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INHIBITORS OF FIMH AGAINST UROPATHOGENIC ESCHERICHIA COLI: COMBINATION THERAPY, ANTI-VIRULENCE MECHANISMS, AND RESISTANCE BIOLOGY

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ABSTRACT

The majority of urinary tract infections (UTIs) are caused by Uropathogenic Escherichia coli (UPEC), which are difficult to treat due to recurrence and growing antibiotic resistance. FimH, the mannose-binding adhesin at the tip of type 1 pili, is an appealing target for anti-virulence because it promotes bladder colonization, invasion, and the creation of intracellular biofilm-like communities. The structural biology of FimH, the ways in which competitive antagonists block it, and the medicinal chemistry that advanced the field from simple alkyl mannosides to ortho-substituted biphenyl, C-linked, and heterocyclic molecules with nanomolar potency are all included in this study. After that, check how resistance and adaptation could develop in response to an anti-adhesion medication, which in vitro and animal evidence support the anti-virulence effects, and how FimH antagonists could be used with antibiotics or inhibitors of other adhesins like FmlH. Pharmacokinetic and safety factors are explored, with special focus to the trade-off between potency and permeability, and computational and experimental evaluation techniques are described. Lastly, highlight the primary gaps direct resistance data, thorough combination studies, and human efficacy trials and offer recommendations for next-generation design.

KEYWORDS: FimH; Uropathogenic Escherichia Coli; Mannosides; Anti-Virulence; Urinary Tract Infection Antibiotic Resistance; Combination Therapy.

1. INTRODUCTION

1.1 Uropathogenic Escherichia coli (UPEC) Infections and Their Clinical Burden

Approximately half of all women will experience at least one episode of a urinary tract infection (UTI) during their lifetime, making it one of the most common bacterial illnesses observed in clinical practice.[1, 2] Most community-acquired cases and a significant portion of hospital-associated cases are caused by uropathogenic Escherichia coli.[2, 3, 4] The financial aspect is as startling: according to a recent medicinal chemistry research, UTI-related medical expenses in the US total approximately $2.5 billion annually, with over 10% of all antibiotic courses administered for this indication.[5] Recurrence is a more difficult issue than a straightforward acute sickness since many people relapse months after what appeared to be a clear cure.[1, 6]

1.2 Conventional Antibiotic Therapy's Limitations

Although they are still the mainstay of care, antibiotics are becoming less effective. According to a global review, drug-resistant bacterial infections directly caused well over a million fatalities in 2019, with Enterobacterales being one of the most common problematic pathogens.[7, 8] Guideline committees have been forced to retire or caveat a number of erstwhile first-line agents due to the increasing resistance in uncomplicated UTI over the past 20 years.[9, 10] It isn't only about resistance. Broad-spectrum medications also disrupt the gut flora that serves as a reservoir for UPEC[13], and bacteria that retreat inside bladder cells can withstand antibiotic exposure and subsequent seed recurrence.[11, 12]

1.3 Rationale for Anti-Virulence Strategies Targeting FimH

Instead of eliminating the organism, anti-virulence therapy disarms the characteristics that allow it to colonize a host.[14, 15] The evolutionary reasoning is more complex than early enthusiasm suggested, but the basic attraction is a weaker selective pressure for resistance.[16] The earliest application of this concept is anti-adhesion therapy. It is theoretically possible to allow the organisms to be washed out by normal urine flow by blocking the carbohydrate-binding adhesins that bind bacteria to host surfaces.[17] FimH, the mannose-specific adhesin at the tip of type 1 pili, is the apparent target for UPEC, and oral active small-molecule FimH antagonists have already eliminated bacteria from the mouse bladder.[18]

1.4 Scope and Objective

It summarizes the current understanding of FimH inhibitors against UPEC, including the structural biology of the adhesin and the medicinal chemistry used to create oral mannosides. It focus on three issues that are often addressed separately: how resistance and adaptation may develop in response to an anti-adhesion medication; which anti-virulence effects are supported by experimental data; and how FimH antagonists may be used in conjunction with antibiotics or inhibitors of other adhesins. Because the optimization of the FmlH series provides useful lessons for the entire field, also compare FimH with the galactose-specific adhesin FmlH.[19, 20]

2. FimH's Biological Importance in the Pathophysiology of UPEC

2.1 Structure and Function of Type 1 Pili

The chaperone-usher pathway, in which a periplasmic chaperone transports pilin subunits to an outer-membrane usher that constructs the fiber without the need for an external energy source, is responsible for the assembly of type 1 pili, which resemble hair.[21] In addition to type 1, E. coli possesses other chaperone-usher systems; a pan-genome survey revealed hundreds of different types, with individual strains carrying multiple at once.[22, 23] The rod is composed of repeated FimA subunits and ends in a short tip fibrillum that bears the adhesin FimH. The pilus is necessary for bladder colonization in mice, and type 1 pili are still the most well-characterized of these in the urinary tract.[24, 25]

2.2 Mannose-Binding Pocket and FimH Architecture

The protein FimH has two domains. The adhesin is anchored to the pilus by the C-terminal pilin domain, whereas the N-terminal lectin domain contains the carbohydrate-binding site.[26] Hydrophobic residues, such as the so-called tyrosine gate formed by Tyr48 and Tyr137, border the entrance of the mannose pocket, which is deep and lined with polar residues that form hydrogen bonds to the sugar hydroxyls.[27, 28] Alkyl and aryl aglycones that reach those entrance residues bond much more firmly than methyl mannoside, which proved to be the key to affinity.[27] Additionally, crystal structures demonstrate that the gate's layout can change between conformations, which is an important element for inhibitor design.[28]

FimH doesn't act as a static lock. The lectin domain shifts from a low-affinity to a high-affinity state and the interdomain linkage loosens under mechanical shear, resulting in the adhesin catch-bond behavior that keeps bacteria attached while urine flows.[29, 30] According to ensemble studies, natural sequence variations alter the equilibrium between these conformations, adjusting a strain's binding strength in various host environments.[31] The key takeaway for drug research is that the pocket found in numerous crystal structures represents a single state of a dynamic protein.

2.3 FimH role in Bacterial Adhesion and Invasion

In the bladder, FimH binds N-linked glycans on β1 and α3 integrins and recognizes mannosylated glycoproteins on the luminal surface of the urothelium, including uroplakins.[25, 32] Actin rearrangement and bacterial absorption into superficial umbrella cells are triggered by binding; this process is dependent on type 1 pili.[33, 34] The host fights back, thus the invasion is not the end of the story. Through a TLR4-dependent mechanism controlled by cyclic AMP, infected cells can eliminate bacteria.[35, 36] They can also exfoliate, which removes bacteria but reveals deeper tissue layers.[34]

2.4 Biofilm Formation Mediated by FimH and Recurrent UTIs

After escaping expulsion, bacteria grow in the cytoplasm and form intracellular bacterial communities (IBCs) that resemble biofilms and are protected from numerous host defenses.[37, 38] FimH inhibitors are evaluated in biofilm experiments in addition to binding assays[40] because IBC growth is dependent on type 1 pili.[39] The bacteria spread, reinfect nearby cells, and, in mice, establish quiescent reservoirs that can last for weeks following a spike in replication.[12, 41] Urine samples from women with UTIs have shown similar communities, demonstrating the model's clinical applicability.[42] Relapse may be explained by the fact that antibiotic therapy can lower bacterial levels without eliminating these reservoirs.[43, 44]

3. FimH Inhibition's Molecular Mechanisms

3.1 Mannose Binding Competitive Inhibition

Every FimH antagonist that has been created thus far functions as a competitive inhibitor. They prohibit the adhesin from interacting with host glycans because they occupy the mannose pocket.[27, 45] Potency is largely dependent on how strongly the aglycone engages the hydrophobic entry because the mannose ring provides the anchor and the aglycone provides the additional affinity.[46, 47] The chemicals circumvent the porin and efflux processes that restrict many antibiotics since the location is extracellular and they do not need to pass through the bacterial membrane.[15, 17]

3.2 Host-Pathogen Interaction Disruption

It is anticipated that a FimH antagonist will stop bacteria from attaching to uroplakin and integrin receptors, which is the first stage of the infection cycle.[32, 33] When administered prior to challenge, mannoside therapy reduced bladder bacterial burdens and avoided infection in the mouse.[18] Noteworthy is a second effect. Blocking FimH-dependent attachment should also lessen the invasion-associated processes mentioned above because it triggers downstream signaling in the host cell.[33, 34] It is still unclear and has only been indirectly investigated if pharmacological treatment actually modifies the host response.

3.3 Impacts on Intracellular Reservoirs and Bacterial Colonization

Anti-adhesion medications are more effective against extracellular microorganisms. One reason preventive and early treatment are more promising than clearing established reservoirs is that once UPEC are within a cell, a polar, sugar-like inhibitor has restricted access to them.[12, 44] However, the reservoir is not isolated from the lumen; an inhibitor can catch bacteria when they periodically emerge to reinfect new cells.[12, 38] The stages of the cycle are mapped onto the locations where FimH antagonists are believed to function in Figure 1.

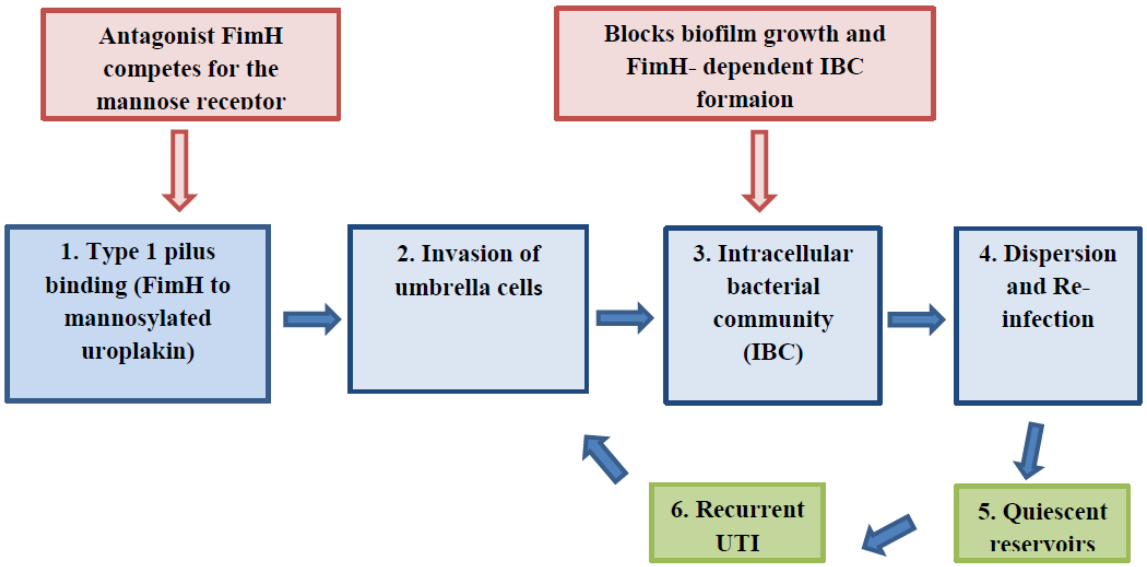


Figure 1: A simplified cycle of UPEC infection in the bladder that illustrates the expected action of FimH antagonists.

3.4 Biofilm formation inhibitors

The functional readout provided by biofilm prevention assays has a strong correlation with FimH binding. In one optimization campaign, the addition of an ortho substituent to a biphenyl mannoside increased the biofilm IC50 from 1.35 μM to 0.16 μM, approximately eight times the gain observed in hemagglutination testing.[48] Biofilm inhibition is now regarded as a standard secondary assay because related work with various chemotypes revealed the same trend.[20, 49]

4. FimH Inhibitor Classification and Medicinal Chemistry

4.1 Mannosides, both natural and artificial

Simple sugars are where the story starts. Although D-mannose is commonly used as a supplement and a small randomized study found benefit for prophylaxis, the therapeutic effect of D-mannose and its methyl glycoside is restricted since they only block adhesion at high concentrations.[17, 50] Alkyl mannosides significantly improved the situation. Because its chain reaches the tyrosine gate, the n-heptyl derivative binds with a dissociation constant in the low nanomolar range.[20, 27] The expanded site's recognition of oligomannose was further elucidated by trimannose complexes cocrystallized with FimH.[51]

4.2 Aryl Mannosides and C-Mannosides

The biphenyl series provided the first compounds with actual oral potential, followed by aryl mannosides. Structure-guided biphenyl mannosides from two separate groups demonstrated that the second ring stacks against Tyr48 and that a meta-substituted hydrogen-bond acceptor on the distal ring might interact with Arg98.[45, 52] One early finding of this effect dates back to research on aryl mannosides in the 1980s.[52, 53] Ortho substitution on the ring linked to mannose then produced a significant increase in potency. The Ernst group's studies of the link between potency, urine concentration, and efficacy shown that pharmacokinetic balance was just as important as binding.[54, 55]

Additionally, the O-glycosidic link is vulnerable to hydrolysis by glycosidases or acids. To get around this, C-mannosides were created, in which a carbon linker takes the place of the anomeric oxygen. After oral treatment in mice, an R-hydroxymethylene linker maintained efficacy and, in an isoquinolone-based C-mannoside, provided around a 100-fold lower bladder bacterial load than the comparable O-glycoside.[20, 56]

With one N-linked derivative achieving a hemagglutination titre of roughly 1 nM, isoquinolone aglycones were also beneficial on their own.[49]

4.3 Glycomimetic Inhibitors and Thiomannosides

A third line of work consists of heterocyclic and sulfur-containing substitutes. Mannosyl triazoles were investigated as bioisosteres that alter polarity and metabolic destiny while maintaining the amide's hydrogen-bonding architecture.[55, 57] Although the chemistry of thiazolylmannosides is easily transferred to the urinary context, they were primarily designed for adherent-invasive E. coli in Crohn's disease.[58, 59] Beyond FimH, the glycomimetic idea has been examined in the larger framework of medications based on carbohydrates; the common problem is how to maintain affinity while removing a sugar's polarity.[60, 61]

4.4 Inhibitors of Multivalent FimH

Multivalent mannosides were a clear early tactic since bacteria carry hundreds of pili. In binding and aggregation tests, mannosylated dendrimers and multimeric heptyl mannosides demonstrated nanomolar potency.[62, 63] The increases in avidity are highlighted in reviews of multivalent glycoconjugates, but they also come with bulk, heterogeneity, and poor drug-likeness.[61,64] The field shifted toward monovalent tiny compounds since these large molecules are challenging to create, especially for oral therapy.[61]

4.5 FimH Antagonists' Structure–Activity Relationship (SAR)

Four guidelines can be used to summarize the SAR when taken as a whole. Recognition depends on the mannose ring. By interacting with the tyrosine gate, a biaryl aglycone becomes more potent than alkyl chains. Arg98 is engaged by a hydrogen-bond acceptor at the distal ring's meta position. Lastly, the glycosidic link is protected and affinity is increased by tiny hydrophobic ortho substituents on the proximal ring.[65, 66] The primary classes are compared in Table 1, and the degree to which the ortho substituent altered potency in a single matched series is displayed in Table 2 and Figure 2.

Table 1: Main classes of FimH antagonists and their typical strengths and weaknesses.

Class	Key Features	Main limitation	Representative references
Biphenyl O-mannosides	Biaryl π-stacking with Tyr48; meta acceptor binds Arg98	Glycoside hydrolysis; permeability–potency trade-off	[45], [52], [65]
Alkyl mannosides	Chain reaches the tyrosine gate; low nM binding for heptyl	Limited drug-likeness and oral exposure	[27], [20]
Multivalent mannosides	High avidity, nanomolar activity	High molecular weight, heterogeneous, poor oral profile	[62], [63], [64]
Isoquinolone and heterocyclic aglycones	Improved potency and half-life; low nM HAI values	Optimisation of exposure still required	[49], [57]
Thiazolyl mannosides	Developed for E. coli in Crohn's disease	Less data in UTI models	[58], [59]
C-Mannosides	Stable anomeric linker; R-hydroxymethylene retains potency	More demanding synthesis	[56]

Table 2: Effect of ortho substitution in biphenyl mannosides (data adapted from Han et al., 2012). HAI = hemagglutination inhibition titre (EC>90).

Compound	Ortho group/ amide	HAI EC >90 (μM)	Biofilm IC50 (μM)	CLogD 7.4	PAMPA log Pe
1	H	1.00	0.94	1.17	- 5.42
5b	Me (amide)	0.06	0.16	0.93	- 3.89
4b	Cl (ester)	0.03	0.26	1.64	- 4.29
4d	CF_3 (ester)	0.03	0.17	1.62	- 3.91
7	CF_3 (diamide)	0.01	0.043	1.15	- 6.27
3	H (diamide)	0.37	0.74	0.71	- 4.51
8	Me (diamide)	0.02	0.073	1.35	- 8.46

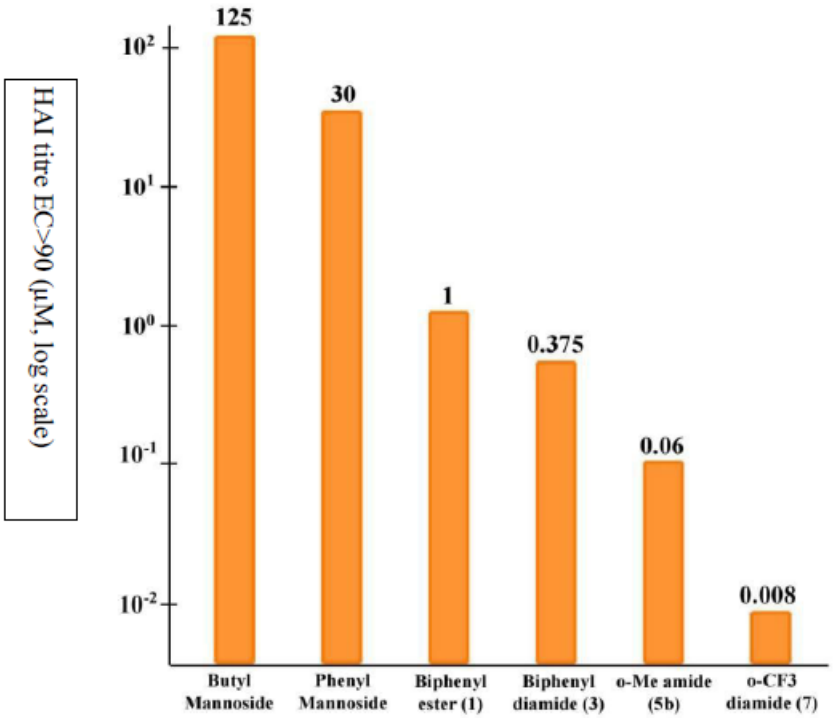


Figure 2: FimH antagonist potency (HAI titre) changes from phenyl and alkyl mannosides to ortho-substituted biphenyl mannosides. values derived from Han et al. (2012)'s tables.

5. Inhibition of FimH and Biology of Bacterial Resistance

5.1 Anti-Adhesion Resistance vs. Antibiotic Resistance

Antibiotic resistance is usually easy to characterize: the organism withstands drug exposure that would otherwise kill it. Since the substance does not initially endanger bacterial viability, the concept of an anti-adhesion medication is less precise. Instead, selection would favor variations that colonize through a different pathway or that bind the host effectively when the inhibitor is present.[15, 16] Therefore, the assays used to determine resistance must take into account the possibility that it may manifest as altered colonization rather than growth in the presence of a medication.

5.2 Polymorphism and Genetic Variation in FimH

FimH varies depending on the strain. The pathogenic adaption of E. coli was connected to natural sequence variation in the late 1990s[67], and genomic analyzes revealed signs of positive selection in the fimH gene of clinical UPEC isolates.[68] The way the protein alternates between conformations is altered by a number of the chosen residues, and the virulence of the mutant strains in the mouse bladder varies.[31, 69] The binding pocket itself seems to be widely conserved despite this diversity, and FimH's affinity for mannose is said to be mostly independent of pathotype.[70]

5.3 Possible Reasons for Decreased FimH-Inhibitor Susceptibility

There are a number of potential pathways to decreased susceptibility, however the majority of them lack direct experimental support. The way the aglycone fits against the tyrosine gate may be altered by a mutation close to the pocket entrance, which would be particularly important for molecules that rely significantly on aglycone interactions.[28, 65] Conformational equilibrium-shifting mutations may change binding under flow.[29, 30] The mannose pocket's small size and the requirement to maintain mannose recognition likely restrict how much FimH can alter before losing its functionality.[70] Consequently, consider high-level resistance as conceivable but unproven; Table 3 enumerates the potential mechanisms and the supporting data.

Table 3: Current evidence and potential pathways to decreased susceptibility to FimH antagonists.

Mechanism	Rationale	Evidence status	References
Pocket or gate mutations in FimH	Natural variants and Positively selected Residue exist	Variation documented; effect on inhibitors not established	[67], [68]
Use of alternatives adhesins	Strains encode several chaperone- usher pili with other receptors	Conceptually supported	[22], [71]
Sequestration inside host cells	Intracellular bacteria are shielded from extracellular inhibitors	Observed for antibiotics	[12], [11]
Altered conformational equilibrium	Residues outside the pocket tube low-versus high- affinity series	Demonstrated for virulences; untested for drugs	[69],[31]

5.4 Compensatory Virulence Mechanisms and Bacterial Adaptation

UPEC has multiple adhesion systems. In addition to type 1 pili, they can express Fml pili, whose FmlH adhesin binds N-acetylgalactosamine and galactose on the inflammatory bladder epithelium, improving fitness during long-term infection.[71, 72] Through a host receptor, type 1 pili also contribute to kidney infection, expanding the possible locations of action.[73] It has not been directly investigated whether bacteria under FimH inhibition can upregulate such systems, but this is a clear rationale to use many inhibitors instead of just one.[22, 23]

5.5 Experimental Evaluation and Resistance Monitoring

A realistic resistance-monitoring strategy would integrate phenotypic and genotypic research. While hemagglutination inhibition and biofilm assays would reveal if those variants react to the medication, sequencing fimH from isolates with recurring infections could identify developing variants.[67, 68] Thermal-shift assays and biolayer interferometry offer a more direct way to determine if a mutant protein still binds inhibitors.[55, 66] Then, animal infection models can verify if any change made in vitro has an impact in vivo.[42, 44]

6. FimH Inhibitors' Anti-Virulence Effects

6.1 Bacterial Adhesion and Colonization Inhibition

Studies on mice provide the most convincing in vivo data. When taken orally, mannosides decreased bladder CFU in cases of established infection and provided prophylactic protection against challenge.[18] The bladder was not the only organ affected. The restricted, non-bactericidal mode of action is supported by the finding that a biphenyl mannoside reduced gut colonization by UPEC without appreciably altering the broader microbiota.[13] Since these results were obtained in mice, care must be taken before extrapolating to humans.

6.2 Impacts on Intracellular Bacterial Communities and Invasion

Interfering with FimH should reduce the first invasion events that result in IBCs because type 1 pili are necessary for IBC development.[38, 39] In the biofilm experiment used for compound ranking, optimized mannosides were found to stop bacteria from developing IBCs.[48] It is more challenging to directly image IBCs in treated animals, and the majority of the information that is now accessible is indirect. Nevertheless, the reasoning aligns with the accepted etiology model.[37, 44]

6.3 Biofilm Development Modulation

Numerous chemotypes, including isoquinolones and biphenyl mannosides, have been shown to suppress biofilm in vitro; the best compounds have IC50 values in the low to mid nanomolar range.[48, 49] FimH inhibitors are positioned alongside lectin inhibitors for Pseudomonas aeruginosa and other adhesion-targeting strategies in a more comprehensive assessment of carbohydrate-based antibiofilm medicines.[20] The general idea is that while disturbing a mature matrix is more difficult, preventing lectin-mediated adhesion is an appealing method of interfering with early biofilm growth.[74, 75]

6.4 Inflammatory Signaling and Host Immune Reactions

The host reaction is impacted by FimH engagement. It has been demonstrated that type 1-piliated UPEC cause urothelial exfoliation and an inherent defense reaction in the bladder.[34] This interaction also involves the TLR4 and cyclic AMP pathways that promote bacterial ejection.[35, 36] Therefore, blocking FimH may suppress some of the host-damaging responses in addition to the bacterial invasion; however, no clean investigation has yet distinguished these effects from decreased bacterial load.[3, 25]

6.5 Bacterial Fitness and Virulence Effects

The idea that anti-virulence drugs should only decrease fitness in the host and not in the lab is one of their distinguishing characteristics. Because mannosides do not impede development in culture, FimH inhibitors meet that profile.[14, 15] However, fimH mutants are significantly reduced in the host, and positive selection on the gene implies that adhesion tuning is essential for fitness.[68, 69] The same reasoning holds true for Fml pili in chronic cystitis, where loss of the operon caused a competitive deficiency in the kidney and bladder in mice.[71].

7. Combination Therapy: Antimicrobial Agents and FimH Inhibitors

7.1 Justification for Combination Treatment

There are three reasons to consider combinations. First, a second agent with intracellular activity may be required because an anti-adhesion medication cannot eradicate bacteria that have already entered cells.[12, 44] Second, inhibitors of many adhesins may accumulate because UPEC may use multiple adhesins.[71, 72] Third, the likelihood that a single mutation can save the organism is typically decreased when agents with distinct mechanisms are combined.[15, 16]

7.2 Combination with Traditional Antibiotics

The first study of oral active FimH inhibitors found that a mannoside administered in conjunction with trimethoprim–sulfamethoxazole was more successful in eliminating germs in mice than either treatment alone.[18] This confirms a previous finding that persistent bacteria in the bladder cannot be eliminated by antibiotic therapy alone.[43] In order to minimize collateral harm to the microbiota, practical combinations may combine a FimH antagonist with a conventional drug at a lower dose or for a shorter duration.[13]

7.3 Additive and Synergistic Antimicrobial Impacts

There is still little proof of genuine synergy. Complementary targeting of two adhesins is suggested by the fact that co-administration of the FmlH inhibitor with a strong mannoside FimH inhibitor reduced bacterial titres in the kidney and bladder more than the FmlH inhibitor alone.[5, 72] Similar research on other pathogens indicates that anti-virulence substances, such as quorum sensing inhibitors, may make biofilms more susceptible to antibiotics.[76, 77] Since these objectives and species are distinct, they offer proof of concept rather than concrete proof of UPEC.

7.4 Impacts on Recurrent Infections and Biofilms

Preventing recurrence is the most intriguing clinical option. FimH antagonists may reduce antibiotic exposure and relapse rates if they are able to prevent reinfection by newly developing bacteria.[47, 78] Adhesin antagonists may find partners in small-molecule pilicides and curlicides that prevent pilus assembly or the formation of amyloid curli.[40, 79] A controlled human trial that assesses recurrence instead of short-term bacterial counts is still the most important piece of evidence.[3]

7.5 Drug Combination Experimental Evaluation

Checkerboard tests and fractional inhibitory concentration indicators are typically used to evaluate combinations in vitro. Anti-adhesion medications, which lack a minimum inhibitory concentration, are not well suited for that strategy. It is more appropriate to use functional readouts as hemagglutination inhibition, biofilm tests, and mouse bladder CFU counts.[18, 40] Pharmacokinetic compatibility presents another challenge: as concentration-time profiles determine efficacy, each partner's exposure in urine and plasma must be determined before a combination is investigated.[54, 55] Representative combination notions are summarized in Table 4.

Table 4: FimH inhibitor-related combination concepts that are representative.

Partner	Model	Reported outcomes	References
Pilicides / curlicides	In vitro and mouse biofilm models	Reduced pilus or curli assembly and biofilm formation	[79], [40]
Trimethoprim–sulfamethoxazole	Mouse UTI	Mannoside plus antibiotic more effective than either alone	[18]
Quorum sensing inhibitors	S. aureus, other biofilms	Increased antibiotic susceptibility (other species)	[76], [77]
Lectin-directed antibiotic conjugates	P. aeruginosa in vitro	Targeted delivery concept; potency trade-offs	[80]
FmlH inhibitor	Mouse chronic cystitis	Further reduction in bladder and kidney titres	[72], [5]

8. Experimental and Computational Methods for FimH Inhibitor Assessment

8.1 Molecular Docking and Structure-Based Drug Design

The field has relied heavily on structure-based design. The first biphenyl series was guided by cocrystal structures of FimH with mannosides, which defined the pocket.[27, 45] Ortho-trifluoromethyl substitution increased efficacy, with the group orientated toward Ile13, according to docking models, incorporating electrostatic surfaces computed using a Poisson–Boltzmann solver.[48] Docking was employed in the C-mannoside work to explain why the R-hydroxy isomer was preferred because it could form a hydrogen-bond network mediated by water.[56]

8.2 Binding Free-Energy Analysis and Molecular Dynamics

Molecular dynamics provides information that static structures cannot because FimH is conformationally dynamic. The allosteric transition and the catch-bond mechanism have been studied through structural research and simulations.[29, 30] Complementary information about how aglycone binding disrupts the pocket entrance is

provided by NMR and crystallographic investigations of the tyrosine gate.[28] The majority of published rankings for FimH antagonists rely on experimental affinities because free-energy approaches are currently less frequently reported.[66]

8.3 Assays for Biochemical and Biophysical Binding

Hemagglutination inhibition, biolayer interferometry for kinetics, and differential scanning fluorimetry for rating extremely tight binders are all included in a typical panel. Thermal shift measurements (melting temperatures of 74–76 °C compared with around 60 °C for apo-protein) were utilized in the ortho-substituted mannoside series because off-rates were too slow to quantify for the best compounds.[48] These techniques have been used with additional biophysical measurements to investigate the role of aglycone π-stacking in affinity.[55, 66]

8.4 Assays for Bacterial Adhesion and Biofilm Inhibition

Assays based on cells link binding to function. Biofilm prevention assays gage a compound's capacity to halt surface growth, while yeast or erythrocyte hemagglutination assays gage a compound's capacity to inhibit piliated bacterial agglutination.[40, 45] Curlicides and other anti-virulence substances are evaluated based on biofilm development.[40] Although these tests are cheap and suitable for screening, they do not simulate host receptors or urine flow.[30]

8.5 UPEC Infection Models in Vivo

The workhorse for effectiveness is the mouse cystitis model. IBC development and the durability of quiescent reservoirs are two characteristics of human UTI that it mimics.[38, 44] Galactoside antagonists of FmlH are used in chronic-cystitis models[71, 72], while treatment trials assess bladder and kidney CFU following oral or intraperitoneal dosage.[13, 56] The standard disclaimers apply: human data is needed for clinical translation because mouse urine is more diluted and the animals' bladder physiology and flora differ from those of humans.

9. Safety, Therapeutic Development, and Pharmacokinetics

9.1 Distribution, Metabolism, Excretion, and Absorption

Sugars' strong polarity and poor membrane crossing are the main ADME issues for glycomimetics.[60] The parallel artificial membrane permeability assay (PAMPA) offers a fast ranking tool, and increasing lipophilicity is helpful. The more powerful diamides 7 and 8 were significantly less permeable than amide 5b, which exhibited the best permeability (log Pe −3.89 cm²/s) in the ortho-substituted mannoside series and provided prolonged plasma and urine exposure after a 50 mg/kg oral dosage in mice.[48] The trade-off between potency and permeability in this series is depicted in Figure 3.

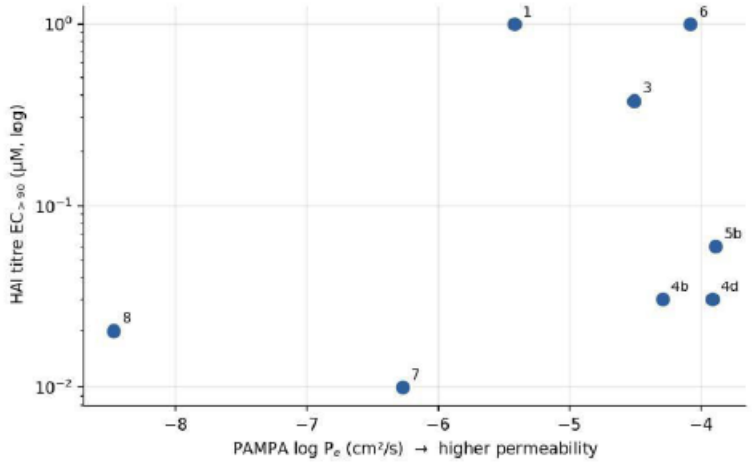


Figure 3: Correlation between PAMPA permeability and hemagglutination inhibition potency for specific biphenyl mannosides. Han et al. (2012) provided the data.

The other side of the question is metabolic stability. Early mannosides were known to cause glycoside hydrolysis in the gut and in tissue, with a phenolic hydrolysis product seen in urine following oral administration.[18, 48] This was addressed by either adding ortho substituents that protect the link or substituting carbon for the glycosidic oxygen.[54, 55]

9.2 Pharmacological Optimization and Urinary Exposure

High urine concentration is beneficial for UTIs because the chemical is delivered right to the infection site. In mice, ortho-substituted mannosides were about ten times more concentrated in urine than in plasma, which is consistent with quick renal clearance.[48] In the early anti-adhesion literature, balanced pharmacokinetics and pharmacodynamics were previously emphasized as the

secret to success.[54, 55] A galactosaminoside with 53% oral bioavailability in mice and urine levels more than 300 times higher than its IC50 was generated in the FmlH series by optimizing the aglycone for smaller polar surface area and increased lipophilicity.

9.3 Evaluation of Toxicity and Safety

There is little published safety data for FimH antagonists. Since they function outside of the cell and are not bactericidal, they have a conceptual advantage over broad-spectrum antibiotics in that they are not predicted to disrupt the microbiota or apply selective pressure through death.[13, 14] The oral bioavailability and tolerability of related lectin inhibitors have been evaluated in animals.[74] Selectivity profiling is particularly listed by the FmlH authors as future work, and comprehensive toxicity, including off-target binding to human lectins, is required for any clinical candidate.[5]

9.4 Status of Preclinical and Clinical Development

A number of initiatives are heading toward the clinic. GSK3882347, an oral bioavailable FimH inhibitor created by Fimbrion and GSK, was being assessed in phase 1b trials in women with simple UTIs, according to the 2024 FmlH report.[19] Since that statement represents the time of the article, readers should examine the most recent trial registries. When evaluating the evidence, it is important to keep in mind that some of the authors of the underlying medicinal chemistry studies disclosed financial interests in a business that commercializes mannoside FimH antagonists.[5] On the other hand, D-mannose is already accessible as a supplement; yet, its effectiveness is based on a small number of studies.[50, 78]

10. Difficulties and Prospects

10.1 Current FimH Inhibitors' Limitations

There are three notable restrictions. First, as the 7 and 8 diamides demonstrate, potency does not ensure permeability, and sugar-derived inhibitors have a persistent issue with oral exposure.[48] Second, the half-life can be shortened by breaking the glycosidic bond.[56] Third, a large portion of the efficacy evidence is restricted to molecules from a limited number of laboratories and a few mice models.[47, 78] All of this explains why translation has been slower than the early mouse evidence predicted, but it does not refute the idea.

10.2 Translational Difficulties in the Management of Recurrent UTIs

Recurrent UTIs are a complex issue. In certain situations, such as Fml-mediated chronic infection, alternative adhesins predominate, and not all strains depend on type 1 pili to the same extent.[22, 71] The FmlH program, which is summarized in Table 5, provides a helpful contrast. Galactoside antagonists encountered the same permeability barrier and demonstrated that rational property-based design could overcome it (Figure 4).[5, 19]

Table 5: The FimH and FmlH adhesin programs are contrasted.

Feature	FmlH (F9/Fml pilus)	FimH (type 1 pilus)
Niche	Inflamed bladder in chronic infection [71]	Bladder and kidney epithelium [73]
Receptor specificity	Terminal Gal and GalNAc; Thomsen–Friedenreich antigen [72]	α-D-mannose-bearing glycoproteins[27]
Best potency reported	IC50 34 nM(compound 90)[5]	HAI EC>90 in the single-digit nM range [48]
Oral exposure	<1% (rat) for 90; 53% (mouse) for AM4085 [19]	Good for some analogues (5b)[48]
Lead chemistry	Ortho-biphenyl GalNAc sulfonamides [5]	Ortho-substituted biphenyl mannosides [48]

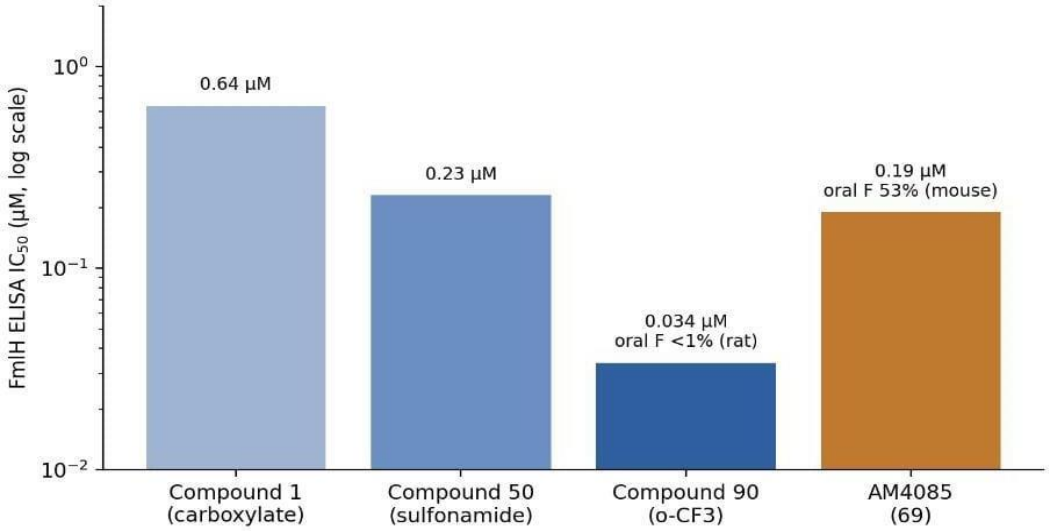


Figure 4: Progression of FmlH antagonist potency and oral bioavailability. Values from Maddirala et al. (2019, 2024.

10.3 Design and Optimization of Next-Generation Inhibitors

Several of the above lessons will likely be combined in next-generation compounds. The oral bioavailability of galactosides was enhanced by adding aryl fluorine or fluorinated alkyl groups, which reduced polar surface area and increased lipophilicity.[19] FimH antagonists with sub-nanomolar affinity have been generated through enhanced aglycone π-stacking[66], and C-linked or heterocyclic frameworks provide better stability.[49, 57] Although considerable cross-reactivity is rare due to structural differences across lectins, selectivity against human lectins is another issue that should be addressed early.[60]

10.4 FimH Inhibitors as Treatments That Spare Antibiotics

FimH antagonists are most attractive when used as antibiotic-sparing medicines, either in conjunction with shorter antibiotic courses or as a preventative measure for individuals who experience recurrent infections.[3, 47] At a time when pharmaceutical investment in traditional antibiotics has been decreasing, this aligns with larger attempts to create anti-virulence medicines.[15, 78] Clinical investigations focused on recurrence will determine whether this potential is realized.

11. CONCLSION

More than fifteen years of structure-guided medicinal chemistry has produced mannosides with nanomolar and even sub-nanomolar efficacy and reliable oral profiles.[49, 56] FimH is a well-validated target for UPEC. A consistent model of UPEC pathogenesis and mice results support the anti-virulence argument.[18, 44] Important gaps still exist, including clear proof of antibiotic synergy in suitable models, direct evidence of resistance, and most importantly, human efficacy data. Adhesin antagonists can be optimized for oral exposure, according to the parallel FmlH program[19], and the combination of several adhesin inhibitors with traditional antibiotics merits systematic testing.[3, 72]

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