4,5,6,7-Tetrahydropyrazolo[1,5-a]pyrazine: Lead-oriented scaffold with three diversity points

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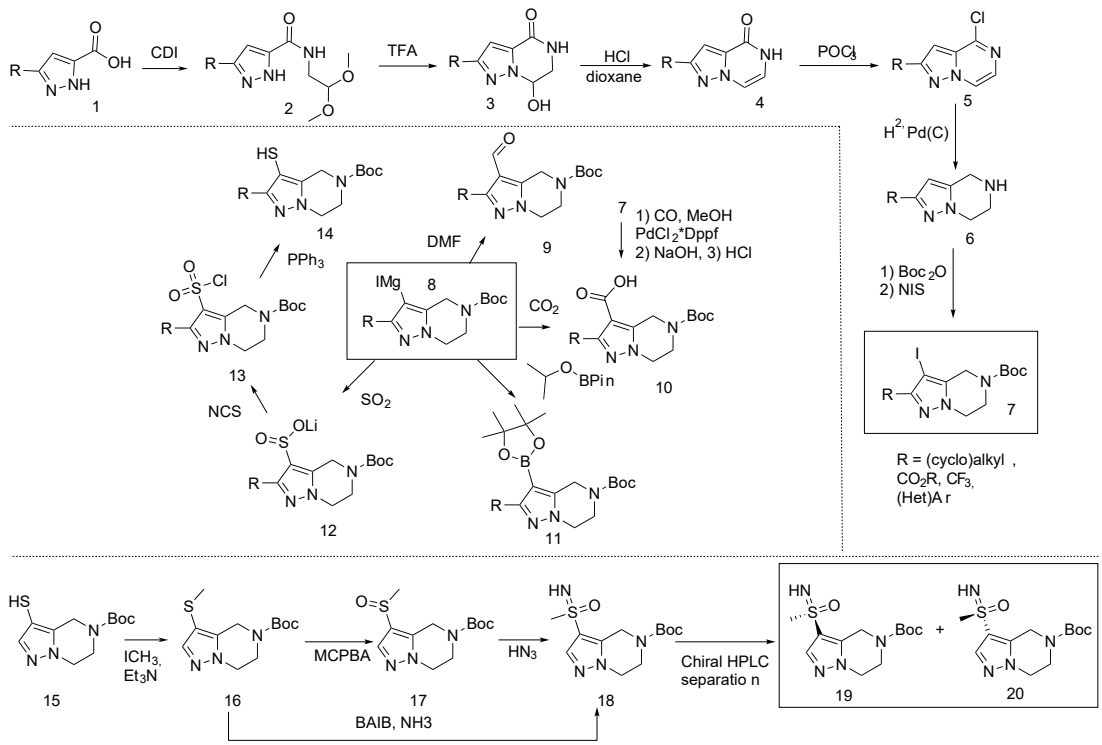
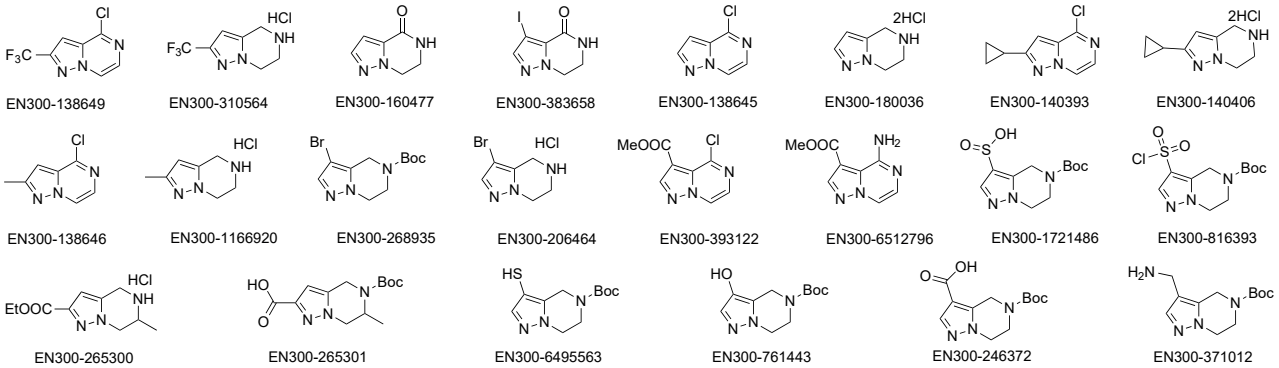
Introduction and Aim

The quest for lead-oriented synthesis proposed by medicinal chemists from GSK in early 2010s have prompted for design and study of low-molecular-weight, hydrophilic, conformationally restricted and sp3-enriched molecular scaffolds. This trend led to the creation of the criteria for the building blocks design in 2015 by AstraZeneca co-workers. The 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazines bearing orthogonally protected functional groups meet the above mentioned criteria and was highlighted in the paper of AstraZeneca. In spite of plenty papers and patents which described synthetic approaches to the scaffold, the convenient, flexible and appropriate for easy scale up approach is still needed. As a part of our ongoing efforts on a design and synthesis of advanced building blocks for the medicinal chemistry, we have turned our attention to tetrahydropyrazolo[1,5-a]pyrazines. The new approach towards multigram preparation of these compounds was developed based on commercially available substituted 1H-pyrazole-5-carboxylic acids **1**. The assembling of the unsaturated pyrazine ring with subsequent catalytic hydrogenation leads to desired building blocks having one functional amino group **6**. The following iodation of the Boc-derivatives with NIS led to iodinated derivatives **7**, which rapidly transmetallated with *i*-PrMgCl, forming the corresponding Grignard reagent **8** able to transformation into wide range of additional functional groups such COOH, CHO, SO_2Na, BPin and SO_2Cl. Also the carbonylation of the corresponding iodides **7** with CO in the presence of $Pd(dppf)Cl_2$ leads carbonyl derivatives **10**, which have been performed with better yields. Taking into account the new trend of the using of sulfenylimines in MedChem, the corresponding thiol **15** was converted to the compound **18** with imino-group for further functionalization. Also the conditions for the separation of racemic compound **18** to both enantiomers by chiral HPLC were found.

Synthesis & Functionalizations



Results



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