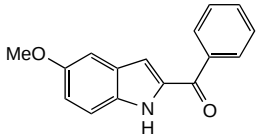
demonstrated a better pharmacokinetic profile, dose-dependent *in vivo* activity and a threefold increase in the lifespan of tumour-implanted mice after oral dosing (28-day study) [5].

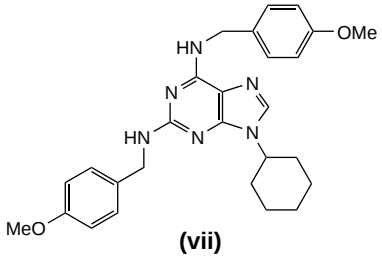
Mahboobi and co-workers at the University of Regensburg (Regensburg, Germany) have reported a new class of anti-mitotic compounds based on 2-aroylindoles [6]. Compound **(vi)** (as well as several others in the series) had a nanomolar IC_{50} value against the growth of human HeLa/KB cervical, SK-OV-3 ovarian and U373 astrocytoma carcinoma cell lines *in vitro*. Inhibition of proliferation correlated with arrest during the G2 and M phases of the cell cycle and inhibition of tubulin polymerization. Notably, compound **(vi)** did not significantly affect the GTPase activity of β-tubulin, as is the case for colchinine, vincristine, nocodazole and taxol. Of particular interest was the observation that selected compounds in the series also inhibited angiogenesis in the chorioallantoic membrane (CAM) assay, which suggests another potential anticancer target for these compounds.



(vi)

In xenograft studies, compound **(vi)** was highly active against human amelanocytic melanoma MEXF989 cells (oral administration, athymic nude mice). 2-Arolylindoles, therefore, constitute an interesting class of antitumour agent for further preclinical development.

Chang and co-workers (New York University and Scripps Research Institute, La Jolla, CA, USA) have reported the development of a series of trisubstituted purines, based on the lead structure myoseverin, as anti-mitotic agents [7]. Notably compound **(vii)** (myoseverin B) was found to be a significantly improved



(vii)

inhibitor of microtubule assembly (IC_{50} for tubulin polymerization inhibition = 2 μM) and exhibited low cytotoxicity in most cell types *in vitro* (using the National Cancer Institute 60-cell panel), suggesting that this molecule might be useful as a cytostatic antitumour agent.

5 Szczepankiewicz, B.G. *et al.* (2001) New anti-mitotic agents with activity in multidrug-resistant cell lines and *in vivo* efficacy in murine tumor models. *J. Med. Chem.* 44, 4416–4430

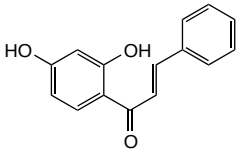
6 Mahboobi, S. *et al.* (2001) Synthetic 2-aroylindole derivatives as a new class of potent tubulin-inhibitory, anti-mitotic agents. *J. Med. Chem.* 44, 4535–4553

7 Chang, Y-T. *et al.* (2001) Synthesis and biological evaluation of myoseverin derivatives: microtubule assembly inhibitors. *J. Med. Chem.* 44, 4497–4500

Flavonoids: anti-proliferative activity against breast cancer cells

Naturally occurring flavonoids occur in many foods including fruits, vegetables, spices, tea and soy-based products, and have attracted widespread interest as anti-proliferative, anti-aromatase, anti-estrogenic and cancer chemopreventative agents.

Chulia and co-workers at the Faculté de Pharmacie (Limoges, France) have synthesized a range of 2′-hydroxychalcones, flavanones, flavones and flavan-4-ols with wide variation in A-ring substitution patterns (H, OH, OMe) and evaluated their antitumour activity *in vitro* against human MCF-7 breast cancer cells [8],



(viii)

In general, 2′-hydroxychalcones (e.g. compound **(viii)**; IC_{50} = 16 μM) and methoxylated flavonones were found to exhibit the most potent anti-proliferative activity in MCF-7 cells.

8 Chulia, C. *et al.* (2001) Flavonoids: structural requirements for anti-proliferative activity on breast cancer cell lines. *Bioorg. Med. Chem. Lett.* 11, 3095–3097

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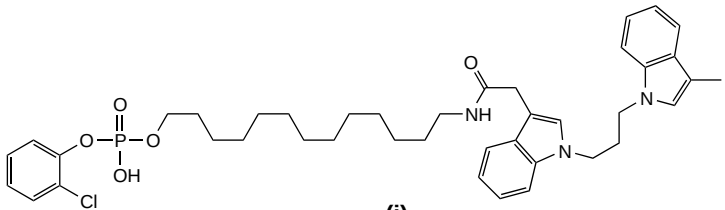
Combinatorial chemistry

Telomerase inhibitors

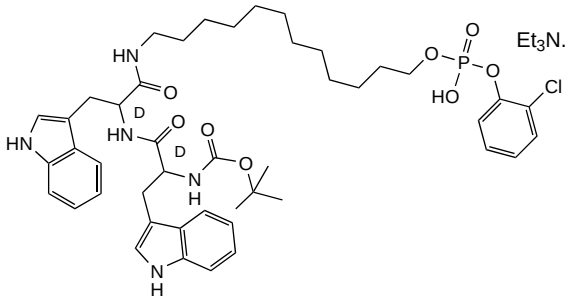
Telomerase is the enzyme responsible for maintaining telomere length and its activity is not observed in normal somatic cells. By contrast, high expression of telomerase is observed in approximately 85–90% of human tumour cells; therefore, telomerase is regarded as a specific target for the development of cancer chemotherapeutic agents. There are several types of inhibitor known, for example, antisense oligodeoxynucleotides and compounds that exhibit potent inhibition of telomerase in the picomolar range. Despite this research, there have been no clinical trials of inhibitors, to date.

Recent developments have highlighted new telomerase inhibitors based on the bisindole unit **(i)** [1]. These new inhibitors are a simple assembly of a phosphate with a hydrophobic group and the bisindole unit, with a long alkyl spacer between them. The simple structural feature of these inhibitors has led to the search for more potent inhibitors [2].

A small library of 42 single compounds was synthesized on Merrifield solid-phase resin. Upon cleavage, evaluation of the library compounds' ability to inhibit telomerase, by testing in a quantitative stretch PCR assay using telomerase



(i)



extracted from the HCT116 cell line, revealed several potent compounds. One of the most potent isolated was **(ii)**, which possessed an IC_{50} value against telomerase of 300 nM. As other stereoisomers were either inactive or much less active, this dependency on the stereochemistry has suggested that there should be a stereospecific demand in the binding site of telomerase for this series of inhibitors. This information, as well as other structure–activity relationships generated in this library, could contribute to the future development of potent telomerase inhibitors.

1 Sasaki, S. *et al.* (2001) Development of novel telomerase inhibitors based on a bisindole unit. *Bioorg. Med. Chem. Lett.* 11, 583–585

2 Sasaki, S. *et al.* (2001) Solid-phase synthesis of a library constructed of aromatic phosphate, long alkyl chains and tryptophane components, and identification of potent dipeptide telomerase inhibitors. *Bioorg. Med. Chem. Lett.* 11, 2581–2584

Library design biased against mutagenic compounds

The use of HTS has represented a major shift in the lead discovery process. Whenever the paradigm is applicable, the use of robotics and large chemical-library screening has yielded uneven results that are dependent on the families of targets, but could result in the identification of multiple hits for an assay. In many cases, the hits found have had to be subsequently discarded because of their toxicological profile or poor bioavailability. If compounds are to be used as drugs, certain biases are necessary to limit the range of properties of the compounds used for building up a library to those relevant to pharmaceuticals. Toxicology, such as mutagenicity, is important in defining the viability of a chemical as a candidate for drug development.

A comparative analysis of simple physical characteristics of compounds that have been reported to be mutagenic or non-mutagenic has been carried out, to search for differences that can lead to the development of knowledge-based biases in libraries designed for mass screening [3].

For each of four *Salmonella* strains, TA-98, TA-100, TA-1535 and TA-1537, an analysis of the statistical significance of the deviation of the averages for several global properties was carried out. The properties studied included topological indices and bit-strings representing the presence or absence of certain chemical moieties. The results with the majority of *Salmonella* strains suggested that mutagenic compounds have a larger number of hydrogen-bond acceptor centres. Moreover, the use of bit-strings points to the importance of certain molecular fragments, such as a nitro group, for the outcome of a mutagenicity study. The development of multivariate models based on global molecular properties or bit-strings suggests a small advantage of bit-strings for the prediction of mutagenicity.

The purpose of this work was the analysis of biases in the structure and molecular properties of the compounds that are found to be mutagens. The properties most commonly used for library design, bit-strings and global properties, showed the ability to discriminate between compounds that test positive and negative in the Ames mutagenicity test for each *Salmonella* strain tested. These properties can then be used for diversity analysis, but also will provide constraints to further tailor libraries towards compounds more likely to be successfully developed into drugs.

3 Villar, H.O. *et al.* (2001) Toward the design of chemical libraries for mass screening biased against mutagenic compounds. *J. Med. Chem.* 44, 2793–2804

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