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Synthesis and structure–activity relationship studies of novel [6,6,5] tricyclic oxazolidinone derivatives as potential antibacterial agents

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ABSTRACT

In our previous Letter, we reported the discovery of a novel benzoxazinyl-oxazolidinone antibacterial candidate **2**. In order to identify a potential backup compound, extensive modifications on the B/C ring and C3 side chain were undertaken. A series of novel [6,6,5] tricyclic analogues were synthesized and their in vitro antibacterial activities were tested against a panel of susceptible and resistant Gram-positive pathogens. Among of them, benzothiazinyl-oxazolidinones with acetamide or thioamide as C3 side chains exhibited moderate to good antibacterial activity, such as compounds **54**, **58**, **59** and **63**. In vitro liver microsomal stability was further evaluated and the results manifested that compounds **54** and **58** were both metabolically stable in rat and human liver microsomes. Additionally, insights gained from this investigation should provide directions for the further research of new oxazolidinone antibiotics.

The continuing emergence of drug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), *S. epidermidis* (MRSE), vancomycin-resistant *Enterococci* (VRE) and penicillin-resistant *Streptococci* (PRSP) have become a worldwide problem in global health.[1–3] Linzolid (**1**, Fig. 1), although played a pivotal role in the treatment of nosocomial resistant Gram-positive infections caused by bacteria mentioned above,[4,5] its resistant organisms have been isolated and treatment failures have been reported after more than a decade clinical use.[6–8] In addition, monoamine oxidase (MAO) inhibition activity and potential bone marrow toxicity restrict its long term use.[9–11] In view of these drawbacks of linezolid, discovery and development of new oxazolidinone antibiotics with improved potency and safety has become increasingly important.

We have previously reported a new series of conformationally restricted [6,6,5] tricyclic fused benzoxazinyl-oxazolidinones as typified by compound **2** (Fig. 1) which exhibited increased in vitro antibacterial activity and excellent pharmacokinetic properties relative to linezolid.[12] What is more important, compound **2** also displayed potent inhibitory activities against linezolid-resistant pathogens and its phosphate salt **3** (YG-056SP, Fig. 1) significantly improved the water solubility. This phosphate salt prodrug has now entered preclinical studies as a drug candidate. These

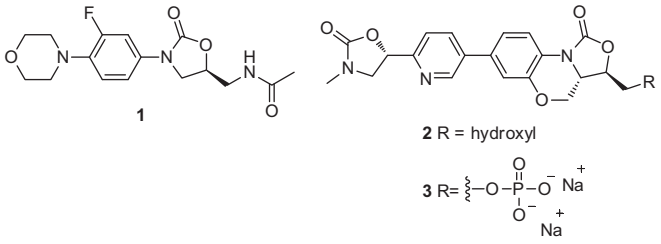

Figure 1. Structure of oxazolidinone compounds.

promising outcomes manifested that this tricyclic fused scaffold is a suitable framework for developing potent antibiotics with improved druggability and worthy of further exploration. In the present investigation, as a backup study, we further explore the [6,6,5] tricyclic fused scaffold and discuss the structure–activity relationship (SAR) hoping to find a potent antibacterial agent.

The preparation of compounds **11**–**13** is described in Scheme 1. A Sharpless asymmetric epoxidation reaction was carried out to convert compound **4**[13] into epoxide **5**, which was subsequently converted to its corresponding thiirane **6** using thiourea as the sulfurating reagent.[14] The hydroxyl group of compound **6** was protected with TBSCl to yield compound **7**. The tricyclic intermediate **8** was constructed through a tandem cyclization of **7** with ^{n}BuLi as the base at −78 °C. Cleavage of the *O*-TBS protective group afforded compound **9**. Then, the Miyaura coupling reaction between **9** and

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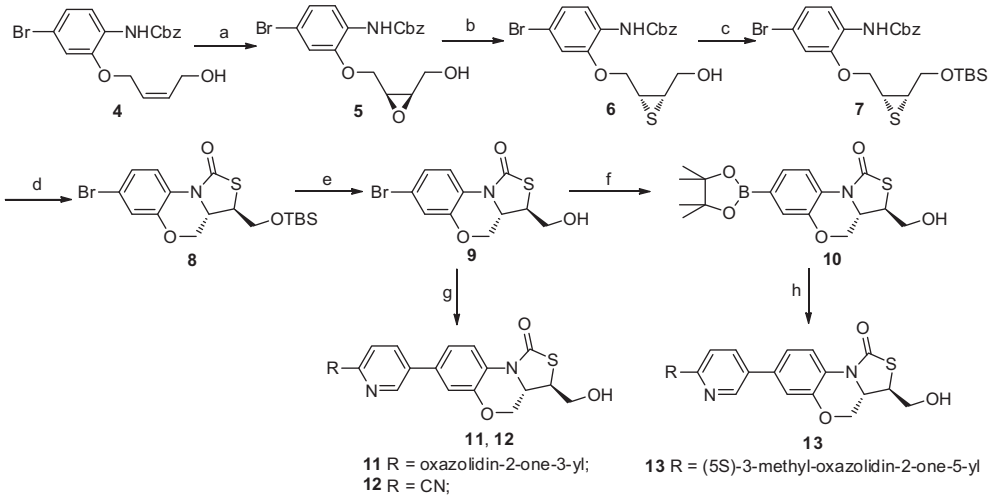
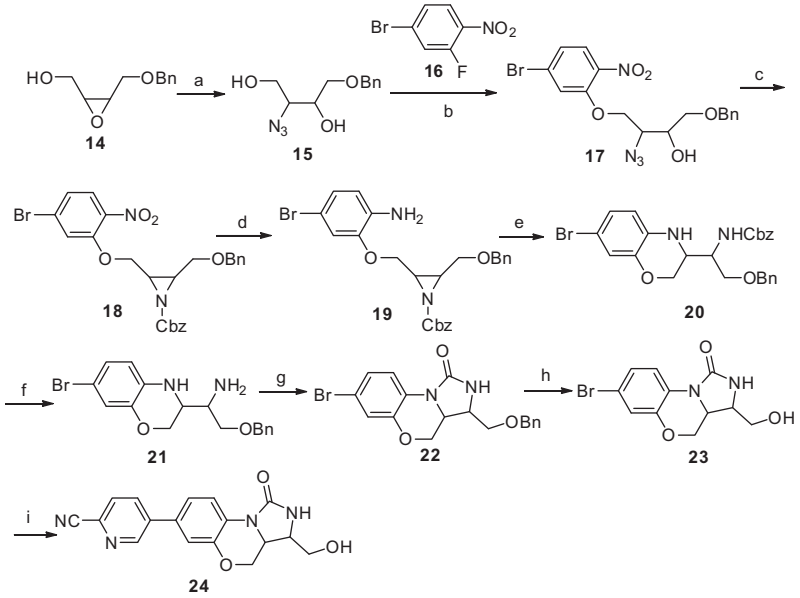


Scheme 1. Reagents and conditions: (a) D-(−)DET, $Ti(O^iPr)_4$, TBHP, 4 Å molecular sieves, extra dry DCM, −25 °C to rt, 24 h; (b) thiourea, MeOH, 60 °C, overnight; (c) TBSCl, imidazole, DMF, rt, 6 h; (d) ^{n}BuLi, THF, −78 °C to rt, 18 h; (e) TBAF, THF, rt, 3 h; (f) bis(pinacolato)diboron, $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, KOAc, dioxane, 80 °C, 2 h; (g) ArB(pin), $Pd(PPh_3)_4$, Cs_2CO_3, dioxane/H_2O, 80 °C, overnight; (h) (*S*)-5-(5-bromopyridin-2-yl)-3-methyloxazolidin-2-one, $Pd(PPh_3)_4$, Cs_2CO_3, dioxane/H_2O, 80 °C, overnight.

bis(pinacolato)diboron, catalyzed with $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, yielded boric acid ester **10**. Finally, the Suzuki coupling reaction was carried out to give the biaryl compounds **11**–**13**.

The synthesis of compound **24** is outlined in Scheme 2. Ring-opening reaction of **14** with sodium azide gave compound **15** which was then subjected to nucleophilic substitution reaction with nitrofluorobenzene **16** to yield intermediate **17**. A tandem azido group reduction/ring-closing reaction using PPh_3 followed by Cbz protection of the resulting amine afforded compound **18**.[15] Reduction of the nitro group in compound **18** yielded aniline intermediate **19**. Intramolecular ring-opening reaction was carried out in refluxing EtOH/H_2O with $LiClO_4$ as the lewis acid catalyst to give compound **20**. The tricyclic intermediate **22** was obtained by deprotection of the *N*-Cbz group and then cyclization using *N*,*N*′-carbonyldiimidazole (CDI) as the reagent. Cleavage of the *O*-Bn group followed by a Suzuki coupling reaction between **23** and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile generated the desired compound **24**.

The convergent synthetic strategy toward compounds **36**–**38** is summarized in Scheme 3. Nucleophilic substitution of 4-bromo-2-fluoro-1-nitrobenzene **16** with *tert*-butyl mercaptan afforded compound **25**. Cleavage of the *t*-butyl group by TFA and then reduction of the nitro group using hydrazine hydrate/$FeCl_3$ in MeOH provided disulfide **27**. *Cis*-2-butene-1,4-diol **28** was protected by trityl and then Sharpless asymmetric epoxidation reaction was performed to provide epoxide **30** which was subsequently converted to its corresponding mesylate **31**. Cleavage of the disulfide bond in compound **27** by 1,4-dithiothreitol (DTT)[16] and in situ alkylation with mesylate **31** afforded compound **32**, which was protected further by Cbz to yield compound **33**. Next, treatment of compound **33** with ^{n}BuLi afforded the desired intermediate **34**. After deprotection of the *O*-trityl group of **34** using TFA, target compounds **36**–**38**



Scheme 2. Reagents and conditions: (a) sodium azide, NH_4Cl, DMF, 80 °C, 14 h; (b) 4-bromo-2-fluoro-1-nitrobenzene, Cs_2CO_3, DMF, rt, 5 h; (c) (i) PPh_3, acetonitrile, 70 °C, 5 h; (ii) CbzCl, TEA, 0 °C to rt, 2 h; (d) Zn powder, NH_4Cl, THF, 45 °C, 8 h; (e) $LiClO_4$, EtOH/H_2O, reflux, 10 h; (f) $BF_3{\cdot}Et_2O$, Me_2S, DCM, rt, 5 h; (g) CDI, DMAP, DMF, 100 °C, 10 h; (h) BCl_3, DCM, rt, 3 h; (i) 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) picolinonitrile, $Pd(PPh_3)_4$, Cs_2CO_3, dioxane/H_2O, 80 °C, overnight.

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