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Synthesis and in vitro antibacterial activity of novel fluoroalkyl-substituted pyrazolyl oxazolidinones

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A series of novel oxazolidinone derivatives bearing fluoroalkyl-substituted pyrazole as the C-ring structure were designed, synthesized and evaluated for their antibacterial activity against six Gram-positive bacterial pathogens. Most of the target compounds have good antibacterial activity. Especially, compounds **13f**, **13i** and **13l** show excellent activity comparable to linezolid.

1 Introduction

Common multi-drug-resistant Gram-positive bacterial pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE), *vancomycin-resistant Enterococci* (VRE), and penicillin-resistant *Streptococcus pneumoniae* (PRSP) have become serious health threats.[1-3] Oxazolidinones, as exemplified by linezolid, are a new class of synthetic antibacterial agents that have high activity against a broad range of Gram-positive Bacteria.[4] Linezolid was developed by Pharmacia and Upjohn Company and approved in 2000 for the treatment of serious infections caused by the above-mentioned strains.[5] However, bacterial resistance to linezolid has been found recently in Gram-positive bacteria *Staphylococcus aureus* and *Enterococcus faecium*.[6] Hence, numerous researches on the synthesis and bioassay of various oxazolidinones have been developed.[7-11] These studies have focused mainly on the modification of A-ring (oxazolidinone), B-ring (phenyl), C-ring (morpholine), and the C-5 side chain on the A-ring substructure of linezolid. Among them, series of oxazolidinones containing nitrogen heterocyclic structures as C-ring unit were reported and some analogues have good activity comparable or superior to linezolid against Gram-positive bacterial pathogens (Figure 1).[12-13] Oxazolidinones containing a pyrroloaryl substituent have been synthesized by J&J Pharmaceutical, and one compound was approved to begin phase I clinical trial.[14] Gyochang Keum has disclosed some oxazolidinones with 3-azabicyclo[3.3.0]octanyl rings as C-ring exhibit potent in vitro antibacterial activity.[15] Potent oxazolidinone antibacterials with pyrazolo[1,5-a]pyridines as the C-ring substructure were described by Hideyuki Suzuki et al.[16] Youfu Luo's group have synthesized an oxazolidinone compound with 4-(pyridin-2-yl)-1H-pyrrole, which has formed nanoassemblies without any carrier and display antimicrobial activity on MRSA.[17]

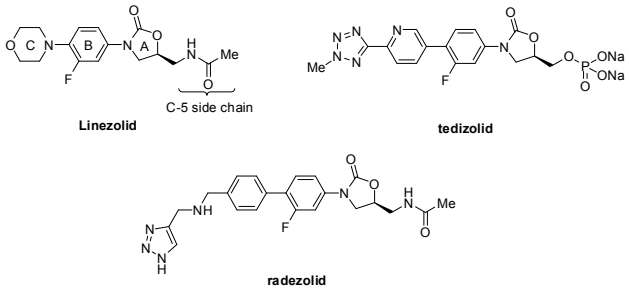

Figure 1 Structure of linezolid and its analogs.

For decades, there is considerable interest in introducing fluorine-containing groups into organic molecules since the growing application of organic fluorine compounds in pharmaceuticals.[18,19] Many commercial drugs containing trifluoromethyl and difluoromethyl groups have come to market.[19] However, literature survey showed that the incorporation of these fluoroalkyl groups into oxazolidinones has not been studies systematically. Consequently, we are interested in developing fluoroalkyl-containing oxazolidinones and expect these compounds might result in potent antibacterial activity. According to the literature, pyrazole cycle has been broadly used as a biologically active scaffold in medicine science.[20] Herein, we reported the synthesis of novel oxazolidinone derivatives bearing fluoroalkyl-substituted pyrazole as the C-ring structure and their antibacterial activities against methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-sensitive *Staphylococcus epidermidis* (MSSE), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and

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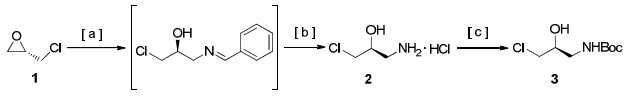
† Electronic supplementary information (ESI) available: Copies of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and mass spectra of the target compounds can be found as supplementary material. See DOI: 10.1039/x0xx00000x

Enterococcus faecium (EF). Three target compounds show good activity comparable to linezolid.

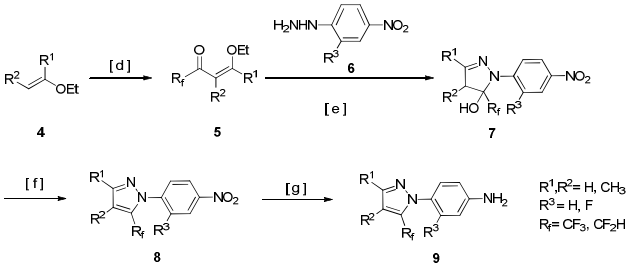
2 Result and discussion

2.1 Chemistry

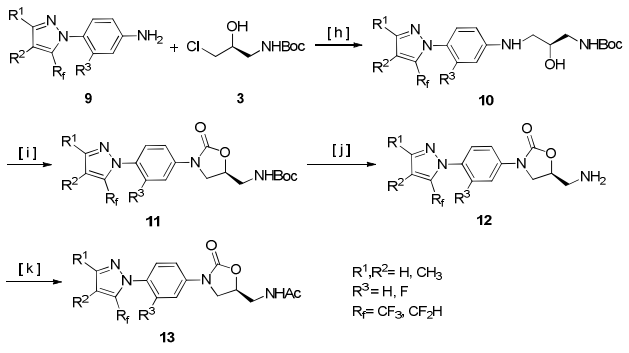
The synthetic routes to fluoroalkyl-substituted pyrazolyl oxazolidinone analogues are outlined in Schemes 1-3. The key intermediate **3** was prepared following literature procedures and described in Scheme 1.[21] (*S*)-Epichlorohydrin **1** reacted with benzaldehyde and aqueous ammonia in ethanol to form compound **2** after the addition of a solution of hydrochloric acid. The reaction of compound **2** and di-*tert*-butyldicarbonate provided the key intermediate **3** in high yield.



Scheme 1 *Reagents and conditions:* (a) PhCHO, NH_3, CH_2Cl_2, 40 °C for 6 h, then 25 °C for 14 h; (b) HCl, H_2O, toluene, 40-45 °C, 3.5 h; (c) $(Boc)_2O$, Et_3N, CH_2Cl_2, 25 °C, 12 h.



Scheme 2 *Reagents and conditions*: (d) $(RfCO)_2O$, Pyridine, CH_2Cl_2, 0 °C for 1 h, then 20 °C for 12 h; (e) EtOH, , reflux with stirring, 24h; (f) TFA, CH_2Cl_2, 25 °C , 12 h; (g) H_2, Pd/C, MeOH, 25 °C , 3 h.

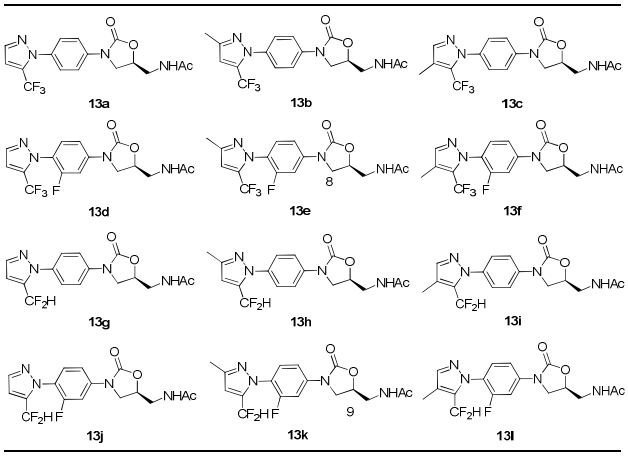


Scheme 3 *Reagents and conditions*: (h) neat, 150 °C, 12 h; (i) CDI, Et_3N, THF, 25 °C , 12 h; (j) TFA, CH_2Cl_2, 25 °C , 12 h; (k) Ac_2O, Et_3N, CH_2Cl_2, 25 °C , 12 h.

The synthesis of key intermediates **9** is depicted in Scheme 2. β-ethyloxyvinyl fluoroalkyl ketones **5** were prepared from ethyl vinyl ether and its derivatives with fluoroalkylacetic anhydride under base condition.[22] Treatment of compounds **5** with *p*-nitrophenylhydrazines **6** in ethanol gave exclusively the 5-hydroxy-4,5-dihydropyrazoles **7**. Dehydration and reduction of the nitro group afforded the corresponding pyrazoles **9**.[23]

Scheme 3 indicated the synthetic route of the target compounds **13**.[24] The preparation involved a coupling reaction between the compound **3** and intermediates **9** to give compounds **10**, which then underwent cyclization in the presence of carbonyl diimidazole (CDI) to form the 2-oxazolidinones **11**. Access to the fluoroalkyl-substituted pyrazolyl oxazolidinones **13** were achieved via the *N*-Boc deprotection and subsequent acetylation reaction. The structures of these target compounds are shown in Table 1. All the ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR and Mass data of compounds **13a-l** were in accordance with the proposed molecular structures.

Table 1 Structure of the target compounds **13a-l**.



2.2 Antibacterial activity

The antibacterial activity of the target compounds **13a-l** and linezolid, known for comparison were evaluated against Gram-positive bacterial strains: methicillin-resistant *Staphylococcus aureus* (MRSA) (5 strains), methicillin-sensitive *Staphylococcus aureus* (MSSA) (5 strains), methicillin-resistant *Staphylococcus epidermidis* (MRSE) (5 strains), methicillin-sensitive *Staphylococcus epidermidis* (MSSE) (5 strains), penicillin-resistant *Streptococcus pneumoniae* (PRSP) (5 strains), *Enterococcus faecium* (EF) (5 strains) and *Staphylococcus aureus* ATCC43300 and ATCC29213, as quality-control strains, using two-fold agar dilution method. The minimum inhibitory concentrations (MIC) of these compounds against the above bacteria are presented in Table 2.

The results revealed that most of the compounds exhibited good to moderate antibacterial activity. Compounds **13f**, **13i** and **13l** appear to exhibit similar antibacterial activity in comparison with linezolid, while compounds have 5-fluoroalkyl pyrazole moiety such as **13b**, **13d**, **13g**, **13k** showed poor activity against all the tested bacterial strains with MIC values greater than 8 μg mL^{-1}. In addition, compounds **13a**, **13c**, **13e** and **13h** were 2-fold less active than linezolid. According to the above result, it is found that compounds have 5-fluoroalkyl-4-methyl pyrazole moiety showed higher MIC value against Gram-positive bacteria than those have 5-fluoroalkyl-3-methyl pyrazole and 5-fluoroalkyl pyrazole moiety. When 4-methyl-5-triflurometh yl pyrazole was used as C-ring, compound with a fluorine atom at the 3-position of phenyl ring **13f** showed 2-4 fold potency advantages compared to compound with no fluorine atom on phenyl ring **13c**. Compounds with 5-

difluoromethyl-4-methyl pyrazole as C-ring have equal activity no matter the fluorine atom substituted at the phenyl ring or not (**13i** vs **13l**).

Table 2 Minimal-Inhibitory Concentrations (MICs) of Oxadiazolesa 1**3a-l**.

Compound	Minimum inhibitory concentrations (MIC) (μg mL^{-1})							
	MRSA	MSSA	MRSE	MSSE	PRSP	EF	ATCC43300	ATCC29213
13a	2-4	2-4	4	2-4	2-4	4	4	2
13b	>16	>16	>16	>16	>16	>16	>16	16
13c	2-4	2-4	4	2-4	2-4	4	4	2
13d	8-16	8-16	8-16	8-16	8	8	8	8
13e	2-4	2-4	4	2-4	2-4	4	4	2
13f	0.5-2	0.5-1	1-2	1-2	1-2	1-2	2	0.5
13g	8-16	8-16	8-16	16	8-16	8-16	8	8
13h	2-4	2-4	4	2-4	2-4	4	4	2
13i	1-2	1-2	1-2	1-2	1-2	1-2	2	1
13j	4-8	4-8	4-8	4-8	4	4	8	4
13k	>16	>16	>16	>16	>16	>16	>16	>16
13l	1-2	1-2	1-2	1-2	1-2	1-2	2	1
Linezolid	1-2	1-2	1-2	1-2	1-2	1-2	2	1

2.3 Molecular docking

To elucidate the antibacterial activity of the target compounds at the molecular level, we explored the interaction mode between the representative compounds **13f**, **13l**, linezolid and the *Deinococcus radiodurans* linezolid-bound 50S ribosomal subunit crystal structure (Protein Data Bank accession codes 3DLL) using Surflex-dock.[25] The predicted binding affinity (total scores) of docking studies was shown in Table 3. The scores of linezolid, **13f** and **13l** are with values of 6.47, 7.92 and 8.29, respectively. The docking result was shown in Figure 2. The figure 1A depicted the docking result of **13f** and linezolid. From the figure 1A, we found the $–CF_3$ group occupy more space than the –H atom, which make the $–CF_3$ group combine with the residues of binding site very easy and result in high antibacterial activity of **13f**. The figure 1B showed the docking result of **13l** and linezolid, according to the figure, the $–CHF_2$ group has a huger space compared to the –H atom. Therefore compound **13l** also showed high antibacterial activity comparable to linezolid. The steric space of $–CF_3$ is bigger than $–CHF_2$, and it is not conductive to the antibacterial activity. Hence, the docking result showed that compound **13l** exhibit higher antibacterial activity than that of compound **13f**. The molecular docking result, along with the biological assay data, suggests that compounds **13f** and **13l** prove to be potential antibacterials.

Next, we applied the molecular docking protocol to predict the affinity of compounds **13b** and **13k**, which both show lower antibacterial activity in the bioassay, to the *Deinococcus radiodurans* linezolid-bound 50S ribosomal subunit crystal structure. The scores of **13b** and **13k** are both lower than linezolid (Table 3). It might due to that in both two compounds, the trifluoromethyl group and methyl group in the pyrazole ring occupy in meta position, which lead to a large steric space and make the target compounds hard to fit into the binding pocket of the subunit.

Table 3 Total-score of compounds 13f, 13l and linezolid

Compound	Total-score
13f	7.92
13l	8.29
linezolid	6.47
13b	4.66
13k	6.10

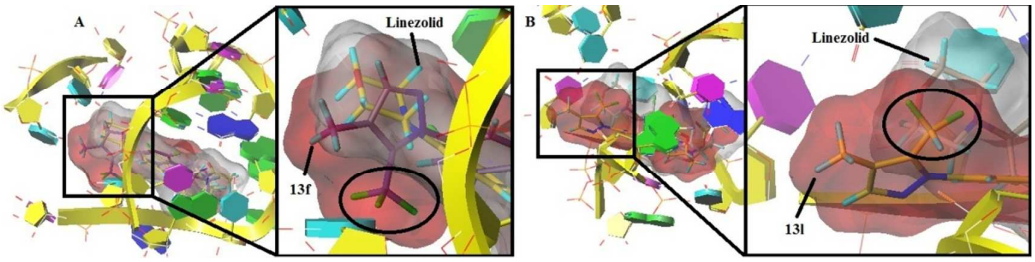


Figure 2 The docking results of linezolid, **13f** and **13l**.

3 Conclusion

In summary, we have synthesized a series of oxazolidinone-type antibacterials bearing fluoroalkyl-substituted pyrazole as the C-ring structure and evaluated their activity against a panel of Gram-positive bacterial pathogens. Most of the target compounds exhibited potent in vitro antibacterial activity. Compounds have 5-fluoroalkyl-4-methyl pyrazole moiety **13f**, **13i** and **13l** showed high antibacterial activity comparable to linezolid with minimum inhibitory concentration (MIC) values of 1-2, 1-2, 1-2 μg mL^{-1}. Molecular docking studies of linezolid

and the representative compounds with most high activity **13f, 13l** and low activity **13b**, **13k**, was performed and gave 6.47, 7.92, 8.20, 4.66, 6.10 total-score respectively. The synthesis of more fluoroalkyl-containing oxazolidinone analogues is ongoing for structure–activity relationship studies.

4 Experimental

4.1 Materials and measurements

All reagents were obtained from commercial suppliers and used without further purification. All NMR spectra were recorded on a Bruker Avance 500 (resonance frequencies 500 MHz for ^{1}H and 126 MHz for ^{13}C) equipped with a 5 mm inverse broadband probe head with z-gradients at 295.8K with standard Bruker pulse programs. The samples were dissolved in 0.6 ml CDCl3 (99.8% D.TMS). Chemical shifts were given in values of δ_H and δ_C referenced to residual solvent signals (δ_H 7.26 for ^{1}H, δ_C 77.0 for ^{13}C in $CDCl_3$). The ^{19}F NMR spectra were obtained using a 500 spectrometer (471 MHz) using trifluorotoluene as external standard. Conventional pulse sequences for NOESY, HMQC and HMBC with standard Bruker pulse programs; 200-ms mixing time for NOESY; J in Hz. High resolution mass spectra (HRMS) were recorded on a Bruker solan X 70 FT-MS (samples was dissolved in CH_3OH and the ion source was ESI), and the energy was 22.5eV at MS/MS. Melting points are uncorrected.

4.2 Synthesis of key intermediate (*S*)-*tert*-butyl (3-chloro-2-hydroxypropyl)carbamate 3

The synthesis of (*S*)-*tert*-butyl (3-chloro-2-hydroxypropyl) carbamate **3** had been reported by William R. Perrault. We prepared this compound completely according to the literature procedure and obtained compound **3** in high yield.[23]

4.3 General procedure for the preparation of 4-(5-(fluoroalkyl)-1*H*-pyrazol-1-yl)anilines 9a-l

To a stirred solution of pyridine (1.58 g, 20 mmol) and ethyl vinyl ether derivatives (22 mmol) in CH_2Cl_2 (50 mL) was dropwise added 2,2,2-trifluoroacetic anhydride or 2,2-difluoroacetic anhydride (20 mmol) at -5°C. The reaction mixture was stirred for 1 h at 0 °C, and then for another 12h at 20°C. After the completion of reaction, the mixture was concentrated in vacuo, diluted with ethylene chloride (50 mL) and poured into saturated sodium bicarbonate solution (50 ml). The two phases were separated and the organic layer was washed with water, dried by anhydrous Na_2SO_4. The solvent was removed in reduced pressure to provide oil products 4-ethoxy-1-fluoroalkyl-but-3-en-2-ones **5a-f** in high yields. Compounds **5a-f** were used for next step without further purification.

Compound **5** (15 mmol) and (4-nitrophenyl)hydrazine **6** (15 mmol) in 50 mL ethanol was heated at reflux for 24 h, followed by cooling and concentration in vacuo. The residue was dissolved in EtOAc (100 mL), washed with water (3 × 100 mL) and brine (100 mL). The organic layer was dried by anhydrous Na_2SO_4 and concentrated in vacuo to afford the brown solid **7a-l**. Then, the compounds **7a-l** was dissolved in CH_2Cl_2 and added trifluoroacetic acid (3.42 g, 30 mmol) dropwise. The mixture was stirred for 12 h at room temperature. The reaction was quenched with water and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography using petroleum ether/ethyl acetate (8:1) as eluent to give the pure products **8a-l** in good yields.

A mixture of compound **8** (10 mmol) and 5 % Pd/C (0.25 g) in methanol (30 mL) was stirred under H_2 for 3h at room temperature. The reaction mixture was filtered through diatomaceous earth, and the residue was washed with methanol. The filter was concentrated under reduced pressure. The crude liquid was purified by flash column chromatography using petroleum ether/ethyl acetate (3:1) as eluent to yield the pure products **9a-l**.

4.3.1 4-(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)aniline (9a). Light yellow liquid, yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.64-7.62 (m, 1H, pyrazole-H), 7.23-7.21 (m, 2H, ArHs), 6.75-6.73 (m, 2H, ArHs), 6.67-6.65 (m, 1H, pyrazole-H), 3.81 (br, 2H, NH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 147.7, 139.0, 132.7 (q, $^{2}J_{C\text{-}F}$ = 39.0 Hz), 129.8, 127.0, 120.0 (q, $^{1}J_{C\text{-}F}$ = 268.7 Hz), 114.7, 108.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.3 (s, 3F).

4.3.2 4-(3-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl) aniline (9b). Light yellow liquid, yield: 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.21-6.69 (m, 4H, ArHs), 6.54 (s, 1H, pyrazole-H), 3.53 (br, 2H, NH_2), 2.34 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 148.3, 147.3, 133.1 (q, $^{2}J_{C\text{-}F}$ = 39.0 Hz), 130.0, 127. 4, 120.5 (q, $^{1}J_{C\text{-}F}$ = 268.9 Hz), 114.7, 107.8, 13.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.7 (s, 3F).

4.3.3 4-(4-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl) aniline (9c). Light yellow liquid, yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.45-7.42 (m, 1H, pyrazole-H), 7.18-7.16 (m, 2H, ArHs), 6.65-6.62 (m, 2H, ArHs), 3.89 (br, 2H, NH_2), 2.22 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 147.5, 140.6, 130.6, 129.2 (q, $^{2}J_{C\text{-}F}$ = 37.1 Hz), 127.3, 120.9 (q, $^{1}J_{C\text{-}F}$ = 269.6 Hz), 119.1, 114.6, 9.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.7 (s, 3F).

4.3.4 3-fluoro-4-(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)aniline (9d). Light yellow liquid, yield: 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm)7.73-7.70 (m, 1H, pyrazole-H), 7.14-7.11 (m, 1H, ArHs), 6.79-6.76 (m, 1H, pyrazole-H), 6.43-6.40 (m, 2H, ArHs), 4.01 (br, 2H, NH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 158.7 (d, $^{1}J_{C\text{-}F}$ = 250.8 Hz), 150.1 (d, $^{3}J_{C\text{-}F}$ = 10.6 Hz), 139.8, 134.2 (q, $^{2'}J_{C\text{-}F}$ = 39.0 Hz), 129.8, 119.8 (q, $^{1'}J_{C\text{-}F}$ = 264.6 Hz), 116.4, 110.0, 108.0, 101.8 (d, $^{2}J_{C\text{-}F}$ = 27.7 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.8 (s, 3F), -121.9 (s, 1F).

4.3.5 3-fluoro-4-(3-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)aniline (9e). Light yellow liquid, yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.14-7.11 (m, 1H, ArH), 6.57-6.55 (m, 1H, pyrazole-H), 6.44-6.39 (m, 2H, ArHs), 3.93 (br, 2H, NH_2), 2.35(s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 158.6 (d, $^{1}J_{C\text{-}F}$ = 250.9 Hz), 149.8 (d, $^{3}J_{C\text{-}F}$ = 10.7Hz), 149.1, 134.6 (q, $^{2'}J_{C\text{-}F}$ = 38.8 Hz), 130.0, 119.7 (q, $^{1'}J_{C\text{-}F}$ = 269.6 Hz), 116.6, 110.0, 107.6, 101.8 (d, $^{2}J_{C\text{-}F}$ = 23.0 Hz), 13.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.7 (s, 3F), -121.9 (s, 1F).

4.3.6 3-fluoro-4-(4-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)aniline (9f). Light yellow liquid, yield: 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.53-7.50 (m, 1H, pyrazole-H), 7.16-7.12 (m, 1H, ArH), 6.57-6.53 (m, 1H, ArH), 6.47-6.44 (m, 1H, ArH), 3.82 (br, 2H, NH_2), 2.36 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 158.8 (d, $^{1}J_{C\text{-}F}$ = 250.8 Hz), 149.6 (d, $^{3}J_{C\text{-}F}$ = 10.8 Hz), 149.1, 141.4, 135.1 (q, $^{2'}J_{C\text{-}F}$ = 36.6 Hz), 130.0, 120.2 (q, $^{1'}J_{C\text{-}F}$ = 264.5 Hz), 110.0, 107.6, 101.9 (d, $^{2}J_{C\text{-}F}$ = 22.9 Hz), 13.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.8 (s, 3F), -121.6 (s, 1F).

4.3.7 4-(5-(difluoromethyl)-1*H*-pyrazol-1-yl)aniline (9g). Light yellow liquid, yield: 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm)7.67-7.64 (m, 1H, pyrazole-H), 7.23-7.21 (m, 2H, ArHs), 6.75-6.70 (m, 2H, ArHs), 6.58 (t, $^{2}J_{H\text{-}F}$ = 49.5 Hz, 1H, CF_2H), 6.48-6.44 (m, 1H, pyrazole-H),3.88 (br, 2H, NH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 147.4, 139.5, 136.3 (t, $^{2}J_{C\text{-}F}$ = 30.1 Hz), 129.6, 126.5, 115.0, 108.7 (t, $^{1}J_{C\text{-}F}$ = 235.0 Hz), 106.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -110.1 (s, 2F).

4.3.8 4-(5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl) aniline (9h). Light yellow liquid, yield: 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.21-7.19 (m, 2H, ArHs), 6.69-6.67 (m, 2H, ArHs), 6.52 (t, $^{2}J_{H\text{-}F}$ = 53.9 Hz, 1H, CF_2H), 6.49-6.48 (m, 1H, pyrazole-H), 3.77 (br, 2H, NH_2), 2.35(s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 148.8, 147.1, 136.9 (t, $^{2}J_{C\text{-}F}$ = 29.9 Hz), 129.6, 126.5, 115.0, 108.7 (t, $^{1}J_{C\text{-}F}$ = 234.7 Hz), 105.9, 13.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -110.1 (s, 2F).

4.3.9 4-(5-(difluoromethyl)-4-methyl-1*H*-pyrazol-1-yl) aniline (9i). Light yellow liquid, yield: 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.47-7.46 (m, 1H, pyrazole-H), 7.18-7.16 (m, 2H, ArHs), 6.67-6.66 (m, 2H, ArHs), 6.57 (t, $^{2}J_{H\text{-}F}$ = 53.1 Hz, 1H, CF_2H), 3.92 (br, 2H, NH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 147.3, 140.7, 132.4 (t, $^{2}J_{C\text{-}F}$ = 29.1 Hz), 129.8, 126.6, 117.8, 114.9, 109.7 (t, $^{1}J_{C\text{-}F}$ = 233.5 Hz), 8.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -111.4 (s, 2F).

4.3.10 4-(5-(difluoromethyl)-1*H*-pyrazol-1-yl)-3-fluoro aniline (9j). Light yellow liquid, yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.72-7.71 (m,1H, pyrazole-H), 7.17-7.16 (m, 1H, ArH), 6.57 (t, $^{2}J_{H\text{-}F}$ = 53.6 Hz, 1H, CF_2H), 6.46-6.44 (m, 2H, ArHs), 6.43-6.40 (m, 1H, pyrazole-H),4.05 (br, 2H, NH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 157.8 (d, $^{1}J_{C\text{-}F}$ = 249.4 Hz), 149.9 (d, $^{3}J_{C\text{-}F}$ = 10.7 Hz), 140.2, 137.9 (t, $^{2'}J_{C\text{-}F}$ = 29.6 Hz), 129.6, 116.3 (d, $^{3'}J_{C\text{-}F}$ = 13.0 Hz), 110.5, 108.5 (t, $^{1'}J_{C\text{-}F}$ = 237.0 Hz), 106.4, 101.8 (d, $^{2}J_{C\text{-}F}$ = 22.9 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -112.4 (s, 2F), -122.7 (s, 1F).

4.3.11 4-(5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl)-3-fluoroaniline (9k). Light yellow liquid, yield: 88%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.12-7.11 (m, 1H, ArH), 6.51 (t, $^{2}J_{H\text{-}F}$ = 54.3 Hz, 1H, CF_2H), 6.40-6.39 (m, 2H, ArHs), 6.38-6.37 (m, 1H, pyrazole-H),4.17 (br, 2H, NH_2), 2.33 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 157.8 (d, $^{1}J_{C\text{-}F}$ = 249.4 Hz), 158.9, 156.9, 149.7, 138.4 (t, $^{2'}J_{C\text{-}F}$ = 29.4 Hz), 116.3 (d, $^{1}J_{C\text{-}F}$ = 13.6 Hz), 110.4, 107.7 (t, $^{1'}J_{C\text{-}F}$ = 236.6 Hz), 107.0, 101.8(d, $^{2}J_{C\text{-}F}$ = 22.9Hz), 13.4; ^{19}F NMR(471 MHz, $CDCl_3$) δ (ppm) -112.4 (s, 2F), -122.7 (s, 1F).

4.3.12 4-(5-(difluoromethyl)-4-methyl-1*H*-pyrazol-1-yl)-3-fluoroaniline (9l). Light yellow liquid, yield: 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.58-7.55 (m, 1H, pyrazole-H), 7.53-7.48 (m, 1H, ArH),6.77 (t, $^{2}J_{H\text{-}F}$ = 54.3 Hz, 1H, CF_2H), 6.48-6.45 (m, 2H, ArHs), 3.97 (br, 2H, NH_2), 2.25 (s,3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 155.2 (d, $^{1}J_{C\text{-}F}$ = 247.6 Hz), 147.6 (d, $^{3}J_{C\text{-}F}$ = 10.6 Hz), 145.1 (t, $^{2'}J_{C\text{-}F}$ = 28.6 Hz), 131.4 (d, $^{4}J_{C\text{-}F}$ = 6.1Hz), 126.0, 119.0 (d, $^{3'}J_{C\text{-}F}$ = 10.4 Hz), 116.8, 112.6 (t, $^{1'}J_{C\text{-}F}$ = 232.5k Hz), 110.9 102.3 (d, $^{2}J_{C\text{-}F}$ = 23.2 Hz), 8.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -112.1 (s, 2F), -124.7 (s, 1F).

4.4 General procedure for the preparation of (*S*)-*tert*-butyl (2-hydroxy-3-((4-(5-(fluoroalkyl)-1*H*-pyrazol-1-yl)phenyl)amino) propyl)carbamates 10a-l

The mixture of compound **9** (10 mmol) and compound **3** (3.14 g, 15 mmol) was heated to 150 °C and stirred overnight. After the completion of reaction, the residue was purified by flash column chromatography using petroleum ether/ethyl acetate (8:1) as eluent to give the pure products **10a-l**.

4.4.1 (*S*)-*tert*-butyl (2-hydroxy-3-((4-(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)amino)propyl) carbamate (10a). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.67 (br, 1H, NHCO), 7.20-7.19 (m, 1H, pyrazole-H), 7.20-7.17 (m, 2H, ArHs), 6.80-6.70 (m, 2H, ArHs), 6.70-6.60 (m, 1H, pyrazole-H), 5.10-5.09 (m, 1H, Ar-NH) 4.01-4.00 (m, 1H, CH), 3.40-3.21 (m, 4H, $2CH_2$*),* 1.48 (s, 9H, $3CH_3$).

4.4.2 (*S*)-*tert*-butyl (2-hydroxy-3-((4-(3-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)amino) propyl) carbamate (10b). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.67 (br, 1H, NHCO), 7.21-7.15 (m, 2H, ArHs), 6.90-6.85 (m, 2H, ArHs), 6.84-6.80 (m, 1H, pyrazole-H) ,5.61-5.60 (m, 1H, Ar-NH), 4.00-3.98 (m, 1H, CH), 3.40-3.21 (m, 4H, $2CH_2$*),* , 2.37 (s, 3H, pyrazole-CH_3), 1.50 (s, 9H, $3CH_3$).

4.4.3 (*S*)-*tert*-butyl (2-hydroxy-3-((4-(4-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)amino) propyl) carbamate (10c). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.67 (br, 1H, NHCO), 7.43-7.40 (m, 1H, pyrazole-H), 7.21-7.15 (m, 2H, ArHs), 6.92-6.83 (m, 2H, ArHs) , 6.00-5.98 (m, 1H, Ar-NH), 4.00-3.99 (m, 1H, CH), 3.39-3.18 (m, 4H*),* 2.26 (s, 3H, pyrazole-CH_3), 1.49 (s, 9H, $3CH_3$).

4.4.4 (*S*)-*tert*-butyl (3-((3-fluoro-4-(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)amino)-2-hydroxypropyl) carbamate (10d). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.69 (br, 1H, NHCO), 7.44-7.41 (m, 1H, pyrazole-H), 7.40-7.37 (m, 1H, ArH), 6.88-6.82 (m, 2H, ArHs), 6.77-6.75 (m, 1H, pyrazole-H), 5.12-5.10 (m, 1H, Ar-NH), 4.04-4.02 (m, 1H, CH), 3.37-3.18 (m, 4H, $2CH_2$*),* 1.49 (s, 9H, $3CH_3$).

4.4.5 (*S*)-*tert*-butyl (3-((3-fluoro-4-(3-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)amino)-2-hydroxy propyl) carbamate (10e). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.72 (br, 1H, NHCO), 7.33-7.30 (m, 1H, ArH), 6.64-6.60 (m, 2H, ArHs), 6.23-6.20 (m, 1H, pyrazole-H), 4.03-4.01 (m, 1H, CH), 3.39-3.18 (m, 4H, $2CH_2$*),* 2.38 (s, 3H, pyrazole-CH_3), 1.51 (s, 9H, $3CH_3$).

4.4.6 (*S*)-*tert*-butyl (3-((3-fluoro-4-(4-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)amino)-2-hydroxypropyl) carbamate (10f). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.70 (br, 1H, NHCO), 7.44-7.41 (m, 1H, pyrazole-H), 6.64-6.60 (m, 3H, ArHs), 4.01-3.99 (m, 1H, CH), 3.37-3.14 (m, 4H*),* 2.27 (s, 3H, pyrazole-CH_3), 1.50 (s, 9H, $3CH_3$).

4.4.7 (*S*)-*tert*-butyl (3-((4-(5-(difluoromethyl)-1*H*-pyrazol-1-yl)phenyl)amino)-2-hydroxypropyl)carbam-ate (10g). ^{1}H NMR

(500 MHz, $CDCl_3$) δ (ppm) 7.70 (br, 1H, NHCO), 7.54-7.52 (m, 1H, pyrazole-H), 7.50-7.48 (m, 2H, ArHs), 6.77-6.68 (m, 2H, ArHs), 6.64-6.62 (m, 1H, pyrazole-H), 6.43 (t, $^2J_{H\text{-}F}$ = 53.4 Hz, 1H, CF_2H), 4.00-3.99 (m, 1H, CH), 3.40-3.25 (m, 4H, $2CH_2$), 1.51 (s, 9H, $3CH_3$).

4.4.8 (*S*)-*tert*-butyl (3-((4-(5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl)phenyl)amino)-2-hydroxypropyl) carbamate (10h). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.70 (br, 1H), 7.40-7.32 (m, 2H, ArHs), 6.65-6.63 (m, 2H, ArHs), 6.62-6.60 (m, 1H, pyrazole-H), 6.31 (t, $^2J_{H\text{-}F}$ = 53.8 Hz, 1H, CF_2H), 4.00-3.99 (m, 1H, CH), 3.40-3.25 (m, 4H, $2CH_2$), 2.33 (s, 3H, pyrazole-CH_3), 1.48 (s, 9H, $3CH_3$).

4.4.9 (*S*)-*tert*-butyl (3-((4-(5-(difluoromethyl)-4-methyl-1*H*-pyrazol-1-yl)phenyl)amino)-2-hydroxypropyl) carbamate (10i). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.71 (br, 1H, NHCO), 7.15-7.13 (m, 1H, pyrazole-H), 7.10-7.02 (m, 2H, ArHs), 6.67-6.60 (m, 2H, ArHs), 6.44 (t, $^2J_{H\text{-}F}$ = 52.8 Hz, 1H, CF_2H), 4.02-4.01 (m, 1H, CH), 3.45-3.30 (m, 4H, $2CH_2$), 2.23 (s, 3H, pyrazole-CH_3), 1.49 (s, 9H, $3CH_3$).

4.4.10 (*S*)-*tert*-butyl (3-((4-(5-(difluoromethyl)-1*H*-pyrazol-1-yl)-3-fluorophenyl)amino)-2-hydroxypropyl) carbamate (10j). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.73 (br, 1H, NHCO), 7.50-7.48 (m, 1H, pyrazole-H), 7.40-7.28 (m, 1H, ArH), 6.72-6.65 (m, 2H, ArHs), 6.62-6.60 (m, 1H, pyrazole-H), 6.42 (t, $^2J_{H\text{-}F}$ = 54.4 Hz, 1H, CF_2H), 4.02-4.00 (m, 1H, CH), 3.44-3.32 (m, 4H, $2CH_2$), 1.50 (s, 9H, $3CH_3$).

4.4.11 (*S*)-*tert*-butyl (3-((4-(5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl)-3-fluorophenyl)amino)-2-hydr-oxypropyl) carba- mate (10k). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.69 (br, 1H, NHCO), 7.24-7.16 (m, 2H, ArHs), 6.72-6.64 (m, 1H, ArH), 6.62-6.60 (m, 1H, pyrazole-H), 6.44 (t, $^2J_{H\text{-}F}$ = 54.4 Hz, 1H, CF_2H), 4.00-3.99 (m, 1H, CH), 3.39-3.30 (m, 4H, $2CH_2$), 2.30 (s, 3H, pyrazole-CH_3), 1.53 (s, 9H, $3CH_3$).

4.4.12 (*S*)-*tert*-butyl (3-((4-(5-(difluoromethyl)-4-methyl-1*H*-pyrazol-1-yl)-3-fluorophenyl)amino)-2-hydroxypropyl) carba- mate (10l). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.67 (br, 1H, NHCO), 7.19-7.16 (m, 1H, pyrazole-H), 7.12-7.08 (m, 1H, ArH), 6.80-6.55 (m, 2H, ArHs), 6.64 (t, $^2J_{H\text{-}F}$ = 54.2 Hz, 1H, CF_2H), 4.00-3.99 (m, 1H, CH), 3.39-3.30 (m, 4H, $2CH_2$), 2.20 (s, 3H, pyrazole-CH_3), 1.47 (s, 9H, $3CH_3$).

4.5 General procedure for the preparation of (*S*)-*tert*-butyl ((2-oxo-3-(4-(5-(fluoroalkyl)-1*H*-pyrazol-1-yl)phenyl)oxazolidin-5-yl) methyl)carbamates 11a-l

Triethylamine (1.62 g, 16 mmol) and carbonyl diimidazole (CDI) (2.59 g, 16 mmol) was added dropwise to a solution of compound **10** (8 mmol) in THF (50 mL) at room temperature. The mixture was stirred for 14 h. After the completion of reaction, the reaction was quenched with water and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography using petroleum ether/ethyl acetate (4:1) as eluent to give the pure products **11a-l**.

4.5.1 (*S*)-*tert*-butyl ((2-oxo-3-(4-(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)oxazolidin-5-yl)methyl)car-bamate (11a). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.75-7.74 (m, 1H, pyrazole-H),7.73-7.71 (m, 2H, ArHs), 7.56-7.53 (m, 2H, ArHs), 6.79-6.77 (m, 1H, pyrazole-H), 6.19-6.18 (m, 1H, NH), 4.85-4.84 (m, 1H, CH), 4.10-4.09 (m, 1H, NCH_2-H_a), 3.89-3.86 (m, 1H, NCH_2-H_b), 3.73-3.70 (m, 2H, CH_2), 1.43 (s, 9H, $3CH_3$).

4.5.2 (*S*)-*tert*-butyl ((3-(4-(3-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl) carbamate (11b). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.71-7.59 (m, 4H, ArHs), 6.70 (s, 1H, pyrazole-H), 6.52-6.43 (m, 1H, NH), 4.93-4.90 (m, 1H, CH), 4.09-4.07 (m, 1H, NCH_2-H_a), 3.76-3.69 (m, 1H, NCH_2-H_b), 3.62-3.59 (m, 2H, CH_2), 1.97 (s, 3H, pyrazole-CH_3), 1.47 (s, 9H, $3CH_3$).

4.5.3 (*S*)-*tert*-butyl ((3-(4-(4-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl) carbamate (11c). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.69-7.65 (m, 1H, pyrazole-H), 7.64-7.60 (m, 1H, ArH), 7.32-7.30 (m, 3H, ArHs), 6.86-6.83 (m, 1H, NH), 4.72-4.70 (m, 1H, CH), 4.09-4.01 (m, 1H, NCH_2-H_a), 3.77-3.75 (m, 1H, NCH_2-H_b), 3.60-3.57 (m, 2H, CH_2), 1.99 (s, 3H, pyrazole-CH_3), 1.47 (s, 9H, $3CH_3$).

4.5.4 (*S*)-*tert*-butyl ((3-(3-fluoro-4-(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)carbamate (11d). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.69-7.67 (m, 1H, pyrazole-H), 7.65-7.63 (m, 1H, ArH), 7.34-7.30 (m, 2H, ArHs), 6.87-6.86 (m, 1H, pyrazole-H), 6.85-6.84 (m, 1H, NH), 4.74-4.72 (m, 1H, CH), 4.09-4.05 (m, 1H, NCH_2-H_a), 3.84-3.81 (m, 1H, NCH_2-H_b), 3.70-3.65 (m, 2H, CH_2), 1.45 (s, 9H, $3CH_3$).

4.5.5 (*S*)-*tert*-butyl ((3-(3-fluoro-4-(3-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin- 5-yl)methyl)carbamate (11e). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.74-7.71 (m, 1H, ArH), 7.54-7.50 (m, 1H, ArH), 7.40-7.37 (m, 1H, ArH), 6.76-6.74 (m, 1H, pyrazole-H), 6.34-6.31 (m, 1H, NH), 4.78-4.75 (m, 1H, CH), 4.09-4.06 (m, 1H, NCH_2-H_a), 3.86-3.84 (m, 1H, NCH_2-H_b), 3.77-3.68 (m, 2H, CH_2), 1.98 (s, 3H, pyrazole-CH_3), 1.49 (s, 9H, $3CH_3$).

4.5.6 (*S*)-*tert*-butyl ((3-(3-fluoro-4-(4-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin- 5-yl)methyl)carbamate (11f). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.71-7.68 (m, 1H, pyrazole-H), 7.50-7.48 (m, 1H, ArH), 7.42-7.39 (m, 1H, ArH), 6.78-6.76 (m, 1H, ArH), 5.94-5.92 (m, 1H, NH), 4.24-4.22 (m, 1H, CH), 4.02-4.00 (m, 1H, NCH_2-H_a), 3.79-3.76 (m, 1H, NCH_2-H_b), 3.68-3.65 (m, 2H, CH_2), 1.97 (s, 3H, pyrazole-CH_3), 1.47 (s, 9H, $3CH_3$).

4.5.7 (*S*)-*tert*-butyl ((3-(4-(5-(difluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)carbamate (11g). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.69-7.67 (m, 1H, pyrazole-H), 7.66-7.60 (m, 2H, ArHs), 7.59-7.56 (m, 2H, ArHs), 6.68-6.66 (m, 1H, pyrazole-H), 6.58 (t, $^2J_{H\text{-}F}$ = 55.7 Hz, 1H, CF_2H), 6.49-6.45 (m, 1H, NH), 4.83-4.80 (m, 1H, CH), 4.04-4.01 (m, 1H, NCH_2-H_a), 3.86-3.84 (m, 1H, NCH_2-H_b), 3.67-3.64 (m, 2H, CH_2), 1.43 (s, 9H, $3CH_3$).

4.5.8 (*S*)-*tert*-butyl ((3-(4-(5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl) carbamate (11h). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.70-7.68 (m, 2H, ArHs), 7.51-7.48 (m, 2H, ArHs), 6.86-6.83 (m, 1H, pyrazole-H), 6.50 (t, $^2J_{H\text{-}F}$ = 54.9 Hz, 1H, CF_2H), 6.41-6.39 (m, 1H, NH), 4.77-

4.74 (m, 1H, CH), 4.09-4.06 (m, 1H, NCH_2-H_a), 3.78-3.75 (m, 1H, NCH_2-H_b), 3.63-3.61 (m, 2H, CH_2), 1.97 (s, 3H, pyrazole-CH_3), 1.50 (s, 9H, $3CH_3$).

4.5.9 (*S*)-*tert*-butyl ((3-(4-(5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl) carbamate (11i). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.69-7.67 (m, 1H, pyrazole-H), 7.58-7.54 (m, 3H, ArHs), 7.10-7.07 (m, 1H, ArH), 6.70 (t, $^2J_{H\text{-}F}$ = 53.7 Hz, 1H, CF_2H), 6.43-6.41 (m, 1H, NH), 4.71-4.68 (m, 1H, CH), 4.11-4.07 (m, 1H, NCH_2-H_a), 3.76-3.73 (m, 1H, NCH_2-H_b), 3.54-3.50 (m, 2H, CH_2), 1.93 (s, 3H, pyrazole-CH_3), 1.46 (s, 9H, $3CH_3$).

4.5.10 (*S*)-*tert*-butyl ((3-(4-(5-(difluoromethyl)-1*H*-pyrazol-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)carbamate (11j). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.71-7.70 (m, 1H, pyrazole-H), 7.69-7.68 (m, 1H, ArH), 7.53-7.35 (m, 2H, ArHs), 6.77-6.75 (m, 1H, pyrazole-H), 6.68 (t, $^2J_{H\text{-}F}$ = 54.6 Hz, 1H, CF_2H), 6.55-6.53 (m, 1H, NH), 4.76-4.72 (m, 1H, CH), 4.09-4.07 (m, 1H, NCH_2-H_a), 3.78-3.74 (m, 1H, NCH_2-H_b), 3.61-3.59 (m, 2H, CH_2), 1.48 (s, 9H, $3CH_3$).

4.5.11 (*S*)-*tert*-butyl ((3-(4-(5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl) carbamate (11k). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.69-7.37 (m, 3H, ArHs), 6.75-6.73 (m, 1H, pyrazole-H), 6.65 (t, $^2J_{H\text{-}F}$ = 54.8 Hz, 1H, CF_2H), 6.57-6.53 (m, 1H, NH), 4.89-4.85 (m, 1H, CH), 4.11-4.09 (m, 1H, NCH_2-H_a), 3.78-3.76 (m, 1H, NCH_2-H_b), 3.59-3.55 (m, 2H, CH_2), 1.97 (s, 3H, pyrazole-CH_3), 1.51 (s, 9H, $3CH_3$).

4.5.12 (*S*)-*tert*-butyl ((3-(4-(5-(difluoromethyl)-4-methyl-1*H*-pyrazol-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl) carbamate (11l). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.77-7.75 (m, 1H, pyrazole-H), 7.74-7.70 (m, 2H, ArHs), 7.30-7.29 (m, 1H, ArH), 6.97-6.95 (m, 1H, NH), 6.83 (t, $^2J_{H\text{-}F}$ = 53.6 Hz, 1H, CF_2H), 4.90-4.88 (m, 1H, CH), 4.06-4.03 (m, 1H, NCH_2-H_a), 3.76-3.73 (m, 1H, NCH_2-H_b), 3.65-3.62 (m, 2H, CH_2), 1.96 (s, 3H, pyrazole-CH_3), 1.49 (s, 9H, $3CH_3$).

4.6 General procedure for the preparation of (*S*)-*N*-((2-oxo-3-(4-(5-(fluoroalkyl)-1*H*-pyrazol-1-yl)phenyl)oxazolidin-5-yl)methyl) acetamides 13a-l

To a solution of compound **11** (6 mmol) in CH_2Cl_2 (50 mL) was added dropwise trifluoroacetic acid (1.37g, 12 mmol). The mixture was stirred for 12h at room temperature. The solvent was removed in reduced pressure to provide the crude products **12a-l**, which were used for next step without further purification.

Acetic anhydride (1.23g, 12 mmol) was added dropwise to a mixture of compound **12** (6 mmol) in CH_2Cl_2 (50 mL) and triethylamine (1.82 g, 18 mmol). The resulting solution was stirred for 12h at room temperature. After the completion of reaction, the reaction was quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate as eluent to give the pure target products **13a-l**.

4.6.1 (*S*)-*N*-((2-oxo-3-(4-(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)oxazolidin-5-yl)methyl)acetamide (13a). Light yellow solid, yiled: 85%, m.p: 145.2-147.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.72-7.71 (m, 1H, pyrazole-H), 7.70-7.68 (m, 2H, ArHs), 7.53-7.51 (m, 2H, ArHs), 6.83-6.82 (m, 1H, pyrazole-H), 6.21-6.20 (m, 1H, NH), 4.84-4.83 (m, 1H, CH), 4.16-4.12 (m, 1H, NCH_2-H_a), 3.90-3.87 (m, 1H, NCH_2-H_b), 3.76-3.61 (m, 2H, CH_2), 2.05 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.2, 154.3, 139.7, 138.8, 135.0, 132.6, 126.5, 119.9 (q, $^1J_{C\text{-}F}$ = 268.3 Hz), 118.3, 109.0, 72.1, 47.5, 41.9, 23.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.8 (s, 3F). HRMS calcd. for $C_{16}H_{15}F_3N_4O_3Na$ $[M+Na]^+$: 391.0994, found: 391.0999

4.6.2 (*S*)-*N*-((3-(4-(3-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (13b). Light yellow solid, yiled: 83%, m.p: 148.4-150.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.66-7.48 (m, 4H, ArHs), 6.61 (s, 1H, pyrazole-H), 6.41-6.32 (m, 1H, NH), 4.83-4.82 (m, 1H, CH), 4.14-4.10 (m, 1H, NCH_2-H_a), 3.88-3.85 (m, 1H, NCH_2-H_b), 3.71-3.63 (m, 2H, CH_2), 2.37 (s, 3H, pyrazole-CH_3), 2.04 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.2, 154.3, 149.1, 138.5, 135.1, 133.1 (q, $^2J_{C\text{-}F}$ = 37.8 Hz), 126.1, 119.8 (q, $^1J_{C\text{-}F}$ = 268.9 Hz), 118.2, 108.7, 72.1, 47.2, 41.9, 23.0, 13.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.8 (s, 3F). HRMS calcd. for $C_{34}H_{34}F_6N_8O_6Na$ $[2M+Na]^+$: 787.2403, found: 787.2412.

4.6.3 (*S*)-*N*-((3-(4-(4-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (13c). Off-white solid, yiled: 82%, m.p: 179.4-180.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.66-7.64 (m, 1H, pyrazole-H), 7.63-7.62 (m, 1H, ArH), 7.44-7.42 (m, 3H, ArHs), 6.75-6.73 (m, 1H, NH), 4.81-4.80 (m, 1H, CH), 4.12-4.08 (m, 1H, NCH_2-H_a), 3.88-3.85 (m, 1H, NCH_2-H_b), 3.69-3.60 (m, 2H, CH_2), 2.26 (s, 3H, pyrazole-CH_3), 2.02 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.3, 154.4, 141.4, 138.6, 135.6, 129.2 (q, $^2J_{C\text{-}F}$ = 37.6 Hz), 126.7, 120.7 (q, $^1J_{C\text{-}F}$ = 269.4 Hz), 119.9, 118.2, 72.1, 47.5, 41.9, 23.0, 9.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.8 (s, 3F). HRMS calcd. for $C_{17}H_{17}F_3N_4O_3Na$[M+Na]$^+$: 405.1150, found: 405.1149.

4.6.4 (*S*)-*N*-((3-(3-fluoro-4-(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (13d). Off-white solid, yiled: 80%, m.p: 165.1-167.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.74-7.71 (m, 1H, pyrazole-H), 7.70-7.67 (m, 1H, ArH), 7.44-7.30 (m, 2H, ArHs), 6.88-6.86 (m, 1H, pyrazole-H), 6.84-6.82 (m, 1H, NH), 4.84-4.82 (m, 1H, CH), 4.13-4.09 (m, 1H, NCH_2-H_a), 3.88-3.85 (m, 1H, NCH_2-H_b), 3.68-3.63 (m, 2H, CH_2), 2.01 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.5, 158.9 (d, $^1J_{C\text{-}F}$ = 253.3 Hz), 154.2, 141.0 (d, $^3J_{C\text{-}F}$ = 10.6 Hz), 140.3, 134.1 (q, $^{2'}J_{C\text{-}F}$ = 38.8 Hz), 129.7, 122.1 (d, $^{3''}J_{C\text{-}F}$ = 13.2 Hz), 119.6 (q, $^{1'}J_{C\text{-}F}$ = 268.8 Hz), 113.0, 108.5, 106.3 (d, $^2J_{C\text{-}F}$ = 25.4 Hz), 72.3, 47.4, 41.8, 22.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.8 (s, 3F), -118.8 (s, 1F). HRMS calcd. for $C_{16}H_{14}F_4N_4O_3Na$[M+Na]$^+$: 409.0900, found: 409.0913.

4.6.5 (*S*)-*N*-((3-(3-fluoro-4-(3-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl) acetamide (13e). Off-white solid, yiled: 87%, m.p: 153.5-155.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.71-7.68 (m, 1H, ArH), 7.45-7.42 (m, 1H, ArH), 7.33-7.30 (m, 1H, ArH), 6.64-6.60 (m, 1H, pyrazole-H), 6.23-6.20 (m, 1H, NH), 4.85-4.84 (m, 1H, CH),

4.13-4.10 (m, 1H, NCH_2-H_a), 3.88-3.84 (m, 1H, NCH_2-H_b), 3.76-3.65 (m, 2H, CH_2), 2.38 (s, 3H, pyrazole-CH_3), 2.05 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.2, 158.0 (d, $^1J_{C-F}$ = 253.4 Hz), 153.9, 149.8, 140.7 (d, $^3J_{C-F}$ = 10.5 Hz), 134.6 (q, $^{2'}J_{C-F}$ = 39.1 Hz), 129.8, 122.4 (d, $^{3'}J_{C-F}$ = 12.5 Hz), 119.5 (q, $^{1'}J_{C-F}$ = 269.6 Hz), 112.8, 108.2, 106.3 (d, $^2J_{C-F}$ = 25.6 Hz), 72.1, 47.4, 41.9, 23.1, 13.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.8 (s, 3F), -118.6 (s, 1F). HRMS calcd. for $C_{17}H_{16}F_4N_4O_3Na$ $[M+Na]^+$: 423.1056, found: 423.1055.

4.6.6 (*S*)-*N*-((3-(3-fluoro-4-(4-methyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl) acetamide (13f). Off-white solid, yiled: 83%, m.p: 160.3-162.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.69-7.66 (m, 1H, pyrazole-H), 7.65-7.28 (m, 3H, ArHs), 6.65-6.61 (m, 1H, NH), 4.85-4.83 (m, 1H, CH), 4.13-4.09 (m, 1H, NCH_2-H_a), 3.88-3.84 (m, 1H, NCH_2-H_b), 3.68-3.65 (m, 2H, CH_2), 2.36 (s, 3H, pyrazole-CH_3), 2.03 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.4, 158.0 (d, $^1J_{C-F}$ = 253.1 Hz), 154.1, 149.8, 142.0, 140.7 (d, $^3J_{C-F}$ = 11.6 Hz), 134.6 (q, $^{2'}J_{C-F}$ = 38.8 Hz), 129.7 (d, $^{3'}J_{C-F}$ = 11.4 Hz), 120.5 (q, $^{1'}J_{C-F}$ = 269.2 Hz), 112.9, 108.2, 106.3 (d, $^2J_{C-F}$ = 25.6 Hz), 72.2, 47.4, 41.9, 23.0, 13.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -62.8 (s, 3F), -118.6 (s, 1F). HRMS calcd. for $C_{17}H_{16}F_4N_4O_3Na[M+Na]^+$: 423.1056, found: 423.1055.

4.6.7 (*S*)-*N*-((3-(4-(5-(difluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (13g). Light yellow solid, yiled: 82%, m.p: 154.4-154.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.73-7.71 (m, 1H, pyrazole-H), 7.70-7.68 (m, 2H, ArHs), 7.55-7.51 (m, 2H, ArHs), 6.77-6.72 (m, 1H, pyrazole-H), 6.64 (t, $^2J_{H-F}$ = 53.4 Hz, 1H, CF_2H), 6.59-6.55 (m, 1H, NH), 4.86-4.80 (m, 1H, CH), 4.14-4.10 (m, 1H, NCH_2-H_a), 3.90-3.86 (m, 1H, NCH_2-H_b), 3.70-3.67 (m, 2H, CH_2), 2.04 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.3, 154.4, 140.2, 138.4, 136.3 (t, $^2J_{C-F}$ = 29.7 Hz), 134.9, 125.8, 118.7, 108.5 (t, $^1J_{C-F}$ = 236.1 Hz), 107.6, 72.2, 47.6, 42.0, 23.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -109.9 - -109.8 (m, 2F). HRMS calcd. for $C_{16}H_{16}F_2N_4O_3Na[M+Na]^+$: 373.1088, found: 373.1098.

4.6.8 (*S*)-*N*-((3-(4-(5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (13h). Off-white solid, yiled: 78%, m.p: 148.0-149.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.64-7.63 (m, 2H, ArHs), 7.49-7.47 (m, 2H, ArHs), 6.75-6.72 (m, 1H, pyrazole-H), 6.57 (t, $^2J_{H-F}$ = 53.8 Hz, 1H, CF_2H), 6.53-6.51 (m, 1H, NH), 4.83-4.80 (m, 1H, CH), 4.11-4.08 (m, 1H, NCH_2-H_a), 3.88-3.85 (m, 1H, NCH_2-H_b), 3.68-3.64 (m, 2H, CH_2), 2.35 (s, 3H, pyrazole-CH_3), 2.02 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.3, 154.4, 149.6, 138.1, 136.7 (t, $^2J_{C-F}$ = 29.2 Hz), 135.0, 125.6, 118.7, 108.4 (t, $^1J_{C-F}$ = 235.5 Hz), 107.3, 72.1, 47.5, 41.9, 23.0, 13.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -109.9 - -109.8 (m, 2F). HRMS calcd. for $C_{17}H_{18}F_2N_4O_3Na[M+Na]^+$: 387.1245, found: 387.1249.

4.6.9 (*S*)-*N*-((3-(4-(5-(difluoromethyl)-4-methyl-1*H*-pyrazol-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (13i). Off-white solid, yiled: 83%, m.p: 156.3-158.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.63-7.62 (m, 1H, pyrazole-H), 7.62-7.61 (m, 1H, ArH), 7.48-7.43 (m, 3H, ArHs), 7.06-7.02 (m, 1H, NH), 6.59 (t, $^2J_{H-F}$ = 52.8 Hz, 1H, CF_2H), 4.80-4.76 (m, 1H, CH), 4.09-4.05 (m, 1H, NCH_2-H_a), 3.85-3.83 (m, 1H, NCH_2-H_b), 3.64-3.60 (m, 2H, CH_2), 2.23 (s, 3H, pyrazole-CH_3), 1.98 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.5, 154.5, 141.4, 138.3, 135.1, 132.2 (t, $^2J_{C-F}$ = 28.2 Hz), 125.9, 118.9, 118.7, 109.2 (t, $^1J_{C-F}$ = 235.5 Hz), 72.2, 47.5, 41.9, 22.9, 8.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -111.0 (s, 2F). HRMS calcd. for $C_{34}H_{36}F_4N_8O_6Na$ $[2M+Na]^+$: 751.2592, found: 751.2590.

4.6.10 (*S*)-*N*-((3-(4-(5-(difluoromethyl)-1*H*-pyrazol-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (13j). Light yellow solid, yiled: 79%, m.p: 149.5-152.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.74-7.73 (m, 1H, pyrazole-H), 7.72-7.70 (m, 1H, ArH), 7.50-7.28 (m, 2H, ArHs), 6.72-6.71 (m, 1H, pyrazole-H), 6.70-6.68 (m, 1H, NH), 6.59 (t, $^2J_{H-F}$ = 54.4 Hz, 1H, CF_2H), 4.86-4.82 (m, 1H, CH), 4.13-4.11 (m, 1H, NCH_2-H_a), 3.89-3.85 (m, 1H, NCH_2-H_b), 3.70-3.66 (m, 2H, CH_2), 2.03 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.4, 156.8 (d, $^1J_{C-F}$ = 251.5 Hz), 154.1, 140.8, 140.4 (d, $^3J_{C-F}$ = 10.5 Hz), 137.8 (t, $^{2'}J_{C-F}$ = 27.8 Hz), 129.3, 122.4 (d, $^{3'}J_{C-F}$ = 12.9 Hz), 113.4, 108.5 (t, $^{1'}J_{C-F}$ = 237.0 Hz), 107.3, 106.4 (d, $^2J_{C-F}$ = 25.4 Hz), 72.2, 47.4, 41.8, 23.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -112.6 (s, 2F), -119.9 (s, 1F). HRMS calcd. for $C_{16}H_{15}F_3N_4O_3Na[M+Na]^+$: 391.0994, found: 391.1010.

4.6.11 (*S*)-*N*-((3-(4-(5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl) acetamide (13k). Light yellow solid, yiled: 81%, m.p: 151.3-152.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.64-7.27 (m, 3H, ArHs), 7.26-7.24 (m, 1H, pyrazole-H), 6.54 (t, $^2J_{H-F}$ = 54.4 Hz, 1H, CF_2H), 6.47-6.42 (m, 1H, NH), 4.80-4.76 (m, 1H, CH), 4.08-4.05 (m, 1H, NCH_2-H_a), 3.83-3.78 (m, 1H, NCH_2-H_b), 3.62-3.57 (m, 2H, CH_2), 2.29 (s, 3H, pyrazole-CH_3), 1.96 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 172.1, 156.8 (d, $^1J_{C-F}$ = 251.0 Hz), 154.3, 150.2, 140.2 (d, $^3J_{C-F}$ = 9.9 Hz), 138.3 (t, $^{2'}J_{C-F}$ = 28.9 Hz), 129.3, 122.4 (d, $^{3'}J_{C-F}$ = 12.6 Hz), 113.4, 108.5 (t, $^{1'}J_{C-F}$ = 236.6 Hz), 107.0, 106.3 (d, $^2J_{C-F}$ = 26.0 Hz), 72.2, 47.4, 41.8, 22.7, 13.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -112.7 (s, 2F), -120.1 (s, 1F). HRMS calcd. for $C_{17}H_{17}F_3N_4O_3Na[M+Na]^+$: 405.1150, found: 405.1166.

4.6.12 (*S*)-*N*-((3-(4-(5-(difluoromethyl)-4-methyl-1*H*-pyrazol-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl) acetamide (13l). Light yellow solid, yiled: 80%, m.p: 163.2-165.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.79-7.77 (m, 1H, pyrazole-H), 7.76-7.64 (m, 2H, ArHs), 7.21-7.19 (m, 1H, ArH), 6.84-6.83 (m, 1H, NH), 6.74 (t, $^2J_{H-F}$ = 54.2 Hz, 1H, CF_2H), 4.86-4.82 (m, 1H, CH), 4.10-4.06 (m, 1H, NCH_2-H_a), 3.86-3.83 (m, 1H, NCH_2-H_b), 3.70-3.68 (m, 2H, CH_2), 2.24 (s, 3H, pyrazole-CH_3), 2.03 (s, 3H, $COCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 171.5, 154.3, 153.4 (d, $^1J_{C-F}$ = 248.4 Hz), 145.9 (t, $^{2'}J_{C-F}$ = 29.2 Hz), 137.7 (d, $^3J_{C-F}$ = 10.1 Hz), 131.2 (d, $^4J_{C-F}$ = 9.7 Hz), 124.4, 123.8 (d, $^{3'}J_{C-F}$ = 9.8 Hz), 118.6, 113.7, 112.3 (t, $^{1'}J_{C-F}$ = 237.0 Hz), 106.8 (d, $^2J_{C-F}$ = 26.5 Hz), 72.2, 47.4, 41.8, 23.0, 8.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -112.6 (s, 2F), -122.4 (s, 1F). HRMS calcd. for $C_{17}H_{17}F_3N_4O_3Na[M+Na]^+$: 405.1150, found: 405.1167.

4.7 Antibacterial activity assay

The antibacterial activities of the target compounds were tested against six Gram-positive bacterial strains using linezolid as a positive control. The strains were isolated and identified by Jiangsu Province People's Hospital and kept in this

laboratory at -80 °C. In vitro activities of the compounds were tested in nutrient broth (NB) for bacteria by two-fold serial agar dilution method using the method recommended by National Committee for Clinical Laboratory Standards (NCCLS). Compounds were dissolved in 50% water in DMSO to prepare a stock solution that had a concentration of 320 μg/mL. Serial 2-fold dilutions were prepared from the stock solution with sterile water and then 10-fold diluted with Mueller–Hinton (MH) agar medium to provide concentration ranges of 16–0.0312 μg/mL. The tested organisms were grown in MH broth medium (containing 5% sheep serum) at 35 °C for 8 h and were adjusted to the turbidity of the 0.5 McFarland standard to a concentration of 10^8 CFU ml^{-1}. The bacterial suspensions were inoculated onto the drug-supplemented MH agar plates with a multipoint inoculator and incubated at 35 °C for 16-20 h. The minimum inhibitory concentrations (MIC) values were determined at the end of the incubation period. The lowest concentration of the compound that prevented visible growth was considered as MIC.

4.8 Molecule docking

Energy minimization: The conformations of compounds **13b**, **13f**, **13l**, **13k** and linezolid were optimized using the minimize module of SYBYL-X 2.1.[26] The force field was calculated with tripos field and the atom charges were also calculated using Gasteiger-Huckel method.[27]

Docking calculations: The docking studies of compounds **13b**, **13f**, **13l**, **13k** and linezolid were performed by the surflex-dock method.[25] The three compounds were docked into the *Deinococcus radiodurans* 50S ribosomal subunit crystal structure (PDB ID: 3DLL) by a posteriori scoring function in Surflex-dock. Before the docking program was performed, the ligand of the crystal structure was used to build the protomol, which is the representation of a ligand making every potential interaction with the binding pocket. In this paper, the protomol of SYBYL was built by automatic docking and other setups were default setting up. The binding affinity was characterized by the total-scores and expressed in $-\lg K_d$ unit.

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References

1 B. Spellberg, R. Guidos, D. Gilbert, J. Bradley, H. W. Boucher, W. M. Scheld, J. G. Bartlett and J., Jr. Edwards, *Clin. Infect. Dis.*, 2008, **46**, 155–164.
2 Y. Fukuda, *Drugs Future*, 2009, **34**, 127–136.
3 R. Leclercq, *Clin. Microbiol. Infect.*, 2009, **15**, 224–231.
4 S. J. Brickner, D. K. Hutchinson, M. R. Barbachyn, P. R. Manninen, D. A. Ulanowicz, S. A. Garmon, K. C. Grega, S. K. Hendges, D. S. Toops, C. W. Ford, and G. E. Zurenko, *J. Med. Chem.*, 1996**, 39***,* 673–679.
5 R. Norrby, *Expert Opin. Pharmacother.* 2001, **2**, 293–302.
6 S. Ager and K. Gould, *Infect Drug Resist*. 2012, **5**, 87–102.
7 Q. Xin, H. Fan, B. Guo, H. He, S. Gao, H. Wang, Y. Huang and Y. Yang, *J. Med. Chem.*, 2011, **54**, 7493−7502.
8 M. F. Gordeev and Z. Y. Yuan, *J. Med. Chem.*, 2014, **57**, 4487−4497.
9 B. Guo, H. Fan, W. Chu, H. Wang, Y. Huang, X. Chen and Y. Yang, *J. Med. Chem.*, 2013, **56**, 2642−2650.
10 E. Spink, D. Ding, Z. Peng, M. A. Boudreau, E. Leemans, E. Lastochkin, W. Song, K. Lichtenwalter, P. I. O'Daniel, S. A. Testero, H. Pi, V. A. Schroeder, W. R. Wolter, N. T. Antunes, M. A. Suckow, S. Vakulenko, M. Chang and S. Mobashery, *J. Med. Chem.*, 2015, **58**, 1380−1389.
11 T. Yang, J. Chen, Y. Fu, K. Chen, J. He, W. Ye, Z. Sang and Y. Luo, *Org. Process Res. Dev.*, 2014, **18**, 511−519.
12 P. Philippe, D. A. Carisa, F. Edward, M. Purvi and D. Anita, *J. Am. Med. Assoc.*, 2013, **309**, 559−569.
13 K. Michalska, I. Karpiuk, M. Krol and S. Tyski, *Bioorg. Med. Chem.*, 2013, **21**, 577−591.
14 S. D. Paget, B. D. Foleno, C. M. Boggs, R. M. Goldschmidt, D. J. Hlasta, M. A. Weidner-Wells, H. M. Werblood, E. Wira, K. Bush and M. J. Macielag, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 4173−4177.
15 D. Bhattarai, S. H. Lee, S. H. Seo, G. Nam, S. B. Kang, A. N. Pae, E. E. Kim, T. Oh, S.-N. Cho and G. Keum, *Chem. Biol. Drug. Des.*, 2012, **80**, 388−397.
16 H. Suzuki, I. Utsunomiya, K. Shudo, T. Fujimura, M. Tsuji, I. Kato, T. Aoki, A. Ino and T. Iwaki. *ACS Med. Chem. Lett.*, 2013, **4**, 1074−1078.
17 C. Gong, T. Yang, X. Yang, Y. Liu, W. Ang, J. Tang, W. Pi, L. Xiong, Y. Chang, W. Ye, Z. Wang, Y. Luo, X. Zhao and Y. Wei, *Nanoscale*, 2013, **5**, 275−283.
18 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320−330.
19 J. Wang, M. Sánchez-Roselló, J. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432−2506.
20 K. A. Kumar and P. Jayaroopa, *Int. J. PharmTech Res.*, 2013, **5**, 1473−1486.
21 W. R. Perrault, B. A. Pearlman, D. B. Godrej, A. Jeganathan, K. Yamagata, J. J. Chen, C. V. Lu, P. M. Herrinton, R. C. Gadwood, L. Chan, M. A. Lyster, M. T. Maloney, J. A. Moeslein, M. L. Greene and M. R. Barbachyn. *Org. Process Res. Dev.*, 2003, **7**, 533–546.
22 X. Fang, Y. Chen, D. He, X. Yang and F. Wu, *J. Fluorine Chem.*, 2008, **129**, 1167−1172.
23 S. P. Singh, D. Kumar, B. G. Jones and M. D. Threadgill, *J. Fluorine Chem.*, 1999, **94**, 199−203.
24 A. Greco, R. De Marco, S. Tani, D. Giacomini, P. Galletti, A. Tolomelli, E. Juaristi and L. Gentilucci, *Eur. J. Org. Chem.*, 2014, 7614–7620.
25 R. Spitzer and A. N. Jain, *J. Comput. Aided Mol. Des.*, 2012, **26**, 687–699.
26 Z. Kai, Y. Ling, W. Liu, F. Zhao and X. Yang, *Biochim. Biophys. Acta*, 2006, **1764**, 70–75.
27 J. Gasteiger and M. Marsili, Tetrahedron, 1980, **36**, 3219–3228.