

# A Biocatalytic Approach to the Synthesis of Pharmacologically Active Compounds

S. Ciceri\*, B. Guidi, S. Reza Elahi and P. Ferraboschi

\*e-mail: samuele.ciceri@guest.unimi.it

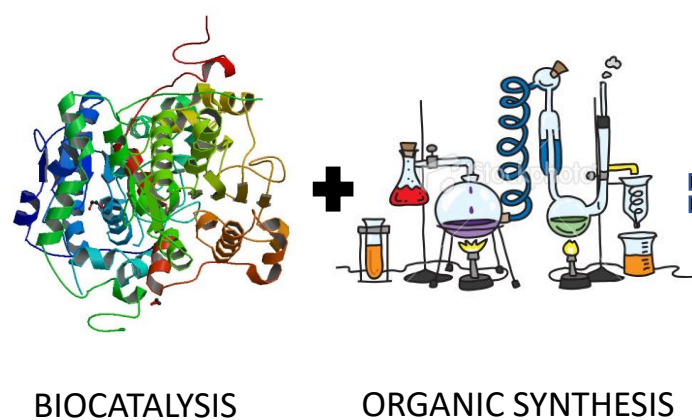
BIOMETRA, Università degli Studi di Milano, Via Saldini 50, 20133 Milano, Italy

## INTRODUCTION

**BIOLOGICALLY ACTIVE COMPOUNDS** are usually polyfunctional and/or chiral molecules and their synthesis requires chemo- regio- and stereoselective transformations.

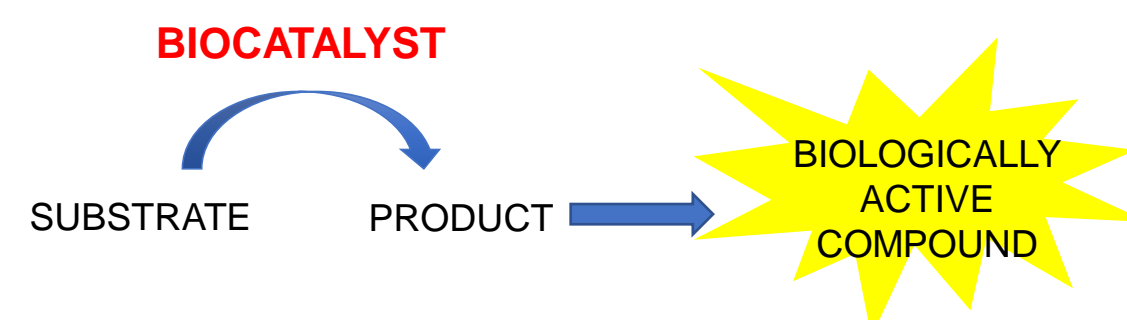
The **USE OF BIOCATALYSTS**, isolated enzymes or whole cells, in organic synthesis can help us to obtain this compounds with:

- high regio-, chemo-, stereoselectivity
- mild experimental conditions
- green processes



## AIM OF THE WORK

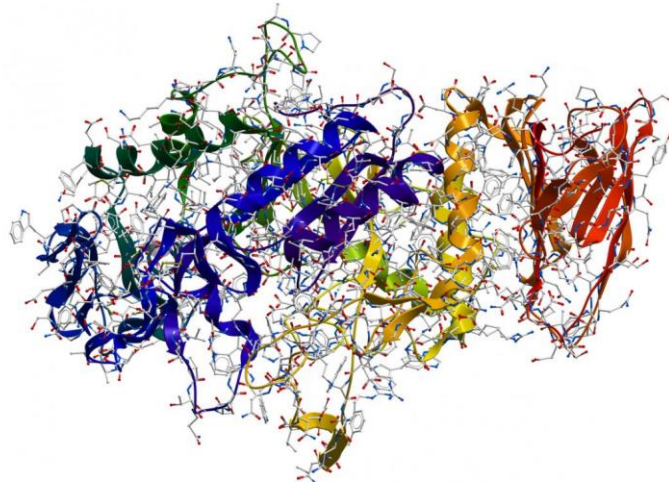
The main topic of our researches is the detection of the biocatalyst and of the substrate more suitable in the crucial step of the preparation of biologically active compounds with high purity and good yields.



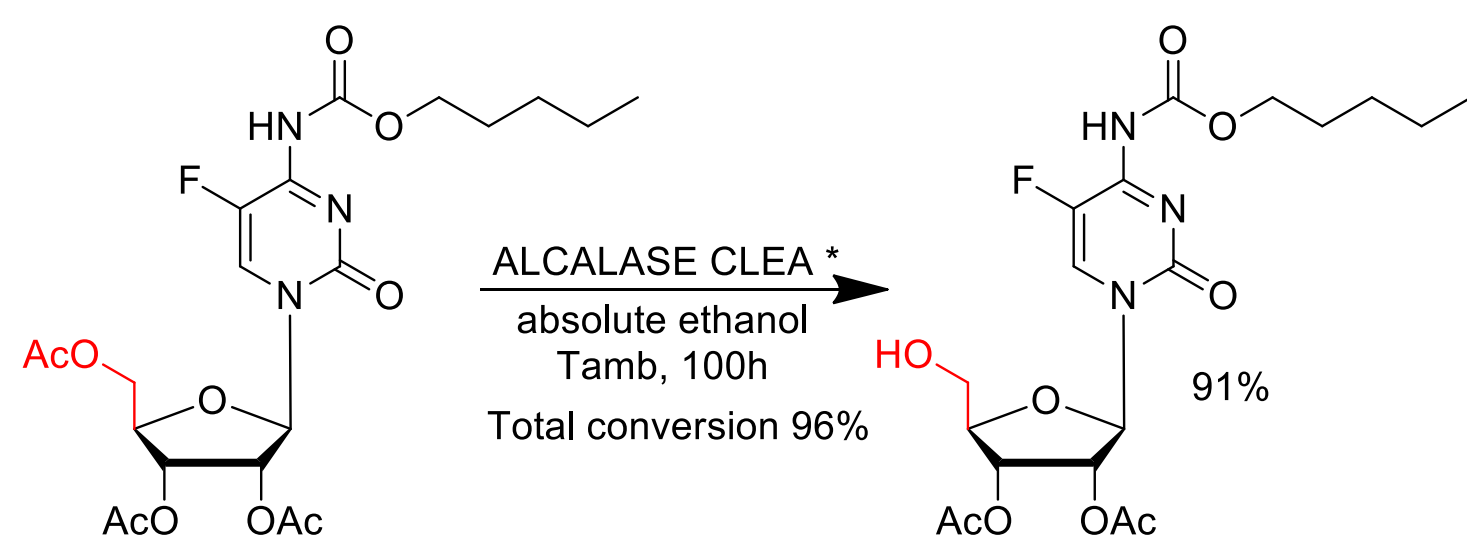
## RESULTS OBTAINED THROUGH BIOCATALYSIS

### ENZYMES

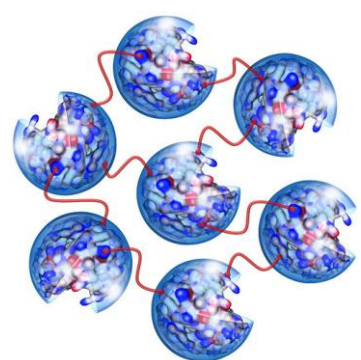
Hydrolases, particularly lipases and proteases, are the most used enzymes for preparative purposes since they don't require cofactors and often are stable also in organic solvents, *i.e.*, the most suitable medium for lipophilic compounds.



### CAPECITABINE antitumor 5-fluorouracil pro-drug



With an enzyme mediated **REGIOSELECTIVE ALCOHOLYSIS** only the primary alcohol was deprotected in order to have the proper modified sugar moiety.

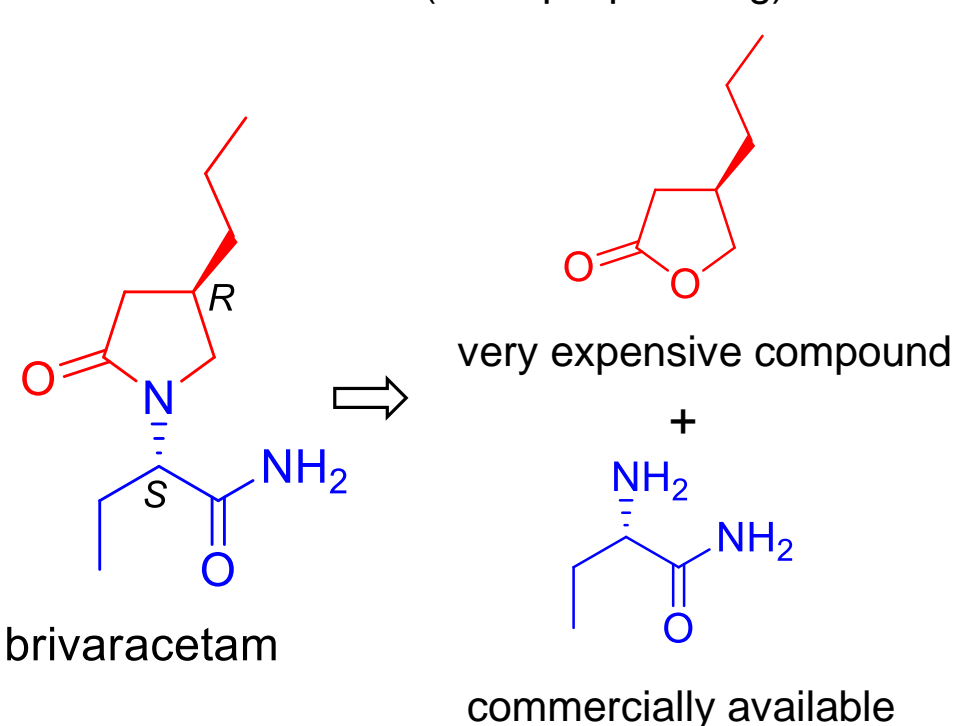


\* CLEA (cross linked enzyme aggregate) make the enzyme more stable towards denaturation, more active and easy to recover and recycle.

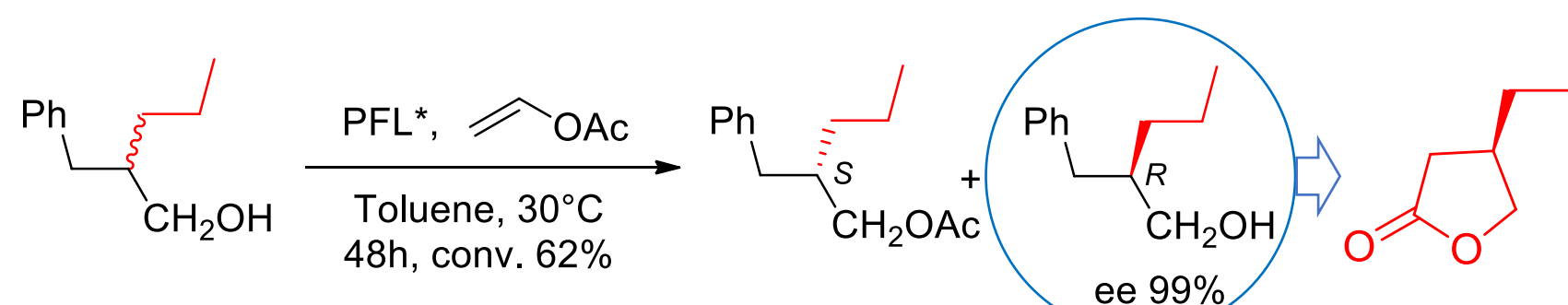
*Tetrahedron Letters* (2015), 56, 5909–5913

*Org. Prep. Proced. Int.* (2017), 49, 69–154

### BRIVARACETAM (anti-epileptic drug)



*Molecules* (2018), 23, 2206



The **KINETIC RESOLUTION** in irreversible transesterification conditions of the racemic alcohol led to the enantiopure alcohol with the proper configuration (*R*) to obtain the expensive chiral lactone in an alternative way with good yield and high optical purity.

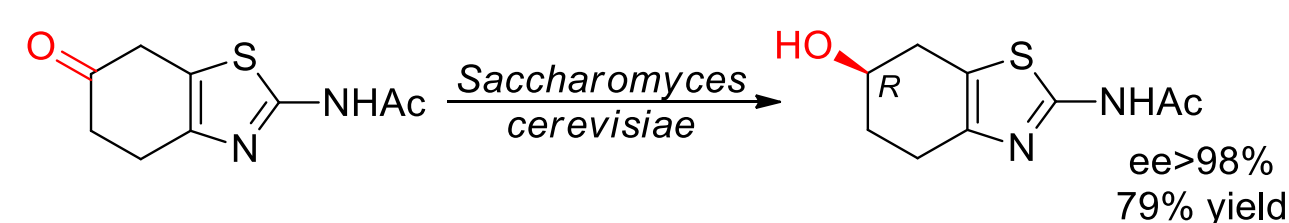
\*PFL=lipase from *Pseudomonas fluorescens*

### MICROORGANISMS

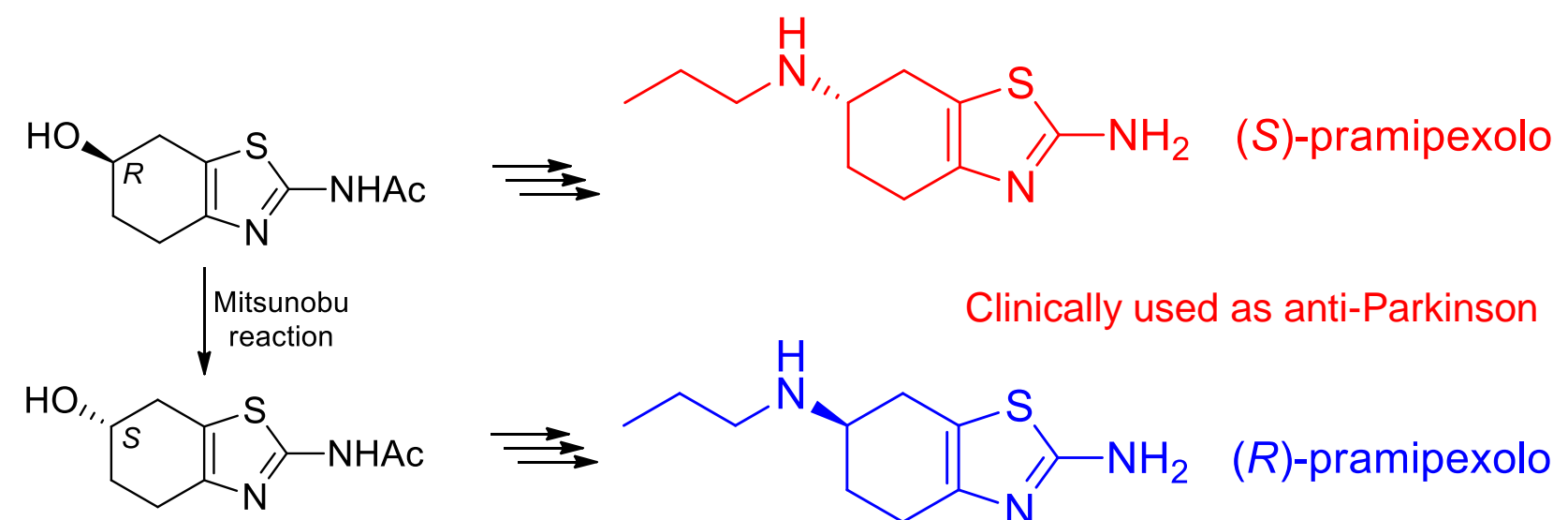
*Saccharomyces cerevisiae* (baker's yeast) is a widely used microorganism for preparative purposes since it doesn't require a microbiologist experience and dedicated equipment. *Saccharomyces cerevisiae* is able to stereoselectively reduce ketones and activated double bonds.



### PRAMIPEXOLE (2 enantiomers, 2 different activities)



Thanks to **THE STEREOSELECTIVE REDUCTION** made by baker's yeast, the enantiopure (*R*)-alcohol was obtained, precursor for enantiopure (*S*) and (*R*) pramipexole.

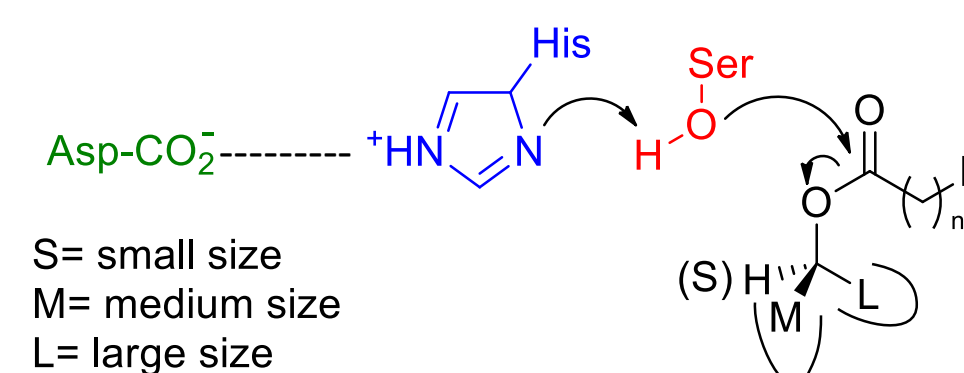


*Tetrahedron: Asymmetry* (2014), 25, 1239–1245

## CONCLUSIONS

The use of biocatalysts allowed us to obtain in good yields:

- **CAPECITABINE** with a **REGIOSELECTIVE TRANSFORMATION** of a polyfunctional molecule;
- **OPTICALLY PURE PRAMIPEXOLE** and **KEY INTERMEDIATE** of **BRIVARACETAM** starting from racemic molecules.



Active-site model for *Pseudomonas* lipase

Once again the synergy between biocatalysis and organic chemistry reveals its power.