Supporting Information

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1. MTT Antiproliferative Assay in SW480, A549 and Hek293 cell lines – lines 1

Approximately 5 × 10^3 SW480 colon adenocarcinoma cells, 3 × 10^3 A549 human lung adenocarcinoma cells and 1 × 10^4 Hek293 human embryonic kidney cells were cultured in 200 µl culture medium per well (Dulbecco's Modified Eagle's Medium (DMEM) for SW480 and A549 cells and Eagle's Minimum Essential Medium (EMEM) supplemented with 1% of non-essential aminoacids for Hek293 cells), both supplemented with 10% newborn calf serum and 1% amphotericin-penicillin-streptomycin solution in 96-well plates and incubated at 37 °C under a 5% CO_2 atmosphere. The cells were grown for 24h and then exposed to different concentrations of the tested drugs (dissolved in culture medium) for 72h. Then,

the treatment was removed and the cells were incubated with 100 µl of MTT (3-(4,5-dimethyltiazol-2-yl)-2,5-diphenyltetrazoliumbromide) (Sigma Aldrich) dissolved in culture medium (500 µg/ml). After 3h, 100 µl of solubilizing solution (10% (w/v) SDS, 0.01 M HCl) were added to each well and incubated for other 18 h. Absorbance was read at 590 nm in a microplate reader (Cytation 5 Cell Imaging Multi-Mode Reader - Biotek Instruments, USA). Four replicates per dose were included. The IC_{50} values, that is, the concentrations which produced 50% inhibition of cell viability were calculated from MTT data using the GraphPadPrism Software Inc. (version 6.01) (USA).

2. MTT Anti-proliferative Assay in MCF7, MDA-MB-231 and MCF-10A cell lines: lines 2

Around 1 × 10^4 cells from each cell line were cultured on a 96-well plate, containing 200 µl per well of Dulbecco's Modified Eagle's Medium (DMEM, Gibco™) supplemented with 10% fetal bovine serum and 1% antibiotic solution penicillin-streptomycin (pen-strep, Gibco™) and incubated at 37 °C under a 5% CO_2 atmosphere. Afterwards, the cells were grown for 24h before being exposed to different concentrations of the tested drugs (ranging from 20 µM to 0 µM), dissolved in culture medium, for 72h. Thereupon, the drug treatments were removed and cells were incubated with 100 µl of 3-(4,5-dimethyltiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT, Sigma Aldrich) dissolved in culture medium (500 µg/ml) for 3h. Upon incubation, 100 µl of solubilizing solution (10% (w/v) SDS, 0.01 M HCl) were added to each well and incubated for 18 h. Absorbance reading was performed at 590 nm using a microplate reader (Synergy™ Mx Monochromator-Based Multi-Mode Microplate Reader, BioTek Instruments, Inc.). All experiments were performed in triplicate. DMSO was used as vehicle control. The IC_{50} values were calculated from MTT data using the GraphPadPrism Software Inc. (version 6.01) (USA).

3. *Gene expression analysis on Breast Cancer cell lines MCF7 and MDA-MB-231*

To assess whether gene expression of the target genes was altered, cell lines MCF7, MDA-MB-231[1] and MCF-10A were grown on a 12-well plate containing Dulbecco's Modified Eagle's Medium (DMEM, Gibco™). The medium for the breast cancer cell lines was supplemented with 10% fetal bovine serum and 1% antibiotic solution penicillin-streptomycin (pen-strep, Gibco™), while the medium for MCF-10A was supplemented with 5% of horse serum, human insulin (40µg/mL), human EGF (20ng/mL), cholera toxin (100ng/mL), hydrocortisone (500ng/mL), and 1% antibiotic solution penicillin-streptomycin (pen-strep, Gibco™). All the cells were incubated at 37 °C under a 5% CO_2 atmosphere. Upon 24h, each cell line was treated with each compound dissolved in medium, to the concentration of their respective IC50 value. Hereupon, cells were incubated for 72h, before initiating the RNA extraction protocol. All experiments were performed in triplicate.

Total RNA extraction was performed using the NZY Total RNA Isolation kit (NZYtech ™), followed by cDNA synthesis, using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems), following the manufacturer's instructions. Afterwards, the synthetized cDNA was subject to qPCR amplification, using the iTaq™ Universal SYBR® Green Supermix (Bio-rad), performed on the real-time cycler CFX96™ (Bio-rad). Each reaction was carried out using 2µL of cDNA diluted 1:4, 0,5µL of the respective primer sequence (Forward and Reverse); 2µL of DNAse/RNAse free treated H_2O and 5µL of 2x SYBR Green, comprising a total of 10µL per reaction, in each well of a 96-well PCR plate. All experiments were performed in triplicate, and glyceraldehyde-3-phosphate dehydrogenate (GAPDH) gene amplification was used as reference for normalization. The CFX Manager 3.1 software (Bio-Rad) was used to visualize amplification and melting curves, define the cycle amplification threshold (CT) and to assign each sample and negative control to its plate location. This data was exported as an excel file and analyzed using the formula "Ratio= E target $^{-(CT\ sample\ target\ gene)}$ / E GAPDH$^{-(CT\ sample\ GAPDH)}$", where E corresponds to primer efficiency. Statistical analysis was carried out through One-Way ANOVA, using Brown-Forsythe and Welch ANOVA test with Dunnett

T3 correction, using the GraphPadPrism Software Inc. (version 6.01). Primer sequences described on Table S1.

		Sequence (5'-3')	Product bp
EP300	FW	GACCCTCAGCTTTTAGGAATCC	353
	RV	TGCCGTAGCAACACAGTGT	
LYPLA2	FW	GTAACACCATGTCTGTGCCC	222
	RV	GTCAAACCAGGAGGGCAT	
GAPDH	FW	ACTGGCGTCTTCACCACCAT	142
	RV	TCTTGAGGCTGTTGTCATACTTC	

Table S1: EP300, LYPLA2 and GAPDH primer sequences and product length. Primer sequences for EP300 and GAPDH were obtained in accordance to the following methods (T. Li, H. Huang, B. Huang, B. Huang, J. Lu, *J. Genet. Genomics*, 36 (2009) 335-342 and S.A.d.B. Garcia, M. Araújo, R. Freitas, *Data in brief*, 30 (2020) 105572-105572). LYPLA2 primers were designed using primer3 online software. Bp, base pair; FW, forward primer; RV, reverse primer.

4. *In Silico* Studies

SEA[2] provided suggestions for targets for the compounds by relating compounds to proteins using a similarity ensemble approach (SEA) based on the similarities of sets of ligands. Protein X-ray crystal structures were obtained from the Protein Data Bank. The crystal structures corresponded to the p300 acetyltransferase domain with allosteric inhibitor CPI-076 and CoA (6pgu, 1.72 Å[3]), as well as to human tryptophan 2,3-dioxygenase in complex with PF-06840003 in active site and exo site (5syn, 2.4 Å[4]). All protein structures were determined at high resolution. Hydrogen atoms were added with Maestro software.[5] Docking was then performed by extra precision Glide XP[5] with the default settings.

Molecular properties and PAINS filters were determined with SwissADME.[6]

5. References

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