Bioorganic & Medicinal Chemistry Letters 26 (2016) 4070–4076

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and antibacterial evaluation of macrocyclic diarylheptanoid derivatives

Hao Lin [a], David F. Bruhn [b,†], Marcus M. Maddox [b], Aman P. Singh [b], Richard E. Lee [b], Dianqing Sun [a,*]

[a] Department of Pharmaceutical Sciences, The Daniel K. Inouye College of Pharmacy, University of Hawai'i at Hilo, 34 Rainbow Drive, Hilo, HI 96720, USA
[b] Department of Chemical Biology & Therapeutics, St. Jude Children's Research Hospital, 262 Danny Thomas Place, MS#1000, Memphis, TN 38105, USA

ARTICLE INFO

Article history:
Received 8 June 2016
Revised 24 June 2016
Accepted 25 June 2016
Available online 27 June 2016

Keywords:
Antituberculosis
Antibacterial
Diarylheptanoid
Macrocycle
SAR

ABSTRACT

Bacterial infections, caused by *Mycobacterium tuberculosis* and other problematic bacterial pathogens, continue to pose a significant threat to global public health. As such, new chemotype antibacterial agents are desperately needed to fuel and strengthen the antibacterial drug discovery and development pipeline. As part of our antibacterial research program to develop natural product-inspired new antibacterial agents, here we report synthesis, antibacterial evaluation, and structure–activity relationship studies of an extended chemical library of macrocyclic diarylheptanoids with diverse amine, amide, urea, and sulfonamide functionalities. Results of this study have produced macrocyclic geranylamine and 4-fluorophenethylamine substituted derivatives, exhibiting moderate to good activity against *M. tuberculosis* and selected Gram-positive bacterial pathogens.

The continuing emergence and spread of multidrug resistant bacterial pathogens including *Mycobacterium tuberculosis* is a major global health care concern.[1,2] According to the World Health Organization, approximately one third of the world's population is infected with latent *M. tuberculosis*, the bacterium causing tuberculosis (TB).[1] In 2014, there were about 9.6 million new cases of TB and 1.5 million deaths worldwide from this infectious disease.[1] This problem is compounded by mounting bacterial resistance to existing antibiotic chemical classes and the low rate of discovery of new agents.[3,4] As such, the discovery and development of new chemotype antibacterial agents are urgently needed to combat clinically problematic bacterial infections.

Natural products represent the most valuable source of novel bioactive molecules in antimicrobial drug discovery, as the majority of clinically used antibiotics are natural products and/or their semisynthetic derivatives in their origin.[5–7] Natural and synthetic macrocycles have attracted a growing attention in drug discovery and medicinal chemistry due to their favorable pharmacological properties.[8–11] Among them, the cyclic diarylheptanoids belong to a chemical class of plant secondary metabolites and have been reported to mediate diverse biological activities.[12,13] As examples, acerogenin A and analogs have been reported to possess osteogenic activity and may serve as potential biomarkers for osteoblast differentiation.[14,15] In addition, acerogenins A and B (Fig. 1) were also found to function as Na^+-glucose co-transporter (SGLT) inhibitors with therapeutic potential for type 2 diabetes.[16] The benzoyl ester derivative of acerogenin C was found to inhibit nitric oxide (NO) production (IC_{50} = 13 μM) from lipopolysaccharide (LPS)-activated macrophages with no cytotoxicity.[17] The dimethyl ether derivative **7** of engelhardione was reported to function as a micromolar inhibitor (IC_{50} = 14.3 μM) against NF-κB by Natarajan and coworkers.[18]

In our continued efforts to develop natural product-inspired antibacterial agents, we previously reported the synthesis and preliminary structure–activity relationship (SAR) of macrocyclic diarylheptanoids with antibacterial activity.[19] Antibacterial evaluation revealed that the *N*-substituted secondary amine derivatives (**1** in Fig. 1) exhibited moderate antitubercular and antibacterial activities with minimum inhibitory concentrations (MIC) of 12.5–50 μg/mL.[19] In this current study, we explore the further synthesis and optimization of *N*-substituted macrocyclic diarylheptanoids in an effort to obtain compounds with improved antibacterial properties. Specifically, an extended chemical library of macrocyclic amine derivatives **9**–**35** was synthesized to expand the scope of amine substrates. We also designed and synthesized a series of new macrocyclic derivatives **36**–**48** with various ester, amide, urea, carbamate, sulfonamide, and sulfonate functionalities. Finally on the basis of a newly obtained antibacterial lead, a focused set of macrocycles **49**–**53** with different ring systems was also synthesized to expand the SAR.

* Corresponding author.
E-mail address: dianqing@hawaii.edu (D. Sun).
† Present address: Avista Pharma Solutions, 3501 Tricenter Boulevard, Suite C, Durham, NC 27713, USA.

http://dx.doi.org/10.1016/j.bmcl.2016.06.075
0960-894X/

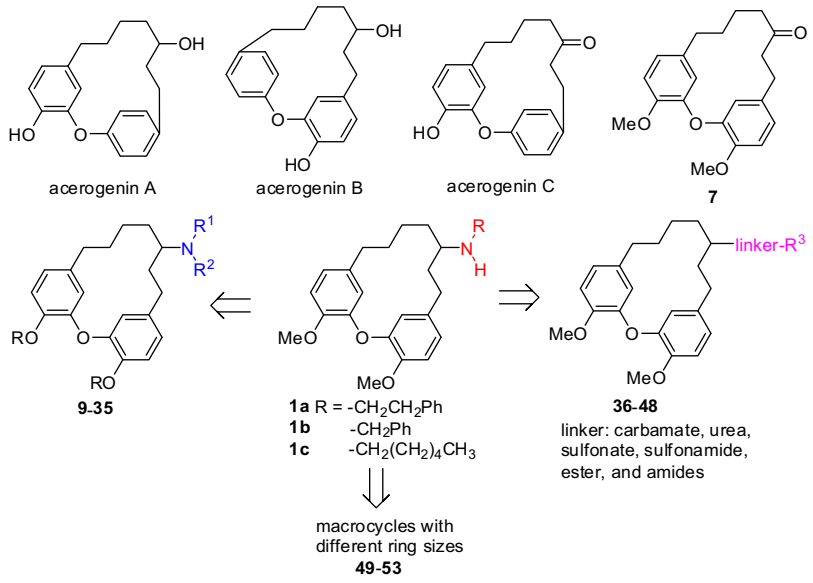

Figure 1. Selected examples of bioactive cyclic diarylheptanoids and an overview of library design.

Synthesis of the key macrocycle intermediates **7** and **8** is shown in Scheme 1. Briefly, 3-(benzyloxy)-4-methoxybenzaldehyde was first transformed into **2** via a 3-step sequence. This improved protocol can be easily scaled up in gram scales compared to our previously reported method.[20] Next, in the presence of 10% sodium hydroxide solution, the aldol condensation of **2** and **3** yielded **4** as a yellow solid in 74% yield. Subsequent hydrogenation of **4** gave both **5** and **6**, which could be easily separated by flash column chromatography. Under microwave irradiation, final intramolecular copper-catalyzed Ullmann coupling[21] of **5** or **6** afforded the corresponding macrocyclic product **7** or **8** in 77% and 80% yields, respectively.

Once the key intermediate **7** was in hand, we next expanded the chemical diversity of macrocyclic amine derivatives by employing various amine substrates (Table 1). The reduction of in situ formed imines with $NaBH_4$ gave their corresponding amine products. Specifically, reduction of **7** in concentrated ammonia solution (7 N in methanol) gave primary amine **9** in 50% yield. In the cases of amine derivatives **12**, **15**, **19**, **22**, and **23** (Table 1, entries 4, 7, 11, 14 and 15), low to moderate yields (19–58%) were obtained under this reaction condition due to the simultaneous formation of the reduced alcohol by-product **8** from starting material **7**. We subsequently found that the yield and selectivity of this reductive amination reaction can be greatly improved by using a milder reductant $NaBH_3CN$, resulting in the desired macrocyclic amine derivatives in good yields with no or only trace amounts of **8** for most primary amine substrates.

With the optimized conditions, compounds **10** and **11** (Table 1, entries 2 and 3), with a 3- and 4-carbon linker, respectively, were designed and synthesized to probe the effect of the spacer length of the alkyl side chain. Compounds **12**–**18** (Table 1, entries 4–10) were synthesized to evaluate different groups and substitution patterns of the phenyl ring by using substituted phenethyl amines as the substrates. The amine derivatives **19**–**21** (Table 1, entries 11–13) with different aromatic/heterocyclic ring systems (pyridine, naphthalene, and 1,3-benzodioxole) were also prepared in moderate to good yields. Compounds **19**, **22**, and **32** (Table 1, entries 11, 14, and 22) with two basic nitrogen functionalities on the side chain of the macrocyclic scaffold were also synthesized. Accordingly, reaction of **7** with optically pure (*R*)-(−)-1,2,3,4-tetrahydro-1-naphthylamine or (*S*)-(+)-1,2,3,4-tetrahydro-1-naphthylamine gave a pair of diastereomers **25** and **26** (Table 1, entry 17) or **27** and **28** (Table 1, entry 18), respectively.

In addition, **24** with the geranyl amine motif was also synthesized in 79% yield. Ethylamine was used to synthesize **29** (Table 1, entry 19) to understand the effect of the phenyl group by comparing to **1a**. Meanwhile, secondary amines diethylamine, diethanolamine, and 1-methylpiperazine were used as substrates to give **30**–**32** (Table 1, entries 20–22) in 15–40% yields. Overall, secondary amines were found to be less reactive in this reductive amination reaction with generally lower yields presumably due to steric effects.

The reaction of 4-chloroaniline with **7** proceeded smoothly to yield the desired product **33** in 57% yield (Table 1, entry 23). However, the reaction of **7** with bulky amine 1-adamantylamine (Table 1, entry 24) gave no desired product under the optimized reaction conditions.

To further evaluate the effect of phenolic hydroxyl groups in cyclic amine derivatives, two selected amine compounds **1a** and **1b** were demethylated using boron tribromide to give free phenols **34** and **35** in 74% and 26% yields, respectively (Scheme 2).

In addition to introducing the basic amine moieties on the macrocyclic ring, a series of macrocyclic derivatives with other functionalities including ester, amide, urea, carbamate, sulfonamide, and sulfonate were also synthesized from **8** or **9** (Table 2). Briefly, reaction of secondary alcohol **8** with substituted isocyanate gave the corresponding carbamates **36**–**38**, in which 4-fluorophenyl isocyanate (Table 2, entry 1) gave a higher yield comparing to phenethyl and benzyl isocyanates (Table 2, entries 2 and 3). Accordingly, macrocyclic urea derivatives **39** and **40** were obtained by reacting primary amine **9** and phenethyl or 4-fluorophenethyl isocyanate (Table 2, entries 4 and 5). Furthermore, **8** or **9** reacted with substituted sulfonyl chloride, carbonyl chloride, or carboxylic acid led to the formation of corresponding sulfonate **41**, sulfonamides **42**–**43**, esters **44**–**46**, and amides **47**–**48** in a range of 26–99% yields (Table 2, entries 6–13).

Finally, based on the promising antibacterial activity of **15** (described below), a focused set of structural analogs **49**–**53** (Fig. 2) with 12, 14, and 15-membered ring systems as well as different methoxy substitution patterns were next prepared to probe the SAR. These compounds were synthesized from their corresponding ketone macrocycles and 4-fluorophenethyl amine under