Drug Discovery Engine DDE based on natural products

INS, ISAS, MPI-Do, WTZ, LDC, **Taros Chemicals**

Ministerium für Innovation, Wissenschaft und Forschung des Landes Nordrhein-Westfalen

EUROPÄISCHE UNION
Investition in unsere Zukunft
Europäischer Fonds für regionale Entwicklung

Abstract

Abstract

The "NRW Drug Discovery Engine DDE based on natural products" aims to discover innovative drug candidates with therapeutic potential for cancer or metabolic diseases by medicinal chemistry optimization of hits towards preclinical candidates and validation of these candidates. The basis of this project was a collection of natural products with associated biological activity data compiled in the IMD BIOPROFILING® database.

A team of experienced experts (INS, LDC) selected promising target-compound combinations with potential applications in the treatment of cancer and metabolic diseases from the IMD BIOPROFILING database. This database contained more than 12 million data points for structures of chemical compounds with associated activity data. Biological assays for multiple cancer and metabolic targets were established and used to validate initial hits. These assays provided also the basis for further SAR studies and med-chem optimization. Significant efforts were invested in mechanistic studies to further validate or de-validate initial hits. In order to identify the most promising hit-target combinations the consortium employed synthesis of chemical analogs (Taros, LDC), proteomic analysis (ISAS) and functional analysis of cellular hits (MPI-Do, LDC, WTZ).

TAROS CHEMICALS ROLE IN DDE: SYNTHETIC PARTNER

- **HIT VALIDATION: synthesis of reference compounds (known biological activity) for the corresponding target. Proof of concept.**
- **HIT TO LEAD: synthesis of analogues based on structural and biological parameters.**
- **BIO-ASSAYS "IN VIVO": synthesis of compounds in bigger scales.**
- **LEAD OPTIMISATION: synthesis of analogues based on the results of biological assays. Modulation of the activity by modification of the structure (SAR).**

SYNTHESIS OF INHIBITORS FOR SPECIFIC TARGETS

CDC25 ← TAROS → HiF1α

↓

STEROID SULFATASE

WORK-FLOW DIAGRAMM: ITERATIVE WORKING PROCESS

TAROS

Synthesis of reference compounds and new analogues for bio-assays.

synthesis → Bio-assays

Proposal of new compounds based on the results from bio-assays.

Lead Discovery Center LDC

About Taros Chemicals

Taros, an independent and privately owned contract research company based in Dortmund, Germany, has been serving the needs of pharmaceutical, chemical, agrochemical and biotech companies since 1999. More than 8.000 synthesis, research and process chemistry projects have successfully been delivered to the ever growing global customer base. Taros operates state-of-the art lab facilities and employs a team of scientists (65% of whom hold post-graduate degrees in Chemistry) who are committed to supporting the diverse needs of its customers in efficient drug discovery, medicinal chemistry and classical synthetic chemistry.

Taros' scientists combine more than 140 years industrial organic chemistry experience and over 60 years of active drug discovery experience from big pharmas and biotechs. For more information see: www.tarosdiscovery.com

Scientic Engagements:

Taros Chemicals is actively managing and/or participating in numerous scientific cooperation projects and grant proposals.

EUROPEAN LEAD FACTORY

Taros Chemicals is coordinating the chemistry consortium of the **European Lead Factory** drug discovery platform, a novel, open-innovation platform funded under the European **Innovative Medicine Initiative** (IMI).

UIMA-HPC

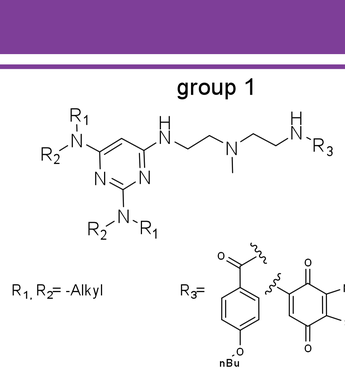
Unstructured Information Management Architecture- High-Performance Computing. Project focused on efficient analysis of chemical and pharmaceutical data bases and documents.

OPTIBIOCAT

Optimized Esterase Biocatalysts for Cost-Effective Industrial Production. Project focused on developing biocatalysts based on feruloyl esterases (FAEs) and glucoronyl esterases (GEs) for production of phenolic fatty- and sugar- esters with antioxidant activity for cosmetic industry.

CDC25 Inhibitors

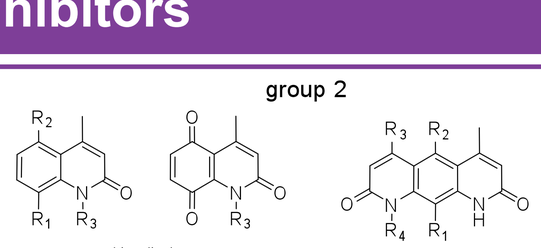
group 1



R_1, R_2= -Alkyl

R_3=

group 2

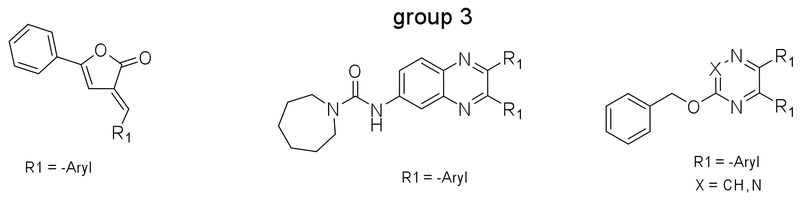


bicyclische

tricyclische

R_1= diverse Substituents
R_2= diverse Substituents
R_3= diverse Substituents
R_4= diverse Substituents

group 3

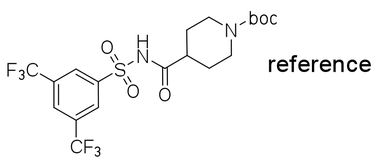


R1 = -Aryl

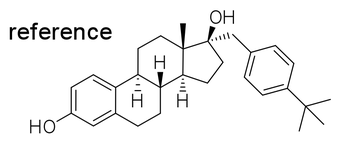
R1 = -Aryl

R1 = -Aryl
X = CH, N

Steroid Sulfatase Inhibitors

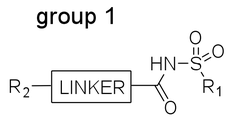


reference



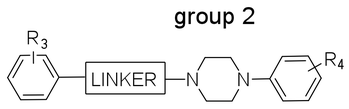
reference

group 1



LINKER = different structural core

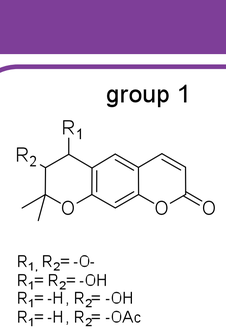
group 2



R_1, R_2, R_3, R_4= diverse substituents or moieties

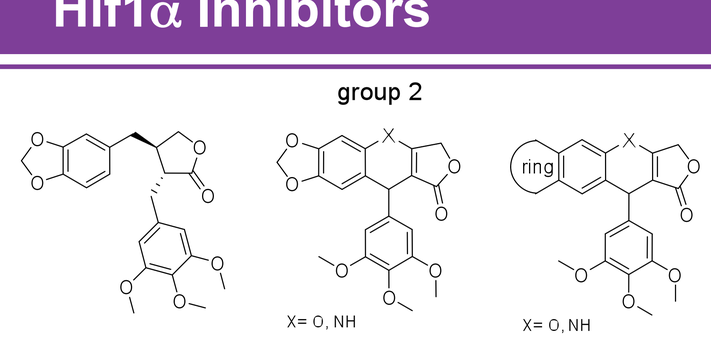
Hif1α Inhibitors

group 1



R_1, R_2= -O-
R_1= R_2= -OH
R_1= -H, R_2= -OH
R_1= -H, R_2= -OAc

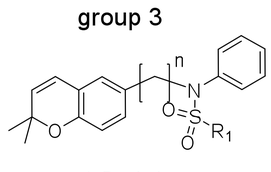
group 2



X= O, NH

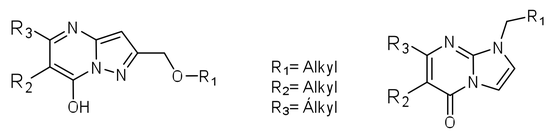
X= O, NH

group 3



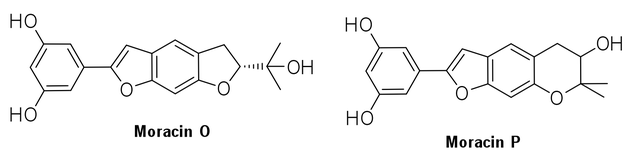
n=1, R_1= Aryl
n=2, R_1= Ary
n=1, R_1= Aryl

group 4



R_1= Alkyl
R_2= Alkyl
R_3= Álkyl

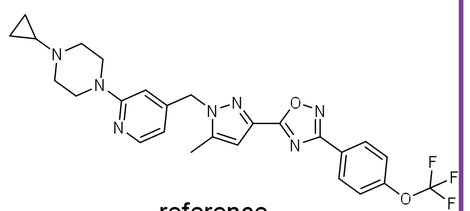
group 5



Moracin O

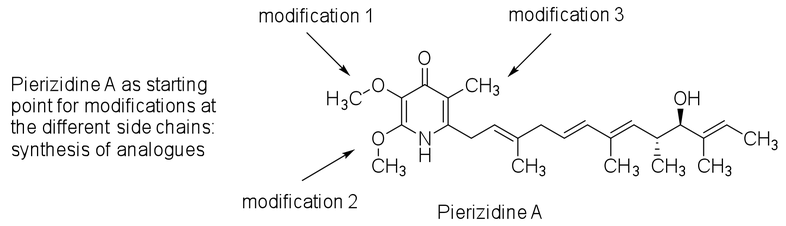
Moracin P

reference



reference

group 6



Pierizidine A as starting point for modifications at the different side chains: synthesis of analogues

group 1

LINKER = different structural core

group 2

R_1, R_2, R_3, R_4= diverse substituents or moieties

CONCLUSIONS

- **~200 compounds have been synthesized for three different biological targets. Some of the compounds were already described in the literature as inhibitors for the corresponding target, and they were used for the validation of the bio-assay and "*a priori*" calculations (Proof of concept). Other compounds were synthesized based on the obtained results from bio-assays for the improvement of the bioactivity through structural modifications based on medicinal chemistry parameters.**
- **CDC25: 52 final compounds were synthesized and delivered for bio-assays.**
- **STS: 70 final compounds were synthesized and delivered for bio-assays.**
- **HiF1α: 69 final compounds were synthesized and delivered for bio-assays.**

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