Bioorganic & Medicinal Chemistry Letters 28 (2018) 1758–1764

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and biological evaluation of aryl-oxadiazoles as inhibitors of *Mycobacterium tuberculosis*

Maria Angeles Martinez-Grau [a], Isabel C. Gonzalez Valcarcel [b], Julie V. Early [c], Richard Klaus Gessner [d,e,f], Candice Soares de Melo [d,e,f], Eva Maria Martin de la Nava [a], Aaron Korkegian [c], Yulia Ovechkina [c], Lindsay Flint [c], Anisa Gravelle [c], Jeff W. Cramer [b], Prashant V. Desai [b], Leslie J. Street [d,e,f], Joshua Odingo [c], Thierry Masquelin [b], Kelly Chibale [d,e,f], Tanya Parish [c,*]

[a] Lilly Research Laboratories, Eli Lilly and Company, Avda. de la Industria 30, 28108-Alcobendas, Madrid, Spain
[b] Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA
[c] TB Discovery Research, Infectious Disease Research Institute, 1616 Eastlake Ave E, Suite 400, Seattle, WA 98102, United States
[d] Drug Discovery and Development Centre (H3D), Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa
[e] South African Medical Research Council Drug Discovery and Development Research Unit, Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa
[f] Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Rondebosch 7701, South Africa

ARTICLE INFO

Article history:
Received 9 March 2018
Revised 6 April 2018
Accepted 11 April 2018
Available online 13 April 2018

Keywords:
Mycobacterium tuberculosis
Oxadiazoles
Phenotypic screening
Antibacterial

ABSTRACT

Despite increased research efforts to find new treatments for tuberculosis in recent decades, compounds with novel mechanisms of action are still required. We previously identified a series of novel aryl-oxadiazoles with anti-tubercular activity specific for bacteria using butyrate as a carbon source. We explored the structure activity relationship of this series. Structural modifications were performed in all domains to improve potency and physico-chemical properties. A number of compounds displayed sub-micromolar activity against *M. tuberculosis* utilizing butyrate, but not glucose as the carbon source. Compounds showed no or low cytotoxicity against eukaryotic cells. Three compounds were profiled in mouse pharmacokinetic studies. Plasma clearance was low to moderate but oral exposure suggested solubility-limited drug absorption in addition to first pass metabolism. The presence of a basic nitrogen in the linker slightly increased solubility, and salt formation optimized aqueous solubility. Our findings suggest that the 1,3,4-oxadiazoles are useful tools and warrant further investigation.

Tuberculosis is the leading cause of death from infectious disease.[1] Although the number of tuberculosis cases decreased during the 20th century, the emergence of HIV and the incidence of multiple-drug resistance have increased the difficulty of treating many new cases.[1,2] Despite efforts to improve the outcome of tuberculosis care, the discovery of new antibiotics against the causative agent *Mycobacterium tuberculosis* has been insufficient to eradicate the disease.[3] New and more effective drugs with novel mechanisms of action are required to shorten treatment, improve patient adherence, and reduce the appearance of resistance.

Mycobacterium tuberculosis can adapt metabolically to host environments and can catabolize multiple carbon sources simultaneously.[4] Fatty acids are the major carbon source available during infection,[5] although carbohydrates, lipids, and carbon dioxide can also be utilized as carbon sources.[6]

We recently reported the identification of a family of oxadiazoles **1**–**5** (Fig. 1)[7] from a whole cell screen against *M. tuberculosis* using butyrate as the carbon source. The compounds were active in medium containing butyrate, but not glucose and lacked mammalian cytotoxicity.[7,8] The lack of cytotoxicity and the low molecular weight prompted us to undertake structure activity relationship (SAR) investigations around this series.

Aryl-oxadiazoles, the common structural motif in compounds **1**–**5**, have been widely applied in medicinal chemistry for the development of new drugs. Compounds containing the 1,2,4- and 1,3,4-oxadiazole motif have been evaluated against a broad spectrum of pharmacological activities, with special attention to their properties as antimicrobial and antitubercular agents.[9–12]

Synthetic methods for the preparation of differently functionalized 1,3,4-oxadiazoles have been recently reviewed.[13] Compound 2 was resynthesized and compounds **13**–**18** and **24**–**41** were made in three steps by the method previously published for making compound **2**, starting from the corresponding hydrazide and then

* Corresponding author.
E-mail address: tanya.parish@idri.org (T. Parish).

https://doi.org/10.1016/j.bmcl.2018.04.028
0960-894X/

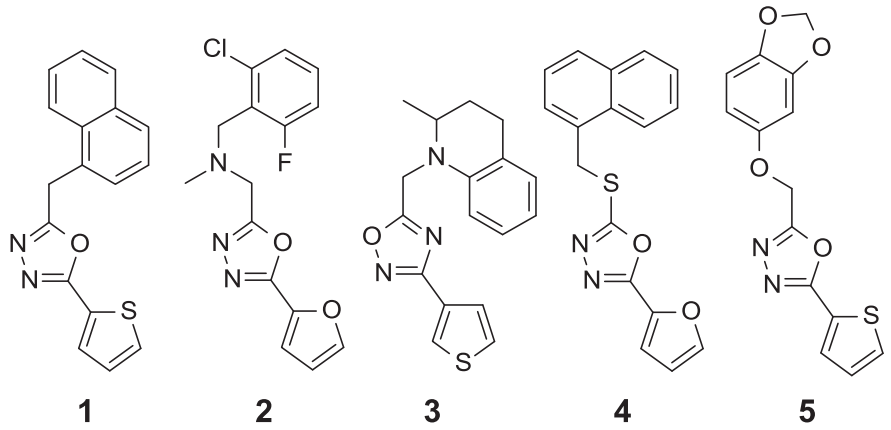
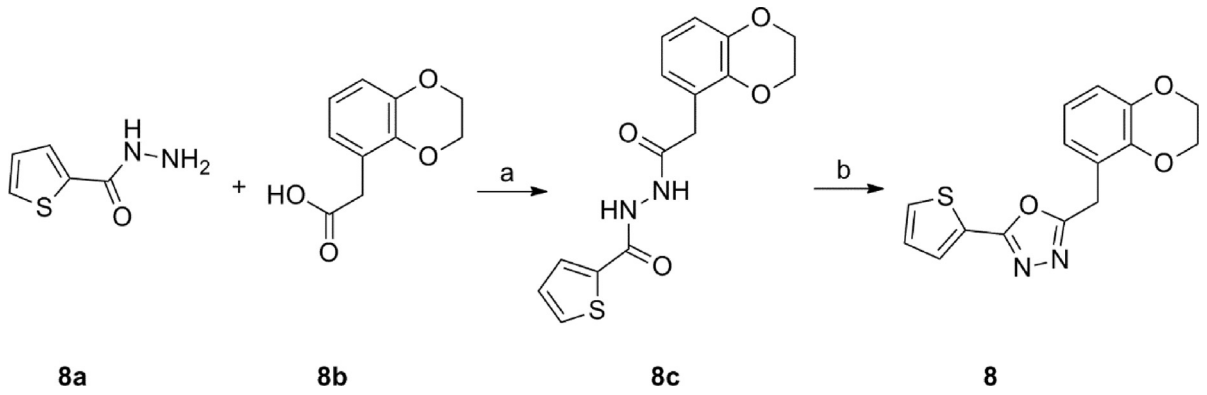


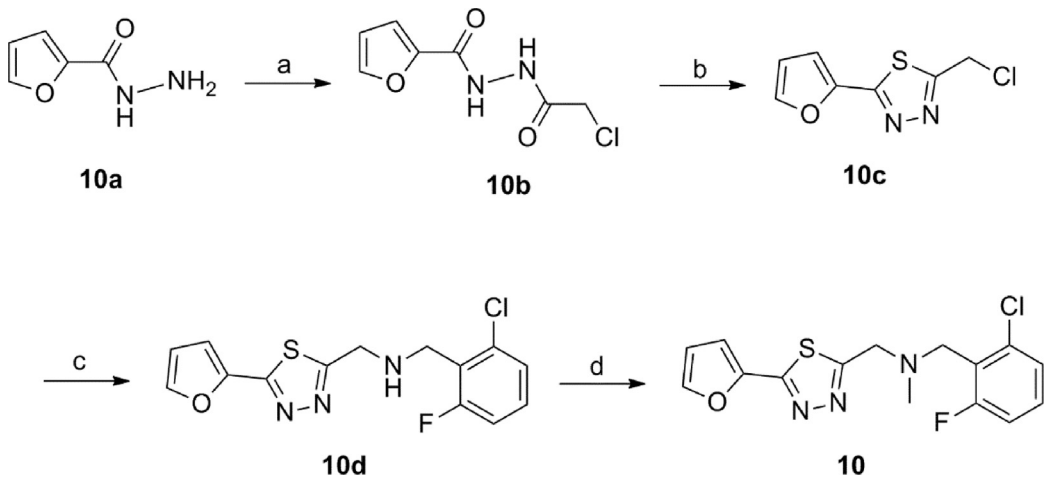
Fig. 1. Oxadiazoles previously identified from whole cell screening against *Mycobacterium tuberculosis*, adapted from Early et al.[7]

reacting the intermediate chloride with the appropriate secondary amine.[7] Compounds **6**–**9** were prepared according to the representative procedure exemplified in Scheme 1 for compound **8**. Hydrazide **8a** was coupled with carboxylic acid **8b** using EDC and HOBt to obtain the intermediate **8c**. Cyclodehydration of semicarbazide **8c** by refluxing with phosphoryl chloride yielded compound **8**.

In order to prepare thiadiazole **10**, reaction of furan-2-carbohydrazide **10a** with chloroacetyl chloride in the presence of *N*-methylmorpholine produced the intermediate acylsemicarbazide **10b** (Scheme 2). Acylsemicarbazide **10b** was refluxed with Lawesson's reagent in THF to obtain the intermediate chloride **10c**. Chloride replacement by 2-chloro-6-fluorobenzylamine at reflux in the presence of DIPEA and sodium iodide generated the secondary amine **10d** which was treated with sodium hydride and methyl iodide to give compound **10**. Compounds **11**, **12** and **19** were prepared from the corresponding oxadiazole analogue to chloride **10c**



Scheme 1. Synthesis of compound **8**. Reagents and conditions: (a) EDC, HOBt, DMF; (b) $POCl_3$, 110 °C.



Scheme 2. Synthesis of compound **10**. Reagents and conditions: (a) *N*-methylmorpholine, chloroacetyl chloride, CH_2Cl_2; (b) Lawesson's reagent, THF, reflux; (c) 2-Chloro-6-fluorobenzylamine, DIPEA, NaI, CH_3CN, reflux; (d) MeI, NaH, DMF.