

Condensed chiral heterocycles: Stereochemistry and activity

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Abstract

The majority (~80%) of secondary metabolites are chiral and they occur as a single enantiomer containing five stereogenic elements in average. More than half of all the new approved drugs in the period 1981-2014 were derived directly or indirectly from natural products and the distribution of chiral drugs has increased from 30-40% in the 1990s to above 60% in the 2000s. In order to aid exploring the stereochemistry-activity and structure-activity relationship in natural products, the relative and absolute configuration of bioactive natural products have been determined by the combination of electronic (ECD) and vibrational circular dichroism (VCD), optical rotation (OR) and NMR measurements and quantum mechanical calculations. The potential of this approach is demonstrated on the examples of several complex natural products containing isolated blocks of stereogenic elements, e.g. both axial and central chirality or existing as stereoisomeric mixtures, which requires the combination of different approaches to differentiate more than two stereoisomers. For the efficient synthesis of molecular libraries consisting of condensed chiral O- and O,N-heterocycles with 4-6 rings, the scope of Knoevenagel-cyclization domino reactions is presented, which can afford novel complex skeletons from fairly simple starting materials in step- and atom-economic transformations. Different mechanisms of domino sequences such as Knoevenagel-intramolecular hetero Diels-Alder (IMHDA), Knoevenagel-[1,5]-hydride shift-cyclization, Knoevenagel-[2+2] cycloaddition or Knoevenagel-Diels-Alder reactions are applied and explored to afford versatile condensed bioactive heterocycles. New multistep domino reactions are identified to increase the diversity of the compound library. Structure-activity and stereochemistry-activity relationships are studied in relation with antiproliferative, neuroprotective and protein tyrosine phosphatase 1B (PTP1B) inhibitory activity.

Biography

Tibor Kurtán, professor of chemistry, head of the Department of Organic Chemistry at the University of Debrecen. His research interests focus on the synthesis, stereochemical and chiroptical studies of O- and O,N-heterocycles and natural products with potential pharmacological activities. He developed a solid-state TDDFT-ECD method for the stereochemical analysis of natural and synthetic derivatives and established general ECD rules for the configurational assignment of heterocycles. He is author of over 170 papers and two book chapters with over 2100 independent citations. He was the recipient of several awards, including the George Oláh Award of the Hungarian Academy of Sciences.

Publications

1. Azacoccones F-H, new flavipin-derived alkaloids from an endophytic fungus *Epicoccum nigrum* MK214079
2. An optically active isochroman-2H-chromene conjugate potently suppresses neuronal oxidative injuries associated with the PI3K/Akt and MAPK signaling pathways
3. Determination of the Absolute Configuration of Super-Carbon-Chain Compounds by a Combined Chemical, Spectroscopic, and Computational Approach: Gibbosols A and B
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5. Alternarin A, a Drimane Meroterpenoid, Suppresses Neuronal Excitability from the Coral-Associated Fungi *Alternaria* sp. ZH-15
6. Correction to Pigments of the Moss *Paraleucobryum longifolium* : Isolation and Structure Elucidation of Prenyl-Substituted 8,8'-Linked 9,10-Phenanthrenequinone Dimers
7. [1,5]-Hydride Shift-Cyclization versus C(sp²)-H Functionalization in the Knoevenagel-Cyclization Domino Reactions of 1,4- and 1,5-Benzoxazepines
8. Isolation and identification of sapotexanthin 5,6-epoxide and 5,8-epoxide from red mamey (*Pouteria sapota*)
9. Furoic acid derivatives from the endophytic fungus *Coniothyrium* sp
10. Synthesis and antiproliferative activity of 6-naphthylpterocarpanes

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