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Design and synthesis of biaryloxazolidinone derivatives containing a rhodanine or thiohydantoin moiety as novel antibacterial agents against Gram-positive bacteria

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Abstract:

Novel biaryloxazolidinone derivatives containing a rhodanine or thiohydantoin moiety were designed, synthesized and evaluated for their antibacterial activity. The key compounds **7** and **9** were synthesized by the knoevenagel condensation of intermediate aldehyde **5** with rhodanine derivatives **6a-6b**. The preliminary study showed that compounds **7**, **9** and **10e** exhibited potent antibacterial activity with MIC values of 0.125 ug/mL against *S.aureus*, MRSA, MSSA, LREF and VRE pathogens, using linezolid and radezolid as the positive controls. The most promising compound **10e** exhibited potent antibacterial activity against tested clinical isolates of MRSA, MSSA, VRE and LREF with MIC values in the range of 0.125–0.5 μg/mL, and the potency of **10e** against clinical isolates of LREF was 64-fold higher than that of linezolid. Moreover, compound **10e** was non-cytotoxic with an IC_{50} value of 91.04 μM against HepG2 cell. Together, compound **10e** might serve as a novel antibacterial agent for further investigation.

Keywords: biaryloxazolidinone; rhodanine derivatives; antibacterial activity; Gram-positive bacteria

Antibiotic-resistant infections of pathogenic bacteria are increasingly prevalent worldwide and become a critical global problem [1-3]. Resistant Gram-positive bacteria such as vancomycin-resistant *Enterococci* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE) are pandemic and become the main concern [4-7]. There is an urgent need to find new antibacterial drugs to combat these bacterial pathogens. However, many major pharmaceutical companies have abandoned the discovery of new antibiotics due to commercial challenges, which led to the dwindling discovery of new antibiotics over the past 25 years [8-9]. Developing new antibacterial drugs is increasingly becoming a big challenge for drug chemists.

The oxazolidinones are a new structural class of totally synthetic antibacterial agents which inhibit bacterial protein biosynthesis by binding to 23S RNA of the 50S ribosomal subunit [10]. Linezolid **1** (Zyvox; Fig.1), the first antibacterial agent of the oxazolidinone family, is used for the treatment of antibiotic-resistant infections caused by Gram-positive bacteria such as MRSA, PRSP, and VRE [11-12]. Unfortunately, linezolid-resistant bacteria such as *Staphylococcus aureus* and other bacteria have already been reported [13-15]. Modifying the scaffold of old drugs to develop novel antimicrobial agents with the same target is an important strategy to overcome bacterial resistance [16]. The modification of scaffolds can improve properties of parental compounds and usually increase affinity for mutated or modified targets.

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Tedizolid phosphate **2** (Fig.1), a second-generation oxazolidinone, was approved by FDA in 2014 to treat patients with acute bacterial skin and skin structure infections (ABSSSIs) caused by certain susceptible bacteria [17-18]. Radezolid **3** (RX-1741, Fig.1), designed from the X-ray structures of linezolid, was a non-selective antibiotic sparsomycin bound to the 50s ribosome [19-20]. Linezolid and sparsomycin share an overlapping region within the RNA bases of the peptidyl transferase center, which inspire Rib-X to develop new antibiotics enhancing the binding to the bacterial ribosome and having a broader and more potent spectrum of antibacterial activity by molecular hybridization and further modification. Radezolid have potential activity against resistant Gram-positive bacteria and even some Gram-negative bacteria.

Rhodanine and its five-membered multiheterocyclic derivatives have broad spectrum of anti-infective activities, such as anti-bacterial [21], anti-malarial [22], anti-tubercular [23], anti-HIV [24] and anti-fungal [25] activities. As depicted in **Figure 2**, compounds **4-8** show excellent antibacterial activity against *Staphylococcus aureus*, MRSA and *Mycobacterial tuberculosis* [26-30].

Since oxazolidinones and many other antibiotics share an overlapping region within the binding site of RNA bases at the C-ring and D-ring portion[16,19-20], in previous researches, our group have designed and synthesized a series of biaryloxazolidinone analogues containing a hydrazone moiety at the D-ring portion (9, Fig. 3), which showed excellent antibacterial activity [31]. The SAR studies about those compounds suggested that biaryl scaffold and hydrazone moiety appear to be critical for antibacterial activity. With the goal of improving the potency and expanding the antibacterial spectrum, due to rhodanine and hydrazone moiety having similar conformations, we inserted rhodanine moiety to the biaryloxazolidinone at D-ring portion in target compounds, as depicted in **Figure 3**.

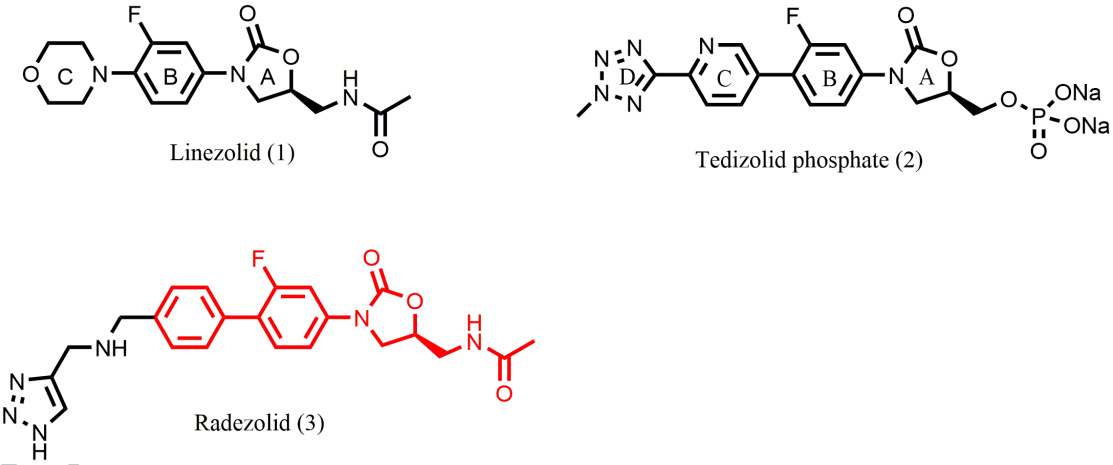


Figure 1. Chemical structures of linezolid and other oxazolidinones.

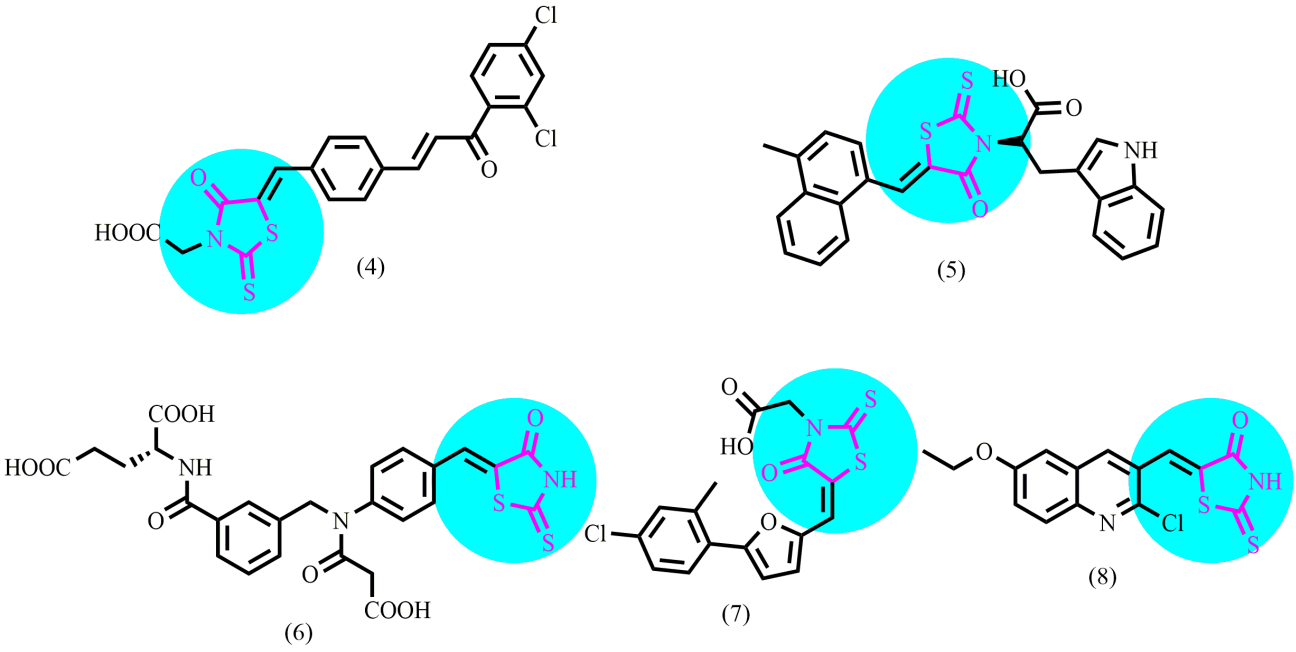


Figure 2. Chemical structures of reported rhodanine derivatives

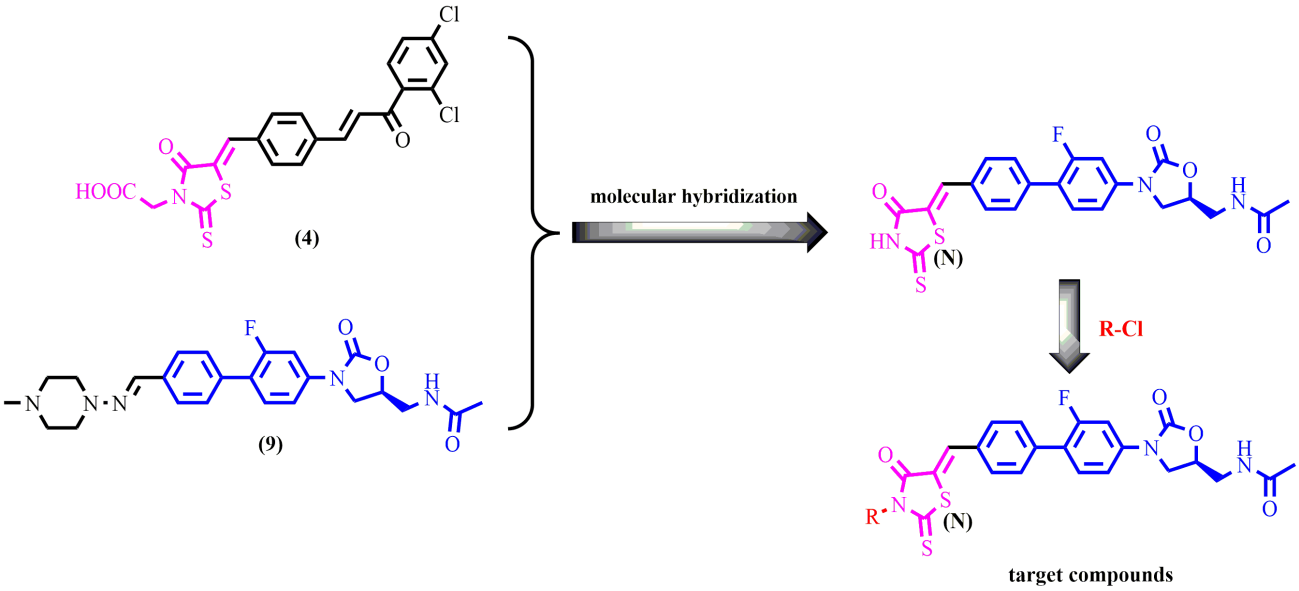


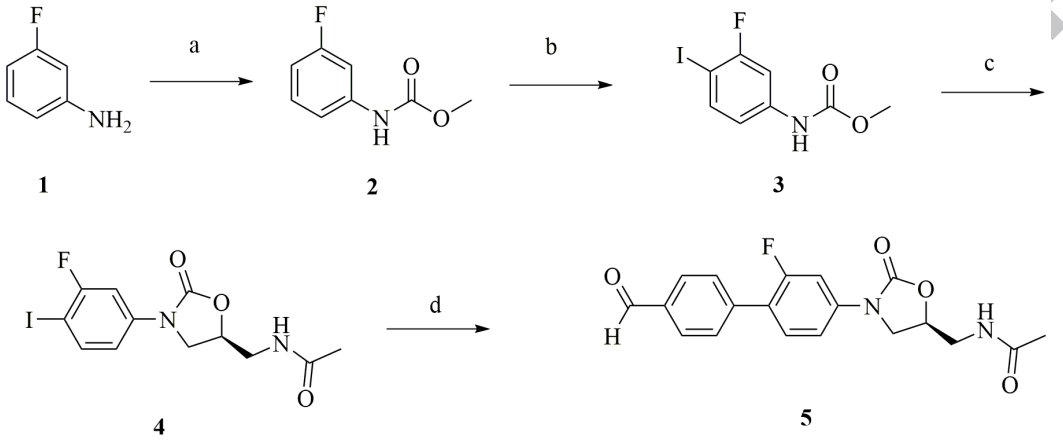
Figure 3. Design strategies for the novel oxazolidinone analogues containing a rhodanine or thiohydantoin moiety

In this paper, all the biaryloxazolidinone derivatives bearing a rhodanine or thiohydantoin moiety were evaluated for their antibacterial activity in *vitro* against five Gram-positive bacteria (*S.aureus* ATCC29213, MRSA, MSSA, LREF and VRE). Antibacterial activity in *vitro* against four clinical isolates (MRSA, MSSA, VRE and LREF) was also carried out. Additionally, the in *vitro* cytotoxicity and inhibition of MAO-A test were also performed from a safety viewpoint. Furthermore, molecular superposition model was built to better understand the potency of the synthesized compounds.

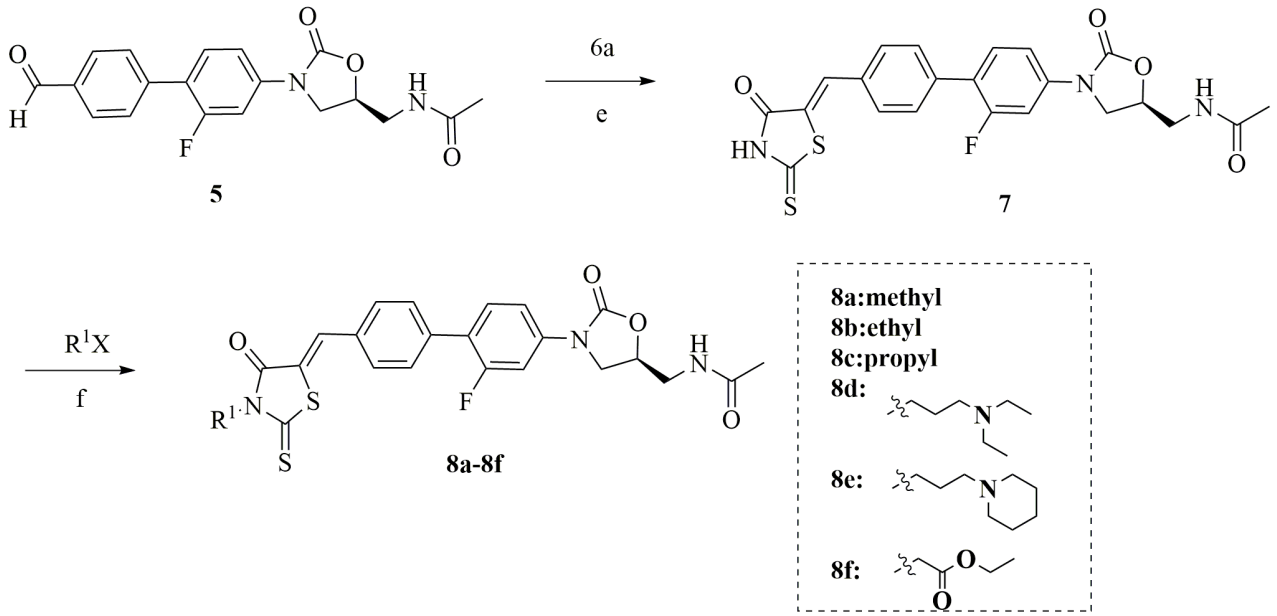
The synthesis of key intermediate **5** is depicted in **Scheme 1**, which had been reported in our previous work [31]. The general synthesis of compounds **8a-8f** and **10a-10h** is illustrated in **Scheme 2-3**. Compound **7** was synthesized by the knoevenagel condensation of intermediate **5** with rhodanine using sodium acetate as base in acetic acid. Compounds **8a-8f** were prepared through nucleophilic substitution of various halogenated hydrocarbons with **7** in the presence of NaOH in DMF. Rhodanine analogue 1-acetyl-2-thioxoimidazolidin-4-one **6b** was prepared by

cyclization of glycine with NH_4SCN in the presence of acetic anhydride in 63 % yield, using a known preparation method [32]. Compounds **10a-10h** were prepared from **5** in the same manner as described for the general synthesis of compounds **8a-8h** by knoevenagel condensation and nucleophilic substitution.

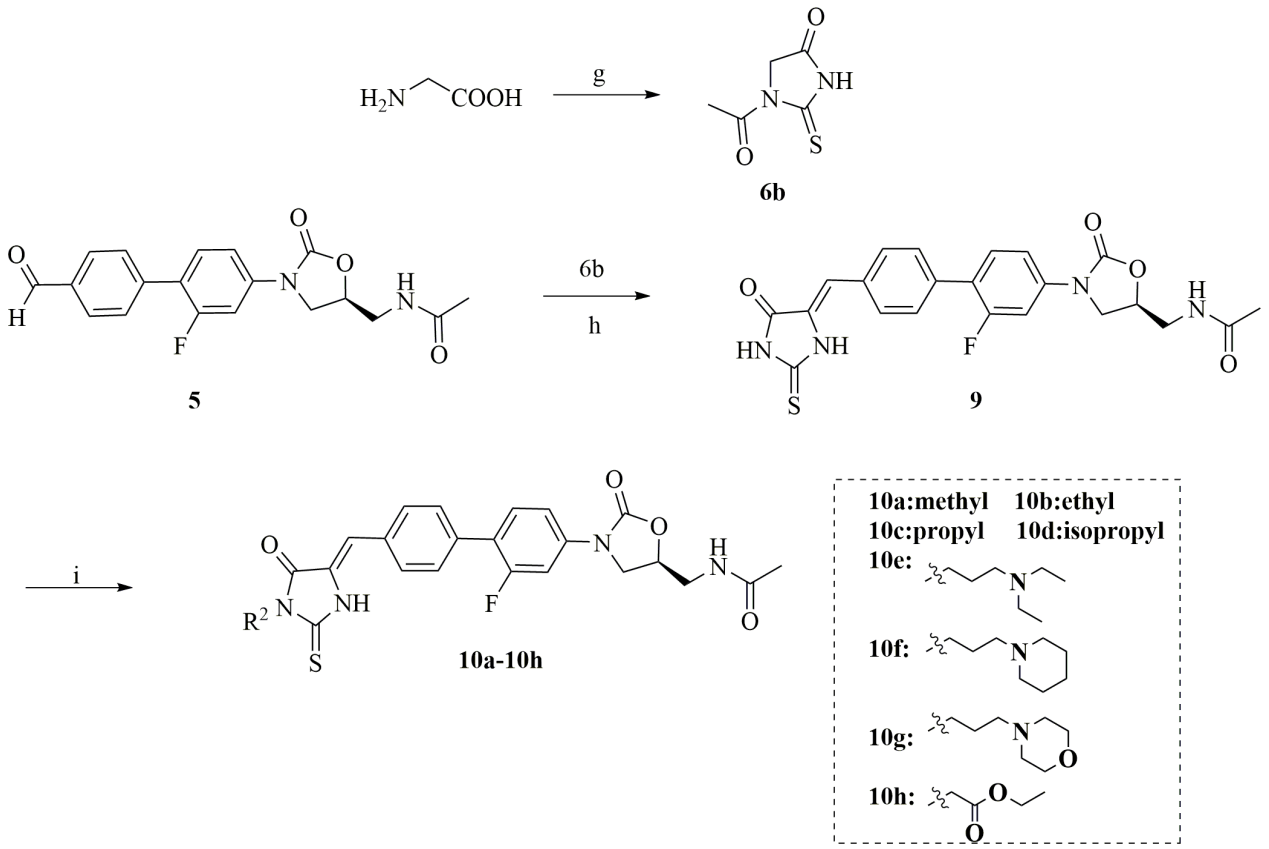
The synthesis of compounds **15a-15c** is depicted in **Scheme 4**. The key intermediates **13a-13c** and **14** were synthesized *via* a two-step reaction from commercially available substituted amines (**11a-11c**) respectively. **11a-11c** were reacted with CS_2 to afford isothiocyanates **12a-12c,** which were subjected to ethyl mercaptoacetate or glycine to give **13a-13c** by ring closure. Compounds **15a-15c** were prepared from **5** by knoevenagel condensation.



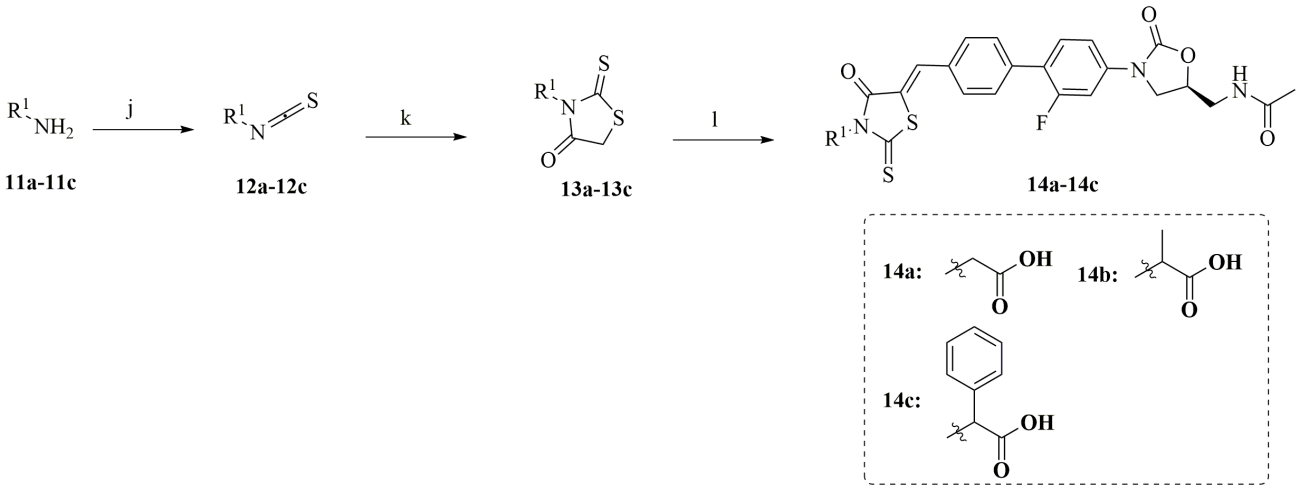
Scheme 1. Reagents and conditions: (a) methyl chloroformate, pyridine, DCM, 25 °C, 2 h; (b) KI, NCS, HI (45%), H_2O, 30 °C, 3 h; (c) (*S*)-1-((acetylamino)methyl)-2-chloroethyl acetate, *t*-BuOLi/CH_3OH, 25 °C, 24 h; (d) 4-formylphenylboronic acid, $Pd(PPh_3)_2Cl_2$, K_2CO_3, Tol/ EtOH/ H_2O, 60 °C, 12h.



Scheme 2. Reagents and conditions: (e) rhodanine (**6a**), sodium acetate, acetic acid, 100 °C, 2-4 h; (f) RX, NaOH, DMF, 55 °C, 2-5 h.



Scheme 3. Reagents and conditions: (g) ammonium thiocyanate, acetic anhydride, 100°C, 2-4 h; (h) **6b**, CH_3COOH, 100 °C, 2 h; (i) R-Cl, NaOH, DMF, 55 °C, 2-5 h.



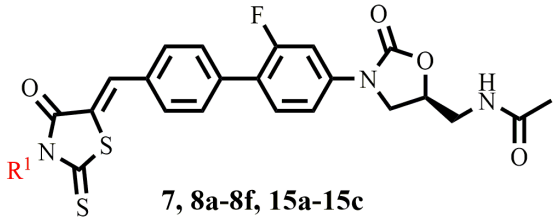
Scheme 4. Reagents and conditions: (j) CS_2, TEA, ethyl acetate/ H_2O, 25 °C, 1h. (k) ethyl mercaptoacetate, TEA, DCM, 25 °C, 2 h; (l) sodium acetate, acetic acid, 100 °C, 2-4 h.

All of the target compounds (**7**, **8a-8f**, 9, **10a-10h**, **15a-15c**) were evaluated for in *vitro* antibacterial activity by the double dilution method using linezolid and radezolid as positive control. Minimum inhibitory concentration (MIC) was calculated and summarized in **Table 1**.

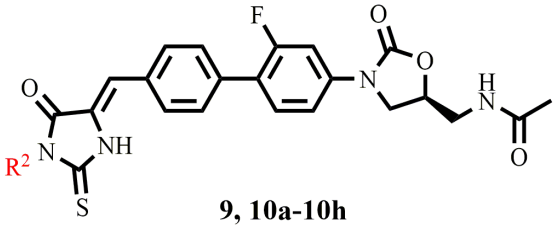
As illustrated in **Table 1**, most target compounds showed moderate to significant antibacterial activities against

selected gram-positive bacteria in comparison with linezolid and radezolid, which indicated that the rhodanine moiety maintained or even enhanced the antibacterial activity of oxazolidinones. Compound **7** showed 4-fold more potent antibacterial activity than radezolid, having a MIC value of 0.125 μg/mL. Notably, compound **9** with a thiohydantoin moiety showed the same antibacterial activities with compound **7**. Thus, rhodanine and thiohydantoin derivatives, including compounds **8a-8f**, **10a-10h**, **15a-15c** with different substituents including carboxyl, ester, acyclic and cyclic alkyl were further synthesized to probe the impact of steric hindrance, hydrophilicity and lipophilicity on antibacterial activity. The MIC values of compounds **8a-8c** and **10a-10d** indicated that substituents on the terminal rhodamine part had great effect on the antibacterial activity. The steric hindrance of these substituents correlated with antibacterial activity, and the smaller substituent was a better preference for enhanced antibacterial activity. Compounds **15a** to **15c** showed in *vitro* activities slightly weaker than radezolid, which indicated that strong polar carboxyl group had negative effect on the antibacterial activity. Compound **8f** with 2-ethoxy-2-oxoethyl group and **15a** with carboxymethyl group exhibited similar levels of in *vitro* antibacterial activity. To our delight, compound **10e** with 3-(diethylamino) propyl group showed superior activity against all tested bacteria, with a MIC value of 0.125 μg/mL. Interestingly, compound **8d** with the same group showed 4-fold weaker in *vitro* antibacterial activity compared to **10e**, but exhibited similar levels of in *vitro* antibacterial activity with radezolid. These results implied that a small flexible aliphatic amino group is beneficial for the antibacterial activity. Overall, Most compounds exhibited more potent antibacterial activity against *S.aureus*, MRSA, MSSA, LREF and VRE pathogens as compared with linezolid and radezolid. Then, three of the most potent compounds (**7**, **9**, and **10e**) were selected for further clinical isolates investigation.

Table 1. *In vitro antibacterial activity of biaryloxazolidinone analogues.*



7, 8a-8f, 15a-15c



9, 10a-10h

Compounds	MICs, ug/mL				
	S.aureus[a]	MRSA[b]	MSSA[c]	LREF[d]	VRE[e]
7	0.125	0.125	0.125	0.125	0.125
9	0.125	0.125	0.125	0.125	0.125
8a	0.25	0.25	0.25	0.25	0.25
8b	0.25	0.25	0.25	0.5	0.5
8c	2	2	2	2	2
8d	0.5	0.5	0.5	0.5	0.5
8e	1	1	1	1	1
8f	1	1	1	1	1
10a	0.5	0.5	0.5	0.5	0.5
10b	0.25	0.25	0.25	0.25	0.25
10c	2	2	2	2	2
10d	1	1	1	0.5	0.5
10e	0.125	0.125	0.125	0.125	0.125
10f	1	1	1	1	1
10g	2	2	2	2	2

10h	1	1	1	1	1
15a	1	1	1	1	1
15b	1	1	1	1	1
15c	1	1	1	1	1
linezolid	1	1	1	＞16	2
radezolid	0.5	0.5	0.5	0.5	0.5

[a] Standard *Staphylococcus aureus* (29213).

[b] Methicillin-resistant *Staphylococcus aureus*.

[c] Methicillin-sensitive *Staphylococcus aureus*.

[d] Linezolid-resistant *Enterococcus faecalis*.

[e] Vancomycin-resistant *Enterococcus faecium.*

Based on the in *vitro* antibacterial activity, three optimal compounds were selected for further evaluation against several clinical isolates which were collected in PLA 309 hospital. These antibiotic-susceptible and antibiotic-resistant clinical isolates included *S.aureus* (4 isolates of MRSA and 4 isolates of MSSA), *E. faecalis* (4 isolates of LREF) and *E.faecium* (4 isolates of VRE), and the results are listed in **Table 2**. Compounds **7** showed slightly weaker in *vitro* antibacterial activities against tested clinical isolates, with MIC values in the range of 1–2 μg/mL. Compound **9** had MIC values of 0.25-1 μg/mL against tested clinical isolates. Significantly, compound **10e** exhibited potent antibacterial activity against tested clinical isolates with MIC values in the range of 0.125–0.5 μg/mL, and the potency of **10e** against clinical isolates of LREF was much more higher than that of linezolid.

Table 2. In *vitro* antibacterial activity against clinical isolates

Compounds	MICs, μg/mL			
	MRSA[a](4)[b]	MSSA[c](4)	LREF[d](4)	VRE[e](4)
7	1-2	1-2	1-2	1-2
9	0.5-1	0.5-1	0.25-0.5	0.25-0.5
10e	0.125-0.5	0.125-0.25	0.125-0.25	0.25-0.5
linezolid	1-4	1-4	＞16	1-4

[a] Clinical strains of methicillin-resistant *Staphylococcus aureus*.

[b] Number of bacterial strains tested are given in parentheses.

[c] Clinical strains of methicillin-sensitive *Staphylococcus aureus*.

[d] Clinical strains of vancomycin-resistant *Enterococcus faecium.*

[e] Clinical strains of linezolid-resistant *Enterococcus faecalis*.

In order to evaluate the toxicity issues and safety profile of novel antibacterial agent, the most potent compounds **7**, **9** and **10e** were tested for cytotoxicity against HepG2 cell and inhibition *against* MAO-A. As illustrated in **Table 3**, Compounds **7**, **9** and **10e** displayed low cytotoxicity with IC_{50} values (63.9, 61.7 and 91.04 μM, respectively) against HepG2 cell, meanwhile linezolid presented low cytotoxicity with IC_{50} values (＞**25**μM). However, three compounds both showed high MAO-A kinase inhibitory activity.

Table 3. *Cytotoxicity and MAO-A inhibition of compounds **7**, **9**, **10e***

Compounds	logD (pH7.4)[a]	HepG2 cytotoxicity IC_{50} (μM)	MAO-A inhibition (%) (30 μM)
7	**2.76**	**63.9**	**99**
9	**1.72**	**61.7**	**99**
10e	**0.46**	**91.04**	**98**
linezolid	**0.49**	**＞25**	**76**

[a]Calculated using instant JChem.

ADME profile and drug-likeness are significantly important in the drug discovery process, so *in silico* ADME and drug-likeness prediction of compounds **7**, **9**, **10e** were performed using the free web tool (http://www.swissadme.ch/) [33], and the results are listed in **Table 3**. Compound **10e** violated Lipinski's rule of five because of the too much molecular weight (＞ 500), but the partition coefficient between n-octanol and water (Log Po/w) and predicted aqueous solubility (logS) suggested that all the three compounds are hydrophilic [33]. Moreover, compound **9** and **10e** showed high GI valves and lower value of TPSA, which suggested they may show good bioavailability. Low values of BBB permeant showed that it is difficult for these compounds to cross the blood-brain barrier. The favorable ADME profile and drug-likeness suggest that **10e** deserve further study.

Table 4. *In silico* ADME prediction of *compounds **7**, **9**, **10e***

Compounds	MW[a]	Log Po/w[b]	Hbond donor[c]	Hbond acceptor[d]	GI[e]	TPSA (Å2)[f]	Lipinski[g]	logS[h]	BBB permeant[i]
7	471.52	3.20	2	5	Low	145.13	0	-4.81	No
9	454.47	2.31	3	5	High	131.86	0	-4.00	No
10e	567.67	3.59	2	6	High	126.31	1	-5.08	No
Linezolid	337.35	1.20	1	5	High	71.11	0	-2.22	No

[a] Molecular weight

[b] Logarithm of compound partition coefficient between n-octanol and water (< 5).

[c] Number of hydrogen bond donor (< 5).

[d] Number of hydrogen bond acceptors (< 10).

[e] Human gastrointestinal absorption.

[f] Topological polar surface area (≤ 140).

[g] Lipinski's rule of five.

[h] Predicted aqueous solubility.

[i] Predicted brain/blood partition coefficient.

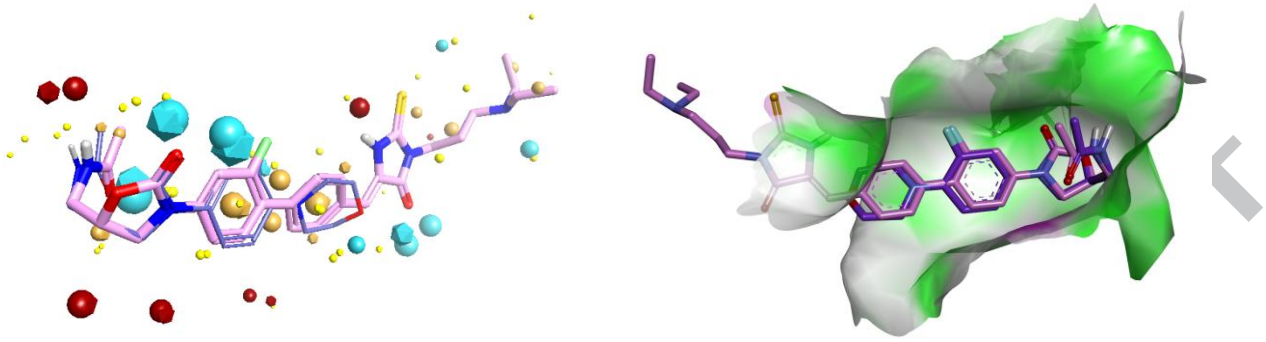


Figure 4. Superposition of compound **10e** and linezolid

To further elucidate the binding mode of novel biaryloxazolidinone antibacterial agent with 50S ribosome unit, a molecular superposition was conducted based on the crystal structure of 50S ribosome unit of *E. coli* with linezolid (PDB: 3CPW [21]), and the results are shown in Figure 4. It can be observed that conformations of **10e** and linezolid showed very good overlay. However, the thiohydantoin part of compound **10e** extended beyond the morpholine ring of linezolid. Jiacheng Zhou *et al*. reported the molecular superposition model of linezolid with the non-selective antibiotic sparsomycin [19-20]. Based on this model, due to there are number of hydrogen bond acceptor groups in the thiohydantoin part, we speculated that this part may forms hydrogen bonds with the binding site of other antibiotics, thus increases intrinsic affinity for the ribosome.

In summary, a series of biaryloxazolidinone derivatives bearing a rhodanine or thiohydantoin moiety were designed and synthesized. Our preliminary antibacterial activity investigation showed that compounds **7**, **9** and **10e** exhibited potent antibacterial activity with MIC values of 0.125 ug/mL against *S.aureus*, MRSA, MSSA, LREF and VRE pathogens, using linezolid and radezolid as the positive controls. The exploration of preliminary structure-activity study showed that the introduction of rhodanine and thiohydantoin moiety to the biaryloxazolidinone at D-ring portion can improve the potency against linezolid-susceptible and linezolid-resistant Gram-positive bacteria. Additionally, three optimal compounds **7**, **9**, and **10e** were selected for further evaluation against clinical isolates, and compound **10e** exhibited potent antibacterial activity against tested clinical isolates with MIC values in the range of 0.125–0.5 μg/mL, and the potency of **10e** against clinical isolates of LREF was 64-fold higher than that of linezolid. Moreover, compound **10e** was non-cytotoxic with an IC_{50} value of 91.04 μM against HepG2 cell. However, compounds **10e** exhibited better MAO-A kinase inhibitory activity compared to linezolid. Further optimization of the structure to reduce MAO-A kinase inhibitory activity is in progress and will be reported in the future.

Acknowledge

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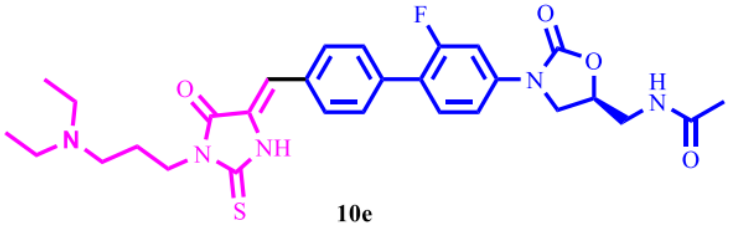

10e

S.aureus	**MIC= 0.125** ug/mL
MRSA	**MIC= 0.125** ug/mL
MSSA	**MIC= 0.125** ug/mL
LREF	**MIC= 0.125** ug/mL
VRE	**MIC= 0.125** ug/mL

Compounds	logD (pH7.4)	HepG2 cytotoxicity IC_{50} (μM)	MAO-A inhibition (%) (30 μM)
10e	**0.46**	**>60(91.04)**	**98**
linezolid	**0.49**	**>60**	**76**

Highlights

1, Biaryloxazolidinone derivatives containing a rhodanine or thiohydantoin moiety.

2, Compound **10e** exhibited a MIC value of 0.125 μg/mL against all tested bacteria.

3, The potency of compound **10e** against LREF was 64-fold higher than that of linezolid.

4, Compound **10e** was non-cytotoxic with an IC_{50} value of 91.04 μM against HepG2 cell.

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