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Original article

Synthesis and *in vitro* antibacterial activities of novel oxazolidinones☆

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Abstract

Design and synthesis of novel piperazinylaryloxazolidinones possessing heteroaryl groups are described and their *in vitro* antibacterial activities have been evaluated by MIC assay. Compounds (*S*)-*N*-[3-{3-fluoro-4-[4-[3-(5-nitrofuran-2-yl)-acryloyl]-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6o**), (*S*)-*N*-[3-{3-fluoro-4-[4-[3-(5-nitrothien-2-yl)-acryloyl]-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6p**) and *N*-oxide of (*S*)-*N*-[3-{3-fluoro-4-[4-[3-(5-nitrofuran-2-yl)-acryloyl]-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**9**) showed superior antibacterial activities than linezolid and also active against the linezolid resistant *Staphylococcus aureus* strains.
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Keywords: Piperazinylaryloxazolidinone; Antibacterial activity; Linezolid resistant *Staphylococcus aureus* strain; *In vitro* MIC

1. Introduction

Multi drug-resistant strains of Gram-positive clinical pathogens are increasingly posing a serious threat to society, particularly methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococci* (VRE) [1–3]. As a result, interest in antibacterial research to combat these organisms is growing. Furoxone **1** an oxazolidinone class of compound was initially reported in 1953 to possess antibacterial activity [4]. In the late 1980s scientists at DuPont developed Dup 721 **2** [5], which was discontinued because of toxicity in rodents [6]. The first few oxazolidinones to emerge as potential drug candidates from biological testing were linezolid **3** and eperezolid **4** (Fig. 1) [7].

Hence oxazolidinone class of antibacterials has attracted considerable attention of a number of research groups [8–30] during the last decade in order to get more efficacious and less toxic drug. Presently, linezolid **3** (Zyvox™) is the first and the only oxazolidinone class of compound in clinical use since 2000 after US-FDA approval [31]. Linezolid acts *via* a novel mechanism of action by inhibiting protein synthesis at the initiation phase *via* binding to 23S rRNA of the 50S ribosomal subunit of prokaryotes [32–34]. Unfortunately, linezolid resistant *Enterococcus* and *S. aureus* have been isolated from patients receiving prolonged treatment [35–38]. This has led to an urgent need to develop useful antibacterial chemotherapy, through extensive modifications of oxazolidinones [39,40].

Eperezolid, a piperazine analogue has been subjected to major modification and has been used for further optimization by several researchers such as a 5-nitrofuryl derivative ranbezolid **5** (**RBx 7644**) in clinical development by Ranbaxy Research Laboratories [41,42].

Earlier, we have reported novel piperazinylaryloxazolidinone having interesting antibacterial activity [43–50], however, none of the compounds could be studied further due to their poor solubility and bioavailabilty.

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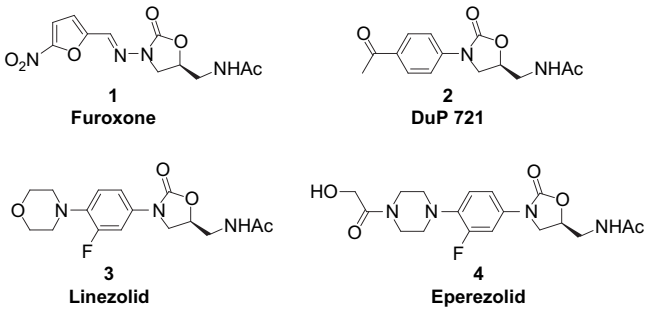


Fig. 1.

Recently, number of groups have reported oxazolidinone analogs substituted with different heteroaryls, which have shown impressive antibacterial activities [41,51–54]. The objective of the present study is to evaluate new oxazolidinones featuring different heteroaryls substituted alkenones **6**, alkenes **7** and **8** and *N*-oxide **9** (Fig. 2) at the 4-position of piperazinylaryloxazolidinones, with a view to identify antibacterials effective against linezolid resistant strains. The minimum inhibitory concentration (MIC) for bacterial growth was determined by microbroth dilution technique using the Clinical and Laboratory Standards Institute Guidelines (formerly, National Committee for Clinical Laboratory Standards, NCCLS) [55].

2. Chemistry

The piperazinylaryloxazolidinones **6** have been synthesized as outlined in Scheme 1 and described in our earlier communications [46]. The acrylic acids **10** and acrolein **12** were prepared by literature methods [56,57]. Piperazinylaryloxazolidinone derivative **11** was synthesized by standard methods [6]. The piperazinylaryloxazolidinone derivative **11** was coupled with acrylic acid derivative **10** using 1-hydroxy-benzotriazole monohydrate and [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide] hydrochloride in the presence of triethylamine at 27–28 °C to afford **6**. Oxazolidinone **6o** was converted into *N*-oxide derivative **9** using magnesium monoperoxyphthalate (Scheme 1) [58]. On the other hand, reductive amination of the piperazinylaryloxazolidinone derivative **11** with acrolein derivative **12** gave compounds **7** and **8** (Scheme 2) [41].

3. Results and discussion

Recently, we have reported the synthesis and SAR of piperazinylaryloxazolidinone compounds containing the unsubstituted cinnamoyl moiety as well as compounds with different substitutions on the phenyl ring of cinnamoyl group [46]. In order to see the effect of heteroaryl groups in the place of phenyl ring of the cinnamoyl moiety, we prepared several heteroaryl analogs (Fig. 2, Schemes 1and 2). Small changes in the structure of aromatic ring have been found to impart large effects on their antibacterial activity. Furanyl and thienyl groups rendered better antibacterial activity to the compounds.

The thiophene and furan derivatives **6a** and **6c**, respectively, exhibited nearly equal activity as that of linezolid and eperezolid (Table 1). When the point of attachment of these heterocycles were varied to get compounds **6b** and **6d**, they were found to be equipotent as their position isomers **6a** and **6c**, respectively. Among the five membered heterocycles, pyrrole moiety containing compound (**6e**) showed activities with MIC values in the range of 1–2 μg/mL in various Gram-positive strains. Similarly, six membered heterocycle groups such as pyridine containing compounds (**6f** and **6g**) were also found to be equipotent as compounds with five membered heterocycles (Table 1).

Oxazolidinones with 3-indolyl moiety resulted in compound **6h**, which was found to be slightly superior in antibacterial activity against *Bacillus cereus* and *Streptococcus pyogenes,* than rest of the heterocycles examined. In a bid to further see the effect of different substituents on the heterocyclic ring, especially furan ring, we synthesized the compounds, a methyl derivative of furan **6i**, a formyl derivative of furan **6j**, hydroxymethyl derivative of furan **6k** and the corresponding acetoxymethyl derivative **6l**.

The compounds **6i** and **6j** showed antibacterial activities in MIC assay but derivatives **6k** and **6l** showed inferior antibacterial activities as compared to linezolid and eperezolid.

The carboxylic acid **6m** and sodium salt of carboxylic acid **6n** when screened against selected Gram-positive bacteria, they remained inactive upto a concentration of 16 μg/mL. However, when a nitro group was introduced in furan ring to get **6o** and in thiophene ring to get **6p**, the compounds showed far superior *in vitro* activity than that of linezolid. However, an electron donating $-CH_3$ group at position 5 of the furan ring,

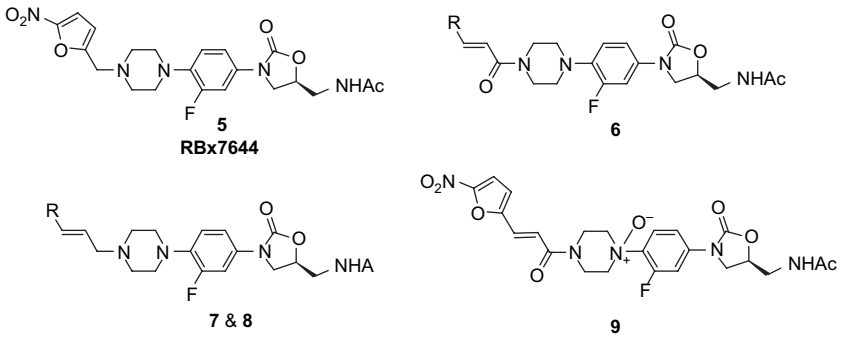
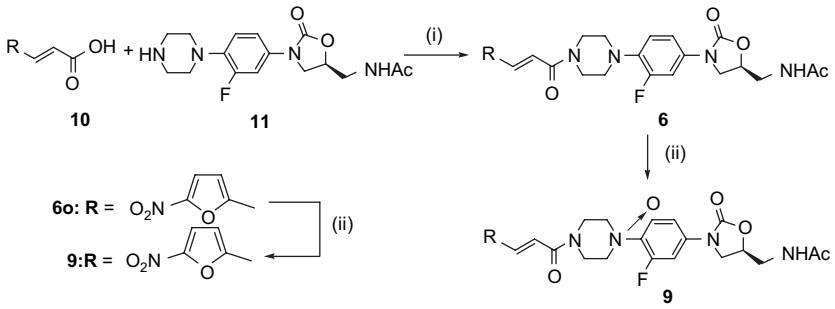


Fig. 2.

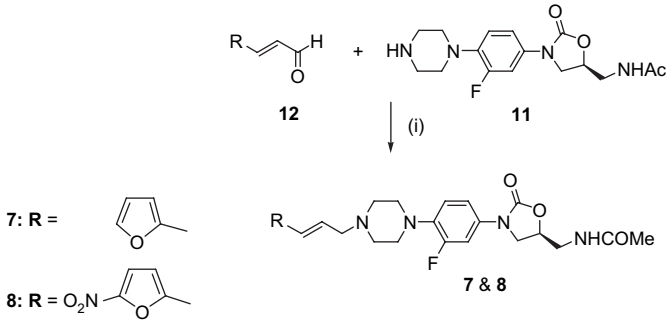


Scheme 1. Reagents and conditions: (i) EDC-HCl, HOBt.H_2O, TEA, CH_2Cl_2, 27–28 °C, 0.5–1 h, (method A); (ii) magnesium monoperoxyphthalate, MeOH, 29–30 °C, 1 h, (method B).

diminished the antibacterial activity (compare **6i** and **6c**), whereas an electron withdrawing $-NO_2$ group at position 5 of the furanyl ring increased the activity (compare **6o** and **6i**). Furthermore, we attempted to replace the −C═O group linked to piperazine ring by $-CH_2-$ to get compounds **7** and **8** (Fig. 2). The compound **7** was inferior in its potency in MIC assay compared to **6c**, similarly compound **8** was found to be much inferior to **6o**. However, both the compounds **7** and **8** exhibited almost similar antibacterial activities to that of linezolid and eperezolid (Table 2).

Some of the selected compounds such as **6o** and **6p**, which showed MIC values in the range of 0.125–1 μg/mL against the strains mentioned in Table 1, were further evaluated in an extended panel of Gram-positive susceptible strains like *Enterococcus faecalis* and *S. aureus* and against resistant organisms such as methicillin resistant *S. aureus*, vancomycin resistant *E. faecalis*, penicillin resistant S*treptococcus pneumoniae* and linezolid resistant *S. aureus*. Both the compounds were found to be superior to linezolid in these bacterial strains (Table 3).

In view of emerging resistance to linezolid, Gordeev et al. have reported compounds which are active against linezolid resistant *S. aureus* [24,25] and we also tested few selected oxazolidinone derivatives against linezolid resistant *S. aureus* **NRS 119** and **NRS 120**, which has G 2576T mutations in DNA encoding the central loop of domain V of 23S rRNA and these mutations have been reported to develop microorganism having linezolid resistance [60] (we are registered user of Network on Antimicrobial Resistance in *S. aureus*, www.narsa.net). Compounds **6o** and **6p** showed good antibacterial activity with *in vitro* MIC values in the range of 2–4 μg/mL against linezolid resistant *S. aureus* (Table 3, linezolid ≥ 16 μg/mL). Thus, appropriate substitution on oxazolidinone would give compounds, which may work even in linezolid resistant organisms. However, at this stage the correlation between SAR and antibacterial activity of compounds against linezolid resistant organisms could not be established.



Scheme 2. Reagents and conditions: (i) $NaBH(OAc)_3$, MS 4A, THF, 29–30 °C, 15 h, (method C).

Compound **6o**, which showed *in vitro* MIC values in the range of 0.125–0.25 μg/mL (Table 1) and remained active in the broader panel of Gram-positive strains as well as found to have activity against resistant organisms (Table 3), was selected for pharmacokinetic studies. However, the compound **6o** remained unabsorbed *via* per-oral route in Sprague–Dawley rats. It has been reported that several amines, which generally show poor bioavailability, can be converted into *N*-oxide derivatives resulting in improvement of pharmacokinetic parameters [58]. These *N*-oxides although act as pro-drug become water-soluble and are expected to improve bioavailability. The most potent compound having amide side chain on the 5 position of oxazolidinone ring **6o** was converted to its corresponding *N*-oxide affording **9** (Fig. 2). The compound **9** was found to be 2–4 times more active than linezolid in MIC assay in several Gram-positive strains (Table 4).

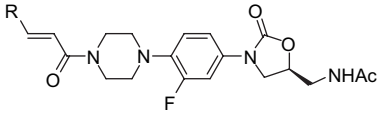
Pharmacokinetic behavior of *N*-oxide **9** was done in male Sprague–Dawley rats to study the effect of this modification. The rate of conversion of *N*-oxide **9** *via* per-oral and intravenous routes to **6o** was very fast and **9** itself was absent in plasma samples. The parent amine **6o** appeared in plasma immediately and quantifiable levels persisted for about 40 min after intravenous and 1.0 h after per-oral administration of the corresponding *N*-oxide **9**.

The pharmacokinetic parameters were calculated for the parent amine **6o** rather than that of the corresponding *N*-oxide (Table 5). The overall per-oral bioavailability of **6o** was found to be 60%, whereas linezolid is known to be 100% bioavailable (Table 5) [59]. The data suggests that **9** could serve as a pro-drug for the parent amine **6o**.

4. Conclusion

In summary, we have studied a series of heteroaryl substituted piperazinyloxazolidinones as antibacterial agents.

Table 1
In vitro MIC [minimum inhibitory concentration in μg/mL] values of oxazolidinones **6** in various Gram-positive bacteria[a]



6

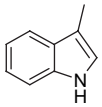
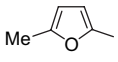
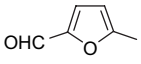
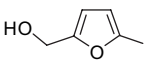
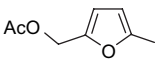
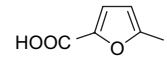
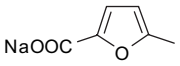
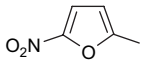
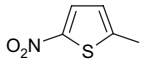
Compound	R	B.p.	B.c.	S.p.	S.e.	E.f.	S.a.
6a		0.5–1	0.5–1	1–2	0.5–1	0.5–1	1–2
6b		0.5–1	0.5–1	ND	1–2	0.5–1	0.5–1
6c		0.5–1	0.5–1	ND	1–2	0.5–1	0.5–1
6d		1–2	1–2	0.5–1	0.5–1	1–2	1–2
6e		1–2	1–2	1–2	0.5–1	1–2	1–2
6f		1–2	1–2	0.5–0.25	2–4	2–4	4–8
6g		1–2	1–2	0.5–1	0.5–1	2–4	1–2
6h		0.5–1	0.25–0.5	0.12–0.25	1–2	0.5–1	2–4
6i		1–2	1–2	0.5–1	0.5–1	1–2	2–4
6j		1–2	2–4	1–2	2–4	2–4	4–8
6k		4–8	2–4	1–2	1–2	2–4	4–8
6l		4–8	4–8	2–4	2–4	4–8	2–4

Table 1 (*continued*)

Compound	R	B.p.	B.c.	S.p.	S.e.	E.f.	S.a.
6m		>16	>16	>16	>16	>16	>16
6n		>16	>16	>16	>16	>16	>16
6o		≤0.12	≤0.12	≤0.12	≤0.12	0.25–0.5	0.12–0.25
6p		0.5–1	1–2	0.12–0.25	≤0.12	0.5–1	0.25–0.5
3		0.5–1	2–4	1–2	1–2	1–2	2–4
4		1–2	2–4	0.5–1	2–4	2–4	2–4

[a] MIC were determined by broth microdilution technique. B.p. = *Bacillus pumilus* **ATCC 14884**, B.c. = *Bacillus cereus* **ATCC 11778**, S.p. = *Streptococcus pyogenes* **ATCC 14289**, S.e. = *Staphylococcus epidermidis* **ATCC 155**, E.f. = *Enterococcus faecalis* **ATCC 35550**, S.a. = *Staphylococcus aureus* **ATCC 25923**, N D = **Not done.**

The antibacterial activity of the compounds **6o**, and **9** against a large variety of Gram-positive strains, methicillin resistant *S. aureus*, vancomycin resistant *E. faecalis* and penicillin resistant *S. pneumoniae* has been found good. A few selected compounds **6o**, **6p** and **9** were also found to be effective against linezolid resistant organisms.

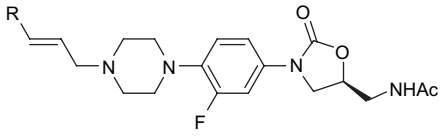
The most active compound **6o** is 4–16 times more active than linezolid and eperezolid in different strains. The compound **6o** which is orally unabsorbed could be made 60% bioavailable by converting it to its *N*-oxide **9**. Further studies of some of the active compounds are under progress.

5. Experimental protocols

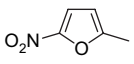
5.1. In vitro antibacterial activities (MIC)

The *in vitro* (MIC) antibacterial activity of the compounds against Gram-positive *Bacillus pumilus*, *B. cereus, S. aureus*, *Staphylococcus epidermidis*, *S. pyogenes*, *Streptococcus pneumoniae*, *E. faecalis* was tested as growth inhibition with the use of broth microdilution method according to NCCLS [55]. Compounds were dissolved in DMSO and water was added to get stock solution in 80% DMSO. The working

Table 2
In vitro MIC values of oxazolidinones **7** and **8** in various Gram-positive bacteria[a]



7 & 8

Compound	R	B.p.	B.c.	S.p.	S.e.	E.f.	S.a.
7		2–4	0.5–1	0.5–1	8–16	2–4	2–4
8		0.25–0.5	0.25–0.5	0.12–0.25	0.5–1.0	1–2	1–2
3		0.5–1	2–4	1–2	1–2	1–2	2–4
4		1–2	2–4	0.5–1	2–4	2–4	2–4

[a] Please see the foot notes of Table 1.

Table 3
In vitro MIC values of selected oxazolidinones against broader panel of both susceptible and resistant Gram-positive strains[a]

Compound	E.f. 1	E.f. 2	E.f. 3	S.a. 1	S.a. 2	S.a. 3	S.a. 4	S.a 5	S.a 6	S.p 1
6o	0.25–0.5	0.5–1	0.12–0.25	0.12–0.25	0.12–0.25	0.12–0.25	0.12–0.25	2–4	2–4	0.25–0.5
6p	0.25–0.5	0.5–1.0	0.5–1.0	0.25–0.5	0.25–0.5	0.25–0.5	0.25–0.5	4–8	4–8	≤0.125
3	1–2	1–2	1–2	2–4	2–4	1–2	1–2	>16	>16	0.25–0.5
4	1–2	1–2	1–2	2–4	2–4	1–2	1–2	>16	>16	0.5–1

[a] MIC were determined by broth microdilution technique. E.f. 1 = *E. faecalis* **ATCC 14506**, E.f. 2 = multi-resistant *E. faecalis* **ATCC 700802**, E.f. 3 = vancomycin resistant *Enterococcus faecium* **ATCC 700221**, S.a. 1 = *S. aureus* **ATCC 29213**, S.a. 2 = *S. aureus,* **ATCC 9144**, S.a. 3 = *S. aureus* **ATCC 14154**, S.a. 4 = methicillin resistant *S. aureus* **ATCC 700699**, S.a 5 = linezolid resistant *S. aureus* NRS **119**, S.a 6 = linezolid resistant *S. aureus* NRS **120,** S.p 1 = multi-resistant *Streptococcus pneumoniae* **ATCC 700904**, N D = Not done.

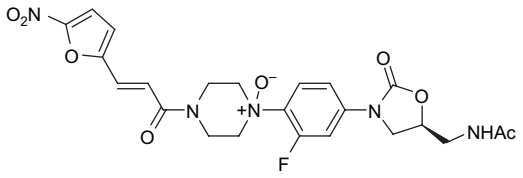
solution was prepared by diluting the stock solution 1:10 times in 4–8% DMSO in water or medium. With each set of experiment concurrent sterility controls and inoculum (bacterial culture) viability controls were examined. Sterility controls meant to check sterility of each component of the test which contains sterility conformation for media, vehicle, working drug solution and saline. While inoculum viability controls were done to evaluate the growth inhibitory action of the vehicle itself to each bacterial strain. They contain positive control (plain medium) and highest three dilutions of the vehicle (i.e., 4%, 2% and 1% of DMSO) in presence of the final inoculum and the dissolved compounds were evaluated in the concentrations of 0.125, 0.25, 0.5, 1, 2, 4, 8, and 16 μg/mL.

5.2. Pharmacokinetics

Pharmacokinetics of the test compounds (**6o** and **9**) was studied *via* per-oral and intravenous routes of administration in male Sprague–Dawley rats of 8–10 weeks of age. Animals were fasted for 18 h and food was supplied after 4.0 h of administration of the test compound. There was free access to water throughout the study. A homogenous suspension of the test substance was prepared in 0.5% w/v CMC in normal saline and a per-oral dose of 30 mg/kg was administered. For intravenous administration, the test compounds were dissolved in a cocktail (polyethylene glycol PEG-400 17.48%, cremophore ELP 4.85% v/v, ethanol 4.85% v/v, propylene glycol 9.7% v/v and normal saline 63.11% v/v) to obtain a clear solution and a dose of 10 mg/kg was administered through tail vein. After the administration of the test compounds, blood samples were withdrawn at various time intervals through retro-orbital plexus and collected into heparinized micro-centrifuge tubes. Plasma was separated by centrifugation at 4000 rpm for 5 min at ambient temperature and analyzed immediately. Remaining samples were stored at −20 °C until analyzed.

Analysis was carried out by taking aliquots of 180 μL plasma and 20 μL of internal standard (Atorvastatin) and was extracted with 2.5 mL of extracting solvent (ethyl acetate:acetonitrile, 80:20, v/v) in glass test-tube by vortexing with spinix vortex mixture for a minute. This was then centrifuged at 2000 rpm for 2.0 min. The supernatant was transferred to another glass test-tube and the solvent was evaporated under nitrogen using Zymark evaporator at 40 °C. Finally, the tubes were reconstituted with 0.1 mL diluent (acetonitrile:methanol:water 40:40:20). The reconstituted samples were analyzed on Agilent 1100 Series HPLC system with a mobile phase of 0.05% v/v trifluoroacetic acid in water:acetonitrile (32:68, v/v); flowing at a flow rate of 1.0 mL/min through a Kromasil 250 mm × 4.6 mm × 5 μm column maintained at 30 °C. Chromatographic separation was achieved within 15 min. Agilent software version Chemstation Rev.A.09.01 (1206) was used to acquire and process all chromatographic data. Quantification was based on a series of calibrators ranging from 0.031 to 32 μg/mL, prepared by adding test compound to drug free rat plasma. Quality control samples were analyzed in parallel to verify that the system

Table 4
In vitro MIC values of oxazolidinone **9** against broader panel of both susceptible and resistant Gram-positive strains[a]



9

Compd.	S.p.	S.e.	E.f.	S.a.	S.a. 1	S.a. 3	S.a. 4	E.f. 2	E.f. 3	S.p 1	S.a 5	S.a 6
9	0.12–0.25	0.12–0.25	1–2	0.5–1	1–2	1–2	0.5–1	1–2	0.5–1	0.25–0.5	2–4	2–4
3	1–2	1–2	1–2	2–4	2–4	1–2	1–2	1–2	1–2	0.25–0.5	>16	>16
4	0.5–1	2–4	2–4	2–4	2–4	1–2	1–2	1–2	1–2	0.5–1	>16	>16

[a] Please see the footnotes of Tables 1 and 3.

Table 5
Mean pharmacokinetic parameters of **9** and linezolid in male Sprague–Dawley rats[a]

Compound	Route	Dose (mg/kg)	t_{max} (h)	C_{max} (μg/mL)	$t_{1/2}$ (h)	AUC (0–∞) (h. μg/mL)	Bioavailability %
9	i.v	10	0.00	9.18 ± 1.96	0.95 ± 0.05	1.03 ± 0.22	60
	p.o	30	0.17 ± 0.01	1.21 ± 0.37	0.97 ± 0.36	1.87	
Linezolid [59]	i.v	10	0.00	n	0.95 ± 0.08	n	100
	p.o	25	0.31 ± 0.17	15.8 ± 3.3	1.05 ± 0.03	n	

[a] Compound **9** gets converted to **6o** *in vivo* and hence concentration of **6o** can only be measured, n = not reported.

performs in control. Pharmacokinetic parameters namely; maximum plasma concentration (C_{max}), time point of maximum plasma concentration (t_{max}), area under the plasma concentration–time curve from 0 h to infinity ($AUC_{0-\infty}$) and half-life of drug elimination during the terminal phase ($t_{1/2}$) were calculated from plasma concentration *versus* time data, by standard non-compartmental methods, using the WinNonLin software version 4.0.1 procured from Pharsight Corporation, USA.

5.3. Chemistry

^{1}H spectral data are recorded using a 300 MHz ^{1}H NMR spectrometer (M-300) and reported in δ scale, using tetramethyl silane as an internal standard. IR spectra are recorded on FTIR 8300 Shimadzu in KBr pellets. Mass spectra are recorded on Perkin Elmer Sciex API 3000. HPLC analysis were carried out at λ_{max} 220 nm using column ODS C-18, 150 mm × 4.6 mm × 4 μm on AGILENT 1100 series. Melting points were recorded on scientific melting point apparatus and are uncorrected. The oxazolidinones evaluated in antibacterial screening assay were ca. 90–99% in purity by HPLC analysis and ^{1}H NMR spectrophotometry. Considering the intrinsic variability to the standard broth microdilution assay, which is generally considered accurate within one dilution, ≥90% chemical purity supports the meaningful SAR studies.

5.3.1. Typical procedure for the synthesis of (*S*)-*N*-[3-{3-fluoro-4-[4-(3-thien-2-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6a**), method A

To a stirred solution of 3-thien-2-yl-acrylic acid **10** (45.8 mg, 0.2974 mmol) in dichloromethane (20 mL) 1-hydroxy benzotriazole-hydrate (102 mg, 0.7548 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (104 mg, 0.5425 mmol), and *N*-(3-{3-fluoro-4-piperazin-1-yl-phenyl}-2-oxo-oxazolidin-5-yl-methyl)acetamide **11** (100 mg, 0.2976 mmol) was added followed by triethylamine (0.2 mL, 1.5536 mmol). The reaction mixture was stirred at 28–29 °C for 2 h. The progress of the reaction was monitored by TLC using the mobile phase $CHCl_3$:MeOH (7:3). The reaction mixture was poured into demineralised water (80 mL) and extracted with dichloromethane (2 × 50 mL). The dichloromethane layer was separated and dried over anhydrous Na_2SO_4 and filtered.

The solvents were evaporated on a rotatory evaporator under reduced pressure to afford an off-white solid (140 mg, 100%). The solid was taken in EtOAc (10 mL) and heated on a water bath at 40–45 °C for 15 min. The hot slurry of the compound in EtOAc was filtered on a Buchner funnel under suction and the residue obtained was washed with diethyl ether (10 mL) to afford *N*-[3-{3-fluoro-4-[4-(3-thien-2-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide as a white solid (75 mg, 78%), 97.3% purity by HPLC; mp: 225 °C; IR (KBr): 3292, 1693, 1554, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.84 (d, J = 15.09 Hz, 1H, vinyl-*H*), 7.46 (dd, J = 16.20, 2.56 Hz, 1H, phenyl-*H*), 7.33 (d, J = 5.06 Hz, 1H, phenyl-*H*), 7.23 (d, J = 3.48 Hz, 1H, phenyl-*H*), 7.06–7.03 (m, 2H, thienyl-*H*), 6.92 (t, J = 9.05 Hz, 1H, thienyl-*H*), 6.70 (d, J = 15.06 Hz, 1H, vinyl-*H*), 6.20 (bs, 1H, –N*H*CO–), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.02 (t, J = 9.06 Hz, 1H, –CH_2–), 3.81–3.74 (bs, 4H, piperazine-*H*), 3.72 (m, 1H, –CH_2–), 3.30–3.23 (m, 2H, –CH_2 of oxazolidinone ring), 3.08 (bs, 4H, piperazine-*H*), 2.27 (s, 3H, –COCH_3); ESI-MS: 473 $(M + H)^+$.

The following compounds have been prepared as per method A.

5.3.1.1. (*S*)-*N*-[3-{3-Fluoro-4-[4-(3-thien-3-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6b**).

Yield: 82%; 98% purity by HPLC; mp: 250 °C; IR (KBr): 3294, 1733, 1647, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3 + CD_3OD$): δ 7.68 (d, J = 15.08 Hz, 1H, vinyl-*H*), 7.51–7.48 (m, 3H, phenyl-*H*), 7.34 (m, 2H, thienyl-*H*), 6.97 (t, J = 9.06 Hz, 1H, thienyl-*H*), 6.75 (d, J = 15.27 Hz, 1H, vinyl-*H*), 6.07 (s, 1H, –N*H*CO–), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.04 (t, J = 9.03 Hz, 1H, –CH_2–), 3.89–3.83 (bs, 4H, piperazine-*H*), 3.74 (m, 1H, –CH_2–), 3.62 (m, 2H, –CH_2– of oxazolidinone ring), 3.09 (bs, 4H, piperazine-*H*), 2.01 (s, 3H, –COCH_3); ESI-MS: 473 $(M + H)^+$.

5.3.1.2. (*S*)-*N*-[3-{3-Fluoro-4-[4-(3-furan-2-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6c**).

Yield: 47%; 94% purity by HPLC; mp: 124–126 °C; IR (KBr): 3292, 1735, 1643, 1517, 1409 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.48 (d, J = 15.09 Hz, 1H, vinyl-*H*), 7.46 (m, 2H, phenyl-*H*), 7.08 (dd, J = 10.41, 1.56 Hz, 1H, phenyl-*H*), 6.92 (t, J = 9.02 Hz, 1H, furyl-*H*), 6.83 (d, J = 15.06 Hz, 1H, vinyl-*H*), 6.56 (d, J = 3.33 Hz, 1H, furyl-*H*), 6.46 (dd, J = 5.13, 1.77 Hz, 1H, furyl-*H*), 5.98 (s, 1H, –N*H*CO–), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.02 (t, J = 9.06 Hz, 1H, –CH_2–), 3.89–3.82 (bs, 4H, piperazine-*H*), 3.74 (m, 1H, –CH_2–), 3.70

(m, 2H, –CH_2– of oxazolidinone ring), 3.08 (bs, 4H, piperazine-*H*), 2.08 (s, 3H, –COCH_3); ESI-MS: 457.4 $(M + H)^+$.

*5.3.1.3. (S)-N-[3-{3-Fluoro-4-[4-(3-furan-3-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6d**).* Yield: 41%; 99% purity by HPLC; mp: 250–255 °C; IR (KBr): 3313, 1739, 1654, 1598, 1550 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.23 (bs, 1H, –N*H*CO–), 8.03 (s, 1H, phenyl-*H*), 7.70 (s, 1H, phenyl-*H*), 7.43 (d, *J* = 15.16 Hz, 1H, vinyl-*H*), 7.41 (s, 1H, phenyl-*H*), 7.17 (dd, *J* = 10.97, 2.14 Hz, 1H, furyl-*H*), 7.11–7.00 (m, 3H, vinyl-*H* and furyl-*H*), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.07 (t, *J* = 8.96 Hz, 1H, –CH_2–), 3.81–3.71 (bs, 4H, piperazine-*H*), 3.68 (m, 1H, –CH_2–), 3.38 (m, 2H, –CH_2– of oxazolidinone ring), 2.97 (bs, 4H, piperazine-*H*), 1.81 (s, 3H, –COCH_3); ESI-MS: 457.4 $(M + H)^+$.

*5.3.1.4. (S)-N-[3-{3-Fluoro-4-[4-(3-1H-pyrrol-2-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6e**).* Yield: 10%; 94% purity by HPLC; mp: 198–200 °C; IR (KBr): 3280, 1751, 1641, 1550, 1517 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.47 (bs, 1H, pyrrolyl-N*H*), 7.49–7.44 (dd, *J* = 17.07, 2.14 Hz, 1H, phenyl-*H*), 7.12–7.08 (m, 1H, phenyl-*H*), 6.95–6.91 (m, 2H, phenyl-*H* and pyrrolyl-*H*), 6.73 (d, *J* = 12.62 Hz, 1H, vinyl-*H*), 6.46 (t, *J* = 1.69 Hz, 1H, pyrrolyl-*H*), 6.24 (t, *J* = 2.92 Hz, 1H, pyrrolyl-*H*), 6.02 (s, 1H, –N*H*CO–), 5.82 (d, *J* = 12.50 Hz, 1H, vinyl-*H*), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.07 (t, *J* = 8.95 Hz, 1H, –CH_2–), 3.71 (bs, 4H, piperazine-*H*), 3.66 (m, 1H, –CH_2–), 3.39 (m, 2H, –CH_2– of oxazolidinone ring), 2.97 (s, 4H, piperazine-*H*), 1.82 (s, 3H, –COCH_3); ESI-MS: 456 $(M + H)^+$.

*5.3.1.5. (S)-N-[3-{3-Fluoro-4-[4-(3-pyridin-4-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6f**).* Yield: 46%; 95% purity by HPLC; mp: 244–246 °C; IR (KBr): 3292, 1733, 1651, 1546 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.60 (d, *J* = 5.65 Hz, 2H, pyridinyl-*H*), 8.23 (bs, 1H, –N*H*CO–), 7.69 (d, *J* = 6.05 Hz, 2H, pyridinyl-*H*), 7.56 (dd, *J* = 15.48 Hz, 1H, vinyl-*H*), 7.52 (m, 1H, phenyl-*H*), 7.47 (d, *J* = 14.45 Hz, 1H, vinyl-*H*), 7.16 (dd, *J* = 12.77, 2.27 Hz, 1H, phenyl-*H*), 7.08 (t, *J* = 9.21 Hz, 1H, phenyl-*H*), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.07 (t, *J* = 8.94 Hz, 1H, –CH_2–), 3.87–3.73 (bs, 4H, piperazine-*H*), 3.67 (m, 1H, –CH_2–), 3.38 (m, 2H, –CH_2– of oxazolidinone ring), 2.99 (bs, 4H, piperazine-*H*), 1.81 (s, 3H, –COCH_3); ESI-MS: 468.3 $(M + H)^+$.

*5.3.1.6. (S)-N-[3-{3-Fluoro-4-[4-(3-pyridin-3-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6g**).* Yield: 80%; 97% purity by HPLC; mp: 248–250 °C; IR (KBr): 1730, 1649, 1604, 1517 cm^{-1}; ^1H NMR ($CD_3OD + CDCl_3$): δ 8.74 (d, *J* = 1.71 Hz, 1H, pyridinyl-*H*), 8.49 (dd, *J* = 6.21, 1.38 Hz, 1H, pyridinyl-*H*), 8.09 (d, *J* = 8.04 Hz, 1H, pyridinyl-*H*), 7.69 (d, *J* = 15.57 Hz, 1H, vinyl-*H*), 7.51–7.44 (m, 2H, pyridinyl-*H* and phenyl-*H*), 7.28 (d, *J* = 15.57 Hz, 1H, vinyl-*H*), 7.11 (m, 1H, phenyl-*H*), 7.01 (t, *J* = 8.97 Hz, 1H, phenyl-*H*), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.09 (t, *J* = 9.01 Hz, 1H, –CH_2–), 3.89 (bs, 4H, piperazine-*H*), 3.77 (m, 1H, –CH_2–), 3.53 (m, 2H, –CH_2 of oxazolidinone ring), 3.10 (bs, 4H, piperazine-*H*), 1.95 (s, 3H, –COCH_3); ESI-MS: 468 $(M + H)^+$.

*5.3.1.7. (S)-N-[3-{3-Fluoro-4-[4-(3-1H-indol-3-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6h**).* Yield: 73%; 97% purity by HPLC; mp: 218–220 °C; IR (KBr): 3323, 1743, 1614, 1560 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.61 (s, 1H, indolyl-N*H*), 8.21 (s, 1H, –N*H*CO–), 7.93 (d, *J* = 9.02 Hz, 1H, indolyl-*H*), 7.83 (d, *J* = 2.58 Hz, 1H, indolyl-*H*), 7.76 (d, *J* = 15.27 Hz, 1H, vinyl-*H*), 7.45–7.40 (m, 2H, indolyl-*H*), 7.15–7.10 (m, 4H, indolyl-*H* and phenyl-*H*), 6.98 (d, *J* = 15.36 Hz, 1H, vinyl-*H*), 4.80 (m, 1H, oxazolidinone ring C_5-*H*), 4.09 (t, *J* = 9.06 Hz, 1H, –CH_2–), 3.88–3.79 (bs, 4H, piperazine-*H*), 3.76 (m, 1H, –CH_2–) and 3.72–3.69 (m, 2H, –CH_2– of oxazolidinone ring), 3.00 (bs, 4H, piperazine-*H*), 2.42 (s, 3H, –COCH_3); ESI-MS: 506.3 $(M + H)^+$.

*5.3.1.8. (S)-N-[3-{3-Fluoro-4-[4-(3-methylfuran-2-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6i**).* Yield: 33%; 96% purity by HPLC; mp: 205–206 °C; IR (KBr): 3301, 1733, 1643, 1517 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.49–7.43 (m, 2H, phenyl-*H* and vinyl-*H*), 7.06 (dd, *J* = 10.41, 1.59 Hz, 1H, phenyl-*H*), 6.92 (t, *J* = 9.04 Hz, 1H, phenyl-*H*), 6.73 (d, *J* = 14.97 Hz, 1H, vinyl-*H*), 6.45 (d, *J* = 3.18 Hz, 1H, furyl-*H*), 6.06 (m, 2H, furyl-*H* and –N*H*CO–), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.02 (t, *J* = 8.98 Hz, 1H, –CH_2–), 3.87 (bs, 4H, piperazine-*H*), 3.75 (m, 1H, –CH_2–), 3.72–3.68 (m, 2H, –CH_2– of oxazolidinone ring), 3.07 (bs, 4H, piperazine-*H*), 2.35 (s, 3H, –COCH_3), 2.02 (s, 3H, –CH_3); ESI-MS: 471.3 $(M + H)^+$.

*5.3.1.9. (S)-N-[3-{3-Fluoro-4-[4-(5-5-formylfuran-2-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6j**).* Yield: 50%; 93% purity by HPLC; mp: 191–193 °C; IR (KBr): 3276, 1728, 1676, 1598 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.61 (s, 1H, –C*H*O), 8.22 (bs, 1H, –N*H*CO–), 7.59 (d, *J* = 3.69 Hz, 1H, furyl-*H*), 7.47 (m, 1H, phenyl-*H*), 7.43 (d, *J* = 15.35 Hz, 1H, vinyl-*H*), 7.26 (d, *J* = 15.36 Hz, 1H, vinyl-*H*), 7.14 (d, *J* = 3.64 Hz, 2H, phenyl-*H* and furyl-*H*), 7.07 (t, *J* = 9.24 Hz, 1H, phenyl-*H*), 4.69 (m, 1H, oxazolidinone ring C_5-*H*), 4.07 (t, *J* = 8.98 Hz, 1H, –CH_2–), 3.85–3.81 (bs, 4H, piperazine-*H*), 3.69 (m, 1H, –CH_2–), 3.39 (m, 2H, –CH_2– of oxazolidinone ring), 2.99 (bs, 4H, piperazine-*H*), 1.81 (s, 3H, –COCH_3); ESI-MS: 485 $(M + H)^+$.

*5.3.1.10. (S)-N-[3-{3-Fluoro-4-(4-[3-(5-hydroxymethylfuran-2-yl-acryloyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6k**).* Yield: 45%; 95% purity by HPLC; mp: 190–192 °C; IR (KBr): 3307, 1751, 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 (dd, *J* = 16.66, 2.45 Hz, 1H, phenyl-*H*), 7.43 (d, *J* = 15.04 Hz, 1H, vinyl-*H*), 7.06 (d, *J* = 8.73 Hz, 1H, phenyl-*H*), 6.90 (t, *J* = 9.03 Hz, 1H, phenyl-*H*), 6.81 (d, *J* = 15.05 Hz, 1H, vinyl-*H*), 6.50 (d, *J* = 3.41 Hz, 1H, furyl-*H*), 6.36 (m, 2H, furyl-*H* and –N*H*CO–), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.64 (s, 2H, –CH_2OH), 4.02 (t, *J* = 9.12 Hz, 1H,

–CH_2–), 3.86 (bs, 4H, piperazine-*H*), 3.76 (m, 1H, –CH_2–), 3.66 (m, 2H, –CH_2– of oxazolidinone ring), 3.06 (bs, 4H, piperazine-*H*), 2.02 (s, 3H, –$COCH_3$); ESI-MS: 487 $(M+H)^+$.

*5.3.1.11. Acetic acid (S)-[3-(4-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-3-oxo-propenyl}furan-2-yl-methyl ester (**6l**).* Yield: 55%; 98% purity by HPLC; mp: 200–202 °C; IR (KBr): 3280, 1726, 1643, 1596, 1550 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.47 (dd, $J = 16.68$, 2.55 Hz, 1H, phenyl-*H*), 7.45 (d, $J = 15.06$ Hz, 1H, vinyl-*H*), 7.08 (dd, $J = 10.68$, 1.86 Hz, 1H, phenyl-*H*), 6.92 (t, $J = 9.03$ Hz, 1H, phenyl-*H*), 6.85 (d, $J = 15.09$ Hz, 1H, vinyl-*H*), 6.49 (dd, $J = 20.07$, 3.33 Hz, 2H, furyl-*H*), 6.02 (bs, 1H, –N*H*CO–), 5.07 (s, 2H, –CH_2OAc), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.02 (t, $J = 6.02$ Hz, 1H, –CH_2–), 3.88–3.82 (bs, 4H, piperazine-*H*), 3.74 (m, 1H, –CH_2–), 3.64 (m, 1H, –CH_2– of oxazolidinone ring), 3.08 (bs, 4H, piperazine-*H*), 2.11 (s, 3H, –$OCOCH_3$), 2.02 (s, 3H, –$COCH_3$); ESI-MS: 529.3 $(M+H)^+$.

*5.3.1.12. (S)-5-[3-(4-{4-[5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-3-oxo-propenyl}-furan-2-carboxylic acid (**6m**).* Yield: 35%; 96% purity by HPLC; mp: 213–216 °C; IR (KBr): 3276, 1728, 1676, 1598 cm^{-1}; ^1H NMR (DMSO-d_6): δ 13.29 (bs, 1H, –COO*H*), 8.20 (bs, 1H, –N*H*CO–), 7.49(dd, $J = 17.19$, 2.34 Hz, 1H, phenyl-*H*), 7.37 (d, $J = 15.27$ Hz, 1H, vinyl-*H*), 7.27 (d, $J = 3.64$ Hz, 1H, furyl-*H*), 7.17 (dd, J = 11.7 and 2.2 Hz, 1H, phenyl-*H*), 7.10 (m, 1H, phenyl-*H*), 7.07 (d, J = 15.33 Hz, 1H, vinyl-*H*), 7.02 (d, $J = 3.64$ Hz, 1H, furyl-*H*), 4.69 (m, 1H, oxazolidinone ring C_5-*H*), 4.07 (t, $J = 8.97$ Hz, 1H, –CH_2–), 3.79–3.71 (bs, 4H, piperazine-*H*), 3.68 (m, 1H, –CH_2–), 3.36 (m, 2H, –CH_2– of oxazolidinone ring), 2.99 (bs, 4H, piperazine-*H*), 1.81 (s, 3H, –$COCH_3$); ESI-MS: 501 $(M+H)^+$.

*5.3.1.13. Sodium salt of (S)-5-[3-(4-{4-[5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-3-oxo-propenyl]furan-2-carboxylic acid (**6n**).* Yield: 60%; 98% purity by HPLC; mp: 222–223 °C; IR (KBr): 3276, 1728, 1676, 1598 cm^{-1}; ^1H NMR (DMSO-d_6): δ 13.29 (bs, 1H, –COO*H*), 8.20 (bs, 1H, –N*H*CO–), 7.49 (dd, $J = 17.19$, 2.34 Hz, 1H, phenyl-*H*), 7.37 (d, $J = 15.27$ Hz, 1H, vinyl-*H*), 7.17 (dd, J = 11.7 and 2.2 Hz, 1H, phenyl-*H*), 7.10 (m, 1H, phenyl-*H*), 7.07 (d, J = 15.33 Hz, 1H, vinyl-*H*), 7.02 (d, $J = 3.64$ Hz, 1H, furyl-*H*), 4.69 (m, 1H, oxazolidinone ring C_5-*H*), 4.07 (t, $J = 8.97$ Hz, 1H, –CH_2–), 3.79–3.71 (bs, 4H, piperazine-*H*), 3.68 (m, 1H, –CH_2–), 3.36 (m, 2H, –CH_2– of oxazolidinone ring), 2.99 (bs, 4H, piperazine-*H*), 1.81 (s, 3H, –$COCH_3$); ESI-MS: 501 $(M-Na)^+$.

*5.3.1.14. (S)-N-[3-{3-Fluoro-4-[4-[3-(5-nitrofuran-2-yl)-acryloyl]-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6o**).* Yield: 27%; 98% purity by HPLC; mp: 170 °C; IR (KBr): 3084, 1751, 1602, 1487 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.48 (d, $J = 15.12$ Hz, 1H, vinyl-*H*), 7.49 (s, 1H, phenyl-*H*), 7.35 (d, $J = 3.75$ Hz, 1H, furyl-*H*), 7.17 (d, $J = 15.18$ Hz, 1H, vinyl-*H*), 7.09 (dd, $J = 10.56$, 1.83 Hz, 1H, phenyl-*H*), 6.92 (t, $J = 9.06$ Hz, 1H, phenyl-*H*), 6.70 (d, $J = 3.78$ Hz, 1H, furyl-*H*), 5.99 (bs, 1H, –N*H*CO–), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.02 (t, $J = 8.91$ Hz, 1H, –CH_2–), 3.91–3.84 (bs, 4H, piperazine-*H*), 3.75 (m, 1H, –CH_2–), 3.68–3.62 (m, 2H, –CH_2– of oxazolidinone ring), 3.10 (bs, 4H, piperazine-*H*), 2.02 (s, 3H, –$COCH_3$); ESI-MS: 502.2 $(M+H)^+$.

*5.3.1.15. (S)-N-[3-{3-Fluoro-4-[4-[3-(5-nitrothien-2-yl)-acryloyl]-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**6p**).* Yield: 22%; 93% purity by HPLC; mp: 235–237 °C; IR (KBr): 3284, 1726, 1662, 1517, 1448 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.85 (d, $J = 4.26$ Hz, 1H, thienyl-*H*), 7.73 (d, $J = 15.24$ Hz, 1H, vinyl-*H*), 7.48 (dd, $J = 16.65$, 2.43 Hz, 1H, phenyl-*H*), 7.14 (m, 1H, phenyl-*H*), 7.08 (dd, $J = 8.97$, 2.01 Hz, 1H, phenyl-*H*), 6.91 (m, 1H, thienyl-*H*), 6.89 (d, $J = 15.12$ Hz, 1H, vinyl-*H*), 5.93 (bs, 1H, –N*H*CO–), 4.76 (m, 1H, oxazolidinone ring C_5-*H*), 4.02 (t, $J = 8.94$ Hz, 1H, –CH_2–), 3.91–3.79 (bs, 4H, piperazine-*H*), 3.72 (m, 1H, –CH_2–), 3.68–3.63 (m, 2H, –CH_2– of oxazolidinone ring), 3.10 (bs, 4H, piperazine-*H*), 2.02 (s, 3H, –$COCH_3$); ESI-MS: 518 $(M+H)^+$.

*5.3.2. Typical procedure for synthesis of N-oxide of (S)-N-[3-{3-fluoro-4-[4-[3-(5-nitrofuran-2-yl)-acryloyl]-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**9**)), method B*

To a stirred solution of [*N*-[3-{3-fluoro-4-[4-[3-(5-nitrofuran-2-yl)-acryloyl]-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide] **6o** (0.237 g, 0.482 mmol) in dry methanol (25 mL) at 29–30 °C magnesium monoperoxyphthalate hexahydrate (0.286 g, 0.577 mmol) was added and the mixture was stirred at 29–30 °C over a period of 1 h. The progress of the reaction was monitored by TLC using the mobile phase $CHCl_3$:MeOH (9:1). The reaction mixture was filtered through celite and the filtrate was concentrated on a rotatory evaporator under reduced pressure to afford oil. To the oil, diisopropyl ether (10 mL) and diethyl ether (5 mL) are added and triturated to get a crude solid (0.150 mg). The crude compound was purified using column chromatography on silica gel (100–230 mesh) with 0–0.6% methanolic-NH_3 in chloroform as eluent. The fractions were pooled and the solvents were evaporated on a rotatory evaporator to afford *N*-oxide of (*S*)-*N*-[3-{3-fluoro-4-[4-[3-(5-nitrofuran-2-yl)-acryloyl]-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide as a white solid.

Yield: 37% (0.090 g), 99% purity by HPLC; mp: 162–163 °C; IR (KBr): 3084, 1751, 1602, 1487 cm^{-1}; ^1H NMR ($CD_3OD + CDCl_3$): δ 8.38 (bs, 1H, –N*H*CO–), 7.83 (dd, $J = 18.12$, 2.30 Hz, 1H, phenyl-*H*), 7.48 (d, $J = 15.29$ Hz, 1H, vinyl-*H*), 7.47 (d, $J = 3.83$ Hz, 1H, furyl-*H*), 7.41 (dd, $J = 11.23$, 2.01 Hz, 2H, phenyl-*H*), 7.33 (d, $J = 15.36$ Hz, 1H, vinyl-*H*), 6.99 (d, $J = 3.82$ Hz, 1H, furyl-*H*), 4.77 (m, 1H, oxazolidinone ring C_5-*H*), 4.17 (t, $J = 9.06$ Hz, 1H, –CH_2–), 3.90–3.8 (bs, 4H, piperazine-*H*), 3.63 (m, 1H,

–CH_2–), 3.55 (m, 2H, –CH_2– of oxazolidinone ring), 3.20 (bs, 4H, piperazine-*H*), 1.95 (s, 3H, –COCH_3); ESI-MS: 518 $(M+H)^+$.

*5.3.3. Typical procedure for synthesis of (S)-N-[3-{3-fluoro-4-[4-(3-(5-nitrofuran-2-yl)-allyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide hydrochloride (**8**)), method C*

(a) *3-(5-Nitrofuran-2-yl)-2-propenal*: to a stirred solution of 5-nitrofurfural (5 g, 35.46 mmol) in benzene (12 mL) acetaldehyde (3 g, 54.5 mmol) at 0–5 °C was added over a period of 10 min. To this, catalytic mixture of piperidine (0.1 g, 1.17 mmol) and acetic acid (0.075 g, 11.16 mmol) in benzene (10 mL) were added drop wise over a period of 3 h at 0–5 °C. The mixture was stirred at 26–27 °C for 8 h and then heated on steam bath at 72–74 °C for 6 h. Reaction mixture was cooled to 26–27 °C. The benzene layer was decanted and the mixture was extracted with hot benzene (2 × 100 mL). The combined organic layer was treated with animal charcoal and filtered on a Buchner funnel through a bed of hy-flow (0.2 g). The filtrate was concentrated on a rotary evaporator to afford [3-(5-nitrofuran-2-yl)-2-propenal] **12** (R = 5-nitro-2-furyl) as a brown solid (0.6 g, 9%). Mp: 114–116 °C; IR (KBr): 3327, 1676, 1521, 1471 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.70 (d, $J = 7.63$ Hz, 1H, –C*H*O), 7.78 (d, $J = 3.93$ Hz, 1H, furyl-*H*), 7.21 (d, $J = 15.96$ Hz, 1H, vinyl-*H*), 7.43 (d, $J = 3.92$ Hz, 1H, furyl-*H*), 6.78 (dd, $J = 23.58$, 7.63 Hz, 1H, vinyl-*H*); ESI-MS: 168 $(M+H)^+$.

(b) *(S)-N-[3-{3-Fluoro-4-[4-(3-(5-nitrofuran-2-yl)-allyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide hydrochloride* (**8**): to a stirred solution of *N*-[3-(3-fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-yl-methyl] acetamide **11** (0.5 g, 1.49 mmol) in dry tetrahydrofuran (50 mL) molecular sieves (10 g, 4) were added followed by [3-(5-nitrofuran-2-yl)-2-propenal] **12** (R = 5-nitro-2-furyl) (0.25 g, 1.49 mmol) and the reaction mixture was stirred at 26–27 °C for 3 h. To this sodium triacetoxy borohydride (1.25 g, 5.91 mmol) was added and stirred at 26–27 °C for 12 h. The progress of the reaction was monitored by TLC using the mobile phase chloroform: methanol (9:1). The precipitate formed was filtered on a Buchner funnel through a bed of hy-flow. The filtrate was washed with water (200 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and filtered. The solvents were evaporated on a rotatory evaporator to afford a gummy mass. The crude gummy mass was purified by column chromatography on silica gel (230–400 mesh) using eluent 0–4% methanol in chloroform. The required fractions were pooled and the solvents were evaporated on a rotatory evaporator under reduced pressure to give a white solid (0.25 g, 34%). The solid obtained was converted into hydrochloride salt. Thus, *N*-[3-{3-fluoro-4-[4-(3-(5-nitrofuran-2-yl)-allyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (0.1 g, 0.205 mmol) was taken in diethyl ether (10 mL) and added ethereal-HCl (0.5 mL) at 0–5 °C and stirred for 2 h. Filtration on a Buchner funnel afforded the title compound as a white solid. Yield: 84% ((0.09 g), 96.7% purity by HPLC; mp: 158–160 °C; IR (KBr): 3398, 2231, 1726, 1541 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46–7.40 (d, $J = 14.24$, 1H, furyl-*H*), 7.30 (d, $J = 15.70$ Hz, 1H, vinyl-*H*), 7.08–7.05 (dd, $J = 8.75$, 1.75 Hz, 1H, phenyl-*H*), 6.93 (t, $J = 9.06$ Hz, 1H, phenyl-*H*), 6.85–6.65 (m, 1H, phenyl-*H*), 6.48–6.42 (d, 2H, vinyl-*H* and furyl-*H*), 6.02 (bs, 1H, –N*H*CO–), 4.78 (m, 1H, oxazolidinone ring C_5-*H*), 4.01 (t, $J = 8.98$ Hz, 1H, –CH_2–), 3.76–3.73 (m, 1H, –CH_2–), 3.71–3.67 (m, 2H, –CH_2– of oxazolidinone ring), 3.25 (d, 2H, –CH_2–CH=CH–), 3.12 (bs, 4H, piperazine-*H*), 2.70 (bs, 4H, piperazine-*H*), 2.02 (m, 3H, –COCH_3); ESI-MS: 488 $(M+H)^+$.

The following compound has been synthesized as per method C.

*5.3.3.1. (S)-N-[3-{3-Fluoro-4-[4-(3-furan-2-yl-allyl)-piperazin-1-yl]-phenyl}-2-oxo-oxazolidin-5-yl-methyl] acetamide (**7**).* Yield: 50%; 96% purity by HPLC; mp: 125–128 °C; IR (KBr): 3292, 1735, 1643, 1517, 1409 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.43 (dd, $J = 16.76$, 2.46 Hz, 1H, phenyl-*H*), 7.34 (m, 1H, vinyl-*H*), 7.04 (d, $J = 2.05$ Hz, 1H, phenyl-*H*), 6.93 (t, $J = 9.06$ Hz, 1H, phenyl-*H*), 6.37 (m, 2H, furyl-*H*), 6.46 (m, 2H, furyl-*H* and vinyl-*H*), 6.10 (bs, 1H, –N*H*CO–), 4.81 (m, 1H, oxazolidinone ring C_5-*H*), 4.01 (t, $J = 8.98$ Hz, 1H, –CH_2–), 3.76–3.73 (m, 1H, –CH_2–), 3.70–3.66 (m, 2H, –CH_2– of oxazolidinone ring), 3.20 (d, 2H, –CH_2–CH=CH–), 3.12–3.09 (bs, 4H, piperazine-*H*), 2.70 (bs, 4H, piperazine-*H*), 2.01 (s, 3H, –COCH_3); ESI-MS: 443 $(M+H)^+$.

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