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Novel and potent oxazolidinone antibacterials featuring 3-indolylglyoxamide substituents☆

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Abstract—Novel oxazolidinone antibacterials bearing a variety of 3-indolylglyoxamide substituents have been explored in an effort to improve the spectrum and potency of this class of agents. A subclass of this series was also made with the diversity at C-5 terminus. These derivatives have been screened against a panel of clinically relevant Gram-positive pathogens and fastidious Gram-negative organisms. Several analogs in this series were identified with in vitro activity superior to linezolid (MIC = 0.25–2 μg/mL). Compounds **10a**, **10c**, **10e** and **10f** displayed activity against linezolid resistant Gram-positive organisms (MIC = 2–4 μg/mL). Selected oxazolidinones were evaluated for in vivo efficacy against a mouse systemic infection model.

The oxazolidinones, exemplified by linezolid **1** and eperezolid **2**, are a group of promising antibacterials active against a variety of susceptible and resistant Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), and penicillin-resistant *Streptococcus pneumoniae* (PRSP).[1] This class is known to inhibit the bacterial protein synthesis by binding to the 50S ribosomal subunit and prevents the formation of a functional 70S initiation complex.[2] Due to this unique mechanism of action, no cross-resistance is expected between the oxazolidinones and the other families of antibacterials. Linezolid, the first oxazolidinone to receive FDA approval, has become an important clinical option for the treatment of nosocomial resistant Gram-positive bacterial infections. However, a few cases of linezolid-resistant pathogens in clinical isolates have been reported.[3] The emergence of early resistance and safety concerns in terms of myelosupression emphasize the need for the development of more effective oxazolidinones.[4] (see Fig. 1).

In the course of research to enhance the spectrum and potency of oxazolidinones,[5] we embarked on relatively less explored glyoxamide derivatives. There are only two examples reported in the literature carrying 3-thienyl and methyl glyoxamide substituents on piperazine scaffold of eperezolid analogs.[6] This type of modification resulted in compounds with improved antibacterial activity against Gram-positive pathogens. For example, MIC values are in the range of 0.25–0.5 μg/mL and 0.5–2 μg/mL against *S. aureus* organisms for 3-thienyl and methyl glyoxamide derivatives, respectively. On the other hand, indole ring provides instant access to a variety of 3-indolylglyoxamides. The synthetic ease and diversity of indole derivatives as well as the reported potency of glyoxamides prompted us to investigate the effect of indolylglyoxamides **3** on the antibacterial activity of oxazolidinones. Thus, a focused library was made wherein hydroxyacetamido group in eperezolid has been replaced initially with various substituted 3-indolylglyoxamides. In the second variation, acetamide at C-5 terminus has been modified with various N-and O-linked substituents keeping 5-bromoindole fixed on the left hand side. The synthesis and antibacterial activity of these compounds are reported herein.

The advanced intermediates **4**, **5**, **6**, and **7** were prepared conveniently following the reported procedure as depicted in Scheme 1.[7] The 3-indolylglyoxalyl chlorides

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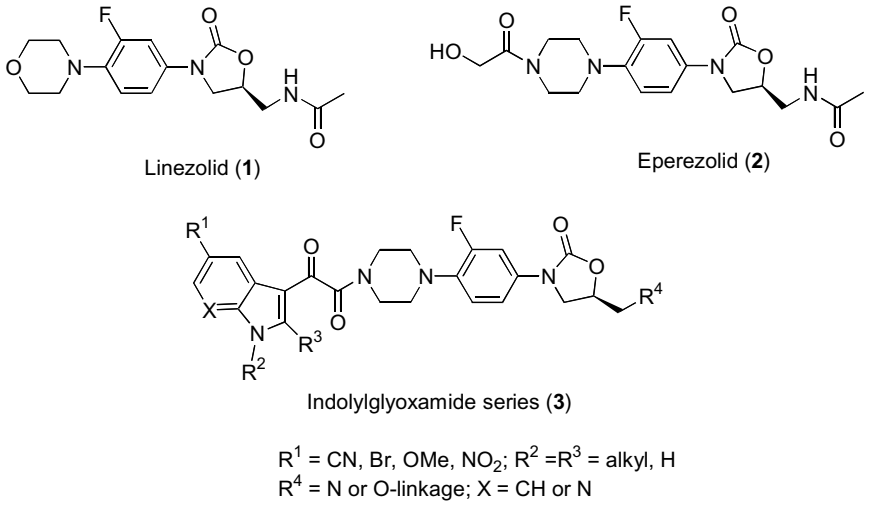
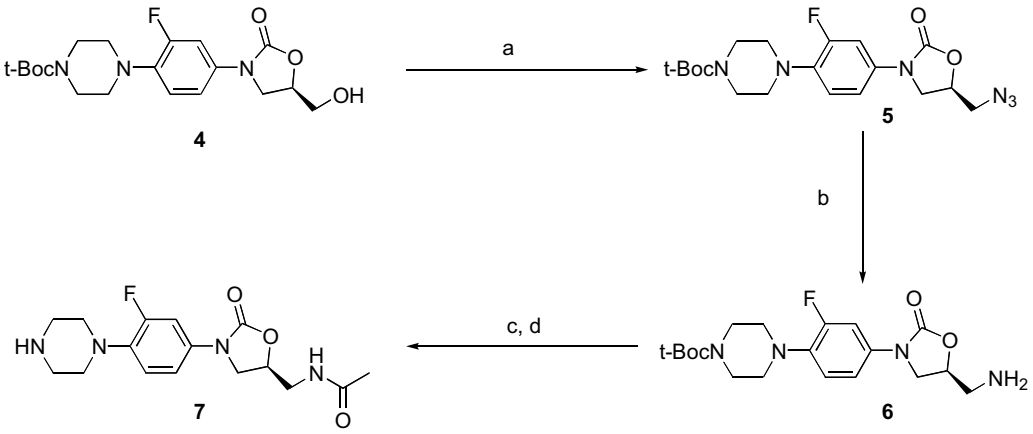


Figure 1.



Scheme 1. Reagents and conditions: (a) i—MsCl, Et_3N, CH_2Cl_2, rt, ii—NaN_3, DMF, 90 °C, 80%; (b) PPh_3, THF–H_2O, 78%; (c) Ac_2O, Et_3N, CH_2Cl_2, 82%; (d) TFA, CH_2Cl_2, rt, 86%.

have been made by the treatment of corresponding indoles **8a**–**h** with oxalyl chloride. Subsequently, the reaction of these 3-indolylglyoxalyl chlorides with **7** in the presence of Hunig's base produced targeted oxazolidinones **9a**–**h** in good yields.[8]

A series of C-5 acetamide compounds was screened against a panel of susceptible and resistant Gram-positive and fastidious Gram-negative strains.[9] As per the data summarized in Table 1, most of the analogs exhibited superior activity compared to linezolid against MSSA, MRSA, *E. faecalis* and *E. faecium*. The simple indole analog **9a** exhibited onefold better activity compared to linezolid against most of the organisms. Among the 5-substituted indole derivatives (**9b**, **9c**, **9e**, and **9h**), 5-bromoindole **9h** displayed 1-2-fold superior potency compared to linezolid across the panel of organisms. The MIC values of this derivative against *S. aureus*, *E. faecalis* and *E. faecium* are in the range of 0.5–1 μg/mL. The antibacterial activity was minimally impacted when indole moiety in **9a** was substituted by azaindole **9d**. In vitro activities of 2-methylindole **9f** and *N*-methylindole **9g** were onefold better than linezolid against two enterococcal strains. However, none of these molecules showed antibacterial activity against a representative Gram-negative CAP (community acquired pneumonia) pathogen such as *H. influenzae*. The preliminary SAR indicates that the position and electronic nature of substituents on indole ring have little influence on the antibacterial activity. Thus, the in vitro activities of simple indole analog **9a** and the rest of the molecules in Table 2 are comparable (see Scheme 2).

In the next phase, SAR on a relatively potent compound **9h** from the above series was undertaken at C-5 side chain of oxazolidinone pharmacophore. Previous studies had identified various cyclic and acyclic surrogates for the privileged acetamidomethyl side chain.[10–13] Accordingly, acetamide group in **9h** has been replaced with a variety of substituents including amides, carbamates and azoles. As illustrated in Scheme 3, primary amine **6** was reacted with ethyl dithioacetate to yield the corresponding thioacetamide. Subsequently, trifluo-

Table 1. In vitro antibacterial activity (MIC (μg/mL)) of oxazolidinone derivatives **9a–h**

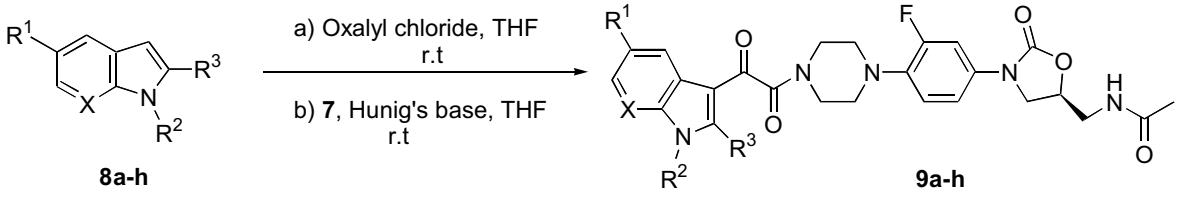
Compound	Sa[a]	Sa[b]	Ef[c]	Ef[d]	Ef[e]	Hi[f]
9a	1	1	1	1	1	16
9b	1	1	1	0.5	1	>32
9c	2	1	1	1	2	>32
9d	2	1	1	0.5	1	>32
9e	2	1	1	0.5	1	>32
9f	2	1	1	1	2	>32
9g	2	1	1	1	2	>32
9h	1	0.5	1	0.5	1	>32
LNZ	2	1	2	2	2	8

LNZ—linezolid.
MIC—minimum inhibitory concentration.
[a] S.a., *Staphylococcus aureus* DRCC 035 (methicillin-susceptible *S. aureus*).
[b] S.a., *Staphylococcus aureus* DRCC 019 (methicillin-resistant *S. aureus*).
[c] E.f., *Enterococcus faecalis* DRCC 034 (vancomycin susceptible *E. faecalis*).
[d] E.f., *Enterococcus faecalis* DRCC 153 (vancomycin-resistant *E. faecalis*).
[e] E.f., *Enterococcus faecium* DRCC154 (vancomycin-resistant *E. faecium*).
[f] H.i., *Haemophilus influenzae* DRCC 433 (β-lactamase –ve).

Table 2. In vitro antibacterial activity (MIC (μg/mL)) of oxazolidinone derivatives **10a–h**

Compound	Sa[a]	Sa[b]	Sa[c]	Ef[d]	Ef[e]	Ef[f]	Ef[g]	Mc[h]	Hi[i]
9h	1	0.5	8	1	0.5	1	8	2	>32
10a	0.5	0.25	2	0.5	0.12	0.25	2	2	>32
10b	1	0.5	16	1	0.5	1	32	2	>32
10c	1	1	2	1	0.5	1	2	1	>32
10d	1	2	8	2	1	2	8	4	>32
10e	2	1	4	1	0.25	0.5	4	2	>32
10f	1	1	4	1	0.25	0.5	4	2	>32
10g	2	0.5	8	1	0.5	0.5	16	4	>32
10h	>32	32	32	32	32	>32	32	32	>32
LNZ	2	1	32	2	2	2	32	4	8

[a] S.a., *Staphylococcus aureus* DRCC 035 (methicillin-susceptible *S. aureus*).
[b] S.a., *Staphylococcus aureus* DRCC 019 (methicillin-resistant *S. aureus*).
[c] S.a., *Staphylococcus aureus* DRCC 564 (linezolid resistant *S. aureus)*.
[d] E.f., *Enterococcus faecalis* DRCC 034 (vancomycin susceptible *E. faecalis*).
[e] E.f., *Enterococcus faecalis* DRCC 153 (vancomycin-resistant *E. faecalis*).
[f] E.f., *Enterococcus faecium* DRCC154 (vancomycin-resistant *E. faecium*).
[g] E.f., *Enterococcus faecalis* DRCC 632 (linezolid resistant *E. faecalis*).
[h] M.c., *Moraxella catarrhalis* DRCC 300 (β-lactamase –ve).
[i] H.i., *Haemophilus influenzae* DRCC 433 (β-lactamase –ve).

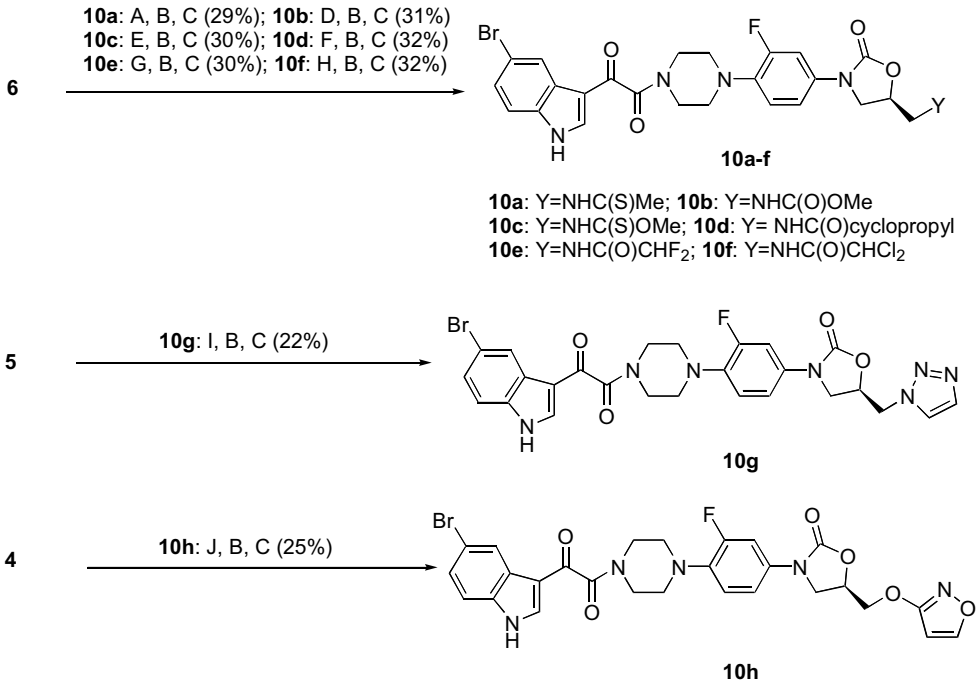


8a: R^1=R^2=R^3=H, X=CH; **8b**: R^1=CN, R^2=R^3=H, X=CH
8c: R^1=NO_2, R^2=R^3=H, X=CH; **8d**: R^1=R^2=R^3=H, X=N
8e: R^1=OMe, R^2=R^3=H, X=CH; **8f**: R^1=R^2=H, R^3=Me, X=CH
8g: R^1=R^3=H, R^2=Me, X=CH; **8h**: R^1=Br, R^2=R^3=H, X=CH

Yields: **9a** (40%), **9b** (65%),
9c (24%), **9d** ((55%)
9e (83%), **9f** (40%)
9g (39%), **9h** (45%)

Scheme 2.

roacetic acid treatment followed by the reaction of 3-indolylglyoxalyl chloride derived from 5-bromoindole **8h** furnished the desired oxazolidinone **10a**. Amine **6** was treated with methyl chloroformate in the presence of Hunig's base to furnish methylcarbamate **10b**. Thiocarbamate **10c** was prepared by the reaction of amine



Scheme 3. Reagents and conditions: (A) $CH_3C(S)SC_2H_5$, Et_3N, THF, rt, 80%; (B) TFA, CH_2Cl_2, rt; (C) 5-bromo-3-indolylglyoxalyl chloride, *N*-diisopropyl ethylamine, THF; (D) ClC(O)OMe, *N*-diisopropyl ethylamine, CH_2Cl_2, rt, 72%; (E) $C(S)Cl_2$, $NaHCO_3$, CH_2Cl_2 then MeOH, reflux, 67%; (F) cyclopropyl carboxylic acid, EDC·HCl, NMM, CH_2Cl_2, rt, 65%; (G) CHF_2COOH, EDC·HCl, NMM, CH_2Cl_2, rt, 55%; (H) $CHCl_2COOH$, EDC·HCl, NMM, CH_2Cl_2, rt, 52%; (I) bicyclo[2.2.1] hepta-2,5-diene, dioxane, 100 °C, sealed tube, 94%; (J) PPh_3, DEAD, 3-hydroxy isooxazole, THF, rt, 70%.

6 with thiophosgene to produce the corresponding isothiocyanate, which in turn reacted with excess of methanol under reflux. The cyclopropyl amide **10d** was fashioned by the sequential treatment of **6** with cyclopropyl carboxylic acid in the presence of EDC·HCl, trifluoroacetic acid and then 5-bromo 3-indolylglyoxalyl chloride obtained from **8h**. Similarly, difluoroacetamide **10e** and dichloroacetamide **10f** have been accessed by using difluoroacetic acid and dichloroacetic acid, respectively. The triazole derivative **10g** was made by the reaction of azide **5** with bicyclo[2.2.1] hepta-2,5-diene at 100 °C in a closed vial.

The isooxazole ring was appended at C-5 position by exposing alcohol **4** to Mitsunobu conditions. The t-Boc group was cleaved by acid treatment and the resulting amine was derivatized with 5-bromo 3-indolylglyoxalyl chloride to afford ether derivative **10h**.

All of the analogs were tested in vitro against a broader panel of Gram-positive bacteria including linezolid-resistant organisms[14] and fastidious Gram-negative bacteria such as *M. catarrhallis* and *H. influenzae*. The results are presented in Table 2. In general, C-5 modifications based on N-linkage were well tolerated and furnished potent molecules. The analogs **10a**, **10b**, **10c**, **10e**, **10f** and **10g** showed excellent in vitro activity against key Gram-positive pathogens (MICs = 0.25–2 μg/mL). The thiocarbonyl compounds **10a** and **10c** were more potent than the corresponding oxocarbonyl compounds **9h** and **10b** as observed in many other oxazolidinone series.[10] The enhancement in potency could be the result of subtle changes in electronic character and lipophilicity of the molecules.[10a–c] The dihaloacetamides **10e** and **10f** have shown improved potency compared to simple acetamide **9h**. This characteristic is reminiscent to the C-5 modifications reported by Vicuron and Pfizer groups using various haloacetamides.[11]The noteworthy feature of thioacetamide **10a**, thiocarbamate **10c**, difluoroacetamide **10e** and dichloroacetamide **10f** analogs is their activity against linezolid-resistant *S. aureus* and *E. faecalis* (MICs = 2–4 μg/mL). This result exemplifies that appropriate substitution around oxazolidinone would result in compounds active against linezolid-resistant organisms. Though the rational behind this activity feature is not very clear, it can be attributed to distinct binding mode to oxazolidi-

Table 3. In vivo efficacy in a murine systemic infection model by oral route[13]

Compound	ED_{50} (mg/kg/day)
9a	19.4 (5.3–70.5)[a]
9b	>30
9d	>30
9h	27.0 (18.0–40.4)
10a	>30
10c	>30
10d	18.9 (9.4–37.9)
10e	>30
10f	>30
10g	28.9 (19.3–43.3)
Linezolid	5.3 (2.6–9.0)

[a] Numbers in parentheses are 95% confidence ranges.

Table 4. Pharmacokinetic parameters of selected compounds in Swiss Albino mice[a]

Parameters	9b	9d	9h	10d	Linezolid
$AUC_{(0-t)}$ (μg h/mL)	1.90	3.36	2.25	1.26	10.98
T_{max} (h)	3.00	0.50	2.00	2.00	0.25
C_{max} (μg/mL)	0.43	1.05	0.68	0.30	6.31
$t_{1/2}$ (h)	1.19	0.87	2.17	1.13	1.37
K_{el} (h−1)	0.58	0.79	0.32	0.61	0.51

[a] Pharmacokinetic experiments were performed by single dose (10 mg/kg) using oral route of administration.

none site and/or binding to additional site on ribosome. Cyclopropyl amide **10d** derivative showed 1-2-fold less potency than acetamide congener **9h**. Among the C-5-linked azoles, the activity of triazole derivative **10g** was comparable to acetamide **9h** and superior to standard. The result is in accordance with the early work on C-5 heterocyclic groups.[12] However, the *O*-isooxazole substitution at C-5 terminus in **10h** proved to be detrimental to the antibacterial activity. This observation is in contrast to the report disclosing tetrahydropyranyl and tetrahydropyridyl series where O-linked isooxazole was found to be optimal.[13] Most of the analogs exhibited respectable activity against fastidious Gram-negative bacterium *M. catarhalis* (MIC = 2–4 μg/mL). However, these molecules were devoid of antibacterial activity against other Gram-negative organism *H. influenzae*. The lack of activity against this Gram-negative organism in both series could be due in part to active efflux, effectively lowering the intracellular concentration of the test compound.[15] In general the SAR at C-5 terminus followed the trend as reported earlier in most of the cases and showed improvement in in vitro activity except for the *O*-isooxazole analog **10h**. These results once again prove that C-5 side chain can accommodate diverse functionalities depending upon the nature of other substituents in the molecule.

Selected oxazolidinones **9a**, **9b**, **9d**, **9h**, **10a**, **10c**, **10d**, **10e**, **10f**, and **10g** from both the series have been tested in vivo against *S. aureus* DRCC 035 organism in a murine systemic infection model by oral route.[16] The ED_{50} values are presented in Table 3. Compounds **9a**, **9h**, **10d**, and **10g** protected mice from infection at higher doses compared to linezolid despite the good in vitro activity against this organism. Subsequently, pharmacokinetic studies of representative molecules **9b**, **9d**, **9h** and **10d** in mice were taken up. The pharmacokinetic parameters are summarized in Table 4. Upon oral administration, the absorption from mouse gastrointestinal tract was slow and the maximum plasma concentration reached at 2–3 h (T_{max}) in all the compounds except for **9d**. The elimination half-life ($t_{1/2}$) and rate of elimination (K_{el}) were in the range of linezolid for most of the compounds. However, the mean plasma concentration (C_{max}) and systemic exposure ($AUC_{(0-t)}$) of these oxazolidinones were poor compared to linezolid. Thus, the higher ED_{50} values can be attributed to poor pharmacokinetics exhibited by these compounds.

In summary, a novel series of oxazolidinones bearing indolylglyoxamides active against resistant and susceptible Gram-positive pathogens has been identified. These analogs with acetamide moiety at C-5 position were found to be 1-2-fold more potent compared to linezolid against the tested organisms. Notable improvements in terms of potency and spectrum have been made through the introduction of halogenated amides, thioamides and 1,2,3-triazole at C-5 side chain. Compounds **10a**, **10c**, **10e** and **10f** exhibited excellent activity against Gram-positive organisms such as MSSA, MRSA, *E. faecalis* and *E. faecium*. The activity of these four molecules against linezolid-resistant *S. aureus* and *E. faecalis* is an additional trait of the present series (MIC = 2–4 μg/mL). A few members of this series also showed in vivo efficacy in a lethal murine infection model at higher doses.

Acknowledgments

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8. *Preparation of compound* **9a**. To a solution of indole (80 mg, 0.68 mmol) in THF was added oxalyl chloride (0.065 mL, 0.75 mmol) dropwise at 0 °C and the reaction mixture was stirred at rt for 4 h. The solvent was removed under reduced pressure to obtain indole-3-glyoxalyl chloride as a yellow solid. To a suspension of **7** (150 mg, 0.44 mmol) and above-prepared indole-3-glyoxalyl chloride (140 mg, 0.66 mmol) in THF, *N*,*N*-diisopropylethylamine (0.155 mL, 0.89 mmol) was added dropwise and stirred at rt overnight. Finally it was quenched with 10% aq $NaHCO_3$ (20 mL) and extracted with ethyl acetate (2× 20 mL). The combined organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel (eluent: 4% MeOH/$CHCl_3$) to obtain oxazolidinone **9a** as light green solid (90 mg, 40%). ^{1}H NMR (DMSO-d_6): δ12.31 (d, J = 2.9 Hz, 1H), 8.24–8.18 (m, 2H), 8.16–8.11 (m, 1H), 7.57–7.52 (m, 1H), 7.48 (dd, J = 2.4 Hz, 14.6 Hz, 1H), 7.32–7.24 (m, 2H), 7.18 (dd, J = 2.4 Hz, 8.8 Hz, 1H), 7.08 (t, J = 9.2 Hz, 1H), 4.73–4.66 (m, 1H), 4.07 (t, J = 8.8 Hz, 1H), 3.78 (t, J = 4.8 Hz, 2H), 3.69 (dd, J = 6.3 Hz, 9.2 Hz, 1H), 3.50 (t, J = 3.9 Hz, 2H), 3.42–3.37 (m, 2H), 3.10 (t, J = 4.8 Hz, 2H), 2.94 (t, J = 4.3 Hz, 2H), 1.82 (s, 3H); IR (KBr): 3284, 2924, 1751, 1630, 1518, 1425, 1377, 1325, 1281, 1236, 1155, 1034, 953, 840, 773, 754, 640 cm^{-1}; MS: (*m*/*z*) 508 (M+1).
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16. Cleeland, R.; Squires, E. *Antibiotics in Laboratory Medicine*; The Williams and Witkins Co.: Baltimore, MD, 1991, 739–786. *In vivo experiment.* The infecting inoculum (0.5 mL) was adjusted to yield approximately 100 times LD_{50} and injected intraperitoneally (10^8 cfu/mL). The test compounds were formulated in sterile Tween and carboxy methyl cellulose (CMC) and then administered by oral route for 1 day at 1 and 5 h post-infection. A treatment group of six mice was used for each antibiotic dose level. Death in each treated and untreated group was monitored daily for 5 days. The ED_{50} values were calculated by Probit analysis.