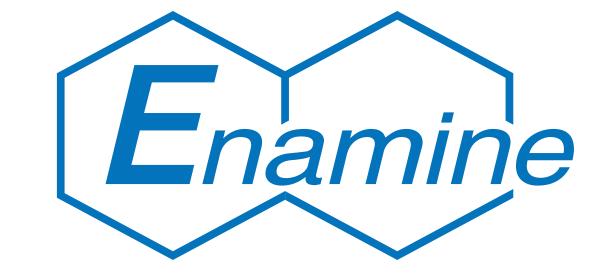
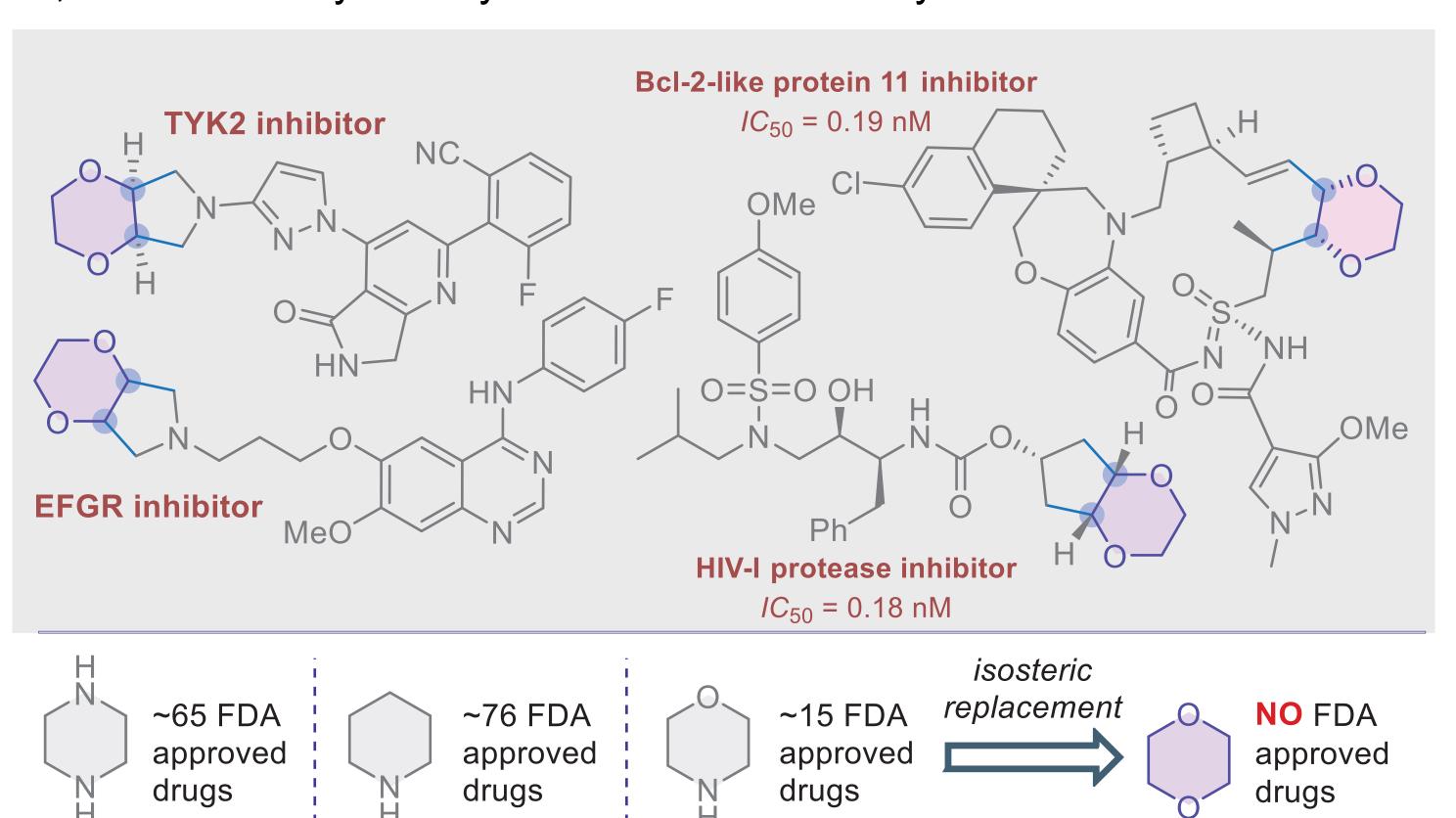
Diastereoselective synthesis of 2,3-disubstituted 1,4-dioxanes



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Background of the project

- 1,4-dioxane moiety is an integral part of several reported bioactive molecules demonstrating antiviral and anticancer properties
- wide application of the core in MedChem projects is currently limited by commercial availability and synthetic protocols often offering either symmetric 1,4-dioxanes only or unsymmetric ones with low yield.



Pool of commercially available 2,3-substituted functionalized 1,4-dioxanes

Route to key dioxane building blocks

OBJECT IN FOCUS: a concise route to 2,3-disubstituted functionalized dioxanes exploiting readily available commercial substances

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Diversity of products supplied by the synthetic strategy

• the protocol toward 1,4-dioxenes works well for anhydrides with alkyl, aryl, and organofluorine substituents

 there is room for further expanding the scope of the reaction due to the synthetic and commercial availability of the starting compounds

- dehydrodioxanes were efficiently reduced by catalytic hydrogenation (H2 100 atm., 20% Pd(OH)2/C, 100°C) with almost quantitative yields
- exclusive formation of products with formal cis-configuration was confirmed by 2D NMR.
- further acidic hydrolysis yielded carboxylic acids with no inversion of the configuration or ring-opening by-products observed
- no additional purification was required at these steps, except for CHF2-substituted compounds.

Further functionalization of the constructed dioxanes

- chemical and stereochemical stability of the core was proven during amidation, dehydration, and Grignard synthesis
- a set of non-symmetrical MedChem-relevant 1,4-dioxane-based building blocks, including amides, amines, and ketones was obtained
- currently, we are expanding the range of 1,4-dioxanes bearing a functionalized fragment in position 2 and various substituents in position 3 or 2,3-bifunctional counterparts, including organofluorine building blocks