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# Novel tetrahydro-thieno pyridyl oxazolidinone: an antibacterial agent☆

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**Abstract**—Synthesis of a number of 4,5,6,7-tetrahydro-thieno[3,2-*c*]pyridine substituted oxazolidinones have been reported. They have been screened against a panel of Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*. A SAR has been developed. Compound **15** showed comparable activity (MIC) to linezolid and superior to eperezolid.


## 1. Introduction

Despite a number of antibiotics available for the treatment of bacterial infections, emergence of multi-drug resistant organism has posed a great challenge to the scientists. The latest addition to the armory for treating antibacterial infections has been oxazolidinone, linezolid **1** (Fig. 1) by Pharmacia and UpJohn, based on the lead molecule DuP 721 **2** (Fig. 1) discovered at DuPont in 1987.[1] Linezolid (Zyvox)[2] was launched as the only drug of choice, for the treatment of infections associated with vancomycin-resistant *Enterococcus faecium* including blood stream infections, hospital acquired *pneumonia* and methicillin-resistant *Staphylococcus aureus*.[3] However, toxicity as well as emergence of resistance in some patients receiving prolonged treatment has been reported.[4]

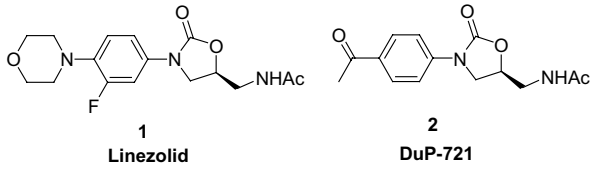


**Figure 1.**

A number of attempts have been made by various research groups to obtain potent and safer analogues without much success.[5] There appears to be a need for second generation oxazolidinone with improved drug efficacy and better toxicity profile. We have also recently reported some of our interesting findings of oxazolidinones.[6,7] Recently, Paget et al.[8] reported 6:5 fused ring pyrrolopyridine substituted oxazolidinones, in which **3** and **4** (Fig. 2) have been shown to have 2–4-fold better antibacterial (MIC) activity to linezolid and similar to linezolid against *Staphylococcus aureus* in in vivo experiment.[8]

In the present article, we would like to disclose a few oxazolidinones **11**–**21** (Fig. 3) having 4,5,6,7-tetrahydro-thieno[3,2-*c*]pyridine ring systems and their antibacterial activity.

## 2. Chemistry

The syntheses of compounds have been outlined in Scheme 1. 4,5,6,7-Tetrahydro-thieno[3,2-*c*]pyridine **5** and its derivatives were synthesized by methods described in the literature.[9] Reaction of **5** with 3,4-difluoronitrobenzene **6** was carried out under basic conditions leading to the nucleophilic substitution at 4-position to yield a nitro compound **7** (Scheme 1).

*Keywords*: Oxazolidinone; 4,5,6,7-Tetrahydro-thieno[3,2-*c*]pyridine; Linezolid; In vitro activity.
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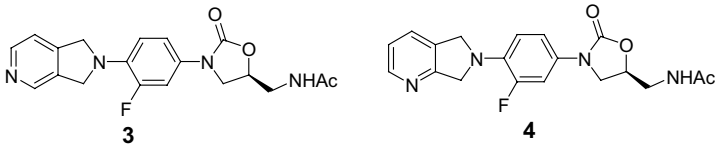



**Figure 2.**

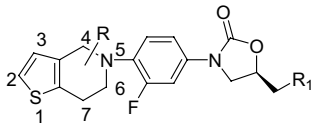
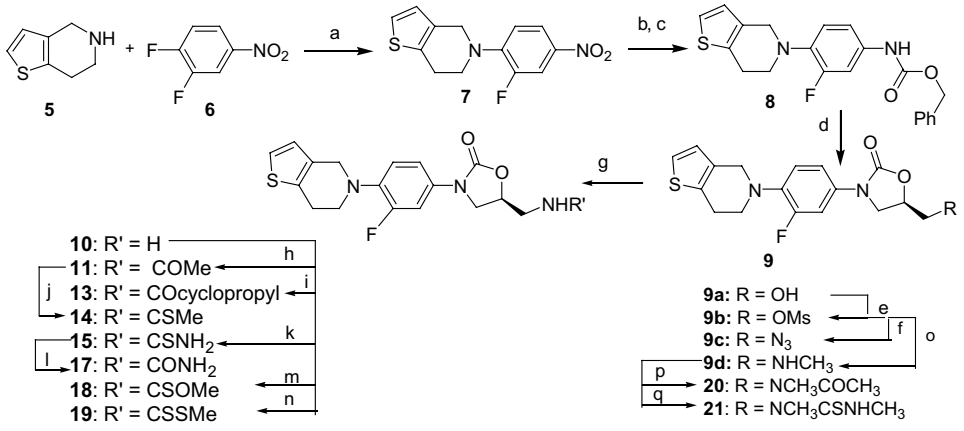



**Figure 3.**

The nitro group of compound **7** was then reduced by hydrazine/Raney-Ni at 30 °C to afford amino compound which was protected by carboxybenzyloyl group to furnish compound **8**. Reaction of **8** with *n*-BuLi followed by reaction with (*R*)-glycidyl butyrate lead to the formation of oxazolidinone alcohol **9a**. Alcohol **9a** was then converted into azide **9c** or methylamino derivative **9d** via mesylated intermediate **9b** by standard method.[3,10,11] The azide **9c** or amine **9d** can be converted into various substituted oxazolidinones **11**–**21** as shown in Scheme 1.

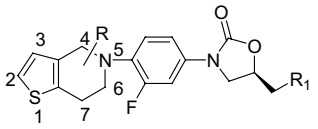
## 3. Results and discussion

The results of in vitro antibacterial activities (MIC) against various bacterial strains are summarized in Table 1. Tetrahydro-thienopyridine substitution at 4-position of the phenyl ring gave compound **11**, which showed antibacterial activities. Any substitution of the tetrahydro-thienopyridine ring did not show any improvement in antibacterial activity, such as 7-methyl (**12**) or 4-methyl (**16**) were inferior to linezolid. When the methyl group of acetamide side chain of compound **11** was replaced by a cyclopropyl group to give compound **13**, inferior antibacterial activity was observed, when compared to compound **11**. Recently, it has been shown in several studies that replacement of acetamide side chain with thioacetamide, thiourea or carbamate lead to improvement in their antibacterial potential.[10–12] Thus, we synthesized thioamide **14**, thiourea **15** and **16**, urea **17**, thiocarbamate derivative **18** and dithiocarbamate derivative **19** and evaluated their antibacterial activity in panel of Gram-positive strains. The thioacetamide derivative **14** showed an improved antibacterial activity as compared to compounds **11**, **12** and **13**, however, it remains inferior to linezolid and eperezolid in MIC value. Thiourea derivatives **15** was equally potent and showed comparable antibacterial activity to linezolid and eperezolid; however, methyl substituted analogue **16** was relatively inferior. When '**S**' atom of thiourea of compound **15** is replaced by '**O**' atom to furnish urea derivative **17** a dramatic decrease in the antibacterial activity was observed. Based on the result of **15** and **16**, we envisioned that introduction of one more 'S' atom in the compound **15** will give superior compound **19**, however, it was much inferior to **15** and **16**. Interestingly, substitution of –NH of acetamide, thioacetamide or thiourea with a methyl group, which led to the formation of compounds **20** and **21**

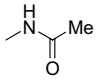
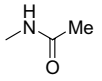
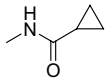
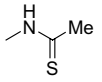
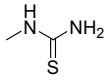
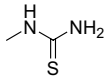
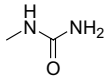
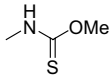
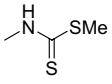
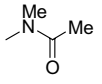
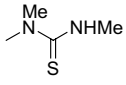



**Scheme 1.** Reagents and conditions: (a) acetonitrile, 75–78 °C, 2 h. (b) Raney-Nickel, $NH_2NH_2{\cdot}H_2O$, 28–30 °C, 1 h. (c) Benzyl chloroformate (50% in toluene), 10% $Na_2CO_3$, acetone, 27–30 °C, 18 h. (d) *n*-BuLi (1.6 M in hexane), (*R*)-glycidyl butyrate, THF, −78 °C, 3 h. (e) $MeSO_2Cl$, TEA, $CH_2Cl_2$, 0–5 °C, 3 h. (f) $NaN_3$, DMF, 70–75 °C, 2 h. (g) $P(Ph)_3$, $NH_4OH$, MeOH, 1,4-dioxane, 25–27 °C, 2 h. (h) $Ac_2O$, pyridine, 25–27 °C, 30 min. (i) Cyclopropanoic acid, HOBt–$H_2O$, EDC–HCl, TEA, $CH_2Cl_2$, 26–28 °C, 30 min. (j) Lawesson's reagent, 1,4-dioxzane, 95–100 °C, 4 h. (k) $CS_2$, TEA, THF, Ethyl chloroformate, 30% $NH_3$ in MeOH, 26–28 °C, 2 h. (l) $Hg(OAc)_2$, $CH_2Cl_2$, 38–40 °C, 3 h. (m) NaH (60% in oil), MeOH, 0–5 °C, 3 h. (n) $CS_2$, TEA, MeI, THF, 0–5 °C, 4 h. (o) 40% methyl amine in methanol, 60–65 °C, 24 h. (p) Pyridine, $Ac_2O$, 25–28 °C, 1.5 h. (q) TEA, MeNCS, $CH_2Cl_2$, 26–28 °C, 2 h.

**Table 1.** MIC (minimum inhibitory concentration in microgram per litre) values of new oxazolidinones in various Gram-positive bacteria



**11 - 21**

| Compd | R | R1 | B.p. | B.c. | S.p. | S.e. | E.f. 1 | E.f. 2 | S.a. 1 | S.a. 2 | S.a. 3 | S.a. 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **11** | H |  | 4–8 | 8–16 | 1–2 | 4–8 | 4–8 | 8–16 | 4–8 | 8–16 | 8–16 | 8–16 |
| **12** | 7-$CH_3$ |  | ND | 8–16 | ND | >16 | >16 | ND | >16 | >16 | ND | ND |
| **13** | H |  | 8–16 | 8–16 | 2–4 | 4–8 | 8–16 | >16 | 8–16 | >16 | >16 | >16 |
| **14** | H |  | 1–2 | >16 | 1–2 | 0.5–1 | 1–2 | >16 | 2–4 | 2–4 | 2–4 | 8–16 |
| **15** | H |  | 1–2 | 1–2 | 2–4 | 1–2 | 2–4 | 1–2 | 0.5–1.0 | 2–4 | 2–4 | 2–4 |
| **16** | 4-$CH_3$ |  | 2–4 | 2–4 | 1–2 | 1–2 | 2–4 | 2–4 | 2–4 | 2–4 | 4–8 | 8–16 |
| **17** | H |  | 8–16 | 8–16 | 1–2 | 4–8 | 8–16 | 8–16 | 8–16 | >16 | 8–16 | >16 |
| **18** | H |  | 1–2 | >16 | 0.5–1 | 0.5–1 | 1–2 | >16 | 4–8 | 4–8 | >16 | >16 |
| **19** | H |  | >16 | >16 | 2–4 | 1–2 | >16 | >16 | >16 | >16 | >16 | >16 |
| **20** | H |  | >16 | >16 | >16 | >16 | >16 | >16 | >16 | >16 | >16 | >16 |
| **21** | H |  | ND | 64 | ND | >64 | 32 | ND | >64 | ND | ND | ND |
| Linezolid | | | 1–2 | 2–4 | 0.25–0.5 | 0.5–1 | 1–2 | 1–2 | 1–2 | 2–4 | 2–4 | 2–4 |
| Eperezolid | | | 1–2 | 1–2 | 0.5–1 | 2–4 | 2–4 | 1–2 | 2–4 | 2–4 | 2–4 | 2–4 |

B.p. = *Bacillus pumilus* **MTCC 1607**, B.c. = *Bacillus cereus* **MTCC 430**, S.p. = *Streptococcus pyogenes* **MTCC 442**, S.e. = *Staphylococcus epidermidis* **MTCC 155**, E.f. 1 = *Enterococcus faecalis* **MTCC 439**, E.f. 2 = *Enterococcus faecalis* **ATCC 14506**, S.a. 1 = *Staphylococcus aureus* **MTCC 96**, S.a. 2 = *Staphylococcus aureus* **ATCC 14154**, S.a. 3 = *Staphylococcus aureus*, **ATCC 25923**, S.a. 4 = *Staphylococcus aureus* **ATCC 29213**, ND = not done.

were totally devoid of any activity suggesting the importance of NH group in the side chain for their antibacterial activity.

## 4. Conclusion

In summary, unsubstituted tetrahydro-thienopyridine substitution at *p*-position of the aromatic ring in oxazolidinone skeleton furnishes active antibacterial compound **11**, however, best antibacterial activity can be obtained with thiourea as side chain, compound **15**. Thus, it appears that most potential antibacterial activity of a compound can be achieved with appropriate combination of heterocyclic moiety at 4-position of aromatic ring as well as appropriate modification of acetamide side chain. The compound **15** is showing promising results, and studies to establish its safety are being planned for its further development.

## 5. In vitro MIC

The in vitro (MIC) antibacterial activity of the compounds against Gram-positive (*Bacillus pumilus*, *Bacillus cereus*, *Staphylococcus aureus*, *Staphylococcus*

*epidermidis*, *Enterococcus faecalis*) bacteria was tested as growth inhibition with the use of microdilution broth method according to NCCLS.[13] Compounds were dissolved in concentrated DMSO and water was added to get stock solution in 80% DMSO. The working solution was prepared by diluting the stock solution 1:10 times in 4–8% DMSO in water or medium, and the dissolved compounds were evaluated in the concentrations of 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32 and 64 μg/mL.

## 6. Experimental

$^1$H spectral data are recorded using a 300 MHz $^1$H NMR spectrometer (M-300) and reported in $\delta$ scale, using tetramethyl silane as the internal standard. IR spectra are recorded on FTIR 8300 Shimadzu in KBr pellets. Mass spectra are recorded on a Perkin Elmer Sciex API 3000. HPLC of the pure compounds are done at $\lambda_{max}$ 220 nm using column ODS C-18, 150 mm × 4.6 mm × 4μ on AGILENT 1100 series. Melting points are taken on scientific melting point apparatus and are uncorrected. 25 DC-Alufolien 20 × 20 cm kieselgel 60 $F_{254}$ Merck plates were used for TLC unless specified.

### 6.1. Pyridin-5-(2-fluoro-4-nitro-phenyl)4,5,6,7-tetrahydro-thieno[3,2-*c*]pyridine (7)

A solution of 3,4-difluorobenzene **6** (2.28 g, 143.0 mmol) in acetonitrile (30 mL) was added to 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine **5** (5.0 g, 35.0 mmol) and heated at temperature 75–78 °C for 2 h. The reaction mixture was cooled to temperature 27–28 °C and solvents were removed under reduced pressure to afford a crude oil. Water (100 mL) was added to this and extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed with saturated sodium chloride solution (100 mL) and dried over anhydrous $Na_2SO_4$. The solvents were removed on a rotatory evaporator under reduced pressure to afford compound **7** as a yellow solid (3.99 g, 100%) (99.0% purity by HPLC). Mp 135 °C. $^1$H NMR ($CDCl_3$): $\delta$ 8.00 (m, 2H), 7.17 (d, 1H, $J$ = 5.13 Hz), 6.95 (t, 1H, $J$ = 8.64 Hz), 4.43 (s, 2H), 3.70 (t, 2H, $J$ = 5.58 Hz), 3.00 (t, 2H, $J$ = 5.52 Hz); IR (KBr): 3107, 2891, 2821, 2337, 1604, 1498, 1454, 1330, 1265, 1207, 1047 cm$^{-1}$. ESI-MS: 279 $(M+H)^+$.

### 6.2. [4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluorophenyl]-carbamic acid benzyl ester (8)

To a solution of compound **7** (2 g, 7.19 mmol) in MeOH (15 mL) was added Raney-Nickel (2.5 g) followed by hydrazine hydrate 99% (3 mL) dropwise over a period of 5 min. The mixture was stirred at 28–30 °C for 1 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (9:1). The reaction mixture was filtered through celite and the celite bed was washed with MeOH (15 mL). The filtrate was concentrated on a rotatory evaporator under reduced pressure to afford a yellow solid. The solid was dissolved in acetone (20 mL) and treated with 10% $Na_2CO_3$ (aq) solution (5 mL) dropwise and cooled to 0–5 °C. To this benzyl chloroformate (5 mL) was added dropwise at 0–5 °C. The reaction was warmed to 26–28 °C and stirred at this temperature for 18 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (9:1). The solvent was evaporated on a rotatory evaporator under reduced pressure to afford oil. Water (75 mL) was added to oil, and extracted with ethyl acetate (3 × 75 mL). The organic layer was treated with activated charcoal (1 g), warmed for 10 min at temperature 45–50 °C and filtered through hy-flow. The solvents were evaporated on a rotatory evaporator under reduced pressure to afford an oil. The oil was triturated with hexane (10 mL) to give the title compound **8** as an off-white solid (1.3 g, 47%) (99.1% purity in HPLC). Mp 100–103 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.39 (m, 5H), 7.12 (d, 1H, $J$ = 5.1 Hz), 6.81 (d, 1H, $J$ = 5.1 Hz), 6.61 (m, 2H), 6.57 (s, 1H), 5.19 (s, 2H), 4.18 (s, 2H), 3.43 (t, 2H, $J$ = 5.64 Hz), 2.95 (t, 2H, $J$ = 5.52 Hz). IR (KBr): 3330, 2922, 2777, 1697, 1587, 1527, 1456, 1417, 1375, 1301, 1217, 1072, 711 cm$^{-1}$. ESI-MS: 383.0 $(M+H)^+$.

### 6.3. [4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-5-oxazolidinyl methanol (9a)

To a solution of compound **8** (3.5 g, 9.16 mmol) in freshly distilled THF (40 mL) at −78 °C under nitrogen atmosphere was added dropwise, *n*-BuLi (1.6 M in hexane, 11.1 mL, 9.3 mmol) and mixture was stirred for 1.5 h. To this (*R*)-glycidyl butyrate (1.34 mL, 9.4 mmol) was added at −78 °C and stirred for 1 h. The reaction mixture was warmed to 27–28 °C and stirred for 3.5 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (9:1). Saturated aqueous solution of ammonium chloride (5 g) was added to the reaction mixture followed by ethyl acetate (50 mL) and water (5 mL). The layers were separated and aqueous layer was extracted with ethyl acetate (3 × 25 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The solvents were evaporated on a rotatory evaporator under reduced pressure to afford a solid. The solid was further taken in ethyl acetate (10 mL) and warmed on a water bath at 50–55 °C for 30 min. The solid was filtered to give compound **9a** as a white solid (1.3 g, 41%) (94% purity in HPLC). Mp = 158–160 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.43 (dd, 1H, $J$ = 2.55 Hz, 11.6 Hz), 7.13 (m, 2H), 6.98 (t, 2H, $J$ = 9.18 Hz), 6.81 (d, 1H, $J$ = 5.13 Hz), 4.74 (m, 1H), 4.21 (s, 2H), 4.00 (m, 3H), 3.77 (dd, 2H, $J$ = 4.0 Hz, 8.58 Hz), 3.46 (t, 2H, $J$ = 5.64 Hz), 3.11 (s, 3H), 2.96 (t, 2H, $J$ = 5.49 Hz). IR (KBr): 3431, 2900, 2823, 1732, 1631, 1569, 1517, 1479, 1423, 1325, 1224, 1193, 1101, 991, 937, 831, 804, 752 cm$^{-1}$. ESI-MS: 349.0 $(M+H)^+$, 371 $(M+Na)^+$, 387 $(M+K)^+$.

### 6.4. [4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-5-oxazolidinyl methyl methane sulfonate (9b)

To the solution of compound **9b** (1 g, 2.87 mmol) and triethylamine (0.78 mL) in dichloromethane at 0–5 °C was added methane sulfonyl chloride (0.3 mL) dropwise within 2 min. The mixture was stirred at 0–5 °C for 3 h and the completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (9:1). The reaction

mixture was diluted with water (50 mL) and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$ and the solvents were evaporated on a rotatory evaporator under reduced pressure to afford a crude solid product. The solid was crystallized from acetonitrile (10 mL) and water (20 mL) to get **9b** as a white solid. (1.03 g, 84%) (93% purity in HPLC). Mp 140–144 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.45 (dd, 1H, $J$ = 2.55 Hz, 11.5 Hz), 7.00 (m, 2H), 6.99 (t, 2H, $J$ = 9.12 Hz), 6.82 (d, 1H, $J$ = 5.13 Hz), 4.45 (m, 2H), 4.31(m, 1H), 4.21(s, 2H), 4.09 (t, 1H, $J$ = 9.12 Hz), 3.93 (m, 1H), 3.47 (t, 2H, $J$ = 5.64 Hz), 2.97 (t, 2H, $J$ = 5.55 Hz). IR (KBr): 1743, 1517, 1419, 1365, 1172, 997 cm$^{-1}$. ESI-MS: 427.2 $(M+H)^+$, 465 $(M+K)^+$.

### 6.5. [4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-5-oxazolidinylmethyl azide (9c)

Compound **9b** (0.9 g, 2.11 mmol) in dimethyl formamide (17 mL) was treated with $NaN_3$ (0.520 g, 8.0 mmol) and heated to 70–75 °C with stirring for 2 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (8.5:1.5). The heat source was removed and the reaction mixture was cooled to 25–26 °C. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 25 mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$ and the solvents were evaporated on a rotatory evaporator under reduced pressure to afford oil. The oil was triturated with $CHCl_3$–IPE (1:2) to give compound **9c** as white solid (0.5 g, 41%) (95% purity in HPLC). Mp 158–160 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.47 (dd, 1H, $J$ = 2.58 Hz, 11.55 Hz), 7.13 (m, 2H), 6.99 (t, 1H, $J$ = 9 Hz), 6.82 (d, 1H, $J$ = 5.13 Hz), 4.78 (m, 1H), 4.21 (s, 2H), 4.05 (t, 1H, $J$ = 8.91 Hz), 3.83 (m, 1H), 3.69 (m, 2H), 3.57 (t, 2H, $J$ = 5.61 Hz), 2.96 (t, 2H, $J$ = 5.58 Hz). IR (KBr): 2119, 1733, 1517, 1419, 1326 1193, 1168 cm$^{-1}$. ESI-MS: 374 $(M+H)^+$, 411 $(M+K)^+$.

### 6.6. 3-[4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-5-methyloxazolidin methylamine (10)

Compound **9c** (1.77 g, 4.7 mmol) in dioxane (20 mL) and methanol (4 mL) was treated with triphenyl phosphine (2.47 g, 9.4 mmol) and stirred at 25–27 °C for 1 h. The completion of the reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (8.5:1.5). The solvents were evaporated on a rotatory evaporator under reduced pressure to afford a brown gummy compound. The compound was taken in diisopropyl ether (10 mL) and heated on a warm water bath at 65–70 °C for 15 min. The solvent was decanted and this operation was done 2–3 times. The crude compound was purified by column chromatography over silica gel (100–230 mesh) using 0–25% ethyl acetate as eluant. The required fractions were collected and the solvents were removed on a rotatory evaporator to give compound **10** as a pale yellow solid. (0.986 g, 61%) (99% purity in HPLC). $^1$H NMR ($CDCl_3$): $\delta$ 7.48 (dd, 1H, $J$ = 2.52 Hz, 11.7 Hz), 7.12 (t, 2H, $J$ = 5.10 Hz), 6.98 (t, 1H, $J$ = 9.0 Hz), 6.81 (d, 1H, $J$ = 5.16 Hz), 4.71 (m, 1H), 4.21 (s, 2H), 4.00 (t, 1H, $J$ = 9.1 Hz), 3.82 (m, 1H), 3.46 (t, 2H, $J$ = 4.62 Hz), 3.13 (dd, 1H, $J$ = 4.02 Hz, $J$ = 9.60 Hz), 2.94 (m, 3H). IR (KBr): 3392, 2823, 1732, 1517, 1421, 1325, 1222, 1193, 864, 804, 752 cm$^{-1}$.

### 6.7. 1-{3-[4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-yl-methyl}-acetamide (11)

Compound **10** (0.25 g, 0.72 mmol) in dry pyridine (0.4 mL) was treated with acetic anhydride (0.71 mL) and the mixture was stirred at 25–27 °C for 1.5 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (9:1). The reaction mixture was poured into chilled water (40 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$ and the solvents were evaporated on a rotatory evaporator under reduced pressure to afford compound **11** as a white solid (0.217 g, 77%) (94% purity in HPLC). Mp 135–140 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.47 (dd, 1H, $J$ = 2.46 Hz, 11.64 Hz), 7.13 (d, 1H, $J$ = 5.13 Hz), 7.04 (dd, 1H, $J$ = 2.22 Hz, 6.60 Hz), 6.97 (t, 1H, $J$ = 8.91 Hz), 6.82 (d, 1H, $J$ = 5.13 Hz), 5.92 (s, 1H), 4.75 (s, 1H), 4.21(s, 2H), 4.05 (t, 1H, $J$ = 9.0 Hz), 3.74 (m, 2H), 3.59 (m, 1H), 3.47 (t, 2H, $J$ = 5.64 Hz), 2.96 (t, 2H, $J$ = 5.49 Hz), 2.02 (s, 3H). IR (KBr): 3093, 2923, 2815, 1741, 1641, 1517, 1431, 1328, 1228, 1132, 1014, 850, 815, 756 cm$^{-1}$. ESI-MS: 390 $(M+H)^+$, 428 $(M+K)^+$.

### 6.8. N-{3-[3-Fluoro-4-(7-methyl-6,7-dihydro-4H-thieno-[3,2-*c*]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (12)

The title compound was synthesized by a procedure identical to the procedure described for the synthesis of compound **11**.

Yield: 27% (87% purity in HPLC). Mp 102–106 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.46 (dd, 1H, $J$ = 16.50 Hz), 7.14 (d, 1H, $J$ = 5.13 Hz), 7.07 (dd, 1H, $J$ = 10.11 Hz), 6.82 (d, 1H, $J$ = 5.13 Hz), 6.02 (br s, 1H), 4.77 (br s, 1H), 4.31 (m, 1H), 4.03 (t, 1H, $J$ = 6.0 Hz,), 4.01 (m, 2H), 3.77 (m, 2H), 3.59 (m, 1H), 3.18 (m, 1H), 2.67 (m, 1H), 2.02 (s, 3H), 1.14 (m, 3H). IR (KBr): 3093, 2923, 2815, 1741, 1641, 1517, 1431, 1328, 1228, 1132, 1014, 850, 815, 756 cm$^{-1}$. ESI-MS: 404.2 $(M+H)^+$.

### 6.9. Cyclopropanecarboxylic acid {3-[4-(6,7-dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-yl-methyl}-amide (13)

A solution of cyclopropanecarboxylic acid (0.123 g, 1.43 mmol) in 25 mL of dichloromethane was treated with compound **10** (0.5 g, 1.44 mmol), 1-hydroxybenzotriazole hydrate (0.510 g, 3.86 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.522 g, 2.73 mmol) and triethylamine (0.1 mL, 1.35 mmol) in dichloromethane (25 mL). The reaction mixture was stirred at 26–28 °C for 30 min. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (9:1). The reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (3 × 25 mL). The organic layer was separated, dried over

anhydrous $Na_2SO_4$ and the solvents were evaporated on a rotatory evaporator under reduced pressure to afford compound **13** as a solid (0.476 g, 80%) (99% purity in HPLC). Mp 185 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.46 (dd, 1H, $J$ = 2.33 Hz, 11.69 Hz), 7.13 (d, 1H, $J$ = 5.13 Hz), 7.04 (m, 2H), 6.82 (d, 1H, $J$ = 5.13 Hz), 6.00 (m, 1H), 4.76 (m, 1H), 4.31 (m, 1H), 4.05 (m, 3H), 3.71 (m, 3H), 3.18 (d, 1H, $J$ = 4.92 Hz), 2.65 (m, 1H), 2.02 (s, 3H), 1.25 (s, 1H), 1.10 (m, 3H). IR (KBr): 3344, 1733, 1670, 1515, 1427, 1328, 1224, 1193, 1163, 1058, 906, 871, 744 cm$^{-1}$. ESI-MS: 416.2 $(M+H)^+$, 454.2 $(M+K)^+$.

### 6.10. N-{3-[4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-yl-methyl}thioacetamide (14)

Compound **11** (0.250 g, 0.64 mmol) was treated with Lawesson's reagent (0.259 g, 0.16 mmol) in 1,4-dioxane (6 mL) under an atmosphere of nitrogen. The reaction mixture was refluxed at 95–100 °C for 4 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (9:1). The solvents were evaporated on a rotatory evaporator under reduced pressure to afford the crude product. The crude product was triturated with diisopropyl ether (10 mL) and the solid was filtered, which was further purified by column chromatography using silica gel (100–230 mesh) and 0–25% ethyl acetate in hexane as eluant. The required fractions were pooled and the solvents were evaporated on a rotatory evaporator to give compound **14** as a yellow solid (190 mg, 73%) (91% purity in HPLC). Mp 162–164 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.47 (dd, 1H, $J$ = 2.04 Hz, 12.03 Hz), 7.14 (d, 1H, $J$ = 4.98 Hz), 7.06 (m, 1H), 6.96 (t, 1H, $J$ = 9.03 Hz), 6.82 (d, 1H, $J$ = 4.98 Hz), 6.36 (s, 1H), 4.76 (s, 1H), 4.20 (s, 2H), 4.03 (t, 1H, $J$ = 8.88 Hz), 3.79 (t,1H, $J$ = 8.87 Hz), 3.70 (d, 2H, $J$ = 5.25 Hz), 3.46 (t, 2H, $J$ = 5.37 Hz), 2.96 (s, 2H), 2.62 (s, 2H). IR (KBr): 1745, 1569, 1517,1226, 1118 cm$^{-1}$. ESI-MS: 406.2 $(M+H)^+$.

### 6.11. N-{3-[4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-yl-methyl}thiourea (15)

Compound **10** (1 g, 2.88 mmol) in tetrahydrofuran (50 mL) was treated with $CS_2$ (0.18 mL, 2.916 mmol) and triethylamine (0.4 mL, 0.114 mmol) and stirred at 26–28 °C for 5 h. Ethyl chloroformate (0.26 mL, 2.68 mmol) was added and further stirred at 26–28 °C for 2 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (8.5:1.5). The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 25 mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$ and the solvents were evaporated on a rotator evaporator under reduced pressure to afford 3-[4-(6,7-dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-5-isothiocyanatomethyl-oxazolidin-2-one as an oil. The oil (0.3 g, 0.7 mmol) was taken in methanol (10 mL) and the solution was treated with 30% $NH_3$ in methanol (10 mL) and stirred at 26–28 °C for 2 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (8.5:1.5). The solid separated out was filtered, washed with diisopropyl ether (15 mL) to afford compound **15** as an off white solid (0.140 g, 44%) (97% purity in HPLC). Mp 80–85 °C. $^1$H NMR ($CDCl_3$): $\delta$ 8.01 (s, 1H), 7.46 (dd, 1H, $J$ = 2.14 Hz, 11.85 Hz), 7.14 (d, 1H, $J$ = 5.07 Hz), 7.03 (m, 2H), 6.82 (d, 1H, $J$ = 5.08 Hz), 4.98 (m, 1H), 4.21 (m, 3H), 4.03 (t, 2H, $J$ = 8.93 Hz), 3.81 (m, 1H), 3.47 (t, 2H, $J$ = 5.55 Hz), 2.98 (d, 2H, $J$ = 5.17 Hz), 2.61 (s, 3H). IR (KBr): 3458, 3317, 1743, 1602, 1577, 1326, 1228 cm$^{-1}$. ESI-MS: 407 $(M+H)^+$, 445 $(M+K)^+$.

### 6.12. {3-[3-Fluoro-4-(4-methyl-6,7-dihydro-4H-thieno-[3,2-*c*]pyridin-5-yl)-phenyl]-2-oxo-oxazolidin-5-yl-methyl}-thiourea (16)

The title compound was synthesized by a procedure identical to the procedure described for the synthesis of compound **15**.

Yield: 61% (95.2% purity in HPLC). Mp 118–120 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.11(s, 1H), 7.52 (dd, 1H, $J$ = 2.01 Hz, 12.01 Hz), 7.14 (d, 1H, $J$ = 5.0 Hz), 7.03 (m, 2H), 6.82 (d, 1H, $J$ = 5.05 Hz), 5.20 (s, 2H), 4.86 (d 1H, $J$ = 3.02 Hz), 4.19 (s, 2H), 4.01 (m, 4H), 3.46 (t, 2H, $J$ = 5.36 Hz), 2.96 (s, 2H), 2.49 (s, 2H). IR (KBr): 3313, 2925, 2854, 1735, 1618, 1514, 852, 748 cm$^{-1}$. ESI-MS: 421 $(M+H)^+$, 459 $(M+K)^+$.

### 6.13. N-{3-[4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-yl-methyl}urea (17)

Compound **15** (0.250 g, 0.61 mmol) was treated with $Hg(OAc)_2$ (0.197 g, 0.61 mmol) in dichloromethane (15 mL) and refluxed at 38–40 °C for 2 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (9:1). The reaction mass was cooled to 26–28 °C, with the formation of solid residue. The solid formed was filtered over buchner funnel and the filtrate was diluted with water (50 mL), extracted with 3 × 20 mL of dichloromethane. Organic layer was separated, dried over anhydrous $Na_2SO_4$ and solvents were removed on a rotatory evaporator to afford crude solid. The Crude product was purified through column chromatography using silica gel (100–230 mesh) and 0–10% methanol in chloroform as eluant. The required fractions were collected and solvents were removed under reduced pressure to give title compound **17** as white solid (0.03 g, 12%) (98% purity in HPLC). Mp 138 °C (with decomposition). $^1$H NMR ($CDCl_3$): $\delta$ 7.57 (s, 1H), 7.34 (dd, 1H, $J$ = 1.95 Hz, 1.7 Hz), 7.12 (d, 1H, $J$ = 5.13 Hz), 6.99 (m, 2H), 6.80 (dd, 1H, $J$ = 1.32 Hz, 3.81 Hz), 6.18 (s, 2H), 4.82 (m, 1H), 4.65 (q, 1H, $J$ = 6.6 Hz), 4.35 (s, 1H), 4.07 (m, 3H), 3.92 (m, 1H), 3.48 (q, 2H, $J$ = 4.14 Hz), 2.84 (m, 2H), 2.34 (m, 2H). IR (KBr): 3392, 1728, 1654, 1517, 1228, 1191 cm$^{-1}$. ESI-MS: 391.1 $(M+H)^+$, 429.2 $(M+K)^+$.

### 6.14. N-{3-[4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-yl-methyl}thiocarbamate (18)

Compound **10** (0.5 g, 1.44 mmol) in tetrahydrofuran (5 mL) was treated with $CS_2$ (0.1 mL, 1.62 mmol) and tri-

ethylamine (0.2 mL, 1.427 mmol), stirred at 26–28 °C for 2 h. Ethyl chloroformate (0.26 mL, 2.68 mmol) was added and further stirred at 26–28 °C for 2 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (8.5:1.5). The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate ($3 \times 50$ mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$ and the solvents were evaporated on a rotatory evaporator under reduced pressure to afford 3-[4-(6,7-dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-5-isothiocyanatomethyl-oxazolidin-2-one as an oil. To this oil, methanol (10 mL) was added and treated with NaH (100 mg) at 0–5 °C. The reaction mixture was stirred at 0–5 °C for 1 h and then brought to 26–28 °C and stirred for 2 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (9:1). The reaction mixture was quenched with ice and the solid separated out was filtered and dried to give a yellow crude product as granules (0.90 g). The crude product was taken in ethyl acetate (10 mL) and heated on warm water bath at 45–50 °C for 10 min. The solid was filtered to give yellow solid (0.350 g, 31.2%). The solid was further purified by column chromatography using silica gel (100–230 mesh) and eluant 0–25% ethyl acetate in hexane. The required fractions were mixed and the solvents were removed on a rotatory evaporator to afford compound **18** as white crystalline solid (0.200 g, 17.8%) (99% purity in HPLC). Mp 160–165 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.46 (dd, 1H, $J = 2.34$ Hz, 11.76 Hz), 7.13 (d, 1H, $J = 5.1$ Hz), 7.01 (m, 2H), 6.96 (t, 1H, $J = 8.73$ Hz), 6.82 (d, 1H, $J = 5.16$ Hz), 6.49 (m, 2H), 4.75 (m,1H), 4.20 (s, 2H), 4.05 (t, 1H, $J = 8.97$ Hz), 3.85 (m, 1H), 3.53 (t, 2H, $J = 3.93$ Hz), 2.96 (t, 2H, $J = 5.61$ Hz). ESI-MS: 422.1 $(M+H)^+$.

### 6.15. 3-[4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-yl-methyl}thiocarbamic acid methyl ester (19)

Compound **10** (0.5 g, 1.44 mmol) in freshly distilled tetrahydrofuran (10 mL) was treated with $CS_2$ (0.16 mL) and triethylamine (0.2 mL). The reaction mixture was stirred at 0–5 °C for 4 h. The completion of reaction was checked by TLC using mobile phase EtOAc–hexane (8:2). Methyl iodide (0.1 mL) was added to the reaction mixture at 0 °C and maintained at 0 °C for 30 min. The reaction mixture was warmed to 26–28 °C by removing ice bath and stirred at this temperature for 2 h. The completion of reaction was checked by TLC using mobile phase EtOAc–hexane (8:2). The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate ($3 \times 20$ mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$ and the solvents were evaporated on a rotatory evaporator under reduced pressure to afford a brown oil (0.4 g). This crude product was chromatographed over silica gel (100–230 mesh) using eluant 0–25% ethyl acetate in hexane. The required fractions were pooled and the solvents were evaporated to give the title compound as a white solid (0.055 g, 8.4%) (96% purity in HPLC). Mp 174–176 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.47 (dd, 1H, $J = 2.37$ Hz, 11.76 Hz), 7.13 (d, 1H $J = 5.13$ Hz), 7.07 (dd, 1H, $J = 2.19$ Hz, 6.63 Hz), 6.97 (t, 1H, $J = 9.09$ Hz), 6.82 (d, 1H, $J = 5.16$ Hz), 6.74 (s, 1H), 4.95 (m, 1H), 4.20 (s, 2H), 4.08 (m, 5H), 3.85 (m, 1H), 3.46 (t, 2H, $J = 5.61$ Hz,), 2.96 (t, 2H, $J = 4.3$ Hz). IR (KBr): 3236, 1733, 1514, 1423, 1190 and 1056 $cm^{-1}$. ESI-MS: 438.1 $(M+H)^+$, 476.2 $(M+K)^+$.

### 6.16. 1-{3-[4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-yl-methyl}-N-methyl-acetamide (20)

Compound **9b** (2.24 g, 5.25 mmol) was treated with methyl amine in methanol (12 mL) and refluxed at 60–65 °C for 24 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (9:1). The reaction mixture was diluted with water (50 mL) and the aqueous layer was extracted with chloroform ($2 \times 25$ mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$ and the solvents were evaporated on a rotatory evaporator under reduced pressure to afford compound **9d** which was further used in the synthesis of title compound. Thus, compound **9d** (0.90 g, 2.5 mmol) in dry pyridine (1.9 mL) was treated with acetic anhydride (3.3 mL) and mixture was stirred at 25–28 °C for 1.5 h. The completion of reaction was checked by TLC using mobile phase $CHCl_3$–MeOH (9:1). The reaction mixture was poured into chilled water (40 mL) and extracted with ethyl acetate ($3 \times 50$ mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$ and the solvents were evaporated on a rotatory evaporator under reduced pressure to afford compound **20** as a white solid (0.841 g, 84%) (98% purity in HPLC). Mp 114–116 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.46 (dd, 1H, $J = 2.49$ Hz, 11.58 Hz), 7.26 (m, 1H), 7.13 (d, 1H, $J = 5.16$ Hz), 7.05 (dd, 1H, $J = 2.19$ Hz, 6.72 Hz), 6.95 (t, 1H, $J = 9.09$ Hz), 6.82 (d, 1H, $J = 5.13$ Hz), 4.95 (m, 1H), 4.45 (m, 1H), 4.21 (s, 2H), 4.07 (m, 2H), 3.80 (m, 1H), 3.47 (t, 2H, $J = 5.6$ Hz), 2.96 (t, 2H, $J = 5.58$ Hz), 2.65 (m, 3H). IR (KBr): 3093, 2923, 2815, 1741, 1641, 1517, 1431, 1328, 1228, 1132, 1014, 850, 815, 756 $cm^{-1}$. ESI-MS: 404.3 $(M+H)^+$, 442 $(M+K)^+$.

### 6.17. 1-{3-[4-(6,7-Dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)-3-fluoro-phenyl]-2-oxo-5-oxazolidinyl methyl}1,3-dimethyl thiourea (21)

Compound **9d** (0.70 g, 1.9 mmol) was treated with triethyl amine (0.57 mL) and MeNCS (0.388 g, 5.3 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at 26–28 °C for 2 h. The reaction mixture was diluted with water (40 mL) and the aqueous layer was extracted with dichloromethane ($2 \times 20$ mL). The organic layers were combined, dried over anhydrous $Na_2SO_4$ and the solvents were evaporated on a rotatory evaporator to afford compound (**21**) as a white solid (0.5 g, 59%) (95% purity in HPLC). Mp 90–92 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.47 (dd, 1H, $J = 2.49$ Hz, 11.7 Hz), 7.13 (d, 1H, $J = 5.13$ Hz), 7.06 (m, 1H), 6.97 (t, 1H, $J = 9.12$ Hz), 6.82 (d, 1H, $J = 5.13$ Hz), 4.87 (m, 1H), 4.20 (s, 2H), 4.02 (t, 1H, $J = 9.0$ Hz), 3.99 (m, 1H), 3.75 (m, 1H), 3.48 (m, 3H), 3.18 (s, 2H), 2.98 (t, 2H, $J = 5.31$ Hz), 2.12 (s, 3H). IR (KBr): 3356, 1747, 1515, 1327, 1224, 1055, 750 $cm^{-1}$. ESI-MS: 435.2 $(M+H)^+$.

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