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The discovery and structure–activity relationships leading to CE-156811, a difluorophenyl cyclopropyl fluoroether: A novel potent antibacterial analog derived from hygromycin A

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ABSTRACT

SAR studies and optimization of various modified Hygromycin A fluoroalkyl ethers, which led to the discovery of the highly potent 4′-(2-cyclopropyl-2-fluoroethyl ether) antibacterial CE-156811 (**1**) derived from truncation of the ribose ring and difluorination of the phenyl found in Hygromycin A, are discussed.

Infections with bacterial pathogens that have developed resistance to a number of important classes of antibiotics continue to present highly challenging treatment problems for physicians.[1,2,8–10] As a consequence, discovery of novel antibacterial agents to combat these resistant strains remains of high interest due to high medical need.

The natural product Hygromycin A, discovered in 1953, has only weak activity against medically important Gram-positive organisms.[3,4] It demonstrates potent activity against the organism implicated in swine dysentery. From mode of action studies carried out a number of years ago, it was established that Hygromycin A interferes with bacterial growth by inhibition of protein synthesis involving inhibition of peptide bond formation.[5] Our study concerning Hygromycin A analogs as potential new leads within the Human Health anti-infective group at Pfizer was initiated as a consequence of an intensive examination of a broad selection of known natural products published in the literature. Earlier efforts reported a series of modified Hygromycin A analogs, resulting from investigations during a Pfizer Animal Health research program that was ultimately terminated. Hecker, Jaynes, and coworkers established that the Hygromycin A furanose ring could be effectively replaced by simple alkyl ether substituents, for example, 4′-allyl ether, and that the phenol hydroxyl could be replaced with fluorine. The 2,5-difluorophenyl analog in particular demonstrated improved activity against the animal pathogens of interest, as well as significant improvement against key Gram-positive human pathogens.[6,7]

CE-156811 (**1**) is a novel truncated Hygromycin A derivative possessing potent in vitro activities against important Gram-positive bacterial pathogens. It also demonstrated efficacy commensurate with linezolid in several in vivo infection models with subcutaneously (sc) dosing (Fig. 1).

The preparation of **5** started with condensation between phosphonate **3**[7] and commercially available aldehyde **2** under basic conditions (Scheme 1). Different ether substituents at the 4-aryl position of **5** were appended in a reasonably straightforward manner using nucleophilic aromatic substitution with a variety of alcohols on the trifluorophenyl intermediate **4**. This typically gave the desired *para* substituted analogs as the primary products in low-to-modest (15–45%) yields; minor amounts of the product of *ortho* substitution were also isolable. The selectivity can be inferred to arise from steric hindrance at the *ortho* site. As the isomers were separable by chromatography, the use of this method allowed us to prosecute the SAR in an expeditious manner.

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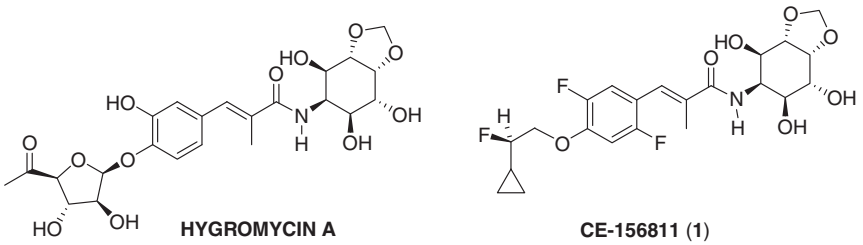
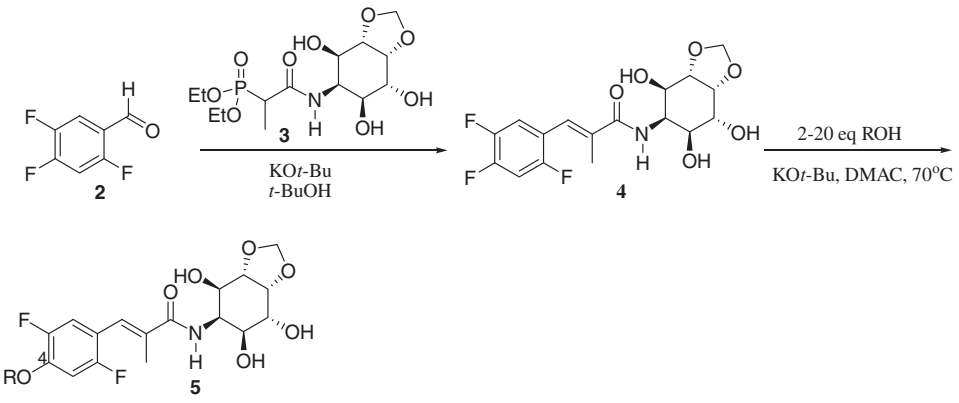


Figure 1. The structures of Hygromycin A and CE-156811 (**1**).



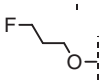
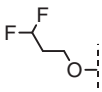
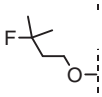
Scheme 1. Synthesis of 2,5-difluorophenyl 4-ethers.

Using this approach, the compounds in Table 1 were prepared. In the acyclic 4′-alkyl ether series, as exemplified in the generic structure **5**, going from ethyl ether **6** to hydroxyl ethyl ether **7**, potency dropped across species. However, when fluorine was introduced in place of the hydroxyl found in **7** to give **8**, the potency was regained; 3-fluoropropyl ether **9** provided the optimal antibacterial activity in this acyclic series. Based on this finding, we prepared additional 3-fluoropropyl analogs in an attempt to broaden the SAR. These efforts were generally unsuccessful, as a number of additional compounds demonstrated an overall weaker antibacterial activity spectrum (e.g., compounds **10** and **11**).

A more promising avenue became evident when we examined the addition of substituents to the C2-carbon of the 2-fluoroethyl ether moiety of **8**; it is to be noted that the parent 2-fluoroethyl ether itself has only modest antibacterial activity. However, placement of small alkyl moieties at this site proved to considerably boost the in vitro potency; for example, **12** demonstrated an 8- to 20-fold improvement in activity compared with **8**. In a similar manner, the importance of fluorination at the 2-ethyl ether position in potentiating activity was demonstrated; for example, **13** is 2-fold more potent than cyclobutylmethyl ether **14** (Table 2).

Due to these observations, we hypothesized that there was potentially a small binding pocket at the site of activity that accommodated these small alkyl substituents and the 2-fluoro heteroatom on the ethyl ether template. We therefore targeted a broader examination of related compounds to better understand

Table 1
In vitro antibacterial activities (MIC, μg/mL) of early analogs

Compound	R	*S. aureus* 1095[a]	*E. faecalis* 1085[b]	*E. faecium* 1022[c]	*S. pneumo* 1016[d]
6		100	25	12.5	NA
7		100	>100	>100	NA
8		50	25	25	6.2
9		1.56	1.56	0.78	2
10		12.5	12.5	3.13	1.56
11		100	100	50	25

[a] *S. aureus, Staphylococcus aureus.*
[b] *E. faecalis, Enterococcus faecalis.*
[c] *E. faecium, Enterococcus faecium.*
[d] *S. pneumo, Streptococcus pneumoniae.*