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Novel synthesis of isoxazoline indolizine amides for potential application to tropical diseases

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ABSTRACT

Synthetically challenging isoxazoline indolizine amide compounds were designed and prepared for potential application to tropical diseases. Indolizine core structures were synthesized strategically as common intermediates for efficient derivatization. The chemistry for the syntheses of 8-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-*N*-(2-oxo-2-((2,2,2-trifluoroethyl)amino)ethyl) indolizine-5-carboxamide (**3**) and 5-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-*N*-(2-oxo-2-((2,2,2-trifluoroethyl)amino)ethyl)-indolizine-8-carboxamide (**4**) is described in this Letter.

Introduction

Tropical neglected diseases have drawn increasing attention in recent years from academic institutions, non-profit organizations, pharmaceutical industry, and government agencies. Such attention from various parties provides strong support to the enrichment of future new treatments for tropical neglected diseases. Anacor is interested in research in this field and has active research programs of neglected diseases. One of the strategies used for discovering new treatments for human neglected diseases is to research established animal drugs as a starting point for improvement. Albendazole, as an example, was first discovered at an animal health laboratory in 1970s and now has application in humans for the treatment of worm infestations.[1] It was rationalized that a long acting animal ectoparasiticide may interrupt the transmission between vectors, such as mosquitoes and flies, and humans with potential application for human use.

Isoxazoline compounds as a new class of ectoparasiticide agents have recently been discovered and drawn broad attention.[2] Structures of two efficacious isoxazoline compounds (**1** and **2**) are shown as examples in Figure 1.

During our research program, isoxazoline indolizine amide target compounds (**3** and **4** in Fig. 2) were designed to use the indolizine scaffold to replace the lipophilic moiety of methylphenyl in **1** and naphthyl in **2**. These synthetically challenging compounds were prepared by first building indolizine core structures (synthons **5**–**8** in Fig. 2) as common intermediates for efficient derivatization for the structure-activity relationship study on the structure variation of the left side isoxazoline and right side amide.[3] These synthons are functionalized with the acetyl or aldehyde group on the left side for assembling an isoxazoline ring and with the carboxylic ester group on the right side for building an amide moiety. Herein, the chemistry for the syntheses of **3** and **4** is described in this article.

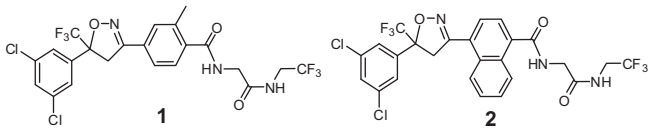

Figure 1. Chemical structures of typical isoxazoline compounds.

Results and discussion

As shown in Scheme 1, the acetyl indolizine intermediate **5** was used as key intermediate to synthesize target compound **3**. The chemistry started with the substitution reaction of pyrrole **9** with the lactone, 5-methyldihydrofuran-2(3*H*)-one, to give compound

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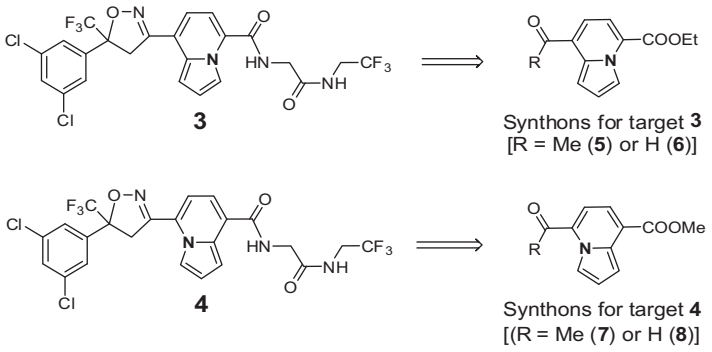
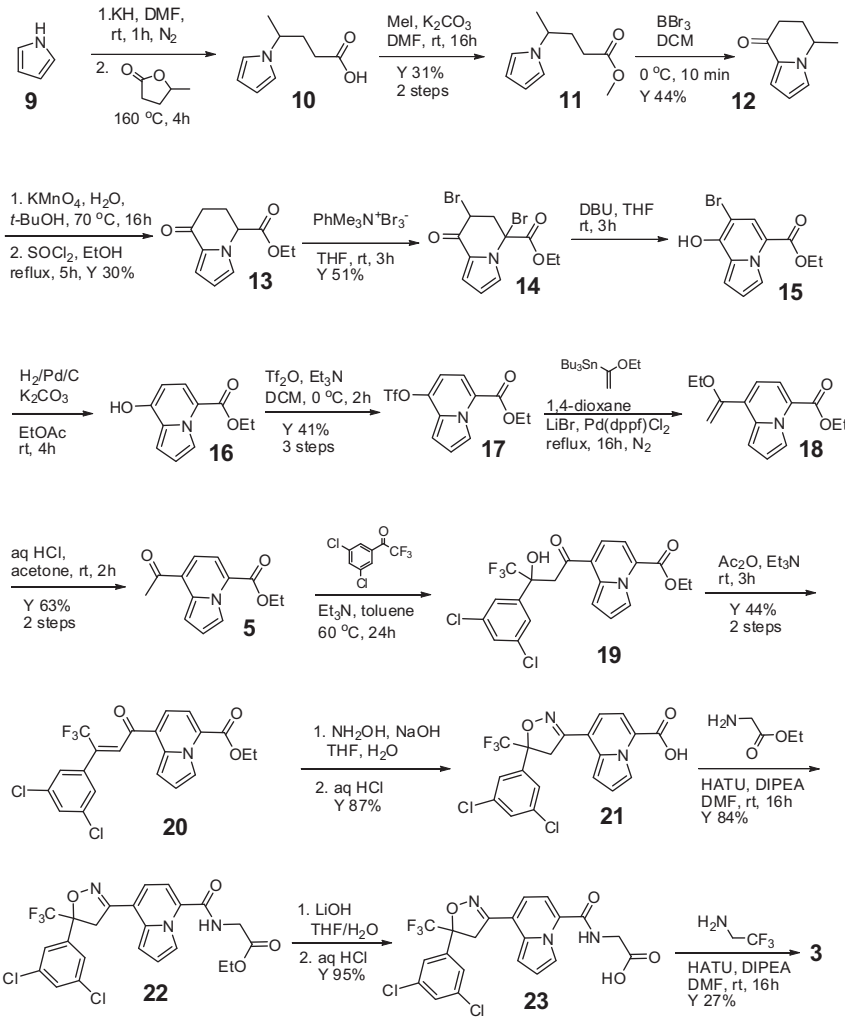


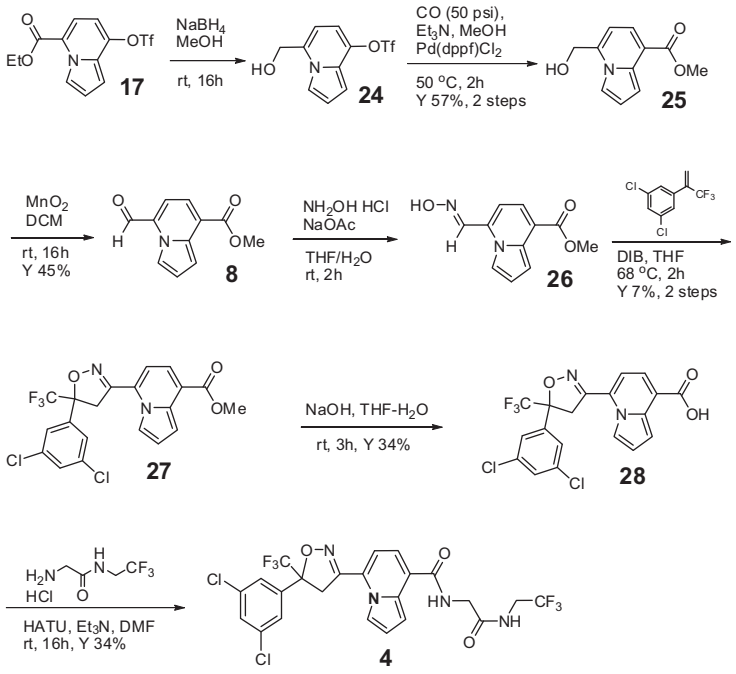
Figure 2. Structures of two isoxazoline indolizine amide target compounds and their synthons for chemistry plan.



Scheme 1. Synthesis of isoxazoline indolizine amide compound **3**.

10.[4] It was then esterified and cyclized to provide the fused compound **12**, of which the methyl group was oxidized and then esterified to generate compound **13**. Compound **13** was brominated using phenyltrimethylammonium tribromide (PTT) to afford the bisbromo intermediate **14**, which was de-acidified and debrominated stepwise to yield the hydroxyl indolizine ester **16**. The hydroxyl group was then triflated and coupled with tributyl(1-ethoxyvinyl)stannane to give the ethoxyvinyl compound **18**. Removal of the ethyl group in **18** by aqueous hydrochloric acid provided the key indolizine intermediate **5**. Addition of **5** to 1-(3,5-dichlorophenyl)-2,2,2-trifluoroethanone and then dehydration generated compound **20**, which was treated with hydroxylamine under basic condition to give the isoxazoline indolizine acid **21**. It reacted with ethyl glycine to form the amide **22** and then hydrolyzed to give **23**. This acid went through amide formation to afford the final compound **3**.

Similarly the chemistry for the synthesis of isoxazoline indolizine amide compound **4** is shown in Scheme 2. In this case, the aldehyde indolizine **8** was used as a key intermediate to test a different synthetic methodology for isoxazoline ring formation. Starting from compound **17**, the ester group was reduced to the hydroxylmethyl group to afford compound **24**. The triflate group



Scheme 2. Synthesis of isoxazoline indolizine amide compound **4**.

in **24** was converted to methoxycarbonyl of **25** by reacting with carbon monoxide in methanol in the presence of a catalyst, 1,1′-bis(diphenylphosphino)ferrocene-palladium(II)dichloride. The hydroxylmethyl group of **25** was oxidized to aldehyde and then reacted with hydroxylamine to give the oxime intermediate **26**. It was oxidized with diacetate iodobenzene (DIB) and then went through an addition-cyclization reaction with 1,3-dichloro-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene to form the isoxazoline indolizine ester **27**. The ester was hydrolyzed to the carboxylic acid **28** and then reacted with 2-amino-*N*-(2,2,2-trifluoroethyl)acetamide to form the final amide **4**.

The experimental procedures for the preparation of compounds **3** and **4** are described in the Supporting information.

In summary, new synthetic methods for the preparation of two isoxazoline indolizine amide compounds **3** and **4** have been established. These compounds are being tested to evaluate their biological activities. The biological results may be disclosed in the future publication.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.003.

References and notes

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