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From Nature to Medicinal Chemistry: Anti-Cancer Activity of Novel Indane Scaffolds

Tao Zhang

Technological University Dublin, tao.zhang@tudublin.ie

Vilmar Bandero-Filho

Trinity College Dublin

Kit Chan

Trinity College Dublin

Lorraine O'Driscoll

Trinity College Dublin

Neil Frankish

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Authors

Tao Zhang, Vilmar Bandero-Filho, Kit Chan, Lorraine O'Driscoll, Neil Frankish, and Helen Sheridan



Bandero-Filho VC[#], Zhang T, Chan K, O'Driscoll L, Frankish N and Sheridan H^{*}

Drug Discovery Group, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin; Trinity Biomedical Sciences Institute (TBSI); Dublin 2, Ireland

[#]Correspondence: banderv@tcd.ie

Background

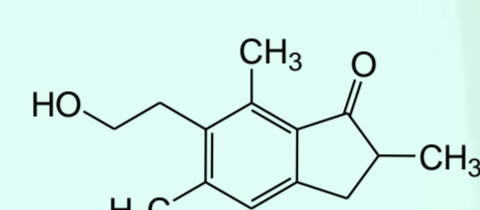
The indane scaffold is of key importance in the natural world. It occurs in a range of biologically active natural products. The natural structures range from simple indanes and indanones with antibacterial activity e.g. indanone isolated from the cyanobacterium *Nostoc*¹ to the pterosin family of fern and fungal metabolites, 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. 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).

Results and Discussion

A novel scaffold designed around an indane nucleus was identified as the chemical target in this study (Fig.1). The scaffold was synthesised by combining a series of small chemical fragments using a range of spacer molecules. The second major 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 and products were evaluated using the Acid Phosphatase assay, in a series of *in vitro* cancer cell lines. Coupling of the main molecular fragments and spacers gave rise to 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 (Figs.2 and 3). Compounds with the new scaffold induce apoptosis to varying degrees and also demonstrate either inhibition of ROS production or act as a free radical scavenger (Figs. 4 and 5) and cell cycle arrest. A lead compound has been identified within the series which has displayed the highest IC₅₀ value (1.0 μM) against the HER2+ cell line SKBR3. Current studies are now focussed on this cell line.

Naturally occurring Indane structures

Pteridophyta



Dipterocarpaceae

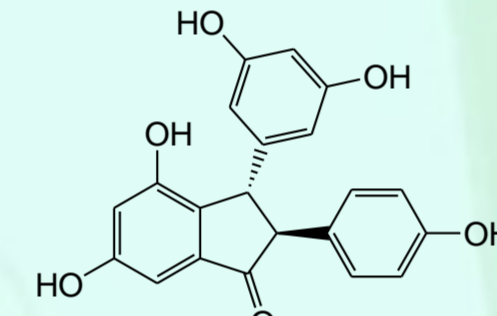


Figure 1: Target Hybrid Scaffold

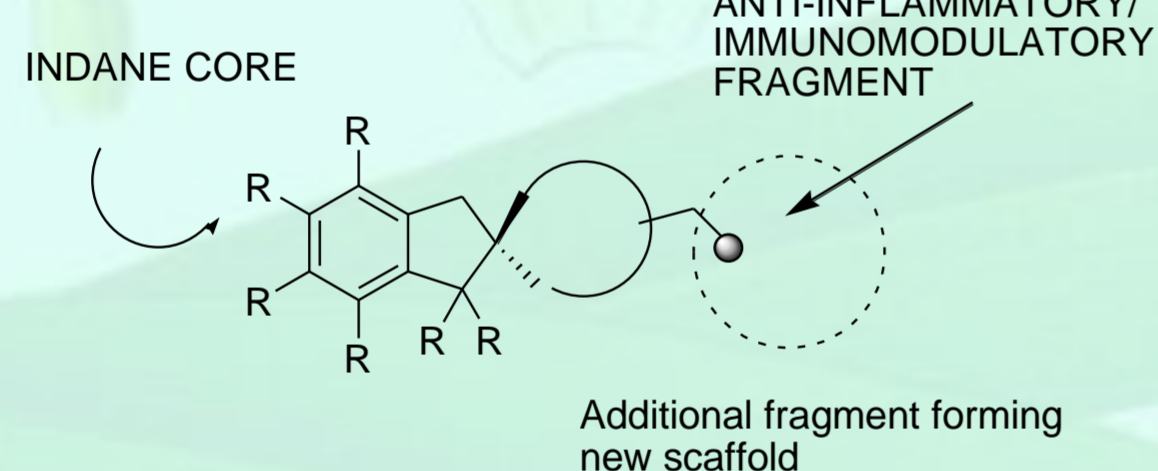


Figure 3: IC₅₀ comparison of lead compounds in HER2+ SKBR3 breast cancer cell line

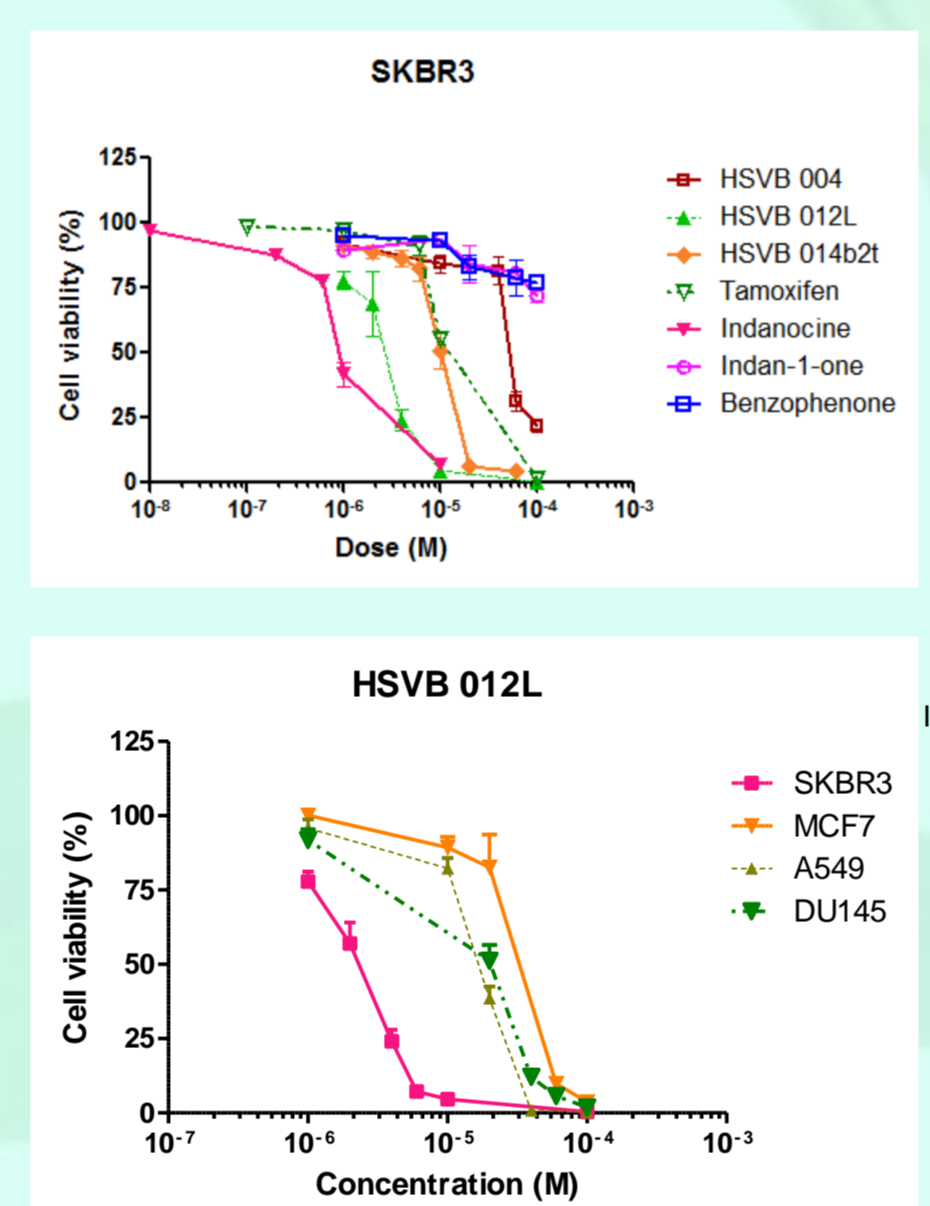


Figure 4: Flow cytometry analysis of Apoptosis induction of lead compound over time in SKBR3 cells

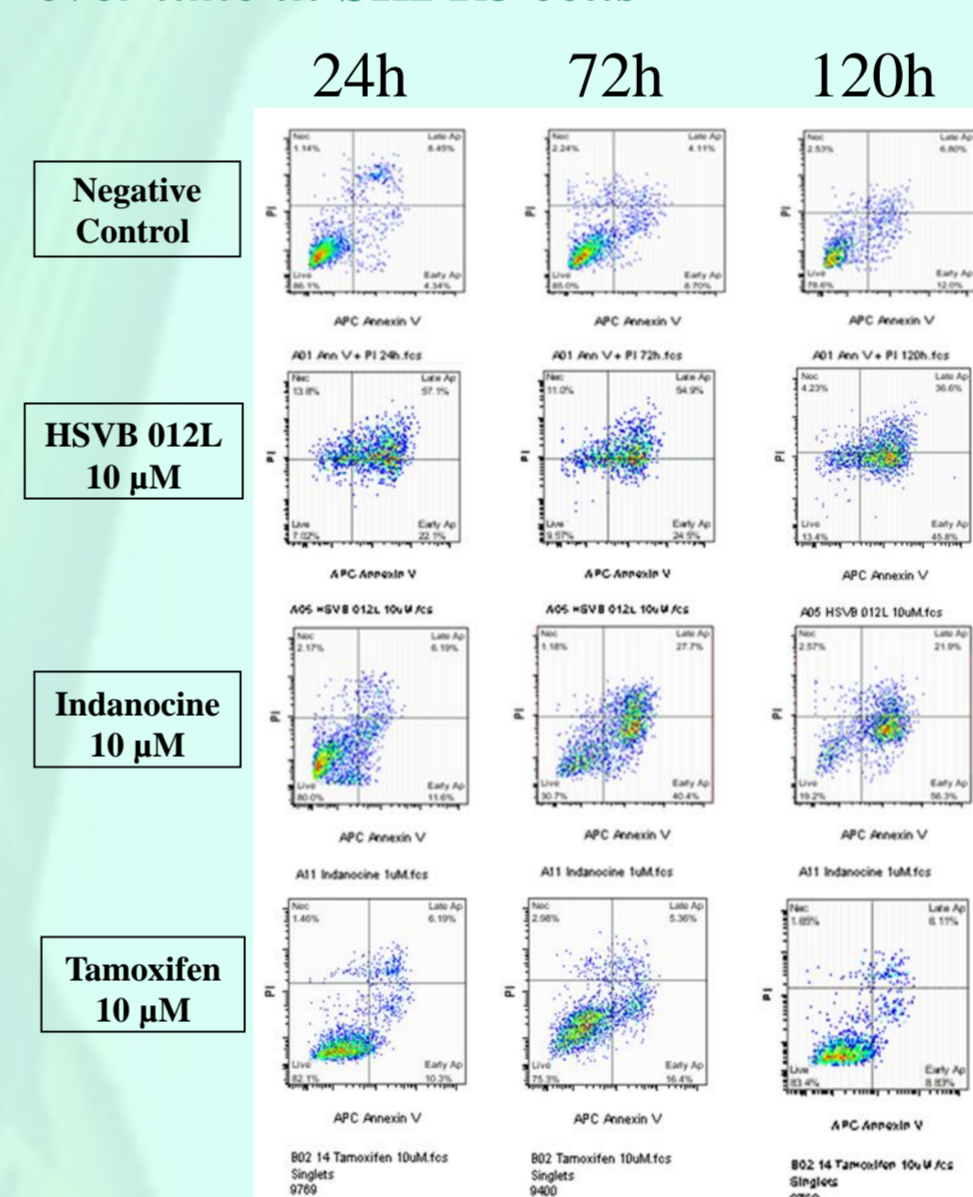


Figure 5: Flow cytometry analysis of ROS accumulation of leading compounds in SKBR3 cells (24 h, n=3)

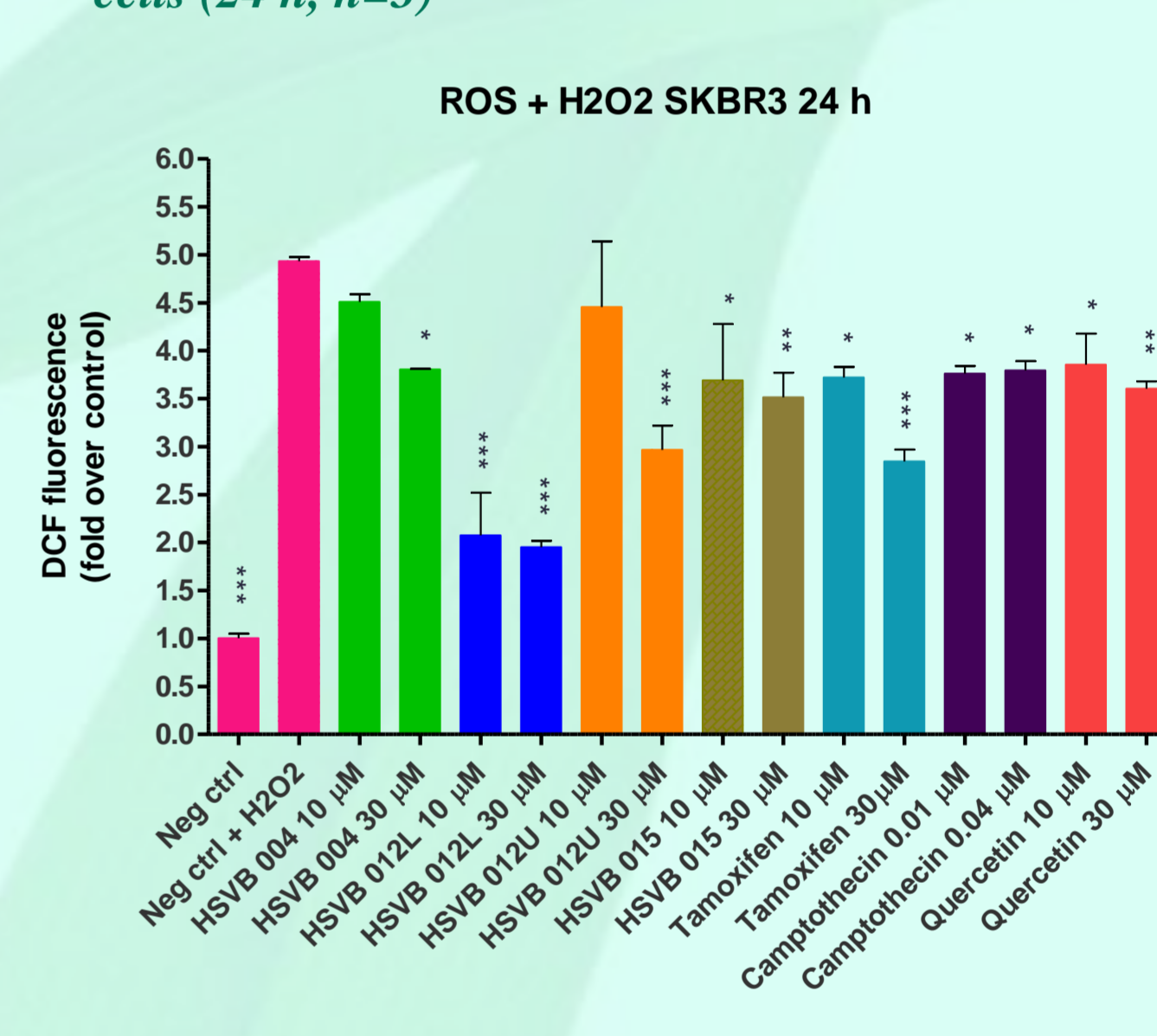
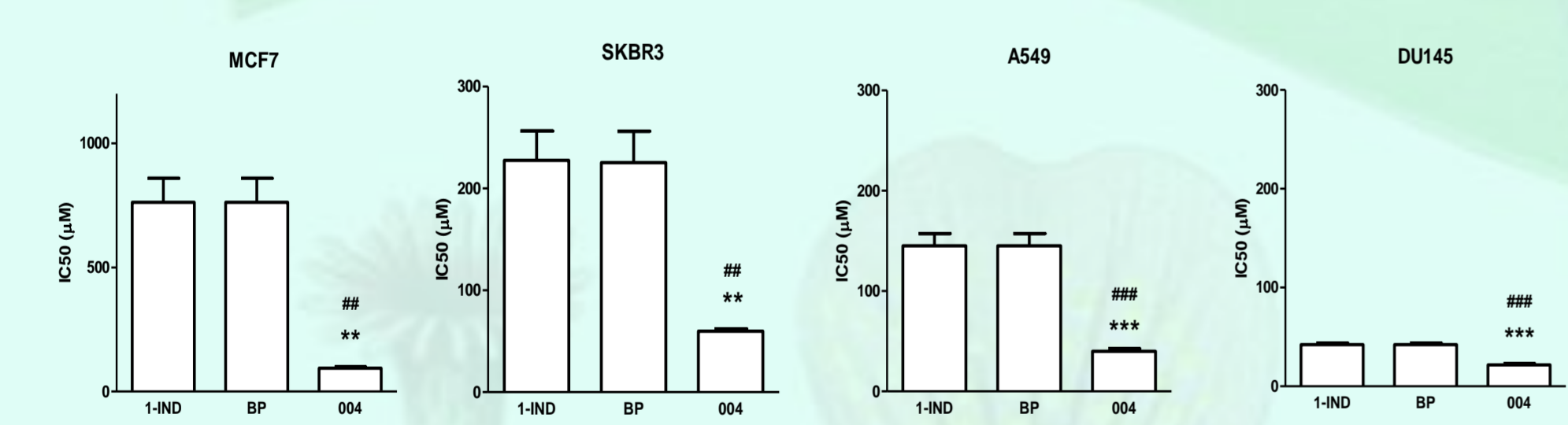
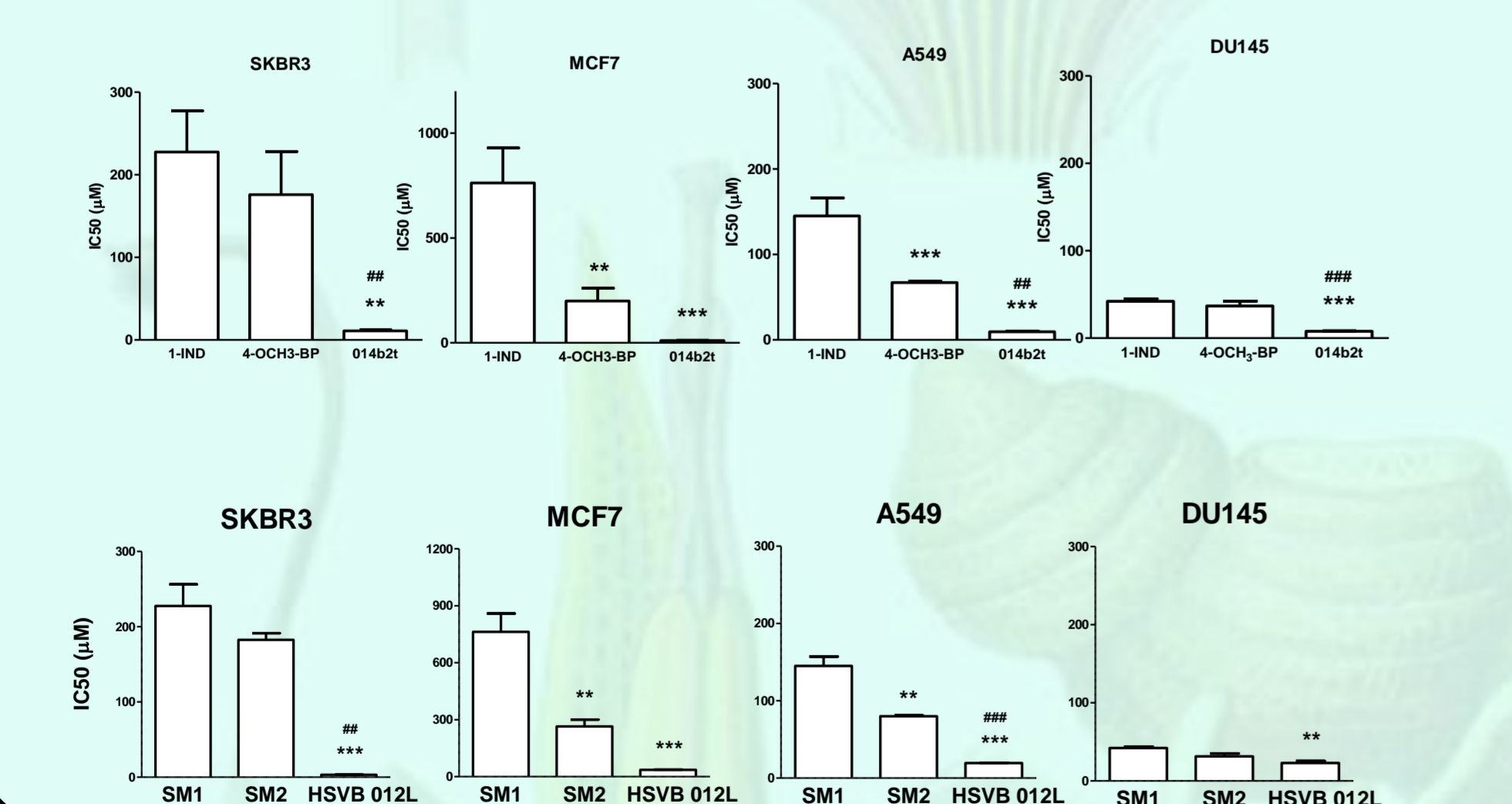


Figure 2: Cytotoxicity of parent hybrid and natural precursors in MCF7 and SKBR3 (Breast), DU145 (Prostate) and A549 (Lung) cell lines



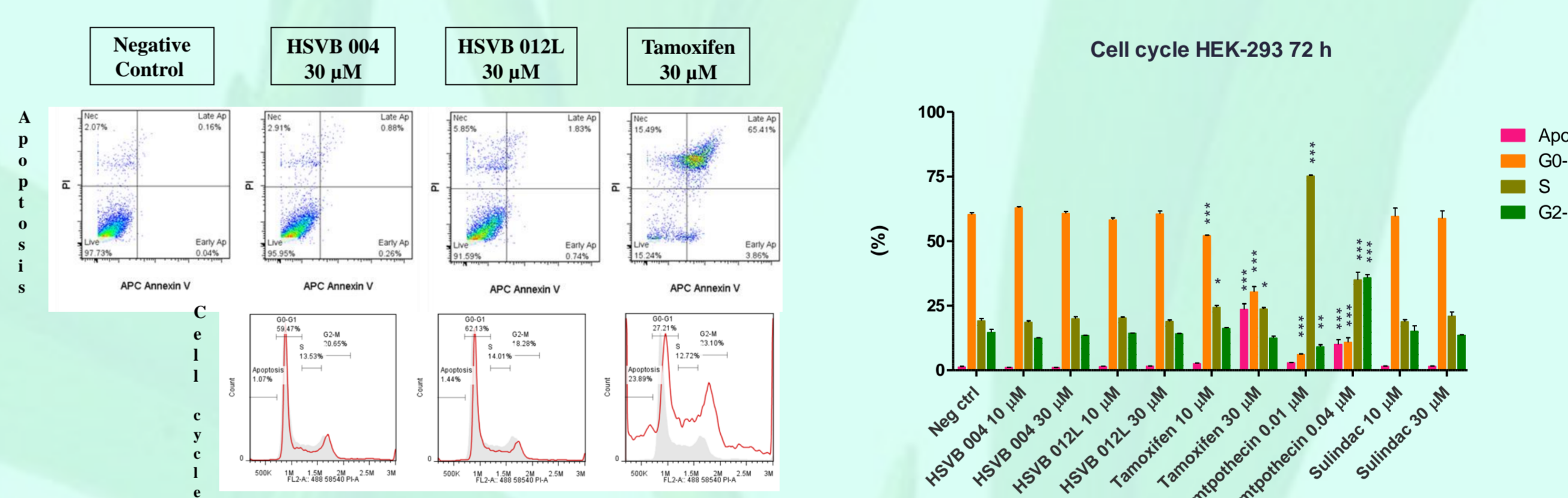
Cytotoxicity of optimised hybrid and natural precursors in MCF7 and SKBR3 (Breast), DU145 (Prostate) and A549 (Lung) in vitro cell lines



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Figure 6: Flow cytometry analysis of Apoptosis induction and Cell cycle arrest in HEK-293 cells (72 h, n=3)



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). Excitingly, 012L has not shown cytotoxicity to normal HEK cells even at a concentration 30 times higher than its IC₅₀ on SKBR3. Tamoxifen, on the other hand, at its IC₅₀ concentration, has induced apoptosis on 85% of the HEK cells. The decrease in ROS accumulation in a dose-dependent manner for the compounds of this novel indane scaffold suggests that it might be involved on the cellular apoptosis induction. 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 μM in SKBR3, A549, MCF7 and IC₅₀ 40.88 μM in DU145) with fragment A (IC₅₀ 100 μM in SKBR3 and MCF7; and IC₅₀ 46.4 μM in A549, and IC₅₀ 33.54 μM in DU145) yields a novel chemical scaffold with (IC₅₀ 1.04 μM in SKBR3, 14.9 in A549, 26.9 in DU145 (Prostate) and 35.7 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 preparing 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 effects of scaffolds against other HER2+ breast cancer cells, including resistant to conventional treatments. A series of *in vitro* anti-cancer assessments and *in vivo* and *in vitro* anti-inflammatory studies will be carried out over the next months, to establish MOE 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. HEK(ATCC CRL-1573TM; embryonic kidney cells) was grown in Minimum Essential Medium Eagle supplemented with 10 % 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.