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Drug Discovery: Novel Indane Scaffolds with Anticancer Activity

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Drug discovery: Novel indane scaffolds with anticancer activity

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Background

The indane scaffold is of key importance in the natural world. It occurs in a range of biologically active natural products. The natural structures range from simple indanes and indanones with antibacterial activity e.g. indanone **1** isolated from the cyanobacterium *Nostoc*¹ to the pterosin family of fern and fungal metabolites e.g. **2**, which show cytotoxicity toward the Human leukaemia HL-60 cell line^{2,3}, to oligomers of resveratrol (3,5,4'-trihydroxystilbene) e.g. the indane Pauciflorol F isolated from the Dipterocarpaceae.⁴ The therapeutic potential of indanes becomes more evident in the area of medicinal chemistry where this scaffold is incorporated into structures that demonstrate therapeutic properties e.g. the indanone Sulindac (ClinorilTM; Merck), a non-steroidal anti-inflammatory that has recently demonstrated anti-proliferative and apoptotic effects.^{5,6} More recently the tubulin polymerisation inhibitor Indanocine (NIH) has been receiving attention.⁷ During the course of our research on indane monomers and dimers, we have noted that the potential of novel indane scaffolds for the treatment of inflammatory disease and cancer has not been fully exploited. Inflammatory disease is responsible for, or implicated in, a wide range of conditions including, but not limited to, Rheumatoid Arthritis, Cardiovascular Disease, Multiple Sclerosis, inflammatory bowel disease (IBD) and Psoriasis. It is also well established that inflammation plays a significant role in the development of cancer.⁸ The aim of this research project is to combine, experience led and evidence based, theories with our knowledge of small molecule drug development to generate novel hybrid scaffolds with therapeutic potential for the treatment of cancer and inflammatory disease. The second fragment of interest, in this study comes from the naturally occurring benzophenones.⁹ This class of molecules features widely in plants used as anti-tumour agents in Traditional Herbal Medicinal systems. A range of bioactivities has been established for members of this chemical class, including tubulin binding and P-glycoprotein (P-gp) modulating activity, the prototypical efflux transporter, implicated in multidrug resistance (MDR).¹⁰

Results and Discussion

A novel scaffold designed around an indane nucleus was identified as the chemical target in this study (Figure 1). The scaffold was synthesised by combining a series of small chemical fragments using a range of spacer molecules. A second fragment incorporated into the molecule is centered on the small naturally occurring bioactive benzophenone moiety, which depending on substitution pattern demonstrates a variety of biological properties. Initial studies have led to the development of a synthetic approach that has thus far yielded eight final products with the desired final chemical scaffold. All products and intermediates have been characterized spectroscopically. The cytotoxicity of the starting fragments was evaluated using the Acid Phosphatase assay, in a series of *in vitro* cancer cell lines: MCF7 and SKBR3 (Breast), DU145 (Prostate) and A549 (Lung). The individual fragments displayed low levels of cytotoxicity (Table 1) in A549, MCF7 and SKBR3 cell lines, but do have low micro-molar activity in the DU145. Some fragments with significant cytotoxicity (in red, Table 1) have been prepared and await coupling. Coupling of the main molecular fragments and spacers gave rise to a series of compounds with a novel chemical scaffold. These molecules displayed significant increases in IC₅₀ values in the cell lines under investigation, relative to their component fragments (Figure 2). Initial and ongoing studies have demonstrated inhibition of tubulin binding at micro molar levels.

Naturally occurring Indane structures

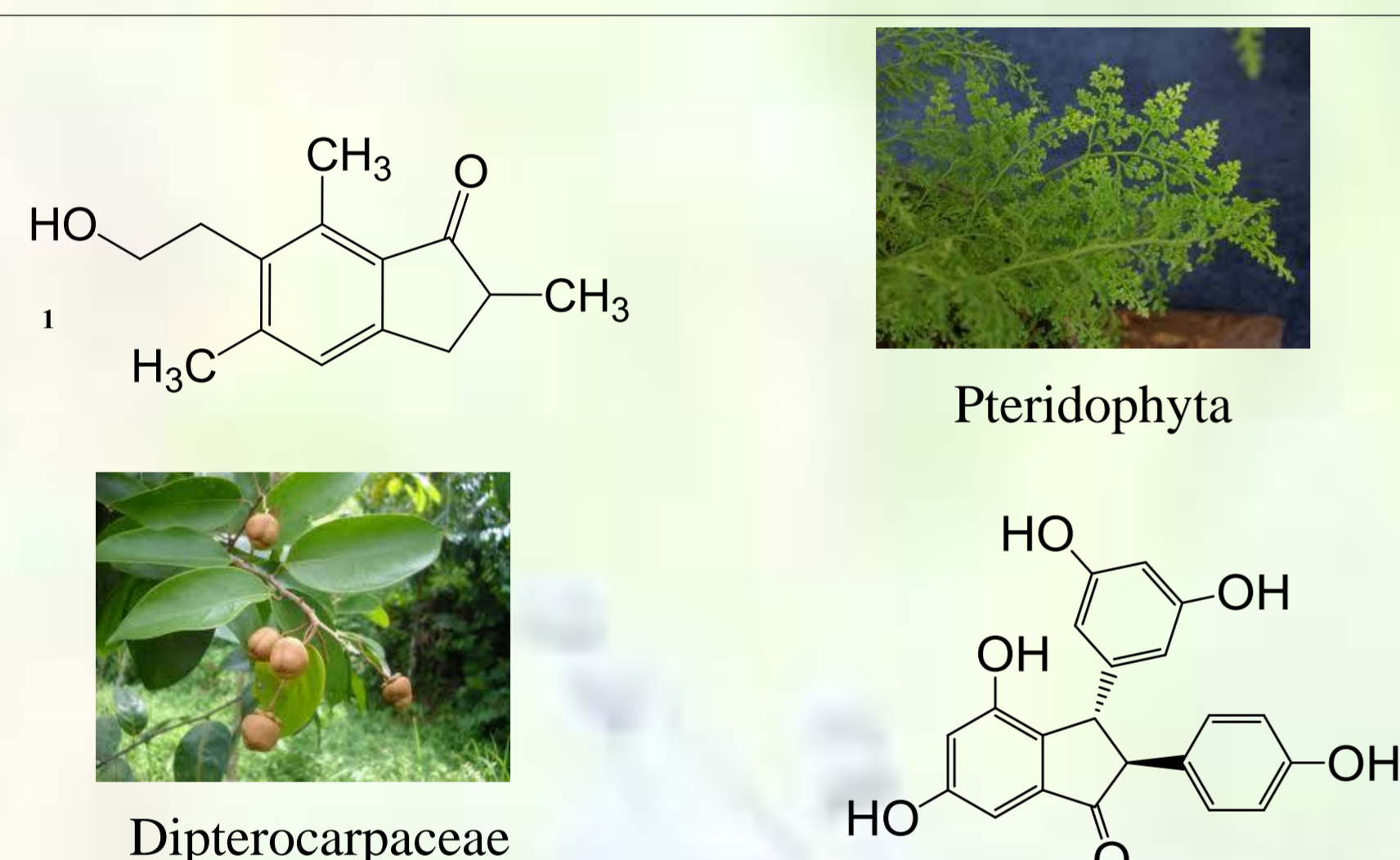


Figure 1: Target Hybrid Scaffold

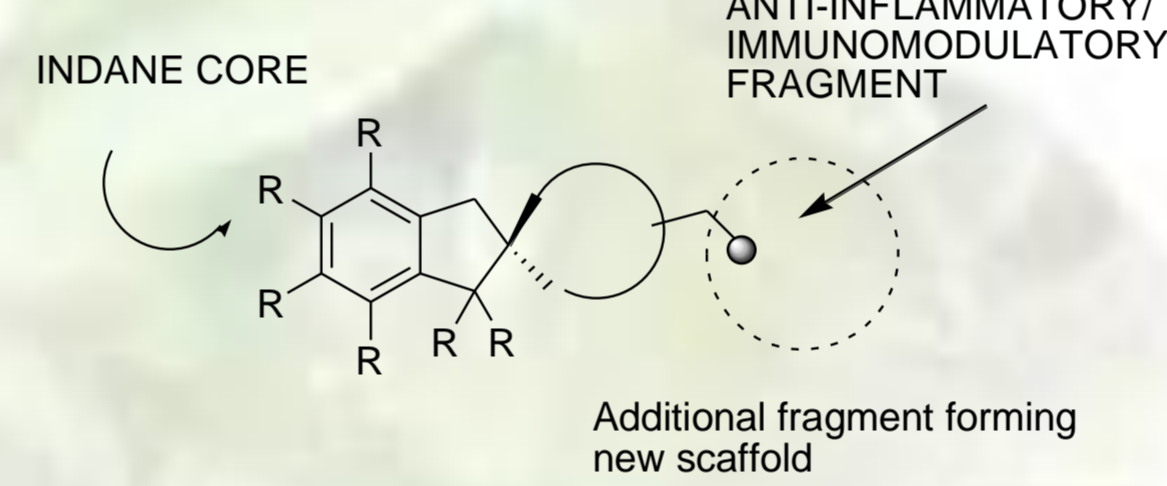


Figure 2: Modification of one fragment increased activity of hybrid all cell lines

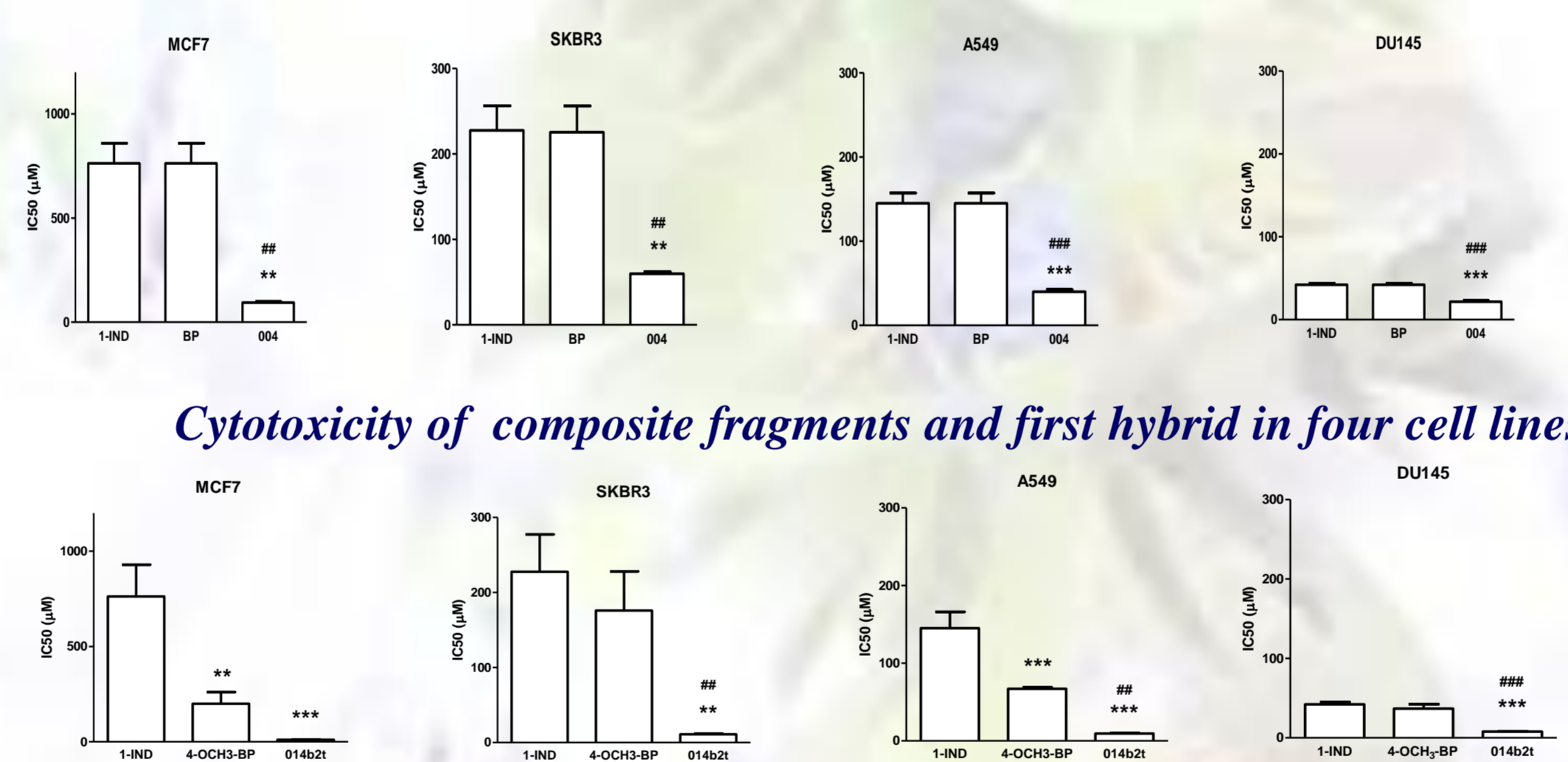
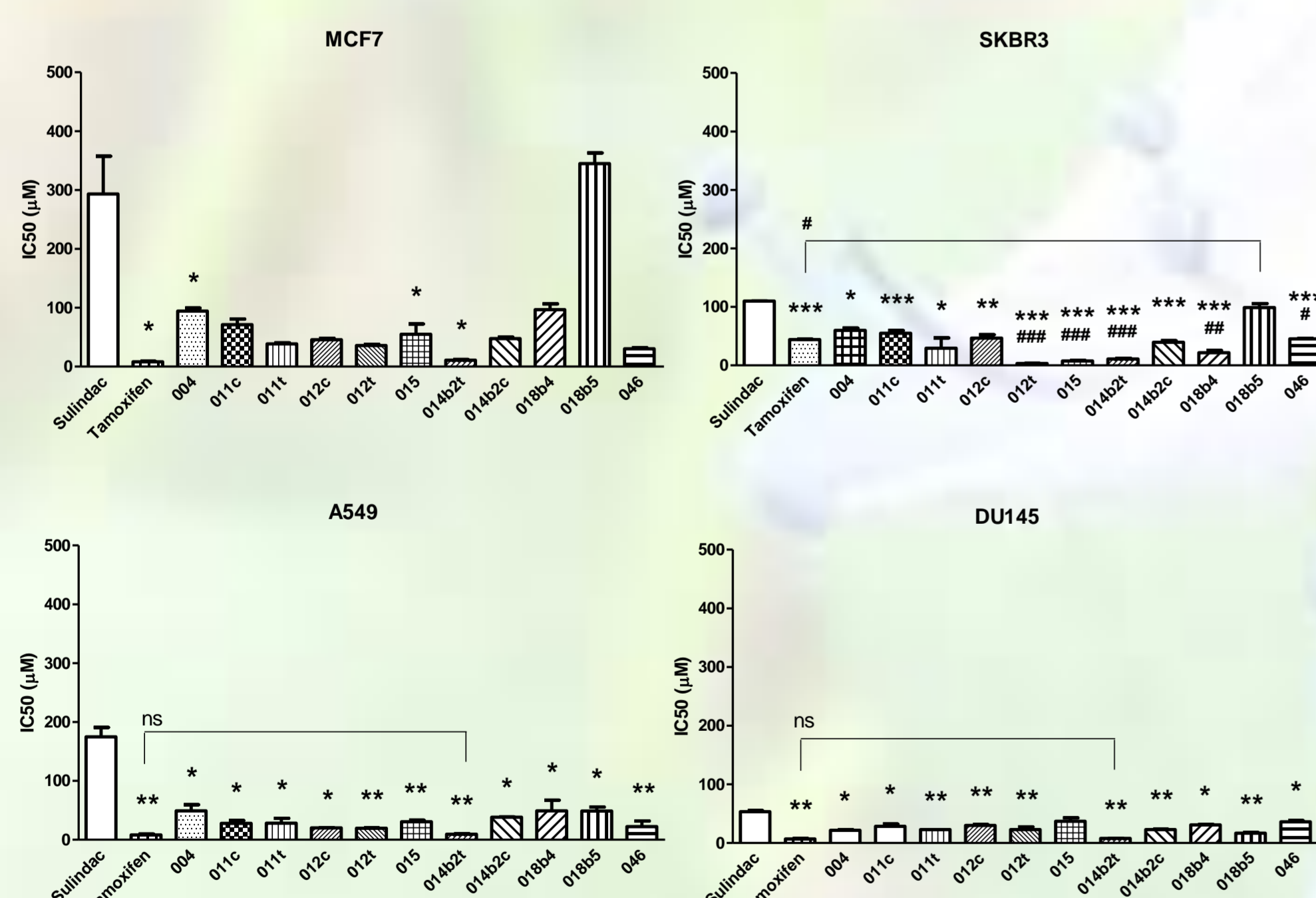


Table 1: Cytotoxicity of some fragments before coupling to form hybrids

Fragments IC ₅₀	MCF7 μM	SKBR3 μM	A549 μM	DU145 μM
	> 100	> 100	> 100	40.88
	> 100	> 100	> 100	28.41
	> 100	> 100	46.42	33.50
	> 100	> 100	56.63	19.74
	> 100	> 100	26.60	24.52
		514 nM	17.4 nM	6.16 nM

***Fragments have been synthesised and await coupling. We expect significant increases in activity for the final hybrids.

Figure 3: Cytotoxicity of lead hybrids compared with Tamoxifen



Conclusion and Perspectives: We have identified a novel chemical scaffold, that demonstrates cytotoxic activity *in vitro* in a range of human cell lines, including MCF7 and SKBR3 (Breast), DU145 (Prostate) and A549 (Lung). Our working hypothesis has been that hybridization of several bioactive fragments results in synergized bioactivity (Figure 2 and 3). The results demonstrate the validity of this hypothesis, showing that the nature and position of substitution together with stereo-isomeric specificity results in significant increases in bioactivity: e.g. coupling of indan-1-one (IC₅₀ 100 micromolar in SKBR3, A549, MCF7 and IC₅₀ 40.88 micromolar in DU145) with fragment A (IC₅₀ 100 micromolar in SKBR3 and MCF7; and IC₅₀ 46.4 micromolar in A549, and IC₅₀ 33.54 micromolar in DU145) yields a novel chemical scaffold with (IC₅₀ 1.04 micromolar in SKBR3, 14.9 in A549, 32.1 in DU145 (Prostate) and 30.5 in MCF7. One hybrid 14b2t compares well with Tamoxifen across the cell lines. Several hybrids are more potent in the SKBR3 cell line. **Future chemical synthesis:** We are working to couple indanone nuclei with new fragments we have prepared, that display nanomolar activity across the four cell lines, to generate what we believe will be derivatives with significant nanomolar dual activities. **Future bioactivity evaluation:** Initial studies also support the tubulin binding effects of scaffolds. This activity will be further evaluated in collaboration with the CNRS, Gif-Sur-Yvette in March. In addition P-glycoprotein (P-gp) modulating activity will be evaluated. A series of *in vitro* anticancer assessments and *in vivo* and *in vitro* anti-inflammatory studies will be carried out over the next six months, to establish MOA and selectivity of these scaffolds.

Methods:

Synthesis and specific compounds: Will not be discussed at this point. **Cell Culture:** All the cell lines were maintained in a humid chamber at 37 °C and 5% CO₂ atmosphere. SKBR3 (ATCC HTB-30), MCF7 (ATCC HTB-22), and DU145(ATCC HTB-81) cells were cultured in RPMI-1640 Medium containing 10% fetal bovine serum (FBS) and 1% L-Glutamine. A549 (ATCC CCL-185) lung carcinoma cells were grown in Dulbecco's Modified Eagle's Medium supplemented with 5% FBS. **Acid Phosphatase assay:** After 5 days of incubation of cells with the drugs, the medium was removed and each well was washed with 100 μL of PBS. Then, 100 μL of freshly prepared phosphatase substrate (10 mM p-nitrophenol phosphate, Sigma) in 0.1 M sodium acetate (Sigma), 0.1 % triton X-100 pH5.5 (BDH) was added to each well. The plates were wrapped in tin foil and incubated in the dark at 37° C for 1 hour. The reaction was stopped by the addition of 50 μL of NaOH 1 M to each well and measuring was obtained in a dual beam plate reader at 405 nm with a reference wavelength of 620 nm.

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