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Novel ureido-dihydropyridine scaffolds as theranostic agents

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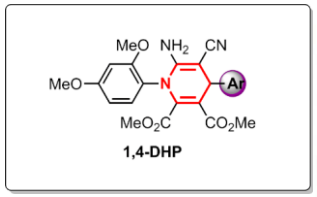
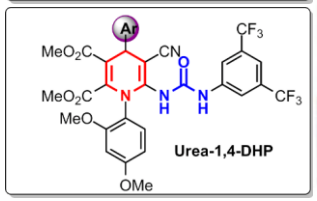
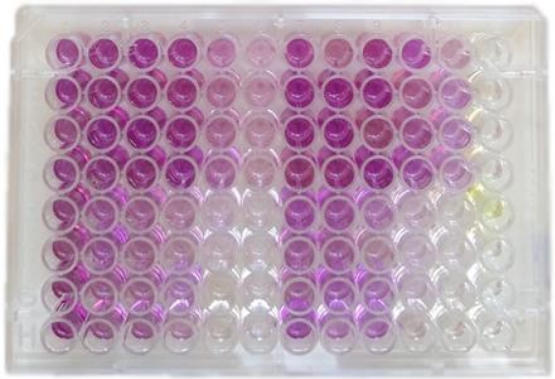
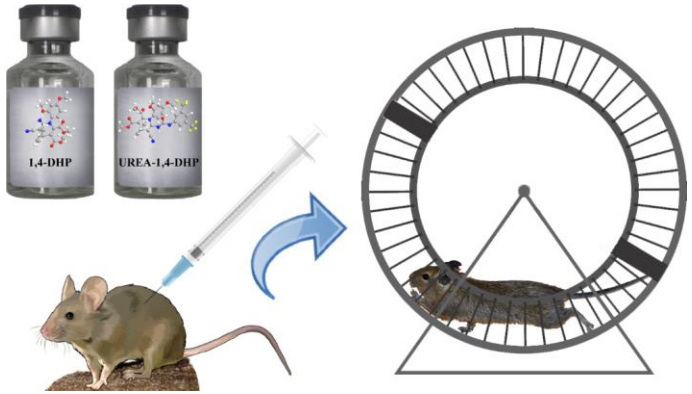
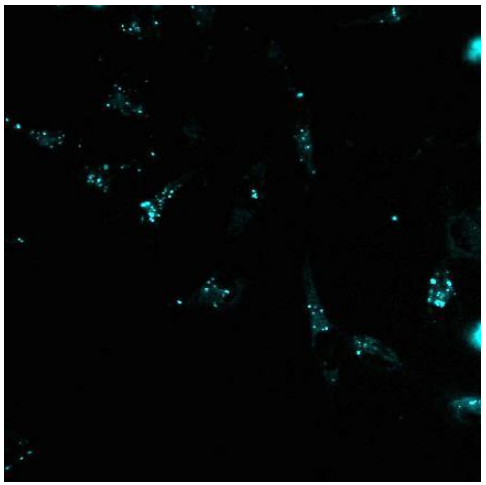
Novel ureido-dihydropyridine scaffolds as theranostic agents

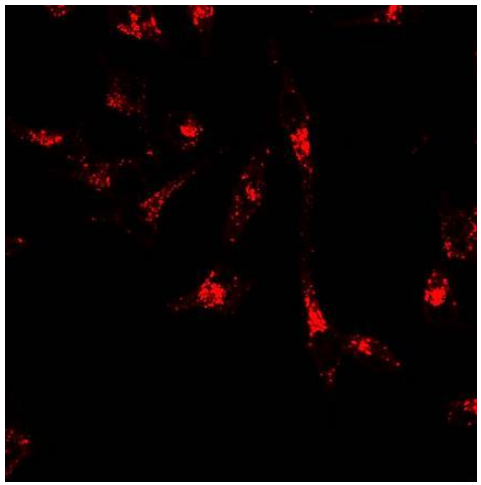


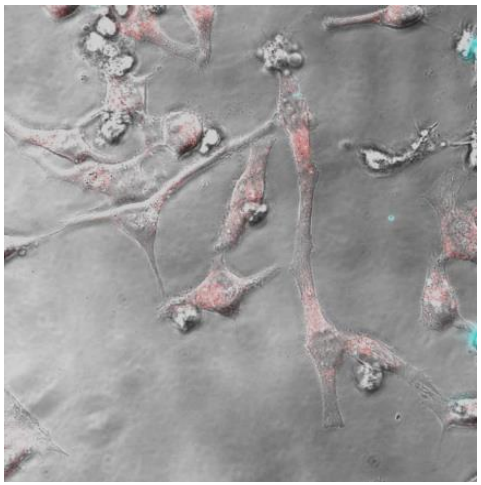










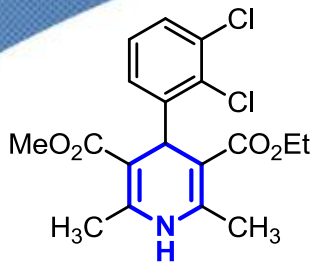


Abstract

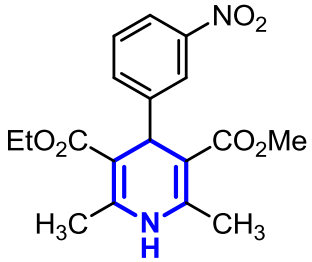
The potential as anticancer agents of 1,4-dihydropyridines (1,4-DHPs) and their pioneering urea derivatives have been evaluated.in HeLa (cervix), Jurkat (leukaemia) and A549 (lung) cancer cell lines as well as on healthy mice. 1,4-DHPs show moderate cytotoxicity. However, when the urea moiety is introduced, an extraordinary increase in their antiproliferative activity is observed, proving an interesting synergy between these two scaffolds. Remarkably, when enantiomerically enriched samples are examined, they result to be in almost all cases less to equally active. This effect could be caused by a complex amalgam of physical and chemical contributions. The studied compounds present luminescent properties and a biodistribution study in cancer cells has been performed. Fluorescence microscopy showed that some of the 1,4-DHP derivatives accumulated in the lysosomes, whilst their urea counterparts targeted the cell membrane, which can be key to explain the different cytotoxic activity and imply a different mechanism of action. Finally, a preliminary *in vivo* study regarding the acute toxicity of some of these compounds on healthy mice has been conducted, using a concentration up to 7200 times higher than the corresponding IC_{50} value. No downgrade in the welfare of the test subjects was observed, which could support their use in preclinical tumour models. Recently, we have been exploring the biological properties of 1-benzamido-1,4-dihydropyridine derivatives and the preliminary results on cytotoxicity will be commented.

Keywords: Cancer; 1,4-Dihydropyridine; Fluorescence; Mice; Theranosis; Urea.

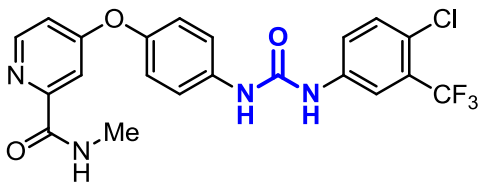
Introduction



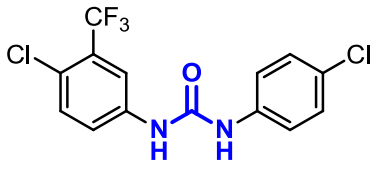
Felodipine



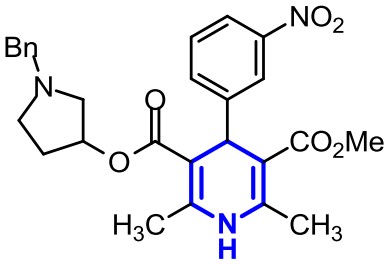
Nitrendipine



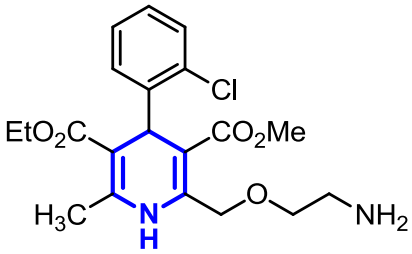
Sorafenib



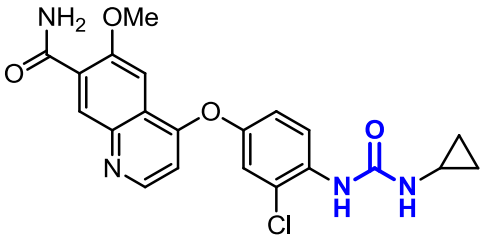
Cloflucarban



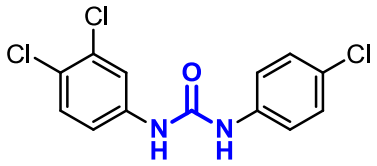
Barnidipine



Amlodipine



Lenvatinib

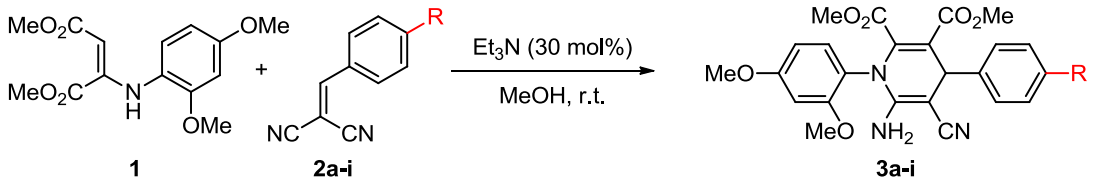


Triclocarban

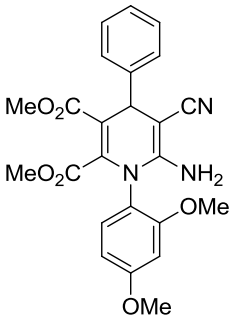
- Calcium chanel blockers.
- Multiple Drug Resistance (MDR) inhibitors.
- Other properties.
- Protein kinase inhibitors.
- Antimicrotubule agents.
- Other properties.

F. Auria-Luna *et al*. *Bioorg. Chem*. **2020**, *105*, 104364.

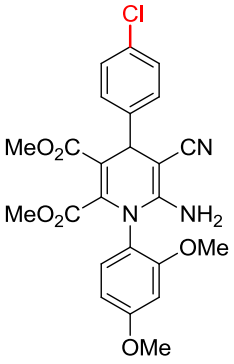
Results and discussion



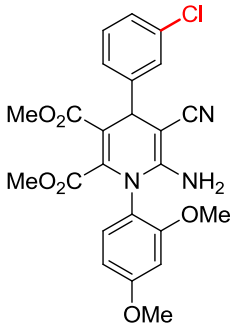
1 **2a-i** **3a-i**



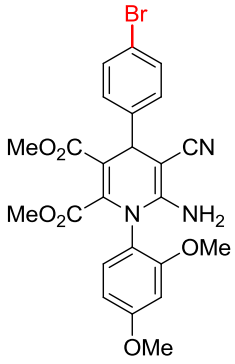
3a
42% yield



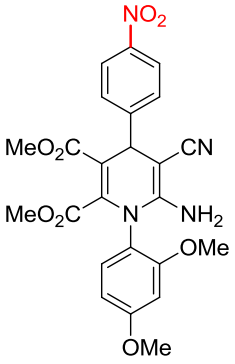
3b
60% yield



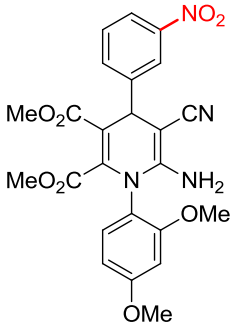
3c
99% yield



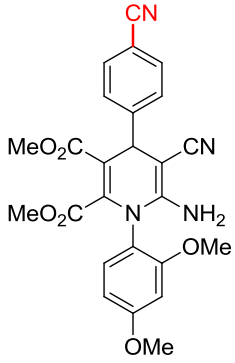
3d
38% yield



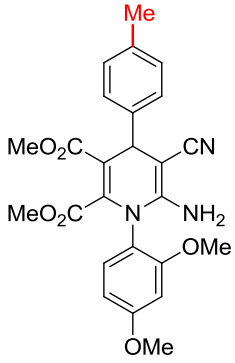
3e
99% yield



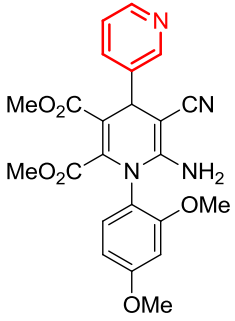
3f
91% yield



3g
99% yield

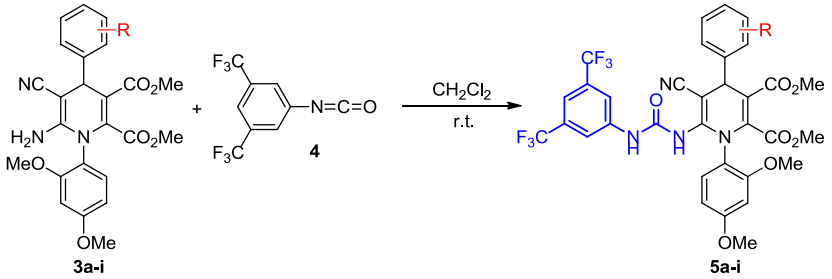


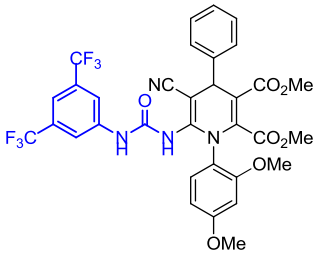
3h
37% yield



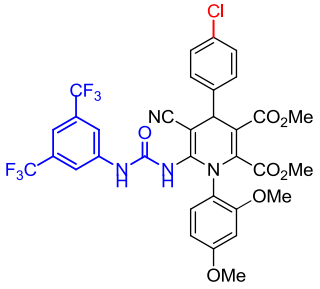
3i
99% yield

Results and discussion

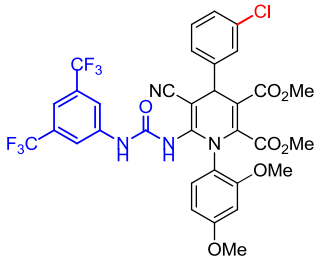




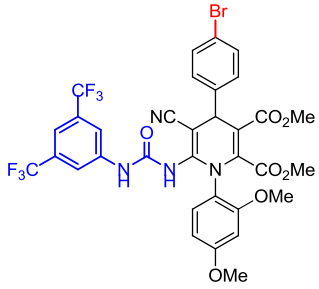
5a
61% yield



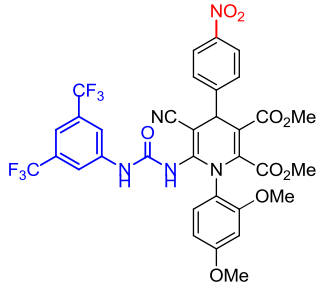
5b
99% yield



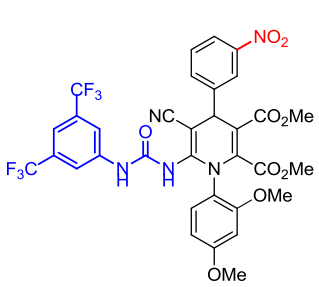
5c
83% yield



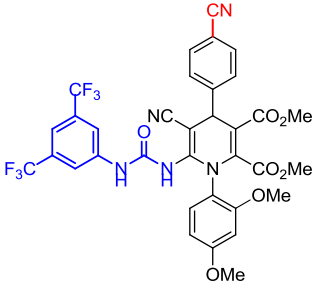
5d
54% yield



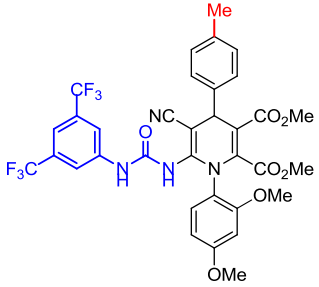
5e
78% yield



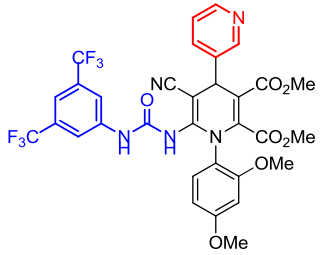
5f
50% yield



5g
99% yield

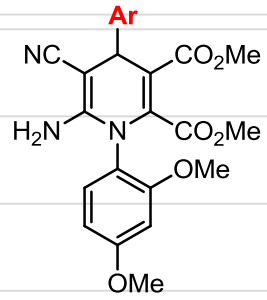


5h
71% yield



5i
89% yield

Results and discussion

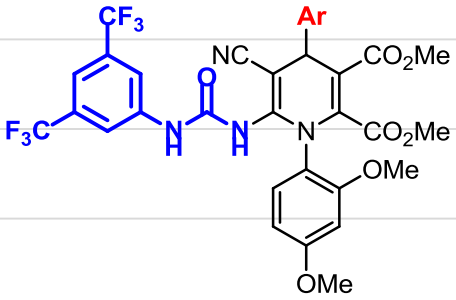


IC_{50} moderate values

Selectivity against different cell lines

	3a	3b	3c	3d	3e	3f	3g	3h	3i
HeLa	159,08	48,87	47,17	52,31	79,96	87,51		144,70	22,08
Jurkat	81,95	30,67	22,35	24,56		76,45		62,47	
A549									58,22

Results and discussion

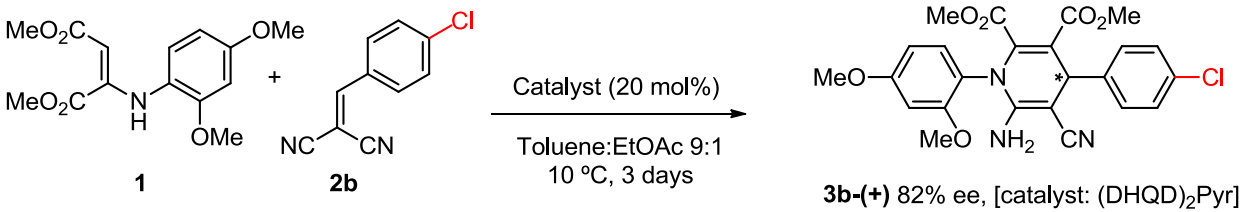


Upgrade of the IC_{50} values

Maintained selectivity

	5a	5b	5c	5d	5e	5f	5g	5h	5i
HeLa	3,97	1,04	0,97	0,96		1,00	3,56	0,97	
Jurkat	3,91	9,82	1,00	1,00				29,84	66,58
A549		3,86						73,51	

Results and discussion



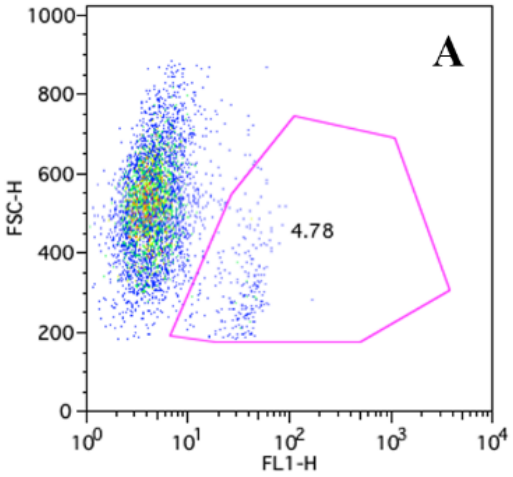
3b-(+) 82% ee, [catalyst: $(DHQD)_2Pyr$]
3b-(–) 98% ee, [catalyst: $(DHQ)_2Pyr$]

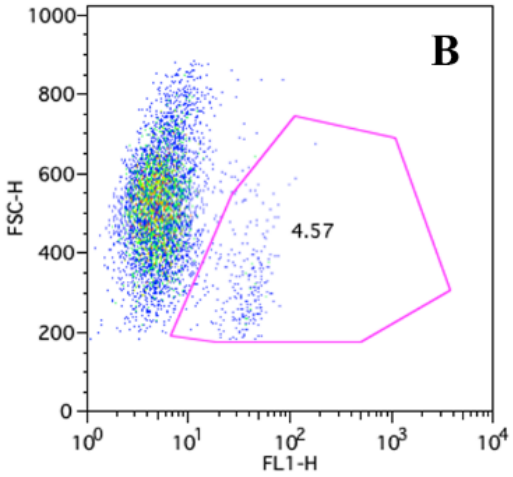
3b	HeLa	Jurkat	A549
L	>50	43.20 ± 4.78	>50
D	>50	77.46 ± 15.83	>50
Rac.	47.87 ± 1.22	31.23 ±3.34	>50

5b	HeLa	Jurkat	A549
L	>50	>50	>50
D	>50	16.49 ± 2.42	0.28 ± 0.01
Rac.	1.07 ± 0.16	8.17 ± 1.43	2.99 ± 0.86

Results and discussion

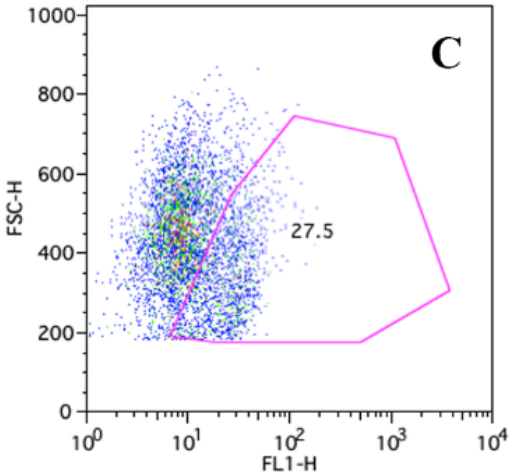
Control experiment

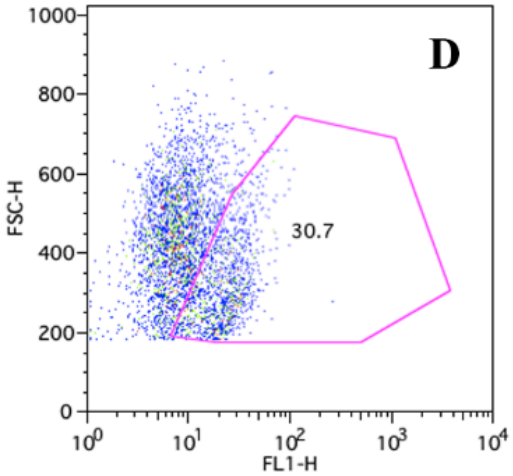




Control experiment with z-VAD-fmk caspase inhibitor

Assay compound

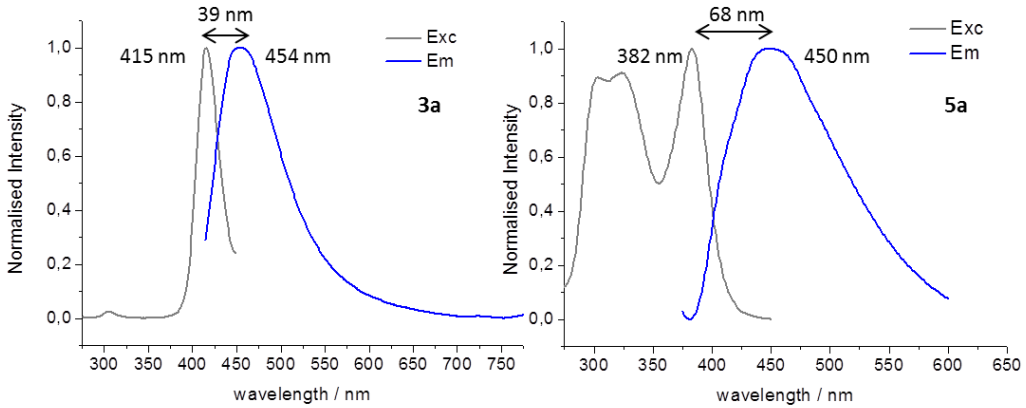




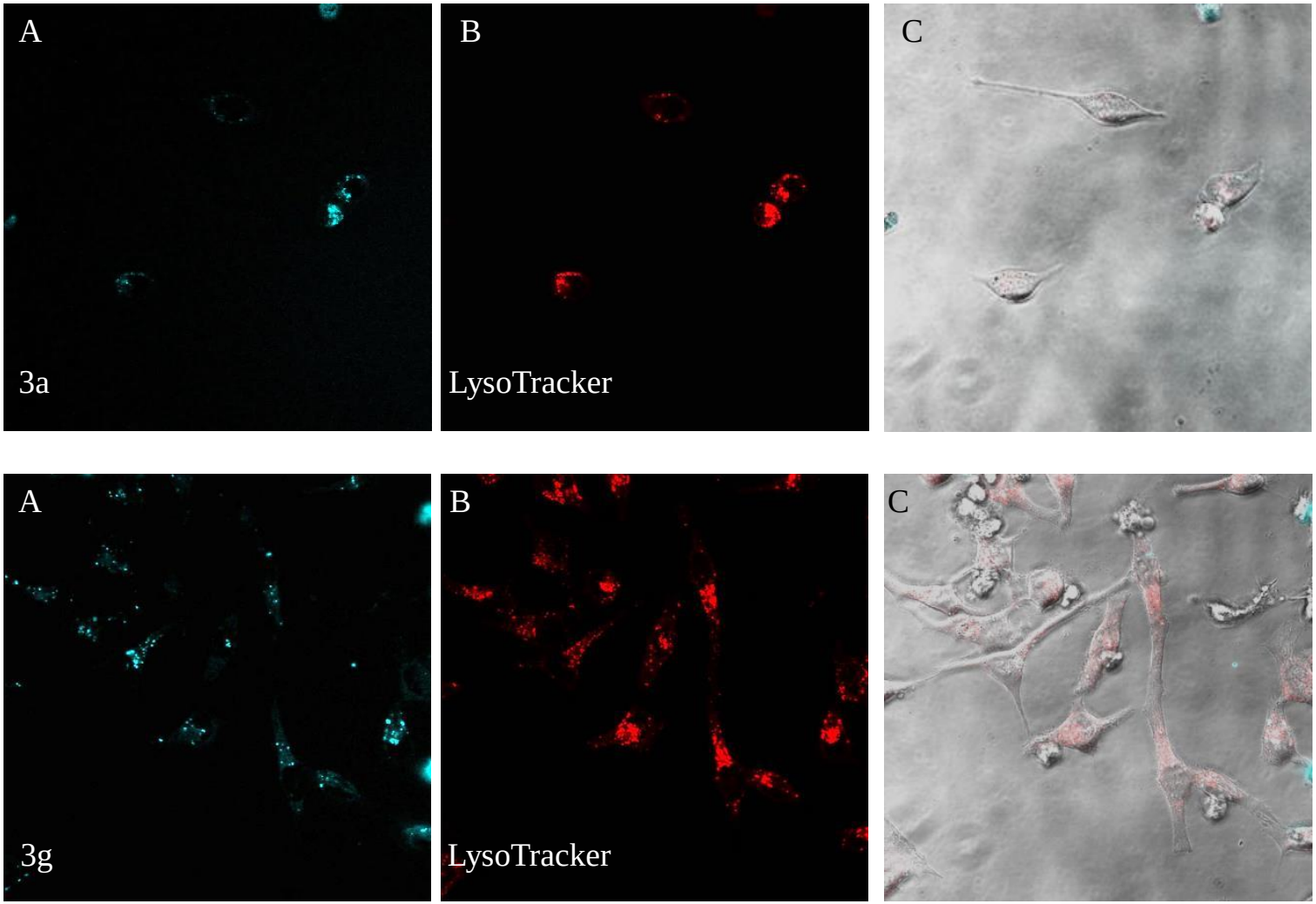
Assay compound with z-VAD-fmk caspase inhibitor

Results and discussion

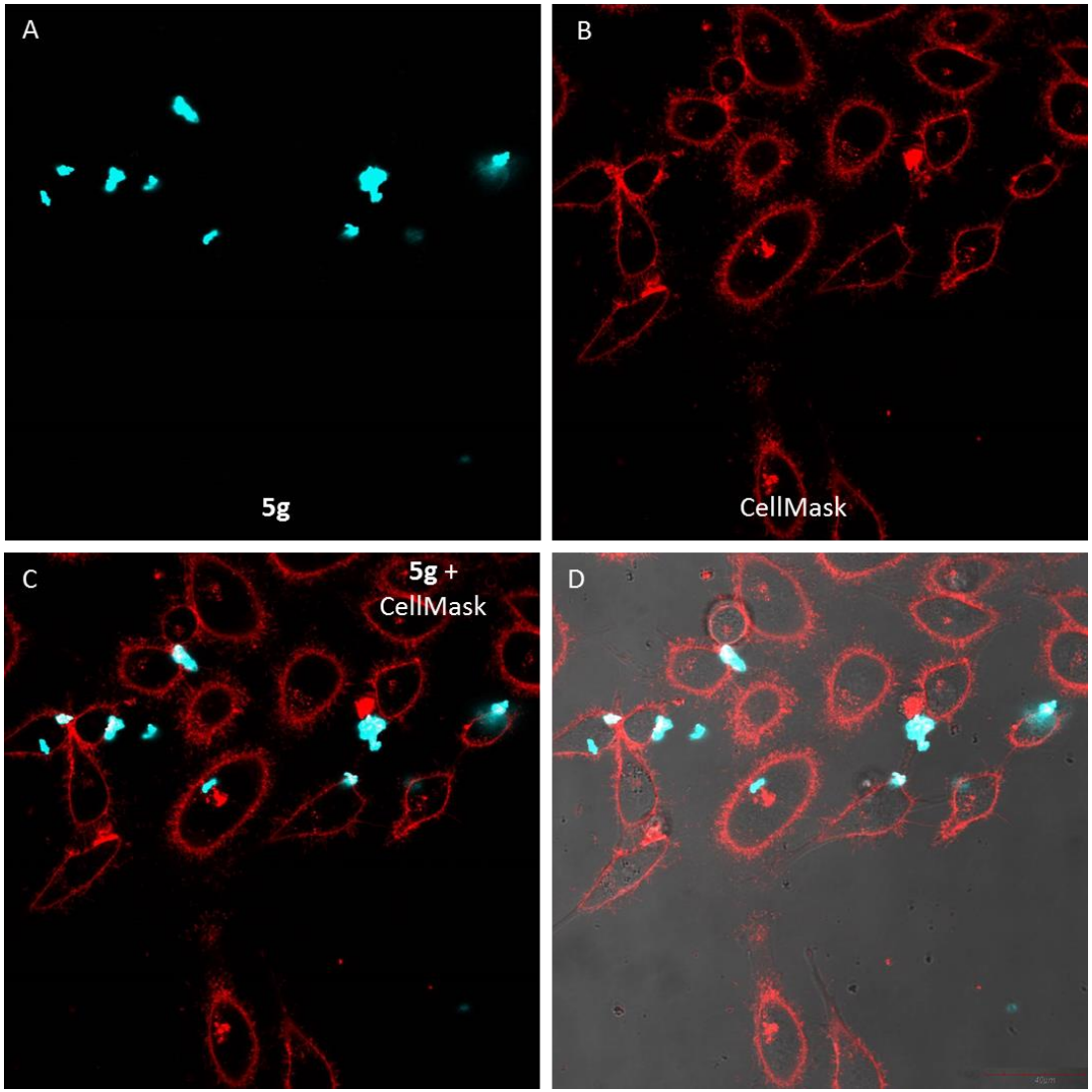
DHP	λ_{exc} (nm)	λ_{em} (nm)	Stokes shift/nm	Urea-DHP	λ_{exc} (nm)	λ_{em} (nm)	Stokes shift/nm
3a	415	454	39	5a	382	450	68
3b	>420	425	≈ 5	5b	391	436	45
3c	>422	428	≈ 6	5c	389	456	67
3d	>415	420	≈ 5	5d	391	437	46
3g	416	471	55	5g	398	465	67
3h	>416	424	≈ 8	5h	389	460	71
3i	>420	425	≈ 5	5i	393	440	47



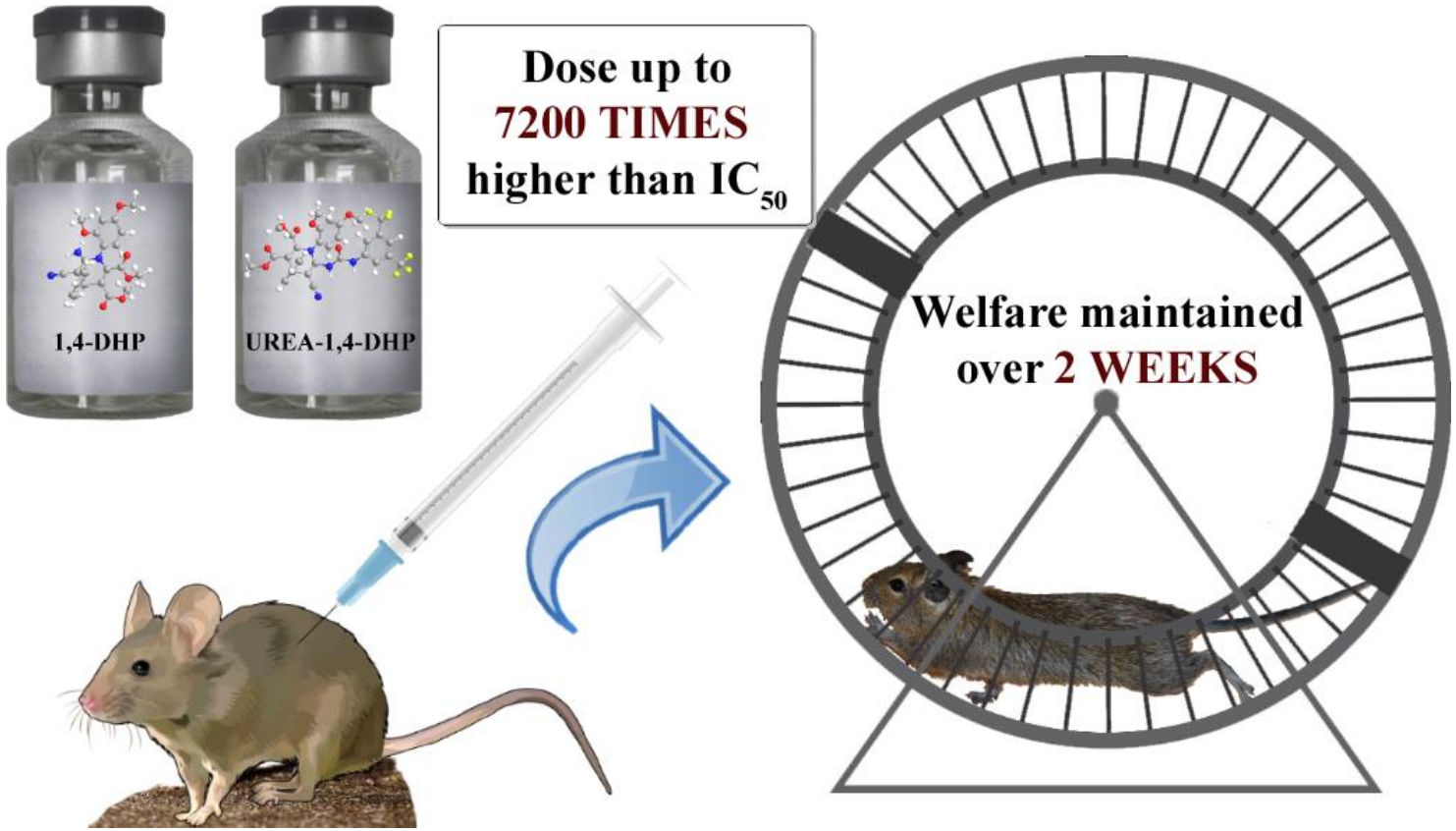
Results and discussion



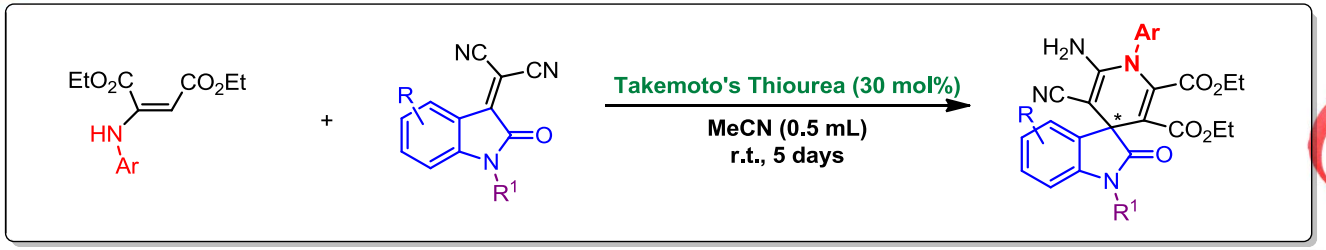
Results and discussion



Results and discussion

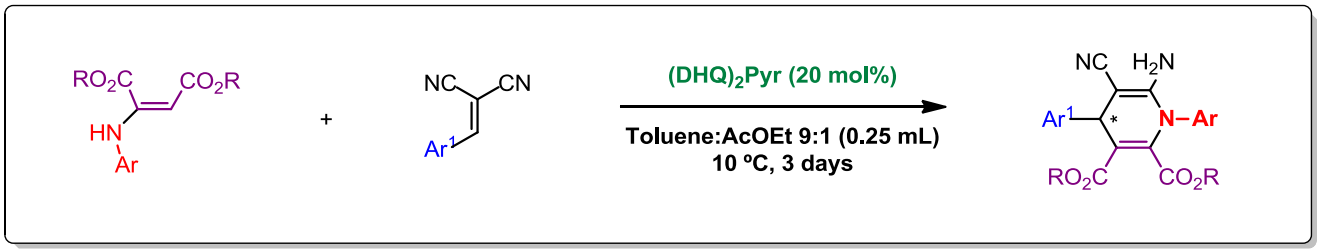


Results and discussion



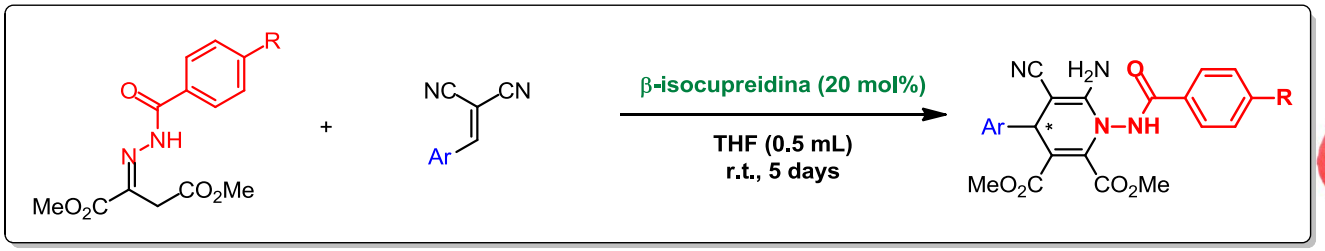
11 examples
up to >82% yield
up to 58% ee

Auria-Luna, F. *et al. Molecules* **2015**, *20*, 15807-15826.



17 examples
up to >95% yield
up to 82% ee

Auria-Luna, F. *et al. J. Org. Chem.* **2017**, *82*, 5516-5523.

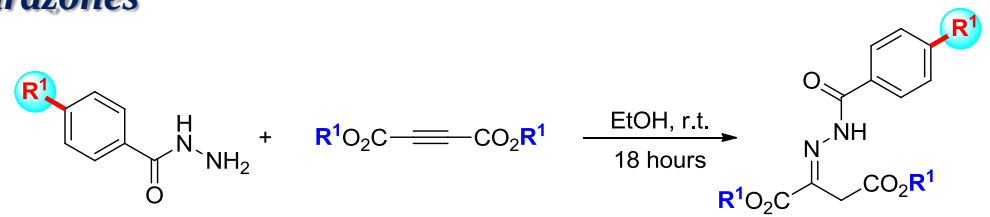


18 examples
up to >99% yield
up to 54% ee

Auria-Luna, F. *et al. Molecules* **2018**, *23*, 2692

Auria-Luna, F. et al. Adv. Synth. Catal. **2017**, *359*, 2161.

Synthesis of Hydrazones



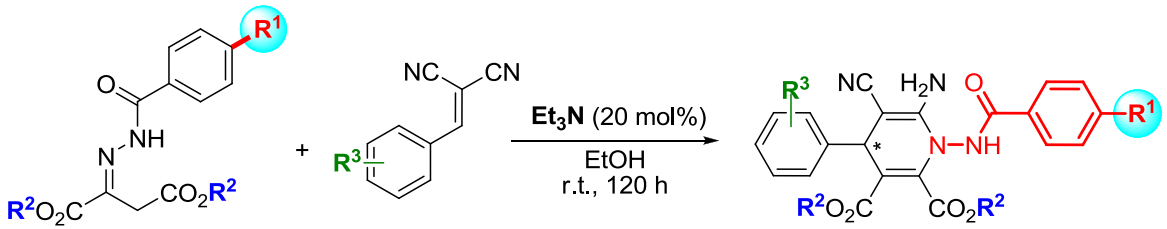
6a R = H
6b R = NO_2
6c R = Cl
6d R = Br
6e R = *t*-Bu
6f R = OMe

7a,b

7a R^2 = Me
7b R^2 = Me

8
up to 99% yield

Synthesis of 1-Benzamido-1,4-Dihydropyridines



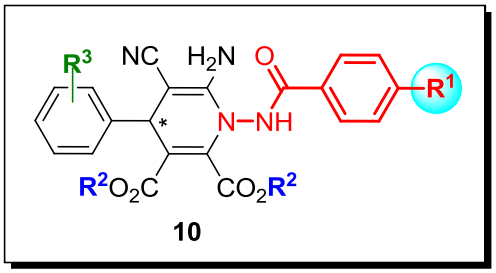
8

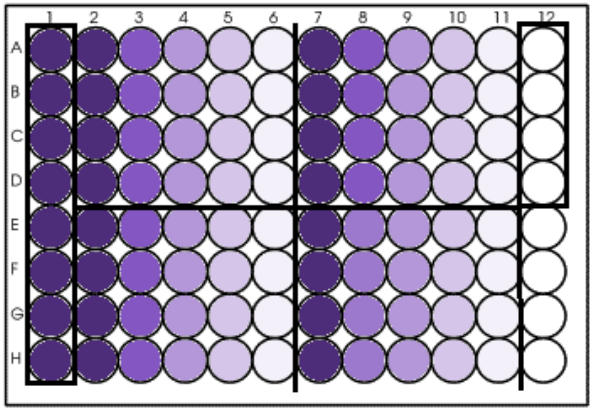
9a-m

9a R^3 = H
9b R^3 = 4-NO_2Ph
9c R^3 = 3-NO_2Ph
9d R^3 = 3-ClPh
9e R^3 = 4-ClPh
9f R^3 = 4-BrPh
9g R^3 = 4-CNPh
9h R^3 = 1-naphthyl
9i R^3 = 4-MePh
9j R^3 = 4-MeOPh
9k R^3 = 2-furyl
9l R^3 = 2-thienyl
9m R^3 = 3-pyridyl

10
up to 99% yield

Cytotoxic Activity





HeLa / Jurkat / A549 cell lines

- **IC_{50} moderate values**
- **Selectivity against different cancer cell lines**
- **Interesting behavior for drug discovery**

Conclusions

- **Synthesis of novel urea-DHP derivatives 5.**
- **1,4-DHPs 3 and their urea derivatives 5 are cytotoxic. The introduction of the urea moiety causes an activity enhancement.**
- **Both families show an apparent selectivity against different cancer cell lines.**
- **In most cases, the compounds are luminescent, enabling their use as theranostic agents.**
- **Preliminary results of the *in vivo* assay show no toxicity over 2 weeks using a concentration up to 7200 times higher than IC_{50}.**
- **A novel family of 1-benzamido-1,4-dihydropyridines has provided interesting cytotoxic results.**

Acknowledgements

https://asymmetricorganocatalysis.com/

GOBIERNO DE ARAGON

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MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

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