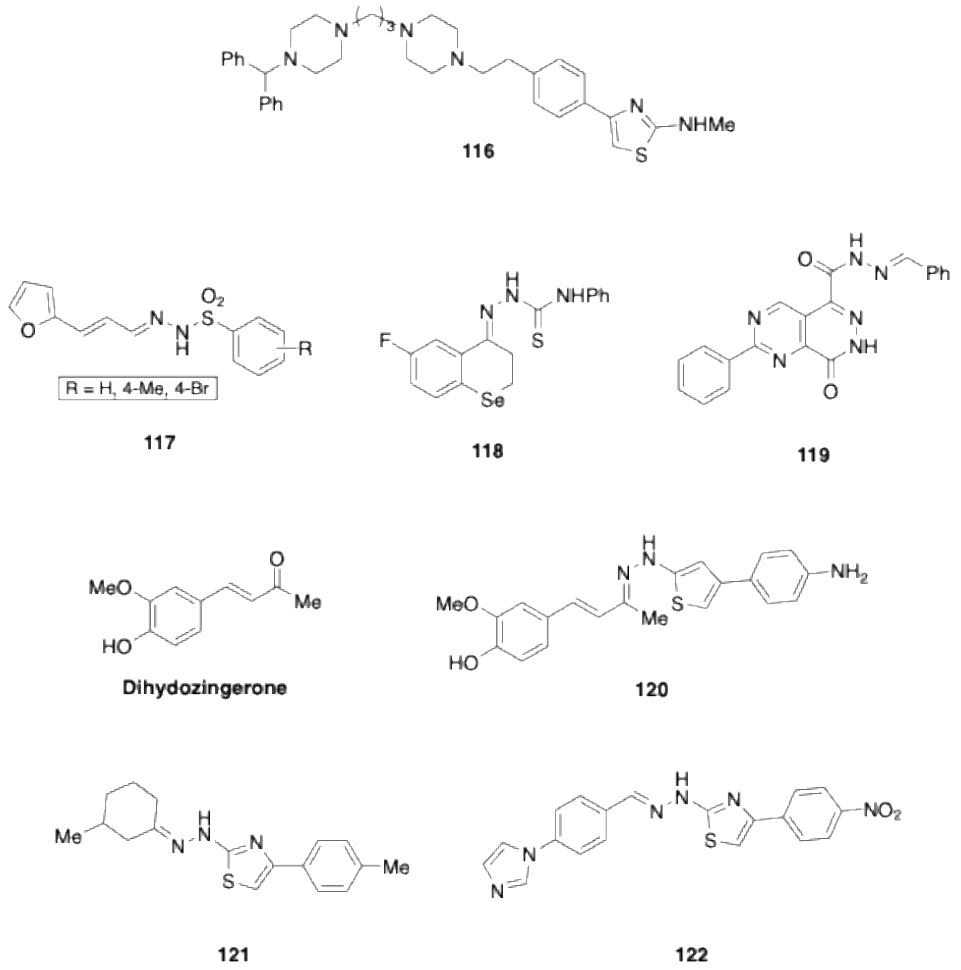


Fig. (15). Antifungal hybrids derived from thiazoles and hydrazine.

hybrid **120**. This compound demonstrated significant antifungal activity with an MIC of 1.5 μM and an IC_{50} of 0.48 μM against *M. tuberculosis* H37Rv [166, 167]. Thiazolylhydrazone hybrids were further studied for their antimycobacterial properties by Bizzarri *et al*. and Ozadali *et al*. Bizzarri's study, which compared the effects of these hybrids on 22 *Candida* isolates with clotrimazole, found compound **121** to be highly inhibitory. Ozadali's research revealed that another group of hybrids had MICs ranging from 1.03 to 72.46 μM against *M. tuberculosis* H37Rv, with compound **122** being the most potent, though slightly toxic. Both studies reported that the hybrids exhibited low overall toxicity (Fig. **15**) [168, 169].

5.6. Assorted Antifungals Inhibitory of *Candida albicans*

Candida albicans, along with related species like *C. tropicalis*, *C. parapsilosis*, and *C. glabrata*, is a common pathogen that forms biofilms and often infects immunocompromised individuals, such as those with HIV. This yeast is frequently used as a model organism for testing potential antifungal agents. Novel alkyl 1H-azole-1-carbodithioates (compounds **123a-c**) have demonstrated dual antimicrobial and spermicidal activities, inhibiting *Trichomonas vaginalis*, *Candida* species, and human sperm [170]. Carvacrol-thiourea hybrids (*e.g.*, **124**), which are known for their role as insect growth regulators, also showed potent antifungal properties [171]. Indoline and indole-based antifungal hybrids, represented by **125**, exhibited effective antibiofilm activity [172]. Quinoline-chalcone hybrids (compound **126**), when combined with fluconazole, displayed promising results against drug-resistant *Candida albicans* [173]. Among these, compound **127**, in combination with fluconazole, was the most effective against 14 strains of resistant *C. albicans*, working by inducing reactive oxygen species (ROS) accumulation and damaging mitochondrial membrane potential [174]. Benzamidine-based hybrids, such as compound **128**, offer a novel strategy to restore antifungal activity against drug-resistant fungi by counteracting efflux pump mechanisms [175]. Purinylthiazolylethanone hybrids, exemplified by compound **129**, exhibited potent

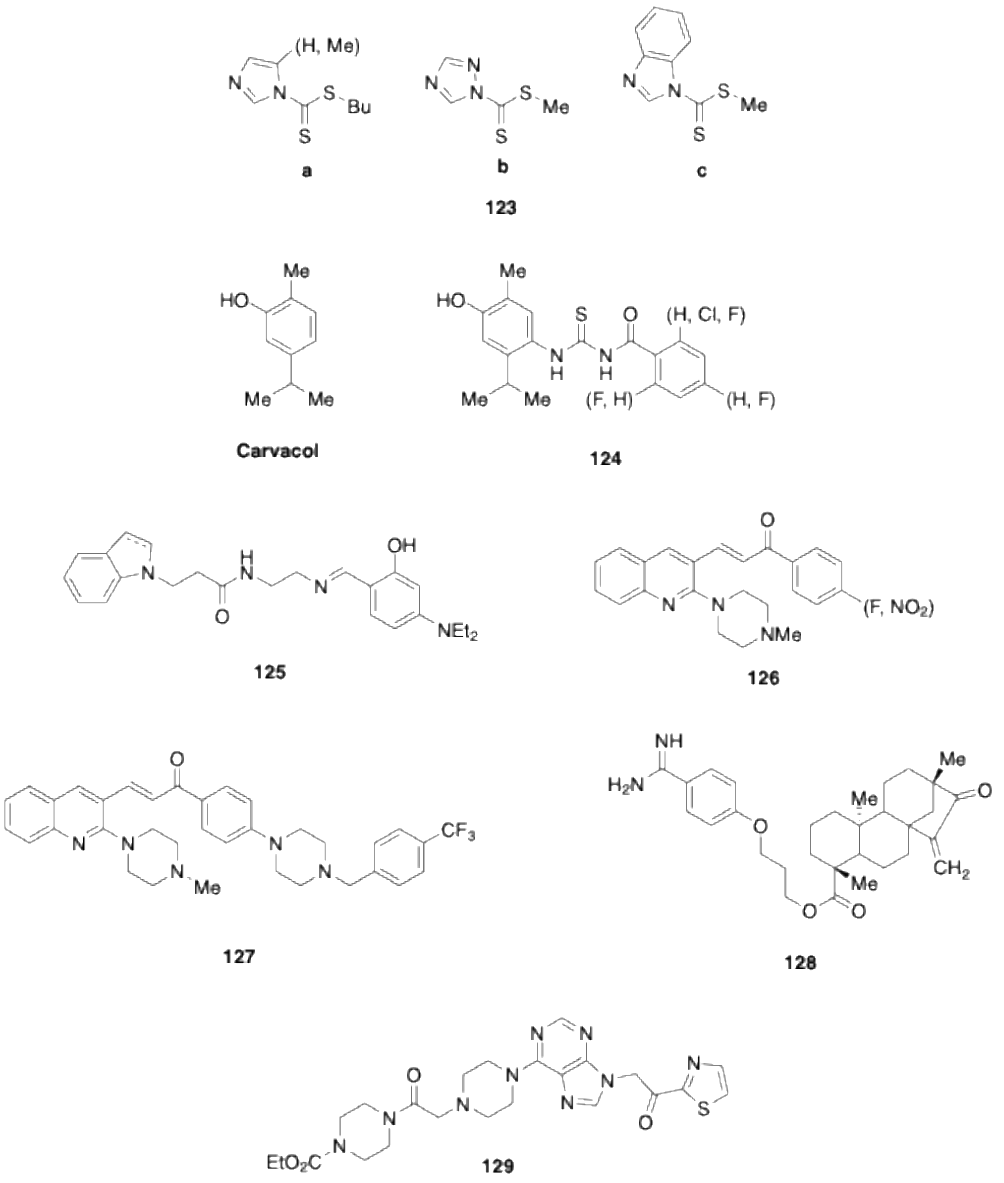


Fig. (16). Miscellaneous antifungals.

inhibition of *C. albicans* with an MIC of 1 mg/mL. This compound was non-toxic, showed no detectable resistance, and caused significant bacterial cell membrane damage, leading to protein leakage, increased ROS and reactive nitrogen species (RNS), and an overall fungicidal effect (Fig. **16**) [176].

5.7. Assorted Antifungal Hybrids

Hybrid **130**, created by coupling fenfuram and aniline fragments, exhibited potent fungicidal activity, with EC_{50} values of 0.223 and 0.037 mg/mL against the plant pathogenic fungus *Rhizoctonia solani* [177]. Hybrid **131** showed inhibition of inosine-5′-monophosphate dehydrogenase (IMPDH), highlighting its potential as an antitubercular agent [178]. The bis-4-chlorophenyl azetidine-2-one hybrid **132** emerged as the most potent antifungal within a series of cinnamamide analogs, displaying efficacy against the tomato and potato pathogen *Alternaria solani* [179]. Structure-activity relationship (SAR) studies on antitubercular agents BM212 and SQ109 revealed that incorporating a cyclohexylmethyl group into compounds like **133** resulted in more potent candidates [180]. Structural rigidification of early *N*-phenylpyrroles **134**, which were active against *M. tuberculosis*, led to the development of indole derivatives. Substituting with lipophilic groups produced indole hybrids, such as compound **135**, which exhibited potent activity (MIC 0.96 μg/mL) against both *M. tuberculosis* and drug-resistant isolates [181]. Among a series of pyrrole-derived hybrids tested against *M. tuberculosis*, compound **136** was the most active, with an MIC of 0.50 μg/mL [182]. Novel ben-

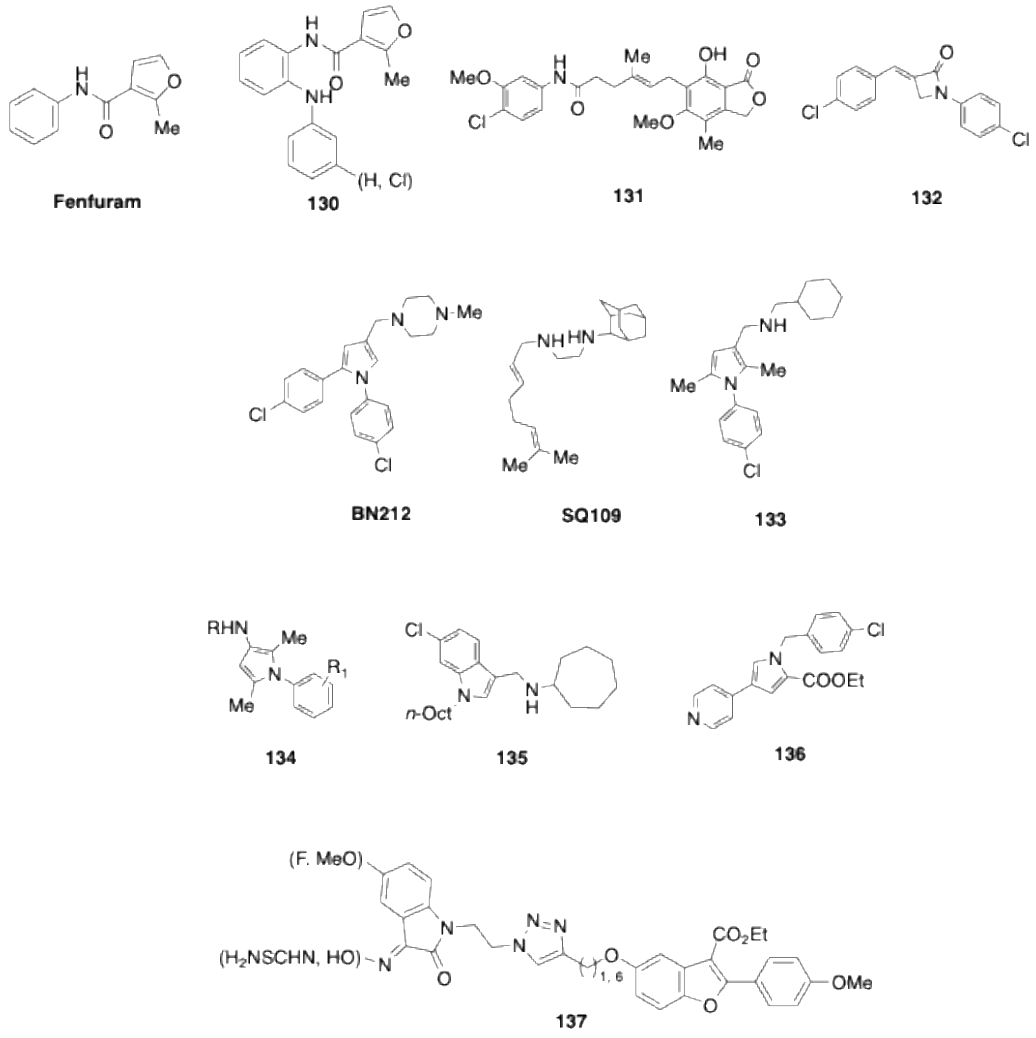


Fig. (17). Assorted antifungal hybrids.

zofuran-isatin conjugates, showing favorable toxicity profiles, proved effective against MDR *M. tuberculosis* strains, with hybrids like **137** providing the highest activity (Fig. **17**) [183, 184].

6. ANTITUBERCULAR HYBRIDS

6.1. Antitubercular Heterocyclic Azole-Derived Hybrids

A range of hybrids incorporating "azole" rings has demonstrated promising antitubercular activity. Isoniazid, the most effective approved antitubercular drug, inhibits 2-trans-enoyl-acyl carrier protein reductase (InhA). The free NH_2 group in isoniazid has facilitated the formation of various hybrids by linking it to different functional groups. Compounds **138-145** [185-190] have shown efficacy against *M. tuberculosis* (*Mtb*) strains, including H37Rv and *M. marinum*. Subsequent modifications involved replacing the pyridyl group of isoniazid with heterocyclic groups such as pyrrole **146** [191], benzofuran **147** [189] and other groups like phenyl, thienyl, furyl, and thiadiazolyl **148** [192]. Some hybrids containing the isoniazid unit have demonstrated significant antitubercular activity. For instance, triazole-bridged hybrids **149** exhibited low toxicity and potent inhibition of *Mtb* H37Rv (MIC = 0.78 mg/mL) [193]. Hybrids such as **150**, which incorporate aminoquinoline, isoindoline, and isoniazid, displayed promising antimycobacterial properties against the mc26230 strain of *M. tuberculosis* with an MIC of 5.1 μM [194]. The CQ-hydrazone-ferrocene hybrid **151**, where the pyridyl group of isoniazid is replaced with a chloroquinolyl group, also demonstrated antitubercular activity. This suggests that similar hybrids incorporating ferrocene and chloroquine (CQ) warrant further investigation (Fig. **18**) [195].

6.2. Benzimidazoles and Imidazoles

Ethionamide (ETH), an isoniazid analog and second-line anti-TB drug, along with its derivatives, has shown activity against *M. tuberculosis* H37Rv, with

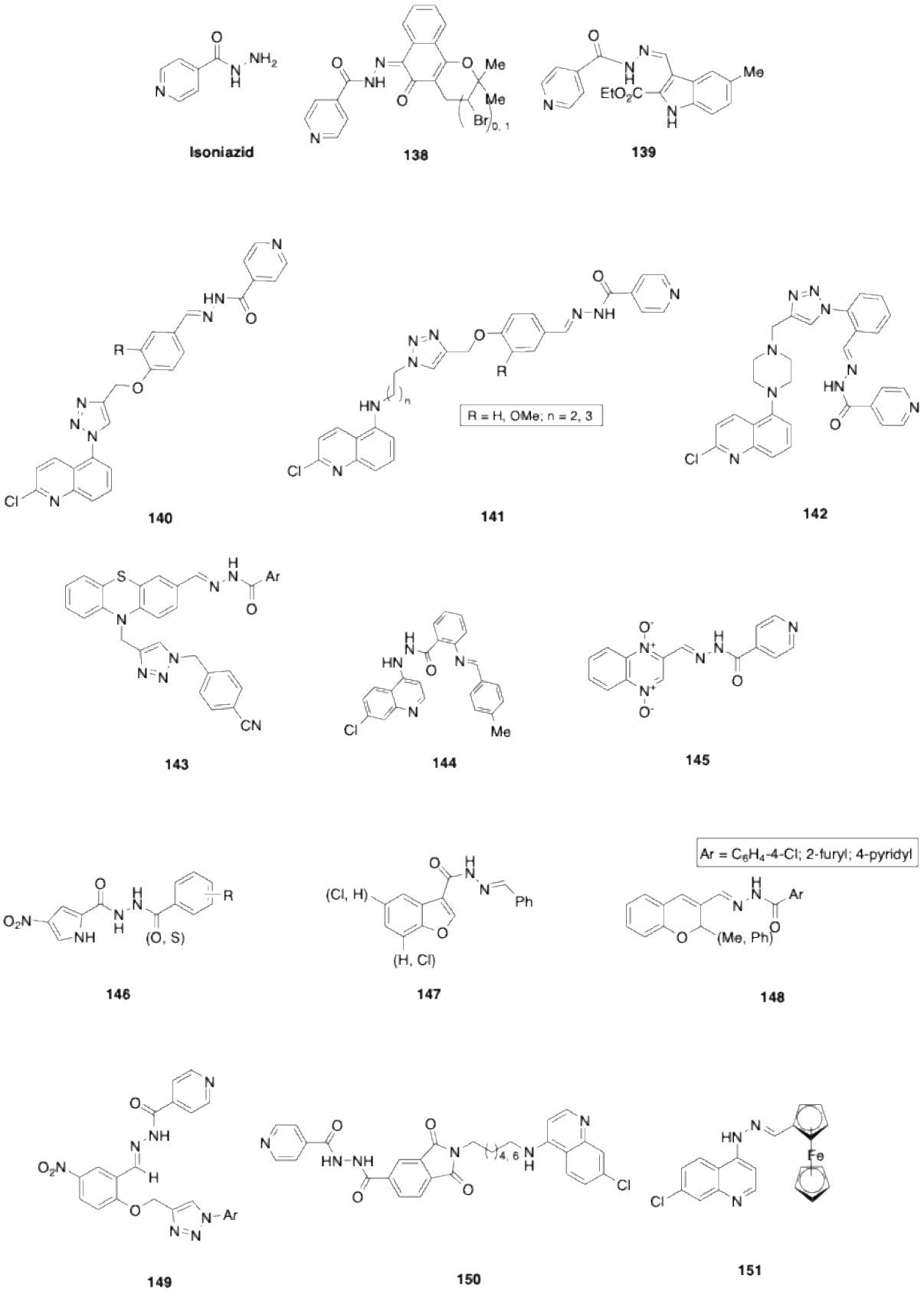


Fig. (18). Isoniazid-derived antitubercular conjugates.

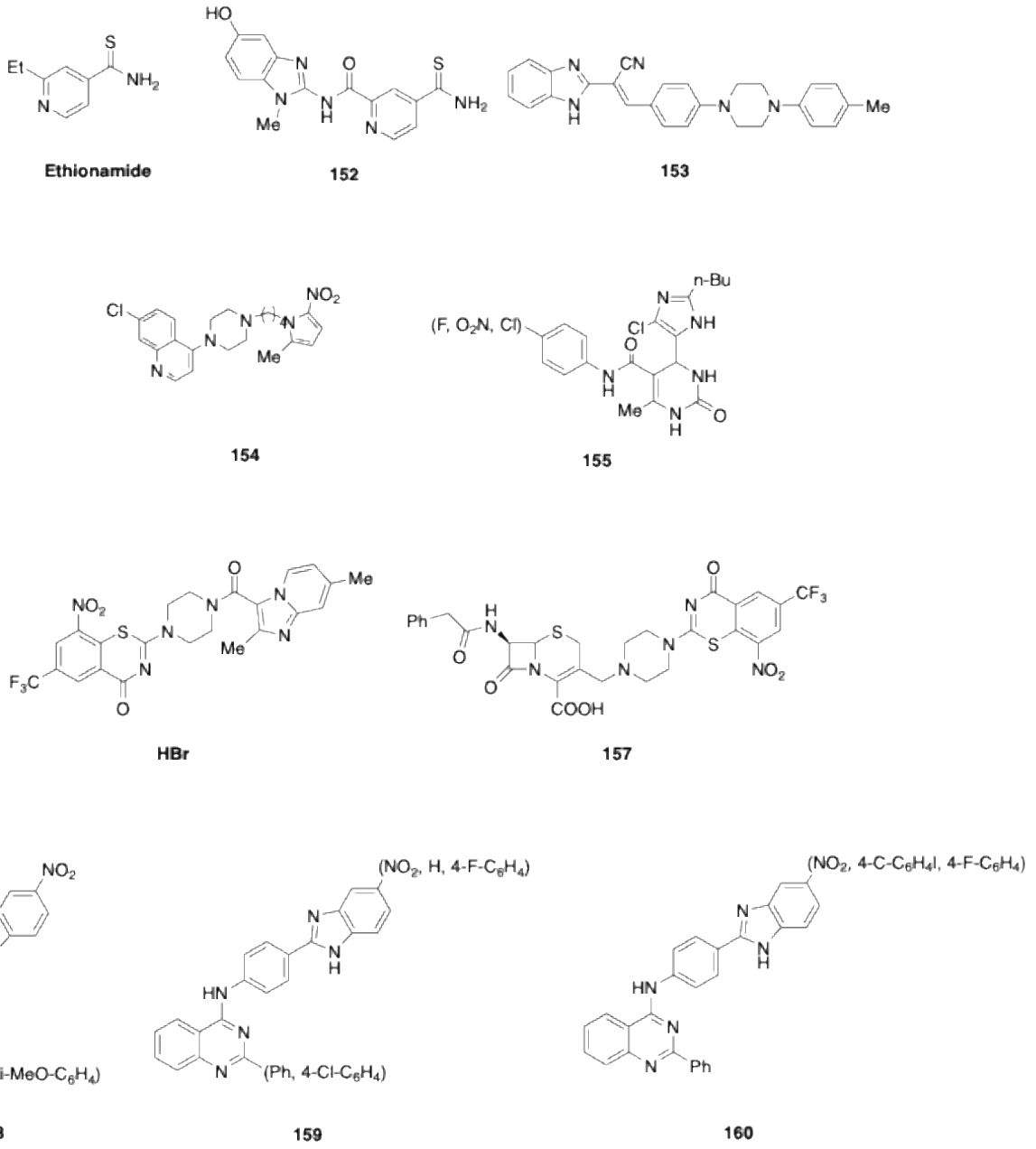


Fig. (19). Antitubercular hybrids based on benzimidazoles and imidazoles.

MICs ranging from 0.27 to 2.532 μM. Among these, compound **152** was found to be the most potent and minimally toxic [196]. Benzimidazole-acrylonitrile hybrids, such as compound **153** (MIC = 0.78 mg/mL), exhibited superior activity compared to standard drugs like isoniazid, ciprofloxacin, rifampicin, and moxifloxacin [197]. The methylated chloroquinoline-nitroimidazole conjugate **154** showed promising activity against *M. tuberculosis*, with an MIC of 2.2 μg/mL [198]. Imidazolyl dihydropyrimidine hybrids (**155**) effectively reduced *M. tuberculosis* growth in an infected macrophage model, likely through inhibition of dihydrofolate reductase [199]. Conjugates **156** and **157**, formed by coupling imidazopyridines and cephalosporins with piperzino-1,3-benzothiazin-4-ones, demonstrated some antitubercular activity, though their efficacy was limited. [200]. Non-toxic quinazoline-benzimidazole hybrids **158** provided inhibition of various mycobacterial species, including *M. tuberculosis* H37Rv and *M. abscessus* ATCC 19977, with MICs ranging from 8 to 16 μg/mL. Additionally, analogs **159** displayed antibacterial activity against *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* with an MIC of 8 μg/mL, while compound **160** inhibited *S. aureus* with an MIC of 4 to 8 μg/mL (Fig. **19**) [201].

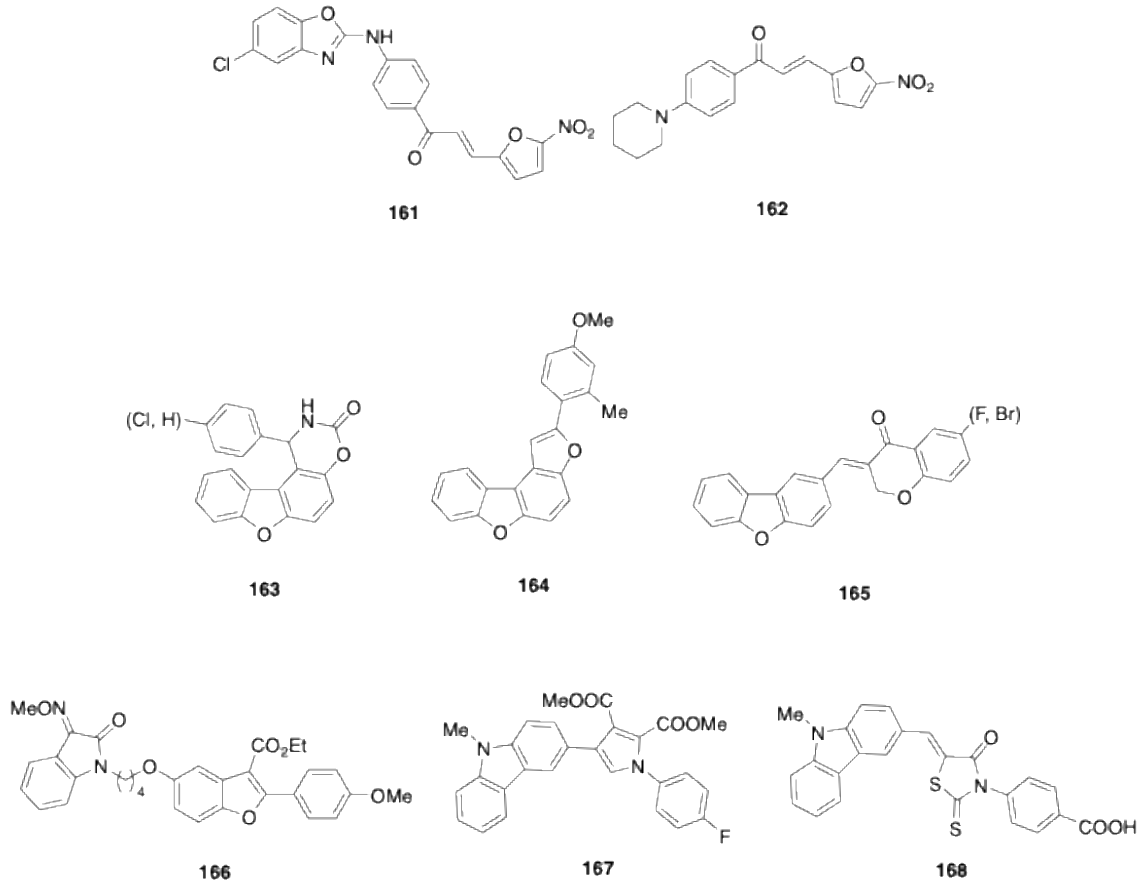


Fig. (20). Hybrids of benzoxazoles, benzofurans, benzoxazines and carbazoles.

6.3. Benzoxazoles, Benzofurans, and Benzoxazines

The benzoxazole-nitrofuranylchalcone hybrid **161** [202] and its analog **162** [203] exhibited potent inhibition of *M. tuberculosis* bacilli. Benzofuran derivatives **163** and **164** also demonstrated significant antitubercular activity, though compound **165** was approximately ten times less potent [204-206]. Benzofuran-isatin-imine hybrids **166** showed enhanced antitubercular activity (<0.016-0.218 μg/mL) and exhibited promising antibacterial effects against both G+ and G- pathogens (<0.03-8 μg/mL) [207]. Carbazole-derived hybrids **167** and **168**, obtained from *N*-methylcarbazoles, displayed strong antitubercular activity with low toxicity against *M. tuberculosis* [208-210].

6.4. 1,2,4- and 1,3,4-Oxadiazoles, Oxazoles, and Thiadiazoles

Reviews by Degani *et al*., Verma, and Rakesh *et al*. have highlighted the potential of oxadiazole isomers in tuberculosis treatment [210, 211]. The 1,2,4-oxadiazole hybrid **169** displayed an MIC of 0.31 μM against *M. tuberculosis* [212]. 1,2,4-Oxadiazole derivatives linked to quinoline, such as compound **170**, showed promising antitubercular activity [213]. Additionally, 1,3,4-oxadiazole hybrids **171**, featuring a substituted phenyl group attached to the oxadiazole unit, exhibited greater potency against *M. tuberculosis* compared to those with cycloalkyl or heterocyclic rings [214]. Analogous hybrids **172** were found active against *Mycobacterium bovis* BCG at concentrations below 3 μg/mL [215]. A set of 1,3,4-oxadiazole compounds, represented by **173**, displayed activity against *M. tuberculosis* when utilizing butyrate as a carbon source, but not glucose [216]. Further antitubercular 1,3,4-oxadiazole-derived hybrids, including **174** and **175**, have also been reported [217]. Screening of 45,000 compounds led to the discovery of an oxazole hybrid as a potent *Mtb* inhibitor, and further structural modifications produced non-toxic hybrids **176** with MICs of 1-64 mg/L against *M. tuberculosis* [218]. Hybrids **177**, incorporating imidazo[2,1-*b*][1,3,4]thiadiazoles tethered to triazoles, exhibited significant activity against *M. tuberculosis* with an MIC of 3.125 μg/mL (Fig. **21**) [219].

6.5. Pyrazoles, Tetrazoles, and Thiazoles

Pyrazole derivatives are key components in several promising antitubercular hybrid candidates, such as compounds **178**-**181** [220-223]. Non-toxic hybrids **182**,

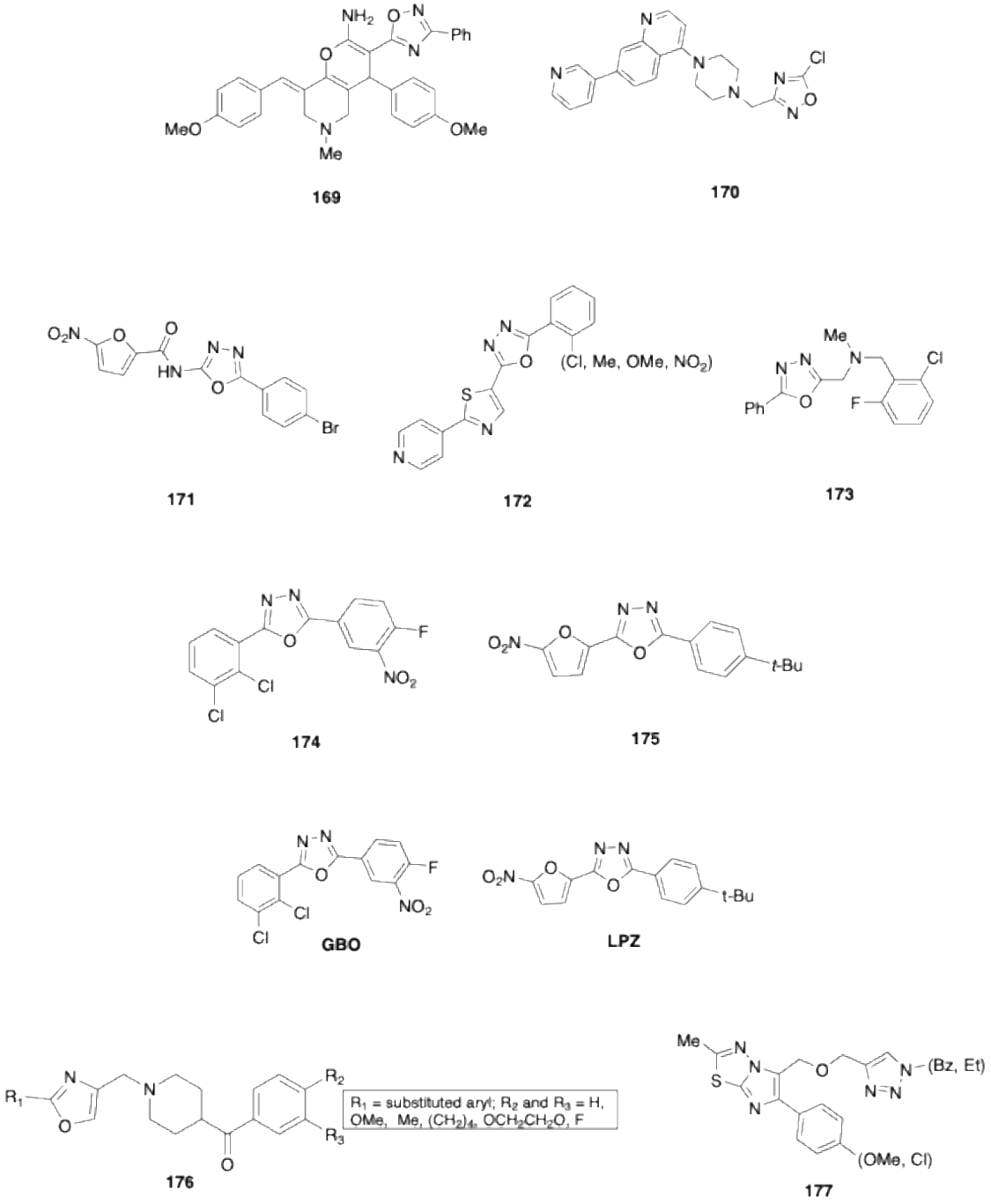


Fig. (21). Antitubercular conjugates of 1,2,4- and 1,3,4-oxadiazoles, oxazoles and thiadiazoles.

featuring a methyl tetrazole group, enhanced potency as antitubercular agents compared to standard drugs like ethambutol and pyrazinamide [224]. Tetrazole derivatives **183**, despite showing favorable antifungal activity, exhibited high reactivity towards thiol nucleophiles, leading to toxicity [225]. Various spiro-derived heterocycles, such as dispiroindenopyrrolidine/pyrrolothiazole-thiochroman hybrids (compound **184**), demonstrated potent antimycobacterial activity against *M. tuberculosis* H37Rv, as well as anticancer activity and acetylcholinesterase (AchE) inhibition [226]. Similar antitubercular effects were observed with 2-arylidene-1,3-indanediones **185** [227] and novel spirooxindolpyrrolothiazoles **186** [228]. Additional antimycobacterial thiazole derivatives, exemplified by **187**, also showed promise as antitubercular agents [229]. Among hybrids incorporating a benzothiazole-hydrazide group, compound **188** emerged as the most effective inhibitor of *M. tuberculosis* H37Rv (Fig. **22**) [230].

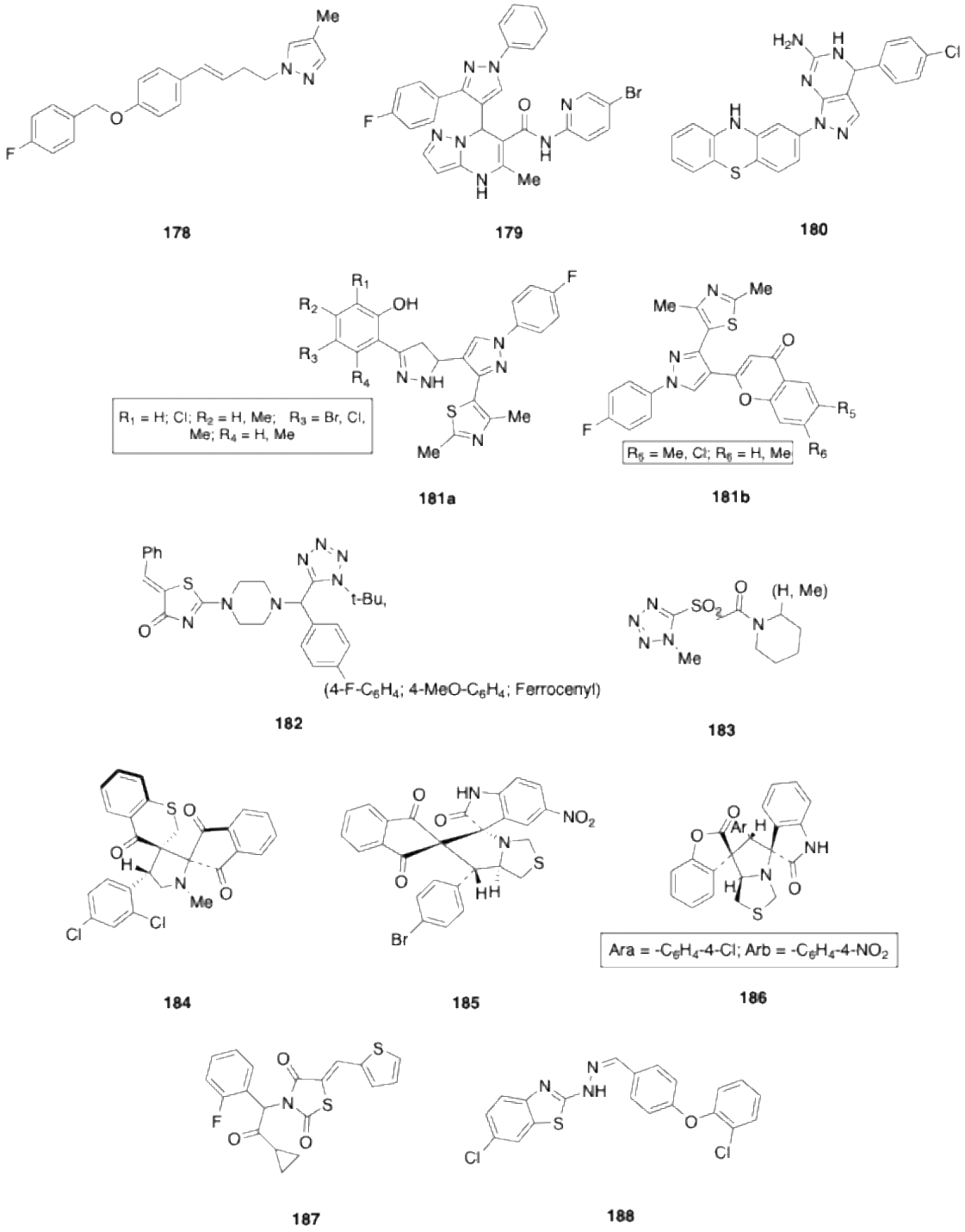
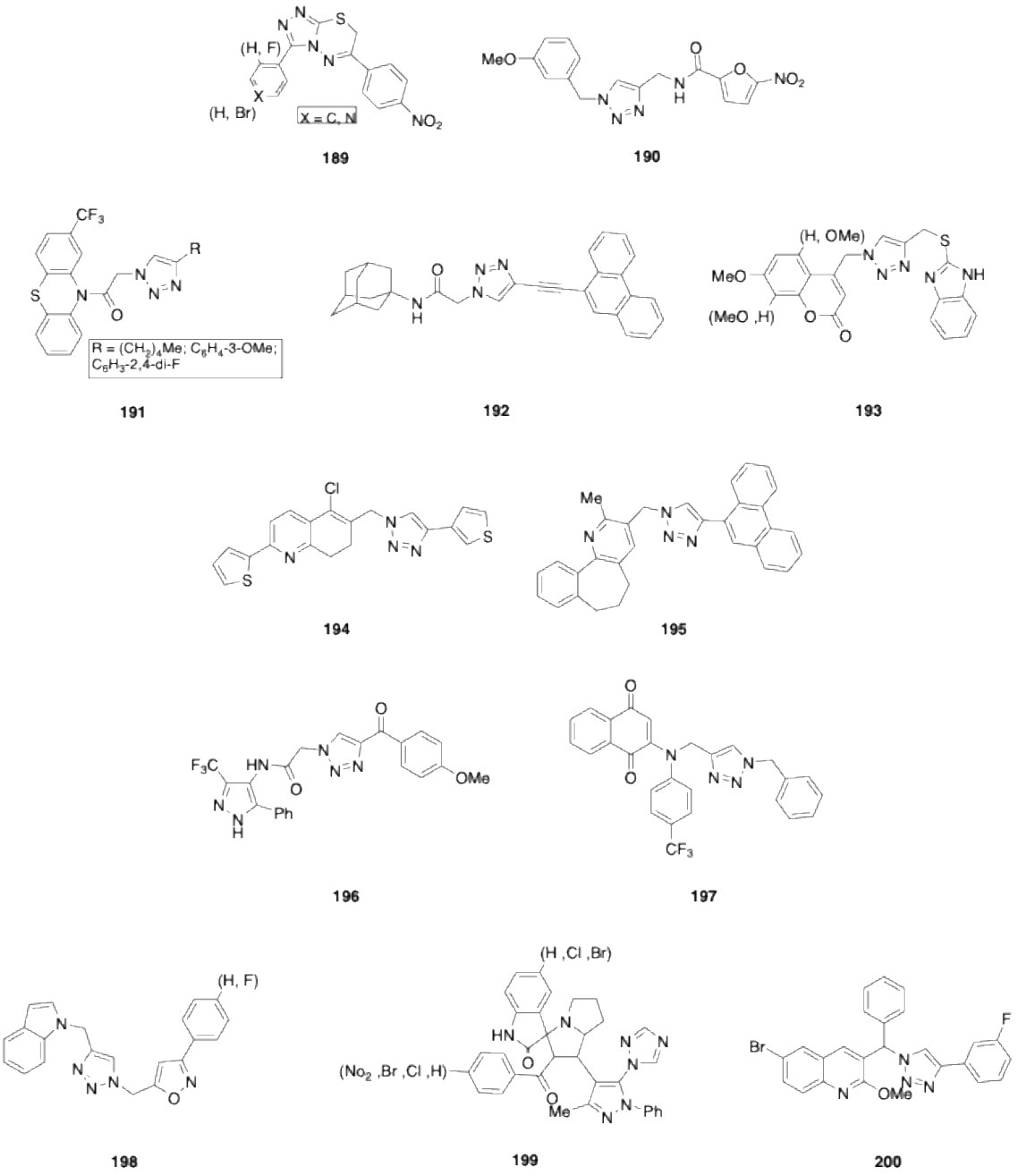


Fig. (22). Antitubercular chimeras of pyrazoles, tetrazoles and thiazoles.

6.6. Triazoles

While nitro-containing drugs often suffer from high toxicity, triazolothiadiazine hybrids, such as compound **189** (with a -C_6H_4-4-NO_2 substitution), were of low toxicity and effectiveness against drug-resistant *M. tuberculosis* strains [231]. Other nitro-derived hybrids, *e.g.*, **190**, displayed promising antibacterial activity against MRSA and effectively inhibited biofilm formation [232]. Triazole-derived hybrids **191-194** exhibited *in vitro* antitubercular activity against *M. tuberculosis* H37Rv (ATCC 27294), with MICs ranging from 3.12 to 19.5 μg/mL [233-236]. Hybrid **195**, tested against *Mtb*, showed low toxicity with an MIC of 1.56 μg/mL, and also exhibited antiviral activity against the influenza virus A/Puerto Rico/8/34 (H1N1) [237]. Pyrazolo hybrids **196** were effective antituberculars against *Mycobacterium smegmatis* with low cytotoxici-

ty against the A549 cancer cell line [238]. The naphthoquinone-triazole hybrid **197** was active against *Mtb* with an IC_{50} of 1.87 μM [239]. The diverse antitubercular and antimicrobial activities of triazole-containing hybrids are reflected in various chemical structures, including compounds **198-204** [240-246]. For instance, a gatifloxacin-fluoroquinolone hybrid **205**, tethered *via* a 1,2,3-triazole bridge to indolones, exhibited activity against *Mtb* [247]. A group of synthetic hybrids having artemisinin conjugated with a fluoroquinolone (conjugate **206**) were active against *Mtb* H37Rv with an MIC of 0.0625 μg/mL, comparable to moxifloxacin and more potent than ofloxacin [248]. Hybrids linking 1,2,3-triazole and moxifloxacin fragments were evaluated as inhibitors of *Mtb* strains, showing activity with MICs ranging from 0.05 to 2 μg/mL. Notably, compound **207** displayed potency 2-8 times greater than moxifloxacin or rifampicin [249]. Non-toxic diarylether hybrids, linked *via* a triazole-containing bridge, such as conjugate **208**, functioned as direct enoyl-ACP reductase (InhA) inhibitors, like isoniazid, proving effective against *Mtb*. Mechanistic studies suggest these hybrids disrupt the biosynthesis of mycolic acids in *M. tuberculosis* H37Rv (Fig. **23**) [250].



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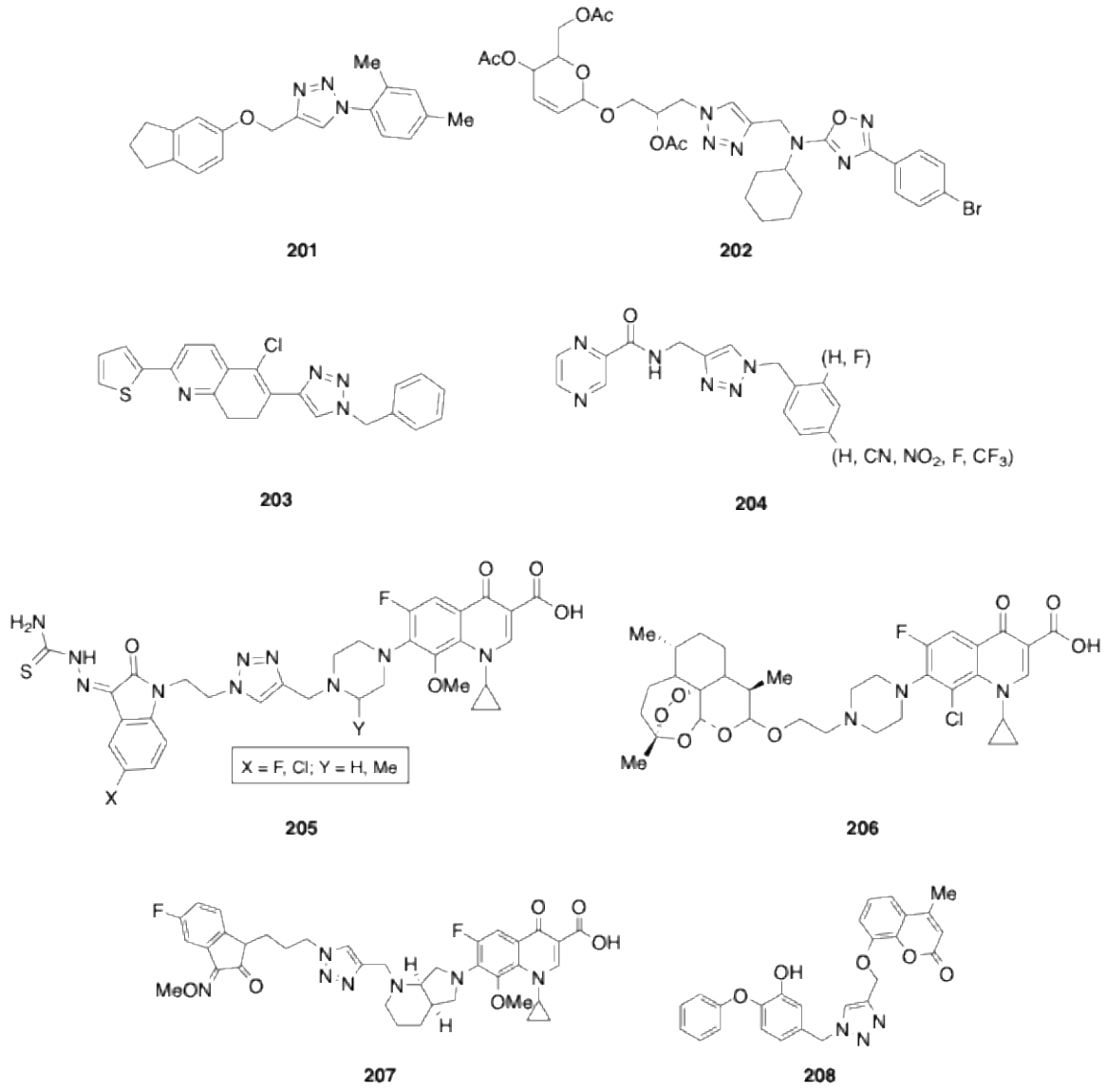


Fig. (23). Triazole platform of antitubercular hybrids.

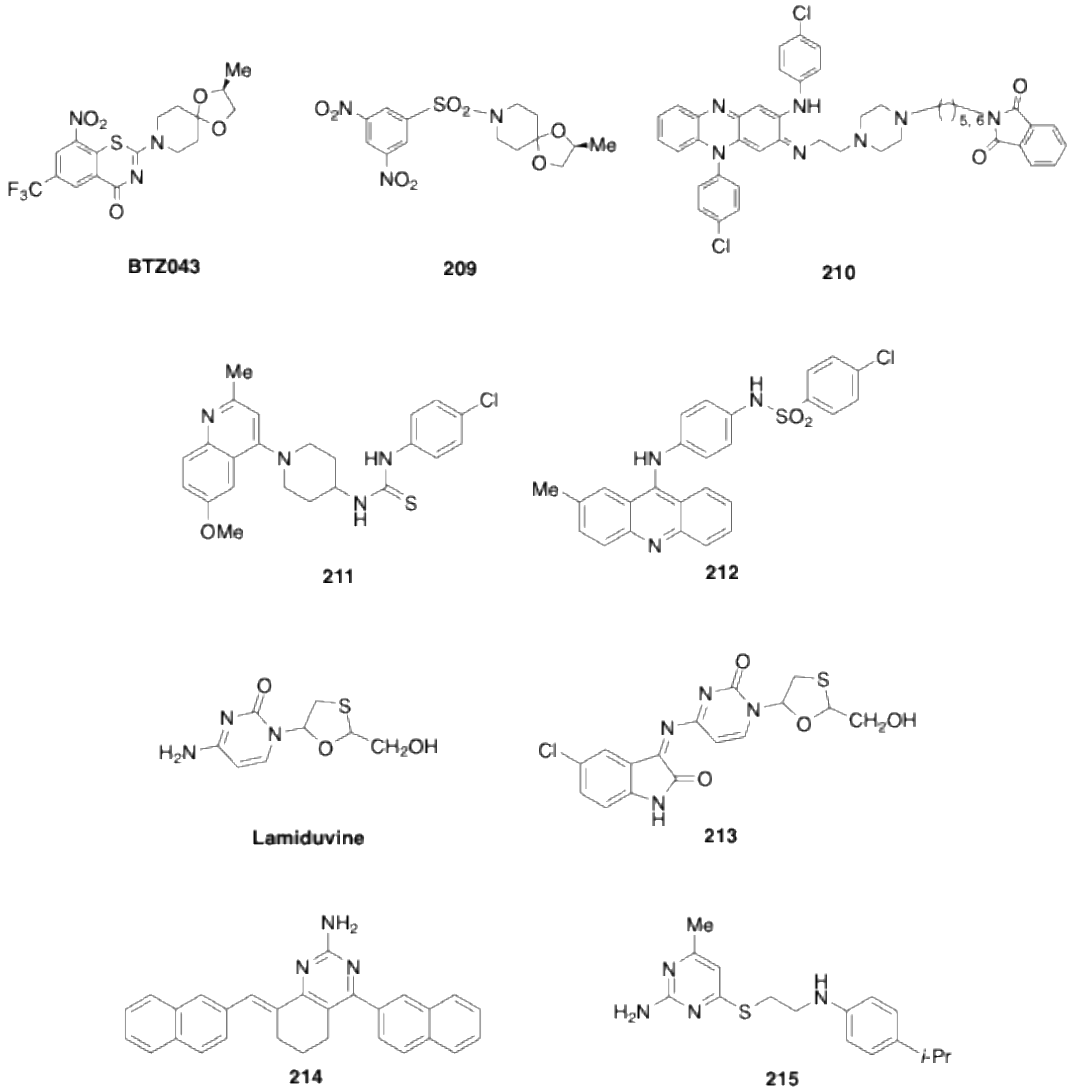
6.7. Assorted Antitubercular Hybrids

The active antitubercular compound 1,3-benzothiazinone (BTZ043) has served as a foundation for the development of novel and potent dinitro-aryl hybrids, such as compound **209** [251]. Additional hybrids were synthesized by bridging phthalimido units with phenazines, exemplified by compound **210** [252]. The aminoquinoline-thiourea hybrid **211** and the acridine hybrid with a sulfonamido group (compound **212**) were identified as non-toxic, potent inhibitors of *Mtb* DNA gyrase supercoiling, affecting both *Mycobacterium smegmatis* GyrB and *M. tuberculosis* DNA gyrase [253, 254]. Compound **213**, derived from the coupling of isatin with the antiretroviral drug lamivudine, exhibited significant antitubercular properties, with 92-100% inhibition against the *Mtb* H37Rv strain at 6.25 μg/mL, alongside its anti-HIV activity [255, 256]. Two families of hybrids derived from 2-aminopyrimidines also showed antitubercular activity. The non-toxic diaryl pyrimidine **214** inhibited α-glucosidase and glycogen phosphorylase enzymes *in vitro* and showed about 58% *ex vivo* activity against *Mtb*, with an MIC up to 3.12 μg/mL. This suggests potential efficacy in treating diabetic patients with tuberculosis [257]. Among 2-[(2-amino-6-methylpyrimidin-4-yl)sulfanyl]-N-arylacetamide hybrids, conjugate **215** was three times more potent than the standard antitubercular drug ethambutol [258]. *In vitro* screening of phthalide derivatives against *Mtb* revealed that four compounds had IC_{50} values ranging from 0.81 to 1.24 μg/mL, indicating their potential as new antitubercular agents. The enhanced activity of compound **216a** is attributed to the presence of halogen groups, while the improved activity of compound **216b**

is linked to the substitution of phenyl groups with isosteric furan and thiophene rings [259]. Chalcone-derived hybrids tested against *Mtb* H37Rv proved that compound **217** was the most potent, exhibiting 16 times greater selectivity for tubercular cells compared to normal cells [260]. Compound **218**, a (-)-fenchone analog linked to a cinnamyl group, exhibited significant antitubercular activity with an MIC of 0.3 μg/mL [261]. The pyrazine-thiazolidinone hybrid **219** presented limited antitubercular activity, with an IC_{50} of 0.337 μg/mL against *Mtb* H37Ra [262]. The pyrrolo[1,2-*a*]quinoxaline tricyclic system served as a basis for the design of novel antitubercular compounds. Hybrid **220**, with an MIC of 5 μg/mL, demonstrated good bioavailability and high permeability across the blood-brain barrier [263]. 3-Methoxy-2-phenylimidazo[1,2-*b*]pyridazine hybrids **221** were active *in vitro* against *M. tuberculosis* and *Mycobacterium marinum*, but were found to be inactive *in vivo* due to rapid metabolism [264]. Compound **222**, derived from formononetin by replacing the OMe group with other substituents, inhibited 95% of the *Mtb* H37Rv strain (Fig. **24**) [265].

6.8. Hydrazine- and Hydrazone-Derived Antitubercular Conjugates

Hybrid compounds incorporating guanylhydrazone, thiosemicarbazide, or semicarbazide moieties, such as substances **223-225**, have demonstrated potent inhibition against fungal, bacterial, and tubercular pathogens. Notably, the most active candidates exhibit low toxicity and show promising efficacy against MRSA (Fig. **25**) [266, 267].



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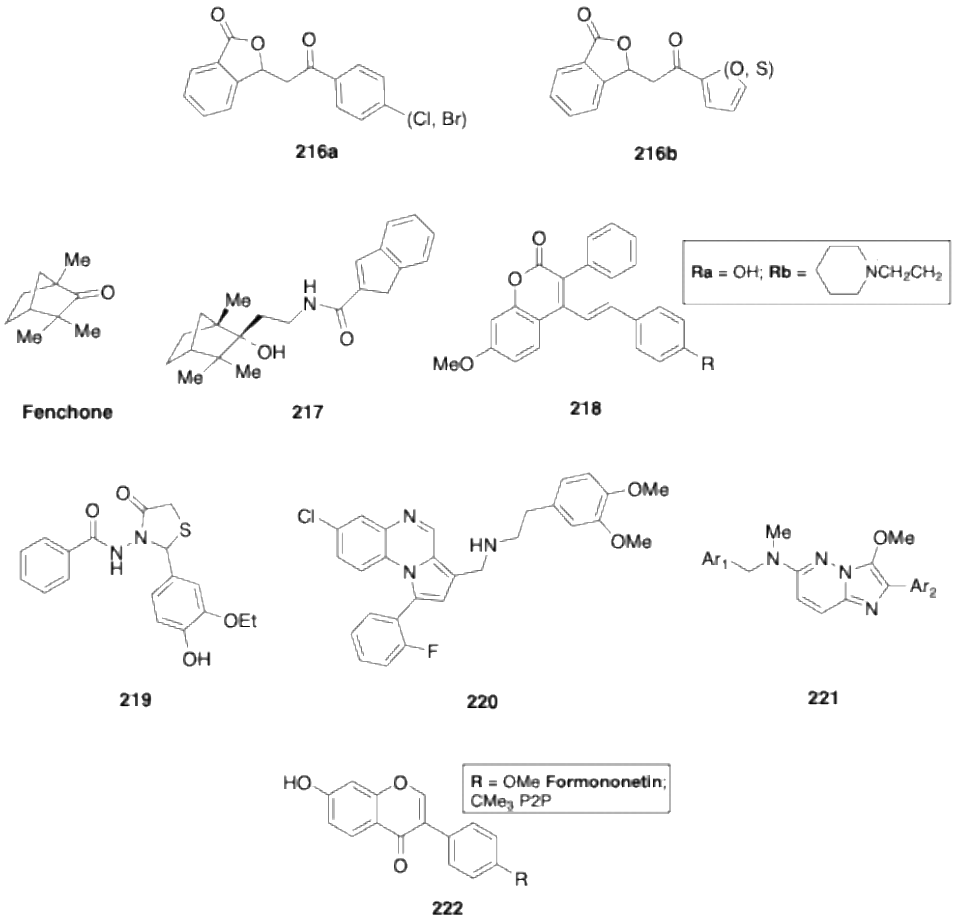

Fig. (24). Structurally unrelated *Mtb* inhibitory hybrids.

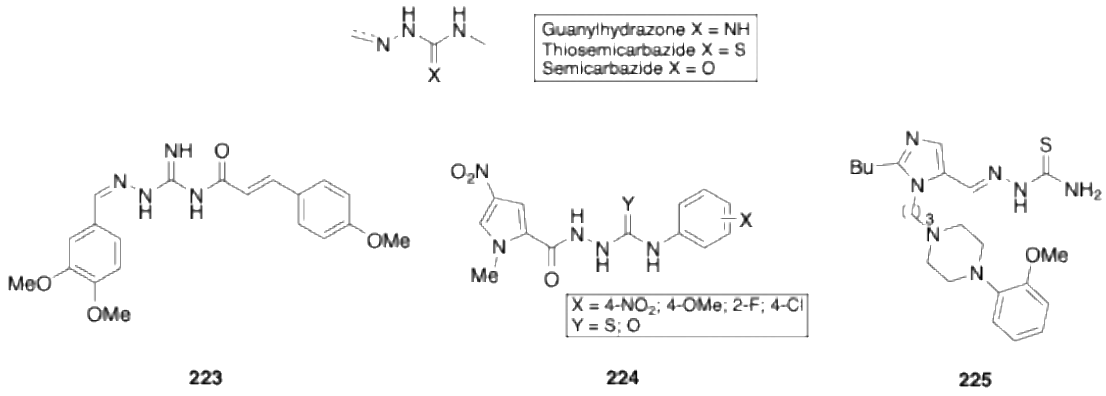

Fig. (25). Hydrazine- and hydrazone-derived inhibitors of *Mtb.*

7. ANTIMALARIAL HYBRIDS

Compounds developed to treat malaria caused by *Plasmodium falciparum* generally fall into three main categories: quinoline derivatives, trioxanes, and ferrocene derivatives (Fig. **26**). The first category includes classic quinoline-based drugs such as the natural product quinine and its synthetic analogs-chloroquine (CQ), hydroxychloroquine, mefloquine, primaquine, and amodiaquine. The second major class consists of trioxanes, with artemisinin being the most prominent example, discovered by Youyou Tu, who was awarded the 2015 Nobel Prize for her work. Artemisinin has led to a variety of analogs, including endoperoxide trioxanes such as artemether and artesunic acid. Despite extensive research into the chemistry, biology, and mechanisms of these drugs, their widespread use has contributed to the development of resistance, prompting the need for new therapeutic strategies. As a result, signifi-

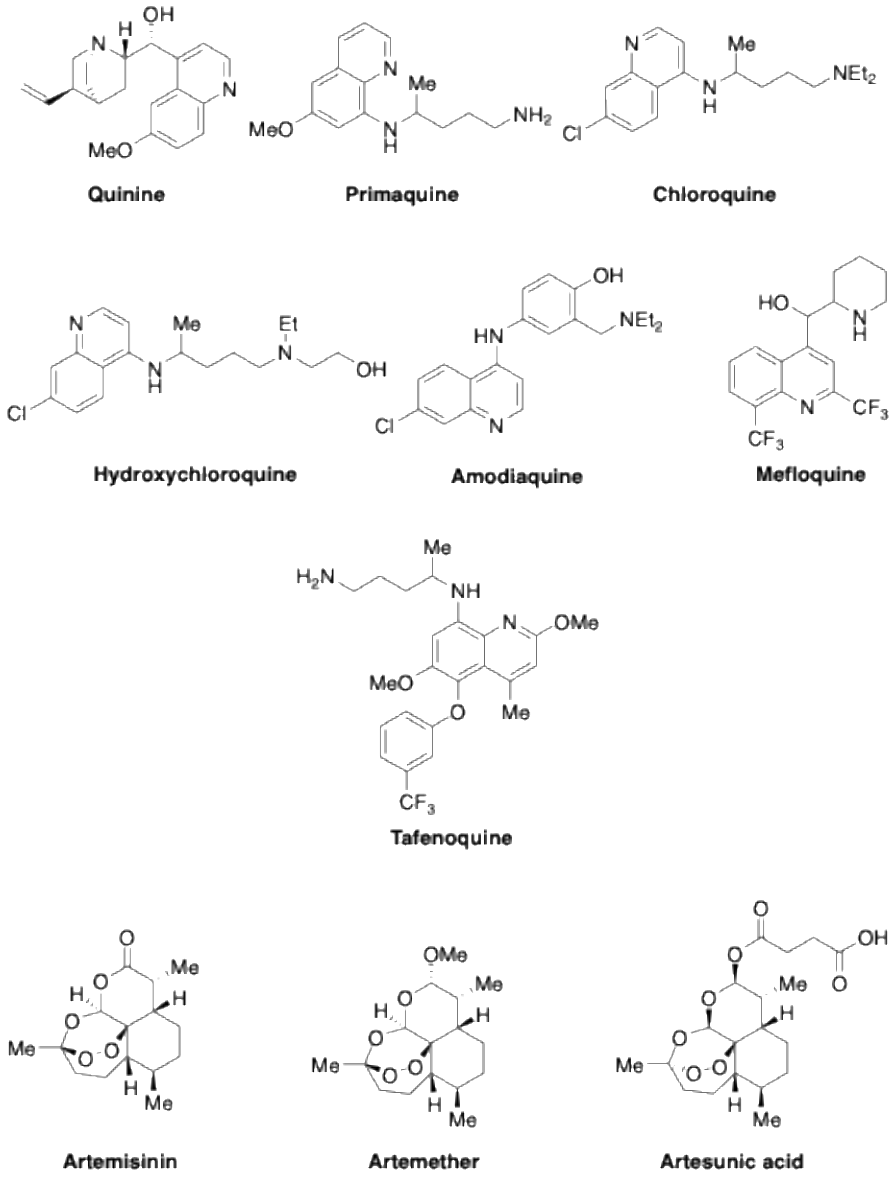

Fig. (26). Clinically approved antimalarial drugs.

cant attention has shifted to the development of hybrid compounds that combine the potent antimalarial activity of traditional drugs with mechanisms aimed at minimizing resistance. Given the urgent need for effective treatments, numerous studies have been published, exploring diverse approaches to discovering novel antimalarial agents. Many reviews have focused on the development of these hybrid compounds, highlighting their potential to overcome existing drug resistance while maintaining efficacy against *Plasmodium falciparum* (Fig. **26**).

7.1. Antimalarial Reviews

A selection of reviews on antimalarial hybrids includes works by Bell [268]; Muregi and Ishih**,** who focused on aminoquinoline hybrids [269]; Aberibghe and Alven**,** who reviewed quinoline and endoperoxide hybrids [270] and ferrocene-derived antimalarial hybrids [271]. Gao *et al*. also reviewed ferrocene-derived antimalarials [272]. Gómez-Barrio and Kouznetsov concentrated on hybrids of 4-amino-7-chloroquinoline, an analog of chloroquine [273]. D'hooghe and Vandekerckhove summarized numerous antimalarial hybrids containing quinoline fragments [274]. Awasthi *et al*. discussed challenges encountered with antimalarial hybrids and summarized endoperoxides, including efforts to overcome MDR parasites and toxicity, while seeking better pharmacokinetic properties and formulations [275, 276]. Additional reviews by Patel and Legoabe focused on synthetic antimalarial peroxides, [277] and Maunier specifically reviewed peroxide hybrids [278]. Lopes *et al*. emphasized the significance of

antimalarial hybrids with different mechanisms of action [279], and Qin and Rakesh described hybrids involving chalcone entities [280]. Jain *et al***.** presented new hybrid structures with antimalarial activity [281] while Hoda and Madhav analyzed clinical targets for antimalarial hybrids [282]. Ng and Cheong discussed multi-target antimalarial hybrids, referring to their activity as "covalent biotherapy" [283]. Reviews dedicated to specific molecular scaffolds for antimalarial hybrids include quinoline [284, 285], indoles [286], β-carbolines [287], spiral molecules [288] and hybrids related to falcipains [289]. Additional general reviews of antimalarial hybrids can be found in several sources [290-292].

7.2. Hybrids of Chloroquine (CQ) and Primaquine

Derivatives of CQ-chalcone hybrids **226** showed enhanced antimalarial activity against both CQ-resistant *P. falciparum* (K1) and chloroquine-susceptible (3D7) strains, effectively inhibiting *in vitro* β-hematin formation [293]. The non-toxic hybrid **227**, termed "reverse quinoline," was orally effective at low nanomolar concentrations against resistant *P. falciparum* strains [294]. To target different stages of *P. falciparum* development, the combined CQ-primaquine hybrid **228** was tested and showed activity against both asexual and sexual blood stages, as well as *P. berghei* sporozoites and liver stages [295]. CQ-based hybrids demonstrated potent i*n vitro* activity against *P. falciparum*, with dimeric hybrid **229** showing IC_{50} values of 31.3 ± 4.9 nM and 80.9 ± 14.6 nM against 3D7 and Dd2 strains, respectively. The CQ-mortiamide hybrid **230** exhibited an IC_{50} of 80.1 ± 9.2 nM against the 3D7 strain, with part of the activity attributed to the cyclic peptide portion [296]. A modified CQ hybrid linked to a pyrimidine **231** showed comparable activity to CQ against D10 and Dd2 strains of *P. falciparum* [297]. Compound **232**, a triazolopyrimidine hybrid linked to CQ, exhibited an IC_{50} of 0.2 μM against CQ-resistant strains, with potent inhibition of hemozoin formation and dihydroorotate dehydrogenase [298]. The CQ-hydrazine hybrid **233** demonstrated activity against malarial blood parasites (Fig. **27a**) [299].

A click reaction-based synthesis led to conjugates of chloroquine linked to isatin and indole units, with the most active compound **234** showing an IC_{50} of 69 nM against *P. falciparum* [300]. β-Carboline-containing hermiquin hybrids, such as **235**, linked to CQ, exhibited high antiplasmodial activity against the Pf3D7 strain [301-305]. Quinoxaline 1,4-dioxide-N-oxide hybrids (**236** and **237**), containing CQ or primaquine pharmacophores, demonstrated potent blood-stage activity and were the most active and selective at this stage. The primaquine hybrid was particularly effective against the exoerythrocytic stages, displaying enhanced liver activity against *P. berghei*.[7] [306]. Investigations into quinoline-pyrimidine hybrids led to compound **238**, which showed antiplasmodial properties with an IC_{50} of 0.32 ± 0.06 μM [307]. Studies by Rawat *et al*. on hybrid **239** and compound **240** indicated promising antimalarial activity [308-311]. Among hybrids derived from CQ and a pyrimidine nucleus, compound 241b exhibited the lowest IC_{50} against both CQ-sensitive and CQ-resistant strains, through mechanisms involving heme and DNA binding. Analogous compounds **241a** and **241c** also showed effectiveness against feline coronavirus and herpesvirus [312]. Singh *et al*. reported that CQ-pyrimidine hybrid **242** had reduced plasmodial activity [313], while primaquine-pyrimidine hybrid **243** exhibited effective blood- and liver-stage antiplasmodial effects (Fig. **27b**) [314].

CQ-cyano-substituted pyrimidine hybrids **244** displayed antiplasmodial activity against the Dd2 strain through inhibition of hemozoin formation [315-316]. The 8-aminoquinoline-pyrazolopyrimidine hybrid **245** demonstrated IC_{50} values of 5-10 nM against *P. falciparum* [317]. Aminoquinoline-triazine hybrids, reported by Rawat *et al*. and Chauhan *et al*., included compound **246**, which inhibited *P. falciparum* clones D6 and W2 with IC_{50} values of 0.21 and 0.28 μM, respectively [318-321]. Compound 247 was orally active at 100 mg/kg for 4 days in Swiss mice infected with the CQ-resistant N-67 strain of *P. yoelii*. Compound **248** exhibited promising *in vivo* antimalarial activity against *P. yoelii via* intraperitoneal administration at 50 mg/kg/day (Fig. **27c**).

Compound **249** displayed an IC_{50} of 5.23 ng/mL against the CQ-sensitive 3D7 strain of *P. falciparum* [322]. An acridine analog of CQ tethered to a substituted triazine, compound **250**, achieved 98.73% inhibition of the CQ-resistant N-67 strain of *P. yoelii* in Swiss mice at 100 mg/kg for 4 days [323]. Another acridine analog with an amino group at position 4 linked to an *m*-F-cinnamyl group, hybrid **251**, was 20- and 120-fold more potent against the hepatic and gametocyte stages of *Plasmodium* infection compared to primaquine [324]. Compared to CQ, the adamantane amine-chloroquine hybrid **252** showed an 18-fold increase in activity against resistant *P. falciparum* strains [325]. Moderate *in vitro* activity and acceptable cytotoxicity were observed for compound **253** [326]. Amino-analogs **254** of kojic acid were effective inhibitors of β-hematin and exhibited antiplasmodial activity against both resistant

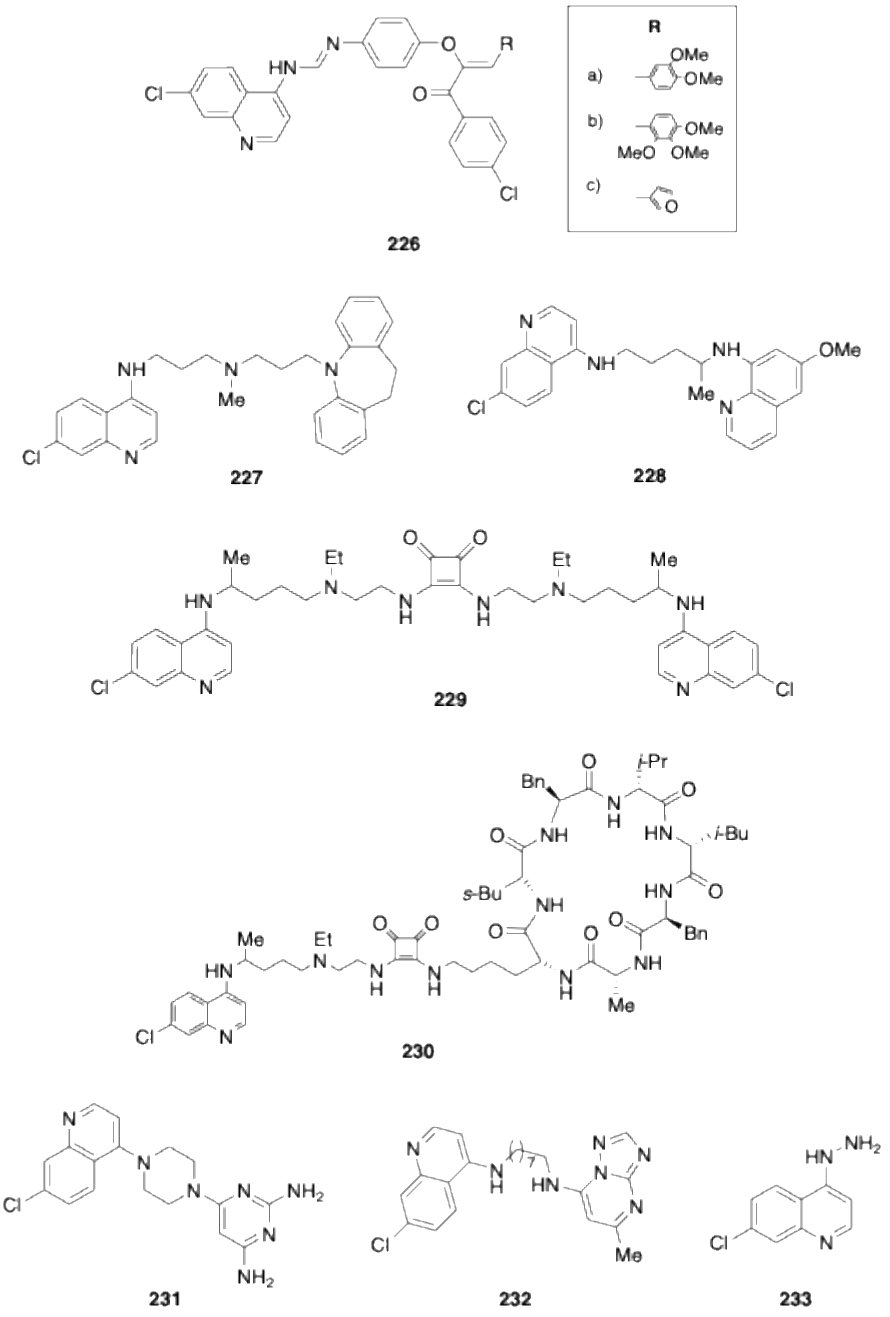

Fig. (27a). Extensive variety of hybrids of chloroquine (CQ) and primaquine.

and sensitive strains of *P. falciparum* [327-328]. [299]. Bridging ciprofloxacin to a CQ derivative yielded a potent, non-toxic antimalarial hybrid, compound **255** [329]. Similar activity was observed for sulfonamide-CQ hybrids **256** [330]. Novel and potent hybrids **257a,b**, where CQ is bound to substituted naphthylamides, exhibited IC_{50} values of 15 nM and 0.07 μM against CQ-susceptible 3D7 and CQ-resistant W2 strains of *P. falciparum*, respectively [331-332]. Hybrids where CQ is linked to various heterocyclic moieties were also reported. Hybrid **258**, with CQ linked to a thiazolidine ring, and its analogs were better inhibitors of the Dd2 MDR strains of *P. falciparum* compared to CQ [333]. Compound **259** effectively suppressed 99% parasitemia on day 4 (Fig. **27d**) [334].

Hybrid **260**, which integrates a CQ unit, an isoniazid fragment, and a phthalimide, exhibited approximately an order of magnitude higher potency than CQ against the resistant W2 strain of *P. falciparum* [335]. Conjugate **261**, composed of a CQ-triazole unit linked to a chalcone, showed sub-micromolar IC_{50} values against the D10, Dd2, and W2 strains of *P. falciparum* [336]. Additionally, a range of CQ- and primaquine-

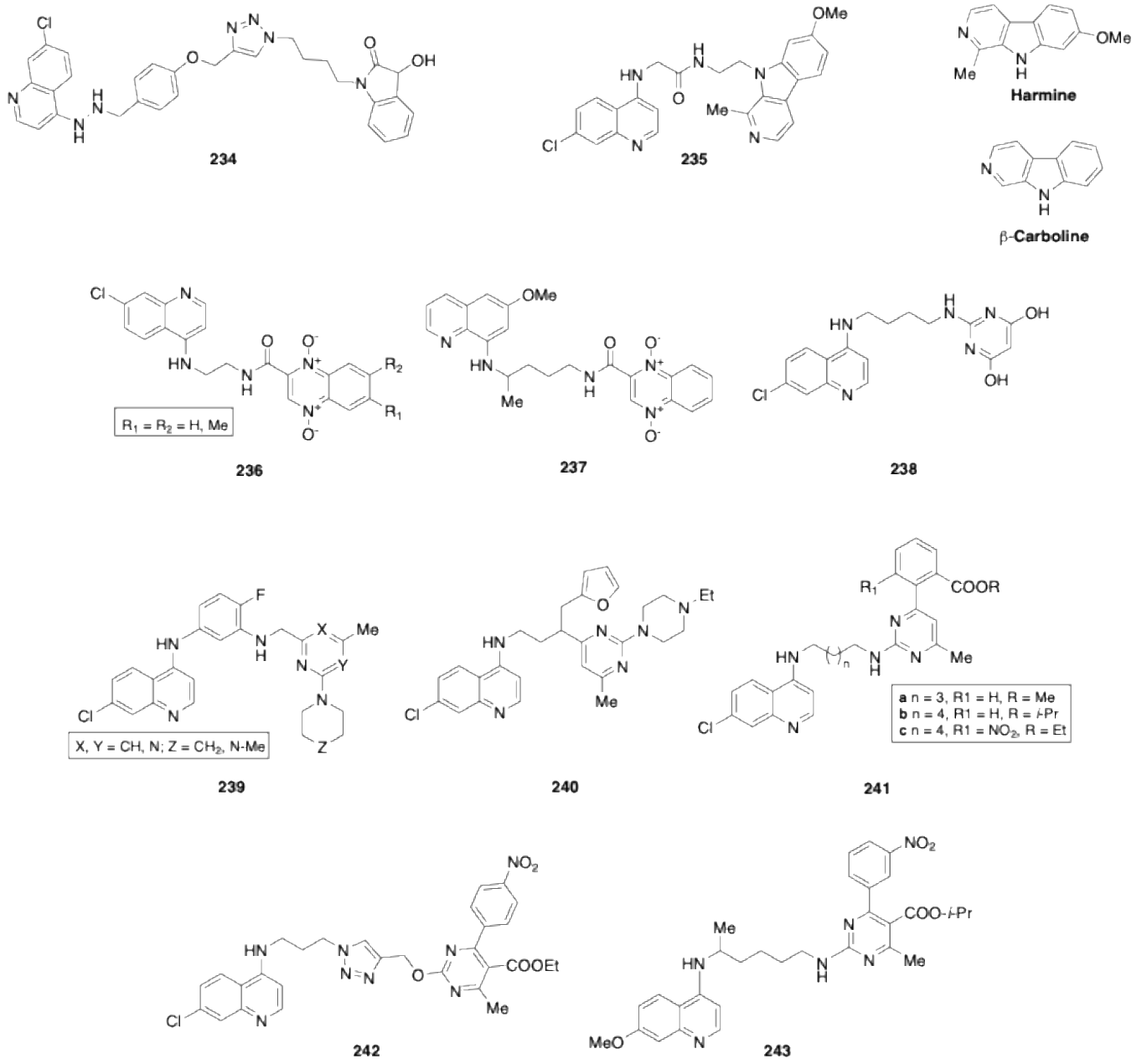

Fig. (27b). Extensive variety of hybrids of chloroquine (CQ) and primaquine.

derived hybrids, including compounds **262-266**, displayed notable antimalarial activity. These hybrids were effective *in vitro* against *P. berghei*, *PfFP2*, *PfFP3*, *Pf3D7*, and *PfW2*, encompassing both CQ-sensitive and CQ-resistant strains of *P. falciparum* (Fig. **27e**) [337-342].

7.3. Quinoline, Quinolone, and Quinolinone Hybrids

Linking *N*-hydroxyquinolinones to various aromatic residues led to the formation of hybrids **267**, which presented notable antiplasmodial activity (with IC_{50} values in the μM range), as well as antibacterial and Fe^{2+}-chelation properties [343]. *In vitro* evaluation of quinoline hybrids **268** revealed significant antiplasmodial effects against *P. falciparum* 3D7 [344]. The chimeric hybrid **269**, formed by conjugating an anticholesterolemic atorvastatin fragment with an aminoquinoline, exhibited potent antiplasmodial efficacy, with an IC_{50} of 0.40 μM against *P. falciparum* [345]. Various trifluoromethylated quinolines linked to 1,3,4-triazole units, represented by hybrid **270**, displayed antiplasmodial activity within a range of 0.083-33.0 μM [346]. Brominated 4-quinolones, such as hybrid **271**, exhibited moderate antiplasmodial activity against a chloroquine-sensitive (CQS) *P. falciparum* strain (NF54) (Fig. **28**) [347].

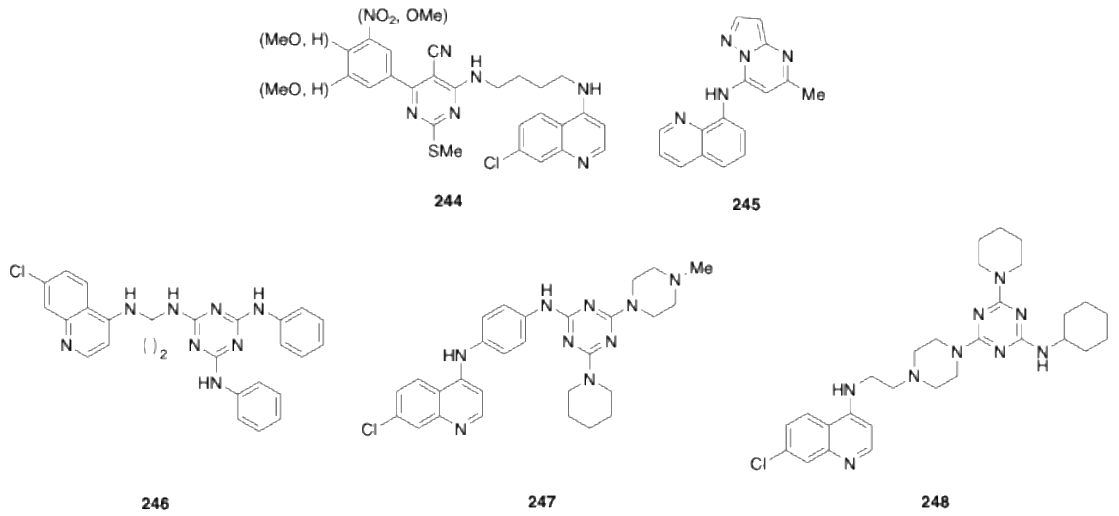

Fig. (27c). Extensive variety of hybrids of chloroquine (CQ) and primaquine.

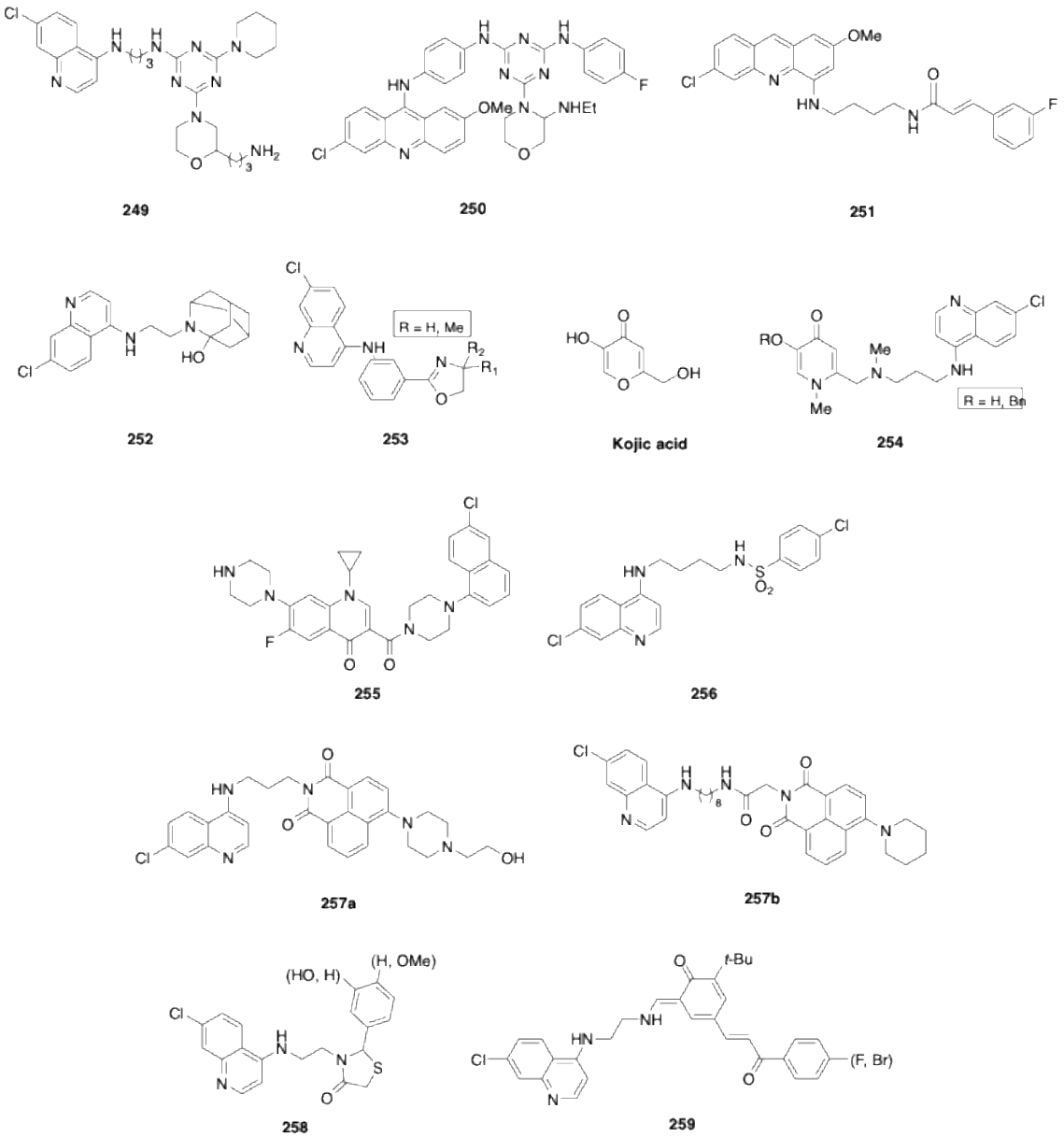

Fig. (27d). Extensive variety of hybrids of chloroquine (CQ) and primaquine.

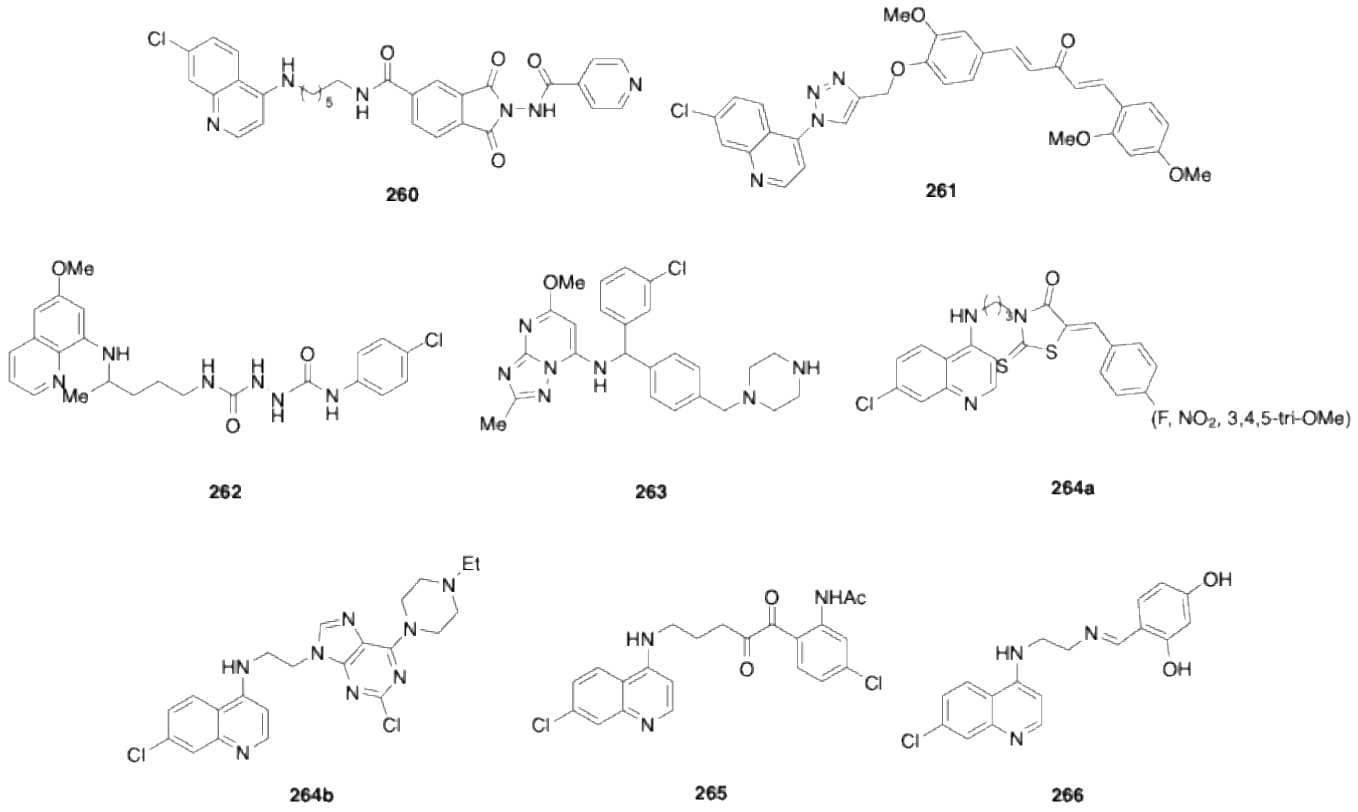

Fig. (27e). Extensive variety of hybrids of chloroquine (CQ) and primaquine.

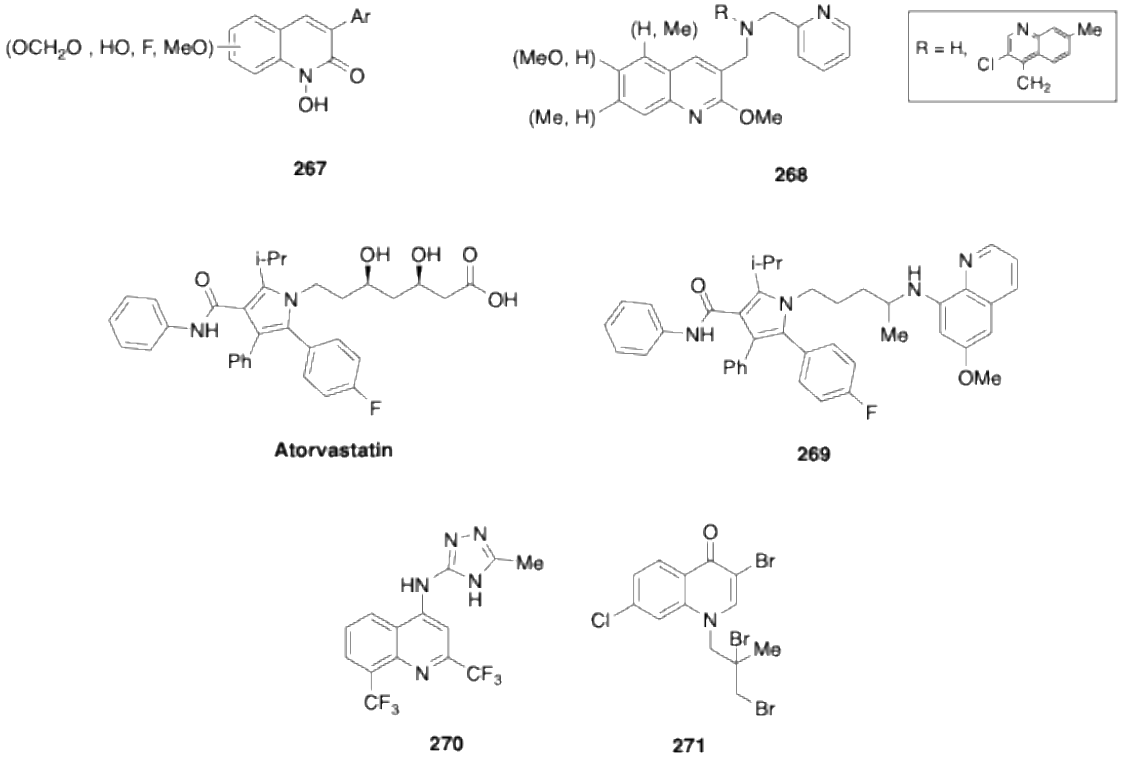

Fig. (28). Quinoline, quinolone and quinolinone antimalarial hybrids.

7.4. Peroxide Antimalarials

The artemisinin-quinine hybrid **272**, which functions more as a prodrug due to its ester linkage, demonstrated strong inhibitory activity against both the 3D7 and drug-resistant FcB1 strains of *Plasmodium falciparum*, outperforming either artemisinin or a mixture of the individual components [348]. Hybrids **273a** and **273b**, derived from primaquine and artemisinin, exhibited enhanced antimalarial activity by targeting distinct mechanisms of action [349]. Conjugate **274**, created by linking artemisinin to estrogen, displayed polypharmacological activity. It showed superior antiplasmodial efficacy compared to chloroquine and artesunic acid and outperformed ganciclovir against human cytomegalovirus. Additionally, it inhibited the growth of a range of breast tumor cells (including MCF7, MDA-MB-231, MDA-MB-361, and T47D) and cervical cancer cells (HeLa, SiHa, and C33A) [350]. Artesunate-indoloquinoline hybrids, such as compound **275**, demonstrated reduced cytotoxicity and enhanced antimalarial activity. It exhibited IC_{50} values of 0.45 nM against CQ-sensitive (NF54) strains and 0.42 nM against CQ-resistant strains, with a resistance index (RI) of 0.93. This hybrid also significantly reduced parasitemia by 89.6% and prolonged survival to 7.7 days [351]. The hybrid **276**, formed by linking artemisinin to the local antiseptic 9-aminoacridine, when tested against chloroquine-sensitive, gametocytocidal, and CQ-resistant strains of *P. falciparum*, demonstrated seven-fold higher anti-gametocytocidal activity compared to chloroquine and was seven times more potent against the Dd2 strain. Furthermore, it showed 3- to 8-fold increased anticancer activity over melphalan in HeLa cells (Fig. **29a**) [352].

The dimeric artemisinin-triazine hybrid **277** exhibited robust antigametocytocidal activity against the *P. falciparum* NF54 strain, with an IC_{50} in the nM range, and comparable potency to artesunate against the Dd2 strain [353]. The artemisinin-CQ hybrid **278**, in its oxalate salt form, outperformed CQ against the chloroquine-resistant (CQR) strain of *P. falciparum*, while the artemisinin-CQ dimeric hybrid **279** demonstrated high antiplasmodial efficacy [354, 355]. Compound **280**, which combines DHA with an NO-donating unit, proved effective in dilating rat aorta and preserving antiplasmodial activity *in vitro* and *in vivo* against *P. berghei* ANKA. Its effectiveness was comparable to artesunate and artemether, and also increased the survival of mice with late-stage disease [356]. Conjugate **281**, a hybrid of DHA and azidothymidine (AZT), exhibited *in vitro* antiplasmodial activity like that of DHA (IC_{50} = 26 nM) and moderate HIV activity (IC_{50} = 2.9 μM) without cytotoxicity to HeLa cells [357]. Dual-acting hybrids like **282** and **283** (comprising artemisinin and vinyl phosphonate) and **284** (linking artemisinin and vinyl sulfone) showed potent antimalarial efficacy against various sensitive and resistant *P. falciparum* strains with EC_{50} values in the nanomolar range. The antifalcipain-2 activity from the vinyl peptide pharmacophore boosted the antiplasmodial efficacy of artemisinin. These hybrids cleared parasitemia in infected mice and provided complete protection, extending survival beyond 60 days. Compounds **282** and **283** also demonstrated synergistic effects and a lower likelihood of inducing resistance. Their diastereomers exhibited potent *in vitro* antiplasmodial activity (Fig. **29b-c**) [358-359].

Hybrid **285**, formed by coupling (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine with artemisinin, displayed nanomolar antiplasmodial IC_{50} values [360]. The artemisinin-quinone hybrid 286 exhibited better polypharmacological properties than artemisinin and thymoquinone alone, showing activity as antimalarial, antiviral, and antileukemic agents [361]. Hybrid **287**, combining an adamantyl-1,2,4-trioxalane unit with CQ, was more potent than both CQ and artemisinin against the 3D7 and K1 strains of *P. falciparum* [362]. Tetraoxane endoperoxides have been developed into various hybrids to combat *P. falciparum* resistance. Notable dual-acting hybrids, such as **288**, which integrates an endoperoxide with a vinyl sulfone inhibitor (IC_{50} = 175±15.1 nM) targeting cysteine protease falcipain, reduced parasitemia and increased survival in mice infected with *P. berghei* [363]. Similarly, hybrid **289**, featuring a toxic tetraoxane endoperoxide linked to a pyrimidine falcipain inhibitor, also reduced parasitemia and improved survival in infected mice [364]. The amidic hybrid **290**, synthesized from a tetraoxane and primaquine, effectively cleared *P. berghei* infection in mice following intraperitoneal administration (Fig. **29c**) [365, 366].

The endoperoxide **291**, combined with artemisinin, produced compound **292**, the most potent antimalarial combination against chloroquine-resistant *P. falciparum* [367]. Synthetic trioxaquine hybrids, exemplified by compound **293**, which links a trioxane unit to an aminoquinoline fragment, showed potent antiplasmodial activity with IC_{50} values ranging from 4 to 32 nM against both asexual and sexual stages of *P. falciparum*. *In vivo*, they were effective against *P. vinckei petteri* and *P. yoelii nigeriensis* strains [368]. Several novel trioxane-coumarin hybrids **294**, though limited in solubility, were active against the CQ-sensitive 3D7 strain of *P. falciparum* [369]. Linking artemisinin to

the plant metabolite egonol resulted in hybrid **295**, which exhibited potent antimalarial, antiviral, and antileukemic activities [370]. Trioxaferroquines, such as compound **296**, represent a new class of antimalarial hybrids that combine a trioxane peroxide unit with a CQ fragment. These hybrids *in vitro* were efficacious against resistant *P. falciparum* strains, and treatment of mice infected with *P. vinckei petteri* resulted in undetectable parasite levels with a low dose of **296** (Fig. **29d**) [371].

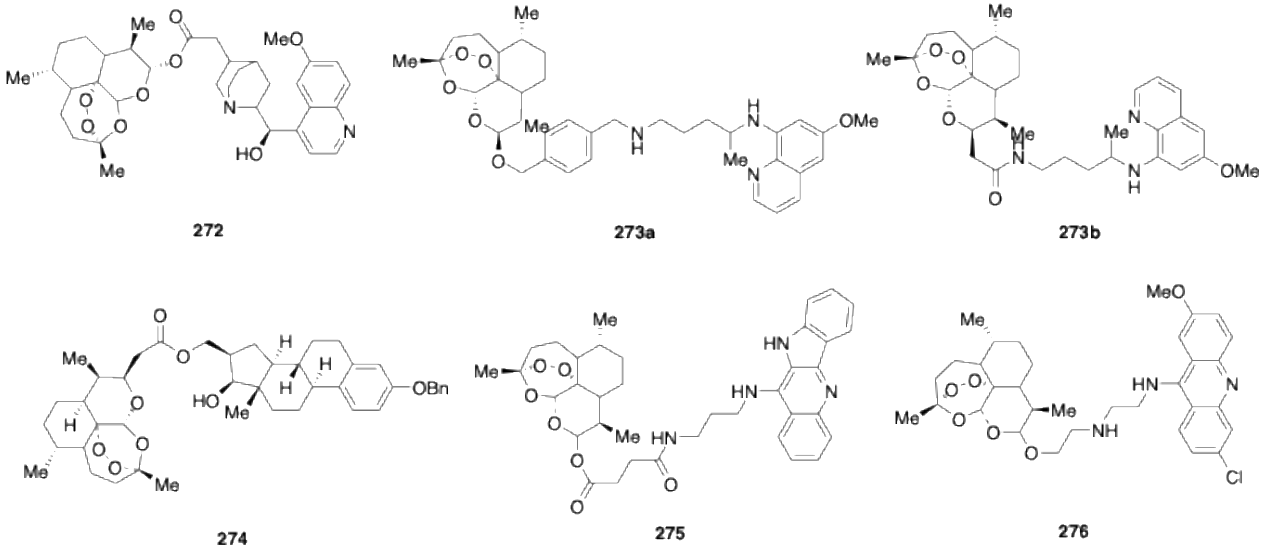

Fig. (29a). Artemisinin-inspired peroxide structures of antimalarial conjugates.

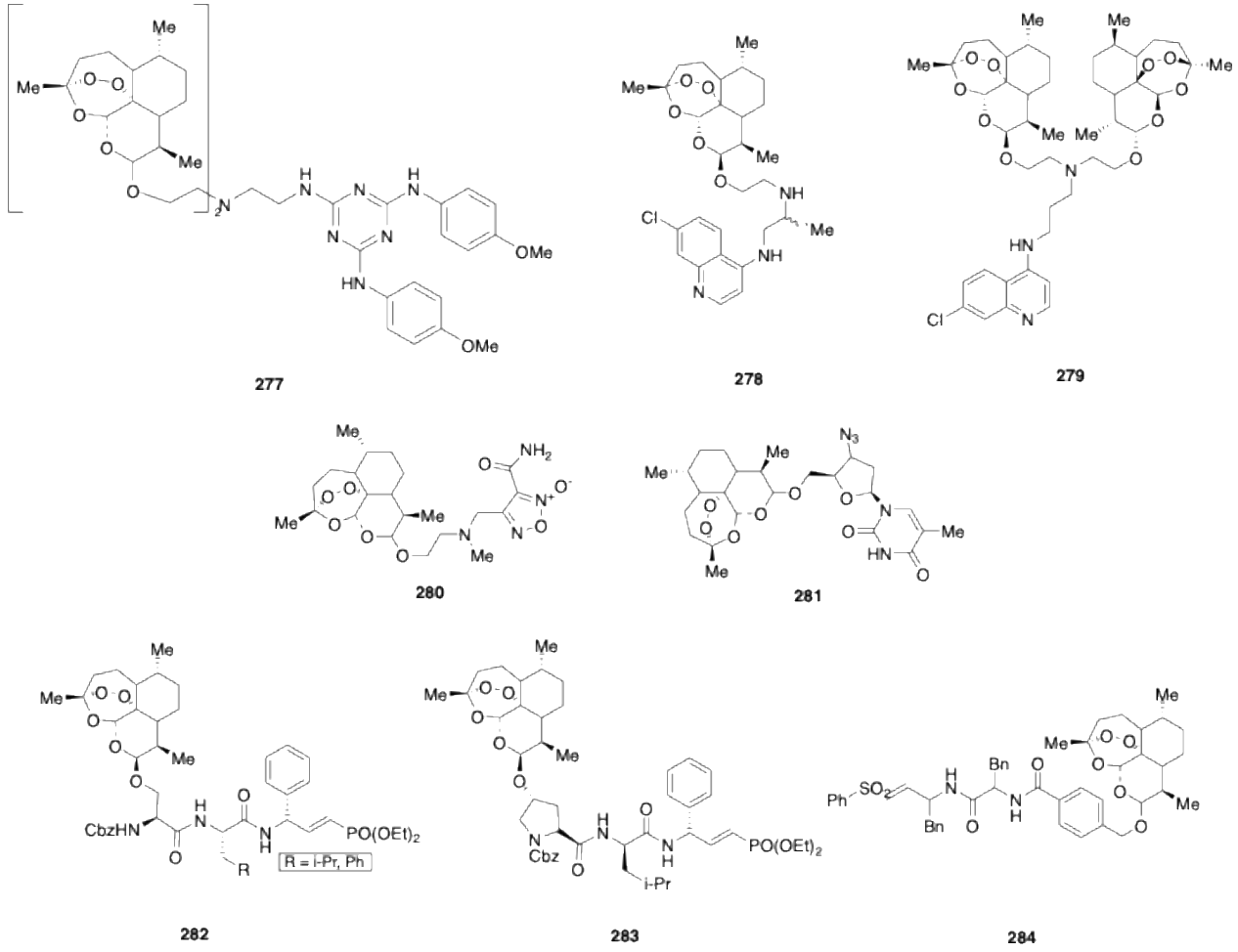

Fig. (29b). Artemisinin-inspired peroxide structures of antimalarial conjugates.

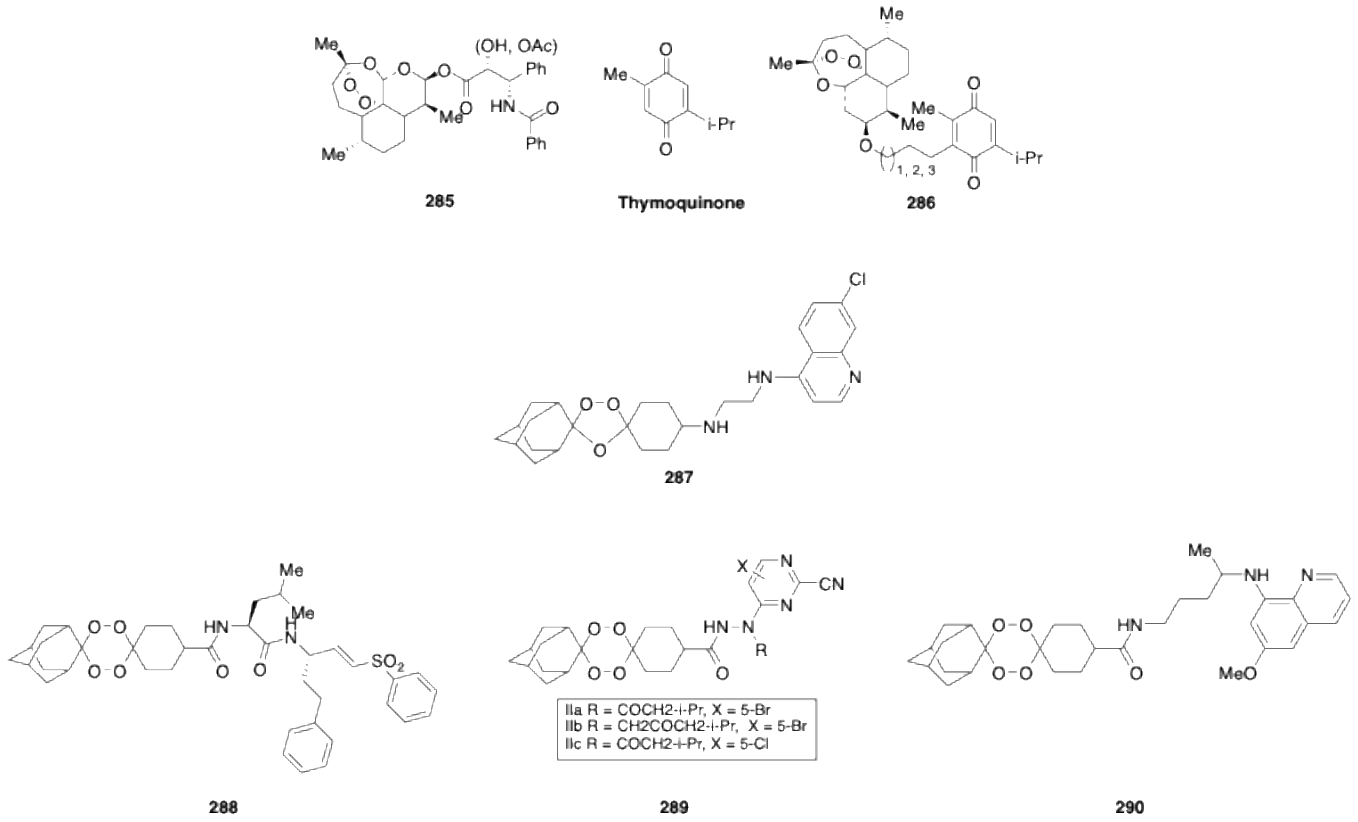

Fig. (29c). Artemisinin-inspired peroxide structures of antimalarial conjugates.

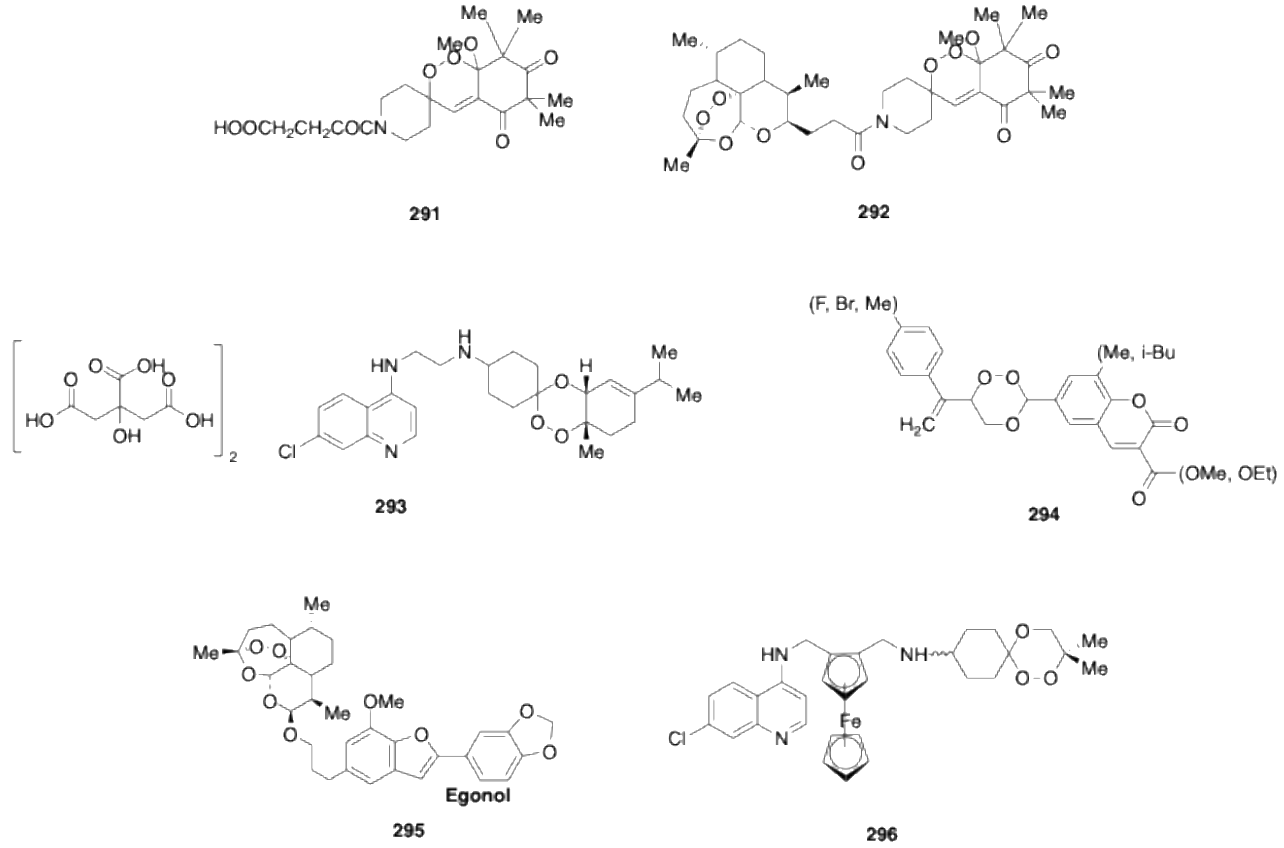

Fig. (29d). Artemisinin-inspired peroxide structures of antimalarial conjugates.

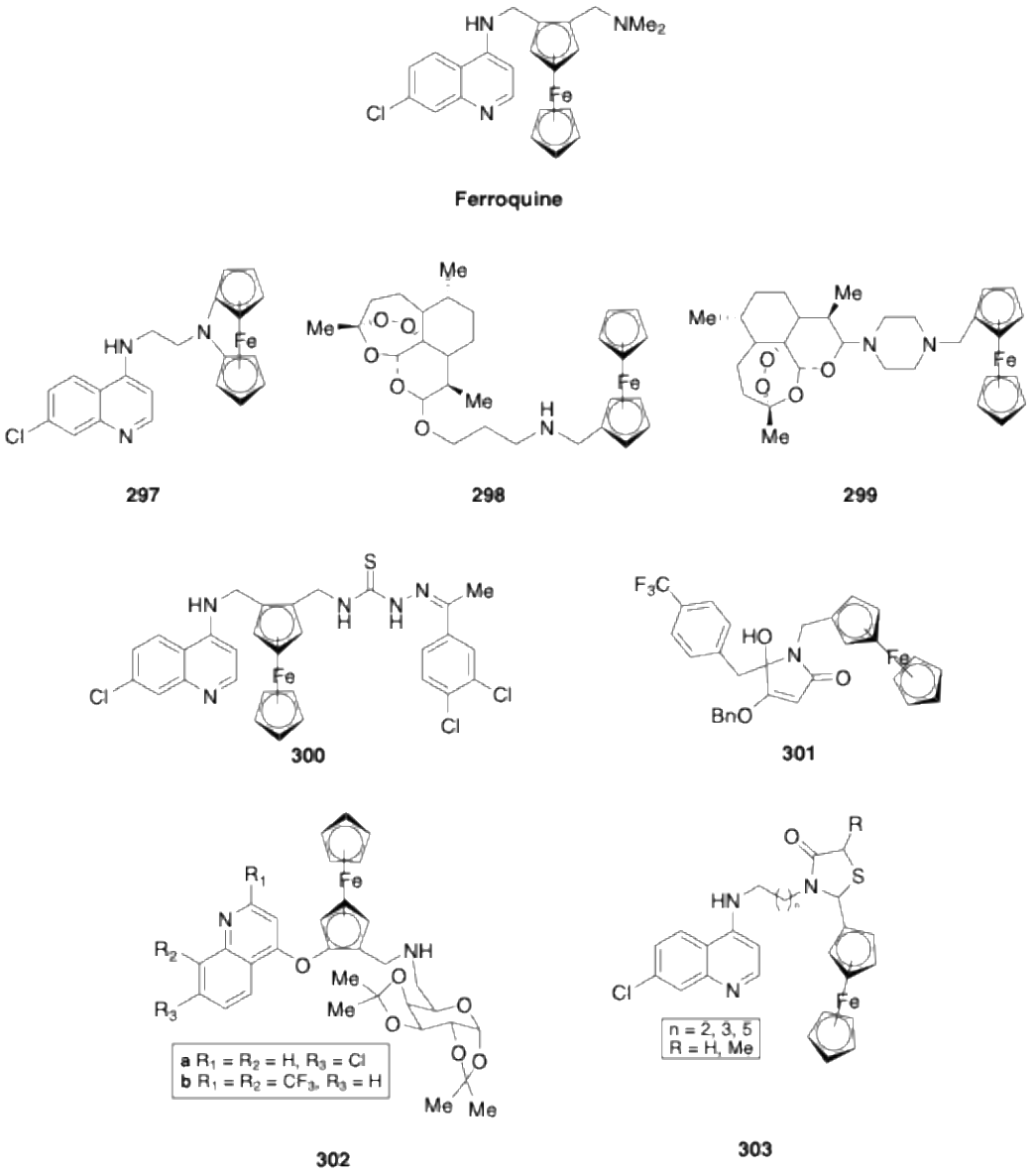

Fig. (30). Ferrocene-based antimalarial hybrids.

7.5. Ferrocene-Derived Antimalarial Hybrids

Ferroquine, a hybrid derived from chloroquine (CQ) and ferrocene, is the most advanced compound in clinical trials. It has shown no *in vivo* toxicity and proved effective against CQ-resistant *Plasmodium falciparum*. [372, 373]. Ferrocene-CQ hybrids, such as compound **297**, where the CQ moiety is linked to both rings of ferrocene, are active against both CQ-sensitive and CQ-resistant parasite strains [374]. Hybrids combining artemisinin with a ferrocenic nucleus, like compounds **298** and **299**, also afforded promising antimalarial activity [375, 376]. Thiosemicarbazone-ferrocene-aminoquinoline hybrids (*e.g.*, compound **300**), which are capable of coordinating metal ions, were developed with the aminoquinoline fragment playing a key role in their antimalarial efficacy [377]. The novel ferrocene-containing compound **301**, though water-insoluble and unstable, represents an example of a compound with a distinct mechanism of action compared to CQ [378]. Triple hybrids **302a** and **302b**, derived from disubstituted ferrocene linked to either glucofuranose or galactopyranose and to mefloquine or CQ fragments, exhibited low activity against both D10 (CQ-sensitive) and Dd2 (CQ-resistant) strains [379]. CQ hybrids linked to 1,3-thiazolidin-4-one units and ferrocenyl groups, such as structure **303**, showed antiplasmodial activity as well as antibacterial properties against G+ *Staphylococcus aureus* and *Bacillus cereus*, with MIC values ranging from 3 to 12 mg/mL (Fig. **30**) [380].

7.6. Assorted Antimalarial Hybrids

Like antitubercular hybrids, antimalarial hybrids encompass a broad range of structurally diverse compounds. Most of these hybrids have been primarily tested *in vitro*, demonstrating potent antiplasmodial activity against *Plasmodium falciparum*, including its drug-resistant strains. However, only a few have been evaluated *in vivo*, and those that were tested did not progress to clinical trials. For instance, the novel antimalarial hybrid **304**, which links a stilbene to a chalcone, exhibited IC_{50} values of 2.2, 1.4, and 6.4 μM against the 3D7 (CQ-sensitive), Indo, and Dd2 (CQ-resistant) strains of *P. falciparum*, respectively. In comparison, the individual stilbene (IC_{50} > 100 μM) and chalcone (IC_{50} = 11.5 μM), or their equimolar mixture (IC_{50} = 32.5 μM), were significantly less potent than hybrid **304** [381]. Additionally, the amidoxime-thiazolium hybrid **305** showed enhanced oral antimalarial activity [382]. Indole-derived hybrids, such as those based on pyrimethamine analogs **306**, were found to be ten times more potent than pyrimethamine itself, which had been previously discontinued due to resistance issues [383]. The tetracyclic hybrid **308**, derived from a thionolactone-isatin combination **307**, demonstrated strong activity against the chloroquine-resistant W2 strain of *P. falciparum* [384]. Hybrids combining coumarin and pyrazoline units, like compound **309**, effectively inhibited both sensitive (MRC-02) and resistant (RKL9) strains of malaria parasites (Fig. **31a**) [385].

Furthermore, a number of structurally diverse hybrids **310-315** [386-391] have been reported to exhibit antimalarial properties, including inhibition of both CQ-sensitive strains (3D7, Pf3D7, RKL-9) and resistant strains (RKL9, Pf3K1, W2). Some of these compounds also enhanced survival in a murine model of *P. berghei* ANKA and displayed anticancer activity against A549 and MDA-MB-231 cell lines (Fig. **31b**).

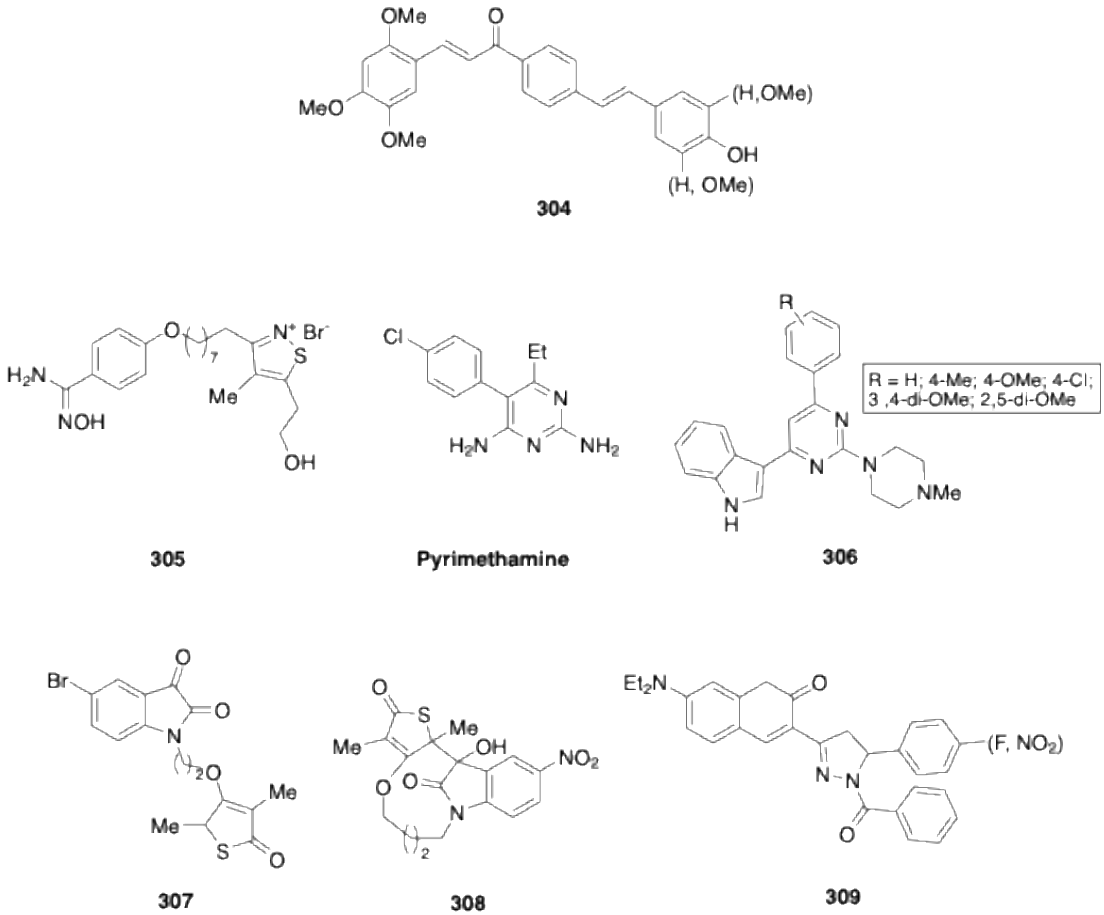

Fig. (31a). Assorted antimalarial hybrids of unrelated structures.

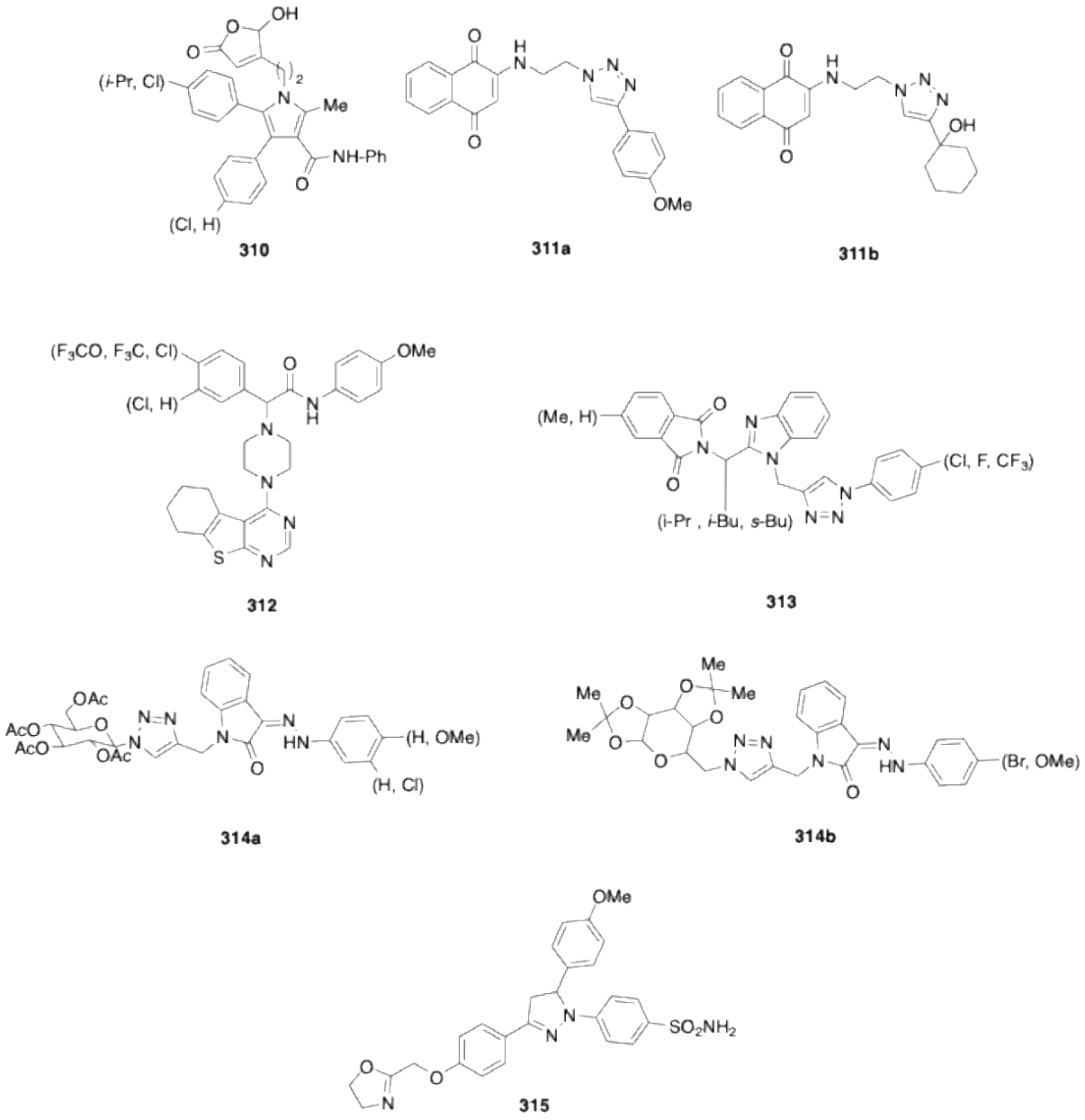

Fig. (31b). Assorted antimalarial hybrids of unrelated structures.

CONCLUSION

The literature on hybrid compounds primarily focuses on antimicrobial hybrids designed to treat widespread diseases such as malaria, fungal infections, and tuberculosis. Other hybrids aim to fill the significant gap in clinically effective treatments for certain diseases. While hundreds of hybrids have demonstrated *in vitro* activity against a range of microbial targets, only a few have been tested *in vivo*, and even fewer have progressed to clinical trials. Additionally, due to the vast structural diversity within each category of hybrids and the broad variety of microbes across different parasitic groups, it is nearly impossible to make meaningful comparisons of activity between these hybrids.

AUTHORS' CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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