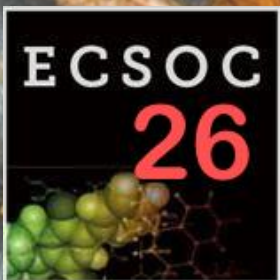


Ivana Todorovska¹, Katerina Dragarska², Jane Bogdanov³

**^{1,2,3}Institute of Chemistry, Faculty of Natural Sciences and Mathematics,
„Ss. Cyril and Methodius“ University - Skopje**

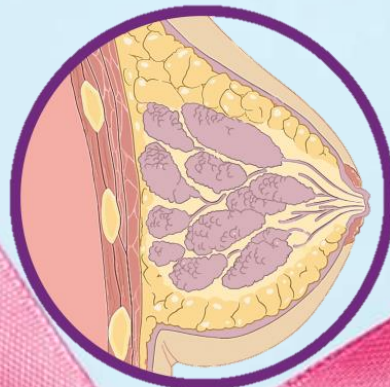
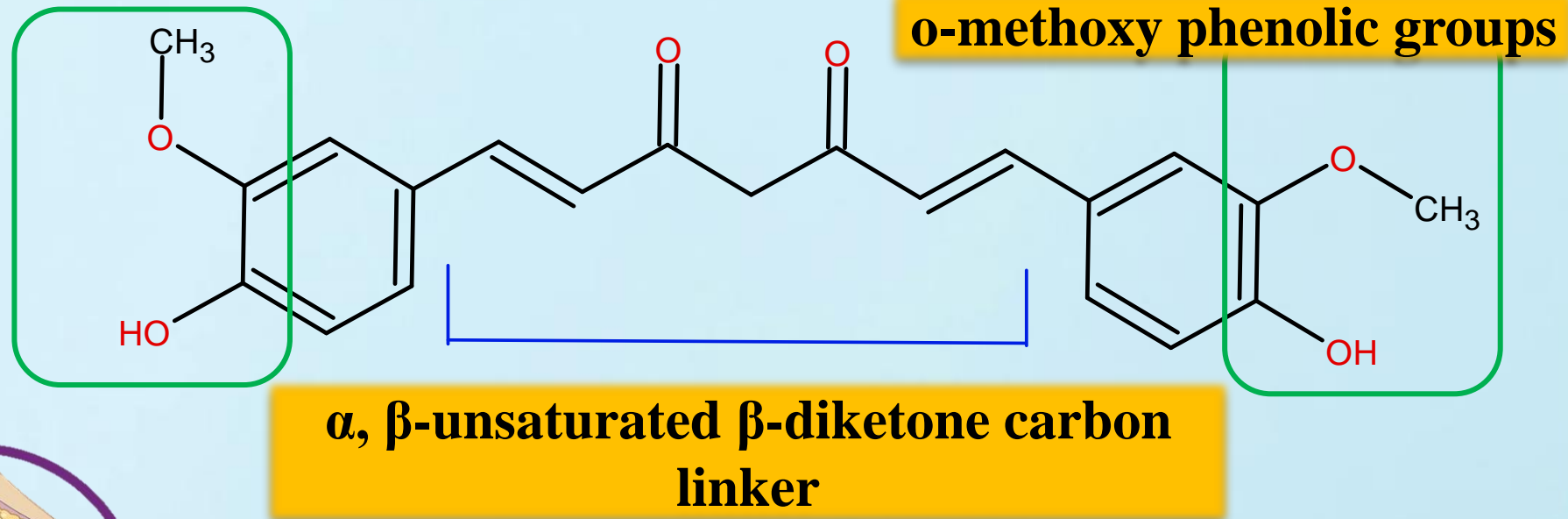
**A combined 2D- and 3D-QSAR study, design and synthesis of some
monocarbonyl Curcumin analogs as potential inhibitors of MDA-
MB-231 breast cancer cells**



15-30 November 2022

Curcumin

(1E,6E)-1,7-bis (4-hydroxy- 3-methoxyphenyl) -1,6- heptadiene-3,5-dione



Curcuma longa

Antioxidant

Antimicrobial

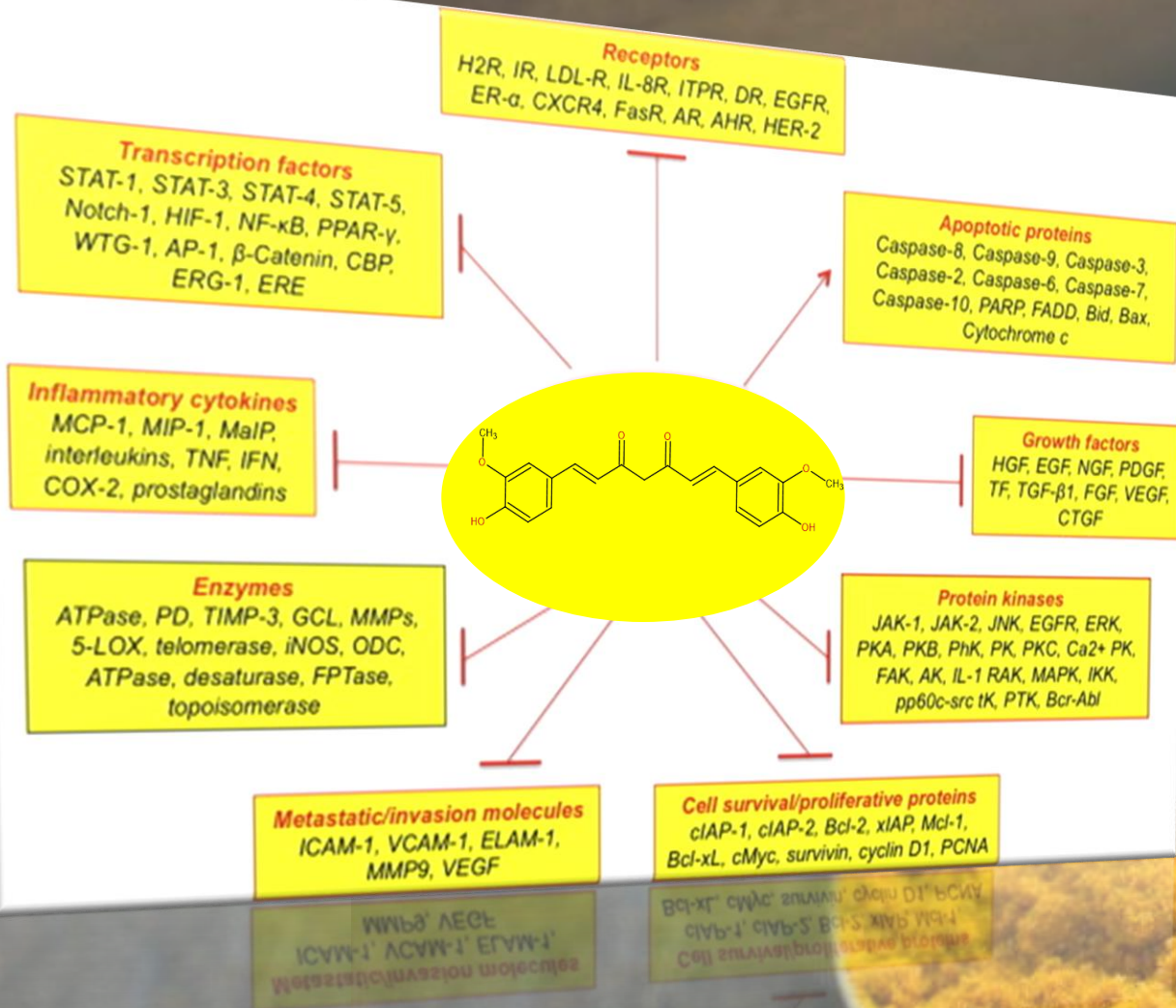
Antidiabetic

Anti-inflammatory

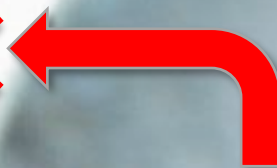
Antiviral

Anti-cancer

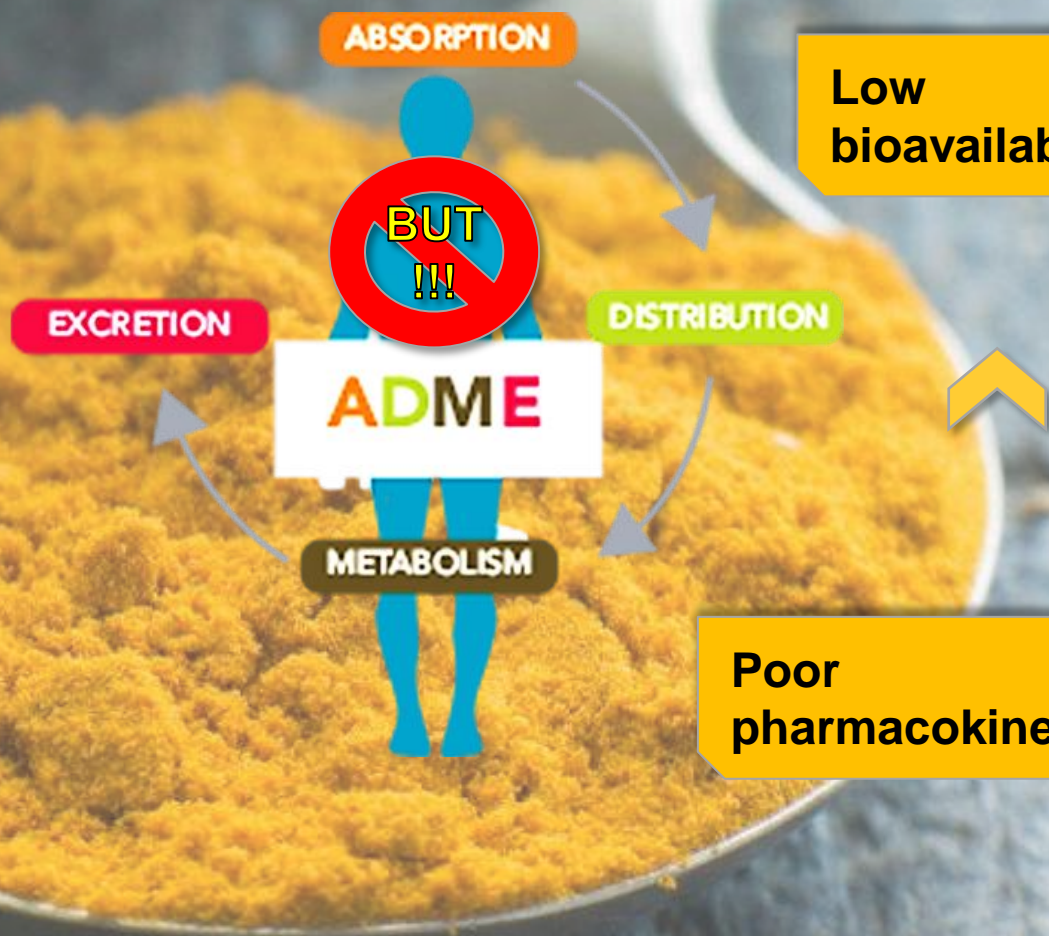




Potential
therapeutic
candidate

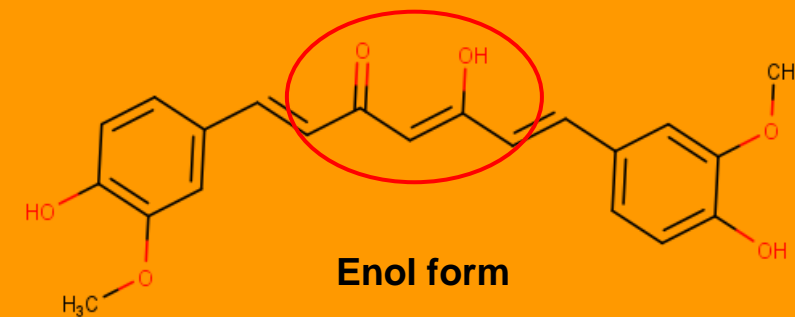
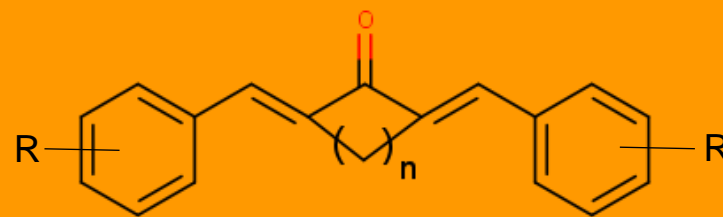


Low
bioavailability

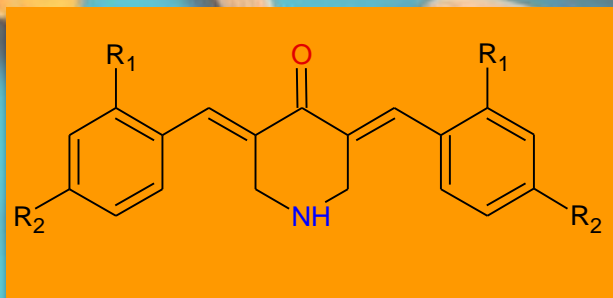


MACs

Structural modification

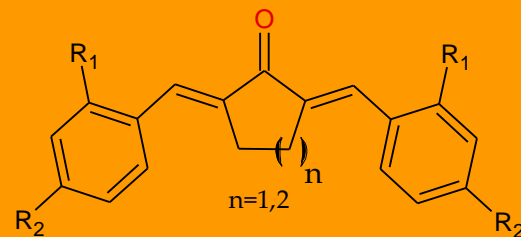


4-piperidone



cyclohexanone

cyclopentanone



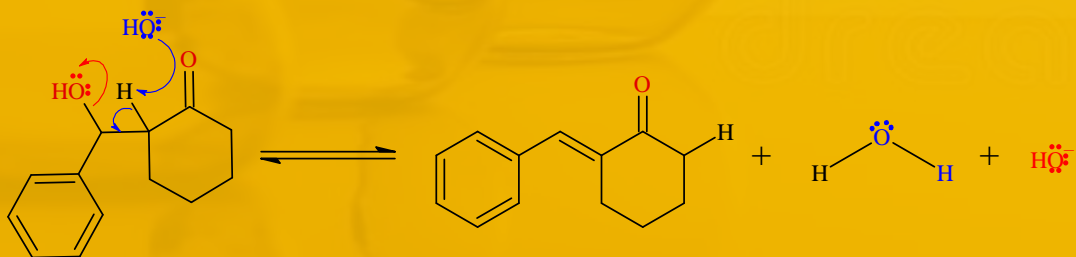
Physiological conditions



Claisen-Schmidt condensation

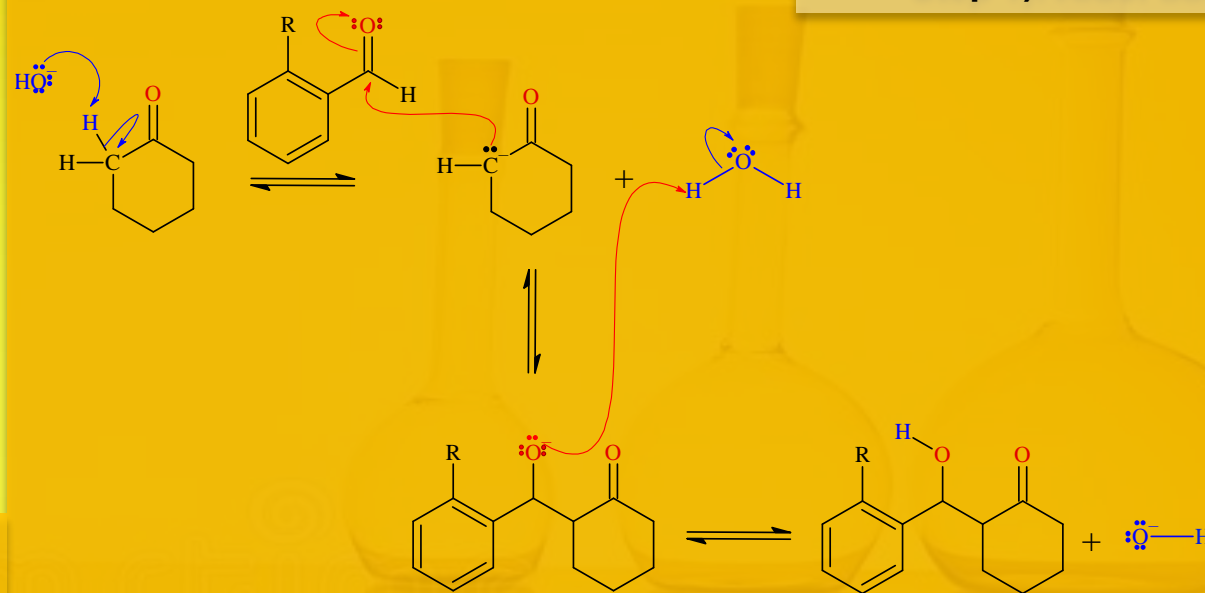
➤ cross-aldol reaction

Step 2): Dehydration via E2 elimination



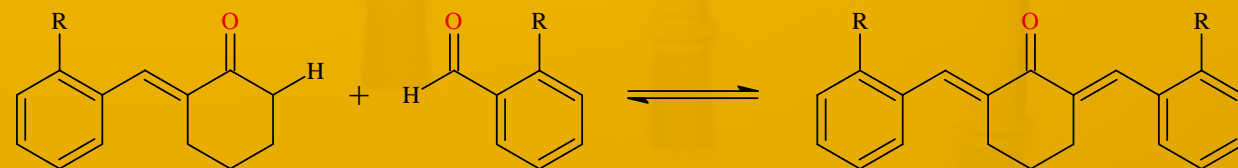
Conjugated enone

Step 1): Aldol addition



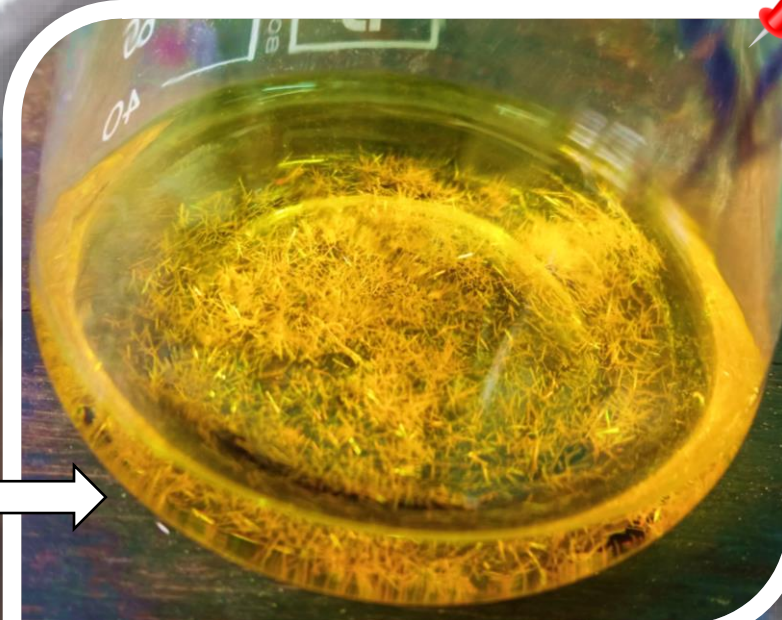
β -hydroxy ketone

Reaction with 2nd eq. of benzaldehyde



Symmetrical MAC

Experimental procedure



Characterization

Mel-Temp II



Measuring and comparing the MP to their literature values

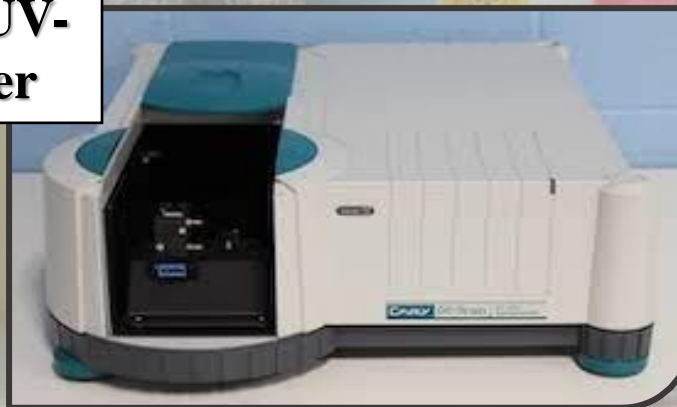
Perkin Elmer 2000 FT-IR spectrophotometer



Golden gate sapphire/diamond system

Recording FTIR spectra with KBr pellet method and ATR technique (range: 4000-650 cm^{-1})

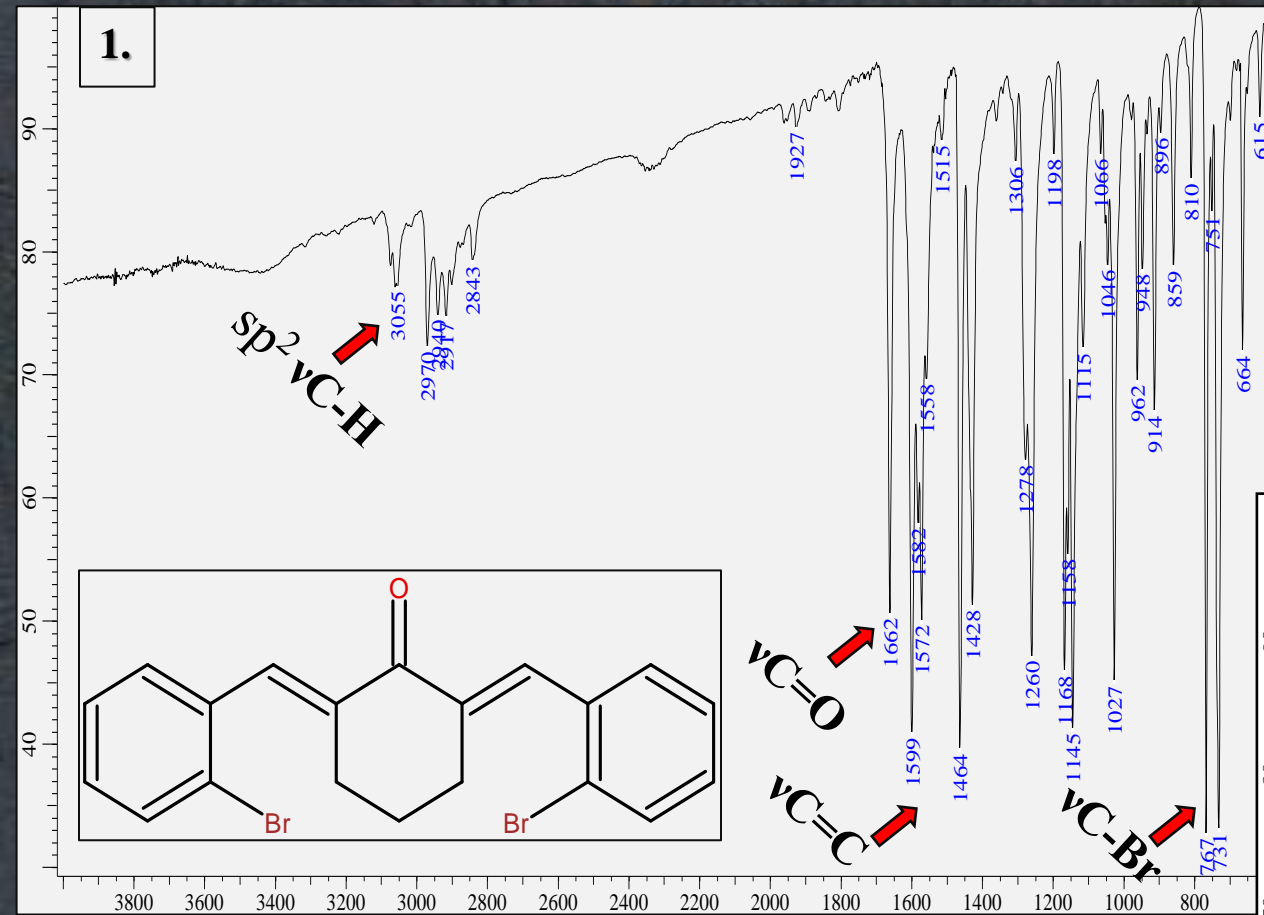
Varian Cary 50 Scan UV-Vis spectrophotometer



Recording UV/Vis spectra in pure acetonitrile (range: 200-800 nm)

Spectroscopic analysis:

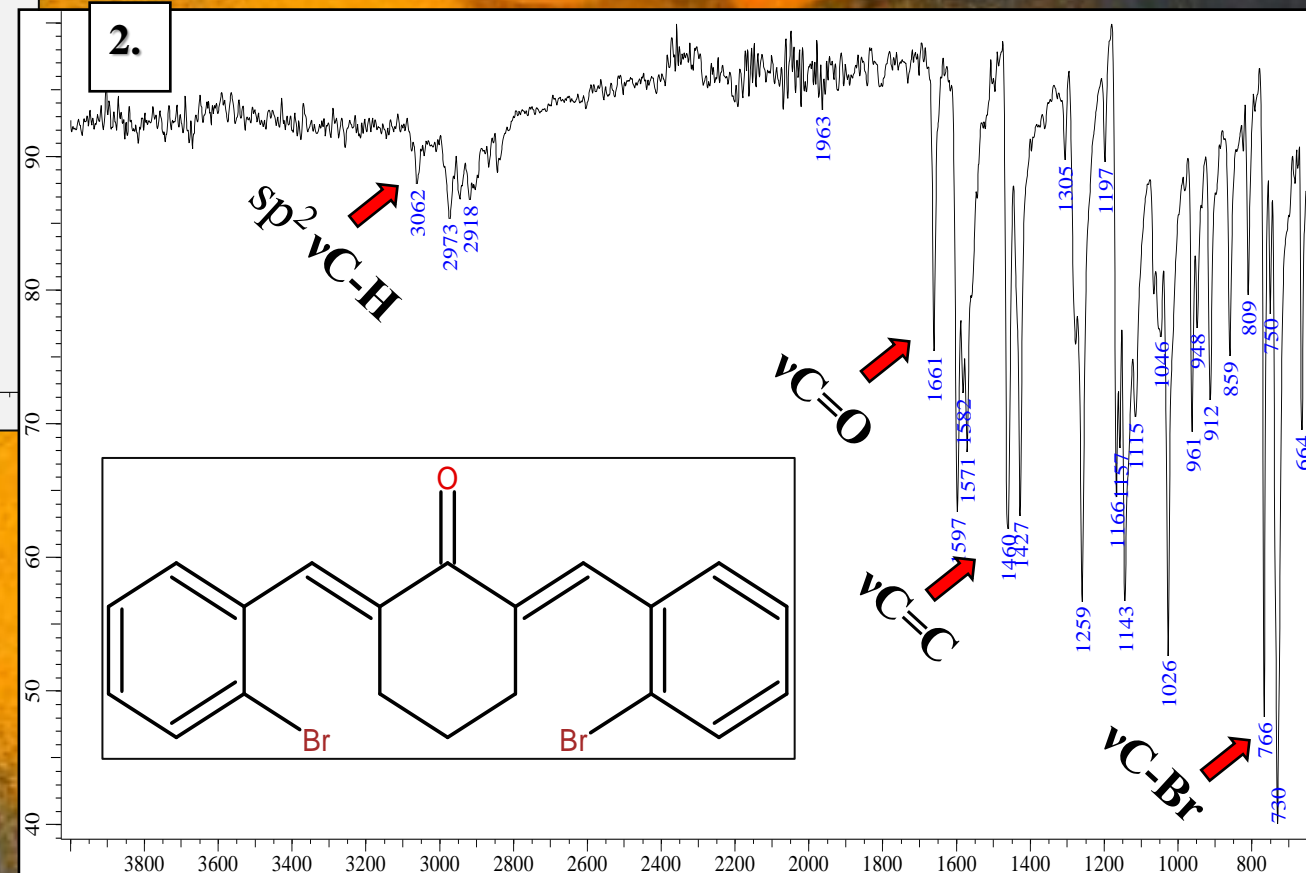
1.



1. FTIR spectrum of (2E,6E)-2,6-bis(2-bromobenzylidene)cyclohexanone prec. 5:2 CH₃OH/CH₂Cl₂ (KBr)

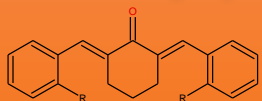
2. ATR-FTIR spectrum of (2E,6E)-2,6-bis(2-bromobenzylidene)cyclohexanone prec. 5:2 CH₃OH/CH₂Cl₂

2.



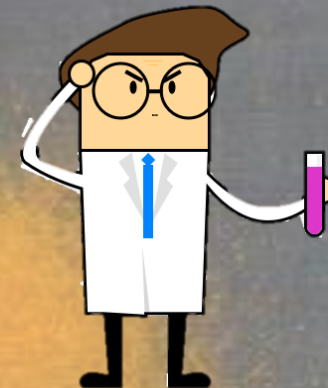
QSAR (Quantitative structure-activity relationship)

Original
scientific paper



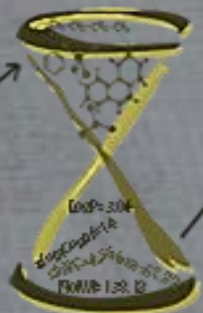
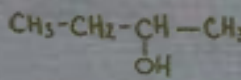
**pIC50 values against
MDA-MB-231 breast
cancer cells**

How can I predict the
anti-breast cancer activity
of my novel compounds?

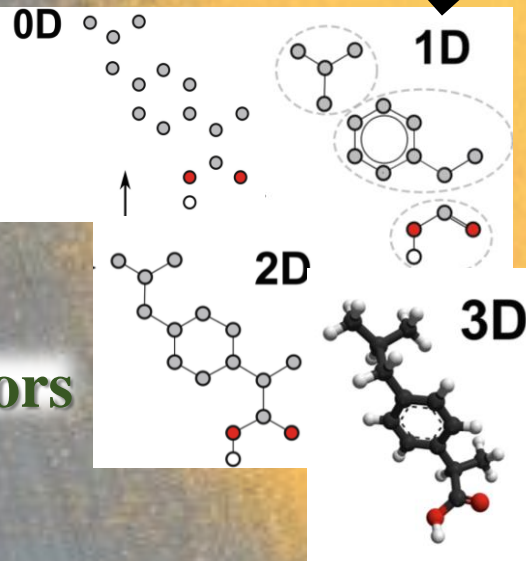


**Construction of statistical
models (MLR and PLS)**

**Internal and external
validation**



0D	MolWt	138.12
1D	nrot	14
2D	LogP	3.04
3D	chi0C	4.96
	tpsa	57.22



36 molecules

Molecular descriptors

**Train set-29
Test set-7**

2D-QSAR model

➔ ChemDes and HyperChem

➔ SPSS statistical software

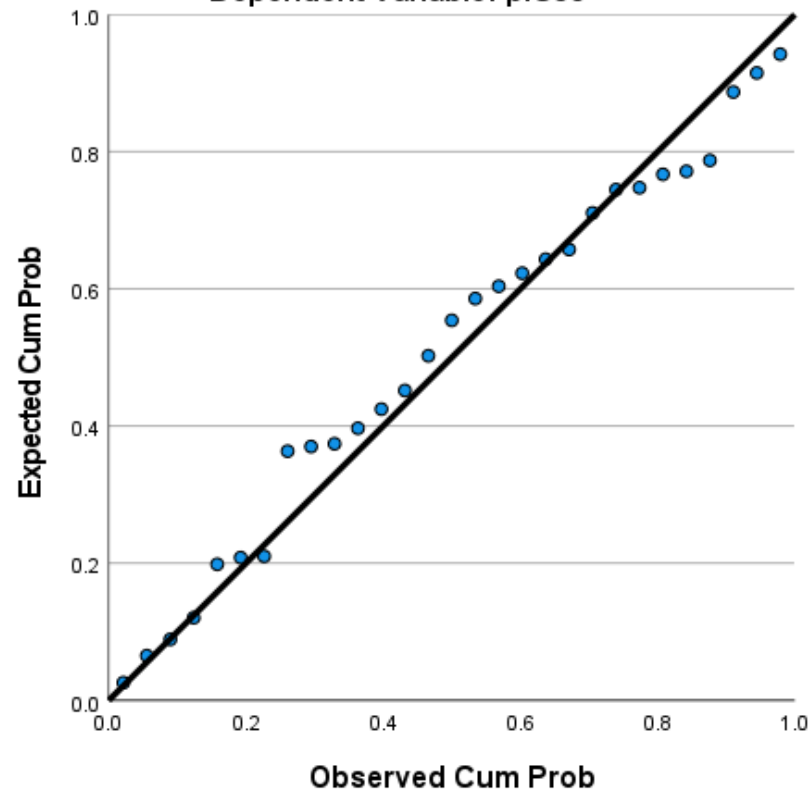
Multi linear regression equation

$$pIC50 = -1.63 * MATS3s + 0.83 * TDB10u + 0.1 * RDF60p - 2.88 * SCH6 + 2.32 * BIC4 + 0.1 * nHBint6 - 0.188 * CrippenLogP - 4.04$$

- *pIC50*-dependent variable
- descriptors-independent variable
- α (numbers)- regression coefficients

Normal P-P Plot of Regression Standardized Residual

Dependent Variable: pIC50



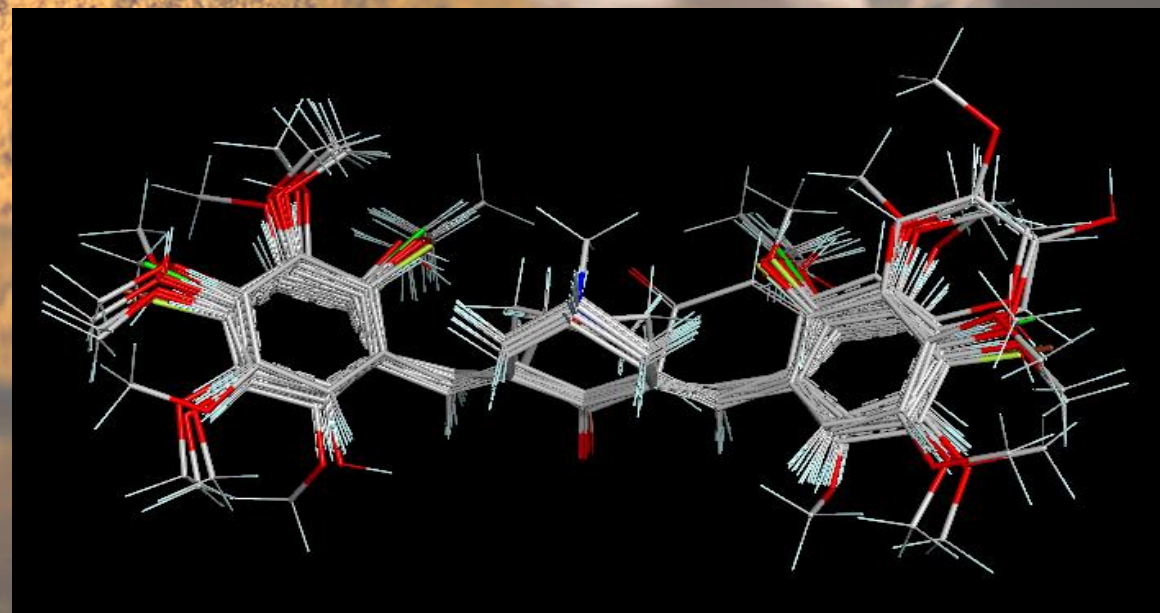
Validation parameters:

Parameter	N	R ²	SE	P	F	R ² pred
Value	36	0.78	0.266	<0.001	10.336	0.783

3D-QSAR model

➡ Comparative molecular field analysis
(CoMFA) method

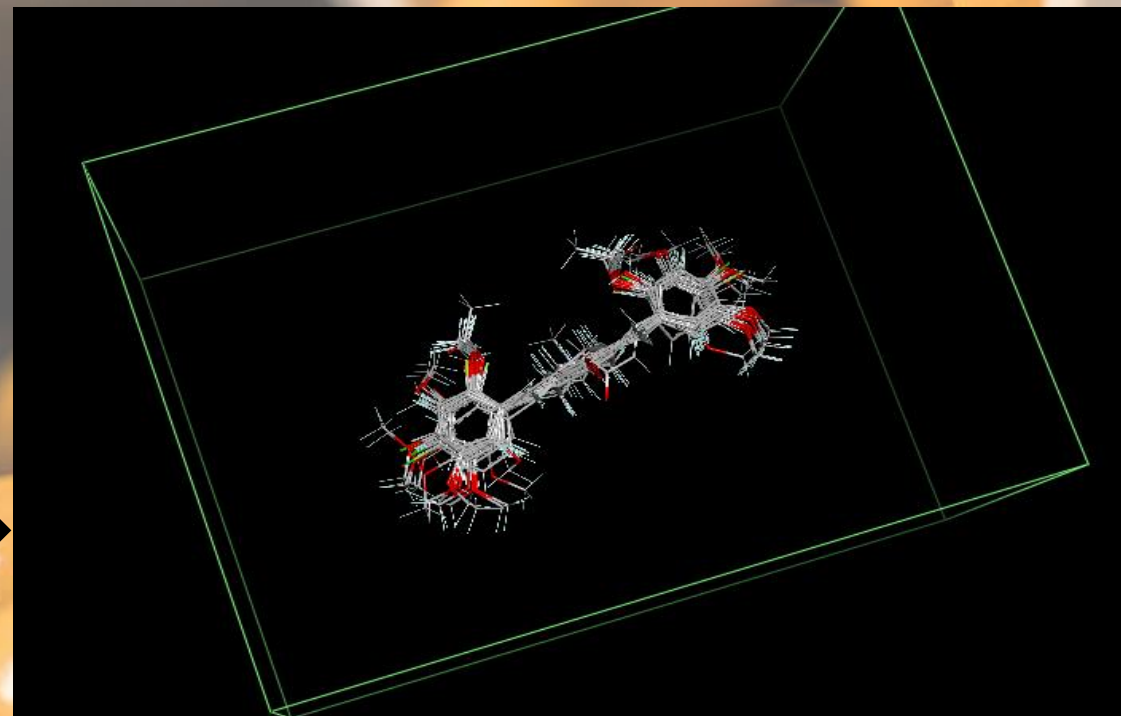
➡ Open3DQSAR program



Alignment of the molecules



Calculation of electrostatic and steric energies (descriptors)

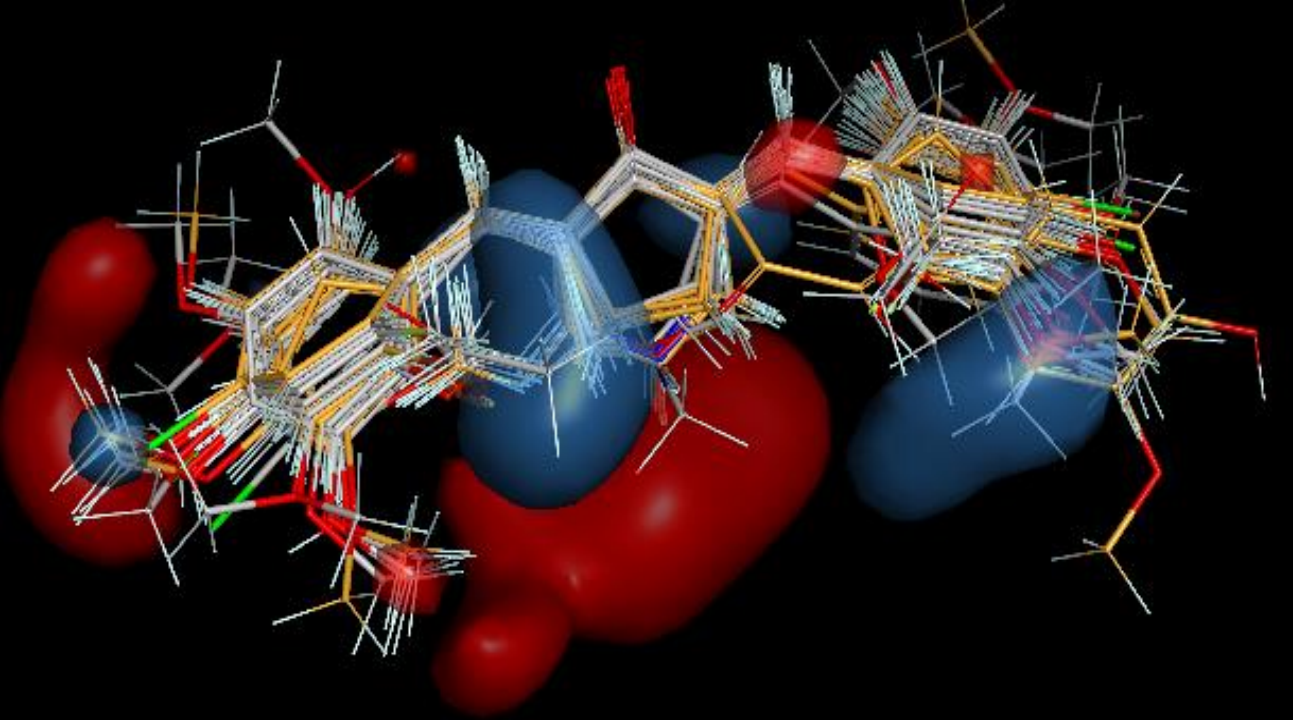
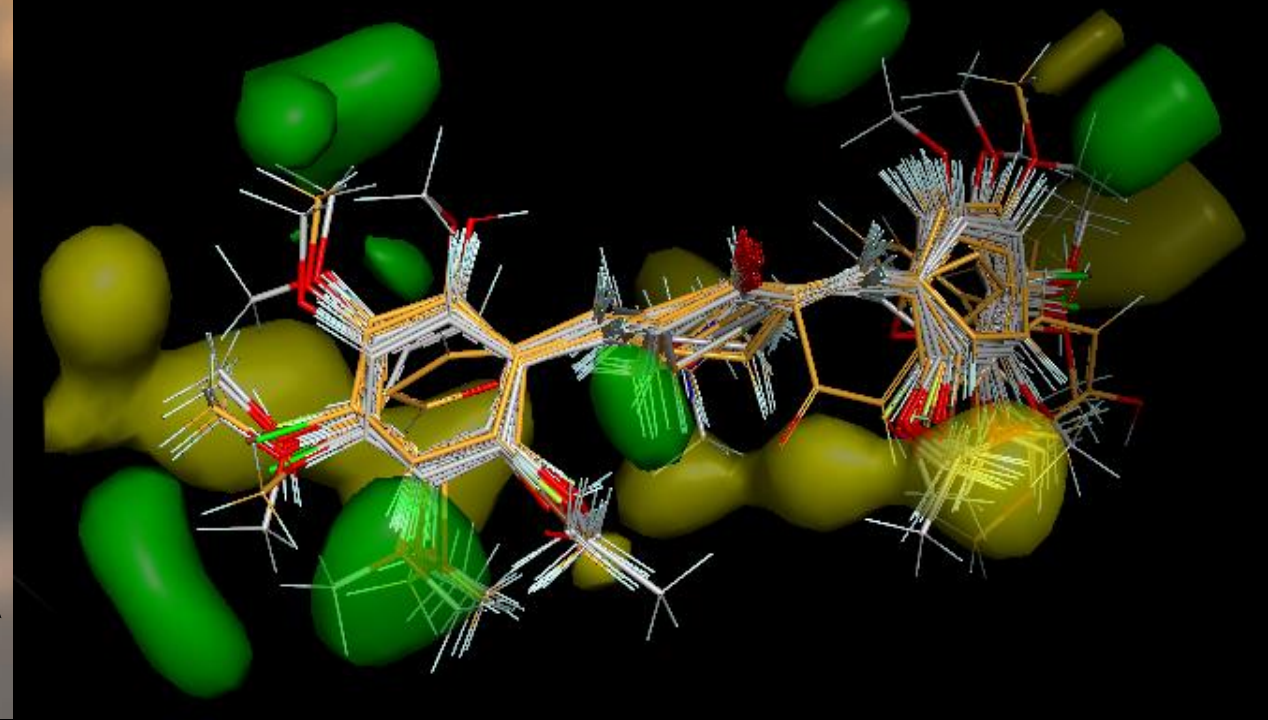
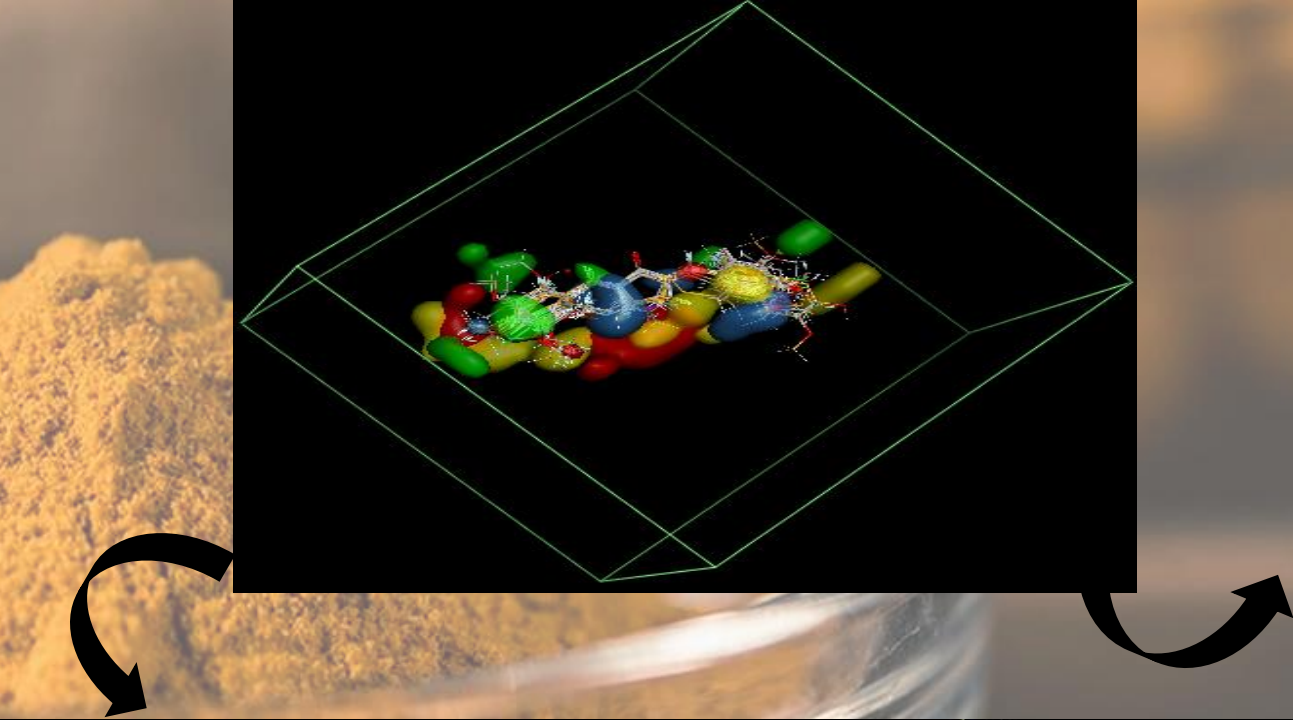


CoMFA color contour maps



Partial least square regression





Validation parameters:

Parameter	N	R ²	SE	R ² pred
Value	36	0.96	0.097	0.91

The predicted activities of the synthesized MACs

Analogue	Predicted pIC50 values (μmol/L)
(3E, 5E)-3,5-bis(2-fluorobenzylidene)-4-piperidone	5.46
(3E, 5E)-3,5-bis(2-bromobenzylidene)-4-piperidone	5.19
(2E, 6E)-2,6-bis(2-fluorobenzylidene)cyclohexanone	5.15
(2E, 6E)-2,6-bis(2-bromobenzylidene)cyclohexanone	5.14
(3E, 5E)-3,5-bis(2-trifluoromethylbenzylidene)-4-piperidone	5.13
(2E,5E)-2,5-Bis(2-furylmethylene)cyclopentanone	5.07
(2E, 6E)-2,6-bis(4-dimethylaminobenzylidene)cyclohexanone	4.54
(2E, 6E)-2,6-bis(2-fluorobenzylidene)cyclopentanone	4.36
(2E, 6E)-2,6-bis(2-bromobenzylidene)cyclopentanone	4.29

≥

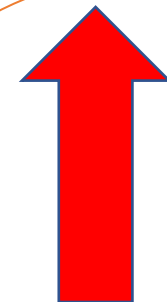
Curcumin

**pIC50 = 4.577
μmol/L**

**↑ Number of
carbon atoms in
the central core**

**Presence of a
heterocyclic structure
moiety**

**↑ Electron
acceptors in the
ortho positions**



**pIC50
value**

A top-down photograph of turmeric ingredients on a dark, textured surface. In the upper left, a wooden spoon is filled with bright yellow turmeric powder. To its left, a small terracotta bowl also contains the powder. Several pieces of fresh turmeric root are scattered around; some are whole, showing their knobby, light brown skin, while others are sliced to reveal the vibrant orange interior. A fine mist of yellow powder is scattered across the dark background, particularly concentrated around the spoon and bowl. The lighting is soft, highlighting the textures of the powder, the roots, and the dark surface.

Thank you for your attention!!