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Synthesis of Novel Oxazolidinone Derivatives Bearing Benzo[*b*]thiophene Moiety and their Antimicrobial Evaluation

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Literature survey revealed that the oxazolidinone derivatives exhibit pharmacological significance. Thus, by targeting to design new antimicrobial agent, a novel series of oxazolidinone derivatives (**11a-t**) having benzo[*b*]thiophene moiety were synthesized. Chemical structures of the synthesized compounds were confirmed through spectroscopic techniques such as IR, NMR and Mass spectroscopy. All the new synthesized compounds were subjected to *in vitro* antimicrobial testing by estimating zone of inhibition toward Gram-positive pathogens like *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 25923 and *Streptococcus pyogens* ATCC 8668.

Keywords: Oxazolidinone, Benzo[*b*]thiophene, Linezolid, Antimicrobial activity.

INTRODUCTION

Discovery of antibiotic is one kind of boon for human life. This innovation is nothing but the one type of achievement of modern science and technology, which has assured the revolution of human beings and better-quality life. However, with widespread use and abuse of antibiotics, multi-drug resistant and superbug bacteria have emerged across the world which could reduce the effectiveness of treatment of a large number of drugs [1-3]. To combat such types of multi-drugs resistance, the invention of novel, potent and safe compounds has become today's important task. Presently the numbers of new antimicrobial drugs from different classes are in practices [4-6]; out of these, oxazolidinone is important class of heterocyclic compounds and moreover well-known scaffold for the medicinal chemists [7].

Oxazolidinones are synthetic antibacterial agents which having unique mode of action. It shows promising activity against multiple resistance Gram-positive pathogens including, methicillin resistant *Staphylococcus aureus*, penicillin resistant *Streptococci* and *Vancomycin* resistant *enterococci* [8-17].

Linezolid (**1**) was the first branded antibiotic from the class of oxazolidinone, which enjoyed as a drug since 2000 and having remarkable worldwide sale of $ 1.3 billion in 2011 [18,19]. Eperezolid (**2**) was the second generation oxazolidinone developed contemporarily with linezolid, up to phase II study. Linezolid and eperezolid (Fig. 1) require multi dosing regimen during the period of treatment, which increases the serious side effects [20]. In order to overcome unwanted hitch of linezolid and eperezolid, discovery of new safe oxazolidinone derivatives with superior potency has become urgent requirement. However, several major pharmaceutical organizations stopped the discovery of new antibiotics due to its commercial or regulatory challenges. Hence, now a days, discovery and development of new antimicrobial drugs are big challenge for drug chemists [21].

On the other hand, benzo[*b*]thiophene molecule found to be important scaffolds in synthetic medicinal chemistry. Literature

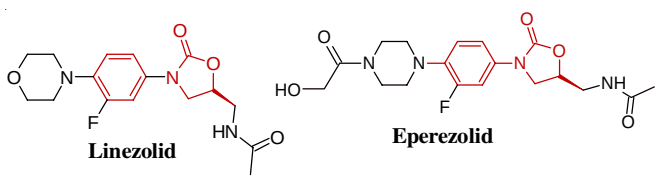


Fig. 1. Structure of linezolid (**1**) and eperezolid (**2**)

survey of benzo[*b*]thiophene derivatives indicates that benzo[*b*]thiophene and its multi-heterocyclic derivatives have wide range of biological/pharmacological activities like analgesic, anti-inflammatory [22], estrogen receptor modulating [23,24], antimitotic [25], enzyme inhibitors [26], anticancer [27,28], kinases inhibitors [29], antimalarial [30], anthelmintic [31], antihyperglycemic [32] and pesticides [33]. Further, numerous benzothiophene-based compounds as clinical drugs have been extensively used to treat various types of diseases with high therapeutic potency, which has led to their extensive developments. Some of the benzothiophene derivatives those are available in the market as depicted [34-38] in Fig. 2.

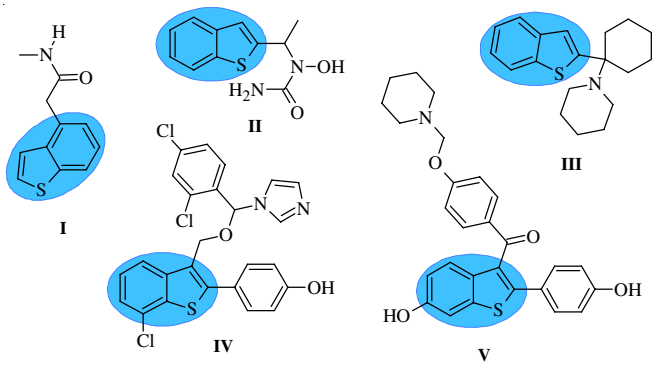


Fig. 2. Biologically active compounds containing benzothiophene

Changing the framework of old medications to create the novel antimicrobial specialists with same objective is a significant methodology to minimize the bacterial obstruction [39]. As eperezolid structure permitted scope for auxiliary refinement, the piperazinyl-phenyl-oxazolidinone core structure of eperezolid was attached to benzo[*b*]thiophene heterocycle. With a goal of improving the antimicrobial spectrum, benzo[*b*]-thiophene moiety inserted in the target compounds, as depicted in Fig. 3.

EXPERIMENTAL

Different chemicals and solvents of analytical reagent grade quality were procured from commercial vendors. These chemicals were used without further purification. Melting points were determined on digital melting point apparatus (Sr. No. ZXII-02-332) and are uncorrected. All the reactions were monitored by thin layer chromatography (TLC) on 25 mm silica gel 60 F_{254} plates (Merck, Germany) using UV light (254 & 366 nm) for visualization. All the synthesized compounds were purified by column chromatography using solvents system (methanol and dichloromethane). The NMR spectral data was recorded using BRUKER AVANCE II 300 MHz, chemical shifts were reported in ppm relative to TMS. The mass spectra were recorded on a Shimadzu Nexara 2020 LC-MS and the IR spectra of the compounds were recorded on Bruker FTIR-TENSOR-II.

1-(1-Benzo[*b*]thiophen-4-yl)-4-(2-fluoro-4-nitrophenyl)piperazine (5): To a well stirred mixture of compound **4** (5 g, 0.019 mol) and potassium carbonate (5.4 g, 0.039 mol) in acetonitrile (25 mL) was added compound **3** (3.12 g, 0.019 mol) then the resulting mixture was heated at reflux temperature for 10-12 h. After the completion of reaction, reaction mixture was allowed to cool at room temperature and solvent was distilled under reduced pressure up to residue, purified water (25 mL) was added and mixture allowed to stir for 30 min. Precipitated solid was filtered, followed by washing with purified water (10 mL). Crude solid was recrystallized in ethanol to furnish compound **5** as a yellow solid. Yield 5.61 g, 80%, IR (KBr, ν_{max}, cm^{-1}): 3064 (C-H), 1601 (C=C), 1562 and 1380 (nitro), 1449 (C=C), 1256 (Ar-F), 1206 (C-N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.06-8.02 (m, 2H, C-H of phenyl ring), 7.75-7.73 (d, 1H, *J* = 5.7 Hz, C-H of thiophene ring), 7.68-7.65 (d, 1H, *J* = 8.1 Hz, C-H of phenyl ring), 7.51-7.49 (d, 1H, *J* = 6 Hz, C-H of thiophene ring), 7.33-7.20 (m, 2H, C-H of phenyl ring), 6.97-6.94 (d, 1H, *J* = 7.5 Hz, C-H of phenyl ring), 3.53-3.52 (d, 4H, *J* = 4.5 Hz, CH_2-piperazine ring), 3.24-3.23 (d, 4H, *J* = 4.2 Hz, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ146, 142, 139, 137, 135, 129, 128, 124, 122, 119, 117, 114, 113, 108, 63, 58; ESI-MS, *m/z* calculated for $C_{18}H_{16}FN_3O_2S$, 357.40; found 358 $[M]^+$.

4-[4-(1-Benzo[*b*]thiophen-4-yl)piperazin-1-yl]-3-fluoroaniline (6): A mixture of compound **5** (4.0 g, 0.011 mol), iron (6.2 g, 0.11 mol) and aqueous ammonium chloride (5.98 g, 0.11 mol) in ethanol (40 mL) was micro refluxed for 6-8 h. After completion of reaction, hot reaction was mass filtered through hyflow bed and filtrated concentrated up to solid appeared. Purified water (40 mL) was added to obtain solid and pH of mixture basified by using 10% aq. sodium bicarbonate solution. Precipitated solid isolated by filtration and washed

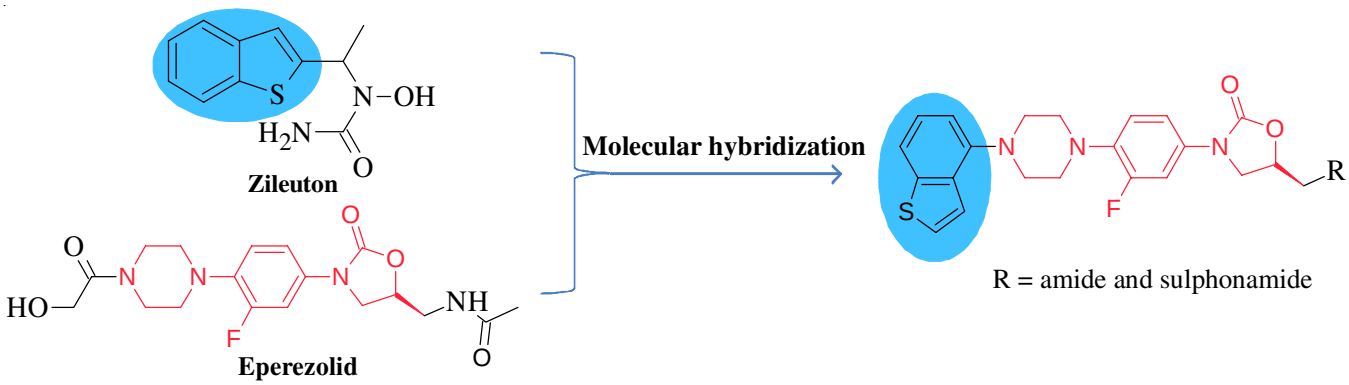


Fig. 3. Approach for the novel oxazolidinone derivatives bearing benzo[*b*]thiophene moiety

with purified water to get dark brown coloured solid **6**; obtained solid used for next reaction without further purification. Yield 3.48 g, 95%; IR (KBr, ν_{max}, cm^{-1}): 3403 and 3314 (NH_2), 3061 (C-H), 1623 and 1449 (C=C), 1274 (Ar-F), 1237 (C-N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.70-7.64 (d, 2H, C-H of phenyl ring), 7.45-7.298 (d, 2H, C-H of phenyl ring), 6.94-6.87 (d, 2H,C-H of thiophene ring), 6.36 (s, 2H, C-H of phenyl ring), 5.03 (s, 2H, NH_2), 3.184 (s, 4H, CH_2-piperazine ring), 3.08 (s, 4H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 143, 142, 139, 136, 135, 130, 128, 123, 121, 119, 116, 113, 111, 107, 65, 59; ESI-MS, *m/z* calculated for $C_{18}H_{18}FN_3S$, 327.41; found 328 $[M]^+$.

2-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenylamino]-2-hydroxy-propyl}-isoindole-1,3-dione (8): A mixture of compound **6** (3.0 g, 0.0091 mol) and 2-[(2S)-oxiran-2-ylmethyl]-1*H*-isoindole-1,3(2*H*)-dione (2.3 g, 0.011 mol) in isopropyl alcohol (30 mL) was heated at 80 ºC for 10-12 h. After total conversion of starting material into product; the reaction mixture was allowed to attain room temperature and stir for 60-90 min. Precipitated solid was filtered and wash with isopropyl alcohol (10 mL), obtained crude material crystallized from isopropyl alcohol; a light cream coloured solid. Yield 4.37 g, 90%; IR (KBr, ν_{max}, cm^{-1}): 3300 (NH), 3066 (C-H), 1631 and 1452 (C=C), 1719 and 1769 (anhydride), 1259 (Ar-F), 1237 (C-N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.85 (s, 4H, C-H of phenyl ring), 7.71-7.65 (m, 2H, C-H of phenyl ring), 7.46-7.30 (m, 2H, C-H of phenyl ring), 6.95 (s, 2H, C-H of thiophene ring), 6.42 (s, 2H, C-H of phenyl ring), 5.55 (s, 1H, C-H of aliphatic region), 5.16 (s, 1H, C-H of aliphatic region), 3.99 (s, 1H, C-H of aliphatic region), 3.62 (s, 1H, C-H of aliphatic region), 3.19-3.01 (m, 10H, CH_2-piperazine and aliphatic region); ^{13}C NMR (300 MHz, DMSO-d_6): δ 163, 148, 144, 138, 136, 133, 128, 126, 125, 123, 120, 116, 114, 111, 108, 106, 103, 73, 65, 61, 60, 50; ESI-MS, *m/z* calculated for $C_{29}H_{27}N_4O_3SF$, 530.61; found 531 $[M]^+$.

2-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-isoindole-1,3-dione (9): To a well stirred mixture of compound **8** (2.0 g, 0.0037 mol) and potassium carbonate (0.78 g, 0.0056 mol) in dichloromethane (25 mL), N,N′-carbonyldiimidazole (0.91 g, 0.0056 mol) was charged and stirred overnight at 30-35 ºC. After completion of reaction, purified water (25 mL) was added and lower dichloromethane layer separated. Aqueous layer back washed with dichloromethane (20 mL), combined dichloromethane layers were dried with sodium sulfate. Filtration of dichloromethane layer for removal of sodium sulfate followed by evaporation of dichloromethane to afford oxazolidinone compound. Obtained crude solid was further recrystallized from tetrahydrofuran; to get a light yellow solid. Yield 1.98 g, 94.4%; IR (KBr, ν_{max}, cm^{-1}): 3107 (C-H), 1628 and 1448 (C=C), 1718 and 1740 (phthalamide), 1235 (C-N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.93-7.88 (m, 4H, C-H of phenyl ring), 7.73-7.72 (d, 1H, C-H of thiophene ring), 7.67-7.64 (t, 1H, C-H of phenyl ring), 7.50-7.45 (dd, 2H, C-H of phenyl ring), 7.33-7.28 (d, 1H, C-H of thiophene ring), 7.22-7.12 (m, 2H, C-H of phenyl ring), 7.02-6.96 (t, 1H, C-H of phenyl ring), 4.97-4.93 (m, 1H, CH-oxazolidinone ring), 4.22-4.16 (t, 1H, diastereotopic proton of oxazolidinone ring), 4.05-3.88 (m, 3H, diastereotopic proton of oxazolidinone ring), 3.24 (s, 8H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 159, 153, 148, 143, 139, 135, 133, 132, 128, 125, 124, 122, 120, 117, 115, 112, 109, 103, 80, 67, 62, 50, 42; ESI-MS, *m/z* calculated for $C_{30}H_{25}N_4O_4SF$, 556.60; found 557 $[M]^+$.

(*S*)-5-(Aminomethyl)-3-[4-(4-(benzo[*b*]thiophen-4-yl)-piperazin-1-yl)-3-fluorophenyl]-oxazolidin-2-one hydrochloride salt (10): Solution of compound **9** (1.5 g, 0.0026 mol) and 40% aqueous methyl amine solution (15 mL) in THF (25 mL) was stirred at room temperature for overnight. After overnight stirring solvent was removed under reduced pressure up to residue, methanol (10 mL) was added in residue and stirred for 30 min. Precipitated solid filtered and washed with prechilled methanol to get white coloured solid **10**, obtained solid used for next reaction without further purification. Yield 0.51 g, 45%; IR (KBr, ν_{max}, cm^{-1}): 3434 (NH_2), 3107 (C-H), 1628 and 1448 (C=C), 1235 (C-N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.70-7.71 (d, 1H, *J* = 7.2 Hz, C-H of thiophene ring), 7.57-7.40 (m, 2H, C-H of phenyl ring), 7.35-7.32 (m, 2H, C-H of phenyl ring), 7.30-7.27 (m, 2H, C-H of phenyl ring), 6.90-6.92 (d, 1H, *J* = 7.8 Hz, C-H of thiophene ring), 6.13 (s, 2H, NH_2), 4.88-4.86 (m, 1H, CH-oxazolidinone ring), 4.20-4.16 (t, 1H, *J* = 9.3 Hz, diastereotopic proton of oxazolidinone ring), 3.89-3.83 (t, 1H, *J* = 6.3 Hz, diastereotopic proton of oxazolidinone ring), 3.68-3.55 (m, 2H, CH_2-aliphatic region), 3.26 (s, 8H, CH_2-piperazine ring); ESI-MS, *m/z* calculated for $C_{22}H_{23}N_4O_2SF$, 426.50; found 427 $[M]^+$.

Synthesis of novel amide oxazolidinone (11a-p)

Part A: general procedure for synthesis of compounds (11a-b): To a stirred solution of (5*S*)-5-(aminomethyl)-3-[4-(4-(benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-oxazolidin-2-one (0.00035 mol) in dichloromethane (10 mL) was added triethyl amine (0.0007 mol) resultant solution cool to 10 to 15 ºC. Appropriate acid chloride (0.00035 mmol) was added at same temperature and maintained for 60 to 90 min. The reaction progress was monitored by TLC and after the completion of reaction; it was diluted with purified water (20 mL) and stirred for 10 to 15 min. The organic and aqueous layers were separated out and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure obtained crude product, which has been purified by silica gel column chromatography to afford the pure oxazolidinone amide (**11a-b**).

(*S*)-*N*-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}acetamide (11a): Cream powder, 0.43 g, yield: 80%; m.p.: 125-127 ºC; IR (KBr, ν_{max}, cm^{-1}): 3068, 2822, 1750; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.25-8.22 (t, 1H, *J* = 4.2 Hz, -NH-C=O), 7.73-7.64 (dd, 2H,*J* = 3.9 & 6 Hz, C-H of phenyl ring), 7.54-7.49 (dd, 1H, *J* =1.8 & 1.8 Hz, C-H of phenyl ring), 7.48-7.46 (d, 1H, *J* =3.9 Hz, C-H of phenyl ring), 7.33-7.29 (t, 1H, *J* = 6 Hz, C-H of thiophene ring), 7.23-7.14 (m, 2H, C-H of phenyl ring), 6.98-6.96 (d, 1H, *J* = 5.7 Hz, C-H of thiophene ring),

4.74-7.68 (m, 1H, CH-oxazolidinone ring), 4.12-4.07 (t, 1H, *J* = 6.9 Hz CH-oxazolidinone ring), 3.74-3.70 (m, 1H, diastereotopic proton of oxazolidinone ring), 3.42-3.39 (t, 2H, *J* =4.2 Hz, CH_2 of near to oxazolidinone ring), 3.23 (s, 8H, CH_2-piperazine), 2.8 (s, 3H, CH_3 of acetyl group); ^{13}C NMR (300 MHz, DMSO-d_6): δ 171, 153, 147, 145, 138, 137, 135, 133, 128, 126, 124, 121, 119, 116, 115, 84, 67, 62, 46, 42, 22; ESI-MS, *m/z* calculated for $C_{24}H_{25}FN_4O_3S$, 468.54; found $[M]^+$ 469.

(*S*)-*N*-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-chloroacetamide (11b): Beige white powder, 0.22 g, yield: 75%; m.p.: 117-119 ºC; IR (KBr, ν_{max}, cm^{-1}): 3300, 2940, 1727; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.69-8.67 (t, 1H, *J* = 6 Hz, -NH-C=O), 7.79-7.77 (d, 1H, *J* = 6 Hz, C-H of phenyl ring), 7.72-7.70 (d, 1H, *J* = 6 Hz, C-H of thiophene ring), 7.59-7.52 (m, 2H, C-H of phenyl ring), 7.38-7.35 (t, 1H, *J* = 3 Hz, C-H of phenyl ring), 7.28-7.20 (m, 2H, C-H of phenyl ring), 7.04-7.02 (d, 1H, *J* = 6 Hz, C-H of thiophene ring), 4.83-4.82 (m, 1H, CH-oxazolidinone), 4.17-4.16 (d, 2H, *J* = 3 Hz, diastereotopic proton of oxazolidinone ring), 3.81-3.78 (dd, 1H, diastereotopic proton of oxazolidinone ring), 3.54 (s, 3H, CH_2 and CH of aliphatic region), 3.29 (s, 8H, CH_2-piperazine); ^{13}C NMR (300 MHz, DMSO-d_6): δ 171, 154, 147, 145, 139, 137, 133, 132, 128, 125, 123, 121, 119, 117, 115, 114, 84, 67, 61, 47, 45, 42; ESI-MS, *m/z* calculated for $C_{24}H_{24}ClFN_4O_3S$, 502.98; found $[M+NH_4]^+$ 521.

Part B: General procedure for synthesis of compounds (11c-p): To a stirred solution of appropriate aromatic or aliphatic carboxylic acid (1.25 mol) in dichloromethane (25 mL), EDC·HCl (1.5 mol), HOBt (1 mol) and triethyl amine (1.5 mol) was added to the reaction mass, formed clear suspension was stirred at ambient temperature for 20 to 30 min. (5*S*)-5-(Aminomethyl)-3-[4-(4-(benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-oxazolidin-2-one (1 mol) was added and stirred for 45 to 60 min. After the completion of reaction by TLC, reaction mass diluted with purified water (25 mL) and stirred for 10 to 15 min. The organic and aqueous layers were separate out and aqueous layer back extracted with 15 mL of dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure; obtained crude product has been purified by silica gel column chromatography to afford the pure oxazolidinone amide (**11c-p**).

(*S*)-5-Chlorothiophene-2-carboxylicacid-{3-[4-(4-(benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}amide (11c): Cream powder, 0.20 g, yield: 60%; m.p.: 189-191 ºC; IR (KBr, ν_{max}, cm^{-1}): 3298, 2914, 1704; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.87 (s, 1H, NH-C=O), 7.67-7.64 (d, 1H, thiophene ring), 7.57-7.40 (m, 4H, C-H of phenyl ring and thiophene ring), 7.38-7.31 (m, 3H, C-H of phenyl ring and thiophene ring), 7.28-7.14 (m, 2H, C-H of phenyl ring and thiophene ring), 4.90-4.87 (m, 1H, CH-oxazolidinone ring), 4.21-4.15 (t, 1H, *J* = 9.3 Hz, diastereotopic proton of oxazolidinone ring), 3.90-3.85 (t, 1H, *J* = 6.3 Hz, diastereotopic proton of oxazolidinone ring), 3.71-3.57 (m, 2H, CH_2-aliphatic region), 3.23 (s, 8H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 163, 155, 147, 146, 142, 136, 134, 133, 131, 130, 128, 126, 122, 120, 119, 118, 116, 109, 107, 84, 67, 62, 44, 42; ESI-MS, *m/z* calculated for $C_{27}H_{24}ClFN_4O_3S_2$, 571.02; found $[M]^+$ 572.

(*S*)-*N*-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-3-phenyl-propionamide (11d): Cream powder, 0.27 g, yield: 85%; m.p.: 128-130 °C; IR (KBr, ν_{max}, cm^{-1}): 3299, 2910, 1750; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.29-8.27 (t, 1H, *J* = 6 Hz, -NH-C=O), 7.73-7.72 (d, 2H, *J* = 3 Hz, C-H of phenyl ring), 7.66-7.65 (d, 1H, *J* = 3 Hz,C-H of phenyl ring), 7.53-7.47 (m, 2H, C-H of phenyl ring), 7.33-7.29 (t, 1H,C-H of phenyl ring), 7.28-7.21 (m, 7H, C-H of phenyl ring), 6.98-6.97 (d, 1H, *J* = 4.5 Hz, C-H of thiophene ring), 4.74-7.68 (m, 1H, CH-oxazolidinone ring), 4.07-4.03 (t, 1H, diastereotopic proton of oxazolidinone ring), 3.66-3.65 (m, 1H, diastereotopic proton of oxazolidinone ring), 3.48-3.44 (m, 2H, CH_2-aliphatic region), 3.24 (s, 8H, CH_2-piperazine ring), 2.44-2.41 (t, 2H, *J* = 9 Hz, CH_2-aliphatic propionic), 2.37-2.34 (t, 2H, *J* = 9 Hz, CH_2-aliphatic propionic); ^{13}C NMR (300 MHz, DMSO-d_6): δ 172, 154, 148, 147, 144, 141, 139, 137, 131, 128, 127, 125, 118, 117, 114, 112, 110, 107, 105, 103, 84, 64, 61, 50, 45, 42, 31; ESI-MS, *m/z* calculated for $C_{31}H_{31}FN_4O_3S$, 558.66; found $[M]^+$ 559.

(*S*)-*N*-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-3-phenyl-acrylamide (11e): White powder, 0.29 g, yield: 90%; m.p.: 119-121 ºC; IR (KBr, ν_{max}, cm^{-1}): 3246, 2921, 1695; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.55-8.51 (t, 1H, *J* = 4.2 Hz, -NH-C=O), 7.73-7.72 (d, 1H, *J* = 5.7 Hz, C-H of thiophene ring), 7.67-7.64 (d, 1H, *J* = 8.1 Hz, C-H of phenyl ring), 7.57-7.40 (m, 6H, C-H of phenyl ring), 7.37-7.35 (t, 1H, *J* = 6 Hz, C-H of thiophene ring), 7.28-7.12 (m, 2H, C-H of phenyl ring), 6.98-6.96 (d, 1H, *J* = 6 Hz, C-H of phenyl ring), 6.72-6.67 (d, 1H, *J* = 15 Hz, CH-*trans* proton of cinnamic acid) 4.83-4.79 (m, 1H, CH-oxazolidinone ring), 4.18-4.12 (t, 1H, *J* = 9 Hz, diastereotopic proton of oxazolidinone ring), 3.80-3.75 (t, 1H, *J* = 6 Hz, diastereotopic proton of oxazolidinone ring), 3.60-3.57 (t, 2H, *J* = 6 Hz, CH_2-aliphatic region), 3.23 (s, 8H, CH_2-piperazine ring); ESI-MS, *m/z* calculated for $C_{31}H_{29}FN_4O_3S$, 556.66, found $[M]^+$ 557.

(*S*)-*N*-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-3-(3,4-difluorophenyl)-acrylamide (11f): White powder, 0.26 g, yield: 75%; m.p.: 179-181 ºC; IR (KBr, ν_{max}, cm^{-1}): 3380, 2966, 1738; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.55-8.53 (t, 1H, *J* = 3 Hz, -NH-C=O), 7.73-7.72 (d, 1H, *J* = 5.7 Hz, C-H of thiophene ring), 7.70-7.65 (m, 2H, Ar-H, C-H of phenyl ring), 7.55-7.45 (m, 5H, C-H of phenyl ring), 7.33-7.29 (t, 1H, *J* = 6 Hz, C-H of thiophene ring), 7.24-7.21 (dd, 1H, *J* = 3 & 3 Hz, C-H of phenyl ring), 7.17-7.14 (t, 1H, *J* = 6 Hz, C-H of phenyl ring), 6.98-6.97 (d, 1H, *J* = 9 Hz, CH-trans proton of cinnamic acid), 4.83-4.80 (m, 1H, CH-oxazolidinone ring), 4.15 (t, 1H, diastereotopic proton of oxazolidinone ring), 3.79-3.77 (t, 1H, *J* = 3 Hz, diastereotopic proton of oxazolidinone ring), 3.61 (t, 2H, CH_2-aliphatic region), 3.23 (s, 8H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 172, 154, 148, 146, 144, 141, 137, 130, 129, 127, 125, 120, 118, 116, 115, 113, 112, 111, 107, 104, 103, 101, 84, 67, 63, 46, 42; ESI-MS, *m/z* calculated for $C_{31}H_{27}F_4N_4O_3S$; 592.63, found $[M]^+$ 593.

(*S*)-*N*-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-3-(3-trifluoromethyl-phenyl)acrylamide (11g): White powder, 0.31 g, yield: 85%; m.p.: 139-141 ºC; IR (KBr, ν_{max}, cm^{-1}): 3310, 2875, 1790; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.58-8.54 (t, 1H, *J* = 6 Hz, NH-C=O), 7.93-7.87 (t, 2H, C-H of phenyl ring), 7.74-7.64 (m, 4H, C-H of phenyl ring), 7.56-7.46 (m, 3H, C-H of phenyl ring), 7.33-7.28 (t, 1H, *J* = 6 Hz, C-H of thiophene ring), 7.24-7.15 (m, 2H, C-H of phenyl ring), 6.98-6.96 (d, 1H, *J* = 7.8 Hz, C-H of thiophene ring), 6.87-6.82 (d, 1H, C-H of phenyl ring), 4.85-4.83 (m, 1H, diastereotopic proton of oxazolidinone ring), 4.18-4.12 (t, 1H, *J* = 9 Hz, diastereotopic proton of oxazolidinone ring), 3.80-3.75 (t, 1H, *J* = 6.6 Hz, diastereotopic proton-oxazolidinone ring), 3.62-3.61 (d, 2H, CH_2-aliphatic region), 3.22 (s, 8H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 172, 154, 148, 146, 144, 142, 139, 137, 131, 128, 126, 125, 123, 121, 119, 117, 116, 113, 112, 110, 105, 103, 102, 101, 64, 66, 62, 46, 46; ESI-MS, *m/z* calculated for $C_{32}H_{28}F_4N_4O_3S$, 624.64; found $[M+ACN]^+$ 665.

(*S*)-N-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzamide (11h): White powder, 0.20 g, yield: 65%; m.p.: 181-183 °C; IR (KBr, ν_{max}, cm^{-1}): 3259, 2958, 1735; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.87-8.84 (t, 1H, *J* = 5.7 Hz, NH-C=O), 7.87-7.85 (d, 2H, *J* = 7.2 Hz, C-H of phenyl ring), 7.74-7.20 (d, 1H, *J* = 5.4 Hz, C-H of thiophene ring), 7.67-7.64 (d, 1H, *J* = 6 Hz, C-H of thiophene ring), 7.57-7.44 (m, 5H, C-H of phenyl ring), 7.33-7.28 (t, 1H, *J* = 8.4 Hz, C-H of phenyl ring), 7.25-7.15 (m, 2H, C-H of phenyl ring), 6.98-6.96 (d, 1H, *J* = 6 Hz, C-H of phenyl ring), 4.89-4.83 (m, 1H, diastereotopic proton of oxazolidinone ring), 4.20-4.14 (t, 1H, *J* = 9 Hz, diastereotopic proton-oxazolidinone ring), 3.90-3.85 (m, 1H, diastereotopic proton of oxazolidinone ring), 3.64-3.63 (d, 2H, CH_2-aliphatic region), 3.23 (s, 8H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 168, 157, 151, 146, 142, 138, 136, 134, 132, 131, 129, 127, 126, 119, 118, 113, 111, 109, 107, 84, 64, 60, 46, 42; ESI-MS, *m/z* calculated for $C_{29}H_{27}FN_4O_3S$, 530.61; found $[M]^+$ 531.

(*S*)-*N*-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-4-fluoro-benzamide (11i): Cream powder, 0.14 g, yield: 45%; m.p.: 160-162 ºC; IR (KBr, ν_{max}, cm^{-1}): 3314, 2940, 1754; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.74 (s, 1H, -NH-C=O), 8.11-8.07 (t, 2H, *J* = 6.9 Hz, Ar-H), 7.60-7.55 (m, 2H, Ar-H),7.55-7.51 (d, 2H, *J* = 2.6 Hz, Ar-H), 7.48-7.33 (m, 4H, Ar-H), 7.24-7.20 (t, 1H, Ar-H), 7.15-7.09 (t, 1H, Ar-H), 4.80-4.74 (m, 1H, CH-oxazolidinone ring), 4.16-4.10 (t, 1H, *J* = 9 Hz, diastereotopic proton-oxazolidinone ring), 3.80-3.75 (dd, 1H, diastereotopic proton-oxazolidinone ring), 3.61 (s, 4H, CH_2-piperazine), 3.49-3.46 (t, 2H, *J* = 5.1 Hz, CH_2-alkyl), 3.20 (s, 4H, CH_2-piperazine); ^{13}C NMR (300 MHz, DMSO-d_6): δ 169, 162, 157, 150, 144, 142, 139, 136, 135, 133, 131, 129, 127, 125, 123, 119, 116, 114, 112, 110, 107, 83, 64, 61, 45, 42; ESI-MS, *m/z* calculated for $C_{29}H_{26}F_2N_4O_3S$, 548.60; found $[M]^+$ 549.

(*S*)-N-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-3,4-difluoro-benzamide (11j): White powder, 0.29 g, yield: 88%; m.p.: 169-171 ºC; IR (KBr, ν_{max}, cm^{-1}): 3365, 2934, 1722; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.71 (s, 1H, -NH-C=O), 8.11-8.07 (m, 2H, C-H of phenyl ring), 7.60-7.10 (m, 9H, C-H of phenyl and thiophene ring), 4.80-4.76 (m, 1H, CH-oxazolidinone ring), 4.16-4.10 (t, 1H, *J* = 9 Hz, diastereotopic proton of oxazolidinone ring), 3.80-3.75 (dd, 1H, diastereotopic proton of oxazolidinone ring), 3.61 (s, 4H, CH_2-piperazine ring), 3.49-3.47 (d, 2H, CH_2-aliphatic region), 3.21 (s, 4H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 169, 156, 155, 153, 151, 144, 142, 141, 139, 136, 135, 132, 131, 128, 126, 125, 119, 117, 114, 112, 107, 84, 66, 61, 45, 42; ESI-MS, *m/z* calculated for $C_{29}H_{25}F_3N_4O_3S$, 566.59; found $[M]^+$ 567.

(*S*)-N-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-2,4-difluorobenzamide (11k): Light yellow powder, 0.28 g, yield: 85%; m.p.: 171-173 ºC; IR (KBr, ν_{max}, cm^{-1}): 3348, 2960, 1740; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.03-9.01 (t, 1H, *J* = 3 Hz, -NH-C=O), 8.11-8.07 (t, 2H, *J* = 7.2 Hz, C-H of phenyl ring), 7.60-7.52 (m, 2H, C-H of phenyl ring), 7.38-7.36 (m, 3H, Ar-H, C-H of phenyl ring), 7.24-7.10 (m, 4H, C-H of phenyl ring), 6.92-6.87 (t, 1H, *J* = 7.2 Hz, C-H of phenyl ring), 6.51-6.47 (t, 1H, *J* = 5.7 Hz, C-H of thiophene ring), 4.80-4.78 (m, 1H, CH-oxazolidinone ring), 4.16-4.10 (t, 1H, *J* = 9 Hz, diastereotopic proton of oxazolidinone ring), 3.80-3.74 (dd, 1H, diastereotopic proton of oxazolidinone ring), 3.61 (s, 4H, CH_2-piperazine ring), 3.47 (d, 2H, CH_2-aliphatic region), 3.21 (s, 4H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 169, 165, 162, 157, 151, 145, 142, 141, 138, 136, 134, 133, 131, 128, 127, 125, 119, 116, 115, 112, 108, 106, 84, 65, 62, 45, 42; ESI-MS, *m/z* calculated for $C_{29}H_{25}F_3N_4O_3S$, 566.59; found $[M]^+$ 567.

(*S*)-Cyclohexane carboxylic acid {3-[4-(4-(benzo[*b*]-thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}amide (11l): Cream powder, 0.24 g, yield: 77%; m.p.: 204-206 ºC; IR (KBr, ν_{max}, cm^{-1}): 3396, 2904, 1733; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.10 (t, 1H, -NH-C=O), 7.74-773 (d, 1H, *J* = 3 Hz, C-H of phenyl ring), 7.67-7.65 (d, 2H, *J* = 6 Hz, C-H of thiophene ring), 7.53-7.47 (m, 2H, C-H of phenyl ring), 7.33-7.30 (t, 1H, *J* = 6 Hz, C-H of phenyl ring), 7.20-7.16 (m, 2H, C-H of phenyl ring), 6.99-6.97 (d, 1H, *J* = 6 Hz, C-H of thiophene ring), 4.74-4.71 (m, 1H, CH-oxazolidinone ring), 4.11-4.08 (t, 1H, *J = 6* Hz, diastereotopic proton of oxazolidinone ring), 3.80-3.74 (dd, 1H, diastereotopic proton of oxazolidinone ring), 3.61 (s, 4H, CH_2-piperazine ring), 3.47 (d, 2H, CH_2-aliphatic region), 3.21 (s, 4H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 172, 157, 150, 145, 139, 133, 132, 129, 127, 125, 123, 116, 114, 111, 108, 106, 84, 64, 62, 61, 45, 43, 42, 31, 28, 23; ESI-MS, *m/z* calculated for $C_{29}H_{33}FN_4O_3S$, 536.66; found [M+Na] 559.

(*S*)-*N*-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-4-methyl-benzamide (11m): Beige white powder, 0.27 g, yield: 85%; m.p.: 173-175 ºC; IR (KBr, ν_{max}, cm^{-1}): 3398, 2960, 1740; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.46 (s, 1H, -NH-C=O), 8.09-8.07 (t, 2H, Ar-H), 7.57-7.45 (m, 3H, Ar-H), 7.26-7.23 (m, 3H, *J* = 7 Hz, Ar-H), 7.16-7.10 (m, 1H, Ar-H), 7.03-7.01 (d,

2H, *J* = 7.2 Hz, Ar-H), 6.44 (s, 1H, Ar-H), 4.78-4.77 (m, 1H, CH-oxazolidinone ring), 4.15-4.09 (t, 1H, *J* = 8.7 Hz, diastereotopic proton-oxazolidinone ring), 3.79-3.74 (t, 1H, diastereotopic proton-oxazolidinone ring), 3.61 (s, 4H, CH_2-piperazine), 3.46 (s, 2H, CH_2-alkyl), 3.21 (s, 4H, CH_2-piperazine), 2.20 (s, 3H, CH_3-phenyl); ^{13}C NMR (300 MHz, DMSO-d_6): δ 169, 157, 151, 145, 142, 139, 135, 134, 133, 131, 139, 137, 125, 123, 119, 117, 113, 112, 109, 107, 84, 64, 60, 45, 42, 23; ESI-MS, *m/z* calculated for $C_{30}H_{29}FN_4O_3S$, 544.63; found $[M]^+$ 544.

(*S*)-*N*-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-4-methoxybenzamide (11n): White powder, 0.29 g, yield: 90%; m.p.: 210-212 ºC; IR (KBr, ν_{max}, cm^{-1}): 3358, 2973, 1750; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.76-8.74 (t, 1H, *J* = 6 Hz, NH-C=O), 7.91-7.89 (d, 2H, *J* = 6 Hz, C-H of phenyl ring), 7.78-7.77 (d, 1H, *J* = 3 Hz, C-H of phenyl ring), 7.72-7.70 (d, 1H, *J* = 6 Hz, C-H of thiophene ring), 7.59-7.52 (m, 2H, C-H of phenyl ring), 7.38-7.35 (t, 1H, *J* = 6 Hz, C-H of thiophene ring), 7.29-7.27 (dd, 1H, *J* = 1.5 & 1.2 Hz 1.5, C-H of phenyl ring), 7.22-7.19 (t, 1H, *J* = 6 Hz, C-H of phenyl ring), 7.06-7.05 (m, 3H, C-H of phenyl ring), 4.92-4.89 (m, 1H, CH-oxazolidinone ring), 4.23-4.19 (t, 1H, *J* = 6 Hz, diastereotopic proton of oxazolidinone ring), 3.93 (m, 1H, diastereotopic proton of oxazolidinone ring), 3.67-3.65 (m, 2H, CH_2-aliphatic region), 3.29 (s, 8H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 168, 163, 156, 150, 145, 142, 138, 135, 134, 132, 131, 128, 126, 125, 123, 118, 116, 113, 111, 108, 106, 84, 64, 62, 60, 46, 42; ESI-MS, *m/z* calculated for $C_{30}H_{29}FN_4O_4S$, 560.63; found $[M]^+$ 561.

(*S*)-*N*-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-chlorobenzamide (11o): White powder, 0.26 g, yield: 80%; m.p.: 151-153 ºC; IR (KBr, ν_{max}, cm^{-1}): 3388, 2896, 1769; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.87 (s, 1H, NH-C=O), 7.73-7.72 (d, 1H, *J* = 7.2 Hz, C-H of thiophene ring), 7.67-7.64 (d, 1H, C-H of phenyl ring), 7.57-7.40 (m, 4H, C-H of phenyl ring), 7.38-7.31 (m, 3H, C-H of phenyl ring), 7.28-7.14 (m, 2H, C-H of phenyl ring), 6.99-6.96 (d, 1H, *J* = 7.8 Hz, C-H of thiophene ring), 4.90-4.87 (m, 1H, CH-oxazolidinone ring), 4.21-4.15 (t, 1H, *J* = *9.3* Hz, diastereotopic proton of oxazolidinone ring), 3.90-3.85 (t, 1H, *J* = 6.3 Hz, diastereotopic proton of oxazolidinone ring), 3.71-3.57 (m, 2H, CH_2-aliphatic region), 3.23 (s, 8H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 169, 158, 149, 144, 141, 139, 137, 135, 134, 133, 131, 129, 127, 125, 122, 119, 115, 113, 111, 108, 84, 67, 61, 46, 42; ESI-MS, *m/z* calculated for $C_{29}H_{26}ClFN_4O_3S$, 565.05; found $[M]^+$ 566.

(*S*)-Pent-4-yonic acid-{3-[4-(4-(benzo[*b*]thiophen-4-yl)-piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}amide (11p): Light yellow powder, 0.23 g, yield: 78%; m.p.: 154-156 ºC; IR (KBr, ν_{max}, cm^{-1}): 3382, 2961, 1755; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.34-8.32 (t, 1H, *J* = 6.9 Hz, NH-C=O), 7.73-7.72 (d, 1H, *J* = 3.3 Hz, C-H of phenyl ring), 7.67-7.65 (d, 1H, *J* = 6 Hz, C-H of thiophene ring), 7.54-7.47 (m, 2H, C-H of phenyl ring), 7.33-7.30 (t, 1H, *J* = 6 Hz, C-H of thiophene ring), 7.22-7.15 (m, 2H, C-H of phenyl ring), 6.99-6.97 (d, 1H, *J* = 6 Hz, C-H of phenyl ring), 4.74-7.71 (m, 1H, CH-oxazolidinone ring), 4.12-4.10 (t, 1H, *J* = *8.5* Hz, diastereotopic proton of oxazolidinone ring), 3.74-3.71 (m, 1H, diastereotopic proton of oxazolidinone ring), 3.48 (s, 2H, CH_2-aliphatic region), 3.24 (s, 8H, CH_2-piperazine ring), 2.70-2.69 (d, 1H, *J* = 3.1 Hz, CH-aliphatic region), 2.35-2.32 (m, 4H, CH_2-aliphatic region); ^{13}C NMR (300 MHz, DMSO-d_6): δ 173, 154, 147, 145, 139, 137, 135, 134, 129, 127, 124, 121, 119, 117, 116, 115, 87, 84, 73, 64, 61, 45, 42, 33, 23; ESI-MS, *m/z* calculated for $C_{27}H_{27}FN_4O_3S$, 506.59, found $[M]^+$ 507.

Part C: General procedure for synthesis of compounds (11q-t): To a stirred solution of (5*S*)-5-(aminomethyl)-3-[4-(4-(benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-oxazolidin-2-one (1 mol) in dichloromethane (25 mL) was added triethyl amine (2 mol) resultant solution cool to 10 to 15 ºC. Appropriate amount of sulfonyl chloride (1 mol) was added at the same temperature and maintained for 60 to 90 min. Reaction progress was monitored by TLC and after the completion of reaction; reaction mass was diluted with purified water (50 mL) and stirred for 10 to 15 min. The organic and aqueous layers were separated out and the aqueous layer back extracted with 25 mL of dichloromethane. Combined organic extracts were dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure obtained crude product, which has been purified by silica gel column chromatography to afford the pure oxazolidinone sulphonamide (**11q-t**).

(*S*)-Ethane sulfonicacid-{3-[4-(4-(benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-amide (11q): Beige white powder, 0.22 g, yield: 70%; m.p.: 159-161 ºC; IR (KBr, ν_{max}, cm^{-1}): 3210, 2856, 1680; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.74-7.73 (d, 1H, *J* = 3.3 Hz, C-H of phenyl ring), 7.67-7.65 (d, 1H, *J* = 4.8 Hz, C-H of thiophene ring), 7.56-7.53 (m, 2H, C-H of phenyl ring), 7.48-7.47 (d, 1H, *J* = 3.3 Hz, C-H of phenyl ring), 7.33-7.30 (t, 1H, *J* = 9 Hz, NH-SO_2), 7.24-7.22 (dd, 1H, C-H of phenyl ring), 7.20-7.18 (d, 1H, *J* = 5.4 Hz, C-H of thiophene ring), 6.99-6.98 (d, 1H, *J* = 4.5 Hz, C-H of phenyl ring), 4.76-4.74 (m, 1H, CH-oxazolidinone ring), 4.13 (s, 1H), 3.84-3.82 (t, 1H, *J* = 6 Hz, diastereotopic proton of oxazolidinone ring), 3.24 (s, 10H, CH_2-piperazine and aliphatic ring), 3.06-3.05 (q, 2H, *J* = 4 Hz, CH_3-aliphatic region), 1.22-1.18 (t, 3H, *J* = 4.5 Hz, CH_3-aliphatic region); ^{13}C NMR (300 MHz, DMSO-d_6): δ 154, 147, 145, 138, 136, 135, 134, 129, 127, 124, 121, 119, 117, 116, 115, 87, 84, 73, 64, 61, 45, 42, 33, 23; ESI-MS, *m/z* calculated for $C_{24}H_{27}FN_4O_4S_2$, 518.62; found $[M]^+$ 519.

(*S*)-N-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-trifluoromethyl-benzenesulfonamide (11r): White powder, 0.31 g, yield: 85%; m.p.: 120-122 ºC; IR (KBr, ν_{max}, cm^{-1}): 3296, 2940, 1650; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.73-7.72 (d, 1H, *J* = 7.2 Hz, C-H of thiophene ring), 7.67-7.64 (d, 1H, C-H of phenyl ring), 7.57-7.40 (m, 4H, C-H of phenyl ring), 7.38-7.31 (m, 3H, C-H of phenyl ring), 7.28-7.14 (m, 2H, C-H of phenyl ring), 6.99-6.96 (d, 1H, *J* = 7.8 Hz, C-H of thiophene ring), 6.42-6.45 (t, 1H, *J* = 9 Hz, NH-SO_2), 4.90-4.87 (m, 1H, CH-oxazolidinone ring), 4.21-4.15 (t, 1H, *J* = 9.3 Hz, diastereotopic proton of oxazolidinone ring), 3.90-3.85 (t, 1H, *J* = 6.3 Hz, diastereotopic proton of oxazolidinone ring), 3.71-3.57 (m, 2H, CH_2-aliphatic region), 3.23 (s, 8H, CH_2-piperazine

ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 154, 146, 143, 141, 139, 137, 134, 133, 131, 139, 127, 125, 123, 121, 119, 118, 116, 114, 112, 84, 64, 62, 46, 42; ESI-MS, *m/z* calculated for $C_{29}H_{26}F_4N_4O_4S_2$, 634.66; found [M + Formic acid]$^+$ 680.

(*S*)-N-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-4-methyl-benzenesulfonamide (11s): White powder, 0.28 g, yield: 85%; m.p.: 185-187 ºC; IR (KBr, ν_{max}, cm^{-1}): 3211, 2945, 1654; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.09-8.07 (t, 2H, Ar-H), 7.57-7.45 (m, 3H, Ar-H), 7.26-7.23 (m, 3H, *J* = 7 Hz, Ar-H), 7.16-7.10 (m, 1H, Ar-H), 7.03-7.01 (d, 2H, *J* = 7.2 Hz, Ar-H), 6.44-6.47(t, 2H, *J* = 9 Hz, NH-SO_2, Ar-H), 4.78-4.77 (m, 1H, CH-oxazolidinone ring), 4.15-4.09 (t, 1H, *J* = 8.7 Hz, diastereotopic proton-oxazolidinone ring), 3.79-3.74 (t, 1H, diastereotopic proton-oxazolidinone ring), 3.61 (s, 4H, CH_2-piperazine), 3.46 (s, 2H, CH_2-alkyl), 3.21 (s, 4H, CH_2-piperazine), 2.20 (s, 3H, CH_3-phenyl); ESI-MS, *m/z* calculated for $C_{29}H_{29}FN_4O_4S_2$, 580.69; found [M+ACN]$^+$ 621.

(*S*)-*N*-{3-[4-(4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}-4-bromo-3-fluoro-benzenesulfonamide (11t): Cream powder, 0.21 g, yield: 55%; m.p.: 199-201 ºC; IR (KBr, ν_{max}, cm^{-1}): 3310, 2965, 1700; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.11-8.07 (m, 2H, C-H of phenyl ring), 7.60-7.10 (m, 9H, C-H of phenyl and thiophene ring), 6.63-6.66(t, 1H, *J* = 9 Hz, NH-SO_2), 4.80-4.76 (m, 1H, CH-oxazolidinone ring), 4.16-4.10 (t, 1H, *J* = 9 Hz, diastereotopic proton of oxazolidinone ring), 3.80-3.75 (dd, 1H, diastereotopic proton of oxazolidinone ring), 3.61 (s, 4H, CH_2-piperazine ring), 3.49-3.47 (d, 2H, CH_2-aliphatic region), 3.21 (s, 4H, CH_2-piperazine ring); ^{13}C NMR (300 MHz, DMSO-d_6): δ 157, 155, 145, 143, 141, 139, 136, 133, 132, 131, 129, 126, 125, 123, 122, 121, 119, 117, 114, 113, 110, 84, 67, 62, 46, 42; ESI-MS, *m/z* calculated for $C_{28}H_{25}BrF_2N_4O_4S_2$, 664.55; found [M]$^+$ 665.

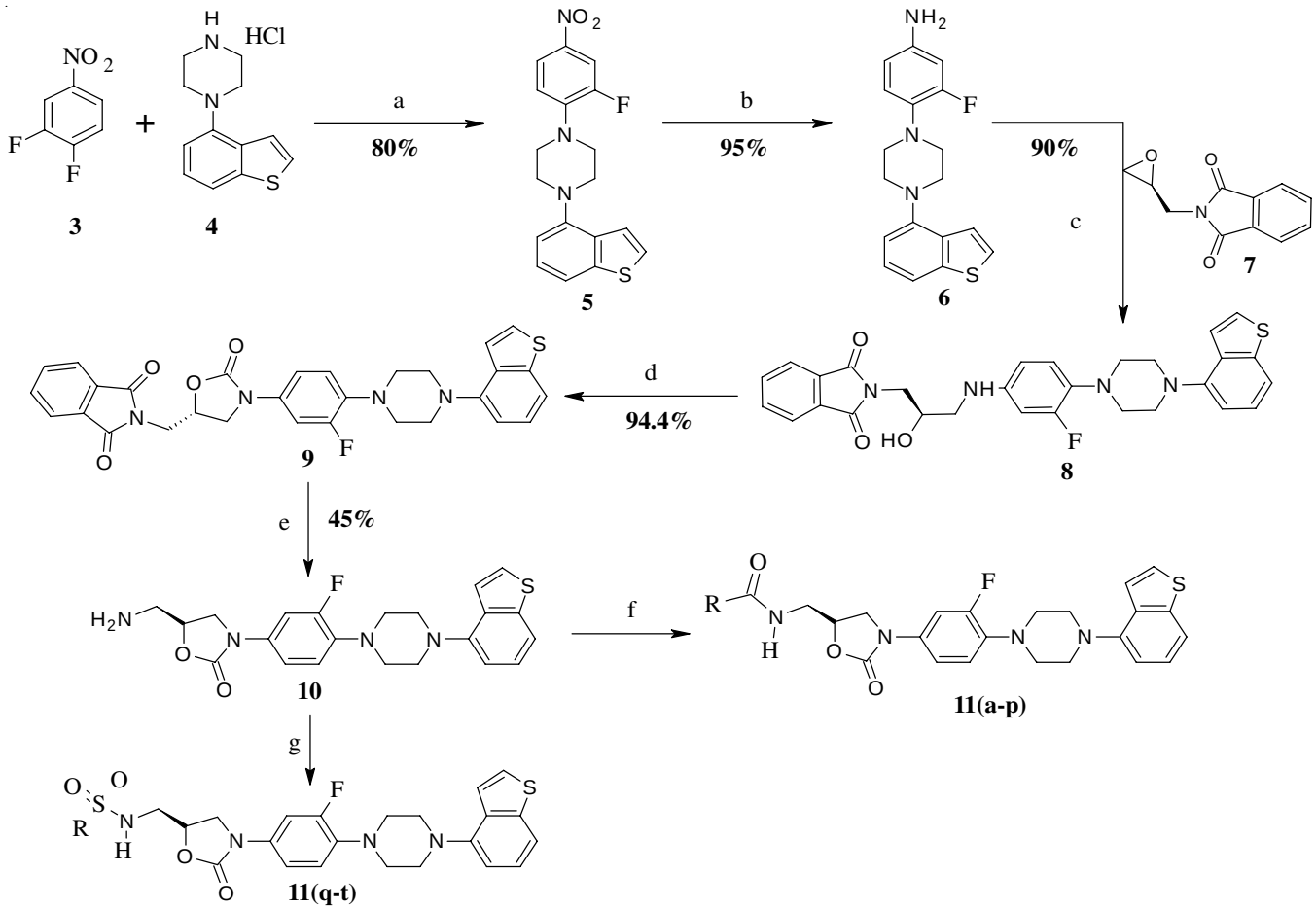
Biological activity: The newly synthesized molecules (**11a-t**) were screened for their *in vitro* antimicrobial activity using Muller-Hinton broth method against Gram-positive pathogens like *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 25923 and *Streptococcus pyogens* ATCC 8668 [40]. The standard strains required for antimicrobial assay were obtained from microbial type culture collection (MTCC) at the NCIM, Pune, India. The bacterial suspensions were spread over nutrient agar plates and the well with of 6 mm diameter was punched with sterile cork borer. The compounds were tested at concentration 25 µg/mL in DMSO for bioassay. Linezolid was used as standard to evaluate the potency of the tested compounds in DMSO under the same conditions. The zone of inhibition in mm were compared after 24 h of incubation at 37 °C and measured as per National Committee for Chemical Laboratory Standards. Linezolid was used as a reference drug and the obtained results were expressed in terms of zone of inhibition (mm) values.

RESULTS AND DISCUSSION

The synthetic route for target compounds **11a-11t** outlined in **Scheme-I**. Briefly, 1-(1-benzo[*b*]thiophen-4yl)piperazine hydrochloride (**4**) reacted with 3,4-difluoronitrobenzene (**3**) in acetonitrile at reflux temperature containing K_2CO_3 as base to give nitro compound (**5**). The obtained nitro compound converted into primary amine (**6**) through radical mechanism by using iron and aq. NH_4Cl at mild reflux temperature in ethanol as a solvent for 6 to 8 h. Further, refluxing the obtained primary amine with 2-[(2*S*)-oxiran-2-ylmethyl]-1*H*-isoindole-1,3(2*H*)-dione in isopropyl alcohol, for 10 to 12 h to get hydroxy amine compound (**8**). The key oxazolidinone intermediate (**9**), obtained after the reaction of hydroxy amine with *N*,*N*′-carbonyl-diimidazole (CDI) under basic condition at room temperature in dichloromethane. Deprotection of phthalamide group with 40% aq. methyl amine solution in methanol at reflux temperature produced amine (**10**). Finally, targeted compounds obtained after the treatment of compound **10** with appropriate acetyl chlorides, acids and sulphonyl chlorides by customary approach. The chemical constitution of all above compounds was proven with the help of spectroscopic techniques such as NMR, IR spectroscopy and mass spectrometry.

IR spectrum of nitro compound **5** confirmed the presence of nitro functional group with peaks at 1380 and 1562 cm^{-1}. Moreover, proton NMR of this compound, revealed the appearance of proton peaks at δ 8.06 to 8.03 ppm due to presence of nitro group. The chemical conversion of nitro (**5**) to amine (**6**) was elucidated by IR spectra, which confirmed the presence of NH_2 peaks of compound at 3314 and 3215 cm^{-1}. In addition, the ^{1}H NMR of this compound revealed the presence of peak at 5.03 ppm corresponding to NH_2 group. The formation of compound **8** clarified by the presence of NH and OH functional groups at 3365 to 3300 cm^{-1}. Additionally, the ^{1}H NMR of this compound showed the peak at δ 5.55 ppm corresponding to OH, in addition to the presence of a peak at δ 5.16 ppm concerned with NH group. The construction of oxazolidinone (**9**) elucidated by the presence of CO peak in the range of 1718 to 1740 cm^{-1}. Proton NMR indicated CH_2 group for diastereotopic protons of oxazolidinone at δ 4.22 to 4.16 ppm and 4.05 to 3.97 ppm. Deprotection of phthalamide and generation of primary amine (**10**) confirmed by IR spectra, which showed the NH_2 peak at 3434 cm^{-1}. Additionally, the protons related to the phthalamide disappeared from the ^{1}H NMR spectra, also supports for the complete deprotection of phthalamide group.

Biological activity: Among the synthesized compounds **11a**, **11f**, **11g**, **11n** and **11p** exhibited comparable antimicrobial activity. Further, the structural activity relationship study was investigated for these compounds (**11a-t**). From antimicrobial activity data (Table-1), it is observed that compound **11a** with acetyl group exhibited more potent activity than other synthesized compounds. Compound **11n** having 4-methoxy substitution on phenyl ring showed good activity but less than **11a**. Removal of methoxy group from phenyl ring resulted **11h** showed the lower activity than **11n**. However, replacement of methoxy group **11n** with trifluromethyl group on the phenyl ring resulted compound **11g**, which showed lower activity than **11n**. Introduction of difluro substitution at 3 and 4-positions on the phenyl ring resulted **11f** showed loss of activity compared to **11n**. Furthermore, sulphonamide derivatives showed the negative results corresponding to the antimicrobial activity against the tested pathogens.



Reagents and conditions: (a) K_2CO_3, ACN, 75-80 °C, 6-8 h; (b) Fe/aq.NH_4Cl, ethanol, 75-80 °C, 6-8 h; (c) compound 7, IPA, 75-80 °C, 10-12 h; (d) CDI, K_2CO_3, DCM, 25-30 °C, 10-12 h; (e) 40 % aq. methyl amine solution, methanol, 25-30 °C, 1-2 h; (f) Aliphatic and aromatic acid, TEA, EDC·HCl, HOBT, DCM, 25-30 °C, 1-2 h or Aliphatic and aromatic acid chloride, TEA, DCM, 25-30 °C, 1-2 h; (g) Aliphatic and aromatic sulphonyl chloride, TEA, DCM, 25-30 °C, 1-2 h

Scheme-I: Synthesis of novel 1-(1-benzo[*b*]thiophen-4-yl)piperazine oxazolidinones (**11a-t**)

TABLE-1
ZONE OF INHIBITION (DIAMETER) mm OF NEWLY SYNTHESIZED COMPOUNDS **11a-t**

Compound	Zone of inhibition in mm at 25 µg/mL			Compound	Zone of inhibition in mm at 25 µg/mL		
	B. subtilis[a]	*S. aureus*[b]	*S. pyogens*[c]		*B. subtilis*[a]	*S. aureus*[b]	*S. pyogens*[c]
11a	14 ± 0.2	20 ± 0.2	12 ± 0.2	**11l**	10 ± 0.2	12 ± 0.2	13 ± 0.2
11b	11 ± 0.2	12 ± 0.2	12 ± 0.2	**11m**	10 ± 0.2	12 ± 0.2	12 ± 0.2
11c	11 ± 0.2	12 ± 0.2	12 ± 0.2	**11n**	13 ± 0.2	13 ± 0.2	18 ± 0.2
11d	11 ± 0.2	13 ± 0.2	13 ± 0.2	**11o**	13 ± 0.2	14 ± 0.2	14 ± 0.2
11e	9 ± 0.2	12 ± 0.2	11 ± 0.2	**11p**	13 ± 0.2	14 ± 0.2	14 ± 0.2
11f	13 ± 0.2	13 ± 0.2	13 ± 0.2	**11q**	13 ± 0.2	12 ± 0.2	12 ± 0.2
11g	11 ± 0.2	13 ± 0.2	15 ± 0.2	**11r**	10 ± 0.2	15 ± 0.2	13 ± 0.2
11h	11 ± 0.2	12 ± 0.2	13 ± 0.2	**11s**	11 ± 0.2	13 ± 0.2	14 ± 0.2
11i	11 ± 0.2	12 ± 0.2	14 ± 0.2	**11t**	12 ± 0.2	11 ± 0.2	11 ± 0.2
11j	11 ± 0.2	12 ± 0.2	14 ± 0.2	Linezolid	23 ± 0.2	24 ± 0.2	21 ± 0.2
11k	11 ± 0.2	12 ± 0.2	13 ± 0.2	Eperezolid	18 ± 0.2	15 ± 0.2	16 ± 0.2

Bacilus subtilis ATCC 6633; *Staphyloccus aureus* ATCC 25923 and *Streptococcus pyogens* ATCC 8668; Concentration of linezolid 25 µg/mL; Inhibition zone = 9-15 mm: slight activity; 16-20 mm: moderate activity; 21 -25 mm: high activity; >26 mm: excellent activity

Conclusion

In conclusion, a series of novel (*S*)-N-{3-[4-(4-(benzo[*b*]-thiophen-4-yl)piperazin-1-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl}amides (**11a-11p**) and sulphonamides (**11q-11t**) derivatives were synthesized. The synthesized compounds were further evaluated for their *in vitro* antimicrobial for the first time. As a result, several derivatives exhibited good antimicrobial activity in comparison with used reference drug. Among the synthesized compounds **11a**, **11f**, **11g**, **11n** and **11p** exhibited comparable antimicrobial activity. However,

sulphonamide derivatives showed the negative results corresponding to the antimicrobial activity against the tested pathogens.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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