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Synthesis of two novel regioisomeric oxospiropyrazole piperidine scaffolds

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ABSTRACT

The synthesis of two unprecedented regioisomeric oxospiropyrazole piperidine scaffolds is detailed. Their potential utility as templates for drug discovery is also exemplified. Chemical stability and solid state conformation were also evaluated.

The preparation of structurally novel templates for use in active pharmaceutical ingredients is one of the numerous challenges faced by drug discovery chemists. In addition to providing opportunities for modifying physicochemical properties (e.g., lipophilicity, solubility, permeability), rationally designed cores can incorporate conformational restrictions that reduce systemic entropy and thereby may lead to improved potency or selectivity.[1] Such restriction can also provide useful information that help to better define a specific pharmacophore. Herein, we report the synthesis of two constrained regioisomeric oxospiropyrazole piperidine scaffolds and their application toward the discovery of small molecule agonists of the G-protein coupled receptor 119 (GPR119).[2,3] GPR119 is expressed at the surface of L-cells (gut) and β-cells (pancreas) and plays a key role in glucose homeostasis. As such, GPR119 agonism has recently emerged as a very promising mechanism to the treatment of type 2 diabetes.

Analysis of targets containing constrained oxospiropyrazole ring systems (e.g., **1** and **2**) suggested that such analogs would be limited to two major conformations at the piperidine; however, it was unclear whether the alkyl or pyrazole substituent would occupy the axial or equatorial positions in the ground state (Fig. 1). Thus, we embarked on the synthesis of **1** and **2** to probe the utility of these analogs as potential agonists and to confirm their relative conformation. Surprisingly, substructure searches of the available chemical literature did not reveal procedures detailing the synthesis of such heterocyclic scaffolds, hence it was necessary to design a de novo route to such structures.[4]

We reasoned that both **1** and **2** could be derived from a divergent route stemming from the known *N*-benzyl piperidyl hydrazine **3**.[5] Condensation of this building block with appropriate regioisomeric dicarbonyls or related reagents followed by intramolecular *O*-alkylation would readily provide access to the desired scaffolds, primed for further analog synthesis (Fig. 2).

The synthesis of **1** is described in Scheme 1. Condensation of hydrazine **3** with 4-benzyloxy ethyl acetoacetate **4** under the various conditions tested gave only low yield of pyrazole **5**.[6] Hence, an alternative condensation was explored. Butynoate **6** was treated with **3** under mildly basic conditions to afford the conjugate adduct **7** in 90% yield.[7] Treatment of intermediate **7** under acidic conditions and microwave irradiation provided the corresponding intermediate pyrazole ester, which was used crude in the subsequent reduction step ($LiBH_4$, THF, 80 °C) to provide intermediate **8** in 65% yield after acidic methanolysis of the borate complex. One-pot *O*-tosylation and intramolecular S_N2 displacement promoted effective cycloetherification to provide spirocyclic scaffold **9** in 82% yield. Approaches relying on Mitsunobu conditions to promote

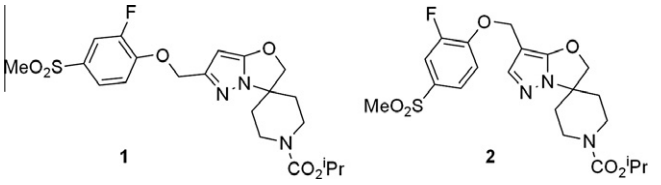

Figure 1. Targets **1** and **2** containing regioisomeric oxospiropyrazole piperidine scaffolds.

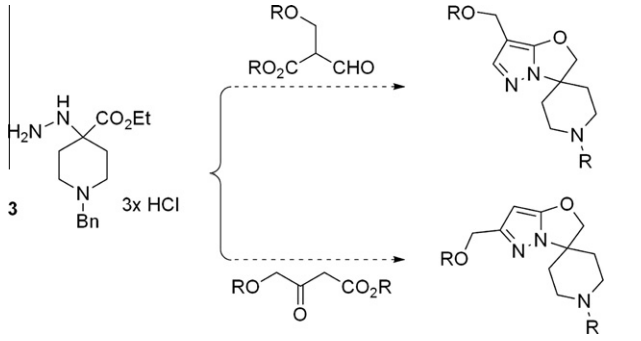

Figure 2. Hydrazine 3 as a common precursor to regioisomeric oxospiropyrazole scaffolds.

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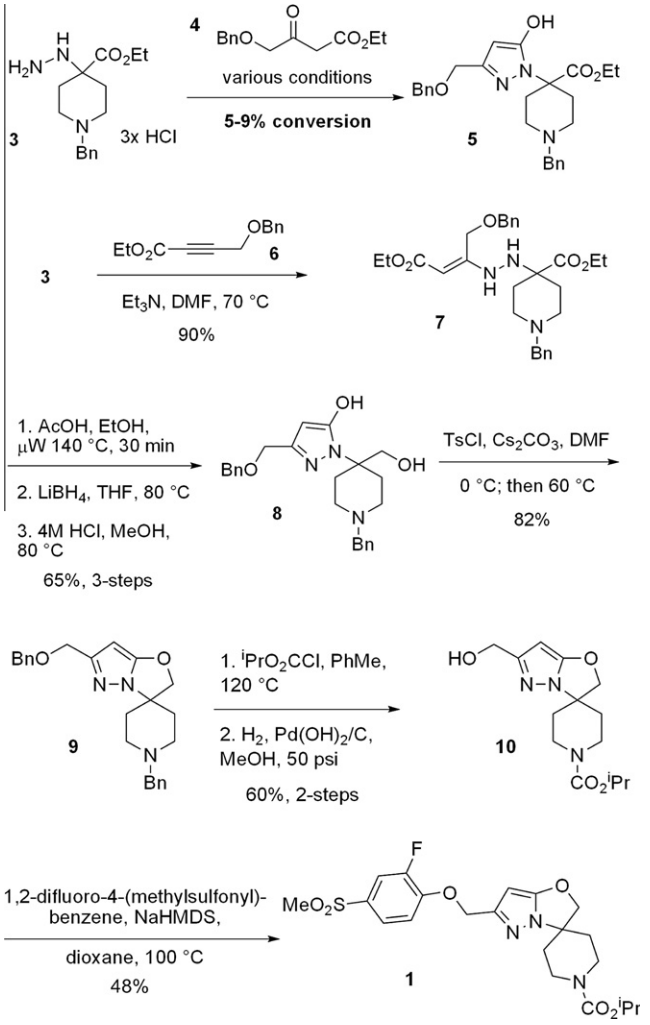
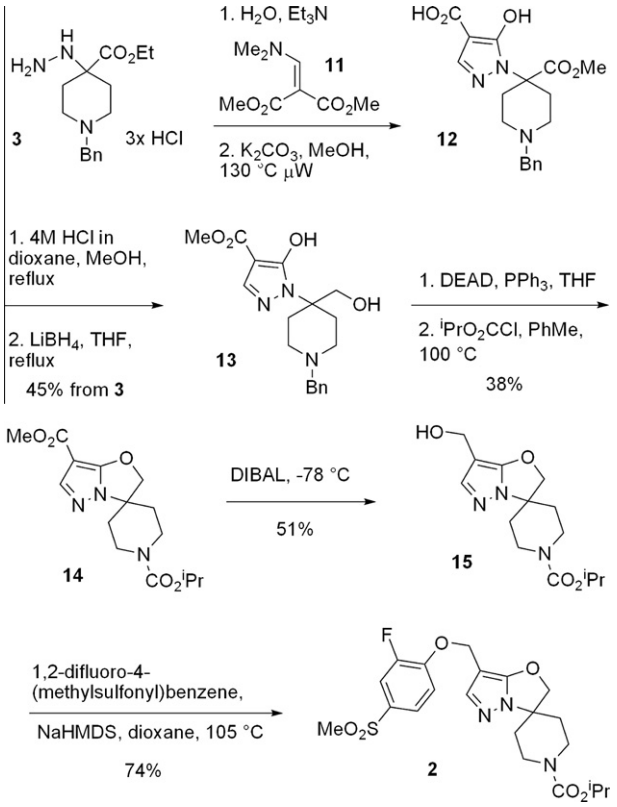


Scheme 1. Synthesis of oxospiropyrazole piperidine regioisomer **1**.



Scheme 2. Synthesis of oxospiropyrazole piperidine regioisomer **2**.

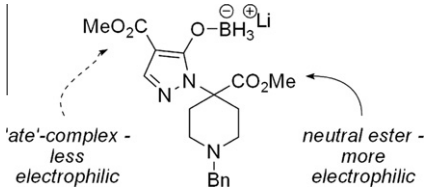


Figure 3. Possible origin of reduction selectivity.

cycloetherification proved ineffective presumably due to the relatively high pK_a of the hydroxypyrazole. Tandem deprotection of the *N*-benzyl group and isopropyl carbamate formation followed by catalytic hydrogenolysis of the benzyl ether proceeded uneventfully to afford the free primary alcohol **10** in 60% overall yield. The final target **1** was subsequently prepared in 48% yield via S_NAr of 1,2-difluoro-4-(methylsulfonyl)-benzene with the sodium alkoxide of **10** (unoptimized).[8]

The synthesis of **2** is described in Scheme 2. Condensation of **3** with malonyl alkylidene **11** proved sluggish under a variety of conditions; of those screened only microwave irradiation in basic methanol facilitated good conversion to intermediate **12** in which the pyrazole and piperidine esters had been, respectively, hydrolized and transesterified (Scheme 2).[9] Attempts to reduce the alkalinity of the reaction medium to afford direct access to the ester were unsuccessful, highlighting the crucial nature of a 4:1 base-to-reactant stoichiometry. As a result of these considerations, the requisite ester was reformed through a standard Fischer esterification (MeOH, HCl, dioxane). Reduction of this diester intermediate (excess $LiBH_4$, THF, reflux) proceeded with exclusive regiocontrol to produce **13** (45% yield from **3**). The preference for the complete regioselective reduction of the most hindered ester is believed to arise from the intervention of a boron-'ate' species involving the oxygen in C-5 of the pyrazole that renders the pyrazole ester in C-4 highly electron rich, and thus less reactive toward nucleophilic attack (Fig. 3).

In contrast to the regioisomer, exposure of **13** to standard Mitsunobu conditions resulted in rapid cycloetherification; the presence of the electron withdrawing ester likely modulates the hydroxypyrazole pK_a rendering it an effective nucleophile in this case. A one-pot N-debenzylation and isopropylcarbamate formation gave the desired product **14** in 38% overall yield from **13**. DIBAL-H was discovered to be an optimal reducing reagent for the preparation of spirocyclic scaffold **15**.[10] Scaffold **15** was easily converted into compound **2,** the regioisomer of compound **1**, via S_NAr of 1,2-difluoro-4-(methylsulfonyl)-benzene.[11]

Although structurally similar and nearly identical in Rf by thin layer chromatography (silica gel), **1** and **2** exhibited distinct characteristics. While oxospiropyrazole **1** was quite stable under

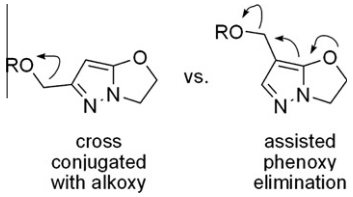


Figure 4. Potential explanation for differential stability of **1** and **2**.

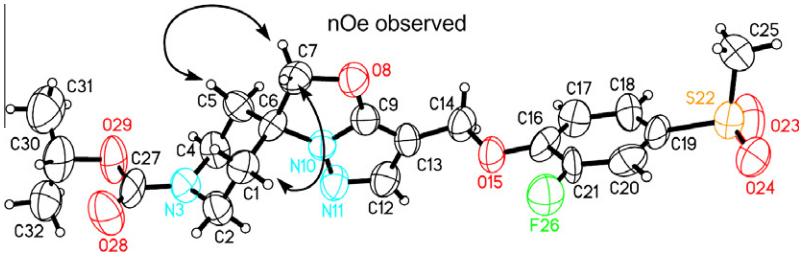


Figure 5. X-ray structure of **2** with observed NOEs indicated for axial and equatorial hydrogens.

typical workup and storage conditions, **2** proved to be quite sensitive to prolonged weak acid exposure (e.g., stirring in aq ammonium chloride, standing on silica oxide); decomposition of **2** led to recovery of **15** and the corresponding phenol.[12] It is, therefore, possible that resonance donation of the pyrazole nitrogen or alkoxy group assists in elimination of the phenoxide leaving group in the case of isomer **2**, while in isomer **1**, cross conjugation of the putative benzylic cation with either of these donating groups would reduce the likelihood of this decomposition pathway (Fig. 4).[13]

Single crystals of isomer **2** prepared by slow evaporation from ethyl acetate were obtained for X-ray diffraction analysis (Fig. 5). As pictured above, the solid state conformation of the piperidine places the pyrazole substituent in the axial position, while the methylene group is projected in the equatorial position; this is likely due to the restricted rotation around the pyrazole–piperidine C–N linkage that would be expected to dramatically reduce the effective steric bulk for this group thereby minimizing diaxial interactions in this conformer. Analysis of the NOESY spectra for **2** confirms that solution state conformation is identical to that observed in the solid state.

When evaluated in vitro at human GPR119, both compounds **1** and **2** proved inferior to other agonists profiled in our program. This result indicates that the conformation occupied by these constrained analogs is suboptimal when compared to more flexible variants, suggesting that they are not representative of the bioactive conformation.

In conclusion, we have described the synthesis and stability of two novel constrained regioisomeric oxospiropyrazole piperidine scaffolds. Although these compounds were not immediately suitable for continued pursuit within our lead discovery program, the work described around the preparation of these constrained spirocyclic scaffolds provided further information and understanding of the GPR119 pharmacophore. We also expect that these general synthetic strategies will find further application for other small molecule drug discovery programs.

Acknowledgments

We would like to thank Brian Samas for the generation of the X-ray structure for **2** and Geeta Yalamanchi for the NOESY spectra interpretation. We also thank Kevin Filipski and Dr. Michael Green for correction of the manuscript.

References and notes

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2. For general information regarding the GPR119 receptor as a therapeutic target, see: (a) Semple, G.; Fioravanti, B.; Pereira, G.; Calderon, I.; Uy, J.; Choi, K.; Xiong, Y.; Ren, A.; Morgan, M.; Dave, V.; Thomsen, W.; Unett, D. J.; Xing, C.; Bossie, S.; Carroll, C.; Chu, Z.-L.; Grottick, A. J.; Hauser, E. K.; Leonard, J.; Jones, R. M. *J. Med. Chem.* **2008**, *51*, 5172; (b) Shah, U. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 519; (c) Lauffer, L.; Iakoubov, R.; Brubaker, P. L. *Endocrinology* **2008**, *149*, 2035;.
3. For examples of known GPR119 agonists see: (a) Jones, R. M.; Leonard, J. N. *Annu. Rep. Med. Chem.* **2009**, *44*, 149; (b) Jones, R. M.; Leonard, J. N.; Buzard, D. J.; Lehmann, J. *Expert Opin. Ther. Patents* **2009**, *19*, 1339.
4. We were unable to find any closely related ring structures through substructure searches in the chemical literature.
5. Jenkins, S. M.; Wadsworth, H. J.; Bromidge, S.; Orlek, B. S.; Wyman, P. A.; Riley, G. J.; Hawkins, J. *J. Med. Chem.* **1992**, *35*, 2392.
6. *For example*: Et_3N (5 equiv), β-ketoester (1.2 equiv), EtOH (0.1 M), 70 °C, 16 h, conventional heating; Et_3N (5 equiv), β-ketoester (1.2 equiv), EtOH (0.1 M), 130 °C, 30 min, microwave heating; NaOAc (5 equiv), β-ketoester (1.2 equiv), EtOH (0.1 M), 70 °C, 16 h, conventional heating; NaOAc (5 equiv), β-ketoester (1.2 equiv), EtOH (0.1 M), 130 °C, 30 min, microwave heating; Et_3N (5 equiv), β-ketoester (1.2 equiv), EtOH (0.5 M), 70 °C, 16 h, conventional heating; NaOAc (5 equiv), β-ketoester (1.2 equiv), EtOH (1 M), 70 °C, 16 h, conventional heating.
7. For the preparation of **6** see: Marmsaeter, F. P.; Vanecko, J. A.; West, F. G. *Org. Lett.* **2004**, *6*, 1657.
8. *Spectral data for* **1**: ^{1}H NMR (chloroform-d, 500 MHz): δ (ppm) 7.65–7.69 (m, 2H) 7.32 (t, J = 7.80 Hz, 1H), 5.51 (s, 1H), 5.13 (s, 2H), 4.96 (septet, J = 6.10 Hz, 1 H), 4.75 (s, 2H), 3.93–3.98 (m, 2H), 3.50–3.60 (m, 2H), 3.05 (s, 3H), 2.05–2.15 (m, 2H), 1.75–1.85 (m, 2H), 1.28 (d, J = 6.35 Hz, 6H); MS (M+1): 468.0.
9. Although treatment with ethyl ethoxymethylene-malonate for extended reaction times (~24–48 h) in refluxing EtOH with potassium carbonate gave reasonable conversions, the reaction could not be driven to completion without the increased formation of the carboxylic acid. The presence of base was absolutely necessary for the reaction to proceed. Overall, the use of the described procedure afforded rapid conversion to the acid, which immediately recrystallized out of the reaction medium with cooling and could be recovered conveniently by filtration. It appears as if hydrolysis only occurs at the heteroaryl ester while transesterification only occurs at the alkyl ester.
10. Careful control of reaction stoichiometry was necessary to prevent reduction of the carbamate to the *N*-methyl piperidine. This consideration led to suboptimal yields of the desired alcohol.
11. *Spectral data for* **2**: ^{1}H NMR (chloroform-d, 500 MHz): δ (ppm) 7.70 (d, J = 8.8 Hz, 1H), 7.65 (dd, J = 10.0, 2.2 Hz, 1H), 7.46 (s, 1H), 7.20 (t, J = 8.2 Hz, 1H), 4.99 (s, 2H), 4.92–4.98 (m, 1H), 4.81 (s, 2H), 3.91 (ddd, J = 13.2, 8.8, 3.7 Hz, 2H), 3.61 (br s, 2H), 3.05 (s, 3H), 2.06–2.14 (m, 2H), 1.78–1.88 (m, 2H), 1.27 (s, 3H), 1.26 (s, 3H); MS (M+1): 468.0.
12. An NMR sample of **2** was left for >5 d at ambient temperature in DMSO-d_6 and very little decomposition was observed. It therefore appears very likely that weak acid is a critical component of the decomposition.
13. The authors thank the editors for noting that resonance donation of the pyrazole nitrogen lone pair would also be expected to behave analogously to the ether participation invoked in Figure 4 and that in all likelihood it is a combination of both donating groups that results in this instability.