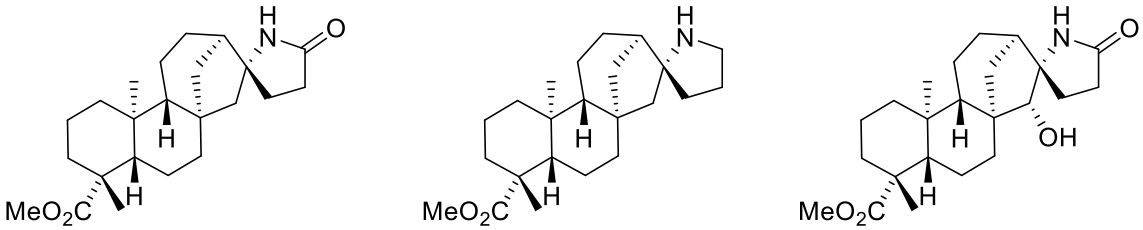
Preparation of Antiproliferative Terpene-Alkaloid Hybrids of *ent*-Kauranic Derivatives

Elena Pruteanu[1,2], Vladilena Gîrbu[1], Nicon Ungur[1], Leentje Persoons[3], Dirk Daelemans[3], Philippe Renaud[2], Veaceslav Kulciţki[1]

[1]Institute of Chemistry (MECC), Str. Academiei, 3, MD-2028 Chișinău, Moldova
[2]Department of Chemistry, Biochemistry and Pharmaceutical Sciences, University of Bern, Freiestrasse 3, 3012 Bern, Switzerland
[3]KU Leuven, Department of Microbiology, Immunology and Transplantation, Laboratory of Virology and Chemotherapy, Rega Institute for Medical Research, Herestraat 49, 3000 Leuven, Belgium
elena.pruteanu@unibe.ch

A convenient strategy for molecular editing of available *ent*-kauranic natural scaffolds has been developed based on radical mediated C–C bond formation [1]. Free radical modifications represent an ideal tool for molecular editing within SAR studies of complex molecules. The kauranic family of diterpenes [2,3] is widespread in diverse plant sources. Some representatives are readily available of large-scale processing. The most known examples of the diterpene family are: *ent*-kaurenoic acid and steviol, which can be conveniently isolated from industrial crop derived products or residues.



$IC_{50\ min}$ 0.8±0.2 μM
SI_{max} 9.5
(for colorectal carcinoma)

$IC_{50\ min}$ 1.0±0.1 μM
SI_{max} 32.2
(for lung carcinoma)

$IC_{50\ min}$ 1.9±0.2 μM
SI_{max} 14.6
(for lung carcinoma)

Scheme 1. Selected examples with relevant cytotoxic activity parameters

The described processes resulted in a small library of new compounds with modified *ent*-kaurane skeletons. The cytotoxic activity of newly formed products has been investigated. Some of the examples showed relevant biological activity, which was demonstrated by *in vitro* cytotoxicity tests on several tumor cell lines (eg: NCI-H460 (lung carcinoma), HCT-116 (colorectal carcinoma), K-562 (chronic myeloid leukemia) and others). The hybrid terpene-nitrogen containing heterocycles with unprecedented spiro-junction (Scheme 1.) have shown relevant cytotoxicity and promising selectivity indexes. These results represent a solid basis for following research on the synthesis of such derivatives based on available natural product templates

[1] For this work: E. Pruteanu, et.all. *Molecules*, **2021**, 26, 4549.
[2] E. Kataev, R.N. Khaybullin, R.R. Sharipova, I.Y. Strobykina, *Rev. J. Chem*. **2011**, 1, 93–160.
[3] L. Wang, D. Li, C. Wang, Y. Zhang, J. Xu, *Mini Rev. Med. Chem*. **2011**, 11, 910–919.