Programa Cooperación Farma-Biotech

8º encuentro (7 de mayo de 2013)

Novel proapoptotic compounds for cancer treatment

A project of:

Universitat de Barcelona

IDIBELL
Institut d'Investigació Biomèdica de Bellvitge

IRB BARCELONA
INSTITUTO DE INVESTIGACIÓN BIOMÉDICA

Parc Científic de Barcelona

Managed by:

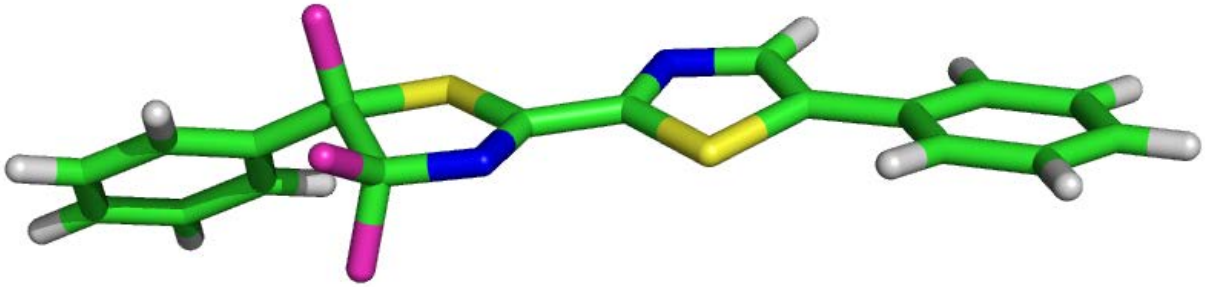
Fundació Bosch i Gimpera
Universitat de Barcelona

Madrid, 7 de mayo de 2013

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

farmaindustria



1. The Institutions

Universitat de Barcelona

IRB BARCELONA
INSTITUTO DE INVESTIGACIÓN BIOMÉDICA

IDIBELL
Institut d'Investigació Biomèdica de Bellvitge

Parc Científic de Barcelona

1. The Institutions

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Apoptosis and cancer (IDIBELL). Molecular mechanisms of apoptosis and its alteration in cancer. Biology and medicine
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Prof. Fernando Albericio research group.
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Combinatorial and Peptide Chemistry for the Discovery of New Compounds. Chemistry
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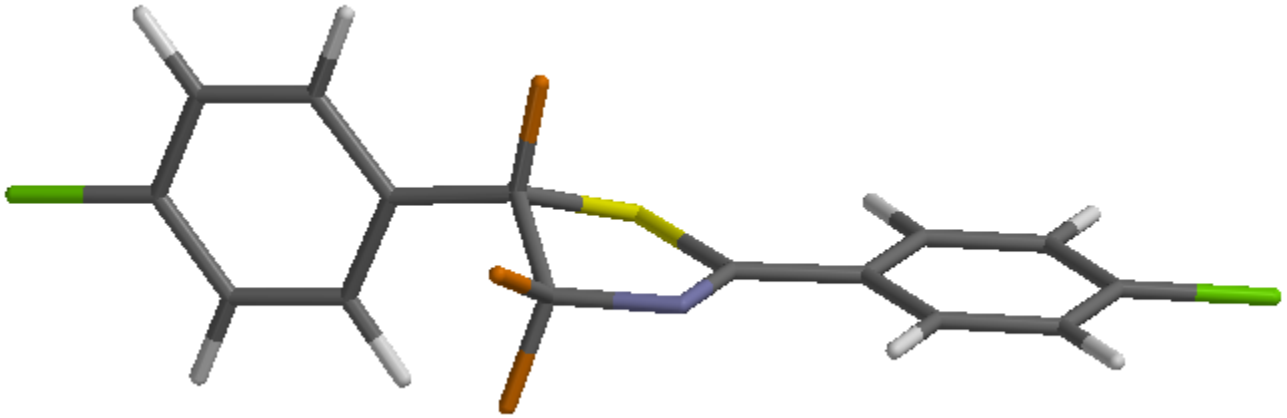
Professor of Organic Chemistry at UB.
Multicomponent Reactions in Heterocyclic & Medicinal Chemistry . Chemistry
rlavilla@pcb.ub.es

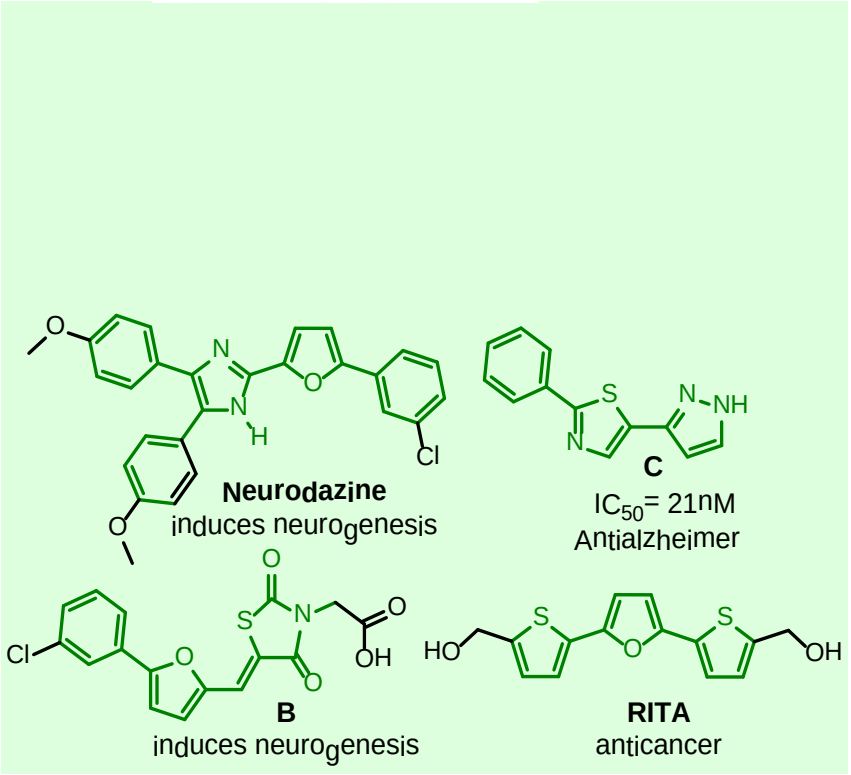
2. The Product

Introduction

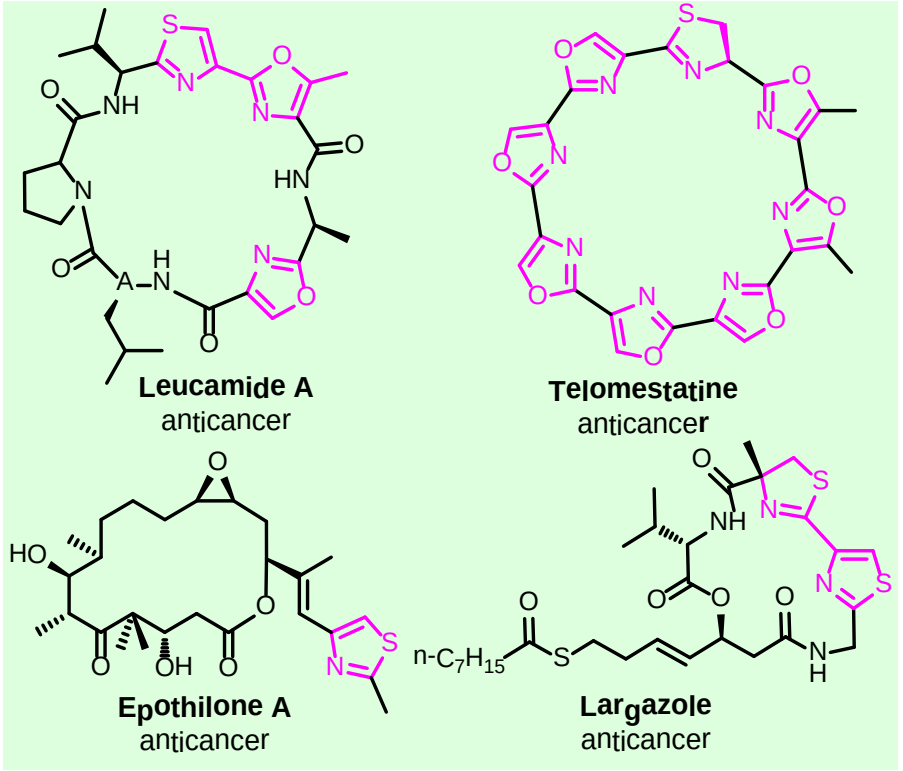
Fluorinated Thiazolines as Proapoptotic Antitumoral Agents



Introduction

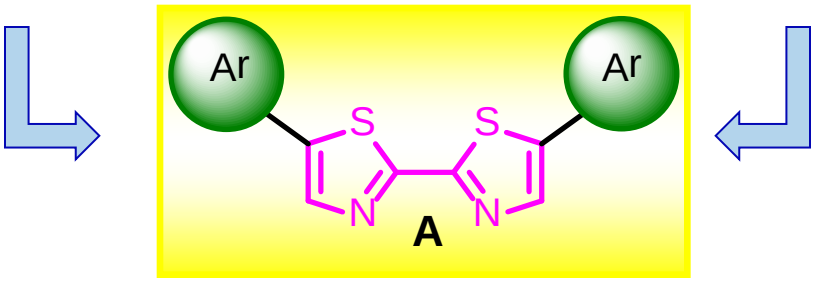


Polyarylated motifs as new scaffolds in medicinal chemistry



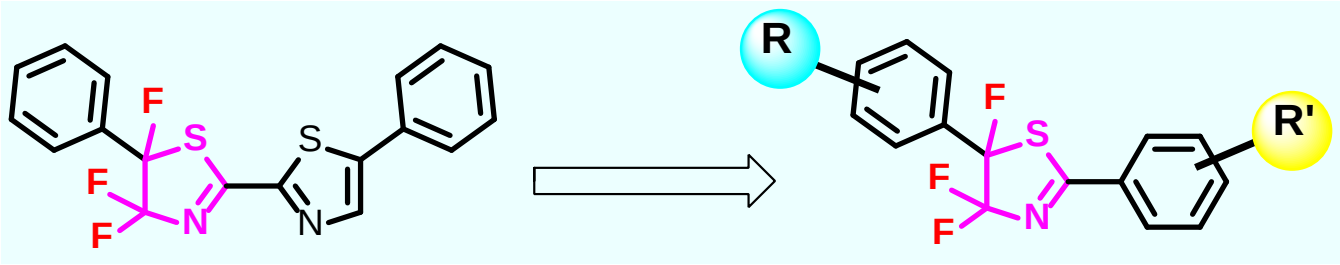
Bioactive natural products containing 1,3-oxa/thiazoles moieties in their structures

Andrew D. Hamilton et al.
Angew. Chem. Int. Ed.
2005, *44*, 2704 –2707

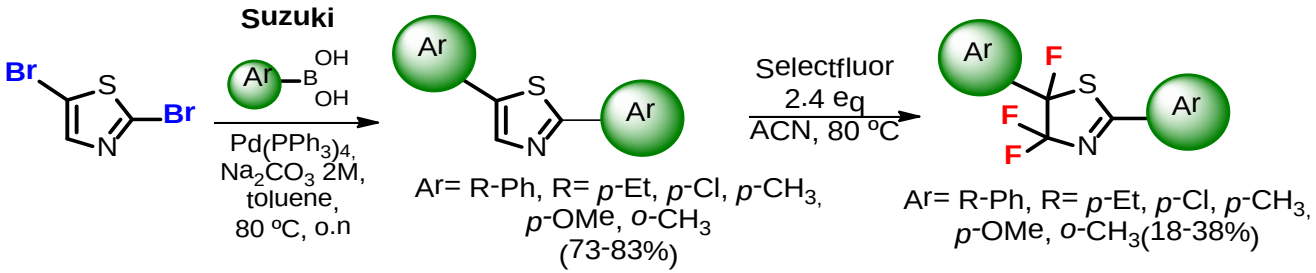


Merging of privileged structures

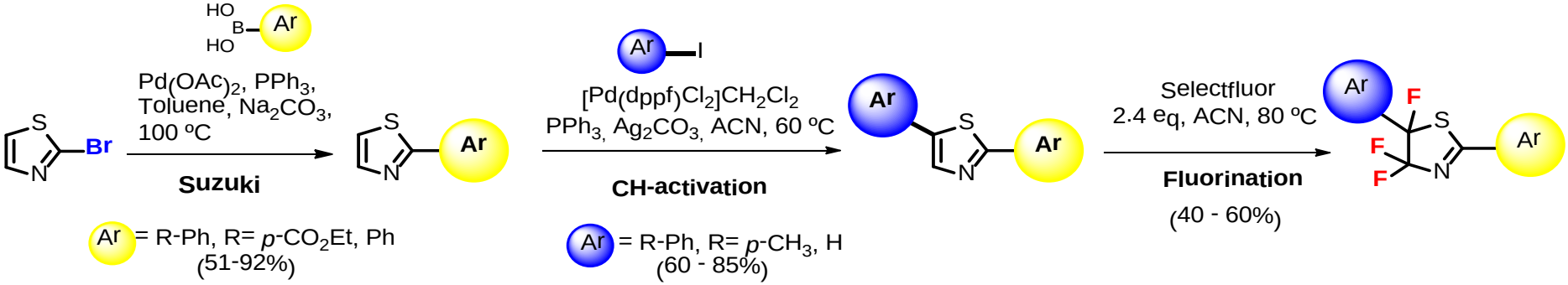
Synthesis of the trifluorothiazolines scaffold



Symmetrically arylated thiazoles:



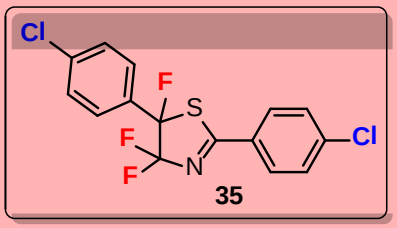
Non-symmetrically arylated thiazoles:



Biological evaluation: Proapoptotic activity

➢ **Viability in Jurkat cells (acute T cell leukemia)**

PROAPOPTOTICS
EC_{50}<5µM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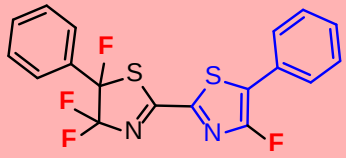
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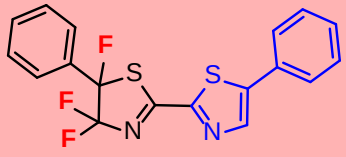
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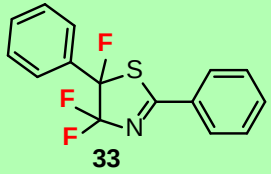
EC_{50} 5-20µM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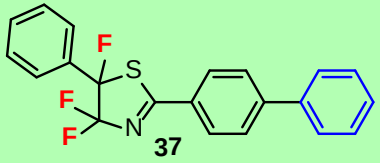
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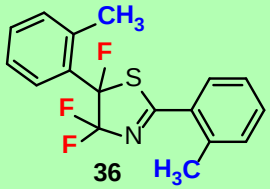
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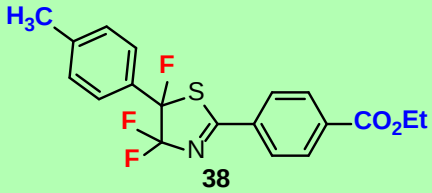
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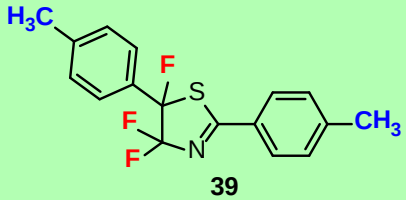
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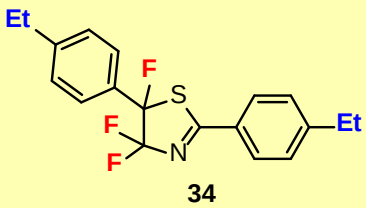
INACTIVE
EC_{50}>40µM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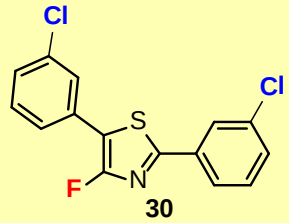
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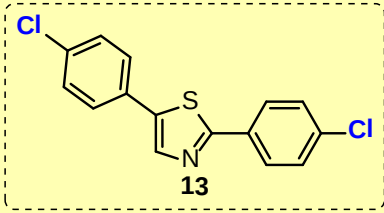
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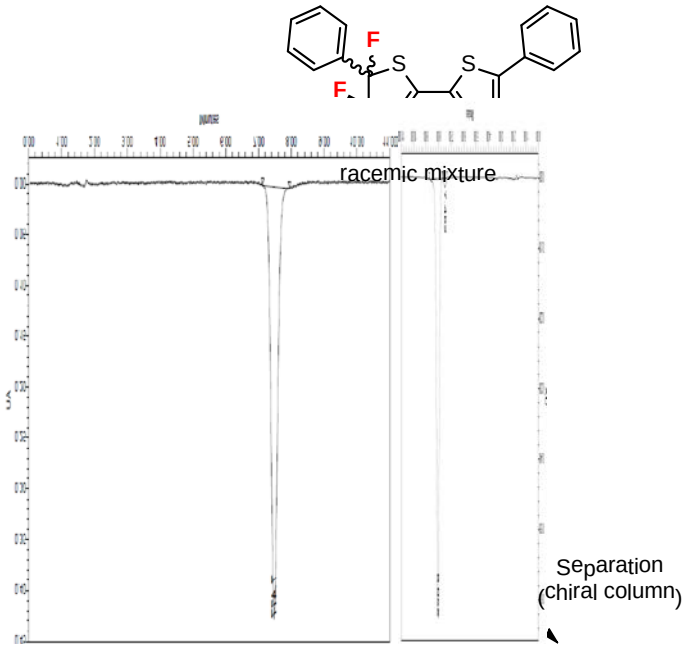
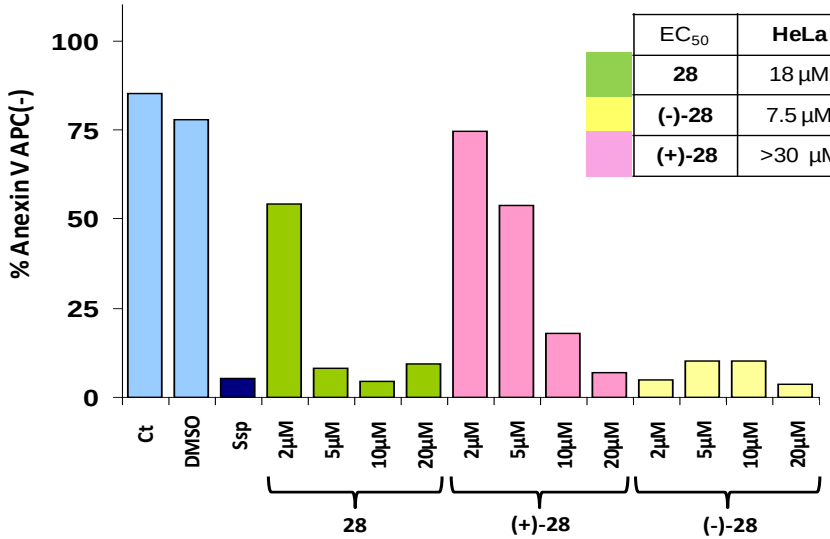
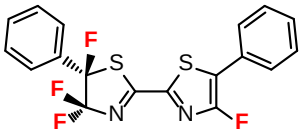
- Reliable and Fast Synthetic Access
- Diversified Library, Restrictions Known
- Scalable (multigram) Processes

Enantiomer separation





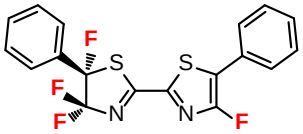
EC_{50}	HeLa	z-138
28	18 μM	3.9 μM
(-)-28	7.5 μM	1.1 μM
(+)-28	>30 μM	>5 μM



$(^{+})$-28

$[\alpha]_D$= +31.29 (c 0.075, CH_2Cl_2) t_R= 7.5 min

ee>99%

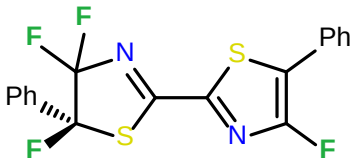


$(^{-})$-28

$[\alpha]_D$=-16.47 (c 0.05, CH_2Cl_2) t_R= 8.1 min

ee>97%

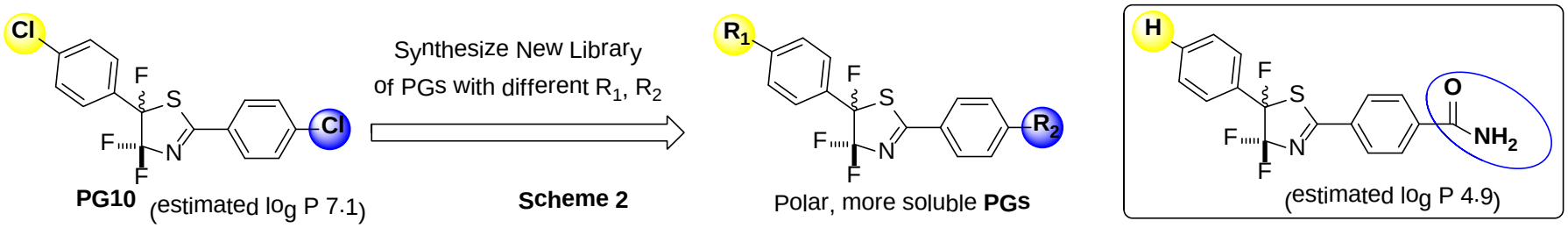
X-ray structure of $(^{-})$-28



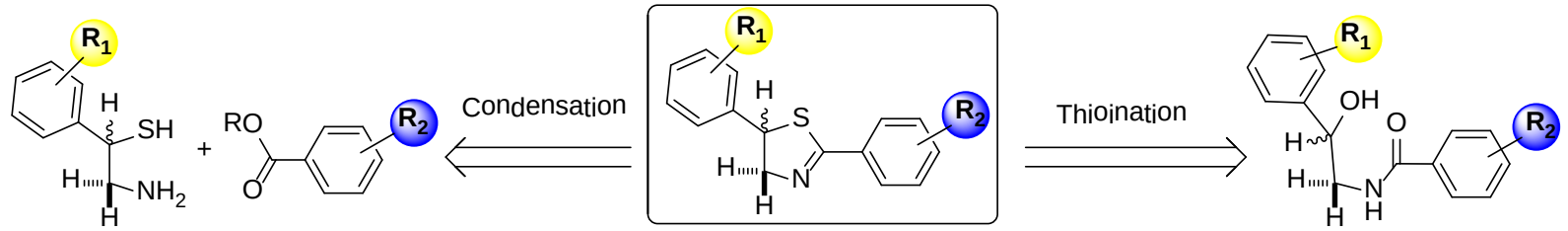
(*R*)

Problems, Solutions and Perspectives in MedChem

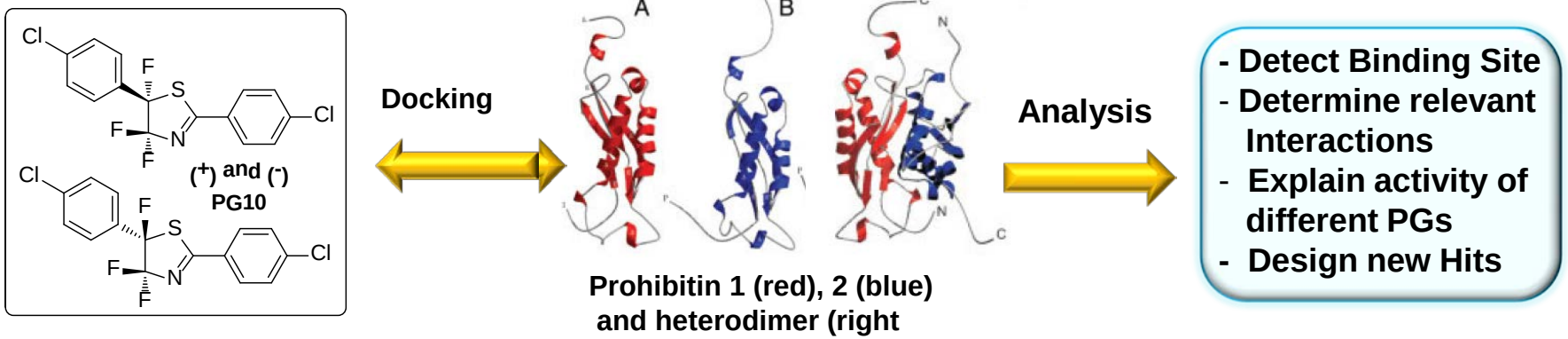
More Polar (Soluble) Compounds



Alternative Scaffold (non fluorinated)



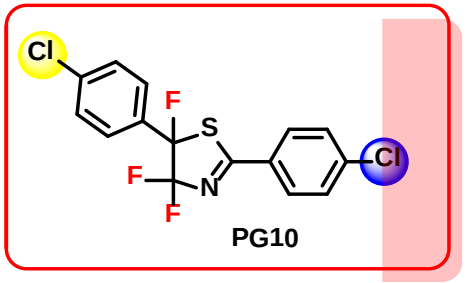
Computational Studies



b) Target indications: CANCER

Screening: Cell Viability assay in Jurkat T and HeLa cell lines (p53 mutated)

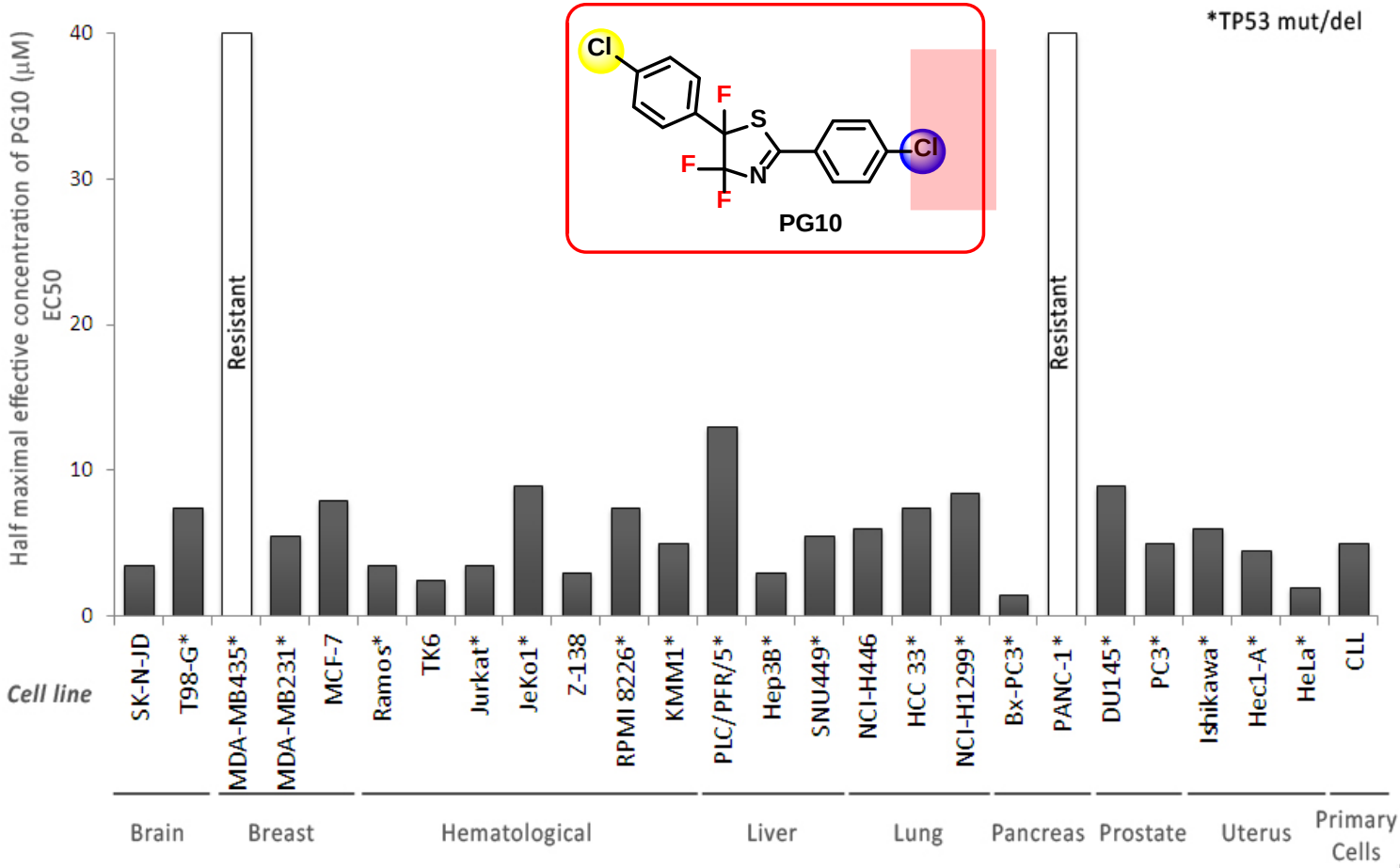
Compound	IC_{50} (μM)	
	Jurkat	HeLa
PG0	4	20
PG7	3	8
PG8	8	10
PG10	3,5	1,75
PG11	20	3,5
PG12	8	17



PG10

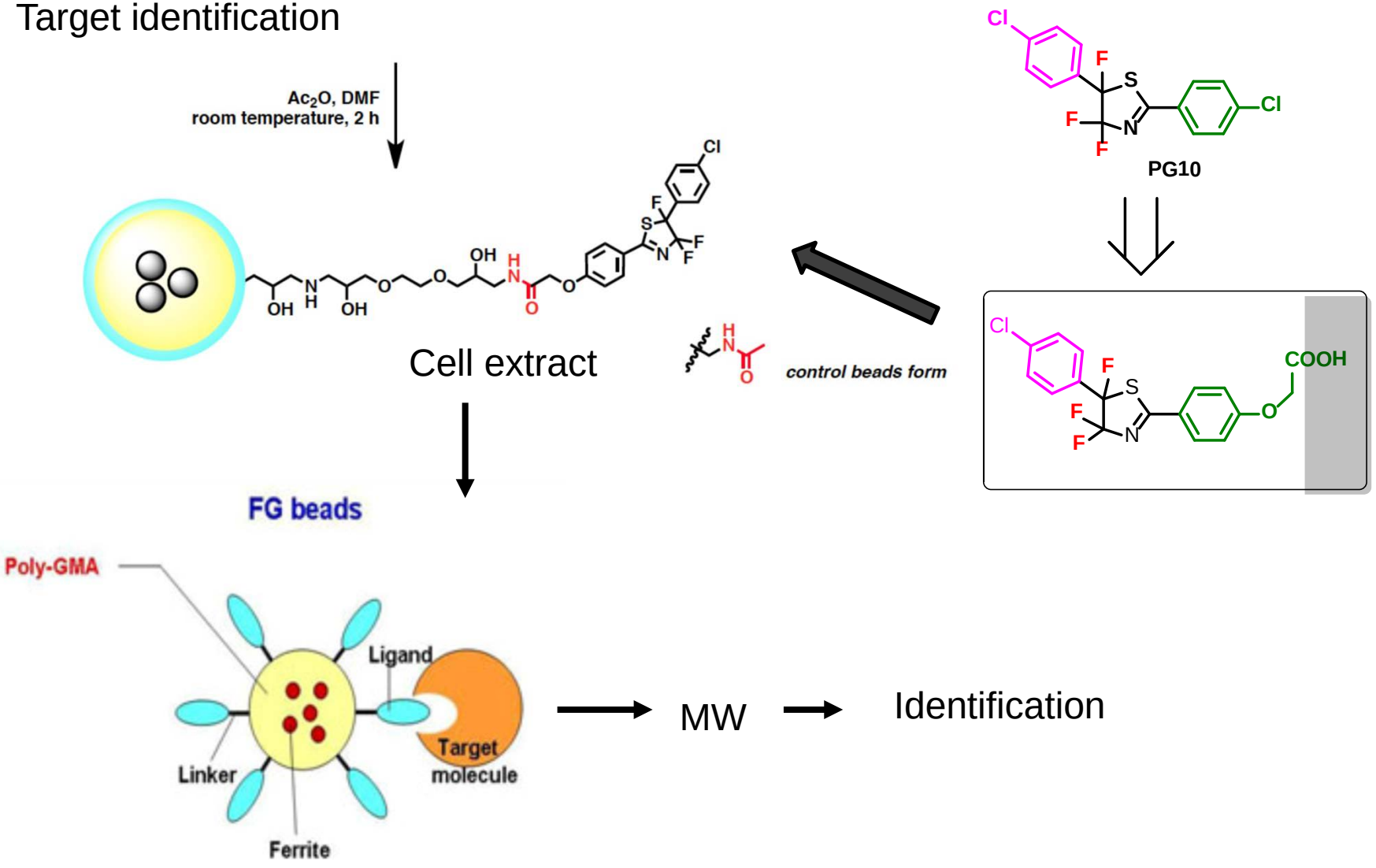
Cell Viability assays in different cancer cell lines

PG10: Active in most tumor cells independently of p53 status

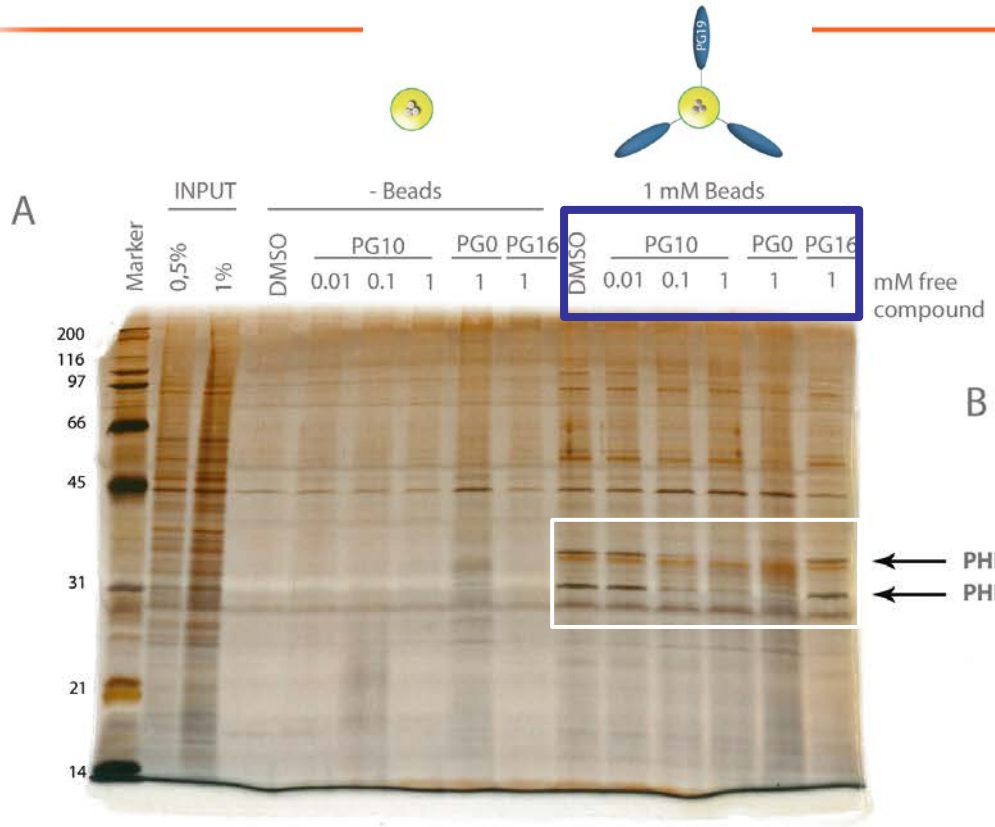


b) Innovative mechanism of action

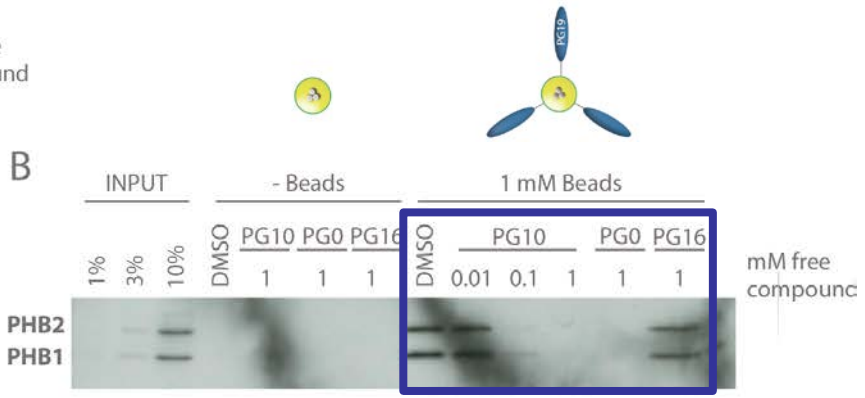
Target identification



TARGET IDENTIFICATION

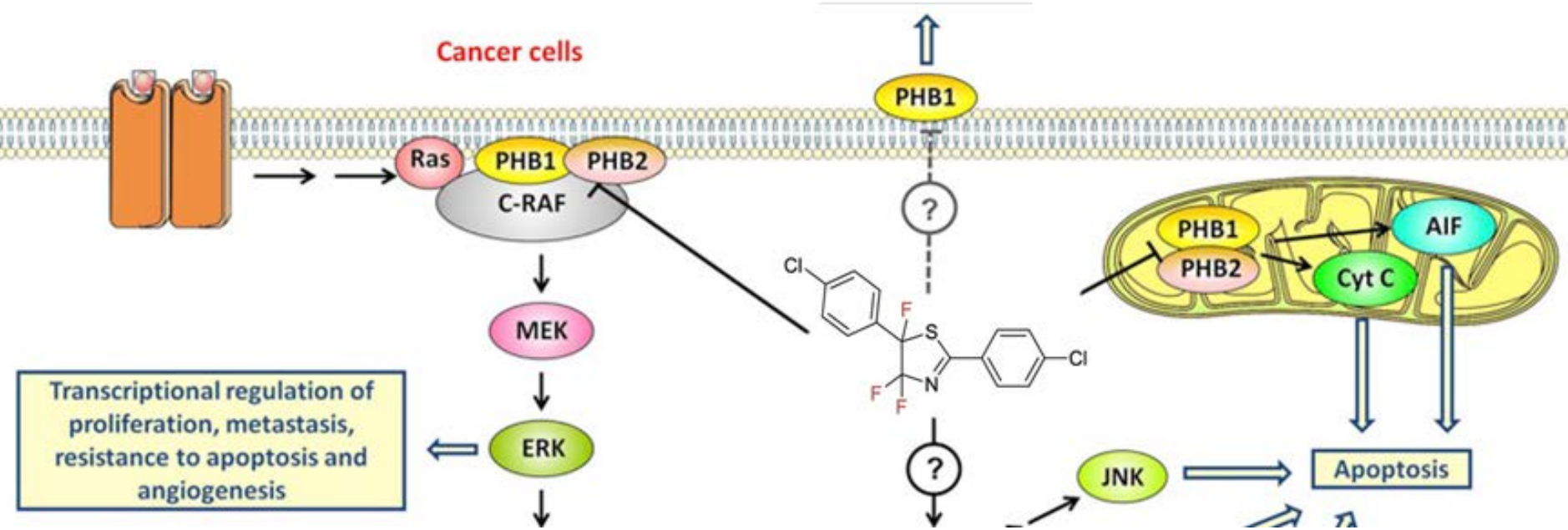


TARGET PROTEIN IDENTITY VALIDATION



PROHIBITIN 1 (PHB1) AND PROHIBITIN 2 (PHB2) ARE FLUORINATED THIAZOLES-SPECIFIC INTERACTING PROTEINS

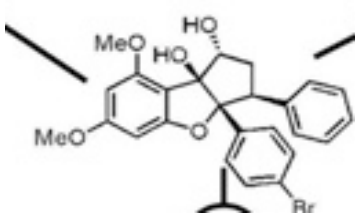
Prohibitins in cell signalling and apoptosis



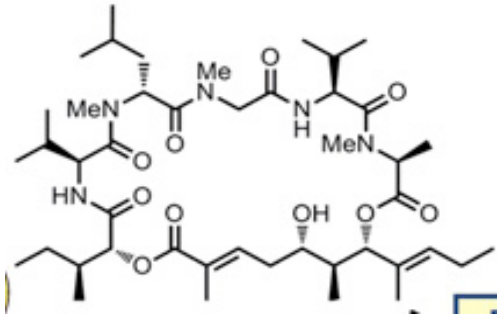
Adapted from **Chemistry & Biology, March 21, 2013**

b) Innovative mechanisms of action:

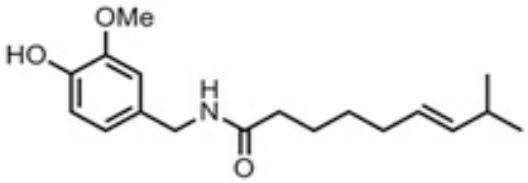
first synthetic compounds and only 3 natural compounds that Target **Prohibitin**



flavaglines

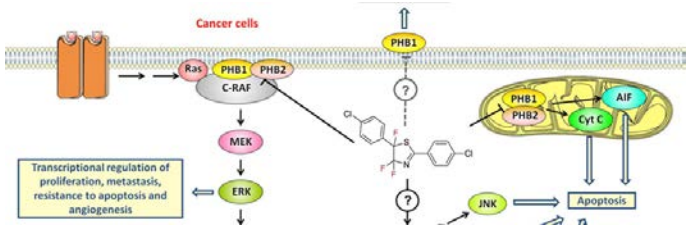


aurilide

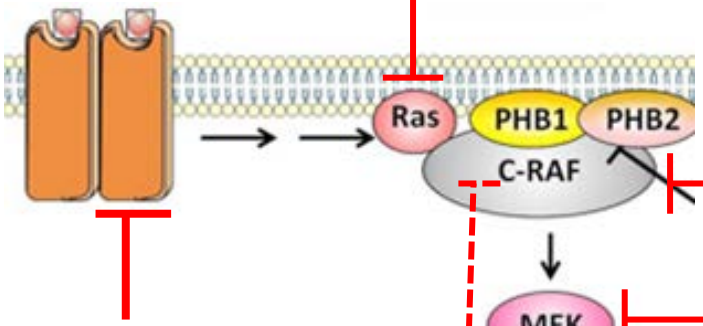


capsaicin

Which drugs are “competitors” of PG10?



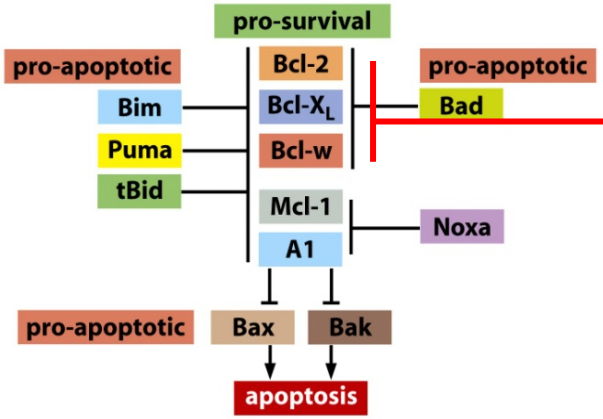
BMS-214662 (BMS)
TIPIFANIB (J&J)



Vemurafenib (ROCHE)

CI-1040 (PFIZER)

IRESSA (ASTRA ZENECA)
TARCEVA (ROCHE)
LAPATINIB (GSK)
AEE788 (NOVARTIS)
BMS-214662 (BMS)
CI-1033 (PFIZER)
SORAFENIB (BAYER)

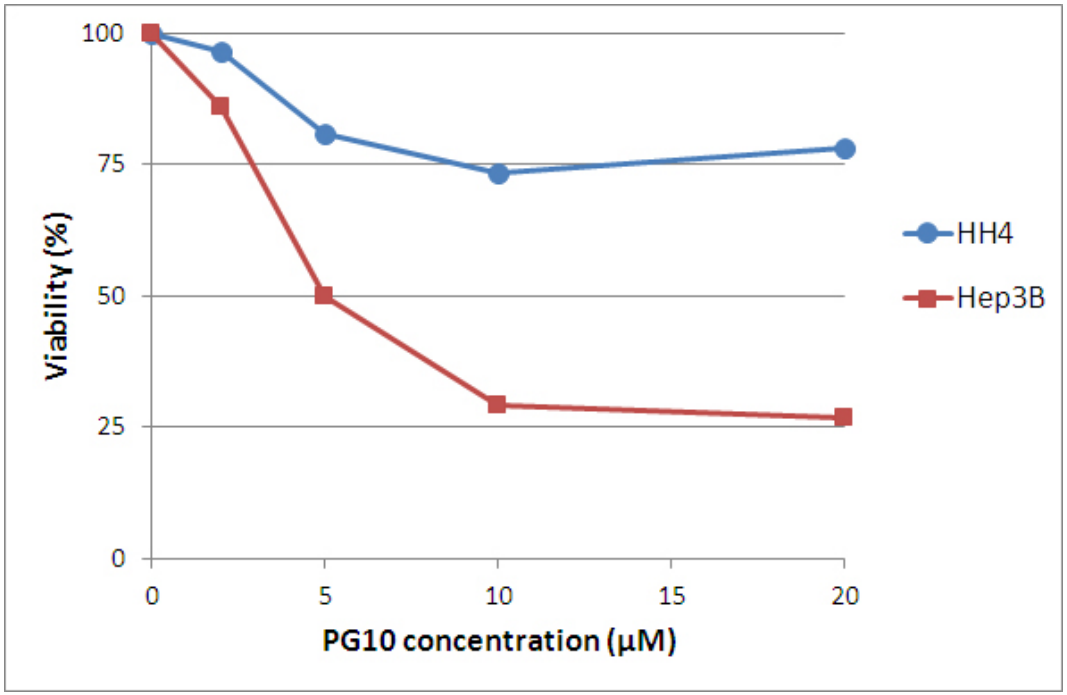


ABT-263/737
(ABBOTT)

C) Differential features facing the market

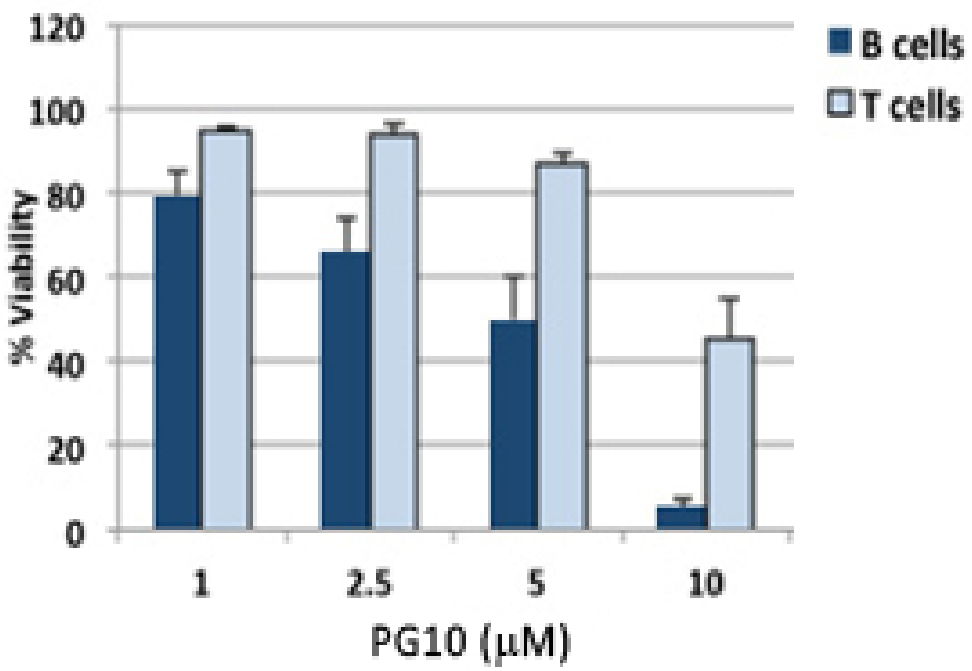
C1) Selective action in cancer cells vs normal cells

PG10: Induces apoptosis in hepatoma cells (Hep3B9) but not in hepatocytes (HH4)

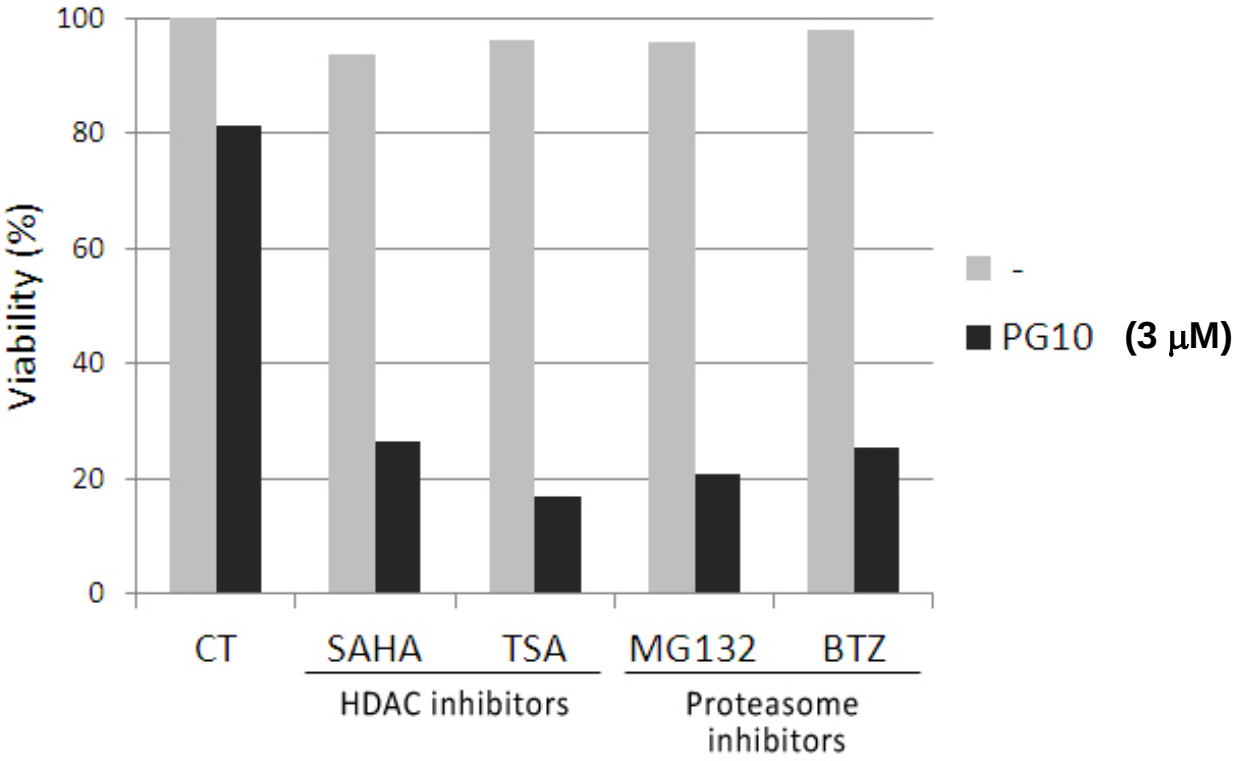


C1)Selective action in cancer cells vs normal cells

PG10 selective induction of apoptosis in CLL cells (B cells) versus normal T cells



C2) Synergism with other drugs



d) Current status of development

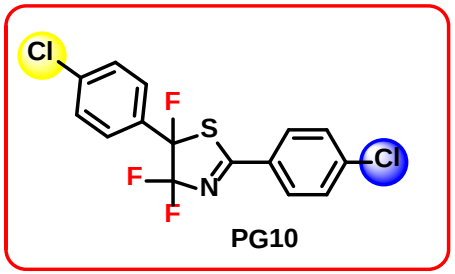
d1)Toxicology studies (PG10 compound)

Up & Down assay
LD50 > 50mg/kg. This is the maximum concentration used because of the solubility of the molecule.

Subacute toxicity – 14 days
Weight of organs, hematologic parameters, biochemical parameters
Commet assay, histophatology

- The compound is not genotoxic and it has a reasonable toxicity profile.

d2) Activity in "in vivo" model



PG10

Compounds with antitumoral activity

Active in different cancer cell lines: glioblastoma, lung, breast, cancer, prostate, pancreas, mantle cell lymphoma, multiple myeloma, endometrium, hepatocellular, colon, CLL

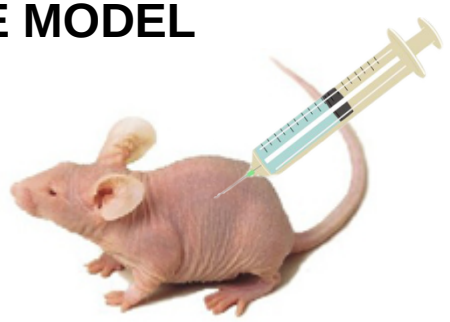
Proof of concept

Hepatocellular carcinoma

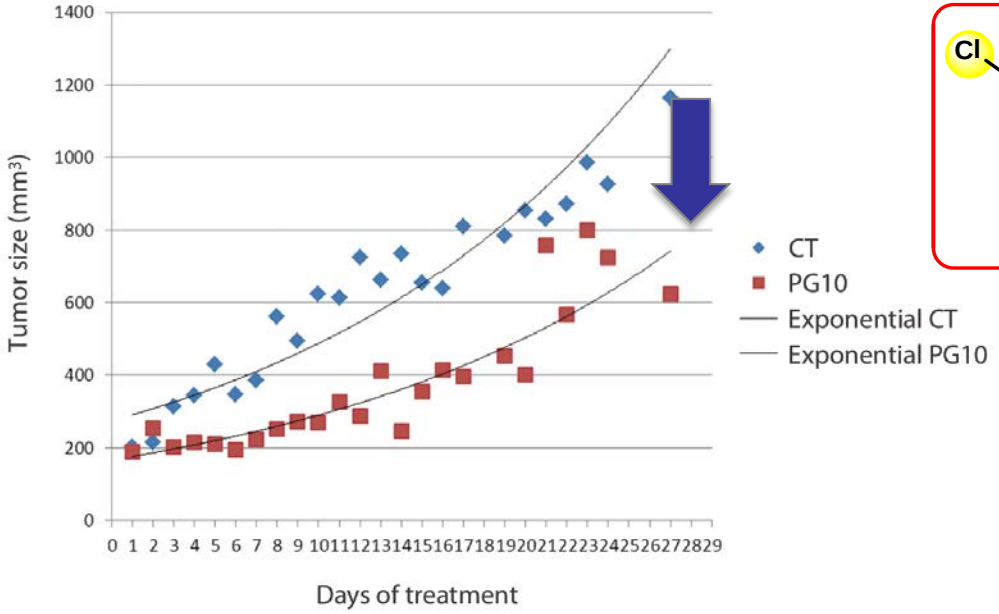
Unmet medical need

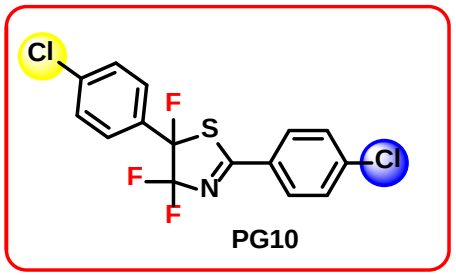
ANTITUMOR EFFICACY OF PG10

SUBCUTANEOUS HEPATOCELLULAR CARCINOMA MOUSE MODEL
(COLLABORATION WITH ISABEL FABREGAT, IDIBELL)



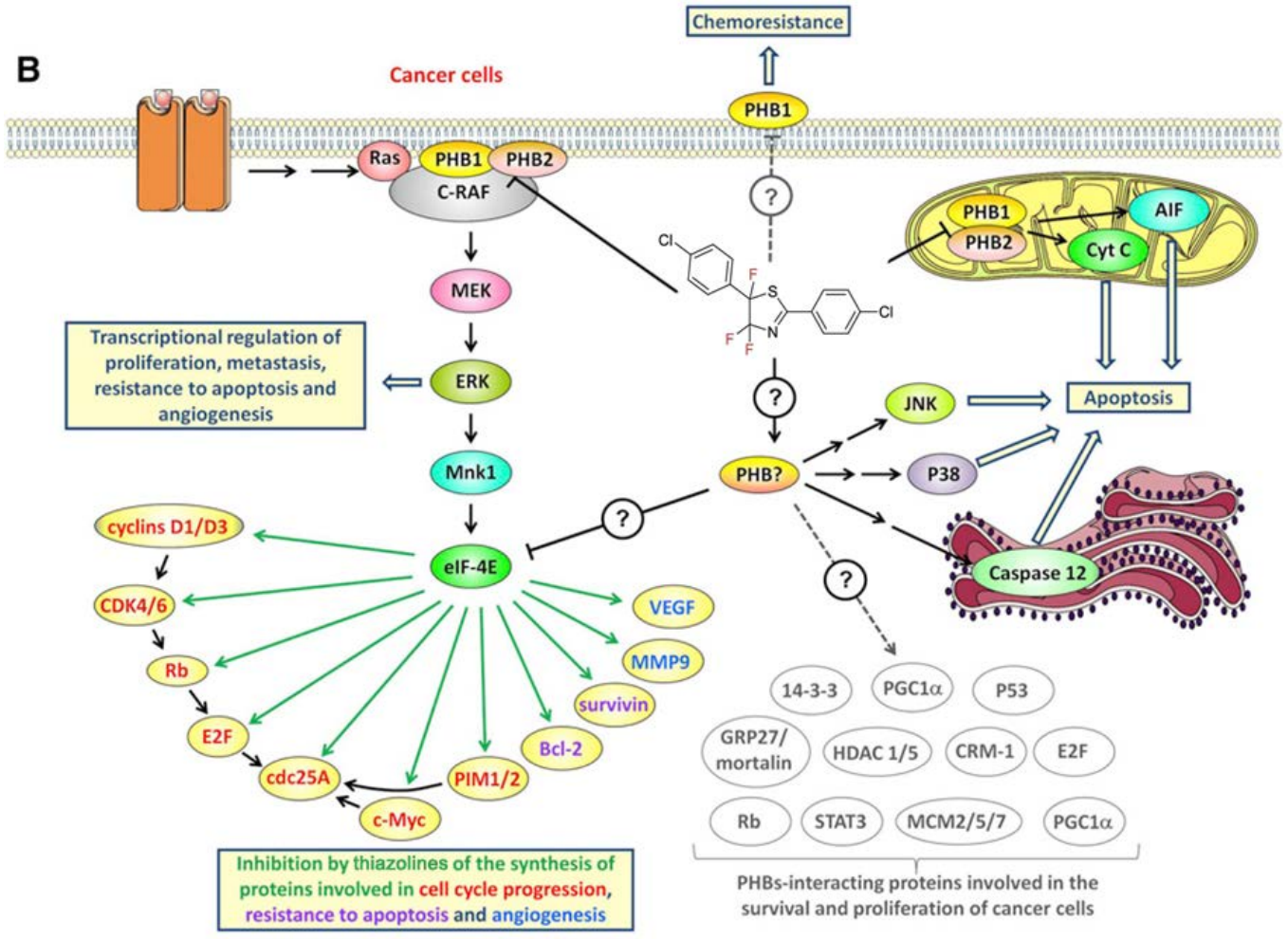
- **Human HCC cell line Hep3B injected subcutaneously**
- **Subcutaneous administration of vehicle or PG10 15 mg/Kg every 2 days**





PG10 DELAYED TUMOR GROWTH RATES

d3) Ongoing studies of elucidation of the mechanism of action.



Adapted from **Chemistry & Biology, March 21, 2013**

2. The Product

e) IPR protection

• PCT/ES2011/070605	ISR positive National phases in Europe & USA Protection of product (fluorinated thiazoles), method of preparation, cancer application
• EP12382498.9	Filed - Priority December 2012 Worldwide Protection of combination of fluorinated compounds with other drugs, cancer Application

Ownership: UB, IDIBELL, PCB, IRB. Management: FBG (TTO of UB)

2. The Product

f) Pitfalls & Risks to be considered

Threats

- Efficacy in *in vivo* model.
- PK/PD & ADME development

Weaknesses

- Solubility of compounds to be improved.
- i.v. administration not yet confirmed..

2. The Product

f) Strengths & Opportunities to be considered

Strengths

- MoA independent of p53 protein.
- Easy Synthesis.
- Positive ISR from PCT/ES2011/070605.

Opportunities

- Market Needs of new anti-cancer drugs.
- First-in-class (no anti-prohibitin drug in oncology market)

2. Partnering Opportunities

The project is available to licensing out through a collaboration and license agreement.

Potential research collaboration in:
-Chemical Development
-- Metabolic Studies
-- Drug Delivery
- Animal Studies

2. Partnering Opportunities

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