UNIVERSITAT DE BARCELONA

FACULTAT DE FARMÀCIA I CIÈNCIES DE L'ALIMENTACIÓ

New therapeutic targets for neurodegenerative diseases

Carmen Escolano + Collaborators

Laboratory of Medicinal Chemistry

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INTRODUCTION

Neurodegenerative diseases
Social impact

IMIDAZOLINE I_2 RECEPTORS

New strategy for Alzheimer's disease
I_2-IR Ligands

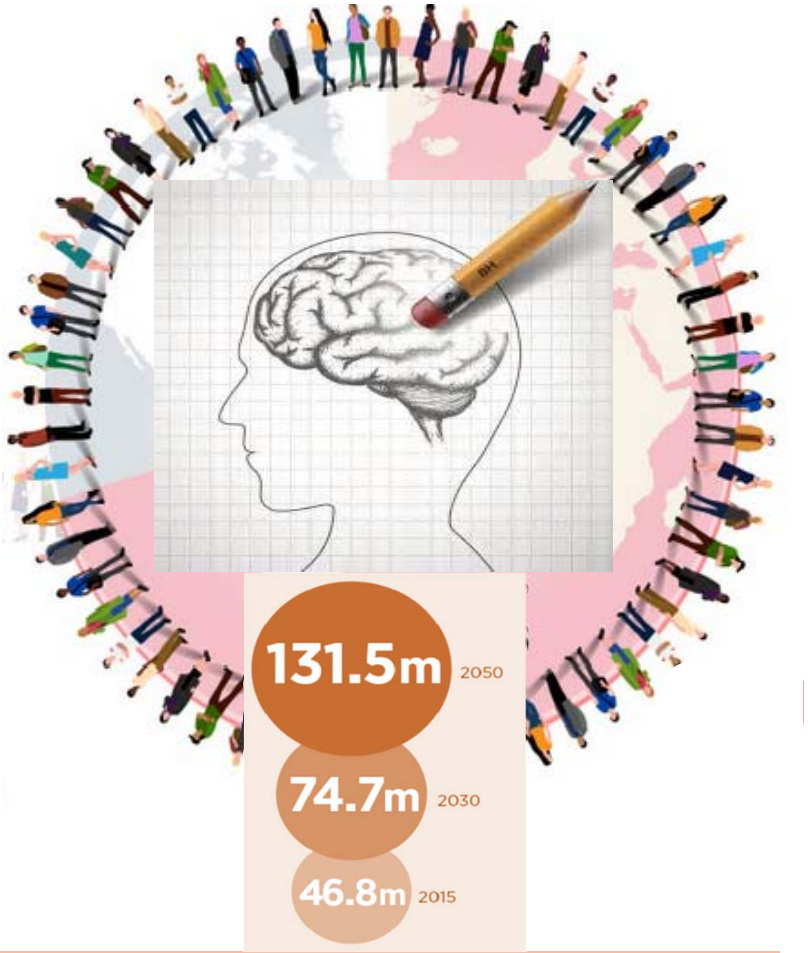
MULTICOMPONENT REACTIONS

Concept MCR
Green chemistry
Synthesis of new compounds

NEW ACTIVE COMPOUNDS

New MCR I_2-IR ligands
New [3+2]cycloaddition I_2-IR ligands
Application in neurodegenerative diseases
Unmet medical needs (neuropathic pain, glioblastoma).

Neurodegenerative diseases



Crucial challenge for humankind

World Health Organization

Dementia

50 million

Approximately 50 million people worldwide have dementia.

Dementia cost

$818 billion

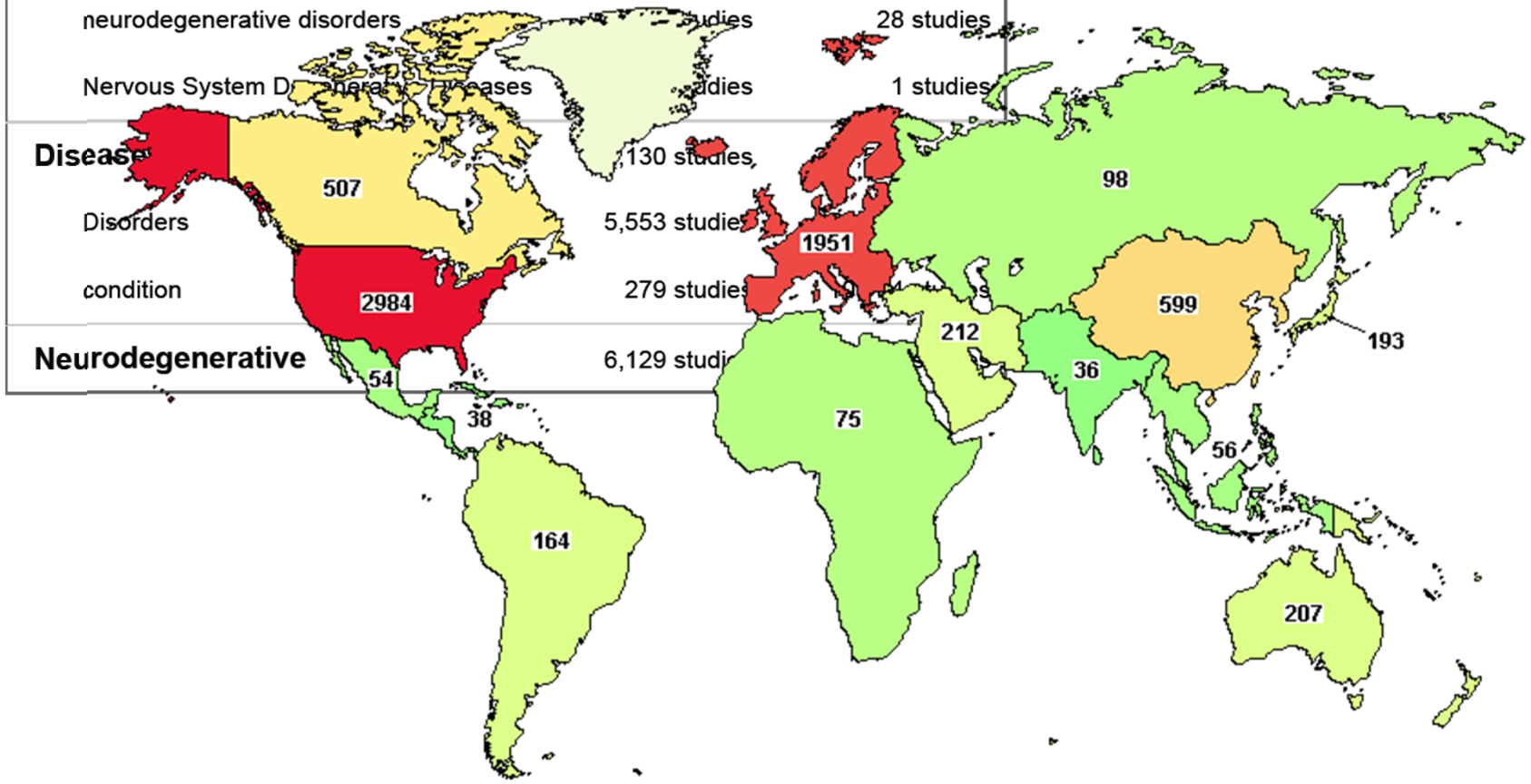
The majority of care is provided by family carers.

1 June 2018 – Only a few countries currently have formulated national dementia plans, despite approximately fifty million people worldwide living with dementia.

NIH U.S. National Library of Medicine

ClinicalTrials.gov

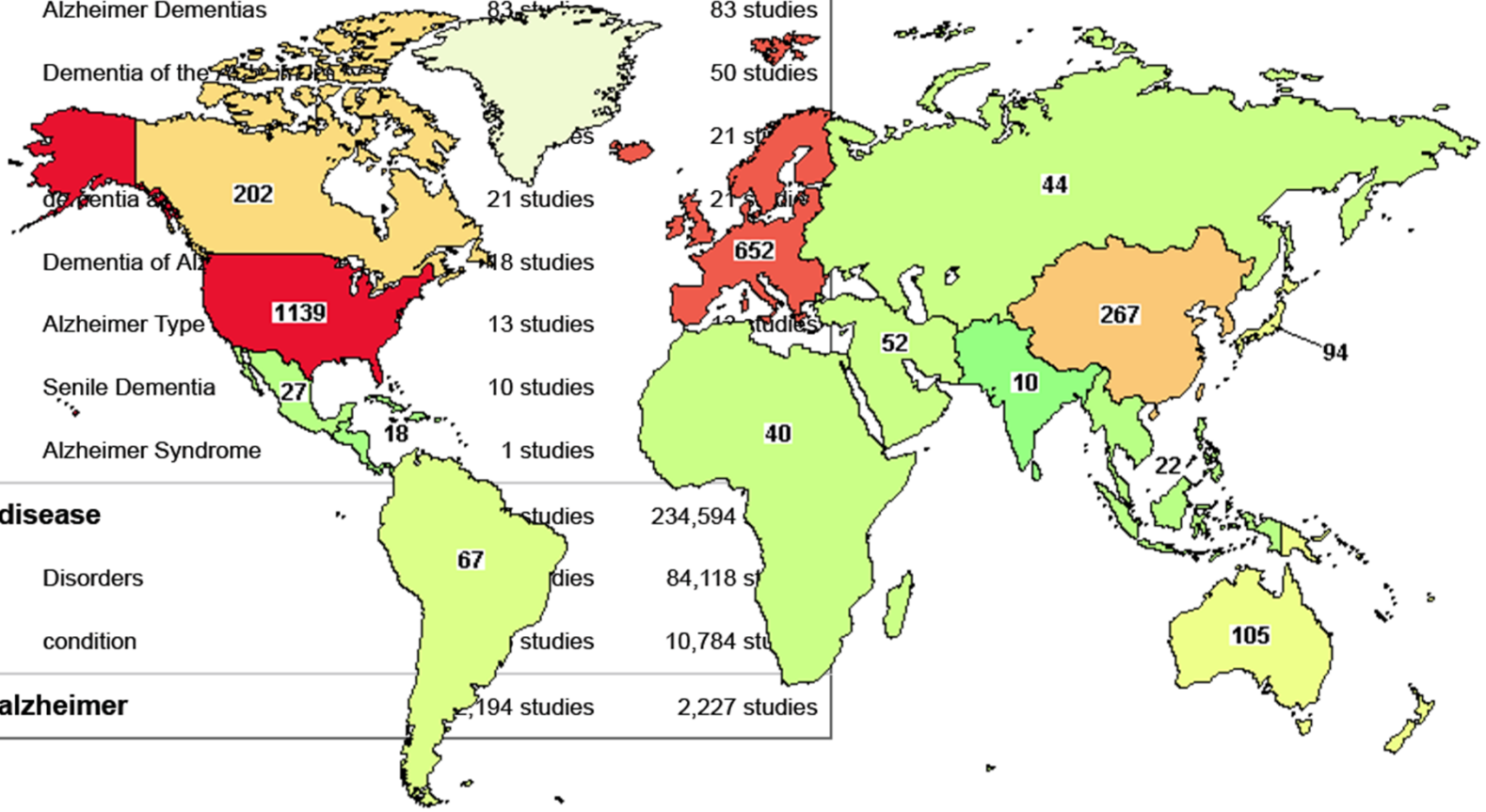
Terms	Search Results*	Entire Database**
Synonyms		
Neurodegenerative Diseases	6,129 studies	6,129 studies
neurodegenerative disorders	udies	28 studies
Nervous System D eneral Diseases	udies	1 studies
Disease	130 studies	
Disorders	5,553 studie	
condition	279 studie	
Neurodegenerative	6,129 studi	

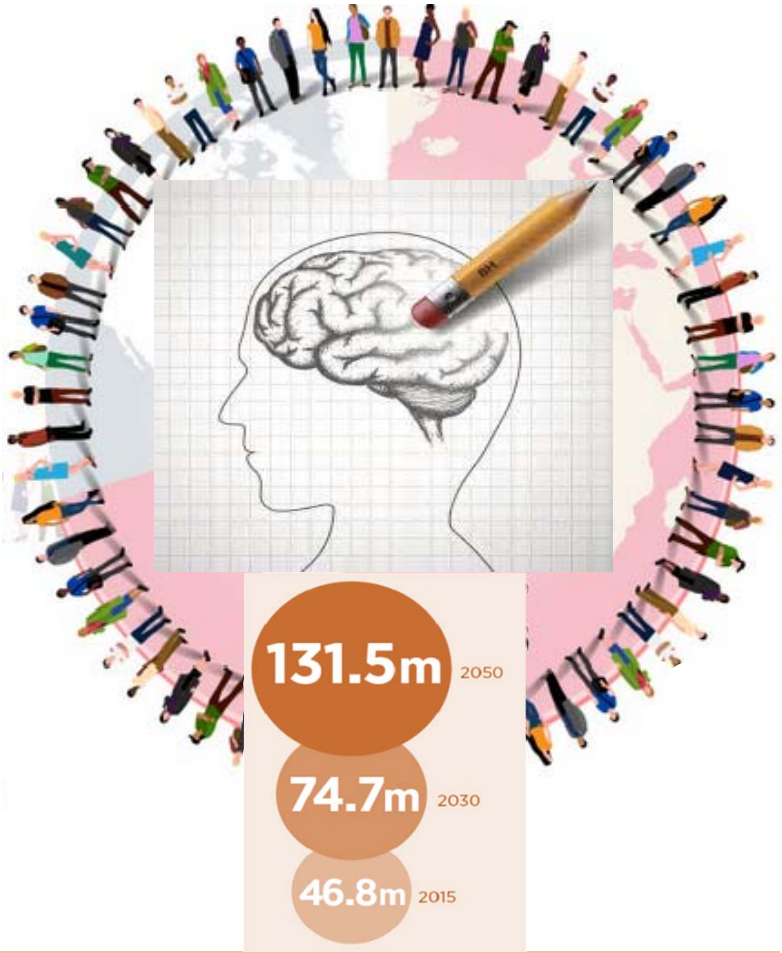


NIH U.S. National Library of Medicine

ClinicalTrials.gov

Terms	Search Results*	Entire Database**
Synonyms		
alzheimer disease	2,210 studies	2,210 studies
Alzheimer Dementias	83 st	83 studies
Dementia of the		50 studies
	es	21 st
de entia	21 studies	21
Dementia of Al	18 studies	
Alzheimer Type	13 studies	
Senile Dementia	10 studies	
Alzheimer Syndrome	1 studies	
disease	studies	234,594
Disorders	dies	84,118 st
condition	studies	10,784 st
alzheimer	,194 studies	2,227 studies





Crucial challenge for humankind

- ***Scarce***
- ***Limited efficacy***
- ***No new cognitive enhancer drug***

Inappropriate *therapeutic target*?

Solution:

- **Look for *NEW THERAPEUTIC TARGETS***

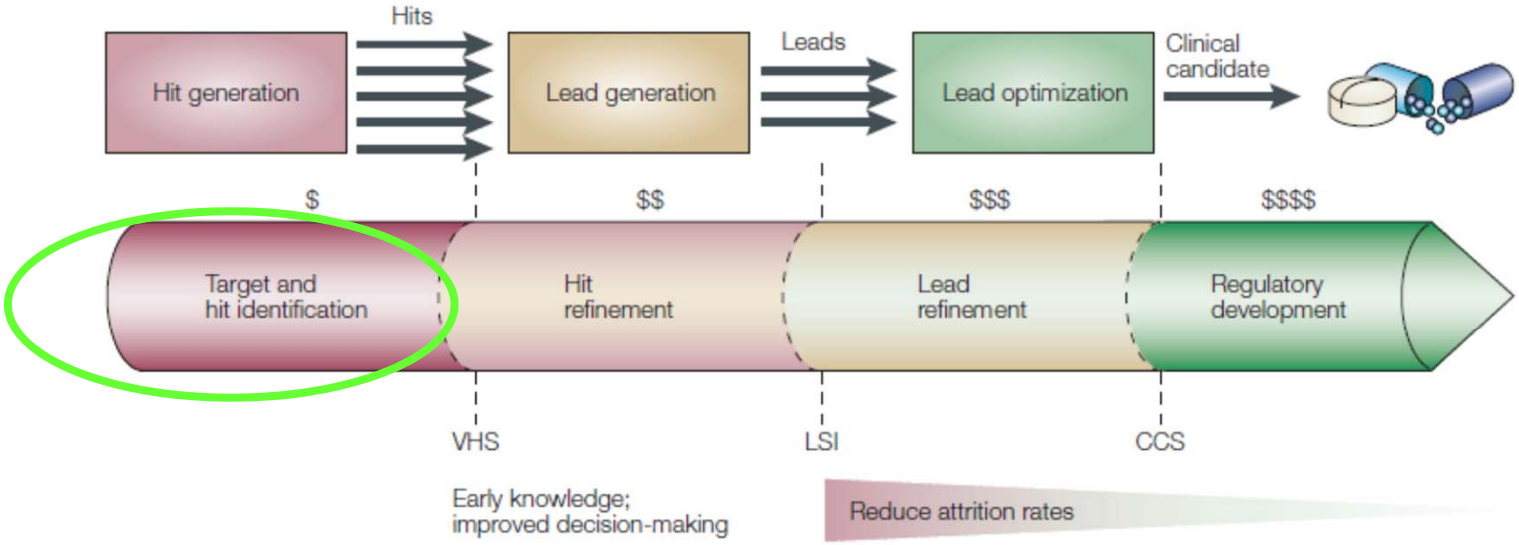
- **Understand the mechanisms involved in neurodegeneration**

→ **To address the multiple etiologies and pathophysiological processes of AD**

Solution:

- **Look for *NEW THERAPEUTIC TARGETS***

Steps in the process of discovery and development



Solution:

- **Look for *NEW THERAPEUTIC TARGETS***

Know your target, know your molecule

Imidazoline I_2 receptors

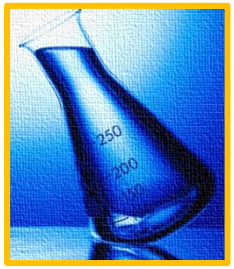
Solution:

- **Look for *NEW THERAPEUTIC TARGETS***
- **Understand the mechanisms involved in neurodegeneration**

➡ **To address the multiple etiologies and pathophysiological processes of AD**

Imidazoline I_2 receptors (I_2-IR)

- **Relatively unexplored target**
- **Widely distributed in the brain**
- **Increased in the brain of Alzheimer's patients**

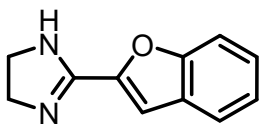


Known I_2–IR ligands

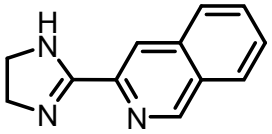
The nature of I_2-IR and their respective signalling patways have not been characterized

Competition binding studies against the selective I_2-IR radioligand [^{3}H]-2-BFI and the selective α_2-adrenoceptor (α_2-AR) radioligand [^{3}H]RX821002.

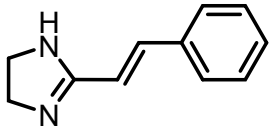
2-imidazoline-containing compounds



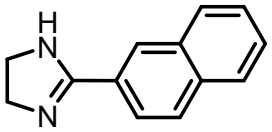
2-BFI



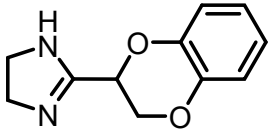
BU-224



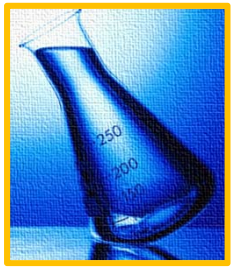
tracizoline



benazoline



idazoxan



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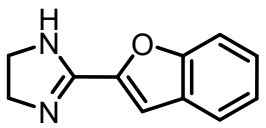
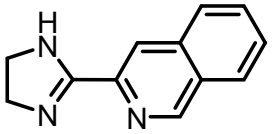

2-BFI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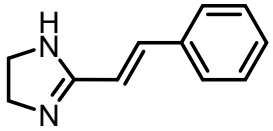
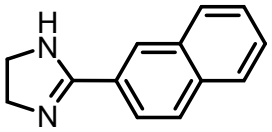
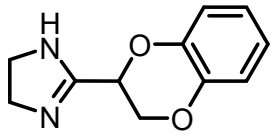
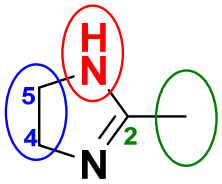

tracizoline


benazoline

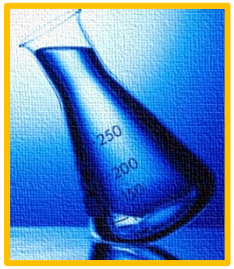

idazoxan

unsubstituted nitrogen



2-substituted

4,5-nonsubstituted



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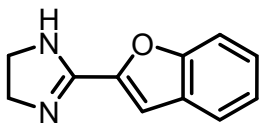
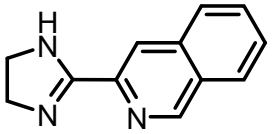

2-BFI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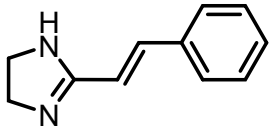
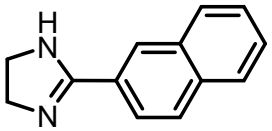
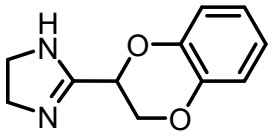

tracizoline


benazoline


idazoxan

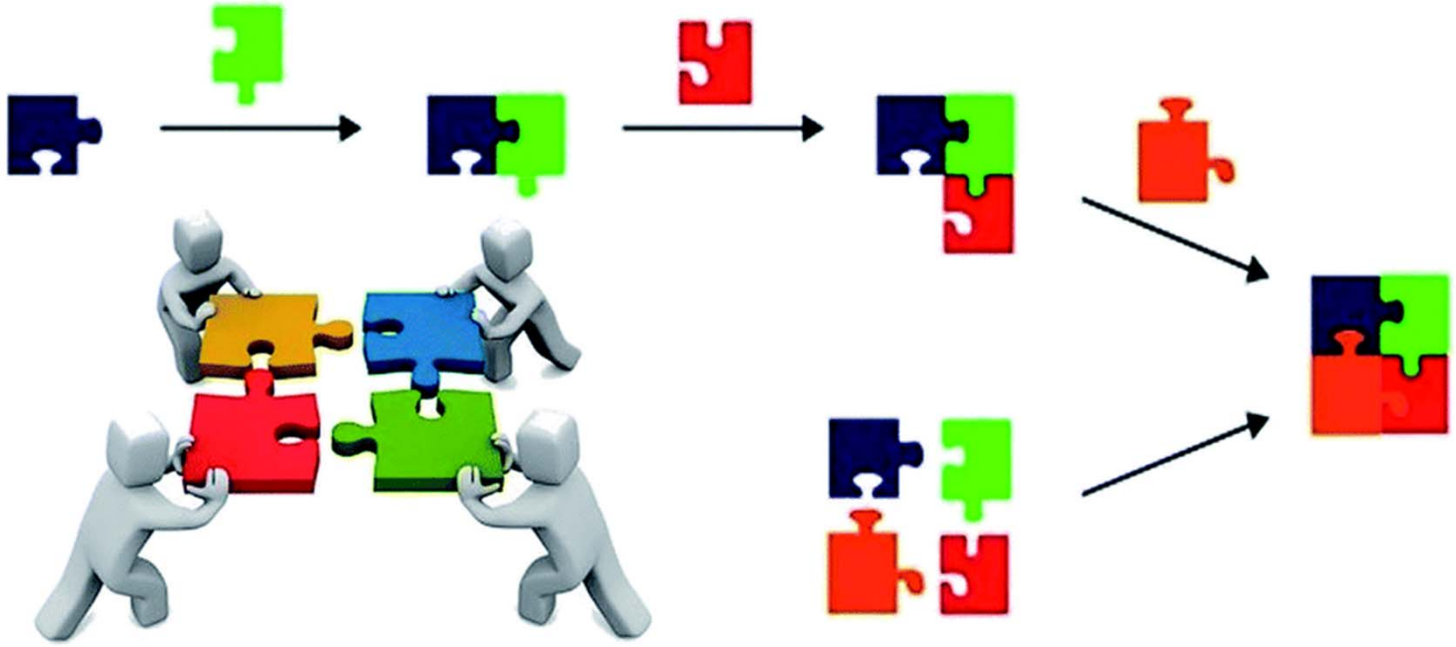
- Structurally restricted
- Low selectivity for I_2-IR/α_2-AR

New 2-imidazoline derivatives with a different substitution pattern

Multicomponent reactions

Reactions in which more than two starting compounds react to form a product in such a way that the majority of the atoms of the starting material can be found in the product.

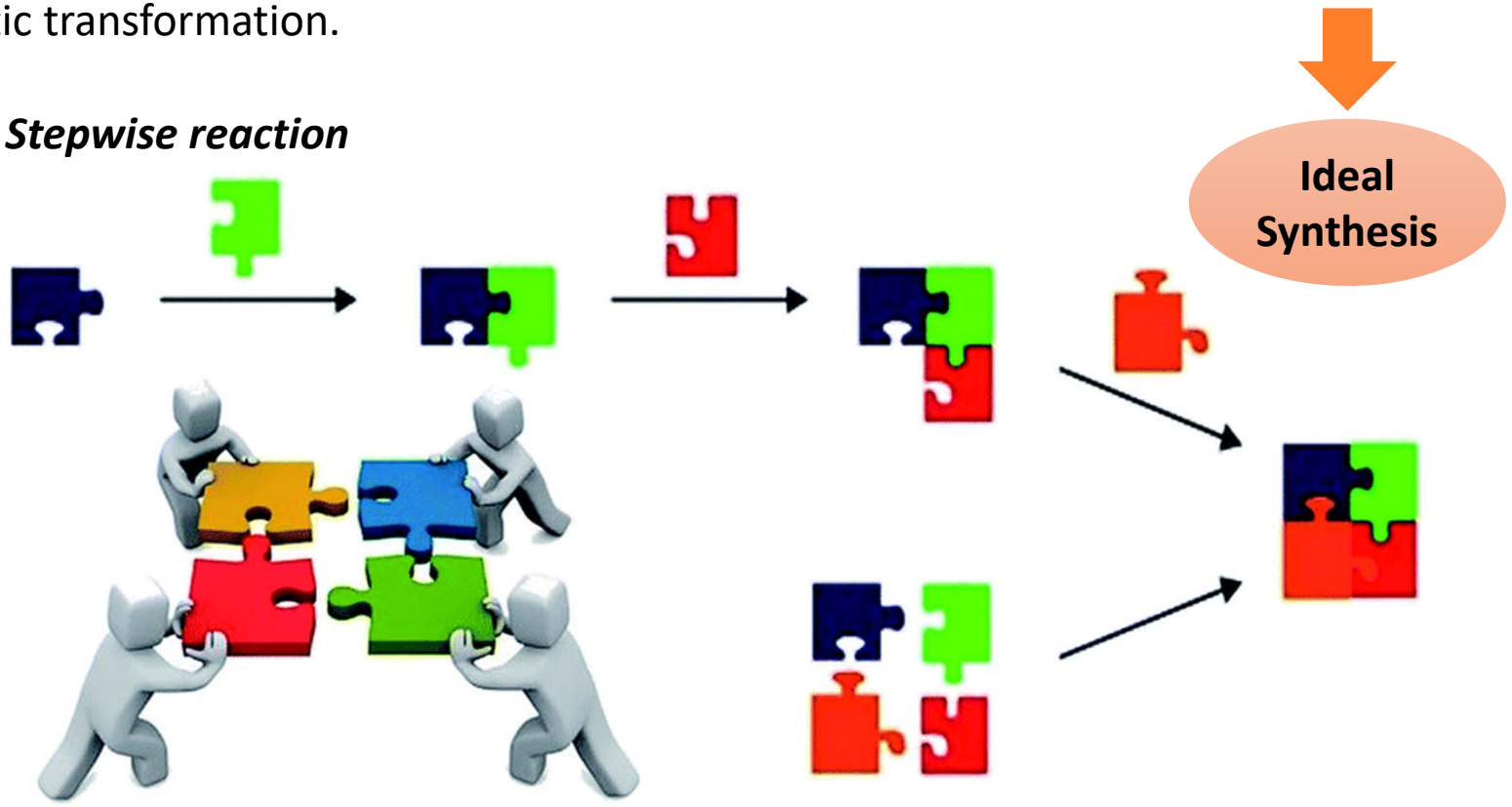
Stepwise reaction

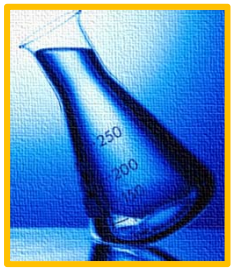


Multicomponent reaction

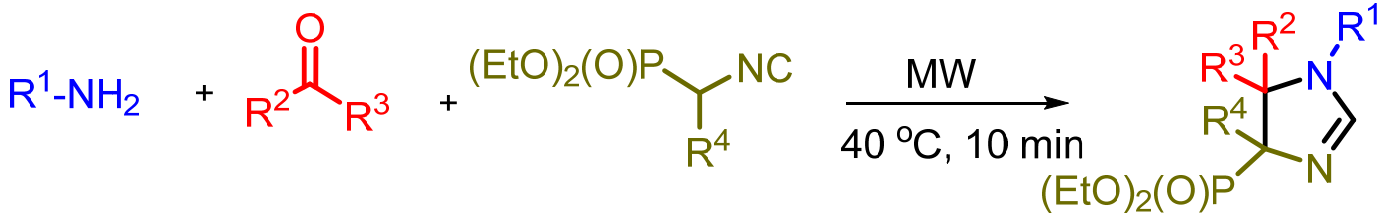
Multicomponent reactions

- ***Atom economy***, the majority if not all of the atoms of the starting materials are incorporated in the product;
- ***Efficiency***, the product is formed in one-step instead of multiple sequential steps;
- A very ***high bond-forming index***, several non-hydrogen atom bonds are formed in one synthetic transformation.





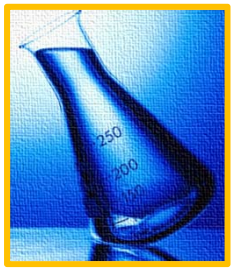
New 2-imidazoline phosphonates



ISOCYANIDE-BASED MULTICOMPONENT REACTION

SOLVENT FREE/NON ANHYDROUS ATMOSPHERE
ATOM ECONOMY
MICROWAVE ASSISTED

Abás, S.; Estarellas, C.; Luque, F. J.; Escolano, C. *Tetrahedron* **2015**, *71*, 2872.



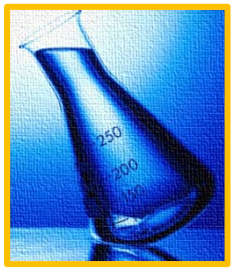
Receptor binding affinities/new ligands

Competition binding studies against the selective I_2-IR radioligand [^{3}H]-2-BFI and the selective α_2-AR radioligand [^{3}H]RX821002.

Membranes from postmortem human frontal cortex.

Blood Brain Penetration by PAMPA assays.

Abás, S.; Erdozain, A. M.; Keller, B.; Rodríguez-Arévalo, S.; Callado, L. F.; García-Sevilla, J. A.; Escolano, C. *ACS Chem. Neurosci*. 2017, *8*, 737.



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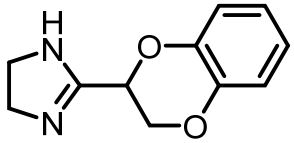
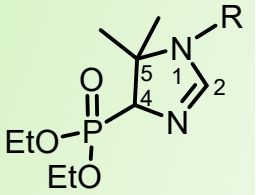
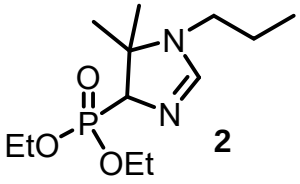


idazoxan **pK_i 7.27/ non I_2/α_2 selectivity**



Series 1



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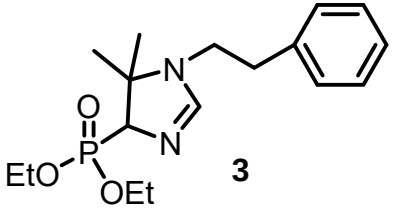

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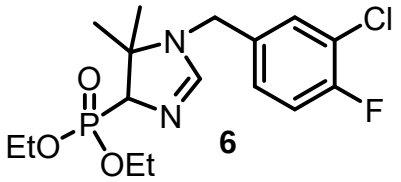
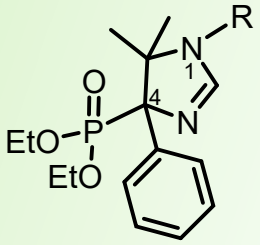
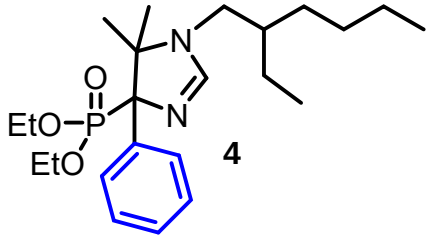


6

	2	**3**	**6**
pK_i	**7.84**	**8.19**	**8.31**
Selectivity I_2/α_2	**7762**	**10233**	**316**



Series 2



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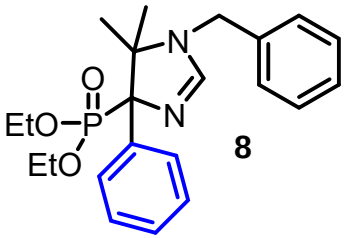

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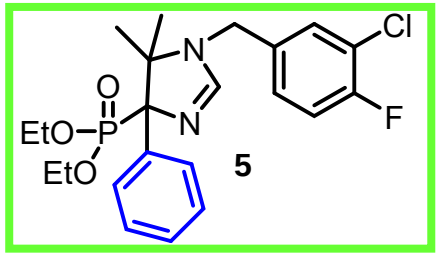
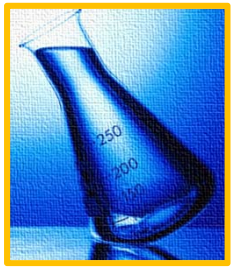


5

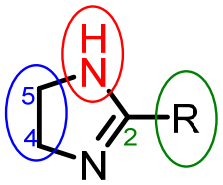
	4	**8**	**5**
pK_i	**7.61**	**8.89**	**9.42**
Selectivity I_2/α_2	**955**	**23**	**457**



New 2-imidazoline phosphonates

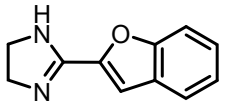
Known I_2-IR ligands

unsubstituted nitrogen

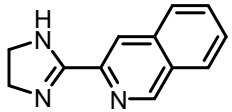


2-substituted

4,5-nonsubstituted



2-BFI



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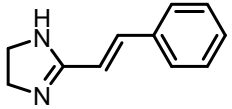
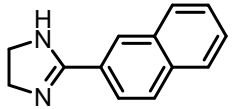
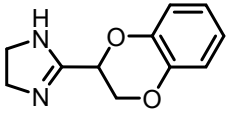


tracizoline



benazoline



idazoxan

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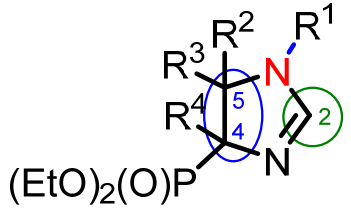


2-nonsubstituted

4,5,5-tri- or 4,4,5,5-tetrasubstituted

Competitive advantages

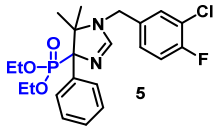
I_2-IR ligands

NIH U.S. National Library of Medicine
ClinicalTrials.gov

CR-4056 (Rottapharm Biotech)
the first-in-class imidazoline-2 receptor ligand
Osteoarthritis-Clinical Trial Phase II

[^{11}C]BU99008 (Imperial College London/GlaxoSmithKline)
PET studies for AD-Clinical Trial Early Phase I

Advantages of 5:



5

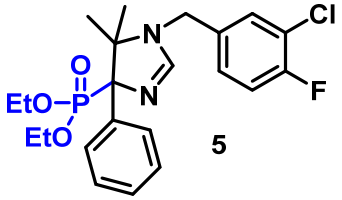
- *vs* other I_2-IR ligands: Higher affinity/selectivity against human brain I_2-IR

- *vs* current AD treatments (AchEI, $NMDA_{ant}$): new mechanism of action
  new therapeutic opportunities

No companies or academic groups are working on I_2-IR ligands for AD therapeutics

Stability studies

- Solubility
- Chemical stability: light, solid, solution, temperature…



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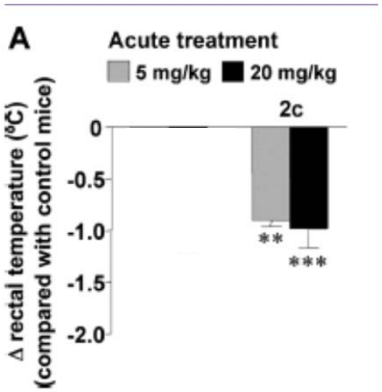
ADMET studies

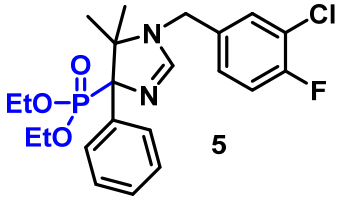
- Inhibition of cytochrome P450 enzymes
- Microsomal stability
- Inhibition of hERG channels
- Preliminary cytotoxicity: Cell lines tested: MRC-5, HEL, HeLa, MDCK and MT4

No warnings!!!!

Hypothermia

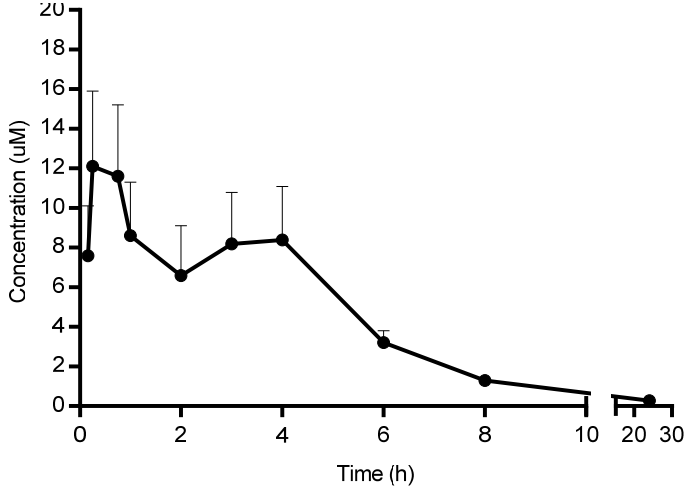
Induces hypothermic effects
→ neuroprotection





Pharmacokinetics

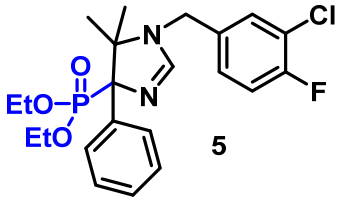
Plasma concentration and standar error after oral administration in mice (n=4) IP at 5 mg/Kg



Good bioavailability

Pharmacokinetic parameters
AUC_0^{∞} (ug*h/ml): 28,8
AUC_0^{t} (ug*h/ml): 27,8
T_{max}: 0,25h
C_{max}: 5,49 ug/ml;
$t_{1/2\,\beta}$:5,76 h

In vivo cognitive studies



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In drinking water at 5 mg/Kg
for 1 month

Female 12 months-old

SAMP8 Ct (n=8)

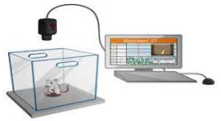
SAMP8 MCR 5 (n=8)

BEHAVIOURAL AND COGNITIVE TESTS

BEHAVIOUR

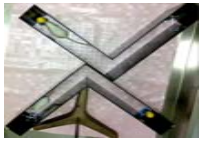
EPM

OF

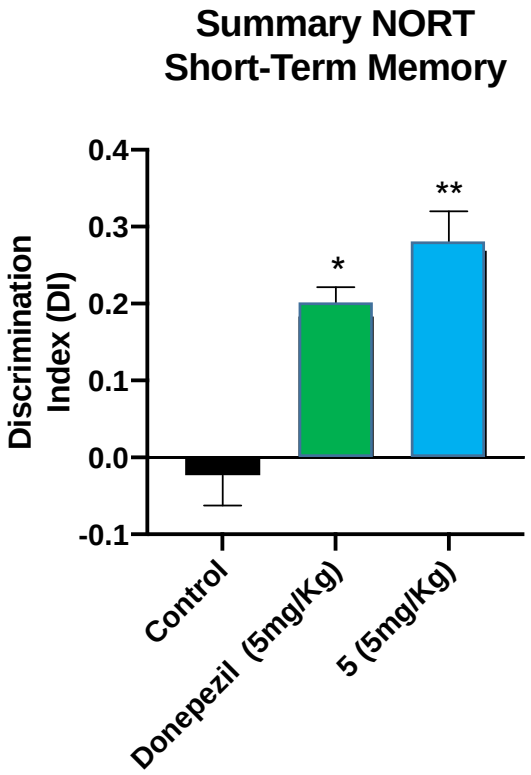


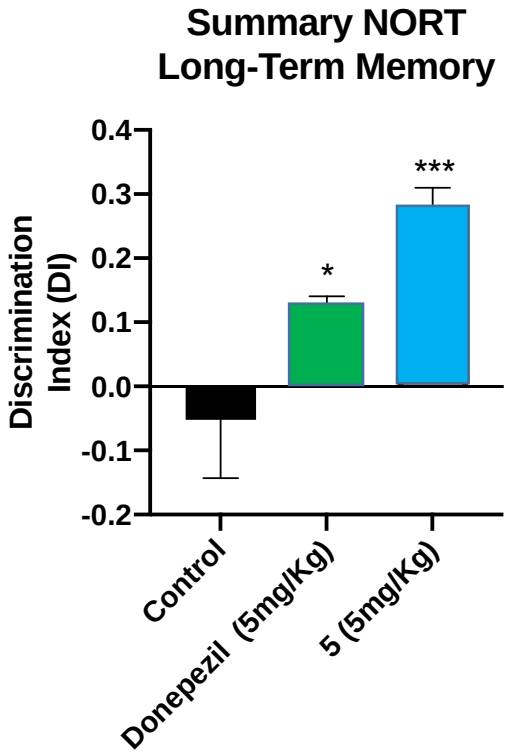
MEMORY

NORT



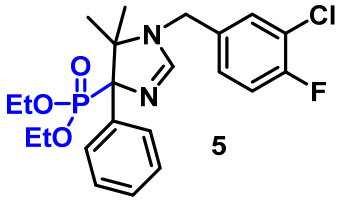
In vivo cognitive studies/donepezil





Between 6- and 8-month-old and Males SAMP8 (n = 10-12; each group).
One Way ANOVA followed by Dunnett posthoc test; *p<0.05; **p<0.01; ***p<0.001

In vivo cognitive studies



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In drinking water at 5 mg/Kg
for 1 month

Female 12 months-old

SAMP8 Ct (n=8)

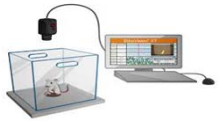
SAMP8 MCR 5 (n=8)

BEHAVIOURAL AND COGNITIVE TESTS

BEHAVIOUR

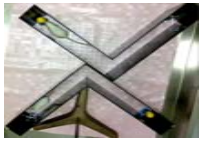
EPM

OF



MEMORY

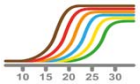
NORT



MOLECULAR ANALYSIS

WB

qPCR



Reduction of inflammatory markers and anti-oxidant enzymes increase

Griñán, C.; Vasilopoulou, F.; Abás, S.; Rodríguez-Arévalo, S.; Bagán, S.; Sureda, F. X.; Pérez, B.; Callado, L. F.; García-Sevilla, J. A.; Escolano, C. *Neurotherapeutics* 2019, *16*, 416.

Ligand based approach-3D QSAR

Data set preparation

- I_2 - 38 compounds; pKi: 9.42-3.64
- $Alpha_2$- 39 compounds; pKi: 7.52-3.95

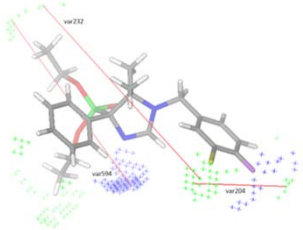
3D-QSAR model building

- Calculation of GRID independent descriptors
- Training set 70% - building PLS model; test set 30% - model validation

Model validation

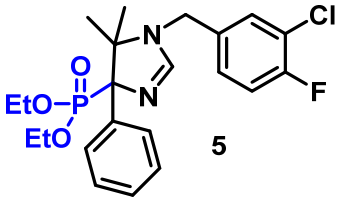
- Internal and external validation → to ensure the reliability and predictability of created QSAR models.

Pharmacophore analysis



3D-QSAR approach was used to find crucial structural features responsible for high binding affinity and selectivity of I_2-IR ligands.

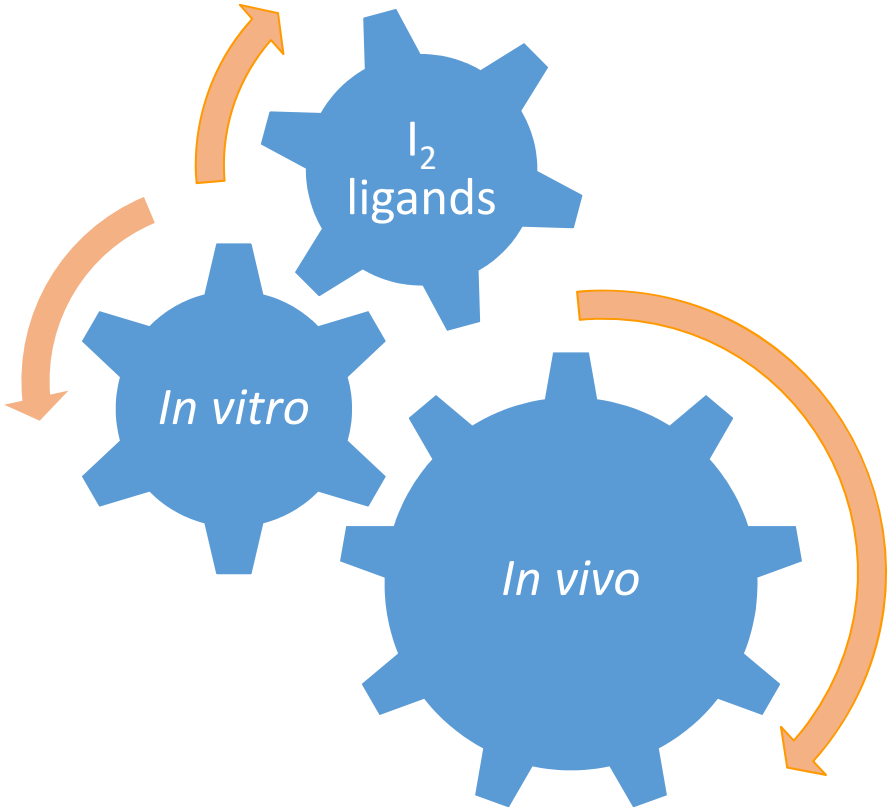
Conclusions 2-imidazoline phosphonates



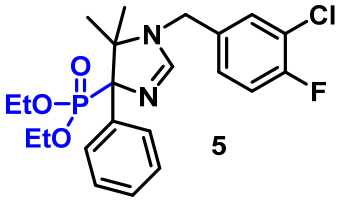
5 improves the cognitive decline in SAMP8

First experimental evidence

I_2-IR new target for AD



Conclusions

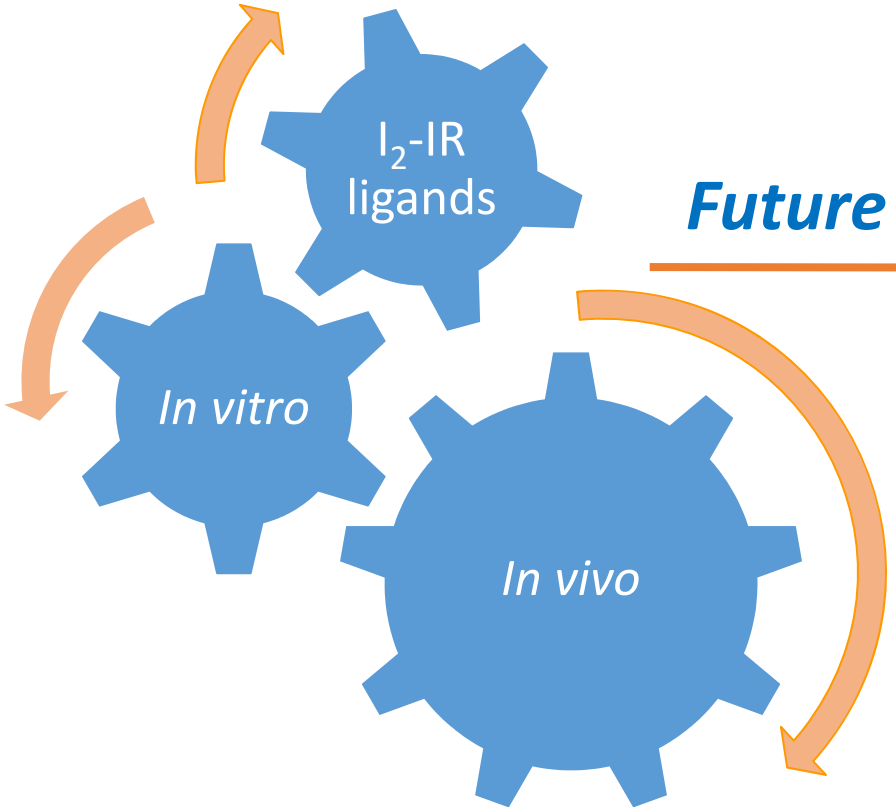


5 improves the cognitive decline in SAMP8

First experimental evidence

I_2-IR new target for AD

Future perspectives



- ***Target engagement***

Definition of the signalling pathways of I_2-IR

Read-out for new of I_2-IR ligands (*in vitro* test)

Imidazoline I_2 receptors

- Target engagement

- Relatively unexplored target

- Widely distributed in the brain

- Increased in the brain of Alzheimer's patients

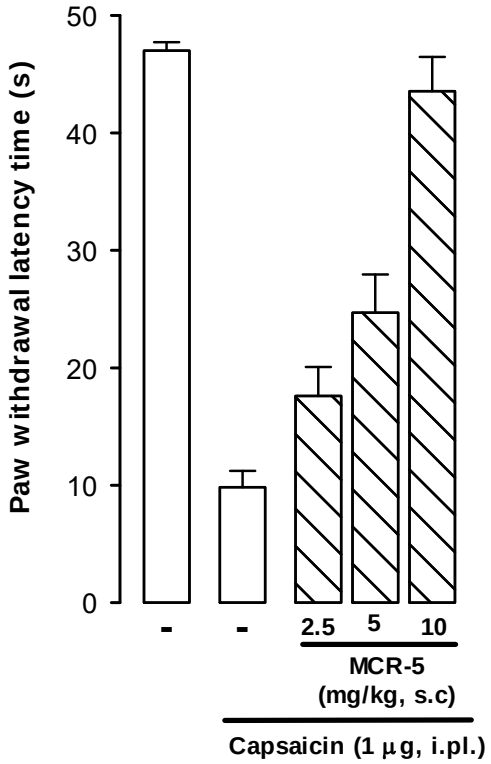
NIH U.S. National Library of Medicine

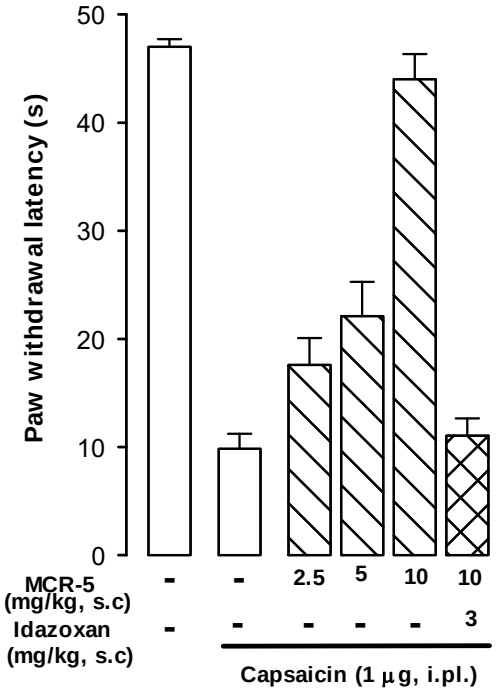
ClinicalTrials.gov

CR-4056 (Rottapharm Biotech)
the first-in-class imidazoline-2 receptor ligand
Osteoarthritis-Clinical Trial Phase II

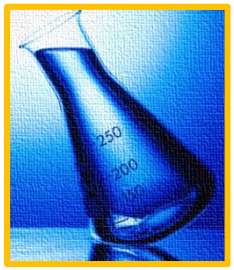
→ Neuropathic pain **UNMET MEDICAL NEED**

Imidazoline I_2 receptors

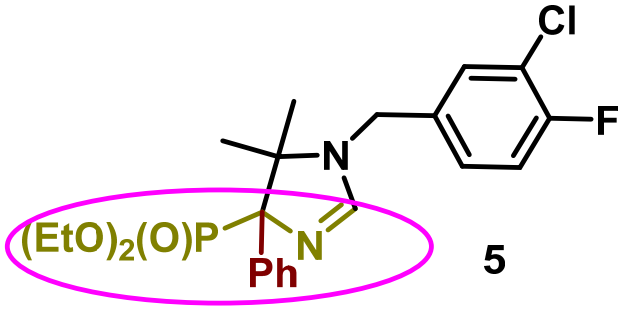




→ Neuropathic pain **UNMET MEDICAL NEED**



New bicyclic α-iminophosphonates



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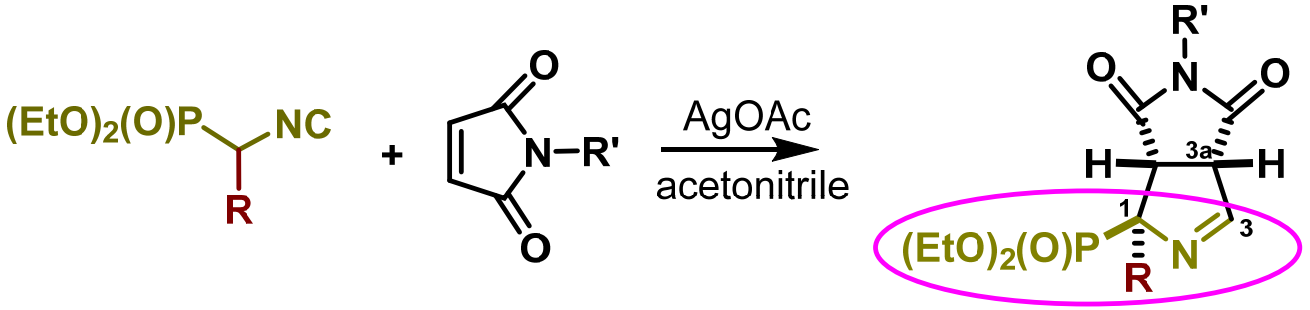
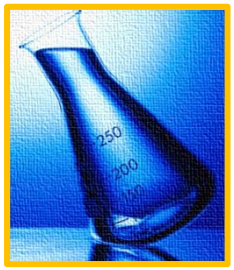
α-iminophosphonate moiety

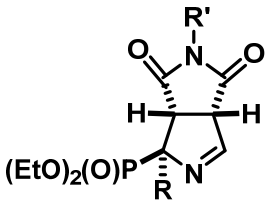


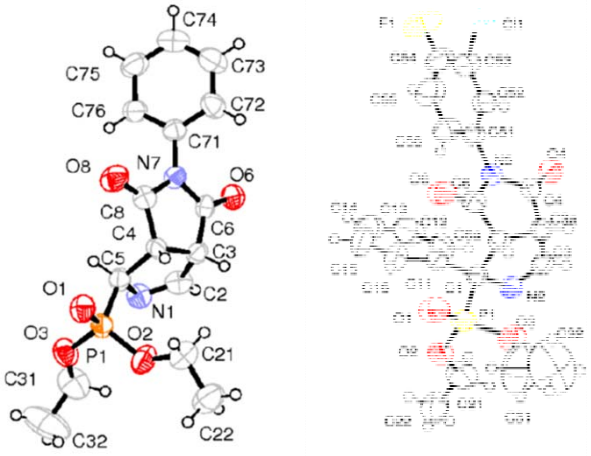
Diastereoselective [3+2] cycloaddition reaction

Arróniz, C.; Molina, J.; Abás, S.; Molins, E.; Campanera, J. M.; F. J. Luque; Escolano, C. *Org. Biomol. Chem*. **2013**, *11*, 1640.

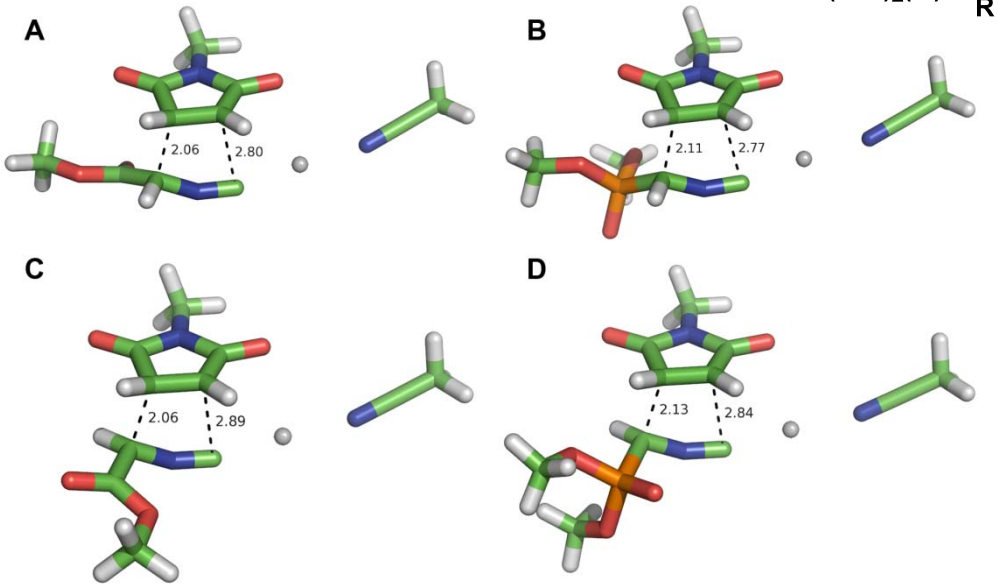


New bicyclic α-iminophosphonates

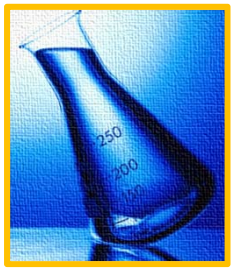




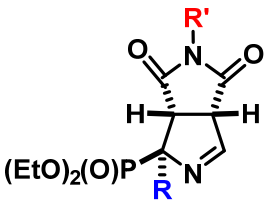
X-Ray crystallography



Theoretical calculations



New bicyclic α-iminophosphonates



R'-	R- = H-	Ph-	4-FPh-	4-MeOPh-	$PhCH_2$-	$4FPhCH_2$-
Me	**8a**	**9a**				
cyclohexyl	**8b**	**9b**				
Ph	**8c**	**9c**	**12c**	**13c**	**14c**	**15c**
3-Cl,4-FPh	**8d**	**9d**	**12d**	**13d**		
4-MeOPh	**8e**	**9e**				

R' =

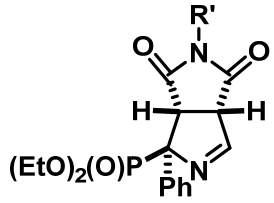
9f, Et
9g, propyl
9h, *t*-butyl
9i, (1-adamantyl)methyl-

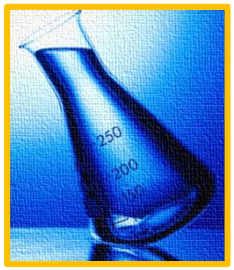
9j, $PhCH_2$-
9k, $PhCH_2CH_2$-
9l, $4\text{-}FPhCH_2CH_2$-
9m, $Ph(CH_2)_2CH$-

9n, $4\text{-}CF_3Ph$-
9o, $3\text{-}CF_3Ph$-
9p, 4-FPh-
9q, 4-ClPh-
9r, 2-ClPh-
9s, 3-ClPh-
9t, 4-BrPh-
9u, 3,5-diClPh-
9v, 3,4-diClPh-
9w, 2,4,6-triClPh-
9x, $3\text{-}NO_2Ph$-
9y, $3\text{-}NO_2,6\text{-}CH_3Ph$-

9z, 4-PhPh-
9aa, $4\text{-}CH_3Ph$-
9ab, 4-PhOPh-

9ac, 1-naphthyl
9ad, 2-Cl,3-pyridyl



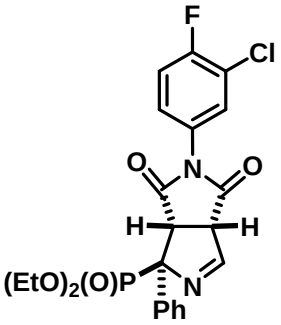


Receptor binding affinities/new ligands

Our asset

New family of **small molecules**

- **Short** synthetic process
- **High affinity** and **selectivity** for the human I_2-IR
- **Good Blood Brain Barrier penetration** properties



B06

B06 (Ki 3 nM)

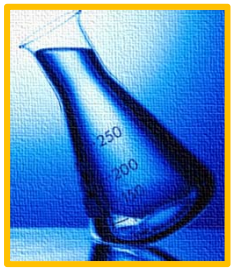
Non-cytotoxicity
(human fibroblasts, CC_{50}>100 µM)

No inhibition of hERG channels (IC_{50}> 10 µM)
→ no cardiac side-effects

Induces hypothermic effects
→ neuroprotection

Improves the behavior and cognition
in two murine models,
neurodegeneration (SAMP8)
and AD (5xFAD)

Bosch i Gimpera
UNIVERSITAT DE BARCELONA



Receptor binding affinities/new ligands

Protected by European patent application (WO 2019/121853 A1 , December 2018)

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WIPO | PCT

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(74) Common Representative: **UNIVERSITAT DE BARCELONA**; Centre de Patents de la UB, Baldiri Reixac 4 - Torre D, 08028 Barcelona (ES).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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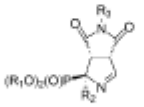
Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*

WO 2019/121853 A1

(54) Title: SYNTHETIC I_2 IMIDAZOLINE RECEPTOR LIGANDS FOR PREVENTION OR TREATMENT OF HUMAN BRAIN DISORDERS

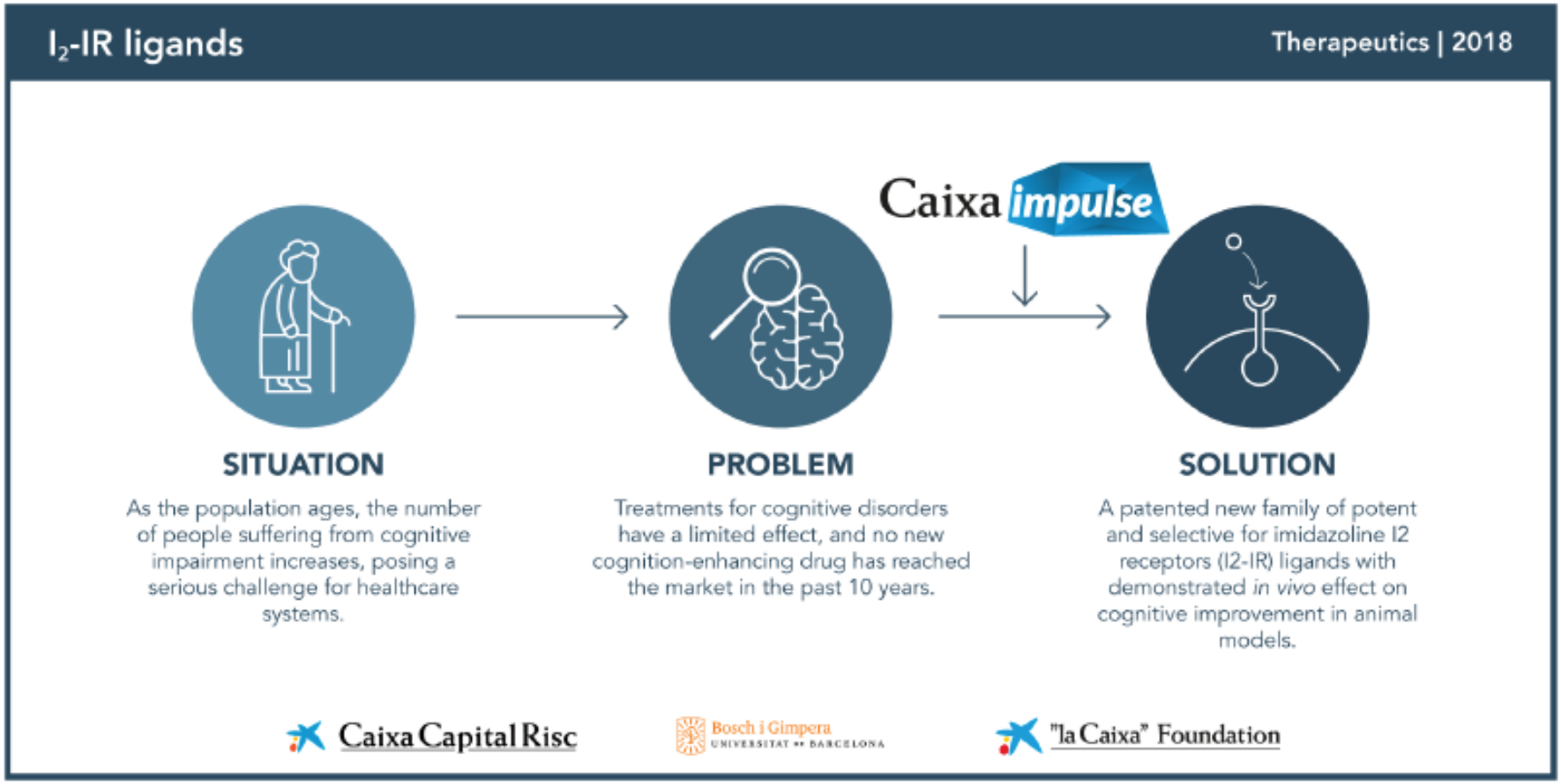


(I)

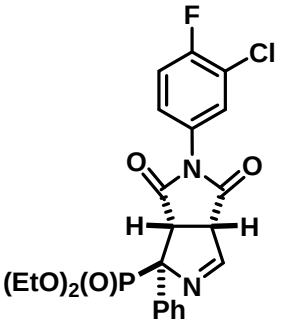
(57) Abstract: Compounds of formula I, their respective mirror-image enantiomers, and mixtures-preferably racemic- of both enantiomers, wherein R_1 is ethyl or phenyl; R_2 is methyl, phenyl, monosubstituted phenyl, benzyl, or monosubstituted benzyl; R_3 is selected from the group consisting of: $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-cycloalkyl, -$[CH_2]_n$-phenyl, -$[CH_2]_n$-1-naphtyl, -$[CH_2]_n$-2-naphtyl, and -$[CH_2]_n$-[substituted phenyl]; wherein [substituted phenyl] is a phenyl radical with one, two or three substituents independently selected from: F, Cl, Br, $(C_1\text{-}C_3)$-alkyl, $(C_1\text{-}C_3)$-alkyloxy, phenyl, phenoxy, $-CF_3$, $-OCF_3$, nitro, -CN, $-CO\text{-}(C_1\text{-}C_3)$-alkyl and benzoyl, and n is an integer between 0 and 4; have a high affinity for imidazoline receptors of the I_2 type, i.e. they are I_2-IR ligands. Consequently they are applicable in the prevention or treatment of brain disorders in animals, including humans, particularly of neurodegenerative disorders, and more particularly of Alzheimer's disease (AD).

Valorization for TechTransfer

I2-IR ligands



Pharmacokinetics



B06

Fundación MEDINA
Centro de Excelencia
en Investigación de
Medicamentos Innovadores
en Andalucía

Metabolic profiling

- Levels of **B06** in CNS
- Determination of metabolites
  - Microsomal stability
  - Plasmatic stabilty
  - Structure (mass spectrometry)

Future perspectives

Synthesis of metabolites and pharmacological evaluation
Modification of the molecule

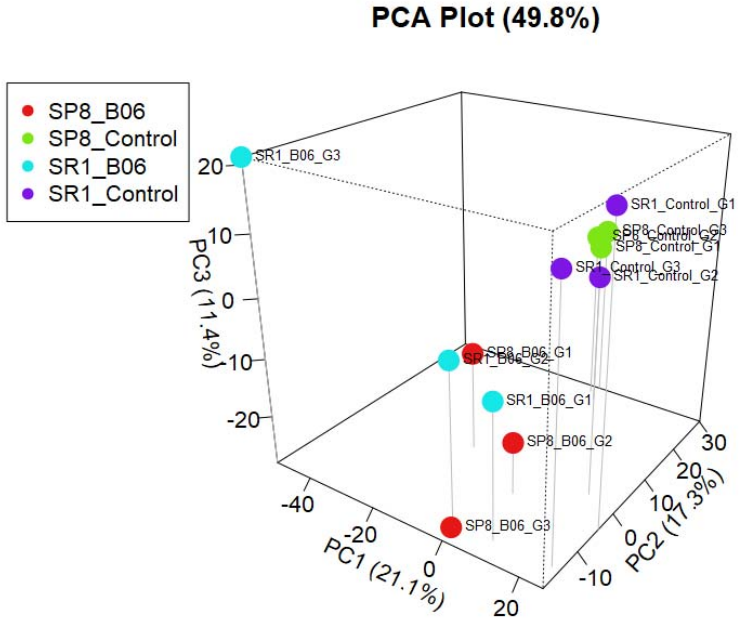
Future perspectives

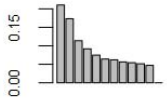
- Target engagement

Proteomics

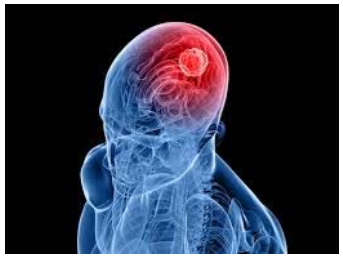
Parc Científic de Barcelona
UNIVERSITAT DE BARCELONA

CRG
Centre for Genomic Regulation

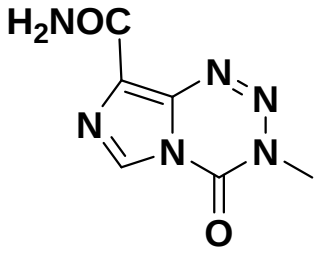




SP8_B06	Phenotype SP8 Control
SP8_Control	Phenotype SP8 Control
SR1_B06	Phenotype SR1 B06
SR1_Control	Phenotype SR1 Control

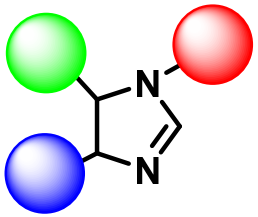


orphanet **Glioblastoma**



temozolomide

Gold standard
IC_{50} de 14.5 µM en LN-229 cells



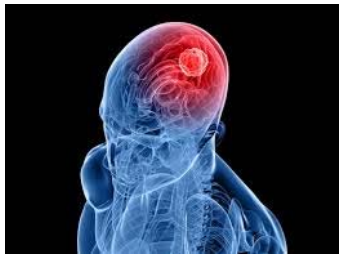
New family
embodying 2-imidazoline nucleus
Synthesis MCR

KATHOLIEKE UNIVERSITEIT LEUVEN
Rega Instituut

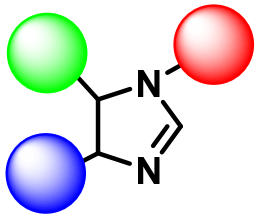
IC_{50} 7 µM in LN-229 cells ✓

PAMPA BBB permeation ✓

Bosch i Gimpera
UNIVERSITAT DE BARCELONA



Glioblastoma



New family
embodying 2-imidazoline nucleus
Synthesis MCR

IC_{50} 7 µM in LN-229 cells ✓

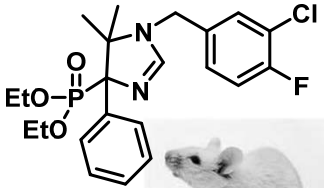
PAMPA BBB permeation ✓

CONCLUSIONS

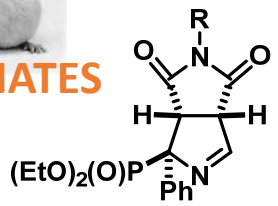
NEW STRATEGY FOR NEURODEGENERATIVE DISEASES (AD)

NEW IMIDAZOLINE I_2 RECEPTORS LIGANDS
MULTICOMPONENT REACTIONS

FIRST *IN VIVO* EVIDENCE I_2-IR LIGANDS FOR AD

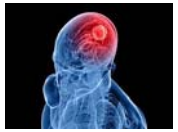


NEW FAMILY OF I_2-IR LIGANDS: BICYCLIC α-IMINOPHOSPHONATES



I_2-IR LIGANDS FOR NEUROPATHIC PAIN

MCR compounds for GLIOBLASTOMA



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THANK YOU