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Preparation, antibacterial evaluation and preliminary structure–activity relationship (SAR) study of benzothiazol- and benzoxazol-2-amine derivatives

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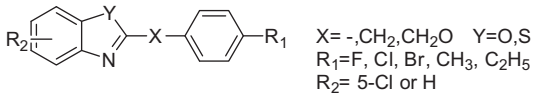
ABSTRACT

In this study, a novel benzothiazol- and benzooxazol-2-amine scaffold with antibacterial activity was designed and synthesized. Preliminary structure–activity relationship analysis displayed that compound **8t** with a 5,6-difluorosubstituted benzothiazole was found to be a potent inhibitor of Gram-positive pathogens, and exhibited some potential against drug-resistant bacteria and without cytotoxicity in therapeutic concentrations. In addition, molecular docking studies indicated that *Staphylococcus aureus* methionyl-tRNA synthetase might be the possible target of these compounds. Taken together, the present study provides an effective entry to the synthesis of a good lead for subsequent optimization and a new small molecule candidate drug for antibacterial therapeutics.

Nosocomial infections caused by multi-drug resistant bacteria have been the most deleterious to the public health and a continuous increase in infections in the worldwide poses a significant threat.[1] Although several classes of antibacterial agents are presently available, the multi-drug resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant *Enterococcus faecalis* (VRE) present a considerable challenge in the clinic.[2] To solve this serious global medical problem, the development of new antibacterial agents with new mechanism should be urgently carried out. In the recent decade, different biochemical pathways that are used as targets for new antibacterial agents in the key areas of the bacterial cell cycle have been well studied, such as aminoacyl tRNA synthetase family; DNA type IIA topoisomerases and FtsZ guanosine triphosphatase and so on.[3–6] Meanwhile, many novel chemical structures with new scaffolds completely different from the beta lactam or quinolone were reported[7–9,30] For example, a series of 2-substituted benzoxazoles and benzothiazoles were found to be associated with various antibacterial activities by Yildiz and co-workers (the chemical structures were shown in Fig. 1) and this kind of structures exhibited high activity against drug-resistant Gram-positive bacteria.[10–13] Continuous studies focused on benzoxazoles and benzothiazoles derivatives showed that substituted benzothiazole was identified as capable of curing *Caenorhabditis elegans* nematodes infected with *Enterococcus faecalis*[14] and benzoxazole-2-thione derivatives exhibited high inhibition rate to bacterial hyaluronan lyase.[15]

A heterocyclic derivative has been identified by high throughput screening as a competitive inhibitor of drug-resistant staphylococci. Optimized compound SB-299683 showed remarkable activities against staphylococcal and enterococcal pathogens with low MIC value[16] and this kind of heterocyclic diamine compounds were considered as bacterial methionyl-tRNA synthetase (MetRS) inhibitors.[17,18] Jarvest et al.[16,19,20] in GlaxoSmithKline provided an efficient entry in structural modification based upon this kind of compounds, they proposed that the class structure was divided into LHS (Left-hand side), RHS (Right-hand side) and the amide linker (Fig. 2). Some pharmacophore models or QSAR studies based on the crucial chemical features were reported in literature of the subsequent years,[21,22] proposed that LHS (quinolones or other heterocyclic) were fitted hydrophobic sites and the amine linker provided hydrogen bonds with the MetRS protein. So, the structural modification of SB-299623 was mostly focused on the amine linker and RHS (with different substituted benzene rings),[23,24] nearly no liter-



Antimicrobial Benzoxazoles and Benzothiazoles

Figure 1. The antimicrobial active multisubstituted benzoxazole or benzothiazole derivatives as previous reported.

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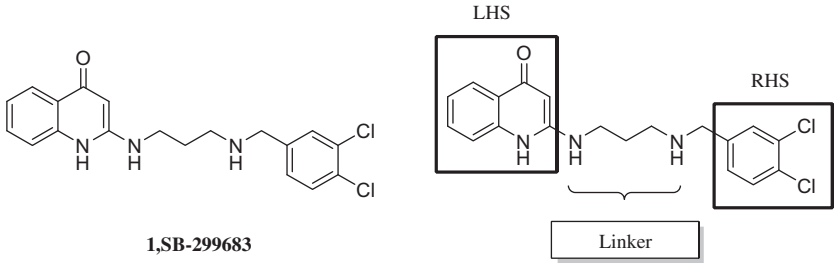


Figure 2. The chemical structure of leading compound **1**, SB-299683.

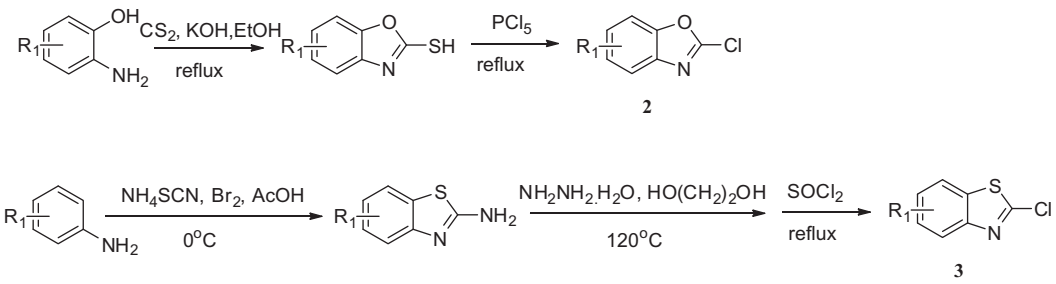
atures reported about the LHS. Lee and co-workers and Finn et al.[25,26] put forward some modification strategies about LHS by pharmacophore identification and virtual screening methods. They suggested that some benzo heterocyclic structure as benzothiazoles or benzoxazoles might exhibit more binding activity than quinolones. The benzoxazole or benzothiazole functionalities fitted tightly into the aromatic site and the pharmacophore features were retrieved in the top scoring docking results.[26] These results provided us some novel information or ideas to further design some new structural analogues of SB-299683 used as antibacterial agents.

Therefore, originated from the pioneer work of Jarvest et al. and the discovery of benzothiazole or benzoxazole nucleus with important antimicrobial activity, we synthesized a series derivates with benzothiazol- and benzoxazol-2-amine scaffold based on the leading compound SB-299683. All synthetic compounds were characterized by NMR and ESI-TOF-HRMS spectra and their antibacterial activities were preliminary evaluated against ATCC strains of *S. aureus*, *E. faecalis*, and *Escherichia coli* using the standard broth dilution method. The most promising compound **8t** was further assessed against many important clinical isolates including that was resistant to commonly used antimicrobial drugs. Compared with the lead compound, we tried to analyze the structure–activity relationship of these derivates and to explore the possibility of obtaining efficient novel antibacterial lead compounds.

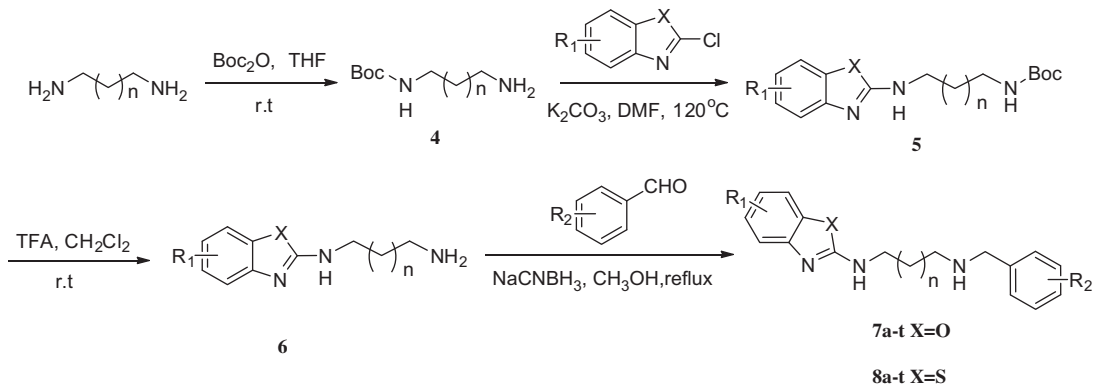
The synthesis of these two series of intermediates, 2-chloro substituted benzoxazoles and benzothiazoles (compounds 2 and **3**) were shown in Scheme 1. The condensation of 5-chloro-2-aminophenol with carbon disulfide in ethanol afforded 2-thiolbenzoxazoles, which was then treated with thionyl chloride to give the intermediate 2 in a total yield of 44–67%.[27] On the other hand, substituted anilines were cyclized with ammonium thiocynate and bromine to give 2-aminobenzothiazole (yield: 35–44%) which was converted into intermediate **3** by a chlorination reaction with hydrazine, then treated with thionyl chloride and the total yield in the two steps was about 72–87%.[28,29]

The diamines were treated with Boc_2O in THF to obtain mono Boc-protected ethane-1,2-diamine or propane-1,3-diamine (compound **4**, yield: 71% and 79%) which were then reacted with 2-chloro substituted benzoxazoles and benzothiazoles intermediates **2** and **3** in the presence of K_2CO_3 to afford compound **5** (yield: 44–69%). After the amine displacement reaction, compound **5** was treated with TFA to remove the BOC group to compound **6 (yield:** almost 100% without additional purification) and the final products compounds **7a–t** and **8a–t** were synthesized via an amide coupling strategy with substituted benzaldehyde and purified by silica gel column chromatography using ethyl acetate–petroleum ether with a little ammonia as an eluent (yield: 39–75%). The synthetic procedure was outlined in Scheme 2. The high degree of symmetry in these molecules enabled facile confirmation by NMR techniques. For example, in the ^1H NMR spectrum, the benzyl proton generated in reductive amination was observed the resonance signal at 3.81(s) which was clearly distinguishable from the resonances arising from amine linkers at 2.61 (t) and 3.64 (m) ppm. The purity of all compounds was above 97.0% determined by HPLC normalization method (A Waters XTerra RP18 column (250 mm × 4.6 mm, 5 μm) was eluted at flow rate of 1.0 mL/min. The mobile phase was a mixture of water and methanol containing 0.1% triethylamine (60:40). The eluate was monitored in the absorption at 254 nm with a UV detector). Furthermore, the molecular weight of the desired target structures .was confirmed by ESI-TOF high resolution mass spectrum (HRMS). All the spectra displayed a very prominent peak corresponding to the compounds complexed with protons or sodium cations. The analytical data were documented in the Supplementary data.

All the compounds were preliminary tested in vitro against our panel of three ATCC bacterial strains (*S. aureus* 25923, *E. faecalis* 29212 and *E. coli* 29425) using the standard broth dilution method.[22] As shown in Tables 1 and 2, this two series exhibited antibacterial activity with MIC (minimum inhibitory concentration) ranging from 0.5 to >64 μg/mL. From the initial results, we could see that among all the compounds, only some which still had more substituted halogen groups and propanediamine linker, was more active. For example, compounds **7c–7f** and **7k–7t** (R_2 = halogen groups or multsubstituted halogen groups) was slightly more effective compared with the non halogen substituted compound **7a–7b** and **7g–7h**. Moreover, we found that the scaffold containing the benzoxazole and benzothiazole retained the antibacterial

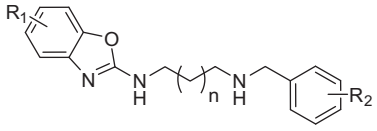


Scheme 1. The synthesis of 2-chloro substituted benzoxazoles and benzothiazoles.



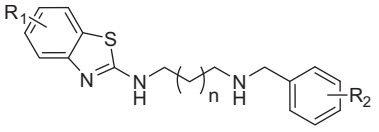
Scheme 2. The synthesis of the target molecules **7a–t** and **8a–t**.

Table 1
Antibacterial activity of benzoxazoles **7a–t**



Compound	*n*	R_1	R_2	MIC (μg/mL)		
				S. aureus	*E. faecalis*	*E. coli*
7a	0	H	H	>64	>64	>64
7b	1	H	H	>64	>64	>64
7c	0	H	4-Cl	8	32	>64
7d	1	H	4-Cl	16	16	>64
7e	0	H	3-Br	8	64	>64
7f	1	H	3-Br	16	8	32
7g	0	H	4-OH	32	32	>64
7h	1	H	4-OH	32	32	>64
7i	0	H	4-OMe	64	64	>64
7j	1	H	4-OMe	32	32	>64
7k	0	H	3,4-diCl	16	8	>64
7l	1	H	3,4-diCl	16	2	32
7m	0	H	2,4-diCl	8	8	>64
7n	1	H	2,4-diCl	8	4	>64
7o	1	6-OMe	3,4-diCl	8	16	32
7p	1	6-Cl	3,4-diCl	2	4	32
7q	1	5-Cl	3,4-diCl	2	4	32
7r	1	6-F	3,4-diCl	1	4	32
7s	1	5-F	3,4-diCl	1	4	32
7t	1	5,6-Difluoro	3,4-diCl	1	2	32
SB-299683	—	—	—	4	0.5	>64

Table 2
Antibacterial activity of benzothiazole **8a–t**



Compound	*n*	R_1	R_2	MIC (μg/mL)		
				S. aureus	*E. faecalis*	*E. coli*
8a	0	H	H	>64	>64	>64
8b	1	H	H	>64	>64	>64
8c	0	H	4-Cl	8	32	>64
8d	1	H	4-Cl	16	8	>64
8e	0	H	3-Br	8	64	64
8f	1	H	3-Br	16	8	32
8g	0	H	4-OH	16	32	>64
8h	1	H	4-OH	16	32	>64
8i	0	H	4-OMe	32	32	>64
8j	1	H	4-OMe	64	64	>64
8k	0	H	3,4-diCl	32	64	>64
8l	1	H	3,4-diCl	4	16	32
8m	0	H	2,4-diCl	2	8	32
8n	1	H	2,4-diCl	8	8	>64
8o	1	6-OMe	3,4-diCl	4	4	>64
8p	1	6-Cl	3,4-diCl	4	2	32
8q	1	5-Cl	3,4-diCl	2	2	32
8r	1	6-F	3,4-diCl	1	2	32
8s	1	5-F	3,4-diCl	1	2	32
8t	1	5,6-Difluoro	3,4-diCl	0.5	1	32
SB-299683	—	—	—	4	0.5	>64

activity and especially, the activity of the benzothiazole derivatives with halogen substitution at the end-carbon was greater than or equal to the lead compound SB-299633. This study might confirm the results of the previous pharmacophore virtual screening and molecular design.[18,19,23] The benzothiazoles **8** with the best MIC 0.5 μg/mL exhibited more potent than benzoxazoles **7** with the best MIC 1 μg/mL. Furthermore, the antibacterial spectrum of benzothiazol- and benzooxazol-2-amine derivatives was very similar to SB-299633: the effect on the Gram-positive bacteria was much better than the Gram-negative bacteria. MIC values were lower <8 μg/mL for *S. aureus* and *E. faecalis*, but >64 μg/mL for *E. coli.*

For the further determination of the antibacterial spectrum of our compounds, the most promising agent **8t** was tested against many important clinical isolates including that was susceptible or resistant to commonly used antimicrobial agents. SB-299683, Ampicillin and cefotaxime frequently used in antimicrobial therapeutic, were taken as positive control. Among *S. aureus,* **8t** was active against both methicillin-susceptible and methicillin-resistant isolates, with MICs of 0.5 and 1 mg/L, respectively. Compound **8t** also exhibited activity against clinical isolates of *Streptococcus pneumoniae* with MICs both 4 mg/L for penicillin-susceptible isolates and for penicillin-resistant strains. Moreover, compound **8t** demonstrated low MICs against both *E. faecalis* (MICs, 1–2 μg/mL) and *E. faecium* (MICs 1–2 μg/mL), including strains that were resistant to vancomycin. The results from these in vitro data (Table 3) suggest several trends. First, compound 8t and SB299683 were very effective against Gram-positive bacteria, but not active against Gram-negative enterobacteriaceae family and di-F benzothiazol-substituted compound **8t** was slightly more effective compared to the leading compound SB299683 with a similar antibacterial spectrum and lower MICs. Second, compounds **8t** showed higher MICs against the susceptible strains than the clinical used antibiotics ampicillin and cefotaxime, but the activity of compound **8t** was not affected in the screening of drug-resistant strains. This means that compound **8t** exhibited excellent MICs in MRSA and VRE much better than ampicillin and cefotaxime. Third, the safety

Table 3
Anti-clinical isolates activity and toxicity of compound **8t**

Organism, phenotype	MIC (μg/mL)			
	8t	SB-299683	Ampicillin	Cefotaxime
Gram-positive				
S. aureus				
Methicillin-susceptible	0.5	2	0.0625	1
Methicillin-resistant	1	2	>64	>64
S. pneumoniae				
Penicillin-susceptible	4	4	0.125	1
Penicillin-resistant	4	8	>64	64
E. faecalis				
Vancomycin-susceptible	1	1	0.125	1
Vancomycin-resistant	1	2	>64	>64
E. faecium				
Vancomycin-susceptible	2	1	0.25	1
Vancomycin-resistant	2	1	>64	>64
Gram-negative				
E. coli	>64	>64	0.25	0.25
Cytotoxic activity				
HEK293[a]	>64	>64	–	–

[a] IC_{50} values obtained with viability assays for 48 h. Each value is representative of three independent determinations.

profiles of compounds **8t** and SB299683 were tested on Human Embryonic Kidney 293 cells in 64 μg/mL using the standard MTT methods. The two compounds exhibited good safety profile with inhibitory rates as low as 15% and IC_{50} were >64 μg/mL in three independent experiments. In addition, we did a preliminary BSA (bovine serum albumin) binding assay to further descript the protein binding of compound **8t** using centrifugal ultrafiltration and liquid chromatography.[32] The binding degrees with BSA could be defined as follow equation: Binding degree = (Cb−Ca)/Cb where Cb and Ca are the concentrations of the compound before and after the interaction with the BSA standard solution in HPLC. As a result, we found that the compound **8t** showed not any interaction with BSA (Binding degree = 1.4%).

A preliminary structure–activity SAR study was showed in Figure 3. It appeared that propanediamine and 3,4-dichlorobenzol derivative substitution at RHS provided much better antibacterial activity when consistent LHS groups. When RHS groups were kept constant, more halogen substitutions in benzothiazoles and benzooxazoles provided good antibacterial activity. It was concluded that the activity was significantly effected by the length of the linker and halogen atom in heterocyclic also played a crucial role. We also observed that different substituents on benzene ring significantly alter the *C*log*P* value and may play an important role in antibacterial activity of these compounds.[33] For example, compound **8h**: R_2 = 4-OH, *C*log*P* = 3.81, MIC to SA = 16 and compound **8l**: R_2 = 3,4-diCl, *C*log*P* = 5.82, MIC to SA = 4. But this correlation can not be fully applicable for all compounds: compound **8j**, R_2 = 4-OMe, *C*log*P* = 4.43, MIC to SA = 64, compound **8h**: R_2 = 4-OH, *C*log*P* = 3.81, MIC to SA = 16). Therefore, we think that such a result may indicate that some correlation of *C*log*P* and antibacterial activities, but *C*log*P* is not the main reason for these compounds work. The main mechanism of these compounds maybe that specific structure was binding to a specific receptor or protein (enzymes).

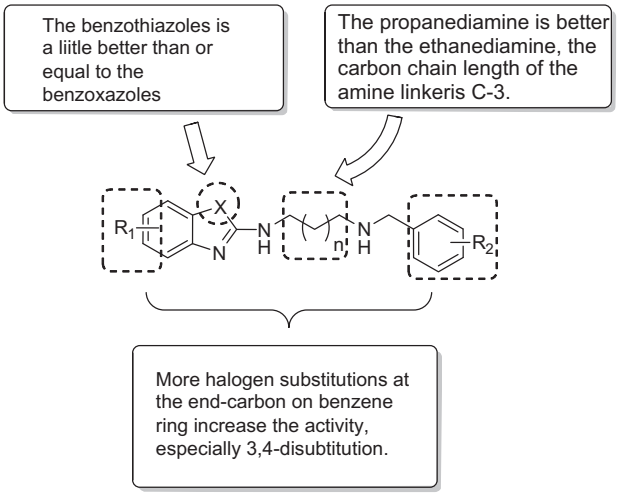


Figure 3. SAR study of benzothiazol- and benzooxazol-2-amine derivatives.

Although the cellular target is not defined in the experimental antimicrobial investigations of these molecules, it was desirable to find out the interactions of the active compounds with the MetRS enzymes targeted by leading compound SB-299623. So, we developed the 3D-model structure of *S. aureus* MetRS using homology modeling method as Lee and co-workers and Finn et al. reported.[25,26,31] PDB structure 2CSX was used as the template. The Uniprot Accession Number of MetRS was Q5HII6.[34,35] The compound **8t** occupy a long groove, largely lined by hydrophobic residues, adjacent to the methionine binding site of the protein (Fig. 4 b). In addition to making several hydrophobic interactions, compound **8t** utilize their amino head group to interact with the protein through some hydrogen bonds also (Fig. 4a). Interactions involving Asp51 seem to be particularly important as Finn et al. previous reported.[26] SB-299683, the known MetRS inhibitor showed −51.05 Grid Score, −19.27 Amber Score and formed H-bonding with the active site residues of Asp51. Compound **8t** also showed −49.51 Grid scores, −31.42 Amber Score and formed similar type of interactions with the active site amino acid Asp51 His23 and Try 14. These two molecules showed extraordinary results with respect to all properties like estimated activity, binding affinity, calculated drug-like properties (see Supplementary data). Docking results indicate the probability of these compounds to interfere *S. aureus* MetRS.

In conclusion, we designed and prepared a series of benzothiazol- and benzooxazol-2-amine derivatives based on previous QSAR and pharmacophore modeling analysis of a leading methionyl-tRNA synthetase inhibitor SB-299683. Our assays showed that the benzothiazole derivatives with halogen substitution at the end-carbon displayed significant antibacterial activity equal to the lead compound SB-299633. As a further MIC result, compound **8t** exhibited better activities on the Gram-positive bacteria, though

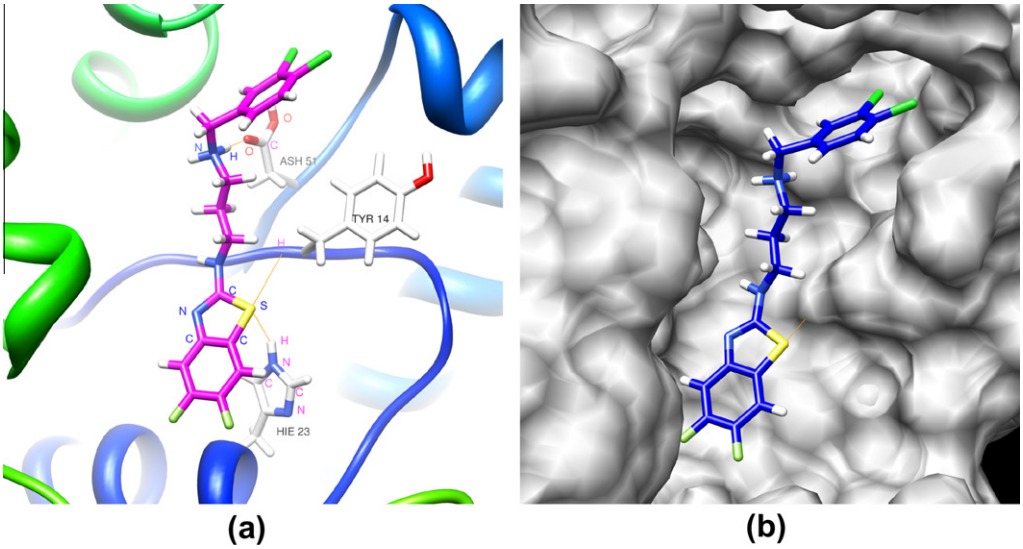


Figure 4. Compound **8t** docked in the active site of *S. aureus* methionyl-tRNA synthetase. (a) Residues involved in interaction with the ligand. (b) The protein molecule is shown in the surface representation, whereas docked compounds are illustrated in the stick representation

standard drug Ampicillin and Cefotaxime displayed better activity on the non-resistant bacteria. Impressively, the new compound **8t** seems to be more potential on drug-resistant bacteria especially methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecalis*. From the results of molecular docking, we speculated that compound **8t** might be a new MetRS inhibitor. Importantly, our study provided an effective entry for the synthesis of a new small molecule and a good lead for subsequent optimization used as antibacterial agents. The preliminary results seem to be very promising and we are continuing to develop more suitable methods for the comprehensive evaluation of methionyl-tRNA enzyme inhibitory activity and in vivo animal models.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.03.079.

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