UNIVERSIDAD SAN SEBASTIAN
Ilumina el futuro

MOLECULAR DYNAMICS AND PHARMACOPHORE MODELING OF THE INACTIVE MINERALOCORTICOID RECEPTOR FOR ANTAGONIST DISCOVERY

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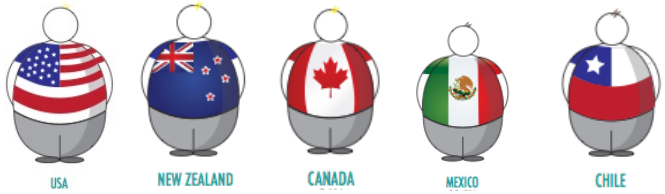
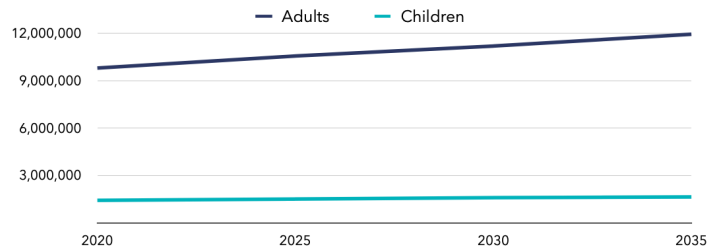
Obesity: a global epidemic with local urgency

Worldwide Prevalence (WHO)

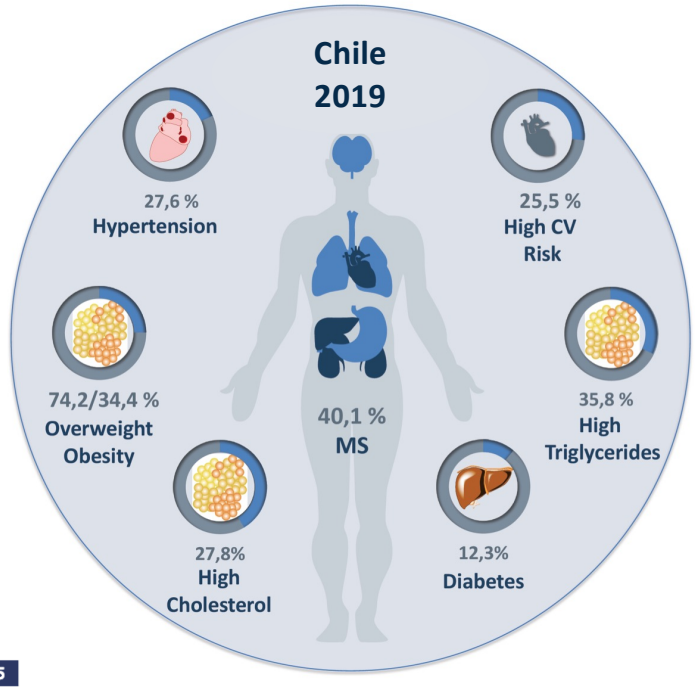


36,2% 30,8% 29,4% 28,9% 34,4%

Projected numbers of adults and children with high Body Mass Index (BMI)



Almost ¾ of the population is overweight !!!!



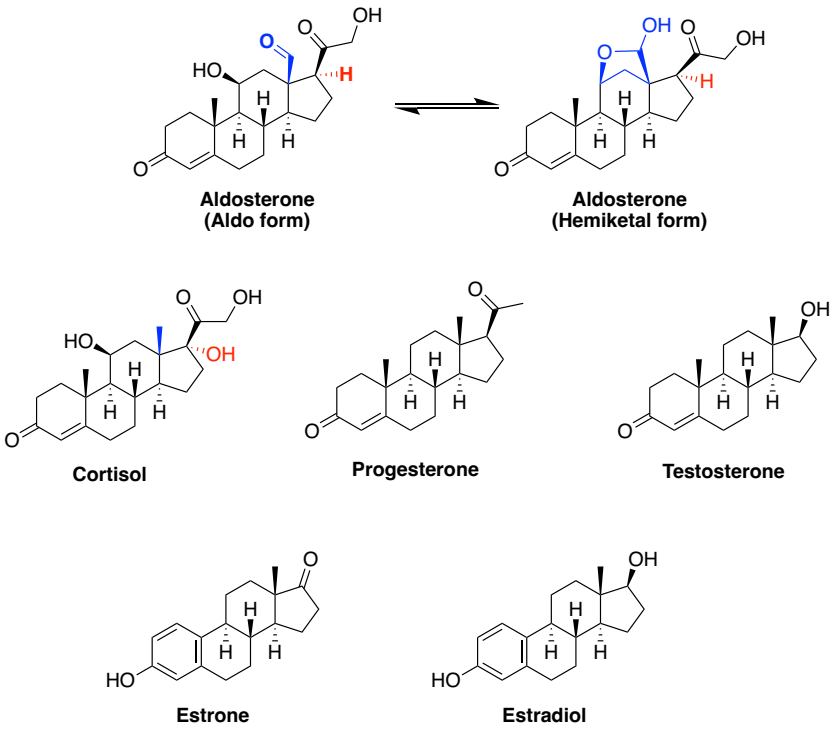
Early signs of NCDs in children aged 5–19 years, 2020 and 2035[1][2]

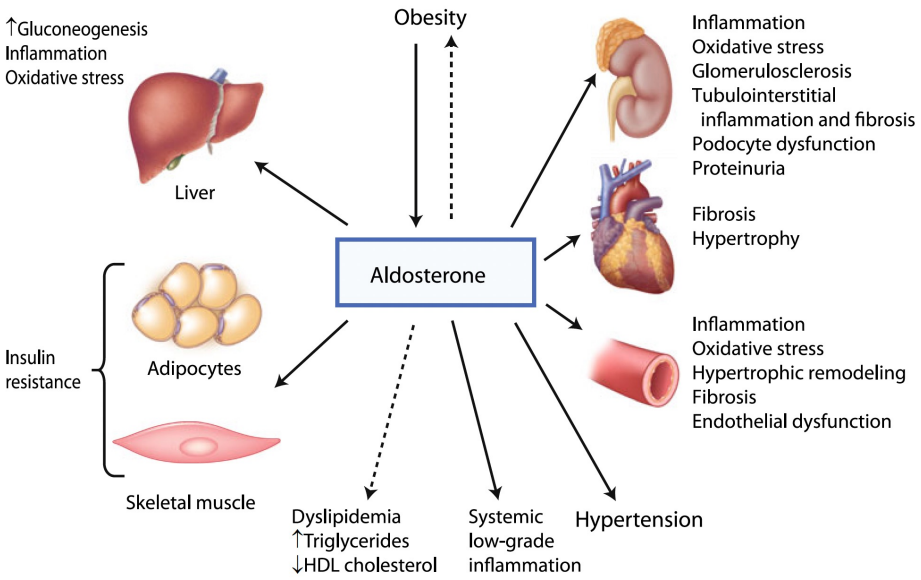
	2020	2035
Prevalence of children with high BMI	**38%**	**49%**
Numbers of children with high BMI	**1,415,728**	**1,630,339**
of which, children with high blood pressure attributable to high BMI	118,952	150,706
of which, children with hyperglycaemia attributable to high BMI	49,038	57,470
of which, children with low HDL cholesterol attributable to high BMI	137,210	163,748

World Obesity Atlas 2024

Aldosterone, MR and the Metabolic Syndrome

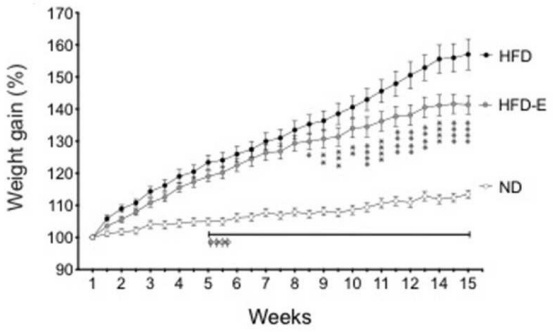
NHR receptor ligands

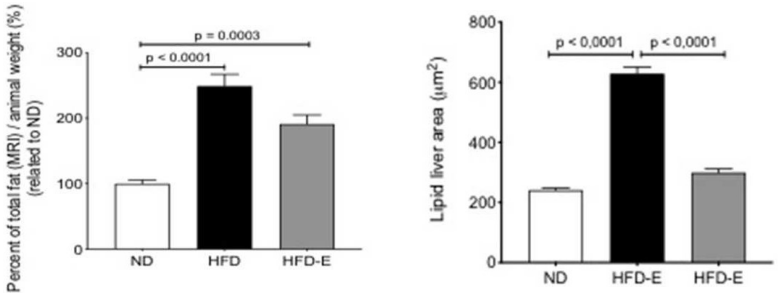


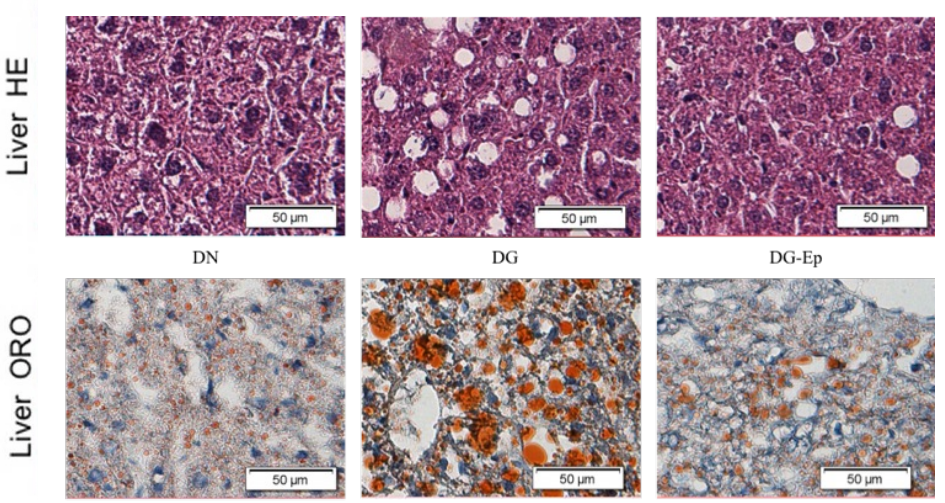


(Briet & Schiffrin, 2011).

The mineralocorticoid receptor (MR) in obesity and fatty liver disease



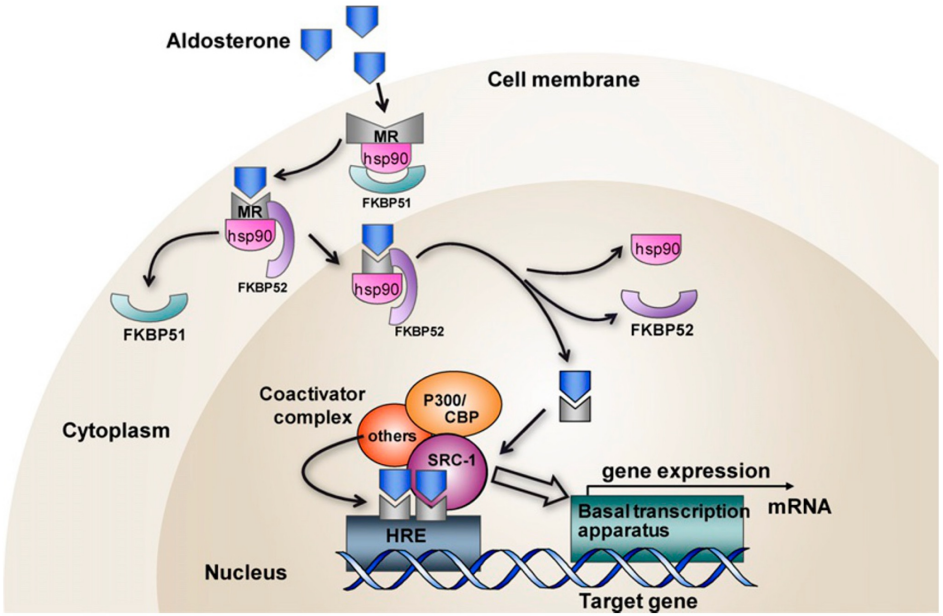




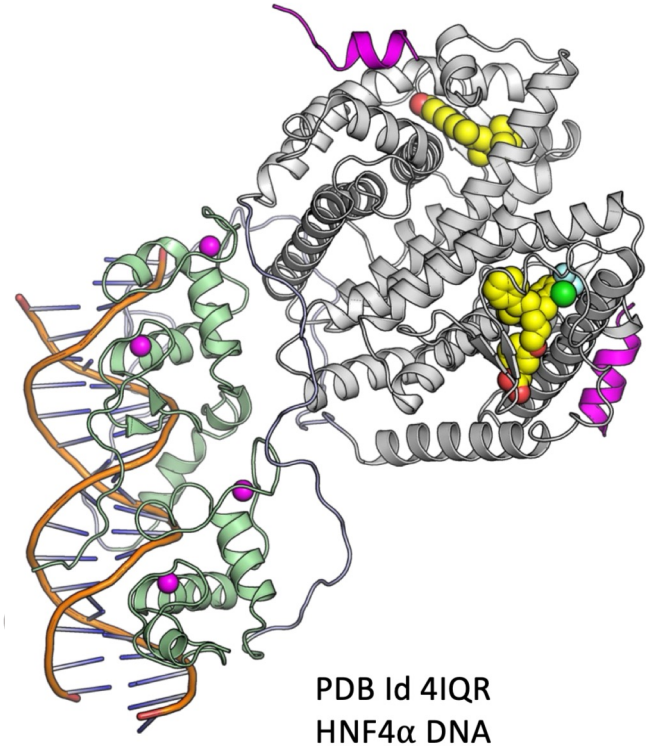
Eplerenone, an MR antagonist reduces body weight gain, fat accumulation, and hepatic lipid accumulation in HFD model of obesity.

Vecchiola et al. *Frontiers in Endocrinology* **2020,** 11, (223).

MR: structure and function (why domains matter)

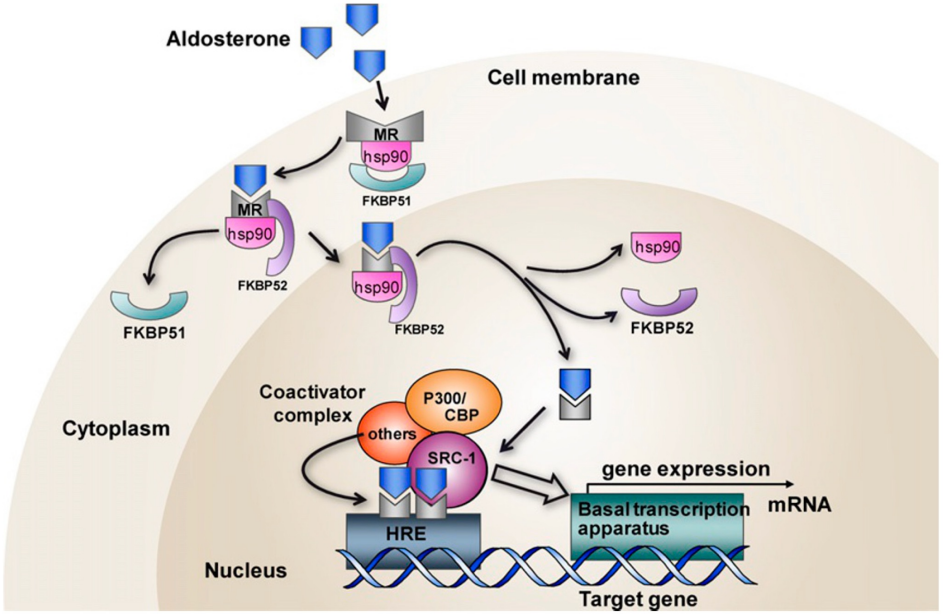


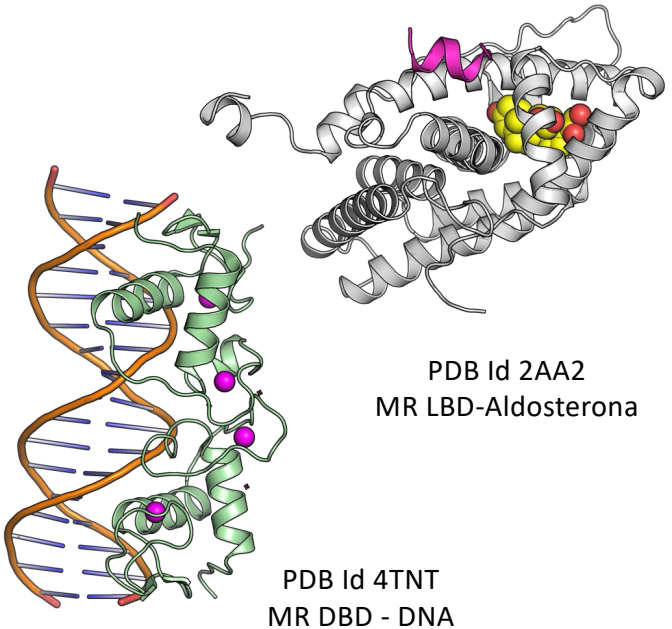
(Baker & Katsu, 2017).



PDB Id 4IQR
HNF4α DNA

MR: structure and function (why domains matter)



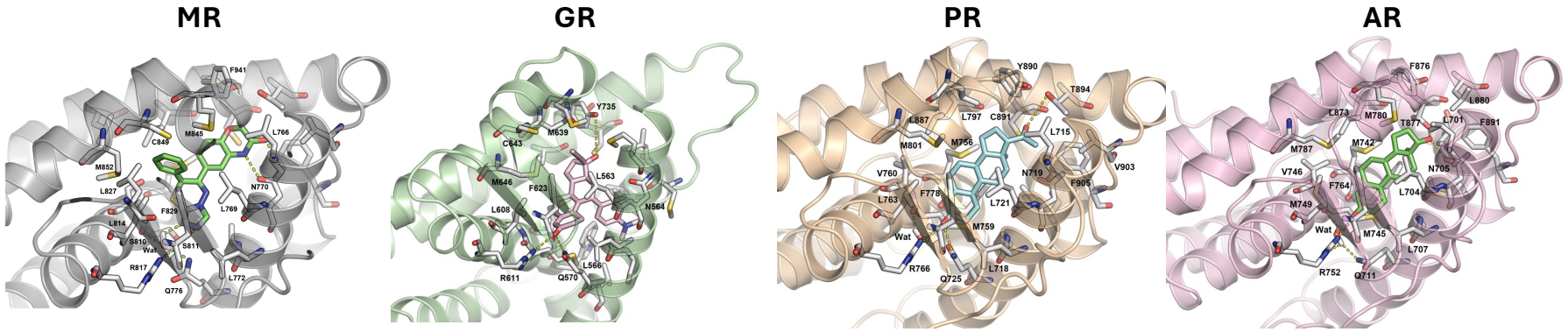


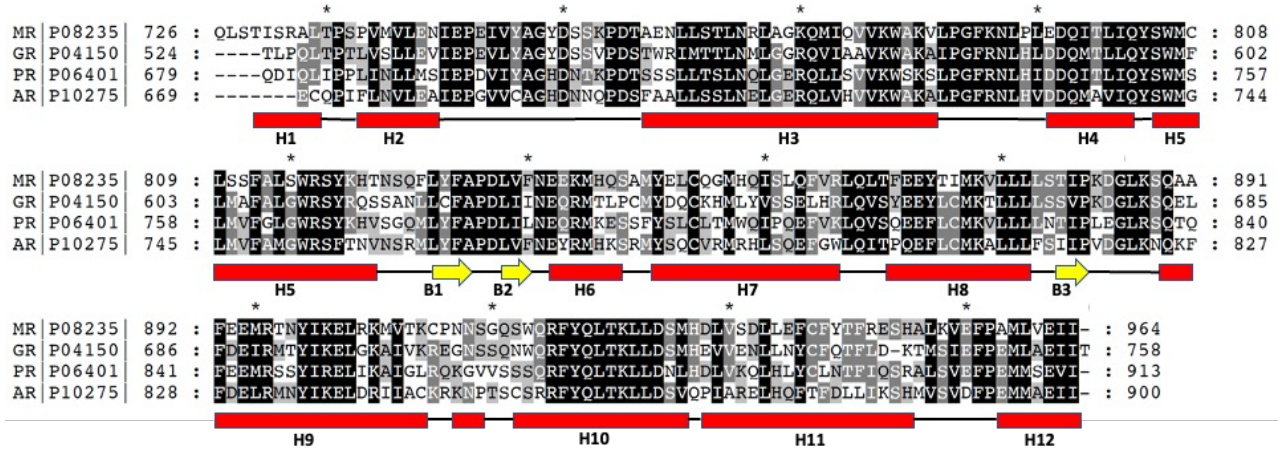
PDB Id 2AA2
MR LBD-Aldosterona

PDB Id 4TNT
MR DBD - DNA

(Baker & Katsu, 2017).

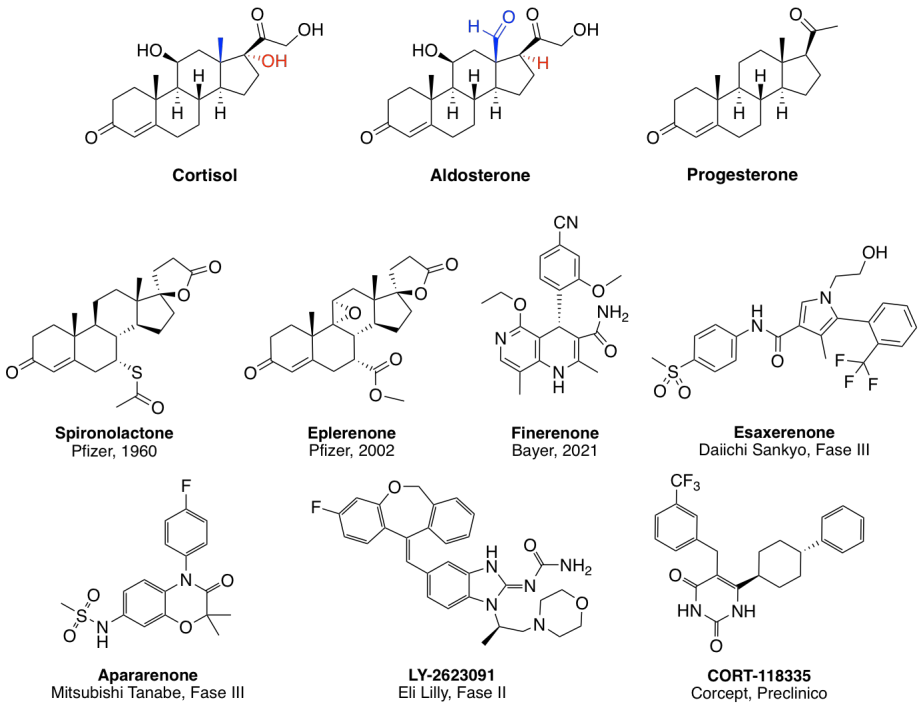
LBD architecture and AF-2 mechanics

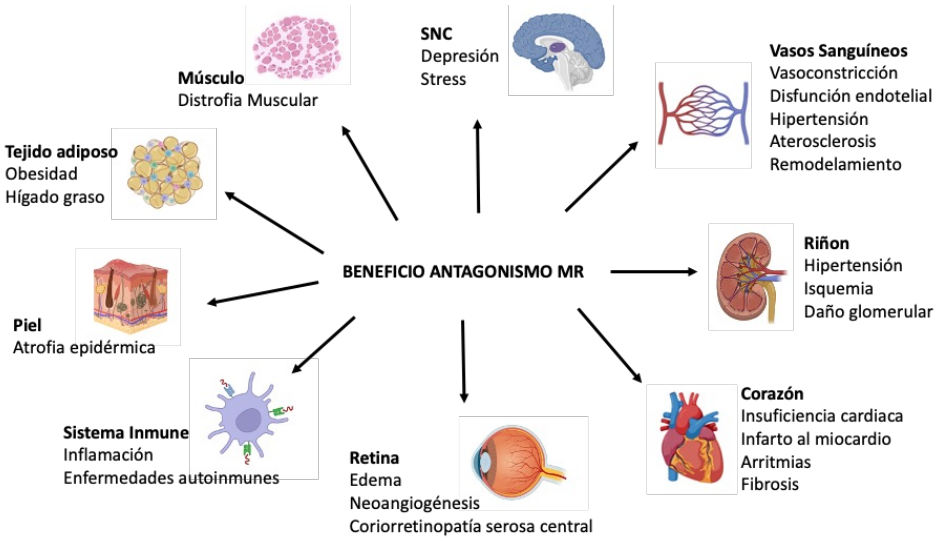




MR residues	GR	PR	AR
Identical	55%	53%	49%
Similar	74%	73%	69%
Gaps	2%	1%	2%

Current MR antagonists: utility and limitations



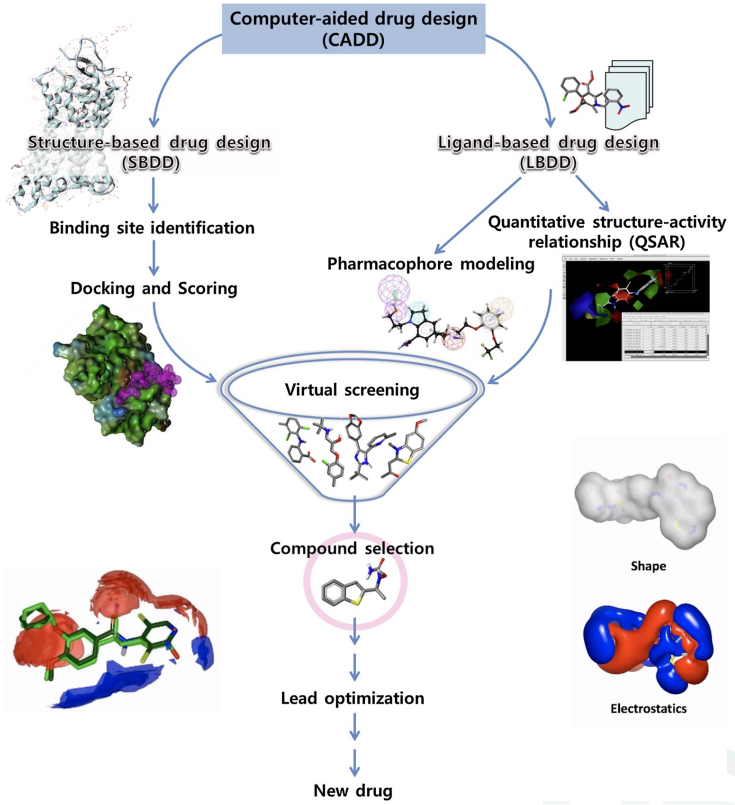


(Agarwal et al., 2021)

Computer-aided drug discovery (CADD) frame

Drug design tools are used to estimate the affinity of the ligand for the protein; in addition to accelerating the speed of drug discovery and decreasing the cost.

Structural bioinformatics approaches use structure-based or ligand-based methods. These methods are used for structural optimization to improve potency and identification.



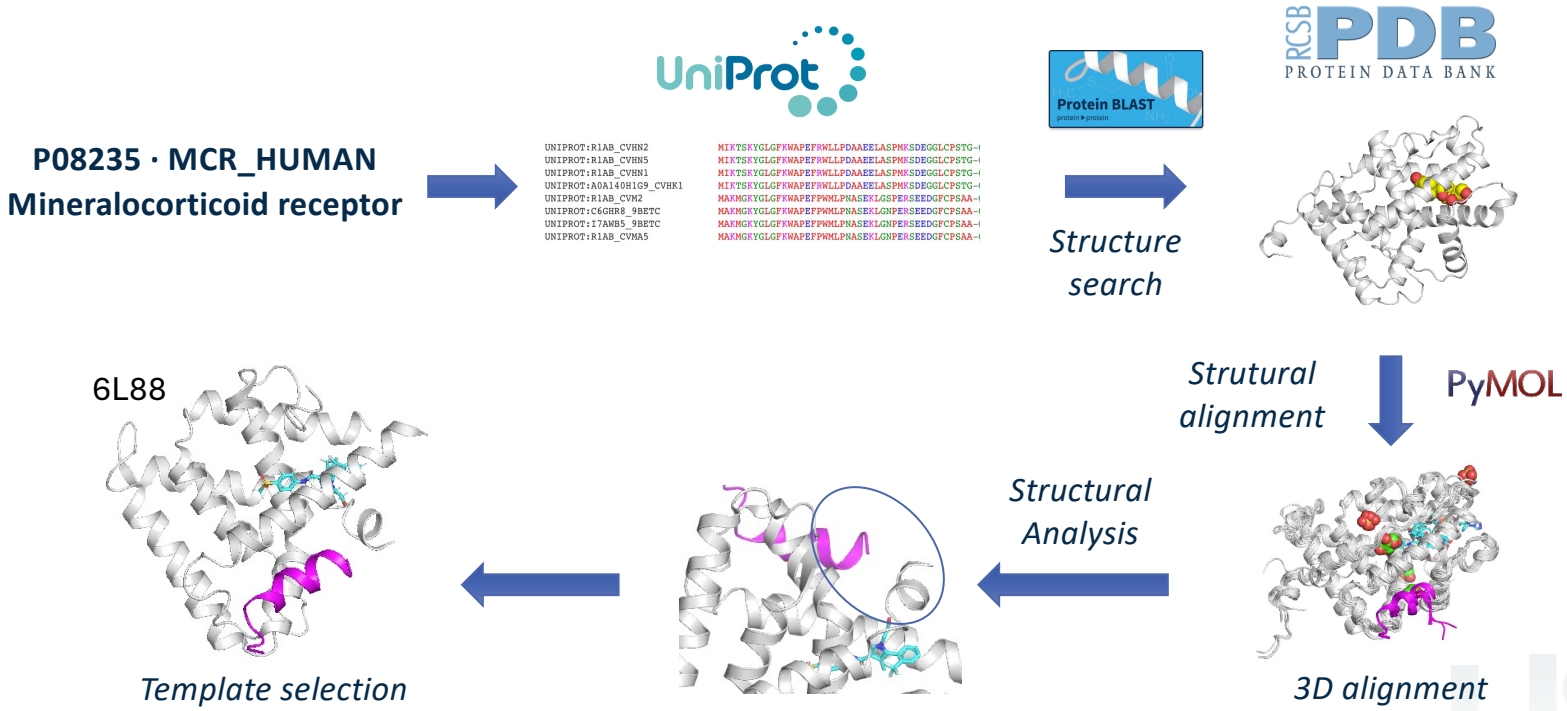
Strategy: concept to workflow

Combined ligand and structure virtual screening emerges as a valuable strategy for the identification of MR pure antagonists modulators with potential biological activity.

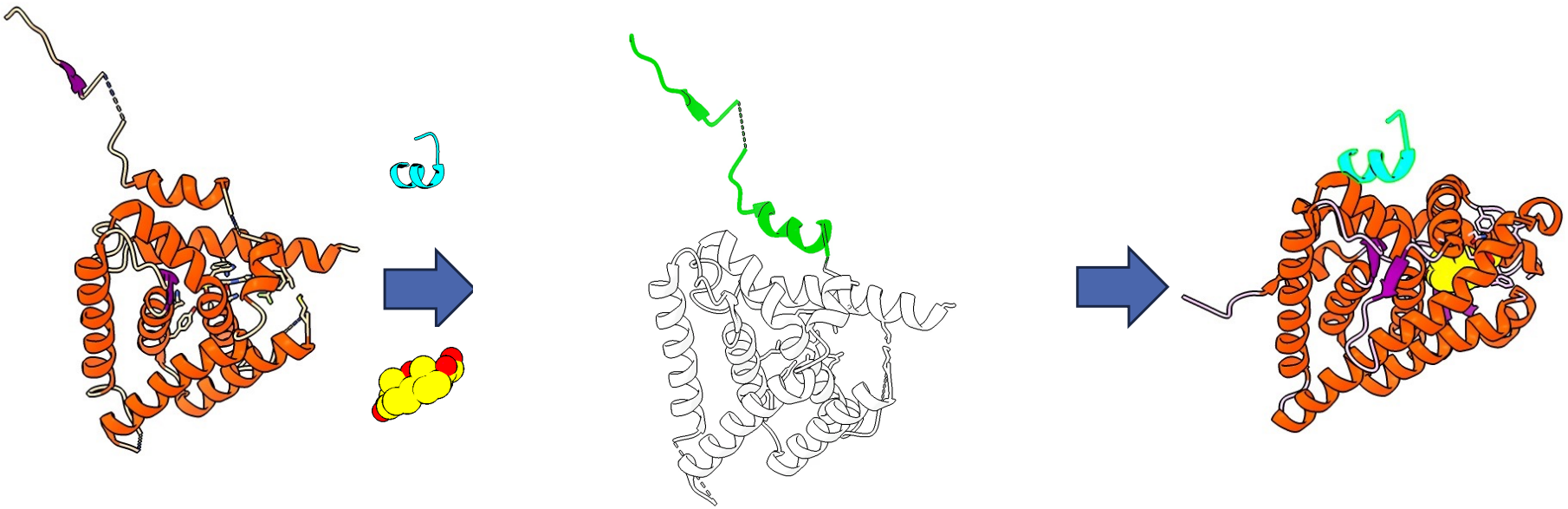
- Complete crystallographic structure of the MR-Esaxerenone complex, enabling the exploration of MR in its inactive state.
- Identify ligands that may bind with high affinity the orthosteric sites of the MR using virtual screening approaches.
- Select compounds with potential allosteric modulatory activity and adequate physicochemical properties for human administration.
- Perform biological evaluations of selected compounds using *in vitro* models of adipogenesis.

Results and Discussion

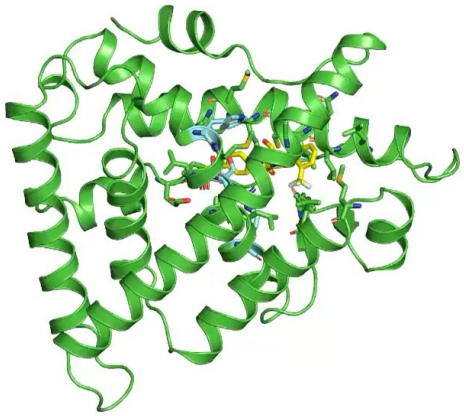
Complete crystallographic structure of the MR-Esaxerenone complex, enabling the exploration of MR in its inactive state.

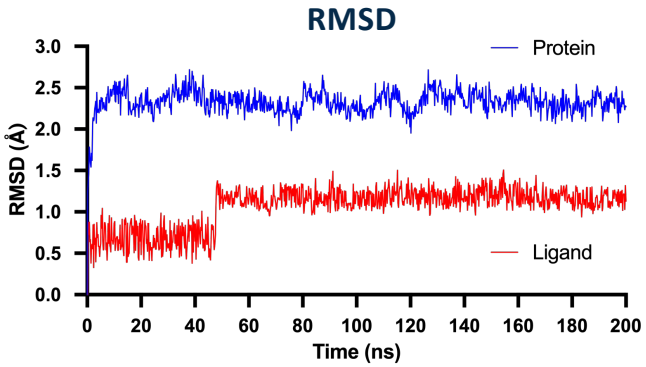


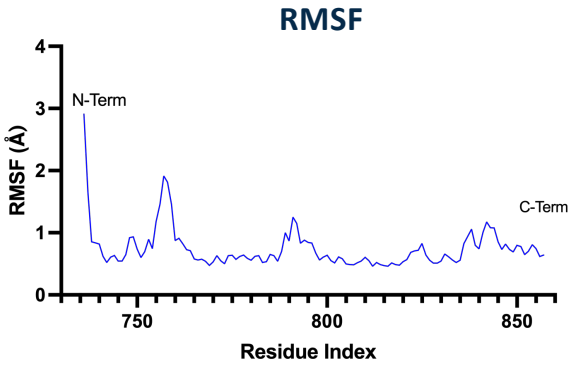
Modeling and validating the inactive MR state

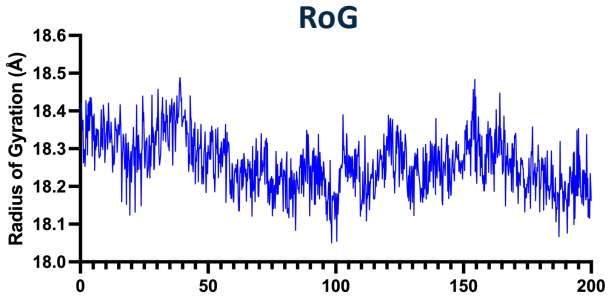


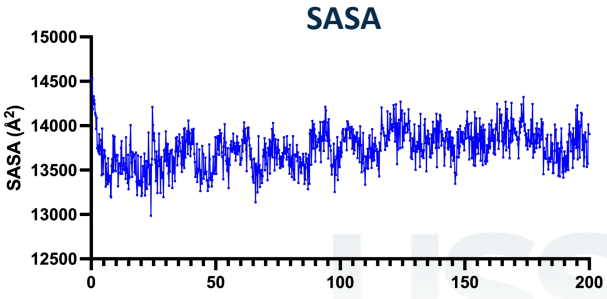
Modeling and Validation of an inactive state of MR Molecular Dynamics of the MR-Esaxerenone complex



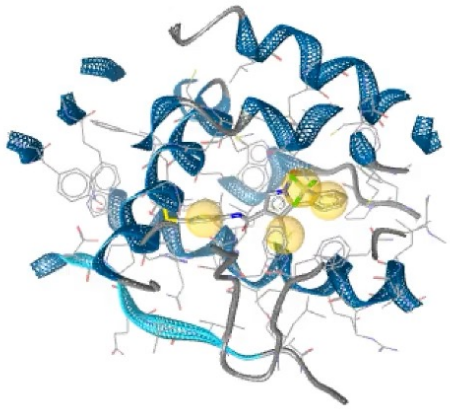


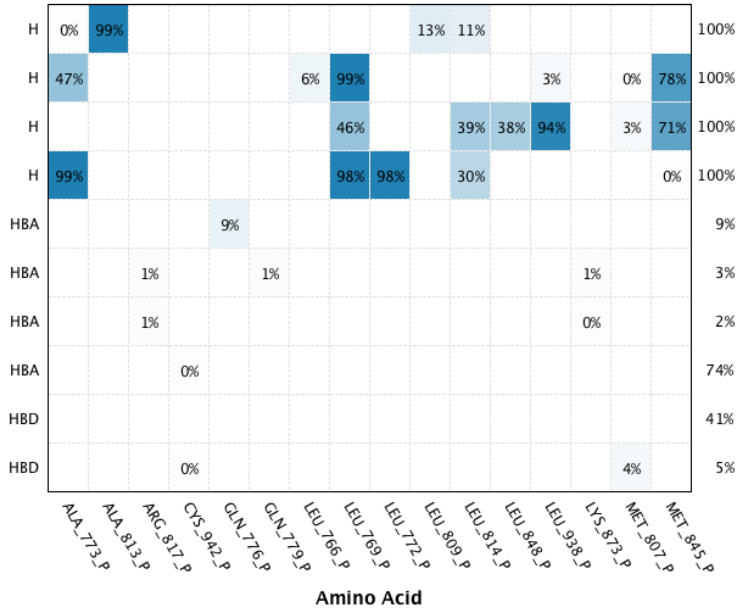






MD with esaxerenone: from trajectories to features





LigandScout

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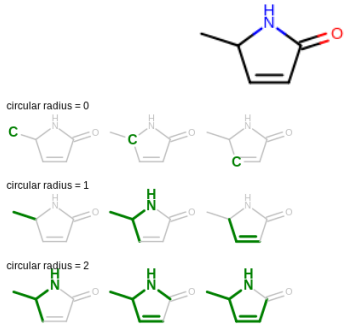
Identify ligands that may bind with high affinity towars inactive conformation of MR using 2D and 3D virtual screening

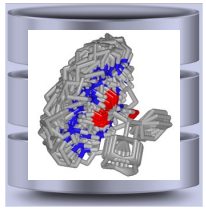
Chemical Compounds Databases (100 million)

Canonization & ADME/Tox filtering
FILTER

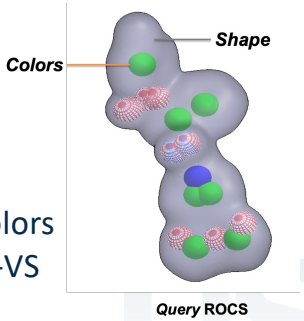


Fingerprint based 2D-VS

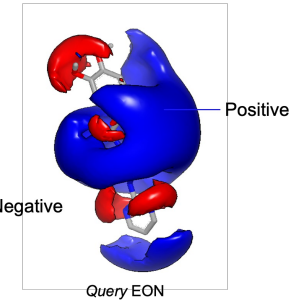
3D conformer generation



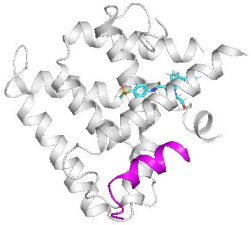
Tanimoto = $\frac{A \cap B}{A \cup B}$



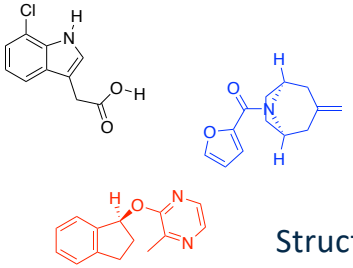
Shape & Colors based 3D-VS ROCS



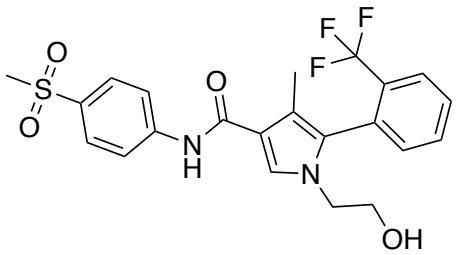
Electrostatic based 3D-VS EON



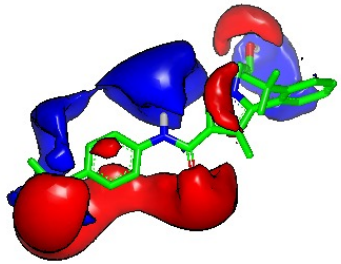
Structure Based Virtual Screening
FRED

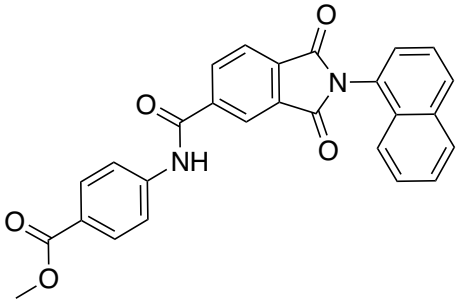


Identify ligands that may bind with high affinity over MR inactive conformation using virtual screening approaches.

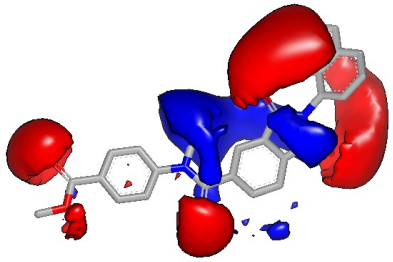


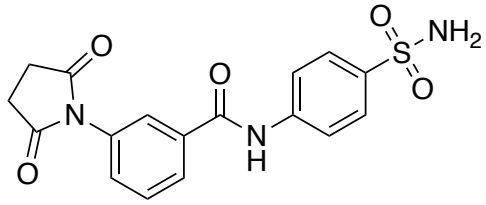
Control Esaxerenone
FRED ChemGauss4 Score: -11,167





LIG1
FRED ChemGauss4 Score: -15,646
Shape + Charge Tanimoto: 0,796

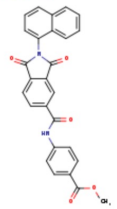


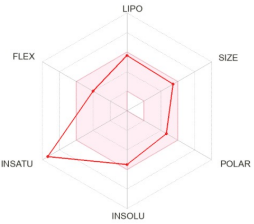


LIG4
FRED ChemGauss4 Score: -14,345
Shape + Charge Tanimoto: 0,796

Select compounds with potential allosteric modulatory activity and adequate physicochemical properties for human administration :ADME triage

LIG1

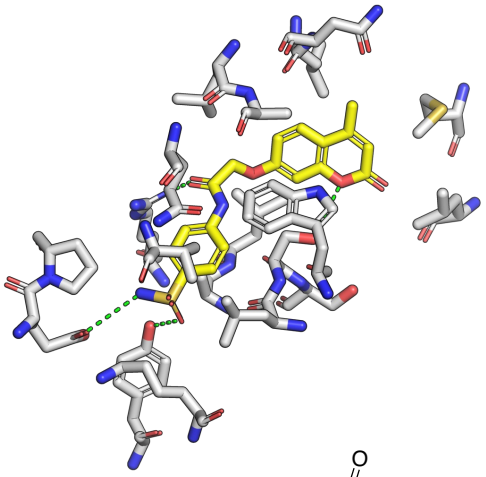


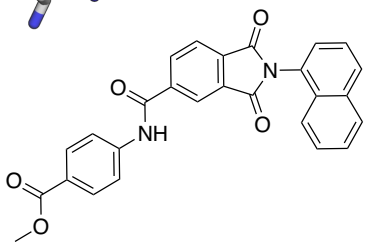


SMILES COC(=O)c1ccc(cc1)NC(=O)c1ccc2c(c1)C(=O)N(C2=O)c1cccc2c1cccc2

Physicochemical Properties	
Formula	C27H18N2O5
Molecular weight	450.44 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	22
Fraction Csp3	0.04
Num. rotatable bonds	6
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	129.96
TPSA	92.78 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.08
Log $P_{o/w}$ (XLOGP3)	4.40
Log $P_{o/w}$ (WLOGP)	4.11
Log $P_{o/w}$ (MLOGP)	3.86
Log $P_{o/w}$ (SILICOS-IT)	4.18
Consensus Log $P_{o/w}$	3.93

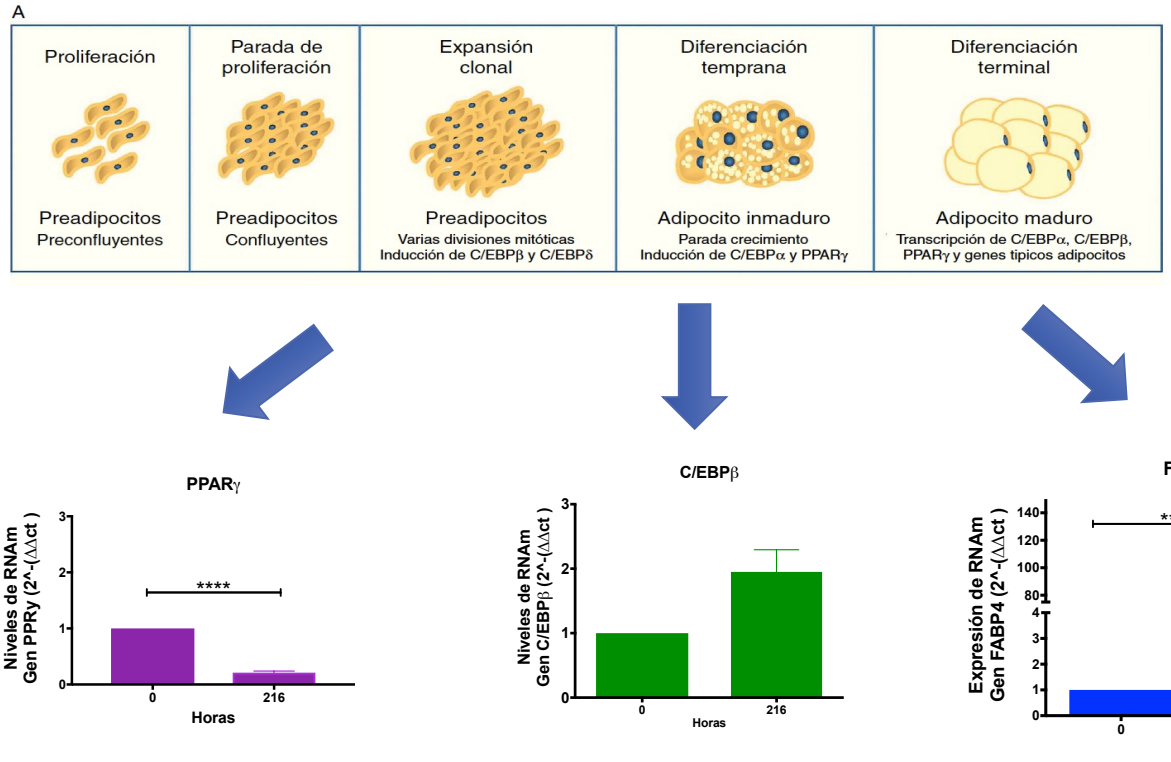
Water Solubility	
Log *S* (ESOL)	-5.49
Solubility	1.47e-03 mg/ml ; 3.25e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-6.07
Solubility	3.87e-04 mg/ml ; 8.60e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-8.72
Solubility	8.52e-07 mg/ml ; 1.89e-09 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.92 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: phthalimide
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	2.72

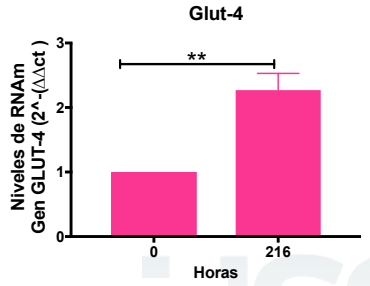




LIG1
FRED ChemGauss4 Score: -15,646
Shape + Charge Tanimoto: 0,796

Validating the human adipogenesis model



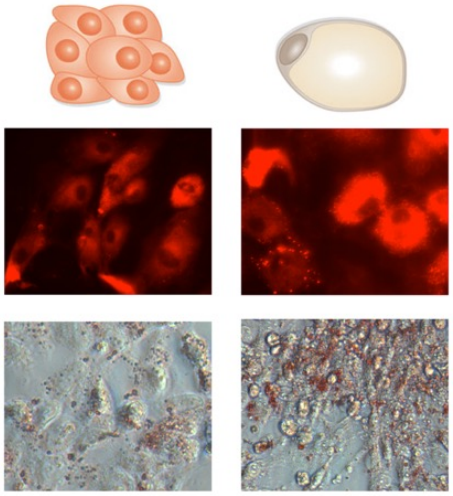


Early / Intermediate Markers

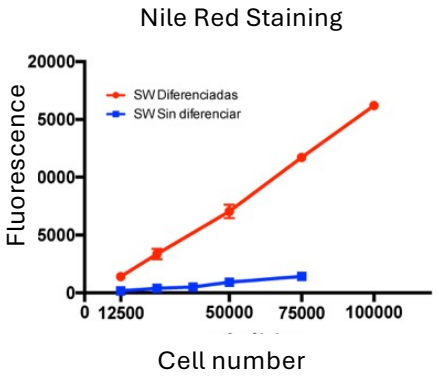
Late Markers

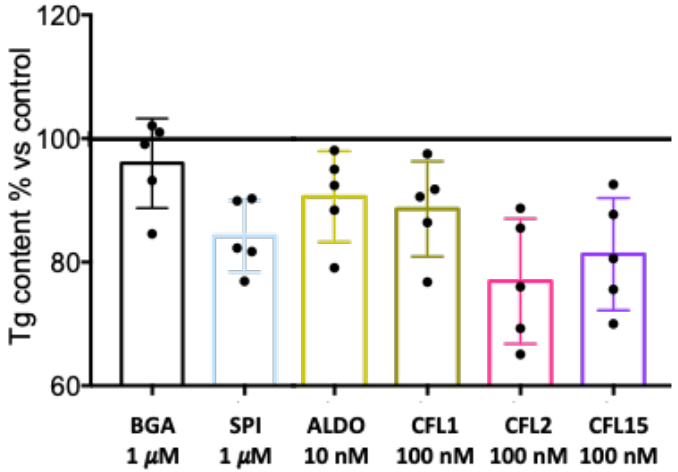
Morphology and lipid readouts (Nile Red / Oil Red)

SW-872 cells

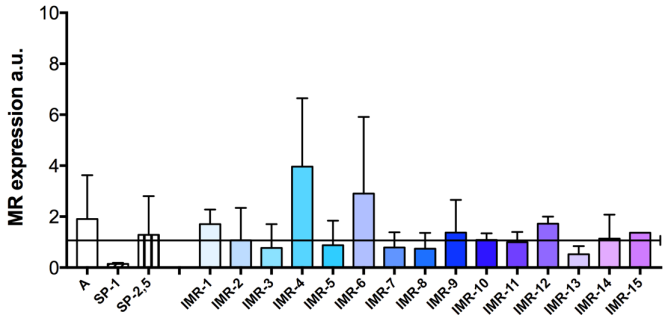


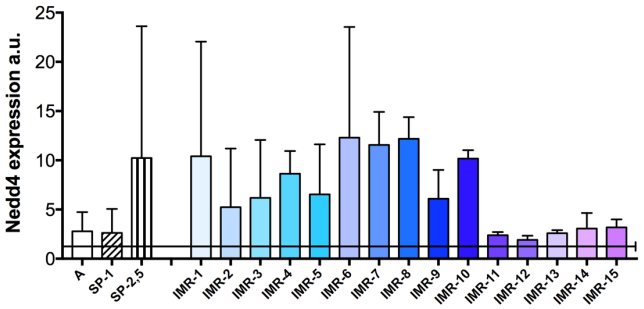
Undifferentiated Differentiated

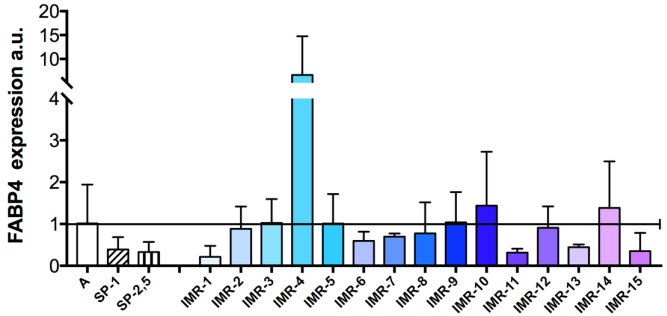


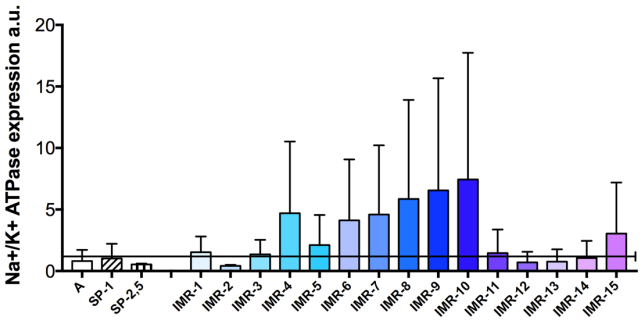


Preliminary MR-responsive transcriptional effects









Conclusions

A combined ligand and structure-based virtual screening approach to identify novel non-steroidal ligands targeting the inactive conformation of MR was developed.

The methods allow us to identified novel non-steroidal scaffolds with desirable physicochemical properties and predicted to have better affinity to MR than for other NRs.

Gene expression analysis of MR target genes by RT-qPCR identified several compounds that showed significant effect over FABP4 and Na+/K+ ATPase expression and similar profile to that of Spironolactone.

Selected MR modulators some of the selected compounds are shown to decrease lipid accumulation in adipocytes in culture. Selectivity assays and confirmation of binding to the LBP site is underway.

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Emerging Challenges and Opportunities for In Silico Drug Discovery

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