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ORGANOCATALYTIC SYNTHESIS OF *N*-BENZAMIDO-1,4-DIHYDROPYRIDINE DERIVATIVES AND THEIR EFFECT AGAINST DIFFERENT CANCER CELL LINES

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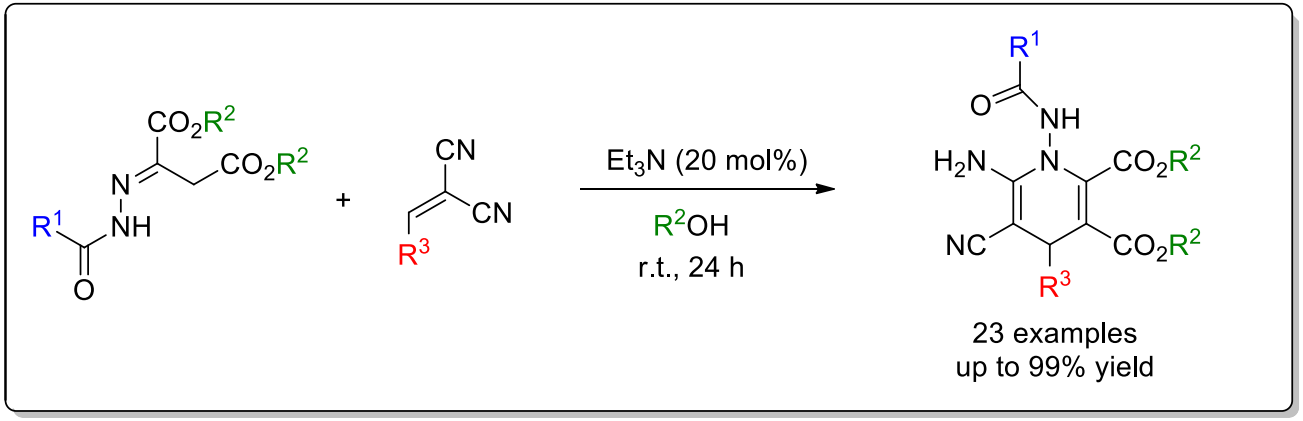
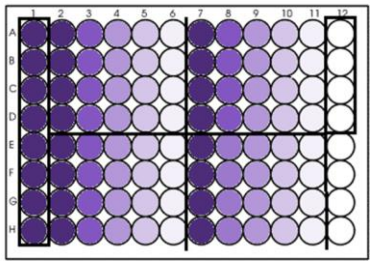
OrganoCatálisis Asimétrica
Asymmetric OrganoCatalysis

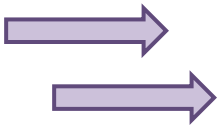
Organocatalytic synthesis of *N*-benzamido-1,4-dihydropyridine derivatives and their effect against different cancer cell lines

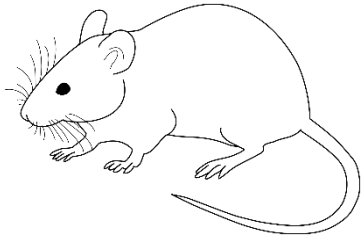
Graphical abstract



- Moderate IC_{50} values.
- Selectivity against different cancer cell lines.







Abstract

Dihydropyridines (DHPs) have a wide presence in nature, which makes them privileged structures with possible chemical and biological properties. They are found as part of the cofactors NADH and NADPH (energy transporters in cellular metabolic reactions) and since these compounds are part of a large number of biological processes, DHPs have become molecules of high interest for attacking these potential therapeutic targets.

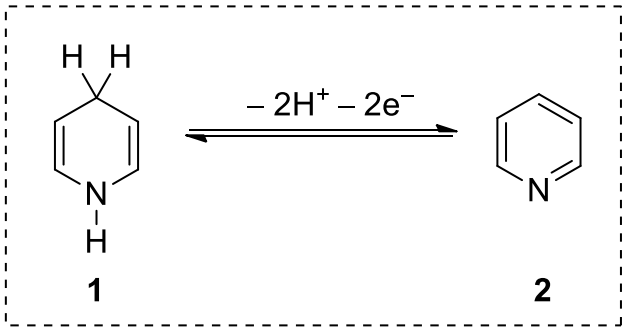
In this work we want to show the toxicity results obtained in four different tumor lines: HeLa (cervix), Jurkat (leukemia), A549 (lung) and MIA-PaCa-2 (pancreas); using the racemic 1,4-DHPs obtained from different derivatives of alkylidenemalononitrile and hydrazone through an organocatalytic process.

Since some of these molecules are luminescent, we have also studied their ability as diagnostic cell visualization agents.

The *in vitro* cytotoxicity values and the luminescent properties studied encouraged us to go one step further in our research and we carried out the tests *in vivo* as well.

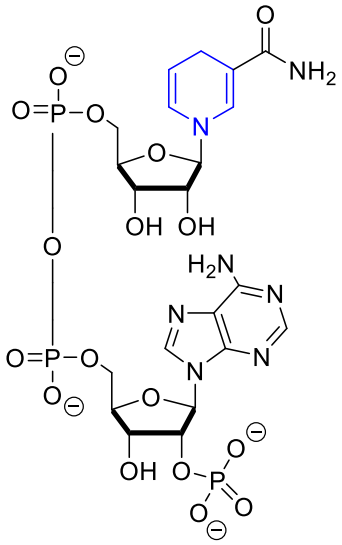
Keywords: organocatalysis / dihydropyridines / cytotoxicity / *in vitro* assays / *in vivo* studies

Introduction

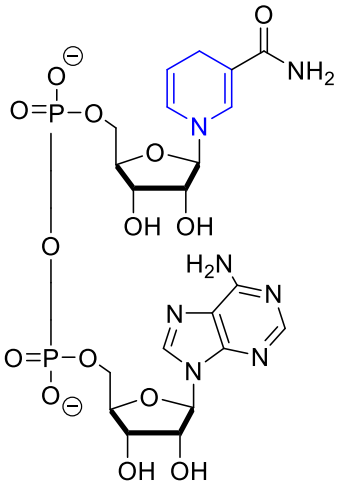


Dihydropyridines (**1**) are heterocyclic structures based on the pyridine (**2**) molecule with which they share a *redox* equilibrium.

These mono-nitrogen molecules are doubly unsaturated and are widely spread in nature, which makes them interesting systems due to their chemical and biological properties.



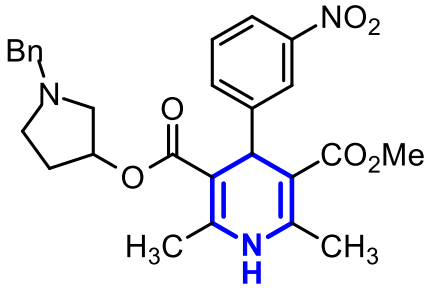
NADPH



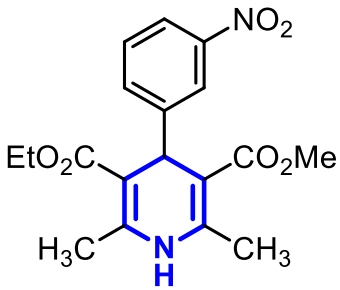
NADH

Oxid. Med. Cell. Longev. **2016**, 1892412.

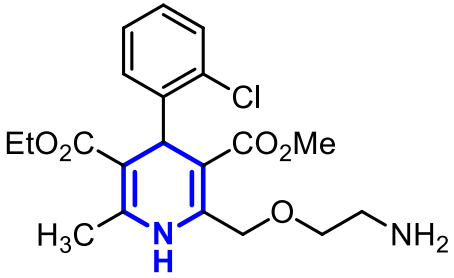
Introduction



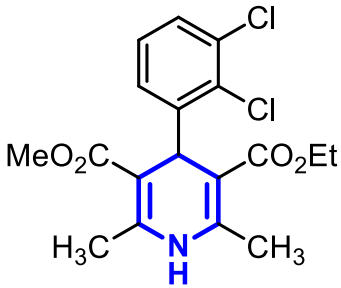
Barnidipine



Nitrendipine



Amlodipine



Felodipine

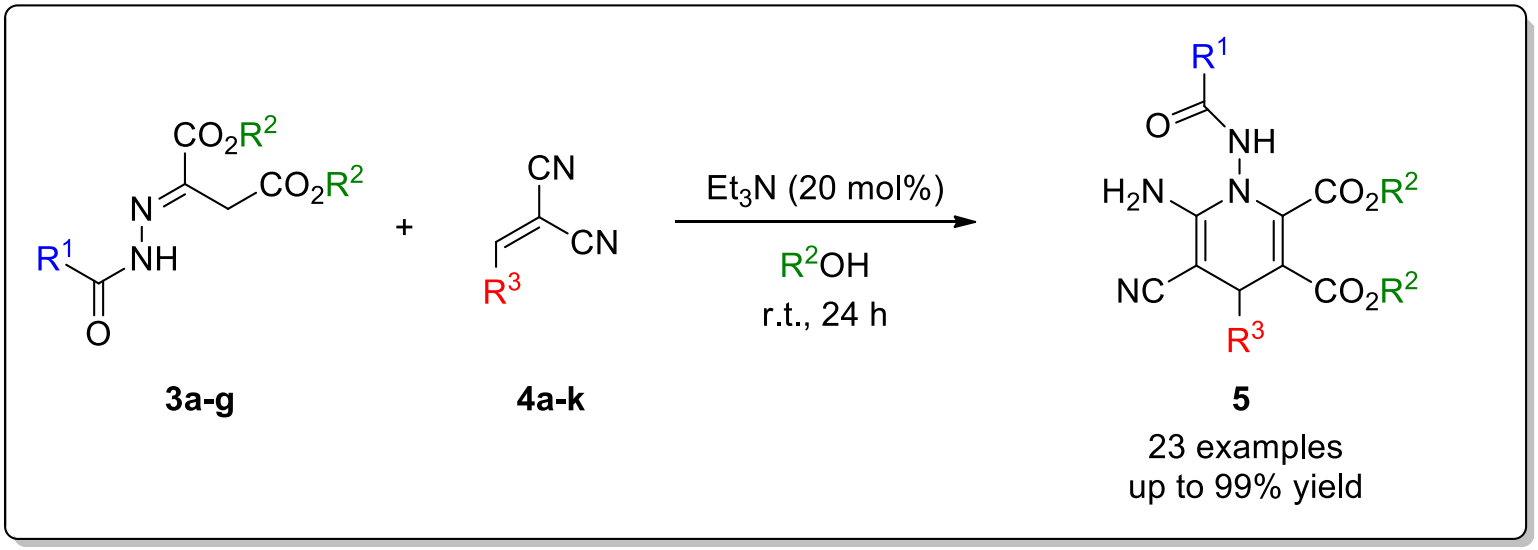
- ✓ Calcium channel blockers
- ✓ Anti-inflammatory activity
- ✓ Antihistamine activity
- ✓ Multiple Drug Resistance (MDR) inhibitors
- ✓ **Antitumor activity**

Bioorg. Chem. **2020**, *105*, 104364.

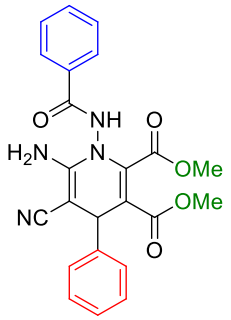
Organocatalytic synthesis of the new family of

N-benzamido-1,4-dihydropyridine derivatives

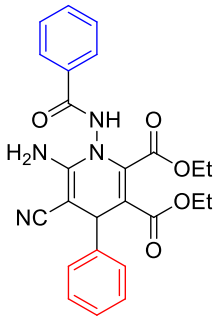
starting from their alkylidenemalononitrile and hydrazone precursors



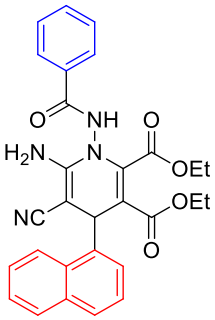
Results and discussion



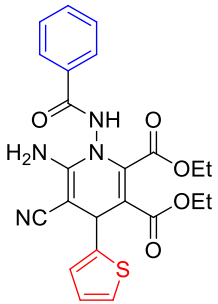
5aa
85% yield



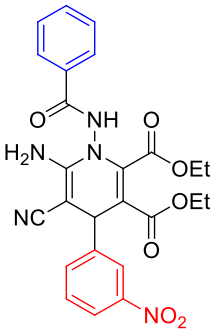
5ba
19% yield



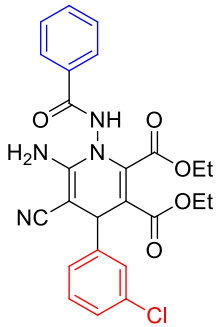
5bb
83% yield



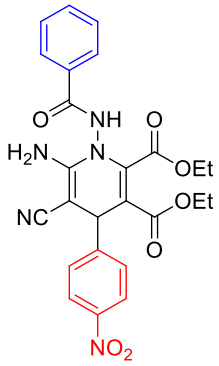
5bc
40% yield



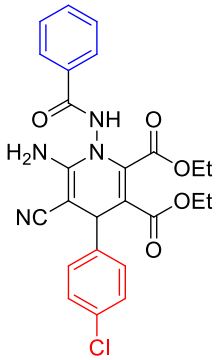
5bd
92% yield



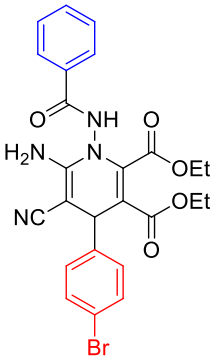
5be
89% yield



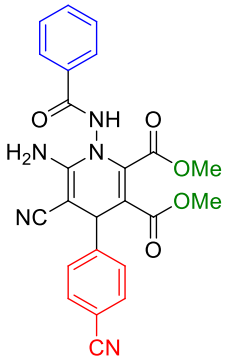
5bf
94% yield



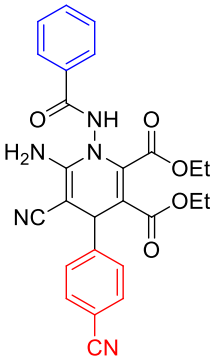
5bg
80% yield



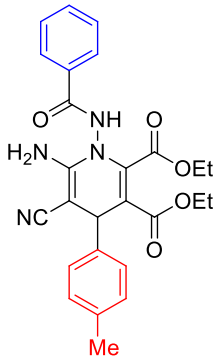
5bh
74% yield



5ai
96% yield

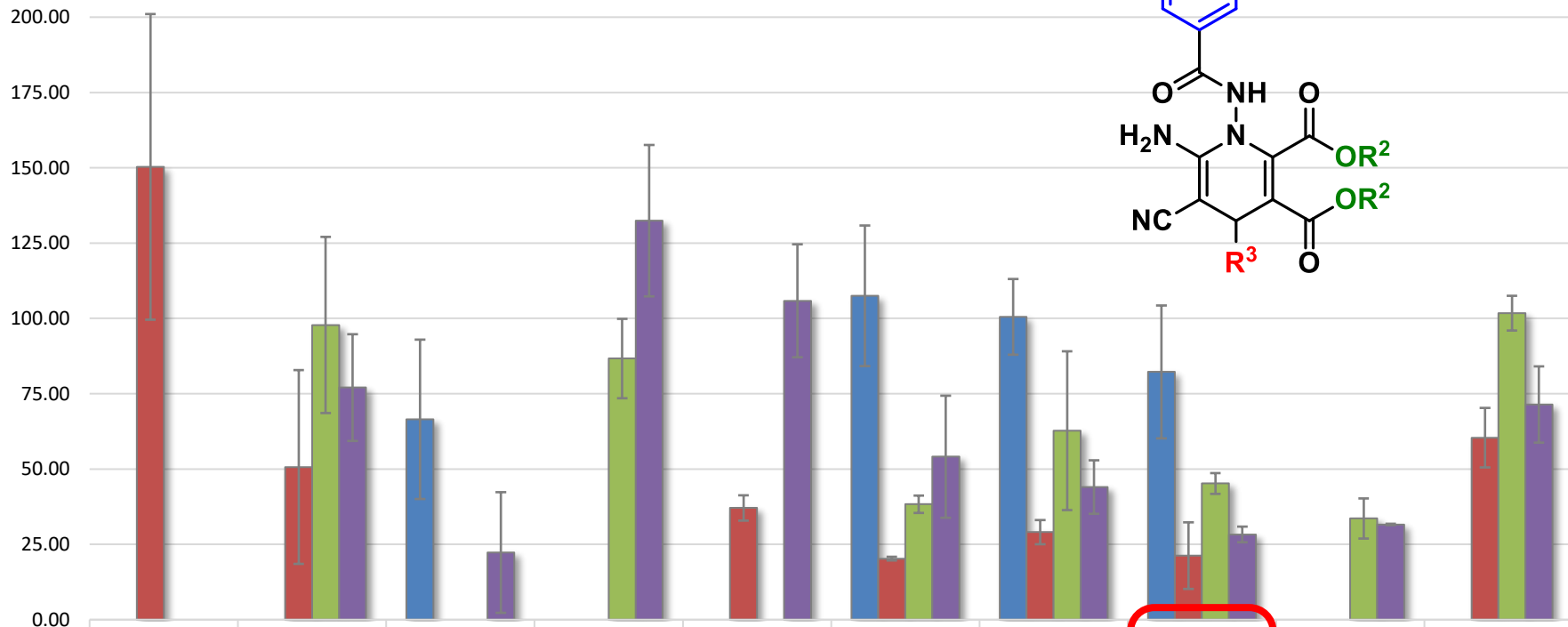


5bi
46% yield



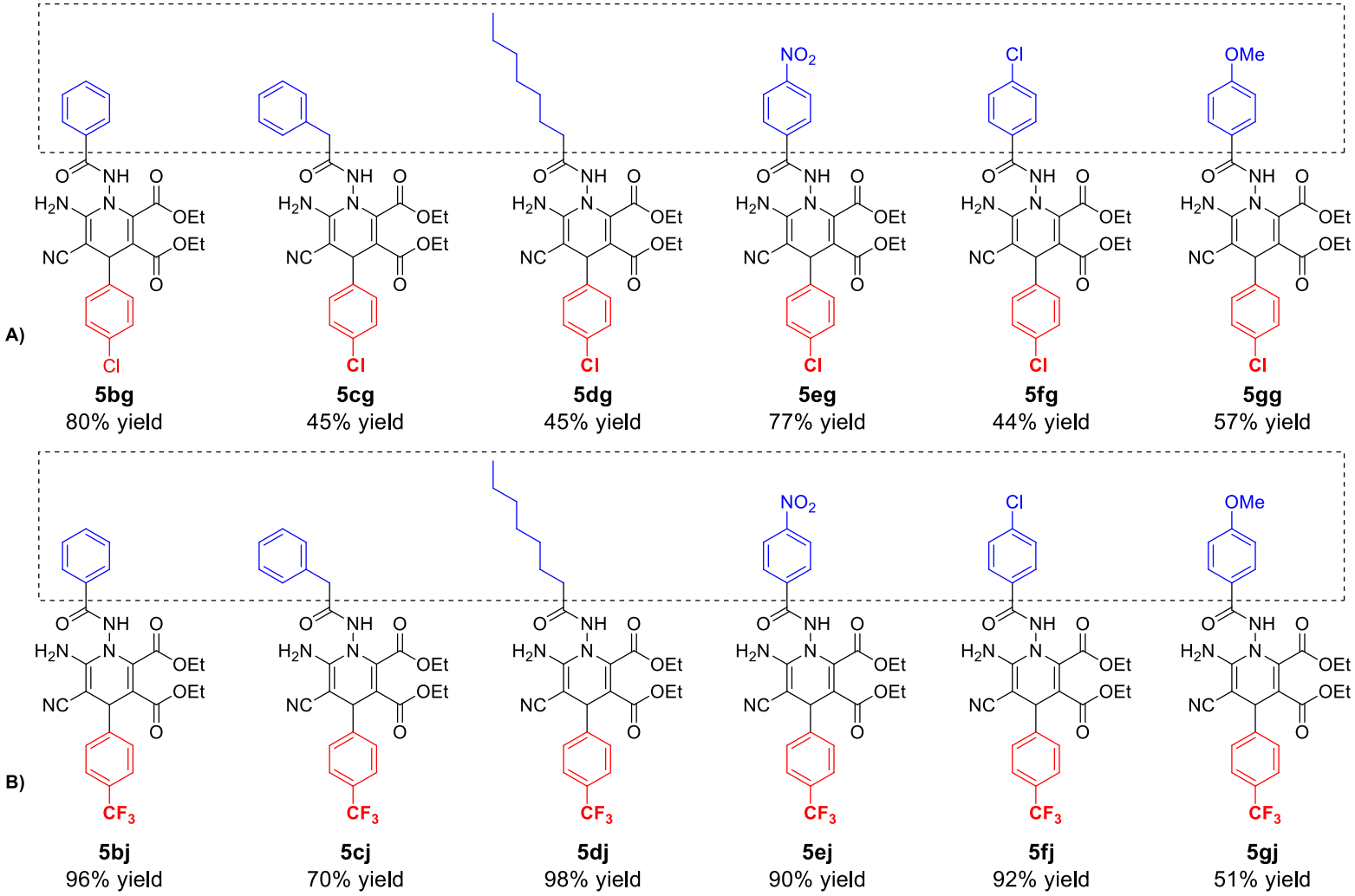
5bk
93% yield

Results and discussion

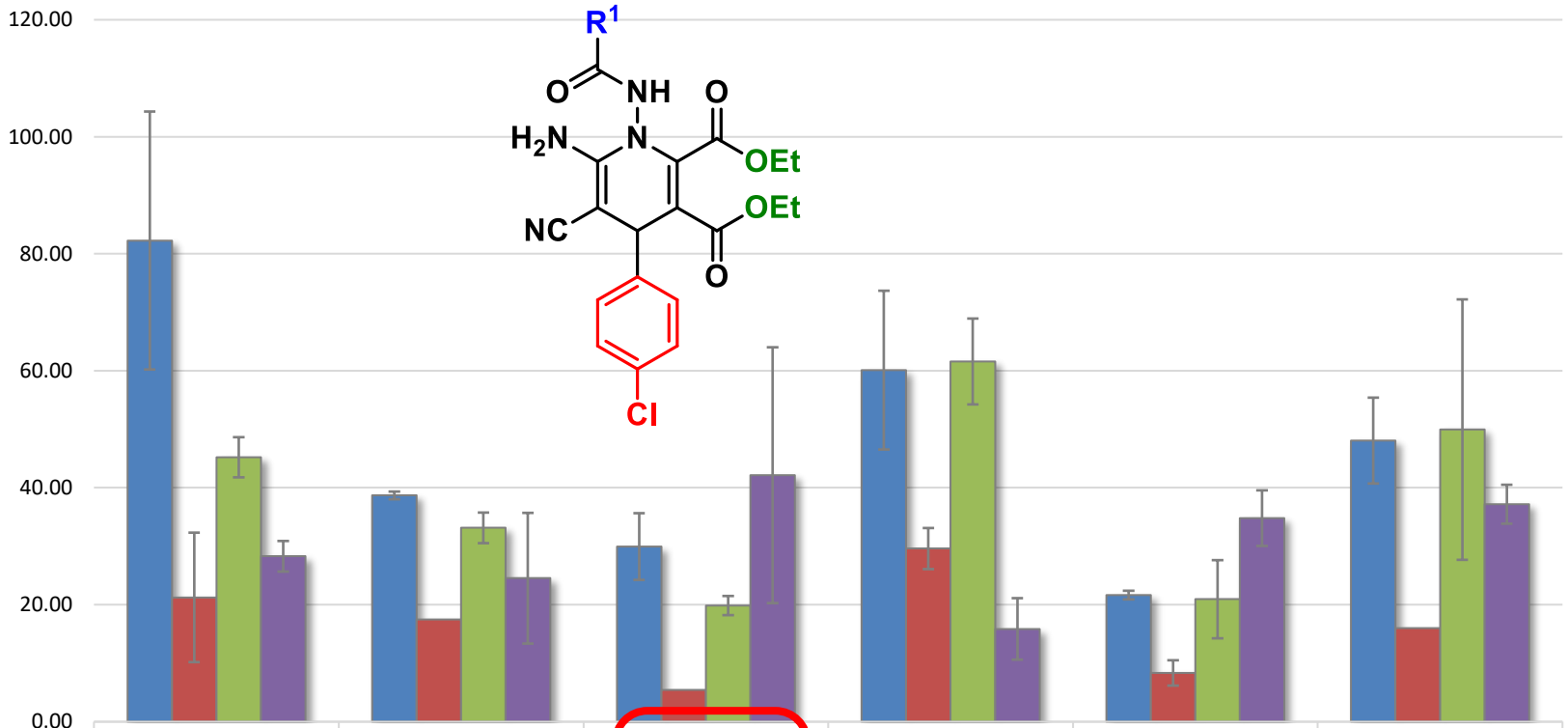


	Me (5aa)	Et (5ba)	1-naftil (5bb)	2-tiofen (5bc)	3-NO2Ph (5bd)	3-ClPh (5be)	4-NO2Ph (5bf)	4-ClPh (5bg)	4-BrPh (5bh)	4-MePh (5bk)
HeLa			66.50			107.515	100.50	82.25		
Jurkat	150.30	50.65			37.11	20.25	29.05	21.22		60.40
A549	0	97.8	0	86.70		38.30	62.73	45.20	33.58	101.75
MIA-PaCa-2		77.05	22.31	132.49	105.86	54.08	44.01	28.28	31.57	71.40

Results and discussion

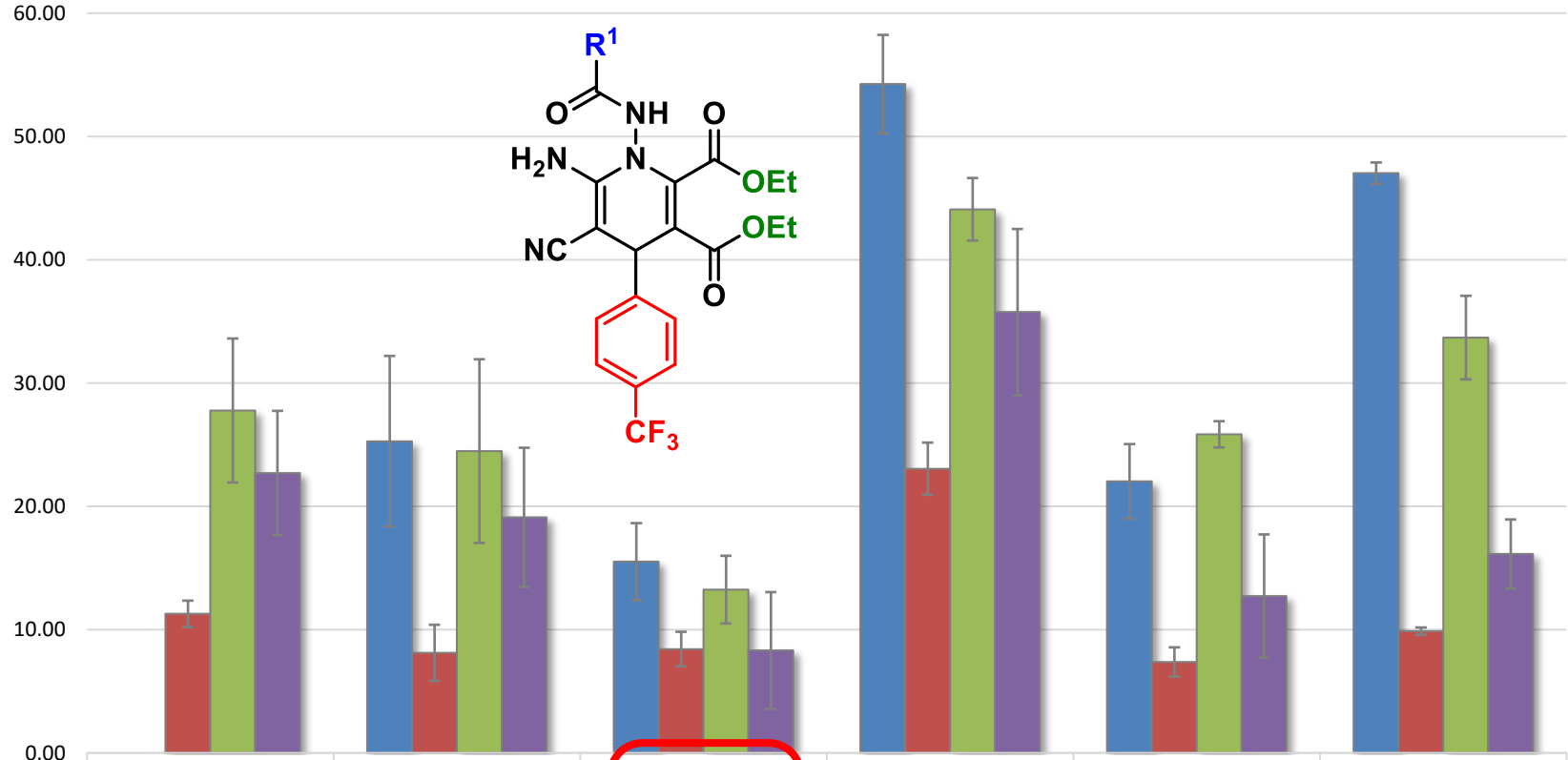


Results and discussion



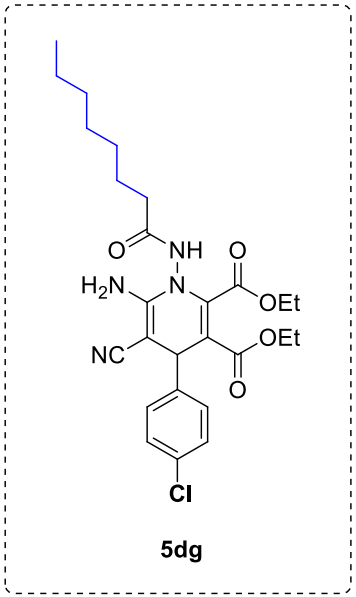
	Ph (5bg)	CH2Ph (5cg)	heptil (5dg)	4-NO2Ph (5eg)	4-ClPh (5fg)	4-OMePh (5gg)
HeLa	82.25	38.68	29.93	60.12	21.64	48.05
Jurkat	21.22	17.47	5.41	29.6	8.33	15.98
A549	45.20	33.15	19.85	61.57	20.93	49.93
MIA-PaCa-2	28.28	24.54	42.16	15.85	34.80	37.19

Results and discussion

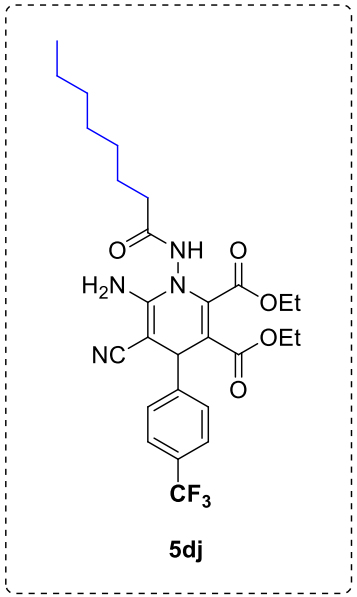


	Ph (5bj)	CH2Ph (5cj)	heptil (5dj)	4-NO2Ph (5ej)	4-ClPh (5fj)	4-OMePh (5gj)
HeLa		25.28	15.52	54.26	22.04	47.03
Jurkat	11.29	8.13	8.44	23.06	7.39	9.89
A549	27.78	24.50	13.25	44.10	25.85	33.70
MIA-PaCa-2	22.72	19.12	8.32	35.76	12.74	16.15

The two **best compounds** of *in vitro* tests were selected for *in vivo* assays

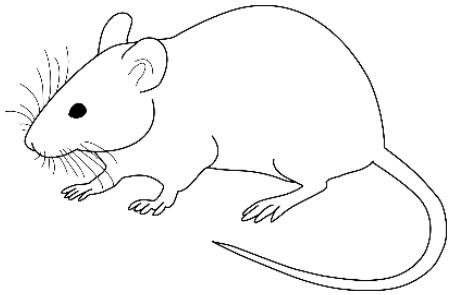


5dg



5dj

1700 and 3200 times more concentrated than the corresponding IC_{50} values



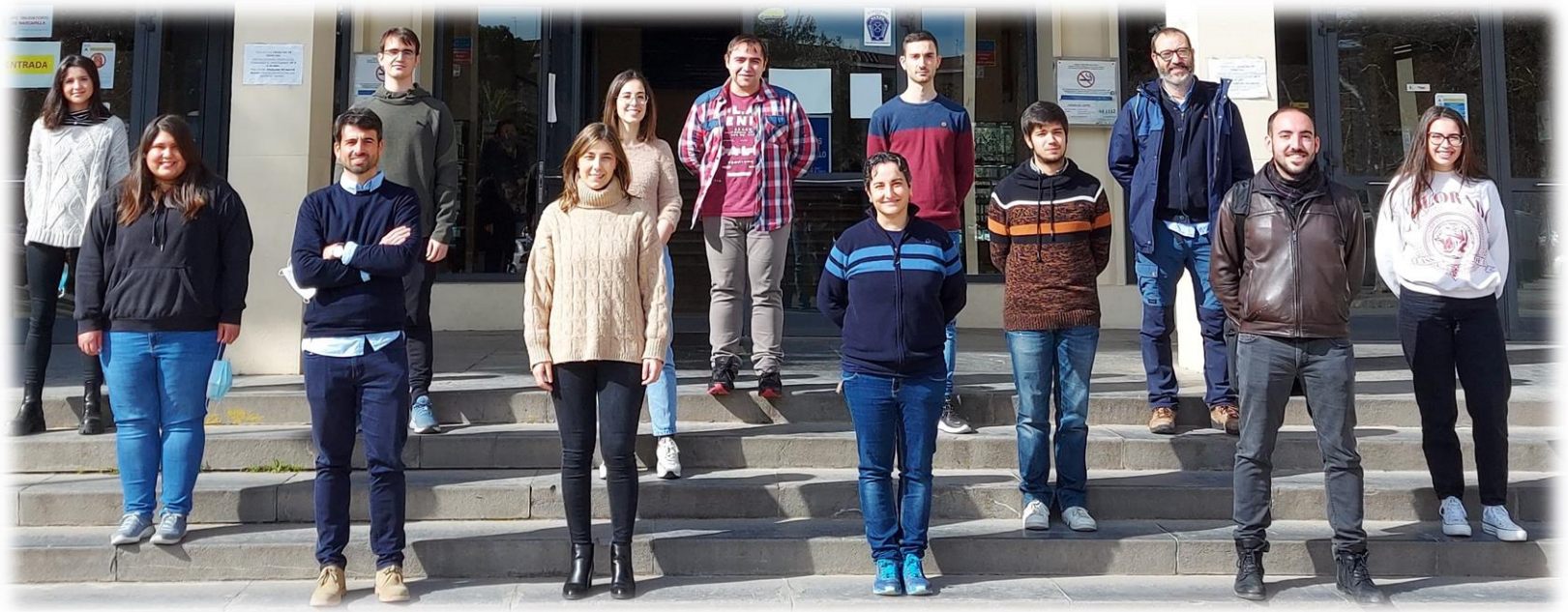
Conclusions

The synthesis of a battery of 1,4-dihydropyridine derivatives from hydrazone precursors and malononitrile derivatives has been carried out in a **simple procedure**, under **mild reaction conditions** and in **good yields**.

The **cytotoxic properties** of this family of compounds have been studied for the first time.

The good results of the *in vitro* tests have allowed a further step **towards *in vivo* studies**, starting acute cytotoxicity tests on healthy male mice, which have also **concluded positively**.

Acknowledgments



https://asymmetricorganocatalysis.com/

OrganoCatálisis Asimétrica
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