Bioorganic & Medicinal Chemistry Letters 28 (2018) 1198–1206

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Design, synthesis and biological evaluation of spiropyrimidinetriones oxazolidinone derivatives as antibacterial agents

Asher M. Siddiqui [a,b,*], Jitendra A. Sattigeri [a], Kalim Javed [b,*], Syed Shafi [b], M. Shamim [b], Smita Singhal [a], Zubbair M. Malik [c]

[a] Daiichi Sankyo India Pharma Pvt. Ltd., Gurgaon, Haryana 122015, India
[b] Department of Chemistry, Faculty of Science, Jamia Hamdard (Hamdard University), New Delhi 110062, India
[c] Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi 110025, India

ARTICLE INFO

Article history:
Received 17 August 2017
Revised 7 January 2018
Accepted 27 February 2018
Available online 6 March 2018

Keywords:
Spiropyrimidinetrione
Oxazolidinone
[1,5]-Hydride shift
Drug resistance

ABSTRACT

Gram-positive bacteria are among the most common human pathogens associated with clinical infections which range from mild skin infections to sepsis. Resistance towards existing class of drugs by Gram-positive bacteria including methicillin resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (MRSE) and vancomycin resistant *enterococci* (VRE) is a growing concern. There is an urgent need to discover new antibiotics which are active against resistant strains of Gram positive bacteria. We report herein a novel class of spiropyrimidinetrione oxazolidinone derivatives as novel antibacterial agents. Key step towards the synthesis of title compounds involved the use of *tert*-amino reaction with [1,5]-hydride shift leading to the new C—C bond formation. Compound **30n** has demonstrated potent antibacterial activity against a panel of Gram-positive microbial strains including MRSA, MRSE, and LNZ and vancomycin resistant strains of *E. faecalis*. Further, molecular docking studies suggest that **30n** has binding mode similar to that of LNZ in 50S RNA ribosome.

© 2018 Elsevier Ltd. All rights reserved.

The emergence of antibacterial resistance to existing antibiotics is posing a serious concern in hospital settings and community.[1–4] Infections caused by multidrug-resistant Gram-positive bacteria represent a major public health burden, not just in terms of morbidity and mortality, but also in terms of increased financial burden on exchequer.[5–7] In recent decades, the discovery and development of new antibiotics have slowed dramatically as scientific barriers to drug discovery; regulatory challenges and diminishing returns on investment have led major drug companies to scale back or abandon their antibiotic research. Consequently, the antibiotic discovery-which peaked in the 1950s-has dropped precipitously resulting in a lack of new antibiotics coming to the market.[8,9] Treatment of infections caused by Gram-positive bacteria including Methicillin Resistant *Staphylococcus aureus*[10,11] (MRSA), Methicillin Resistant *Staphylococcus epidermidis*[12] (MRSE) and vancomycin resistant *enterococci*[13](VRE) [*E. faecalis and E. faecium*] is increasingly becoming a big challenge to health care professionals.

Linezolid (LNZ) **1** (Fig. 1), an oxazolidinone class of synthetic antibiotic, was introduced into the clinic around 20 years[14,15] back for treating serious infections caused by Gram positive bacteria such as *S. aureus, S. epidermis* and *VRE.*[16] Unfortunately, the resistance to LNZ started to appear soon after its implementation for therapeutic use with the rate of resistance being high especially among *Enterococci* and *Staphylococcus epidermidis* strains.[17,18] The most common mechanism by which these pathogens develop resistance to LNZ is by manifesting G2576T/U mutation in the 23S rRNA sub-unit. The second mechanism of resistance involves the plasmid-encoded *cfr* gene, an enzyme with 23S rRNA

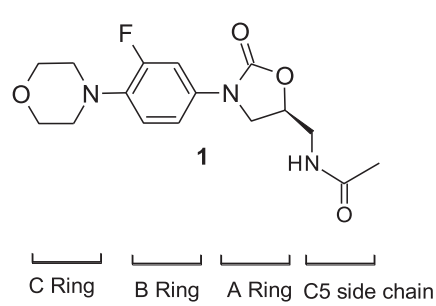

Fig. 1. Linezolid.

* Corresponding authors at: School of Chemical & Life Sciences, Department of Chemistry, Jamia Hamdard (Deemed to be University), New Delhi 110062, India (A.M. Siddiqui).

E-mail addresses: mohd.asher@gmail.com (A.M. Siddiqui), kjaved@jamiahamdard.ac.in (K. Javed).

https://doi.org/10.1016/j.bmcl.2018.02.055
0960-894X/© 2018 Elsevier Ltd. All rights reserved.

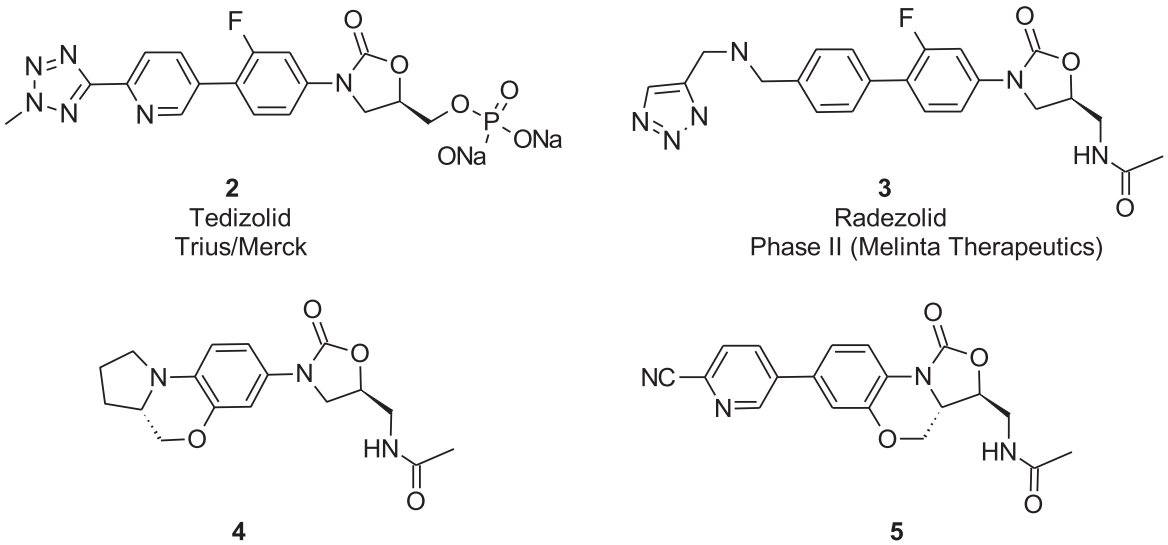

Fig. 2. Oxazolidinone based potent antibacterials.

methyltransferase activity, which confers a pan-resistant phenotype involving chloramphenicol, clindamycin and LZD.[19]

The most common approach to overcome antibacterial resistance is the modification of existing classes of antibacterial agents to provide new analogues with improved attributes.[20] Since its discovery, a number of second generation oxazolidinones (eg. **2** & **3**, Fig. 2) have been reported.[21,22] Additionally, a number of conformationally restricted oxazolidinone analogues[23,24] (e.g. **4** & **5**, Fig. 2) having potent activity against Gram positive bacteria have also been reported. Recently, AstraZeneca and Pfizer disclosed compounds **6** & **7** (Fig. 3)[25,26] containing unique Spiropyrimidinetrione (tetracyclic) structural framework which exhibited potent antibacterial activity.

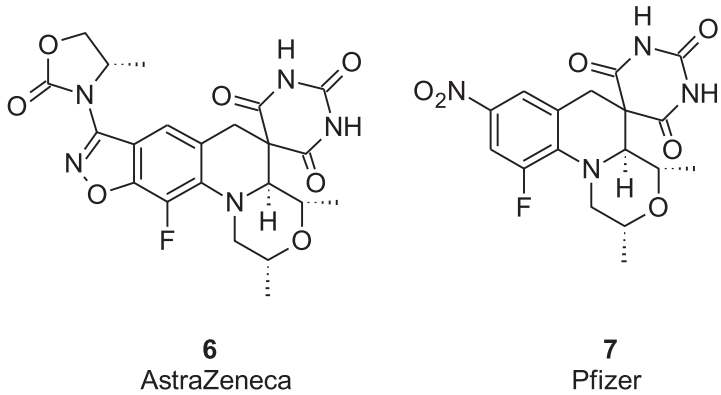

Fig. 3. Recently reported spiropyrimidinetriones based antibacterials.

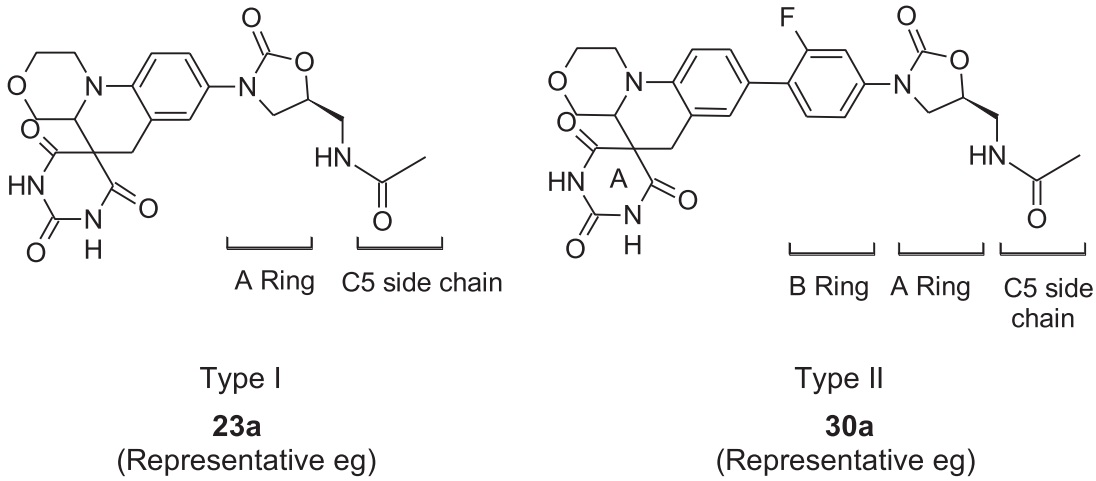

Fig. 4. Spiropyrimidinetrione oxazolidinone derivatives.

Download English Version:

https://daneshyari.com/en/article/7779154

Download Persian Version:

https://daneshyari.com/article/7779154

Daneshyari.com