

REVIEW



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Advances in antibacterial agents for *Mycobacterium fortuitum*†

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Mycobacterium fortuitum is an emerging human pathogen, characterized by an increase in prevalence and antibacterial resistance over the years, highlighting the need for the development of new drugs against this rapidly growing nontuberculous mycobacterium (NTM). To support this crusade, this review summarizes findings from the past two decades concerning compounds with antimycobacterial activity against *M. fortuitum*. It identifies the most promising and effective chemical frameworks to inspire the development of new therapeutic alternatives for infections caused by this microorganism. Most compounds effective against *M. fortuitum* are synthetic, with macozinone, featuring a 2-piperazine-benzothiazinone framework, standing out as a notable drug candidate. Among natural products, the polyphenolic polyketide clostrubin and the sansanmycin peptide analogs have shown efficacy against this NTM. Some compounds' mechanisms of action on *M. fortuitum* have been studied, including NITD-916, which acts as an enoyl-acyl carrier protein reductase inhibitor, and TBAJ-5307, which inhibits F-ATP synthase. Moreover, this review discusses the pathogenic molecular mechanisms and potential therapeutic targets within this mycobacterium.

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Introduction

Mycobacterium fortuitum, also known as *Mycolicibacterium fortuitum*,^{1,2} is a rapidly growing nontuberculous mycobacterium (NTM) associated with opportunistic infections in humans and animals.³ Considered an emerging



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human pathogen, its infections have been increasingly prevalent in recent years.^{4–6} The NTM can withstand a wide range of environmental temperatures,⁷ and its infection incidence varies by country, ranging from 1 to 40 cases per 100 000 population,⁸ with 3–30% attributable to *M. fortuitum*.^{9–12}

Commonly found in the environment, *M. fortuitum* can cause respiratory, skin, or soft tissue infections in both immunodeficient and immunocompetent individuals.^{13,14} In terms of microbial susceptibility and therapeutic regimen, infections caused by different NTM present some particularities, despite susceptibility tests being indicated.¹⁵ An official guideline for the management of pulmonary diseases related to NTM recommends an oral or parenteral regimen with drugs such as macrolides, clofazimine, linezolid, amikacin, imipenem, ceftazidime, or tigecycline to treat infections by *M. abscessus*, and macrolides, rifamycin, ethambutol, amikacin, or streptomycin for infections by the *M. avium* complex.^{16,17}

To date, there is no specific guideline for the therapy of pulmonary infections associated with *M. fortuitum*. However, susceptibility studies have shown that *M. fortuitum* clinical isolates are sensitive to amikacin, imipenem, moxifloxacin, ciprofloxacin, and doxycycline.^{18,19} *M. fortuitum* isolates may be intrinsically resistant to macrolides.^{20,21} Additionally, some cases of *M. fortuitum* resistance to quinolones^{22,23} and omadacycline²⁴ have been reported. *M. fortuitum* and *M. abscessus* are the most common NTM isolated in skin infections.²⁵ For skin and soft tissue infections caused by NTM, surgery may be necessary in conjunction with drug therapy.^{25,26} This may involve a combination of ceftazidime, imipenem, amikacin, and macrolides for *M. abscessus* skin infections or fluoroquinolones, macrolides, doxycycline, or antifolate for *M. fortuitum* skin infections.²⁷



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In addition to commercial issues,²⁸ challenges in the development of new drugs for NTM stem from the microorganism's characteristics, such as its lipid-rich outer membrane and the ability to adhere to surfaces to form biofilms.^{29,30} Additionally, the lack of animal models that accurately mimic human infection^{31–33} and the limited physiological similarities between NTM and *M. tuberculosis* restrict the applicability of drugs developed for *M. tuberculosis* to NTM.³⁴ While recent reviews have discussed molecular targets and new antimicrobial agents for *M. tuberculosis*,^{35–39} only a few have focused on NTM,^{40–42} and none exclusively on *M. fortuitum*.

Additionally, limited information is available on the biochemical pathways of *M. fortuitum* that can be used as targets for new antimycobacterial compounds.⁴³ Given the urgency of developing new treatments for NTM,⁴⁴ including *M. fortuitum*, this review aims to present information from the last two decades on compounds known for their antimicrobial activity against *M. fortuitum*, analyzing their *in vitro* activity, uncovering structural and physicochemical insights for the development of new effective agents, and discussing potential targets involved in the pathogenicity molecular mechanism of this microorganism.

In vitro activity against *M. fortuitum*

The *in vitro* evaluation of antimicrobial activity is a critical step in the early phases of drug discovery. It provides quick, reproducible, and cost-effective data on how a chemical structure affects biological activity.^{45,46} Though it has some limitations,⁴⁷ it serves as a benchmark to determine if a chemical entity will succeed in the drug development process.

Drugs aimed at treating *M. fortuitum* infections show low micromolar values in *in vitro* tests (Table 1), consistent with other anti-infective drugs.⁴⁸ This micromolar range activity can serve as a criterion during the drug development process. In this study, we applied these parameters to identify promising compounds from a range of diverse compounds already tested against *M. fortuitum*. For clarity, we have divided them into compounds derived from natural sources and synthetic ones. The graphs illustrating the relationship

Table 1 Antimicrobial drug activity for *M. fortuitum*^{49–52}

Drug	Class	MIC ^{Strain} [μM]
Amikacin	Aminoglycoside	MIC ^{ATCC6841} = 3.41
		MIC ^{ATCC49404} = 5.33
Moxifloxacin	Quinolone	MIC ^{ATCC6841} = 0.15
Clarithromycin	Macrolide	MIC ^{ATCC6841} = 1.34
Doxycycline	Tetracycline	MIC ^{ATCC6841} = 0.56
Imipenem	Carbapenem	MIC ^{ATCC6841} = 13.36
Sulfamethoxazole	Sulfonamide	MIC ^{ATCC6841} = 126.3
Linezolid	Oxazolidinone	MIC ^{ATCC6841} = 23.71
Clofazimine	Riminophenazine	MIC ^{ATCC6841} = 4.22

MIC = minimum inhibitory concentration as the lowest concentration at which no bacterial growth was observed.

between biological activity and physicochemical properties are presented in the ESI.†

Natural products related compounds

Natural products showing promising activity against *M. fortuitum* cover a wide range of classes, including fatty acids, alkaloids, steroids, terpenes, phenolic derivatives, peptides, and polyamides. The minimum inhibitory concentrations (MIC) of fatty acids evaluated against *M. fortuitum* range from 14.26 μM to 2 mM.^{53–56} The activity of these natural products is influenced by their degree of unsaturation (Fig. 1), as evidenced by linolenic acid being two to four times more active than oleic acid.^{53,54} A reduction in chain length from eighteen to sixteen carbon atoms, as well as the absence of unsaturation (palmitic acid), significantly decreases the activity.⁵³ The position of unsaturation also plays a crucial role in antimicrobial efficacy, as demonstrated by the lower activity of 3(ζ)-hydroxy-octadeca-4(*E*),6(*Z*)-dienoic acid compared to linoleic acid. Moreover, the introduction of a hydroxyl group at C3 has been shown to be unfavorable.^{55,56}

Fatty acid derivatives have been explored as well, such as 3-(*S*)-faltarinol, a derivative of oleic acid.⁵⁷ The MIC of 3-(*S*)-faltarinol was approximately threefold lower than that of its precursor,⁵⁸ highlighting the critical role of unsaturation in the antimycobacterial activity of fatty acids and related compounds. The enantiomer, 3-(*R*)-faltarinol, exhibited a similar MIC value of 16.4 μM ,⁵⁹ indicating comparable activity. However, the dihydroxylated derivative, 3-(*R*),8-(*S*)-faltarindiol, was shown to be less active, suggesting that the addition of a hydroxyl group at C8 is detrimental to its activity.⁵⁹ The stearic acid derivative, harmonine,⁶⁰ also displayed comparable activity to that of oleic acid,⁶¹ which has a single unsaturation.

Interestingly, the FabI enzyme (enoyl-acyl carrier protein reductase), critical in fatty acid biosynthesis in bacteria, has been identified as a molecular target for linoleic acid and other unsaturated fatty acids in *Staphylococcus aureus* and *Escherichia coli*.⁶² This enzyme is also a target of isoniazid in *Mycobacterium tuberculosis*.⁶³

A similar relationship between unsaturation and anti-*M. fortuitum* activity is observed in some natural 2-alkylquinolones (Fig. 2).⁶⁴ Various alkyl chains have been

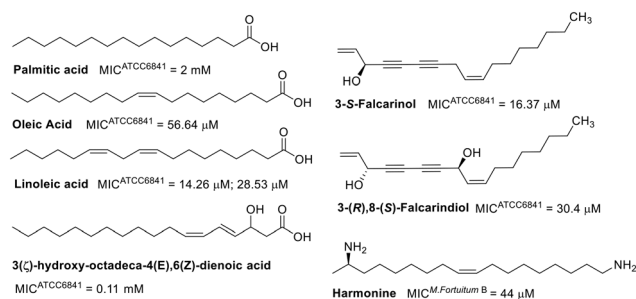
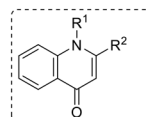
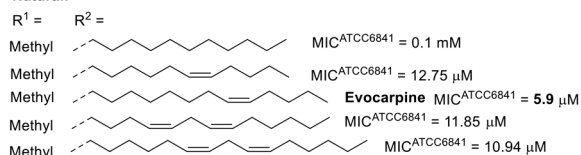


Fig. 1 Fatty acid-related compounds.



Natural:



Synthetic



Fig. 2 2-Alkylquinolones related to fatty acid.

examined, with the alkaloid evocarpine (a biosynthetic derivative of myristoleic acid) displaying the best activity in this group, featuring a thirteen-carbon chain and a single unsaturation at the substituent at position 2. Either reducing the length of the alkyl chain or introducing a second unsaturation diminished the activity by approximately half. Furthermore, the absence of unsaturation led to a substantial reduction in activity.⁶⁴ Synthetic 2-alkylquinolones with unsaturated chains showed encouraging results, with some being more active than evocarpine.^{65–67} Compounds with double bonds conjugated to the quinolone ring were particularly promising, with their activity appearing to depend more on the substituent at position 1 than on the size of the alkyl chain at position 2. Smaller alkyl chains (containing up to four carbons) at position 1 generally led to more active derivatives.^{65–67}

Alkylquinolones have been identified as inhibitors of MurE ligase (UDP-*N*-acetylmuramoylalanyl-D-glutamate-2,6-diaminopimelate ligase) in *M. tuberculosis*.⁶⁵ This ATP-dependent ligase plays a crucial role in the synthesis of cell wall peptidoglycan and has emerged as a target for new antimicrobial agents.^{68,69}

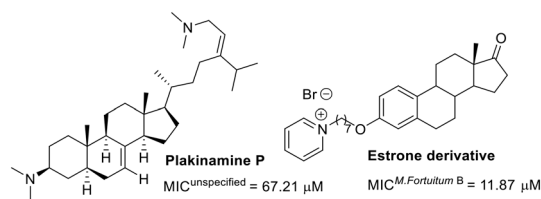


Fig. 3 Steroid-related compounds.

Regarding steroid-related compounds, the limited number of molecules evaluated against *M. fortuitum* suggests that this area is ripe for exploration in drug discovery (Fig. 3). Adamec and colleagues discovered estrone derivatives exhibiting noteworthy activity. The series substituted with pyridines at C3 showed similar efficacy.⁷⁰ Exploring other substitutions at C3 might optimize this hit. In another study, plakinamine P, isolated from a sponge, exhibited modest activity against *M. fortuitum*, despite its significant activity against *M. tuberculosis* (MIC = 3.81 μ M).⁷¹

An intriguing correlation was noted when assessing the activity of another class of isoprene derivatives. Lipophilicity seems critical for the anti-*M. fortuitum* activity of certain evaluated terpenoids (Fig. 4). The hydroxylated sesquiterpenes, laurinterol and nerolidol displayed comparable activities,^{72,73} as well as $\log P$ values (4.18 and 5.40, respectively).⁷⁴ Muzigadial, the most hydrophilic sesquiterpene in this group ($\log P = 1.16$),⁷⁴ was less active.⁵⁴ Longifolene, consisting only of carbon and hydrogen atoms, is one exception; despite its high $\log P$ value (4.06),⁷⁴ it showed reduced activity.⁷⁵

The activity of a small selection of diterpenes also demonstrated this correlation. The diterpene totarol ($\log P = 5.34$)⁷⁴ was more active than ent-Kaur-16-en-19-al^{73,75} ($\log P = 4.11$)⁷⁴ and a pimarane diterpene⁷⁶ ($\log P = 3.7$).⁷⁴ Substituting a hydroxyl group for a carbonyl in a pimarane diterpene decreased its activity eightfold.⁷⁶ A triterpene from African Combretaceae ($\log P = 5.54$)⁷⁴ exhibited significant activity against *M. fortuitum*. Incorporating rhamnose into this framework negatively affected the activity,⁷⁷ emphasizing the importance of lipophilicity. Although natural products with higher lipophilicity showed better *in vitro* activity, this is unlikely to translate to *in vivo* models due to low aqueous

solubility, high metabolism, and promiscuity-related off-target toxicity.⁷⁸

Coumarins and alkaloids with isoprene units displayed notable activity, as shown in Fig. 4. Geranyl and farnesyl coumarins achieved similar MIC values.^{79,80} Ferulenol derivatives, modified at the end of the alkyl chain (with hydroxyl, benzoyloxy, or acetyl groups), were less effective than the hit compound.⁷⁹

SQ-109, a diamine with a geranyl group, showed a MIC of 3.02 μ M against *M. fortuitum*,⁸¹ comparable to that of amikacin (refer to Table 1), and is under investigation in clinical trials for tuberculosis treatment.^{82–84} In *M. tuberculosis*, this compound targets MmpL3 (mycobacterial membrane protein large 3), a crucial protein for transporting cell wall components.^{85,86} Furthermore, SQ-109 has recently been reported to exhibit immunomodulatory properties.⁸⁷

Phenols represent another significant class of natural products with antibacterial activity.^{88,89} Despite the phenolic compounds' issues of low bioavailability due to high metabolism,^{90,91} a diverse collection has been evaluated against *M. fortuitum*, as indicated in Fig. 5.

Among the neolignans, licarin A exhibits superior activity, with MICs against clinical isolates comparable to those of linezolid (Table 1). However, against the standard strain ATCC 6841, licarin A demonstrated poor activity. Enhancing the lipophilicity of derivatives from the licarin

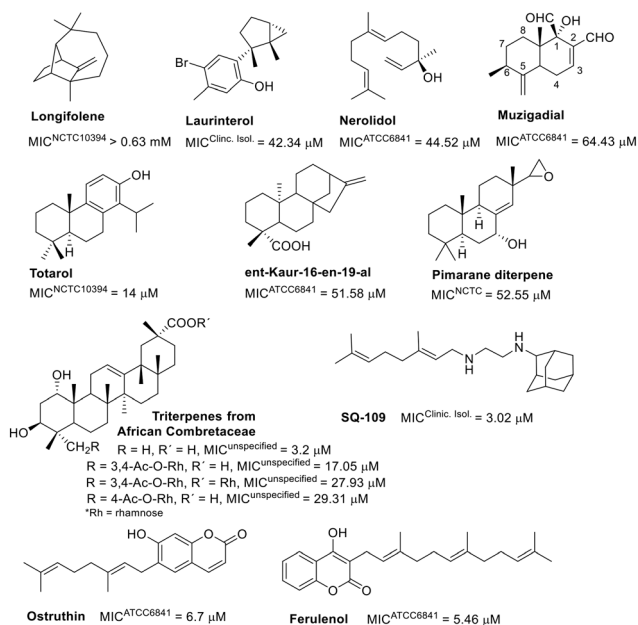


Fig. 4 Terpenoid-related compounds.

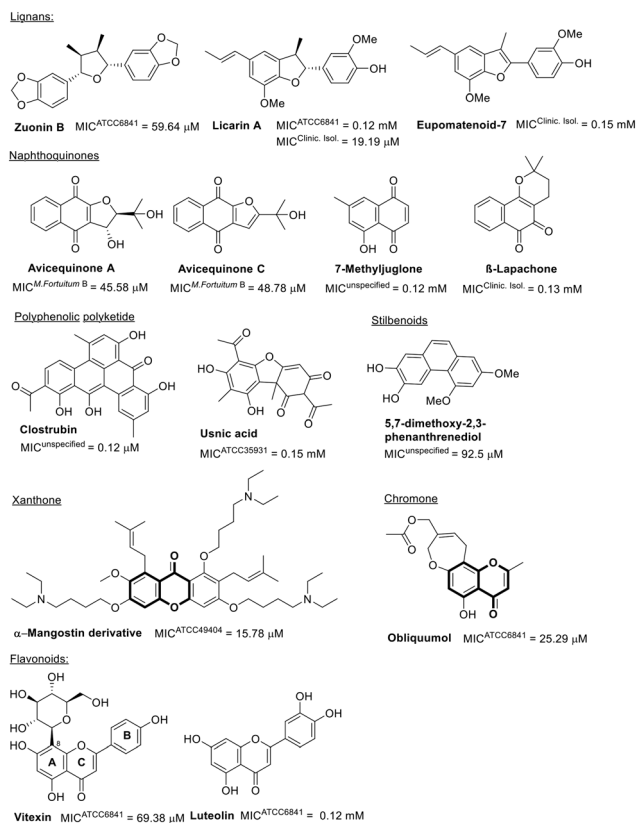


Fig. 5 Phenolic compounds.

A hydroxyl group can potentially improve its antimicrobial efficacy (ESI⁺).⁹² Saturation in the furan moiety within the central core of this natural product is crucial for activity, as illustrated by eupomatenoid-7, which has an unsaturated benzofuran, exhibiting even weaker antimicrobial effects.⁹³ Beyond this class of natural products, the lignan zuorin B also modestly impacts *M. fortuitum* growth.⁷³

Another group of phenolic compounds evaluated biologically against *M. fortuitum* is the naphthoquinones, all of which displayed modest to weak activity. Notably, the furonaphthoquinones found in the twigs of *Avicennia marina*, avicequinone A and C, differ from neolignans in that saturation of the furan moiety is not essential for antimicrobial activity (Fig. 5).^{94–96}

The natural polyketides, considered among the most significant microbial metabolites in human antibiotic medicines (e.g., erythromycin and doxycycline), are noteworthy.⁹⁷ Clostrubin, a polyphenolic polyketide antibiotic featuring a unique benzo[*a*]tetraphene scaffold, has shown excellent antimicrobial activity against *M. fortuitum* (Fig. 5).⁹⁸

Other polyphenolic natural products, including usnic acid⁹⁹ and compounds with stilbenoid or flavonoid scaffolds, have demonstrated moderate to poor activity against *M. fortuitum* (Fig. 5).¹⁰⁰ Interestingly, the presence of glucopyranoside in C8 of ring A in the flavonoid vitexin seems beneficial for activity against *M. fortuitum*,¹⁰¹ a benefit not observed with the disaccharide rutinose bonded to C3 in ring C.¹⁰²

Xanthone and chromone, two other phenolic compound classes active against *M. fortuitum* that share a benzopyrone moiety, are also of interest (Fig. 5). A semisynthetic xanthone

derivative from alpha-mangostin exhibits good *in vitro* activity against *M. fortuitum* and its biofilm formation.¹⁰³ Obliquumol, a chromone isolated from *Ptaeroxylon obliquum* common in Southern Africa, is slightly less active.¹⁰⁴

Among alkaloids, polyamides, and peptide natural products, the latter two are highlighted as potent antibacterial agents against *M. fortuitum*, whereas the former shows moderate activity (Fig. 6).

Sansanmycin A, a known uridylpeptide natural product, has been used as a scaffold inspiration in developing *M. tuberculosis* translocase inhibitors. These inhibitors prevent the formation of a lipid compound, a key intermediate in mycobacterial peptidoglycan synthesis.¹⁰⁵ Recently, the same research group described new analogues of this natural uridylpeptide (Fig. 6) and identified the critical role of the appended neopentylamide moiety in the antimycobacterial activity of these compounds.¹⁰⁶ The low micromolar anti-*M. fortuitum* activity of these sansanmycin A analogues is comparable to some of the most active known drugs (Table 1).

Unlike sansanmycin A, netropsin is a non-peptidic polyamide but has also been used as a scaffold for developing analogues with effective activity against *M. fortuitum* growth (Fig. 6), possibly due to DNA minor groove binding.¹⁰⁷ For these polyamide compounds, replacing the methyl-piperazine with a morpholine ring results in inactive compounds (MIC > 77.7 μM).¹⁰⁷

Alkaloids, as a class, do not appear to be effective antibiotics against *M. fortuitum* (Fig. 6). The indole alkaloids canthin-6-one and cryptolepine exhibited weak anti-*M. fortuitum* activity.^{56,108} Not significantly different, halicyclamine A, a marine sponge alkaloid, was the most potent among them against *M. fortuitum* (Fig. 6).¹⁰⁹ Although alkaloids alone seem ineffective against *M. fortuitum*, evidence suggests that their combination with known antibiotics can potentiate anti-mycobacterial activity.¹¹⁰

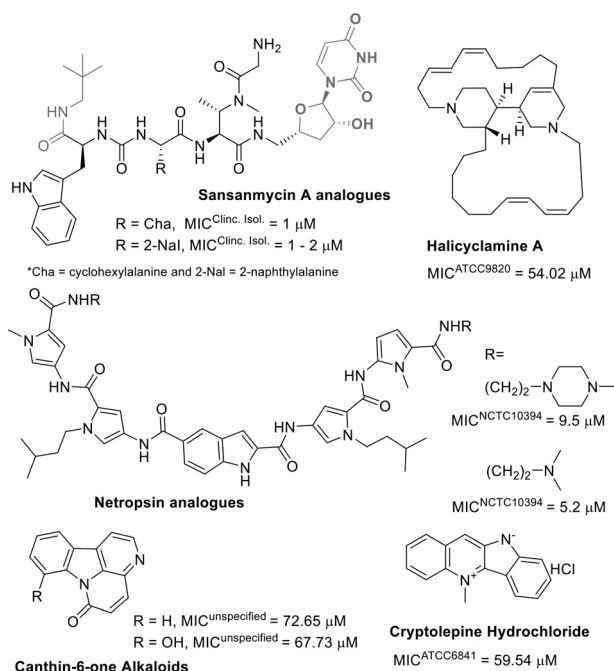


Fig. 6 Alkaloids and peptides/polyamides.

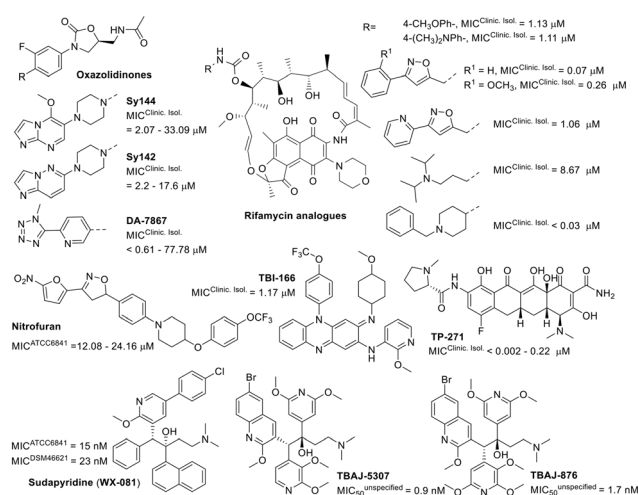


Fig. 7 Various compounds related to anti-infective drugs.

Synthetic compounds

The development of new drugs often employs the “me-too” strategy to produce what are known as “follow-on drugs”. This approach leverages the structure of existing drugs, implementing modifications to enhance activity and/or aspects related to absorption, distribution, metabolism, excretion, and toxicity (ADMET).^{111,112} This strategy has been used to develop new antimycobacterial agents, evaluating compounds related to known anti-infective medications against *M. fortuitum* (Fig. 7). One example is DA-7867, an oxazolidinone derivative with a tetrazole moiety, demonstrating greater activity than linezolid against twenty-four clinical isolates of *M. fortuitum* with MICs ranging from <0.61 to 19.45 μM .¹¹³ Oxazolidinones Sy142 and Sy144 also showed greater activity than the control drug linezolid, with MICs of 23.41–189.72 μM .¹¹⁴ These findings suggest that the isosteric substitution of a morpholine ring with a piperazine and the incorporation of fused N-heterocycles, such as imidazo[1,2-*a*]pyrimidine (Sy142) and imidazo[1,2-*b*]pyridazine (Sy144), are beneficial modifications.

The bedaquiline analogue sudapyridine (WX-081) demonstrated significant anti-*M. fortuitum* activity, comparable to the control drug, with MIC values in the nanomolar range.¹¹⁵ This compound has been the subject of clinical trials for the treatment of tuberculosis, showing advantages in safety and pharmacokinetics compared to bedaquiline.^{116,117} The other two bedaquiline analogues, TBAJ-5307 and TBAJ-876, were recently described as F-ATP synthase inhibitors. This enzyme provides the biological energy ATP and maintains ATP homeostasis under hypoxic stress conditions. These two drug candidates showed broad-spectrum anti-NTM activity with excellent *in vitro* performance against *M. fortuitum* in the low nanomolar range.¹¹⁸

Another compound displaying noteworthy activity was TP-271, a tetracycline analogue, exhibiting superior activity to doxycycline (Table 1) against *M. fortuitum*.¹¹⁹ TP-271 has undergone phase I clinical trials as a potential pneumonia treatment.¹²⁰

Rifamycin analogues featuring a substituted carbamate group at the C25 position exhibited significant activity against *M. fortuitum*, with MIC values ranging from <0.03 to 8.67 μM .¹²¹ Within this series, the compound with a 1-benzyl-4-methylpiperidinyl substituent as the carbamate

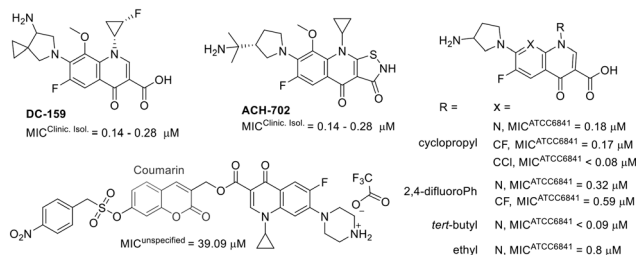


Fig. 8 Compounds related to fluoroquinolone.

group was found to be the most active. The presence of aromatic ring substituents in these derivatives appears to enhance activity, although only a single aliphatic substituent was investigated (Fig. 7).¹²¹

Other studies have investigated analogues within the nitrofurans and riminophenazine classes, which have demonstrated promising anti-*M. fortuitum* activity and efficacy in tuberculosis animal models.^{122,123}

Furthermore, studies on fluoroquinolone-related compounds against *M. fortuitum* have revealed that derivatives retaining the quinolone pharmacophore (the carboxylic acid at C3) exhibited comparable activity against *M. fortuitum* (Fig. 8).^{124–126}

Interestingly, compound ACH-702, which contains an isothiazol-3(2*H*)-one moiety fused to C2/C3, showed activity similar to that of its analogue DC-159, which incorporates the quinolone pharmacophore at C3.^{124,127} A coumarin-quinolone hybrid exhibited reduced activity, highlighting the importance of the carboxylic acid at C3.¹²⁸ This compound was designed to function as a prodrug, being activated by nitroreductases.¹²⁸ Structural modifications at positions 1, 7, and 8 were also explored. The structure-activity relationship studies indicate that bulky substituents at position 1 generally decrease activity. Furthermore, alterations at position 1 and other substituted heterocycles at position 7 appear to be tolerable.¹²⁵

In addition to compounds inspired by known drugs, a diverse range of synthetic compounds was also developed to combat *M. fortuitum* infection. These compounds, focusing on five-membered heterocycles, showed promising activity against *M. fortuitum* (Fig. 9).

Among the non-aromatic five-membered rings, tetrahydrofuran in a galactofuranose with a lipophilic sulfenamide demonstrated significant activity against *M. fortuitum*. A smaller lipophilic side chain in the structure had a detrimental effect on the antimycobacterial activity of these compounds.¹²⁹ Lipophilicity also seemed to

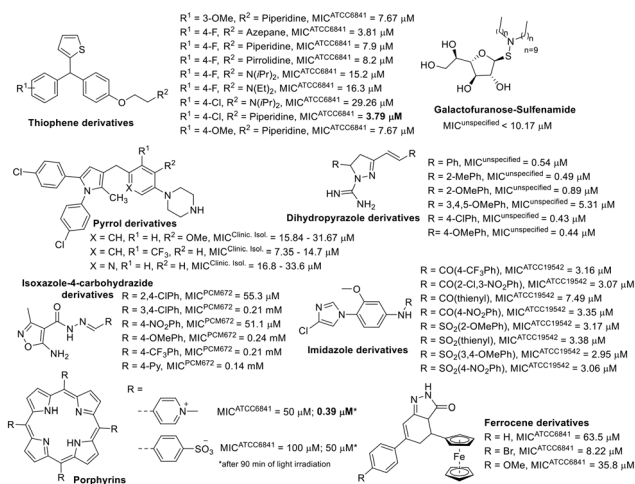


Fig. 9 Compounds focusing on five-membered heterocycles.

influence the activity of dihydropyrazole derivatives evaluated against *M. fortuitum*. Compared to the previously mentioned sugar derivative, the dihydropyrazole performed better against *M. fortuitum* (Fig. 9) despite being less lipophilic. This could be attributed to the free amidine in the structure, which is essential for anti-*M. fortuitum* activity.¹³⁰ The lipophilic balance derived from the benzene ring supports various substituents, except for the trimethoxy substitution that reduces the *clogP* of this class of compounds to less than 3, diminishing the activity tenfold (ESI[†]).

Considering compounds based on aromatic five-membered rings, isoxazole derivatives exhibited the lowest anti-*M. fortuitum* activity (Fig. 9).¹³¹ Pyrrole derivatives also showed moderate activity,¹³² except when part of the porphyrin structure was activated by irradiation.¹³³ The ferrocene derivatives did not stand out as excellent agents against *M. fortuitum*.¹³⁴

Generally, the thiophene-containing trisubstituted methane evaluated against *M. fortuitum* had good activity (Fig. 9) but was not as potent as moxifloxacin (Table 1), a drug used as a positive control.¹³⁵ However, two thiophene compounds from this set also demonstrated *in vivo* activity, clearing mice of bacilli in acute infections,¹³⁵ and one of them was the less active

thiophene derivative (Fig. 9). Regarding compounds with an imidazole ring active against *M. fortuitum*, amide derivatives did not significantly differ from sulphonamide derivatives, except for the thienyl amide, which was less active than its related sulphonamide. Nevertheless, all the imidazole derivatives in Fig. 9 showed good anti-*M. fortuitum* activity, comparable to rifampicin, another positive control drug.¹³⁶

In addition to the five-membered heterocyclic derivatives, compounds centered on 6,6-fused heterocycles also displayed excellent antimycobacterial activity (Fig. 10).

The most extensively investigated core was quinoline, where compounds with a C4 substitution by triazole exhibited only modest anti-*M. fortuitum* activity.¹³⁷ Compounds featuring a carbohydrazone moiety at C2 and an amino-phenyl-thio butanamide at C3 achieved low micromolar range activity against *M. fortuitum* (Fig. 10).¹³⁸ Quinoxaline derivatives were also evaluated for their anti-*M. fortuitum* activity, with di-*N*-oxide quinoxalines that have smaller esters at C7 showing more conducive activity (Fig. 10).^{139,140}

Benzothiazinone represents another 6,6-fused heterocycle used in antimycobacterial agents, notable in the drug candidate macozinone, which is undergoing clinical trials for *M. tuberculosis*.¹⁴¹ It has demonstrated excellent *in vitro*¹⁴² and *in vivo*¹⁴³ activity against *M. fortuitum* (Fig. 10). The mechanism of action of macozinone against *M. tuberculosis* involves the inhibition of decaprenyl-phosphoryl-ribose 2'-epimerase (DprE1), a critical enzyme in the biosynthesis of vital cell wall polysaccharides.¹⁴⁴

Interestingly, simple frameworks have also shown low micromolar MICs for *M. fortuitum*, including benzylamide, dihydrotriazolopyrimidine, and thiocarbamate derivatives (Fig. 10).^{145–147} However, a diverse set of compounds exhibited moderate to poor activity against *M. fortuitum*, among them benzothiophene SK-03-92, bis-benzimidazole, keto ester, thioxindolinones, and thiocyanate derivatives.^{148–153}

Compounds featuring tricyclic fused-ring system cores were identified among those with low micromolar MICs for *M. fortuitum*. Diphenyleneiodonium chloride (DPIC, Fig. 10), discovered during an *in vitro* screening of the LOPAC®¹²⁸⁰ small molecule library, showed potential *in vivo* activity comparable to the amikacin control.¹⁵⁴ Another notable compound, the triazaacenaphthylene antibiotic gepotidacin, which, (Fig. 10) by inhibiting DNA replication through topoisomerase inhibition,¹⁵⁵ showed a significant reduction in the bacterial load in various organs at a concentration ten times lower than that of amikacin.^{156,157}

Lastly, the enoyl-ACP reductase (InhA) inhibitor,¹⁵⁸ NITD-916 (Fig. 10), with a low micromolar MIC against *M. fortuitum*, demonstrated anti-*M. fortuitum* activity in a macrophage model and was highly effective in protecting infected zebrafish larvae during short-duration treatments.¹⁵⁹

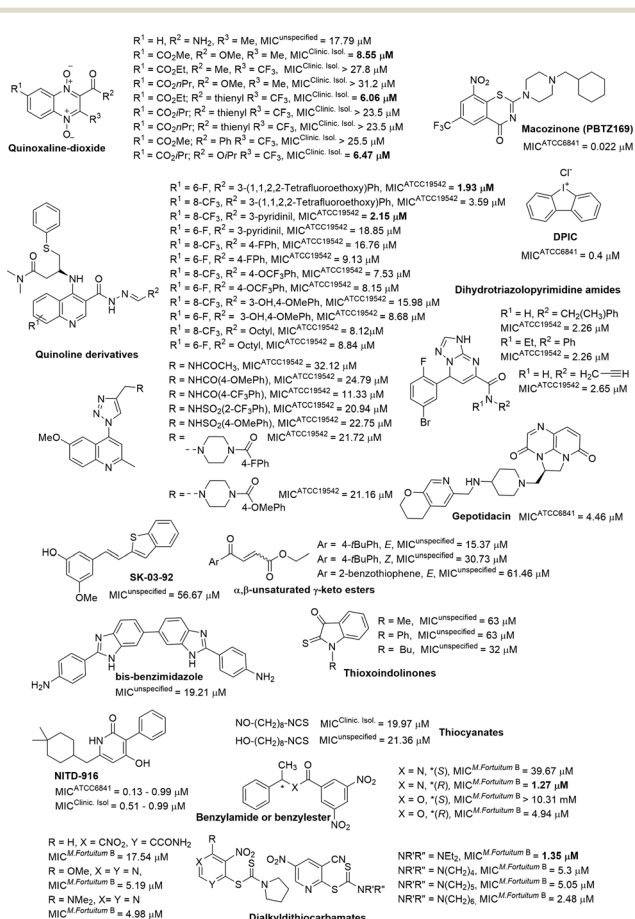


Fig. 10 Miscellaneous compounds.

Pathogenic molecular mechanism and potential therapeutic targets

Although a recent study explored the proteomics for *M. fortuitum*,⁴³ structural biological data for *M. fortuitum* remain scarce. To date, the Protein Data Bank (PDB) repository contains only seven 3D structures related to *M. fortuitum*, of which two (PDB: 5K21 and 7PDA) are enzymes involved in the biotransformation of phenazine-related compounds.¹⁶⁰ Most of the remaining structures have not been described in publications.

Mycobacterium species have lipid mycolic acids that play essential roles in physiology and virulence.¹⁶¹ In this context, enoyl-acyl carrier protein reductase InhA is a crucial enzyme for fatty acid synthesis; its inhibition halts mycolic acid biosynthesis. As previously mentioned, NITD-916 directly inhibits the InhA of *M. fortuitum*, and the chemical interactions with the target are elucidated in the resolved crystal structures available (PDB: 7U0O and 7K73), where the pyridone central core is responsible for three hydrogen bonds while the cyclohexyl occupies a hydrophobic pocket.¹⁵⁹

Other type II fatty acid components have been evaluated in knockdown studies for *M. fortuitum*. While the 3-hydroxyacyl-ACP dehydratase (HadC) is not essential for the survival and growth of *M. fortuitum*,¹⁶² the fabG4 gene is crucial for maintaining cell envelope physiology and is required for the formation of the *M. fortuitum* pellicle and biofilm.¹⁶³

While much basic mycobacterial research has focused on lipid composition, carbohydrate features are underexplored in drug discovery, with only two enzymes having 3D information available: glycosyl hydrolase (PDB: 4W65) and shikimate 5-dehydrogenase (PDB: 4XIJ). Glycoside hydrolases are important for the persistence, virulence, and general biology of these microorganisms and are promising drug targets.¹⁶⁴ Similarly, the shikimate pathway, absent in humans but essential for mycobacteria, is an attractive target for developing new selective antimycobacterial drugs.¹⁶⁵

Like other microorganisms, *M. fortuitum* has shown drug resistance, and the cleavage of β -lactam antibiotics is one of the mechanisms. In mycobacteria, β -lactam resistance is primarily due to the production of class-A β -lactamase,¹⁶⁶ which has been described in *M. fortuitum* (PDB: 2CC1) with structural features that confer more efficient cephalosporinase activity.¹⁶⁷ The rRNA methylase gene is another mechanism of resistance against macrolides in *M. fortuitum*.²⁰ Resistance to isoniazid is related to two unrelated catalase-peroxidases (KatGI and KatGII) in *M. fortuitum*.¹⁶⁸

Few studies discuss the pathogenic mechanisms of *M. fortuitum*. One mechanism is the ability of *M. fortuitum* to produce porins to facilitate nutrient uptake through the mycobacterial cell wall, which also increases the colony size of this microorganism.¹⁶⁹ Understanding these pathogenic mechanisms is crucial, as is recognizing those not involved in this process. For example, extracellular DNA (eDNA), an

essential component of biofilm formation, is scarcely present in the rapidly growing mycobacteria *M. fortuitum*.¹⁷⁰

Conclusions

This review summarizes the major findings of the last two decades on active compounds against *Mycobacterium fortuitum*. During this period, around two hundred compounds have shown some level of anti-*M. fortuitum* activity, with a quarter originating from natural sources and the majority from synthetic origins. Among natural products, the polyphenolic polyketide clostrubin and the sansanmycin peptide analogs have emerged as the most promising and effective against *M. fortuitum*. However, more potent compounds were identified in the synthetic category.

In only a few cases there were enough data to establish a structure–activity relationship, and even fewer compounds were also tested *in vivo*. Notably, analogs of antibiotics approved for other uses demonstrated significant activity against this microorganism. The drug candidates macozinone, gepotidacin, TBAJ-5307, and NIT-916 deserve special mention for their outstanding *in vitro* and/or *in vivo* anti-*M. fortuitum* activity. It is important to note that no strict correlation exists between the *in vitro* anti-*M. fortuitum* activity and the physicochemical properties of the evaluated compounds (ESI†).

For most active compounds discussed, there is a lack of information on their mechanism of action on *M. fortuitum*. Moreover, only recently studies begun to identify potential *M. fortuitum* targets, which are primarily associated with mycobacterial lipid composition, although carbohydrate-related targets are also being recognized as potentially significant. Despite our promising findings, much remains to be done to develop a new drug. A consideration will be whether a new agent has sufficiently broad NTM spectrum coverage to increase patient recruitment in future clinical trials and help attract pharmaceutical companies' interest.

Data availability

No primary research results, software or code have been included as part of this review. Furthermore, any data supporting this article have been included as part of the ESI.†

Author contributions

The manuscript was written through contributions of all authors and all authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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