# Synthesis of Conformationally Constrained Analogues of Linezolid: Structure−Activity Relationship (SAR) Studies on Selected Novel Tricyclic Oxazolidinones†

Natesan Selvakumar, Deekonda Srinivas, Manoj Kumar Khera, Magadi Sitaram Kumar, Rao N. V. S. Mamidi, Hemanth Sarnaik, Chandrashekar Charavaryamath, Bonthu Srinivasa Rao, Mohammed A. Raheem, Jagattaran Das, Javed Iqbal,* and Ramanujam Rajagopalan*

*Anti-Infectives Discovery Group, Dr. Reddy's Research Foundation, Bollaram Road, Miyapur, Hyderabad 500 050, India*

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In an effort to discover potent antibacterials based on the entropically favored "bioactive conformation" approach, we have designed and synthesized a series of novel tricyclic molecules mimicking the conformationally constrained structure of the oxazolidinone antibacterial, Linezolid **1**. The structure **3** obtained by this approach was synthesized and found to be moderately active against a panel of Gram-positive organisms tested. Further introduction of a fluorine atom in the aromatic ring of compound **3** as in Linezolid resulted in some excellent compounds possessing potent antibacterial activity. The thus obtained lead molecule **16** was further fine-tuned by structure−activity relationship studies on the amide functionality leading to a number of novel tricyclic oxazolidinone derivatives. Some particularly interesting compounds include the thioamides **36** and **37**, thiocarbamate **41**, and thiourea **45**. The in vitro activity results of amide homologues of **16** (compounds **25**−**30**) revealed that compounds up to four carbon atoms on the amide nitrogen retain the activity. In general, thioamides and thiocarbamates are more potent when compared to the corresponding amides and carbamates.

## Introduction

The emergence of bacterial resistance to the antibiotics poses a serious concern for medical professionals during the past decade.[1] In particular, multidrug resistant Gram-positive bacteria[2,3] including methicillin resistant *Staphylococcus aureus* (MRSA)[4] and *Staphylococcus epidermitis* (MRSE) and Vancomycin resistant enterococci (VRE)[5] are of major concern. In addition, an alarming situation has been created by the emergence of strains of glycopeptide intermediate resistant *S. aureus* (GISA) with reduced susceptibility to Vancomycin.[6,7] Strains of common intestinal bacteria *Enterococcus faecalis* and *Enterococcus faecium* have been resistant to Vancomycin for several years. The most worrisome bacteria are the MRSA, a particularly virulent organism that causes a broad array of problems starting from pimples to life-threatening bacteremia, osteomyelitis, etc. These are resistant to many of the common antibiotics except Vancomycin, and if they develop or acquire Vancomycin resistance as well, physicians have nothing in their arsenal to fight them.[8]

Oxazolidinones are a new class of synthetic antibacterials with activity against Gram-positive bacteria and anaerobic bacteria.[9] They have been shown to selectively bind to the 50S ribosomal subunit and inhibit bacterial translation at the initiation phase of the protein synthesis.[10−12] Linezolid **1**, developed by Pharmacia and Upjohn, is the first compound commercialized in the United States from the oxazolidinones class of antibacterials.[13,14] This class of compounds is particularly active against Gram-positive organisms such as MRSA, MRSE, and VRE. The novel mechanism of action combined with their biological activity against resistant organisms aroused widespread attention worldwide to develop newer antibacterials of this class.[15−19] In an ongoing project on antiinfectives in our laboratory, we have explored the possibility of design and synthesis of novel antibacterials based on the conformationally constrained analogues of Linezolid. Herein, we describe a detailed account of our observations on novel tricyclic oxazolidinones as potent antibacterial agents.

The binding of a drug molecule to its target is governed by subtle stereoelectronic compatibility, and these factors play a dominant role in the pharmacodynamics of the process. In addition, another important factor that plays a profound role in host−guest interaction is the "bioactive conformation" of the drug molecule. This conformation is the one that a drug molecule adopts when it binds to the target, and its interaction is greatly influenced by the entropic factors that are related to the structural flexibility present in the molecule. It is axiomatic that every chemical structure and consequently a drug are expected to have free rotation along the bonds, thereby contributing to the degrees of freedom that will in turn favor the increase in entropy of the molecule. However, out of numerous possible conformations of a given structure, only one of the conformations (i.e., bioactive conformation) is expected to bind to the receptor. In such a scenario, a flexible drug molecule, comprised of several conformers, will provide an entropically disadvantageous situation as it would have to forego several degrees of freedom prior to binding with the target. In view of these considerations, we pursued the approach of conformationally constrained molecules as a mimic of the bioac-

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* To whom correspondence should be addressed. Tel: 91-40-3045439. Fax: 91-40-3045438. E-mail: javediqbal@drreddys.com and rajagopalanr@drreddys.com.

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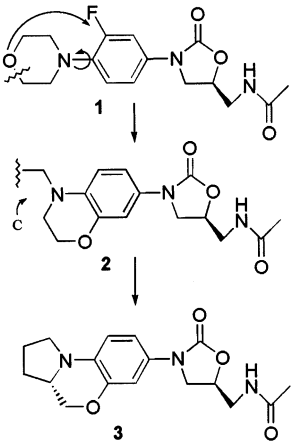
**Chart 1**

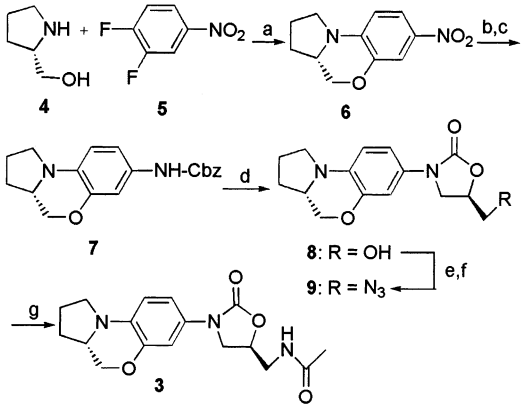


tive conformation as the basis for designing potent antibacterial agents. The designed conformationally constrained structure patterned on well-known potent molecules offers exciting prospects for this concept. On the basis of the above considerations, Linezolid **1**, because of its proven commercial viability, appears a good molecule on which one could apply the concept of conformationally constrained structures as mimics of the bioactive conformation. As evident from its structure, one could easily conceive constraining the free rotation along the carbon−nitrogen bond connecting the aromatic ring with morpholine (Chart 1). Such constrain would also reduce the number of conformers associated with the six-membered morpholine ring. Thus, we envisioned conformationally rigid analogues of Linezolid by freezing the free rotation along the C−N bond connecting the aromatic and the morpholine ring. Conceptually, the marked C−O bond in Linezolid **1** could be chopped and the resultant oxygen could be cyclized onto the aromatic ring leading to the novel structure **2** as illustrated in Chart 1. It is evident that the resultant structure **2** still possesses a morpholine skeleton that is fused to the aromatic ring. As the pendant ethyl group in structure **2** would have flexibility leading to further conformational freedom, it may be fused further onto the newer morpholine ring by incorporating a carbon atom. The overall modification would lead to a novel tricyclic oxazolidinone **3** that may represent a conformationally constrained analogue of Linezolid and could be a mimic of its bioactive conformation.

## Synthesis

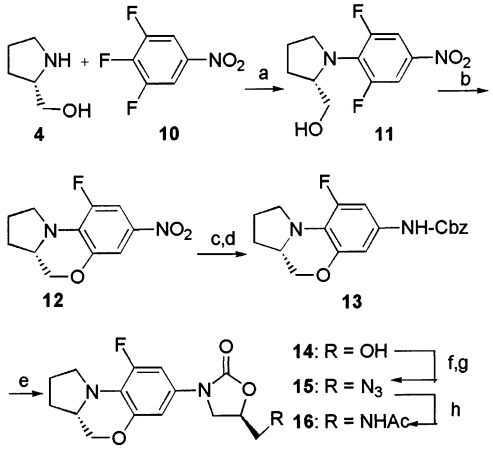
**Tricyclic Compound 3.** The general method of assembling the tricycle involved the aromatic nucleophilic substitution of an appropriate proline derivative with di- or trifluro nitrobenzenes. Thus, substitution of L-prolinol **4** onto 3,4-difluronitrobenzene **5** under strong basic conditions resulted in the displacement of both the fluorine atoms leading to the nitro compound **6** in one step (Scheme 1). Having obtained the nitro compound **6**, further steps for the synthesis of **3** were carried out along the lines of established protocol.[13] This compound **6** upon reduction followed by protection afforded the Cbz-protected tricyclic compound **7**. Deprotonation of the Cbz compound **7** followed by reaction with (*R*)-glycidyl butyrate yielded the tricyclic oxazolidinone

**Scheme 1**[a]



[a] Reagents and conditions: (a) Aqueous KOH, DMSO, 60 °C, 4 h. (b) Fe, HCl, EtOH, 0 °C to room temperature, 45 min. (c) Cbz-Cl, aqueous $Na_2CO_3$, acetone, 0 °C to room temperature, 5 h. (d) BuLi, (*R*)-glycidyl butyrate, THF, −78 °C to room temperature, 4 h. (e) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C to room temperature, 2 h. (f) $NaN_3$, DMF, 80 °C, 2 h. (g) MeCOSH, room temperature, 18 h.

**Scheme 2**[a]



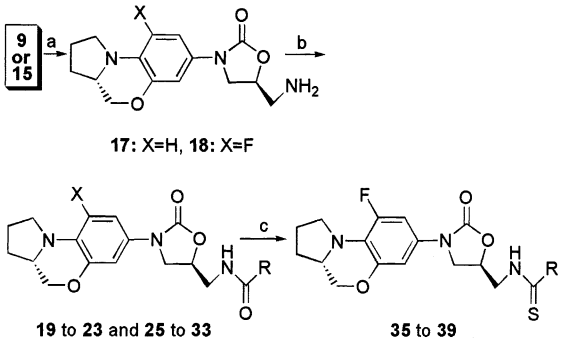
[a] Reagents and conditions: (a) $Et_3N$, $CH_3CN$, room temperature, 14 h. (b) KOH, DMSO, 80 °C, 2 h. (c) Fe, HCl, EtOH, 0 °C to room temperature, 2 h. (d) Cbz-Cl, aqueous $Na_2CO_3$, acetone, 0 °C to room temperature, 4 h. (e) BuLi, (*R*)-glycidyl butyrate, THF, −78 °C to room temperature, 14 h. (f) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 1 h. (f) $NaN_3$, DMF, 60 °C, 2 h. (g) MeCOSH, room temperature, 14 h.

alcohol **8**, which was converted into the corresponding azide **9** by standard procedures. The treatment of the azide **9** with thiolacetic acid produced the target acetamide **3** in good yields.

**Tricyclic Compound 16.** The tricyclic compound **16** was prepared by a route shown in Scheme 2 that is similar to the synthesis of tricyclic compound **3**. The attempted one step preparation of the tricyclic nitro compound **12** from L-prolinol **4** and 3,4,5-trifluro nitrobenzene **10** resulted only in complex mixtures. However, the desired compound **12** was prepared by a stepwise displacement of fluorine atoms on **10**. Addition of L-prolinol to 3,4,5-trifluoro nitrobenzene **10** under mild basic conditions afforded the alcohol **11** by single fluorine displacement. The second fluorine atom of **11** was displaced by a relatively stronger basic condition to afford the nitro compound **12** in very good yields. The conversion of the nitro compound **12** to the acetamide **16** followed essentially the same route as in Scheme 1.

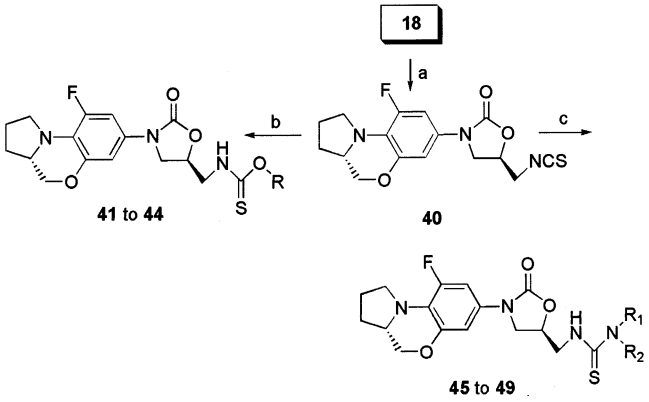
**Preparation of Derivatives of 3 and 16 for Structure−Activity Relationship (SAR) Studies.**

**Scheme 3**[a]




[a] Reagents and conditions: (a) $Ph_3P$, THF, room temperature, 4 h and then $H_2O$, reflux, 12 h. (b) For compounds **19** and **25**, ethyl formate, reflux, 2 h; for all other compounds, acid chlorides, $Et_3N$, $CH_2Cl_2$, 0 °C, 14 h. (c) Lawesson's reagent, dioxane, reflux, 2 h.

**Scheme 4**[a]




[a] Reagents and conditions: (a) $CSCl_2$, $Et_3N$, $CH_2Cl_2$, 0 °C to room temperature, 14 h. (b) Alcohols, 80−100 °C, 12 h. (c) Ammonia or amines, THF, room temperature, 14 h.

The tricyclic azides **9** and **15** were converted to the corresponding amines **17** and **18** under standard conditions (Scheme 3).[20] The amines **17** and **18** were converted to the respective formamides **19** and **25** in refluxing ethyl formate.[21] However, the alkyl amide derivatives such as **20**−**23** and **26**−**33** were obtained from the respective amines by the conventional treatment with appropriate acid chlorides under basic conditions. The amides **25**−**28** and **16** were converted to the respective thioamides **35**−**39** smoothly using Lawesson's reagent.[22]

To obtain the thiocarbamate and thiourea derivatives of the above tricyclic oxazolidinones, it was necessary to prepare the isothiocyanate **40**. This was achieved by treating the amine **18** with thiophosgene under basic conditions (Scheme 4). Exposure of the isothiocyanate **40** to appropriate alcohols afforded the corresponding thiocarbamates **41**−**44** under heating conditions. The thiourea **45** was synthesized by bubbling ammonia gas to a tetrahydrofuran (THF) solution of the isothiocyanate **40**. On the other hand, the remaining thioureas **46**−**49** were obtained by treatment of appropriate amines with isothiocyanate **40**.

The methyl and ethyl carbamate analogues **50** and **51** were prepared from the amine **18** by reacting with the respective alkylchloroformates (Scheme 5). The fluorinated amide derivatives **24** and **34** were prepared from the respective acids using DCC. The dithio carbamate analogue **52** was obtained under standard conditions. The imide **53** was achieved by exposure to succinic anhydride at high temperature.

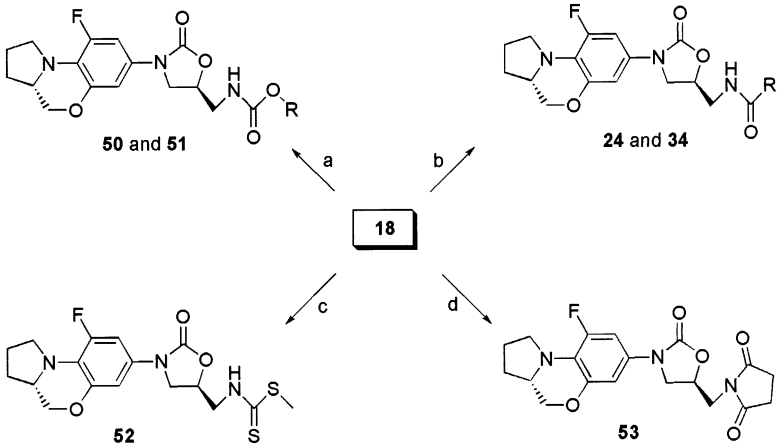
## Results and Discussion

The constrained analogues of Linezolid prepared above were screened for in vitro activity against a panel of Gram-positive organisms. The first constrained structure **3** showed moderate in vitro activity (Table 1). In a bid to improve potency, we prepared several analogues by modifying the amide portion. However, within the limited number of modifications performed, we could not achieve a compound better than Linezolid, although compounds **22** and **24** exhibited nearly equal activity to that of Linezolid.

After we carried out a number of changes in the tricyclic core of compound **3**, we opted to introduce a fluorine atom as present in Linezolid at the ortho position with respect to the nitrogen atom of the tricyclic structure. This particular move was very fruitful as the resultant compound **16** was a few folds more potent than the parent compound **3**, with MIC values in the range of 1−4 $\mu$g/mL.

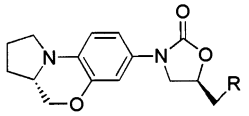
After we achieved a potent compound, we turned our attention toward performing an extensive SAR studies

**Scheme 5**[a]




[a] Reagents and conditions: (a) Alkylchloroformate, $Et_3N$, $CH_2Cl_2$, 0 °C, 14 h. (b) Acid, DCC, DMAP, $CH_2Cl_2$. (c) $CS_2$, $Et_3N$, EtOH, MeI. (d) Succinic anhydride, toluene, DMSO, reflux.

**Table 1.** In Vitro Antibacterial Activity (MIC, $\mu$g/mL)[a] of Selected Tricyclic Oxazolidinones[b]



| compd | R | S.a 019 | S.a 213 | S.a 035 | E.f 034 | E.f 153 | E.fm 154 |
|---|---|---|---|---|---|---|---|
| **3** | $NHCOCH_3$ | 4 | 4 | 8 | 16 | 16 | 16 |
| **19** | NHCHO | 4 | ND | 8 | 16 | 16 | 16 |
| **20** | $NHCOCH{=}CH_2$ | 4 | ND | 8 | 8 | 8 | 8 |
| **21** | $NHCOCH(CH_3)_2$ | 8 | ND | 16 | 32 | 32 | 32 |
| **22** | $NHCOCH_2Cl$ | 2 | ND | 4 | 4 | 8 | 8 |
| **23** | $NHCOCHCl_2$ | 4 | ND | 4 | 8 | 8 | 8 |
| **24** | $NHCOCHF_2$ | 2 | ND | 4 | 4 | 4 | 4 |
| Linezolid | | 1 | 2 | 2 | 2 | 2 | 2 |
| Vancomycin | | 2 | 1 | 1 | 2 | >32 | >32 |

[a] S.a 019 = *S. aureus* ATCC 33591 (methicillin resistant); S.a 213 = *S. aureus* ATCC 49951; S.a 035 = *S. aureus* ATCC 29213; E.f 034 = *E. fecalis* ATCC 29212 (Vancomycin sensitive); E.f 153 = *E. fecalis* NCTC 12201 (Vancomycin resistant); and E.fm 154 = *E. fecium* ATCC 12202 (Vancomycin resistant). [b] ND denotes not determined.

on the amide functionality by keeping the tricyclic core unchanged (Table 2). The first systematic SAR study was to increase the length of the alkyl chain of the amide **16**. Thus, compounds **25**−**30** were prepared and tested for in vitro activity from which the acetamide **16** was found to be the best among all amides. In addition, there was a clear downward trend in terms of potency upon increasing the length of the alkyl chain. It was clear from this study that the alkyl chain length of the amide was acceptable up to four carbon atoms, and compounds possessing more than four carbons (**29** and **30**) exhibited poor activity. Thus, we have recorded the complete SAR study concerning the length of the alkyl chain on the amide functionality although a limited such study is reported.[15] In addition, the amide **31** where the alkyl group is branched also showed poor activity. Several other derivatives such as compounds **32**−**34** were prepared that did not produce any compound better than Linezolid barring one exception to the chloroacetyl derivative **32**.

After we studied the activity pattern of various amide derivatives of tricycle **16**, we then turned our focus toward the thioamide analogues **35**−**39** of the corresponding amides **25**, **16**, and **26**−**28**. This particular change had produced excellent compounds in almost all of the analogues, as the thioamides were many-folds better than their oxygen counterparts. Similar findings were reported by Bayer, Pharmacia, and others while our work was going.[23] The key compounds here are the thioamides **36** and **37** whose MIC values are in the range of 0.5−1 $\mu$g/mL against the Gram-positive organisms tested, and that is 4-fold better than that of Linezolid. This SAR study indicates that the analogues having longer carbon chain (compounds **38** and **39**) also retain the activity due to the higher potency of thio compounds.

Yet another series of useful analogues is the monothiocarbamates (compounds **41**−**44**) in place of amides.[19] These derivatives exhibited excellent in vitro activities as indicated by the MIC values of the order of 0.5 $\mu$g/mL for its methyl thiocarbamate derivative **41**. The thiourea derivatives **45**−**49** were prepared,[23] in which the unsubstituted thiourea derivative **45** exhibited an excellent in vitro activity of the order of 0.5 $\mu$g/mL. However, the analogous thiourea derivatives where the second nitrogen is branched to accommodate a ring (compounds **47**−**49**) showed dramatic reduction in potency. The carbamate analogues **50** and **51** also exhibited interesting activity, and the dithiocarbamate **52** was found to be yet another potent compound.[24] Finally, we prepared a cyclic imide **53** that was found to be inactive. We believe that the hydrogen atom of the amide functionality is essential for the biological activity presumably due to the possibility of engaging in hydrogen bonding and that the hydrogen bonding responsible for activity is more pronounced in cases where the carbamates and ureas have linear alkyl or amine terminals allowing greater degrees of freedom to approach the site when compared to the cyclic ones. A similar observation has also recently been reported.[23]

The in vivo efficacies of selected analogues matched with that of Linezolid as exemplified by their $ED_{50}$ values (Table 2). The $ED_{50}$ values of methyl thiocarbamate **41** and methyl carbamate **50** matched the value of Linezolid.

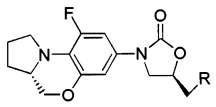
## Conclusions

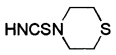
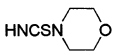
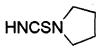
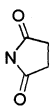
In essence, we achieved excellent antibacterial activities for compounds obtained by making conformationally rigid analogues of Linezolid **1** based on the entropically favored bioactive conformation approach. In addition, a systematic SAR study on the amide functionality of compound **16** produced several compounds with improved in vitro results than that of the parent amide. The compounds of particular interest are the thioamides **36** and **37**, thiocarbamate **41**, and thiourea **45** whose MIC values are fractional and more significantly are several-fold better than Linezolid. We have also arrived at conclusions on the number of atoms that could be accommodated on the nitrogen atom of the amide functionality. Yet another important observation is that the hydrogen atom on the amide nitrogen and shorter open chain terminals thereon are essential for the biological activity. It is also proposed that thioamides and thiocarbamates are more potent with respect to their oxygen counterparts.

## Experimental Section

**General.** Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1650 spectrophotometer. All $^1H$ NMR and $^{13}C$ NMR were recorded at 200 and 50 MHz, respectively, on a Varian Gemini spectrometer. Chemical shifts

**Table 2.** In Vitro (MIC, $\mu$g/mL) and In Vivo ($ED_{50}$, mg/kg) Antibacterial Activity of Selected Fluorine-Containing Tricyclic Oxazolidinones[a]




| Compound | R | S.a 019 | S.a 213 | S.a 035 | Ef 034 | Ef 153 | Efm 154 | $ED_{50}$ |
|---|---|---|---|---|---|---|---|---|
| **25** | NHCHO | 4 | 4 | 8 | 4 | 4 | 8 | |
| **16** | $NHCOCH_3$ | 1 | 2 | 2 | 2 | 2 | 4 | 8.6 |
| **26** | $NHCOCH_2CH_3$ | 2 | 4 | 4 | 4 | 8 | 8 | 16.0 |
| **27** | $NHCOCH_2CH_2CH_3$ | 4 | 4 | 4 | 4 | 4 | 4 | |
| **28** | $NHCO(CH_2)_3CH_3$ | 8 | 16 | 16 | 16 | 16 | 32 | |
| **29** | $NHCO(CH_2)_4CH_3$ | 16 | 32 | 32 | 32 | 32 | 32 | |
| **30** | $NHCO(CH_2)_5CH_3$ | 32 | 32 | 32 | 32 | 32 | 32 | |
| **31** | $NHCOCH(CH_3)_2$ | 8 | 8 | 8 | 16 | 16 | 16 | |
| **32** | $NHCOCH_2Cl$ | 1 | ND | 1 | 2 | 2 | 2 | |
| **33** | $NHCOCH{=}CH_2$ | 4 | 4 | 4 | 4 | 4 | 4 | 30 |
| **34** | $NHCOCH_2CF_3$ | 4 | 8 | 8 | 4 | 4 | 4 | |
| **35** | NHCHS | 1 | 1 | 1 | 1 | 1 | 2 | 9.07 |
| **36** | NHCSMe | 0.5 | 0.5 | 0.5 | 1 | 1 | 1 | 30 |
| **37** | $NHCSCH_2CH_3$ | 0.5 | 0.5 | 1 | 0.5 | 0.5 | 0.5 | 30 |
| **38** | $NHCSCH_2CH_2CH_3$ | 1 | 2 | 2 | 1 | 1 | 1 | 30 |
| **39** | $NHCS(CH_2)_3CH_3$ | 2 | 2 | 4 | 2 | 2 | 2 | |
| **41** | NHCSOMe | 0.5 | 1 | 1 | 0.5 | 0.5 | 0.5 | 4.85 |
| **42** | NHCSOEt | 1 | 2 | 2 | 2 | 2 | 2 | |
| **43** | $NHCSOCH(CH_3)_2$ | 8 | 8 | 8 | 8 | 16 | 8 | |
| **44** | $NHCSO(CH_2)_3CH_3$ | >32 | >32 | >32 | >32 | >32 | >32 | |
| **45** | $NHCSNH_2$ | 05 | 0.5 | 0.5 | 1 | 1 | 1 | |
| **46** | NHCSNHMe | 2 | 4 | 4 | 2 | 4 | 4 | |
| **47** |  | 16 | 16 | 16 | 16 | 16 | 16 | |
| **48** |  | 16 | 16 | 16 | 16 | 16 | 16 | |
| **49** |  | 32 | 32 | 32 | 32 | 32 | 32 | |
| **50** | $NHCO_2Me$ | 2 | 2 | 2 | 2 | 2 | 2 | 3.3 |
| **51** | $NHCO_2Et$ | 8 | 8 | 8 | 8 | 8 | 8 | |
| **52** | $NHCS_2Me$ | 1 | 1 | 2 | 1 | 1 | 1 | 30 |
| **53** |  | >32 | >32 | >32 | >32 | >32 | >32 | |
| Linezolid | | 1 | 2 | 2 | 2 | 2 | 2 | 3.91 (2.40-5.42)[b] |
| Vancomycin | | 2 | 1 | 1 | 2 | >32 | >32 | 3.93[c] (3.59-4.27) |

[a] See the footnote of Table 1 for the details regarding the organisms. [b] Values in the parentheses denote 95% confidence limits. [c] $ED_{50}$ of Vancomycin administered by SC route.

are reported in $\delta$ units with respect to tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a HP-5989A spectrometer. Combustion analyses were obtained using a Perkin-Elmer 2400 analyzer. All analytical work was carried out by the Analytical Research Department of Dr. Reddy's Research Foundation. Unless otherwise mentioned, all of the solvents used were of LR grade. Usually, the flash chromatography was performed using 100−200 mesh silica gel. All of the organic extracts were dried over sodium sulfate after work up. All high-performance liquid chromatographies (HPLC) were run either with "system 1", which consisted of an Inertsil ODS 3V column (250 mm), 0.01 M $KH_2PO_4$/$CH_3CN$ 50:50 at 1 mL/min flow rate, 225 nm, or with "system 2", which consisted of a Hichrom RPB column (250 mm), 0.01 M $KH_2PO_4$/$CH_3CN$ 50:50 at 1 mL/min flow rate, 220 nm.

**(6a*S*)-3-Nitro-6a,7,8,9-tetrahydro-6H-azolo[1,2-d]benzo-[*b*][1,4]oxazine 6.** To a solution of L-prolinol (0.761 g, 7.54 mmol) in dry DMSO (10 mL) was added KOH (1.05 g, 18.8 mmol) followed by 3,4 difluoronitrobenzene (1.0 g, 6.28 mmol) dropwise over a period of 2 min. The reaction mixture was heated to 60 °C for 4 h and then allowed to cool to room temperature. The nitro compound **6** precipitated upon addition of ice pieces that were filtered to give a yellow solid (1.1 g, 72% yield); mp 159 °C. IR (KBr): 1600, 1487, 1292 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.85 (dd, $J$ = 8.8, 2.4 Hz, 1H), 7.72 (d, $J$ = 2.4 Hz, 1H), 6.42 (d, $J$ = 9.3 Hz, 1H), 4.55 (dd, $J$ = 10.3, 3.4 Hz, 1H), 3.28−3.72 (m, 4H), 2.22−1.94 (m, 3H), 1.53−1.39 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 141.0, 140.7, 135.1, 119.9, 110.3, 109.6, 67.6, 55.4, 47.1, 27.8, 23.0. MS 220 ($M^+$), 190, 174. Anal. ($C_{11}H_{12}N_2O_3$) C, H; N: calcd, 12.73; found, 12.55.

**Benzyl(6a*S*)-6a,7,8,9-tetrahydro-6H-azolo[1,2-d]benzo-[*b*][1,4]oxazine-3-carboxylate 7.** To a solution of nitro compound **6** (1.1 g, 5 mmol) in ethanol (8 mL) at 0 °C was added hydrochloric acid (35%, 8 mL) followed by electrolytic iron powder (2.8 g, 50 mmol) portionwise over a period of 5 min. The reaction mixture was stirred at room temperature while monitoring by thin-layer chromatography (TLC) and was worked up after 1 h by adding saturated $K_2CO_3$ solution (pH 8) followed by extraction with ethyl acetate. The combined organic extracts were washed with water and brine, and dried. The intermediate amine was obtained upon evaporation of solvent as a gum (800 mg, 84% yield), which was directly taken up for the next step without any purification. IR (neat): 3348, 1514, 1169 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 6.49 (d, $J$ = 8.2 Hz, 1H), 6.30−6.26 (m, 2H), 4.38−4.20 (m, 1H), 3.50−2.95 (m, 4H), 2.20−1.80 (m, 3H), 1.55−1.30 (m, 1H). MS 190 ($M^+$), 161.

To a solution of the above amine (800 mg, 4.21 mmol) in acetone (15 mL) at 0 °C was added aqueous $Na_2CO_3$ (10%, 892 mg, 8.42 mmol) followed by benzylchloroformate (50% solution in toluene, 1.5 mL, 5.25 mmol) dropwise over a period of 3 min. The reaction mixture was stirred at room temperature for 4 h and was worked up by adding water followed by extraction with ethyl acetate. The combined organic extracts were washed with water and brine and dried. The residue obtained upon evaporation of solvent was chromatographed over silica gel and eluted with 40% ethyl acetate:pet-ether to afford the protected amine **7** as a white solid (1 g, 73% yield); mp 82 °C. IR (film): 1705, 1522, 1218 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.37 (s, 5H), 6.89 (bs, 1H), 6.60−6.45 (m, 2H), 5.17 (s, 2H), 4.38 (d, $J$ = 8.1 Hz, 1H), 3.60−3.10 (m, 4H), 2.20−1.85 (m, 3H), 1.55−1.30 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 153.5, 142.6, 136.9, 131.0, 128.8, 128.4 (2C), 128.0 (2C), 127.9, 112.8, 112.3, 107.1, 68.0, 65.4, 55.0, 48.2, 27.6, 23.2. MS 324 ($M^+$), 216, 189, 108, 91. Anal. ($C_{19}H_{20}N_2O_3$) C, H, N.

**(5*R*)-3-[(6a*S*)-6a,7,8,9-Tetrahydro-6H-azolo[1,2-d]benzo-[*b*][1,4]oxazin-3-yl]-5-hydroxymethyl-1,3-oxazolan-2-one 8.** To a solution of tricyclic compound **7** (1.0 g, 3.08 mmol) in dry THF (20 mL) at −78 °C under argon atmosphere was added butyllithium (1.6 M in hexanes, 2.3 mL, 3.69 mmol) dropwise over a period of 5 min. The reaction mixture was stirred at −78 °C for 1 h followed by addition of (*R*)-(−)-glycidylbutyrate (0.53 mL, 3.69 mmol). The reaction mixture was stirred initially at −78 °C for 1 h and then at room temperature for 5 h. The reaction mixture was quenched by addition of saturated $NH_4Cl$ solution and then extracted with ethyl acetate. The combined organic extracts were washed with water and brine and dried. The residue obtained upon evaporation of solvent was chromatographed over silica gel and eluted with ethyl acetate to give the oxazolidinone alcohol **8** as a solid (510 mg, 56% yield); mp 173 °C. IR (KBr): 3396, 1708, 1529, 1133 $cm^{-1}$. $^1H$ NMR ($CDCl_3$ + DMSO-$d_6$): $\delta$ 7.06 (d, $J$ = 2.4 Hz, 1H), 6.96 (dd, $J$ = 8.6, 2.4 Hz, 1H), 6.53 (d, $J$ = 8.5 Hz, 1H), 4.88 (bs, 1H), 4.75−4.55 (m, 1H), 4.42 (dd, $J$ = 9.5, 2.4 Hz, 1H), 4.05−3.10 (m, 8H), 2.25−1.90 (m, 3H), 1.60−1.35 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 154.6, 142.5, 131.9, 128.1, 112.4, 112.3, 107.1, 72.9, 68.0, 61.8, 55.1, 48.0, 46.6, 27.7, 23.2. MS 290 ($M^+$), 216, 114. Anal. ($C_{15}H_{18}N_2O_4$) C, H, N.

**(5*R*)-3-[(6a*S*)-6a,7,8,9-Tetrahydro-6H-azolo[1,2-d]benzo-[*b*][1,4]oxazin-3-yl]-5-azidomethyl-1,3-oxazolan-2-one 9.** To a solution of the alcohol **8** (510 mg, 1.75 mmol) in dry dichloromethane (15 mL) at 0 °C under argon atmosphere was added triethylamine (0.61 mL, 4.39 mmol) followed by methanesulfonyl chloride (0.16 mL, 2.1 mmol) dropwise over a period of 2 min. The reaction mixture was stirred at 0 °C for 1 h and was worked up by adding water followed by extraction with dichloromethane. The combined organic extracts were washed with water and brine and dried. The solvent was evaporated to give the mesylate as a gum (600 mg, 93% yield), which was taken up for the next step without any purification. IR (KBr): 1736, 1521, 1176 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.05−6.90 (m, 2H), 6.54 (d, $J$ = 8.3 Hz, 1H), 4.75−4.90 (m, 1H), 4.55−4.30 (m, 4H), 4.06 (t, $J$ = 9.1 Hz, 1H), 3.92−3.75 (m, 1H), 3.60−3.10 (m, 4H), 3.09 (s, 3H), 2.20−1.90 (m, 3H), 1.55−1.35 (m, 1H). MS (CI method) 369 ($M + H)^+$, 91.

To a solution of the above mesylate (600 mg, 1.63 mmol) in dry dimethyl formamide (DMF, 10 mL) under argon atmosphere was added sodium azide (212 mg, 3.26 mmol), and the resulting mixture was stirred at 80 °C for 2 h. The reaction mixture was allowed to cool to room temperature and worked up by addition water followed by extraction with ethyl acetate. The combined organic extracts were washed with water and brine and dried. The residue obtained upon evaporation of solvent was chromatographed over silica gel and eluted with 70% ethyl acetate:pet-ether to give the azide **9** as a white solid (300 mg, 58% yield); mp 180 °C. IR (KBr): 2096, 1725, 1518 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.10−6.95 (m, 2H), 6.57 (d, $J$ = 9.3 Hz, 1H), 4.85−4.65 (m, 1H), 4.44 (dd, $J$ = 9.5, 2.4 Hz, 1H), 4.04 (t, $J$ = 8.9 Hz, 1H), 3.85−3.10 (m, 7H), 2.25−1.90 (m, 3H), 1.60−1.35 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 153.7, 142.2, 131.9, 127.4, 112.5, 112.2, 107.2, 70.8, 67.8, 54.9, 52.7, 47.8, 47.4, 27.6, 23.1. MS 315 ($M^+$), 287, 216, 202.

**N1-{(5*S*)-3-[(3a*R*)-1,2,3,3a,4,9b-Hexahydrocyclopenta-[c]chromen-7-yl]-2-oxo-1,3-oxazolan-5-ylmethyl}acetamide 3.** A solution of the azide **9** (300 mg, 0.952 mmol) in thiolacetic acid (1.5 mL) was stirred under argon atmosphere for 14 h at room temperature. The contents were adsorbed on silica gel and purified on a column of silica gel and eluted with ethyl acetate to give the tricyclic acetamide **3** (200 mg, 63% yield); mp 182 °C. IR (KBr): 3365, 1750, 1520, 1226 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.05−6.85 (m, 2H), 6.52 (d, $J$ = 8.4 Hz, 1H), 6.20 (bt, 1H), 4.80−4.60 (m, 1H), 4.41 (dd, $J$ = 9.6, 2.5 Hz, 1H), 3.98 (t, $J$ = 9.1 Hz, 1H), 3.80−3.10 (m, 7H), 2.20−1.85 (m, 6H), 1.55−1.30 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 170.0, 154.3, 142.5, 132.1, 127.9, 112.7, 112.4, 107.5, 71.2, 68.0, 55.1, 48.0, 47. 9, 41.5, 27.7, 23.2, 22.4. MS 331 ($M^+$), 287, 228, 203.

**(2*S*)-1-(2,6-Difluoro-4-nitrophenyl)azolan-2-ylmethanol 11.** To a solution of L-prolinol (9.7 g, 96 mmol) in dry acetonitrile (100 mL) was added triethylamine (33.46 mL, 240 mmol) followed by 3,4,5-trifluoronitrobenzene **10** (16.99 g, 96 mmol) dropwise over a period of 5 min under argon atmosphere. The reaction mixture was stirred at room temperature for 14 h and worked up by adding water followed by extraction with ethyl acetate. The combined organic extracts were washed with water and brine and dried. The residue obtained upon evaporation of solvent was chromatographed over silica gel and eluted with 30% ethyl acetate:pet-ether to afford the nitro alcohol **11** as viscous oil (15 g, 60% yield); mp 82 °C. IR

(neat): 3384, 1510, 1320 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.85−7.60 (m, 2H), 4.38 (bs, 1H), 4.00−3.30 (m, 4H), 2.30−1.50 (m, 4H). MS 258 ($M^+$), 227, 181, 139. Anal. ($C_{11}H_{12}N_2O_3F_2$) C, H; N: calcd, 10.85; found, 10.31.

**(6a*S*)-1-Fluoro-3-nitro-6a,7,8,9-tetrahydro-6H-azolo-[1,2-d]benzo[*b*][1,4]oxazine 12.** To a solution of the nitro alcohol **11** (15.0 g, 58 mmol) in dry DMSO (100 mL) was added powdered KOH (9.78 g, 174.41 mmol). After it was stirred for 2 h at 80 °C, the reaction mixture was worked up by adding water and extracting with ethyl acetate. The combined organic extracts were washed with water and brine and dried. The residue obtained upon evaporation of solvent was chromatographed over silica gel and eluted with 40% ethyl acetate:pet-ether to obtain the tricyclic nitro compound **12** as yellow solid (12.5 g, 90% yield); mp 135 °C. IR (KBr): 1498, 1306 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.63−7.55 (m, 2H), 4.48 (dd, $J$ = 10.3, 3.2 Hz, 1H), 4.10−3.95 (m, 1H), 3.60−3.33 (m, 3H), 2.25−1.95 (m, 3H), 1.60−1.35 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 148.6 (d, $J$ = 238.4 Hz, 1C), 143.0 (d, $J$ = 8.0 Hz, 1C), 134.0 (d, $J$ = 13.1 Hz, 1C), 130.5 (d, $J$ = 14.2 Hz, 1C), 107.9, 105.9 (d, $J$ = 25.9 Hz, 1C), 67.0, 55.5, 50.6 (d, $J$ = 9.5 Hz, 1C), 26.5, 23.4. MS 238 ($M^+$), 208, 192, 162.

**Benzyl(6aS)-1-fluoro-6a,7,8,9-tetrahydro-6H-azolo[1,2-d]benzo[*b*][1,4]oxazine-3-carboxylate 13.** The nitro compound **12** (12.5 g, 52.52 mmol) was reduced as per the earlier procedure for the reduction of compound **6** in ethanol (40 mL) using hydrochloric acid (35%, 40 mL) and electrolytic iron powder (14.7 g, 262.6 mmol). The intermediate amine was obtained (10.5 g, 96% yield) that was used in the next step without purification. IR (KBr): 3459, 3310, 3192, 1648, 1505 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 6.15−6.05 (m, 2H), 4.20−3.95 (m, 1H), 3.90−3.20 (m, 4H), 2.81−2.68 (m, 1H), 2.30−1.75 (m, 3H), 1.60−1.35 (m, 1H). MS 208 ($M^+$), 179.

The above amine in acetone (150 mL) was converted to the protected amine **13**, using aqueous $Na_2CO_3$ (10%, 6.42 g, 60.58 mmol) and benzylchloroformate (50% solution in toluene, 10.2 mL, 60.58 mmol) as described before for compound **7**, as a colorless solid (13.2 g, 76% yield); mp 137 °C. IR (KBr): 3333, 1730, 1540, 1229 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.35 (s, 5H), 6.86 (d, $J$ = 13.4 Hz, 1H), 6.62 (s, 1H), 6.50 (s, 1H), 5.15 (s, 2H), 4.18−4.12 (m, 1H), 3.90−3.75 (m, 1H), 3.50−3.20 (m, 2H), 2.97−2.84 (m, 1H), 2.25−1.80 (m, 3H), 1.55−1.35 (m, 1H). MS 342 ($M^+$), 234, 207, 91. Anal. ($C_{19}H_{19}N_2O_3F$) C, N; H: calcd, 5.59; found, 5.44.

**(5*R*)-3-[(6a*S*)-1-Fluoro-6a,7,8,9-tetrahydro-6H-azolo-[1,2-d]benzo[*b*][1,4]oxazin-3-yl]-5-hydroxymethyl-1,3-oxazolan-2-one 14.** To a solution of the compound **13** (8.0 g, 23.39 mmol) in dry THF (150 mL) at −78 °C under argon atmosphere was added butyllithium (1.6 M in hexanes, 18.73 mL, 28 mmol) dropwise over a period of 30 min. The reaction mixture was stirred at −78 °C for 1 h followed by addition of (*R*)-(−)-glycidylbutyrate (3.97 mL, 28 mmol). The reaction mixture was further stirred at −78 °C for 1 h and then at room temperature for 14 h. The resultant mixture was worked up and purified as before to give the oxazolidinone alcohol **14** as a colorless solid (5.0 g, 69% yield); mp 195 °C. IR (KBr): 3435, 1714, 1510 $cm^{-1}$. $^1H$ NMR ($CDCl_3$ + DMSO-$d_6$): $\delta$ 7.06 (dd, $J$ = 13.4, 2.4 Hz, 1H), 6.74 (s, 1H), 4.70−4.55 (m, 1H), 4.40−4.10 (m, 2H), 3.95−3.29 (m, 6H), 3.00−2.85 (m, 1H), 2.30−1.80 (m, 3H), 1.60−1.35 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 153.4 (d, $J$ = 237.2 Hz, 1C), 154.3, 146.1 (d, $J$ = 8.1 Hz, 1C), 130.3 (d, $J$ = 13.1 Hz, 1C), 119.7 (d, $J$ = 14.4 Hz, 1C), 102.3, 98.9 (d, $J$ = 25.6 Hz, 1C), 73.1, 65.8, 61.7, 54.2, 51.7, 46.1, 26.1, 23.2. MS 308 ($M^+$), 234.

**(5*R*)-3-[(6a*S*)-1-Fluoro-6a,7,8,9-tetrahydro-6H-azolo-[1,2-d]benzo[*b*][1,4]oxazin-3-yl]-5-azidomethyl-1,3-oxazolan-2-one 15.** The alcohol **14** (5.0 g, 16.23 mmol) was treated with triethylamine (5.66 mL, 40.58 mmol) and methanesulfonyl chloride (15.4 mL, 19.48 mmol) in dry $CH_2Cl_2$ (100 mL) as described before to obtain its corresponding mesylate as viscous oil (5.8 g, 93% yield). IR (neat): 1753, 1510, 1176 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 6.99 (dd, $J$ = 13.7, 2.4 Hz, 1H), 6.73 (s, 1H), 4.95−4.80 (m, 1H), 4.60−3.75 (m, 6H), 3.50−3.20 (m, 2H), 3.20−2.90 (m, 4H), 2.25−1.80 (m, 3H), 1.60−1.30 (m, 1H). MS 386 ($M^+$), 245.

To a solution of the above mesylate in dry DMF (50 mL) under argon atmosphere was added sodium azide (1.95 g, 30 mmol), and the resultant mixture was stirred at 60 °C for 2 h. The work up and purification as before afforded the azide **15** as a colorless solid (4.8 g, 96% yield); mp 124 °C. IR (KBr): 2095, 1733, 1508 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.05 (dd, $J$ = 13.4, 2.4 Hz, 1H), 6.76 (s, 1H), 4.95−4.65 (m, 1H), 4.23 (dd, $J$ = 9.8, 2.4 Hz, 1H), 4.10−3.20 (m, 7H), 3.10−2.90 (m, 1H), 2.30−1.90 (m, 3H), 1.60−1.40 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 153.3 (d, $J$ = 237.7 Hz, 1C), 153.6, 146.0 (d, $J$ = 8.65 Hz, 1C), 129.8 (d, $J$ = 13.15 Hz, 1C), 119.9 (d, $J$ = 14.5 Hz, 1C), 102.6 (d, $J$ = 2.4 Hz, 1C), 99.1 (d, $J$ = 26.0 Hz, 1C), 71.1, 65.8, 54.1, 52.7, 51.7 (d, $J$ = 6.6 Hz, 1C), 47.0, 26.1, 23.2. MS 333 ($M^+$), 305, 260, 234, 220. Anal. ($C_{15}H_{16}N_5O_3SF$) H; C: calcd, 54.03; found, 53.52; and N: calcd, 21.02; found, 20.51.

**N1-{(5*S*)-3-[(6a*S*)-1-Fluoro-6a,7,8,9-tetrahydro-6H-azolo-[1,2-d]benzo[*b*][1,4]oxazin-3-yl]-2-oxo-1,3-oxazolan-5-ylmethyl}acetamide 16.** A solution of the azide **15** (150 mg, 0.45 mmol) in thiolaceticacid (0.5 mL) was stirred at room temperature under argon atmosphere for 14 h. The contents were adsorbed on silica gel and purified by column chromatography (elution with ethyl acetate) to give the acetamide **16** (110 mg, 70% yield); mp 162 °C. IR (KBr): 3341, 1741, 1662, 1511 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.00 (dd, $J$ = 13.7, 2.4 Hz, 1H), 6.73 (s, 1H), 6.30 (bt, 1H), 4.85−4.65 (m, 1H), 4.21 (dd, $J$ = 9.8, 2.4 Hz, 1H), 4.05−3.25 (m, 7H), 3.10−2.90 (m, 1H), 2.30−1.80 (m, 3H), 2.01 (s, 3H), 1.60−1.35 (m, 1H). MS 349 ($M^+$), 305, 246, 221. HPLC (system 1) 95.3% purity.

**General Procedure for the Conversion of Azides 9 and 15 to the Corresponding Amines 17 and 18.** Triphenylphosphine (1.3 equiv) was added portionwise to a solution of the azide in dry THF, and the resultant mixture was stirred at room temperature for 6 h. Water (few drops) was added, and the reaction mixture was heated to 60 °C overnight. The solvent was evaporated, and the residue was passed through a column of silica gel to afford the respective amine.

**Amine 17.** On the basis of the above procedure, the azide **9** (3.5 g, 11.1 mmol) afforded the amine **17** (3.08 g, 96% yield); mp 115 °C. IR (KBr): 3379, 3308, 1737, 1523, 1197 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.10−6.95 (m, 2H), 6.60−6.45 (m, 1H), 4.70−4.55 (m, 1H), 4.41 (dd, $J$ = 9.7, 2.7 Hz, 1H), 4.05−2.90 (m, 8H), 2.20−1.90 (m, 3H), 1.55−1.35 (m, 1H). MS (CI method) 290 $(M + 1)^+$.

**Amine 18.** On the basis of the above procedure, the azide **15** (2.8 g, 8.4 mmol) afforded the amine **18** (2.3 g, 89% yield); mp 132 °C. IR (KBr): 3405, 1732, 1510, 1231 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.07 (dd, $J$ = 13.8, 2.4 Hz, 1H), 6.75 (s, 1H), 4.75−4.55 (m, 1H), 4.21 (dd, $J$ = 10.0, 2.4 Hz, 1H), 4.00−2.85 (m, 8H), 2.40−1.80 (m, 3H), 1.60−1.40 (m, 1H). MS (CI method) 308 $(M + 1)^+$.

**General Procedure for the Preparation of Formamides 19 and 25.** A solution of amine **17** or **18** in ethyl formate was heated to 80 °C overnight. The volatiles were removed under reduced pressure, and the residue obtained was passed through column to yield the formamides **19** and **25**, respectively.

**Compound 19.** mp 160 °C. IR (KBr): 3327, 1733, 1872, 1521 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 8.20 (s, 1H), 6.95−6.86 (m, 2H), 6.47 (d, $J$ = 8.6 Hz, 1H), 6.31 (bs, 1H), 4.80−4.60 (m, 1H), 4.36 (dd, $J$ = 14.1, 2.6 Hz, 1H), 3.99−3.10 (m, 8H), 2.09−1.82 (m, 3H), 1.50−1.30 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 161.9, 154.3, 142.5, 132.2, 127.8, 112.7, 112.4, 107.5, 71.1, 68.1, 55.1, 48.0, 47. 9, 40.1, 27.7, 23.2. MS 317 ($M^+$), 227, 185.

**Compound 25.** mp 171 °C. IR (KBr): 3308, 1741, 1510 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 8.27 (s, 1H), 6.99 (dd, $J$ = 13.7, 2.4 Hz, 1H), 6.74 (s, 1H), 6.48 (bs, 1H), 4.83−4.70 (m, 1H), 4.30−2.90 (m, 9H), 2.28−1.75 (m, 3H), 1.60−1.40 (m, 1H). MS 335 ($M^+$), 291, 246, 241. HPLC (system 2) 97.9% purity.

**General Procedure for the Conversion of Amines 17 and 18 to the Amides 20−23 and 26−33.** To a solution of the appropriate amine (1 equiv) in dry dichloromethane at 0 °C under argon was added $Et_3N$ (2.5 equiv) followed by the

respective acid chloride (1.2 equiv) dropwise. After it was stirred at room temperature for 1−6 h (TLC control), the reaction mixture was diluted with dichloromethane and washed with water twice followed by brine. The organic extract was dried, was evaporated, and was passed through a column to afford the acylated product.

**Compound 20.** mp 171 °C. IR (KBr): 3329, 1724, 1673, 1520 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.00−6.85 (m, 2H), 6.50 (d, $J$ = 8.3, 1H), 6.40−6.00 (m, 3H), 5.75−5.60 (m, 1H), 4.90−4.65 (m, 1H), 4.39 (dd, $J$ = 9.5, 2.4 Hz, 1H), 4.10−2.90 (m, 8H), 2.20−1.85 (m, 3H), 1.60−1.35 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 165.2, 154.2, 142.4, 132.0, 131.2, 127.7, 125.7, 112.7, 112.3, 107.5, 71.2, 68.0, 55.0, 48.0, 41.6, 27.7, 23.2. MS 343 ($M^+$), 299, 227, 203.

**Compound 21.** mp 158 °C. IR (KBr): 3326, 2930, 1732, 1628 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.00−6.85 (m, 2H), 6.52 (d, $J$ = 9.7, 1H), 6.05−5.90 (bt, 1H), 4.80−4.65 (m, 1H), 4.45−4.35 (m, 1H), 3.97 (t, $J$ = 9.0 Hz, 1H), 3.75−3.10 (m, 7H), 2.45−1.85 (m, 4H), 1.60−1.10 (m, 7H). MS 359 ($M^+$), 315, 224, 143, 99.

**Compound 22.** mp 148 °C. IR (KBr): 3314, 1734, 1679, 1520 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.15−6.85 (m, 3H), 6.52 (d, $J$ = 8.8, 1H), 4.80−4.65 (m, 1H), 4.39 (dd, $J$ = 9.5, 2.4 Hz, 1H), 4.15−3.10 (m, 10H), 2.20−1.80 (m, 3H), 1.60−1.35 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 166.8, 154.2, 142.5, 132.1, 127.8, 112.8, 112.4, 107.6, 70.9, 68.0, 55.1, 48.0, 47. 9, 42.5, 41.9, 27.7, 23.2. MS 367 ($M + 2$)$^+$, 365 ($M^+$), 228, 203, 185.

**Compound 23.** mp 194 °C. IR (KBr): 3327, 2930, 1627 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.10−6.90(m, 3H), 6.52 (d, $J$ = 8.6 Hz, 1H), 5.95(s, 1H), 4.85−4.70(m, 1H), 4.41(dd, $J$ = 9.5, 2.7 Hz, 1H), 4.20−3.10 (m, 8H), 2.10−1.95 (m, 3H), 1.60−1.35 (m, 1H). MS 399 ($M - 1$)$^+$, 224, 143, 99. HPLC (system 1) 95.6% purity.

**Compound 31.** mp 192 °C. IR (KBr): 3323, 1742, 1663, 1512 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.02 (dd, $J$ = 13.7, 2.4 Hz, 1H), 6.73 (s, 1H), 6.40−6.00 (m, 4H), 5.71 (d, $J$ = 9.8 Hz, 1H), 4.85−4.70 (m, 1H), 4.22 (dd, $J$ = 9.8, 2.4 Hz, 1H), 4.05−2.90 (m, 8H), 2.30−1.80 (m, 3H), 1.60−1.40 (m, 1H). MS 361 ($M^+$), 317, 246, 221. HPLC (system 1) 99.2% purity.

**Compound 32.** mp 152 °C. IR (KBr): 3319, 1740, 1681, 1512 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.10−6.95 (m, 2H), 6.70 (s, 1H), 4.85−4.65 (m, 1H), 4.20 (dd, $J$ = 9.8, 2.4 Hz, 1H), 4.05 (s, 2H), 3.99−2.90 (m, 8H), 2.30−1.80 (m, 3H), 1.60−1.40 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 201.4, 153.3 (d, $J$ = 237.4 Hz, 1C), 153.8, 146.0 (d, $J$ = 8.8 Hz, 1C), 129.9 (d, $J$ = 13.2 Hz, 1C), 120.0 (d, $J$ = 14.6 Hz, 1C), 102.7, 99.3 (d, $J$ = 25.7 Hz, 1C), 70.1, 65.8, 54.2, 51.7 (d, $J$ = 6.4 Hz, 1C), 48.1, 47.5, 32.8, 26.1, 23.2. MS 383 ($M^+$), 339, 246, 221. HPLC (system 1) 96.7% purity.

**Compound 33.** mp 182 °C. IR (KBr): 3323, 1742, 1663, 1512 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.02 (dd, $J$ = 13.7, 2.4 Hz, 1H), 6.73 (s, 1H), 6.40−6.00 (m, 4H), 5.71 (d, $J$ = 9.8 Hz, 1H), 4.85−4.70 (m, 1H), 4.22 (dd, $J$ = 9.8, 2.4 Hz, 1H), 4.05−2.90 (m, 8H), 2.30−1.80 (m, 3H), 1.60−1.40 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 165.2, 153.3 (d, $J$ = 237.4 Hz, 1C), 153.9, 145.9 (d, $J$ = 8.3 Hz, 1C), 131.2, 129.9 (d, $J$ = 13.2 Hz, 1C), 125.7, 119.8 (d, $J$ = 14.6 Hz, 1C), 102.6, 99.2 (d, $J$ = 26.0 Hz, 1C), 71.3, 65.8, 54.1, 51.7 (d, $J$ = 5.9 Hz, 1C), 47.4, 26.1, 23.2. MS 361 ($M^+$), 317, 246, 221. HPLC (system 1) 99.2% purity.

**General Procedure for the Preparation of Thioamides 35−39.** A solution of the amide (1 equiv) and Lawesson's reagent (0.6 equiv) in dry dioxane was heated to 55−90 °C over 3−10 h (TLC control). The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate. The resultant mixture was washed with water (four times) followed by brine and dried. The residue obtained upon evaporation of solvent was passed through a column of silica gel to afford the respective thioamide.

**Compound 35.** mp 149 °C. IR (KBr): 3440, 1746, 1511 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 9.54 (d, $J$ = 6.2 Hz, 1H), 8.42 (s, 1H), 6.95 (dd, $J$ = 13.4, 2.4 Hz, 1H), 6.72 (s, 1H), 5.05−4.95 (m, 1H), 4.26−4.18 (m, 3H), 4.06−3.73 (m, 3H), 3.48−3.28 (m, 2H), 3.07−2.94 (m, 1H), 2.30−1.90 (m, 3H), 1.60−1.40 (m, 1H). HPLC (system 2) 95.0% purity.

**Compound 36.** mp 149 °C. IR (KBr): 3296, 1743, 1511, 1241 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 8.11 (bs, 1H), 7.01 (dd, $J$ = 13.2, 2.0 Hz, 1H), 6.74 (s, 1H), 5.05−4.85 (m, 1H), 4.40−2.90 (m, 9H), 2.62 (s, 3H), 2.30−1.90 (m, 3H), 1.60−1.40 (m, 1H). HPLC (system 2) 95.2% purity.

**Preparation of Isothiocyanate 40.** Thiophosgene (200 mg, 1.8 mmol) was added dropwise to a solution of the amine **18** (450 mg, 1.5 mmol) and $Et_3N$ (0.5 mL, 3.7 mmol) in dry dichloromethane at ice bath temperature under argon. The reaction mixture was warmed to room temperature over 3 h, and then, the volatiles were removed. The residue obtained was directly charged on to a column of silica gel to afford the product **40** (350 mg, 68% yield); mp 164 °C. IR (KBr): 2117, 1748, 1512, 1247 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.04 (dd, $J$ = 13.7, 2.4 Hz, 1H), 6.77 (s, 1H), 4.90−4.70 (m, 1H), 4.35−3.25 (m, 8H), 3.10−2.90 (m, 1H), 2.30−1.90 (m, 3H), 1.60−1.35 (m, 1H). MS (CI method) 350 ($M + 1$)$^+$.

**Preparation of Thiocarbamates 41−44.** A solution of the isothiocyanate **40** in the respective alcohol was heated to 80−100 °C while monitoring by TLC. At the complete consumption of starting material, the reaction mixture was allowed to cool to room temperature. The crystals formed were separated, washed with ether, and dried at vacuum to yield the pure product.

**Compound 41.** mp 201 °C. IR (KBr): 3247, 1752, 1512 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.03 (d, $J$ = 12.7 Hz, 1H), 6.85−6.70 (m, 2H), 4.95−4.60 (m, 1H), 4.30−2.90 (m, 12H), 2.30−1.40 (m, 3H), 1.60−1.40 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 161.9, 152.9 (d, $J$ = 237.9 Hz, 1C), 154.0, 146.1 (d, $J$ = 8.7 Hz, 1C), 130.0 (d, $J$ = 13.3 Hz, 1C), 120.0 (d, $J$ = 14.4 Hz, 1C), 102.7, 99.2 (d, $J$ = 25.8 Hz, 1C), 71.2, 65.8, 54.2, 51.8 (d, $J$ = 6.5 Hz, 1C), 47.4, 26.1, 23.2. MS 381 ($M$)$^+$, 349, 337, 221. HPLC (system 1) 97.5% purity. Anal. ($C_{17}H_{20}N_3O_4FS$) C, N; H: calcd, 5.29; found, 5.62.

**Preparation of Thiourea 45.** Ammonia gas was bubbled to a solution of isothiocyanate **40** in THF at −10 °C over 20 min. The resultant mixture was stirred at room temperature for 1 h and then diluted with ethyl acetate. The organic layer was washed with water (two times) and brine and dried. The residue obtained upon evaporation of the solvent was passed through a column of silica gel to afford the thiourea **45**; mp 157 °C. IR (KBr): 3357, 1752, 1511, 1246 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.60 (bs, 1H), 6.95−6.80 (m, 2H), 6.24 (bs, 2H), 5.00−4.80 (m, 1H), 4.30−2.90 (m, 11H), 2.35−1.90 (m, 3H), 1.60−1.20 (m, 1H). MS 409.

**Preparation of Thiourea 46−49.** A neat solution of isothiocyanate **40** in the appropriate amine (1 mL for 100 mg isothiocyanate) was stirred at room temperature over 4 h, and water was added to the reaction mixture followed by extraction with ethyl acetate. The residue obtained upon evaporation of the solvent was passed through a column of silica gel to afford the respective thiourea.

**Compound 46.** mp 148 °C. IR (KBr): 3376, 1731, 1512, 1240 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 6.94 (d, $J$ = 13.2 Hz, 1H), 6.80−6.40 (m, 2H), 5.00−4.90 (m, 1H), 4.35−2.90 (m, 12H), 2.30−1.80 (m, 3H), 1.60−1.40 (m, 1H).

**Compound 47.** mp 158 °C. IR (KBr): 3348, 1746, 1510, 1246 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.01 (dd, $J$ = 13.7, 2.4 Hz, 1H), 6.75 (s, 1H), 6.30−6.10 (bs, 1H), 4.40−2.90 (m, 13H), 2.68 (t, $J$ = 5.4 Hz, 4H), 2.30−1.80 (m, 3H), 1.60−1.40 (m, 1H). HPLC (system 1) 98.1% purity.

**General Procedure for the Preparation of Carbamates 50 and 51.** To a solution of the amine **18** (1 equiv) and $Et_3N$ (2.2 equiv) in dry dichloromethane was added alkyl chloroformate (1.2 equiv) under argon atmosphere at 0 °C. The reaction mixture was stirred at room temperature overnight and worked up by diluting with dichloromethane followed by washing with water and brine. The residue obtained after evaporation of the dried organic layer was passed through a column to afford the carbamate.

**Compound 50.** mp 204 °C. IR (KBr): 1754, 1708, 1511, 1246 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.04 (dd, $J$ = 13.7, 2.4 Hz, 1H), 6.73 (s, 1H), 5.30−5.10 (bs, 1H), 4.80−4.65 (m, 1H), 4.30−

2.90 (m, 11H), 2.30−1.80 (m, 3H), 1.60−1.40 (m, 1H). MS 365 $(M)^+$, 333, 246. HPLC (system 1) 98.9% purity.

**Preparation of Compound 52.** To an ice-cold mixture of amine **18** (1 equiv), $Et_3N$ (2 equiv), and water (few drops) in EtOH was added $CS_2$ (1 equiv) under argon. After the mixture was stirred overnight at room temperature, methyl iodide (1.1 equiv) in EtOH was added and the stirring was continued for 12 h. The volatiles were removed, and the residue was taken up in ethyl acetate. The organic mixture was washed with saturated $NaHCO_3$ solution, water, and brine and dried. The residue obtained upon evaporation of the solvent was passed through a column to afford the product **52**; mp 185 °C. IR (KBr): 3241, 1739,1513 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.60−7.45 (bs, 1H) 7.00 (dd, $J$ = 13.4, 2.0 Hz, 1H), 6.72 (s, 1H), 5.00−4.85 (m, 1H), 4.40−2.90 (m, 9H), 2.65 (s, 3H), 2.30−1.80 (m, 3H), 1.60−1.40 (m, 1H). HPLC (system 1) 96.7% purity.

**Preparation of Compounds 24 and 34.** To a solution of the amine **18** (250 mg, 0.81 mmol) in dry dichloromethane (20 mL) was added successively DCC (167 mg, 0.81 mmol) and DMAP (10 mg, 0.081 mmol) followed by 3,3,3-trifluoropropionic acid (149 mg, 0.98 mmol) at room temperature under argon atmosphere. After it was stirred for 6 h, the reaction mixture was diluted with chloroform, washed with water and brine, and dried. The residue obtained upon evaporation of the solvent was passed through a column of silica gel to afford compound **34** (150 mg, 44% yield); mp 183 °C. IR (KBr): 3342, 1742, 1680, 1514 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.00−6.80 (m, 1H), 6.72 (s, 1H), 4.85−4.70 (m, 1H), 4.23 (dd, $J$ = 9.8, 2.4 Hz, 1H), 4.05−2.90 (m, 10H), 2.30−1.80 (m, 3H), 1.60−1.40 (m, 1H). MS 417 $(M)^+$, 246, 221. HPLC (system 2) 92.94% purity.

The compound **24** was obtained using a similar procedure starting from amine **17** and difluroacetic acid; mp 146 °C. IR (KBr): 3330, 2930, 1700, 1518 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.05−6.85 (m, 3H), 6.52 (d, $J$ = 8.06 Hz, 1H), 5.92 (t, $J$ = 54.0 Hz, 1H), 4.85−4.65 (m, 1H), 4.41 (dd, $J$ = 9.5, 2.4 Hz, 1H), 4.10−3.10 (m, 8H), 2.20−1.85 (m, 3H), 1.60−1.35 (m, 1H). MS 367 $(M)^+$, 227, 185. HPLC (system 1) 95.7% purity.

**Preparation of Compound 53.** A solution of the amine **18** (250 mg, 0.81 mmol) and succinic anhydride (49 mg, 0.48 mmol) in toluene (15 mL) and DMSO (3 mL) was heated to 100 °C for 8 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate. The organic mixture was washed with water and brine and dried. The residue obtained upon evaporation of the solvent was passed through a column of silica gel to afford the product **53** (50 mg, 15% yield); mp 184 °C. IR (KBr): 1746, 1694, 1508 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 7.03 (dd, $J$ = 13.7, 2.4 Hz, 1H), 6.74 (s, 1H), 4.95−4.80 (m, 1H), 4.30−2.90 (m, 9H), 2.77 (s, 4H), 2.30−1.80 (m, 3H), 1.60−1.40 (m, 1H). MS 389 $(M)^+$, 345, 246. HPLC (system 1) 95.0% purity.

**In Vitro Tests.** The MICs of the test compounds were determined by the broth microdilution method as per the guidelines prescribed by National Committee for Clinical and Laboratory Standards (NCCLS).[25] Doubling dilution of the test compound in the range of 256−1 $\mu$g/mL was carried out in Mueller Hinton Medium (Difco). The organisms were added to obtain $(1-5) \times 10^5$ CFU/mL, and the plates were incubated overnight in ambient air at 35 °C. MIC was defined as the lowest concentration of compound that completely inhibits the growth of organism. Linezolid and Vancomycin were used as controls.

**In Vivo Tests.** The efficacy ($ED_{50}$) of selected compounds was evaluated in a murine systemic infection model. Overnight growth of *S. aureus* ATCC 29213 was inoculated into fresh brain heart infusion broth (BHIB, Difco) and incubated for 2−3 h on a rotary shaker (Innova, NBS) at 150 rpm at 35 °C. The inoculum was adjusted to $100 \times LD_{50}$ in 5% hog gastric mucin (Difco), and 0.5 mL was injected intraperitoneally to female Swiss Albino mice weighing 22−25 g ($n$ = 6). The test compound was suspended in 0.25% carboxy methyl cellulose and administered orally 1 and 6 h postinfection. The control group of mice ($n$ = 6) was administered saline. The mice were observed for 48 h, and the cumulative mortality was recorded. $ED_{50}$ was calculated by linear regression analysis. The mortality rate in untreated mice was 85−100%.

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