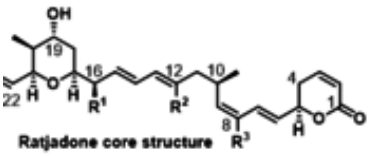
Technology Offer

# Novel Ratjadones as payloads in folate-, peptide-, and antibody-drug conjugates for the treatment of cancer

Reference Number 02-00350

## Challenge

Cancer is an extremely complex disease with a multitude of different origins as well as forms of occurrence in various human tissues. The high heterogeneity of tumors often causes cancer relapse after putatively successful chemotherapeutic treatment. Furthermore, tumors not responding to established single- or multi-drug administration are still a big challenge in cancer therapy.
In order to be able to attack cancer cells individually and specifically, extracellular targeted carrier-drug conjugates (EDCs) have been established as a new approach for a selective treatment of cancer. Such EDCs comprise a highly cytotoxic drug attached via an intracellular cleavable linker to a carrier molecule with a high affinity for a target overexpressed specifically on the surface of cancer cells. Thus, the EDC can be selectively directed to the tumor where the toxic payload is taken up by the cancer cells via endocytosis resulting in the apoptosis of the respective cells.




*Ratjadone core structure*

## Technology

Ratjadones are polyketidic natural products produced by the myxobacterium *Sorangium cellulosum*. These small molecules have been found to be highly potent anti-proliferative agents showing sub-nanomolar $IC_{50}$ values for the growth inhibition of several cancer cell lines. Their anti-proliferative activity is based on the covalent inhibition of Crm1, an evolutionary highly conserved protein, which is responsible for the nuclear export of several proteins as well as mRNA into the cytoplasm. The inactivation of Crm1 leads to a major inhibition of central cellular functions and finally to cell death. This so far under-investigated mode of action renders ratjadones highly interesting for the development of targeted anti-cancer drugs.
The synthesized derivatives of ratjadone A present different functionalities such as ketones, amino groups, terminal alkynes, cyclooctyne moieties or reactive disulfides, which allow bio-orthogonal or orthogonal coupling to biologically active carrier molecules (e.g. folates, peptides, antibodies). Therefore, these compounds enable the development and construction of EDCs using ratjadone derivatives as cytotoxic payloads with a new mode of action for the targeted therapy of cancer.

## Commercial Opportunity

The technology is offered for in-licensing and/or co-development.

## Development Status

Proof of principle was obtained in different cancer cell lines. A reliable and scalable access to the natural product is given.

## Patent Situation

A European priority application was filed in August 2017 (EP17185598.4), an international application was filed in August 2018 (WO/2019/030284).

## Further Reading

Klahn, Philipp & Fetz, Verena & Ritter, Antje & Collisi, Wera & Hinkelmann, Bettina & Arnold, Tatjana & Tegge, Werner & Rox, Katharina & Hüttel, Stephan & I. Mohr, Kathrin & Wink, Joachim & Stadler, Marc & Wissing, Josef & Jänsch, Lothar & Brönstrup, Mark. (2019). The Nuclear Export Inhibitor Aminoratjadone is a Potent Effector in Extracellular-Targeted Drug Conjugates. Chemical Science. 10.1039/C8SC05542D.

HZI HELMHOLTZ Centre for infection research

**Licensing Contact:**
Dr Sabina Heim
Senior Technology Manager
T: +49 531 618120-90
heim@ascenion.de

**Ascenion GmbH**
Herzogstraße 64
D-80803 München
T: +49 89 318814-0
info@ascenion.de
www.ascenion.de