

REVIEW

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Oxazolidinones as versatile scaffolds in medicinal chemistry

Guilherme Felipe Santos Fernandes, ^{†*a} Cauê Benito Scarim, ^{†b}
Seong-Heun Kim, ^{ac} Jingyue Wu ^a and Daniele Castagnolo ^{*a}

Oxazolidinone is a five-member heterocyclic ring with several biological applications in medicinal chemistry. Among the three possible isomers, 2-oxazolidinone is the most investigated in drug discovery. Linezolid was pioneered as the first approved drug containing an oxazolidinone ring as the pharmacophore group. Numerous analogues have been developed since its arrival on the market in 2000. Some have succeeded in reaching the advanced stages of clinical studies. However, most oxazolidinone derivatives reported in recent decades have not reached the initial stages of drug development, despite their promising pharmacological applications in a variety of therapeutic areas, including antibacterial, antituberculosis, anticancer, anti-inflammatory, neurologic, and metabolic diseases, among other areas. Therefore, this review article aims to compile the efforts of medicinal chemists who have explored this scaffold over the past decades and highlight the potential of the class for medicinal chemistry.

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Introduction

Oxazolidinones are a class of five-membered heterocyclic compounds containing both nitrogen and an oxygen atom in their structure and find broad application in organic and medicinal chemistry. Oxazolidinones can exist as different structural isomers depending on the reciprocal position of oxygen and nitrogen atoms in the five-membered ring. Consequently, different nomenclatures are used to represent the different isomers, namely 2-, 3-, and 4-oxazolidinone. Oxazolidinones constitute an important class in medicinal chemistry, since they can act as bioisosteres of different chemical groups, *e.g.*, carbamates, thiocarbamates, ureas, and amides. This structural similarity between oxazolidinones (especially 2-oxazolidinone) and the aforementioned groups confers on the former certain critical druglike characteristics such as the formation of hydrogen bonds with amino acid residues and a higher metabolic and chemical stability because carbamate is cyclized in a five-membered ring, unlike noncyclic carbamates, for example, that are more prone to hydrolysis.¹

The first drug that contained the oxazolidinone scaffold was furazolidone (2-oxazolidinone) (1) (Fig. 1). Furazolidone,

a synthetic nitrofur-oxazolidinone, was discovered in the 1940s as an antimicrobial agent targeting bacterial DNA.² Furazolidone was likely the initial candidate that led to the genesis of further development of the class of oxazolidinone as antibacterials.³ Later, the oxazolidinone cycloserine (3-oxazolidinone) (2) (Fig. 1), was developed and used as an antitubercular drug since 1956.⁴ Nevertheless, it was only after the discovery in the late 1980s of *N*-aryl-oxazolidinones, a new class of synthetic antibacterial agents, that oxazolidinones gained notoriety in medicinal chemistry.⁵ The first representatives of this new class of antibacterial agents were compounds (3) (Dup-105) and (4) (DuP-721) (Fig. 1), formally reported by E.I. du Pont de Nemours & Company (DuPont) at the 1987 Interscience Conference on Antimicrobial Agents and Chemotherapy.⁶ Subsequently, researchers from the Pharmacia & Upjohn company started an iterative medicinal chemistry campaign aimed at further developing novel oxazolidinones as commercially available antibiotics.⁷ Linezolid (LZD) (5) (Fig. 1), the first commercially available member of this new class of compounds, was discovered in 1996 by Pharmacia & Upjohn and approved in 2000 for clinical use by the US Food and Drug Administration (FDA) for the treatment of infectious diseases caused by Gram-positive bacteria resistant to other antibiotics.^{8,9} LNZ displays potent activity against a wide range of Gram-positive bacteria, including streptococci, vancomycin-resistant *Enterococci* (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA).⁷ Recently, LZD was included in the list of antitubercular drugs recommended by the World Health Organization (WHO) for use in long

^a Department of Chemistry, University College London, 20 Gordon Street, WC1H 0AJ, London, UK. E-mail: guilherme.fernandes@ucl.ac.uk, d.castagnolo@ucl.ac.uk^b Department of Drugs and Medicines, School of Pharmaceutical Sciences, São Paulo State University, Araraquara, 14800903, Brazil^c School of Cancer and Pharmaceutical Sciences, King's College London, 150 Stamford Street, SE1 9NH, London, UK[†] These authors contributed equally.

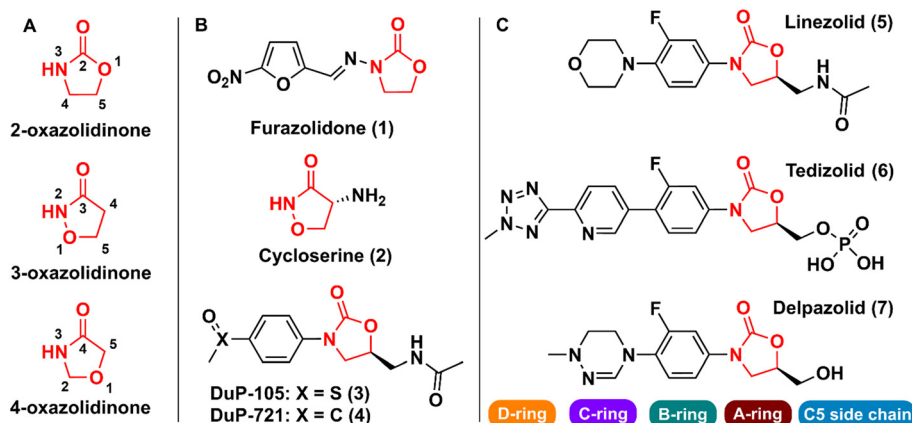


Fig. 1 A) Oxazolidinone isomers; B) first reported bioactive oxazolidinone derivatives reported; C) drugs containing the oxazolidinone scaffold.

multidrug-resistant tuberculosis (MDR-TB) treatment regimens.¹⁰ The mechanism of action of LZD involves binding to the 50S subunit of the bacterial ribosome, more specifically, at the A site of the peptidyl transferase active centre, thus preventing the interface with the 30S subunit, and consequently the formation of the 70S initiation complex, ultimately leading to the inhibition of bacterial protein synthesis.^{11–14} In 2014, the FDA approved the second-generation representative of the oxazolidinone class, namely tedizolid (6) (Fig. 1), for the treatment of acute bacterial skin and skin structure infections caused by certain susceptible bacteria, including *Staphylococcus aureus*, several *Streptococcus* species, and *Enterococcus faecalis*.¹⁵

Shortly after LZD approval, drug-resistant strains began to appear. This phenomenon led to the research of a new generation of oxazolidinones.¹⁶ Various analogues were developed, and some were able to reach clinical studies, including posizolid, ranbezolid, radezolid, and cadazolid, just to name a few. Currently, three new derivatives of oxazolidinones are undergoing clinical trials for the treatment of drug-resistant tuberculosis (TB), namely delpazolid (7) (Fig. 1), sutezolid, and TBI-223.¹⁷ The structural difference between these drug candidates and LZD is mainly in the C- and D-rings (Fig. 1).

During last decades, multiple studies have highlighted the potential of oxazolidinones to exert multifaceted biological activities. The majority of the studies reported in the literature concern oxazolidinones designed as antibacterial and/or antimycobacterial agents. Several reviews have already been published addressing these derivatives.^{18–20} Nevertheless, there is a lack of reviews covering the oxazolidinones developed for application in other therapeutic areas and, to the best of our knowledge, no review article to date has fully covered these compounds. Therefore, this review will address the oxazolidinone-based derivatives reported since 2011 and discovered for the most diverse therapeutic applications, including antibacterial, antitubercular, anticancer, anti-inflammatory, antiviral, and neurological and metabolic disorders. It should be noted that this review will cover only fully synthetic (so-called small

molecules) 2-oxazolidinone derivatives. Compounds obtained from natural sources^{21,22} are not part of the scope of this review.

Oxazolidinones as antibacterial agents

Bacteria naturally develop resistance over time as they are exposed to antibiotics, which has been observed since antibiotics were first introduced. However, the emergence and spread of antibiotic resistance have been accelerated by the overuse and misuse of antibiotics while a lack of new antibiotics is being developed.²³ The ever-increasing number of resistant bacteria is described as a crisis by many public health organizations. In 2019, it was reported that drug-resistant bacterial infections directly caused 1.27 million deaths worldwide.²⁴ The urgency of this matter was emphasized in the review on antimicrobial resistance, as it predicts 10 million deaths per year by 2050 if there is no intervention.²⁵ There is a growing concern about multidrug-resistant pathogens, *Enterococcus* spp, *S. aureus*, *K. pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp, which were termed ESKAPE, as they have been shown to cause most nosocomial infection.²⁶ Carbapenem-resistant Gram-negative bacteria, classified as critical in the pathogen prioritization report by WHO, drastically increase the cause of severe infection, which represents a global emergency worldwide.²⁷ The rise of the third-generation cephalosporin in *E. coli* and *K. pneumoniae* leaves us with limited antibiotic therapy for Gram-negative bacterial infections.²⁸ Bacterial infections, which have been susceptible to standard antibiotic regimes for decades, are now becoming resistant to all major antimicrobial treatments, undermining the efficacy of available antibiotics. This highlights the urgent need for novel therapeutic agents to tackle drug-resistant bacteria. Due to the success of LZD, oxazolidinones have been extensively investigated as antibacterials.^{18,20} In this section, we will highlight oxazolidinone-based derivatives that have



demonstrated potent and promising activity against several Gram-positive and Gram-negative bacteria.

Oxazolidinone derivatives active against Gram-positive bacteria

In 2011, Khera *et al.* described a series of 1,2,4-triazolo[4,3- α]pyrimidine oxazolidinone with potent inhibitory activity against Gram-positive bacteria.²⁹ Initially, they disclosed a series of 22 derivatives and found compound **8** (Fig. 2) to be the most promising with minimum inhibitory concentration (MIC) values of 1.0 $\mu\text{g mL}^{-1}$ against *E. faecalis* ATCC 29212 and *S. aureus* ATCC 25923 and 0.5 $\mu\text{g mL}^{-1}$ against *S. aureus* MRSA 43300 and *S. epidermidis* ATCC 12228. Compound **8** also showed metabolic stability in the human liver microsome. Subsequently, the same authors reported a second series of related analogues in which an additional aromatic ring (C-ring) was inserted into the 1,2,4-triazolo[4,3- α]pyrimidine and the 3-fluorophenyl oxazolidinone subunit.³⁰ Several aromatic rings were assessed, including 2-fluorophenyl, pyridine, phenyl, methoxy phenyl, and thiophene. Compound **9** (Fig. 2) containing the 2,4-disubstituted thiophene system was shown to be highly potent against Gram-positive strains with MIC values below 0.125 $\mu\text{g mL}^{-1}$. Furthermore, analogues containing 2-fluorophenyl (**10**), and the pyridyl group (**11**) (Fig. 2) also displayed remarkable activity with MIC values below 0.5 $\mu\text{g mL}^{-1}$.³⁰ Compound **12** (RBx 11760) (Fig. 2) is another biaryl oxazolidinone developed against *Clostridium difficile* with potent *in vivo* activity.³¹ *In vitro* evaluation demonstrated MIC₉₀ below 1.0 mg L⁻¹ (range 0.25–1.0 mg L⁻¹) against *C. difficile* ATCC 43255, *C. difficile* ATCC 43596, *C. difficile* NCTC

11223, *C. difficile* NAP1/027/BI type strain 2009155 and clinical isolates from 2004118, and *C. difficile* (45 strains). Further studies revealed that compound **12** exhibited concentration-dependent bactericidal activity and reduced *de novo* toxin production, as well as sporulation in several isolates of *C. difficile*. *In vivo* studies using a hamster model of *C. difficile* gastrointestinal infection demonstrated that compound **12** (at a dose of 50 mg kg⁻¹) led to the survival of 100% of treated animals, while the positive control group treated with metronidazole and vancomycin resulted in 0 and 50%, respectively. Similarly to LZD, compound **12** was also found to be a potent protein synthesis inhibitor.³¹

LegoChem Biosciences, Inc. (Daejeon, South Korea) has developed several oxazolidinone derivatives as antibacterial agents in the last decade.^{32–35} For example, compound **13** (LCB01-0062) (Fig. 2) showed *in vitro* activity against clinical isolates of Gram-positive bacteria compared to several antibacterial drugs, including linezolid, erythromycin, ciprofloxacin, and vancomycin. In a massive effort, compound **13** was evaluated against 400 clinical isolates of Gram-positive bacteria obtained from general hospitals in South Korea. Compound **13** displayed MIC₉₀ values below 0.5 mg L⁻¹ against all strains tested with bacteriostatic activity similar to that of linezolid. Furthermore, *in vivo* studies in a mouse model of infection caused by *S. aureus* Giorgio (methicillin-susceptible) showed that compound **13** was more active than linezolid.³⁵ Compound **14** (LCB 01-0648) (Fig. 2) is another representative that was developed after a lead optimization campaign on delpazolid (**7**) (LCB01-0371).³³ The medicinal chemistry effort aimed to increase the activity against linezolid-resistant strains by modifying the C-5 side chain and the C-ring by adding a pyridinyl ring attached to a

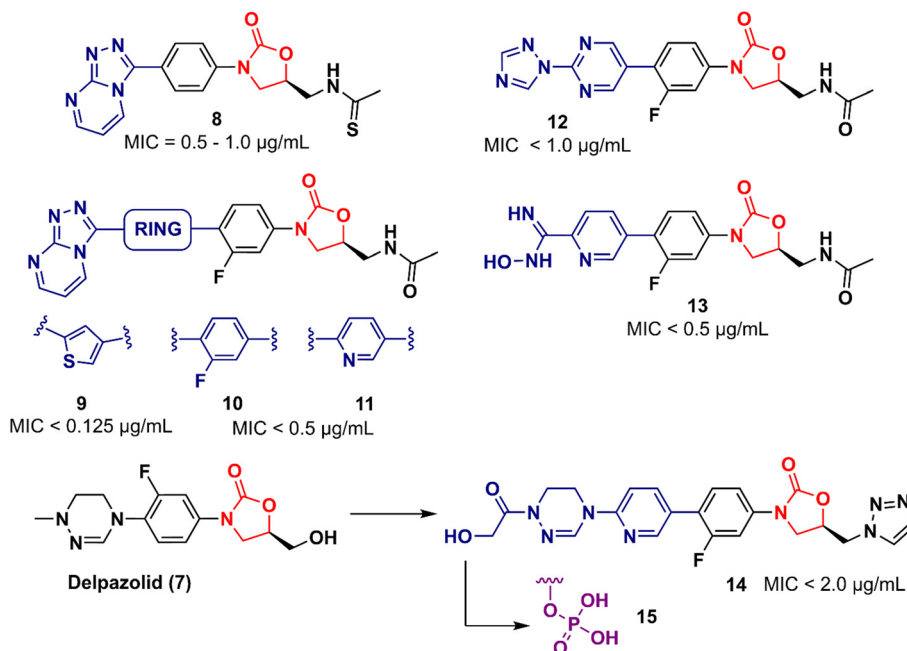


Fig. 2 Oxazolidinones as antibacterial agents.



cyclic amidrazone subunit on the D-ring. Compound **14** displayed MIC values below $2.0 \mu\text{g mL}^{-1}$ against *S. aureus*, *S. aureus* MR, *E. faecalis* linezolid resistant and *E. faecium* linezolid resistant. Although this compound was not the most potent in the series, it was selected for further evaluation because it had the best safety profile in the inhibition and myelotoxicity of monoamine oxidase (MAO). Further *in vitro* studies exhibited MIC₉₀ values below $0.5 \mu\text{g mL}^{-1}$ against 184 clinical isolates of *Enterococci*, highlighting its potential against multidrug-resistant (MDR) Gram-positive cocci.³³ Further development of compound **14** led to its prodrug, compound **15** (Fig. 2).³² Pharmacokinetic (PK) studies in a rat model demonstrated that most of compound **15** was converted to the parent compound **14**. The AUC_{last} (area under the concentration–time curve from time zero to the last sampling time) of compound **15** was found to be 5.08 mg h L^{-1} whilst the AUC_{last} of compound **14** was 85.0 mg h L^{-1} . Compound **15** was more potent than linezolid in both a mouse model with systemic infection and a soft tissue infection model against *S. aureus* Giorgio and *S. aureus* P125 (methicillin-resistant), respectively. Furthermore, it did not show any change in reticulocyte count, suggesting that it was not associated with myelosuppression.³²

Tricyclic oxazolidinone derivatives have also been reported to be promising scaffolds for the development of antibacterial agents. Yang's group has published several analogues containing this nucleus.^{36–39} For instance, benzoxazinyl-oxazolidinone **16** (Fig. 3) was discovered after an extensive medicinal chemistry campaign as a highly potent antibacterial 3 to 4 times more active than linezolid *in vivo*.³⁸ Compound **16** displayed MIC values below $0.5 \mu\text{g mL}^{-1}$ against a large panel of Gram-positive bacteria, including *Staphylococcus aureus* ATCC 29213, MRSA, methicillin-resistant *Staphylococcus epidermidis* (MRSE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and *Enterococcus faecalis*. In addition, it also showed potent activity against a panel of linezolid-resistant bacteria with MIC values ranging from 0.125 to $2.0 \mu\text{g mL}^{-1}$. Compound **16** was also evaluated in a mouse systemic infection model and exhibited an efficacy of 4 times (ED₅₀: 2.5 mg kg^{-1}) and 3-times (ED₅₀: $<5.0 \text{ mg kg}^{-1}$) superior to LZD against *S.*

aureus and MRSA, respectively. PK studies demonstrated a favourable profile for compound **16** for oral and intravenous administration.³⁸

However, compound **16** showed poor solubility that limited its development in an intravenous formulation. Therefore, a lead optimization strategy was carried out to avoid the issue. Three approaches were used for this purpose: the incorporation of polar groups, the disruption of molecular planarity, and the prodrug strategy. Prodrug **17** (YG-056SP) (Fig. 3) emerged as the most promising derivative with improved water solubility ($>22\,000$ -fold greater than compound **16**), good PK profile, and superior *in vivo* activity than linezolid. The ED₅₀ of compound **17** was 5.0 mg kg^{-1} (2-times higher than that of linezolid). Additionally, it showed a significant reduction in hERG inhibition compared to compound **16** (IC₅₀ $> 40 \mu\text{M}$ for the bioactive parent).³⁹ Compounds **18** and **19** (Fig. 3) were later reported as a continuing effort to identify new lead derivatives.^{40,41} The drug design behind these two analogues relied on modification of the C-5 side chain (**18**) and isosteric substitution of previously benzoxazinyl-oxazolidinone with benzothiazinyl-oxazolidinone (**19**). Oxazolidinone **18** exhibited an increase in activity against a panel of resistant and susceptible Gram-positive bacteria compared to LZD. The MIC values against MRSA (six strains), MRSE (five strains), and PRSP (four strains) ranged between 0.25 and $1.0 \mu\text{g mL}^{-1}$.⁴⁰ Benzothiazinyl-oxazolidinone **19**, however, showed a decrease in antibacterial activity (compared to LZD) with MIC values ranging from 2.0 to $4.0 \mu\text{g mL}^{-1}$ against the panel. Interestingly, the substitution of oxygen on the tricyclic ring was also evaluated with different groups, including NH, N-Boc, S=O, and SO₂, and all cases led to a significant loss of antibacterial activity highlighting the importance of the oxygen atom at this position.⁴¹

Gong *et al.* reported in 2013 a carrier-free nano-assemble of an oxazolidinone derivative with promising antibacterial activity.⁴² The authors aimed to develop an analogue and manipulate it into nano-assembles using a self-assembly method without using any carrier to improve the water solubility of the compound. Compound **20** (Fig. 4) showed MIC values between 0.5 and $1.0 \mu\text{g mL}^{-1}$ against a panel of



Fig. 3 Tricyclic oxazolidinone derivatives with activity against Gram-positive bacteria.





Fig. 4 Linezolid derivatives with modification in the C-ring.

MSSA and MRSA. Furthermore, *in vitro*, and *in vivo* toxicity studies showed that the compound was not toxic to HEK293 and L02 cells ($\text{IC}_{20} > 25$ and $50 \mu\text{M}$, respectively) and did not show signs of toxicity in mice. *In vivo* efficacy studies of compound 20 in MSSA and MRSA, systemic infection mouse models demonstrated efficacy greater than 3-times and 2-times greater than LZD against MSSA or MRSA, respectively.⁴² Moreover, compound 20 displayed efficacy in inhibiting biofilm formation *in vitro* and *in vivo*. It reduced the biofilm mass of MSSA (ATCC 25923) by 50% compared to the control group. *In vivo* studies using catheter-associated infection in a murine model showed that compound 20 removed surface bacteria more effectively than LZD.⁴³ More studies were conducted to investigate the metabolism of compound 20. Amide hydrolysis in the acetyl group of compound 20 was shown to be the main metabolic

biotransformation in phase I metabolism.⁴⁴ Subsequent studies turned compound 20 into a phosphate salt to address the solubility problem. The new phosphate salt showed MIC values ranging from 0.25 to $2.0 \mu\text{g mL}^{-1}$ against 120 clinically isolated strains. Furthermore, it did not show significant cytotoxicity in HEK293, L02, THP-1, and K462 cells ($>70 \mu\text{M}$) nor showed inhibition of the hERG K^+ channel ($>40 \mu\text{M}$). *In vivo* studies highlighted its high oral bioavailability ($F = 99.1\%$) and significantly enhanced efficacy compared to LZD.⁴⁵ In 2013, Suzuki *et al.* reported a series of oxazolidinone derivatives with modifications in the C-ring. Several analogues were identified as potent antibacterials with *in vitro* and *in vivo* activity.^{46,47} For example, compounds 21 and 22 (Fig. 4) containing an *N*-hydroxyacetyl-substituted [1,2,5]triazepane C-ring unit and a thiocarbamate C5 side chain displayed MIC values ranging from 0.063 to $4.0 \mu\text{g mL}^{-1}$ against a panel of Gram-positive bacteria. *In vivo* evaluation in a systemic mouse infection model with *S. aureus* SR3637 showed an ED_{50} of 0.94 and 0.77 mg kg^{-1} (intravenous) and 1.05 and 2.07 mg kg^{-1} (oral) for compounds 21 and 22, respectively. These results highlighted the higher efficacy of the compounds tested compared to that of LZD. Moreover, both compounds displayed a reduction in MAO-A and B inhibition compared to LZD.⁴⁶ Further optimization studies identified compounds 23 and 24 (Fig. 4) as new leads with reduced activity against MAO-A and B while maintaining a potent antibacterial effect.⁴⁷ Several other studies have pursued the idea of developing LZD analogues with modifications on the C-ring. For example, compound 25 (Fig. 4) was developed by adding an arylboronic acid moiety to the C- and D-ring sections. It showed MIC values $<0.78 \mu\text{g mL}^{-1}$ against selected Gram-positive strains and *E. coli* JW5503.⁴⁸ Compound 26 is another example with modifications to the C-ring. This compound was designed with a heterocyclic benzoxazinone ring at that position. Compound 26 showed MICs ranging from 0.03 to $1.0 \mu\text{g mL}^{-1}$ against a panel of Gram-positive and negative bacteria. This *in vitro* activity was superior to that of LZD. Additionally, it did not show significant inhibition of cytochrome P450 (CYP450) enzymes ($10 \mu\text{M}$), and showed metabolic stability in mice liver microsomes.⁴⁹ Compound 27 (Fig. 4) is another LZD analogue with modifications to the C-ring. This compound presents a silicon atom incorporated into the C-ring. According to the study, this modification led to a compound with enhanced brain exposure compared to the parental drug, which could be a therapeutic alternative for brain infections. This improvement was related to the strong bond to plasma proteins by the compound, which could be an advantage in improving the penetration of the blood-brain barrier (BBB). Furthermore, compound 27 retained potent *in vitro* antibacterial activity.⁵⁰

Several other oxazolidinone derivatives bearing modifications on the C-ring have been described as promising antibacterials. For example, Khalaj *et al.* reported a nitroimidazolyl-oxazolidinone hybrid with potent activity. The MIC values of compound 28 (Fig. 5) ranged from 0.006





Fig. 5 Oxazolidinone derivatives with antibacterial activity.

to 0.781 $\mu\text{g mL}^{-1}$ against a panel of selected strains. It did not show significant cytotoxicity activity in mouse fibroblast (NIH/3T3) cells ($\text{IC}_{50} > 200 \mu\text{g mL}^{-1}$).⁵¹ Compound **29** (Fig. 5) is another example of an LZD analogue with modifications on the C-ring. It displayed a MIC of 2.0 $\mu\text{g mL}^{-1}$ MSSA and MRSA and an ED_{50} of 2.5 mg kg^{-1} (orally, in the mouse model of septicemia). PK studies in dogs highlighted the superior profile of compound **29** over LZD.⁵² Analogues of LZD with modifications in the C5 side chain are less common in the literature. To date, only a few compounds have been reported. The reason behind this scarcity is mainly due to the mechanism of action of LZD-based derivatives that target the 50S subunit of the bacterial ribosome. Matsingos *et al.* nicely demonstrated this in an interesting study containing a series of LZD derivatives with several modifications on the C5 side chain. After an extensive medicinal chemistry campaign to synthesize and evaluate various analogues, none of the compounds obtained was identified as promising. Molecular docking studies using the 50S ribosomal subunit from *S. aureus* (PDB 6WRS) demonstrated that small modifications in the C5 side chain usually led to a considerable loss of antibacterial activity and in many cases to complete inactivity. This was observed when bulky groups were inserted into that position. Despite the not-so-promising results, this work brings valuable information about the structure–activity relationship (SAR) of LZD derivatives and contributes to the rational design of new generations of analogues.⁵³ On the other hand, some compounds bearing modifications in the C5 side chain have shown remarkable activity even against resistant strains. For example, compound **30** (Fig. 5), a cationic amphiphilic derivative of LZD, showed MIC values ranging from 2.0 to 16.0 $\mu\text{g mL}^{-1}$ against MRSA, *Klebsiella pneumoniae* carbapenemase (KPC) and New Delhi metallo- β -lactamase 1 (NDM-1) producing carbapenem-resistant *Enterobacteriaceae*

(CRE), while LZD ranged from 2.0 to $>64 \mu\text{g mL}^{-1}$. Further studies indicated that compound **30** has rapid bactericidal activity against both Gram-positive and negative bacteria and can inhibit the formation of biofilms (*S. aureus* and *E. coli* biofilms) at high concentrations (64 and 128 $\mu\text{g mL}^{-1}$). Mechanism of action studies suggested that compound **30** acts by permeabilization and depolarization of Gram-positive and Gram-negative bacterial membranes.⁵⁴

In the vast majority of cases, the oxazolidinone derivatives reported in the literature are in the early stages of drug development and frequently present only data from the initial antibacterial screening. Herein are several of these early-stage compounds that, despite their promising antibacterial activity, are still far from the most advanced stages of development due to the lack of critical studies, for example, *in vitro* ADME, *in vivo* PK, and *in vitro* and *in vivo* toxicology. Triazolymethyl oxazolidinones **31** and **32** (Fig. 6) were identified after extensive exploration of different substituents on the D-ring. These compounds showed MIC values compared to LZD in most Gram-positive strains.^{55,56}

Similarly, researchers working with Shenyang Pharmaceutical University conducted an extensive medicinal chemistry project exploring variations in C- and D-rings. Several promising analogues (**33–37**) (Fig. 7) were identified with promising activity against Gram-positive bacteria and are many times more potent than LZD.^{57–61} These compounds (**33–37**) were tested against *S. aureus*, MRSA, MSSA, Linezolid-resistant *Enterococcus faecalis* (LREF), and VRE and MICs ranged from 0.0675 to 1.0 $\mu\text{g mL}^{-1}$. Similarly, compounds **33–37** demonstrated similar MIC values against a panel of clinical isolates. Further *in vitro* cytotoxicity and ADME studies were performed on selected analogues. Compound **33** exhibited an IC_{50} of 0.82 μM (HepG2 cells), a low half-life ($t_{1/2}$ 72.85 min), a high clearance (Cl_{int} 23.86 $\text{mL min}^{-1} \text{kg}^{-1}$), and moderate metabolism in the human liver microsome.⁵⁷ Compound **34** displayed $\text{IC}_{50} > 64 \mu\text{M}$ (HepG2 cells), a long half-life (501.99 min), and a low human liver microsomal Cl_{int} (3.46 $\text{mL min}^{-1} \text{kg}^{-1}$).⁵⁹ Also, compound **35** exhibited $\text{IC}_{50} > 25 \mu\text{M}$ (HepG2 cells), improved water solubility (68 $\mu\text{g mL}^{-1}$), long half-life (409.44 min), and low Cl_{int} (4.25 $\text{mL min}^{-1} \text{kg}^{-1}$) in human liver microsome.⁵⁸

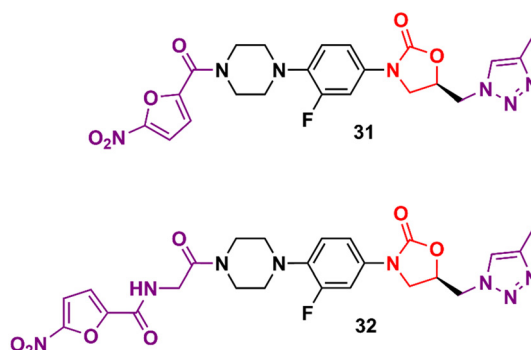


Fig. 6 Oxazolidinone as Gram-positive bacteria inhibitors.





Fig. 7 Gram-positive bacteria inhibitors.

In addition to the examples highlighted above, many other oxazolidinone-based derivatives in the early stages of drug

development have been reported in the literature in recent years (Fig. 8).^{62–66} However, despite promising initial screening, these compounds still lack several studies to advance drug development stages.

Oxazolidinone derivatives active against Gram-negative bacteria

Unlike the oxazolidinones presented in the previous section that were mainly derivatives of LZD, the oxazolidinones disclosed here display a greater structural variety in relation to their peers developed against Gram-positive bacteria. Basarab *et al.* working at AstraZeneca identified a promising oxazolidinone clinical candidate for the treatment of uncomplicated gonorrhoea with DNA Gyrase inhibitory activity.⁶⁷ Compound **43** (Zoliflodacin, ETX0914) (Fig. 9) presents in its structure an oxazolidinone linked to a benzisoxazole fused with a spiropyrimidinetrione. It showed MICs of 0.39 and 6.2 μM against *N. gonorrhoea* and *E. coli*, respectively. Furthermore, it displayed potent activity against selected Gram-positive bacteria with MIC values below 0.78 μM . Structure–activity relationships demonstrated the importance of the methyl group attached to the position 4 of the oxazolidinone for the antibacterial activity. Compound **43** showed a favourable PK profile in rats, dogs, and humans. *In vitro* genotoxic and cytotoxic studies demonstrated its safety profile. Compound **43** was shown to act by inhibiting DNA gyrase and topoisomerase IV of Gram-positive and Gram-negative bacteria.^{67,68} In 2018, compound **43** completed phase II clinical trials⁶⁹ and is currently being developed in phase III by Entasis Therapeutics in partnership with the Global Antibiotic Research and Development Partnership (GARDP). Compound **44** (Fig. 9) is another example of an



Fig. 8 Antibacterial agents containing the oxazolidinone scaffold as the pharmacophore.





Fig. 9 Oxazolidinone with activity against Gram-negative bacteria.

oxazolidinone derivative with activity against Gram-negative bacteria and is not similar to the structure of LZD.⁷⁰ This compound (**44**) was identified as a quorum-sensing inhibitor of *Pseudomonas aeruginosa* PAO1. Quorum-sensing is a system that controls biofilm formation and the release of virulence factors. In fact, *in vitro* studies showed that compound **44** inhibited the biofilm formation of *P. aeruginosa* PAO1 in a concentration-dependent manner. For instance, at 162.5 μM , it inhibited biofilm formation by 40.39%. *In vivo* studies using *Caenorhabditis elegans* N2 infected with *P. aeruginosa* demonstrated that inhibition of QS by compound **44** (165.2 μM) led to an improvement in the survival rates of *C. elegans* N₂ infected by 13.33%.⁷⁰ Oxazolidinone derivatives have also been developed as UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC) inhibitors. LpxC is a zinc metalloenzyme that plays an important role in the biosynthesis of lipid A, a glucosamine disaccharide that anchors lipopolysaccharide (LPS) to the outer membrane of Gram-negative bacteria.^{71,72} Le *et al.* working at Novartis identified by virtual screening an oxazolidinone derivative with potent LpxC inhibitory activity ($K_d = 0.065 \text{ nM}$).⁷³ Compound **45** (Fig. 9) displayed MIC values of 0.125, 0.5 and 1.0 $\mu g \text{ mL}^{-1}$ against *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *K. pneumoniae* ATCC 43816, respectively. The cocrystal structure of compound **45** complexed with the *P. aeruginosa* LpxC enzyme revealed that the oxazolidinone scaffold is critical for the activity by linking the sulfone/hydroxamic acid moiety of the inhibitor with the hydrophobic pocket while retaining a low-energy conformation. *In vivo* studies using a mouse neutropenic thigh infection model infected with *P. aeruginosa* revealed that compound **45** (160 mg kg^{-1}) reduced the bacterial burden to undetectable levels. Interestingly,

compound **45** was also shown to have a potent synergic effect *in vitro* and *in vivo* with other antibiotics.⁷³ In another article, Kurasaki *et al.* working at Kyorin Pharmaceutical,⁷⁴ discovered a similar oxazolidinone with LpxC inhibitory activity ($IC_{50} = 6 \text{ nM}$). Compound **46** (Fig. 9) has a great structural similarity to **45**. However, some differences are worth noting, such as the stereochemistry of the substituent on the C5 side chain and the presence of a fluorine atom on the phenyl ring, which was shown to play an important role in the activity by making additional interactions with C207 and C63 at the binding site. Oxazolidinone **46** showed remarkable *in vitro* activity against *E. coli* TG1, *E. coli* KAM3, and *K. pneumoniae* ATCC 13883 with MICs lower than 0.016 $\mu g \text{ mL}^{-1}$.⁷⁴ Compound **47** (Fig. 9) is another example of an LpxC inhibitor with potent antibacterial activity against Gram-negative strains. It showed MIC values ranging from 0.020 to 16.0 $\mu g \text{ mL}^{-1}$ against a panel of wild-type and clinical isolate strains.⁷⁵

Liu *et al.* reported in 2018 an interesting study on an innovative concept of an oxazolidinone-based derivative linked to a cephalosporin with an attached siderophore.⁷⁶ The design of the not-so-small molecule **48** (Fig. 10) can be divided into three parts. Initially, the siderophore moiety acts as a delivery system for antibiotics, a strategy known as the 'Trojan Horse'.^{76,77} Subsequently, cephalosporin acts as a release system for the oxazolidinone antibiotic after hydrolysis by bacterial β -lactamases. Finally, the released oxazolidinone, a Gram-positive-only drug, can reach its ribosomal target. This approach allowed the delivery of eperezolid to its target in Gram-negative bacteria. It is worth noting that eperezolid cannot cross Gram-negative outer membranes and is quickly effluxed when it does.⁷⁸





Fig. 10 The trojan horse approach: siderophore–cephalosporin–eperezolid conjugate.

Compound **48** was active against clinical isolates of *Acinetobacter baumannii* and strains producing considerable amounts of ADC-1 β -lactamase. MICs against these strains ranged from 0.4 to 6.0 μM . On the other hand, oxazolidinone and cephalosporin alone, siderophore–oxazolidinone, and siderophore–cephalosporin conjugates had no activity (MIC > 50 μM).⁷⁶

Lyons *et al.* also reported an oxazolidinone derivative not related to LZD as a potent Gram-negative antibacterial. Compound **49** (Fig. 11) was identified as a potent bacterial type II topoisomerase inhibitor (DNA gyrase and topoisomerase IV) with IC_{50} values of 0.055 and 0.01 μM against *E. coli* gyrase and topo IV, respectively. It showed MIC values ranging from 0.5 to 4.0 $\mu\text{g mL}^{-1}$ against a large panel of MDR Gram-negative clinical isolates (*A. baumannii*, *P. aeruginosa*, *E. cloacae*, *E. coli* and *K. pneumoniae*). Additional *in vivo* studies using a mouse thigh infection model of *A. baumannii* NCTC13420 (MDR) showed that compound **49** reduced the bacterial burden by >1 log CFU g^{-1} at 60 mg kg^{-1} . However, **49** did not show favourable *in vitro* DMPK

properties, displaying high clearance in both mouse and human liver microsomes (264 and 110 $\mu\text{L min}^{-1} \text{mg}^{-1}$, respectively) and demonstrated high inhibitory activity of the hERG K^+ channel ($\text{IC}_{50} = 5.0 \mu\text{M}$).⁷⁹ LZD analogues have also been reported as antibacterials with potent activity against Gram-negative pathogens. Appropriate modifications on the C-ring appear to be essential for LZD analogues to overcome the permeability barrier of the Gram-negative outer membrane whilst minimizing active efflux. Aggen *et al.* demonstrated that polar and/or charge-carrying groups seem to contribute greatly to the ability of LZD analogues to cross the outer barrier. Furthermore, the zwitterionic character and the presence of ≤ 4 rotatable bonds were also shown to be beneficial in overcoming the outer barrier.^{80,81} Nam *et al.* also identified LZD analogues bearing polar groups in their structures with activity against Gram-negative pathogens. Compound **50** (Fig. 11) showed a MIC of 0.39 $\mu\text{g mL}^{-1}$ against *Haemophilus influenzae* and a low IC_{50} (213 μM) against the hERG K^+ channel. It also showed potent activity against a panel of Gram-positive bacteria (MIC < 1.56 $\mu\text{g mL}^{-1}$).⁸² Zhuang *et al.* demonstrated the synergistic activity of a series of nitroimidazole–oxazolidinone conjugates against Gram-negative anaerobic pathogens. Specifically, two well-known drugs were used as starting points for the design of the series, namely LZD and pretomanid. For example, compound **51** (Fig. 11), an LZD–pretomanid conjugate, showed MICs ranging from 0.03 to 2.0 $\mu\text{g mL}^{-1}$ against selected clinically important anaerobic bacterial strains.⁸³

Recently, Duerfeldt *et al.* reported a library of oxazolidinone derivatives developed against ESKAPE bacteria.⁸⁴ The drug designing direction focused on increasing the accumulation of the new analogues in Gram-negative bacteria by circumventing efflux and increasing their ability to penetrate membranes. The structural modifications focused on the C-ring and a large number of compounds were synthesized and evaluated against wild-type *E. coli*, *A. baumannii*, and *P. aeruginosa*, and isogenic mutants with different grades of efficiency of the outer membrane and/or efflux pump. Three oxazolidinones, **52**, **53** and **54** (Fig. 12), were identified as potent analogues displaying potent activity against all three bacteria. It is worth mentioning that LZD did not show activity against these bacteria. These results highlight how small structural modifications can broaden



Fig. 11 Oxazolidinones as Gram-negative bacteria inhibitors.



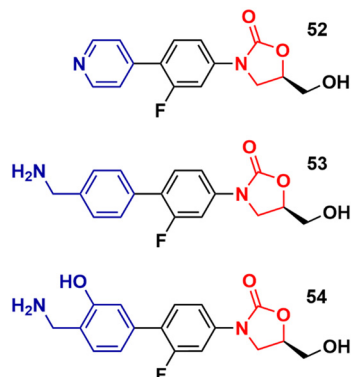


Fig. 12 Oxazolidinone analogues active against ESKAPE bacteria.

the spectrum of action of oxazolidinones against Gram-negative bacteria.⁸⁴

Oxazolidinones as antitubercular agents

Mycobacterium tuberculosis is one of the deadliest pathogens documented in the history of human civilization. TB is currently considered the second leading cause of death from an infectious disease behind only COVID-19.¹⁷ However, this position is likely to reverse as the number of deaths caused by COVID-19 decreases due to the success of immunization programs. Oxazolidinone derivatives, especially LZD analogues, have been extensively studied as anti-TB agents. Huang *et al.* recently reported several of these derivatives.^{85–87} In 2017, benzoxazinyl-oxazolidinone **55** (Fig. 13) was discovered as a potent anti-TB compound with MIC₉₀ of 0.391 µg mL⁻¹ against *M. tuberculosis* H₃₇Rv and less than 0.50 µg mL⁻¹ against drug-resistant strains. It did not show toxicity against HepG2 cells (IC₅₀ > 64 µg mL⁻¹) nor inhibitory activity against the hERG K⁺ channel (IC₅₀ > 30 µM). *In vitro* evaluation of ADME and *in vivo* PK demonstrated its favourable profile with high maximum plasma concentration (*C*_{max} = 30.0 µg mL⁻¹), long elimination half-life (*t*_{1/2} = 4.22 h), and outstanding oral bioavailability (*F* = 102%) after oral administration in Balb/c mice.⁸⁵ Subsequently, compound **55** went through a hit-to-lead optimization medicinal campaign in an attempt to identify an analogue with improved anti-TB activity, reduced toxicity, and improved drug-like properties. The campaign was

successful in identifying compound **56** (Fig. 13) as a new lead oxazolidinone. Analogue **56** displayed improved *in vitro* and *in vivo* efficacy compared to LZD and compound **52**. For instance, it showed MIC₉₀ of 0.03 µg mL⁻¹ against *M. tuberculosis* H₃₇Rv, 13 times lower than the parental compound **55**. The drugability of **56** was extensively evaluated in microsomal stability, cytotoxicity, cytochrome P450 enzyme inhibition, and *in vivo* PK. Compound **56** displayed excellent metabolic stability in liver microsomes of different species, high IC₅₀ values (>45 µM) against several isoforms of CYP450 enzymes, and a favourable PK profile in mice. A further *in vivo* evaluation of efficacy in a mouse model of acute *M. tuberculosis* infection demonstrated the potent activity of **56** (dose 100 mg kg⁻¹ per day) after reducing the bacterial lung load in 3.6 log₁₀ CFU compared to the untreated group. LZD (dose 100 mg kg⁻¹ per day) on the other hand, achieved a reduction of 1.7 log₁₀ CFU. Subsequently, a dose-response study also demonstrated the superior efficacy of compound **56** compared to LZD and sutezolid at different doses.⁸⁶ Recently, the same group reported the discovery of a new tricyclic benzo[1,3]oxazinyl-oxazolidinone **57** (Fig. 13) as a new anti-TB lead. Compound **57** displayed MIC₉₀ values of 0.40, 0.48, and 0.82 µg mL⁻¹ against *M. tuberculosis* H₃₇Rv, and two strains of MDR-TB, respectively. Interestingly, the benzo[1,3]oxazinyl-oxazolidinone derivative showed superior activity than the benzo[1,4]oxazinyl-oxazolidinone isomer. Similarly, to its predecessors, **57** exhibited excellent metabolic stability in human and mouse liver microsomes and no toxicity to Vero cells. However, it showed a lower IC₅₀ value (IC₅₀ = 17.82 µM) against the hERG K⁺ channel compared to analogues **55** and **56**. Further evaluation of the PK profile demonstrated its excellent profile with a high maximum plasma concentration (*C*_{max} = 10.2 µg mL⁻¹), appropriate elimination half-life (*t*_{1/2} = 3.76 h), and good oral bioavailability (*F* = 128%) after oral administration in Balb/c mice.⁸⁷ In summary, these results highlight the tricyclic benzo[1,3]oxazinyl-oxazolidinone as a promising moiety for the discovery of anti-TB drugs.

Several other oxazolidinone derivatives have been reported to act as anti-TB agents. However, most of these compounds have only been evaluated against the standard strain of *M. tuberculosis* H₃₇Rv. Drug discovery of new anti-TB agents is highly unfruitful, and currently, the greatest challenge lies in the identification of new active agents against resistant



Fig. 13 Tricyclic oxazolidinones as antituberculosis agents.



Table 1 Oxazolidinones with activity against *M. tuberculosis*

Cmpd	Structure	MIC ₉₀ (μM)	Ref.
58		2.2	90
59		1.8	90
60		1.3	91
61		1.2	92
62		1.3	93
63		2.8	94
64		0.9	95
65		0.2	96
66		0.6	97
67		7.3	98
68		2.6	99
69		2.6	100
70		0.9	101



Table 1 (continued)

Cmpd	Structure	MIC ₉₀ (μM)	Ref.
71		1.1	102

strains (MDR- and XDR-TB).^{88,89} Often, oxazolidinone derivatives discovered as anti-TB agents show great similarity to LZD, a drug already used in the treatment of TB. Therefore, to avoid extending this section's discussion with limited information regarding only the initial screening of these compounds, we have condensed these LZD derivatives into Table 1 with their respective MIC₉₀ values. Importantly, we converted all the MIC values from μg mL⁻¹ to μM to facilitate the comparison between the compounds.

Oxazolidinones as anti-cancer agents

Cancer is undoubtedly one of the leading causes of death in modern times and it ranks second only to cardiovascular diseases.¹⁰³ Naturally, this scenario attracts the attention of medicinal chemists from both academia and industry, who are constantly searching for new therapeutic alternatives for the treatment of the most diverse types of cancer. Oxazolidinones are one of the classes within the large chemical universe that are systematically researched for the treatment of cancer.¹⁰⁴ Although the number of oxazolidinone derivatives reported as anticancer agents are incredibly lower than that of anti-infective compounds. Mutant isocitrate dehydrogenases 1 (mIDH1) and 2 (mIDH2) have been extensively studied as promising anticancer targets since their identification.^{105,106} Briefly, wild-type IDH1

catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG), using NADP⁺ as a cofactor. Heterozygous mutations at the R132 (Arg132) position of IDH1 and R140 or R172 of IDH2 have been associated with various cancers, including low-grade glioma, glioblastoma, acute myelogenous leukaemia, and solid tumours such as chondrosarcoma, cholangiocarcinoma, colon, pancreatic, and prostate cancer.¹⁰⁷ This mutation (gain-of-function) leads to a loss of normal enzymatic function and reduces α-KG to R-2-hydroxyglutarate (2-HG), resulting in increased levels of this metabolite, which is linked to widespread alterations in histone and DNA methylation, which can contribute to tumorigenesis.^{108,109} Novartis Institutes for BioMedical Research have pioneered the development of the oxazolidinone class as mutant IDH1 inhibitors. In 2017/18, Novartis reported the discovery of several oxazolidinone derivatives with promising anticancer activity. Compound 72 (IDH125) (Fig. 14) was the first hit identified by high-throughput screening (HTS).¹¹⁰ The X-ray cocrystal structure of 72 in the homodimer of IDH1^{R132H} demonstrated the importance that the oxazolidinone ring has in the active binding conformation. Following an iterative hit-to-lead medicinal chemistry campaign exploring the phenyl ring, the researchers developed compound 73 (IDH889) (Fig. 14) as a new lead with improved activity and PK properties. Compound 73 exhibited equipotent inhibition of the



Fig. 14 Oxazolidinone as anticancer agents.



homodimer IDH1^{R132H} (IC₅₀ 0.02 μM) and IDH1^{R132C} (IC₅₀ 0.072 μM) proteins and was less potent for the heterodimer IDH1^{WT}–IDH1^{R132H} (IC₅₀ 1.38 μM) protein. In the HCT116–IDH1^{R132H±} xenograft model, 73 (at 200 mg kg^{−1}) inhibited 2-HG production. PK studies highlighted its excellent permeability through brain tissue.¹¹¹ Despite its potent activity, 73 demonstrated low aqueous solubility (39 μM at pH 6.8) and high *in vivo* clearance in rodents. A lead optimization program that focused on fluoromethyl and fluoroethyl substituted oxazolidinones to improve metabolic stability without compromising physicochemical properties led to the identification of compounds 74 and 75 (IDH305) (Fig. 14).^{112,113} The X-ray structure of compound 75 bound to IDH1^{R132H} homodimer demonstrated the importance of the carbonyl group of the oxazolidinone in binding the backbone amide of Leu120. Both analogues exhibited an outstanding improvement in metabolic stability while maintaining their potent inhibitory efficacy *in vitro* and *in vivo*. Compound 75 exhibited selectivity greater than 200 times for mutant IDH1 isoforms compared to wild-type (IDH1^{R132H} IC₅₀, 0.027 μM; IDH1^{R132C} IC₅₀, 0.028 μM; IDH1^{WT} IC₅₀, 6.14 μM). In the HCT116–IDH1^{R132H/+} xenograft model, 75 dosed at 200 mg kg^{−1}, reduced 2-HG concentration in the tumour with a maximum inhibition of 2-HG of 87.2% compared to the untreated tumours.¹¹³ The promising results of the PK and pharmacodynamic studies of oxazolidinone 75 have paved the way for clinical investigation. Currently, compound 75 has been evaluated in a phase 1 study in patients with advanced malignancies that harbour IDH1^{R132} mutations.¹¹⁴ Zha *et al.* reported a similar derivative during the same period, but independently of Novartis. Compound 76 (Fig. 15) reduced 2-HG production in cells transfected with IDH1^{R132H} and IDH1^{R132C} mutations at 10 and 50 μM. It was also shown to have a good ability to penetrate the BBB.¹¹⁵

Researchers working at Amgen Inc. have also paved the way for oxazolidinone for anticancer therapy.^{116,117} DiMauro *et al.* reported in 2013 the discovery of a new oxazolidinone derivative as a potent, selective, and orally bioavailable tankyrase inhibitor.¹¹⁶ Tankyrases (TNKS1, PARP5a and TNKS2, PARP5b) are members of the poly-ADP-ribose polymerase (PARP) family.¹¹⁸ Tankyrases perform regulatory roles in controlling (in a context-dependent manner) numerous cellular pathways, including the WNT/β-catenin signalling pathway, which abnormal activation has been associated with the development and formation of several

cancers.^{119,120} Compound 77 (Fig. 15) was identified through an iterative structure-based design effort where several scaffolds were tested before landing on the oxazolidinone moiety. It showed IC₅₀ values of 0.001 μM against TNKS1, 0.15 μM against SW480 β-catenin, and >85 μM against PARP1 and PARP2, highlighting its selectivity PARP1/2. Nevertheless, 77 exhibited poor metabolic stability, which was linked to the hydrolysis of the aminoquinazoline amide group.¹¹⁶ Shortly thereafter, Amgen researchers reported the lead optimization work that aimed to improve the metabolic stability of compound 77. The drug design was based on the hypothesis of replacing the aminoquinazoline amide group with a 2-aminopyridine, thus circumventing the stability problem, while persevering two essential hydrogen bond interactions with the protein at Asp1198 and Gly1196. The approach effectively managed to improve the PK properties of the new lead compound 78 (Fig. 15). PK studies in rats and mice revealed moderate clearance and volumes of distribution (*V*_{ss}). For example, after intravenous administration to rats, 78 (dose 0.5 mg kg^{−1}) exhibited Cl_{int} 0.75 L h^{−1} kg^{−1}, *V*_{ss} 2.85 L kg^{−1}, and *t*_{1/2} 3.6 h. Importantly, compound 78 also maintained its selectivity and potency against TNKS1/2 with an IC₅₀ of 0.002 μM against both isoforms. Furthermore, *in vivo* studies revealed that a dose of 78 at 50 mg kg^{−1} reduced Wnt-dependent reporter activity.¹¹⁷

Recently, Miller *et al.* reported the discovery of an *N*-(4-benzamidino)-oxazolidinone with potent inhibitory activity against kallikrein-related peptidase 6 (KLK6).¹²¹ Kallikreins, trypsin-like serine proteases, are a group of trypsin-like serine proteases that are associated with several normal and pathological processes.¹²² KLK6 exerts an essential role in the degradation of extracellular matrix proteins and its differential expression has been associated with carcinogenesis in several cancers, including carcinomas, melanomas, colon, ovarian, and breast cancers.^{123,124} It has been hypothesized that targeting KLK6 inhibition could be a promising therapeutic strategy against some types of cancer, such as colon and squamous cell carcinomas. Compound 79 (Fig. 16) was discovered by an HTS where approximately 350 000 compounds were evaluated for their ability to reduce KLK6-catalyzed hydrolysis of a fluorogenic peptide. After several rounds of funnelling, 76 was identified as a potent KLK6 inhibitor with a pIC₅₀ of 8.6. Additional ADME profiling of 79 showed excellent solubility, high metabolic stability in human and mouse microsomes (Cl_{int} 3.1 and 2.4

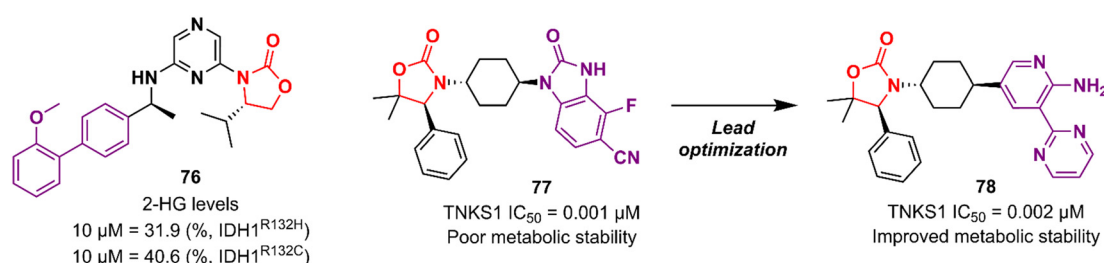


Fig. 15 Anticancer oxazolidinones.



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Fig. 17 Oxazolidinones with antiviral activity.

This was supported by *in vitro* evaluation against two replicons that carry mutations in NS4B (H94N and V105M) with known resistance to similar analogues. There was a considerable loss of potency against these strains (27.3 times and 185 times less potent). *In vitro* ADME profile demonstrated excellent solubility (310 μ g mL⁻¹) and metabolic stability ($t_{1/2}$ 123 min). PK *in vivo* evaluation in rats displayed good clearance (25.7 mL min⁻¹ kg⁻¹) and oral exposure (C_{max} 344 ng mL⁻¹).¹³¹ Oxazolidinones have also been identified as enterovirus inhibitors. The purine-oxazolidinone hybrid **87** (Fig. 17) exhibited potent activity against the Coxsackievirus B3, Nancy strain (CVB3), a frequent cause of acute and chronic viral myocarditis. Compound **87** showed EC_{50} and EC_{90} values of 8.9 and 15.3 μ M against CVB3 in Vero cells. Notably, it did not show significant antiviral activity against other enteroviruses.¹³²

Oxazolidinones as anti-inflammatory agents

Many biological pathways are involved in an inflammatory process. Consequently, there is a wide window of opportunity for potential therapeutic targets (enzymes, G-protein-coupled receptors, nuclear hormone receptors, cytokines and cytokine receptors, cell adhesion molecules, and co-stimulatory molecules) to be explored.¹³³ The chemical space of the oxazolidinone class has also been investigated by targeting different targets in the complex inflammatory pathways. Fujimoto *et al.* working at Takeda discovered an oxazolidinone with potent activity against Δ -5 desaturase (D5D).¹³⁴ D5D is a transmembrane protein associated with polyunsaturated fatty acid biosynthesis, such as dihomo- γ -linolenic acid, which in turn participates in the biosynthesis of arachidonic acid that is ultimately used as a precursor for the synthesis of various unsaturated inflammatory fatty acids, including prostaglandins, leukotrienes, and thromboxanes.¹³⁵ Compound **88** (Fig. 18) was developed in a medicinal chemistry campaign using HTS coupled with pharmacophore modelling. The first hits identified in the HTS were characterized by aromatic rings at each end of the molecule linked by a carbonyl-containing group. Pharmacophore modelling led the researchers to design new analogues containing oxazolidinone as a spacer between the aromatic rings. The rational drug design was successful in identifying compound **88** with high potency against D5D. It exhibited IC_{50} of 1.5 nM in both D5D binding activity (in rat liver microsomes) and D5D inhibitory activity (in HepG2 cells) assays. Furthermore, **88** displayed a high *in vivo* inhibition index for D5D in normal C57BL/6J mice (74%, 3 mg kg⁻¹, po) and an atherosclerosis mouse model (66%, 3 mg kg⁻¹, po). Compound **88** did not show inhibitory activity against CYP isoforms (3A4, 2C8, 2C9, and 2D6). Interestingly, **88** exhibited moderate hERG inhibitory activity (30.7% inhibition at 10 μ M), which naturally raised a red flag; however, it was shown to be safe when its hERG inhibitory effect was evaluated *in vivo* in an electrocardiogram study with dogs.¹³⁴ The LZD derivative **89** (Fig. 18) was discovered as an inhibitor of 5-lipoxygenase (5-LO).¹³⁶ 5-LO plays an essential role in the biosynthesis of leukotrienes (LT) from arachidonic acid.¹³⁷ Compound **89** bears a hydroxamic acid group attached to the oxazolidinone at position 5, which is suggested to act as an iron-chelating moiety of an iron at the active site of the enzyme. A series of *in vitro* assays were carried out to assess the activity of **89**. For example, in cell-based test systems (human whole blood and human monocytes), **89** inhibited the synthesis of 5-LO products (LTB₄ and LTC₄) with IC_{50} values of 0.7 and 0.9 μ M, respectively. In the direct inhibition assay against 5-LO, the IC_{50} was 1.9 μ M. Furthermore, compound **89** was active in a mouse model of peritoneal inflammation (a known model in which LT is known to play an essential role), significantly reducing the LTC₄ content of the lavage



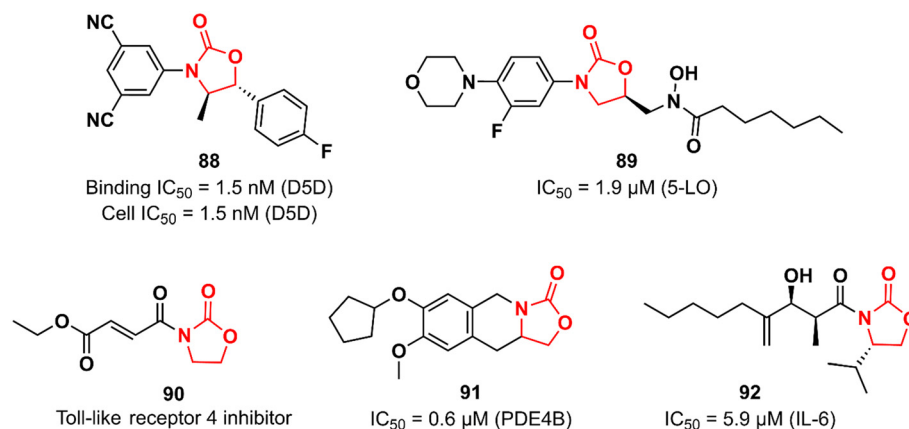


Fig. 18 Oxazolidinones with anti-inflammatory activity.

fluid.¹³⁶ Oxazolidinones have also been investigated as inhibitors of the toll-like receptor 4 (TLR4),¹³⁸ a critical receptor involved in many inflammatory responses, such as LPS recognition.¹³⁹ Oxazolidinone **90** (Fig. 18) was first described as a suppressor of LPS-induced NF- κ B activation.¹⁴⁰ Subsequently studies revealed that compound **90** acts by suppressing LPS-induced dimerization of TLR4, a key step to trigger the activation of TLR4 signalling. Interestingly, it was hypothesized that the α,β -unsaturated carbonyl group presented in **90** could play an essential role in inhibiting TLR4 dimerization by acting as a Michael acceptor.¹³⁸ The oxazolidinone-fused tetrahydroisoquinoline derivative **91** (Fig. 18) was reported as a phosphodiesterase 4 (PDE4) inhibitor. It exhibited IC_{50} values of 0.6 and 5.13 μ M against PDE4B and PDE4D, respectively. *In vivo* profiling demonstrated that **91** has potent suppressing activity against TNF- α release (48%) and LPS-induced neutrophilia inhibition (42%). Importantly, **91** exhibited high selectivity for PDE4, as it was inactive against other human PDE isoforms. Molecular docking analysis suggested

that the catechol group plays an important role in the interaction with the enzyme.¹⁴¹ Choi *et al.* reported the first synthetic small-molecule inhibitor of interleukin 6 (IL-6), a glycoprotein that plays a critical role in inflammatory processes.^{142,143} Oxazolidinone **92** (Fig. 18) emerged as a hit in the screening of a large chemical library tested against IL-6-induced luciferase expression in human hepatocarcinoma HepG2 cells. Compound **92** (50 μ M) decreased IL-6-induced luciferase activity by approximately 90% and showed an IC_{50} of 5.9 μ M. It also inhibited the proliferation of the IL-6-induced human erythroleukemic cell line TF-1 with an IC_{50} of 7.5 μ M. Furthermore, an *in vivo* (mice model) investigation showed that **92** inhibited IL-6-induced TNF- α production, decreased collagen-induced arthritis, and demonstrated a therapeutic effect against pancreatitis by reducing the expression of pro-inflammatory cytokines, including IL1 β , TNF- α , and IL-6. Further studies revealed that compound **92** targets the β subunit of the IL-6 receptor (gp130), responsible for initiating downstream signal transduction.¹⁴²

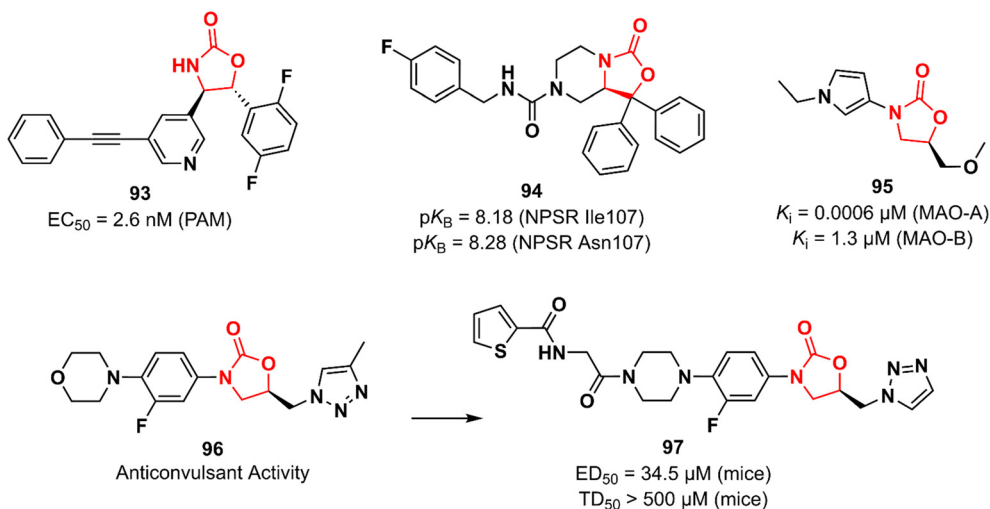


Fig. 19 Oxazolidinones discovered for neurological disorders.



Oxazolidinones in neurological disorders

Huang *et al.* working at Bristol-Myers Squibb Research & Development reported an oxazolidinone acting as a positive allosteric modulator (PAM) of the metabotropic glutamate receptor subtype 5 (mGluR5) for the treatment of schizophrenia.^{144,145} mGluR5 is associated with *N*-methyl-D-aspartate receptors (NMDA) in GABAergic interneurons and its activation has been associated with increased NMDA function, which in turn can restore the imbalance between excitation and inhibition in glutamatergic synapses.¹⁴⁶ Oxazolidinone **93** (BMS-955829) (Fig. 19) exhibited an EC₅₀ value of 2.6 nM against PAM, excellent mGluR5 binding affinity (K_i 1.6 nM), and high selectivity for the mGluR5 subtype. *In vivo* investigation demonstrated that **93** (30 mg kg⁻¹, ip) prevented convulsions in mice, which was associated with its lack of agonist activity (EC₅₀ > 30 μM). Furthermore, it showed *in vivo* efficacy in mice models of schizophrenia. Further drugability profiling highlighted its safety profile and favourable brain penetration.¹⁴⁵ Neuropeptide S receptor antagonist (NPSR) **94** (SHA 68) (Fig. 19) was first described by Takeda researchers as having anxiolytic-like effects.^{147,148} Subsequently, Guerrini *et al.* reported the synthesis and separation of the active enantiomer (*R*). Oxazolidinone **94** showed a high potency (p*K_B*) in HEK293 cells expressing murine NPSR and human NPSR isoforms (Ile107 and Asn107) with p*K_B* values of 8.29, 8.18, and 8.28, respectively. Conversely, the *S* enantiomer was devoid of biological activity.¹⁴⁹ Another oxazolidinone **95** (Fig. 19) was described as a potent and reversible monoamine oxidase A (MAO-A) inhibitor.¹⁵⁰ MAO inhibition is a well-known effect of certain oxazolidinone derivatives and is frequently applied as a toxicity measurement in the early stages of development.^{151,152} Compound **95** exhibited high selectivity

towards MAO-A with a K_i value of 0.0006 *versus* 1.3 μM against MAO-B.¹⁵⁰ MAO-A catalyzes the oxidation of serotonin and norepinephrine and its inhibition is associated with antidepressant effects.¹⁵² Anticonvulsant activity has also been described for oxazolidinones. The LZD derivative **96** (Fig. 19) suppressed chemically induced seizures (*in vitro* seizure model in the rat hippocampus) by reducing action potential firing and excitatory postsynaptic transmission highlighting the potential of the class as antiepileptic agents.^{153,154} In 2019, the same research group reported an analogue of **96** with *in vivo* anticonvulsant activity in rats and mice. Compound **97** (Fig. 19) showed ED₅₀ values of 34.5 and 90 mg kg⁻¹ in mice and rats, respectively, and TD₅₀ > 500 mg kg⁻¹ in mice. The efficacy produced was comparable to that of levetiracetam (ED₅₀ 19.4 mg kg⁻¹).¹⁵⁵

Oxazolidinones in metabolic disorders

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. According to the WHO, approximately 17.9 million people die each year from CVDs, an estimated 32% of all deaths globally.^{156,157} Elevated levels of low-density lipoprotein-cholesterol (LDL-C) and low levels of high-density lipoprotein-cholesterol (HDL-C; the so-called good cholesterol) are considered the main risk factors for CVD. Therefore, drugs that aim to increase HDL-C levels could have a potential therapeutic application. Oxazolidinones have been studied for this purpose. In 2011, researchers working at Merck Research Laboratories discovered a substituted biphenyl oxazolidinone **98** (Fig. 20) as a cholesteryl ester transfer protein (CETP) inhibitor.¹⁵⁸ CETP acts by decreasing HDL-C levels and increasing LDL-C levels.¹⁵⁹ Compound **98** was designed based on a previously identified inhibitor of cholesteryl ester (CE) transfer. Although oxazolidinone **98** had shown good potency *in vitro* in CE transfer inhibition

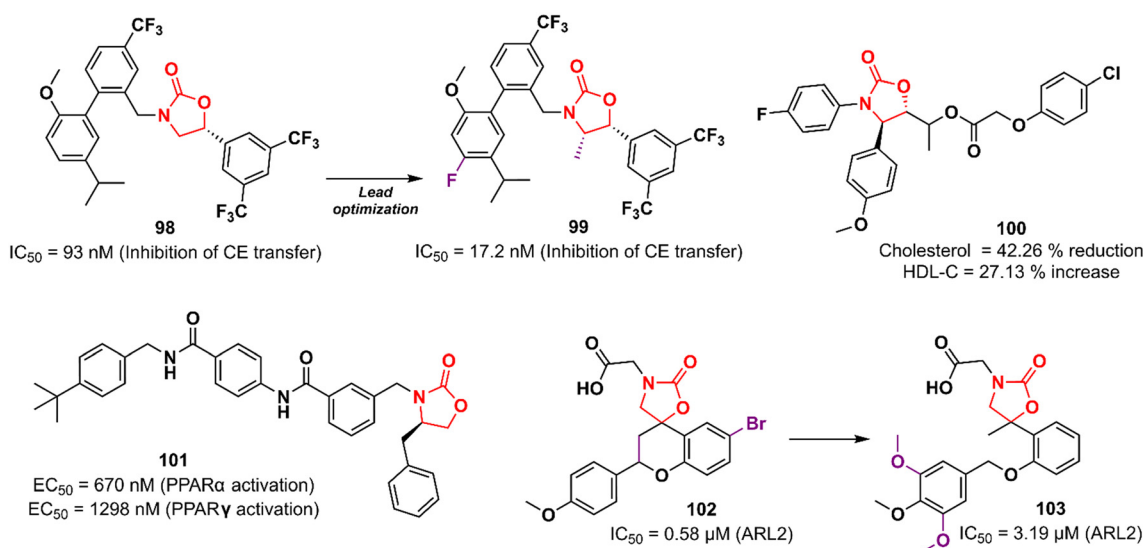


Fig. 20 Oxazolidinones developed for the treatment of metabolic syndromes.



(IC₅₀ 93 nM), it failed to increase HDL-C levels *in vivo*, possibly due to its poor PK profile.¹⁵⁸ Shortly after, Merck disclosed the clinical candidate anacetrapib **99** (Fig. 20) as an optimized lead from **98**.¹⁶⁰ This compound exhibited potent CETP inhibitory activity (IC₅₀ 17.2 nM) and good *in vivo* efficacy in the B6-Tg(CETP) mouse model. PK studies in mice, rats, and rhesus monkeys demonstrated moderate profiles.¹⁶⁰ However, Merck abandoned its development in 2017 due to a lack of efficacy or safety issues in clinical trials, just as several CETP inhibitors have been abandoned since 2006, including torcetrapib (Pfizer), evacetrapib (Lilly), and dalcetrapib (Roche). Oxazolidinone **100** (Fig. 20) was discovered as a cholesterol absorption inhibitor through a pharmacophore modelling study using ezetimibe as a model. *In vivo* studies with cholesterol-fed Sprague–Dawley rats demonstrated that the reduction in total cholesterol and triglyceride levels and increased HDL-C levels after treatment with compound **100** was compared to that of ezetimibe.¹⁶¹ In another study, oxazolidinone **101** (Fig. 20) was identified by molecular docking studies using the peroxisome proliferator-activated receptor (PPAR α) receptor.¹⁶² PPARs are nuclear receptors involved in numerous cellular processes, including adipogenesis, lipid and glucose metabolism, energy levels, and inflammation.¹⁶³ Compound **101** emerged as the most potent PPAR α / γ agonist with EC₅₀ values of 670 and 1298 nM in PPAR α and PPAR γ activation, respectively. *In vivo* investigation revealed that **101** (3.0 mg kg⁻¹) induced a 50% reduction in food intake in food-deprived obese rats.¹⁶² Rapposelli *et al.* reported the spiro-oxazolidinone derivative **102** (Fig. 20) as an aldose reductase (ARL2) inhibitor.¹⁶⁴ ARL2 is a key enzyme of the aldo–keto reductase superfamily, and its activity in pathological conditions is associated with diabetic complications.¹⁶⁵ Compound **102** exhibited an IC₅₀ value of 0.58 μ M against ARL2, which was comparable to sorbinil (IC₅₀ 0.65 μ M), a well-known ARL2 inhibitor.¹⁶⁴ Subsequently, an analogue of **102** lacking the spiro scaffold was reported. However, the new compound **103** (Fig. 20) was shown to be less active against the enzyme (IC₅₀ 3.19 μ M), highlighting the importance of the spiro-oxazolidinone moiety.¹⁶⁶ Together, these results highlight the potential of oxazolidinones in the discovery of drugs for the treatment of metabolic syndromes.

Miscellaneous oxazolidinones

Rivaroxaban (Xarelto®, Janssen Pharmaceuticals) is another drug representative of the oxazolidinone class that is used as an anticoagulant agent to treat deep vein thrombosis and pulmonary emboli by inhibiting protein factor Xa (FXa). FXa is a serine endopeptidase that plays a critical role in the coagulation pathway by cleaving prothrombin to generate thrombin.¹⁶⁷ Yang *et al.* reported in 2015 an analogue of rivaroxaban in which oxazolidinone was merged into a tricyclic scaffold. Compound **104** (Fig. 21) exhibited an IC₅₀ value of 3.41 nM against FXa (selectivity >20 000) and high anticoagulant activity *in vitro*. PK studies in dogs



Fig. 21 Oxazolidinones targeting FXa and T-box riboswitch RNA.

demonstrated an excellent profile for compound **104** with high bioavailability (F = 92%) and excellent oral exposure (C_{\max} = 530 ng mL⁻¹). It is worth mentioning that **104** was superior to rivaroxaban in almost all PK properties. Moreover, compound **104** had excellent antithrombotic activity in three different models of thrombosis in rats: FeCl₃-induced venous thrombosis (ED₅₀ 5.63 mg kg⁻¹), arteriovenous shunt (ED₅₀ 5.28 mg kg⁻¹), and electrically induced rat carotid artery thrombosis (ED₅₀ 2.97 mg kg⁻¹). It is noteworthy that its efficacy *in vivo* was compared with that of rivaroxaban. Additionally, compound **104** did not show inhibition of the hERG K⁺ channel (IC₅₀ 79.75 μ M) and CYP450 isozymes (IC₅₀ > 40 μ M), was not mutagenic in the Ames test and it was well-tolerated in rats upon oral administration of high doses (100 mg kg⁻¹).¹⁶⁸ The oxazolidinone moiety present in rivaroxaban and **104** plays a critical role in the binding affinity to the enzyme by forming two hydrogen bonds with Gly219.¹⁶⁸ Subsequently, Gong *et al.* designed new analogues by replacing the morpholin-3-one moiety with different water-soluble groups. Oxazolidinone **105** (Fig. 21) was identified as the most promising analogue with an IC₅₀ of 2.01 nM against FXa and anticoagulant activities in human and rabbit plasma. This compound has a pyrrole-alkylamino group at the S4 ligand position, which was suggested to be essential for anticoagulant activity.¹⁶⁹



Oxazolidinones have also been developed as ligands that target the T-box riboswitch of non-coding RNA,^{170–173} which in turn could disrupt RNA function. RNA riboswitches control RNA transcription by forming a complex with metabolic effector molecules that ultimately lead to transcription.¹⁷¹ The T-box transcription antitermination riboswitch presented in the 5'-untranslated mRNA region (5'-UTR) presented in several essential genes in Gram-positive bacteria is an example of noncoding RNA with potential application in drug discovery. This non-coding RNA is involved in controlling the transcription of the protein-encoding region of the mRNA.¹⁷⁴ Hines *et al.* described an oxazolidinone derivative **106** (Fig. 21) that binds to the T-box riboswitch RNA (AM1A model), thus altering the function of the riboswitch. RNA binding affinity studies demonstrated that compound **106** has a K_d value of 1.6 μM , which was correlated with the most energetically favourable docking score ($-117.4 \text{ kcal mol}^{-1}$).¹⁷³ Subsequently, the same group reported an iterative medicinal chemistry campaign of a series of oxazolidinones with RNA-binding affinity. Specifically, a SAR study was carried out at the C5 position of the oxazolidinone ring where several substituents were evaluated, eventually leading to compound **107** (Fig. 21) with the strongest binding affinity to AM1A RNA. As a result of the SAR analysis, the importance of hydrogen bonding and hydrophobic properties in oxazolidine binding was demonstrated.¹⁷² These results showing that oxazolidinones bind to AM1A RNA *via* surface binding highlight their application for the discovery of RNA-binding drugs focusing on other medically relevant RNAs.



Fig. 22 Oxazolidinone derivatives with various activities.

In addition to classical Gram-positive and Gram-negative bacteria and *M. tuberculosis*, LZD analogues have also been investigated against other microorganisms. For example, compound **71** (Fig. 22) was tested against a panel of non-tuberculous mycobacteria strains, including *M. avium*, *M. kansasii*, *M. intracellulare*, *M. chelonae*, *M. abscessus*, and *M. fortuitum*. The treatment of infections caused by these mycobacteria is often difficult due to the lack of activity of traditional antitubercular drugs. Oxazolidinone **71** was particularly active against *M. kansasii*, *M. fortuitum* and *M. chelonae* with MIC_{90} values of 1.0, 8.0 and 8.0 μM , respectively.¹⁷⁵ Compound **108** (Fig. 22) was identified with antiparasitic activity against *Hymenolepis nana*, a common parasite responsible for hymenolepiasis, an intestinal parasitosis. *In vitro* analysis showed that after exposure to **108** (20 mg mL^{-1}), the *Hymenolepis nana* worms were paralyzed in 6 min and died after 18 min.¹⁷⁶ Similarly, compound **109** (Fig. 22) was reported with anthelmintic activity against the Indian earthworm *Pheretima posthuman*. This compound, an LZD analogue, induced paralysis in worms in 3.6 min and subsequent death after 8.1 min.¹⁷⁷ It is worth noting that none of the compounds presented significant activity against Gram-positive bacteria, highlighting their high selectivity against parasites. Finally, oxazolidinone **110** (Fig. 22) was found to be a potent inhibitor against several enzymes, including human carbonic anhydrase I and II isoenzymes (hCA I and hCA II), acetylcholinesterase (AChE), and α -glycosidase (α -Gly). These enzymes are involved in a variety of cellular processes, and their inhibition by small molecules has been investigated for the treatment of several diseases, such as glaucoma, leukaemia, epilepsy, Alzheimer's disease, and type-2 diabetes mellitus. Compound **110** exhibited IC_{50} values of 45.6 μM (hCA I), 24.8 μM (hCA II), 58.7 μM (AChE), and 30.5 μM (α -Gly).¹⁷⁸

Future perspectives and conclusions

The discovery of LZD and its approval by the FDA in the 2000 revealed oxazolidinones as important and promising scaffolds in the toolbox of medicinal chemistry. Ever since then, oxazolidinones have been extensively investigated in medicinal chemistry, and numerous LZD analogues have been developed, mainly as antibacterials. LZD was indeed a pioneering drug, being the first fully synthetic small molecule able to inhibit the bacterial protein synthesis. Notwithstanding the great success of oxazolidinones as antibacterial agents, there is still wide potential for this scaffold to be exploited in other therapeutic areas. Indeed, the design and synthesis of LZD analogues, as well as analogues of other oxazolidinone drugs like tedizolid and sutezolid, is an attractive field since such derivatives may find application in the treatment of different diseases. As an example, the tricyclic benzo[1,3]oxazinyl-oxazolidinone **57** shows promise as a potential preclinical anti-TB agent, while Novartis and Amgen have demonstrated the potential of



In conclusion, 2-oxazolidinones are a widely investigated and still fascinating class of compounds in drug discovery and medicinal chemistry. Several oxazolidinones have succeeded in reaching the advanced stages of clinical trials, and others have made their way to the clinic (*e.g.*, linezolid, tedizolid, and rivaroxaban). On the other hand, even if a large number of oxazolidinone derivatives have not been successful in advancing the drug development pipeline, they still represent interesting starting points for future optimization or drug repurposing strategies. This review highlights the versatility of oxazolidinones in medicinal chemistry, as demonstrated by the wide applicability of such compounds in many therapeutic areas, including anticancer, antiviral, anti-inflammatory, neurological disorders, antitubercular, and especially antibacterial. This reinforces the distinguished quote made by Nobel Prize winner Sir James Black that “*the most fruitful basis for the discovery of a new drug is to start with an old drug*”. The goal of this review was thus to provide a comprehensive overview of all the oxazolidinone analogues reported in the literature in the past decade to shed light on this important chemical motif and to stimulate the discussion on their use and future application in drug discovery.

LZD	Linezolid
FDA	Food and Drug Administration
VRE	Vancomycin-resistant <i>Enterococci</i>
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
WHO	World Health Organization
MDR-TB	Multidrug-resistant tuberculosis
TB	Tuberculosis
MIC	Minimum inhibitory concentration
MAO	Monoamine oxidase
MDR	Multidrug-resistant
PK	Pharmacokinetic
AUC	Area under the concentration
MRSE	Methicillin-resistant <i>Staphylococcus epidermidis</i>
PRSP	Penicillin-resistant <i>Streptococcus pneumoniae</i>
<i>F</i>	Bioavailability
CYP450	Cytochrome P450
BBB	Blood brain barrier
SAR	Structure–activity relationship
KPC	<i>Klebsiella pneumoniae</i> carbapenemase
NDM-1	New Delhi metallo- β -lactamase 1

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