Preparation of new sp³ Quinolone Isosteres

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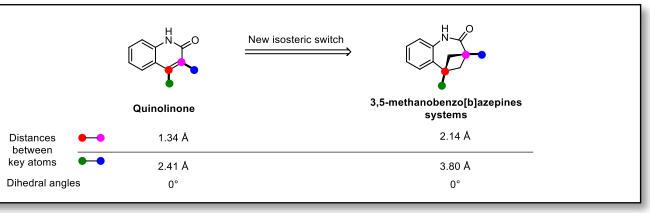
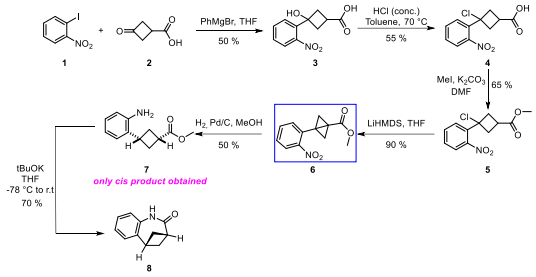
Introduction

The construction of novel scaffolds through design and synthesis constitutes a critical role for organic chemists in the drug discovery process. In line with these goals, our group continue to expand the collection of isosteres available by exploring new chemical space while following the mantra **'escape from flatland'**. With this approach in mind, we turned our focus to the quinoline and more precisely the quinolone systems because of their ubiquity in medicinal chemistry (Quinine, Chloroquine, Ciprofloxacin,...). The drawback of these scaffolds being their overall planarity, we aim for a gain of sp^3 character in order to improve solubility and reduced π-stacking.



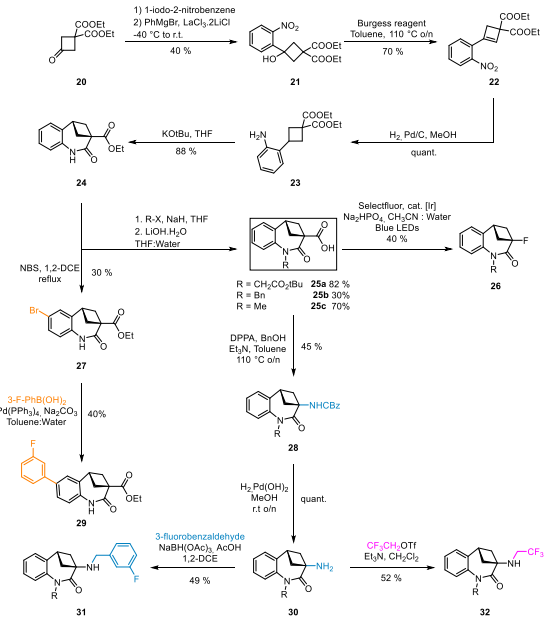
Synthesis of the scaffold

Successful application of bicyclo[1.1.0]butane as cis-cyclobutyl precursor towards the synthesis of (**8**):

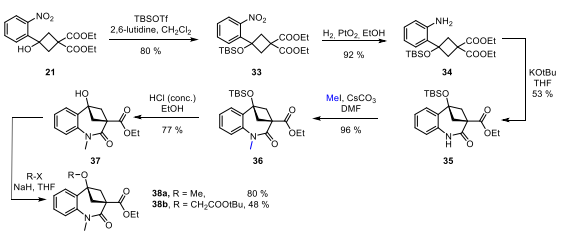


Scaffold functionalization

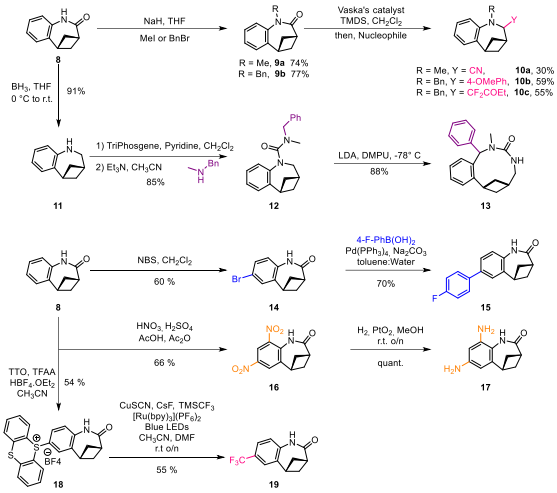
- New synthetic route to access position 3 of the system:



- Taking advantage of the first intermediate (**21**) to access position 5:

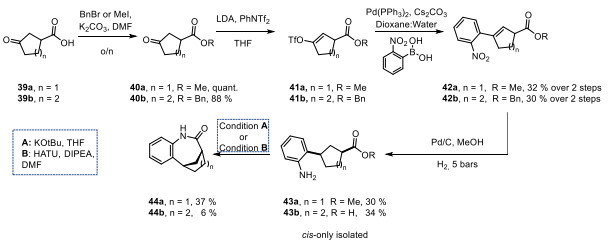


Chemical diversification



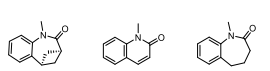
Syntheses of ring-enlarged systems:

The synthetic route had to be adapted to include larger ring-sizes:



Physico-chemical properties: aqueous solubility

The aqueous solubility of the proposed isostere has been compared (using the Beer-Lambert Law) to quinolone **46** and azepine **47**:



Compound	45	46	47
Solubilty (M)	0.145	0.071	0.073

Gratifyingly, the proposed moiety presents a twice enhanced aqueous solubility at pH = 7 and that represents a great starting point to pursue with evaluation of other physico-chemical properties.

Conclusion

To conclude, a novel isostere of quinolone has effectively been synthetized and diversified. Our approach is offering the functionalization of most of the atoms of the system. The initial strategy using bicyclo[1.1.0]butane as a key intermediate for *cis* cyclobutane proved to be successful. An array of methodologies could readily be applied to our system. It ultimately proved the versatility of our new scaffold, enabling the possibility of integrating it in med-chem like structures. The aqueous solubility of the proposed system is twice enhanced to related analogues, which is encouraging for further works.