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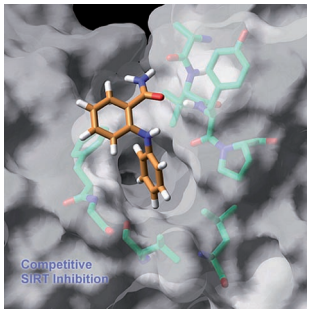
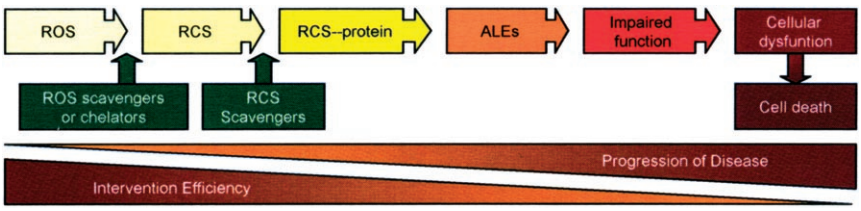
COVER PICTURE



The cover picture shows the model of a SIRT inhibitor, 2-anilinobenzamide, bound to the catalytic core of a SIRT homologue. SIRTs catalyze the deacetylation of several proteins such as histones, p53, and γ-tubulin, and are involved in certain disease states including cancer. SIRT inhibitors can be considered as potential therapeutic agents. This simple compound, which was discovered from a nicotinamide- and benzamide-focused chemical library, shows potent SIRT1 inhibition competitive with the acetylated lysine substrate and causes p53 acetylation in human colon cancer HCT116 cells. For more details, see the Communication by T. Suzuki, N. Miyata et al. on p. 1059 ff.

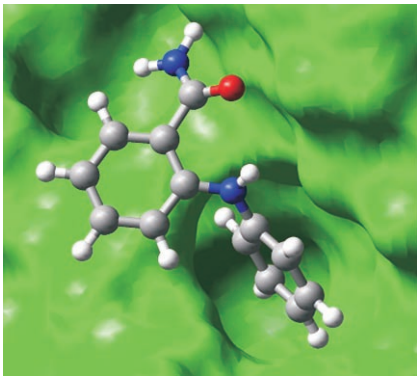
NEWS

MINIREVIEWS

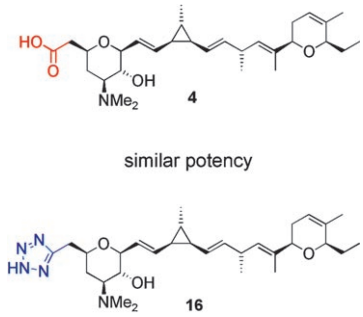


Reactive carbonyl species generated by lipid peroxidation are involved in several human diseases and may represent a novel drug target. RCS therefore represent a new biological target for drug discovery. The reaction mechanisms and structural features characterising effective aldehyde-sequestering agents are highlighted, as are the fundamental biochemical and pharmacological screening tools to be applied in the development of RCS scavengers.

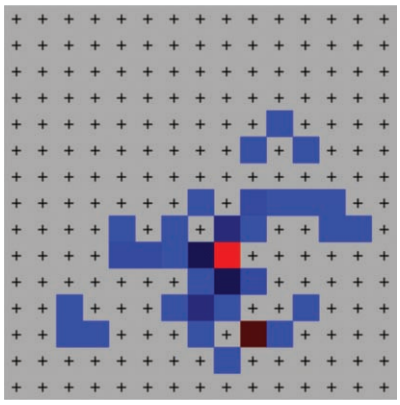
COMMUNICATIONS



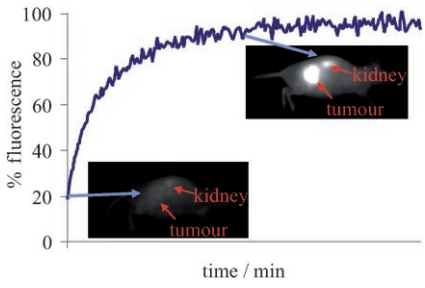
SIRTs, class III histone deacetylases, have been suggested to be associated with certain diseases such as cancer and HIV. Thus, SIRT inhibitors are of interest not only to elucidate the biological functions of the enzyme, but also as potential therapeutic agents. 2-Anilinobenzamide was identified in a nocotinamide- and benzamide-focused compound library as a novel SIRT inhibitor. This compound caused the accumulation of acetylated p53 in HCT116 cells.



Systemic fungal infections have increased significantly in recent years and this is important particularly for immunocompromised patients. A series of ambruticin carboxylic acid analogues have been synthesised through semi-synthesis and tested for their antifungal activity. The results suggest that the carboxylic acid is not crucial for potency, with the tetrazole **16** analogue showing similar antifungal activity to ambruticin VS-3 **4**.



A topological pharmacophore descriptor (CATS) and a self-organizing map (SOM) were used for prediction of multiple receptor interaction of known mGluR antagonists. For a predicted target panel, the tested mGluR ligands exhibited the calculated binding pattern. This virtual screening concept might provide a basis for early recognition of potential side-effects in lead discovery.

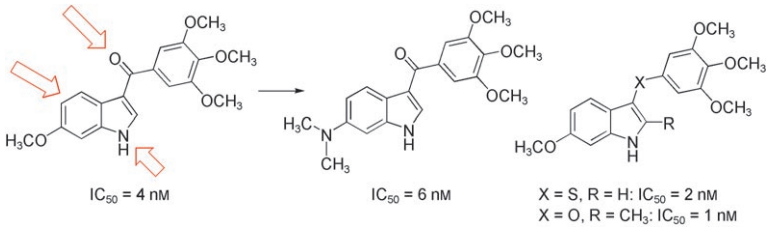


Lighting up tumours in vivo: Activatable probes are designed to image tumour targets and cell internalisation in mice, with improved image contrast. These activatable probes are built on a cyclodecapeptide template with two independent functional domains. The cell-targeting domain allows a multimeric presentation of the RGD motif, and the imaging domain is composed of a dye and a quencher, separated by an intracellular cleavable disulfide bound.

FULL PAPERS

J.-P. Liou, N. Mahindroo, C.-W. Chang, F.-M. Guo, S. W.-H. Lee, U.-K. Tan, T.-K. Yeh, C.-C. Kuo, Y.-W. Chang, P.-H. Lu, Y.-S. Tung, K.-T. Lin, J.-Y. Chang, H.-P. Hsieh**

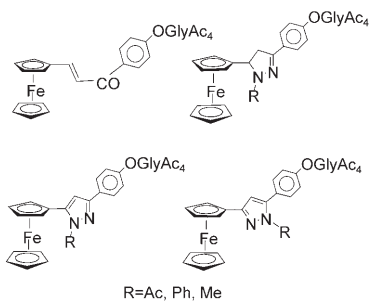
Structure–Activity Relationship Studies of 3-Aroylindoles as Potent Antimitotic Agents



Tubulin assembly blocked: More than 30 analogues of the 3-aroylindole at left were synthesized by introducing variations through three regimens (red arrows) in an effort to further explore the SAR and to improve the potency and solubility of this anticancer drug candidate.

*V. Zsoldos-Mády, A. Csámpai, R. Szabó, E. Mészáros-Alapi, J. Pásztor, F. Hudecz, P. Sohár**

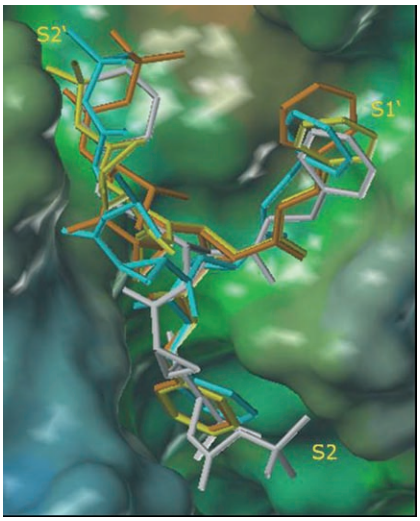
Synthesis, Structure, and in vitro Antitumor Activity of Some Glycoside Derivatives of Ferrocenyl-Chalcones and Ferrocenyl-Pyrazolines



New ferrocene derivatives with cytostatic effect: A series of novel ferrocenyl-(*p*-glycosyloxyphenyl)-chalcones were synthetized and transformed with hydrazines to the corresponding pyrazolines and pyrazoles. Structure was elucidated by NMR spectroscopy, in vitro antitumor activity was studied with human leukemia cells by the MTT method. The new 1-aryl-3-ferrocenyl chalcones showed significant cytostatic effects against HL-60 cells.

*R. Vicik, M. Busemann, C. Gelhaus, N. Stiefl, J. Scheiber, W. Schmitz, F. Schulz, M. Mladenovic, B. Engels, M. Leippe, K. Baumann, T. Schirmeister**

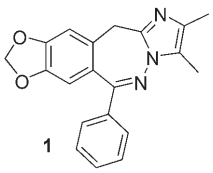
Aziridide-Based Inhibitors of Cathepsin L: Synthesis, Inhibition Activity, and Docking Studies



Docking studies that accounted for the unusual bonding situation in a series of N-acylated aziridines revealed that the most potent cathepsin L inhibitor (shown) adopts a Y-shaped conformation. This binding mode results in the inhibitor spanning across the entire active site cleft of cathepsin L.

B. Elger, M. Schneider, E. Winter, L. Carvelli, M. Bonomi, C. Fracasso, G. Guiso, M. Colovic, S. Caccia, T. Mennini*

Optimized Synthesis of AMPA Receptor Antagonist ZK 187638 and Neurobehavioral Activity in a Mouse Model of Neuronal Ceroid Lipofuscinosis



Two steps toward medicinal use of a novel 2,3-benzodiazepine are reported: 1) Synthesis of ZK 187638 (**1**) was optimized to enable large-scale production for clinical development. 2) Good brain availability and therapeutic efficacy were shown in a mouse model of neuronal ceroid lipofuscinosis, which is a fatal disease with unmet medical need.

SERVICE

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