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7-Oxopyrrolopyridine-derived DPP4 inhibitors—mitigation of CYP and hERG liabilities via introduction of polar functionalities in the active site

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ABSTRACT

Design, synthesis, and SAR of 7-oxopyrrolopyridine-derived DPP4 inhibitors are described. The preferred stereochemistry of these atropisomeric biaryl analogs has been identified as *Sa*. Compound (+)-**3t**, with a K_i against DPP4, DPP8, and DPP9 of 0.37 nM, 2.2, and 5.7 μM, respectively, showed a significant improvement in insulin response after single doses of 3 and 10 μmol/kg in *ob/ob* mice.

In the past few years, inhibitors of dipeptidyl peptidase 4 (DPP4), a member of the serine protease super-family, have attracted considerable attention as novel therapeutic agents for the treatment of diabetes mellitus.[1] Sitagliptin (Januvia™),[2] saxagliptin[3] (Onglyza™), vildagliptin (Galvus™),[4] and linagliptin (Tradjenta™)[5] are approved agents for the treatment of type 2 diabetes, and alogliptin[6] is in advanced stages of clinical trials. While many antidiabetic agents cause weight gain in patients and can cause hypoglycemia, DPP4 inhibitors have shown weight neutrality and are associated with a very low incidence of hypoglycemic events. A considerable amount of effort has thus been focused on the development of DPP4 inhibitors as a novel therapy for the treatment of diabetes.

Earlier work from our laboratories had identified potent and selective DPP4 inhibitors via exploitation of differences in the solvent-exposed region of the DPP4 and DPP8/9 enzymes.[7] Herein, we describe a continuation of this approach through the discovery and development of pyrrolopyridines with the goal of mitigating hERG and CYP liabilities while retaining potency and selectivity. While the significance of DPP selectivity remains a topic of debate in the literature, as a secondary goal, we sought to maximize selectivity for DPP4 versus DPP8/9 in this back-up series to mitigate against any potential issues. Monocyclic DPP4 inhibitors such as **1** have been reported in the literature.[8a] Based on the X-ray co-crystal structure[8b] of a close analog of **1** (not shown) bound to DPP4 and our internal structural studies[7] on cores analogous to the proposed structures (**3–5**, **A**) in Figure 1, we hypothesized that introduction of nitrogen-containing heterocycles such as **3**, **4**, **5**, or **A**, would allow for facile functionalization and variation of R groups in the solvent-exposed region of the enzyme active site. The elaboration of series **A** will be the subject of a separate disclosure from our laboratories.

Synthesis of 7-oxopyrrolopyridine analogs (**3**) followed a literature protocol (Scheme 1), whereby benzylidines **7a** and **7b** were condensed with methyl or ethyl 3-aminocrotonate to give dihydropyridines, which were further oxidized with nitric acid to 7-oxopyrrolopyridine esters **8a** and **8b**, respectively, in good yield.[9] Esters **8a** and **8b** were reduced to alcohols **9a** and **9b**, respectively, with $LiBH_4$, and then converted to the desired primary amines **3a** and **3b** by sequential treatment with mesyl chloride and 7 N NH_3/MeOH under microwave conditions.[10]

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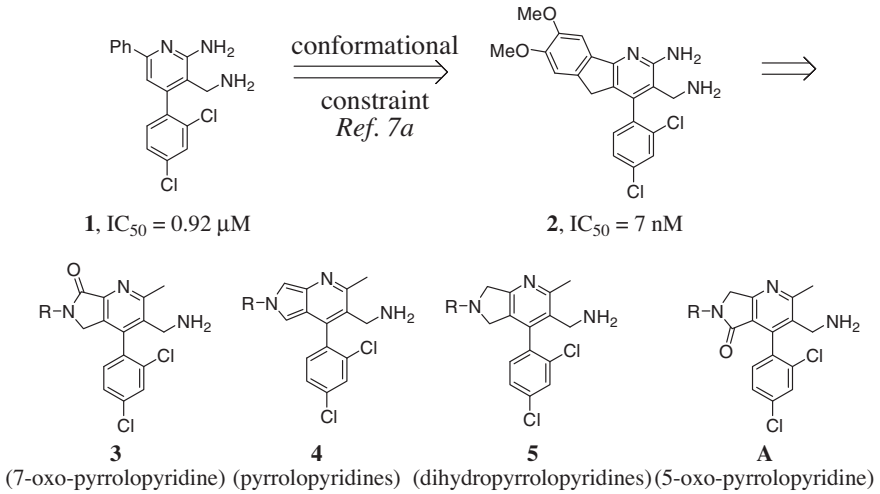
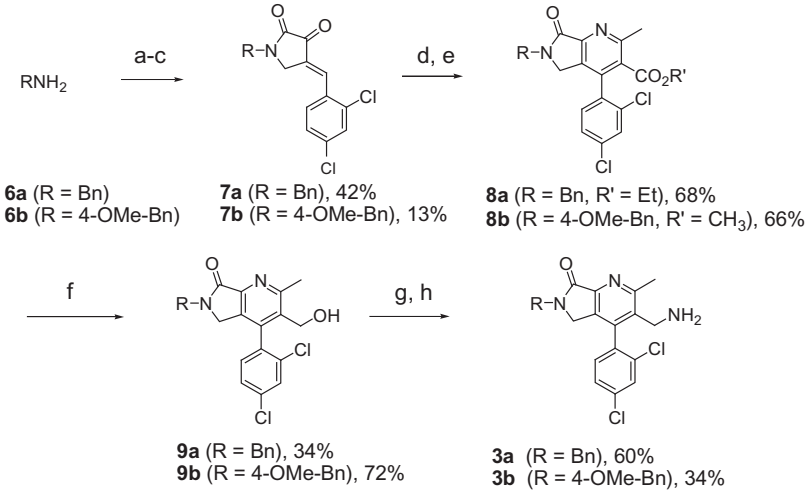
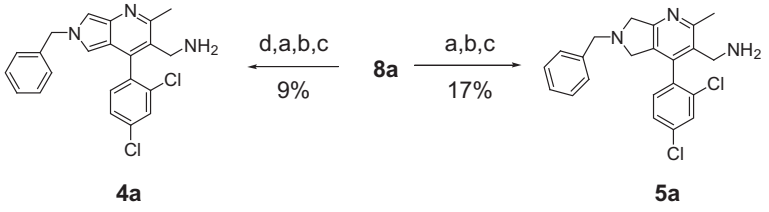


Figure 1. Design of pyrrolopyridines.



Scheme 1. Reagents and conditions: (a) ethyl acrylate, EtOH, rt, 15 h; (b) diethyl oxalate, NaOEt, EtOH, reflux, 1 h; (c) 2,4-dichlorobenzaldehyde aq HCl/EtOH, reflux, 4 h; (d) ethyl 3-aminocrotonate, HOAc, reflux, 1.5 h; (e) 1 N HNO_3, reflux, 30 min; (f) $LiBH_4$, THF, cat MeOH, rt, 15 h; (g) MsCl, Et_3N, DCM, rt, 2 h; (h) 7 N NH_3 in MeOH, microwave, 100 °C, 5 min.



Scheme 2. Reagents and conditions: (a) LAH, THF, 0 °C to rt, 20 min; (b) MsCl, Et_3N, DCM, rt, 3 h; (c) 7 N NH_3 in MeOH, microwave, 100 °C, 15 min; (d) DIBAL-H, THF, rt, 3 h.

Synthesis of pyrrolopyridine **4a** and dihydropyrrolopyridine **5a** (Scheme 2), was low-yielding but expedient. LAH reduction of intermediate **8a** to the corresponding dihydropyrrolopyridine followed by the 2-step treatment with MsCl and NH_3/MeOH afforded primary amine **5a**, whereas use of a milder reducing agent (DIBAL) afforded the pyrrole intermediate with the ester moiety intact. Subsequent treatment with LAH reduced the ester to the alcohol, which was then transformed to pyrrolopyridine **4a** following the usual sequence in 9% overall yield.

We initially sought to identify the most suitable of the three bicyclic cores, represented by compounds **3a**, **4a**, and **5a,** for further SAR elaboration. All three compounds showed moderately potent DPP4 inhibition, and hence could serve as good starting points (Table 1). Compound **4a** was chemically unstable and hence was not progressed further.

Due to compound **3a**'s relatively superior PK properties and CYP profile, 7-oxo-pyrrolopyridine was chosen over **5a** as the bicyclic core for SAR optimization, despite **5a**'s apparent higher peptidase selectivity. All three compounds displayed CYP3A4, hERG and PXR liabilities.

We began by exploring aryl substituents on the lactam nitrogen, taking advantage of Chan-Lam's versatile copper-mediated N-aryla-