Publikationen

Originalarbeiten:

1) Asche, C., Frank, W., Albert, A. und Kucklaender, U.
   DOI: 10.1016/j.bmc.2004.10.038

Abstract
A series of novel 5H-benzo[b]carbazoles related to the ellipticines was obtained from the reactions of p-benzoquinones with 2-aminomethylene-1-indanones. Most of the compounds were evaluated for their antitumour activity in the National Cancer Institute’s in vitro human tumour cell line screening panel. Among them, particularly derivative 15c bearing a p-quinone methide moiety in ring C of the heterocycle was found to show in vitro activity comparable to clinically well established anticancer agents such as amsacrine or mitomycin C. Compounds 9d, 9e and 12k showed increased potency to distinct cell lines like the leukemia or melanoma subpanel of cell lines. Based on the test results, structure-activity relationships for this series of compounds were developed. For instance, it was found that a quinonoid substructure in ring C leads to a noticeable increase in activity. The same observation was made for a 2-hydroxyl substituent at the ring system. 2-Acetoxy and 2-methoxy derivatives as well as 2-unsubstituted 5H-benzo[b]carbazoles either had a decreased potency or were found to be inactive. A COMPARE analysis with some of these compounds showed poor or no correlation with anticancer drugs of the NCI’s standard agents database indicating a novel mechanism of action. Additionally, UV-vis titrations in the series of 5H-benzo[b]carbazoles indicated interactions with calf thymus DNA only for the highly active quinone methide 15c.
2) Asche, C., Dumy, P., Carrez, D., Croisy, A. und Demeunynck, M.

Nitrobenzylcatbamate prodrugs of cytotoxic acridines for potential use with nitroreductase gene-directed enzyme prodrug therapy.


Abstract

The synthesis, solvolytic behaviour and cytotoxicity of novel 4-nitrobenzyl carbamates and carbonates derived from 3-amino-4-hydroxymethylacridine 1 are described. Compounds 2 and 6 are both substrates for Escherichia coli nitroreductase and the highly active lead structure 1 is liberated upon incubation of the two compounds in the presence of NTR and its cofactor NADH. Additionally, the cytostatic activity of 2 and 6 against human HT29 colon carcinoma cell lines is decreased 80-fold and 360-fold, respectively, indicating their suitability and potency as prodrugs for either gene-directed enzyme prodrug therapy or antibody-directed enzyme prodrug therapy.

3) Schenck, L.W., Kuna, K., Frank, W. Albert, A. Asche, C. und Kucklaender, U.

1,4,9,10-Anthradiquinone as precursor for antitumor compounds.

Bioorg. Med. Chem. 2006, 14, 3599-3614

DOI: 10.1016/j.bmc.2006.01.026

Abstract

1,4,9,10-Anthradiquinone 5 was reacted with enamines 6 in the Nenitzescu reaction to yield unexpected 3,3a,6,12-tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-naphtho[2,3-d]indol-1-carboxylates 8A. However, anthracine-like naphtho-condensed 5-hydroxyindoles were not obtained from this diquinone. It yielded similar reaction products of the Nenitzescu reaction like other quinones activated by two electron-withdrawing groups. Furthermore, these new compounds 8A were found to constitute precursors for the synthesis of azonines. The conversion to dibenzoazonines 13 occurred in an unusual and up to now unknown way consisting of isomerization, ring opening, and re-closure. 2-Chloro-anthradiquinone 19 reacted with enamines 6 as vinylogous acid chloride to pyrroloanthraquinone 20. No substitution of chlorine was observed. Naphtho-condensed indoles 26 were obtained by the reactions of unsubstituted 1,4-anthraquinone 25 with enamines 6 via the normal Nenitzescu route. Indoles 26 were converted to Mannich bases, reacting further to dimers by the Diels-Alder reaction of intermediate o-quinone methides. Most of the synthesized heterocycles were evaluated for their anticancer properties in the NCI's human-disease oriented in vitro anticancer screen. Particularly, carbinolamines 8A exhibited inhibitory activity of tumor cell growth and thus they constitute a new class of lead structures for anticancer drug design.

4) Asche, C. und Kucklaender, U.


Pharmazie 2006, 61, 244-245

Abstract

A tumour-selective 4-nitrobenzoyl carbonyl prodrug methyl 5-benzyl-2-hydroxy-11-methylene-6-oxo-5H-benzo[b]carbazole-1-carboxylate was synthesized for gene-directed enzyme prodrug therapy (GDEPT). The compound is a substrate for E. coli nitroreductase.
5) Ouberai, M., Asche, C., Carrez, D., Croisy, A., Dumy, P. und Dmeunynck, M.

3,4-Dihydro-1H-[1,3]oxazino[4,5-c]acridines as a new family of cytotoxic drugs.


DOI: 10.1016/j.bmcl.2006.05.101

Abstract
A series of [1,3]oxazino fused acridines has been prepared as precursors of cytotoxic 3-amino-4-hydroxymethylacridine 2. Their cytotoxic activity has been evaluated against HT29 colon carcinoma cell line and was shown to be dependent on the nature of the substituent located on position 2 of the oxazine ring. Additionally, the nitrophenyl derivative 3f is activated by nitroreductase, indicating its potency as prodrug for either gene-directed or antibody-directed enzyme prodrug therapies.

Reviews:
1) Asche, C.

Antitumour Quinones.


Abstract
Quinones still comprise one of the largest classes of antitumour agents. For example, the anthracycline antibiotics are among the most utilised anticancer agents ever developed. Many other quinones were tested for their anticancer activity. Though there are general and well-established mechanisms for quinone toxicity, the exact contribution of the quinone moiety to the cytotoxic effect remains frequently uncertain. However, DNA represents the main target for quinoid antitumour agents and most of them belong to the groups of DNA intercalating and/or alkylating agents. But also other cellular structures such as heat shock protein 90 or telomerase have been identified as targets for quinoid compounds.

2) Asche, C. und Demeunynck, M.

Antitumor Carbazoles.

Anticancer Agents Med. Chem. 2007, 7, 247-267

Abstract
Natural and synthetic carbazoles, either in a pure substituted or in an annellated substituted form, represent an important and heterogeneous class of anticancer agents, which has grown considerably over the last two decades. Many carbazole derivatives have been tested for cytotoxic activity, some of them have entered clinical trials, but only very few have been approved for the treatment of cancer so far, since the clinical application of many carbazoles has encountered problems like severe side effects or multidrug resistance. Due to their polycyclic, planar and aromatic structure carbazoles are predestined for intercalation into DNA and therefore DNA remains one of the main targets for cytotoxic carbazoles. For many carbazoles cytotoxicity can be related to DNA-dependent enzyme inhibition such as topoisomerase I/II and telomerase. But also other targets such as cyclin-dependent kinases and estrogen receptors have emerged.