Research Group Medicinal Chemistry

Leibniz-Forschungsinstitut für Molekulare Pharmakologie

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The medicinal chemistry group optimizes small molecule hits emerging from screening or from rational drug design approaches by iterative chemical optimization cycles, consisting of molecular modeling, chemical synthesis and biological testing.

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THE PEOPLE

THE PROJECTS

Specifc inhibition of clathrin-mediated endocytosis...

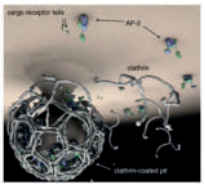
André Horatscheck, Haydar Bulut, Sandra Miksche, Mark J Robertson, Lisa von Kleist, Andreas Oder, Adam McCluskey, Jens Peter von Kries, Volker Haucke, Marc Nazaré

...by disruption of clathrin-endocytic protein interactions with Pitstop derivatives

Background: Clathrin-mediated endocytosis (CME) regulates many key physiological processes for the internalization of growth factors and receptors, entry of pathogens (e. g. HIV-1), and synaptic transmission by formation of so-called 'clathrin-coated vesicles'.

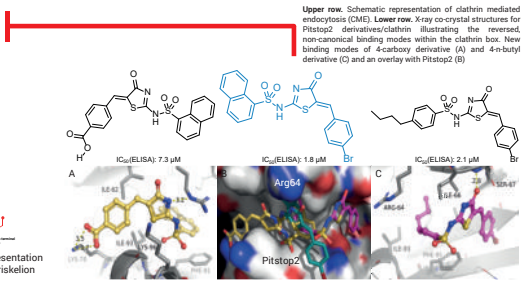
Approach: An ELISA-based high-throughput screen (HTS) using the 17K ChemBioNet library resulted in the identification of Pitstop compounds that inhibit complex formation between the clathrin terminal domain (TD) and amphiphysin B. We synthesized focused libraries of around 150 compounds, providing a first SAR.

Results: X-ray co-crystallization gave insight into the key interactions between these Pitstop ligands and the clathrin TD. Surprisingly, six nearly equipotent inhibitors showed four different binding modes. These non-canonical binding modes of the novel Pitstop analogues revealed the structural basis for the disruption of clathrin TD endocytic protein interactions.



Cryo-electron microscopy image of a clathrin-coated vesicle

Schematic representation of a clathrin triskelion



Upper row. Schematic representation of clathrin mediated endocytosis (CME). **Lower row.** X-ray co-crystal structures for Pitstop2 derivatives/clathrin illustrating the reversed, non-canonical binding modes within the clathrin box. New binding modes of 4-carboxy derivative (A) and 4-n-butyl derivative (C) and an overlay with Pitstop2 (B)

Discovery and Optimization...

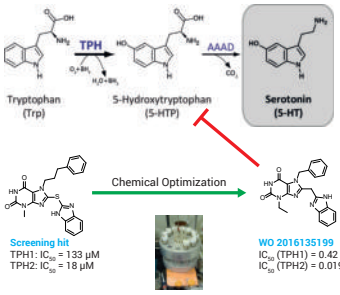
Edgar Specker, Susann Matthes, Anja Schütz, Martin Neuenschwander, Udo Heinemann, Jens von Kries, Michael Bader, Marc Nazaré

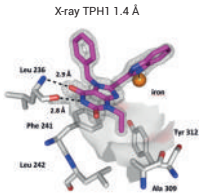
...of Tryptophan hydroxylase (TPH) inhibitors

Background: Serotonin [5-hydroxytryptamine (5-HT)] is causally involved in multiple aspects of mood control in the central nervous system. In peripheral tissues, serotonin regulates vascular tone, gut motility, primary hemostasis, and cell-mediated immune responses, and is associated with diseases like irritable bowel syndrome and carcinoid syndrome.

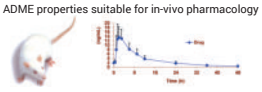
Approach: The biosynthesis of serotonin is a highly regulated two-step process, starting with the essential amino acid L-tryptophan (Trp), while tryptophan hydroxylase (TPH) is the initial and rate-limiting enzyme in the biosynthesis of serotonin.

Results: We have identified and further developed highly active TPH inhibitors that are able to modulate physiological serotonin levels. The X-ray co-crystal structures obtained with our inhibitors allowed us to elucidate the binding mode and to reveal the structural determinants for for efficient protein-ligand interaction. Several inhibitors are currently undergoing in vivo efficacy studies in mice.





ADME properties suitable for in-vivo pharmacology



THE EQUIPMENT

- *Kiwi Store (LiCONiC AG) automated compound store and FreedomEvo Tecan, pipetting workstation*
- *LCMS- SQ and LCMS-TOF*
- *NMR Bruker AV300 and AV600*
- *Automated purification prep HPLC and*
- *Biotage systems*
- *Rayonet photoreactor*
- *Microwave Biotage Initiator*
- *Parallel synthesis equipment*
- *Mnova NMR software, Reaxys database, Chemaxxon, Pipeline-Pilot, MOE and PyMol software.*

THE MEDCHEM

The chemical tools of interest cover a broad range of applications from modulation of protein-ligand and protein-protein interactions, SAR studies, labeling studies for target deconvolution, and in-vivo proof of concept studies.

Each research project is guided by at least one of the following principles:

- New chemical structures of the small molecule modulator
- New unexplored mechanisms of action for a given biological protein target
- New unexplored biological targets or pharmacological applications/ therapeutic concept

- Hit optimization is enabled by state-of-the-art laboratory equipment for solution-phase chemistry, parallel synthesis and automated purification systems
- Rescaffolding, fragment-based approaches and structure-based design by computer modeling and X-ray crystallography
- Compound management of a 66.000 Drug-Like Small Molecule Library
- Co-localized support and collaboration at FMP: Screening Unit, FMP, Jens Peter von Kries and Drug Design group, FMP, Ronald Kühne.

Collaborations (academic/industrial):

international: Uwe Grether, F.Hoffmann-La Roche, Basel, Switzerland; Haiyu Hu, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College; Stefan Krauss, University Hospital, Oslo, Norway;

national: Michael Bader, MDC, Berlin; Walter Birchmeier, MDC, Berlin; Udo Heinemann, MDC, Berlin; Hans-Jürgen Holdt, University of Potsdam, Potsdam; Christoph Rademacher, MPI, Potsdam; K. Lenhard Rudolph, FLI, Jena; Claus Scheidereit, MDC, Berlin; David W. Will, EMBL, Heidelberg

Networks:

Helmholtz Drug Research, ChemBioNet, Berlin-Institute of Health

THE FUTURE

Capacity:
2-3
EU-OPENSCREEN chemical tool optimization projects

THE OUTPUT

1. Ruess, D. A.; Heynen, G. J.; Ciecielski, K. J.; Ai, J.; Berninger, A.; Kabacaoglu, D.; Görgülü, K.; Dantes, Z.; Wörmann, S. M.; Diakopoulus, K. N.; Karpathaki, M. K.; Kowalska, M.; Kaya-Aksoy; E.; Song, L.; Zeeuw van der Laan, E. A.; López-Alberca, M. P.; Nazaré, M.; Reichert, M.; Saur, D.; Erkan, M. M.; Hopt, U. T.; Sainz Jr, B.; Birchmeier, W.; Schmid, R. M.; Lesina, M.; Algül, H. Mutant KRAS-driven cancers depend on PTPN11/SHP2 phosphatase. Nat. Med. 2018, 24, 954-960.
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4. Anumala, U. R.; Waaler, J.; Nkizinkiko, Y.; Ignatev, A.; Lazarow, K.; Lindemann, P.; Olsen, P. A.; Murthy, S.; Obaji, E.; Majouga, A. G.; Leonov, S.; von Kries, J. P.; Lehtiö, L.; Krauss, S.; Nazaré, M. Discovery of a Novel Series of Tankyrase Inhibitors by a Hybridization Approach. J. Med. Chem. 2017, 60, 10013-10025.
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7. Kozian, D. H.; von Haeften, E.; Joho, S.; Czechtizky, W.; Anumala, U. R.; Roux, P.; Dudda, A.; Evers, A.; Nazare, M.; Modulation of Hexadecyl-LPA-Mediated Activation of Mast Cells and Microglia by a Chemical Probe for LPA5. ChemBioChem 2016, 17, 861-865.
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9. Hu, H.-Y.; Lim, N.-H.; Juretschke, H.-P.; Ding-Pfennigdorff, D.; Florian, P.; Kohlmann, M.; Kandira, A.; Peter von Kries, J.; Saas, J.; Rudolphi, K. A.; Wendt, K. U.; Nagase, H.; Plettenburg, O.; Nazare, M.; Schultz, C.; In vivo visualization of osteoarthritic hypertrophic lesions. Chem.Sci. 2015, 6, 6256-6261.

Patents:

1- Krauss, S.; Nazare, M.; Anumala, U. R.; Lehtio, L.; Waaler, J.; Holsworth, D.; Wegert, A.; Leenders, R. G. G. Preparation of triazole derivatives as tankyrase inhibitors useful in treatment and prevention of diseases. WO 2018118868, 2- Scheidereit, C.; Willenbrock, M.; Lindemann, P.; Radetzki, S.; Von Kries, J. P.; Nazare, M.; Preparation of polycyclic nitrogen heterocycles as selective inhibitors of genotoxic stress-induced IKK/NF-kB pathways for the treatment of diseases. WO 2018087389, 3- Bader, M.; Specker, E.; Matthes, S.; Schuetz, A.; Mallow, K.; Grohmann, M.; Nazaré, M. Xanthine derivatives, their use as a medicament, and pharmaceutical preparations comprising the same. WO 2016135199, 4- Hu, H.-Y.; Nazaré, M.; Han Lim, N.; Ding-Pfennigdorff, D.; Plettenburg, O.; Ritzeler, O; Juretschke, H.-P.; Saas, J.; Bartnik, E.; Florian, P.; Wendt, U.; Schultz, C.; Nagase, H. DOTAM derivatives for therapeutic use. WO 2015075699

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