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Chiral Amino-Tetrahydroindazoles: Synthesis and Applications

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A short survey of literature data shows a vivid renaissance in the field of substituted tetrahydroindazoles (THIs). Thus, compounds containing the latter scaffold were very recently reported to be useful corticotropin releasing factor (CRF) receptor antagonists.[1] Down-regulation of increased endogenous levels of CRF is applicable in the treatment of several gastrointestinal disorders, major depressive disorders, and dementia of Alzheimer's type. Cognitive abilities can be improved also by tetrahydroindazolones.[2] The same type of compounds possess also antitumor activity while being less toxic than other available antitumor drugs. Additionally, novel THI-based antituberculosis agents have been reported.[3]

Chiral resolution of amino-THIs is achieved via salt formation with either *O,O'*-dibenzoyl tartaric acid or camphoric acid. Transformation of enantiomerically enriched amino-THIs in corresponding azides proceeds with no erosion of their ee's. Comparison of X-ray structures of the racemic and enantiopure forms of 7-amino-THIs explain the rather large melting point differences between the both series.[4] Enantiopure azides obtained from the aforementioned amines are employed in copper-catalyzed Huisgen 1,3-dipolar cycloaddition reactions with various alkynes. The use of enantiomerically enriched THI scaffolds is demonstrated by preparation of diastereomerically pure products (e.g. **1** and **2**, Fig.1) when the former are conjugated with alkynes arising from natural sources.

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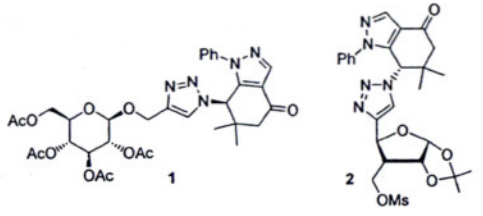

Fig.1 Examples of diastereomerically pure tetrahydroindazole-carbohydrate conjugates