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REVIEW

THIAZOLE HYBRIDS WITH ANTIBACTERIAL POTENTIAL AGAINST *STAPHYLOCOCCUS AUREUS*

Chen YIMEN

Department of Internal Medicine, Wuhan Hospital of Traditional Chinese Medicine, Wuhan, 430000 Hubei, China

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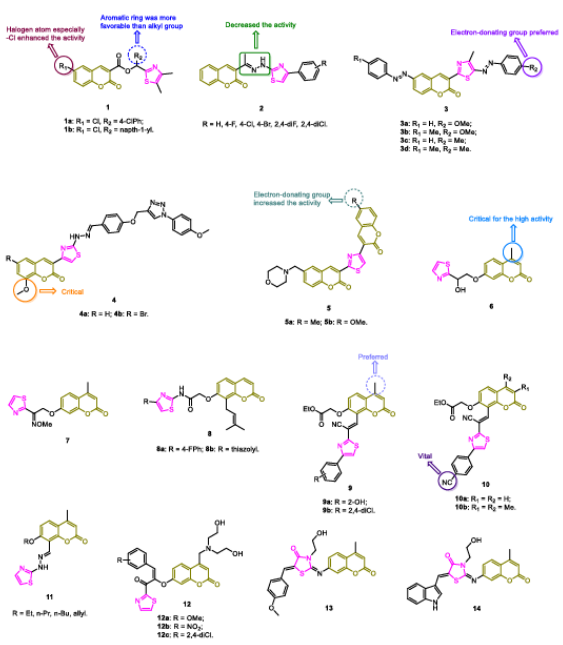
Staphylococcus aureus (*S. aureus*), a typical Gram-positive bacterium, harbors a repertoire of virulence factors that enable it to invade tissues, evade the immune system, and cause diverse infections. Due to its virulence factors, biofilm-forming ability, and rapid antimicrobial resistance development, *S. aureus* is a leading cause of both community- and hospital-acquired infections, including superficial skin abscesses to life-threatening systemic diseases. As traditional antibiotics become less effective against drug-resistant *S. aureus* strains, especially methicillin-resistant *S. aureus* (MRSA), the search for novel antibacterial agents has intensified. Thiazole derivatives, a class of heterocyclic compounds featuring a five-membered ring with sulfur and nitrogen atoms, can disrupt the synthesis of the bacterial cell wall, target the bacterial membrane, inhibit key metabolic pathways, and suppress the efflux pump. Therefore, the thiazole moiety is a promising pharmacophore against *S. aureus*. Hybridization of thiazole with other anti-*S. aureus* pharmacophores to yield multi-targeted agents that address the limitations of single-pharmacophore therapies represents a promising strategy to enhance therapeutic efficacy, leveraging synergistic mechanisms against bacterial virulence and resistance. The present work aims to summarize the current scenario of thiazole hybrids with antibacterial potential against *S. aureus*, covering articles published between 2020 and the present. The structure-activity relationships and the mechanisms of action are also discussed for further rational design of novel effective drug candidates.



INTRODUCTION

Staphylococcus aureus (*S. aureus*) is a Gram-positive pathogen that colonizes the human microbiota, primarily in the nasal cavity, skin, and mucous membranes, with approximately 30% of the population serving as asymptomatic carriers.[1,2] As a versatile pathogen, *S. aureus* harbors a repertoire of virulence factors that enable it to invade tissues, evade the immune system, and cause diverse infections.[3,4] Clinically, *S. aureus* is a leading cause of severe infections, including life-threatening sepsis, necrotizing pneumonia, destructive endocarditis, and chronic osteomyelitis.[5,6] The

* Corresponding author: 18971625553@163.com

therapeutic landscape for *S. aureus* infections has been profoundly reshaped by the rapid acquisition of antimicrobial resistance.[7,8] Resistance mechanisms include genetic mutations (*e.g.*, *gyrA* alterations conferring fluoroquinolone resistance), enzymatic inactivation (*e.g.*, β-lactamase-mediated degradation), and efflux pump-mediated drug extrusion, underscoring the pathogen's adaptive resilience.[9,10] Methicillin-resistant *S. aureus* (MRSA), which emerged in the 1960s, remains a quintessential example of antibiotic resistance, with the *mecA* gene encoding penicillin-binding protein 2a (PBP2a) conferring broad-spectrum β-lactam resistance.[11] More recently, *S. aureus* strains displaying reduced susceptibility to vancomycin (vancomycin-intermediate *S. aureus*/VISA) and complete resistance (vancomycin-intermediate *S. aureus*/VRSA) have emerged, posing a critical threat to the efficacy of last-line glycopeptide therapies.[12,13] The World Health Organization (WHO) lists drug-resistant *S. aureus* as a high-priority pathogen for new antibiotic development, necessitating urgent development of novel therapeutic strategies.[14]

Thiazole derivatives, heterocyclic compounds with a five-membered ring of sulfur and nitrogen, can combat *S. aureus* through multiple mechanisms: (1) binding to penicillin-binding proteins (PBPs), thereby inhibiting cell wall cross-linking and causing bacterial lysis; (2) disrupting the bacterial cell membrane, leading to leakage of ions and proteins, which compromises cell viability; (3) targeting ribosomal subunits or aminoacyl-tRNA synthetases to block protein synthesis; (4) suppressing virulence factors by inhibiting quorum sensing systems or toxin gene transcription; (5) interfering with DNA topoisomerases or RNA polymerase to disrupt nucleic acid replication and transcription; (6) blocking peptidoglycan precursor synthesis or transport, thereby disrupting cell wall assembly; (7) inducing reactive oxygen species (ROS); (8) inhibiting efflux pumps or targeting resistance mechanisms like PBP2a in MRSA.[15–18] Moreover, the thiazole moiety offers vast synthetic flexibility for the design of novel anti-*S. aureus* agents with enhanced efficacy and reduced resistance potential, and hybridization of thiazole with other anti-*S. aureus* pharmacophores can yield multi-targeted agents that address the limitations of single-pharmacophore therapies, representing a promising strategy to enhance therapeutic efficacy, leveraging synergistic mechanisms against bacterial virulence and resistance.[19,20]

The present work aims to systematically summarize the current landscape of thiazole hybrids with demonstrated antibacterial potential against *S. aureus*, focusing on research articles published from 2020 to the present. By curating recent advancements, this review not only highlights the structural diversity of these hybrids but also dissects their efficacy against both susceptible and drug-resistant strains, including MRSA. A detailed analysis of structure-activity relationships (SARs) is integrated to unveil key molecular features that modulate antibacterial potency. Additionally, the review delves into the underlying mechanisms of action to inform rational drug design. Ultimately, these insights aim to guide the development of novel thiazole-based candidates with optimized efficacy, reduced resistance liabilities, and translational potential for clinical applications.

THIAZOLE-COUMARIN HYBRIDS

The ester tethered thiazole-coumarin hybrids **1** (Fig. 1, minimum inhibitory concentration/MIC: 0.05–4.0 μg/mL) exhibited excellent antibacterial activity against *S. aureus* ATCC12600 strain.[21] The SARs disclosed that (1) a halogen atom, especially chloro, at the C-6 position (R1) of the coumarin moiety boosted the activity; (2) the aromatic ring, especially 4-chlorophenyl and naphthyl, at the R2 position was more favorable than an alkyl side chain;[21] (3) the ester linker between thiazole and coumarin moieties was critical for the high activity, and replacement by hydrazone led to significant loss of activity as evidenced by that hybrids **2** (MIC: 100–500 μg/mL) were less potent than norfloxacin (MIC: 10 μg/mL) and ciprofloxacin (MIC: 50 μg/mL) against *S. aureus* ATCC96 strain.[22] In particular, the representative hybrids **1a,b** (MIC: 0.05 μg/mL) not only were 2.5–80 times superior to ciprofloxacin (MIC: 0.125 μg/mL), gatifloxacin (MIC: 0.5 μg/mL), levofloxacin (MIC: 4.0 μg/mL), and novobiocin (MIC: 2.0 μg/mL) against *S. aureus* ATCC12600 strain but also demonstrated potential antibacterial activity against MRSA N315 (MIC: 4.0 and 4.0 μg/mL) and VRSA Mu50 (MIC: 4.0 and 8.0 μg/mL) pathogens, not inferior to that of ciprofloxacin (MIC: 4.0 and 16 μg/mL), gatifloxacin (MIC: 8.0 and 32 μg/mL),

levofloxacin (MIC: 32 and 16 μg/mL), and novobiocin (MIC: 16 and 32 μg/mL). Of particular note, hybrid **1a** (half maximal inhibitory concentration/IC_{50}: 130 nM) was highly active in the inhibition of DNA gyrase, outperforming that of ciprofloxacin (IC_{50}: 750 nM), gatifloxacin (IC_{50}: 10.66 μM), levofloxacin (IC_{50}: 22.14 μM), and novobiocin (IC_{50}: 820 nM). The molecular docking studies revealed that the chloro on the coumarin moiety could form a hydrogen bond with Arg1122, whereas the carbonyl group of the coumarin moiety formed a hydrogen bond with Cys11. Besides, the chloro at the *para*-position of the phenyl ring formed a hydrogen bond with Ser1084. Overall, hybrid **1a,** as a potent DNA gyrase inhibitor, could serve as a promising candidate for fighting against both drug-sensitive and drug-resistant *S. aureus* pathogens.

Further studies indicated that thiazole could also be directly linked to the C-3 position of the coumarin moiety, and hybrids **3** (MIC: 1.0–4.0 μg/mL) showed potent antibacterial activity against *S. aureus* strain.[23] The SARs illustrated that (1) an electron-donating methyl or methoxy group at the R2 position increased the activity, whereas a methyl at the R1 position was also tolerated; (2) introduction of 1,2,3-triazole was permitted, and a significant part of hybrids **4** (MIC: 2.0–8.0 μg/mL) were active against *S. aureus* ATCC96 and *S. aureus* MLS16 ATCC2940 strains;[24] (3) incorporation of the second coumarin moiety was tolerated, and hybrids **5** (MIC: 1.0–8.0 μg/mL) also displayed robust antibacterial activity against *S. aureus*.[25] Among them, the representative hybrids **3a–d** (MIC: 1.0 μg/mL) and **5a,b** (MIC: 2.0 and 1.0 μg/mL) were comparable to ciprofloxacin (MIC: 1.0 μg/mL) against *S. aureus*, whereas hybrids **4a,b** (MIC: 2.0–4.0 μg/mL) were not inferior to ciprofloxacin (MIC: 1.0 μg/mL) against *S. aureus* MLS16 ATCC2940 strains. Notably, hybrids **3a,b** (MIC: 2.0 and 2.0 μg/mL) were also comparable to linezolid (MIC: 2.0 and 1.0 μg/mL) against MRSA ATCC33591 and MRSA ATCC43300 strains. Moreover, hybrids **4a,b** (IC_{50}: 13.5 and 12.0 μM) displayed promising biofilm formation inhibitory activity towards *S. aureus* MTCC96, whereas hybrids **5a,b** (IC_{50}: 122 and 131 nM) demonstrated superior dihydrofolate reductase (DHFR) enzyme inhibitory activity, compared to sulfadiazine (IC_{50}: 138 nM). Molecular docking studies revealed that (1) the oxygen atom in the morpholine moiety formed a hydrogen bond with Arg98 residue; (2) the carbonyl group of the coumarin moiety not only formed a hydrogen bond with Thr46, but also formed a hydrogen bond with Gly97 for hybrid **5a** and with Gly15 for hybrid **5b**; (3) the coumarin unit in hybrid **5a** exhibited hydrophobic π-H contacts with the His45 residue.

The ether tethered thiazole-coumarin hybrid **6** (MIC: 8.0 μg/mL) was comparable to ciprofloxacin (MIC: 8.0 μg/mL) and norfloxacin (MIC: 2.0 μg/mL) against *S. aureus*, and the SAR manifested that the methyl group at the C-4 position of coumarin moiety was critical for the high activity.[26] It was worth noticing that hybrid **6** (MIC: 1.0 μg/mL) demonstrated robust antibacterial activity against MRSA N315, 8.0 times surpassed that of ciprofloxacin (MIC: 8.0 μg/mL) and norfloxacin (MIC: 8.0 μg/mL). Further study showed that incorporation of methoxime between thiazole and coumarin was tolerated, and hybrid **7** (MIC: 1.0 μg/mL) was also highly potent against MRSA N315. Moreover, hybrid **7** (IC_{50}: >16 μg/mL) displayed relatively low cytotoxicity towards normal LO2 cells, and the hemolytic rate was <5% even at 16 μg/mL. Besides, hybrid **7** could eradicate 36.3% biofilm of MRSA at 8.0 μg/mL and decrease MRSA by 10 Log CFU/mL within 6 h at 4.0 μg/mL. The resistance studies showed that the MIC values of hybrid **7** remained nearly stable over 12 passages, whereas those of norfloxacin began to change after 4 passages and increased by 32-fold after 14 passages. Mechanistically, hybrid **7** was able to damage the integrity of the membrane to trigger leakage of protein, insert into MRSA DNA to block its replication, and induce the generation of ROS to inhibit bacterial growth.

Thiazole-osthole hybrids **8a,b** (MIC: 1.0–2.0 μg/mL) were highly potent against *S. aureus* and MRSA, not inferior to that of norfloxacin (MIC: 1.0 μg/mL) and oxacillin (MIC: 0.5 μg/mL) against *S. aureus* and 64 and 128 folds higher than that of norfloxacin (MIC: 128 μg/mL) and oxacillin (MIC: 256 μg/mL) against MRSA.[27] The SAR elucidated that the substituent at the C-4 position of the thiazole moiety had a remarkable influence on the activity, and 4-fluorophenyl or thiazolyl was most favorable to the activity, while a small volume alkyl side chain or phenyl ring with an electron-donating group led to a significant loss of activity.

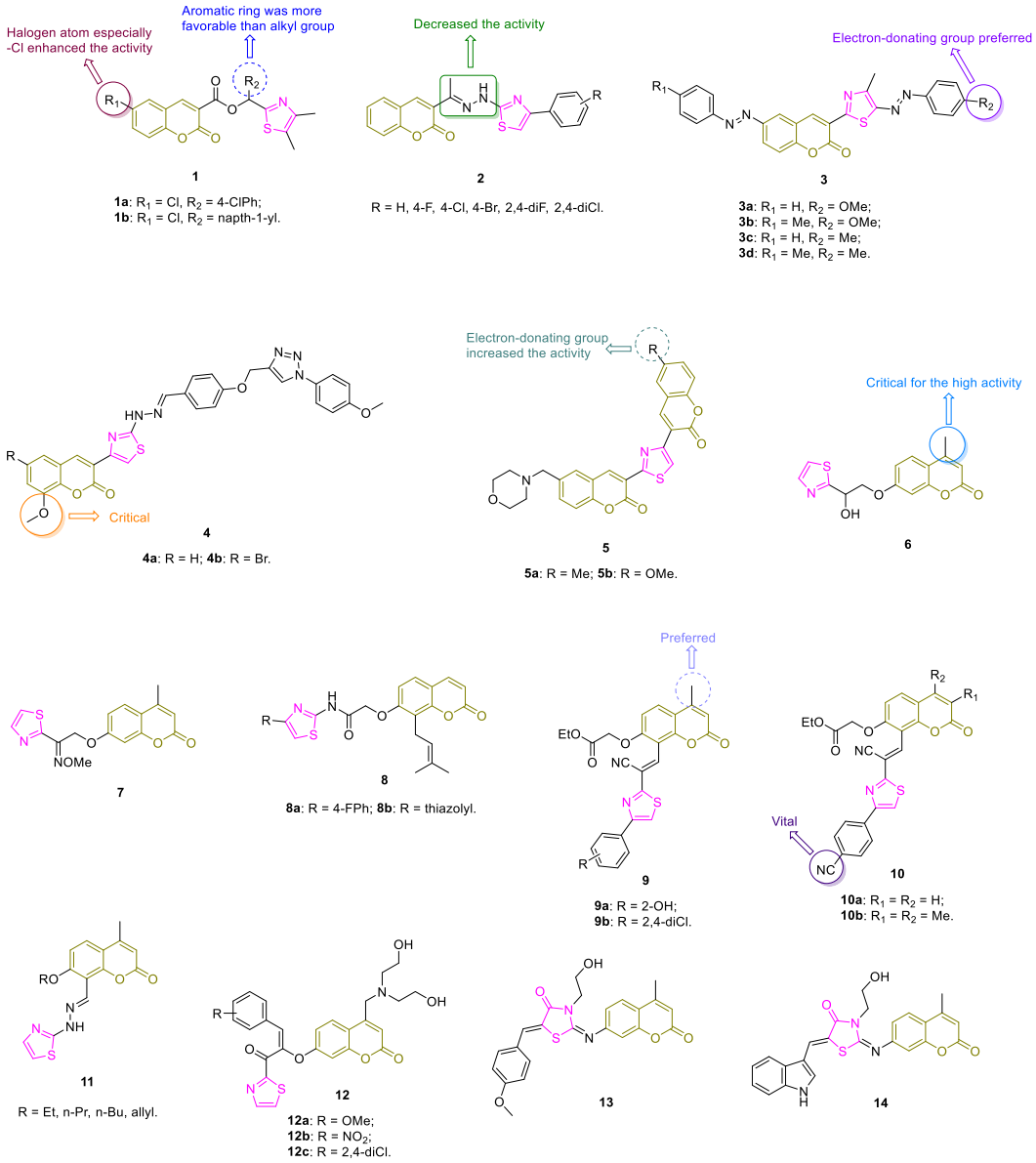


Fig. 1 – Chemical structures of thiazole-coumarin hybrids **1–14**.

Thiazole-coumarin hybrids **9a,b** (MIC: 32 μg/mL) showed moderate activity against MRSA N315, slightly less active than norfloxacin (MIC: 8.0 μg/mL).[28] The SAR revealed that the methyl group at the C-4 position of the coumarin moiety was favorable to the activity against MRSA N315. Further studies demonstrated that (1) incorporation of the cyano group at the *para*-position of the phenyl ring increased the antibacterial activity against *S. aureus* ATCC25923 and *S. aureus* ATCC29213 strains as evidenced by that hybrids **10a,b** (MIC: 1.0–4.0 μg/mL) were comparable to norfloxacin (MIC: 1.0 and 2.0 μg/mL) against the two *S. aureus* strains;[28] (2) the linker between thiazole and coumarin influenced the activity significantly, and hybrids **11** (MIC: 8.0–512 μg/mL) were less active than norfloxacin (MIC: 0.5–8.0 μg/mL) against three *S. aureus* strains and MRSA N315.[29] The resistance studies showed that the MIC values of hybrid **10a** remained almost unchanged after 16 passages, whereas those of norfloxacin increased by 32-fold after 16 passages. Of note, the hemolytic rate of hybrid **10a** was <3% even at 256 μg/mL. Mechanistic studies showed that hybrid **10a** not only intercalated into DNA, forming stable supramolecular complexes that blocked DNA replication, but also bound to DNA gyrase to form biosupramolecular assemblies. Additionally, hybrid **10a** disrupted the cell membrane, perturbed metabolic pathways, and triggered oxidative stress, ultimately leading to bacterial cell death. In the *S. aureus* ATCC 29213-infected mice model, hybrid

10a administered orally achieved a 2.4 Log CFU/mL reduction in bacterial loads at 10 mg/kg and caused a ~4.0 Log CFU/mL decrease in bacterial colony count at 20 mg/kg. Accordingly, hybrid **10a** shows great potential as a candidate for developing novel chemotherapeutics to treat *S. aureus* infections.

Thiazole-coumarin hybrids **12** (MIC: 32–256 μg/mL) showed moderate antibacterial activity against three *S. aureus* strains, but hybrids **12a-c** (MIC: 2.0–4.0 μg/mL) were not inferior to norfloxacin (MIC: 1.0 μg/mL) against MRSA N315.[30] The time-kill kinetic studies revealed that hybrid **12a** had a strong killing ability against MRSA at 4.0 μg/mL and could quickly inactivate the bacteria within 2.0 h. The resistance studies indicated that MRSA remained almost unchanged for 7 consecutive passages and produced slow resistance to hybrid **12a** compared with the reference drug norfloxacin, demonstrating that it was more difficult for the hybrid **12a** to induce the development of MRSA resistance than norfloxacin. Moreover, hybrid **12a** was shown to disrupt the membrane of MRSA and form a PI-DNA complex, which may further penetrate the bacterial membrane to achieve its potent antibacterial effect. Besides, hybrid **12a** could also be inserted into MRSA DNA to inhibit its replication and growth. The molecular docking results indicated that (1) the oxygen atom on the hydroxyl group in hybrid **12a** was adjacent to Cys11, forming a hydrogen bond; (2) hybrid **12a** also formed hydrogen bonds with the Arg1122 residue *via* the nitrogen atom of the thiazole fragment and the oxygen atom on the carbonyl group.

Tiazolidinone-coumarin hybrid **13** (MIC: 0.5 μg/mL) was highly active against *S. aureus* ATCC29213 strain, and the SAR disclosed that the replacement of the benzyl ring by indole increased the activity as evidenced by that hybrid **14** (MIC: 0.25 μg/mL) was 8–16 times outperformed norfloxacin (MIC: 2.0–4.0 μg/mL) against *S. aureus* ATCC25923, *S. aureus* ATCC29213, and MRSA N315 pathogens.[31] Notably, (IC_{50}: >100 μg/mL) displayed relatively low cytotoxicity towards normal endothelial cells, and the hemolytic rate of hybrid **14** was <5% even at 256 μg/mL. Further studies revealed that the MIC values of norfloxacin increased by 16-fold after 14 passages, while the MIC values of indole-derived hybrid **14** did not change dramatically, which indicated that hybrid **14** exhibited a low tendency to develop resistance. Mechanistic studies revealed that hybrid **14** could disrupt the cell membrane, thereby inducing leakage of intracellular proteins and nucleic acids and disrupting normal metabolic processes. Also, hybrid **14** triggered ROS-mediated oxidative damage, ultimately inhibiting bacterial growth. Furthermore, hybrid **14** was found to intercalate into DNA and bind to DNA gyrase B, highlighting its multi-target antibacterial mechanism.

THIAZOLE-PYRIMIDINE/QUINAZOLINE HYBRIDS

Thiazole-pyrimidine hybrids **15** (Fig. 2, MIC: 2.0–4.0 μg/mL) and **16** (MIC: 2.0–4.0 μg/mL) exhibited potent antibacterial activity against 2 methicillin-susceptible *S. aureus* (MSSA), 5 MRSA, and 2 VRSA clinical isolates, not inferior to that of vancomycin (MIC: 0.5–64 μg/mL) and linezolid (MIC: 0.5–32 μg/mL).[32] The SARs disclosed that (1) the substituent at the C-2 position of the pyrimidine moiety significantly influenced activity, with a six-membered ring-containing amino group demonstrating favorable effects on the activity;[32,33] (2) incorporation of an aminomethylene linker between thiazole and pyrimidine led to remarkably loss of activity;[34] (3) replacement of thiazole by thiazolidinedione was permitted, and hybrids **17a,b** (MIC: 4.0 and 4.0 μg/mL against *S. aureus*; 8.0 and 8.0 μg/mL against MRSA) were not inferior to streptomycin (MIC: 8.0 μg/mL against *S. aureus*) and linezolid (MIC: 8.0 μg/mL against MRSA);[35] (4) substitution of pyrimidine with pyrazolo[1,5-a]pyrimidine was also tolerated, giving hybrids **18a,b** (MIC: 3.12 and 3.12 μg/mL), which showed activity equivalent to chloramphenicol (MIC: 3.12 μg/mL) and superior to cephalothin (MIC: 6.25 μg/mL) against *S. aureus* ATCC6538.[36] Hybrid **15** (5 × MIC) displayed rapid bactericidal activity, reducing the total count by >3.0 Log CFU/mL within 2 h and completely eradicating MRSA USA400 after 6 h, whereas hybrid **16** reduced the high MRSA USA400 inoculum by >3.0 Log within 6 h and eradicated it after 8 h. In contrast, vancomycin required 24 h to eradicate the high MRSA count. Unlike rifampicin, to which MRSA developed resistance rapidly, the MIC values for hybrids **15** and **16** increased 2-fold after the 8^{th} and 14^{th} passage, respectively. Besides, hybrid **15** reduced the intracellular MRSA USA400 burden by a 2.08 Log CFU/mL reduction (99.18% reduction) at 4 × MIC (16 μg/mL), whereas hybrid **16** completely eradicated the intracellular MRSA USA400 burden. Mechanistically, hybrid **16** inhibited undecaprenyl diphosphate phosphatase (UppP) with an IC_{50} value of 29 μM. Of particular note, hybrid **16** possessed

desirable pharmacokinetic profiles with half-life ($t_{1/2}$) of 4.28 h, volume of distribution (Vd) of 17.78 L, rate of clearance (CL) of 7.35 L/h, and area under the curve ($AUC_{0-\infty}$) of 3400 h·ng/mL at a dose of 5.0 mg/kg *via* intravenous injection. In an *in vivo* murine MRSA USA300 skin infection model, mice treated with petroleum jelly containing 2% of hybrid **16** exhibited significantly milder lesions and remarkable skin healing, and bacterial colony counts in the hybrid **16**-treated group were significantly lower than those in the petroleum jelly-treated group. Besides, the systemic bacterial invasion, quantified by colony counts in the spleens of infected animals, was substantially reduced. No liver toxicity and body weight loss were observed even after oral administration of up to 250 mg/kg, demonstrating the good safety profile of hybrid **16**. Collectively, hybrid **16** was an excellent therapeutic candidate for invasive MRSA infections.

The antibacterial SAR of thiazole-quinazolinone hybrids (MIC: 0.5–128 μg/mL) against *S. aureus*, *S. aureus* ATCC25923, *S. aureus* ATCC29213, and MRSA N315 pathogens illustrated that the introduction of substituents into the quinazolinone moiety reduced the activity.[37,38] Among them, hybrid **19** (MIC: 1.0–8.0 μg/mL against *S. aureus* strains; 0.5 μg/mL against MRSA N315) showed activity equivalent to norfloxacin (MIC: 1.0–8.0 μg/mL) against 3 *S. aureus* strains and 8 times surpassed norfloxacin (MIC: 4.0 μg/mL) against MRSA N315. In addition, hybrid **19** with low hemolytic toxicity (hemolytic rat: 4.43% at 32 × MIC) developed resistance slowly: the MIC values of hybrid **19** against MRSA remained nearly unchanged after 16 successive cultures, whereas those of norfloxacin showed a dramatic increase after the 9th passage, and the MIC value of MRSA increased 32-fold compared to the first generation. Moreover, hybrid **19** effectively inhibited biofilm formation and reduced MRSA metabolic activity. Mechanistic studies revealed that hybrid **19** induced protein leakage by disrupting membrane integrity and DNA replication *via* DNA intercalation. Notably, hybrid **19** exhibited a synergistic effect with cefdinir, which was attributed to its ability to induce allosteric regulation of MRSA PBP2a. This regulation triggered the opening of the active site, promoting cefdinir binding and inhibiting PBP2a expression, thereby overcoming MRSA resistance and significantly enhancing anti-MRSA activity.

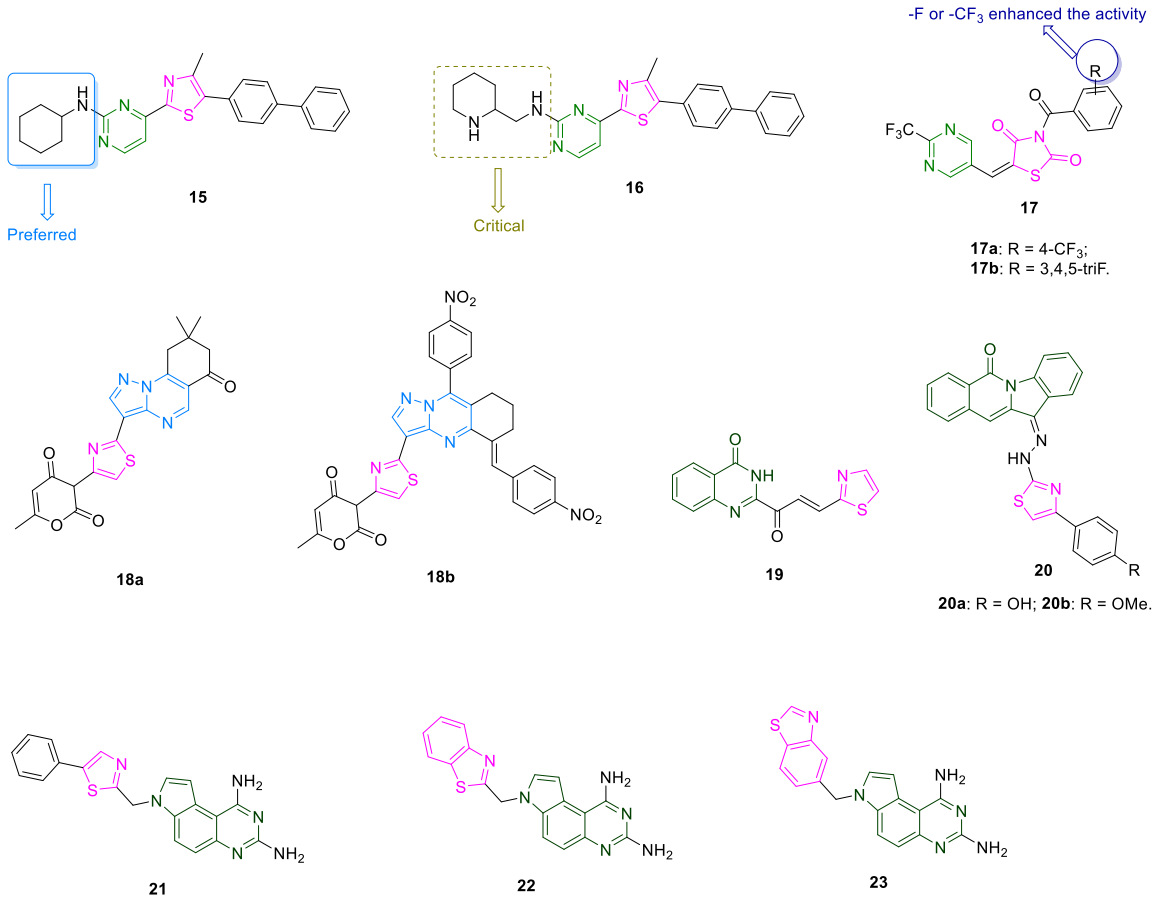


Fig. 2 – Chemical structures of thiazole-pyrimidine/quinazoline hybrids **15–23**.

A significant part of thiazole-tryptanthrin hybrids **20** (MIC: 3.12–50 μg/mL) were active against *S. aureus*, and the SAR manifested that an electron-donating group on the phenyl ring at the C-4 position of the thiazole moiety was beneficial for the activity.[39] Among them, hybrids **20a,b** (MIC: 3.12 and 3.12 μg/mL) were 2 times superior to streptomycin (MIC: 6.25 μg/mL) against *S. aureus*. Of note, replacement of tryptanthrin by pyrrol[3,2-*f*]quinazoline was tolerated, and hybrid **21** (MIC: 2.0 and 4.0 μg/mL) was as potent as norfloxacin (MIC: 2.0 and 4.0 μg/mL) and trimethoprim (MIC: 2.0 and 2.0 μg/mL) against *S. aureus* ATCC29213 and MRSA ATCC43300 strains.[40] In addition, hybrid **21** (half of hemolytic concentration/ HC_{50}: >250 μg/mL) showed poor hemolytic activity, confirming its weak capacity to disrupt red blood cell membranes and induce hemolysis.

Further studies revealed that substitution of thiazole by benzothiazole remarkably enhanced the antibacterial activity, and benzothiazole-pyrazolo[1,5-a]pyrimidine hybrid **22** (MIC: ≤0.03–0.125 μg/mL) exhibited pronounced antibacterial activity against 2 MSSA, 4 MRSA, and 2VISA, outperforming that of levofloxacin (MIC: 0.25–64 μg/mL) and trimethoprim (MIC: 0.25–1.0 μg/mL).[41] Hybrid **23** (MIC: 0.125 and 0.0156 μg/mL), the regio-isomer of hybrid **22**, also showed excellent antibacterial activity against *S. aureus* ATCC29213 and MRSA ATCC43300 strains, 8 and 32 times more potent than that of trimethoprim (MIC: 1.0 and 0.5 μg/mL). After MRSA ATCC 43300 cells were incubated for a period of 10 passages, the MIC values for hybrid **23** were increased 2-fold, whereas trimethoprim (16-fold) showed an obvious increase in the MIC. Moreover, the median lethal dose (LD_{50}) of hybrid **23** was 282.81 mg/kg, demonstrating its low acute toxicity. In the MRSA ATCC43300-infected mice model, hybrid **23** (intraperitoneal injection) provided significant protection to the infected mice with a survival rate of 50% at 7.5 mg/kg and 66% at 15 mg/kg, superior to that of trimethoprim (<50% at 15 mg/kg). In the MRSA ATCC43300-infected mice thigh model, hybrid **23** (intraperitoneal injection) reduced ∼0.60 Log CFU/g bacterial load in thighs at a dose of 60 mg/kg, while trimethoprim only reduced ∼0.30 Log CFU/g bacterial load under the identical conditions.

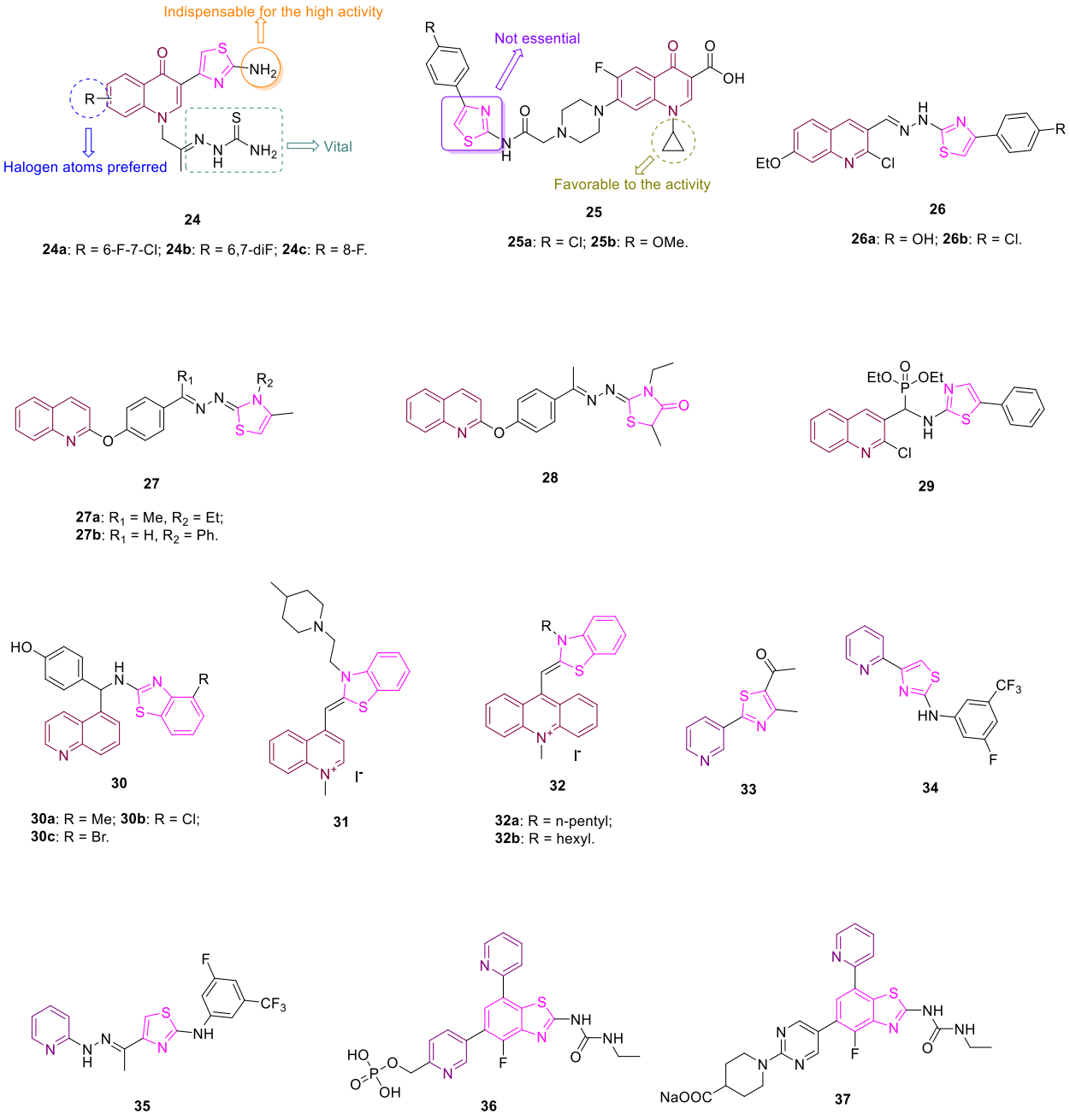
THIAZOLE-PYRIDINE/QUINOLINE HYBRIDS

Thiazole-quinolone hybrids **24** (Fig. 3, MIC: 2.0–64 μg/mL) exhibited considerable antibacterial activity against *S. aureus* ATCC25923, *S. aureus* ATCC29213, MRSA N315, and drug-resistant *S. aureus* pathogens.[42] The SARs elucidated that (1) the amino at the C-2 position of the thiazole moiety and carbothioamidehydrazone at the N-1 position of the quinolone motif were vital for the high activity; (2) halogen atoms at the C-6, C-7, or C-8 position of quinolone boosted the activity.[42,43] Among them, hybrids **24a–c** (MIC: 2.0–16 μg/mL) were found to be most active against the tested organisms and were not inferior to norfloxacin (MIC: 8.0 and 8.0 μg/mL) against MRSA N315 and drug-resistant *S. aureus* pathogens. In particular, hybrid **24a** exhibited negligible hemolysis with the hemolytic rate <1.0% at 8.0 μg/mL and could disrupt the integrity of the bacterial membrane, intercalate into DNA, and inhibit the activity of topoisomerase IV, suggesting a multitargeting mechanism of action. Besides, hybrid **24a** (IC_{50}: >128 μg/mL) displayed relatively low cytotoxicity toward normal mouse fibroblast L929 cells, and no overt toxicity in major organs or significant body weight loss was observed at a dose of 5.0 mg/kg/day, highlighting its good safety profile. Hybrid **24a** (8 × MIC) showed rapid bactericidal activity against drug-resistant *S. aureus*, reducing >1.0 Log CFU/mL bacterial burden within 2 h. After 16 passages, the MIC values of hybrid **24a** remained well constant, while the MIC values of norfloxacin began to significantly increase only after 4 passages. Molecular docking studies revealed that (1) the 2-amino group and carbothioamide fragment of hybrid **24a** could enter the hydrophobic pocket of the DNA-topoisomerase IV complex; (2) the nitrogen atom and amino group at the C-2 position of the thiazole ring formed hydrogen bonds with the DA20 base of DNA.

The antibacterial SARs of thiazole-fluoroquinolone hybrids **25** (MIC: 10.35–315.63 μg/mL) against *S. aureus* ATCC25923 and MRSA disclosed that (1) the cyclopropyl group at the N-1 position of the fluoroquinolone moiety was most favorable to the activity; (2) thiazole moiety was not essential for the activity, and replacement by thiadiazole motif increased the activity.[44] Among them, thiazole-ciprofloxacin hybrids **25a,b** (MIC: 10.35 and 10.35 μg/mL) showed equal antibacterial activity against *S. aureus* ATCC25923 and MRSA, but were less potent than the parent ciprofloxacin (MIC: 1.31 and 1.31 μg/mL).

The hydrazone tethered thiazole-quinoline hybrids **26a,b** (MIC: 5.57 and 7.81 μg/mL) showed higher antibacterial activity than tetracycline (MIC: 62.5 μg/mL) against *S. aureus*, and hybrid **26a**

(MIC: 1.95 μg/mL) was not inferior to vancomycin (MIC: 0.78 μg/mL) and ciprofloxacin (MIC: 3.90 μg/mL) against multidrug-resistant *S. aureus* ATCC33591.[45] The SARs indicated that (1) incorporation of phenyloxy between quinoline and hydrazole was permitted, and hybrids **27a,b** (MIC: 0.24 and 0.24 μg/mL) and **28** (MIC: 0.24 μg/mL) exhibited excellent antibacterial activity against *S. aureus*;[46] (2) replacement of the hydrazone linker by an amino linker was tolerated, and hybrid **29** (MIC: 0.5 and 0.5 μg/mL) showed robust antibacterial activity against *S. aureus* ATCC25923 and ciprofloxacin-resistant *S. aureus* strains.[47] Of note, hybrid **26a** (IC_{50}: 10.02 μM) was more active than trimethoprim (IC_{50}: 18.25 μM) in inhibition of DHFR. Molecular docking studies revealed that (1) the hydrogen of hydrazinyl, oxygen of ethoxy group, and hydroxy group on the phenyl ring of hybrid **26a** formed three hydrogen bonds between the residues Ser59, Arg28, and Glu30; (2) the ethoxy group of quinoline and thiazole core formed hydrophobic interaction as well as one arene-arene interaction between the residue Phe34 and phenyl ring of phenol.



24

24a: R = 6-F-7-Cl; **24b**: R = 6,7-diF; **24c**: R = 8-F.

25

25a: R = Cl; **25b**: R = OMe.

26

26a: R = OH; **26b**: R = Cl.

27

27a: R_1 = Me, R_2 = Et;
27b: R_1 = H, R_2 = Ph.

28

29

30

30a: R = Me; **30b**: R = Cl;
30c: R = Br.

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32

32a: R = n-pentyl;
32b: R = hexyl.

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37

Fig. 3 – Chemical structures of thiazole-pyridine/quinoline hybrids **24**–**37**.

Benzothiazole-quinoline hybrids **30a–c** (MIC: 50 μg/mL) showed moderate antibacterial activity against *S. aureus*,[48] whereas benzothiazole-quinolinium hybrid **31** (MIC: 1.0–2.0 μg/mL) was highly active against 2 *S. aureus* and 4 MRSA strains,[49] not inferior to that of vancomycin (MIC: 1.0–2.0 μg/mL) and ampicillin (MIC: 16->64 μg/mL). The SAR illustrated that the replacement of quinolinium by acridinium was tolerated, and hybrids **32a,b** (MIC: 0.25–2.0 μg/mL and <0.125–1.0 μg/mL, respectively) were more potent than vancomycin (MIC: 1.0–4.0 μg/mL), ciprofloxacin (MIC: 4.0 – >64 μg/mL), and linezolid (MIC: 2.0–4.0 μg/mL) against *S. aureus* ATCC25923, *S. aureus* clinical isolate, MRSA ATCC43300, and penicillin-resistant *S. aureus* (PRSA) pathogens.[50] Moreover, hybrid **32b** achieved 2.07 Log CFU/mL reduction within 3 h (>99% of *S. aureus* ATCC25923 killed) at 4.0 μg/mL (16 × MIC). Besides, hybrid **32b** completely eradicated *S. aureus* after 6 h, and no resistant populations were observed during 24 h. The MIC value of hybrid **32b** increased only 2-fold after *S. aureus* ATCC25923 was incubated (0.5×MIC) for 17 passages. In contrast, ciprofloxacin was shown to induce resistance rapidly, exhibiting a more than 64-fold increase at 0.5 × MIC. Further studies demonstrated that hybrid **31** stimulated filamenting temperature-sensitive mutant Z (FtsZ) polymerization in bacteria, thereby disrupting dynamic assembly and Z-ring formation, with inhibition of this critical step in bacterial cell division likely representing its primary antibacterial mechanism, whereas hybrid **32b** acted as an effective FtsZ inhibitor by modulating the dynamics of FtsZ self-polymerization through a stimulatory mechanism, thereby inhibiting cell division and inducing cell death. In the *S. aureus* ATCC25923-infected murine model, hybrid **32b** (25 mg/kg, intraperitoneal injection) reduced the number of viable bacterial colonies by 0.91 Log CFU/mL, comparable to that of linezolid (1.29 Log CFU/mL) under the same conditions.

AMPT (**33**), a thiazole-pyridine hybrid, demonstrated potent antibacterial activity against 85 MSSA (MIC: 0.25–8.0 μg/mL; mean MIC_{90}: 2.0 μg/mL) and 121 MRSA (MIC: 0.25–8.0 μg/mL; mean MIC_{90}: 4.0 μg/mL) clinical isolates.[51] The activity was not inferior to oxacillin (mean MIC_{90}: 0.50 and 512 μg/mL against MSSA and MRSA, respectively), vancomycin (mean MIC_{90}: 8.0 and 16 μg/mL), and teichoplanin (mean MIC_{90}: 2.0 and 8.0 μg/mL) against MSSA clinical isolates and 2.0–128 folds outperformed the three reference drugs against MRSA. The bactericidal effect of **AMPT** (2 × MIC) was observed after only 4 h of treatment in multidrug-resistant MRSA-C17 and MRSA-C18 isolates, with a 4.0 Log CFU decrease in viable counting achieved after 4 h, and no viable bacteria could be detected after 24 h of incubation, whereas no bactericidal activity was observed for ampicillin-treated cultures. Moreover, **AMPT** exhibited notable inhibitory effects on haemolysin, protease production, and biofilm formation in MRSA, but showed no dispersal activity against preformed biofilms. Molecular docking analysis further revealed favorable interactions between AMPT and key virulence regulators AgrA and SarA in *S. aureus*, confirming its anti-virulence and anti-biofilm properties.

Thiazole-pyridine hybrid **34** (MIC: 1.0 μg/mL) was highly active against MRSA ATCC43300, 2 times superior to that of vancomycin (MIC: 2.0 μg/mL).[52] The SARs illustrated that (1) incorporation of the hydrazone linker between thiazole and pyridine was permitted, and hybrid **35** (MIC: 0.5–4.0 μg/mL) also exhibited excellent antibacterial activity against 8 *S. aureus* and MRSA ATCC43300 pathogens, not inferior to that of vancomycin (MIC: 1.0–2.0 μg/mL);[52] (2) incorporation of thioether linker between hydrazone and pyridine,[53] or introduction of a thiol group into the thiazole ring,[54] or replacement of pyridine by 1,8-naphthyridine,[55] resulted in a notable decrease in antibacterial activity. Further studies indicated that treatment of MRSA ATCC 43300 with hybrid **35** at 0.5 μg/mL and 1.0 μg/mL initially suppressed bacterial growth (0–8 h), followed by regrowth between 8 and 24 h. Significantly, increasing the concentration to 2.0 μg/mL, hybrid **35** resulted in complete growth inhibition, with no detectable bacterial viability after 24 h. These findings demonstrate that hybrid **35** effectively inhibited the growth of MRSA ATCC 43300.

RBx10115912 (**36**; MIC: 0.125–1.0 μg/mL), a urea-containing benzothiazole-bispyridine hybrid, exhibited potent antibacterial activity against a panel of 81 MSSA, MRSA, VISA, VRSA, fluoroquinolone-resistant *S. aureus*, erythromycin-resistant *S. aureus*, linezolid-resistant, and mupirocin-resistant *S. aureus* clinical isolates.[56] The SAR disclosed that the pyridine moiety at the C-5 position of the benzothiazole moiety was not critical for the high activity, and replacement by pyrimidine enhanced the activity, as evidenced by **RBx10080758** (**37**; MIC: 0.015–0.06 μg/mL)

surpassed linezolid (MIC: 1.0 – >32 μg/mL), vancomycin (MIC: 0.5–16 μg/mL), erythromycin (MIC: 0.25 – >16 μg/mL), and ciprofloxacin (MIC: 0.25 – >16 μg/mL) against the above 81 *S. aureus* isolates. Besides, **RBx10080758** was an outstanding dual inhibitor of gyrase B and topoisomerase IV, with IC_{50} values of 130 and 250 nM, respectively. Moreover, **RBx10080758** exhibited a mutation-prevention concentration (MPC) of 0.125 μg/mL against *S. aureus* and MRSA, completely inhibiting the development of spontaneous resistance at this concentration, and showed rapid concentration-dependent killing of MRSA isolates. In a murine systemic infection model of MRSA-562, **RBx10080758** (10 mg/kg, intraperitoneal injection) significantly reduced bacterial load in kidneys (∼3.0 Log CFU/animal kidneys; half effective dose/ED_{50}: 5.0 mg/kg) and promoted 100% survival at day 8. In contrast, all mice in the placebo group died by day 1. In the MRSA WCUH-29-infected mice thigh model, **RBx10080758** (10 mg/kg, intravenous injection) reduced ∼3.5 Log CFU/mL bacterial load in thighs, outperforming that of linezolid (∼3.0 Log CFU/mL) under the identical conditions. Of particular note, **RBx10080758** showed IC_{50} values >10 μM for five CYP enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), indicating low risk of drug-drug interaction. After intravenous injection of 1.0 mg/kg, **RBx10080758** possessed favorable pharmacokinetic properties with $t_{1/2}$ of 1.64 and 1.14 h, C_{max} of 5190 and 4380 ng/mL, and $AUC_{0-\infty}$ of 1500 and 1270 ng/mL•h in rat and dog, respectively. Collectively, **RBx10080758** could serve as a promising candidate for fighting against drug-resistant *S. aureus* infections.

THIAZOLE-AZOLE HYBRIDS

Thiazole-thiazolidinone hybrids **38** (Fig. 4, MIC: 3.12–50 μg/mL) exhibited considerable antibacterial activity against *S. aureus* ATCC7443 strain.[57] The SARs illustrated that (1) the phenyl ring at the C-5 position of the thiazolidinone moiety was more favorable than the furan motif; (2) halogen atoms on the phenyl ring were beneficial for the activity;[57] (3) replacement of the thiazole by benzothiazole resulted in a significant loss of activity.[58] The representative hybrids **38a,b** (MIC: 3.12 μg/mL against *S. aureus* ATCC7443; 0.39–0.78 μg/mL against MRSA ATCC43300 and MRSA 4326/P clinical isolate) were not only comparable to ampicillin (MIC: 3.12 μg/mL) and chloramphenicol (MIC: 6.25 μg/mL) against *S. aureus* ATCC7443 but also were 16–32 times more potent than ampicillin (MIC: 12.5 μg/mL) against MRSA ATCC43300 and MRSA 4326/P clinical isolate. Besides, hybrids **38a,b** did not cause any lysis of human red blood cells at 100 μg/mL and showed the bactericidal potential against *S. aureus* ATCC3160. Molecular docking revealed that (1) the nitrogen atom of the thiazole ring in hybrid **38b** formed two hydrogen bonds with Asn83 and Arg310; (2) the N–H group of the 2-aminothiazole moiety engaged in a hydrogen bond with Asn83; (3) the nitrogen atom of the thiazolidinone ring fromed a hydrogen bond with Arg310; (4) the fluorine atom on the phenyl ring formed a halogen bond with Gly145; (5) the central thiazolidinone ring participated in a π–π stacking interaction with TYR149 and a π-alkyl interaction with Ile84; (6) the sulfur atom of the thiazole ring formed a sulfur-π interaction with Try149, and the thiazole ring itself engaged in a π-sulfur interaction with Met150.

Thiazole-thiadiazole hybrids **39** (MIC: 0.12–0.49 μg/mL) exhibited excellent antibacterial activity against MSSA ATCC29213 and MRSA ATCC700788 strains, and the SAR demonstrated that the thiadiazole moiety was critical for the high activity.[59] In particular, hybrids **39a,b** (MIC: 0.12 μg/mL against MSSA ATCC29213 and 0.24 against MRSA ATCC700788) were 4–8 times superior to vancomycin (MIC: 0.48 and 1.95 μg/mL) against MSSA ATCC29213 and MRSA ATCC700788 pathogens. Notably, hybrid **39a** (MIC: 1.95 μg/mL) also showed robust antibacterial activity against VRSA RCMB28354, and the minimum biofilm eradication concentration against MSSA ATCC29213 was 0.96 μg/mL.

Thiazole-pyrazole hybrids,[60,61] thiazole-pyrazoline hybrids,[62,63] and thiazole-pyrazolinone hybrids[64] typically elicited weak to moderate antibacterial activity against *S. aureus*. In contrast, bis-thiazole-pyrazole hybrids **40a,b** (MIC: 0.12 and 2.0 μg/mL) were not inferior to vancomycin (MIC: 2.0 μg/mL) against *S. aureus* ATCC6538.[65] Moreover, hybrid **40a** (MIC: 0.25 μg/mL) also displayed profound antibacterial activity against MRSA ACL18, outperforming that of vancomycin (MIC: 1.0 μg/mL) and ciprofloxacin (MIC: 2.0 μg/mL). Of particular note, hybrid **40a** demonstrated a synergistic effect with cefoxitin,

vancomycin, and ciprofloxacin against MRSA ACL18. In addition, hybrid **40a** (IC_{50}: 3.81 μM) was more active than trimethoprim (IC_{50}: 8.34 μM) in inhibition of DHFR.

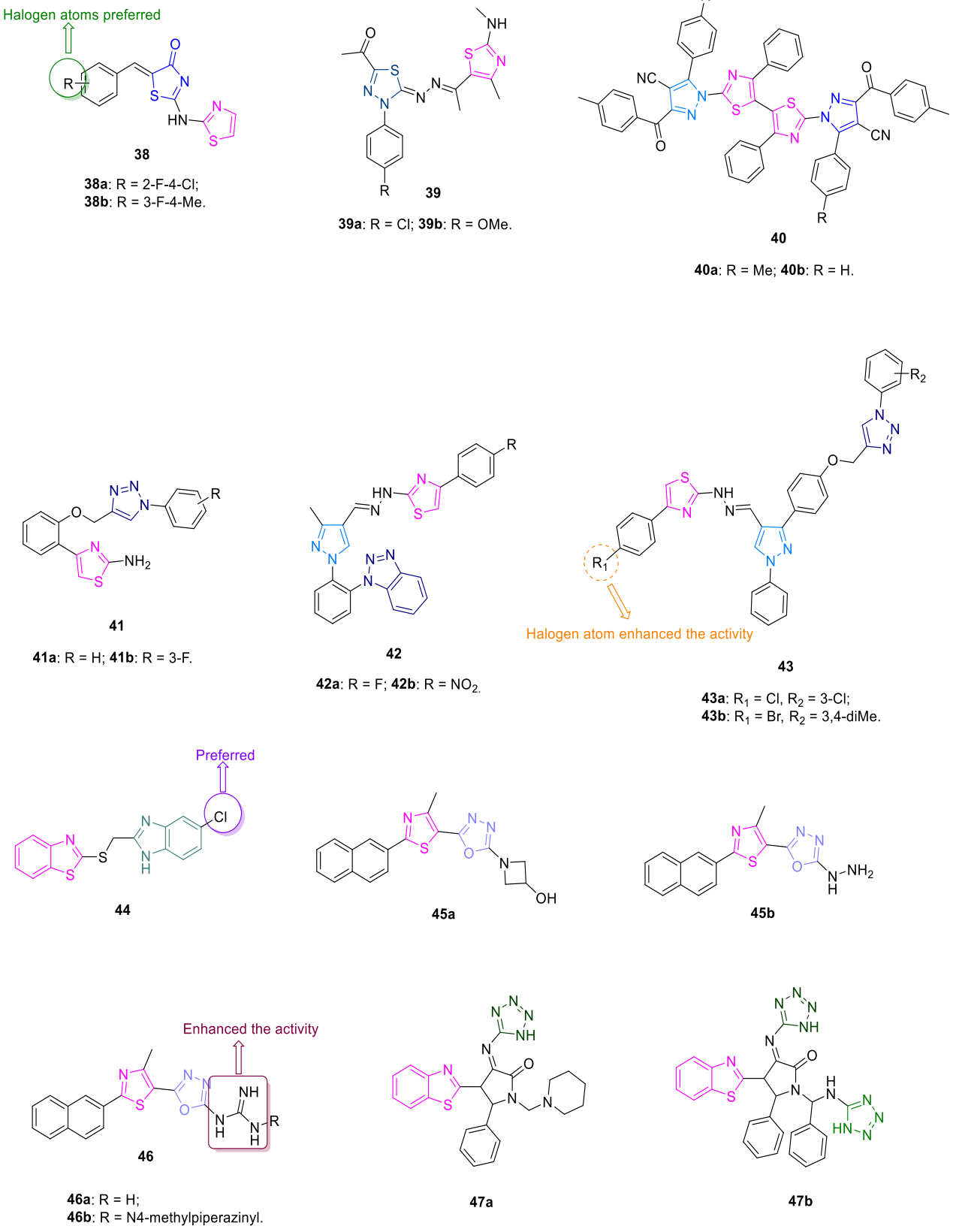

Fig. 4 – Chemical structures of thiazole-azole hybrids **38–47**.

Thiazole-1,2,3-triazole hybrids **41a,b** (MIC: 62.5 and 50 μg/mL) and thiazole-pyrazole-benzotriazole hybrids **42a,b** (MIC: 15.6 and 15.6 μg/mL) showed promising antibacterial activity against *S. aureus*, and the activity of hybrids **41a,b** was 4- and 5-fold more potent than that of ampicillin (MIC: 250 μg/mL) against *S. aureus* MTCC96 strain.[66,67] The SARs revealed that (1) for hybrids **42**, an electron-withdrawing group at the *para*-position of the phenyl ring was favorable to the activity;[67] (2) replacing benzotriazole with benzimidazole did not increase the antibacterial activity against *S. aureus*;[68] (3) replacement of benzotriazole by 1,2,3-triazole enhanced the activity.[69] Especially, thiazole-pyrazole-1,2,3-triazole hybrids **43a,b** (MIC: 4.8 and 4.1 μg/mL) exhibited antibacterial activity against the *S. aureus* MTCC96 strain comparable to that of novobiocin (MIC: 3.9 μg/mL) and ampicillin (MIC: 10 μg/mL).

Thiazole-imidazole hybrids usually displayed weak to moderate antibacterial activity against *S. aureus*[70,71] whereas benzothiazole-benzimidazole hybrid **44** (MIC: 7.81 μg/mL) was not inferior to ampicillin (MIC: 1.95 μg/mL) against *S. aureus*[72] The SARs illustrated that (1) the chloro at the C-5 position of the benzimidazole moiety was critical for the high activity; (2) benzothiazole was not vital for the activity, and replacement by benzoxazole was permitted.[72] The intermolecular interaction studies of hybrid **44** in the active site of *S. aureus* DNA gyrase revealed that (1) the nitrogen of the benzimidazole ring and sulfur atom of the S-linker region formed strong hydrogen bonds with Met1121 and Arg1122; (2) benzimidazole ring formed hydrophobic pi-alkyl contacts with Tyr1087, Ala1120, and Met1121; (3) chloro at the C-5 position of the benzimidazole moiety formed a pi-alkyl interaction with Tyr1087; (4) benzothiazole ring formed several hydrophobic pi-alkyl and pi-sigma interactions with Ala1068, Met1075, and Met1121, as well as a pi-sulfur contact with Met1121.

Thiazole-1,3,4-oxadiazole hybrids **45a,b** (MIC: 3.9 and 3.9 μg/mL) showed potent antibacterial activity against MRSA (2658 RCMB).[73] The SARs manifested that (1) the introduction of guanidine into the C-5 position of the 1,3,4-oxadiazole moiety was beneficial for the activity, and hybrids **46a,b** (MIC: 1.95 and 1.95 μg/mL) showed activity equivalent to vancomycin (MIC: 1.95 μg/mL);[73] (2) replacement of 1,3,4-oxadiazole by oxazolidinone led to significant loss of activity,[74] whereas replacing with tetrazole was tolerated, and benzothiazole-tetrazole hybrids **47a,b** (MIC: 3.12 and 3.12 μg/mL) were not inferior to chloramphenicol (MIC: 3.12 μg/mL) and cephalothin (MIC: 6.25 μg/mL) against *S. aureus*.[75]

THIAZOLE-GUANIDINE HYBRIDS

Thiazole-guanidine hybrids **48a,b** (Fig. 5, MIC: 4.0 and 4.0 μg/mL) were comparable to vancomycin (MIC: 1.0 μg/mL) against MRSA USA300 and displayed a low hemolytic rate (<3%) even at 128 μg/mL.[76] Both hybrids showed post-antibiotic effect (PAE) duration of 2 h, while vancomycin exhibited a 3 h PAE. Resistance studies demonstrated that the MIC values of hybrids **48a,b** against MRSA USA300 increased only 2-fold at the 10^{th} and 12^{th} passages, respectively, with no further increase observed until the final passage, demonstrating their low tendency for resistance. In contrast, MRSA USA300 showed a marked 15-fold increase in MIC to rifampicin. In a MRSA USA300-infected murine model, hybrids **48a,b** showed modest *in vivo* activity in the skin (0.37 and 0.46 Log CFU/mL reduction in bacterial loads) but an acceptable effect in controlling systemic dissemination, preventing the spread of the infection throughout the body.

Further studies indicated that incorporation of the thiophene moiety into the phenyl ring was tolerated, and hybrids **49a,b** (MIC: 0.5–1.0 and 2.0–4.0 μg/mL) were on a par with linezolid (MIC: 0.5–64 μg/mL) and vancomycin (MIC: 0.5 – >64 μg/mL) against 2 MSSA, 4 MRSA, and 3 VRSA clinical isolates.[77] Moreover, hybrids **49a,b** achieved 2.0 and 1.7 Log CFU/mL reduction in MRSA NRS123 burden at 5 × MIC after 24 h, while linezolid resulted in only a 1.1 Log CFU/mL reduction in bacterial burden under the identical conditions. The MIC value of hybrid **49a** against MRSA USA400 increased 2-fold after 14 passages, whereas MRSA rapidly developed resistance to rifampicin, with its MIC increasing 31-fold after just one passage. In a murine model of skin infection, hybrid **49a** resulted in a decrease in the MRSA USA300 burden in skin lesions by ~1.0 Log CFU/mL, revealing its potential in controlling MRSA skin infection.

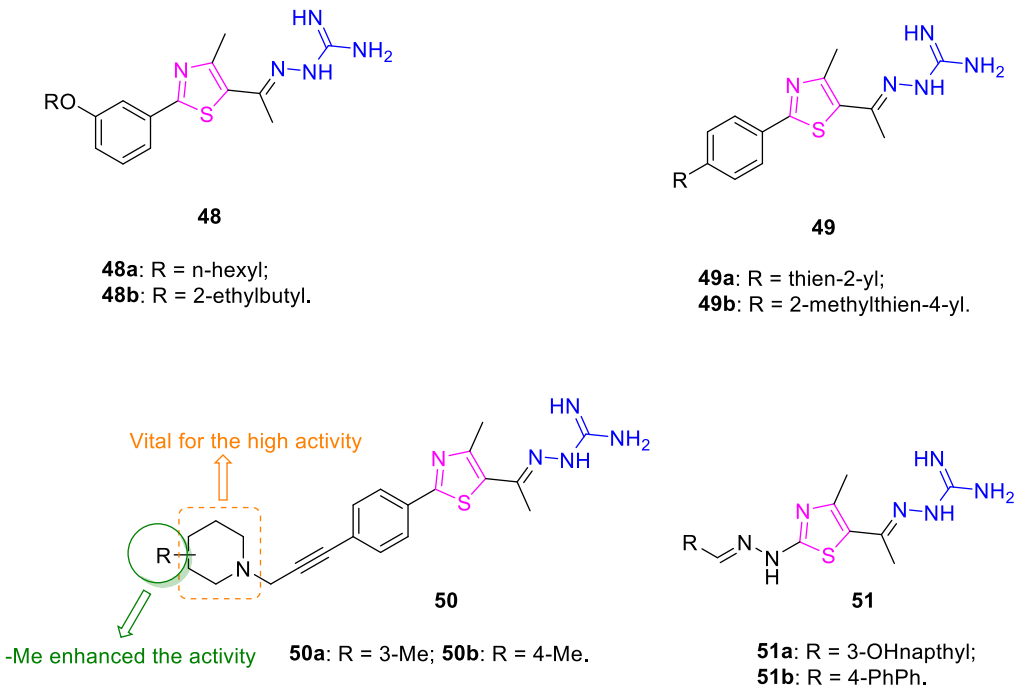

Fig. 5 – Chemical structures of thiazole-guanidine hybrids **48-51**.

The alkynyl-containing thiazole-guanidine hybrids **50a,b** (MIC: 4.0–16 μg/mL and 4.0–8.0 μg/mL, respectively) exhibited promising antibacterial activity against 2 MSSA, 12 MRSA, 3 VISA, and 8 VRSA clinical isolates, not inferior to that of linezolid (MIC: 1.0–64 μg/mL) and vancomycin (MIC: 1.0 –> 64 μg/mL).[78] The SARs illustrated that (1) the piperidinyl ring was vital for the high activity; (2) the methyl group at the C-3 or C-4 position of the piperidinyl ring was favorable to the activity;[78,79] (3) replacement of the phenyl ring at the C-2 position of the thiazole moiety was permitted, and hybrids **51a,b** (MIC: 2.0 and 1.0 μg/mL) were comparable to ampicillin (MIC: 2.0 μg/mL) and ciprofloxacin (MIC: 1.0 μg/mL) against *S. aureus*.[80,81] Further studies revealed that hybrids **50a,b** were as effective as vancomycin, and all three agents reduced the burden of MRSA by 3.0 Log CFU/mL within 24 h. The susceptibility of hybrid **50a** against MRSA USA400 remained consistent and did not change throughout the 14 passages. Besides, hybrid **50a** (disrupted ~31% of MRSA USA300 biofilm mass at 2 × MIC) was superior to vancomycin in MRSA biofilm eradication. After oral administration of 10 mg/kg, hybrid **50a** demonstrated excellent pharmacokinetic profiles with $t_{1/2}$ of 3.0 h, peak time (t_{max}) of 1.5 h, volume of distribution (V_d) of 1.4 L, clearance (CL) of 0.3 L/h, and C_{max} of 18400 ng/mL. Moreover, hybrid **50a** reached a plasma concentration equal to its MIC (4.0 μg/mL) against MRSA USA300 within 30 min and remained at or above this concentration for nearly 8 h. Collectively, hybrid **50a** could serve as a promising candidate for the treatment of infections caused by both drug-sensitive and drug-resistant *S. aureus*.

THIAZOLE-INDOLE/PYRROLE HYBRIDS

Thiazole-oxindole hybrid **52** (Fig. 6, MIC: 0.25–0.5 μg/mL) showed robust antibacterial activity against *S. aureus*, *S. aureus* ATCC25923, *S. aureus* ATCC29213, and MRSA, outperforming that of chloromycetin (MIC: 4.0–16 μg/mL), norfloxacin (MIC: 1.0–4.0 μg/mL), and cefdinir (MIC: 0.5–2.0 μg/mL).[82] The SARs indicated that (1) the n-butyl group at the N-1 of the oxindole moiety was vital for the high activity; (2) introduction of substituents into the C-4, C-5, C-6, or C-7 position of the oxindole moiety led to loss of activity;[82] (3) the hydrazone linker between thiazole and oxindole was favorable to the activity;[83] (4) introduction of phenyl into C-4 position of thiazole moiety decreased the activity;[84] (5) incorporation of sulfonamide fragment was permitted, and hybrid **53** (MIC: 7.8 and 7.8 μg/mL) was 4 and 2 folds more active than levofloxacin (MIC: 32.5 and 16.2 μg/mL) against *S. aureus* ATCC25923 and *S. aureus* ATCC29213;[85] (6) incorporation of the second hydrazone was tolerated, and hybrid **54** (MIC: 1.0 μg/mL) was 8 times superior to chloramphenicol

(MIC: 8.0 μg/mL) against MRSA ATCC43300.[86] Further study demonstrated that hybrid **52** could significantly impede the development of bacterial resistance, as evidenced by that the MIC values of hybrid **52** against MRSA remained stable during 16 passages, but the MICs of norfloxacin presented a 4-fold increment. Besides, the hemolysis rate of hybrid **52** was < 5%, and the morphology of red blood cells incubated with hybrid **52** at 256 × MIC was consistent with that of the control saline, indicating its high safety profile for blood cells. Meanwhile, the number of viable MRSA cells decreased rapidly after being treated with hybrid **52** for 30 min, demonstrating its rapid bactericidal ability against MRSA. Preliminary mechanistic investigations revealed that hybrid **52** could effectively penetrate the cell membrane of MRSA and embed DNA to form a hybrid **52**-DNA supramolecular complex and thus hinder DNA replication. Additionally, hybrid **52** could target the pyruvate kinase of MRSA and interfere with the function of the enzyme, thereby reducing cell metabolic activity.

The antibacterial SARs of thiazole-pyrrole hybrids **55** (MIC: 1.0–8.0 μg/mL) against MRSA/VISA ATCC700699 manifested that (1) halogen atoms on the pyrrole moiety were beneficial for the activity; (2) the 3-bromo-5-trifluoromethyl group on the phenyl ring was critical for the high activity;[87] (3) incorporation of piperidine fragment between thiazole and pyrrole was tolerated, and hybrid **56** (MIC: 0.125 μg/mL) exhibited excellent antibacterial activity against *S. aureus* ATCC29213;[88] (4) replacement of thiazole by tetrahydrobenzo[*d*]thiazole was permitted, and hybrid **57** (MIC: 4.0–8.0 μg/mL) showed promising antibacterial activity against *S. aureus* ATCC29213, MRSA ATCC43300, and VISA ATCC700699 strains.[89] Among them, hybrids **55a,b** (MIC: 1.0 and 1.0 μg/mL) surpassed vancomycin (MIC: 8.0 μg/mL) 8.0 times against MRSA/VISA ATCC700699 strain.

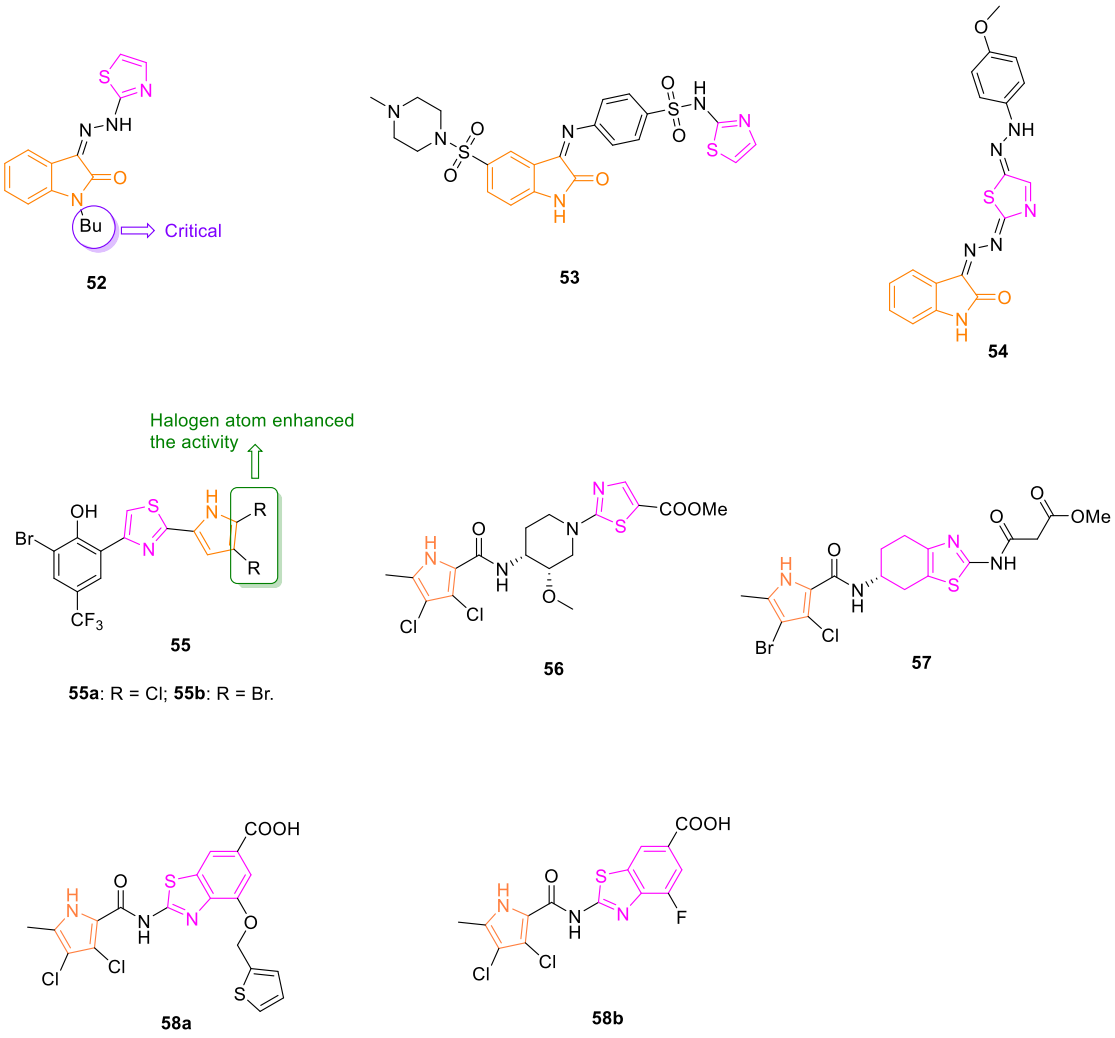

Fig. 6 – Chemical structures of thiazole-indole/pyrrole hybrids **52–58**.

Benzothiazole-pyrrole hybrids **58a,b** (MIC: 0.0625–0.5 μg/mL) were highly active against *S. aureus* ATCC29213 and MRSA ATCC43300, and hybrid **58a** (MIC: 0.0625–0.25 μg/mL) also demonstrated profound antibacterial activity against additional MRSA (GyrB R144I and GyrB T173A mutants) and 3 VISA (wild-type, GyrB R144I and GyrB T173A mutants).[90] Moreover, hybrid **58a** (IC_{50}: <10 and 84 nM) was identified as a potent dual inhibitor of gyrase and topoisomerase IV, outperforming that of novobiocin (IC_{50}: 34 and 27000 nM). Besides, hybrid **58a** displayed no cytotoxicity toward MCF-7 and HepG2 cells at 100 μM, and no *in vitro* genotoxicity was observed at 16 μM.

MISXELLANEOUS THIAZOLE HYBRIDS

Thiazole-urea hybrids **59** (Fig. 7, MIC: 0.39–3.12 μg/mL) showed potent antibacterial activity against *S. aureus* ATCC6538, and the SAR disclosed that fluoro-containing substituents on the phenyl ring enhanced the activity.[91] Amongst them, the representative hybrids **59a-d** (MIC: 0.39–0.78 μg/mL) were comparable to or better than ofloxacin (MIC: 0.78 μg/mL), linezolid (MIC: 3.12 μg/mL), and cefoxitin (MIC: 25 μg/mL) against *S. aureus* ATCC6538. Especially, hybrids **59a** (MIC: 0.39–0.78 μg/mL) and **59d** (MIC: 0.78–1.56 μg/mL) were not inferior to vancomycin (MIC: 0.78–1.56 μg/mL) against MRSA2858, MRSA0101, MRSA05107, and MRSA10105 strains. Moreover, hybrids **59a,d** completely eradicated MRSA2858 within 4 and 8 h, respectively, demonstrating their rapid antibacterial activity. Mechanistically, hybrid **59d** caused the death of bacteria by damaging the cell membrane. After intragastric administration of hybrid **59d** (200 mg/kg), the general condition of the rats was good, and no significant change in appearance, activity, body weight, central necrosis, or steatosis was observed, revealing its good safety profile. In the MRSA2858-infected mouse model, after treatment with 2.0 mg/kg and 5.0 mg/kg of hybrid **59d** for 24 h, MRSA titres decreased by 1.9 and 2.5 Log CFU/mL, respectively.

Further structural modifications revealed that (1) the linker between benzothiazole and urea was not vital for the high activity, as evidenced by the hybrids **60a,b** (MIC: 0.098 and 0.098 μg/mL) were 8-fold more potent than vancomycin (MIC: 0.78 μg/mL) against *S. aureus* ATCC6538; (2) trifluoromethyl group at *para*-position of phenyl ring was essential for the activity;[92] (3) replacement of benzothiazole by thiazole resulted in significant loss of activity.[93] Of particular note, hybrid **60a** (MIC: 0.098 μg/mL) exhibited pronounced antibacterial activity against 5 MRSA clinical isolates, 8-16 times outperforming that of vancomycin (MIC: 0.78–1.56 μg/mL). Mechanistically, hybrid **60a** disrupted the cell wall structure, impaired bacterial lytic growth, and inhibited autolysis. In mice infected with MRSA USA300, the antibacterial effect of hybrid **60a** (~3.4 Log CFU/mL reduction at 5.0 mg/kg *via* intraperitoneal injection) showed *in vivo* efficacy equivalent to vancomycin (~3.4 Log CFU/mL) under the same conditions.

The antibacterial SARs of thiazole-thiourea-glucose hybrids **61** (MIC: 0.78–200 μg/mL) against *S. aureus* elucidated that (1) a methoxy group at the *para*-position of the phenyl ring was critical for the high activity; (2) a nitro group at the *meta*-position of the phenyl ring boosted the activity;[94] (3) replacement of thiazole by benzothiazole was tolerated, and hybrids **62** (MIC: 0.78–200 μg/mL) also demonstrated considerable antibacterial activity against *S. aureus*.[95] Amongst them, hybrids **61a,b** (MIC: 1.56 and 0.78 μg/mL) and **62a,b** (MIC: 1.56 and 0.78 μg/mL) were not inferior to ciprofloxacin (MIC: 3.12 μg/mL) and vancomycin (MIC: 1.56 μg/mL) against *S. aureus*. Besides, hybrids **61a,b** (IC_{50}: 1.37 and 1.25 μM against gyrase; 0.17 and 0.13 μM against dihydrofolate reductase) were comparable to ciprofloxacin (IC_{50}: 1.15 μM) in inhibition of *S. aureus* DNA gyrase and superior to methotrexate (IC_{50}: 0.36 μM) in inhibition of dihydrofolate reductase, whereas hybrid **62b** (IC_{50}: 0.57 and 0.28 μM) was an excellent dual inhibitor of DNA gyrase ATPase and topoisomerase IV ATPase, not inferior to that of ciprofloxacin (IC_{50}: 0.41 and 0.42 μM) and novobiocin (IC_{50}: 0.42 and 0.20 μM). Moreover, hybrid **62b** (IC_{50}: 64.34 μM) also displayed relatively low cytotoxicity toward normal WI-38 cells and was worthy of further investigations.

Thiazole-pleuromutilin hybrids **63** (MIC: 0.25–16 μg/mL) showed promising antibacterial activity against *S. aureus* ATCC25923 and MRSA ATCC43300, and the SAR manifested that a large volume substituent at the R position enhanced the activity.[96] In particular, hybrids **63a,b** (MIC: 0.25–0.50 μg/mL) were comparable to tiamulin (MIC: 0.25 and 0.25 μg/mL) against *S. aureus* ATCC25923 and MRSA ATCC43300. At 6 × MIC,

hybrid **63a** exhibited remarkable killing activity against MRSA and superior antibacterial efficacy compared to tiamulin, with a 3.08 Log CFU/mL reduction in bacterial counts at 24 h. Besides, after exposure at 4 × MIC, hybrid **63a** exhibited a PAE of 1.29 h. In addition, hybrid **63a** showed a 16-fold increase in MIC against MRSA after 21 passages, whereas tiamulin exhibited a more substantial 64-fold increase in MIC. Surprisingly, no cross-resistance was observed in the drug-resistant MRSA isolates between hybrid **63a** and tiamulin, and tiamulin-resistant MRSA showed sensitivity to hybrid **63a**, with a MIC of 0.5 μg/mL. Docking studies demonstrated the strong affinity of hybrid **63a** for the 50S ribosomal subunit by forming 8 hydrogen bonds. In the MRSA ATCC43300-infected mice model, hybrid **63a** (20 mg/kg, intravenous injection) reduced 0.90 Log CFU/g bacteria burden in the lungs, not inferior to valnemulin (0.98 Log CFU/g reduction) under the identical conditions, and the absolute and relative organ weights showed no significant differences. No rats died in the acute oral toxicity study, and the half lethal dose (LD_{50}) value of hybrid **63a** was determined to be >2000 mg/kg by oral administration, demonstrating its good safety profile.

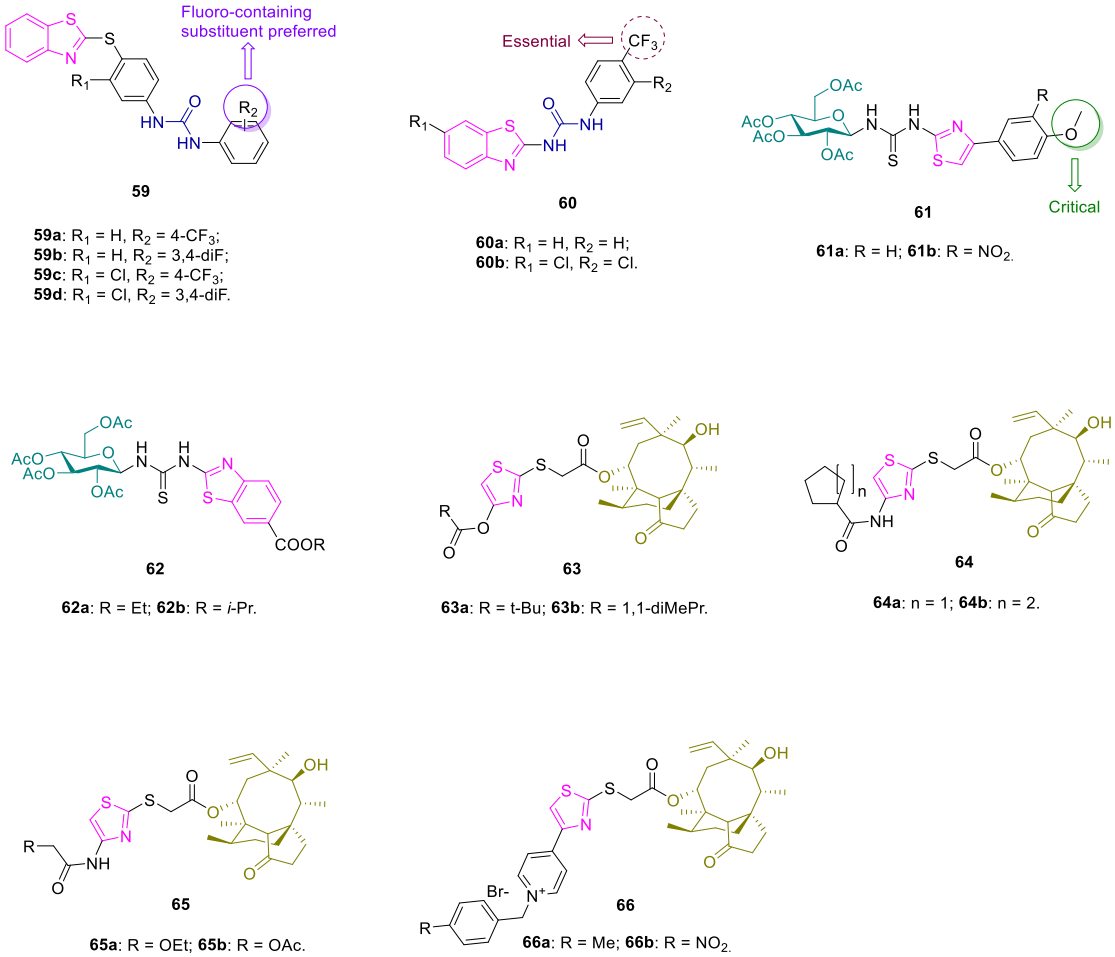

Fig. 7 – Chemical structures of thiazole hybrids **59**–**66**.

Further structural modifications demonstrated that (1) replacement of the ester linker between thiazole and pleuromutilin by an amide linker was tolerated, and hybrids **64** (MIC: 0.0625–0.25 μg/mL) were highly potent against 3 *S. aureus* and 1 MRSA strains; (2) the cycloalkyl group could be replaced by ether or ester as hybrids **65** (MIC: 0.062-0.25 μg/mL) also possessed robust antibacterial activity against the tested 4 pathogens.[97] The representative hybrids **64a,b** (MIC: 0.0625–0.125 μg/mL) and **65a,b** (MIC: 0.0625–0.125 μg/mL) were not inferior to valnemulin (MIC: 0.0625 μg/mL), tiamulin (MIC: 0.25–1.0 μg/mL), and vancomycin (MIC: 1.0–2.0 μg/mL) against all tested organisms. Particularly, hybrid **64a** exhibited bactericidal activity against MRSA, achieving 3.00 and 3.83

Log CFU/mL reduction at 4 × MIC and 8 × MIC after 24 h of incubation, whereas hybrid **64b** reduced 4.62 Log CFU/mL bacteria burden at 8 × MIC after 24 h. After exposure at 4 × MIC, the PAE values of hybrids **64a,b** were found to be 1.29 and 0.65 h, respectively. Notably, hybrid **64a** formed strong hydrogen bonds with the 50S ribosomal subunit. In the MRSA ATCC43300-infected murine neutropenic thigh model, hybrid **64a** (1.78 Log CFU/g reduction at 20 mg/kg *via* intravenous injection) exhibited superior *in vivo* antibacterial efficacy than tiamulin (1.21 Log CFU/g reduction) under the identical conditions.

Introduction of pyridinium into the C-4 position of the thiazole moiety was also permitted, and hybrids **66** (MIC: 0.0625–4.0 μg/mL) exhibited potent antibacterial activity against *S. aureus* ATCC29213, MRSA ATCC43300, and MRSA ATCC33591 strains.[98] Further studies revealed that the phenyl ring at the N-1 position of the pyridinium fragment was critical for the high activity, and replacement by an alkyl side chain led to a significant loss of activity. In particular, hybrids **66a,b** (MIC: 0.0625–1.0 μg/mL) were not inferior to moxifloxacin (MIC: 0.0625–1.0 μg/mL), retapamulin (MIC: 4.0–32 μg/mL), and valnemulin (MIC: 4.0–128 μg/mL) against the above 3 strains, and hybrid **66a** (MIC: 1.0–8.0 μg/mL) was 8–32 times outperformed retapamulin (MIC: 32–128 μg/mL) against 5 MRSA clinical isolates. Besides, hybrid **66a** (IC_{50}: >100 μM) was non-toxic toward normal HEK293 cells, lower than that of retapamulin (IC_{50}: 83.76 μM) and valnemulin (IC_{50}: 65.44 μM). In addition, hybrid **66a** completely eradicated MRSA within 12 and 8 h at 2 × MIC and 4 × MIC, respectively. Mechanistically, hybrid **66a** destroyed bacterial cell membranes to exert its anti-MRSA effects. In a mouse model of systemic MRSA infection, the survival rate in the hybrid **66a**-treated group (10 mg/kg, intraperitoneal injection) was ~71%, higher than that of valnemulin (~45%) under the same conditions, and the ED_{50} was 4.94 mg/kg. These findings demonstrate that hybrid **66a** is a promising candidate for the treatment of MRSA infections.

CONCLUSIONS

S. aureus has evolved diverse virulence mechanisms and strategies to evade the human immune system, while traditional antibiotic therapies currently fail to effectively control infections caused by drug-resistant forms, necessitating the urgent development of novel chemotherapeutic agents. Thiazole hybrids can combat both drug-sensitive and drug-resistant *S. aureus* through multiple mechanisms, and diverse thiazole hybrids have been developed since 2020. Notably, several thiazole hybrids demonstrated robust *in vitro* and *in vivo* antibacterial efficacy against various MRSA strains.

In conclusion, (1) the thiazole moiety is a valuable pharmacophore against *S. aureus*, and almost all positions can be modified; (2) various antibacterial pharmacophores can be hybridized with the thiazole moiety, especially coumarin, pyrimidine, quinazoline, pyridine, quinoline, azole, guanidine, urea, and pleuromutilin. Based on the above points, future work may focus on (1) hybridization of novel antibacterial pharmacophores with thiazole to provide more lead compounds/candidates for further investigations; (2) further investigations of the current available thiazole hybrids with pronounced *in vivo* efficacy to afford more clinical candidates; (3) combination therapies with existing antibiotics can be explored to leverage synergistic effects and reduce resistance risk.

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