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ORIGINAL PAPER

Design, synthesis of novel oxazolidino-amides/sulfonamides conjugates and their impact on antibacterial activity

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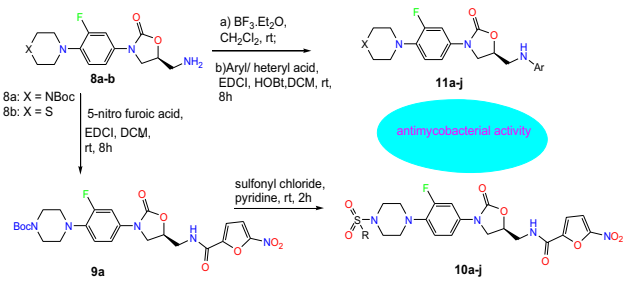
Abstract In view of generating new compounds for future drug development, we have synthesized oxazolidinones library of aryl amides and aryl sulfonamide derivatives. These compounds were screened in vitro against panel of susceptible and resistant Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*), Gram-negative bacteria (*Pseudomonas aeruginosa*), fungi (*Candida albicans*) strains, and Mycobacterium tuberculosis (Mtb). Among them, **10d** and **11a** compounds have been evaluated against 12 fungal strains and have displayed significant antimycotic activities approximately 37 folds more potent than fluconazole.

Graphical Abstract



Keywords Oxazolidinones · Antitubercular activity · Antimycobacterial activity · EDC · Anti-fungal activity

Introduction

The oxazolidinones represent a new class of antimicrobials with a unique mechanism of action. They are having admirable activity against susceptible and resistant Gram-positive organisms such as MRSA (methicillin-resistant *Staphylococcus aureus)*, VRE (vancomycin-resistant *Enterococci*) and PRSP (penicillin-resistant *Streptococcus pneumoniae*), and a good adverse effect profile; they can be administered both intravenously and orally. In addition, oxazolidinone class antibacterials have good activity against multidrug-resistant *Mycobacterium tuberculosis* infections, which are one of the most threatening, widespreading infectious diseases, causative medium for this infection and have resistance to antibiotics (Martone et al. 1998). Patients suffering from these infections do not respond to general antibiotic treatments. Most of these infections are caused by Gram-positive pathogens; among them most problematic are MRSA, VRE, and PRSP.

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Furthermore, certain Gram-negative strains like *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* also develop drug resistance towards leading antibiotics (Fridkin et al. 2001; Leclercq et al. 1988; Whitney et al. 2000).

Oxazolidinones are the first new class of antibiotics to be developed in the past 20 years. In 1978, EI DuPont de Nemours & Company initially discovered that certain oxazolidinones had activity against plant pathogens, but limited activity against human pathogens. Further development of this class in the late 1980s occurred with the description of DuP-721 and DuP-105, which had activity against human pathogens (Brickner 2007; Ford et al. 2001; Hutchinson 2003; Zurenko et al. 1997). The discovery of lethal bone marrow toxicity in drug safety studies performed in rats led to the extinction of development. Observing for this new class of synthetic antibacterial agents, Pharmacia and Upjohn began development and patented many chemical oxazolidinone congeners (Barbachyn et al. 1997; Brickner 1996). Oxazolidinones reveal a novel mechanism of action by inhibiting the initiation of protein synthesis at a site different from other protein synthesis inhibitors. Presently, there are only two oxazolidinones: linezolid (Moise et al. 2002; Peppard and Weigelt 2006), and eperezolid. Linezolid was an approved drug in the United States and is now accessible in Canada. The chemical structures of these two agents differ with their side chains on the benzene ring and the addition of a fluorine atom. Oxazolidinones have activity against many antibiotic-resistant organisms (mostly Gram-positives), even those cross-resistant to other protein synthesis inhibitors (Apodaca and Rakita 2003; Bergeron et al. 2005; Bressler et al. 2004; Gillman 2003; Kalamazoo 2003; Kuter and Tilloston 2001; Wigen and Goetz 2002; Zivkovic and Lacomis 2005). Exploitation of the chemical structure continues to broaden the spectrum of activity and to diminish or eliminate adverse effects.

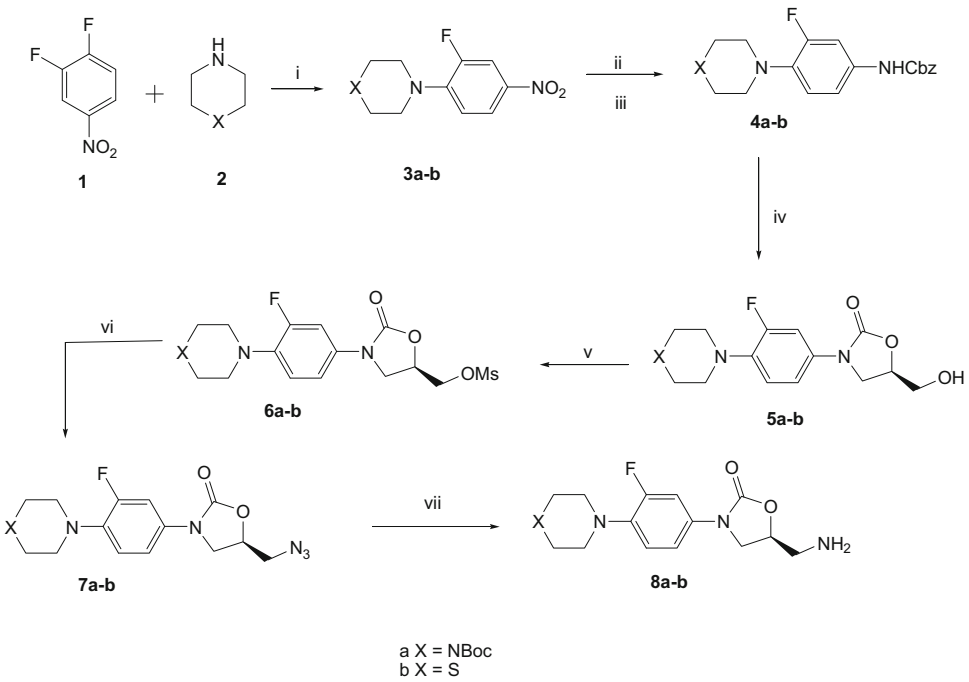
We synthesized and evaluated a focused library of oxazolidinone analogs, a currently narrow spectrum class of antibacterials active only against Gram-positive bacteria. In this series, we have explored the effectiveness for improving Gram-positive activity by identifying and combining beneficial structural modifications in the C-ring region (Boyer et al. 2007) and C-5 substituted (Roehrig et al. 2005; Das et al. 2009; Chen et al. 2015) When combined in hybrid C-ring modified and C-5 arm modified oxazolidino-arylamido/sulfonamides (Aoki et al. 2002; Bobkova et al. 2003; Lin et al. 1997; Matassaova et al. 1999; Park et al. 1992; Patel et al. 2001; Shinabarger et al. 1997; Zhou et al. 2002; Cooper et al. 2017; Cano et al. 2006) analogs, seems to largely overcome the efflux and/or penetrable barriers, resulting in improved anti-bacterial activity. In the present work, the focus has been on improving the activity and limiting the cytotoxicity of oxazolidinone based derivatives. Herein, we describe the synthesis and evaluation of bacterial and anti-tubercular activity of oxazolidino-aryl amides and sulfonamide conjugates particularly for drug resistance bacteria (Barbachyn and Ford 2003; Barbachyn et al. 1999; Johnson et al. 2002; Joseph et al. 2008; Quesnella et al. 2005; Sakoulas et al. 2003; Tsiodras et al. 2001).

Results and discussion

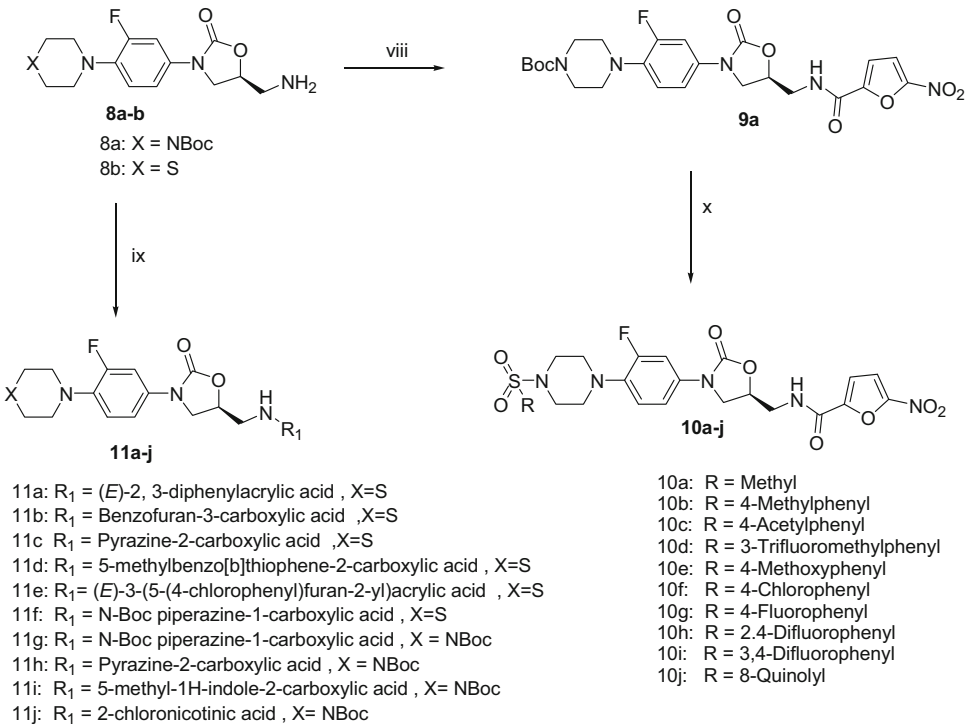
Chemistry

The preparation of intermediates oxazolidinyl methyl amines (Steven et al. 1996) (**8a** and **8b**) had been carried out by the sequence illustrated in Scheme 1. The treatment of commercially available *tert*-butyl piperazine-1-carboxylate (**2**) with **3**, 4-difluoronitrobenzene (1) in acetonitrile in the presence of diisopropyl ethyl amine under reflux at 80 °C affords the compounds **3a-b**. The nitro compounds in the presence of 5% Pd/C and H_2 are reduced to their corresponding amines and protected with benzyl chloroformate to afford compounds **4a-b**. The benzyloxy *N*-protected compounds (**4a-b**) have been treated with (*R*)-glycidyl butyrate in presence of *n*-butyl lithium at −78 °C to gives compounds oxazolidinyl methanol (**5a-b**). The intermediates **5a-b** treated with methyl sulfonyl chloride in the presence of triethylamine in dichloromethane as solvent afford compounds **6a-b**. The mesylated intermediate further undergo in S_N^2 nucleophilic substitution by azide in presence of sodium azide under reflux in dimethyl formamide to afford oxazolidinone azide **7a-b**. Further, on reduction in the presence of hydrogen and palladium carbon in ethyl acetate, azide (**7a-b**) converted into corresponding amines **8a-b**.

The synthesis of target compounds **10a-j** and **11a-j** were achieved by the procedure described in Scheme 2. The amine intermediates (**8a-b**) on coupling reaction with different acids and sulfonyl chlorides to afford final conjugates. The oxazolidinone amines (**8a-b**) treated with 5-nitro furoic acid in the presence of EDC in dry CH_2Cl_2, afforded the amide-coupled compound **9a**. Further, the deprotection of intermediate (**9a**) by $BF_3{\cdot}Et_2O$ in CH_2Cl_2 followed by treatment with the different sulfonyl chloride in dry pyridine at room temperature afforded C-5 modified oxazolo sulfonamide analogs (**10a-j**). The intermediate **8a** reacted with different carboxylic acids and EDC in DCM solvent at room temperature over 8 h time period then afforded corresponding final conjugates **11a-j** in good yields.



Scheme 1 Reagents and conditions: (i) ACN, DIEA, reflux, 3 h; (ii) Pd/C 10%, H_2, methanol, 12 h; (iii) benzyl chloroformate, acetone, aq. $NaHCO_3$, 12 h; (iv) (*R*)-(-)-glycidylbutyrate, THF, *n*-BuLi, −78 °C to rt, 12 h; (v) MsCl, CH_2Cl_2, TEA, 5 h; (vi) NaN_3, DMF, reflux, 5 h; (vii) H_2, Pd/C, methanol, 2 h



Scheme 2 Reagents and conditions: (viii) 5-nitro furoic acid, EDC, CH_2Cl_2, rt, 8 h; (ix) carboxylic acid, EDC, CH_2Cl_2, rt, 8 h; (x) (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt; (b) sulfonyl chloride, pyridines, rt, 2 h

Biological activity

Antimicrobial activity

The compounds **10a-j** and **11a-j** have been screened for their antibacterial activity against Gram-positive strains *S. aureus* (MTCC96), *Bacillus subtilis* (MTCC121), *S. aureus* (MLS-16)(MTCC2940), Gram-negative strain *P. aeruginosa* bacteria (MTCC 2453) and the antifungal activity was evaluated against yeast *Candida albicans* (MTCC 3017). The inhibitory zones (in mm) are determined by agar well method (Amsterdam and Loman 1996; Wallace et al.

1986), Neomycin and fluconazole are used as positive controls against bacteria and fungi, respectively.

The results summarized in Table 1 show that all compounds exhibited moderate to good antibacterial activity. All compounds have shown significant inhibition against all the bacteria tested and were not strain dependent. In the C-ring modified series, the compound and **10a**, **10d**, **10g**, **10h** and **10i** are the most active due to containing fluorine atom; the sensible introduction of fluorine into a molecule can productively influence conformation, pK_a, intrinsic potency, membrane permeability, metabolic pathways, pharmacokinetic properties and shows good activity compared to remaining compounds. The compounds **11b**, **11d** and **11e** showed good anti-bacterial activity due to the presence of benzfuran, benzothiophene and furan structural moieties in the parent structures. The antibacterial screening of the synthesized compounds was determined by the well diffusion method according to Lindsay. Three to five identical colonies from each agar plate were lifted with a sterile wire loop and transferred into a tube containing 5 mL of Nutrient Agar. Nutrient Agar plates were inoculated by streaking the swab over the entire sterile agar surface. This procedure was repeated by streaking two more times, rotating the plate approximately 60 °C each time to ensure even distribution of the inoculums. As a final step, the rim of the agar was also swabbed. After allowing the inoculums to dry at room temperature, 6 mm diameter wells were prepared in the agar with the help of sterilized cork bore. The different concentrations of test compounds (50, 100 μg/ml) were prepared by dissolving in dimethyl sulfoxide (DMSO) and introduced into duplicate wells. The plates were incubated at 37 °C for 24 h. Subsequently, the plates were examined for bacterial growth inhibition and the inhibition zone diameters (IZD) measured to the nearest millimeter.

Based on the above antibacterial study, we performed antifungal screening of two compounds **10d** and **11a** carried out fewer than twelve strains of *C. albicans*. The investigation of antifungal screening data is summarized in Table 2, which reveals that both the compounds showed good fungal inhibition. The oxazolidinone derivatives (**10d** and **11a**) exhibited very good inhibitory activity against fungal strain *C. albicans* (1.17–2.34 μg/mL). The method followed for antifungal assay, where the medium is potato

Table 1 Antibacterial and antifungal activity of oxazolidinones (**10a-j** and **11a-j**)

Compounds	Minimum inhibitory concentration (μg/mL)				
	Staphylococcus aureus (MTCC 96)	*Bacillus subtilis* (MTCC 121)	*Staphylococcus aureus* (MLS-16) (MTCC 2940)	*Pseudomonas aeruginosa* (MTCC 2453)	*Candida albicans* (MTCC 3017)
10a	18.75	1.1	4.68	1.1	1.1
10b	37.5	2.34	18.75	4.68	4.68
10c	37.5	37.5	4.6	4.6	4.6
10d	150	18.75	75	75	37.5
10e	4.68	37.5	–	–	–
10f	4.68	9.37	9.37	4.68	9.37
10g	75	75	37.5	75	37.5
10h	37.5	37.5	18.75	18.75	9.37
10i	37.5	37.5	18.75	18.75	18.75
10j	–	2.34	9.37	4.68	9.37
11a	18.75	9.37	75	3.37	18.75
11b	37.5	37.5	18.75	18.75	4.6
11c	18.75	2.34	4.68	4.68	4.68
11d	37.5	2.34	18.75	4.68	4.68
11e	37.5	2.34	4.68	4.68	4.68
11f	37.5	37.5	18.75	18.75	4.6
11g	–	9.37	75	75	37.5
11h	37.5	37.5	18.75	18.75	4.6
11i	37.5	37.5	4.6	4.6	18.75
11j	–	–	–	–	–
Neomycin	18.75	18.75	18.75	9.45	–
Fluconazole	–	–	–	–	75

Standard drug for bacteria: Neomycin and Standard drug for fungi: Fluconazole (zone of inhibition internal diameter: 6 mm)

Table 2 Antimycotic activity of oxazolidinone derivatives (**10d** and **11a**) against twelve different strains of *Candida albicans*

Test organism	Minimum inhibitory concentration (μg/mL)		
	10d	**11a**	Fluconazole
Candida albicans MTCC 183 (ATCC 2091)	1.17	2.34	37.5
Candida albicans MTCC 227 (ATCC 10231)	2.34	2.34	37.5
Candida albicans MTCC 854	2.34	2.34	37.5
Candida albicans MTCC 1637 (ATCC 18804)	1.17	2.34	75
Candida parapsilosis MTCC 1744	2.34	2.34	18.75
C. albicans MTCC 3018 (ATCC 24433)	2.34	2.34	37.5
Candida albicans MTCC 3958	1.17	2.34	37.5
C. albicans MTCC 3017 (ATCC 90028)	2.34	2.34	75
Candida glabrata MTCC 3019 (ATCC 90030)	2.34	2.34	75
Issatchenkia orientalis MTCC 3020 (ATCC 749)	2.34	2.34	150
Issatchenkia hanoiensis MTCC 4755	2.34	2.34	150
Candida aaseri MTCC 1962 (ATCC 18805)	2.34	2.34	75

dextrose agar (39 g/L). All test compounds were studied for their antifungal activity at concentration 50–100 μg/mL using DMSO as a solvent. The solvent did not exhibit any activity at the concentrations used. The treated and the controls were kept in an incubator at 28 ± 2 °C for 48 h and inhibition zones were measured to the nearest millimeter value. Three replicates were maintained for each treatment for each treatment. Fluconazole (50 μg/mL) was used as positive control.

Antimycobacterial activity

All the synthesized compounds (**10a-j** and **11a-j**) have been evaluated for the antimycobacterial activity and the results are summarized in Table 3. All compounds were initially screened against *M. tuberculosis* H37Rv at the single concentration of 100 (μg/mL). Minimum inhibitory concentrations (MIC in μg/ml) of compounds against of mycobacterium were determined by reference agar dilution method (Ramos et al. 2008) as per the NCCLS-M24-T2 recommendations. The compounds and reference drug were dissolved in DMSO and diluted twofold to obtained ten serial dilutions of compound. Appropriate volumes of compounds were incorporated into duplicate plates of Middle brook 7H10 agar medium supplemented with 10% Middle brook supplement oleic acid-albumin-dextrose-catalase (OADC) enrichment at concentration of 0.03–16 μg/mL. Test organisms (mycobacterium strains) were grown in Middle brook 7H9 broth containing 0.05% Tween-80 and 10% ADC supplement. After 10 days of incubation at 37 °C, the broths were adjusted to the turbidity of 0.5 McFarland standards. The organisms were further diluted tenfold in sterile water containing 0.01% Tween-80. The resulting mycobacterial suspension were spotted (3–5 μl/spot) onto drug-supplemented 7H10 media plates. The MIC was recorded as the highest dilution/lowest concentration of drug that completely inhibited the growth of mycobacterial cultures. Rifampicin was used as reference drug; most of these compounds have shown activity between 1 and 16 μg/mL. Among these, C-5 substituted compounds showed promising in vitro antimyco

Table 3 Anti-mycobacterial activity of oxazolidinones against *M. tuberculosis* (H37Rv) expressed in MIC (μg/mL)

Compound	C log P	CMR	MIC (μg/ml)
9a	3.22	13.06	1
10a	1.25	11.89	2
10b	2.92	13.94	8
10c	3.07	13.95	8
10d	3.14	13.97	8
10e	3.21	13.97	8
10f	3.64	14.43	8
10g	4.05	14.92	16
10h	3.09	14.56	16
10i	2.80	15.17	> 16
10j	2.50	14.90	16
11a	3.42	14.40	8
11b	2.92	15.42	> 16
11c	4.10	15.63	> 16
11d	2.40	15.27	> 16
11e	2.67	14.55	8
11f	4.75	15.79	> 16
11g	3.17	15.01	> 16
11h	3.81	14.45	8
11i	4.95	14.82	16
11j	3.08	13.52	> 16
Linezolid	–	–	1

C log P (hydrophobicity); and CMR (molar refractivity) calculated using the ChemDraw Ultra, version 10.0

bacterial activity than the standard drug linezolid. C log P (Hydrophobicity); and CMR (molar refractivity) was calculated using the ChemDraw Ultra, version 10.0.

Conclusion

In conclusion, we synthesized some oxazolidinones to investigate the effect of the C-ring and C-5 substituents for antibacterial activity. It was proved that the antibacterial activity was greatly affected by an alternation of the C-ring and C-5 substituents has been designed, synthesized and evaluated against *M. tuberculosis* H37Rv, bacterial strains and fungal strains. The compounds **10a**, **10d**, **10g**, **10h**, **10i** and **11b**, **11d**, **11e** and **11f** have shown remarkable antimycobacterial activity better than equal to linezolid. Further, the compounds **10d** and **11a** were found to be more potent against twelve fungal strains than the standard drug "fluconazole". Therefore, it is worth further evaluation for new generation oxazolidinone candidate that will be available for the clinical treatment of serious infections caused by multi-drug Gram-positive bacteria.

Experimental

General: All commercially available chemicals were used without further purification. The ^{1}H NMR spectra were recorded on Bruckner Avance 300 magnetic resonance spectrometer at 300 MHz in $CDCl_3$ and ^{13}C NMR 75 MHz in $CDCl_3$ with TMS as internal standard (chemical shifts and ppm). Coupling constant (*j*) is reported in hertz (Hz). ESI–MS were obtained on Thermo-Finningan MAT-1020B instrument. Elemental analysis was carried out with a Perkin Elmer 2400 Series IICHNS/O elemental analyzer(Elemental Analyzer, Model PE2400 CHNS/O (PerkinElmer, Shelton, CT, USA) with PC based data system, PE Data manager 2400 for Windows and a PerkinElmer AD-6 Ultra Micro Balance. This instrument can be run in three different modes; carbon, hydrogen and nitrogen (CHN) mode, CHNS mode or oxygen mode). All moisture sensitive reactions were conducted under a nitrogen atmosphere in oven-dried glassware.

General procedure for the synthesis of (*R*)-*tert*-butyl-4-(2-fluoro-4-(5-((5-nitrofuran-2-carboxamido) methyl)-2-oxooxazolidin-3-yl) phenyl) piperazine-1-carboxylate (9a)

To a stirred solution of **8a** (394 mg, 1 mmol) in CH_2Cl_2 (15 mL) was added l-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (EDC) (382 mg, 2 mmol) in ice bath followed by the addition of 5-nitro furoic acid (314 mg, 2 mmol). The resulting mixture was stirred at room temperature until completion of the reaction as indicated by TLC. The reaction mixture was neutralized by sodium bicarbonate solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue, thus, obtained was purified by column chromatography on silica gel using ethyl acetate/hexane (7:3) to afford pure compound (**9a**). Yield: 88%; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.99 (1H, t, $J = 6.04$ Hz), 7.39 (1H, dd, $J = 12.27, 2.45$ Hz), 7.33 (1H, d, $J = 3.77$ Hz), 7.26 (1H, d, $J = 3.77$ Hz), 7.06 (1H, dd, $J = 6.98, 1.88$ Hz), 6.89 (1H, t, $J = 9.25, 8.87$ Hz), 4.92 (1H, m), 4.14 (1H, t, $J = 9.06, 8.87$ Hz), 4.00–3.92 (1H, m), 3.84–3.74 (2H,m), 3.58 (4H, m), 2.97 (4H, m), 1.48 (9H, s); ESI–MS: $m/z = 534$ $(M + 1)^+$.

General procedure for the synthesis of (*S*)-*N*-((3-(3-Fluoro-4-(4-(methyl sulfonyl) piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl) -5-nitrofuran-2-carboxamide (10a)

The target compound **10a** was obtained by treating **9a** (533 mg, 1 mmol) with $BF_3{\cdot}EtO_2$ (2 mL, 1.5 mmol) in CH_2Cl_2 in first step, the crude deprotected compound was directly reacted with methyl sulfonyl chloride (1.2 ml, 1 mmol) in the presence of triethyl amine (3.3 mL, 3 mmol) in dry THF (50 ml). After stirring the reaction mixture for 6 h, the reaction mixture was poured on to crushed ice (1.4 g) and the reaction mixture extracted and purified by column chromatography affords final product **10a** as yellow solid. (Yield 400 mg, 78%); ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.51–7.43 (1H, dd, $J = 11.33$, 2.26 Hz), 7.36 (1H, d, $J = 3.7$ Hz), 7.28 (1H, d, $J = 3.7$ Hz), 7.08 (1H, dd, $J = 7.5$,1.5 Hz), 6.93 (1H, t, $J = 9.0$, 8.3 Hz), 4.89 (1H, m), 4.12 (1H, dd, $J = 9.05$, 4.5 Hz), 4.00-3.90 (1H, dd, $J = 11.3$, 7.55 Hz), 3.77 (1H, dd, I = 7.5 Hz), 3.41 (4H, t, $J = 5.2$, 4.5 Hz), 3.14 (4H, t, $J = 5.2$, 4.5 Hz), 2.83 (3H, *S*); ^{13}CNMR (75 MHz, $CDCl_3$): δ 28.90, 42.32, 44.33, 48.14, 50.98, 80.26, 114.23, 119.64, 133.47, 136.96, 143.13, 143.92, 144.70, 148.10, 154.21 (d, $J = 243.6$ Hz), 155.03, 157.50, 164.30;

ESI–MS: $m/z = 512$ $(M + 1)^+$. Elemental analysis Calcd for $C_{20}H_{22}FN_5O_8S$: C, 46.96; H, 4.34; N, 13.69; O, 25.02; S, 6.27; Found: C, 46.98; H, 4.38; N, 13.83; O, 25.12; S, 6.32.

(*S*)-*N*-((3-(3-Fluoro-4-(4-tosylpiperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10b)

The compound (**10b**) was obtained from **9a** (533 mg, 1 mmol) and 4-methylbenzene-l-sulfonyl chloride (380 mg, 2 mmol) according to the procedure as described for **10a**.

Yield: 80%; ^{1}HNMR (300 MHz, $CDCl_3$): δ 8.95 (1H, m), 7.67 (2H, d, $J = 7.5$ Hz), 7.51–7.30 (5H, m), 7.07 (1H, dd, $J = 8.30$ Hz), 6.91 (1H, dd, $J = 9.06$ Hz), 4.89 (1H, m), 4.07 (1H, dd, J = 9.06, 8.30 Hz), 3.7 (6H, m), 3.47 (1H, dd, J = 6.7 Hz), 3.13 (4H, m), 2.46 (3H, s); ^{13}CNMR (75 MHz, $CDCl_3$) δ 27.90, 41.32, 45.33, 48.14, 51.98, 80.26, 115.23, 120.64, 133.47, 136.96, 144.13, 145.92, 144.70, 148.10, 155.03, 155.21(d, $J = 242.6$ Hz), 156.50, 164.30; ESI–MS: $m/z = 588$ $(M + 1)^+$. Elemental analysis Calcd for $C_{26}H_{26}FN_5O_8S$: C, 53.15; H, 4.46; N, 11.92; O, 21.78; S, 5.46; Found: C, 53.18; H, 4.48; N, 11.94; O, 21.82; S, 5.49.

(*S*)-*N*-((3-(4-(4-(4-acetylphenylsulfonyI) piperazin-l-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10c)

The compound (**10c**) was obtained from **9a** (533 mg, 1 mmol) and 4-acetylbenzene-l-sulfonyl chloride (434 mg, 2 mmol) according to the procedure as described for **10a**.

Yield: 82%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (2H, d, $J = 7.99$ Hz), 7.89 (2H, d, $J = 7.99$ Hz), 7.39 (1H, d, $J = 13.99$ Hz), 7.34 (1H, d, $J = 7.99$ Hz), 7.22 (1H, d, $J = 7.9$ Hz), 7.05 (1H, d, $J = 7.99$ Hz), 6.88 (1H, t, $J = 8.99$ Hz), 4.17 (1H, m), 4.08 (1H, dd, $J = 7.99$, 8.99 Hz), 3.95 (2H, m), 3.77 (H, dd, $J = 8.99$, 6.99 Hz), 3.21 (4H, m), 3.12 (4H, m), 2.66(3H, s); ^{13}CNMR (75 MHz, $CDCl_3$): δ 26.02, 41.24, 45.18, 46.94, 49.02, 70.00, 106.11, 106.90, 111.69, 113.06, 115.14, 118.60, 127.14, 128.14, 132.92, 138.02, 139.32, 147.17, 150.54, 153.23, 155.92 (d, $J = 242.6$ Hz), 156.45, 195.61; ESI–MS: $m/z = 616$ $(M + 1)^+$. Elemental analysis Calcd for $C_{27}H_{26}FN_5O_9S$: C, 52.68; H, 4.26; N, 11.38; O, 23.39; S, 5.21; Found: C, 52.71; H, 4.32; N, 11.44; O, 23.42; S, 5.29.

(*S*)-*N*-((3-(3-fluoro-4-(4-(3-(trifluoro methyl)phenyl sulfonyl) piperazin-l-yl) phenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10d)

The compound (**10d**) was obtained from **9a** (533 mg, 1 mmol) and 3-(trifluoromethyl) benzene-l-sulfonyl chloride (366 mg, 1.5 mmol) according to the procedure as described for **10a**.

Yield: 75%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.99 (1H, m), 8.49 (1H, t, $J = 7.65$ Hz), 8.16 (1H, s), 8.08 (1H, d, $J = 5.74$), 7.99 (2H, m), 7.84 (1H, dd, $J = 7.65$ Hz), 7.69 (1H, d, $J = 7.65$ Hz), 7.54 (1H, t, $J = 7.65$ Hz), 7.3 (1H, d, $J = 2.87$ Hz), 7.1 (1H, d, $J = 8.6$ Hz), 4.86 (1H, m), 4.08 (1H, t, $J = 8.92$ Hz), 3.95 (1H, dd, $J = 8.9$, 4.9 Hz), 3.74 (1H, m), 3.21 (4H, m), 3.11 (4H, m); ^{13}CNMR (75 MHz, $CDCl_3$): δ 41.33, 44.10, 45.45, 45.62, 47.73, 111.48, 114.11, 118.03, 123.92, 125.45, 125.67, 128.33, 128.77 (q, $J = 272.4$ Hz), 129.71, 129.96, 130.86, 133.36, 134.91, 140.14, 144.47, 146.31, 152.08, 154.88 (d, $J = 243$ Hz), 156.45, 164.61; ESI–MS: $m/z = 642$ $(M + 1)^+$. Elemental analysis. Calcd for $C_{26}H_{23}F_4N_5O_8S$: C, 48.68; H, 3.61; N, 10.92; O, 19.95; S, 5.00; Found: C, 48.71; H, 3.62; N, 10.94; O, 19.95; S, 5.04.

(*S*)-*N*-((3-(3-Fluoro-4-(4-(4-methoxyphenylsulfonyl) piperazin-1-yl)] phenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10e)

The compound (**10e**) was obtained from **9a** (533 mg, 1 mmol) and 4-methoxybenzene-l-sulfonyl chloride (307 mg, 1.5 mmol) according to the procedure as described for **10a**.

Yield: 80%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (2H, d, $J = 9.00$ Hz), 7.41 (1H, d, $J = 12.0$. 2.02 Hz), 7.34 (1H, d, $J = 4.00$ Hz), 7.21 (2H, dd, $J = 6.00$ Hz), 7.12 (1H, t, $J = 6.0$ Hz), 7.02 (2H, d, $J = 9.0$ Hz), 6.89 (1H, t, $J = 9.00$ Hz), 4.83 (1H, m), 4.06 (1H, m), 3.94 (1H, m), 3.8 (3H, s), 3.7 (2H, m), 3.15 (4H, m), 3.10 (4H, m); ^{13}CNMR (75 MHz, $CDCl_3$): δ 42.67, 47.61, 46.37, 50.45, 70.72, 105.89, 112.12, 115.38, 115.57, 120.08, 127.50, 127.48, 133.32, 134.71, 138.64, 139.75, 147.60, 150.97, 153.10, 153.69 (d, $J = 242.6$ Hz), 157.88, 164.92; ESI–MS: $m/z = 604$ $(M + 1)^+$. Elemental analysis Calcd for $C_{26}H_{26}FN_5O_9S$: C, 51.74; H, 4.34; N, 11.60; O, 23.86; S, 5.31; Found: C, 51.76; H, 4.38; N, 11.70; O, 23.86; S, 5.34.

(*S*)-*N*-((3-(4-(4-(4-Chlorophenylsulfonyl) piperazin-l-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10f)

The compound (**10f**) was obtained from **9a** (533 mg, 1 mmol) and 4-chlorobenzene-1-sulfonyl chloride (313 mg, 1.5 mmol) according to the procedure as described for **10a**.

Yield: 84%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91 (1H, m), 7.79 (2H, d, $J = 8.70$ Hz), 7.49 (1H, dd, $J = 9.18$, 2.26 Hz), 7.36 (1H, d, $J = 4.37$ Hz), 7.13 (2H, d, $J = 5.17$ Hz), 7.02 (1H, t, $J = 5.17$ Hz), 6.96 (2H, d, $J = 8.70$ Hz), 4.81 (1H, m), 4.01 (1H, m), 3.89 (1H, m), 3.65 (2H, m), 3.17 (4H, m), 3.09 (4H, m); ^{13}CNMR (75 MHz, $CDCl_3$): δ 41.67, 45.61, 47.37, 49.45, 70.72, 106.89, 112.12, 113.38, 115.57, 119.08, 127.50, 128.48, 133.32, 134.71, 138.64, 139.75, 147.60, 150.97, 153.10, 153.69 (d, $J = 243.6$ Hz), 156.88, 165.21; ESI–MS: $m/z = 608$ $(M + 1)^+$. Elemental analysis Calcd for $C_{25}H_{23}ClFN_5O_8S$: C, 49.39; H, 3.81; Cl, 5.83; N, 11.52; O, 21.05; S, 5.27; Found: C, 49.41; H, 3.85; N, 11.60; O, 21.06; S, 5.29.

(*S*)-*N*-((3-(3-Fluoro-4-(4-(4-fluorophenylsulfonyl) piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10g)

The compound (**10g**) was obtained from **9a** (533 mg, 1 mmol) and 4-fluorobenzene-l-sulfonyl chloride (289 mg, 1.5 mmol) according to the procedure as described for **10a**.

Yield: 86%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.95 (1H, m), 8.12 (2H, d, $J = 8.00$ Hz), 7.90 (2H, d, $J = 8.00$ Hz), 7.42(1H, dd, $J = 11.99$, 2.00 Hz), 7.35 (1H, d, $J = 4.00$ Hz), 7.22 (1H, m), 7.07 (1H, d, $J = 8.00$ Hz), 6.89 (1H, t, $J = 9.0$ Hz), 4.91 (1H, m), 3.97–3.93 (2H, m), 378–3.74 (2H, m), 3.24–3.21 (4H, m), 3.13-3.11 (4H, m); ^{13}CNMR (75 MHz, $CDCl_3$): δ 41.70, 45.63, 47.47, 49.48, 70.75, 112.18, 115.63, 119.05, 125.37, 127.18, 128.77, 129.19, 132.70, 134.59, 145.30, 145.88, 147.56, 151.03 (d, $J = 243.4$ Hz), 153.76 (d, $J = 242.6$ Hz), 156.88, 162.34; ESI–MS: $m/z = 592$ $(M + 1)^+$. Elemental analysis Calcd for $C_{25}H_{23}F_2N_5O_8S$: C, 50.76; H, 3.92; N, 11.84; O, 21.64; S, 5.42; Found: C, 50.79; H, 3.95; N, 11.88; O, 21.66; S, 5.44.

(*S*)-*N*-((3-(4-(4-(2, 4-Difluorophenylsulfonyl) piperazin-l-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10h)

The compound (**10h**) was obtained from **9a** (533 mg, 1 mmol) and 2, 4-difluorobenzene-l-sulfonylchloride (316 mg, 1.5 mmol) according to the procedure as described for **10a**.

Yield: 86%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.93 (1H, m), 7.67 (1H, d, $J = 3.77$ Hz), 7.50–7.35 (4H, m), 7.31 (1H, d, $J = 3.02$ Hz), 6.91 (1H, t, $J = 8.30$, 2.2.6 H), 4.88 (1H, m), 4.12–4.02 (1H, m), 3.89–3.85 (1H, m), 3.79–3.73 (2H, m), 3.19–3.07 (4H, m), 2.98–2.94 (4H, m); ^{13}C NMR (75 MHz), $CDCl_3$): δ 42.78, 45.47, 47.00, 48.50, 67.71, 115.57, 111.93, 115.51, 118.48, 125.74, 128.78, 130.44, 130.10, 130.40, 131.33, 140.59, 145.05, 146.35, 146.68, 150.01, 152.53 (d, $J = 242.3$ Hz), 153.45 (d, $J = 243.1$ Hz), 155.45 (d, $J = 242.6$ Hz), 156.12, 162.92, 165.31; ESI–MS: $m/z = 610$ $(M + 1)^+$. Elemental analysis Calcd for $C_{25}H_{22}F_3N_5O_8S$: C, 49.26; H, 3.64; N, 11.49; O, 21.00; S, 5.26; Found: C, 49.29; H, 3.65; N, 11.49; O, 21.06; S, 5.27.

(*S*)-*N*-((3-(4-(4-(3, 4-Difluorophenylsulfonyl) piperazin-l-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10i)

The compound (**10i**) was obtained from **9a** (533 mg, 1 mmol) and 2, 4-difluorobenzene-l-sulfonylchloride (316 mg, 1.5 mmol) according to the procedure as described for **10a**.

Yield: 88%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.01 (1H, m), 8.09 (1H, d, $J = 7.65$ Hz), 8.04–7.97 (2H, m), 7.84–7.82 (1H, m), 7.68 (1H, d, $J = 8.68$ Hz), 7.53 (1H, d, $J = 7.65$, 6.7 Hz),7.34–7.29 (1H, m), 7.10 (1H, t, $J = 8.61$ Hz), 4.94–4.90 (1H, m), 4.11 (1H, t, $J = 4.7$ Hz), 3.95 (1H, m), 3.84 (2H, m), 3.67–3.62 (4H, m), 3.49-3.45 (4H, m); ^{13}C NMR (75 MHz), $CDCl_3$): δ 41.78, 44.47, 46.00, 48.18, 69.71, 111.57, 111.93, 114.51, 118.48, 127.74, 128.78, 129.44, 130.10, 130.40, 131.33, 140.59, 145.05, 146.35, 146.68, 150.01, 152.53 (d, $J = 242.6$ Hz), 153.78 (d, $J = 242.4$ Hz), 155.45 (d, $J = 243.2$ Hz), 158.12, 164.29; ESI–MS: $m/z = 610$ $(M + 1)^+$. Elemental analysis Calcd for $C_{25}H_{22}F_3N_5O_8S$: C, 49.26; H, 3.64; N, 11.49; O, 21.00; S, 5.26; Found: C, 49.29; H, 3.65; N, 11.49; O, 21.06; S, 5.29.

(*S*)-*N*-((3-(3-Fluoro-4-(4-(quinolin-8-ylsulfonyl) piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10j)

The compound (**10j**) was obtained from **9a** (533 mg, 1 mmol) and quinoline-8-sulfonyl chloride (339 mg, 1.5 mmol) according to the procedure as described for **10a**.

Yield: 89%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.09 (1H, d, $J = 2.26$ Hz), 8.86 (1H, m), 8.50 (1H, dd, $J = 7.51$, 1.52 Hz), 8.25 (1H, dd, $J = 6.79$, 1.5 Hz), 8.06 (1H, dd, $J = 6.79$, 1.5 Hz), 7.67–7.62 (1H, dd, $J = 8.30$, 7.5 Hz), 7.54 (1H, m), 7.44–7.34 (3H, m), 7.09–7.04 (1H, m), 6.91 (1H, t, $J = 8.30$ Hz), 4.87 (1H, m), 4.14–4.07 (2H, m), 3.80–3.74 (2H, m), 3.63–3.59 (4H, m), 3.12–3.08 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.78, 44.47, 46.00, 48.18, 69.71, 111.57, 111.93, 114.51, 118.48, 127.74, 128.78, 129.44, 130.10, 130.40, 131.33, 140.59, 145.05, 146.35, 146.68, 150.01, 152.53, 153.91 (d, $J = 242.3$ Hz), 155.45, 158.12; ESI–MS: $m/z = 625$ $(M + 1)^+$. Elemental analysis Calcd for $C_{28}H_{25}FN_6O_8S$: C, 53.84; H, 4.03; N, 13.46; O, 20.49; S, 5.13; Found: C, 53.89; H, 4.05; N, 13.49; O, 20.49; S, 5.19.

General procedure for the synthesis of (*S*)-*N*-((3-(3-Fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl)-2, 3-diphenylacrylamide (11a)

Compound **11a** prepared by amide bond formation between (*R*)-5-(amino methyl)-3-(3-fluoro-4-thiomorpholinophenyl) oxazolidin-2-one (**8b**, 155 mg, 0.50 mmol) and (*E*)-2, 3-diphenylacrylic acid (156 mg, 0.7 mmol) in dry CH_2Cl_2. The coupling reagents EDC (1.2 mmol) and HOBt (1.2 mmol) were added, and the reaction mixture was stirred at room temperature for 10 h. After completion of reaction as indicated by TLC, the reaction mixture was quenched with $NaHCO_3$ and extracted in EtOAc (4 × 25 ml) from the ice-cold aqueous layer and dried

over anhydrous $MgSO_4$. The resulting product 10a was purified by column chromatography to afford 232 mg, a yellow solid. Yield: 90%; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.87 (1H, s), 7.47–7.43 (3H, m), 7.27–7.13 (6H, m), 7.00 (2H, d), 6.63–6.55 (2H, m), 5.98 (1H, t, $J = 6.04$ Hz), 4.80 (1H, m), 3.98 (1H, t, $J = 8.87$ Hz), 3.79–3.69 (3H, m), 3.59 (4H, m), 2.69 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.55, 28.11, 42.72, 50.78, 72.36, 103.12, 103.43, 111.35, 127.85, 132.70 135.58, 137.89, 139.32, 139.93, 142.90, 143.80, 150.68,154.17, 156.01 (d, $J = 243.6$ Hz), 159.62, 174.97; ESI–MS: $m/z = 518$ $(M + 1)^+$. Elemental analysis Calcd for $C_{29}H_{28}FN_3O_3S$: C, 67.29; H, 5.45; N, 8.12; O, 9.27; S, 6.19; Found: C, 67.59; H, 5.55; N, 8.19; O, 9.29; S, 6.20.

(*S*)-*N*-((3-(3-Fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl) benzofuran-3-carboxamide (11b)

The compound **11b** was prepared by the method as described for the preparation of the compound **11a**, employing (*R*)-5-(amino methyl)-3-(3-fluoro-4-thiomorpholinophenyl) oxazolidin-2-one (**8b**, 155 mg, 0.50 mmol) and benzofuran-3-carboxylic acid (113 mg, 0.7 mmol) to afford pure compound **11b** as a yellow solid in 193 mg, 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (1H, d, $J = 7.78$ Hz), 7.53 (1H, d, $J = 8.39$ Hz), 7.5 0 (1H, s), 7.44 (1H, t, $J = 7.17$, 1.22 Hz), 7.31 (1H, t, $J = 7.17$, 0.76 Hz), 7.25–7.21 (2H, m), 6.58–6.53 (2H, m), 4.91 (1H, m), 4.07 (1H, t, $J = 9.00$, 8.85 Hz), 4.01–3.96 (1H, m), 3.84–3.77 (2H, m), 3.56 (4H, m), 2.67 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.37, 41.49, 49.20, 50.62, 72.23, 102.98, 103.28, 110.42, 111.43, 122.17, 123.21, 126.63, 127.83, 147.38, 150.59, 154.28, 155.63 (d, $J = 243.4$ Hz), 158.80, 159.44; ESI–MS: $m/z = 456$ $(M + 1)^+$. Elemental analysis Calcd for $C_{23}H_{22}FN_3O_4S$: C, 60.65; H, 4.87; N, 9.23; O, 14.05; S, 7.04; Found: C, 60.69; H, 4.88; N, 9.29; O, 14.09; S, 7.08.

(*S*)-*N*-((3-(3-Fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl) pyrazine-2-carboxamide (11c)

The compound **11c** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-5-(amino methyl)-3-(3-fluoro-4-thiomorpholinophenyl) oxazolidin-2-one (**8b**, 155 mg, 0.50 mmol) and pyrazine-2-carboxylic acid (87 mg, 0.7 mmol) to afford the pure compound **11c** as a yellow solid in 173 mg, 82%yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (1H, s), 8.79 (1H, d, $J = 2.44$ Hz), 8.57 (1H, dd, $J = 1.52$, 0.91 Hz), 8.29 (1H, t, $J = 6.25$ Hz), 7.21 (1H, t, $J = 9.00$, 8.85 HZ), 6.60–6.53 (2H, m), 4.90 (1H, m), 4.06 (1H, t, $J = 9.00$, 8.85 Hz), 3.99–3.94 (1H, m), 8.87–8.82 (1H, m), 3.80–3.77 (1H, dd, $J = 9.00$, 6.25 Hz), 3.58 (4H, m), 2.68 (4H,m); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.98, 42.20, 49.58, 51.18, 72.55, 103.60, 111.76, 115.05, 128.47, 142.72, 144.31, 147.64, 151.14, 155.98 (d, $J = 242.8$ Hz), 157.31, 159.28, 163.81; ESI–MS: $m/z = 418$ $(M + 1)^+$. Elemental analysis Calcd for $C_{19}H_{20}FN_5O_3SC$, 54.67; H, 4.83; N, 16.78; O, 11.50; S, 7.68; Found: C, 54.69; H, 4.84; N, 16.79; O, 11.52; S, 7.69.

(*S*)-3-Chloro-*N*-((3-(3-fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl)-6-methylbenzo[*b*]thiophene-2-carboxamide (11d)

The compound **11d** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-5-(amino methyl)-3-(3-fluoro-4-thiomorpholinophenyl) oxazolidin-2-one (**8b**, 155 mg, 0.50 mmol) and 5-methyl-benzo[*b*]thiophene-2-carboxylic acid (134 mg, 0.7 mmol) to afford the pure compound **11d** as a yellow solid in 194 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, d, $J = 8.39$ Hz), 7.62 (1H, s), 7.57 (1H, t, $J = 5.95$ Hz), 7.31 (1H, d, $J = 7.62$ Hz), 7.23 (1H, t, $J = 9.00$, 8.85 Hz), 6.59–6.53 (2H, m), 4.93 (1H, m), 4.06 (1H, t, $J = 9.00$, 8.85 Hz), 3.99–3.88 (2H, m), 3.79 (1H, dd, $J = 9.00$, 6.45 Hz), 3.56 (4H, m), 2.67 (4H, m), 2.50 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.80, 32.86, 41.92, 49.63, 51.05, 72.66, 103.71, 103.40, 110.84, 111.62, 114.80, 122.82, 123.64, 127.06, 128.26, 147.81, 150.89, 154.70, 156.06 (d, $J = 243.6$ Hz), 156.58, 159.42, 159.87, 162.35; ESI–MS: $m/z = 520$ $(M + 1)^+$. Elemental analysis Calcd for $C_{24}H_{25}ClFN_3O_3S_2$: C, 55.22; H, 4.83; N, 8.05; O, 9.19; S, 12.28; Found: C, 55.24; H, 4.84; N, 8.09; O, 9.19; S, 12.29.

(*S*)-3-(5-(4-Chlorophenyl) furan-2-yl)-*N*-((3-(3-fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl) acrylamide (11e)

The compound **11e** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-5-(amino methyl)-3-(3-fluoro-4-thiomorpholinophenyl) oxazolidin-2-one (**8b**, 155 mg, 0.50 mmol) and (*E*)-3-(5-(4-chlorophenyl)furan-2-yl)acrylic acid (173 mg, 0.7 mmol) to afford the pure compound **11e** as a yellow solid in 243 mg, 90% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (2H, d, $J = 9.06$ Hz), 7.45–7.34 (3H, m), 7.25 (1H, d, $J = 8.30$ Hz), 6.69 (1H, d, $J = 3.02$ Hz), 6.66–6.51 (4H, m), 4.88 (1H, m), 4.02 (1H, t, $J = 8.30$ Hz), 3.84–3.75 (3H, m), 3.54 (4H, m), 2.65 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.62, 41.78, 49.31, 50.79, 72.82, 103.23, 107.63, 111.36, 114.74, 116.03, 117.52, 125.01, 127.58, 128.01, 128.64, 133.50, 150.52, 150.65, 153.90, 156.15 (d,

$J = 242.6$ Hz), 157.00, 158.98, 166.53; ESIMS: $m/z = 542$ $(M + 1)^+$. Elemental analysis Calcd for $C_{27}H_{25}ClFN_3O_4S$: C, 59.83; H, 4.65; N, 7.75; O, 11.81; S, 5.92; Found: C, 59.83; H, 4.66; N, 7.75; O, 11.89; S, 5.93.

(*S*)-*tert*-Butyl4-((3-(3-fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl)methylcarbamoyl) piperazine-1-carboxylate (11f)

The compound **11f** was prepared by the method as described for the preparation of compound **10a**, employing (*R*)-5-(aminomethyl)-3-(3-fluoro-4-thiomorpholinophenyl)oxazolidin-2-one (**8b**, 155 mg, 0.50 mmol) and 4-(*tert*-butoxycarbonyl)piperazine-l-carboxylic acid (161 mg, 0.7 mmol) to afford the pure compound **11f** as a yellow solid in 248 mg, Yield: 95%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, dd, $J = 9.78$, 2.44 Hz), 7.08 (1H, $J = 6.77$, 1.73 Hz), 6.94 (1H, t, $J = 9.00$ Hz), 6.43 (1H, t, $J = 6.27$, 6.04 Hz), 4.79 (1H, m), 4.16–3.98 (3H, m), 3.77 (1H, dd, $J = 6.39$, 2.44 Hz), 3.69 (4H, m), 3.62 (4H,m), 3.01 (4H,m), 2.74 (4H, m), 1.49 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.43, 42.50, 49.10, 72.18, 76.14, 103.41, 111.29, 127.65, 129.33, 134.88, 137.40, 155.50 (d, $J = 243.6$ Hz), 156.17, 159.46, 167.45, 173.41; ESI–MS: $m/z = 524$ $(M + 1)^+$. Elemental analysis Calcd for $C_{23}H_{32}FN_5O_5S$: C, 54.21; H, 6.33; N, 13.74; O, 15.70; S, 6.29; Found: C, 54.23; H, 6.36; N, 13.75; O, 15.74; S, 6.29.

(*S*)-*tert*-butyl4-((3-(4-(4-(tert-butoxycarbonyl) piperazin-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methylcarbamoyl) piperazine-l-carboxylate (11g)

The compound **11g** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-tert-butyl 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-l-carboxylate (**8a**, 197 mg, 0.50 mmol) and 4-(*tert*-butoxycarbonyl) piperazine-l-carboxylic acid (161 mg, 0.7 mmol) to afford the pure compound **11g** as a yellow solid in 260 mg, Yield: 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, dd, $J = 11.7$, 2.45 Hz), 7.04 (1H, $J = 6.98$,1.7 Hz), 6.91 (1H, t, $J = 9.06$ Hz), 6.41 (1H, t, $J = 6.23$, 6.04 Hz), 4.77 (1H, m), 4.16–3.98 (3H, m), 3.76 (1H, dd, $J = 6.41$, 2.4 Hz), 3.69 (4H, m), 3.59 (4H, m), 2.99 (4H, m), 2.72 (4H, m), 1.48 (9H, s), 1.44 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.42, 29.47, 41.98, 47.79, 50.46, 71.50, 79.97, 113.83, 119.29, 142.28, 143.59, 144.35, 147.75, 154.03, 154.91 (d, $J = 243.6$ Hz), 157.15, 163.95; ESI–MS: $m/z = 593$ $(M + 1)^+$. Elemental analysis Calcd for $C_{28}H_{41}FN_6O_7$: C, 56.74; H, 6.97; N, 14.18; O, 18.90; Found: C, 56.75; H, 6.98; N, 14.19; O, 18.94.

(*S*)-*tert*-butyl 4-(2-fluoro-4-(2-oxo-5-((pyrazine-2-carboxamido) methyl) oxazolidin-3-yl) phenyl) piperazine-l-carboxylate (11h)

The compound **11h** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-tert-butyl 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl)-2-fluorophervyl) piperazine-l-carboxylate (**8a**, 197 mg, 0.50 mmol) and pyrazine-2-carboxylic acid (86 mg, 0.7 mmol) to afford the pure compound **11h** as a yellow solid in 232 mg, Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (1H, s), 8.78 (1H, d, $J = 2.44$ Hz), 8.55 (1H, dd, $J = 2.44$, 1.52 Hz), 8.27 (1H, t, $J = 6.40$ Hz), 7.42 (1H, dd, $J = 11.59$, 2.59 Hz), 7.06 (1H, dd, $J = 7.01$, 2.59 Hz), 6.90 (1H, t, $J = 9.00$ Hz), 4.89 (1H, m), 4.09 (1H, t, $J = 9.00$ Hz), 3.99–3.94 (1H, m), 3.88–3.80 (2H, m), 3.58 (4H, m), 2.97 (4H, m), 1.48 (9H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.35, 41.89, 47.88, 50.69, 71.59, 79.82, 107.29, 107.55, 113.75, 119.20, 133.08, 136.52, 142.69, 143.51, 144.26, 147.67, 154.06, 154.71, (d, $J = 243.6$ Hz) 157.06, 163.87;

ESI–MS: $m/z = 493$ $(M + 1)^+$. Elemental analysis Calcd for $C_{23}H_{33}FN_6O_5$: C, 56.09; H, 6.75; N, 17.06; O, 16.24; Found: C, 56.11; H, 6.77; N, 17.19; O, 16.24.

(*S*)-*tert*-Butyl-4-(2-fluoro-4-(5-((5-methyl-lH-indole-2-carboxamido) methyl)-2-oxooxazolidin-3-yl) phenyl) piperazine-l-carboxylate (11i)

The compound **11i** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-tert-butyl 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-l-carboxylate (**8a**, 197 mg, 0.50 mmol) and 5-methyl-1*H*-indole-2-carboxylic acid (122 mg, 0.7 mmol) to afford the pure compound **11i** as a yellow solid in 250 mg, Yield: 91%;

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (1H, s), 7.62-7.41 (2H, m), 7.22-7.02 (4H, m), 6.93 (1H, t, $J = 9.06$ Hz), 4.91 (1H, m), 4.11 (1H, t, $J = 8.87$, 8.68 Hz), 3.92 (1H, m), 3.78 (2H, m), 3.55 (4H, m), 2.96 (4H, m), 2.59 (3H, s), 1.45 (9H, s), 7.76 (1H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 27.80, 40.25, 47.33, 49.99, 77.56, 78.18, 78.56, 103.21, 106.76, 111.88, 113.44, 118.91, 119.37, 121.08, 123.11, 126.67, 130.64, 132.13, 136.27, 138.43, 151.79, 153.68 (d, $J = 243.6$ Hz), 158.16, 161.77; ESI–MS: $m/z = 538$ $(M + 1)^+$. Elemental analysis Calcd for $C_{28}H_{32}FN_5O_5$: C, 62.56; H, 6.00; N, 13.03; O, 14.88; Found: C, 62.57; H, 6.07; N, 13.05; O, 14.89.

(*S*)-*tert*-Butyl4-(4-(5-((2-chloronicotinamido) methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-1-carboxylate (11j)

The compound **11j** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-tert-butyl 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-l-carboxylate (**8a**, 197 mg, 0.50 mmol) and 2-chloronicotinic acid (109 mg, 0.7 mmol) to afford the pure compound **11j** as a yellow solid in 234 mg, Yield: 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (1H, dd, $J = 4.5$, 3.02 Hz), 7.92 (1H, d, $J = 6.04$ Hz), 7.39 (1H, dd, $J = 2.26$, 12.06 Hz), 7.34–7.28 (2H, m), 7.04 (1H, d, $J = 9.06$ Hz), 6.90 (1H, t, $J = 9.06$ Hz), 4.91 (1H, m), 4.09 (1H, t, $J = 9.06$ Hz), 3.98–3.78 (3H, m), 3.58 (4H, m), 2.99 (4H, m), 1.47 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.31, 42.03, 43.94, 47.66, 50.50, 71.86, 79.83, 106.99, 107.38, 113.89, 122.72, 119.35, 131.29, 132.92, 136.13, 138.82, 147.15, 150.77, 153.70, 154.57 (d, $J = 243.4$ Hz), 156.96, 166.33; ESI–MS: $m/z = 534$ $(M + 1)^+$. Elemental analysis Calcd for $C_{25}H_{29}ClFN_5O_5$: C, 56.23; H, 5.47; N, 13.12; O, 14.98; Found: C, 56.25; H, 5.49; N, 13.15; O, 14.99.

Author Contribution M.V.B.Rao and R.S designed and supervised the study, Y.B synthesized and characterized compounds, and measured spectral data, biological activity was carried at CCMB (The Centre for Cellular & Molecular Biology, Hyderabad).

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