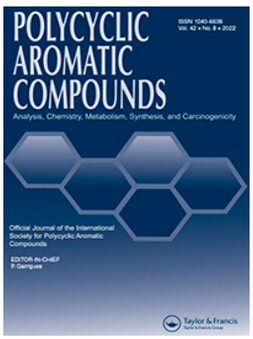

Polycyclic Aromatic Compounds

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Synthesis and Evaluation of Novel (5S)-5-(Aminomethyl)-3-[4-(6,7-Dihydrothieno[3,2-*c*]Pyridin-5(4*H*)-yl)Phenyl]-1,3-Oxazolidin-2-One Derivatives as Potent Antimicrobial Agents

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Synthesis and Evaluation of Novel (5S)-5-(Aminomethyl)-3-[4-(6,7-Dihydrothieno[3,2-*c*]Pyridin-5(4*H*)-yl)Phenyl]-1,3-Oxazolidin-2-One Derivatives as Potent Antimicrobial Agents

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ABSTRACT

In the present work, a series of novel oxazolidinone derivatives containing thieno-pyridine ring system (**11a–n**) were synthesized in six steps. Synthesis of amino oxazolidinone scaffold (**10**) involved nucleophilic substitution of thienopyridine (**4**) with P-chloro-nitrobenzene (**3**) in dimethyl formamide at 65 °C give nitro compound (**5**) which was further reduced in catalytic hydrogenation condition using Raney-Nickel in isopropyl alcohol afforded amine (**6**). Reaction of compound (**6**) with 2-[(2S)-oxiran-2-ylmethyl]-1H-isoindole-1,3(2H)-dione (**7**) at mild reflux condition in isopropyl alcohol gives compound (**8**). Hydroxy amine compound (**8**) further undergo carbonyl insertion reaction with 1, 1′-carbonylbis(1H-imidazole) afforded oxazolidinone compound (**9**). The de-protection of phthalamide group of compound (**9**) carried by treating with aqueous solution of hydrazine hydrate in methanol at room temperature give compound (**10**). Finally, compound (**10**) reacts with acetyl chloride, carboxylic acid, sulfonyl chloride and chloro format by customary method provided amides, sulfonamide and carbamate derivative of (5S)-5-(aminomethyl)-3-[4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)phenyl]-1,3-oxazolidin-2-one.

The developed synthetic approach was operationally simple and high yielding. The structures of the synthesized compounds were elucidated by IR, MS, ^{1}H and ^{13}C-NMR. Synthesized compounds (**11a–n**) were tested for antibacterial activity against a panel of Gram-positive bacteria comprising *Staphylococcus aureus (ATCC5638)*, *Streptococcus pyogenes (ATCC12344)*, *Bacillus subtilis (ATCC6051)*, *Bacillus pumilus (ATCC27142)*, and *Enterococcus faecalis (NCIM5253)*. The investigation of antimicrobial screening data revealed that, most of the compounds tested have demonstrated sensible to good bacterial activity. In summary, preliminary results of activity indicate that, acetyl derivative (**11a**), methane sulfonamide derivative (**11c**) and *p*-toluene sulfonamide derivative (**11e**) found to be good activity and di-(methane sulfonamide) derivative (**11d)** showed comparable activity to reference drug substances.

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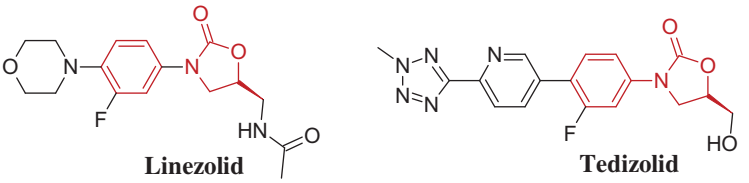


Figure 1. Structure of oxazolidinone.

Introduction

Growing resistance power of microorganisms is now a worldwide anxiety and recognized as a major global public health problem, so that the finding of new antibacterial agent has become gradually critical. This rising problem has reintroduced attention of scientist for discovery of new antibiotic structural classes that inhibit or kill by novel mechanisms. Clearly, this encourage the scientists for discovery and development to design an effective agents against the emerging problematic Gram-positive pathogens, including methicillin-resistant *staphylococcus aureus* (MRSA), penicillin-resistant *streptococci*, and vancomycin-resistant *enterococcus* which are responsible for one third of nosocomial infections.[1]

Oxazolidinones are the totally synthetic antibacterial agents and have a novel mechanism of action wherein bacterial protein synthesis was inhibited at a very early stage prior to chain initiation.[2–6] Linezolid (**1**) is the first drug of this class and approved by various regulatory authorities for the treatment of infections associated with vancomycin-resistant *enterococcus Faecium* including blood stream infections, methicillin-resistant *S. aureus* and penicillin resistant *pneumococci.*[7–8] Tedizolid (**2**) is the second drug of this class and recently approved for the treatment of acute bacterial skin and skin structure infections also known as complicated skin and skin-structure infections (cSSSIs) (Figure 1).[9–10]

At present, utmost efforts are focused on substituted phenyl oxazolidinones since phenyl group is essential for activity (Figure 2). Substitution at phenyl ring is flexible and activity may vary as per substitution. Pyridine derivatives are one of the most important organic compounds used greatly in the pharmaceutical industry and reported as antifungal, antimicrobial, anti-inflammatory, and anticancer agent.[11–14] Thienopyridines are most important fused heterocyclic compounds and are reported as drugs namely: Prasugrel and Clopidogrel, as irreversible ADP receptor/$P2Y_{12}$ inhibitors which are used for their antiplatelet activity.[15–16] Thienopyridines are also reported as anticancer, antibacterial, antifungal, anti-inflammatory and antimicrobial.[17–27]

By considering the above facts and their increasing importance in pharmaceutical and biological field, it was considered of interest to synthesize some new chemical entities incorporating the thienopyridine as a substituent at 4-position of phenyl ring of oxazolidinone wherein two active pharmacophores are present in a single molecular frame.

In the present work, we report herein synthesis of new thienopyridine oxazolidinones (**11a–n**) in six steps and study of their antibacterial activities against representative's strains of Gram-positive bacteria's: *S. aureus* (*ATCC5638*), *Streptococcus pyogenes* (*ATCC12344*), *Bacillus subtilis* (*ATCC6051*), *Bacillus pumilus* (*ATCC27142*), and *Enterococcus faecalis* (*NCIM5253*) by agar diffusion method (Schemes 1 and 2).

Materials and methods

All materials were obtained from commercial suppliers and were used without further purification. All reactions were monitored by thin layer chromatography (TLC) on 25 mm silica gel 60 F254 plates (Merck, Darmstadt, Germany) using UV light (254 and 366 nm) for detection. All synthesized compounds were purified by column chromatography using appropriate solvent

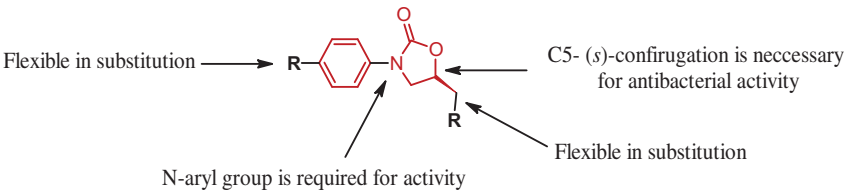
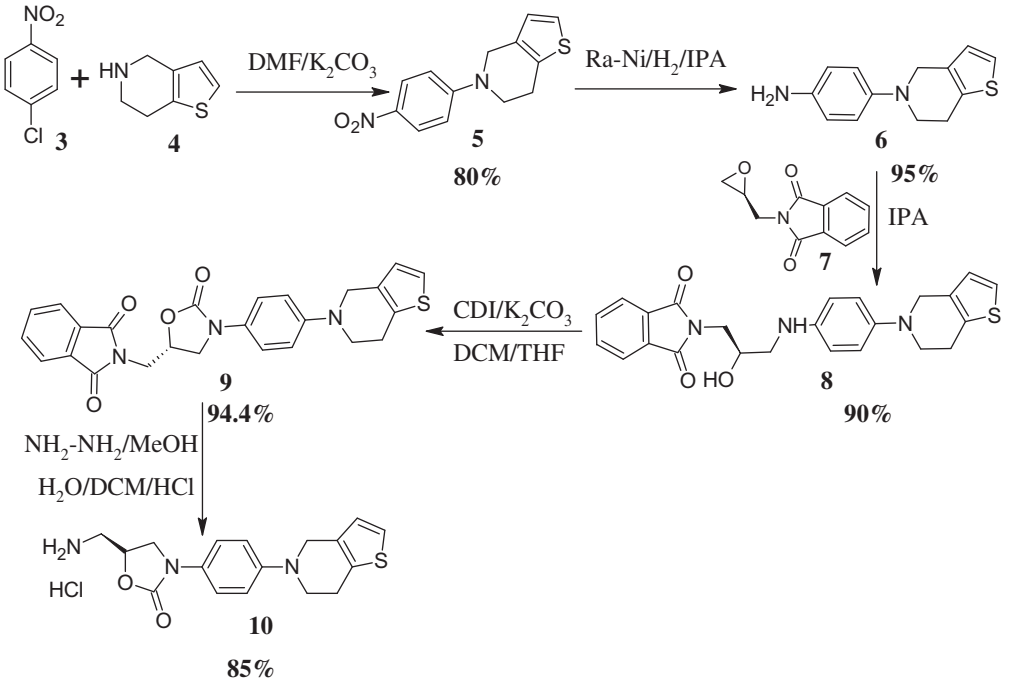
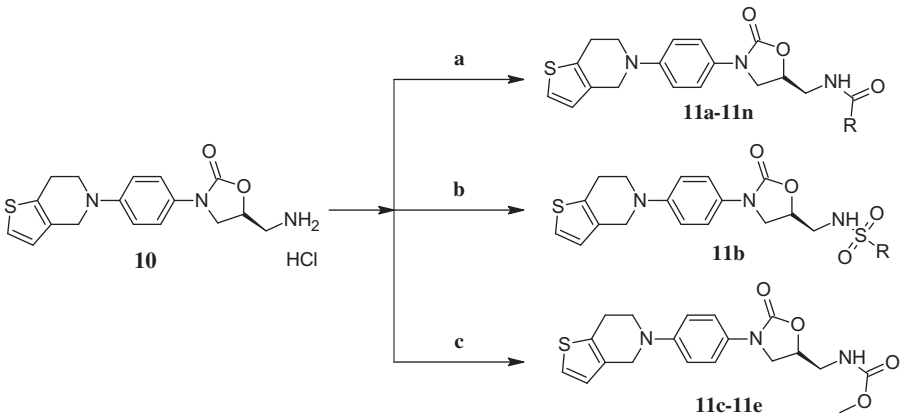


Figure 2. General skeleton of oxazolidinone antibacterial agents.[28]



Scheme 1. Synthesis of intermediate **10**.



Scheme 2. (a) Carboxylic acid, TEA, EDC.HCl, HOBT, DCM, 25 °C, 1–2 h or Carboxylic acid chloride, TEA, DCM, 25 °C, 1–2 h; (b) Aliphatic and aromatic sulfonyl chloride, TEA, DCM, 25–30 °C, 1–2 h. (c) Aliphatic chloro format, TEA, DCM, 25 °C, 1–2 h.

system. ^{1}H NMR and ^{13}C NMR spectral data were recorded using BRUKER AVANCE II 400 MHz and 300 MHz chemical shifts were reported in ppm relative to Tetramethylsilane (TMS) and multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Mass spectra were recorded on a Shimadzu Nexara 2020 LC-MS.

All the bacterial cultures were procured from NCL, Pune, India. The antibacterial activity of the synthesized compounds was evaluated by the agar well diffusion method using Mueller-Hinton agar medium.[29] Zone of inhibition measured for compound **11a–n** against Gram-positive bacterial strain comprising *S. aureus* (*ATCC5638*), *S. pyogenes* (*ATCC12344*), *B. subtilis* (*ATCC6051*), *B. Pumilus* (*ATCC27142*), and *E. faecalis* (*NCIM5253*). The compounds were diluted in DMSO with required concentration for bioassay. DMSO was also loaded as control while Linezolid and Tedizolid were used as standards to evaluate the potency of the tested compounds under the same conditions.

Experimental section

5-(4-Nitrophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (5)

To a solution of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine **4** (50.0 g, 0.359 mol) and potassium carbonate (59.0 g, 0.718 mol) in dimethyl formamide (250.0 mL), 4-chloronitrobenzene **3** (56.1 g, 0.359 mol) was added and mixture was heated to 65 °C for 12 h. Completion of reaction was monitored by TLC, after completion of reaction, mixture was cooled to 30 °C and water (500.0 mL) was slowly added to mixture. Precipitated solid was filtered and washed with water (50.0 mL) to afford compound **5** as a yellow solid. (74.79 g, 80.0%). ^{1}H-NMR (DMSO-d_6): δ 8.07 (d, 2H, $J = 8.7$ Hz, alpha to nitro group), 7.37 (d, 1H, $J = 4.8$ Hz, alpha in thiophene ring), 7.10 (d, 2H, $J = 9$ Hz, beta to nitro group), 6.93 (d, 1H, $J = 4.5$ Hz, beta in thiophene ring), 4.57 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.96 (t, 2H, $J = 5.1$ Hz, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.94 (t, 2H, $J = 5.4$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (300 MHz, DMSO-d_6): δ 154.2, 136.6, 132.94, 132.47, 125.81 (2C's Ar-C), 125.33, 123.65, 112.48 (2C's Ar-C), 47.08, 44.64, 24.10 ppm; ESI-MS, *m/z* calculated for $C_{13}H_{12}N_2O_2S$, 260.3, found 261 $[M+1]^+$, 302 $[M+ACN]^+$.

4-(6,7-Dihydrothieno[3,2-c]pyridin-5(4H)-yl)aniline (6)

A solution of 5-(4-nitrophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine **5** (70.0 g, 0.268 mol) in isopropanol (350.0 mL) and raney-nickel (7.0 g) was charged in autoclave. Reaction mass was maintained under 3–5 kg/cm hydrogen pressure at 40 °C till completion of reaction. After completion of reaction, filtered the reaction mass through celite bed, and obtained filtrated was concentrated to finish light yellow solid of **6** (58.8 g, 95.0%). *Note*: amine compound has very less stability and for analysis purpose it was converted into its hydrochloride salt. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.38 (d, 1H, $J = 6$ Hz, beta to amine group), 7.28 (bs, 4H), 6.92 (d, 1H, $J = 5.1$ Hz), 5.16 (bs, 3H), 4.38 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.70 (t, 2H, $J = 6$ Hz, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.99 (s, 2H); ^{13}C-NMR (300 MHz, DMSO-d_6): δ 146.1, 132.3, 131.4, 126.9, 125.36 (2C's Ar-C), 124.11 (3C's Ar-C), 118.86, 50.5, 48.69, 23.59 ppm; ESI-MS, *m/z* calculated for $C_{13}H_{14}N_2S$, 230.3, found 230 $[M]^+$.

2-{3-[4-(6,7-Dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenylamino]-2-hydroxy-propyl}-isoindole-1,3-dione (8)

To a solution of 4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)aniline **6** (55.0 g, 0.238 mol) in isopropanol, 2-[(2S)-oxiran-2-ylmethyl]-1H-isoindole-1,3(2H)-dione **7** (53.3 g, 0.207 mol) was added.

Reaction mass was heated to 80 °C and maintained for 24 h. Cooled the reaction to 30 °C, solid was filtered, washed with isopropanol and dried to obtain beige colored solid of **8** (93.1 g, 90.0%). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.88–7.81 (m, 4H, Phenyl proton), 7.29 (d, 1H, $J = 5$ Hz), 6.85–6.83 (m, 3H), 6.57 (d, 2H, $J = 8.7$ Hz), 5.13 (d, 1H, $J = 3$ Hz), 5.0 (bs, 1H), 4.0–3.99 (m, 3H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.65–3.58 (m, 2H), 3.34–3.32 (s, 2H), 3.13–3.09 (m, 1H), 2.98–2.94 (m, 1H), 2.86 (bs, 2H); ^{13}C-NMR (300 MHz, DMSO-d_6): δ 168.08, 142.8, 141.9, 134.2, 133.9 (2C's Ar-C), 132.9, 131.8 (2C's Ar-C), 125.4 (2C's Ar-C), 122.8 (3C's Ar-C), 118.4 (2C's Ar-C), 113.2 (2C's Ar-C), 66.4, 50.1, 48.5, 48.1, 42.4, 24.9 ppm; ESI-MS, *m/z* calculated for $C_{24}H_{23}N_3O_3S$, 433.5, found 434 $[M+1]^+$, 475 $[M+ACN]^+$.

2-{3-[4-(6,7-Dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-isoindole-1,3-dione (9)

To a solution of 2-{3-[4-(6,7-Dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenylamino]-2-hydroxy-propyl}-isoindole-1,3-dione **8** (90.0 g, 0.207 mol) and potassium carbonate (42.9 g, 0.311 mol) in dichloromethane, 1, 1′-carbonylbis(1H-imidazole) (50.3 g, 0.310 mol) was added and stirred the mixture at 30 °C for 6 h. completion of reaction was monitored by TLC, filtered the inorganic solid and concentrated the filtrate to obtain residue. Obtained residue was crystallized in tetrahydrofuran to afford off white solid of **9** (90.0 g, 94.4%). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.93–7.88 (m, 4H, phenyl proton), 7.36–7.32 (m, 3H, $J = 8.7$ Hz, alpha to oxazolidinone ring), 7.05–7.02 (d, 2H, $J = 9$ Hz, beta to oxazolidinone ring), 6.91 (d, 1H, $J = 6$ Hz, beta proton of thiophene ring) 4.90–4.88 (m, 1H, CH of oxazolidinone ring), 4.26 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.15 (t, 1H, $J = 9$ Hz, diastereotopic proton-oxazolidinone ring), 4.02–3.84 (m, 3H, diastereotopic proton-oxazolidinone ring), 4.56 (t, 2H, $J = 6$ Hz, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.89 (bs, 2H, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (300 MHz, DMSO-d_6): δ 167.81, 153.98, 146.9, 134.56 (2C's Ar-C), 133.37, 132.98, 131.48 (2C's Ar-C), 129.71, 125.5, 123.24 (2C's Ar-C), 123.14, 119.92 (2C's Ar-C), 115.76 (2C's Ar-C), 69.84, 48.34, 48.21, 46.68, 40.57, 24.4 ppm; ESI-MS, *m/z* calculated for $C_{25}H_{21}N_3O_4S$, 459.5, found 458 $[M-1]^-$.

(5S)-5-(aminomethyl)-3-[4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)phenyl]-1,3-oxazolidin-2-one (10)

To a solution of 2-{3-[4-(6,7-Dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-isoindole-1,3-dione **9** (85.0 g, 0.184 mol) in methanol (200.0 mL), 98% aqueous solution of hydrazine hydrate (30.0 g, 0.91 mol) was added at 30 °C. Mixture was heated for 1 h at 60 °C and cooled to 25 °C. Reaction mixture was diluted with water (500.0 mL) and product was extracted in dichloromethane (2 × 100 mL). The obtained dichloromethane layer was washed with water (100.0 mL) and concentrated to provide light brown colored solid of **10** (51.7 g, 85.0%). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.42 (d, 2H, $J = 9$ Hz, alpha to oxazolidinone ring), 7.32 (d, 1H, $J = 5.1$ Hz, alpha proton of thiophene ring), 7.03 (d, 2H, $J = 9$ Hz, beta to oxazolidinone ring), 6.91 (d, 1H, $J = 5.1$ Hz, beta proton of thiophene ring), 4.58–4.53 (m, 1H, CH of oxazolidinone ring), 4.23 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.95 (t, 1H, $J = 9$ Hz), 3.83–3.79 (m, 1H, diastereotopic proton-oxazolidinone ring), 3.55 (t, 2H, $J = 6$ Hz, CH_2 aliphatic region), 2.9–2.67 (t, 2H, $J = 3$ Hz, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.81 (t, 2H, $J = 6$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine) and 1.73 (bs, 2H, -NH_2); ^{13}C-NMR (300 MHz, DMSO-d_6): δ 154.5, 146.6, 133.3, 132.9, 130.2, 125.4, 123.1, 119.4 (2C's Ar-C), 115.8 (2C's Ar-C), 73.7, 48.4, 47.3, 46.7, 44.3, 24.3 ppm; ESI-MS, *m/z* calculated for $C_{17}H_{19}N_3O_2S$, 329.4, found 330 $[M+1]^+$, 371] $M+ACN]^+$.

N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (11a)

To a solution of 5-aminomethyl-3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]- oxazolidin-2-one **10** (2.0 g, 0.0060 mol) and triethyl amine (1.2 g, 0.012 mol) in dichloromethane (20.0 mL), acetyl chloride (0.56 g, 0.0072 mol) was added and mixture was stirred for 4–5 h at 25 °C. Completion of reaction was monitored by TLC, after completion of reaction, mixture was diluted with water (25.0 mL) and DCM layer was separated. Obtained DCM layer was concentrated to get crude residue and was purified by column chromatography using DCM: MeOH solvent system to obtain white colored solid of **11a**. (1.95 g, 86.6%); MP: 237–239 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.25 (t, 1H, $J = 6$ Hz, NH of amide), 7.37 (d, 2H, $J = 9.2$ Hz, alpha to oxazolidinone ring), 7.26 (d, 1H, $J = 4$ Hz, alpha proton of thiophene ring), 7.01 (d, 2H, $J = 8$ Hz, beta to oxazolidinone ring), 6.88 (d, 1H, $J = 4$ Hz, beta proton of thiophene ring), 4.69–4.65 (m, 1H, CH of oxazolidinone ring), 4.23 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.03 (t, 1H, $J = 8$ Hz, diastereotopic proton-oxazolidinone ring), 3.71–3.67 (m, 1H, diastereotopic proton-oxazolidinone ring), 3.55 (t, 2H, $J = 8$ Hz, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.42–3.37 (m, 2H, CH_2 of aliphatic region), 2.89 (t, 2H, $J = 8$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 1.85 (s, 3H, CH_3 of acetyl group); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 170.02, 154.22, 146.75, 133.21, 132.91, 129.91, 125.3, 122.96, 119.65 (2C's Ar-C), 115.77 (2C's Ar-C), 71.26, 48.39, 47.56, 46.79, 41.46, 24.44, 22.39 ppm; ESI-MS, *m/z* calculated for $C_{19}H_{21}N_3O_3S$, 371.45, found 372 $[M + 1]^+$.

N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-carbamic acid methyl ester (11b)

Off white solid; Yield: 75%; MP: 229–231 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.49 (t, 1H, $J = 4$ Hz, NH of amide), 7.38 (d, 2H, $J = 8$ Hz, alpha to oxazolidinone ring), 7.26 (d, 1H, $J = 4$ Hz, alpha proton of thiophene ring), 7.02 (d, 2H, $J = 8.8$ Hz, beta to oxazolidinone ring), 6.88 (d, 1H, $J = 4$ Hz, beta proton of thiophene ring), 4.68–4.64 (m, 1H, CH of oxazolidinone ring), 4.23 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.04 (t, 1H, $J = 8$ Hz, diastereotopic proton-oxazolidinone ring), 3.75–3.71 (m, 1H, diastereotopic proton-oxazolidinone ring), 3.57–3.55 (m, 5H, CH_2 and CH_3 of aliphatic region), 3.37–3.33 (m, 2H, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.91–2.88 (t, 2H, $J = 8$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 157.14, 154.21, 146.75, 133.22, 132.91, 129.92, 125.31, 122.97, 119.65 (2C's Ar-C), 115.77 (2C's Ar-C), 71.10, 51.46, 48.39, 47.46, 46.79, 43.29, 24.43 ppm; ESI-MS, *m/z* calculated for $C_{19}H_{21}N_3O_4S$, 387.4, found 388 $[M + 1]^+$.

N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-methanesulfonamide (11c)

White solid; Yield: 85%; MP: 239–241 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.49 (t, 1H, NH of amide), 7.39 (d, 2H, $J = 8$ Hz, alpha to oxazolidinone ring), 7.24 (d, 1H, $J = 4$ Hz, alpha proton of thiophene ring), 7.02 (d, 2H, $J = 4$ Hz, beta proton of thiophene ring), 6.89–6.87 (d, 1H, $J = 8$ Hz, beta to oxazolidinone ring), 4.47–4.40 (m, 1H, CH of oxazolidinone ring), 4.24 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.06 (t, 1H, $J = 8$ Hz, diastereotopic proton-oxazolidinone ring), 3.81–3.78 (m, 1H, diastereotopic proton- oxazolidinone ring), 3.56 (t, 2H, $J = 4$ Hz, CH_2 of aliphatic region), 3.28–3.24 (m, 2H, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.93 (s, 3H, CH_3 of sulfonyl group), 2.89 (t, 2H, $J = 4$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 154.12, 146.78, 133.17, 132.90, 129.85, 125.26,

122.93, 119.66 (2C's Ar-C), 115.79 (2C's Ar-C), 71.09, 48.40, 47.22, 46.82, 45.04, 24.45 ppm; ESI-MS, *m/z* calculated for $C_{18}H_{21}N_3O_4S_2$, 407.5, found 408 $[M+1]^+$.

N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-di-(methanesulfonamide) (11d)

White solid; Yield: 88%; MP: 211–212 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.38 (t, 2H, $J=8$ Hz, alpha to oxazolidinone ring), 7.26 (d, 1H, $J=4$ Hz, alpha proton of thiophene ring), 7.02 (d, 2H, $J=8.2$ Hz, beta to oxazolidinone ring), 6.87 (d, 1H, $J=5.2$ Hz, beta proton of thiophene ring), 4.89–4.84 (m, 1H, CH of oxazolidinone ring), 4.25 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.16–4.07 (m, 2H, diastereotopic proton-oxazolidinone ring), 4.01–3.96 (m, 1H, CH of oxazolidinone ring), 3.76–3.73 (m, 1H, diastereotopic proton-oxazolidinone ring), 3.56 (t, 2H, $J=4$ Hz, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.45 (s, 6H, CH_3 of sulfonyl group), 2.89 (t, 2H, $J=5.4$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 153.59, 146.96, 133.19, 132.91, 129.55, 125.30, 122.97, 119.91 (2C's Ar-C), 115.74 (2C's Ar-C), 71.44, 50.13, 48.35, 47.43, 46.74, 42.76. 24.40 ppm; ESI-MS, *m/z* calculated for $C_{19}H_{23}N_3O_6S_3$, 458.6, found 459 $[M+1]^+$.

N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-4-methyl-benzenesulfonamide (11e)

White solid; Yield: 78%; MP: 244–246 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.07 (t, 1H, $J=8$ Hz, NH of sulfonamide), 7.72 (d, 2H, $J=8$ Hz, alpha to oxazolidinone ring), 7.40–7.36 (m, 4H, phenyl ring proton), 7.31 (d, 1H, $J=4$ Hz, alpha proton of thiophene ring), 7.04 (d, 2H, $J=8$ Hz, beta to oxazolidinone ring), 6.91 (d, 1H, $J=4$ Hz, beta proton of thiophene ring), 4.68–4.65 (m, 1H, CH of oxazolidinone ring), 4.24 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.03 (t, 1H, $J=8.8$ Hz, diastereotopic proton-oxazolidinone ring), 3.76–3.72 (m, 1H, diastereotopic proton-oxazolidinone ring), 3.55 (t, 2H, $J=5.2$ Hz, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.12–3.03 (m, 2H, CH_2 of aliphatic region), 2.89 (bs, 2H, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.38 (s, 3H, CH_3 of aliphatic region); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 154.12, 146.78, 142.81, 137.46, 133.35, 132.95, 129.82, 129.67 (2C's, Ar-C), 126.50 (2C's, Ar-C), 125.47, 123.10, 119.67 (2C's Ar-C), 115.79 (2C's Ar-C), 70.94, 48.35, 47.15, 46.70, 45.16, 24.36, 20.94 ppm; ESI-MS, *m/z* calculated for $C_{24}H_{25}N_3O_4S_2$, 483.6, found 484 $[M+1]^+$.

N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-benzamide (11f)

A solution of 5-aminomethyl-3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-oxazolidin-2-one **10** (2.0 g, 0.0060 mol) in DMF (5 mL) was added to a mixture of benzoic acid (0.87 g, 0.0072 mol), EDC.HCl (1.37 g, 0.0072 mol), HOBt (0.98 g, 0.0072 mol) and TEA (1.2 g, 0.012 mol) in DMF (10 mL) at 25 °C. Reaction mass was stirred for 2 h. Completion of reaction was monitored by TLC, after completion of reaction; mixture was diluted with water (75.0 mL). Precipitated solid was filtered, washed with water and purified by column chromatography using DCM: MeOH solvent system to provide off white colored solid of **11f** (2.5 g, 95.0%); MP: 205–207 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.83 (t, 1H, $J=4$ Hz, NH of amide), 7.88–7.86 (m, 2H, phenyl ring proton), 7.53–7.51 (m, 1H, phenyl ring proton), 7.51–7.46 (m, 2H, phenyl ring proton), 7.44–7.38 (m, 2H, phenyl ring proton), 7.26 (d, 1H, $J=5.2$ Hz, alpha proton of thiophene), 7.00 (d, 2H, $J=9$ Hz, beta proton of oxazolidinone), 6.88 (d, 1H, $J=5.2$ Hz, beta proton of thiophene), 4.86–4.80 (m, 1H, CH of oxazolidinone ring), 4.22 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.10 (t, 1H, $J=8.9$ Hz, diastereotopic proton-oxazolidinone ring),

3.86–3.82 (m, 1H, diastereotopic proton-oxazolidinone ring), 3.69–3.60 (m, 2H, CH_2 of aliphatic region), 3.53 (t, 2H, $J = 5.6$ Hz, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.88 (t, 2H, $J = 4$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 167.02, 154.28, 146.77, 134.02, 133.22, 132.93, 131.24, 129.93, 128.16 (2C's, Ar-C), 127.27 (2C's, Ar-C), 125.32, 122.98, 119.68 (2C's Ar-C), 115.76 (2C's Ar-C), 71.05, 48.39, 47.84, 46.76, 42.37, 24.46 ppm; ESI-MS, *m/z* calculated for $C_{24}H_{23}N_3O_3S$, 433.5, found 434 $[M + 1]^+$.

N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-3,4-dimethoxy-benzamide (11g)

White solid; Yield: 90%; MP: 199–201 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.70 (t, 1H, $J = 5.64$ Hz, NH of amide), 7.52–7.49 (dd, 1H, $J = 2$ and 1.8 Hz, proton of methoxy phenyl ring), 7.47 (d, 2H, $J = 1.8$ Hz, proton of methoxy phenyl ring), 7.26 (d, 1H, $J = 5.2$ Hz, alpha proton of thiophene), 7.01–6.97 (m, 3H, phenyl ring proton), 6.88 (d, 1H, $J = 4$ Hz, beta proton of thiophene), 4.83–4.80 (m, 1H, CH of oxazolidinone ring), 4.22 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine) , 4.10 (t, 1H, diastereotopic proton-oxazolidinone ring), 3.86–3.82 (m, 1H, diastereotopic proton-oxazolidinone ring), 3.81 (s, 3H, CH_3 of methoxy group), 3.79 (s, 3H, CH_3 of methoxy group), 3.64–3.62 (m, 2H, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.54 (t, 2H, $J = 5.6$ Hz, CH_2 of aliphatic region), 2.89 (t, 2H, $J = 4$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 166.53, 154.27, 151.31, 148.15, 146.75, 133.21, 132.91, 129.93, 126.23, 125.30, 122.96, 120.56, 119.65 (2C's Ar-C), 115.75 (2C's Ar-C), 110.66 (2C's, Ar-C), 71.19, 55.50, 55.45, 48.38, 47.81, 46.78, 42.39, 24.45 ppm; ESI-MS, *m/z* calculated for $C_{26}H_{27}N_3O_5S$, 439.5, found 494 $[M + 1]^+$.

N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-4-iodo-benzamide (11h)

Light yellow colored solid; Yield: 88%; MP: 194–196 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.90 (s, 1H, NH of amide), 7.82–7.36 (m, 4H, phenyl ring proton), 7.01–6.83 (m, 2H, phenyl ring proton), 4.81–4.80 (m, 1H, CH of oxazolidinone ring), 4.24 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.14 (t, 1H, $J = 8$ Hz, diastereotopic proton-oxazolidinone ring), 3.90–3.86 (m, 1H, diastereotopic proton-oxazolidinone ring), 3.60–3.54 (m, 4H), 2.90–2.33 (m, 2H, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 169.67, 162.27, 154.27, 146.71, 142.48, 138.78, 137.59, 133.56, 132.95, 131.61, 129.96, 128.71 (2C's, Ar-C), 125.48, 123.11, 119.56 (2C's Ar-C), 115.82 (2C's Ar-C), 89.21, 71.01, 48.37, 47.36, 46.73, 41.72 ppm; ESI-MS, *m/z* calculated for $C_{24}H_{22}IN_3O_3S$, 559.42, found 560 $[M + 1]^+$.

N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-2-iodo-4-methyl-benzamide (11i)

Off white solid; Yield: 72%; mp: 206–208 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.76 (t, 1H, $J = 8$ Hz, NH of amide), 7.70 (d, 1H, $J = 8$ Hz, alpha proton of oxazolidinone), 7.43–7.39 (dd, 2H, $J = 4$ and 4 Hz, alpha proton of thiophene and proton of phenyl ring), 7.31 (d, 1H, $J = 4$ Hz, proton of phenyl ring), 7.07–7.03 (m, 3H), 6.99–6.97 (dd, 1H, $J = 4$ and 4 Hz, proton of phenyl ring), 6.90 (d, 1H, $J = 4$ Hz, beta proton of thiophene), 4.84–4.80 (m, 1H, CH of oxazolidinone ring), 4.24 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.14 (t, 1H, $J = 8$ Hz, diastereotopic proton-oxazolidinone ring), 3.90–3.86 (m, 1H, diastereotopic proton-oxazolidinone ring), 3.60–3.54 (m, 4H, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.89 (t, 2H, $J = 8$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.21 (s, 3H, CH_3 of phenyl ring); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 169.67, 162.27, 154.27, 146.71, 142.48, 138.78, 137.59, 133.56, 132.95,

131.61, 129.96, 128.71, 125.48, 123.11, 119.56 (2C's Ar-C), 115.82 (2C's Ar-C), 89.21, 71.01, 48.37, 47.36, 46.73, 41.72, 24.36 ppm; ESI-MS, *m/z* calculated for $C_{25}H_{24}IN_3O_3S$, 573.4, found 574 $[M+1]^+$.

Thiophene-2-carboxylic acid {3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amide (11j)

Off white solid; Yield: 80%; MP: 214–216 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.82 (t, 1H, $J=4$ Hz, NH of amide), 7.78 (d, 1H, $J=4$ Hz, alpha proton of thiophene), 7.65 (d, 1H, $J=4$ Hz, alpha proton of thiophene), 7.36 (d, 2H, $J=8$ Hz, alpha proton of oxazolidinone), 7.22 (d, 1H, $J=4$ Hz, beta proton of thiophene), 7.10–7.08 (dd, 1H, phenyl proton), 6.98 (d, 2H, $J=8$ Hz, beta proton of oxazolidinone), 6.86 (d, 1H, $J=4$ Hz, beta proton of thiophene), 4.81–4.78 (m, 1H, CH of oxazolidinone ring), 4.22 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.08 (t, 1H, $J=8$ Hz, diastereotopic proton-oxazolidinone ring), 3.83–3.79 (m, 1H, diastereotopic proton-oxazolidinone ring), 3.60 (t, 2H, $J=4$ Hz, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.54 (t, 2H, $J=8$ Hz, CH_2 of aliphatic region), 2.89 (t, 2H, $J=4$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 161.83, 154.21, 146.78, 139.28, 133.10, 132.89, 130.65, 129.87, 128.34, 127.62, 125.19, 122.87, 119.72 (2C's Ar-C), 115.75 (2C's Ar-C), 71.08, 48.40, 47.80, 46.85, 42.20, 24.49 ppm; ESI-MS, *m/z* calculated for $C_{22}H_{12}N_3O_3S_2$, 439.5, found 440 $[M+1]^+$, 441 $[M+2]^+$, 481 $[M+ACN]^+$.

5-Chloro-thiophene-2-carboxylic acid {3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-amide (11k)

White solid; Yield: 80%; mp: 160–162 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H, NH of amide), 7.67 (s, 1H), 7.37–7.27 (m, 3H, phenyl ring proton), 7.13–6.89 (m, 4H, phenyl ring proton), 4.78 (s, 1H, diastereotopic proton-oxazolidinone ring), 4.23 (s, 3H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.87 (m, 1H), 3.57 (s, 4H, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.54 (t, 2H, CH_2 of aliphatic region), 2.89 (s, 2H, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 160.79, 154.19, 146.78, 138.31, 133.31, 133.34, 129.83, 128.31, 127.90, 125.34, 123, 119.73 (2C's Ar-C), 115.75 (2C's Ar-C), 71.08, 48.40, 47.80, 46.85, 42.20, 24.49 ppm; ESI-MS, *m/z* calculated for $C_{22}H_{20}ClN_3O_3S_2$, 473.5, found 474 $[M+1]^+$.

N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-3-phenyl-acrylamide (11l)

White solid; Yield: 75%; MP: 181–183 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.51 (t, 1H, $J=4$ Hz, NH of amide), 7.91 (s, 1H), 7.87 (d, 1H, $J=8$ Hz), 7.73 (d, 1H, $J=8$ Hz,), 7.67–7.63 (m, 1H), 7.55 (d, 1H, $J=16$ Hz, alpha proton of cinnamic acid), 7.39–7.36 (m, 2H, phenyl proton), 7.31 (d, 1H, $J=8$ Hz, beta proton of oxazolidinone), 7.04–7.01 (m, 2H), 6.90 (d, 1H, $J=8$ Hz), 6.84 (d, 1H, $J=16$ Hz, beta proton of cinnamic acid), 4.79–4.75 (m, 1H, CH of oxazolidinone ring), 4.23 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.10 (t, 1H, $J=8$ Hz, diastereotopic proton-oxazolidinone ring), 3.76–3.72 (dd, 1H, diastereotopic proton-oxazolidinone ring), 3.59–3.54 (m, 4H, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.88 (t, 2H, $J=8$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 165.25 (amide, C=O), 154.24 (carbamate, C=O), 146.81, 137.53, 135.98, 133.35, 132.94, 131.30, 130.04, 129.88, 125.45, 123.82, 123.09, 119.76 (2C's Ar-C), 115.78 (2C's Ar-C), 71.30, 48.35, 47.64, 46.68, 41.67, 24.34 ppm; ESI-MS, *m/z* calculated for $C_{26}H_{25}N_3O_3S$, 458.5, found 459 $[M+1]^+$.

3-(3,4-Difluoro-phenyl)-N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acrylamide (11m)

Off white solid; Yield: 85%; MP: 221–223 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.49 (t, 1H, $J = 4$ Hz, NH of amide), 7.69–7.66 (m, 1H, phenyl proton), 7.51–7.36 (m, 5H, phenyl proton), 7.31 (d, 1H, $J = 8$ Hz, alpha proton of oxazolidinone), 7.05–7.01 (dd, 2H, $J = 4$ and 4 Hz, phenyl ring proton of 3,4-difluoro ring), 6.90 (d, 1H, $J = 4$ Hz, phenyl ring proton of 3,4-difluoro ring), 6.67 (d, 1H, $J = 12.4$ Hz, beta proton of acid), 4.78–4.73 (m, 1H, CH of oxazolidinone ring), 4.24 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.09 (t, 1H, $J = 12$ Hz, diastereotopic proton-oxazolidinone ring), 3.76–3.72 (dd, 1H, diastereotopic proton-oxazolidinone ring), 3.58–3.54 (m, 4H, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 2.88 (t, 2H, $J = 8$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 165.31, 154.24, 146.81, 137.12, 133.35, 132.94, 129.87, 125.45, 124.66, 123.09, 119.74 (2C's Ar-C), 118.09, 117.92, 116.38, 116.20, 115.78 (2C's Ar-C), 71.30, 48.35, 47.64, 46.68, 41.69, 24.33 ppm; ESI-MS, *m/z* calculated for $C_{26}H_{23}F_2N_3O_3S$, 495.5, found 496 $[M+1]^+$.

N-{3-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-3-(4-trifluoromethyl-phenyl)-acrylamide (11n)

White solid; Yield: 65%; MP: 160–162 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.56 (t, 1H, $J = 8$ Hz, NH of amide), 7.92–7.87 (m, 2H, phenyl ring proton), 7.72 (d, 1H, $J = 8$ Hz, alpha proton of oxazolidinone), 7.67–7.63 (m, 2H, phenyl ring proton), 7.58 (d, 1H, $J = 16$ Hz, alpha proton of acrylic acid), 7.41 (d, 2H, $J = 8$ Hz, beta proton of oxazolidinone), 7.31 (d, 1H, $J = 4$ Hz, alpha proton of thiophene), 7.03 (d, 2H, $J = 8$ Hz), 6.92–6.86 (m, 2H, phenyl ring proton), 4.82–4.78 (m, 1H, CH of oxazolidinone ring), 4.24 (s, 2H, 7 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 4.11 (t, 1H, $J = 8$ Hz, diastereotopic proton-oxazolidinone ring), 3.79–3.75 (dd, 1H, diastereotopic proton-oxazolidinone ring), 3.62 (t, 2H, $J = 8$ Hz, 5 position CH_2 of tetrahydrothieno[3,2-c]pyridine), 3.54 (t, 2H, $J = 8$ Hz, CH_2 of aliphatic region), 2.89 (t, 2H, $J = 4$ Hz, 4 position CH_2 of tetrahydrothieno[3,2-c]pyridine); ^{13}C-NMR (400 MHz, DMSO-d_6): δ 165.29, 154.25, 146.80, 137.55, 135.97, 133.32, 132.94, 131.27, 129.98, 129.90, 129.57, 125.72, 125.42, 125.34, 123.90, 123.86, 123.81, 123.05, 122.63, 119.73 (2C's Ar-C), 115.77 (2C's Ar-C), 71.33, 48.34, 47.64, 46.68, 41.69, 24.36 ppm; ESI-MS, *m/z* calculated for $C_{27}H_{24}F_3N_3O_3S$, 427.5, found 528 $[M+1]^+$.

Results and discussion

(5S)-5-(aminomethyl)-3-[4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)phenyl]-1,3-oxazolidin-2-one **10** is the basic skeleton and its synthesis was started from reaction of 4-chloro nitrobenzene **3** with 4,5,6,7-tetrahydrothieno[3,2-c]pyridine **4** in DMF solvent under basic condition leading to formation of compound 5-(4-nitrophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine **5** (Scheme 1).

The structure of synthesized nitro compound was established by ^{1}H-NMR, ^{13}C-NMR, IR and Mass spectroscopes. The IR spectrum of **5** showed the two absorption bands at 1593 and 1301 cm^{-1} attributable to $-NO_2$ group. In the ^{1}H-NMR spectrum of nitro compound **5**, aromatic ring protons found de-shielded and appeared at δ 8.09–8.06 ppm. Two doublets observed at δ 7.38 and 6.94 ppm corresponding to thiophene ring with coupling constant 4.5 Hz. Three sets of methylene group of tetrahydrothieno[3,2-c]pyridine appears at aliphatic region. The structure of compound **5** confirmed by mass spectrum *m/z* showed 261 $[M+H]^+$. Nitro compound **5** was reduced by using H_2/Raney-Ni under 5–7 kg pressure to afford amino compound **6.** The IR spectrum of compound **6** showed strong band at 3431 cm^{-1} for the free amine group. In the ^{1}H-NMR of compound **6** aromatic protons observed in up filed as compare to protons of compound **5**. The broad singlet observed at 5.16 ppm corresponding to $-NH_2$ group.

Compound 4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)aniline **6** further treated with 2-[(2S)-oxiran-2-ylmethyl]-1H-isoindole-1,3(2H)-dione **7** to furnish compound **8**. The structure of 2-{3-[4-(6,7-Dihydro-4H-thieno[3,2-c]pyridin-5-yl)-phenylamino]-2-hydroxy-propyl}-isoindole-1,3-dione **8** is confirmed from mass spectroscopy where *m/z* value observed 434 $[M+H]^+$. Protons in the NMR spectrum showed two peaks at δ 5.14 and 5.05 ppm corresponds to NH and OH group for one proton each. Further, NMR of compound **8** showed the peaks at 4.04–3.99 ppm only for three protons (two protons for thieno-pyridin and on proton for methine carbon attach to oxygen atom). This clearly indicated that addition of compound **6** with 2-[(2S)-oxiran-2-ylmethyl]-1H-isoindole-1,3(2H)-dione **7** goes with regioselectively to form more stable compound **8.** The ^{13}C-NMR of compound **8** shows the peak at 168.03 ppm which observed due to phthalamide carbonyl group.

Compound **8** was reacted with carbonyl insertion reagent N, N-carbonyldiimidazole lead to formation of oxazolidinone compound **9**. The structure of intermediate **9** is established from IR spectrum of compound **9** showed the presence of absorption band at 1735–1747cm^{-1} providing a strong evidence for the formation of oxazolidinone ring. Another piece of evidence for the cyclization is the appearance of a signal due to two equivalent protons in the ^{1}H-NMR spectrum, at δ 4.18 and 4.02 ppm (diastereotopic protons), which represents the formation of the oxazolidinone ring. The methine proton at C-5 position of oxazolidinone displayed multiplet 4.90–4.88 ppm. In addition, the ^{13}C-NMR of compound **9** oxazolidinone carbonyl carbon appeared at 153.99 ppm. Mass spectrum of compound **9** shown a peak at $m/z = 458$ corresponding to the molecular ion.

Phthalamide de-protection of **9** using hydrazine hydrate in methanol offered vital intermediate (S)-amino oxazolidinone **10**. After completion of reaction compound **10** was isolated in the form of hydrochloride salt and formed by-products are effectively washed out with mother liquor. ^{1}H-NMR spectrum of compound **10** show broad singlet observed integrated for two protons at δ 1.73 ppm recognized to primary amine. The 5th position carbon of oxazolidinone ring displayed at 4.58–4.53 ppm for one proton. The set of two multiplets observed in spectra in the range 4 ppm and 3.55 ppm corresponding to diastereotopic protons of oxazolidinone ring for one proton each.

In ^{13}C-NMR spectrum compound **10** showed peaks at 154.56 ppm confirmed the presence of oxazolidinone moiety. Methylene group adjacent to oxazolidinone ring observed at 44.33 ppm. The set of methylene carbons of piperidine observed at 48.40, 47.37 and 46.76 ppm. The methine carbon of five member ring oxazolidinone observed at 73.77 ppm. The compound **10** confirmed by the mass spectroscopy, it show base peak *m/z* at 330 $[M+1]^+$. All these analytical spectral values confirm the structure of the key intermediate (5S)-5-(aminomethyl)-3-[4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)phenyl]-1,3-oxazolidin-2-one **10**. The physico chemical data of synthesized novel oxazolidinones compounds shown in Table 1.

Antibacterial activity

The results of in-vitro antibacterial activity against various bacterial strains are summarized in Figure 3. As seen in Figure 3, di-sulfonamide derivative (**11d**) was equally potent and showed comparable antibacterial activity to linezolid and torezolid; however, acetamide (**11a**), mono-sulfonamide (**11c**) and p-toluene sulfonamide (**11e**) relatively inferior. When acetyl group (**11a**) replaced with benzoyl (**11f**) and formate (**11b**) group a drastic decrease in the antibacterial activity was observed. Substitution on benzoyl group increases the antibacterial activity wherein iodo group at 4-position of benzoyl ring (**11h**) gives best activity among the di-methoxy (**11g**) and 4-methyl-2-iodo derivatives (**11i**). Thiophene (**11j**) and chloro thiophene (**11k**) derivatives were found inferior than **11a** and **11e**. Acrylamide (**11l**) found very less active but fluoro substitution at 3 and 4-position (**11m**) increases its activity however, tri-fluoromethyl substitution at

Table 1. Some physicochemical and analytical data of the compounds bearing thieno-pyridin.

Compound	Molecular formula	Molecular weight	MP (°C)	Yield (%)
11a	$C_{19}H_{21}N_3O_3S$	371.4	237–239	86.6
11b	$C_{19}H_{21}N_3O_4S$	387.4	229–231	75
11c	$C_{18}H_{21}N_3O_4S_2$	407.5	239–241	85
11d	$C_{19}H_{23}N_3O_6S_3$	458.6	211–212	88
11e	$C_{24}H_{25}N_3O_4S_2$	483.6	244–246	78
11f	$C_{24}H_{23}N_3O_3S$	433.5	205–207	95
11g	$C_{26}H_{27}N_3O_5S$	439.5	199–201	90
11h	$C_{24}H_{22}IN_3O_3S$	559.4	194–196	88
11i	$C_{25}H_{24}IN_3O_3S$	573.4	206–208	72
11j	$C_{22}H_{12}N_3O_3S_2$	439.5	214–216	80
11k	$C_{22}H_{20}ClN_3O_3S_2$	473.5	160–162	80
11l	$C_{26}H_{25}N_3O_3S$	458.5	181–183	75
11m	$C_{26}H_{23}F_2N_3O_3S$	495.5	221–223	85
11n	$C_{27}H_{24}F_3N_3O_3S$	427.5	160–162	65

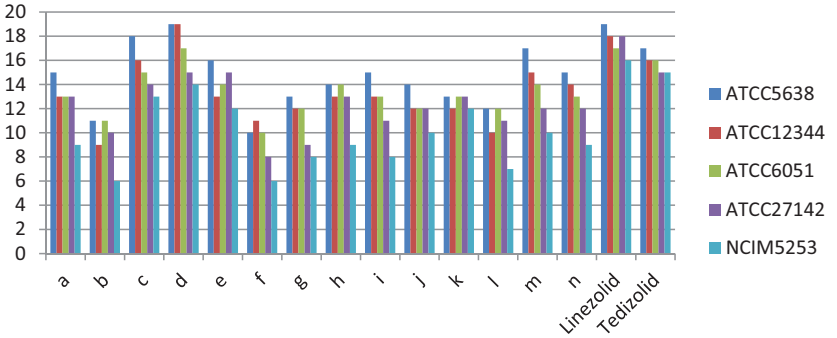
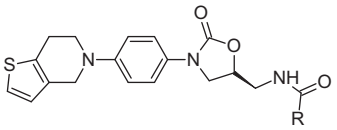
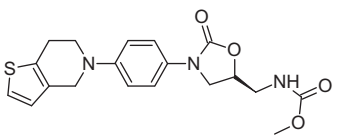


Figure 3. Diameters of zone inhibition of the bacterial strains obtained with novel thienopyridine oxazolidinones (**11a–n**) at 10 μg/mL. *Staphylococcus aureus* (ATCC5638); *Streptococcus pyogenes* (ATCC12344); *Bacillus subtilis* (ATCC6051); *Bacillus pumilus* (ATCC27142) and *E. faecalis* (NCIM5253).

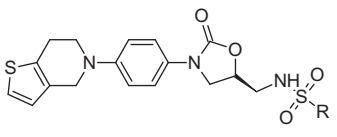
Table 2. The zone of inhibition in mm of synthesized compound (**11a–n**).



11a-11n



11b



11c-11e

	Zone of inhibition (mm)				
Compound	*ATCC5638*	*ATCC12344*	*ATCC6051*	*ATCC27142*	*NCIM5253*
11a	15 ± 0.5	13 ± 0.4	13 ± 0.3	13 ± 0.7	13 ± 0.5
11b	11 ± 0.4	9 ± 0.5	11 ± 0.2	10 ± 0.5	6 ± 0.4
11c	18 ± 0.2	16 ± 0.7	15 ± 0.5	14 ± 0.4	13 ± 0.5
11d	19 ± 0.6	19 ± 0.2	17 ± 0.7	15 ± 0.3	14 ± 0.4
11e	16 ± 0.4	13 ± 0.3	14 ± 0.2	15 ± 0.6	12 ± 0.6
11f	10 ± 0.3	11 ± 0.5	10 ± 0.3	8 ± 0.2	6 ± 0.7
11g	13 ± 0.3	12 ± 0.4	12 ± 0.4	9 ± 0.2	8 ± 0.4
11h	14 ± 0.2	13 ± 0.2	14 ± 0.7	13 ± 0.3	9 ± 0.2
11i	15 ± 0.2	13 ± 0.6	13 ± 0.2	11 ± 0.7	8 ± 0.2
11j	14 ± 0.3	12 ± 0.3	12 ± 0.2	12 ± 0.2	10 ± 0.6
11k	13 ± 0.2	12 ± 0.7	13 ± 0.2	13 ± 0.2	12 ± 0.7
11l	12 ± 0.6	10 ± 0.2	12 ± 0.6	11 ± 0.5	7 ± 0.6
11m	17 ± 0.2	15 ± 0.4	14 ± 0.4	12 ± 0.6	10 ± 0.2
11n	15 ± 0.4	14 ± 0.3	13 ± 0.7	12 ± 0.3	9 ± 0.7
Linezolid	19 ± 0.6	18 ± 0.4	17 ± 0.3	18 ± 0.4	16 ± 0.8
Tedizolid	17 ± 0.3	16 ± 0.4	16 ± 0.2	15 ± 0.5	15 ± 0.4

4-position (**11n**) found equally potent to 4-iodobenzoyl derivative (**11h**). Zone of inhibition of synthesized derivatives were determined for compounds **11a–n** by measuring the diameter (millimeter) on the surface of the plates, and obtained data are tabulated in Table 2 and graphical representation of data shown in Figure 3.

Conclusion

A series of novel oxazolidinone (**11a–n**) derivatives containing thieno-pyridine ring system were synthesized using simple approach with good yield positively. The pharmacological studies against five pathogenic bacteria showed that most of the synthesized compounds exhibited moderate to good activity against panel of Gram-positive bacteria. The enhancement in antibacterial activity is attributed to the presence of pharmacologically active sulfonamides. The present study promises to be very useful to get lead antimicrobial agents. Further modification in these compounds could be anticipated to develop safer and potential antibacterial agents.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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