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Bioorganic & Medicinal Chemistry 14 (2006) 8032–8042
Bioorganic & Medicinal Chemistry

Substituent activity relationship studies on new azolo benzoxazepinyl oxazolidinones☆

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Received 1 July 2006; revised 20 July 2006; accepted 21 July 2006
Available online 10 August 2006

Abstract—In an effort to discover potent antibacterials based on the entropically favored 'bioactive conformation' approach, a series of novel tricyclic molecules mimicking the conformationally constrained structure of Linezolid is reported. Based on the initial tricyclic molecule **1**, the benzazepine derivative **2** was designed where the tricyclic structure had more flexibility around C–N bond compared to **1**. While, the molecule **2** was less active, the molecule **3** showed promising antibacterial activity presumably after having obtained rigidity due to pyrrole ring. The syntheses, SAR studies, and evaluation of **3** as a lead compound are reported.

1. Introduction

The increasing reports of resistance to antibiotics among bacteria, especially Gram-positive bacteria, have compromised the current antibiotic therapies. Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and glycopeptide-resistant *S. aureus* (GISA) are no longer objects of scientific curiosity but a life-threatening proposition that is confronting physicians all over the world. The 'super bugs' are here to stay and in addition to the several measures to control spread of drug resistance, a concerted effort is urgently needed to develop new antibiotics with novel mechanism of action.

Discovery of oxazolidinones, a new class of synthetic antibacterials, opened up an exciting avenue of antibiotic research because of its activity against resistant Gram-positive organisms such as MRSA, VRE, and GISA. Oxazolidinones bind selectively to 50S ribosomal subunit thereby inhibiting bacterial protein biosynthesis at an early stage.[1] Linezolid, the first drug from this class of compounds, was launched by Pharmacia in 2000. In spite of its high potential as an antibiotic and unique mode of action no molecule from oxazolidinone class, except for Linezolid, could make it to the market. Moreover, development of resistance to an antibiotic is inevitable, and Linezolid has been no exception to this rule.[2] Further, due to myelosuppression, Linezolid is not suitable for long-duration therapy, although there are cases where patients receiving Linezolid for more than 2 years are without serious side effects.[3] Therefore, there is a need to pursue development of potent and safer oxazolidinone compounds.

In our earlier communication,[4] we discussed the role of bioactive conformation in a drug molecule, which assists the molecule to bind to a target favorably providing entropic advantage. Every molecule and hence a drug too is expected to have free rotation along the bonds. A drug remains in innumerable energy states (conformations) and out of these innumerable conformations only one, that is, the bioactive form binds to the receptor. In other words, a flexible drug molecule has to limit its rotation along bonds and freeze to the bioactive form in order to bind to the receptor, which is entropically disfavored process. One of the ways to restrict rotation along the bonds is to constrain the drug molecule and by this process if one comes across the bioactive confor-

Keywords: Oxazolidinones; Antibacterial; Tricyclic; Linezolid.
☆ A part of this work was presented in 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, December 16–19, 2001, Chicago, USA.
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doi:10.1016/j.bmc.2006.07.040

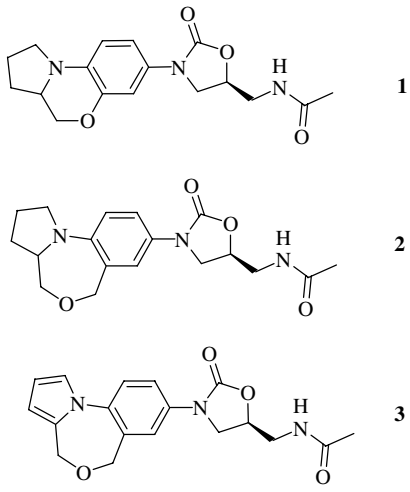


Figure 1.

mation, a potent drug can be delivered. In line with this concept we designed structurally constrained tricyclic molecule **1**,[4] wherein rotation around C–N bond was restricted (Fig. 1). Further, to enumerate more on our concept of bioactive conformation, we designed benzazepine derivative **2**, where the tricyclic structure had more flexibility around C–N bond compared to **1**. However, the molecule was inactive having obtained more freedom of rotation. On the other hand molecule **3**, an intermediate toward **2**, showed promising antibacterial activity having obtained rigidity due to pyrrole ring.[5] Thus, we have carried out SAR study on the right side of the molecule to improve upon the activity. Herein we report the synthesis of molecules **2** and **3**, SAR studies carried out on **3**, and evaluation of **3** as a lead compound.

1.1. Synthesis of azide 13

The nitration of isatoic anhydride **4** to obtain nitro isatoic anhydride **5** (Scheme 1). Methanolysis of the anhydride **5** resulted in the amino-ester **6**. Amino functionality of the compound **6** was then converted to pyrrole ring (**7**) by refluxing in acetic acid with 2,5-dimethoxy tetrahydrofuran. Vilsmeyer–Hack formylation of the compound **7** led to the aldehyde **8**, which on reduction with sodium borohydride followed by acidification of the resulting diol resulted in benz-azulene compound **9**. Usual transformation of nitro to amine and subsequent protection of amine with CBzCl produced compound **11**, which on treatment with (*R*)-glycidyl butyrate in presence of BuLi gave alcohol **12**. Alcohol functionality of **12** was further converted to azide **13** by mesylation followed by displacement with sodium azide.

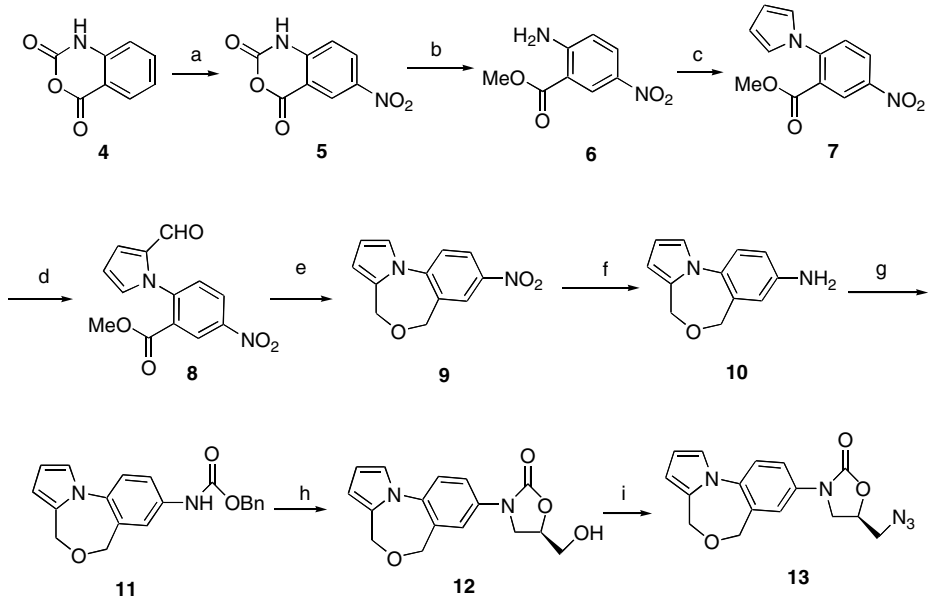
1.2. Synthesis of the derivatives

The amine **14** was obtained by reduction of azide **13** in presence of triphenylphosphine and water (Scheme 2), which was then converted to the derivatives using either corresponding acid chlorides in presence of triethylamine or corresponding acid in presence of DCC and DMAP. The azide **13** upon treatment with thioacetic acid produced the acetamide **3**, which upon hydrogenation yielded the pyrrolidine derivative **2**. The thioacetamide **27** was prepared by treating the amine **14** with ethyldithioacetate and TEA. The carbamate derivatives have been prepared from the amine **14** by treatment with alkylchloroformates and TEA. The isothiocyanate **15** was obtained from the amine **14** by treatment with carbon disulfide, TEA, and ethylchloroformate, which upon refluxing with appropriate alcohols gave the thiocarbamate derivatives (Table 1).

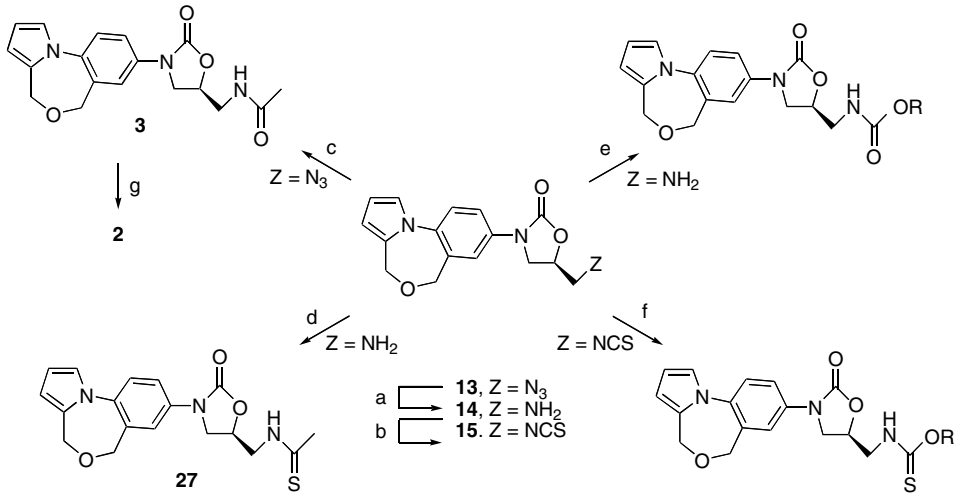
All the compounds synthesized above were screened for in vitro antibacterial activity against a panel of Gram-positive organisms. The compound **2** having more flexibility around C–N bond compared to compound **1** lost its antibacterial activity. However, the compound **3** presumably after having gained rigidity due to the pyrrole ring instead of pyrrolidine exhibited activity similar to Linezolid. Thus, in an attempt to further improve the antibacterial activity, SAR studies on the amine **14** were carried out (Table 2). Increasing the chain length or bulkiness on the acetamide **3** resulted in molecules with inferior activity (e.g., **3** vs **16**–**20**). However, the chloro acetamide compound **21** retained the activity. It is interesting to note that the corresponding bromo derivative **22** was less active. The carbamates **24**–**26** were found to be less active than the corresponding acetamides. But, the thioamide **27** and the thiocarbamate **28** exhibited better activity than the acetamide **3**. However, the homologous thiocarbamate derivative **29** was less active than **28**.

After having completed the SAR studies, the compounds possessing in vitro activity comparable to Linezolid (**3**, **19**, **21**, **27**, and **28**) were taken up for pharmacokinetic and in vivo studies in mice. The mean plasma concentration and ED_{50} values of these compounds and Linezolid are presented in Table 3. Upon oral administration, the absorption from mouse gastrointestinal tract was rapid and the maximum plasma concentration (T_{max}), reached at 0.5 h in all the compounds except for the compound **27** ($T_{max} \sim 1$ h). The data revealed the compound **3** to be superior to other compounds with mean plasma concentration (C_{max}) 11.7 μg/mL and an $AUC_{(0-\infty)}$ of 21.09 μg h/mL. All other compounds exhibited poor pharmacokinetics and this was clearly reflected in the pharmacodynamic study in mice. The ED_{50} in the mouse systemic infection model of compound **3** administered subcutaneously (sc) was 10.10 mg/kg and the ED_{50} by per os (po) administration was 12.5 mg/kg as compared to 2.18 mg/kg (sc) and 5.38 mg/kg (po) for Linezolid. All the other compounds failed to protect mice with $ED_{50} > 30$ mg/kg dose, which correlated well with the poor pharmacokinetics exhibited by these compounds.

The oral pharmacokinetic profile of compound **3** was further evaluated in Wistar rats. The mean plasma concentration versus time profiles of compound **3** and Linezolid, and the pharmacokinetic parameters are presented in Figure 2 and Table 4. After oral administration, the compound **3** reached a maximum level (T_{max}) at 1.5 h, whereas Linezolid was rapidly absorbed and reached T_{max} at 0.5 h, the elimination rate (K_{el}) and



Scheme 1. Reagents and conditions: (a) KNO_3, H_2SO_4, 0–5 °C, 86%; (b) MeOH, NaOH, 90%; (c) 2,5-dimethoxytetrahydrofuran, CH_3COOH, 85%; (d) DMF, $POCl_3$, 86%; (e) $NaBH_4$, MeOH, HCl, 60%; (f) ammonium formate, 10% Pd–C, THF–MeOH, 66%; (g) CBzCl, $NaHCO_3$, 96%; (h) *n*-BuLi, (*R*)-glycidyl butyrate, 85%; (i) MsCl/TEA and NaN_3/DMF, 92%.



Scheme 2. Reagents: (a) Ph_3P/H_2O, 80%; (b) CS_2, TEA, ethylchloroformate; (c) CH_3COSH; (d) ethyldithioacetate, TEA; (e) ROCOCl, TEA; (f) ROH; (g) Pd on charcoal, H_2.

terminal half-life ($t_{1/2}$) were comparable to Linezolid. However, the C_{max} of 12.9 μg/mL and $AUC_{(0-\infty)}$ of 52.90 μg h/mL were inferior to those of Linezolid, which showed a C_{max} of 27.09 μg/mL and $AUC_{(0-\infty)}$ of 83.45 μg h/mL.

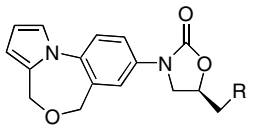
In conclusion, the SAR studies on azolo benzoxazepinyl oxazolidinone resulted in acetamide derivative **3** as a lead compound. The replacement of acetamide of **3** with thioamide and thiocarbamate exhibited better in vitro potency. However, minor changes at the acetamide position of **3**, like replacement of acetamide group with either lengthier or bulkier group, had adverse effect on the in vitro activity. Although the thiocompounds **27** and **28** exhibited good in vitro potency, this was not translated into in vivo efficacy possibly due to poor pharmacokinetic profiles. Complementing the pharmacokinetic profile, the compound **3** showed good in vivo efficacy. It is also interesting to note that the systemic exposure and elimination half-life of **3** was superior in rats compared to that of mice.

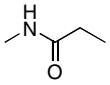
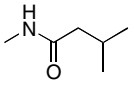
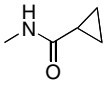
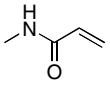
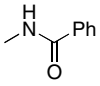
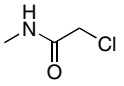
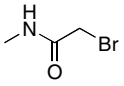
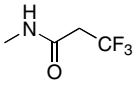
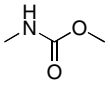
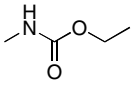
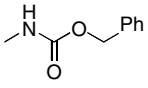
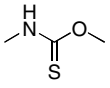
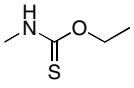
2. Experimental

2.1. General

Melting points were recorded on capillary melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR were recorded at 200 and 50 MHz, respectively. Chemical shifts are reported in δ (delta) units with respect to tetramethylsilane (TMS) as internal standard. Mass

Table 1. SAR studies on the amine 14



Compound	R	Conditions	Yield (%)
16		Propionyl chloride TEA, DCM, 0 °C, 0.5 h	34
17		Isovaleryl chloride TEA, DCM, 0 °C, 0.5 h	41
18		Cyclopropyl carboxylic acid DCC, DMAP, $CHCl_3$, 0 °C, rt, 1 h	41
19		Acryloyl chloride TEA, DCM, 0 °C, 0.5 h	30
20		Benzoyl chloride TEA, DCM, 0 °C, 0.5 h	66
21		2-Chloroacetyl chloride TEA, DCM, 0 °C, 0.5 h	75
22		2-Bromoacetyl chloride TEA, DCM, 0 °C, 0.5 h	43
23		3,3,3-Trifluoropropionic acid DCC, DMAP, $CHCl_3$, 0 °C, rt, 1 h	49
24		Methylchloroformate TEA, DCM, 0 °C, 0.5 h	23
25		Ethylchloroformate TEA, DCM, 0 °C, 0.5 h	29
26		Benzylchloroformate TEA, DCM, 0 °C, 0.5 h	14
27		Ethyldithioacetate TEA, THF, rt, 6 h	21
28		CS_2, NEt_3, THF methylchloroformate, methanol, reflux	40
29		CS_2, NEt_3, THF methylchloroformate, ethanol, reflux	38

spectra were recorded on a HP-5989A spectrometer. Combustion analysis was obtained using a Perkin-Elmer 2400 analyzer. All analytical works were carried out at the Analytical Research Department of Discovery Research.

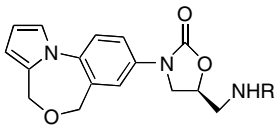
2.2. 6-Nitro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (5)

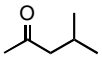
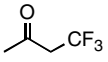
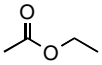
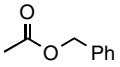
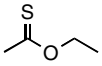
To a solution of isatoic anhydride **4** (20 g, 122.7 mmol) in con. H_2SO_4 (30 mL) at 0 °C was added potassium nitrate (12.40 g, 122.7 mmol) in small batches over a period of 30 min and the stirring was continued for an additional 15 min. The reaction mixture was poured into ice flakes and the precipitate formed was filtered. The solid obtained was washed with water and dried under vacuum to afford the nitro compound **5** as a pale brown solid (24 g, 94%). IR (KBr): 3199, 1779, 1758, 1354, 1336, 1034 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.31 (s, 1H), 8.53 (m, 2H), 7.31 (d, J = 10.0 Hz, 1H). MS: 209 (M^++1), 191, 182, 164, 134, 106, 90.

2.3. Methyl 2-amino-5-nitro-benzoate (6)

A solution of 6-nitro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione **5** (25 g, 120.2 mmol) and NaOH (480 mg, 12.0 mmol) in

Table 2. In vitro potency of azolo benzoxazepinyl oxazolidinones



Compound[a]	R	SA 33591	SA 49951	SA 29213	EF 29212	EF 12201	EFe 12202
1		4	8	16	16	16	16
2		32	32	32	>32	>32	>32
3		2	2	2	2	2	2
16		4	4	4	8	8	8
17		4	8	8	8	8	8
18		16	16	32	32	32	32
19		4	2	2	4	4	4
20		>32	>32	>32	>32	>32	>32
21		1	2	2	2	2	2
22		4	4	4	4	4	4
23		8	8	8	8	8	8
24		4	4	4	8	8	8
25		16	16	16	16	16	16
26		>32	>32	>32	>32	>32	>32
27		0.5	1	1	1	0.5	1
28		0.5	0.5	0.5	2	2	2
29		4	4	4	8	8	8
Linezolid		2	2	2	2	2	4

[a] Compounds 3, 19, 21, 27 and 28 were selected for in vivo studies.

Table 3. Pharmacokinetic and pharmacodynamic parameters of selected compounds in Swiss albino mice[a]

Parameters	**3**	**19**	**21**	**27**	**28**	Linezolid
$AUC_{(0-\infty)}$ (μg h/mL)	21.09	3.83	0.55	1.04	6.72	71.03
T_{max} (h)	0.5	0.5	0.5	1.0	0.5	0.5
C_{max} (μg/mL)	11.7	2.18	0.47	0.18	3.2	28.13
$t_{1/2}$ (h)	0.8	0.6	0.6	0.9	0.8	1.0
ED_{50} (mg/kg)						
sc	10.10	>30	>30	>30	>30	2.18
po	12.50	>30	>30	>30	>30	5.38

[a] Pharmacokinetic experiments were performed by single dose using oral route of administration and the pharmacodynamic results were derived upon doing b.i.d.

Table 4. Single dose oral pharmacokinetic parameters of compound **3** and Linezolid in Wistar rats

Parameters	Compound **3**	Linezolid
Data derived from (*n*)	6	4
$AUC_{(0-\infty)}$ (μg h/mL)	52.90 ± 19.53	84.66 ± 12.17
C_{max} (μg/mL)	12.9 ± 4.07	27.09 ± 2.12
T_{max} (h)	1.50 ± 0.58	0.50 ± 0.00
K_{el} (h^{-1})	0.58 ± 0.21	0.61 ± 0.06
$t_{1/2}$ (h)	1.31 ± 0.40	1.15 ± 0.12

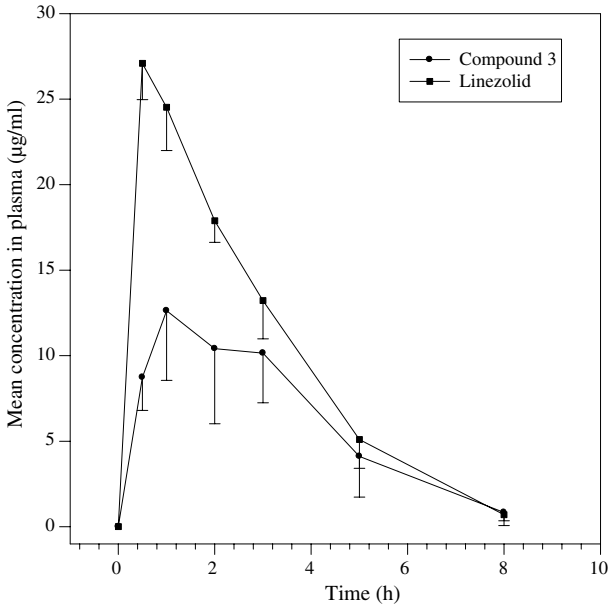


Figure 2. Single dose oral pharmacokinetic parameters of compound **3** and Linezolid in Wistar rats.

methanol was refluxed under N_2 for 15 min. The reaction mixture was allowed to cool to rt, diluted with ethylacetate (750 mL), washed with water, dried over anhydrous Na_2SO_4, and concentrated to obtain **6** as a yellow solid (21 g, 89%). IR (KBr): 3473, 3361, 1707, 1631, 1319 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.62 (s, 1H); 8.14 (d, J = 10.0 Hz, 1H), 7.83 (br s, 1H), 6.89 (br s, 2H), 3.85 (s, 3H). MS: 196 (M^+), 180, 164, 134, 119, 106, 91.

2.4. Methyl 5-nitro-2-pyrrol-1-yl-benzoate (7)

To a solution of methyl 2-amino-5-nitro-benzoate **6** (21 g, 107.1 mmol) in acetic acid (200 mL) was added a solution of 2,5-dimethoxy tetrahydrofuran (14.16 g, 107.1 mmol) in acetic acid (500 mL) and the resulting mixture was heated at reflux under N_2 for 2 h. The reaction mixture was allowed to cool to rt, poured into water (500 mL), and extracted with ethylacetate (500 mL 3×). The combined organic layer was washed with saturated $NaHCO_3$ solution, water, and brine successively. It was then dried over anhydrous Na_2SO_4 and concentrated to afford the compound **7** as a viscous liquid (28 g, 85%). IR (Neat): 1741, 1502, 1335, 738 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.60 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 6.85 (s, 2H) 6.18 (s, 2H), 3.80 (s, 3H). MS: 246 (M^+), 188.

2.5. Methyl 2-(2-formyl-pyrrol-1-yl)-5-nitro-benzoate (8)

Phosphorus oxychloride (17 g, 110.9 mmol) was added dropwise to DMF (250 mL) under N_2 at 0 °C to form a viscous yellow complex. To this reaction mixture was added a solution of methyl 5-nitro-2-pyrrol-1-yl-benzoate (26 g, 105.7 mmol) in DMF at the same temperature over a period of 0.5 h. The reaction mixture was allowed to attain rt and stirred for additional 2 h. It was then poured into water which was basified with Na_2CO_3. The precipitate formed was filtered, washed with water, and dried under vacuum to afford the compound **8** as a white solid (21.6 g, 80%). IR (KBr): 1720, 1661, 1344, 767 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.45 (s, 1H), 8.85 (s, 1H), 8.40 (d, J = 7.0 Hz, 1H), 7.35 (d, J = 7.0 Hz, 1H), 7.11 (s, 1H), 6.95 (s, 1H), 6.45 (m, 1H), 3.75 (s, 3H). MS: 274 (M^+), 246, 215, 169, 140.

2.6. 8-Nitro-4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulene (9)

To a solution of methyl 2-(2-formyl-pyrrol-1-yl)-5-nitro-benzoate **8** (5.00 g, 18.3 mmol) in MeOH (40 mL) was added sodium borohydride (690 mg, 18.3 mmol) in small portions at rt. After stirring the reaction mixture for an additional 1 h, con. HCl (10 mL) was added and was diluted with water (100 mL). After stirring for a further 10 min, the reaction mixture was extracted with ethylacetate (100 mL 3×). The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated to afford the nitro compound **9** as a yellow solid (2.50 g, 60%). IR (KBr): 1522, 1499, 1336, 1087 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.18 (d, J = 10.0 Hz, 2H), 7.58 (d, J = 5.0 Hz, 1H), 7.11 (s, 1H), 6.40 (s, 2H), 4.58 (d, J = 10.0 Hz, 4H). MS: 230 (M^+), 201, 183, 154, 127.

2.7. 4*H*,6*H*-5-Oxa-10b-aza-benzo[*e*]azulen-8-ylamine (10)

To an ice-cold solution of 8-nitro-4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulene **9** (1.00 g, 4.4 mmol) and ammonium formate (1.09 g, 17.4 mmol) in THF–MeOH (1:4, 15 mL) was added 10% Pd–C (500 mg) and stirred at rt under N_2 for 1 h. The reaction mixture was filtered over a pad of Celite and filtrate was concentrated. The residue was diluted with ethylacetate (100 mL), washed with water and brine successively. It was then dried over anhydrous Na_2SO_4 and concentrated to afford the amine **10** as a pale brown solid (580 mg, 66%). IR (KBr): 3356, 2855, 1668, 1625, 1512, 1310, 1268, 1064, 720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.20 (d, J = 1.6 Hz, 1H), 7.01 (s, 1H), 6.64–6.68 (m, 3H), 6.24 (s, 2H), 4.45 (s, 2H), 4.25 (s, 2H). MS: 200 (M^+), 171, 154, 144, 130, 115, 106, 91.

2.8. Benzyl (4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-carbamate (11)

To a solution of amine **10** (4 g, 20.0 mmol) in acetone (20 mL) was added a solution of $NaHCO_3$ (1.69 g, 40.0 mmol) in water (10 mL). Benzylchloroformate (50%, 3.75 g, 22.0 mmol) was added dropwise to the reaction mixture, cooled to 0 °C, over a period of 0.5 h under N_2. The reaction mixture was allowed to attain rt and then poured into water (30 mL). The precipitate formed was filtered and dried under vacuum to afford the compound **11** as an off-white solid (6.00 g, 90%). IR (KBr): 3250, 1728, 1565, 1513, 1317, 1236 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.28 (m, 8H), 7.01 (s, 1H), 6.78 (br s, 1H), 6.25 (s. 2H), 5.20 (s, 2H), 4.42 (d, J = 10.0 Hz, 4H). MS: 334 (M^+), 199, 169, 91.

2.9. (*R*)-5-Hydroxymethyl-3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-oxazolidin-2-one (12)

To a solution of benzyl (4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-carbamate **11** (8.00 g, 24.0 mmol) in dry THF (100 mL) was added *n*-BuLi (15% solution in hexane, 15.33 mL, 36.0 mmol) at −78 °C over a period of 0.5 h and allowed to stir at the same temperature for another 0.5 h. *R*-(−)-Glycidyl butyrate (3.45 g, 26.3 mmol) was added to the reaction mixture and then allowed to come to rt and stirred for additional 4 h. The reaction mixture was then diluted with ethylacetate (300 mL) and water after quenching with saturated NH_4Cl solution. The organic layer was separated and aqueous layer was extracted with ethylacetate (300 mL 2×). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The residue obtained upon concentration was crystallized from ethylacetate–petroleum ether to afford the alcohol **12** as an off-white solid (6.10 g, 85%). IR (KBr): 3398, 1726, 1511, 1062 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.71–7.74 (m, 1H), 7.59 (s, 1H), 7.43 (d, J = 8.9 Hz, 1H), 7.04 (s, 1H), 6.32 (s, 2H), 4.75–4.80 (m, 1H), 4.48 (d, J = 9.4 Hz, 4H), 4.01–4.12 (m, 3H), 3.76–3.82 (m, 1H). MS: 301 (M^++1), 257, 176.

2.10. (*R*)-5-Azidomethyl-3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-oxazolidin-2-one (13)

To a cooled (0 °C) solution of the alcohol **12** (6.10 g, 20.3 mmol) in CH_2Cl_2 (100 mL) was added triethylamine (4.11 g, 41.0 mmol) followed by dropwise addition of methanesulfonylchloride (3.49 g, 30.5 mmol) over a period of 30 min. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and the organic layer was washed with water, brine and dried (Na_2SO_4). Upon concentration the mesylate (7.07 g) was obtained as an off-white solid. To a solution of the mesylate (7.00 g, 18.5 mmol) in DMF (50 mL) was added sodium azide (3.61 g, 55.6 mmol) and heated to 80 °C for 1 h. The reaction mixture was then poured into water (250 mL), extracted with ethylacetate (200 mL 3×), and the combined organic layer was washed with water (200 mL 2×), brine and dried (anhydrous Na_2SO_4). The title compound was obtained as an off-white solid (5.7 g, 95%) after evaporation of the volatiles. IR (KBr): 2104, 1745 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.71–7.74 (m, 1H), 7.57 (s,1H), 7.43 (d, J = 8.6 Hz, 1H), 7.01 (s, 1H), 6.32 (s, 2H), 4.79–4.85 (m, 1H), 4.47 (d, J = 9.4 Hz, 4H), 4.14 (t, J = 8.9 Hz, 1H), 3.90–3.94 (m, 1H), 3.59–3.76 (m, 2H). MS: 326 (M^++1), 300, 298, 201.

2.11. (*S*)-*N*-[3-(4*H*,6*H*-5-Oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide (3)

(*R*)-5-Azidomethyl-3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-oxazolidin-2-one **13** (1.2 g, 3.7 mmol) was treated with thiolacetic acid (8 mL) under nitrogen atmosphere. The excess thiolacetic acid was evaporated after 16 h and the residue obtained was purified on silica gel (100–200 mesh) using a mixture of methanol–chloroform (1:9) as eluent to obtain the product **3** as a white solid (700 mg, 58%): mp 256–258 °C. IR (KBr): 3298, 1737, 1679, 1512, 1321, 1059, 736 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.72–7.43 (m, 3H), 7.06 (s, 1H), 6.36 (s, 2H), 6.17 (m, 1H), 4.48 (m, 1H), 4.51–4.49 (m, 4H), 3.66–4.18 (m, 4H), 2.06 (s, 3H). ^{13}C NMR (DMSO-d_6): 170.0, 154.1, 136.6, 135.5, 129.7, 129.5, 121.5, 120.9, 120.0, 119.5, 109.3, 109.2, 71.6, 66.1, 59.6, 47.3, 41.4, 22.4. MS: 341 (M^+), 312, 297, 254, 209, 154, 127, 105, 91.

2.12. *N*-[2-Oxo-3-(2,3,3a,4-tetrahydro-1*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-oxazolidin-5-ylmethyl]-acetamide (2)

A solution of the amide **3** (100 mg, 0.3 mmol) and 10% Pd–C (31 mg, 10 mol%) in ethylacetate was hydrogenated over 16 h at 50 psi. The catalyst was filtered off over a pad of Celite and the filtrate obtained was concentrated to obtain the title compound **2** (82 mg, 82%) as a colorless solid. Mp 262–264 °C. IR (KBr): 3315, 1746, 1510, 752 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.21 (t, J = 5.8 Hz, 1H), 7.38–7.31 (m, 2H), 6.89 (d, J = 8.9 Hz, 1H), 4.72–4.64 (m, 2H), 4.28 (d, J = 13.2 Hz, 1H), 4.09–4.03 (m, 1H), 3.88 (dd, J = 2.4 and 11.6 Hz, 1H), 3.72–3.67 (m, 1H), 3.39 (t, J = 5.5 Hz, 2H), 3.32–3.18 (m, 3H), 2.97–2.80 (m, 1H), 2.12–2.04 (m, 1H), 1.91–1.78 (m, 5H), 1.52–1.45 (m, 1H). ^{13}C NMR: 169.9, 154.2, 145.4, 130.6, 130.3, 120.0, 118.7, 115.4, 75.2, 73.4, 71.3, 62.6,

51.4, 47.6, 41.4, 27.6, 23.1, 22.4. MS: 346 (M^++1), 296. Anal. Calcd for $C_{18}H_{23}N_3O_4$: C: 62.59; H, 6.71; N, 12.17. Found: C, 63.11; H, 6.63; N, 12.03.

2.13. (*R*)-5-Aminomethyl-3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-oxazolidin-2-one (14)

To a solution of the azide **13** (7.0 g, 21.5 mmol) in THF (60 mL) was added triphenylphosphine (6.22 g, 23.7 mmol). After stirring for 2 h, water (1 mL) was added and the reaction mixture was heated to 40–50 °C for 16 h. The solvent was evaporated and the water was removed azeotropically with benzene. The residue obtained was purified on silica gel (100–200 mesh) column using acetone–chloroform (2:3) system to obtain the amine **14** as a sticky material (5.5 g, 77.62%). IR (KBr): 3386, 1748 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.72–7.75 (m, 1H), 7.58 (s, 1H), 7.42 (d, J = 8.86 Hz, 1H), 7.04 (s, 1H), 6.32 (s, 1H), 4.68–4.74 (m, 1H), 4.47 (d, J = 9.1 Hz, 4H), 4.09 (t, J = 8.7 Hz, 1H), 3.90–3.94 (m, 1H), 2.98–3.17 (m, 2H). MS: 300 (M^++1), 279, 270.

2.14. (*S*)-*N*-[3-(4*H*,6*H*-5-Oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide (16)

To a solution of the amine **14** (100 mg, 0.3 mmol) in chloroform (10 mL) was added triethylamine (93 μL, 0.7 mmol) at 0 °C followed by the addition of propionyl chloride (70.52 mg, 0.5 mmol) and stirred at same temperature for 30 min. The reaction mixture was diluted with chloroform and washed with water and brine successively. It was then dried over anhydrous sodium sulfate and concentrated. The residue obtained was purified on silica gel (100–200 mesh) column using acetone–chloroform (2:3) as eluent to afford the title compound **16** (80 mg, 34%) as a white solid. Mp 256–258 °C. IR (KBr): 3441, 3295, 2924, 1737, 1678, 1513, 732 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.70–7.64 (m, 2H), 7.42 (d, J = 8.5 Hz, 1H), 7.04 (m, 1H), 6.33 (d, J = 2.0 Hz, 2H), 6.17 (br s, 1H), 4.82 (br s, 1H), 4.47 (d, J = 4.4 Hz, 1H), 4.12 (t, J = 8.9 Hz, 1H), 3.91–3.83 (m, 1H), 3.71–3.67 (m, 2H), 2.32–2.27 (m, 2H), 1.14 (t, J = 7.6 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.2, 153.9, 136.3, 135.5, 129.6, 129.4, 121.0, 120.2, 119.8, 119.1, 109.0, 71.4, 66.2, 60.0, 47.2, 39.5, 28.4, 9.6. MS: 356 (M^+), 312. Anal. Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.82. Found: C, 64.77; H, 5.77; N, 12.07.

2.15. (*S*)-*N*-[3-(4*H*,6*H*-5-Oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-isovalerylamide (17)

The title compound was prepared following the procedure reported for the amide **16** using isovaleryl chloride instead of propionyl chloride in 41% yield: mp 206 °C. IR (KBr): 3423, 3305, 2959, 2924, 1736, 1671, 1513, 736 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.69–7.65 (m, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.05 (s, 1H), 6.34 (s, 2H), 6.03 (m, 1H), 4.83 (m, 1H), 4.49 (d, J = 3.9 Hz, 4H), 4.12 (t, J = 9.0 Hz, 1H), 3.87 (dd, J = 6.8 and 8.8 Hz, 1H), 3.73–3.71 (m, 2H), 2.10 (s, 3H), 0.94–0.87 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.7, 154.5, 136.7, 136.1, 130.5, 130.1, 121.5, 120.4, 119.6, 109.6, 72.1, 66.9, 60.4, 47.6, 41.7, 29.6, 26.0, 22.3. MS: 383 (M^+), 339, 213, 127, 91. Anal. Calcd for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.05; H, 6.56, N, 10.36.

2.16. (*S*)-[3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-cyclopropanamide (18)

A solution of the amine **14**, cyclopropane carboxylic acid (0.03 mL, 0.3 mmol), DCC (67 mg, 0.3 mmol), and DMAP (41 mg, 0.3 mmol) in chloroform was stirred for 1 h at rt. The residue obtained upon concentration was purified on silica gel (100–200 mesh) column using acetone–chloroform (2:3) as eluent to obtain the title compound **18** (50 mg, 41%) as a white solid. Mp 240 °C. IR (KBr): 3298, 1736, 1670, 1555, 1513, 1320, 1237, 1062 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz): δ 8.37 (br s, 1H), 7.67 (d, J = 11.2 Hz, 2H), 7.45 (d, J = 8.3 Hz, 1H), 7.09 (s, 1H), 6.26 (s, 2H), 4.79 (br s, 1H), 4.40 (s, 4H), 4.13 (t, J = 9.0 Hz, 1H), 3.88–3.81 (m, 1H), 3.55 (d, J = 4.4 Hz, 2H), 1.61 (br s, 1H), 0.79–0.63 (m, 4H). ^{13}C NMR (50 MHz, DMSO): δ 173.6, 154.2, 136.7, 135.6, 129.8, 129.6, 121.6, 121.0, 120.2, 120.0, 109.4, 109.3, 72.0, 66.1, 59.6, 47.4, 40.3, 13.5, 6.5. MS: 367 (M^+), 323,119, 92. Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 64.79; H, 5.41; N, 11.19.

2.17. (*S*)-*N*-[3-(4*H*,6*H*-5-Oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-acrylamide (19)

The title compound **19** was obtained following the procedure reported for the amide **16** using acryloyl chloride instead of propionyl chloride in 60% yield. Mp 220–221 °C. IR (KBr): 3287, 1737, 1677, 1513, 1321, 1062, 735 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz): δ 8.27 (br s, 1H), 7.64 (t, J = 9.5 Hz, 2H), 7.43 (d, J = 8.3 Hz, 1H), 7.06 (s, 1H), 6.28 (d, J = 6.3 Hz, 3H), 5.62 (t, J = 5.9 Hz, 1H), 4.94–4.71 (m, 1H), 4.45 (d, J = 3.9 Hz, 3H), 4.14 (t, J = 8.8 Hz, 1H), 3.92 (t, J = 7.8 Hz, 1H), 3.70 (br s, 2H), 2.95 (s, 2H). ^{13}C NMR: (50 MHz, DMSO): δ 165.4, 154.0, 136.5, 135.6, 131.2, 129.7, 129.5, 125.6, 123.6, 121.3, 120.7, 120.1, 119.4, 109.2, 71.5, 66.1, 59.6, 47.4, 41.5, 40.8, 40.3. MS: 353 (M^+), 309, 213, 154, 97. Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.56; H, 5.42; N, 11.89. Found: C, 64.88; H, 5.69; N, 11.42.

2.18. (*S*)-*N*-[3-(4*H*,6*H*-5-Oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-benzamide (20)

The title compound **20** was obtained following the procedure reported for the amide **16** using benzoyl chloride instead of propionyl chloride in 49% yield. Mp 234–236 °C (colorless solid). IR (KBr): 3336, 1738, 1663, 1540, 1515, 1319, 1233, 1054, 734 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.70–7.64 (m, 2H), 7.42 (d, J = 8.5 Hz, 1H), 7.04 (m, 1H), 6.33 (d, J = 2.0 Hz, 2H), 6.17 (br s, 1H), 4.82 (br s, 1H), 4.47 (d, J = 4.4 Hz, 1H), 4.12 (t, J = 8.9 Hz, 1H), 3.91–3.83 (m, 1H), 3.71–3.67 (m, 2H), 2.32–2.27 (m, 2H), 1.14 (t, J = 7.6 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.1, 154.2, 136.6, 135.5, 134.0, 131.4, 129.7, 129.5, 128.3,

127.3, 121.5, 120.9, 120.7, 119.4, 109.4, 109.3, 71.4, 66.1, 59.6, 47.6, 42.3. MS: 403 (M^+), 359, 213, 147, 105, 91. Anal. Calcd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.42. Found: C, 69.01; H, 5.05; N, 10.17.

2.19. (*S*)-2-Chloro-*N*-[3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide (21)

The title compound was obtained following the procedure reported for the amide **16** using chloroacetyl chloride instead of propionyl chloride in 75% yield. Mp 160–162 °C (pale brown solid). IR (KBr): 3293, 1736, 1661, 1511, 1409, 1224, 716 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.71 (dd, J = 2.4 and 8.8 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.08–7.06 (m, 2H), 6.35 (d, J = 2.0 Hz, 2H), 4.90–4.84 (m, 1H), 4.50 (d, J = 4.9 Hz, 4H), 4.18 (t, J = 9.3 Hz, 1H), 4.11 (s, 2H), 3.90–3.65 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.2, 154.3, 136.8, 135.8, 129.9, 129.7, 121.7, 121.2, 120.4, 119.8, 109.6, 109.5, 71.6, 66.3, 59.8, 47.5, 42.7, 42.0. MS: 376 (M^+), 342, 298. Anal. Calcd for $C_{18}H_{18}N_3O_4Cl$: C, 57.58; H, 4.83; N, 11.20. Found: C, 57.87; H, 4.46; N, 10.89.

2.20. (*S*)-2-Bromo-*N*-[3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide (22)

To a solution of the amine **14** (300 mg, 1.0 mmol) in chloroform (3 mL) were added DCC (248 mg, 1.2 mmol) and DMAP (61.3 mg, 1.2 mmol), and the reaction mixture was stirred at 0 °C for 30 min. Bromoacetic acid (167 mg, 1.2 mmol) was added at the same temperature and the stirring was continued at rt for 1 h. The reaction mixture was diluted with water and extracted with chloroform (100 mL 2×). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified on silica gel column (100–200 mesh) using acetone–chloroform (2:3) system to obtain the compound **22** (60 mg, 43%). IR (KBr): 3254, 1737, 1718, 1514, 890, 732 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.66 (dd, J = 6.4 and 8.8 Hz, 1H), 7.58 (d, J = 5.9 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.04 (br s, 2H), 6.33 (s, 2H), 4.82 (m, 1H), 4.47 (d, J = 4.4 Hz, 4H), 4.14 (t, J = 9.1 Hz, 1H), 3.89–3.68 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.0, 135.6, 129.6, 129.3, 120.9, 120.0, 119.2, 109.0, 78.4, 77.8, 77.1, 71.0, 66.2, 59.6, 47.0, 41.6, 28.1. MS: 421 (M^++1), 392, 341, 237, 209. 154. Anal. Calcd for $C_{18}H_{18}BrN_3O_4$: C, 51.44; H, 4.32; N, 10.00. Found: C, 50.91; H, 4.44; N, 10.19.

2.21. (*S*)-3,3,3-Trifluoro-*N*-[3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide (23)

The compound was obtained following the procedure reported for **22** using trifluoro propionic acid instead of bromoacetic acid in 49% yield. Mp 203–205 °C. IR (KBr): 3271, 1738, 1695, 1513, 1321, 1238, 1128, 749 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz): δ 7.66 (d, J = 8.8 Hz, 2H), 7.47 (t, J = 4.2 Hz, 1H), 7.09 (s, 1H), 6.34 (s, 2H), 4.85 (br s, 1H), 4.49 (d, J = 3.9 Hz, 4H), 4.18 (t, J = 9.0 Hz, 1H), 3.89 (t, J = 8.0 Hz, 1H), 3.67 (d, J = 4.4 Hz, 2H), 3.36 (s, 1H), 3.15 (q, J = 7.1 and 20.5 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.6, 163.5, 154.1, 136.6, 135.6, 129.8, 129.6, 121.5, 120.9, 120.1, 119.5, 109.4, 109.3, 71.5, 66.1, 50.6, 47.2. MS: 409 (M^+), 380, 213, 154, 91. Anal. Calcd for $C_{19}H_{18}F_3N_3O_4$: C, 55.75; H, 4.43; N, 10.26; Found: C, 56.23; H, 4.36; N, 9.98.

2.22. Methyl (*S*)-[3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamate (24)

To a solution of the amine **14** (250 mg, 0.8 mmol) in DCM was added triethylamine (127 mg, 0.18 mmol) at 0 °C followed by methylchloroformate (95.3 mg, 0.07 mmol). Stirring was continued for an additional 0.5 h and then the reaction mixture was diluted with water and extracted with chloroform (100 mL 3×). The organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was purified on silica gel column (60–120 mesh) using acetone–methanol (93:7 to 85:15) mixture to obtain a sticky compound, which was further washed with diethyl ether and ethylacetate to get the title compound **24** as a colorless solid (70 mg, 23.4%). Mp 187–191 °C. IR (KBr): 3254, 1737, 1718, 1514, 890, 732 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.76 (d, J = 8.5 Hz, 1H), 7.68 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.28 (br s, 1H), 6.31 (s, 2H), 6.28–6.25 (m, 2H), 4.79–4.72 (m, 1H), 4.39 (d, J = 2.7 Hz, 4H), 4.18 (t, J = 9.1 Hz, 1H), 3.84 (t, J = 7.7 Hz, 1H), 3.41–3.30 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.2, 154.1, 136.6, 135.5, 129.7, 129.5, 121.5, 120.9, 120.1, 119.5, 109.4, 109.3, 71.4, 66.1, 59.6, 51.5, 47.2, 43.3. MS: 358 (M^++1), 326. Anal. Calcd for $C_{18}H_{19}N_3O_5$: C, 60.48; H, 5.36; N, 11.76. Found: C, 59.95; H, 5.29; N, 11.90.

2.23. Ethyl (*S*)-[3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamate (25)

The title compound was obtained following the procedure reported for the derivative **24** using ethyl chloroformate instead of methyl chloroformate. It was purified on silica gel column (60–120 mesh) using acetone–chloroform (1:4 to 1:3) to get a sticky compound, which was washed with diethyl ether and ethylacetate to get a colorless powder in 29% yield. Mp 195 °C. IR (KBr): 3259, 3129, 2924, 1738, 1715, 1513, 1321 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.72 (d, J = 6.8 Hz, 1H), 7.60 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.07 (s, 1H), 6.36 (s, 2H), 5.18 (br s, 1H), 4.83 (br s, 1H), 4.50 (d, J = 3.9 Hz, 4H), 4.10–4.17 (m, 3H), 3.92 (t, J = 7.8 Hz, 1H), 3.63 (d, J = 5.4 Hz, 2H), 1.22–1.29 (m, 3H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 156.7, 154.1, 136.7, 135.5, 129.8, 129.5, 121.5, 120.9, 120.1, 119.5, 109.4, 109.3, 71.5, 66.1, 59.9, 59.6, 47.2, 43.2, 14.6. MS: 371 (M^+), 342, 296, 154, 91. Anal. Calcd for $C_{19}H_{21}N_3O_5$: C, 61.43; H, 5.70; N, 11.31; Found: C, 60.99; H, 5.33; N, 10.96.

2.24. Benzyl (*S*)-[3-(4*H*,6*H*-5-Oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamate (26)

The title compound was obtained following the procedure reported for the derivative **24** using benzylchloroformate instead of methylchloroformate. It was purified on silica gel column (60–120 mesh) using acetone–chloroform (1:4 to 3:7) to get a cream color powder in 14% yield. Mp 198 °C. IR (KBr): 3266, 3066, 2961, 2864, 1735, 1718, 1517, 1449, 1264 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.68 (d, J = 8.8 Hz, 1H), 7.55 (s, 1H), 7.32–7.45 (m, 6H), 7.05 (s, 1H), 6.34 (s, 2H), 5.25 (br s, 1H), 5.12 (s, 1H), 4.78–4.90 (m, 3H), 4.48 (d, J = 5.9 Hz, 3H), 4.10 (t, J = 9.0 Hz, 1H), 3.87 (t, J = 7.6 Hz, 1H), 3.59–3.65 (m, 2H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 156.7, 154.1, 136.9, 136.5, 135.5, 129.7, 129.5, 128.3, 127.8, 127.6, 121.5, 120.9, 120.1, 119.4, 109.4, 109.3, 71.5, 66.1, 65.5, 59.6, 47.1, 43.3, 40.7. MS: 433 (M^+), 325, 296, 154, 108, 91.

2.25. (*S*)-*N*-[3-(4*H*,6*H*-5-Oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-thioacetamide (27)

To a solution of the amine **14** (200 mg, 0.67 mmol) in THF (2 mL) was added triethylamine followed by the addition of ethyldithioacetate (43 μL) and stirred for 5–6 h. The residue obtained after evaporation of volatiles was purified on silica gel column (60–120 mesh) using ethylacetate–petroleum ether (3:2) system to obtain the title compound **27** as a white solid (50 mg, 21%). Mp 196–198 °C. IR (KBr): 3251, 2919, 2851, 1749, 1619, 1589, 1511, 1321, 1066 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.03 (br s, 1H), 7.63 (t, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 1H), 7.04 (s, 1H), 6.34 (s, 2H), 5.02 (d, J = 6.8 Hz, 1H), 4.48 (d, J = 4.4 Hz, 4H), 4.05- 4.37 (m, 3H), 3.92 (t, J = 8.0 Hz, 1H), 2.62 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 201.3, 153.0, 135.3, 135.0, 129.0, 128.6, 120.2, 119.2, 118.4, 108.3, 108.2, 69.4, 65.5, 59.0, 46.9, 46.5, 31.9. MS: 357 (M^+), 314, 313, 213, 154, 101.

2.26. *O*-Methyl (*S*)-[3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-thiocarbamate (28)

To a solution of the amine **14** (250 mg, 0.84 mmol) in THF was added carbon disulfide (127.3 mg, 1.67 mmol) in the presence of triethylamine (0.23 mL, 1.7 mmol) and stirred for 6 h at rt. Methylchloroformate was then added to the reaction mixture and stirred for 30–45 min. It was then diluted with water (200 mL) and aqueous layer was extracted with ethylacetate (300 mL 2×). The organic layer was washed with brine, dried, and concentrated. The residue obtained was dissolved in methanol and refluxed for 16 h. The compound obtained after evaporation of volatiles was purified on silica gel (60–120 mesh) column using methanol–chloroform (1:9) as eluent to obtain the title compound **28** (135 mg, 40%). Mp 186–188 °C (colorless powder). IR (KBr): 3222, 3044, 2944, 1738, 1513, 1447, 1319, 1200, 1068, 723 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.70 (dd, J = 2.4 and 6.3 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.05 (s, 1H), 6.89 (br s, 1H), 6.34 (s, 2H), 4.95 (br s, 1H), 4.48 (d, J = 4.4 Hz, 4H), 3.90–4.19 (m, 3H), 4.01 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 192.8, 154.3, 136.7, 136.1, 130.5, 130.1, 121.6, 120.5, 120.4, 119.8, 109.7, 71.4, 66.9, 60.4, 58.6, 57.7, 47.5. MS: 373 (M^+), 341, 312, 213, 117. Anal. Calcd for $C_{19}H_{21}N_3O_4S$: C, 57.90; H, 5.13; N, 11.25. Found: C, 57.49; H, 5.07; N, 11.11.

2.27. *O*-Ethyl (*S*)-[3-(4*H*,6*H*-5-oxa-10b-aza-benzo[*e*]azulen-8-yl)-2-oxo-oxazolidin-5-ylmethyl]-thiocarbamate (29)

The title compound was prepared following the procedure as reported for the compound **28** using ethanol instead of methanol in 38% yield. Mp 200 °C (colorless powder). IR (KBr): 3423, 2924, 1636, 1541, 1509, 1197, 714 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.68 (d, J = 8.8 Hz, 1H), 7.59 (s, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.05 (s, 1H), 6.70 (br s, 1H), 6.34 (s, 2H), 4.93 (br s, 1H), 4.51–4.55 (m, 2H), 4.48 (d, J = 3.9 Hz, 4H), 3.96–4.19 (m, 4H), 1.26–1.36 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 192, 154.2, 136.7, 136.1, 130.5, 130.1, 121.6, 120.5, 120.4, 119.8, 109.7, 71.4, 70.7, 68.2, 67.1, 66.9, 60.4, 47.5, 14.1. MS: 387 (M^+), 343, 341, 213, 131, 102. Anal. Calcd for $C_{19}H_{21}N_3O_4S$: C, 58.90; H, 5.46; N, 10.84. Found: C, 58.69; H, 5.71; N, 10.98.

2.28. Biology: Materials and methods

2.28.1. Organisms. The panel of organisms consisted of six reference Gram-positive bacteria including both sensitive and resistant strains: *S. aureus* ATCC 29213 (MSSA), *S. aureus* ATCC 49951 (Smith), *S. aureus* ATCC 33591 (MRSA), *Enterococcus faecalis* ATCC 29212, *E. faecalis* NCTC 12201 (VRE), and *Enterococcus faecium* NCTC 12202 (VREf).

2.28.2. Susceptibility tests. MIC was determined by agar dilution on Mueller Hinton agar (MHM-Difco) as per the guidelines prescribed by NCCLS.[6] Using a multipoint-inoculating device, 10^4–10^5 bacteria were transferred onto the surface of MHM agar. Plates were incubated for 16–18 h at 35 °C. MIC was defined as the lowest concentration of antibiotic at which no visible growth could be detected on the agar plate.

2.28.3. Pharmacokinetics. Single dose oral pharmacokinetics experiment was carried out for selected compounds (MIC < 4 μg/mL) and Linezolid in Swiss albino mice. All the animal experiments were approved by DRF Institutional Animal Ethics Committee. Single dose oral pharmacokinetics experiment was also carried out for compound **3** and Linezolid in Wistar rats. Studies were conducted under overnight fasted conditions and test compound was administered orally at 30 mg/kg dose in 0.25% carboxy methyl cellulose. Blood samples were collected from orbital plexus at 0.5, 1, 2, 4, 6, and 8 h, and plasma was separated for bio-analysis. Plasma concentration was determined by liquid–liquid extraction followed by HPLC–UV detection with limit of quantitation of 100 ng/mL. Pharmacokinetic parameters were calculated from the mean plasma concentration by non-compartmental analysis.

2.28.4. Systemic infection. Selected compounds were evaluated by mouse systemic infection model using Linezolid as positive control. Overnight growth of *S. aureus* ATCC 29213 was inoculated to fresh BHIB and incubated on a rotary shaker for 2 h at 150 rpm at 35 °C. Inoculum was adjusted to $100 \times LD_{50}$ dose in 5% Hog Gastric Mucin (Difco) and 0.5 mL was injected intraperitoneally to Swiss albino mice weighing 19–21 g ($n = 6$). The test compound suspended in 0.25% sterile CMC was administered orally or subcutaneously 1 and 6 h postinfection. ED_{50} was calculated by linear regression analysis.

Acknowledgment

We are thankful to the analytical department of Discovery Research for their support.

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