Organocatalytic Synthesis of Chiral 1,4-Dihydropyridines with Potential Biological Properties

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Graphical Abstract

**Organocatalysis**

- up to >82% yield
- up to 58% ee

**Biscinchonias**

- up to >99% yield
- up to 82% ee
Abstract:
The 1,4-dihydropyridine core is a widely studied privileged scaffold. Molecules containing this structure are well known calcium channel blockers and are being used already as drugs in the treatment of heart disease. Moreover, recent advances have demonstrated their potential to act against many other diseases. The recent research concerning their activity as multidrug-resistance reversing agents should be highlighted. In the chemistry field, they are soft reducing agents and have been used in asymmetric reductions.
As shown before, these molecules contain a chiral center in their C4 position. Nowadays, it is well known that living matter can discern between stereoisomers of the same compound. Nevertheless, there are scarce examples of procedures leading to enantiomERICALLY enriched 1,4-DHPs, most of them being based on the use of chiral auxiliaries or chiral resolutions. Finding more environmental-friendly processes is also an interesting matter in chemistry, organocatalytic procedures are a perfect tool to achieve this goal. Herein, we report our recent advances in the development of new organocatalytic methodologies to produce enantiomERICALLY enriched 1,4-DHPs. Interestingly, one of them brings out another privileged scaffold, such as the oxindole motif. Our methodologies could be perfect keystones leading to further research on the biological properties of these promising compounds.

Keywords: 1,4-dihydropyridines; 1,4-DHPs; organocatalysis; cinchona; (thio)ureas
Introduction
Introduction

CATALYSIS AS A KEY TOOL

GREEN CHEMISTRY

“The invention, design and application of chemical products and processes to reduce or eliminate the use and the production of harmful substances.”

IUPAC

ORGANOCATALYSIS

“The acceleration of chemical reactions with a substoichiometric amount of organic molecules, which do not contain a metal element.”


Organocatalytic step of the enantioselective synthesis of (S)-Warfarin
Introduction
Privileged scaffolds

DRUGS

Oxipertine
Antidepressant

Nostodione A
Mitotic spindle poison

Nifedipine
Antihypertensive

NADH
Coenzyme

NATURAL PRODUCTS

Nostodione A
Mitotic spindle poison

Quinine
Antimalarial

Quinoline
Antiseptic

Dihydropyridine
Antihypertensive

Introduction

*Classic activity of DHPs: Ca Channel Blockers*

- **Felodipine**

- **Nitredipine**

- **Barnidipine**

- **Amlodipine**
Introduction

*Multidrug-resistance reversing agents*

Classical MDR

Atypical MDR


Introduction

DHPs, more than Ca channel blockers

ANTITUBERCULAR

ANTITUMOR

ALZHEIMER TREATMENT
Introduction

Chirality on pharmacology and 1,4-DHPs

DIFERENTIATION

TERATOGENIC

SEDATIVE

SCARCE EXAMPLES OF ENANTIOSELECTIVE PROCEDURES

Organocatalytic synthesis of chiral 1,4-dihydropyridines.

Herrera, R. P. et al

Results and discussion


SPIROOXINDOLE

horsfiline (X = MeO)
coerulescine (X = H)

(+)-elacomine

alstonisine
Results and discussion

Reaction scope

Up to 82% yield
Up to 58% ee
Results and discussion

**X ray structure**

Prof. Gimeno, M. C. (ISQCH, CSIC)

**Mechanistic proposal**
Results and discussion

Results and discussion

Reaction scope

**Up to 99% yield**

**Up to 82% ee**

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Results and discussion

X ray structure

Prof. Gimeno, M. C. (ISQCH, CSIC)

Mechanistic proposal
Conclusions

- Pioneering catalytic strategies leading to 1,4-DHPs.
- Mild conditions and operational simplicity.
- Promising results.
- Great structural diversity.
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