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Review Article

Role of Synthetic and Natural FtsZ Inhibitors as Antibacterial Agents

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The escalating crisis of antimicrobial resistance (AMR), compounded by the dwindling antibiotic pipeline, necessitates the urgent identification of novel therapeutic targets. Filamenting temperature-sensitive mutant Z (FtsZ), a prokaryotic tubulin homologue and indispensable GTPase mediating bacterial cytokinesis, has emerged as one of the most compelling targets for next-generation antibiotic discovery. FtsZ orchestrates the assembly of the dynamic Z-ring at mid-cell, a structure essential for septum formation and binary fission, and is highly conserved across the bacterial kingdom yet absent from eukaryotes. This review comprehensively examines the structural biology and mechanistic function of FtsZ, its central role in bacterial cell division, and the diverse arsenal of synthetic and natural compound inhibitors that have been developed or identified to date. We critically appraise key inhibitor classes, including benzamide derivatives (PC190723, TXA709), GTP-binding site competitors, allosteric modulators, and natural products such as berberine, sanguinarine, curcumin, totarol, chrysophaentins, and zantrins. Structure-activity relationships (SARs), binding mechanisms, in vitro and in vivo efficacy data, and the translational challenges impeding clinical development are discussed in depth. The review also highlights cutting-edge computational strategies, including virtual screening and machine learning approaches, that are accelerating FtsZ-targeted drug discovery. Collectively, this body of evidence underscores FtsZ as a pharmacologically valid and clinically tractable target for combating multidrug-resistant (MDR) pathogens.

Keywords: FtsZ; bacterial cell division; antimicrobial resistance; GTPase inhibitor; natural compounds; antibiotic targets.

INTRODUCTION

Bacterial infectious diseases remain a leading cause of morbidity and mortality worldwide, accounting for an estimated 1.27 million deaths directly attributable to antimicrobial-resistant (AMR) infections in 2019, with approximately 4.95 million associated with it in that same year [1]. The emergence and global dissemination of multidrug-resistant (MDR) organisms, including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), carbapenem-resistant Enterobacteriaceae (CRE), and extensively drug-resistant Mycobacterium tuberculosis (XDR-TB), have severely eroded the clinical utility of established antibiotic classes [2,3]. Compounding this threat, the antibiotic development pipeline remains critically underpopulated, with few novel chemical entities entering clinical use over the past several decades [4]. This epidemiological and pharmacological impasse has catalyzed an intensive search for antibacterial agents with entirely novel mechanisms of action. Most clinically approved antibiotics target a narrow set of conserved bacterial processes: cell wall biosynthesis (β-lactams, glycopeptides), protein synthesis (aminoglycosides, macrolides, tetracyclines), DNA replication (fluoroquinolones), and membrane integrity (polymyxins) [5]. While

these mechanisms remain relevant, resistance determinants against nearly all of these targets have proliferated, prompting investigators to interrogate previously unexploited pathways [5]. Bacterial cell division, the process by which a mother cell generates two daughter cells with equivalent genetic material represents one such unexploited pathway [5]. Central to this process is the tubulin-like GTPase FtsZ, the product of the highly conserved ftsZ gene present in virtually all eubacteria and many archaea. FtsZ was first identified in Escherichia coli by Bi and Lutkenhaus in 1991, who demonstrated that temperature-sensitive FtsZ mutants failed to divide and formed elongated filamentous cells [6]. Subsequent decades of structural, biochemical, and cell biological research have established FtsZ as the principal organizer of bacterial cytokinesis, functioning as a prokaryotic counterpart of eukaryotic tubulin. FtsZ self-assembles into single-stranded protofilaments in a GTP-dependent manner, which condense into the cytokinetic Z-ring at mid-cell, serving as a scaffold for the sequential recruitment of more than a dozen cell division proteins that collectively constitute the divisome machinery [7,8]. The essential nature of FtsZ, its absolute conservation across pathogenic bacteria, its structural divergence from eukaryotic cytoskeletal proteins, and its lack of a mammalian ortholog collectively render it an ideal antibacterial drug target [9]. The first wave of FtsZ inhibitors emerged from high-throughput screening campaigns in the late 1990s and early 2000s, with compounds such as the benzamide SRI-3072 [10] and the zantrins demonstrating proof-of-concept inhibition [11]. Subsequent rational drug design efforts, guided by the crystal structures of FtsZ from multiple organisms, yielded more potent and selective inhibitors, including the landmark compound PC190723, which demonstrated in vivo efficacy against MRSA in a murine infection model [12]. Parallel efforts in natural product chemistry have identified phytochemicals such as berberine, sanguinarine, curcumin, and chrysophaentins as FtsZ-targeting antimicrobials, some of which exhibit broad-spectrum activity [13]. Despite this substantial body of work, no FtsZ-targeting antibiotic has yet received regulatory approval. Challenges related to pharmacokinetics and bioavailability have impeded clinical translation [14]. Nevertheless, the most advanced candidate, TXA709, a prodrug derivative of the benzamide series, has entered early clinical trials, representing the closest any FtsZ inhibitor has come to clinical use [15,16]. This review provides a comprehensive, PhD-level synthesis of the current state of knowledge on FtsZ inhibitors, encompassing structural biology, mechanisms of inhibition, synthetic and natural compound classes, and future directions for translational development.

2. FtsZ: Structure, Function, And Role In Bacterial Cell Division

2.1. Molecular Architecture of FtsZ

FtsZ is a ~40 kDa, monomeric, GTP-binding protein [17] that occupies a pivotal position in the hierarchy of bacterial cell division proteins [18]. The three-dimensional structure of FtsZ was first elucidated from Methanococcus jannaschii, revealing a structural fold strikingly analogous to that of eukaryotic α- and β-tubulin despite limited primary sequence identity (~17%) [19]. The FtsZ monomer is bilobed, comprising an N-terminal enzymatic domain and a C-terminal domain, interconnected by a central helix, designated H7 [20]. The GTP binding site resides at the interface between the N-terminal domain and the T7 loop—a structural motif strictly analogous to the nucleotide-binding interface of tubulin [21]. The N-terminal domain adopts a Rossmann-fold topology, housing conserved tubulin-signature motifs: the phosphate-binding loop (P-loop or G1 box), the switch I and II elements (T3 and T4 loops), and the G4 box responsible for guanine nucleotide recognition specificity [13,16]. GTP hydrolysis is catalyzed at the interface formed between the T7 loop of one FtsZ subunit and the nucleotide of the next subunit, meaning that the GTPase active site only forms within the polymerized protofilament [22]. This longitudinal, head-to-tail polymerization, wherein the nucleotide-binding domain of one monomer contacts the T7 loop of the next monomer, is thermodynamically coupled to GTP hydrolysis and protofilament dynamics [23,24]. The C-terminal domain of FtsZ, while less structurally conserved than the N-terminal domain, serves as a protein-protein interaction hub, mediating associations with membrane-tethering proteins such as ZipA (in Gram-negative bacteria) and FtsA, as well as with Z-ring stabilizing proteins including ZapA,

ZapB, ZapC, and ZapD [13]. A short, intrinsically disordered C-terminal variable region (CTV) is followed by the conserved core motif (CCM), which engages the FtsA and ZipA interaction surfaces. The hydrophobic cleft between the N-terminal and C-terminal domains, which accommodates the interdomain interface and includes the H7 helix, constitutes an allosteric binding site distinct from the GTP pocket and has become a major focus of structure-guided inhibitor design [25].

2.2. Z-ring Assembly and Dynamics

Within the bacterial cell, FtsZ exists in a dynamic equilibrium between soluble monomers and GTP-bound protofilaments. Upon GTP binding, FtsZ monomers polymerize cooperatively into single-stranded protofilaments approximately 200–1000 nm in length. These protofilaments associate laterally through non-covalent interactions to form bundles and sheets and condense at mid-cell to produce the cytokinetic Z-ring. The Z-ring is not a static structure; rather, it undergoes continuous, rapid treadmilling, a process in which new subunits are added at one end and released from the other, consuming one GTP per turnover cycle [26]. The Z-ring is positioned at mid-cell through the concerted action of two spatial regulatory systems: the Min system, which oscillates between cell poles to preclude division at non-central positions, and nucleoid occlusion, mediated by SlmA (in E. coli) and Noc (in Bacillus subtilis), which prevents Z-ring assembly over unsegregated chromosomes [27]. Once established, the Z-ring serves as a scaffold for the ordered recruitment of downstream division proteins (FtsA, ZipA, FtsEX, FtsK, FtsQ, FtsL, FtsB, FtsW, FtsI/PBP3, and FtsN), which collectively constitute the divisome [28]. The divisome coordinates the synthesis and remodeling of the peptidoglycan septum, culminating in the physical separation of daughter cells [29].

2.3. Conservation across Bacteria and Divergence from Eukaryotic Tubulin

The ftsZ gene is present in virtually all eubacteria, including Gram-positive and Gram-negative pathogens, mycobacteria, spirochetes, and obligate intracellular organisms [13]. Notably, ftsZ is absent from mammalian genomes, and the structural homolog tubulin — while sharing a common evolutionary ancestor — is sufficiently divergent in primary sequence and three-dimensional architecture that FtsZ-targeted compounds typically exhibit minimal cross-reactivity with eukaryotic cytoskeletal proteins [30]. Critically, while the GTP binding sites of FtsZ and tubulin share high sequence similarity, the interdomain cleft of FtsZ has much less sequence and structural similarity with tubulin, making it a better potential target for drugs [16]. This divergence confers a significant safety advantage on FtsZ inhibitors, mitigating concerns about off-target cytotoxicity toward human cells [16]. Despite this selectivity, some natural FtsZ inhibitors, such as sanguinarine, retain residual tubulin-inhibitory activity, which has implications for their therapeutic index [31].

3. Rationale for FtsZ As An Antibiotic Target

The candidacy of FtsZ as an antibiotic target is underpinned by several compelling molecular and microbiological arguments. First, FtsZ is absolutely essential for viability in virtually all bacteria studied to date; deletion or inactivation of ftsZ is lethal, and conditional depletion of FtsZ causes rapid cell death associated with filamentous non-dividing cells [32,33]. Second, the high degree of conservation of FtsZ across diverse bacterial phyla implies that potent inhibitors could exhibit broad-spectrum activity, targeting both Gram-positive and Gram-negative pathogens [15,34]. Third, the absence of any known FtsZ-targeting antibiotic in clinical use means that pre-existing resistance determinants specific to this target are absent from pathogen populations, giving nascent FtsZ inhibitors a significant epidemiological advantage [35]. Structural studies, including high-resolution X-ray crystallography and cryo-electron microscopy, have resolved approximately 2176 FtsZ structures from diverse bacterial species, providing an exceptionally rich structural database for structure-based drug design [17]. The identification of multiple druggable binding sites on FtsZ — the GTP-binding pocket, the T7 loop region, the interdomain allosteric cleft, and the lateral subunit interface — affords various distinct strategies for pharmacological intervention [36]. Moreover, certain FtsZ inhibitors have demonstrated resistance-breaking properties, retaining activity against strains exhibiting resistance to multiple existing antibiotic classes [37],[38]. The

global burden of staphylococcal infections, particularly MRSA, represents a pressing clinical indication for FtsZ-targeted therapy [39]. MRSA is responsible for a disproportionate share of hospital-acquired infections, bacteraemia, pneumonia, and endocarditis, and the current treatment options — vancomycin and linezolid — are increasingly compromised by emerging resistance [40]. FtsZ inhibitors with potent anti-staphylococcal activity and favorable pharmacokinetic profiles would address a critical unmet medical need. Additionally, given the prevalence of FtsZ in Mycobacterium tuberculosis and the global tuberculosis burden, the mycobacterial FtsZ represents an important secondary target [41].

4. Synthetic FtsZ Inhibitors

4.1. Benzamide Derivatives: From 3-Methoxybenzamide to TXA709

4.1.1. Discovery and Characterization of PC190723

The substituted benzamide series represents the most clinically advanced class of FtsZ inhibitors [42]. The prototypical compound, PC190723 (7-benzyl-2-methyl-5-[N-(4-pyridinyl) carbonyloxy]-2,4,5,6-tetrahydropyrazolo[3,4-d][1,3]thiazine), Haydon et al. identified (2008) through a focused medicinal chemistry campaign aimed at optimizing the initial FtsZ-inhibitory benzamide scaffold [12]. PC190723 binds to a pocket at the interface of the N-terminal and C-terminal domains of FtsZ, a site structurally analogous to the taxol-binding site on tubulin, and acts as a polymer-stabilizing agent [43]. Rather than inhibiting polymerization, PC190723 paradoxically promotes FtsZ assembly into stable, non-dynamic protofilament bundles that cannot recapitulate the treadmilling dynamics required for Z-ring function and cytokinesis. PC190723 exhibits potent bactericidal activity against Staphylococcus aureus (including MRSA) and Bacillus subtilis, with minimum inhibitory concentrations (MICs) typically in the range of 0.5-2 μg/mL [12,43]. Whole-cell mechanistic studies demonstrated FtsZ mis-localization and the formation of abnormal cellular morphologies characteristic of division block [43]. Resistance to PC190723 arose at a frequency consistent with single-target inhibition (~10^{-8} per cell per generation), and resistance mutations mapped predominantly to the PC190723-binding site in FtsZ, confirming on-target activity [12]. However, clinical development was hampered by poor aqueous solubility, limited oral bioavailability, and rapid metabolic clearance [44].

4.1.2. Prodrug Strategies: TXY436, TXY541, and TXA709

To address the pharmaceutical liabilities of PC190723, successive generations of N-Mannich base prodrug derivatives were engineered. TXY436, the first prodrug of PC190723, demonstrated approximately 100-fold greater aqueous solubility in acidic media and spontaneously converted to PC190723 at physiological pH, with a half-life of approximately 18 minutes [45]. TXY436 was both intravenously and orally efficacious in murine MRSA infection models, representing the first demonstration of oral efficacy for an FtsZ-targeting benzamide. Subsequent optimization yielded TXY541 with further improvements in formulation and bioavailability, though pharmacokinetics remained suboptimal. The most advanced compound in this series, TXA709, represents a strategic modification in which the labile chlorine substituent on the pyridyl ring of PC190723 was replaced with a trifluoromethyl group resistant to cytochrome P450-mediated metabolism [46]. The active drug TXA707 generated from TXA709 exhibits improved pharmacokinetic properties, including a longer plasma half-life and greater oral bioavailability compared to earlier analogues [46]. TXA709 demonstrates potent activity against MRSA, including vancomycin-intermediate (VISA) and linezolid-resistant isolates, and has demonstrated superior in vivo efficacy in murine systemic and thigh infection models [46,47]. TXA709 has advanced into early-phase clinical evaluation, representing the furthest any FtsZ inhibitor has progressed toward clinical use [48].

4.1.3. Next-Generation Benzamides and TXH9179

Further efforts to optimize the benzamide scaffold have yielded TXH9179, a compound reported to exhibit 4-fold greater potency than TXA707 against a library of 55 MSSA and MRSA clinical isolates, including isolates with resistance to vancomycin and linezolid [49]. TXH9179 also demonstrated a lower frequency of resistance emergence in the majority of

tested strains, offering an improved resistance profile [50]. These data support the continued optimization of benzamide scaffolds toward first-in-class FtsZ-targeting clinical agents.

4.2. GTP-Binding Site Inhibitors

The GTP-binding pocket of FtsZ presents an alternative, orthologous druggable site to the allosteric benzamide-binding cleft. Synthetic inhibitors targeting this site function as competitive antagonists of GTP, displacing the nucleotide substrate and abrogating the assembly-competent conformational state. Compounds UCM05 and UCM44, polyhydroxy aromatic derivatives identified through a fluorescence anisotropy displacement assay, bind specifically to Bacillus subtilis FtsZ monomers with micromolar affinities and perturb normal GTP-dependent assembly [51]. The chlorinated analogue UCM53 exhibited growth inhibitory activity against clinical isolates of antibiotic-resistant Staphylococcus aureus and Enterococcus faecalis, validating the GTP-binding site as a pharmacologically tractable locus [51]. GTP-site inhibitors face intrinsic challenges related to selectivity, as the structural features of purine nucleotide-binding domains are broadly shared across diverse enzyme classes. Achieving selectivity over mammalian GTPases requires careful exploitation of differences in the subunit-interface architecture of FtsZ, where residues from the T7 loop of one monomer contribute to the GTPase active site [10,52]. Nucleotide analogues, including mant-GTP derivatives, have provided important pharmacological tools for probing FtsZ-nucleotide interactions and validating the GTP-binding site as a druggable target, though clinical development of nucleotide-based inhibitors remains challenging due to cellular membrane impermeability.

4.3. Allosteric Inhibitors and Interdomain Cleft Binders

The interdomain cleft of FtsZ, situated at the interface between the N-terminal and C-terminal domains and adjacent to the H7 helix, has emerged as a particularly promising allosteric binding site. Small molecules engaging this site can modulate the conformational dynamics governing FtsZ polymerization cooperativity, potentially offering a mechanism to disrupt the functional Z-ring without competing with the intracellular GTP pool. Virtual screening campaigns have identified multiple chemotypes with predicted binding to this allosteric site, several of which have demonstrated measurable GTPase inhibitory activity and MICs in the low micromolar range [53].

4.4. Quinoline, Quinazoline, and Heterocyclic Derivatives

Quinoline and quinazoline derivatives constitute a structurally diverse class of synthetic FtsZ inhibitors that have received considerable attention due to their well-precedented pharmacological properties and ease of synthetic modification. Studies have demonstrated that several 2-alkoxycarbonylamino-pyridine compounds originally developed as tubulin polymerisation inhibitors, including SRI-3072 and SRI-7614 from Southern Research Institute, exert potent anti-FtsZ activity against Mycobacterium tuberculosis FtsZ [10]. Crucially, SRI-7614 inhibited both FtsZ and tubulin polymerisation, while SRI-3072 demonstrated selectivity for mycobacterial FtsZ, and both compounds showed efficacy against drug-susceptible and drug-resistant M. tuberculosis strains. Benzofuroquinolinium derivatives have been characterized as potent anti-MRSA agents that exert their antibacterial effects through FtsZ inhibition, with selected compounds exhibiting MIC values below 1 µg/mL against S. aureus [37]. Isatin bis-imidathiazole hybrids [54] and 4,5-dihydroisoxazole-containing benzamide derivatives [55] have also been reported as FtsZ-targeting antibacterials capable of killing MDR S. aureus strains, with molecular docking and polymerization assays confirming FtsZ as the primary target.

5. Natural Compound FTSZ Inhibitors

5.1. Alkaloids

5.1.1. Berberine

Berberine, an isoquinoline alkaloid widely distributed among species of Berberis, Coptis, and related genera of the family Berberidaceae, has been a cornerstone of traditional chinese and ayurvedic medicine for millennia. Modern pharmacological investigation has established berberine as an FtsZ inhibitor with

measurable effects on both E. coli FtsZ assembly and GTPase activity in vitro [56]. Molecular modelling predicts that the berberine binding locus overlaps with the GTP-binding pocket of E. coli FtsZ, a prediction consistent with competitive inhibition kinetics [57]. Leveraging the available crystal structure of S. aureus FtsZ, structure-guided design led to a series of 9-phenoxyalkyl berberine derivatives engineered to engage the S. aureus FtsZ interdomain cleft [58]. These berberine derivatives exhibited MIC values of 2-8 µg/mL against S. aureus and 4-16 µg/mL against Enterococcus faecalis, with moderate activity against Gram-negative organisms including Klebsiella pneumoniae and E. coli (MIC 32-128 µg/mL) [58]. While the antibacterial activity of berberine is well documented, the relative contribution of FtsZ inhibition versus other reported mechanisms — including DNA intercalation and membrane disruption — remains a subject of ongoing investigation. The low cytotoxicity of berberine toward mammalian cells [59] and its accessibility from natural sources [59] make it an attractive scaffold for medicinal chemistry optimization.

5.1.2. Sanguinarine

Sanguinarine, a benzophenanthridine alkaloid derived from the rhizomes of Sanguinaria canadensis (bloodroot), is among the most thoroughly characterized natural FtsZ inhibitors. Pioneering studies by Beuria et al. (2005) demonstrated that sanguinarine induces filamentation in both E. coli and B. subtilis through inhibition of cytokinesis, specifically by disrupting Z-ring formation without affecting nucleoid segregation [60]. Mechanistically, sanguinarine directly binds FtsZ with a dissociation constant of 18-30 µM, inhibiting FtsZ protofilament assembly and reducing bundling [60]. Size-exclusion chromatography, fluorescent probe binding assays (1-anilinonaphthalene-8-sulfonic acid), and tryptophan fluorescence measurements of FtsZ mutants collectively confirmed direct FtsZ-sanguinarine interaction [60]. The broad-spectrum antimicrobial activity of sanguinarine, effective against both Gram-positive and Gram-negative pathogens, is partially attributable to its FtsZ-inhibitory mechanism [60], though this compound also inhibits tubulin polymerization, raising concerns about mammalian cytotoxicity [61], [62]. Structurally simplified sanguinarine analogues, including 5-methyl-2-phenylphenanthridium derivatives, have been developed to dissociate FtsZ inhibitory activity from tubulin inhibition, with several compounds exhibiting outstanding activity against both sensitive and resistant bacterial strains (MIC 0.06-2 µg/mL for sensitive, 0.25-4 µg/mL for resistant strains) while demonstrating improved selectivity for FtsZ over tubulin [63].

5.2. Polyphenols and Phenylpropanoids

5.2.1. Curcumin

Curcumin, the principal bioactive polyphenol of Curcuma longa (turmeric), has been studied as an FtsZ inhibitor in addition to its well-documented anti-inflammatory, antioxidant, and antineoplastic properties. Computational docking analyses employing cavity depth analysis and molecular electrostatic potential (MEP) calculations identified two putative curcumin-binding sites on E. coli FtsZ, subsequently validated through site-directed mutagenesis studies [64]. Biochemical characterization demonstrated that curcumin stimulates FtsZ GTPase activity and simultaneously disrupts polymerization, decreasing the steady-state length of FtsZ polymer assemblies [10]. Curcumin is structurally related to the β-diketone pharmacophore that engages tubulin, and indeed exhibits antiproliferative effects on eukaryotic cells through microtubule disruption, warranting selectivity considerations in the context of FtsZ-targeted antibacterial development [65].

5.2.2. Cinnamaldehyde

Cinnamaldehyde, the principal active constituent of cinnamon oil derived from Cinnamomum species, is a phenylpropanoid that has been reported to inhibit FtsZ activity and disrupt Z-ring formation [34,42]. Molecular docking studies predict that cinnamaldehyde binds to the GTP-binding pocket of FtsZ, consistent with competitive inhibition of GTPase activity [66,67]. Like curcumin, cinnamaldehyde interacts with multiple cellular targets and its specificity for FtsZ in whole-cell antibacterial activity has been questioned [68]. Nevertheless, cinnamaldehyde exhibits MIC values in the range of 200-400 µg/mL against E. coli and S.

aureus, and its GRAS (Generally Recognized As Safe) status and wide natural distribution make it an attractive starting point for semi-synthetic modification toward more potent and selective FtsZ inhibitors [69].

5.3 Terpenoids and Diterpenes

5.3.1 Totarol

Totarol, an abietane diterpene phenol isolated from the heartwood of Podocarpus totara and related Gymnosperm species, is reported to have antimicrobial activity [70]. Totarol was reported as an FtsZ inhibitor in early high-throughput screens, appearing to inhibit both GTPase activity and polymerization of FtsZ [34,71]. However, subsequent mechanistic investigations by Anderson et al. (2012) employed rigorous aggregate detection protocols, including Triton X-100 disruption assays and protein concentration-dependence studies, to demonstrate that totarol's apparent FtsZ inhibitory activity arose artifactually from the formation of microscopic colloids or aggregates rather than specific drug-target interactions [71]. The FtsZ inhibitory activity of totarol was abolished in the presence of 0.01% Triton X-100 and exhibited characteristic protein concentration-dependent reduction, both hallmarks of aggregate-based inhibition. This finding, while appearing to undermine totarol as an FtsZ inhibitor, served a broader methodological purpose by establishing stringent experimental controls that should accompany all future reports of FtsZ inhibition by small molecules. The genuine antibacterial activity of totarol against Gram-positive organisms, including S. aureus, may therefore involve mechanisms other than direct FtsZ inhibition potentially including membrane disruption or inhibition of other metabolic targets [72].

5.3.2. Germacrene Terpenoids

Germacrene D-4-ol and germacrene D, sesquiterpenoids extracted from pine needle essential oils, have been identified as candidate FtsZ inhibitors through molecular docking studies predicting engagement with a hydrophobic pocket in the FtsZ protein. These terpenoids exhibit broad-spectrum antimicrobial activity against multiple bacterial species. While computational modelling supports FtsZ as a potential target, rigorous biochemical validation with appropriate aggregate controls is necessary to definitively assign FtsZ inhibition as the primary mechanism of antibacterial action [38].

5.4. Macrolides and Polyketides

5.4.1. Chrysophaentins

Chrysophaentins represent a structurally distinctive class of polyoxygenated, polyhalogenated bisdiarylbutene ether macrocycles isolated from the marine microalga Chrysophaeum taylori. Plaza et al. (2010) characterized chrysophaentins A-H and demonstrated that chrysophaentin A inhibits both the GTPase activity and polymerization of FtsZ, with activity against Enterococcus faecium, S. aureus, and related Gram-positive pathogens [73]. In vitro and in vivo studies established chrysophaentin A as a competitive inhibitor of FtsZ that occupies the GTP-binding site [73,74]. Molecular docking simulations confirmed engagement of a large proportion of the GTP-binding pocket, providing a structural rationale for competitive inhibition kinetics [73]. The complex, densely functionalized macrocyclic architecture of chrysophaentins makes them synthetically challenging to optimize, although their marine origin and unique scaffolds provide valuable starting points for structure-activity relationship studies.

5.4.2. Viriditoxin

Viriditoxin is a bis-naphtho-γ-pyrone natural product discovered through a high-throughput screening campaign of over 100,000 plant and microbial fermentation extracts, in which it was identified as an inhibitor of fluorescently tagged FtsZ polymerization. Initial characterization suggested that viriditoxin prevented FtsZ from forming the Z-ring in B. subtilis and inhibited growth of M. tuberculosis, Haemophilus influenzae, and other organisms. However, subsequent independent evaluation by multiple laboratories failed to reproduce FtsZ inhibitory activity under standardized biochemical assay conditions, raising questions regarding the specificity of the original screening assay [71]. The antibacterial activity of viriditoxin may therefore reflect pleiotropic or off-target mechanisms rather than specific FtsZ inhibition.

5.5. Polyphenols: Zantrins and Related Compounds

The zantrins are a series of five structurally diverse compounds (Z1-Z5) that were identified as FtsZ inhibitors in a targeted screening effort [11]. Zantrins inhibit the GTPase activity of E. coli FtsZ, prevent FtsZ polymerization, and disrupt E. coli Z-ring assembly in whole cells, with broad-spectrum antibacterial activity against both Gram-positive and Gram-negative pathogenic bacteria [11]. Critically, subsequent aggregate formation testing demonstrated that several zantrin analogues, including zantrin Z1, exhibited activity characteristic of colloidal aggregators rather than specific FtsZ binders [71]. In contrast, zantrin Z3 emerged as a reliable, non-aggregating FtsZ inhibitor that maintains activity in the presence of Triton X-100 and lacks the protein concentration-dependence characteristic of aggregate inhibition, establishing it as a validated FtsZ-binding scaffold for further structure-activity relationship studies [71]. Preliminary SAR analyses of zantrin Z3 identified modifications to its two side-chain substituents that modulate inhibitory activity, providing a roadmap for further optimization.

6. Binding Sites And Mechanisms Of FTSZ Inhibition

FtsZ inhibitors can be categorized according to their primary binding site and resultant mechanistic effect on FtsZ assembly dynamics. Three principal binding loci have been characterized: the GTP-binding pocket, the allosteric interdomain cleft (benzamide site), and the T7 loop/subunit interface [75,76]. Inhibitors engaging the GTP-binding pocket function primarily as competitive antagonists, displacing GTP and thereby preventing the nucleotide-induced conformational change that triggers cooperative polymerization. This class includes chrysophaentins, certain zantrins, and GTP analogs. Compounds targeting the allosteric interdomain cleft, typified by the benzamide series and berberine derivatives, modulate the structural communication between the N-terminal GTPase domain and the C-terminal domain. Rather than competitively blocking GTP binding, these molecules lock FtsZ in a conformational state that uncouples productive protofilament assembly from Z-ring dynamics. For PC190723 and related benzamides, this manifests as hyperstabilization of FtsZ polymers into non-functional bundles, analogous to the stabilization of microtubules by taxol [43]. A third mechanistic category consists of inhibitors that perturb lateral interactions between protofilaments, preventing the formation of bundles and sheets required for Z-ring condensation without necessarily disrupting single-protofilament assembly. Peptide inhibitors, including the endogenous inhibitor MciZ (a 40-residue peptide from B. subtilis that blocks C-terminal protofilament interactions during sporulation), and engineered peptide derivatives exemplify this category [77]. Finally, some inhibitors act at the level of FtsZ degradation rather than direct polymerization inhibition, inducing structural perturbations that mark FtsZ for proteolytic turnover by cellular quality control systems [78]..

7. Computational Approaches In FTSZ Inhibitor Discovery

The availability of high-resolution FtsZ crystal structures from pathogenic species, including S. aureus, B. subtilis, E. coli, M. tuberculosis, and Mycobacterium smegmatis, has enabled structure-based virtual screening as a primary discovery strategy [42,79]. Molecular docking campaigns against the GTP-binding pocket and the allosteric benzamide site have identified structurally diverse hit compounds from commercial and natural product-like libraries, several of which have subsequently been validated in biochemical FtsZ inhibition assays [76,80]. Pharmacophore modelling, molecular dynamics simulations, and MM-GBSA free energy calculations have been extensively deployed to rationalize binding affinities, prioritize analogues for synthesis, and understand the conformational dynamics governing FtsZ-inhibitor interactions [75,81]. The inherent flexibility of FtsZ, which adopts distinct conformational states in the GDP-bound (straight protofilament), GTP-bound (curved), and nucleotide-free forms, presents a challenge for rigid-body docking approaches and has motivated the application of ensemble docking and induced-fit docking protocols that account for receptor plasticity [20,26]. Cryo-electron microscopy studies have been instrumental in defining the structural heterogeneity of FtsZ protofilaments and providing structural

models of intermediate assembly states for computational interrogation [23,82]. The integration of machine learning and artificial intelligence approaches, including deep learning-based molecular generation, graph neural networks for property prediction, and reinforcement learning for scaffold optimization, is beginning to transform FtsZ-inhibitor discovery [83,84]. Fragment-based drug discovery approaches, informed by NMR-detected fragment binding to FtsZ in solution, offer an orthogonal strategy for identifying minimal binding motifs that can be elaborated into drug-like leads [17,85].

8. Challenges And Translational Barriers

Despite the compelling scientific rationale for FtsZ as a drug target and the substantial body of inhibitor discovery and development work, no FtsZ inhibitor has successfully completed clinical development. The translational challenges are multifactorial and interrelated. First, the conformational plasticity of FtsZ presents a fundamental challenge for inhibitor binding. FtsZ undergoes substantial conformational changes during its GTPase cycle, transitioning between GDP-bound, GTP-bound, and nucleotide-free states, as well as assuming distinct conformations within monomers, protofilaments, and higher-order assemblies. This structural heterogeneity translates to variable binding affinities for inhibitors that engage conformationally labile sites and complicates the structure-based optimization of binding affinity and selectivity [86]. Second, weak intrinsic binding affinities have historically limited the potency of many FtsZ inhibitors. The high intracellular concentration of FtsZ (~5,000-10,000 molecules per cell) necessitates that an effective inhibitor either bind with high affinity or engage a stoichiometric fraction of the FtsZ pool sufficient to impair Z-ring function [9]. Many natural product FtsZ inhibitors exhibit micromolar binding affinities that translate to inadequate intracellular efficacy or require concentrations associated with cellular toxicity. Third, the spectrum of activity of many advanced FtsZ inhibitors, including the benzamide series, is predominantly restricted to Gram-positive bacteria [87]. FtsZ from Gram-negative pathogens, particularly Enterobacteriaceae and non-fermentative Gram-negatives, frequently contains differences in the benzamide- binding cleft that reduce inhibitor binding affinity. Additionally, the outer membrane permeability barrier of Gram-negative bacteria limits the penetration of lipophilic inhibitors [16]. Overcoming this spectrum limitation is a priority for the field, with some investigators exploring outer membrane permeabilizers as adjuvants [16] or designing amphiphilic analogues with improved Gram-negative penetration [88]. Fourth, the emergence of FtsZ-specific resistance mutations, while occurring at low intrinsic frequencies, represents a manageable but real concern. Point mutations in the benzamide-binding cleft (e.g., G196A in S. aureus FtsZ) reduce affinity for PC190723 and related compounds [16]. Engineering inhibitors capable of engaging multiple binding interfaces or combining FtsZ inhibitors with complementary antibiotic classes may mitigate resistance development. Finally, pharmacokinetic challenges, including limited oral bioavailability, rapid metabolic clearance, and insufficient tissue penetration, must be addressed through prodrug strategies and medicinal chemistry optimization, as exemplified by the evolution from PC190723 to TXA709 [46].

FUTURE DIRECTIONS

The field of FtsZ inhibitor discovery is poised to benefit from several converging technological and scientific advances. The continued expansion of FtsZ structural databases, encompassing structures from clinically relevant pathogens in multiple conformational states and in complex with diverse inhibitor chemotypes, will provide increasingly rich templates for structure-based design. Cryo-electron microscopy approaches capable of resolving transient FtsZ assembly intermediates and capturing the Z-ring in situ within bacterial cells will provide unprecedented mechanistic insights [23]. The integration of high-throughput screening with machine learning-guided compound design is expected to accelerate the exploration of novel chemical scaffolds and circumvent the limited diversity that has characterized the current FtsZ inhibitor landscape. Multi-target approaches, whereby inhibitors simultaneously disrupt FtsZ and a second bacterial target (e.g., bacterial membrane integrity or cell wall biosynthesis), offer a strategy to reduce the emergence of resistance and expand the

spectrum of activity [89]. Dual-mechanism inhibitors that promote FtsZ polymerization hyperstabilization while disrupting bacterial membrane integrity have been reported, demonstrating synergistic bactericidal activity [90]. Peptide and peptidomimetic FtsZ inhibitors, inspired by endogenous regulators such as MciZ, represent an underexplored avenue with the potential to engage extended protein-protein interaction surfaces inaccessible to small molecules. Stapled alpha-helical peptides and macrocyclic peptidomimetics that mimic the FtsZ-interacting domains of divisome proteins may offer new pharmacological modalities [77]. Drug repurposing strategies, exemplified by the identification of the anticancer kinase inhibitors sorafenib and ponatinib as inhibitors of Fusobacterium nucleatum FtsZ, suggest that existing pharmacological diversity may harbor unexplored FtsZ-targeting activity [91]. Finally, the application of FtsZ inhibitors in combination with conventional antibiotics, particularly against persisters and biofilm-forming pathogens, warrants systematic investigation as a strategy to enhance bactericidal activity and overcome phenotypic tolerance.

CONCLUSION

FtsZ occupies a commanding position at the intersection of fundamental bacterial cell biology and translational antimicrobial drug discovery. As the prokaryotic organizer of cytokinesis, a protein conserved across the bacterial kingdom yet absent from mammalian genomes, and the target of no currently approved antibiotic, FtsZ represents a scientifically compelling and clinically opportune drug target [8,48,92]. The two decades of intensive investigation reviewed here have yielded a rich pharmacological landscape encompassing synthetic benzamide inhibitors, natural alkaloids, polyphenols, terpenoids, and macrolide-like compounds, each with distinct binding sites and mechanisms of action [76,87]. The benzamide series, culminating in the clinical candidate TXA709, provides the strongest evidence that FtsZ inhibition is a pharmacologically tractable antibiotic strategy capable of demonstrating in vivo efficacy against MDR pathogens [15,93]. Natural FtsZ inhibitors, while generally exhibiting lower potency and selectivity than optimized synthetic compounds [71,75], have made indispensable contributions to the mechanistic understanding of FtsZ inhibition and continue to provide structural diversity for scaffold-based drug design [17,79]. The methodological lessons learned from the field — particularly regarding the importance of aggregate controls, rigorous target engagement validation, and comprehensive resistance profiling — have strengthened the reproducibility and translational relevance of FtsZ inhibitor research. The path to the first clinically approved FtsZ inhibitor remains challenging but is increasingly well- defined. Multidisciplinary strategies that integrate structural biology, computational chemistry, synthetic medicinal chemistry, and pharmacokinetic optimization, supported by advancing technologies in cryo-EM, machine learning, and high-throughput screening, hold substantial promise for delivering first-in-class antibiotics that address the critical unmet needs posed by the global AMR crisis.

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