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Expedient synthesis of an atypical oxazolidinone compound library

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ABSTRACT

In order to address the current downturn in the drug discovery pipeline, initiatives are being undertaken to synthesise screening libraries of sp^3-rich, low molecular weight compounds. As part of the European Lead Factory initiative, the synthesis and derivatisation of a simple hexahydrooxazolo[5,4-*c*]pyridin-2(1*H*)-one bicyclic carbamate has been achieved. The synthetic route employed involved a telescoped hetero-Diels–Alder/[2,3]-sigmatropic rearrangement/cyclisation sequence to deliver the desired core scaffold containing two points for further diversification. When applied, this synthesis was found to be robust and scalable which allowed the production of a 155 compound library.

1. Introduction

The urgent need for drug discovery programmes to move away from identifying hit compounds using chemical libraries of flat, (hetero)aromatic constituents has been highlighted in a number of publications.[1] It is accepted that flat compounds contribute to high attrition rates due to poor pharmacokinetic profiles and late stage toxicity studies due to off-target effects. Chiral, three-dimensional compounds are more likely to form complementary interactions with specific biological targets, reducing off-target side-effects and potentially providing ligands for more challenging targets.[1] Initiatives have been realised which fund the compilation of new, innovative screening libraries with the aim of injecting novelty back into drug discovery pipelines to tackle the ensuing stalemate with regards to getting new, improved drugs to market.[2] Advances in sp^2–sp^2 coupling reactions led to the creation of the current available libraries and so it is imperative that similar robust and facile chemistry is implemented in analogous sp^3-rich collections. Approaches to the new libraries include fragment-based screening and diversity-orientated synthesis, often with a focus on the synthesis of sp^3-rich, three-dimensional core structures.[3] The aim of the work described herein was to synthesise a small library of sp^3-rich compounds based upon a fused oxazolidinone/piperidine ring scaffold, containing a *cis*-ring junction and at least two functional groups available for diversification.

Carbamates are well precedented in medicinal chemistry as physiologically stable peptidomimetics capable of penetrating cell membranes.[4] Cyclic carbamates, such as the oxazolidinones, are the most metabolically stable carbamates and are a widely known pharmacophore for antibacterial agents.[4] Linezolid (**1**, Fig. 1A) is the archetypal oxazolidonone antibiotic used for the treatment of Gram-positive strains of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE).[5] Antibacterial activity in this series usually requires substitution at the 5-position of the oxazolidinone ring with predictable stereochemistry, as exemplified by the most well developed analogue of **1**, tedizolid (**2**, Fig. 1A) which displays activity in linezolid-resistant bacteria and was approved, as a phosphate prodrug, in 2014 in the USA to treat acute bacterial skin infections.[6] Aside from antibacterial activity, the oxazolidinone pharmacophore is present in rivaroxaban (**3**, Fig. 1A), a factor Xa inhibitor for the treatment of deep vein thrombosis and pulmonary embolism.[7]

It is hoped that inclusion of an oxazolidinone motif in the innovative bicycle **4** could potentially uncover a novel therapeutic opportunity (Fig. 1B). As an addition to our continued interest in scaffold synthesis, discussed herein are results pertaining to the synthesis and derivatisation of the chemical scaffold of the type **4**.[8] N-functionalisation of the oxazolidinone ring nitrogen would

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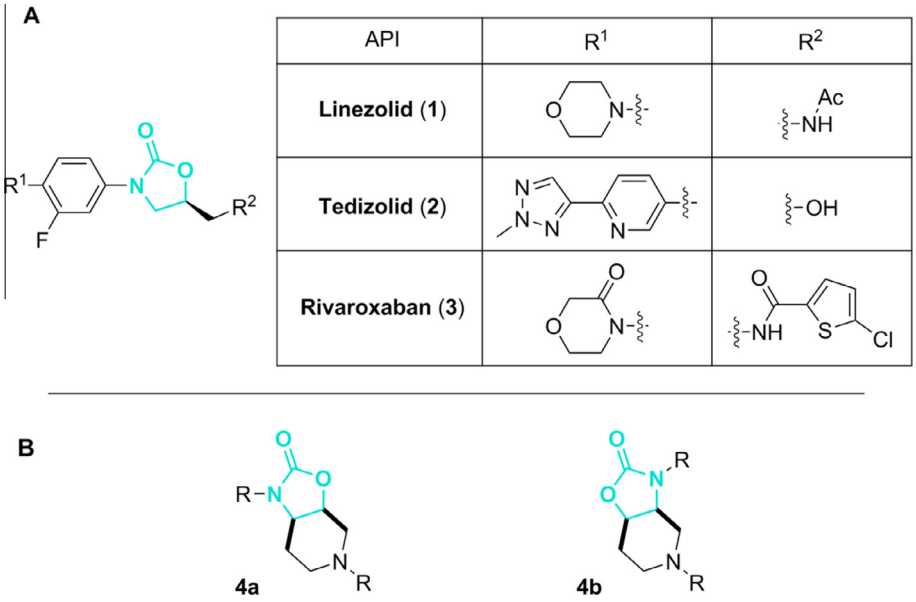
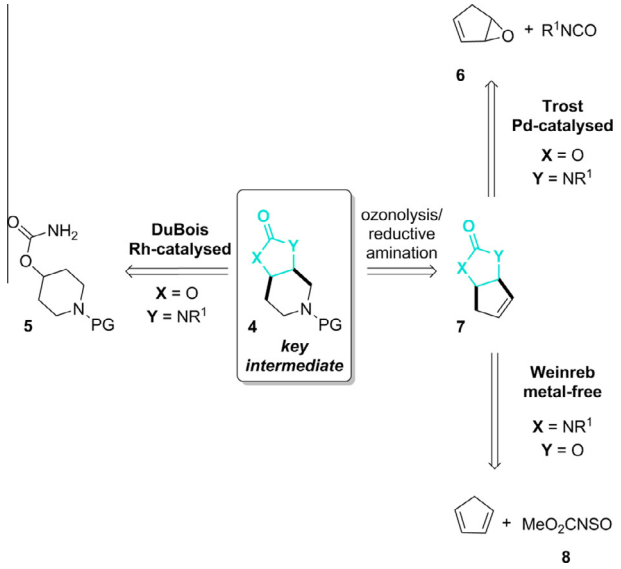


Figure 1. (A) Known cyclic-carbamate containing pharmacophores (**1**–**3**). (B) Targeted bicyclic potential pharmacophores **4a** and **4b**.

provide scaffolds from which novel libraries of compounds could be synthesised, by further derivatisation of the piperidine ring nitrogen. Incorporation of nitrogen atoms as the handle for diversification is desired as this potentially gives access to functional groups such as amines, amides and sulfonamides through facile and high-throughput synthetic methods. The low molecular weight (142 Da) and *c*Log*P* (−1.2) of the unsubstituted scaffold, render this scaffold an excellent starting point for a drug discovery programme if found to possess any biological activity.[9]

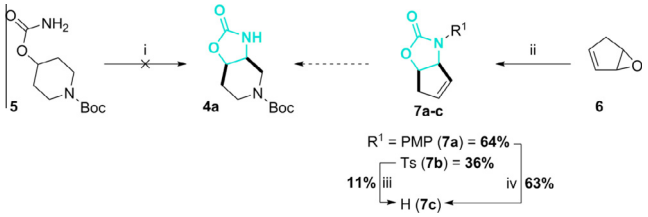
There are two regioisomers of the targeted scaffold which were highlighted as potential targets; **4a** (hexahydrooxazolo[5,4-*c*]pyridin-2(1*H*)-one) and **4b** (hexahydrooxazolo[4,5-*c*]pyridin-2(3*H*)-one). Several routes towards the synthesis of carbamates are known in the literature; however there significantly fewer published syntheses of fused bicyclic oxazolidinones of this class containing a *cis*-ring junction. In order to scale the synthesis of this scaffold to produce a library of hundreds of compounds, the synthetic route chosen must be amenable in terms of cost, safety and expediency. Three potential syntheses towards intermediates **4a** and **4b** were identified (Scheme 1). The use of Du Bois' Rh-catalysed C–H insertion chemistry of a carbamate such as **5**,[10] a Trost-type Pd-catalysed reaction of a vinyl epoxide (**6**) and isocyanate,[11] which would both give rise to regioisomer **4b**, and finally Weinreb's metal-free allylic sulfoxide route which would give alternative regiochemistry seen in **4a** (Scheme 1).[12]



Scheme 1. Retrosynthetic analysis towards the synthesis of scaffold **4**.

2. Results and discussion

Our initial investigations focussed upon applying the two transition metal-catalysed routes to generate cores of the general structure **4a**. The Du Bois method was initially attempted with a number of appropriate carbamates (**5**), which were subjected to typical literature conditions for the C–H insertion reaction.[10] Unfortunately, the cyclised products **4** were not observed in appreciable quantities (Scheme 2). However, the palladium catalysed method for the generation of intermediate **7c**, a precursor to **4a**, was applied with more success. The relevant epoxide **6** was subjected to reaction with a small range of isocyanates.[9] Both the *N*-4-methoxyphenyl and *N*-4-toluenesulfonate protected intermediates **7a** and **7b** were synthesised in 64% and 36% yields respectively and could both be deprotected to provide **7c**. Despite this protocol



Scheme 2. Ineffective routes towards target core **4a**. Representative conditions: (i) $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 36 h; (ii) $Pd_2(dba)_3{\cdot}CHCl_3$, $P(O^iPr)_3$, CH_2Cl_2, R_2NCO, rt, 18 h; (iii) CAN, MeCN, 2 h, rt; (iv) naphthalene, Na, DME, THF, −78 °C–rt, 18 h.

being productive, reproducibility, purification and scalability issues caused by complex reaction mixtures were experienced. These problems forced us to abandon the use of this regioisomer in the remainder of the synthesis.