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Substitution of terminal amide with 1*H*-1,2,3-triazole: Identification of unexpected class of potent antibacterial agents

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ABSTRACT

3-Methoxybenzamide (3-MBA) derivatives have been identified as novel class of potent antibacterial agents targeting the bacterial cell division protein FtsZ. As one of isosteres for the amide group, 1,2,3-triazole can mimic the topological and electronic features of the amide, which has gained increasing attention in drug discovery. Based on these considerations, we prepared a series of 1*H*-1,2,3-triazole-containing 3-MBA analogues via isosteric replacement of the terminal amide with triazole, which had increased antibacterial activity. This study demonstrated the possibility of developing the 1*H*-1,2,3-triazole group as a terminal amide-mimetic element which was capable of both keeping and modulating amide-related bioactivity. Surprisingly, a different action mode of these new 1*H*-1,2,3-triazole-containing analogues was observed, which could open new opportunities for the development of antibacterial agents.

Infections caused by multidrug-resistant (MDR) bacteria are becoming a serious and global threat to public health.[1,2] Furthermore, the number of new therapeutic agents approved or under development is limited in recent years.[3,4] Therefore, there is an urgent need for new antibiotics for fighting against the rampant multidrug-resistant bacteria. The validation of bacterial cell division protein FtsZ as a novel antibacterial drug target has been confirmed by various research groups, and different small-molecule inhibitors targeting FtsZ offer promising candidates for new antibacterial agents development.[5–12] Among those FtsZ-targeting compounds, 3-methoxybenzamide (3-MBA) **1** was identified as a promising lead.[13] In order to improve its potency and optimize drug-like properties, a series of modifications have led to a potent 3-MBA derivative PC190723 (**2**), and other synthetic analogues (Fig. 1).[13–17]

The crystal structure of *S. aureus* FtsZ-PC190723 complex and docking models have shown that the benzamide group plays an important role for antibacterial activity.[17–19] However, little successful modifications on the amide group are achieved through introducing small polar substituents or substituting other close groups for the amide function.[15,20] Nevertheless, considering its key function for antibacterial activity, it is meaningful to further investigate this crucial amide group.

Over the past few years, 1,2,3-trizole has gained increasing attention in all aspects of drug discovery since the introduction of the click chemistry by Sharpless and co-workers.[21] Remarkably, the 1,2,3-triazole serves as a functional moiety that can mimic the topological and electronic properties of an amide bond (Fig. 2).[22–24] What's more, unlike amides, the triazole ring is not sensitive to hydrolytic cleavage or redox modification.[22,25] From the present research, several examples of amide-to-triazole point mutation have been reported and exerted positive results (Fig. 3).[26–28] These findings have initially confirmed that the triazole ring is an effective amide surrogate capable of both sustaining and modulating amide-related bioactivities. Furthermore, to our knowledge, the existent amidomimetic analogues are all 1,4-substituted triazoles, and no information has been reported on the terminal amide isosteric exchange with triazole. Based on the above considerations and the peculiar structure of benzamide antibacterial agents, we designed and synthesized a series of 1,2,3-triazole-substituted 3-MBA analogues, and evaluated their preliminary antibacterial activity.

The brief design route of this program is shown in Fig. 4. Replacing the amide moiety with 1*H*-1,2,3-triazole ring led to series **A**. Further investigation was transferred to non-fluorinated series **B**. Next, we changed the 1,2,3-triazole into 1,2,4-triazole or tetrazole,

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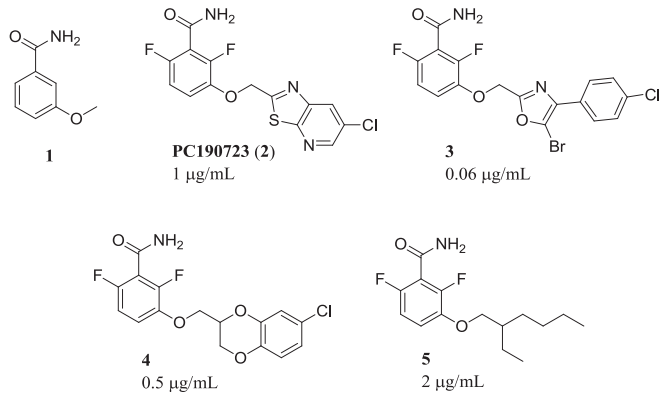

Fig. 1. Chemical structures of some FtsZ inhibitors and their MICs against *S. aureus*.

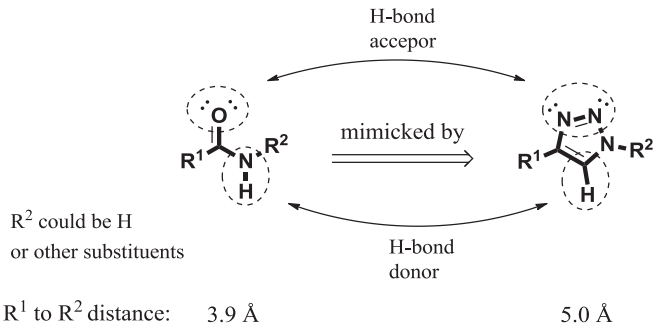

Fig. 2. Topological and electronic similarities of amide and 1,2,3-triazole groups.

leading to series **C** and series **D**. Further exploration was focused on **B6** by changing the 1*H*-1,2,3-triazole and introducing other heteroatoms into this five-membered ring, producing **E1**, **F1** and **G1**. The alkoxy substituent attached to the ortho- or *para*-position of the benzene ring gave **B6-o** and **B6-p**. Methylation of the 1*H*-1,2,3-triazole ring obtained three *N*-methylated analogues, **B6-1m**, **B6-2m**, **B6-3m**. The brief design route of this program is shown in Fig. 4. The chemistry and preliminary bioactivity evaluation of these novel derivatives are presented as follows.

The synthetic routes of the above proposed compounds were illustrated in Schemes 1–4. The synthetic route of the series **A** was outlined in Scheme 1. Commercially available 2,4-difluorophenol **7** was protected by benzyl group, and then treated with DMF in the presence of *n*-BuLi, which was followed by deprotection of the benzyl group, to give the key intermediate **9**. Alkylation of **9** with different alkyl chloride or bromide afforded aldehyde product **10**. Conversion of the aldehyde group of **10** to 1*H*-1,2,3-triazole ring was carried out using two step reactions of treatment with nitromethane and *p*-TsOH-mediated cycloaddition.[29]

As for the synthesis of compound **A7**, at first we tried the alkylation of **9** with bromomethyl thiazole, but this reaction did not work as shown in Scheme 1a, which was consistent with the report previously.[30] Secondly, an alternative route II was that conversion of aldehyde group of **9** to glycol acetal **9a** was followed by alkylation of **9b**. Unfortunately, the attempt to convert **9b** to the desired compound **10** by acid-catalyzed hydrolysis failed because multiple byproducts were observed. Finally, the third route III was explored by conversion of **9** to nitroalkene **9c** and then alkylation of **11** gave **A7** according to the general route. The synthesis of series **B** was achieved in similar method to that of series **A**.

The synthetic route of the series **C** and **D** was outlined in Scheme 2. Bis-benzylation of 3-hydroxybenzoic acid was followed by hydrolysis to produce 3-hydroxy-protected benzoic acid **16**. Benzoic acid **16** was subjected to reduction and then chlorination to benzyl chloride **18**. Substitution reaction of **18** with 1,2,4-triazole or tetrazole was followed by deprotection of benzyl group to generate two key intermediates **20** and **22**, respectively. Alkylation of **20** or **22** with different haloalkanes afforded the target compounds.

The synthesis of the series **E**, **F** and **G** was illustrated in Scheme 3. Treatment of intermediate **16** with oxalyl chloride produced the corresponding acid chloride **23**, which was further converted in the presence of hydrazine or ammonium carbonate to hydrazide **24** and amide **29**, respectively. Cyclization of **24** using trimethyl orthoformate or triphosgene gave **25** or **27**, respectively. The series **E** and **F** were prepared after deprotection and alkylation of hydroxy group. Cyclization of amide **29** to **31** was carried out in two steps of treating with DMF-DMA and hydroxylamine hydrochloride.[31] Finally, through similar procedures mentioned above, the series **G** was obtained.

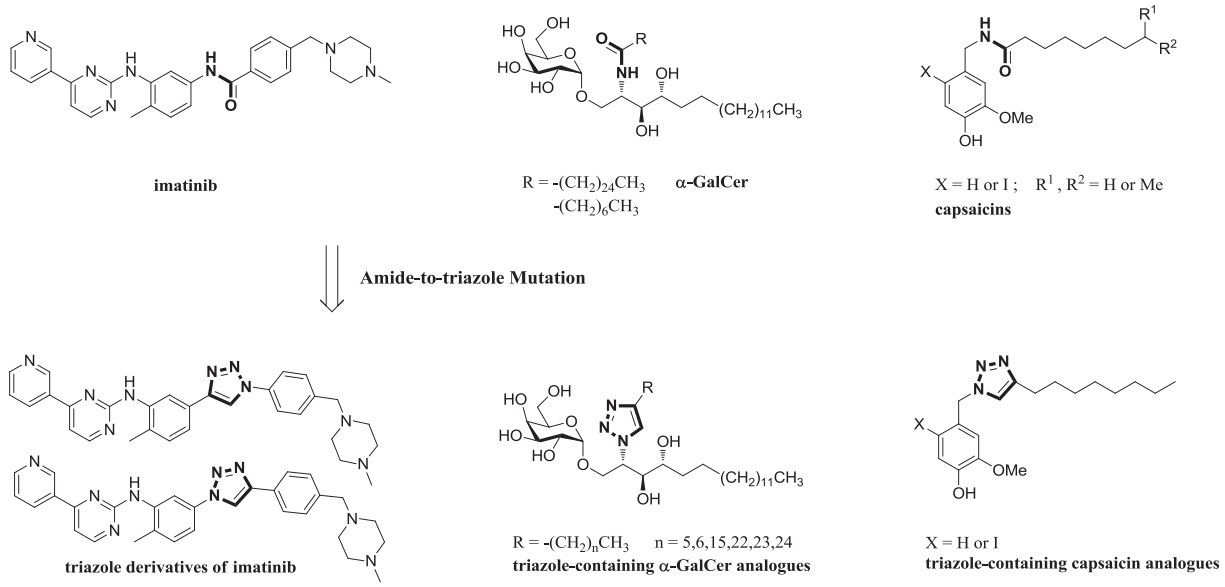

Fig. 3. Structural modifications through changing amide group to 1,2,3-triazole ring.