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Synthesis of novel tricyclic oxazolidinones by a tandem SN_2 and SNAr reaction: SAR studies on conformationally constrained analogues of Linezolid☆

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Abstract—A series of conformationally constrained analogues of Linezolid were synthesised by employing a tandem SN_2 and SNAr reaction as the key step and tested for antibacterial activity. While the hexahydroazolo-quinoxaline compounds were inactive, the tetrahydroazolo-benzothiazine compounds exhibited interesting antibacterial activity. The introduction of fluorine in the aromatic ring further made the compounds more potent in acetamide compounds resulting in an interesting analogue **32**. However, the introduction of fluorine (analogue **34**) on the already potent non-fluorine thiocarbamate **21** did not have any influence on the activity.

The emergence of multidrug-resistant Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermitis* (MRSE) and vancomycin-resistant enterococci (VRE) is of major concern.[1–5] In addition, an alarming situation has been created by the emergence of strains of glycopeptide-intermediate *S. aureus* (GISA) with reduced susceptibility to vancomycin.[6,7] Strains of common intestinal bacteria *Enterococcus faecalis* and *E. faecium* have been resistant to vancomycin for several years. Oxazolidinones are a new class of synthetic antibacterials with activity against Gram-positive bacteria and anaerobic bacteria, including resistant pathogens.[8]

The discovery of Linezolid as a new class of antibacterials particularly active against VREs has triggered widespread research in this area.[9] In an ongoing programme on the discovery of novel second generation oxazolidinones, we have earlier reported certain conformationally constrained analogues of Linezolid (e.g., compound **1**) after an initial lead identification and SAR studies on the right-hand side (Fig. 1).[10] However, we have not undertaken a SAR on the left-hand side of the molecule **1** to vary the oxygen heteroatom to other heteroatoms such as sulfur and nitrogen. In continuation of our efforts in this tricyclic group of oxazolidinones, we now report the synthesis and the SAR studies on the left hand side of the molecule. We have synthesised a number of tricyclic oxazolidinones analogous of **2** and **3** possessing substituted nitrogen and sulfur atom, respectively, instead of oxygen on the tricycle.

Synthesis of hexahydroazolo-quinoxaline compounds: Addition of L-prolinol onto 1-chloro-2,4-dinitrobenzene afforded the dinitro-alcohol **4** (Scheme 1). The compound **4** upon hydrogenation presumably resulted in the corresponding diamine-alcohol, which posed diffi-

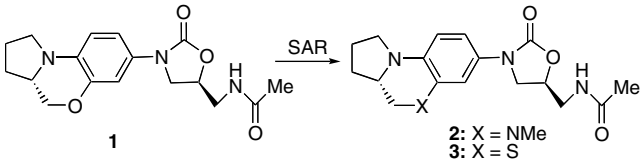

Figure 1.

Keywords: Oxazolidinones; Antibacterial; Tricyclic; Linezolid.
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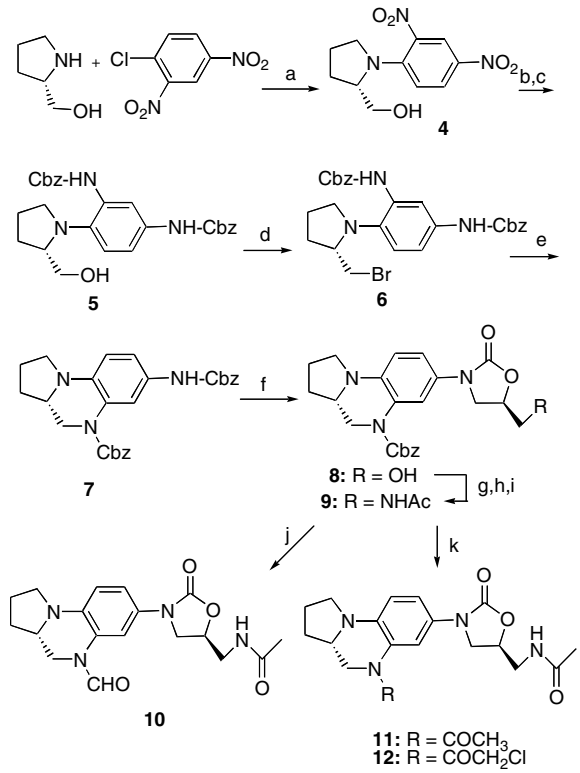
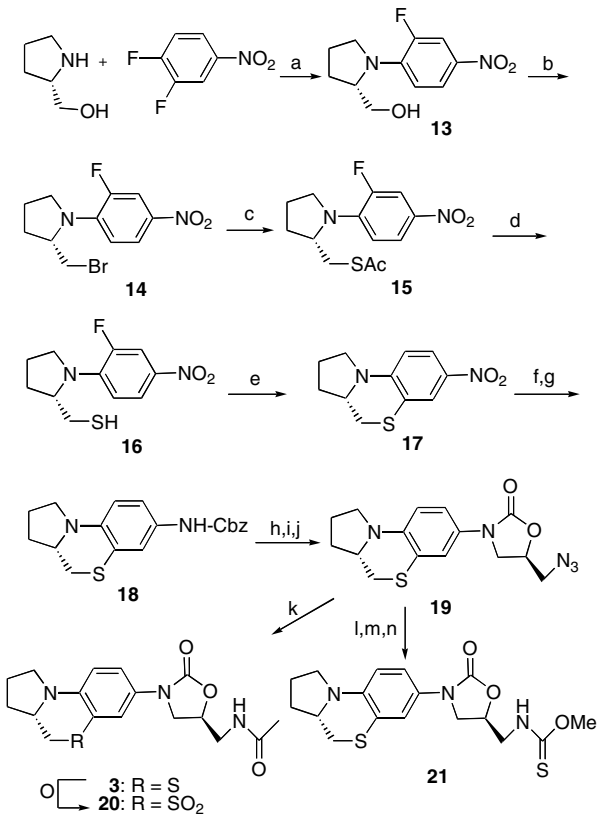


Scheme 1. Reagents and conditions: (a) Et_3N, CH_3CN, rt, 4 h, 94%; (b) 10% Pd on C, H_2, THF, 14 h; (c) Cbz-Cl, aq Na_2CO_3, acetone, rt, 2 h, 75% for two steps; (d) CBr_4, PPh_3, CH_2Cl_2, rt, 48 h, 70%; (e) K_2CO_3, DMF, rt, 28 h, 62%; (f) BuLi, (*R*)-glycidyl butyrate, THF, −78 °C to rt, 14 h, 58%; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C, 4 h, 96%; (h) NaN_3, DMF, 80 °C, 1 h, 91%; (i) MeCOSH, rt, 14 h, 68%; (j) 10% Pd on C, H_2 then HCOOEt, 41%; (k) 10% Pd on C, H_2 then AcCl (62%) or chloroacetyl chloride, Et_3N (55%).

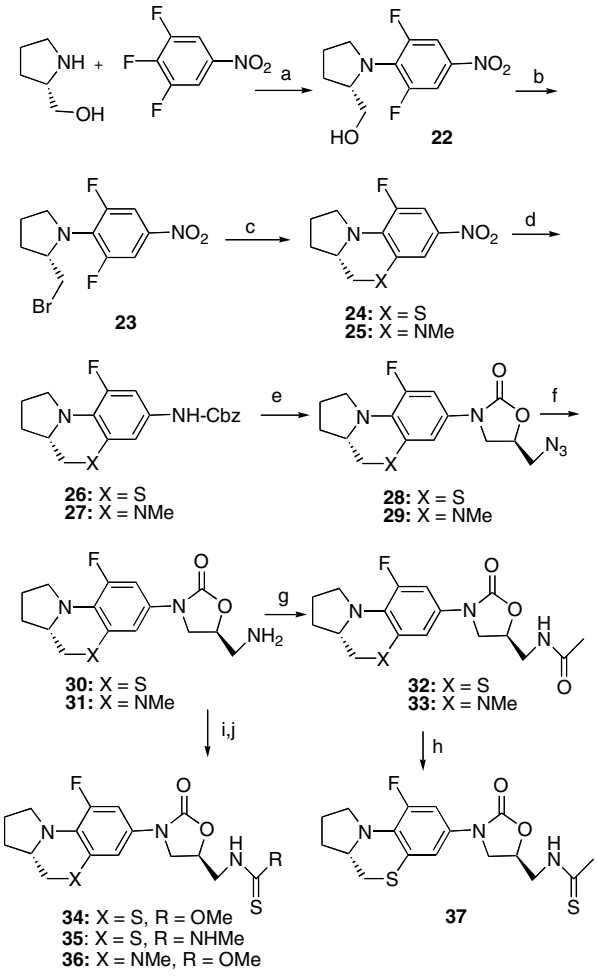


Scheme 2. Reagents and conditions: (a) Hunig's base, CH_3CN, rt, 5 h, 86%; (b) CBr_4, PPh_3, CH_2Cl_2, 0 to 45 °C, 5 h, 93%; (c) MeCOSH, NaH, THF, 8 h, 100%; (d) K_2CO_3, MeOH, reflux, 3 h, 66%; (e) NaH, DMF, 60 °C, 1 h, 46%; (f) Fe, HCl, EtOH, 0 °C to rt, 45 min.; (g) Cbz-Cl, aq Na_2CO_3, acetone, 0 °C to rt, 5 h, 81% for two steps; (h) BuLi, (*R*)-glycidyl butyrate, THF, −78 °C, 4 h, 56%; (i) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 90%; (j) NaN_3, DMF, 80 °C, 2 h, 91%; (k) MeCOSH, rt, 15 h, 65%; (l) PPh_3, H_2O, THF, 68%; (m) $CSCl_2$, Et_3N; (n) MeOH, reflux, 56% for two steps; (o) $NaIO_4$, CH_2Cl_2, 50%.

culty for isolation due to its instability and thus was directly treated with Cbz chloride in situ to produce the di-Cbz compound **5**. The compound **5** was converted into its bromo derivative **6** with CBr_4 and PPh_3, which was cyclised with K_2CO_3 in DMF to result in the tricyclic Cbz compound **7**. After this point, the compound **7** was converted into the acetamide **9** as per the usual literature procedures.[9] The attempts to deprotect the Cbz group to the corresponding free amine or as a salt failed to give the required material because of the instability of the product. Thus, we resorted to installing smaller groups such as formate, acetate and chloroacetate employing usual procedures of treating the amine in situ with the appropriate reagents to give the compounds **10**, **11** and **12**, respectively.

Synthesis of tetrahydroazolo-benzothiazine compounds: Addition of L-prolinol onto 3,4-difluoronitrobenzene resulted in the nitro-alcohol **13** (Scheme 2). The bromo compound **14**, obtained from the nitro-alcohol **13** as above, was converted to the thioacetate **15** with thioacetic acid. The treatment of the thioacetate **15** with K_2CO_3 in MeOH resulted in the thiol **16** that was cyclised with NaH in DMF to yield the tricyclic nitro compound **17**. The nitro compound **17** was converted into the acetamide **3** by essentially following the protocol described in Scheme 1.[11] The acetamide **3** was further converted to the sulfone **20** with sodium metaperiodate. The intermediate azide **19** could be converted to the thiocarbamate **21** following usual reaction conditions.

Synthesis of fluorine containing hexahydroazolo-quinoxaline and tetrahydroazolo-benzothiazine compounds: A new methodology was developed for the preparation of title compounds involving a tandem SN_2 and a SNAr reaction. The nitro-alcohol **22** (Scheme 3), obtained as per our earlier method,[10] was converted to the bromo compound **23** as usual. The analogous bromo compound **14** in Scheme 2 was initially converted to the thiol **16**, by a SN_2 reaction of the anion of thioacetic acid followed by basic hydrolysis, before inducing the cyclisation by a SNAr reaction to result in the tricyclic nitro compound **17**. Instead of this usual three-step protocol, we envisioned a single pot tandem SN_2 and a SNAr reaction involving thioacetic acid and a base as it was anticipated that the anion addition onto bromide followed by the hydrolysis and the subsequent cyclisation should occur



Scheme 3. Reagents and conditions: (a) Ref. 10; (b) CBr_4, PPh_3, CH_2Cl_2, 0 to 45 °C, 5 h, 87%; (c) MeCOSH (42%) or $MeNH_2$ (38%), KOH, DMSO; (d) as in Scheme 2; (e) as in Scheme 1; (f) PPh_3, H_2O, THF, 68%; (g) AcCl, Et_3N, CH_2Cl_2, 89%; (h) Lawesson's reagent, 68%; (i) $CSCl_2$, Et_3N, 87%; (j) MeOH (86% and 82% for **34** and **36**) and $MeNH_2$ (61% for **35**), reflux.

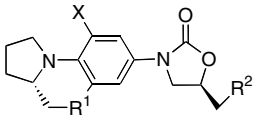
sequentially. Thus, the treatment of the bromide **23** with thioacetic acid and KOH in DMSO afforded the tricyclic nitro compound **24** in one step albeit in modest yield. In a similar manner, employing methylamine in place of thioacetic acid in the above reaction resulted in the tricyclic nitro compound **25** in one pot. Having identified an efficient methodology to prepare the tricyclic nitro compounds **24** and **25** in gram quantities, the synthesis of the corresponding azides **28** and **29** was carried out as discussed in the previous schemes. The amines **30** and **31**, derived from their corresponding azides, were converted to the acetamides **32** and **33**, respectively, under standard conditions. The acetamide **32** was treated with the Lawesson's reagent to get the thioacetamide **37**. Finally, the amines **30** and **31** afforded the thiocarbamates **34** and **36**, respectively, upon treatment with thiophosgene followed by refluxing the intermediate isothiocyanate in methanol. The treatment of the above isothiocyanate intermediate obtained from the amine **30** with methylamine resulted in the thiourea **35**.

The constrained analogues of Linezolid prepared above were screened for in vitro activity against a panel of Gram-positive organisms and the results are summarized in Table 1. The tricyclic oxazolidinone analogues **9**–**12**, possessing nitrogen atom (bearing different substituents) instead of oxygen in the tricycle of compound **1**, exhibited no antibacterial activity. It is relevant to note that the earlier compound **1**, possessing an oxygen atom, had moderate activity (Table 1). Similarly, the analogue **33** containing a *N*-methyl group instead of oxygen in the compound **1** with an additional fluorine atom in the aromatic ring was also found to be inactive. The corresponding thiocarbamate compound **36** of the acetamide **33** was also an inactive compound. Thus, it was concluded that varying the oxygen atom in the constrained analogue **1** to a substituted nitrogen atom results in loss of antibacterial activity.

As the above SAR of varying the oxygen atom in the constrained analogue **1** to substituted nitrogen atom resulted in inactive compounds, we turned our attention in introducing sulfur atom in place of the oxygen. Thus, the acetamide analogue **3** exhibited moderate activity (8 μg/mL) against all the organisms tested, which was more or less comparable to the activity of oxygen analogue **1** (4–16 μg/mL). Encouraged by the observed results, the thiocarbamate analogue **21** was prepared and was found to be highly potent with in vitro activity ranging from 0.25 to 1 μg/mL. But, the conversion of the sulfur atom to the sulfone **20** resulted in the loss of activity. With the view of further increasing the potency, following our earlier report,[10] the tricyclic compounds having fluorine atom in the aromatic ring were synthesised. Thus, the acetamide compound **32** exhibited two- to fourfold more potency (1–2 μg/mL) than the non-fluorine analogue **3**. However, the thiocarbamate analogue **34** was only marginally more potent than the acetamide **32**. In addition, the thioacetamide **37** and the thiourea **35** also possessed similar activity as that of the thiocarbamate **34**. This implies that the introduction of fluorine did not lead to increased potency in the thiocarbamate analogues as observed for the acetamide compounds. The non-fluorine analogue **21** was selected for further development based on in vitro activity.

In conclusion, the SAR studies on the left hand side of the tricyclic analogue **1** in varying the oxygen atom in the tricycle to substituted nitrogen atom and sulfur were completed. While the change to substituted nitrogen resulted in complete loss of activity, introducing sulfur generated some potent compounds. Though the introduction of fluorine in the aromatic ring increased the potency in the acetamide analogue (analogue **32**), the same was not true in the thiocarbamate case (analogue **34**). The thiocarbamate analogue **21** was chosen as the lead compound and further development is in progress.

Table 1. In vitro antibacterial activity (MIC, μg/mL)[a] of selected tricyclic oxazolidinones



Compound No.	X	R^1	R^2	S.a 019	S.a 213	S.a 035	E.f 034	E.f 153	E.fm 154
9	H	N-COOBn	$NHCOCH_3$	>32	>32	>32	>32	>32	>32
10	H	N-CHO	$NHCOCH_3$	>256	>256	>256	>256	>256	>256
11	H	N-$COCH_3$	$NHCOCH_3$	>256	>256	>256	>256	>256	>256
12	H	N-$COCH_2Cl$	$NHCOCH_3$	>256	>256	>256	>256	>256	>256
33	F	N-Me	$NHCOCH_3$	>32	>32	>32	>32	>32	32
36	F	N-Me	$NHCSOCH_3$	>32	>32	>32	>32	>32	32
3	H	S	$NHCOCH_3$	8	8	8	8	8	8
21	H	S	$NHCSOCH_3$	0.25	1	0.5	0.25	0.25	0.5
20	H	SO_2	$NHCOCH_3$	>32	>32	>32	>32	>32	>32
32	F	S	$NHCOCH_3$	1	1	2	2	1	2
37	F	S	$NHCSCH_3$	0.25	0.5	0.5	0.5	0.25	0.25
34	F	S	$NHCSOCH_3$	0.5	1	1	1	0.5	0.5
35	F	S	NHCSNHMe	0.5	0.5	2	1	0.5	1
1	H	O	$NHCOCH_3$	4	4	8	16	16	16
Linezolid				1	2	2	2	2	2
Vancomycin				2	1	1	2	>32	>32

[a] S.a 019 = *Staphylococcus aureus* ATCC 33591 (methicillin-resistant); S.a 213 = *Staphylococcus aureus* ATCC 49951; S.a 035 = *Staphylococcus aureus* ATCC 29213; E.f 034 = *Enterococcus faecalis* ATCC 29212 (vancomycin sensitive); E.f 153 = *Enterococcus faecalis* NCTC 12201 (vancomycin resistant) and E.fm 154 = *Enterococcus faecium* ATCC 12202 (vancomycin resistant).

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11. Analytical data for selected final compounds: Compound **3**: IR (KBr) 3355, 1738, 1666, 1507 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d^6) δ 7.65 (bt, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.10 (dd, J = 8.8, 2.7 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 4.80–4.65 (m, 1H), 3.98 (t, J = 7.6 Hz, 1H), 3.80–3.25 (m, 5H), 3.05 (dd, J = 12.2, 2.4 Hz, 1H), 2.70–2.60 (m, 1H), 2.35–1.85 (m, 4H), 2.01 (s, 3H), 1.70–1.45 (m, 1H). MS (DIP-method) 347 (M^+), 303, 219. HPLC (System 2)[10] 94.04% purity. Compound **21**: IR (KBr) 1744, 1509 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.20 (s, 1H), 7.15 (d, J = 8.8 Hz, 1H), 6.76 (bt, 1H), 6.53 (d, J = 8.8 Hz, 1H), 5.00–4.80 (m, 1H), 4.20–3.20 (m, 9H), 3.04 (dd, J = 12.2, 2.4 Hz, 1H), 2.72 (dd, J = 12.2, 9.8 Hz, 1H), 2.28–1.40 (m, 5H). MS (CI-method) 380 (M^++1), 348, 335. HPLC (System 2)[10] 91.95% purity. Compound **34**: IR (KBr) 3264, 1752, 1492 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.17 (dd, J = 16.6, 2.0 Hz, 1H), 6.85 (s, 1H), 6.76 (bt, 1H), 5.00–4.80 (m, 1H), 4.20–3.10 (m, 10H), 2.85–2.60 (m, 2H), 2.40–1.55 (m, 4H). MS (CI-method) 398 (M^++1), 366, 354. HPLC (System 2)[10] 98.11% purity.