Novel antimicrobials specific against *Helicobacter pylori*

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XVIII Encuentro de Cooperación Farma-Biotech

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Bifi

The labs

1500 m^2 of high tech scientific infrastructure devoted to Biocomputation and Drug Discovery

The People

100 people (60 PhD)

CESAR Centro de Supercomputación de Aragón

LACRIMA Laboratorio Avanzado de Cribado e Interacciones Moleculares de Aragón

Aragón Drug discovery Center

Rapid, target-oriented, screening of thousands of molecules to identify pharmacological activities

Computationally driven Medicinal Chemistry

Repurposing of existing drugs

LACRIMA

Laboratorio Avanzado de Cribado e Interacciones Moleculares de Aragón

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LACRIMA
Laboratorio Avanzado de Cribado e Interacciones Moleculares de Aragón

Year	Target	Type of compound	Application	Patent
2008	PAH	pharmacological chaperons	Phenylketonuria (PKU)	X
2009	**Fld**	**antimicrobials**	***Helicobacter pylori***	**X**
2009	Stem cells	apoptotic cell death	Cell therapy	
2012	Aß(1-42)	aggregation inhibitors	Alzheimer disease	X
2013	NS3 protease	antivirals	Hepatitis C	
2016	hIAPP	aggregation inhibitors	Type II Diabetes	
2016	PEPCK-C	enzyme inhibitors	Isoform phenotyping	
2017	IDP	antitumoral	Pancreatic cancer	
2017	FNR	antimicrobials	*Xanthomonas citri*	
2018	α-syn	aggregation inhibitors	Parkinson disease	X
2018	FAD sintasa	antimicrobials	*C. ammoniagenes/M. tuberculosis/S. pneumoniae*	
2019	AIF	apoptosis regulators	Apoptosis regulation	

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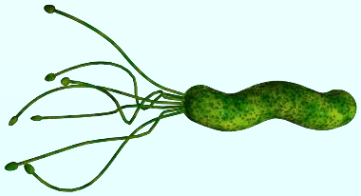
Helicobacter pylori (Hp)

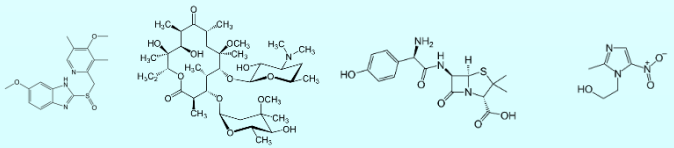


Gram– proteobacteria

~50 % people infected world-wide (47 % in Europe)
(Gastroenterology 2017;153:420-429)

Causes peptic ulcers and stomach cancer

Triple/cuadruple therapy failure: 30 %



OMEPRAZOLE CLARITHROMYCIN AMOXICILLIN METRONIDAZOLE

No new drug has been developed for this indication

There is not a single *H pylori*–specific antimicrobial

Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report
Gut 2017 **66**:6-30

"**Statement 2**: A test-and-treat strategy is appropriate for **uninvestigated dyspepsia**. This approach is subject to regional *H. pylori* prevalence and cost-benefit considerations. It is not applicable to patients with alarm symptoms or older patients.
Level of evidence: high
Grade of recommendation: strong"

"**Statement 12**: *H. pylori* eradication is the first-line treatment for localised stage **gastric MALToma**.
Level of evidence: moderate
Grade of recommendation: strong"

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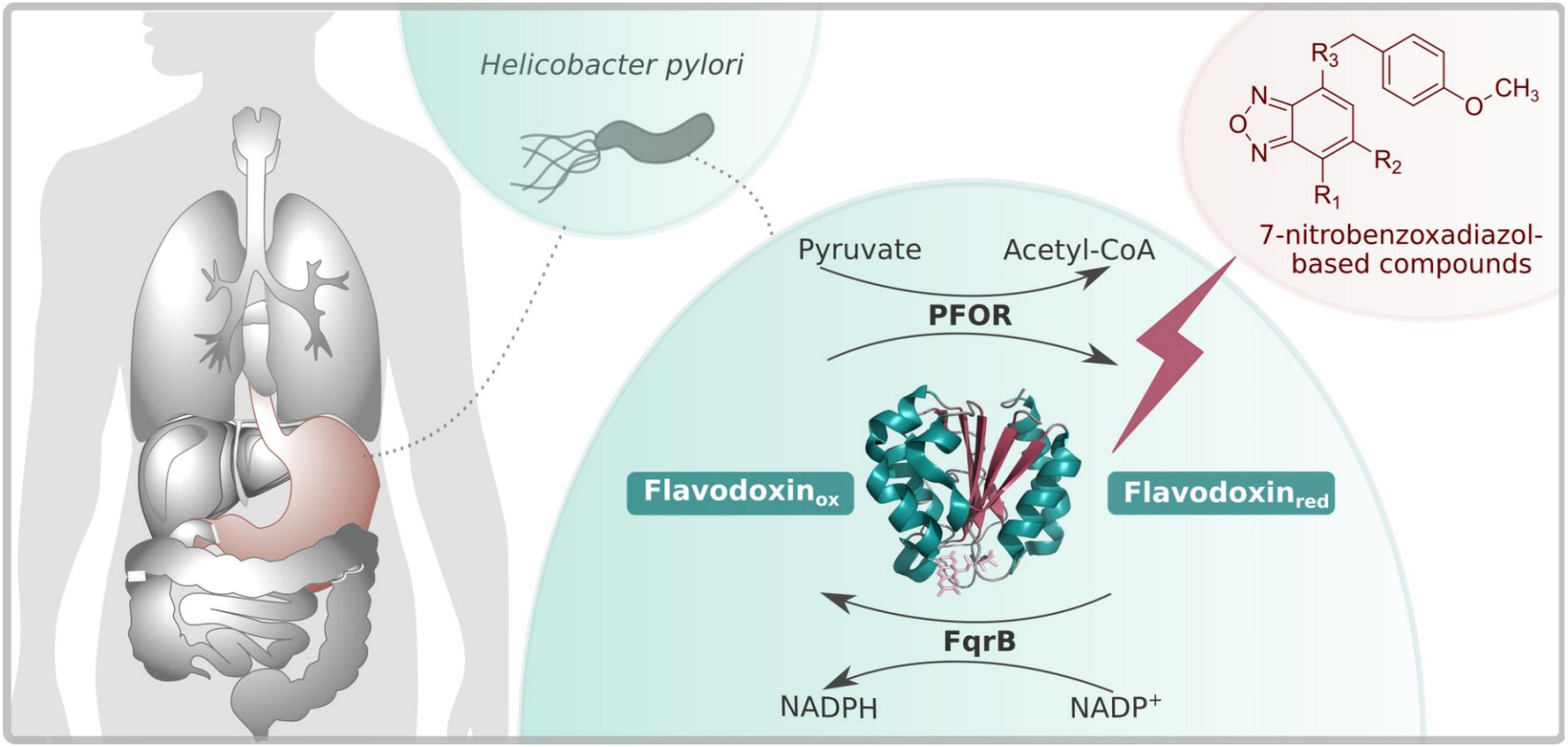
Helicobacter pylori
Pyruvate
Acetyl-CoA
PFOR
Flavodoxin$_{ox}$
Flavodoxin$_{red}$
FqrB
NADPH
NADP$^+$
7-nitrobenzoxadiazol-based compounds

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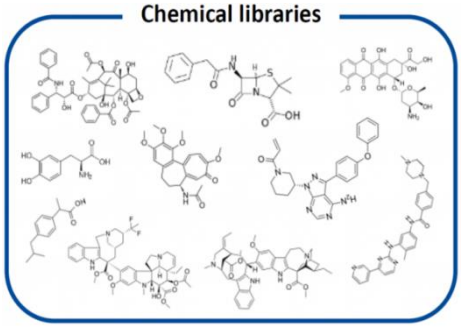
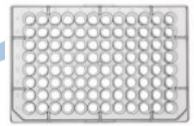
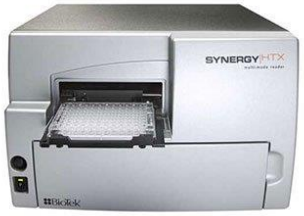
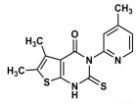
156 M chemicals



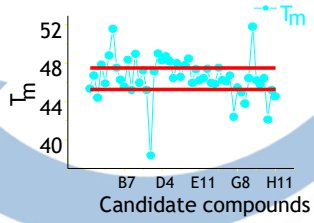
Target to hit screening

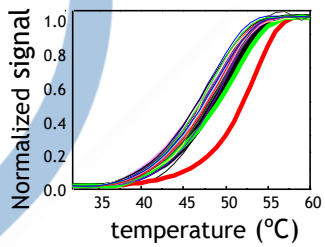




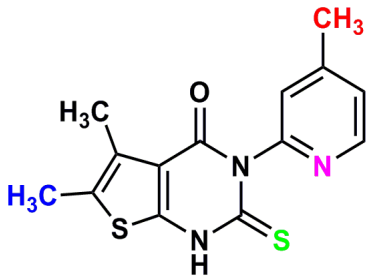


hit





Hit to lead medicinal chemistry



Testing in animal models

1) New compounds: no resistances (yet)

2) *Hp*-specific: presumably less damaging to microbiota

MIC (μg/mL)

	Gram–					Gram+							
Compound	*H. pylori*	*C. jejuni*	*E. coli*	S. thyphimurium	*P. aeruginosa*	*B. subtilis*	*S. pneumoniae*	*L. monocytogenes*	*E. faecalis*	*S. aureus*	*C. diphteriae*	*C. ammoniagenes*	*M. smegmatis*
IV	2	2	>64	>64	>64	4	8	>64	2	16	16	16	>64
IV-a	8	>64	>64	>64	>64	>64	>64	>64	>64	>64	64	>64	>64
IV-b	1	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
IV-c	2	>64	>64	>64	>64	>64	64	>64	>64	>64	8	>64	>64
IV-d	8	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Amp	0,25		0,5	0,5	>64	<0,032	0,063	0,125	8	0,063	0,063	0,063	>64
Mnz	2	1	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Cla	≤0,125	4	16/32	>64	8	0,063	<0,032	0,25	0,25	<0,031	0,063	<0,032	4
	ε proteobacteria		γ proteobacteria			firmicutes					actinobacteria		

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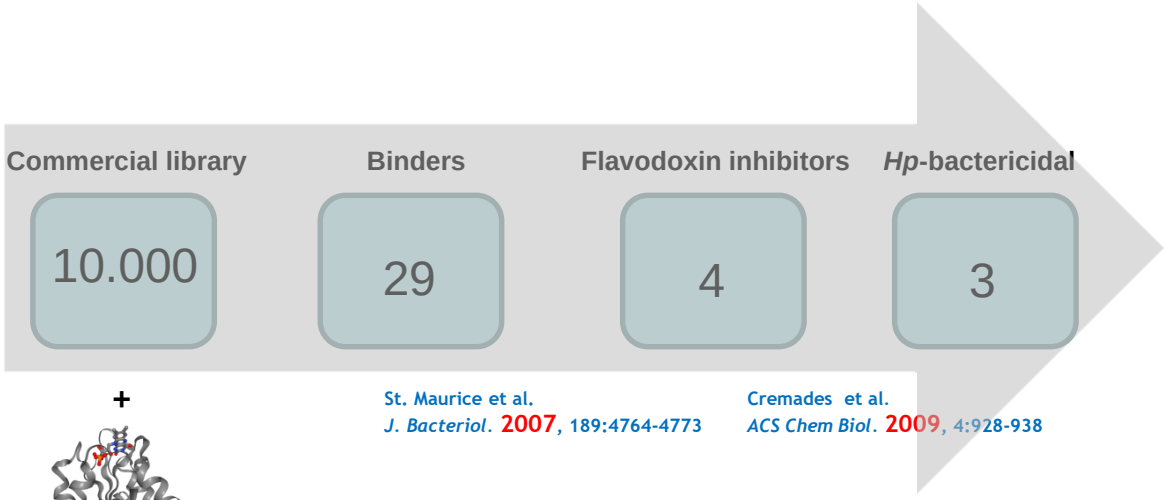
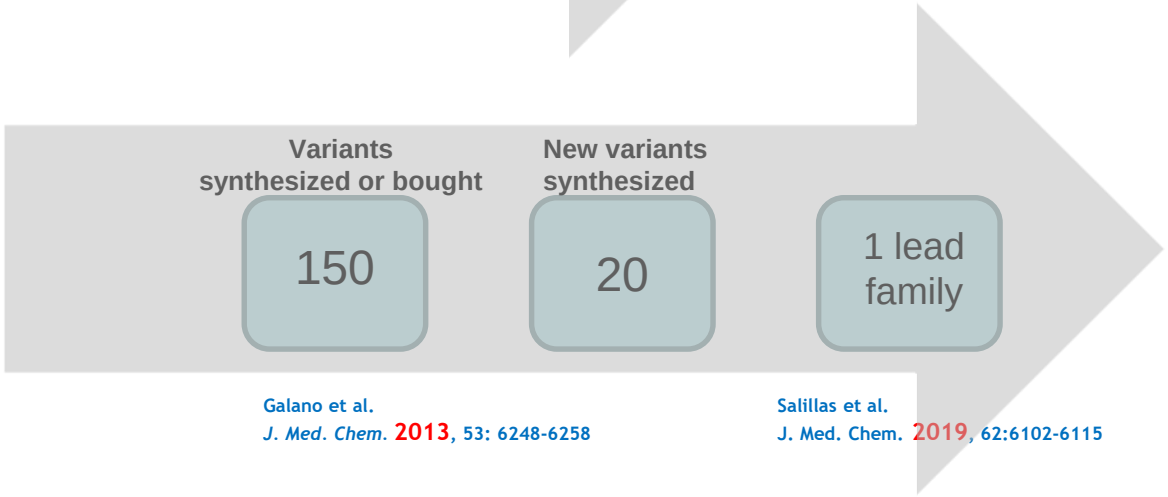


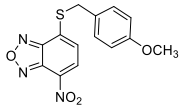
St. Maurice et al.
J. Bacteriol. 2007, 189:4764-4773

Cremades et al.
ACS Chem Biol. 2009, 4:928-938

\+

Purified target:
***Hp*-flavodoxin**





Galano et al.
J. Med. Chem. 2013, 53: 6248-6258

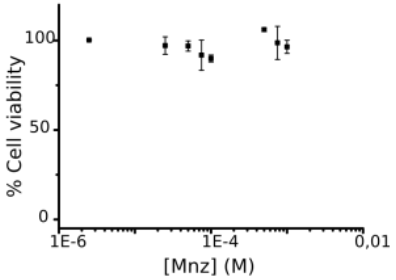
Salillas et al.
J. Med. Chem. 2019, 62:6102-6115

➢**Some variants show very low or no toxicity in vitro toward eukariotic cell (HeLa)**

lead

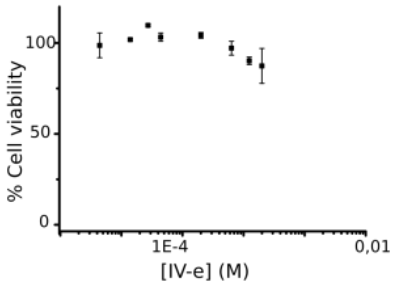
MCC_{50}=7µM

metronidazole



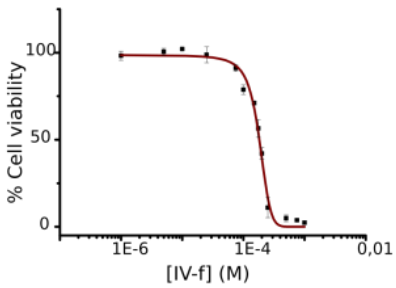
MCC_{50}>1000µM

Compound IV-e



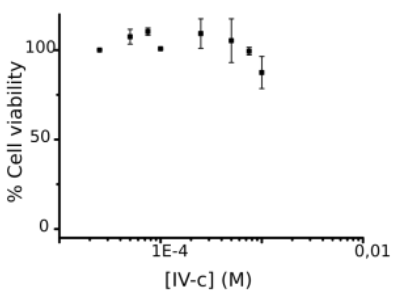
MCC_{50}>1000µM

Compound IV-f



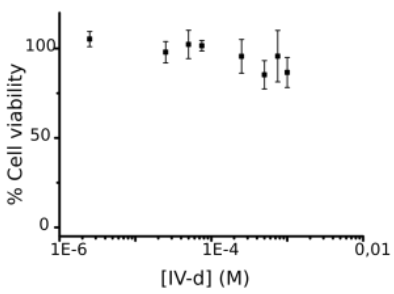
MCC_{50}=179µM

Compound IV-c



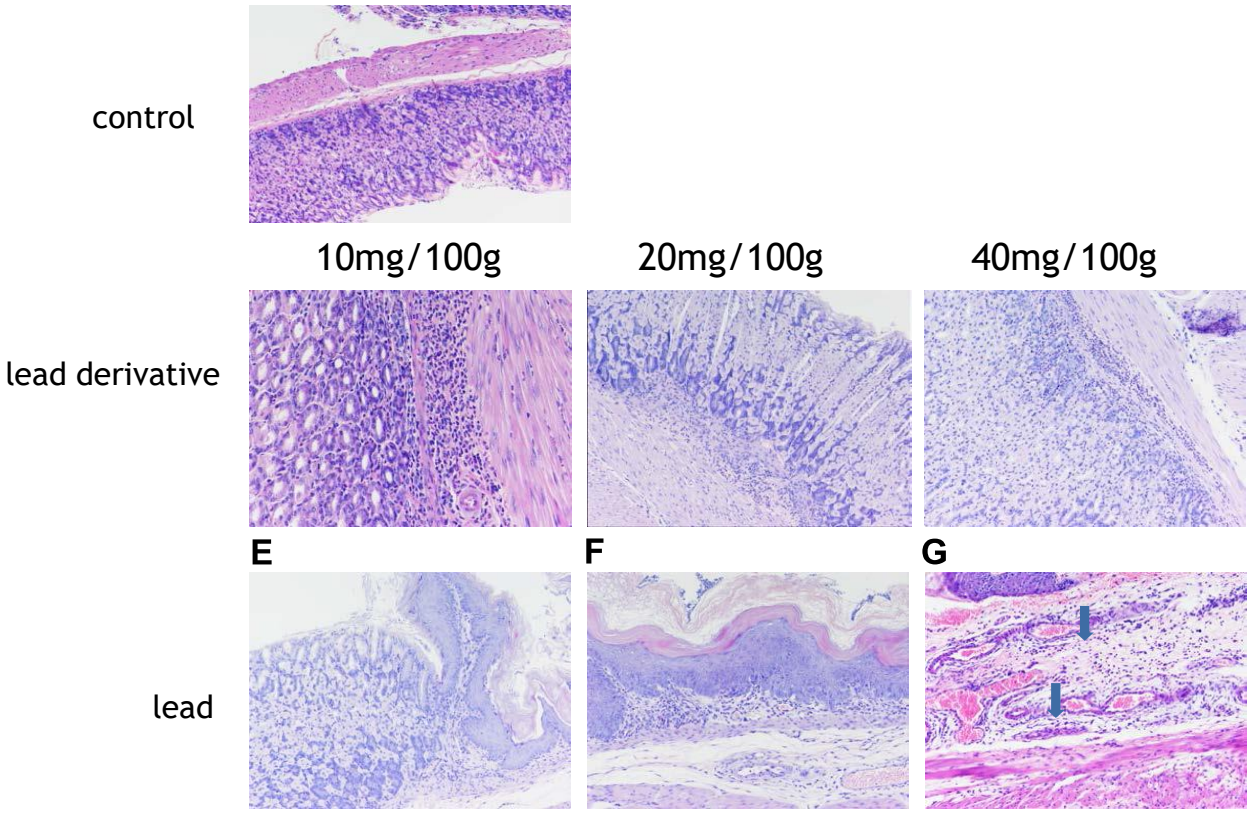
MCC_{50}>1000µM

Compound IV-d



MCC_{50}>1000µM

➢ **Not even the lead is toxic for the mouse model, except at very high concentration**



Histological study of *in vivo* toxicity of inhibitors IV (lead) and IV-a (one representative derivative)

Efficacy *in vitro* against drug-resistant clinical isolates

Table 2. Antimicrobial resistance profiles of *H. pylori* drug-resistant clinical isolates following the EUCAST criteria. (S = sensitive; R = resistant)

Compound	Isolate 1	Isolate 2	Isolate 3	Isolate 4	Isolate 5	Isolate 6
Amoxicillin	S	S	S	S	S	S
Clarithromycin	S	S	S	**R**	S	**R**
Tetracycline	S	S	S	S	S	S
Levofloxacin	S	S	S	S	S	S
Metronidazole	**R**	**R**	**R**	**R**	S	**R**
Rifampicin	S	S	S	S	**R**	S

Efficacy (EUCAST) against resistant isolates

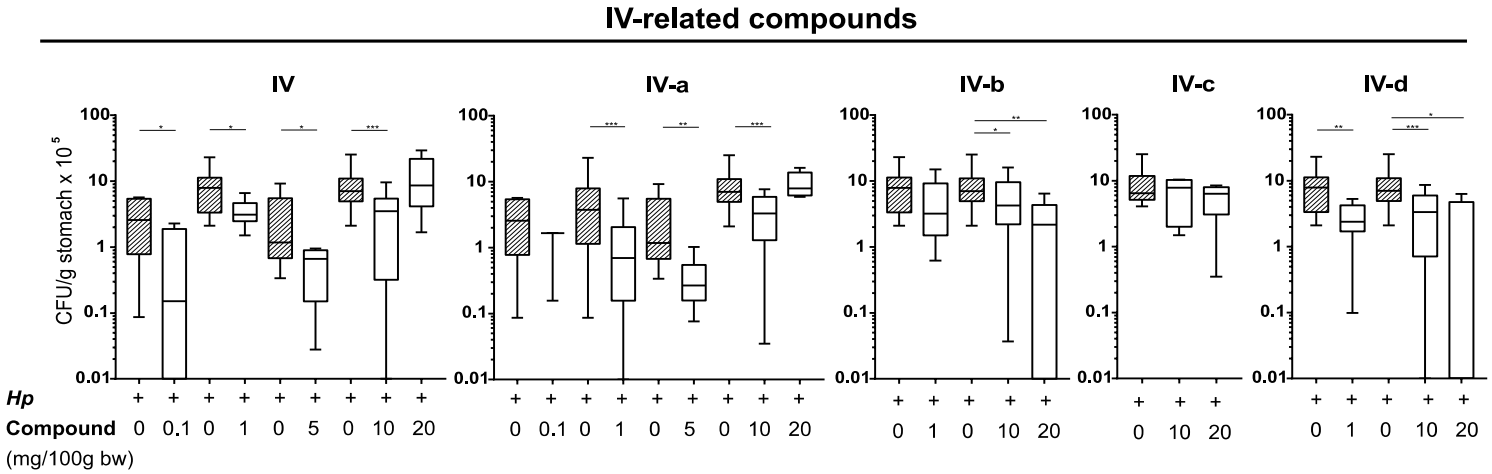
Table 3. TI values (MCC_{50}/MIC) of some developed compounds against *H. pylori* drug-resistant clinical isolates

Compound	Isolate 1	Isolate 2	Isolate 3	Isolate 4	Isolate 5	Isolate 6
IV-a	**144**	**72**	9.0	**144**	9.0	**72**
IV-c	**161**	**322**	10.0	**80**	**40**	**322**
IV-d	9.5	9.5	9.5	9.5	9.5	9.5
IV-e	10.0	10.0	20.0	20.0	10.0	10.0

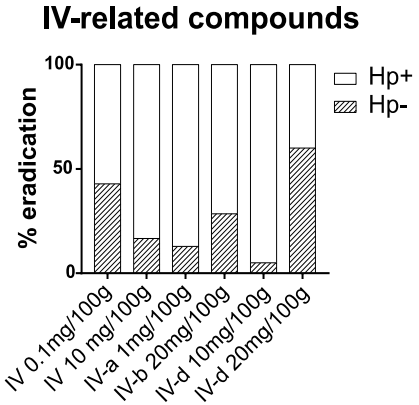
In bold, TI values indicative of effectivity, according to EUCAST (European Committee on Antimicrobial Susceptibility Testing) criteria.

Efficacy *in vivo* on the mouse model of *Hp* infection

Reduction of bacterial load in mice



Erradicacion of *Hp* in mice



- Single daily doses
- 7 days
- Uncombined with other antimicrobials or PPI

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Oficina Española
de Patentes y Marcas

Justificante de presentación electrónica de solicitud de patente

Este documento es un justificante de que se ha recibido una solicitud española de patente por vía electrónica utilizando la conexión segura de la O.E.P.M. De acuerdo con lo dispuesto en el art. 16.1 del Reglamento de ejecución de la Ley 24/2015 de Patentes, se han asignado a su solicitud un número de expediente y una fecha de recepción de forma automática. La fecha de presentación de la solicitud a la que se refiere el art. 24 de la Ley le será comunicada posteriormente.

Número de solicitud:	P201930445
Fecha de recepción:	21 mayo 2019 16:10 (CEST)
Oficina receptora:	OEPM Madrid
Su referencia:	ES1510.112
Solicitante:	UNIVERSIDAD DE ZARAGOZA
Número de solicitantes:	5
País:	ES
Título:	Compounds for the treatment of diseases caused by Helicobacter

Universidad de Zaragoza
CSIC
IIS Aragón
ARAID
Institut Pasteur

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- Risk of non obtaining enough activity in human
  for stand-alone use or in combination with existing antimicrobials or PPIs
- Risk of showing toxicity in human
- Risk of a new therapy for *Hp* suddenly appearing

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3. **Partnering Opportunities**

- We are looking for a business partner to finalize preclinical studies who is interested in a patent license for commercial exploitation

- We offer a patent license with the possibility of international extension

- Open to proposals from business partner

Novel antimicrobials specific against *Helicobacter pylori*

Madrid, 29 de octubre de 2019