Journal of Molecular Structure 1286 (2023) 135630

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Oxazolidinones: Are they only good for the discovery of antibiotics? A worm's eye view

Shelly Pathania, Kseniia Petrova-Szczasiuk, Olli Pentikäinen, Pankaj Kumar Singh *

Integrative Physiology and Pharmacology, Institute of Biomedicine, Faculty of Medicine, University of Turku, FI-20520 Turku, Finland

ARTICLE INFO

Keywords:
Oxazolidinones
O-heterocycles
Antibiotics
Anti-cancer
Pharmacophore

ABSTRACT

Oxazolidinones are one of the well-known classes of *O*-heterocycles which has yielded various potent antibiotics. Several oxazolidinone-based antibiotics are either FDA-approved or are in clinical trials. They act via competitively binding to the 23S rRNA, leading to the inhibition of bacterial protein synthesis. However, this work is an attempt to analyze the other side of oxazolidinone-based pharmacological profile. Herein, we have studied, if most of the recently reported oxazolidinone derivatives are antibiotics, and if so, what are other possible pharmacological profiles attributed to them? And how there is an inadvertent bias to consider oxazolidinones only to design and develop antibiotics. We have attempted to understand and explain the difference between structural and/or pharmacophoric features of potent oxazolidinone-based antimicrobials and other pharmacological profiles. We have highlighted the unused pharmacophoric spaces available in this core, which could be explored to diversify the pharmacological space of this heterocyclic core. This work could provide a crucial realization of bias towards oxazolidinone in drug discovery attempts, which restricts it only to be a core for antibiotics and can promote its use to hit other therapeutic targets.

1. Introduction

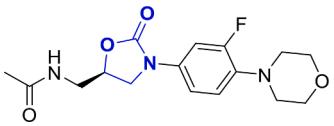
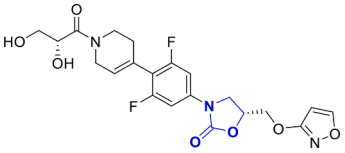
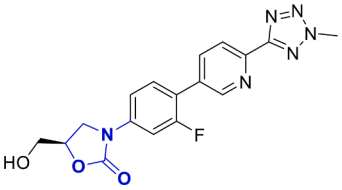
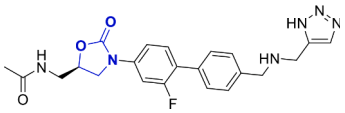
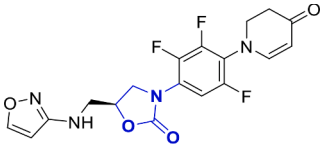
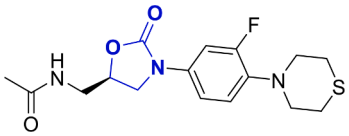
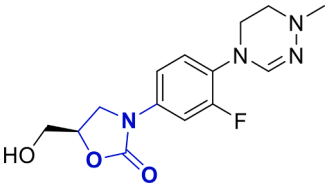
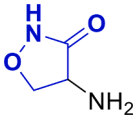
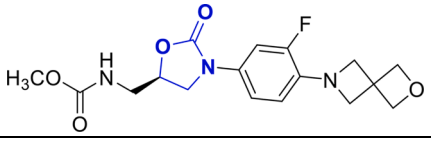
One of the very familiar *O*-heterocycles core used in drug discovery is oxazolidinone [1,2]. Routinely medicinal chemists use this core to design potent antimicrobials [3]. However, a careful investigation of the literature suggests that researchers are tentatively biased towards using oxazolidinones for the discovery of antimicrobials [4]. Recently, in 2021 a review was published that highlighted various aspects of oxazolidinone-based antibiotics and extensively covered their drug-designing aspects [5]. However, what caught our eye was the fact, that most of the well-known work done on oxazolidinones involves the discovery of antibiotics, which made us think, if this core is only good for the discovery of molecules with a similar pharmacological profile.

Oxazolidinones are five-membered heterocycles having both cyclic amide and ester sharing the same carbonyl group [6]. Various procedures have been reported for the synthesis of this heterocyclic core [7]. Pharmacologically, oxazolidinones are a relatively new class of antibacterial agents originally developed for the treatment of gram-positive bacterial infections [8,9]. N-aryl-oxazolidinones, such as linezolid (LZD), constitute the recent family of discovered first-in-class synthetic antibiotics used as the last resort therapy in major infections caused by multidrug-drug resistant (MDR) gram-positive bacteria (GPB) [3,10,11]. This class of compounds inhibits bacterial protein synthesis via competitively binding to the 23S rRNA in the catalytic site of the bacterial 50S ribosomes [12]. Other members of the oxazolidinone class have also shown activity against *Mycobacterium tuberculosis* and are currently under clinical development for the treatment of multidrug-resistant (MDR)- and extensively drug-resistant tuberculosis (XDR)-TB [13]. Sutezolid, originally discovered by Upjohn et al., is in Phase II studies for TB [14]. Sutezolid differs from linezolid by having a thiomorpholine substituent, it has displayed a better antitubercular activity and improved safety profile compared to linezolid [4]. In addition, delpazolid and TBI-223 are also under clinical development for the treatment of TB [15]. Tedizolid (TZD) is another oxazolidinone licensed for acute bacterial skin and skin structure infections that may also be less toxic than LZD at the approved dose [16,17]. The development of AZD5847 by AstraZeneca for the treatment of gram-positive infections and TB has been discontinued [18,19]. A lot of oxazolidinone derivatives in drug discovery phases show serious toxicity mediated by the inhibition of mitochondrial protein synthesis (MPS) and monoamine oxidase (MAO) [14,20,21]. Therefore, there are continued efforts to develop oxazolidinone antibacterial agents having higher antibacterial

* Corresponding author.
E-mail address: pankaj.singh@utu.fi (P.K. Singh).

https://doi.org/10.1016/j.molstruc.2023.135630
Received 30 January 2023; Received in revised form 17 April 2023; Accepted 19 April 2023
Available online 21 April 2023

Table 1
List of FDA approved drugs containing oxazolidinone scaffold.

S. No.	Drug Name	Chemical Structure	Clinical condition	Mechanism of action	Approval/ clinical trials	References
1.	Linezolid		Skin infections, nosocomial pneumonia, drug-resistant tuberculosis	Inhibits protein synthesis	Approved in 2000	[25]
2.	Posizolid		Bacterial Infections	Inhibits protein synthesis	Phase I	[26]
3.	Tedizolid		Skin and skin structure infections	Inhibits protein synthesis	Approved in 2014	[27]
4.	Radezolid		Bacterial acne	Inhibits protein synthesis	Phase II	[28]
5.	Contezolid		Bacterial Infections	Inhibits protein synthesis	Phase II	[17]
6.	Sutezolid		Bacterial Infections	Inhibits protein synthesi	Phase IIa	[17]
7.	Delpazolid		Bacterial Infections	Inhibits protein synthesis	Phase II	[17]
8.	Cycloserine		Drug-resistant tuberculosis	Inhibits cell-wall biosynthesis in bacteria	Approved in 1956	[29]
9.	TBI223		Drug-resistant tuberculosis	Inhibits protein synthesis	Phase I	[17]

activity with increased safety of use to solve these problems [5].

However, anyone can notice, going through the oxazolidinone-based pre-clinical or clinical candidates (Table 1), that all of these molecules are designed to possess antibacterial activity [22]. It seems that very few efforts were made to develop oxazolidinone-based drugs with any other pharmacological profile. Therefore, we made an effort to understand why so? Whether there were really no efforts to design oxazolidinone-based molecules with other pharmacological profiles or researchers are unknowingly biased to consider oxazolidinones exclusively as antibiotics. It is very interesting, because to have any biological activity a molecule should satisfy certain pharmacophoric conditions and no molecule can satisfy every condition simply on the basis of the core heterocycle, so why is it that something like benzimidazole (or any other heterocycle) [23–25] is considered being a "privileged core" having a diverse pharmacological profile on the basis of its varied substitution, while oxazolidinones are only considered to be designed as antibiotics. To understand and answer the same question, herein, we are thoroughly reviewing literature whereby we would be comparing recent oxazolidinone-based molecules as antibiotics with derivatives having a different pharmacological profile and would look out for unexplored pharmacophoric spaces.

1.1. Synthesis route for the FDA approved drugs containing oxazolidinone scaffold

There have been many advances in the chemistry of oxazolidinones [26] and synthetic routes have been improved to yield different oxazolidinone based FDA approved drugs.

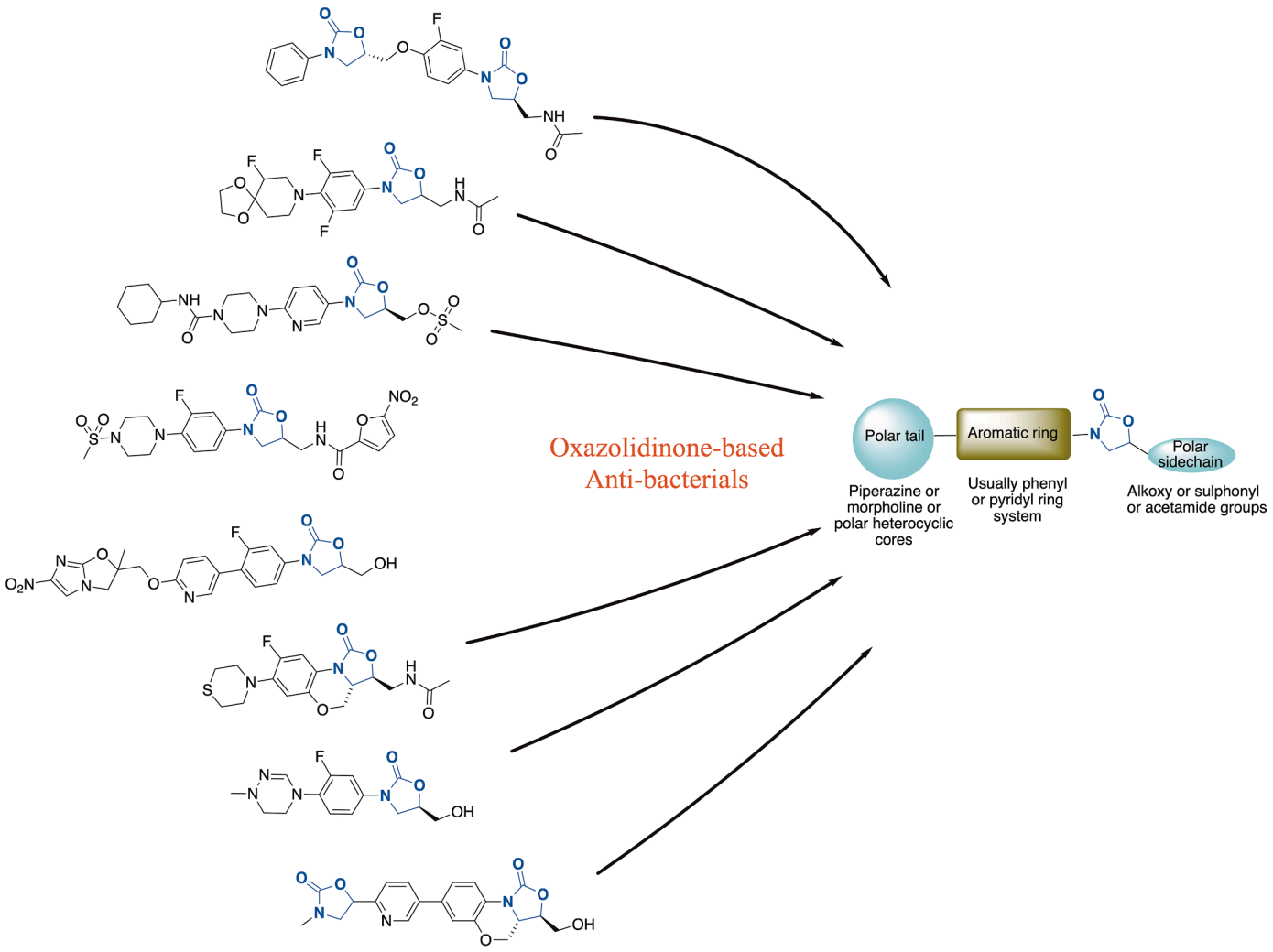
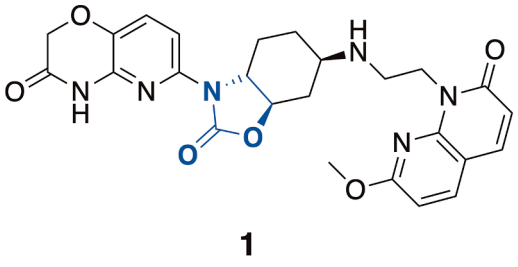


Fig. 1. Common pharmacophoric features identified from structural features of oxazolidinones as antibacterial agent.

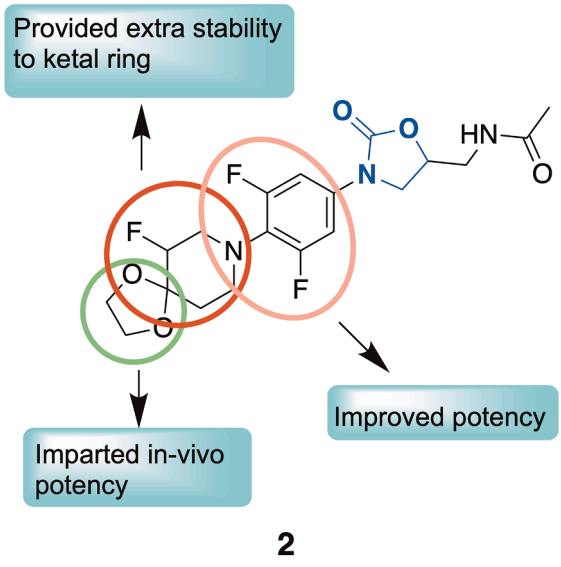


1

Fig. 2. 2D structure of bicyclic oxazolidinone as novel bacterial type II topoisomerase inhibitors.

1.2. Oxazolidinones as antimicrobials: a common sight

Oxazolidinones are commonly known and usually explored for their antibacterial potency. As can be noted in the prior discussion, roughly half of the oxazolidinone-based molecules reported in recent years are developed for antibacterial activities or for improvement of already established antibacterial activities. So, now we will understand the pharmacophoric features which have been explored and established for oxazolidinones to have antibiotic potential. A close inspection of the structures, reported to possess potent antibiotic potential, reveals that most of them possess analogous structural organization having fragments of similar nature swapping places in different molecules and so



2

Fig. 3. Pharmacophoric features of WCK 4034 as gram-positive antibiotic.

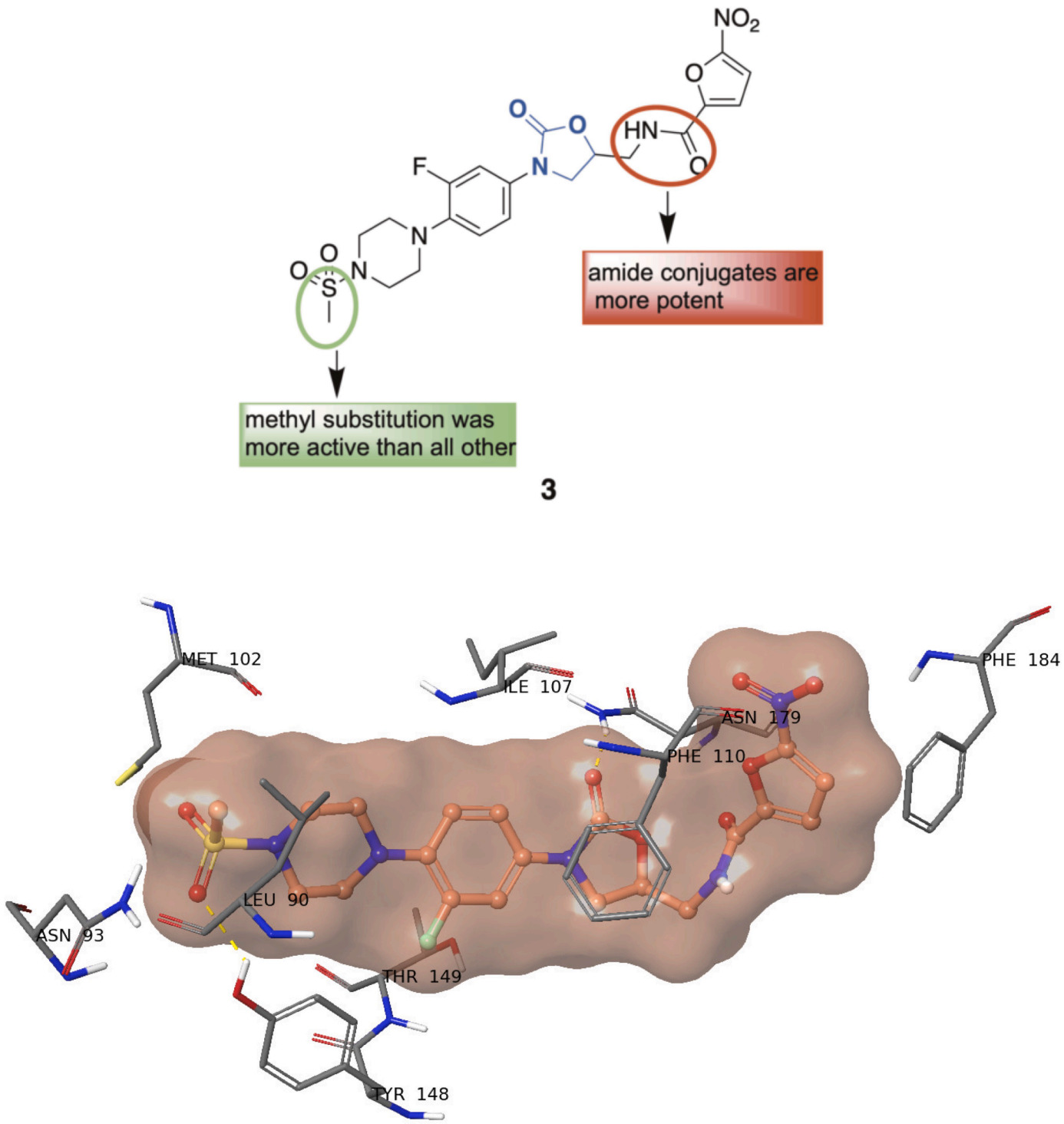


Fig. 4. Pharmacophoric features and molecular docking of linezolid-based oxazolidinones as potent anticandidiasis and antitubercular agents into EthR protein (PDB ID: 5NZ0)

imparting varied levels of potency (Fig. 1). Briefly, almost all of them have substituents on two sites: one on the N of oxazolidinone and the other on the 5th position of the 5-membered ring system. On the N, usually, these antibiotics have been reported to possess an aromatic or heteroaromatic ring system, sometimes with small substituents like halogens. Further, the aromatic rings are extended on the left-hand side via a polar tail in the form of either a substituted morpholine, thiazine or piperazine. While on the 5th position, small polar chains have been reported for the antibacterial agents. These polar extensions usually include acetamide-, alkoxy-, methyl sulphonyl -groups. Detailed discussion on these features and their effect on activity profiles has been published recently [27].

Now we will have a look at the pharmacophoric/structural features of recently reported oxazolidinone-based antibacterial agents, which are a common sight. Lyons et al. in 2022 reported the discovery and structure-activity relationships of a novel oxazolidinone class of bacterial type II topoisomerase inhibitors. They utilized the general conclusions about novel bacterial type II topoisomerase inhibitors (NBTI), such

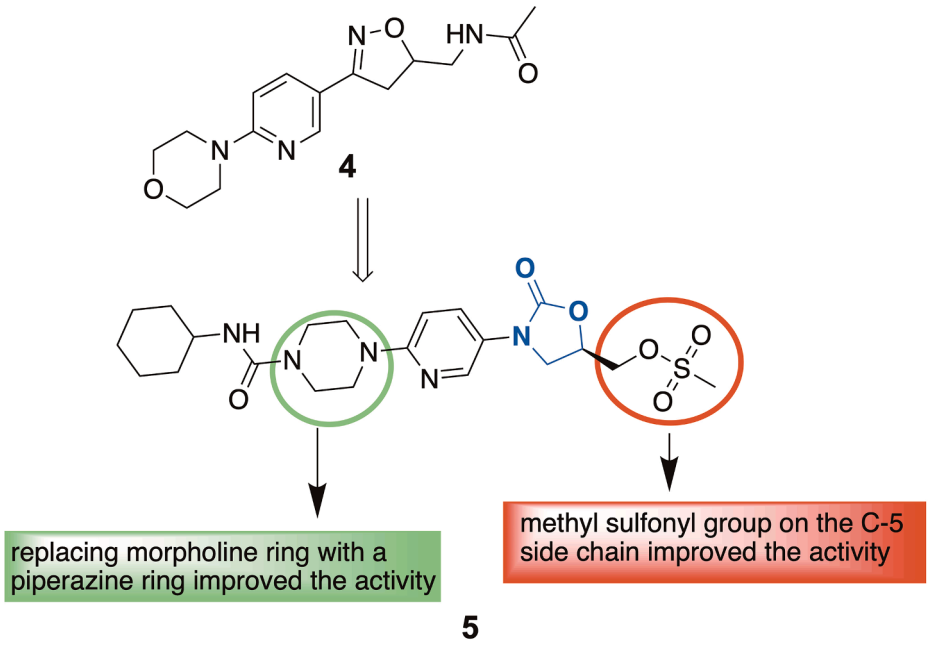


Fig. 5. Pharmacophoric features of 3-(3-pyridyl)-oxazolidinone-5-methyl ester derivatives as antibacterial and anthelmintic activity.

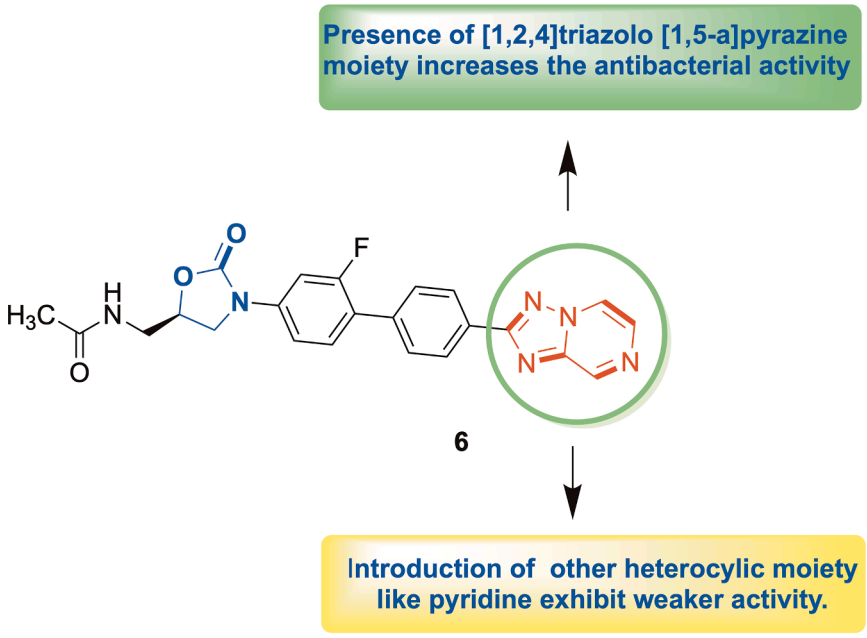


Fig. 6. Oxazolidinone derivative containing [1,2,4]triazolo [1,5-*a*]pyrazine moiety as antibacterial agent..

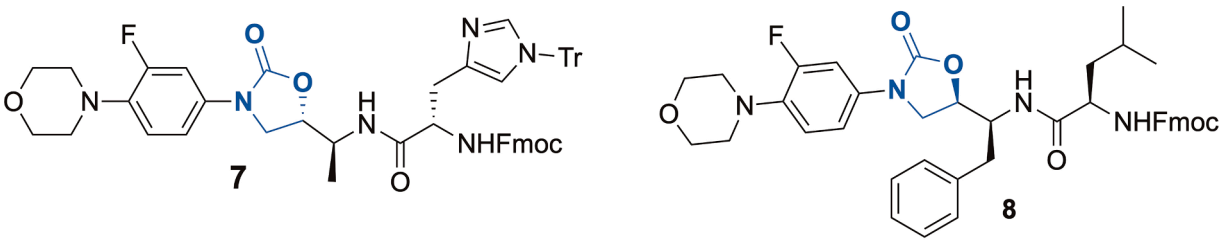


Fig. 7. Linezolid dipeptide-type analogues as antibacterial agent.

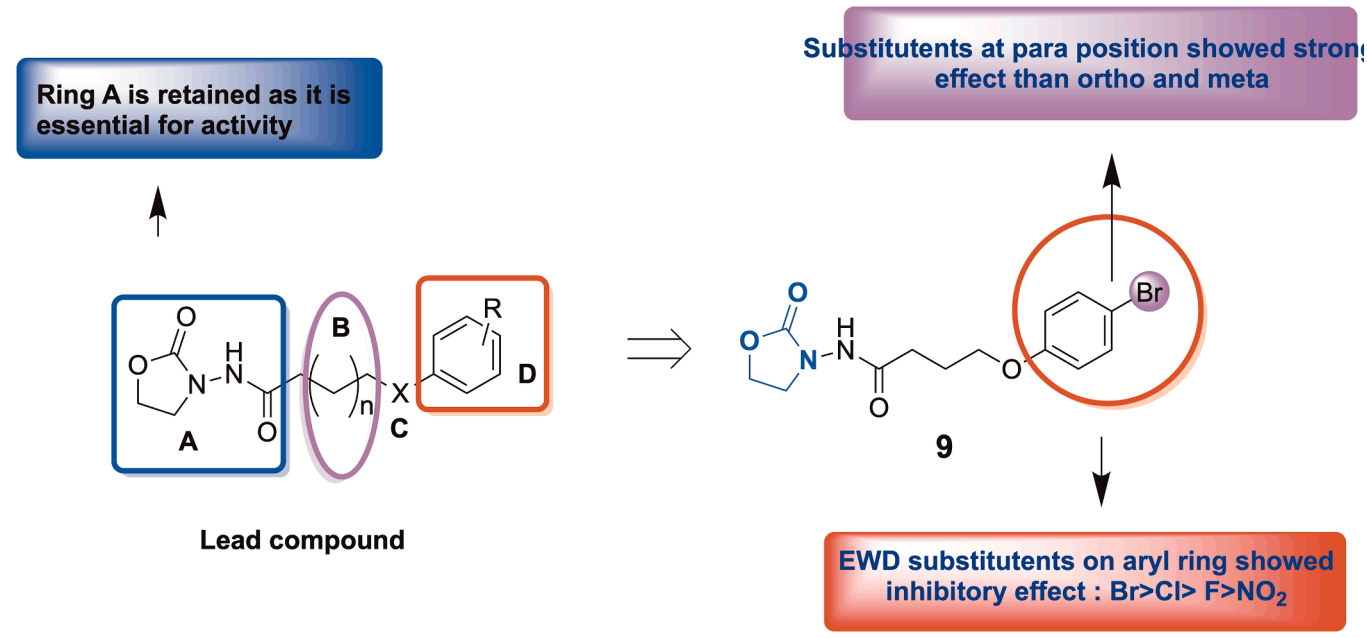


Fig. 8. 3-amino-2-oxazolidinone derivatives as potent quorum-sensing inhibitors of *Pseudomonas aeruginosa* PAO1.

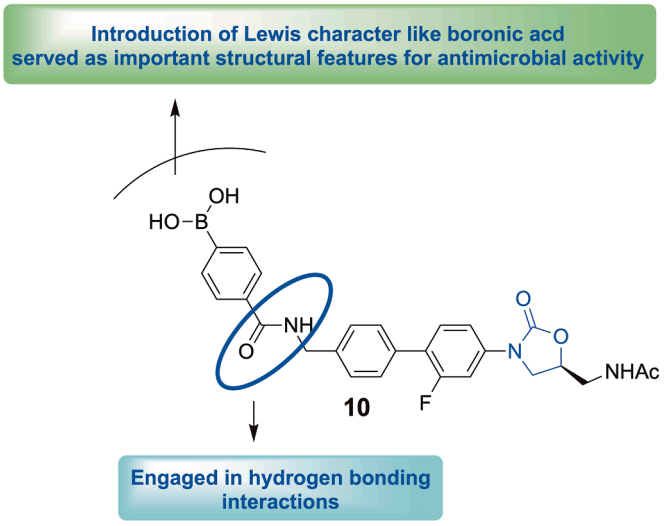


Fig. 9. Aryl boronic substituted *N*-aryl-oxazolidinones analogues with potential antibacterial activity.

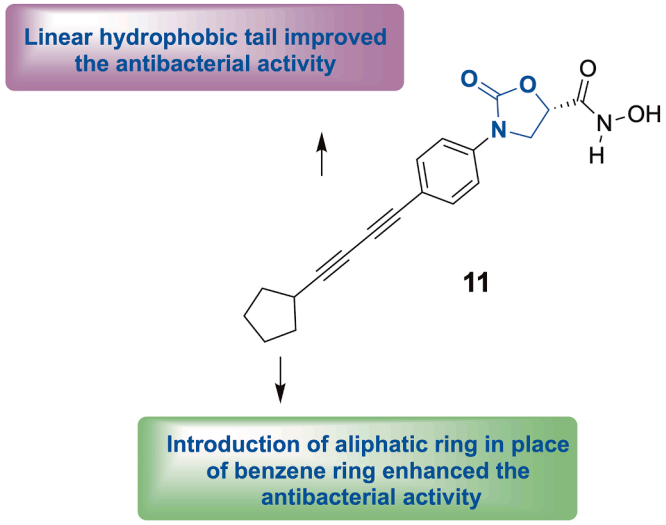


Fig. 10. Oxazolidinone-based compounds with linear hydrophobic tails as antibacterial agents.

as the presence of aromatic left-hand-side, that inserts between two base pairs of DNA, a solvent-exposed central linker (a secondary amine), which interacts with a key aspartate residue, and a right-hand-side, that interacts with the protein, to design a novel series of bicyclic oxazolidinone NBTIs. Out of all designed and synthesized compounds, **1** was found to possess the best *in vivo* efficacy. The limited SAR they could conclude suggested that there was a tricky correlation between logD, antibacterial activity and hERG activity (Fig. 2). Molecular docking analysis of 1 in DNA gyrase showed H-bond interaction between Arg1122 and oxazolidinone motif [28].

Bhawsar et al. in 2022 reported WCK 4034 to be a promising oxazolidinone for treating gram-positive infections. Following the structure of linezolid, they designed various oxazolidinone compounds and identified the lead compound -WCK 4034 (2) as having improved potency and comparable pharmacokinetic parameters to linezolid. SAR analysis highlighted the importance of the 5-member cyclic spiroketal attached at the C-4 carbon of piperidine. The replacement of a hydrogen atom by fluorine on the piperidine ring along with the replacement of two hydrogen atoms on the benzene ring by two fluorine atoms improved the potency (Fig. 3). Overall, WCK 4034 was found to be better against linezolid during *in vivo* efficacy study [29].

Faazil et al. in 2022 reported novel linezolid-based oxazolidinones as potent anticandidiasis and antitubercular agents. In this work, following linezolid, they carried out two significant modifications, first, the morpholine ring was replaced with an *N*-sulphonyl piperazine moiety and the acetamide group was substituted with the 2-nitrofuranamide group, second, the acetamide group was replaced with heteroaryl and biphenylacryl amides. Although, out of all the synthesized derivatives, 3 was found to be the most potent compound, SAR suggested oxazolidinone-amide conjugates to be more potent than their sulphonamide analogues. Also, the conjugate with simple methyl substitution was more active than all the substitutions with an aromatic ring (Fig. 4). The molecular docking analysis of 3 in EthR protein showed the presence of multiple H-bonds with Thr149, Asn179, Asn176, and Phe184 [30].

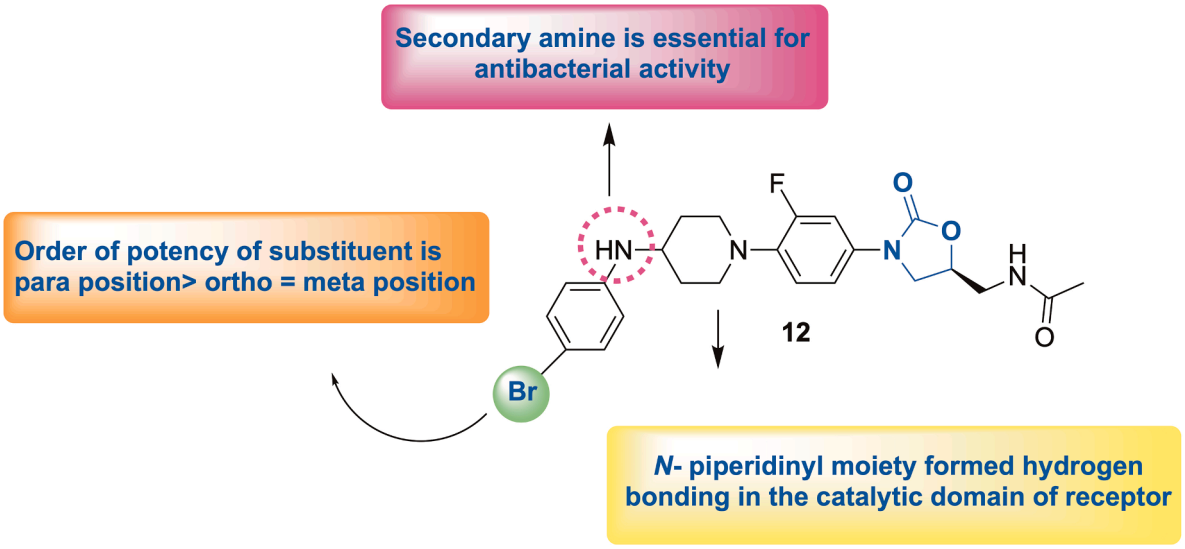


Fig. 11. SAR profile of oxazolidinone derivatives containing a piperidinyl moiety for antibacterial activity.

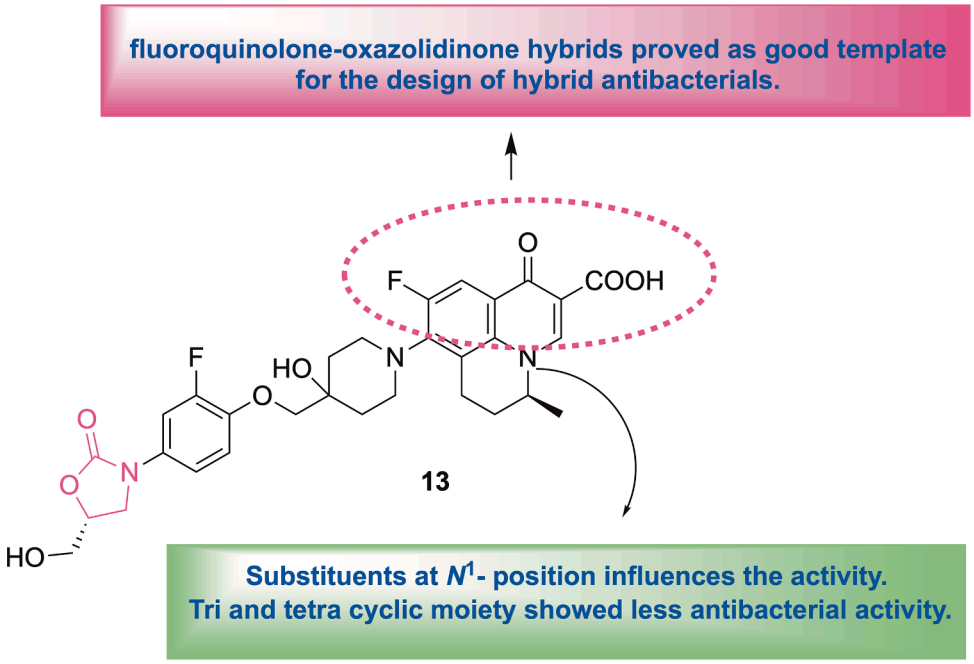


Fig. 12. SAR of oxazolidinone-fluoroquinolone derivatives as antibacterial agents.

Jin et al. in 2022 reported the synthesis, antibacterial and anthelmintic activity of 3-(3-pyridyl)-oxazolidinone-5-methyl ester derivatives. They followed their previous work, where they found pyridine-based heterocycle 4 having good antibacterial and anthelmintic activity and designed new series of compounds replacing the benzene ring with pyridine and a nitrogen atom with an oxygen atom at the 5-position side chain of the oxazolidinone ring. Out of all the synthesized compounds, 5 was found to possess the most potent antibacterial activity. Limited SAR revealed that the presence of methyl sulfonyl group on the C-5 side chain and replacing the morpholine ring with a piperazine ring improved the activity (Fig. 5). Molecular docking analysis in the 50S ribosomal subunit showed 5 to occupy a long and narrow channel with a fully extended state. While the side chain of the oxazolidine ring occupies a relatively small cavity, the piperazine ring extends deeper [31].

Jiang et al. synthesized a series of novel oxazolidinone derivatives with nitrogen-containing fused heterocyclic moiety and evaluated them for antibacterial activity against *S. aureus*, MRSA and MSSA using MIC assay. Most of the compounds displayed potent antibacterial activity when compared to linezolid. Among all, compound 6 showed the most potent antibacterial activity with MIC values of 0.5–1 μg/mL against clinical strains of G^+ including *S. aureus*, which is 32 times more active than linezolid. Molecular docking studies were performed against 50S ribosome unit of *E. coli* with co-crystallized linezolid. It has been shown that the compound exhibits a similar binding pattern as that of linezolid and has π-π interactions with residues U 2619 and U 2620, thus showing good antibacterial action. SAR studies depicts the importance of heteroaromatic moiety, as an introduction of [1,2,4] triazolo [1,5-*a*]pyrazine on the aryl ring of compound 6 increases the antibacterial activity (Fig. 6) [32].

García-Olaiz et al. has reported the structure-modified linezolid substituted with *α*-amino acid substituents in order to increase the

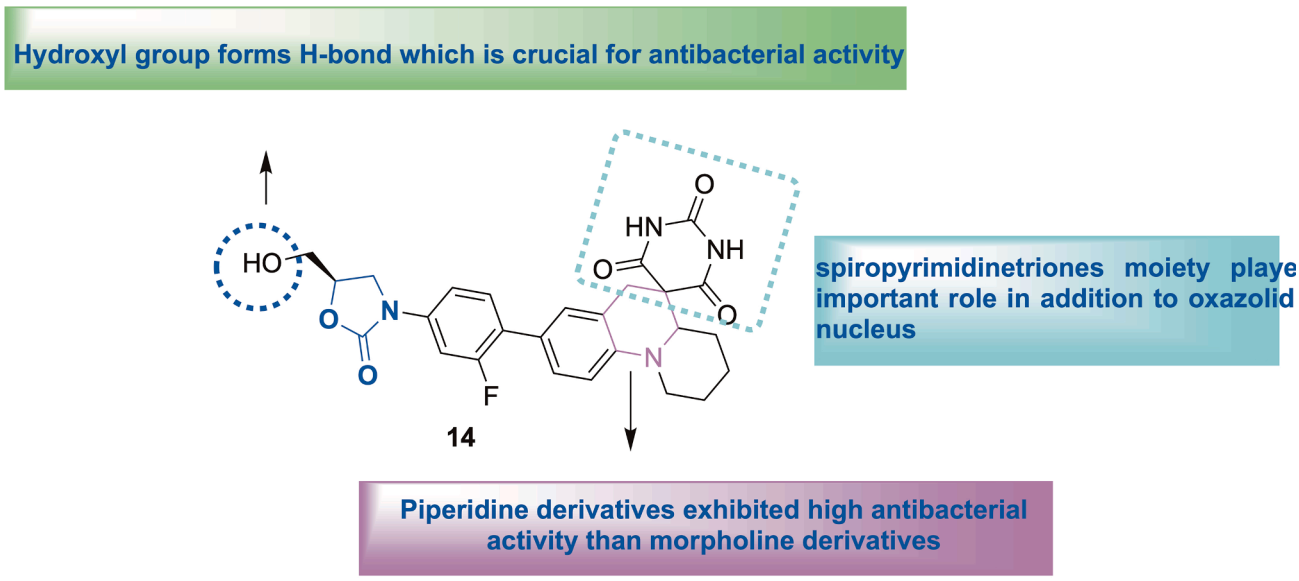


Fig. 13. Spiropyrimidinetrione oxazolidinone derivatives as novel antibacterial agents.

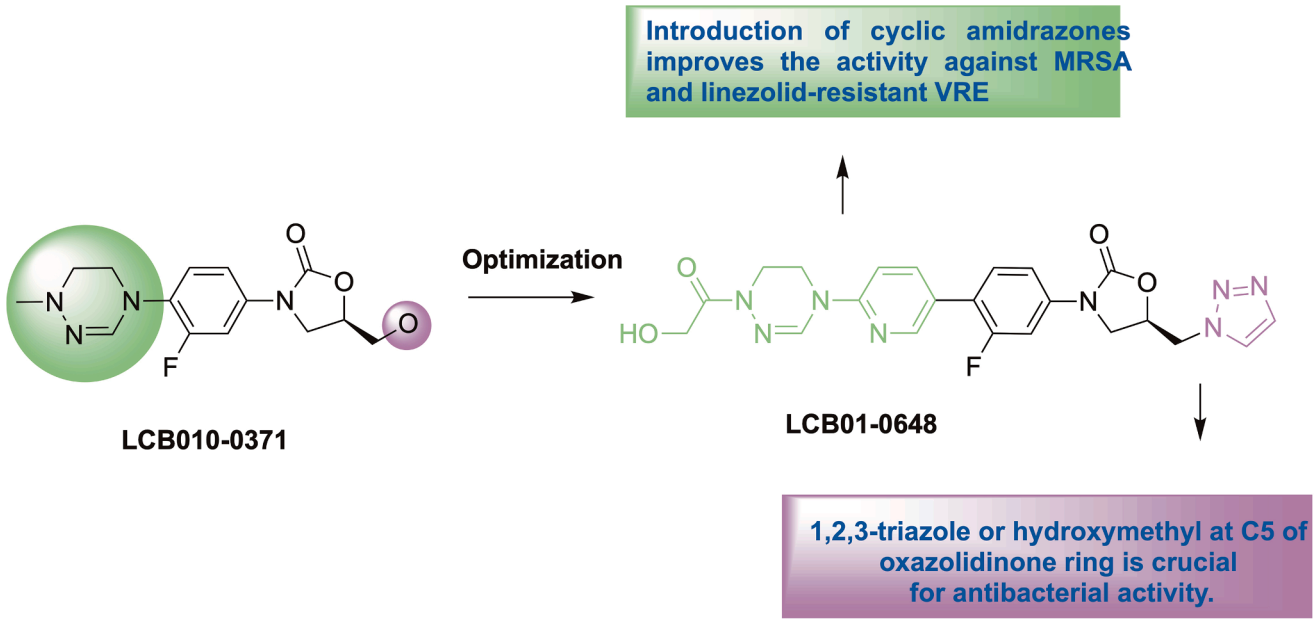


Fig. 14. LCB01–0648 as potent antibacterial agent against linezolid-resistant strains.

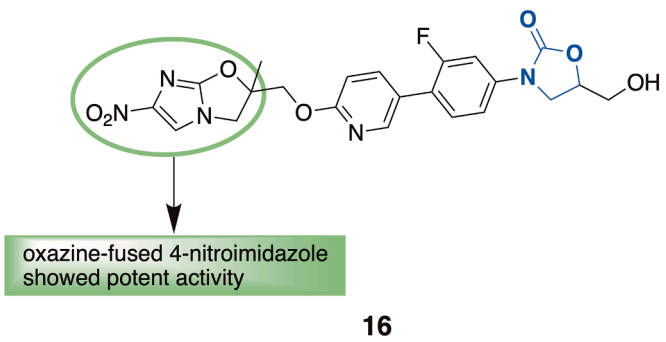


Fig. 15. Pharmacophoric features of nitroimidazole-oxazolidinone conjugates against anaerobic bacteria.

antibacterial activity. During designing, three rings A, B and C of linezolid were preserved while modifications were done on ring A with substituted L-Alanine and L-Phenylalanine, yielding oxazolidinone diastereomers (S,R and S,S), which further coupled to Fmoc-protected amino acid to afford S,R,S and S,S,S diastereomers. These diastereomers were thencoupled with amino acids to obtain a series of 32 compounds, followed by deprotection yielded a database of 64 compounds of linezolid dipeptide-type analogues. All the analogues were subjected to molecular docking against ribosomal RNA (rRNA) of *E. coli* (PDB: 4V4Q) and found extra favourable interactions of linezolid dipeptide-type analogues in the phosphoryl transferase center (PTC) of protein. The chemistry involves the synthesis of 26 compounds, which were then evaluated for antibacterial action against *Streptococcus* and *Staphylococcus* clinical strains using microdilution assay. Among all tested compounds, compound 7 having methyl- substituted amide exhibited significant activity in comparison to a standard, linezolid. The

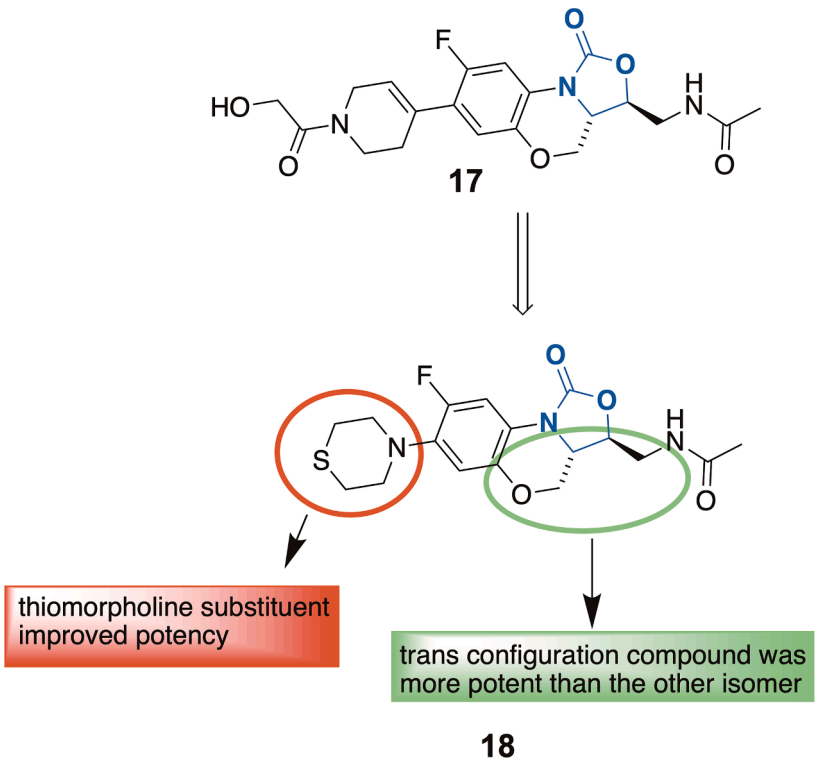


Fig. 16. Pharmacophoric features of conformationally constrained oxazolidinones as antibacterial agents.

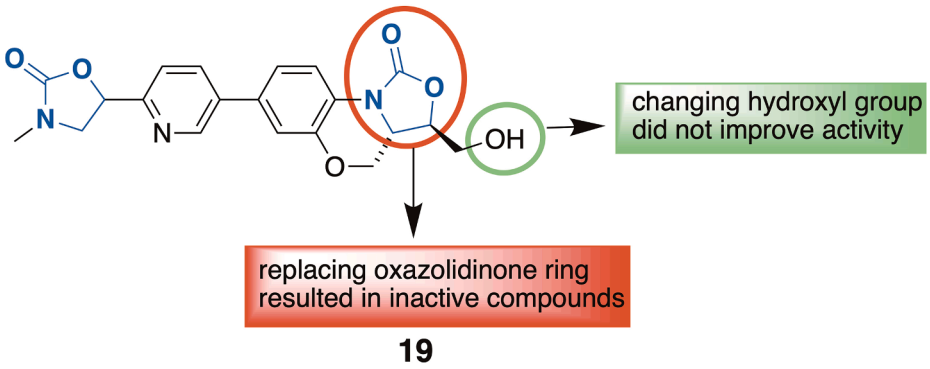


Fig. 17. Pharmacophoric features of [5,6] tricyclic oxazolidinone derivatives as antibacterial agents.

compounds were also evaluated against clinical isolates of multidrug-resistant *Mycobacterium tuberculosis*. Compound 8, which possessed π-π, σ-π and two hydrogen bond interactions with G2505, was found to be the most active when compared to linezolid (Fig. 7). Finally, the active compounds were tested for cytocompatibility assays, which revealed the maintenance of metabolic viability, cellular integrity of the analogues and thus non-cytotoxic effect [33].

Jiang et al. reported a synthesis of eighteen derivatives of 3-amino-2-oxazolidinones and evaluated them for quorum-sensing inhibitory activity against *Pseudomonas aeruginosa* PAO1. Initially, C. *violaceum,* a gram-negative bacteria was used as a reporter strain for preliminary results, followed by *in vitro* and *in vivo* assays. Using 4-p-chlorophenoxy-*n*-(2-oxoxazolidone-3-group)-butylamide as a lead compound, different derivatives were designed by modifying the ring C and D. Preliminary assay displayed that compound 9 exhibited the highest inhibitory action on *C. violaceum* QS with IC_{50} value of 3.686 ± 0.5790 μM (Fig. 8). *In vitro* analysis, also demonstrated compound 9 as an active compound with inhibitory action (ranges from 42.98%−17.67%) on the biofilm formation of PAO1. *In vivo* experiment was carried out using *Caenorhabditis elegans* N2 as a test model to explore further the inhibitory effect of compound 9 on *P. aeruginosa* QS and found that it significantly extended the lifetime of *Caenorhabditis elegans* N2 infected by *P. aeruginosa* PAO1. Overall concluded compound 9 as a viable candidate for antibiotic-resistant *P. aeruginosa* PAO1 and offers a novel approach for the discovery of different antibacterial drugs [34].

Cruz et al. reported a series of *N*-aryl-oxazolidinones derivatives with aryl boronic acid substitution on the external region of oxazolidinones to investigate the effect of acidic substituents on their antimicrobial profile. The compounds synthesized were oxazolidinone analogues coupled with phenylboronic acids with Cl- and F -groups at ortho- and meta -positions on the aryl ring and then tested for antimicrobial activity against bacterial strains. Results displayed that compound 10 has shown eight times to thirty-two times antimicrobial activity against a panel of gram-positive strains. It also exhibited hundred-fold activity against *Escherichia coli* JW5503 with a MIC value of 0.78 μM in comparison to linezolid (MIC = 50 μM). Structural features, including unsubstituted external aryl boronic ring, an amide linkage forming hydrogen bonding interactions and flexible and linear confirmation in compound 10

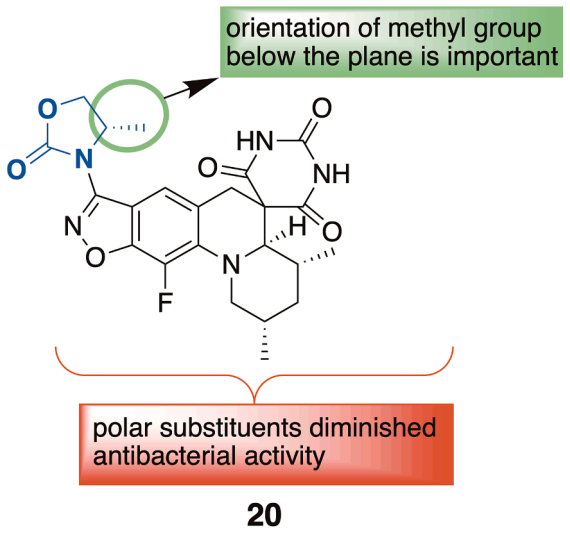


Fig. 18. Pharmacophoric features of *N*-linked oxazolidinone substituted benzisoxazole as antibacterial agents.

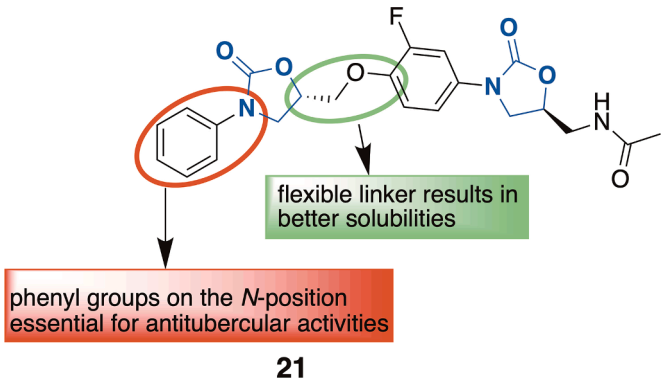


Fig. 19. Pharmacophoric features of bis-oxazolidinone compounds as antitubercular agents.

strengthen the antimicrobial activity (Fig. 9). The presence of an amide linker increased the formation of hydrogen bonding in comparison to ester linkage in the synthesized analogues and thus increased the antimicrobial activity [3].

Ding et al. reported a series of novel oxazolidinone-based UDP-3-*O*-acyl-*N*-acetylglucosamine deacetylase (LpxC) inhibitors as gram-negative antibacterial agents. Compounds containing the oxazolidinone scaffold with linear hydrophobic tails of different lengths were synthesized. Antibacterial evaluation displayed that compounds containing benzene-alkyne-alkyne benzene type structure showed increased antibacterial activity when compared to benzene–alkyne–benzene type structure of molecules (Fig. 10). Further, the replacement of the terminal benzene ring by an aliphatic ring resulted in an active compound 11 with better antibacterial activity against *E. coli* species with MIC of 0.015 μg/ml in comparison to CHIR-090, LpxC inhibitor. However, it did not exhibit an inhibitory effect on *P. aeruginosa* species. Furthermore, metabolic stabilities of the compounds were carried out in liver microsomes. The results indicated weaker metabolic stability of the oxazolidinone derivatives [35].

Hou et al. developed a series of new oxazolidinone derivatives containing a piperidinyl moiety and evaluated them for antibacterial activity against gram-positive bacterial strains including methicillin-resistant *Staphylococcus aureus* (MRSA), MSSA, LREF and vancomycin-resistant *Enterosphere* (VRE) using MIC assay. All the compounds possess potent inhibitory activity against gram-positive strains, when compared to linezolid, a standard drug. Compound 12 was found to be the most active with remarkable antibacterial activity and a MIC value of 0.25–1 μg/mL against *S.aureus,* MRSA, MSSA, LREF and VRE pathogens. SAR study displayed that methylation of the nitrogen atom of derivative 12 decreases the activity, hence, the secondary amine is essential for antibacterial action. The introduction of substituent like bromo at the para position increases the activity, while groups like OCF_3 at the ortho position weaken the antibacterial activity (Fig. 11). The compound was further evaluated against antibiotic-susceptible and antibiotic-resistant clinical isolates including *S.aureus* (4 isolates of MRSA and 4 isolates of MSSA), *E.faecium* (4 isolates of VRE) and *E. faecalis* (4 isolates of LREF). Interestingly, compound 12 showed 64 times more activity against isolates of LREF as compared to linezolid [36].

Liu et al. reported a series of oxazolidinone-fluoroquinolone derivatives with antibacterial activity. The compounds were tested against gram-positive and gram-negative bacterial strains using linezolid, cadazolid and moxifloxacin as reference drugs. Compound 13 emerged as the most active compound among the series with a MIC value of 0.5 μg/ml. The compound was also evaluated for DNA gyrase and Topo IV inhibitory activity by using DNA gyrase supercoiling assay and Topo IV relaxation assay. Compound 13 showed DNA gyrase and topo IV inhibitory activity with IC_{50} value ranges from 1 to 5 μM and 10–15 μM, respectively which was less than the reference drug - ciprofloxacin. The mode of action of the compound was also tested by *in vitro* transcription/translation assay, which displayed that the compound works through protein synthesis inhibition. Molecular docking studies also confirmed that compounds formed, required key interactions, such as hydrogen bonding, within the catalytic domain of the 50S subunit (Fig. 12). In the end, the toxicity study revealed the safety of the compound up to a limit test dose of 2000 mg/kg [37].

Siddiqui et al. reported a new class of spiropyrimidinetrione oxazolidinone derivatives as novel antibacterial agents. Type I and Type II derivatives were designed by modifying the structure of linezolid. In Type I compounds spiropyrimidinetrione moiety was introduced in place of B and C rings, while for Type II derivatives, the C ring (morpholine) of linezolid was replaced with spiropyrimidinetrione moiety (Fig. 13). The derivatives were evaluated against many gram-positive bacteria strains such as *S. aureus*, MRSA 562, MRSA DB-00,026, S. aureus (LNZ resistant), *S. epidermidis*, MRSE and *S. epidermidis*. Results displayed that Type II derivatives exhibited antibacterial activity with MIC value ranges between 1 and 8 μg/mL, whereas Type I did not show any antimicrobial activity. Further, active Type II derivatives were tested against LNZ-resistant and vancomycin-resistant *enterococci* strains and compound 14 bearing piperidine moiety was found as the most active compound of the series. Docking studies of compound 14 on 50S ribosome unit of *E.coli* also suggested the importance of oxazolidinone and spiropyrimidinetriones moiety as they are involved in key interactions, like hydrogen bonding and hydrophobic interactions, important for the antibacterial activity [38].

Sang-Hun Oh et al. reported two novel oxazolidinone compounds LCB01–0062 and LCB01–0371 as antibacterial agents in the year 2010 and 2012 [39,40]. Though the compounds were potent and safe, but not so effective against linezolid-resistant strains. To improve the activity, the authors further modified the structure of previously oxazolidinone compounds with cyclic amidrazone moiety. Four new compounds were synthesized and evaluated against MRSA and linezolid-resistant VRE. Results confirmed that all compounds showed potent activity in tested strains. Out of these 4 compounds, LCB01–0648 (15) was chosen as the lead compound and was further tested against 610 clinically isolated gram-positive cocci strains (Fig. 14). It has been found that LCB01–0648 exhibits the highest activity against *Streptococcus pneumoniae* and *Streptococcus pyogenes* with MIC90s of 0.25 mg/L, which is four to eight times higher than linezolid, a reference drug [41].

In 2020, Zhuang et al. reported synergistic activity of nitroimidazole-oxazolidinone conjugates against anaerobic bacteria. They utilized the

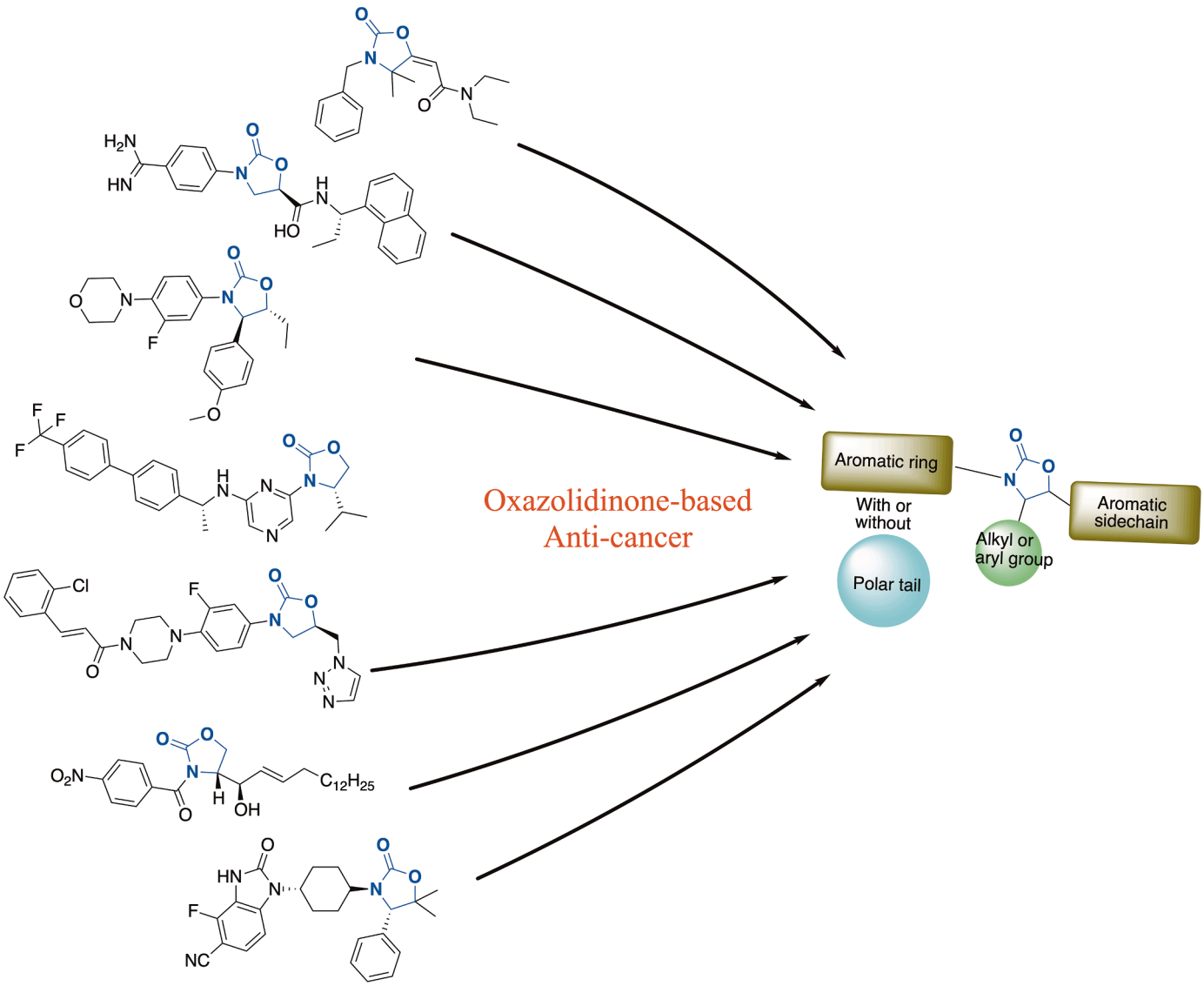


Fig. 20. Common pharmacophoric features identified from structural features of oxazolidinones as anticancer agent.

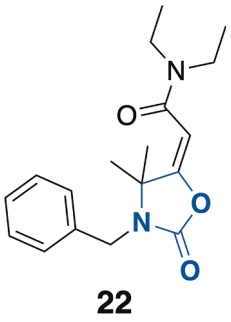


Fig. 21. 2D structure of potent 5-(carbamoylmethylene)-oxazolidin-2-one derivative.

already known SARs and drug designing generalizations of oxazolidinones as antimicrobial agents including H-bonding and hydrophobic interactions between linezolid and binding domain located within the ribosomal peptidyltransferase center of 50S ribosomal subunit. SAR of linezolid suggests that the oxazolidinone ring and the acetamide group on the right side of the molecule are essential. The fluorophenyl moiety in the middle is also important. However, the morpholino ring on the left side does not have significant interactions within the binding site. Therefore, they explored this position to couple a bicyclic 4-nitroimidazole core. A series of conjugates having bicyclic 4-nitroimidazole on the right-hand side and oxazolidinone core on the left-hand side coupled via different linkers were designed synthesized and evaluated for their anitmicrobial property. Out of all, four compounds were highly active against the H37Rv strain with MICs similar to standard drugs, linezolid and pretomanid. Compound 16, having oxazine-fused 4-nitroimidazole and the oxazolidinone core showed more potent activity against the linezolid-resistant strains L1 and L3 (Fig. 15). Overall, nitroimidazole-oxazolidinone coupled compounds showed improved antibacterial potential against anaerobic infections [42].

In 2020, Zhao et al. reported the discovery of conformationally constrained oxazolidinones for the treatment of multidrug-resistant tuberculosis (TB). They followed up their previous work, whereby they identified a benzoxazinyl-oxazolidinone derivative with potent *in vitro* antitubercular activity similar to linezolid. To further improve the activity and drug-like property, they performed lead optimization on the previous top hit 17. Optimization was carried out by varying substituents on both sides of the core. Out of all the compounds, 18 was found to possess the most potent inhibitory activity. SAR analysis suggested that the compound in trans configuration was more potent than

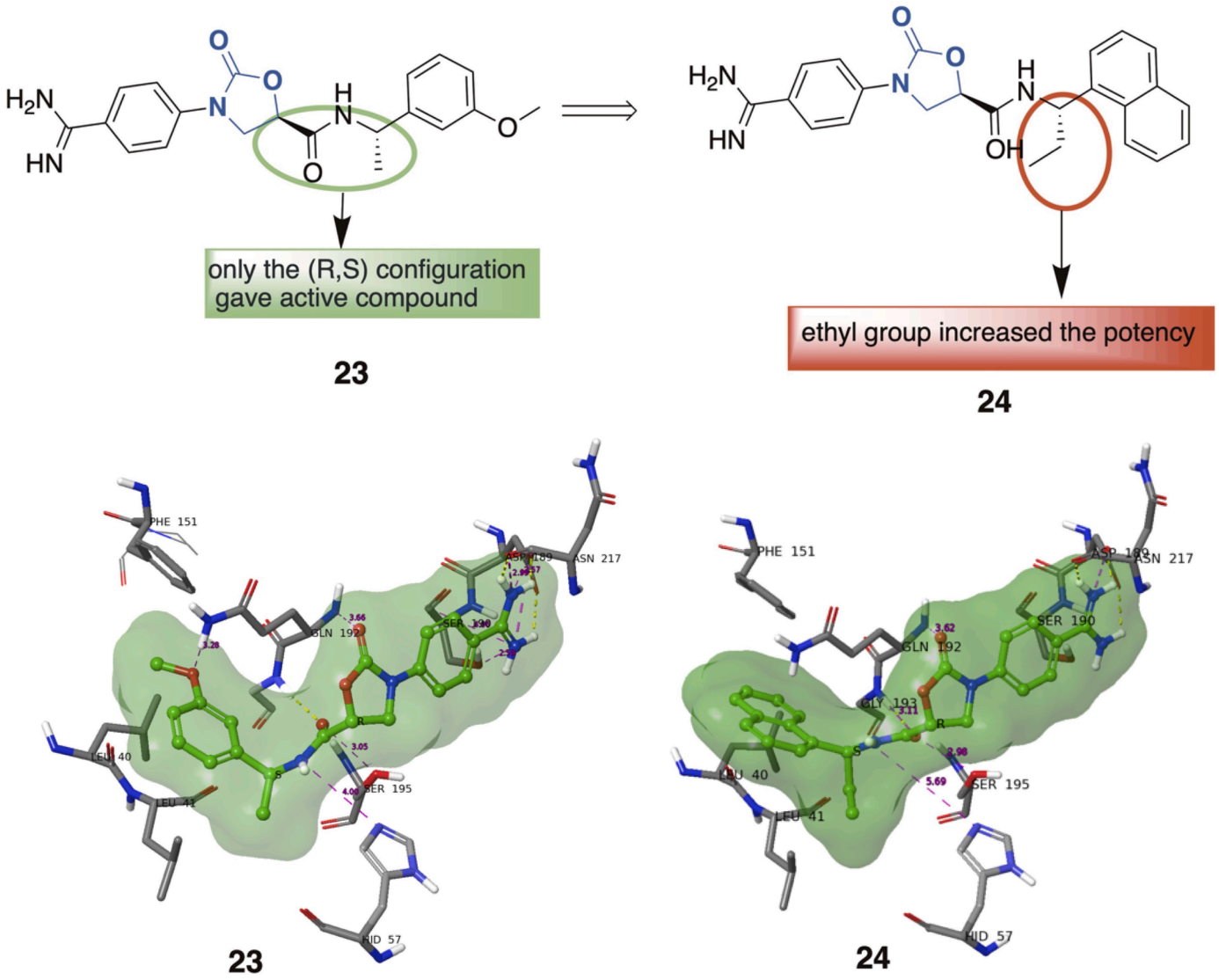


Fig. 22. Pharmacophoric features and molecular docking of *N*-(4-benzamidino)-oxazolidinones as inhibitors of KLK6 (PDB ID: 4D8N).

the other isomer. Also, the thiomorpholine substituent on the benzyl ring of the core resulted in the potent derivative (Fig. 16). Overall, the study supported the claim that oxazolidinone derivatives result in potent antibacterial agents [14].

In 2018, Zong et al. compared the *in vitro* activity of delpazolid (Table 1), a novel oxazolidinone compound, with linezolid against multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis*. They studied 240 MTB -isolates including 120 MDR-TB and 120 XDR-TB isolates and found no significant difference in resistance rate between linezolid and delpazolid among XDR-TB isolates. However, a significantly higher proportion of linezolid-resistant isolates within the MDR group were found. Overall, the study concluded that delpazolid antibacterial activity is comparable to that of linezolid, while a novel mutation identified within rplD resulted in resistance against linezolid (but not against delpazolid) in MTB [43].

In 2015, Xue et al. followed their previous discovery of a novel benzoxazinyl-oxazolidinone- based antibacterial compound 19, to further explore the [5,6] tricyclic fused oxazolidinone scaffold. They synthesized a series of novel [5,6] tricyclic oxazolidinone derivatives and evaluated them for antibacterial activity against a panel of gram-positive bacteria strains. Out of all, four compounds having benzothiazinyl-oxazolidinones with acetamide or thioamide as C3 side chains exhibited moderate to good antibacterial activity. SAR analysis indicated that alterations in B/C rings and C3 side chains resulted in significant variation in antibacterial activity. Further replacement of the oxazolidinone ring resulted in inactive compounds. Also, substituting oxygen atom in the B ring with NH or NBoc resulted in inactive compounds. When the oxygen was further changed to a sulfur atom, in C3 hydroxyl compounds, no activity was observed, while their corresponding C3 acetamide or thioamide compounds gave moderate to good antibacterial activity, which was comparable or slightly superior to that of linezolid (Fig. 17). Long half-life and low liver microsomal clearance both in rat and human liver microsomes suggested that the top compounds of the series were metabolically stable. Binding mode exploration of these [5,6] tricyclic derivatives showed, that these compounds targeted the ribosomal peptidyltransferase center (PTC) in a similar manner as that of linezolid and the benzene ring A and oxazolidinone ring C of the compounds superimposed well, forming shifted-stacking interaction with C2487 and edge-to-face interaction with A2486. Oxazolidinone ring formed stacking interaction with U2539. Moreover, the B ring provided additional shifted-stacking interaction with C2487. The thioamide formed a H-bond with G2540, which was similar to that of linezolid [44].

In 2015, Basareb et al. described *N*-linked oxazolidinone substituted benzisoxazole derivatives with improved antibacterial activity in comparison to previous molecules of the same class. In the previous study,

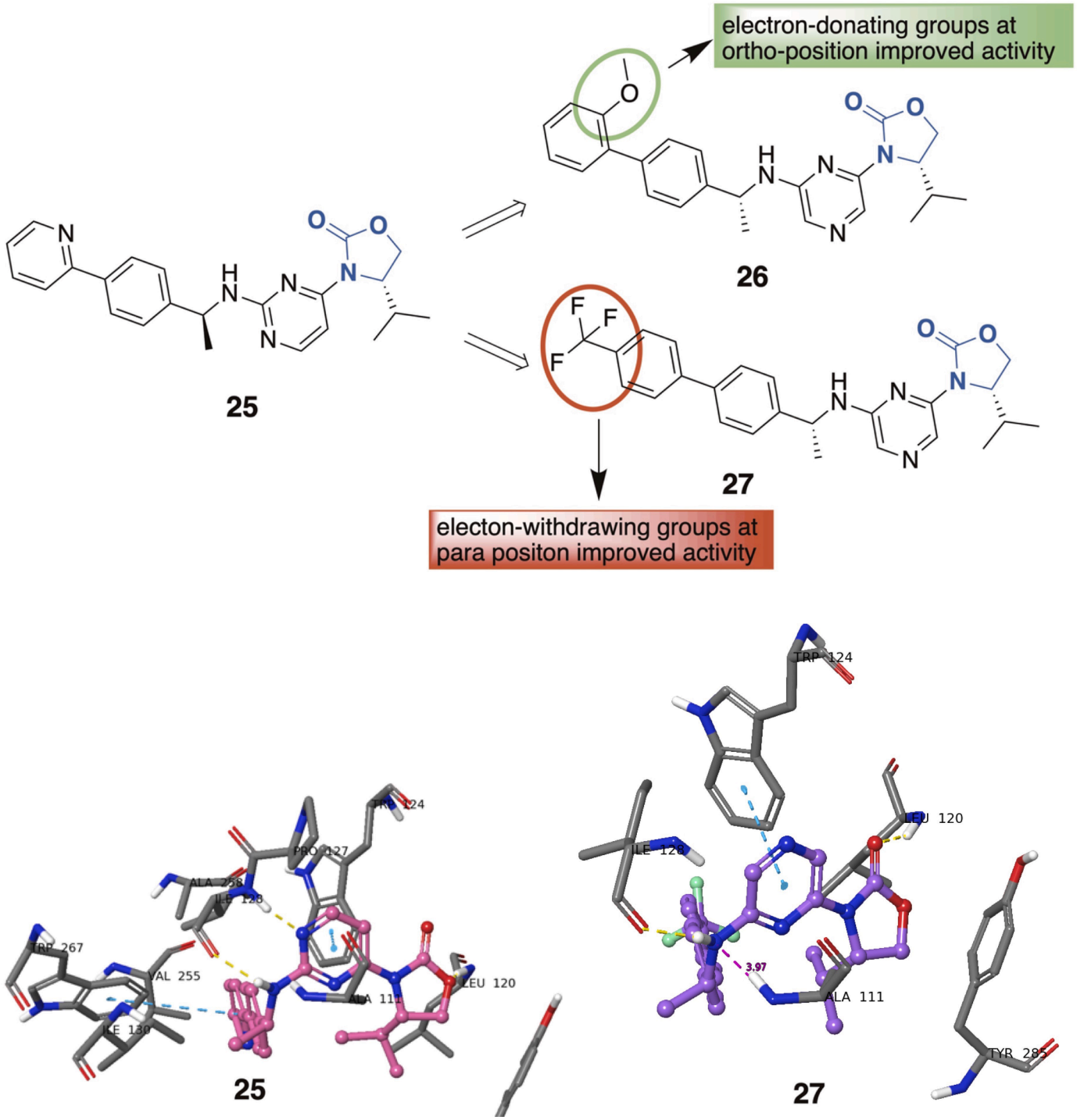


Fig. 23. Pharmacophoric features and molecular docking of 3-pyrazine-4-yl-oxazolidin-2-ones as selective inhibitors of mIDH1 (PDB ID: 5TQH).

the same group reported a novel class of antibacterial agents with a benzisoxazole scaffold fused to a six-membered ring that displays a spirocyclic pyrimidinetrione pharmacophore (ETX0914; 20). The previous SAR study showed that the oxazolidinone substituent averted bone marrow toxicity and genotoxicity seen with other substituents, which led to the selection of ETX0914 for development through phase 1 clinical trials (Clinicaltrials.gov Identifier: NCT01929629). So they continued a detailed analysis of benzisoxazole spiropyrimidinetriones with *N*-linked oxazolidinone substituents as antibacterial agents. Several derivatives and isomers of previous derivatives were synthesized and SAR analysis disclosed that substituents at each of the oxazolidinone 4- and 5-positions showed similar activity. Substitution at both the 4- and 5-positions with methyl groups followed the trend where the overall highest potency was seen with the orientation of both methyl groups below the plane of the oxazolidinone ring (Fig. 18). More polar substituents diminished antibacterial activity presumably due to decreased target potency and/or bacterial membrane permeability. Overall, the profile of ETX0914 and other oxazolidinone analogues were evaluated for the progression of the drug candidate. Gonorrhea was chosen as a gateway indication to evaluate ETX0914 in clinical trials [45].

In 2014 Ang et al. reported the discovery of novel bis-oxazolidinone compounds as potential and selective antitubercular agents. Continuing

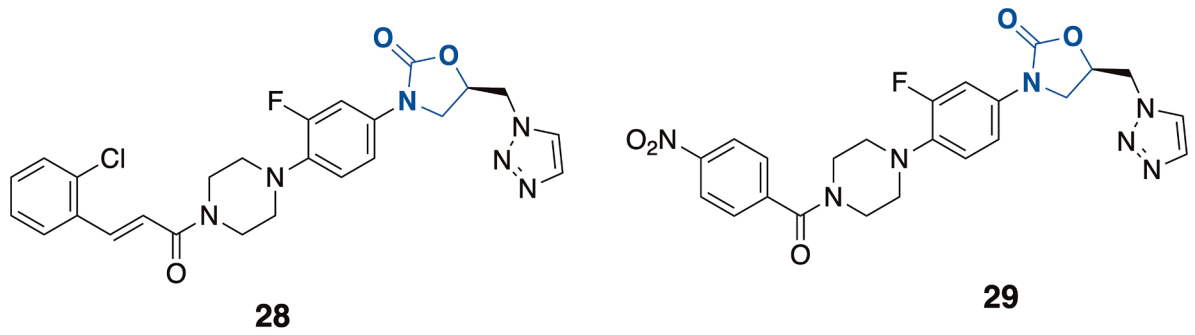


Fig. 24. 2D structure of 5-(1*H*-1,2,3-triazolyl) methyl- and 5-acetamidomethyl-oxazolidinones.

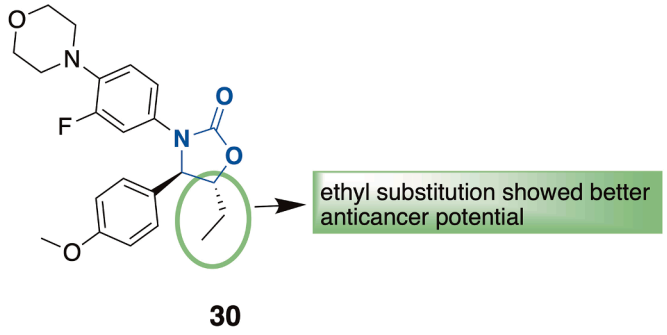


Fig. 25. Pharmacophoric features of linezolid based oxazolidinones as anticancer agents.

their previous work, they modified the C-ring of linezolid and synthesized 26 novel oxazolidinone or bis-oxazolidinone compounds. Compounds were evaluated for *in vitro* antibacterial activities against *Staphylococcus aureus, M.smegmatis, E. coli* and *Pseudomonas aeruginosa*. Out of all, several bis-oxazolidinones showed highly selective potent activities against *M. tuberculosis* H37Rv with excellent safety profile on monkey kidney Vero cells, especially 21, with a selectivity index over 40,000. A preliminary SAR analysis suggested that introduction of a second oxazolidinone ring can significantly improve their selectivity and potency against *M. tuberculosis*. A flexible linker between the second oxazolidinone ring and the B-ring of linezolid results in better solubilities. The introduction of a third oxazolidinone ring does not seem to take effect on the enhancement of antitubercular activities (Fig. 19). Phenyl or substituted phenyl groups on the *N*-position of the second oxazolidinone ring were essential to remain antitubercular activities [46].

Of course, these molecules may have a different mechanism of action for their antibacterial potential, but we are here underlying the structural features, which have been known to impart antibacterial potential to oxazolidinones so, that we can understand what else can be done with this core to explore its full pharmacological potential. This brings us to the next part, now, we will look at the oxazolidinone derivatives having other pharmacological profiles.

1.3. Is it only good for antibacterials: A look at other medicinal attributes

Now we will have a look at oxazolidinone derivates reported to possess other pharmacological profiles and will explore the question if this core is only good for antibacterials.

1.4. Anticancer

Few oxazolidinone derivatives reported to possess anticancer potential suggests that oxazolidinone core having aromatic/heteroaromatic substituent coupled with or without polar cyclic groups on the N of the core, small alkyl or aryl group on the 4th position and alkyl/aryl group on the 5th position can yield potent anticancer agents. Interestingly, these attempts explored the substitutions on the 4th position of the core, which was not that readily observed in studies discussing antibacterial agents (Fig. 20).

In 2020, Armentano et al. claimed that 5-(carbamoylmethylene)-oxazolidin-2-ones increase ROS levels and induce mitochondrial dysfunction leading to apoptosis in breast and cervical cancer. They followed previous reports indicating oxazolidinones to possess antiproliferative potential via different mechanisms as guiding rationale to design 5-(carbamoylmethylene)-oxazolidin-2-ones as anticancer agents against estrogen receptor-positive (ER+) breast cancer (MCF-7) and uterin cervix adenocarcinoma (HeLa) cell lines. Out of all the compounds, only OA, OB, OC, and OI displayed promising antiproliferative potential. OI (22) showed the lowest IC_{50} value in both tested cancer cell lines (Fig. 21) and triggered an increase in ROS -levels and mitochondrial damage-inducing apoptosis [47].

In 2020, De vita et al. reported *N*-(4-benzamidino)-oxazolidinones as potent and selective inhibitors of kallikrein-related peptidase 6 (KLK6) imparting their anticancer activity. KLK6 has been found to be dysregulated in cutaneous malignant melanoma. In this cancer, KLK6 also activate protease-activated receptors (PAR-1), which are overexpressed on melanocytes and have an effect on tumor migration and invasiveness. They first performed a high throughput screening using European Lead Factory and found compounds with oxazolidinone benzamidine core formed the most promising cluster with nine derivatives. SAR analysis considering this pool of compounds suggested that compounds with an amide directly linked to oxazolidinone have better activity as in case of 23. Docking analysis of 23 in the crystal structure of KLK6 revealed that the amidine group of 23 forms H-bonds with Asp189 and Ser190 and results in improved binding. Further, the docking-guided optimization of this scaffold, with a focus on potency against KLK6, resulted in compounds with nanomolar potency and good selectivity. Compound 24 was found to be the most potent inhibitor and showed reduced invasion of HCT116 cells in a dose-dependent manner (Fig. 22). Overall SAR disclosed that ethyl- and 1-naphthyl -substituents on the amide terminal showed the best potency [48].

In 2017, Ma et al. reported the design, synthesis and biological activity of 3-pyrazine-4-yl-oxazolidin-2-ones as selective inhibitors of mutant isocitrate dehydrogenase 1 (mIDH1), an enzyme responsible for the growth of tumor cells, such as gliomas and acute myeloid leukemia. They used NI-1 (25), a 3-pyrimidin-4-yl-oxazolidin-2-one based mIDH1 -inhibitor developed by Novartis, as a template to design a series of 3-pyrazine-4-yl-oxazolidin-2-one based inhibitors. Upon biological evaluation against HEK-293T cell lines expressing IDH1-R132H and IDH1-R132C, compounds 26 and 27 reduced the levels of D-2-hydroxyglutarate in the cells significantly at two concentrations, suggesting compounds with 3-pyrazine-4-yl-oxazolidin-2-ones to have inhibitory potential against mutant IDH1. SAR analysis revealed that electron-withdrawing groups at the para positon and electron-donating groups at meta- and ortho-positions improved activity (Fig. 23). Molecular

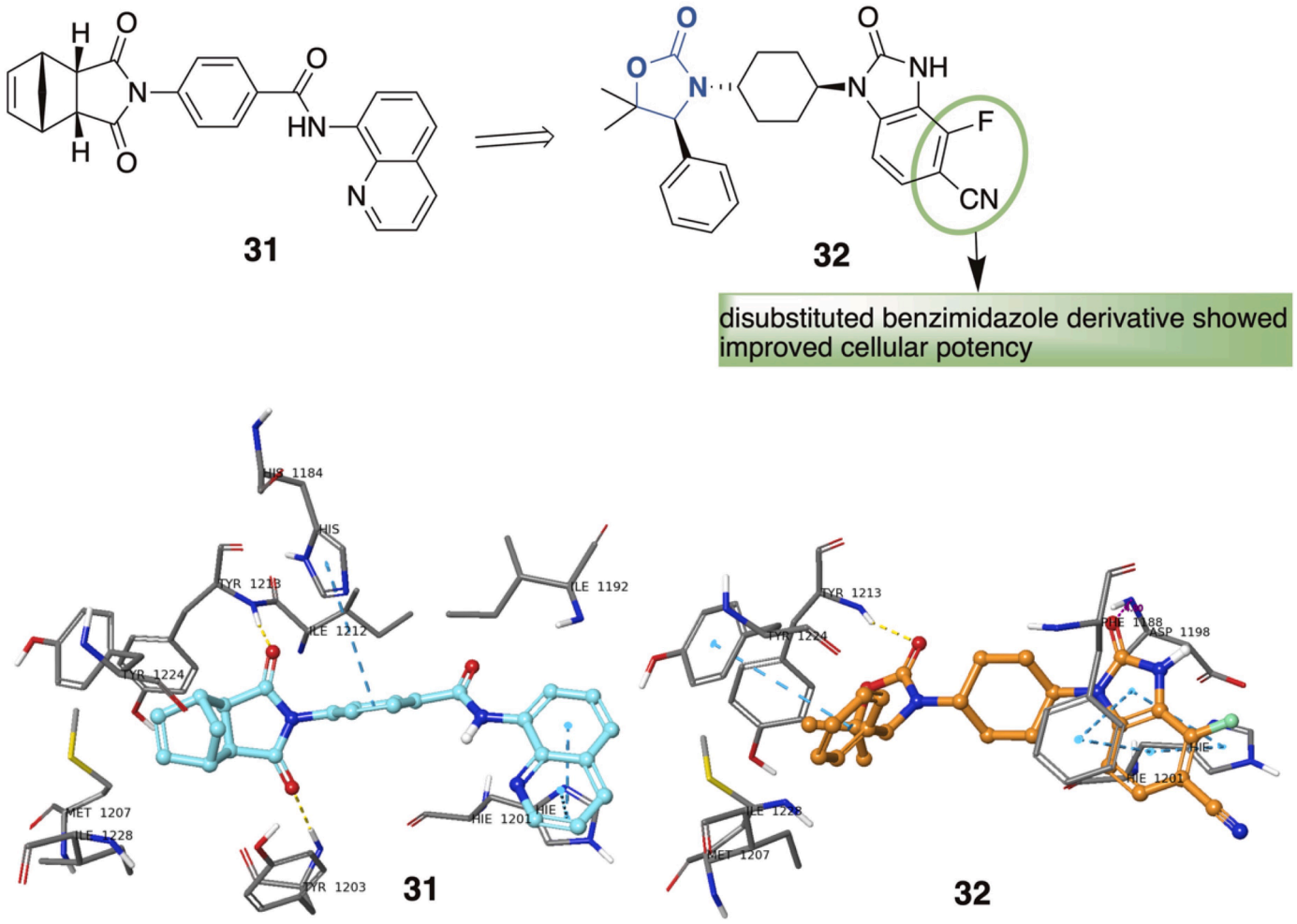


Fig. 26. Pharmacophoric features and molecular docking of oxazolidinones as tankyrase (TNKS) inhibitors. The image on the left represents the X-ray structure of TNKS with co-crystallized inhibitor 31 (PDB ID: 4OA7). Compound 32 - TNKS (PDB ID: 4OA7) docking result is shown on the right.

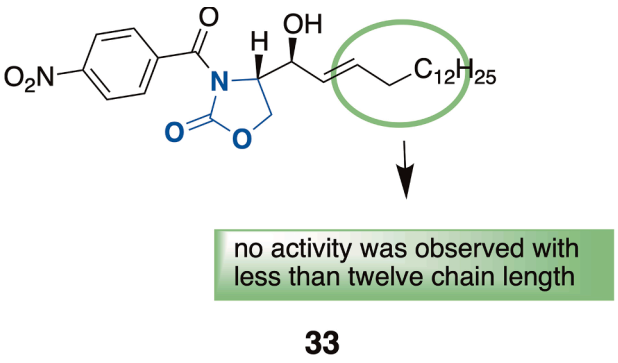


Fig. 27. Pharmacophoric features of oxazolidin-2-ones as constrained ceramide analogs with anticancer activities.

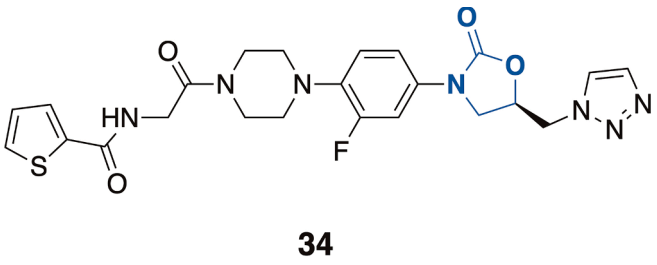


Fig. 28. 2D structure of PH192.

docking analysis revealed that 26 in the allosteric pocket of mIDH1 forms a polar interaction with Ile128 and an H-bond interaction with Leu120 [49].

Hedaya et al. in 2016 reported antiproliferative activity of 5-(1*H*-1,2,3-triazolyl) methyl- and 5-acetamidomethyl-oxazolidinones. They explored the cytotoxic side effect of antibacterial oxazolidinones in mammalian cells to design oxazolidinone-based antiproliferative agents. They synthesized 5-(1*H*-1,2,3-triazoly)-l-methyl-, 5-acetamidomethyl-morpholino and *N*-substituted-piperazino oxazolidinone derivatives and evaluated them via MTT assay, first, against MCF7 human breast cancer cells, whichafter the top three compounds were evaluated against MDA231 breast cancer cells. Out of all, derivatives with 4-*N*-(2-chlorocinnamoyl) (28), 4-*N*-(4-nitrobenzoyl) (29) and 4-*N*-methylsulfonyl substituents exhibited the most potent cytostatic activity against cancer cell lines with 70% inhibition in proliferation (Fig. 24). The cytostatic potential was observed to be in a similar order as the antibacterial potential of these compounds against *Staphylococcus aureus*. Importantly, several derivatives led to proliferation at 100 nM highlighting the need for a more detailed analysis [50].

In 2014, Naresh et al. reported the synthesis of linezolid-based novel oxazolidinone derivatives as anticancer agents. They attempted to study the effect of C-4 substitution of the oxazolidinones, which leads to *erythro*- and *threo* -stereoisomers, on their anticancer potential.

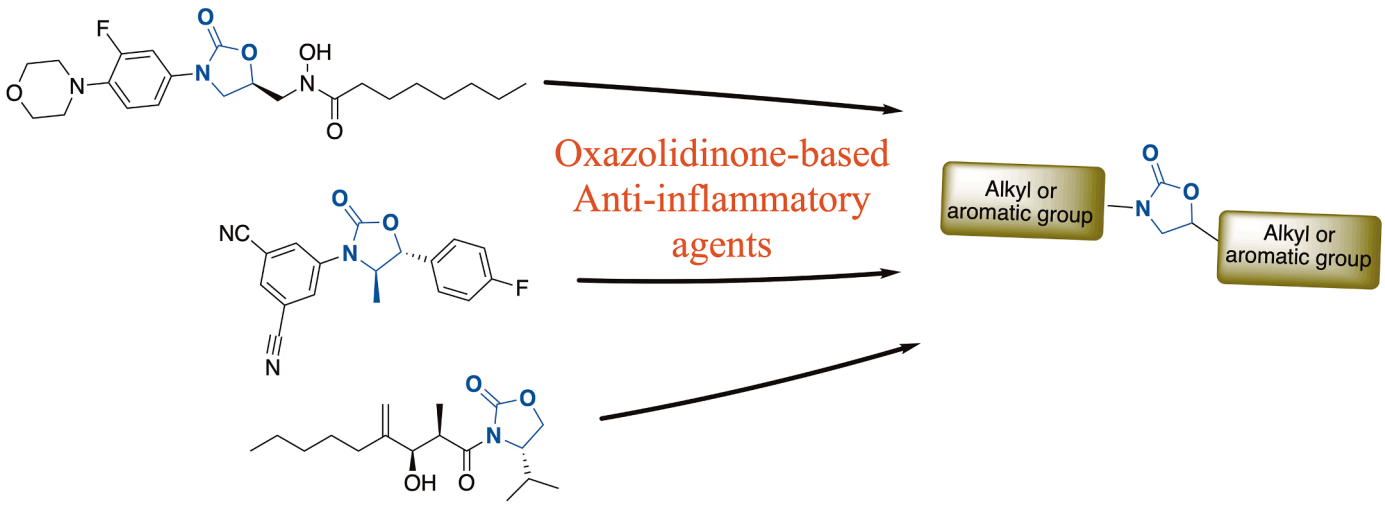


Fig. 29. Common pharmacophoric features identified from structural features of oxazolidinones as anti-inflammatory agent.

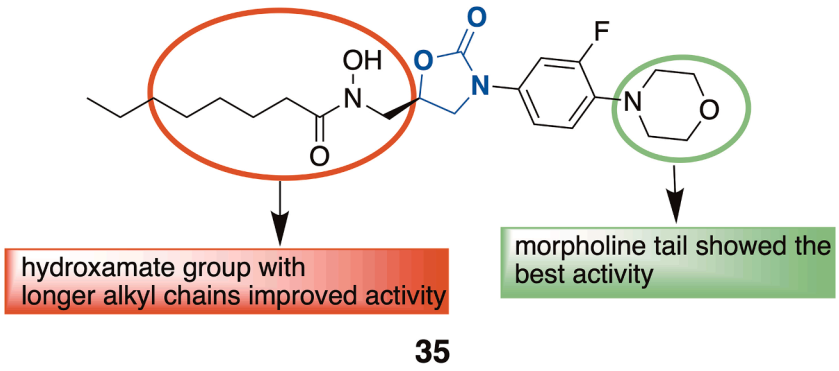


Fig. 30. Pharmacophoric features of 5-(hydroxamic acid)methyl oxazolidinones as 5-LO inhibitors.

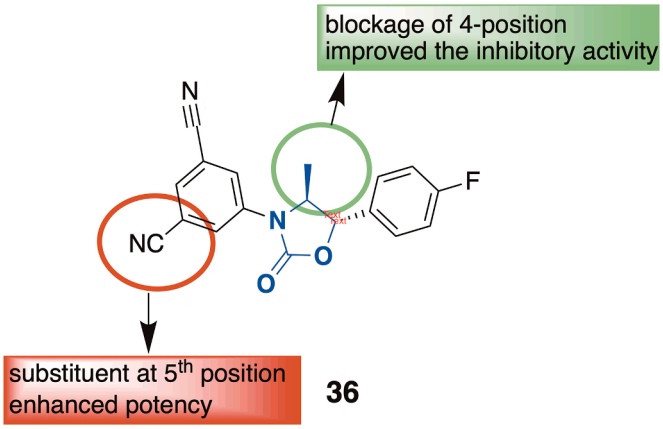


Fig. 31. Pharmacophoric features of 3,5-diphenyl-4-methyl-1,3-oxazolidin-2-ones as D5D inhibitors.

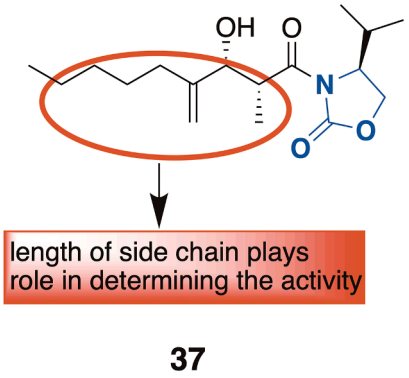


Fig. 32. Pharmacophoric features of oxazolidinone derivatives as IL-6 inhibitors.

Evaluation of anticancer activity using A549, DU145, HELA, and MCF7 cell lines revealed that compound 30 showed better potency in limiting cancer cell proliferation partly by direct targeting cell cycle progression and inducing cellular senescence. SAR analysis suggested that oxazolidinone hybrids with acryl- or ethyl -substitutions showed better anticancer potential than other derivatives (Fig. 25) [51].

In 2013 Bergman et al. reported the discovery of novel oxazolidinones as potent tankyrase (TNKS), a poly-ADP-ribosylating protein, inhibitors. They hypothesized that inhibition of TNKS may lead to better treatment of colorectal cancer. They utilized the known TNKS inhibitor IWR1 (31) as the starting point for SAR evaluations. Careful analysis of IWR1 in complex with TNKS revealed that H-bond with Tyr1213 and Asp1198 are essential for the inhibitory activity. Overall SAR study disclosed that disubstituted benzimidazole derivative (32) showed improved cellular potency and selectivity over PARP1/2 in comparison to IWR1 (Fig. 26) [52].

In 2011, Singh et al. reported 3,4-disubstituted oxazolidin-2-ones as constrained ceramide analogues with anticancer activities. Cell-

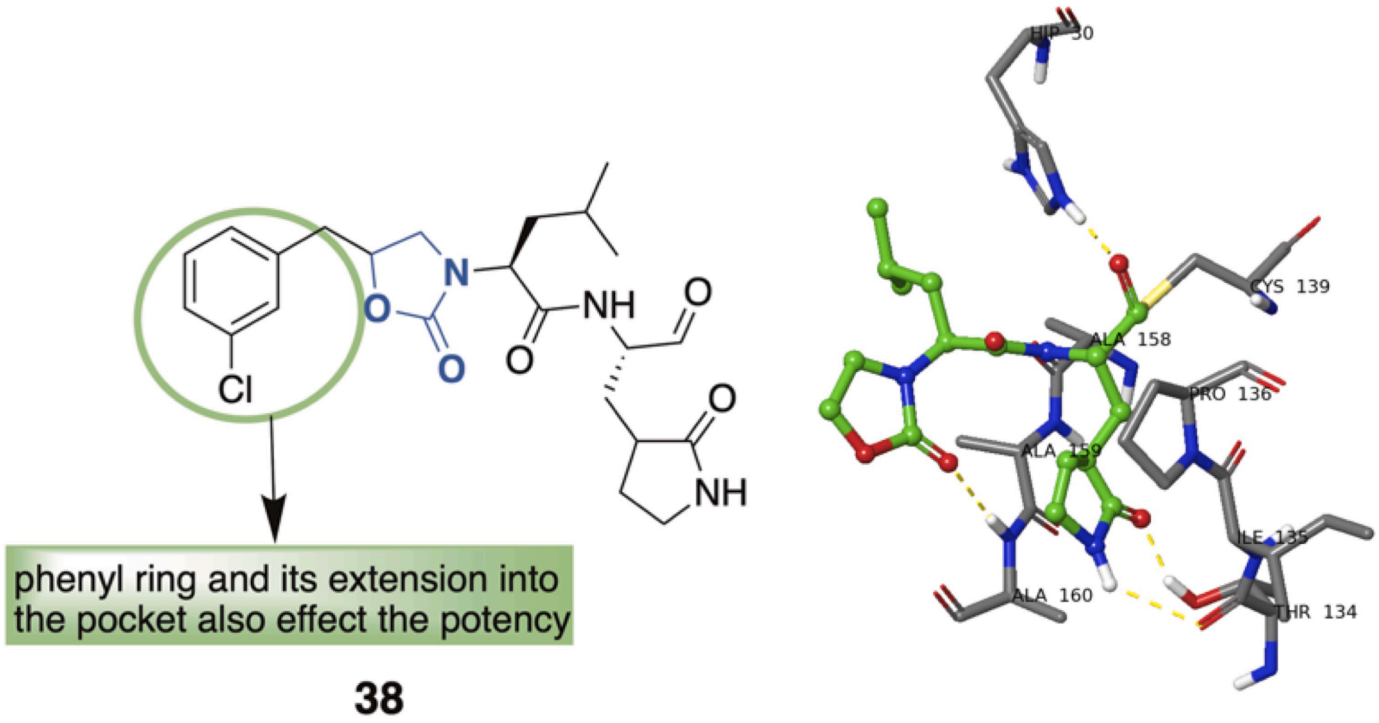


Fig. 33. Pharmacophoric features and molecular visualization of crystal structure for oxazolidinone-based covalent inhibitor of norovirus 3CL protease (PDB ID: 5WEJ).

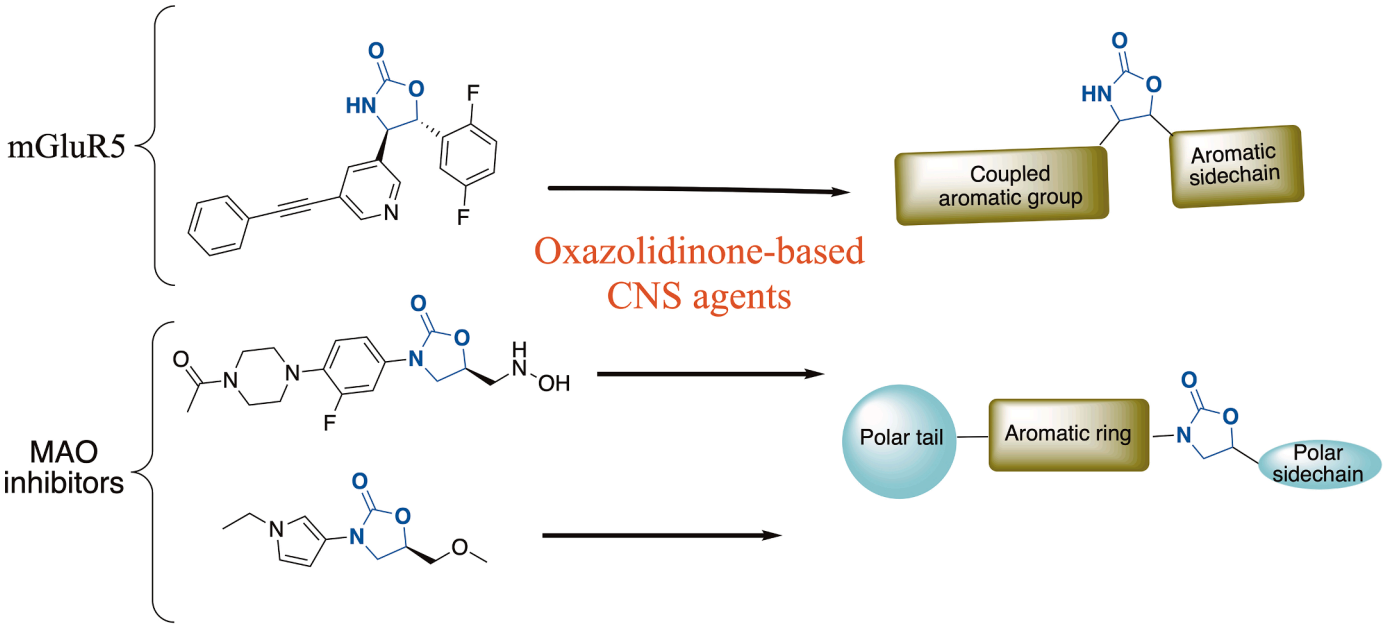


Fig. 34. Common pharmacophoric features identified from structural features of oxazolidinones as CNS agent.

permeable ceramides having short acyl groups are reported to inhibit tumor cell growth and induce apoptosis in leukaemia cell lines. Additionally, constrained ceramide analogues are known to overcome metabolic perturbation. Therefore in this work, Singh et al. followed up their previous work, where they synthesized novel constrained ceramide analogues using the oxazolidin-2-one ring and found them to have similar conformational and electronic properties as ceramide. In this study, they designed 3-alkanoyl or benzoyl-4-(1- hydroxy-2-enyl)-oxazolidin-2-ones as ceramide analogs by binding of primary alcohol and amide in sphingosine backbone as a carbamate. Out of all, the compounds tested against HL-60 cell line, propionyl, cyclopentanoyl and p-nitrobenzoyl-4-(1-hydroxyhexadec-2-enyl)- oxazolidin-2-ones (33) showed better antileukemic activities than natural ceramide with good correlation between cell death and DNA fragmentation. SAR analysis showed that no activity was observed in the compounds with less than twelve chain length of sphingoid backbone (Fig. 27) [53].

1.5. *Anti-convulsant*

In 2019, Qaddoumi et al. reported a novel oxazolidinone derivative,

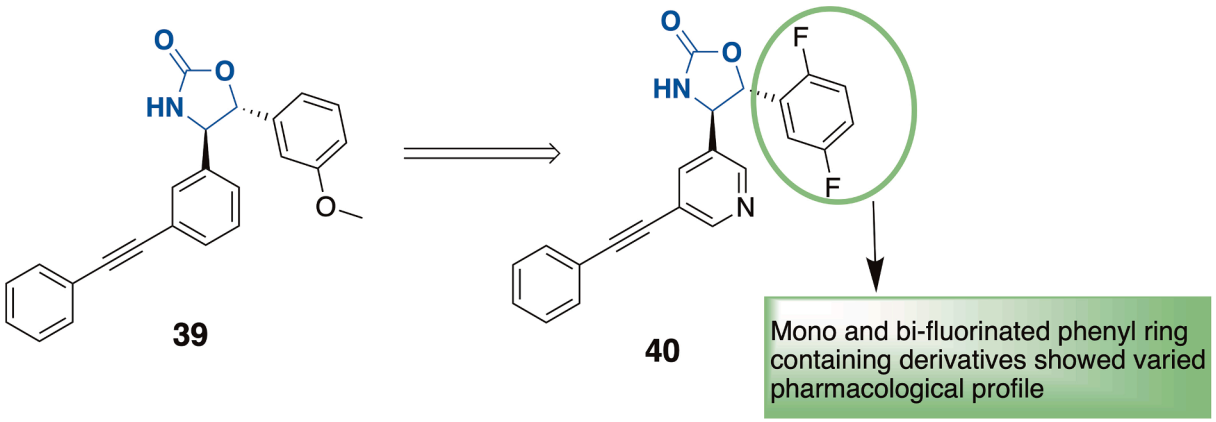


Fig. 35. Pharmacophoric features of oxazolidinone-based allosteric modulators of mGluR5.

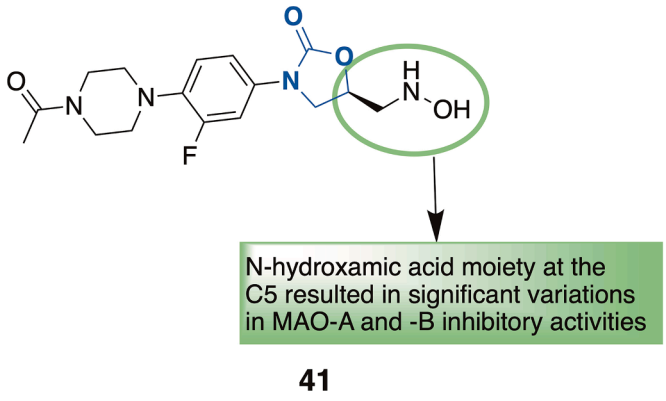


Fig. 36. Pharmacophoric features of 5-(hydroxamic acid)methyl oxazolidinone derivatives as MAO inhibitors.

PH192 to possess anticonvulsant activity *in vivo* in rats and mice (Fig. 28). To identify novel anticonvulsant agents, they synthesized and screened 5-triazolyl oxazolidinone derivatives for their *in vitro* inhibitory potential against seizures. It lead to the identification of some derivatives with anticonvulsant potential *in vivo*. Detailed *in vivo* study revealed that out of five 5-triazolyl oxazolidinone analogues, PH192 (34) showed the most potent activity in both mice and rat models with ED_{50} values of 34 mg/kg in mice and 90 mg/kg in rats along with improved toxicity profile. Overall, this study highlights the potential of oxazolidinone derivatives to be developed as CNS active agents [54].

1.6. *Anti-inflammatory*

Next, oxazolidinone derivatives reported as anti-inflammatory agents suggest that only limited exploration on the N and 5th position of oxazolidinone, with substituted aromatic and alkyl chains has been done (Fig. 29).

In 2020, Philips et al. reported synthesis and structure-activity relationships of 5-(hydroxamic acid)methyl oxazolidinones as 5-lipoxygenase (5-LO) inhibitors. They utilized the pharmacological profile of hydroxamic acid to design oxazolidinone-coupled hydroxamic acid-based 5-LO inhibitors. Out of all the 19 derivatives, compound PH-251 (35) was found to be the most potent with inhibitory activity comparable to zileuton and effective inhibition of mast cell LT release. SAR analysis revealed that derivatives having a hydroxamate group with longer alkyl chains and morpholine tail on the other side showed the best activity. However, increasing the alkyl chain to 7 carbon decreased the activity (Fig. 30). Detailed studies established compounds to possess anti-inflammatory potential without any toxicity [55].

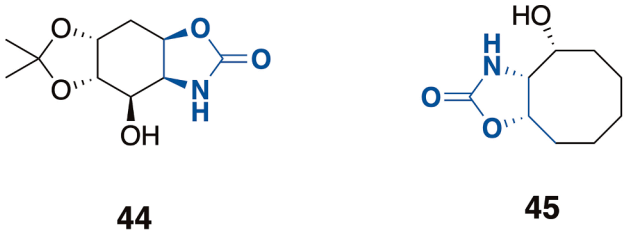


Fig. 38. 2D structure of oxazolidinones as selective hCA, AChE, and α-glycosidase inhibitors.

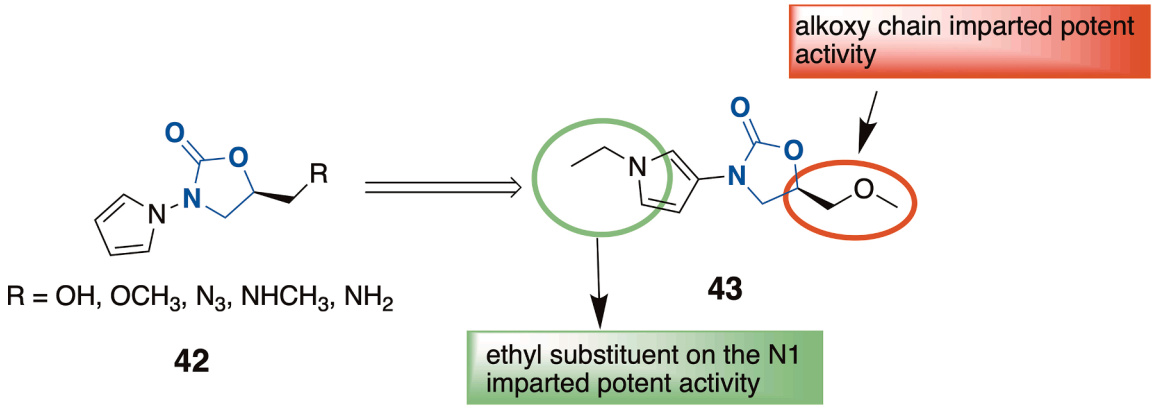


Fig. 37. Pharmacophoric features of 3-(1*H*-Pyrrol-3-yl)−2-oxazolidinones as MAO-A inhibitors.

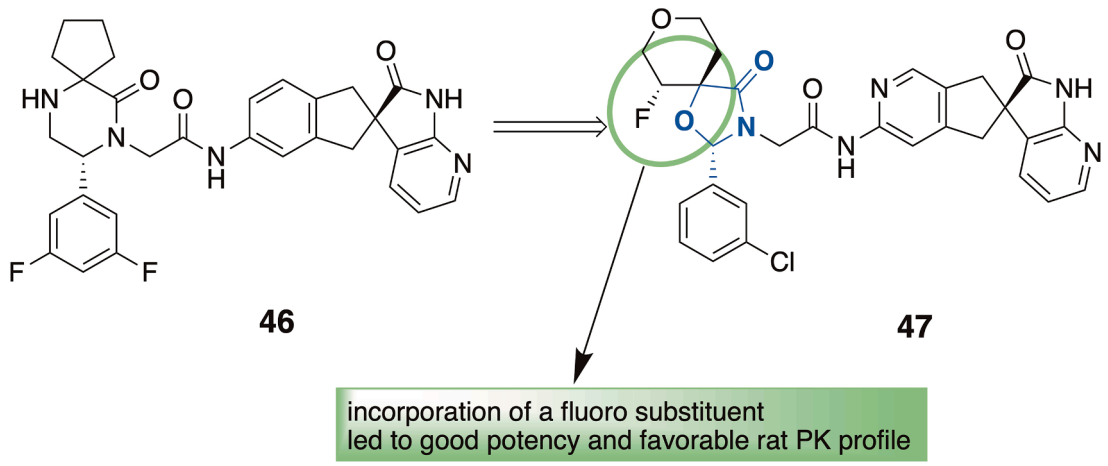


Fig. 39. Pharmacophoric features of oxazolidinone based CGRP receptor antagonists.

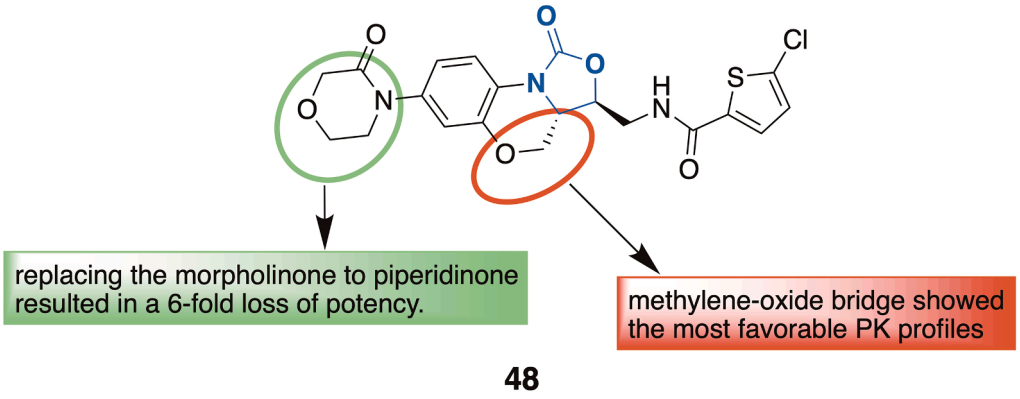


Fig. 40. Pharmacophoric features of [6,6,5] tricyclic fused oxazolidinones as fxa inhibitor.

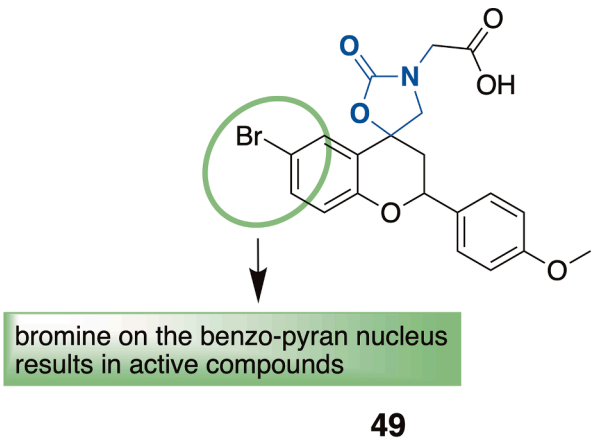


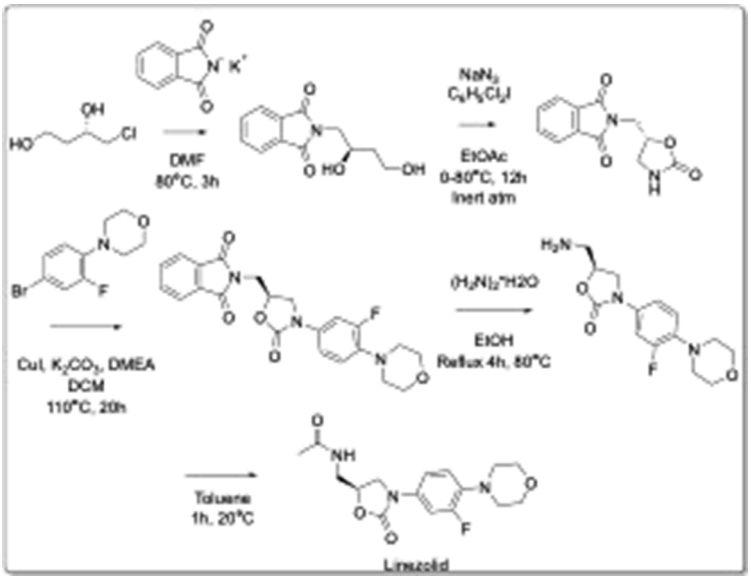
Fig. 41. Pharmacophoric features of 20-oxo-2,3-dihydro- 30h- spiro[chromene-4,50-[1,3]oxazolidin]−30yl]acetic acid derivatives as ALR2 inhibitors.

In 2017, Fujimoto et al. reported discovery of 3,5-diphenyl-4-methyl-1,3-oxazolidin-2-ones as potent delta-5 desaturase (D5D) inhibitors. D5D is a trans-membrane protein mainly expressed in the liver and is involved in the production of arachidonic acid (AA), which is a precursor of anti-inflammatory eicosanoids. They initiated the work by performing a high-throughput screening using a binding assay which led to the identification of some hit compounds. These hits were utilized to develop a pharmacophore model which in turn was used to design 1,3-oxazolidin-2-ones as novel D5D inhibitors. Synthesis and subsequent optimization resulted in several potent derivatives. SAR analysis revealed that the removal of the 2-methoxy substituent and blockage of metabolically susceptible 4-position of the oxazolidin-2-one core improved the inhibitory activity. Also, introducing a substituent at 5th position of benzonitrile moiety enhanced the potency (Fig. 31). Out of all, 36 was found to possess the most potent activity with IC_{50} value of 1.5 nM and 67% inhibition of D5D at the dose of 1 mg/kg *in vivo*. The study provides strong evidence of 3,5-diphenyl-1,3-oxazolidin-2-ones possessing anti-inflammatory potential via D5D inhibition [56].

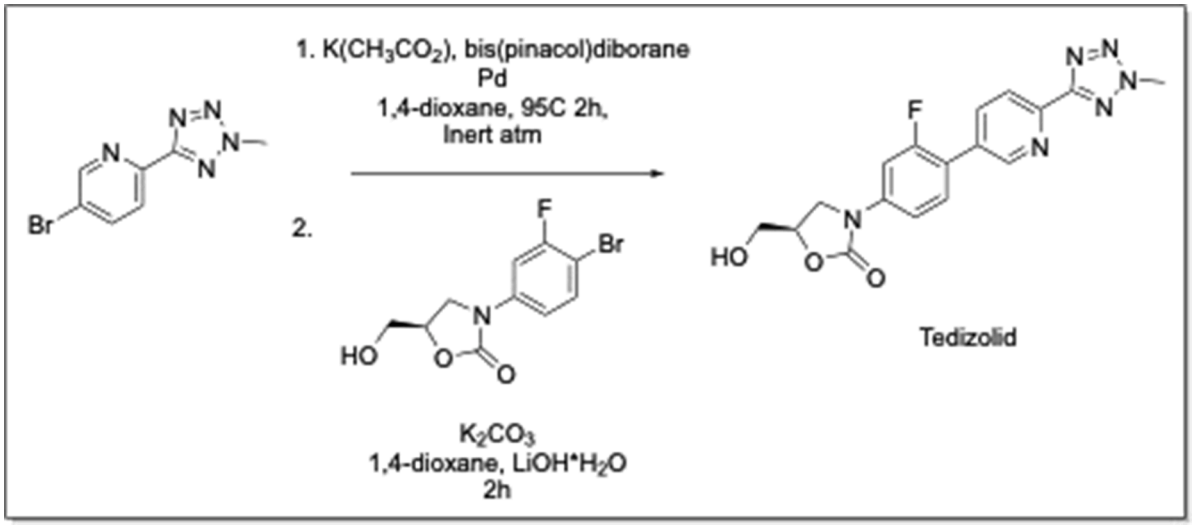
In 2015, Singh et al. reported SAR analysis of oxazolidinone derivatives as IL-6 signalling blockers. In the study, inspired by (+)-Madindoline A, a non-toxic small molecule having IL-6 inhibitory potential, they developed a series of oxazolidinone derivatives to study their binding mode in IL-6 and SAR. Out of all synthesized compounds, 37 having an *n*-pentyl side chain showed potent activity with an IC_{50} value of 5.9 μM. SAR analysis concluded that the length of the side chain plays an important role in determining the activity of these compounds (Fig. 32). Further, molecular docking experiments in the trimeric complex IL-6/IL- 6Rα/GP130D1 revealed that 37 was bound to the GP130D1 domain and formed H- bond interactions with Val93 and Cys6 residues. Compound 37 occupied the "hot spot" region and interrupted interactions between IL-6 and GP130 complex, suggesting a probable inhibitory mechanism [57].

1.7. Anti-viral

In 2017, Damalanka et al. reported structure-guided design, synthesis and evaluation of oxazolidinone-based inhibitors of norovirus 3CL protease. In their study, they focussed on developing peptidomimetics



Scheme 1. Synthetic route for Linezolid.



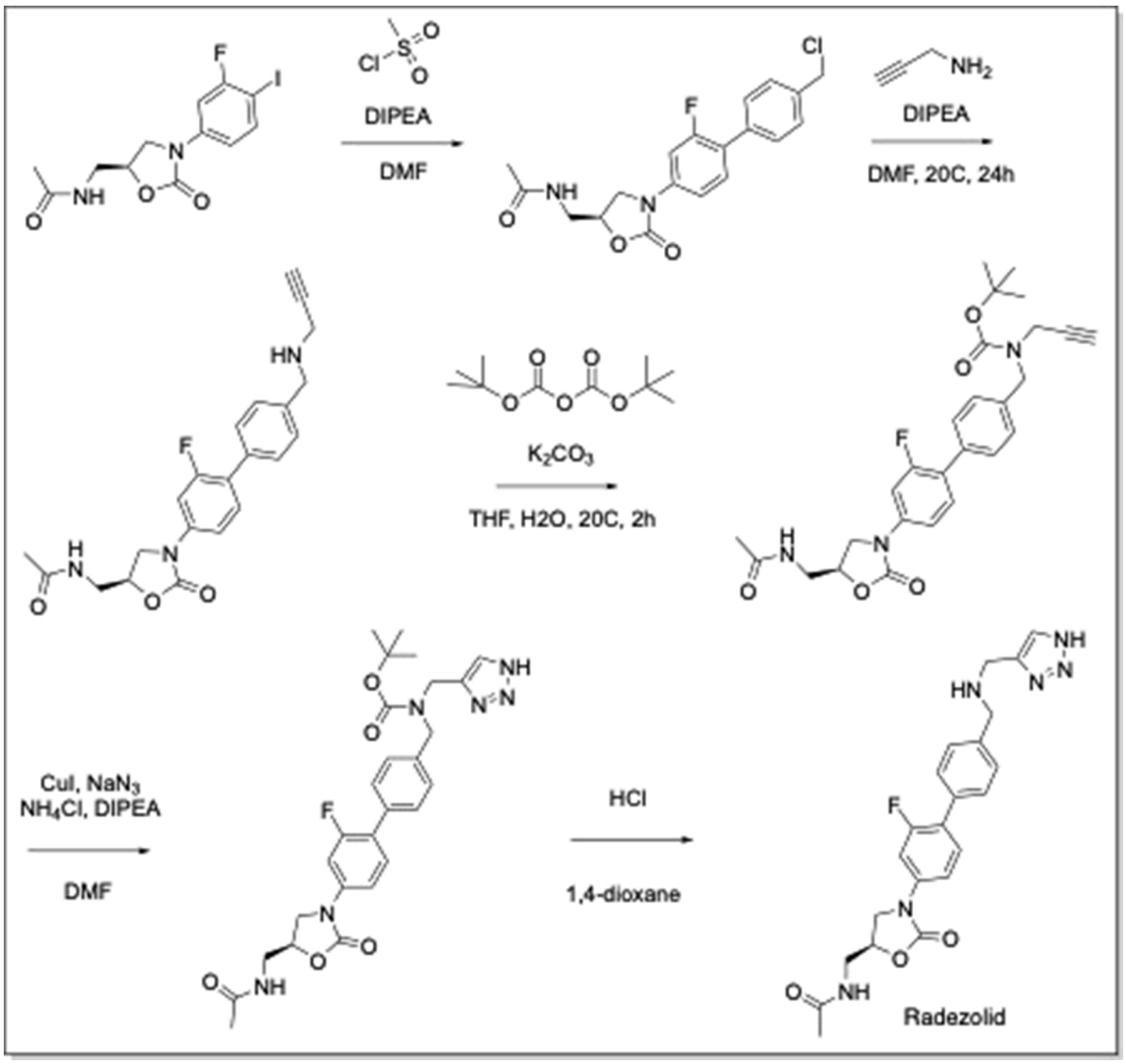
Scheme 2. Synthetic route for Tedizolid.

using an oxazolidinone ring, which could recognize key binding interactions within the active site. Furthermore, rings' chiral center was expected to provide optimal interactions between the S3-S4 subsites and recognition element R3. Although some of the synthesized compounds were biochemically evaluated as diastereomers, they showed submicromolar inhibitory potential. Limited SAR analysis revealed that compounds with cyclohexylalanine showed better activity than compounds with leucine. The position of the phenyl ring and its extension into the pocket also affects the potency (Fig. 33). Finally, X-ray crystallography analysis suggested a covalent bond between 38 (one of the derivatives) and Cys 139 of the pocket. Furthermore, H-bond interactions were observed between the designed inhibitor and His157 and Thr134 [58].

In 2016, Ravichandran et al. explored the relationship of oxazolidinones as HIV-1 protease inhibitors via the generation of QSAR and pharmacophore models. They used a series of *N*-aryl-oxazolidinone-5-carboxamides in their study and found that two aromatic and three hydrogen bond acceptor features were significant for the HIV-1 protease inhibitory activity. Also, they suggested that the number of carbon atoms separated from any specific carbon atom by 2- and 7-bond distances, and the number of fluorine atoms separated from any specific fluorine atom by a 5-bond distance in a molecule, altered the inhibitory activity. 3D QSAR model indicated that the presence of electrostatic and steric field descriptors in *N*-aryl-oxazolidinone-5-carboxamides significantly improved the HIV-1 protease inhibitory potential [59].

1.8. Cardiac agents

In 2020, Bitam et al. generated 2D QSAR models of CETP (Cholesteryl Ester Transfer Protein) inhibitors using a series of (4*S*,5*R*)−5-[3,5-*bis* (*trifluoromethyl*)*phenyl*]−4-methyl-1,3-oxazolidin-2-ones. Basically, Merck disclosed that certain 1,3-oxazolidin- 2-one derivatives show potent CETP inhibitory activity and Bitam et al. went ahead to study the quantitative structure-activity relationship (QSAR). They proposed and validated three linear and non-linear QSAR models (MLR model, SVR model, and FNN-PSO model) with good predictive ability. Overall, the study revealed that the inhibitory activity of oxazolidin-2-ones is dependent on electronegativity, structure and electronic properties [60].



Scheme 3. Synthetic route for Radezolid.

1.9. CNS agents

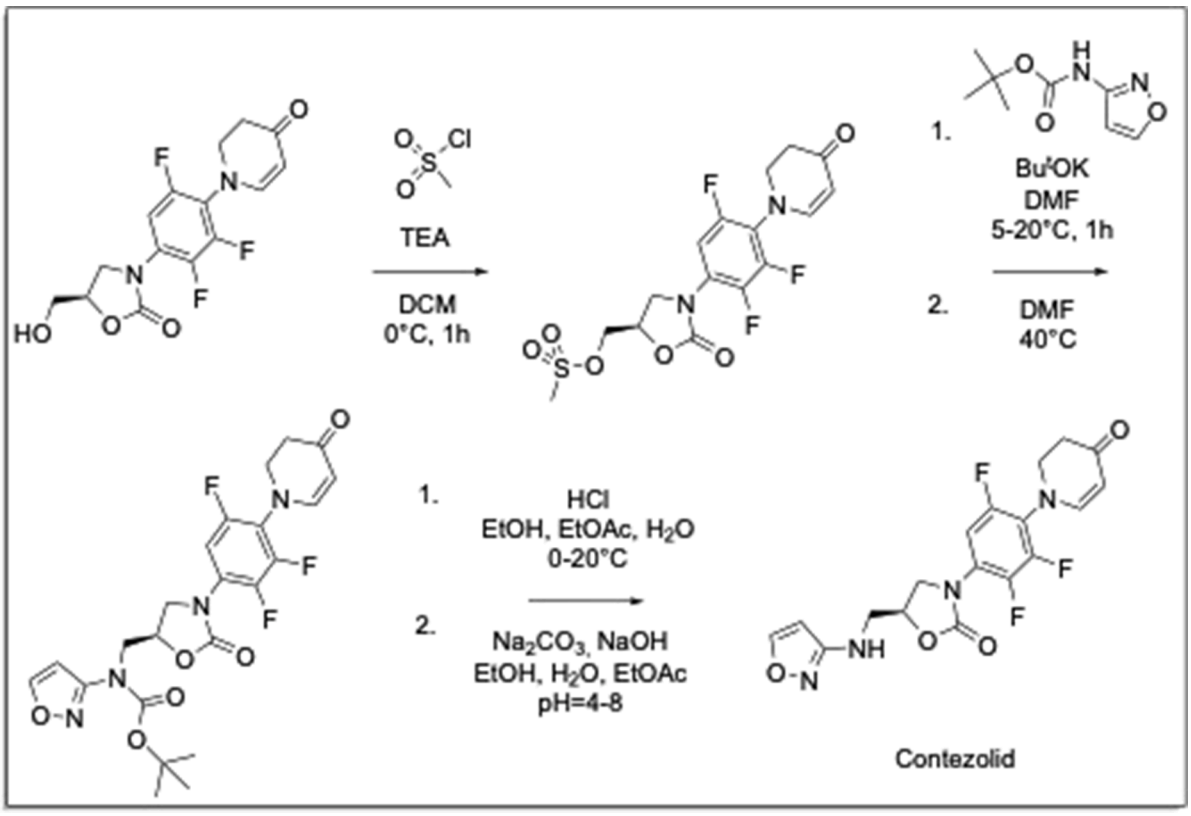
Similarly, oxazolidinone derivatives reported as CNS agents, or more precisely MAO inhibitors have almost similar features as antibacterial oxazolidinone derivatives (Fig. 34) and that is why many oxazolidinone antibacterial agents are reported to have MAO inhibitory side-effects.

Huang et al. in 2016, described oxazolidinone-based allosteric modulators of mGluR5 for the management of schizophrenia. Their work involved optimizing a high throughput screened positive allosteric modulator, an oxazolidinone derivative (39). They replaced the central and left-hand phenyl rings of 39 with pyridine, followed by substituting halogens on the right-hand phenyl ring. Mono- and bi-fluorinated phenyl ring-containing derivatives showed varied pharmacological profiles in the context of inhibitory potential and fold shift (Fig. 35). Detailed *in vivo* studies employing these tool compounds highlighted a need to alter the target profile to prefer a low fold shift PAM devoid of agonist activity. Overall, they found 40 (BMS-955,829) having an optimal profile, which was forwarded for investigational new drug (IND)-enabling toxicology studies [61].

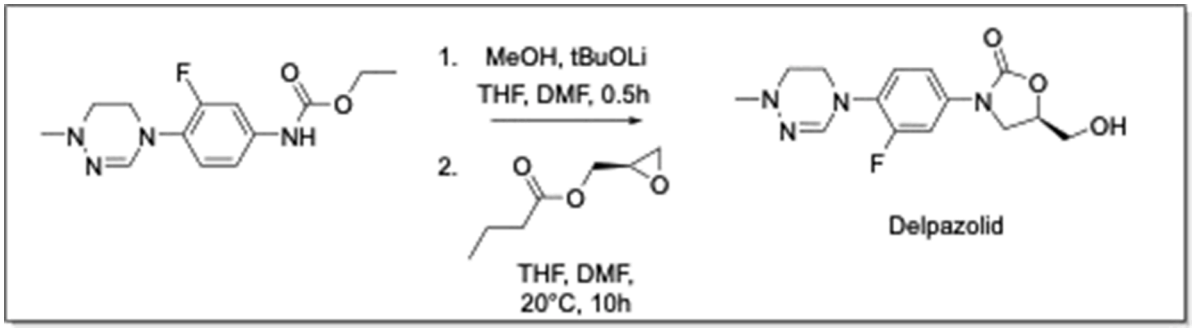
In 2015, Phillips et al. reported the synthesis and biological evaluation of novel 5-(hydroxamic acid) methyl oxazolidinone derivatives both as antibacterial and MAO inhibitors. Out of all derivatives screened for their ability to inhibit both MAO-A and MAO-B *in vitro*, 10 compounds selectively inhibited MAO-B over MAO-A, 4 compounds inhibited both MAO-A and -B and 5 compounds were devoid of both MAO-A and -B inhibitory activity. Compound 41 having 5-(*N*-hydroxylamino) methyl-oxazolidinone, demonstrated $\geq$ 50% MAO-A and MAO-B inhibition. Preliminary SAR analysis suggested that the structural modifications incorporating the *N*-hydroxamic acid moiety at the oxazolidinone C5 position did not favor potent bacteriostatic activity and resulted in significant variations in MAO-A and -B inhibitory activities (Fig. 36) [62].

In 2011, Radhakrishnan et al. evaluated the antidepressant-like activity of linezolid, an oxazolidinone class derivative. Following the report that linezolid is a reversible and non-selective MAO inhibitor, they investigated the anti-depressant potential of linezolid in animal models of depression. All the different models, such as reserpine-induced hypothermia and the ‘‘behavior despair’’ test, suggested that linezolid could be a potential candidate for the management of depression [63].

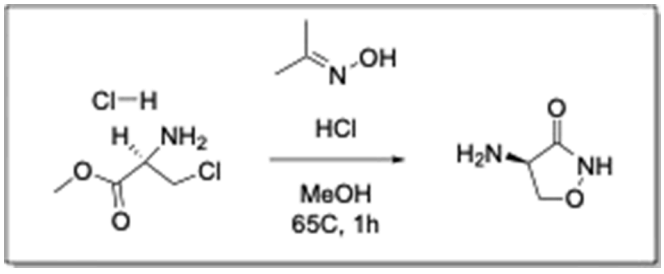
In 2011 Valente et al. reported 3-(1*H*-Pyrrol-3-yl)−2-oxazolidinones as highly potent and selective MAO-A inhibitors. Following their previous work, where they reported 3-(1*H*-pyrrol-1-yl)−2-oxazolidinones (42) as reversible, potent, and MAO-A selective inhibitors, they



Scheme 4. Synthetic route for Contezolid.



Scheme 5. Synthetic route for Delpazolid.

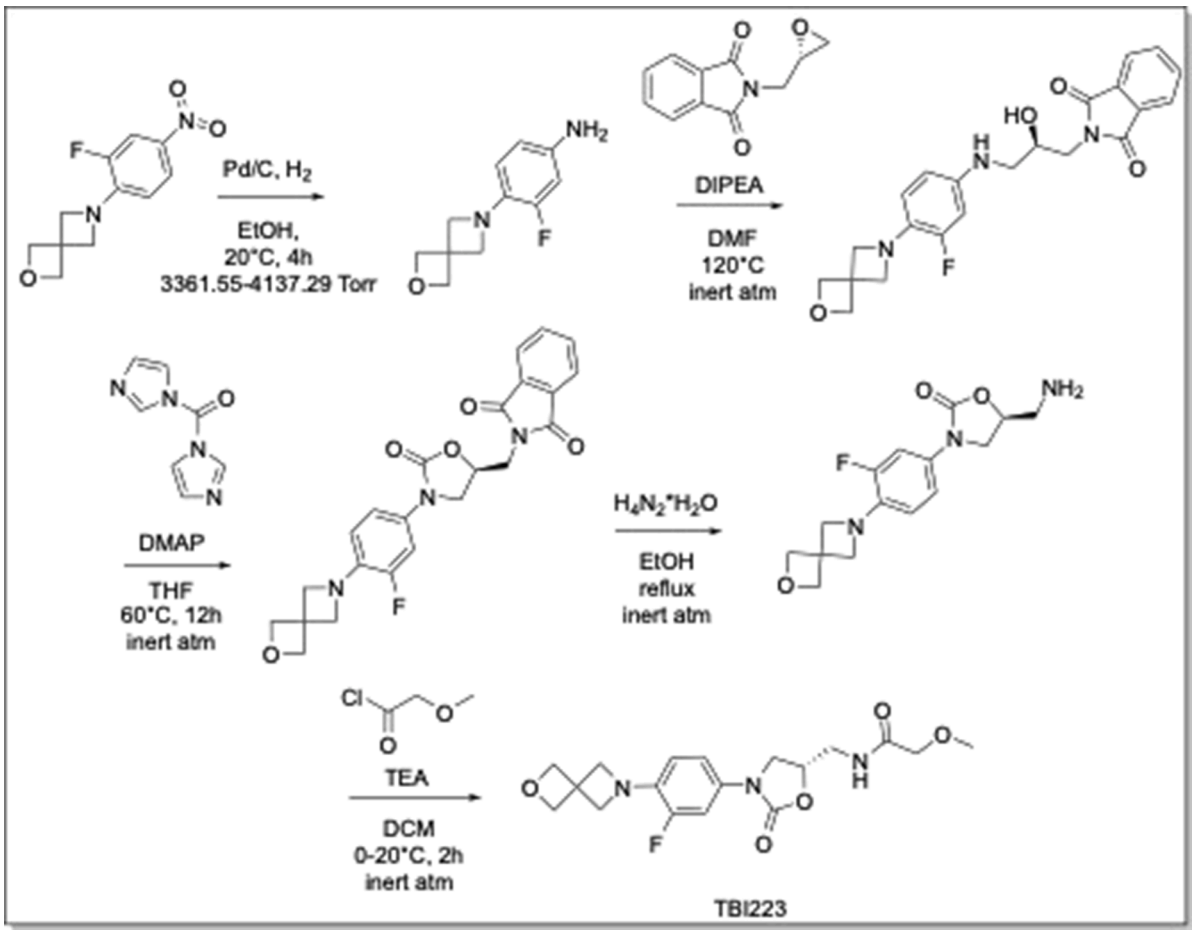


Scheme 6. Synthetic route for Cycloserine.

investigated the C3 position of the pyrrole, shifting the 2-oxazolidinone nucleus at the pyrrole C3 position and introducing alkyl groups at the pyrrole N1 position. Out of all synthesized derivatives, compound 43 having the ethyl group at the pyrrole N1 position showed the most potent, nanomolar range inhibitory activity. Limited SAR analysis indicated ethyl substituent on the N1 position of pyrrole and alkoxy chain on the oxazolidinone ring imparted potent activity and improved selectivity index (Fig. 37) [64].

1.10. Miscellaneous

In 2019, Atmaca et al. reported enantiomerically enriched oxazolidinones as selective hCA, AChE, and α-glycosidase inhibitors (Fig. 38). Out of all the enantiomerically enriched oxazolidinones, three compounds showed low nanomolar range Ki values against hCA I with 44 being the most potent. Limited SAR for this activity suggested that the incorporation of electron-donating groups resulted in a decreased activity. Molecular docking analysis of 44 in hCA showed the presence of



Scheme 7. Synthetic route for TBI223.

an H-bond between the 8-hydroxy group and Gln92. In case of hCA II a similar result was obtained with 44 being the most potent. In molecular docking analysis, different substituents of compound 44 formed H-bond with Asn67, Gln92, Thr200 and Pro201 residues of the hCA II. During the estimation of AchE inhibition, 44 showed the most comparable inhibitory values to the standard drug, tacrine. Functional groups such as -NH, -OH and C=O were indicated to play a role in this activity profile. Docking analysis showed H-bond with Tyr124 and Phe295 residue of the AchE. Finally, against α-glycosidase 45 showed the most potent nanomolar range inhibitory potential. Docking analysis showed an H-bond interaction network between 45 and Asp443, Agr526, Trp539, and His600 residues of α-glycosidase [11].

In 2015, Xu et al. reported molecular modeling studies of tricyclic fused oxazolidinones as FXa inhibitors using 3D-QSAR, Topomer CoMFA, molecular docking and molecular dynamics simulations. They selected 38 new [5,6] tricyclic fused oxazolidinones reported by Yushe Yang [65] as a dataset to generate a 3D-QSAR (Topomer CoMFA) model, followed by molecular docking and dynamics analysis. These models and contour maps obtained from Topomer CoMFA analysis could be used to guide new compounds with high FXa inhibitory activity. The docking and dynamic simulations revealed key residues (Gly219, Gln192, Lys96, Tyr99, Ala190, Cys220, Glu217, Gly216, Trp215 and Glu97) involved in interactions within the binding site [66].

In 2015, Crowley et al. reported novel oxazolidinone-based calcitonin gene-related peptide (CGRP) receptor antagonists for the acute treatment of migraine. They initiated by hoping the scaffold of MK-3207 (46), a clinically efficacious CGRP receptor antagonist, replacing piperazinone core and indanyl spiroazaoxindole with different five-membered saturated and unsaturated heterocycles. Out of all the compounds, 47 was found to possess good potency, off-target selectivity and a favorable pharmacokinetic profile. SAR analysis suggested that incorporation of a C3 fluoro substituent onto the tetrahydropyran ring led to good potency and favorable rat PK profile (Fig. 39). Molecular docking analysis revealed that the 3-chlorophenyl ring occupy the hydrophobic pocket of RAMP1, while the rest of the molecule occupied pocket similar to MK-3207 [67].

Scheme 1
Scheme 2
Scheme 3
Scheme 4
Scheme 5
Scheme 6
Scheme 7

In 2014, Xue et al. reported design, synthesis, and structure-activity and structure-pharmacokinetic relationship studies of novel [5,6] tricyclic fused oxazolidinones leading to the discovery of a potent, selective, and orally bioavailable FXa inhibitor. They explored the X-ray crystal structure of rivaroxaban in complex with human FXa and designed molecules with bridge between benzene ring and oxazolidinone ring by an additional linker to restrict the preferred conformation. Out of all the compounds, 48 was found to possess the most potent *in vitro* FXa inhibitory activity. SAR analysis revealed that replacing the morpholinone with piperidinone resulted in a 6-fold loss of potency. The addition of the second chlorine at the 4th position of the thiophene ring causes a significant loss of activity (Fig. 40). More importantly, compounds carrying a methylene-oxide bridge showed the most favourable PK profiles. Also, the top compound did not show any toxicity in the hERG $K+$ channel, various CYP450 isozymes, Ames mutagenicity test

and micronucleus formation assay [65].

Rapposelli et al. in 2010 reported the synthesis and biological evaluation of 20-oxo-2,3-dihydro- 30h- spiro[chromene-4,50-[1,3] oxazolidin]−30yl]acetic acid derivatives as aldose reductase inhibitors. Aldose reductase (ALR2) is one of the key targets for the management of diabetic complications. They evaluated the effect of small electron-donor and electron-withdrawal groups around the aromatic ring in 2-position and the effect induced by an additional steric hindrance (Fig. 41). Out of all synthesized compounds, 49 was found to be the most potent ALR2 inhibitor with high selectivity against the ALR1 isoform. Limited SAR revealed that the 4-methoxy derivative substituted with a bromine atom on the benzopyran nucleus results in active compounds [68].

1.11. Comparison of structural attributes in antibiotics vs. other activities: Unexplored chemical/pharmacophoric space of oxazolidinones

Overall, a general analysis of all the oxazolidinone-based pharmacological agents suggests that most of them have substitutions at *N* and 5th position and are designed as antibacterials only. One explanation is that initial work on oxazolidinone was done in the context of antibiotics and the most potent antibiotics of this class were found to have these structural attributes, as evident in Table 1, and researchers followed them up with molecules having similar framework but different substituents. However, the interesting thing is that even for oxazolidinones with other activity profiles, similar structural architecture has been explored and there is only a little work available on oxazolidinones, where other structure attributes, for example, substitutions on the 4th position, were explored. Some molecules reported as anticancer agents with a usual framework (substitutions at the 3rd and 5th position) do provide data about substitution on the 4th position, but there are no exhaustive reports. While it seems that oxazolidinones with other frameworks and substitutions can result in highly potent therapeutic agents other than antibiotics, as evidenced by compound 40, an investigational new drug candidate targeted at mGluR5 with free -NH and substitution at the 4th position. There are a few other similar attempts as well, where researchers modified the structural architecture of oxazolidinones and targeted ALR2 or CGRP receptors, as mentioned above. Therefore, it highlights the need to look at the oxazolidinone core from a distinct perspective and it seems that substituting 4th position of the core provides one such attempt. Studies such as compound 40 indicate towards the possibility of successfully identifying potent oxazolidinone-based inhibitors for other pharmacological targets. Medicinal chemists are expected to not be biased towards this core to only think of antibiotics, but to also look for other therapeutic targets like ALR2 or CGRP receptor antagonists or others discussed above in miscellaneous. Overall, this analysis provides information about the difference and similarities between the pharmacophoric features of oxazolidinones as antibiotics and other pharmacological profiles. Also, the identification of the less explored features provides directions to medicinal chemists working on oxazolidinones.

2. Conclusion

Oxazolidinone is one of the most explored *O*-heterocycles in medicinal chemistry and yet it does not get the label of “privileged drug scaffold”. The reason is, that it is more often used to design and develop antibiotics and thus even after giving so many FDA-approved drugs, its pharmacological profile remains quite narrow. Herein, we have attempted to point out this inadvertent bias of the researchers, we have discussed all the recently reported oxazolidinone derivatives as antibiotics and oxazolidinone derivatives with other pharmacological profiles. The structural/pharmacophoric analysis of all the oxazolidinone derivatives reflected that almost all the compounds having antibiotic activity have substitutions on the 3rd and 5th position of the core. While compounds with other pharmacological profiles were also found to be not too diverse from the antibiotic framework of oxazolidinones. Interestingly, compounds from limited attempts with altered architecture *i.e.*, substitutions on the 4th position or oxazolidinone-fused derivatives, resulted in highly potent and drug-like compounds for other therapeutic targets, which indicates towards the multi-facet potential of this core. It also indicates that oxazolidinones, due to their famous antibiotic potential, are probably neglected during the search for heterocyclic cores for other therapeutic targets. This work is simply an attempt to suggest medicinal chemists to look beyond antibiotics when they think of oxazolidinone.

Declaration of Competing Interest

None

Data availability

No data was used for the research described in the article.

Acknowledgement

PKS would like to thank TCSMT for the postdoctoral fellowship.

References

[1] C. Foti, A. Piperno, A. Scala, O. Giuffrè, Oxazolidinone antibiotics: chemical, biological and analytical aspects, Molecules 26 (14) (2021) 4280.
[2] S.K. Verma, R. Verma, F. Xue, P.K. Thakur, Y. Girish, K. Rakesh, Antibacterial activities of sulfonyl or sulfonamide containing heterocyclic derivatives and its structure-activity relationships (SAR) studies: a critical review, Bioorg. Chem. 105 (2020), 104400.
[3] C.D. Cruz, P. Wrigstedt, K. Moslova, V. Iashin, H. Mäkkylä, L. Ghemtio, S. Heikkinen, P. Tammela, J.E. Perea-Buceta, Installation of an aryl boronic acid function into the external section of N-aryl-oxazolidinones: synthesis and antimicrobial evaluation, Eur. J. Med. Chem. 211 (2021), 113002.
[4] R. Kaur, P. Rani, A.G. Atanasov, Q. Alzahrani, R. Gupta, B. Kapoor, M. Gulati, P. Chawla, Discovery and development of antibacterial agents: fortuitous and designed, Mini Rev. Med. Chem. 22 (7) (2022) 984–1029.
[5] Q. Zhao, L. Xin, Y. Liu, C. Liang, J. Li, Y. Jian, H. Li, Z. Shi, H. Liu, W. Cao, Current landscape and future perspective of oxazolidinone scaffolds containing antibacterial drugs, J. Med. Chem. 64 (15) (2021) 10557–10580.
[6] M.M. Rahman, D.J. Pyle, E. Bisz, B.e. Dziuk, K. Ejsmont, R. Lalancette, Q. Wang, H. Chen, R. Szostak, M. Szostak, Evaluation of cyclic amides as activating groups in N–C bond cross-coupling: discovery of N-Acyl-δ-valerolactams as effective twisted amide precursors for cross-coupling reactions, J. Org. Chem. 86 (15) (2021) 10455–10466.
[7] P.K. Singh, O. Silakari, The current status of O-heterocycles: a synthetic and medicinal overview, ChemMedChem 13 (11) (2018) 1071–1087.
[8] H. Lu, H. Wang, H. Zhao, D. Zhang, Recent advances in oxazolidinones as antituberculosis agents, Future Med. Chem. (0) (2022).
[9] G.G. Zhanel, C. Schroeder, L. Vercaigne, A.S. Gin, J. Embil, D.J. Hoban, A critical review of oxazolidinones: an alternative or replacement for glycopeptides and streptogramins? Can. J. Infectious Dis. 12 (6) (2001) 379–390.
[10] S.M.R. Hashemian, T. Farhadi, M. Ganjparvar, Linezolid: a review of its properties, function, and use in critical care, Drug Des. Dev. Ther. 12 (2018) 1759.
[11] U. Atmaca, R. Kaya, H.S. Karaman, M. Celik, İ. Gülçin, Synthesis of oxazolidinone from enantiomerically enriched allylic alcohols and determination of their molecular docking and biologic activities, Bioorg. Chem. 88 (2019), 102980.
[12] H. Li, J. Yuan, S. Duan, Y. Pang, Resistance and tolerance of Mycobacterium tuberculosis to antimicrobial agents—how M. tuberculosis can escape antibiotics, WIREs Mech. Dis. (2022) e1573.
[13] I. Honeyborne, M. Lipman, A. Zumla, T.D. McHugh, The changing treatment landscape for MDR/XDR-TB—can current clinical trials revolutionise and inform a brave new world? Int. J. Infect. Dis. 80 (2019) S23–S28.
[14] H. Zhao, B. Wang, L. Fu, G. Li, H. Lu, Y. Liu, L. Sheng, Y. Li, B. Zhang, Y. Lu, Discovery of a conformationally constrained oxazolidinone with improved safety and efficacy profiles for the treatment of multidrug-resistant tuberculosis, J. Med. Chem. 63 (17) (2020) 9316–9339.
[15] T.A. Black, U.K. Buchwald, The pipeline of new molecules and regimens against drug-resistant tuberculosis, J. Clin. Tuberc. Other Mycobact. Dis. 25 (2021), 100285.
[16] R.G. Hall 2nd, W.J. Smith, W.C. Putnam, S.E. Pass, An evaluation of tedizolid for the treatment of MRSA infections, Expert Opin. Pharmacother. 19 (13) (2018) 1489–1494.
[17] S.-H. Lan, W.-T. Lin, S.-P. Chang, L.-C. Lu, C.-M. Chao, C.-C. Lai, J.-H. Wang, Tedizolid *versus* linezolid for the treatment of acute bacterial skin and skin structure infection: a systematic review and meta-analysis, Antibiotics 8 (3) (2019) 137.

[18] S.R. Tetali, E. Kunapaeddi, R.P. Mailavaram, V. Singh, P. Borah, P.K. Deb, K. N. Venugopala, W. Hourani, R.K. Tekade, Current advances in the clinical development of anti-tubercular agents, Tuberculosis 125 (2020), 101989.
[19] K.T. Angula, L.J. Legoabe, R.M. Beteck, Chemical classes presenting novel antituberculosis agents currently in different phases of drug development: a 2010–2020 review, Pharmaceuticals 14 (5) (2021) 461.
[20] W. Wang, K.M. Voss, J. Liu, M.F. Gordeev, Nonclinical evaluation of antibacterial oxazolidinones contezolid and contezolid acefosamil with low serotonergic neurotoxicity, Chem. Res. Toxicol. 34 (5) (2021) 1348–1354.
[21] D.V. Almeida, T.F. Omansen, S.-.Y. Li, J. Lee, J.H. Grosset, P.J. Converse, E. L. Nuermberger, Oxazolidinones can replace clarithromycin in combination with rifampin in a mouse model of Buruli ulcer, Antimicrob. Agents Chemother. 63 (3) (2019) e02171-18.
[22] L. Farrell, R. Lo, J. Wanford, A. Jenkins, A. Maxwell, L. Piddock, Revitalizing the drug pipeline: antibioticDB, an open access database to aid antibacterial research and development, J. Antimicrob. Chemother. 73 (9) (2018) 2284–2297.
[23] P.K. Singh, O. Silakari, Benzimidazole: journey from single targeting to multitargeting molecule, key heterocycle cores for designing multitargeting molecules, Elsevier (2018) 31–52.
[24] G. Kaur, M. Kaur, O. Silakari, Benzimidazoles: an ideal privileged drug scaffold for the design of multitargeted anti-inflammatory ligands, Mini Rev. Med. Chem. 14 (9) (2014) 747–767.
[25] R. DeSimone, K. Currie, S. Mitchell, J. Darrow, D. Pippin, Privileged structures: applications in drug discovery, Comb. Chem. High Throughput Screen. 7 (5) (2004) 473–493.
[26] F. Sun, E.V. Van der Eycken, H. Feng, Recent advances in the synthesis and ring-opening transformations of 2-oxazolidinones, Adv. Synth. Catal. 363 (23) (2021) 5168–5195.
[27] O.A. Phillips, L.H. Sharaf, Oxazolidinone antimicrobials: a patent review (2012-2015), Expert Opin. Ther. Pat. 26(5) (2016) 591–605.
[28] A. Lyons, J. Kirkham, K. Blades, D. Orr, E. Dauncey, O. Smith, E. Dick, R. Walker, T. Matthews, A. Bunt, Discovery and structure–activity relationships of a novel oxazolidinone class of bacterial type II topoisomerase inhibitors, Bioorg. Med. Chem. Lett. 65 (2022), 128648.
[29] S. Bhawsar, S. Pawar, P. Deshpande, R. Yeole, R. Chavan, M. Nandanwar, S. Bhagwat, M. Patel, WCK 4034: a promising oxazolidinone for treating gram positive infections, Bioorg. Med. Chem. Lett. (2022), 128842.
[30] S. Faazil, M.S. Malik, S.A. Ahmed, R.I. Alsantali, P. Yedla, M.A. Alsharif, I. N. Shaikh, A. Kamal, Novel linezolid-based oxazolidinones as potent anticandidiasis and antitubercular agents, Bioorg. Chem. (2022), 105869.
[31] B. Jin, J.-y. Chen, Z.-l. Sheng, M.-q. Sun, H.-l. Yang, Synthesis, antibacterial and anthelmintic activity of novel 3-(3-pyridyl)-oxazolidinone-5-methyl ester derivatives, Molecules 27 (3) (2022) 1103.
[32] J. Jiang, Y. Hou, M. Duan, B. Wang, Y. Wu, X. Ding, Y. Zhao, Design, synthesis and antibacterial evaluation of novel oxazolidinone derivatives nitrogen-containing fused heterocyclic moiety, Bioorg. Med. Chem. Lett. 32 (2021), 127660.
[33] G. García-Olaiz, E. Alcántar-Zavala, A. Ochoa-Terán, A. Cabrera, R. Muñiz-Salazar, J. Montes-Ávila, A.J. Salazar-Medina, E. Alday, C. Velazquez, J.L. Medina-Franco, Design, synthesis and evaluation of the antibacterial activity of new Linezolid dipeptide-type analogues, Bioorg. Chem. 95 (2020), 103483.
[34] K. Jiang, X. Yan, J. Yu, Z. Xiao, H. Wu, M. Zhao, Y. Yue, X. Zhou, J. Xiao, F. Lin, Design, synthesis, and biological evaluation of 3-amino-2-oxazolidinone derivatives as potent quorum-sensing inhibitors of Pseudomonas aeruginosa PAO1, Eur. J. Med. Chem. 194 (2020), 112252.
[35] S. Ding, J.C. Ji, M.J. Zhang, Y.S. Yang, R. Wang, X.L. Zhu, L.H. Wang, Y. Zhong, L. Gao, M. Lu, Exploration of the structure–activity relationship and druggability of novel oxazolidinone-based compounds as Gram-negative antibacterial agents, Arch. Pharm. (Weinheim) 352 (11) (2019), 1900129.
[36] Y. Hou, Y. Dong, T. Ye, J. Jiang, L. Ding, M. Qin, X. Ding, Y. Zhao, Synthesis and antibacterial evaluation of novel oxazolidinone derivatives containing a piperidinyl moiety, Bioorg. Med. Chem. Lett. 29 (23) (2019), 126746.
[37] L. Liu, L. Shao, J. Li, H. Cui, B. Li, X. Zhou, P. Lv, J. Zhang, Synthesis, antibacterial activities, mode of action and acute toxicity studies of new oxazolidinone-fluoroquinolone hybrids, Molecules 24 (8) (2019) 1641.
[38] A.M. Siddiqui, J.A. Sattigeri, K. Javed, S. Shafi, M. Shamim, S. Singhal, Z.M. Malik, Design, synthesis and biological evaluation of spiropyrimidinetriones oxazolidinone derivatives as antibacterial agents, Bioorg. Med. Chem. Lett. 28 (7) (2018) 1198–1206.
[39] S.-.J. Jung, H.S. Park, H.-.H. Lee, J.-.W. Jeong, Y.-.Z. Kim, Y.-.L. Cho, J.-.H. Kwak, Antibacterial activity of LCB01-0062, a novel oxazolidinone, Int. J. Antimicrob. Agents 40 (6) (2012) 539–543.
[40] J.-.W. Jeong, S.-.J. Jung, H.-.H. Lee, Y.-.Z. Kim, T.-.K. Park, Y.-.L. Cho, S.-.E. Chae, S.-.Y. Baek, S.-.H. Woo, H.-.S. Lee, *In vitro* and *in vivo* activities of LCB01-0371, a new oxazolidinone, Antimicrob. Agents Chemother. 54 (12) (2010) 5359–5362.
[41] S.-.H. Oh, J. Kim, S.-.Y. Baek, S.-.E. Chae, H.-.S. Park, Y.-.L. Cho, J.-.H. Kwak, In vitro activities of LCB 01-0648, a novel oxazolidinone, against gram-positive bacteria, Molecules 22 (3) (2017) 394.
[42] Z. Zhuang, D. Wan, J. Ding, S. He, Q. Zhang, X. Wang, Y. Yuan, Y. Lu, C.Z. Ding, A. S. Lynch, Synergistic activity of nitroimidazole-oxazolidinone conjugates against anaerobic bacteria, Molecules 25 (10) (2020) 2431.
[43] Z. Zong, W. Jing, J. Shi, S.a. Wen, T. Zhang, F. Huo, Y. Shang, Q. Liang, H. Huang, Y. Pang, Comparison of *in vitro* activity and MIC distributions between the novel oxazolidinone delpazolid and linezolid against multidrug-resistant and extensively drug-resistant Mycobacterium tuberculosis in China, Antimicrob. Agents Chemother. 62 (8) (2018) e00165-18.
[44] T. Xue, S. Ding, B. Guo, W. Chu, H. Wang, Y. Yang, Synthesis and structure–activity relationship studies of novel [6, 6, 5] tricyclic oxazolidinone derivatives as potential antibacterial agents, Bioorg. Med. Chem. Lett. 25 (10) (2015) 2203–2210.
[45] G.S. Basarab, P. Doig, V. Galullo, G. Kern, A. Kimzey, A. Kutschke, J.P. Newman, M. Morningstar, J. Mueller, L. Otterson, Discovery of novel DNA gyrase inhibiting spiropyrimidinetriones: benzisoxazole fusion with N-linked oxazolidinone substituents leading to a clinical candidate (ETX0914), J. Med. Chem. 58 (15) (2015) 6264–6282.
[46] W. Ang, W. Ye, Z. Sang, Y. Liu, T. Yang, Y. Deng, Y. Luo, Y. Wei, Discovery of novel bis-oxazolidinone compounds as potential potent and selective antitubercular agents, Bioorg. Med. Chem. Lett. 24 (6) (2014) 1496–1501.
[47] B. Armentano, R. Curcio, M. Brindisi, R. Mancuso, V. Rago, I. Ziccarelli, L. Frattaruolo, M. Fiorillo, V. Dolce, B. Gabriele, 5-(Carbamoylmethylene)-oxazolidin-2-ones as a promising class of heterocycles inducing apoptosis triggered by increased ros levels and mitochondrial dysfunction in breast and cervical cancer, Biomedicines 8 (2) (2020) 35.
[48] E. De Vita, N. Smits, H. van den Hurk, E.M. Beck, J. Hewitt, G. Baillie, E. Russell, A. Pannifer, V. Hamon, A. Morrison, Synthesis and structure-activity relationships of N-(4-benzamidino)-oxazolidinones: potent and selective inhibitors of kallikrein-related peptidase 6, ChemMedChem 15 (1) (2020) 79–95.
[49] T. Ma, F. Zou, S. Pusch, L. Yang, Q. Zhu, Y. Xu, Y. Gu, A. von Deimling, X. Zha, Design, synthesis and biological activity of 3-pyrazine-2-yl-oxazolidin-2-ones as novel, potent and selective inhibitors of mutant isocitrate dehydrogenase 1, Bioorg. Med. Chem. 25 (24) (2017) 6379–6387.
[50] O.M. Hedaya, P.M. Mathew, F.H. Mohamed, O.A. Phillips, Y.A. Luqmani, Antiproliferative activity of a series of 5-(1H-1, 2, 3-triazolyl) methyl-and 5-acetamidomethyl-oxazolidinone derivatives, Mol. Med. Rep. 13 (4) (2016) 3311–3318.
[51] A. Naresh, M.V. Rao, S.S. Kotapalli, R. Ummanni, B.V. Rao, Oxazolidinone derivatives: cytoxazone–Linezolid hybrids induces apoptosis and senescence in DU145 prostate cancer cells, Eur. J. Med. Chem. 80 (2014) 295–307.
[52] H. Bregman, N. Chakka, A. Guzman-Perez, H. Gunaydin, Y. Gu, X. Huang, V. Berry, J. Liu, Y. Teffera, L. Huang, Discovery of novel, induced-pocket binding oxazolidinones as potent, selective, and orally bioavailable tankyrase inhibitors, J. Med. Chem. 56 (11) (2013) 4320–4342.
[53] A. Singh, H.-.J. Ha, J. Park, J.H. Kim, W.K. Lee, 3, 4-Disubstituted oxazolidin-2-ones as constrained ceramide analogs with anticancer activities, Bioorg. Med. Chem. 19 (21) (2011) 6174–6181.
[54] M.G. Qaddoumi, O.A. Phillips, S.B. Kombian, A novel oxazolidinone derivative PH192 demonstrates anticonvulsant activity *in vivo* in rats and mice, Eur. J. Pharm. Sci. 130 (2019) 21–26.
[55] O.A. Phillips, M.A. Bosso, C.I. Ezeamuzie, Synthesis and structure-activity relationships of novel 5-(hydroxamic acid) methyl oxazolidinone derivatives as 5-lipoxygenase inhibitors, J. Enzyme Inhib. Med. Chem. 35 (1) (2020) 1471–1482.
[56] J. Fujimoto, R. Okamoto, N. Noguchi, R. Hara, S. Masada, T. Kawamoto, H. Nagase, Y.O. Tamura, M. Imanishi, S. Takagahara, Discovery of 3, 5-diphenyl-4-methyl-1, 3-oxazolidin-2-ones as novel, potent, and orally available Δ-5 desaturase (D5D) inhibitors, J. Med. Chem. 60 (21) (2017) 8963–8981.
[57] S. Singh, V. Gajulapati, K. Gajulapati, J.-.I. Goo, Y.-.H. Park, H.Y. Jung, S.Y. Lee, J. H. Choi, Y.K. Kim, K. Lee, Structure–activity relationship study of a series of novel oxazolidinone derivatives as IL-6 signaling blockers, Bioorg. Med. Chem. Lett. 26 (4) (2016) 1282–1286.
[58] V.C. Damalanka, Y. Kim, A.C.G. Kankanamalage, A.D. Rathnayake, N. Mehzabeen, K.P. Battaile, S. Lovell, H.N. Nguyen, G.H. Lushington, K.-.O. Chang, Structure-guided design, synthesis and evaluation of oxazolidinone-based inhibitors of norovirus 3CL protease, Eur. J. Med. Chem. 143 (2018) 881–890.
[59] V. Ravichandran, K. Venkateskumar, S. Shalini, R. Harish, Exploring the structure–activity relationship of oxazolidinones as HIV-1 protease inhibitors—QSAR and pharmacophore modelling studies, Chemom. Intell. Lab. Syst. 154 (2016) 52–61.
[60] S. Bitam, M. Hamadache, H. Salah, 2d qsar studies on a series of (4s, 5 r r)-5-[3, 5-*bis* (*trifluoromethyl*) *phenyl*]-4-methyl-1, 3-oxazolidin-2-one as cetp inhibitors, SAR QSAR Environ. Res. 31 (6) (2020) 423–438.
[61] H. Huang, A.P. Degnan, A. Balakrishnan, A. Easton, M. Gulianello, Y. Huang, M. Matchett, G. Mattson, R. Miller, K.S. Santone, Oxazolidinone-based allosteric modulators of mGluR5: defining molecular switches to create a pharmacological tool box, Bioorg. Med. Chem. Lett. 26 (17) (2016) 4165–4169.
[62] O.A. Phillips, R. D'Silva, T.O. Bahta, L.H. Sharaf, E.E. Udo, L. Benov, D.E. Walters, Synthesis and biological evaluation of novel 5-(hydroxamic acid) methyl oxazolidinone derivatives, Eur. J. Med. Chem. 106 (2015) 120–131.
[63] R. Mahesh, A. Jindal, B. Gautam, S. Bhatt, D. Pandey, Evaluation of anti-depressant-like activity of linezolid, an oxazolidinone class derivative–an investigation using behavioral tests battery of depression, Biochem. Biophys. Res. Commun. 409 (4) (2011) 723–726.
[64] S. Valente, S. Tomassi, G. Tempera, S. Saccoccio, E. Agostinelli, A. Mai, Novel reversible monoamine oxidase A inhibitors: highly potent and selective 3-(1 H-pyrrol-3-yl)-2-oxazolidinones, J. Med. Chem. 54 (23) (2011) 8228–8232.
[65] T. Xue, S. Ding, B. Guo, Y. Zhou, P. Sun, H. Wang, W. Chu, G. Gong, Y. Wang, X. Chen, Design, synthesis, and structure–activity and structure–pharmacokinetic relationship studies of novel [6, 6, 5] tricyclic fused oxazolidinones leading to the discovery of a potent, selective, and orally bioavailable FXa inhibitor, J. Med. Chem. 57 (18) (2014) 7770–7791.
[66] C. Xu, Y. Ren, Molecular modeling studies of [6, 6, 5] Tricyclic Fused Oxazolidinones as FXa inhibitors using 3D-QSAR, Topomer CoMFA, molecular

docking and molecular dynamics simulations, Bioorg. Med. Chem. Lett. 25 (20) (2015) 4522–4528.

[67] B.M. Crowley, C.A. Stump, D.N. Nguyen, C.M. Potteiger, M.A. McWherter, D. V. Paone, A.G. Quigley, J.G. Bruno, D. Cui, J.C. Culberson, Novel oxazolidinone calcitonin gene-related peptide (CGRP) receptor antagonists for the acute treatment of migraine, Bioorg. Med. Chem. Lett. 25 (21) (2015) 4777–4781.

[68] S. Rapposelli, F. Da Settimo, M. Digiacomo, C. La Motta, A. Lapucci, S. Sartini, M. Vanni, Synthesis and biological evaluation of 2′-Oxo-2, 3-dihydro-3′ H-spiro [chromene-4, 5′-[1, 3] oxazolidin]-3′ yl] acetic acid derivatives as aldose reductase inhibitors, Arch. Pharm. (Weinheim) 344 (6) (2011) 372–385.