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PPAR~ antagonists as cytotoxic agents in gliomas and pancreatic, colorectal, and renal cancer

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Graphical Abstract

Abstract: Peroxisome Proliferator-Activated Receptors (PPARs) are proteins belonging to the nuclear receptor superfamily, expressed in metabolically active tissues. Three receptor subtypes have been identified, called PPARα, PPARγ and PPARδ, which contribute, each with its peculiarities and functions, to the regulation of lipid and glucose homeostasis.

In recent years, the involvement of the PPARα in the development of tumors has become increasingly evident, although the exact role of this receptor is still controversial. In particular, a reduced PPARα activity has been shown to be beneficial in different types of cancer, like leukemia, prostate, ovarian, and renal cell carcinomas, where a metabolic switch from glucose to fatty acid oxidation occurs. In this context, PPARα antagonists showed cytotoxic activity in different cancer cell lines.

In this presentation the effects of some PPARα antagonists with sulfonimide structure on gliomas and pancreatic, colorectal, and renal cancer will be illustrated.

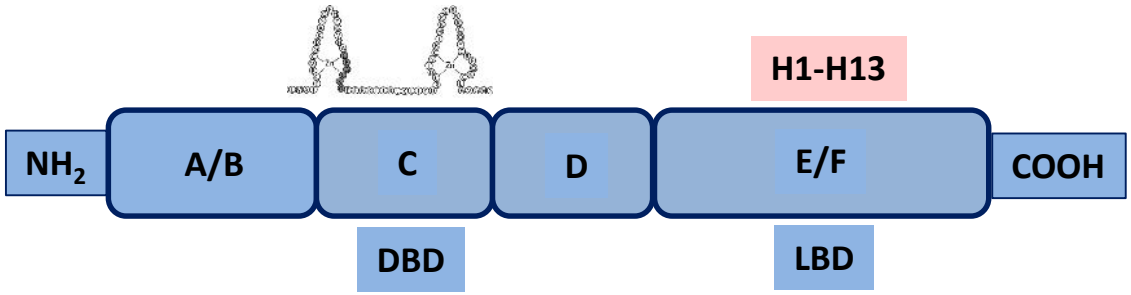
PPARs

PPARα | PPARγ | PPARβ/δ

Lipid metabolism | Glucose homeostasis | Energetic metabolism

Anti-inflammatory action

PPAR modular structure



Introduction

PPAR AGONISTS

coactivator

RXR ligand

PPAR agonist

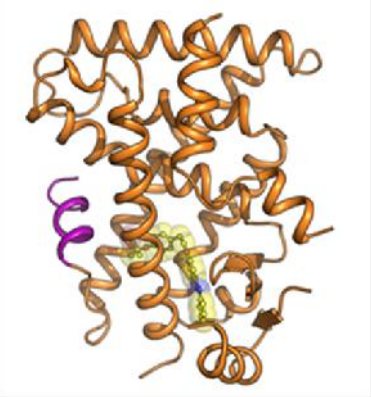
PPAR

RXR

PPRE

DNA

Gene transcription
BIOLOGICAL EFFECT



H12

AGONIST

LBD (closed conformation)

PPAR ANTAGONISTS

corepressors

RXR ligand

PPAR antagonist

PPAR

RXR

PPRE

DNA

Gene transcription block
~~BIOLOGICAL EFFECT~~

ANTAGONIST

H12

LBD (open conformation)

POTENTIAL ANTI-CANCER ACTIVITY OF PPAR~ ANTAGONISTS

PPARs and CANCER: CONTROVERSE ROLE

PPARα overexpression in tumors that use the oxidation of fatty acids for their energy needs

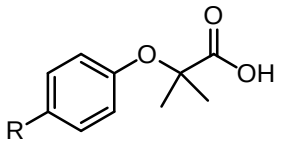
→ Possibility of interfering with the metabolic pathways of cancer cells and blocking tumor progression

↓

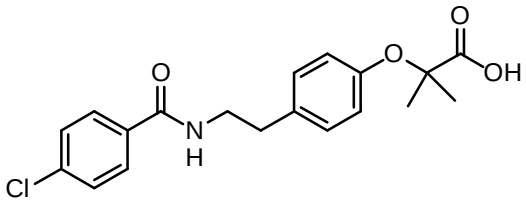
PPAR~ antagonism is emerging as a therapeutic option to interfere with the metabolism of cancer cells

ChemMedChem **2018**, *13*, 209

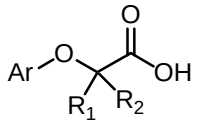
SYNTHETIC STRATEGY FOR DESIGN OF PPAR~ ANTAGONISTS



Fibrate scaffold



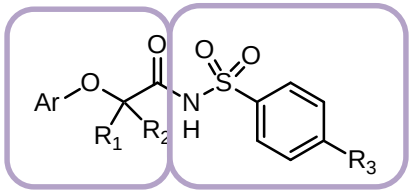
Example of fibrate:
the antilipidemic drug bezafibrate



Fibrate-like scaffold
PPARα AGONIST

Analogue of fibrate

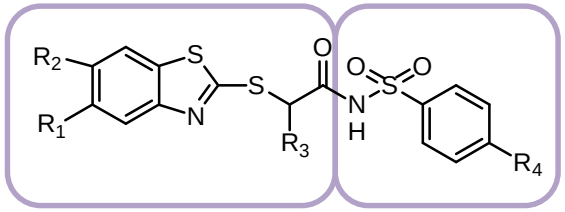
switching strategy



PPARα ANTAGONIST

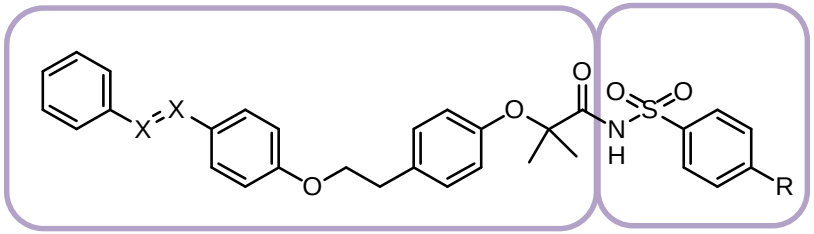
BENZENSULFONIMIDES

BENZOTHIAZOLE-BASED



Fibrate-like scaffold | Benzensolfonamide

STILBENE-BASED



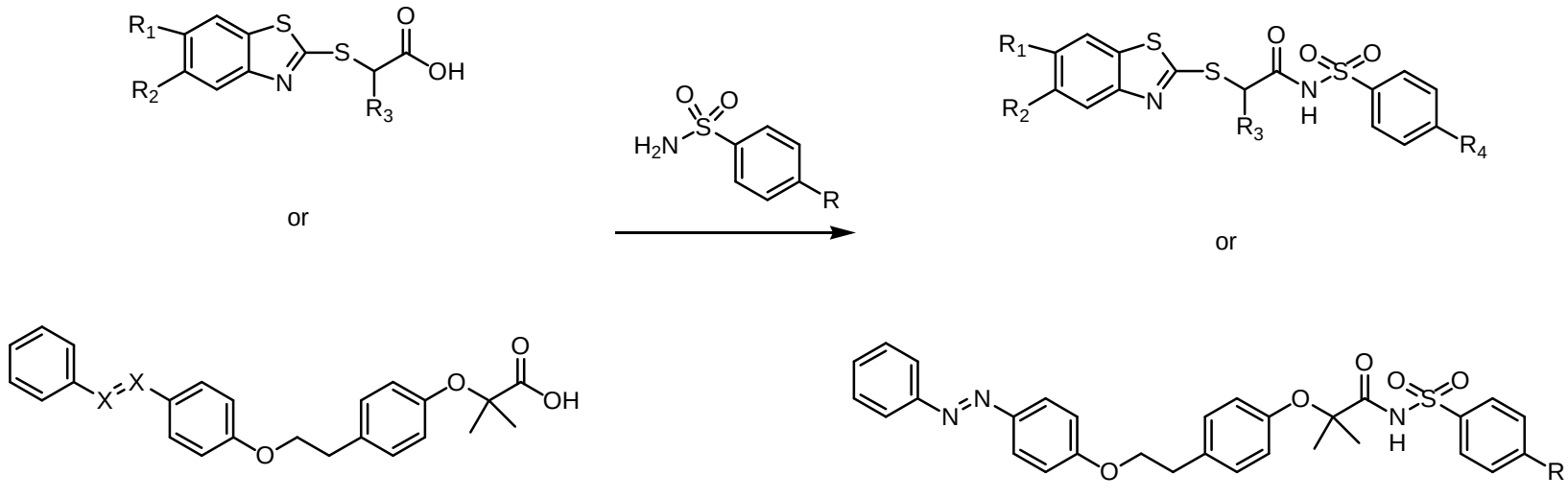
Fibrate-like scaffold | Benzensolfonamide

WORKFLOW

SYNTHESIS
TRANSACTIVATION ASSAYS
CYTOTOXIC ACTIVITY
DOCKING

Results and discussion

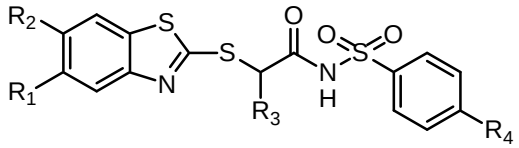
GENERAL SYNTHESIS OF BENZENSULFONIMIDES



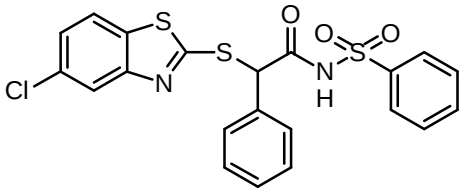
Fibrate-like scaffolds

Reagents and conditions: benzensulfonamide, EDC, DMAP, dry CH_2Cl_2, 0 °C – r.t, 24 h.

BENZOTHIAZOLE-BASED BENZENSULFONIMIDES



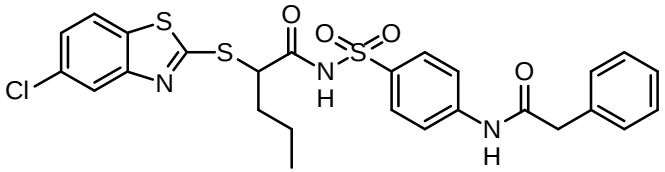
General formula



AA452

PPARα IC_{50} : 6.5 µM

Bioorg Med Chem Lett **2011**, *21,* 4869

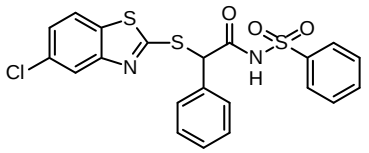


AA493

PPARα IC_{50} : 0.98 µM

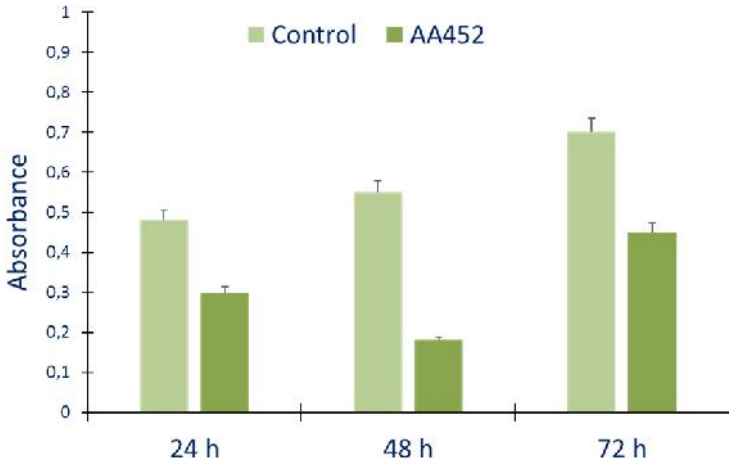
Chem Biol Drug Des **2017**, *90,* 1029

BENZOTHIAZOLE-BASED BENZENSULFONIMIDES

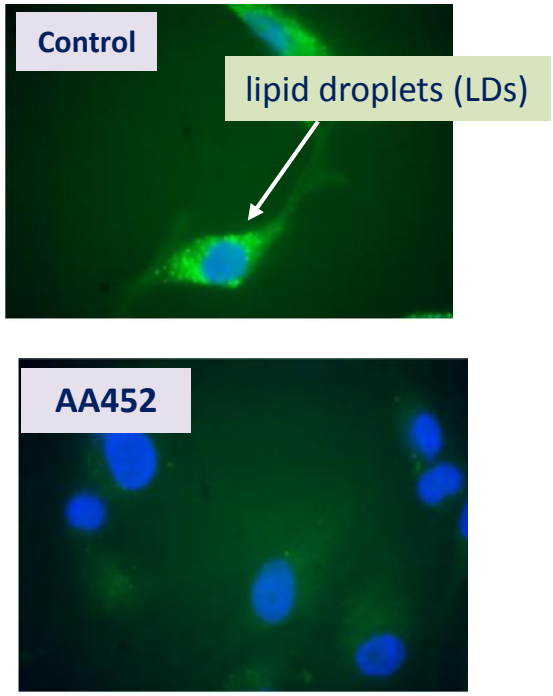


CYTOXICITY OF AA452

CELLULAR VITALITY ON GLIOBLASTOMA PRIMARY CELLS



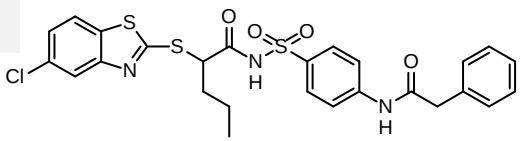
BODIPY STAINING



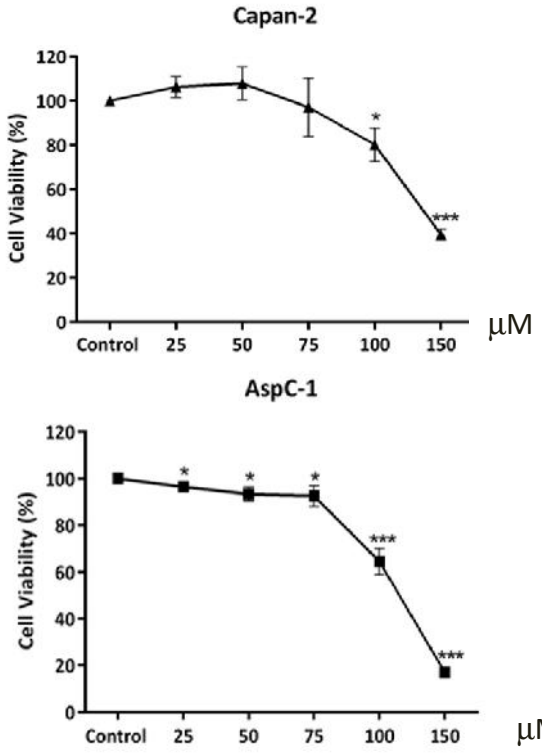
J Cell Physiol **2017**, *232*, 1458

BENZOTHIAZOLE-BASED BENZENSULFONIMIDES

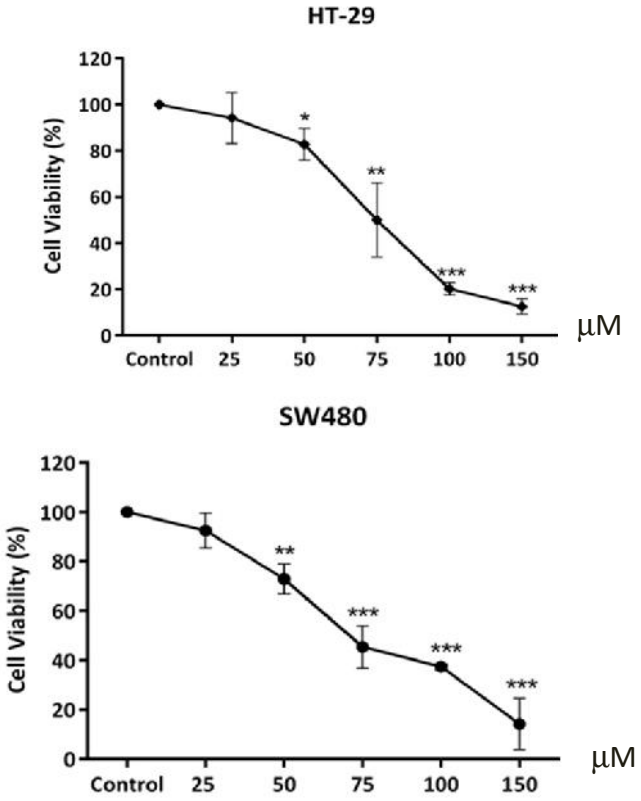
CYTOXICITY OF AA493



CELLULAR VIABILITY ON PANCREAS CANCER LINES

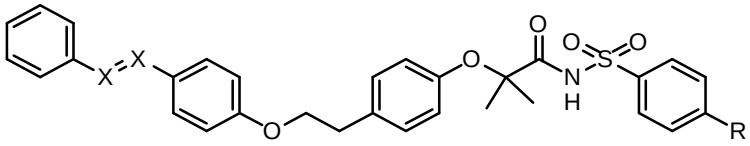


CELLULAR VIABILITY ON COLON CANCER LINES



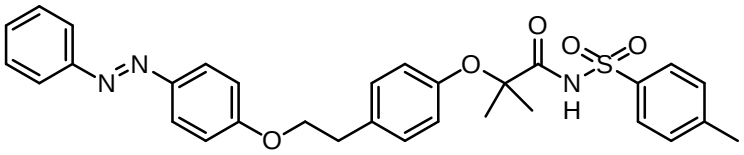
Chem Biol Drug Des **2017**, *90*, 1029

STILBENE-BASED BENZENSULFONIMIDES



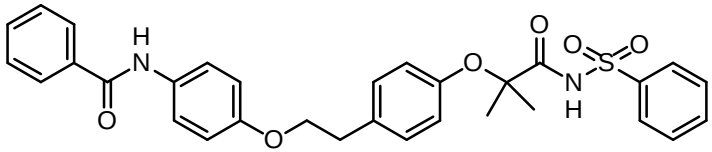
General formula

PPAR~ antagonist



IB40

PPARα IC_{50}: 0.17 μM



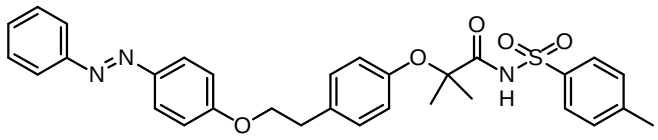
IB66

PPARα IC_{50}: 0.24 μM

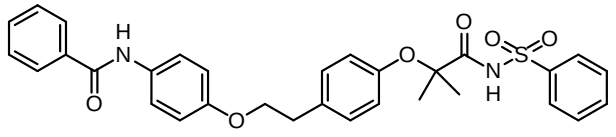
ACS Med. Chem. Lett. **2020**, *11*, 624-632

STILBENE-BASED BENZENSULFONIMIDES

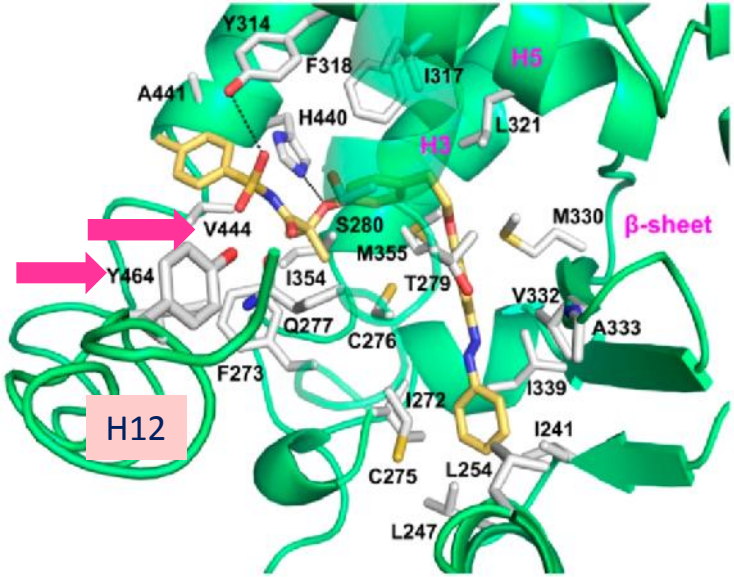
DOCKING STUDIES

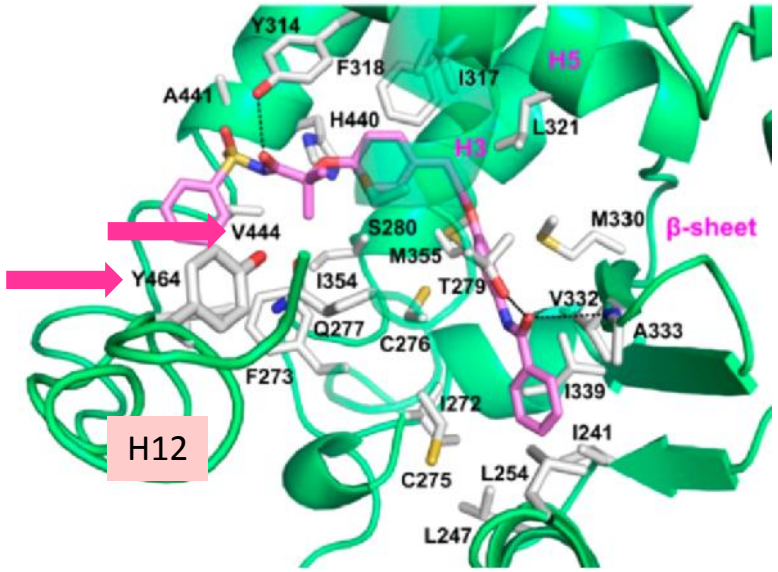


IB40



IB66



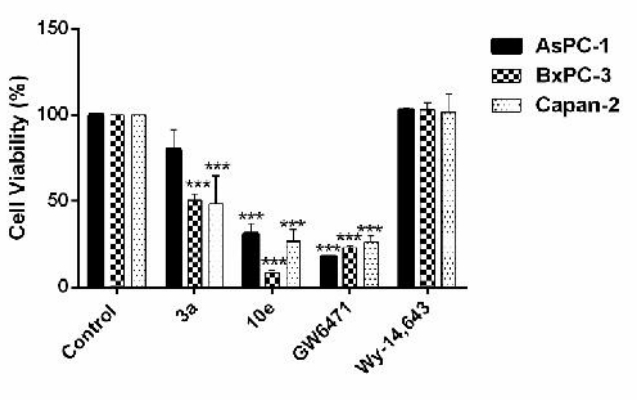


PPARa LBD represented as green ribbon model

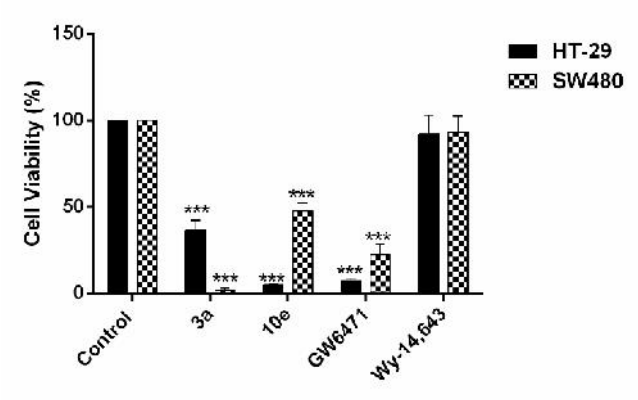
STILBENE-BASED BENZENSULFONIMIDES

CYTOTOXICITY (MTT ASSAYS) OF IB40 AND IB66 (75 μM, 72h)

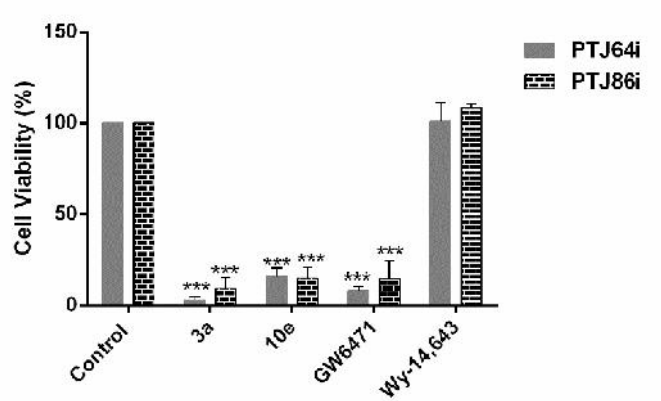
Pancreatic tumor cell lines



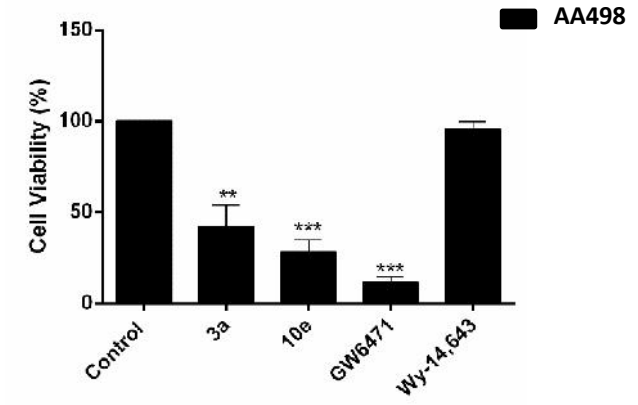
Colorectal tumor cell lines



Paraganglioma cell lines



Renal tumor cell lines



Conclusions

- The synthesis of new benzothiazole- and stilbene-based sulfonimides as PPARα antagonists was performed
- The agonist-to-antagonist switch in activity was confirmed by transactivation assays towards PPARα isoform
- New PPARα antagonists were evaluated in tumor cell lines and all of them showed cytotoxic activity
- Docking studies were performed to elucidate the binding to PPARα
- The results of these in vitro studies deserve to be investigated both from a chemical-pharmaceutical and biological point of view

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