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(54) Title: OXAZOLIDINONE COMBINATORIAL LIBRARIES, COMPOSITIONS AND METHODS OF PREPARATION

(57) Abstract

Oxazolidinones and methods for their synthesis are provided. Also provided are combinatorial libraries comprising oxazolidinones, and methods to prepare the libraries. Further provided are methods of making biologically active oxazolidinones as well as pharmaceutically acceptable compositions comprising the oxazolidinones. The methods of library preparation include the attachment of oxazolidinones to a solid support. The methods of compound preparation in one embodiment involve the reaction of an iminophosphorane with a carbonyl containing polymeric support.

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OXAZOLIDINONE COMBINATORIAL LIBRARIES, COMPOSITIONS AND METHODS OF PREPARATION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation in part of U.S. Patent Application Serial No. 09/012,535, filed January 23, 1998, and a continuation in part of U.S. Patent Application Serial No. 09/086,702, filed May 28, 1998, the disclosures of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present invention is directed to oxazolidinones; oxazolidinone compositions; oxazolidinone combinational libraries; and methods for their preparation and use.

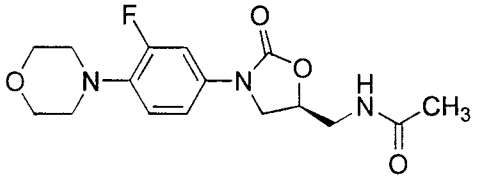
BACKGROUND ART

Oxazolidinones are compounds where an amine group and a hydroxyl group on adjacent carbon atoms have been cyclized to form a 5-membered ring containing a carbonyl group. Certain oxazolidinones have been shown to exhibit a variety of biological activities. For example, some oxazolidinones are inhibitors of monoamine oxidase-B, an enzyme implicated in Parkinson's disease. See, for example, Ding *et al., J. Med. Chem.* 36:3606-3610 (1993).

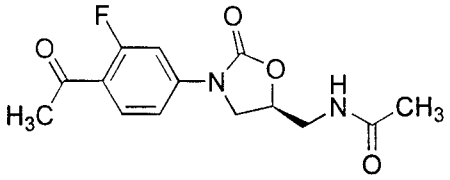
A a ten step synthesis of oxazolidinone antibiotics has been described. U.S. Patent No. 5,547,950. A four step synthesis of the antibacterial compound U-100592 also has been reported. Schauss *et al., Tetrahedron Letters,* 37:7937-7940 (1996). A five step preparation of enantiomerically pure *cis*- and *trans*-N-(propionyl)hexahydrobenzoxazolidin-2-ones further was reported. De Parrodi *et al., Tetrahedron: Asymmetry,* 8:1075-1082 (1997).

Scientists have reported that certain oxazolidinone derivatives exhibit beneficial antibacterial effects. For instance, N-[3-[3-fluoro-4-(morpholin-4-yl)phenyl]2-oxooxazolidin-5(s)-ylmethyl] acetamide (below) has been reported to be useful for the

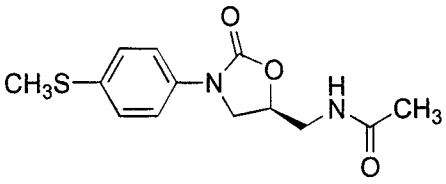
treatment of bacterial infections. Lizondo *et al., Drugs of the Future,* 21:1116-1123 (1996).



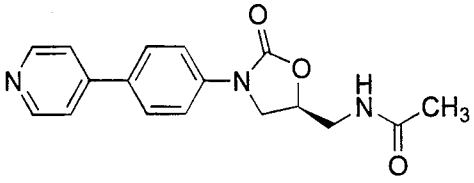
The synthesis of the oxazolidinone antibacterial agent shown below has been reported. Wang *et al., Tetrahedron,* 45:1323-1326 (1989). This oxazolidinone was made using a process that included the reaction of an aniline with glycidol to provide an amino alcohol, and the diethylcarbonate mediated cyclization of the amino alcohol to afford an oxazolidinone.



The synthesis of oxazolidinone antibacterial agents, including the compound shown below has been reported. U.S. Pat. No. 4,705,799. The process used to make the compound shown below included a metal mediated reduction of a sulfonyl chloride to provide a sulfide.



The synthesis of oxazolidinone antibacterial agents, including the pyridyl compound shown below has been reported. U.S. Patent No. 4,948,801. The process used included an organometallic mediated coupling of an organotin compound and an aryl iodide.



Synthetic routes to oxazolidinones often allow a chemist to produce only one compound at a time. These laborious methods can provide a limited number of compounds for evaluation in a biological screen. These methods cannot, however, provide the number of compounds required to supply a high-throughput biological screen, an assay technique whereby the activity of thousands of drug candidates, for example, per week, may be analyzed. This limitation on compound production is of practical importance since high-throughput screens are desirable and efficient for the discovery of new drugs.

SUMMARY OF INVENTION

Provided are oxazolidinones and combinatorial libraries, compositions comprising oxazolidinones, as well as methods of their synthesis and use. Using the methods provided herein, one of skill in the art can rapidly produce the large number of compounds required for high-throughput screening.

In one embodiment, provided are methods for the solid phase synthesis of oxazolidinones.

In one embodiment, the method comprises attaching an olefin to a solid support, oxidizing the olefin to provide an epoxide functionality, opening the epoxide with an amine and cyclizing the resulting amino alcohol using a phosgene equivalent.

In another embodiment, the method comprises attaching an allylic amine to a solid support, oxidizing the olefin of the allylic amine to provide an epoxide, opening the epoxide with an amine, and cyclizing the resulting amino alcohol using a phosgene equivalent.

In another embodiment, the method comprises attaching allylamine to a solid support, oxidizing the olefin of allylamine to provide an epoxide, opening the epoxide with an amine and cyclizing the resulting amino alcohol using a phosgene equivalent.

In another embodiment, the method comprises attaching an olefin to a solid support, oxidizing the olefin to provide an epoxide, opening the epoxide with an amino acid and cyclizing the resulting amino alcohol using a phosgene equivalent.

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