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Synthesis and enantiomeric purity evaluation of a new small library of promising bioactive chiral derivatives of xanthones

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[3]CESPU, Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, Rua Central de Gandra, 1317, 4585-116 Gandra PRD, Portugal
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***** Corresponding author: cfernandes@ff.up.pt

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imfacts

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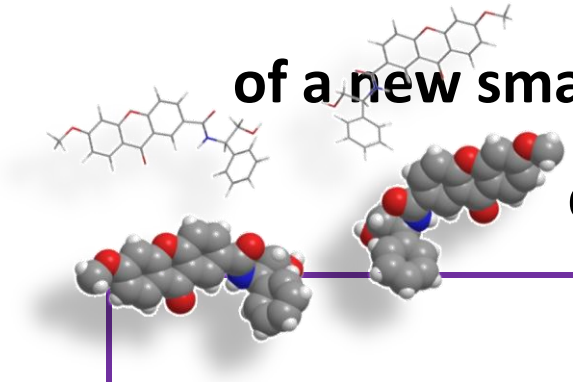
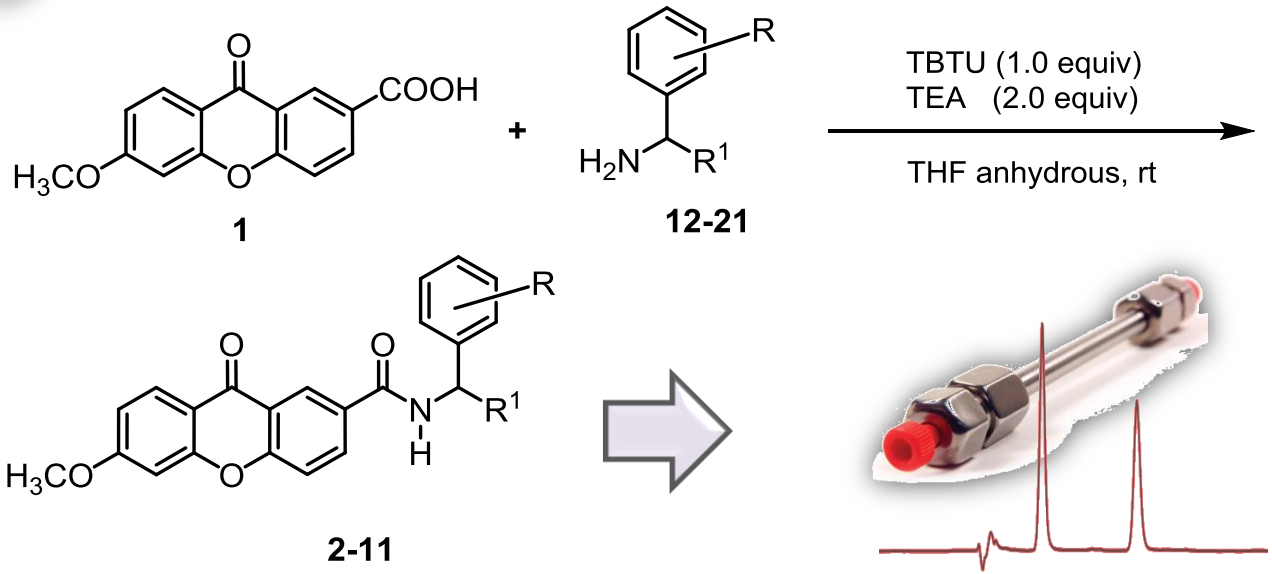
universidade de aveiro

Synthesis and enantiomeric purity evaluation of a new small library of promising bioactive chiral derivatives of xanthones



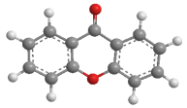


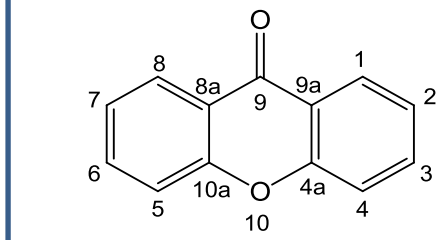
Abstract:
For the last years, searching of new chiral derivatives of xanthones (CDXs) with potential pharmacological properties has remained in the area of interest of our group. Recently, we have described the ability of CDXs to inhibit the growth of different human tumor cell lines. In fact, some of them exhibited interesting dose-dependent growth inhibitory effects on the evaluated cell lines being dependent on the stereochemistry.
Based on this work, herein we describe the synthesis of a new library of promising bioactive analogues, in enantiomerically pure form, with good yields, short reaction times and no racemization. The optimization of the synthetic pathways to obtain the xanthonic derivative used as chemical building block was also described.
The enantiomeric excesses for all synthesized CDXs were measured by HPLC on (*S*,*S*)-Whelk-O1® chiral stationary phase under polar-organic elution conditions, achieving values higher than 99%.
The evaluation of growth inhibitory activity on human tumor cell lines of the synthesized CDXs is in progress.

Keywords: Chiral derivatives of xanthones; Enantiomerically pure; HPLC; Enantioselectivity.

INTRODUTION

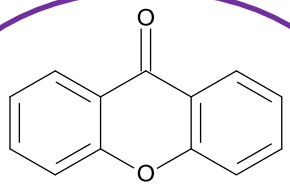
XANTHONES





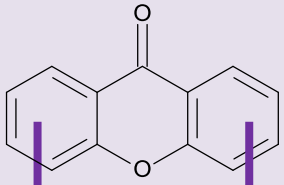
9*H*-xanthen-9-one

Mainly…



Substituent

PHARMACOPHORIC MOIETY

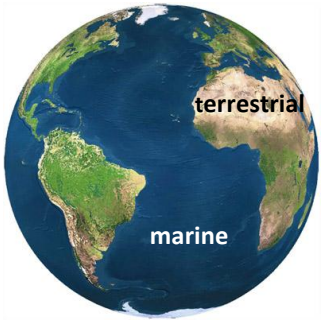


PHARMACOPHORIC MOIETY

Substituents

PRIVILEGED STRUCTURE

NATURAL



From higher plants
fungi, lichens, bacteria, and crude oils

SYNTHETIC

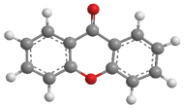
Molecular diversity

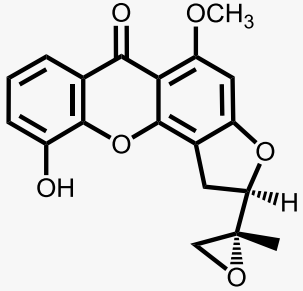
CHIRAL DERIVATIVES OF XANTHONES (CDXS)

- M.M.M. Pinto, M.E. Sousa, M.S J. Nascimento, *Curr.Med. Chem.*, **2005**, *12,* 2517-2538.

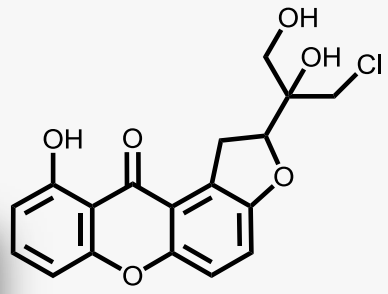
INTRODUTION

CHIRAL XANTHONES IN NATURE - SOME EXAMPLES

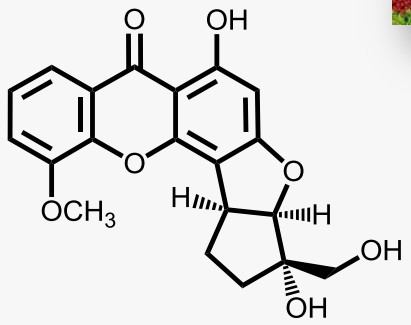




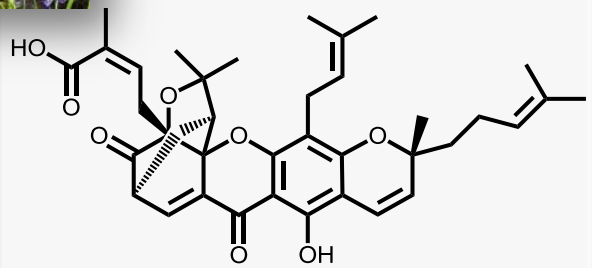
Psorospermin



A furanoxanthone



A difuranoxanthone



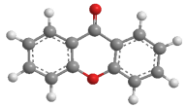
Gambogic acid

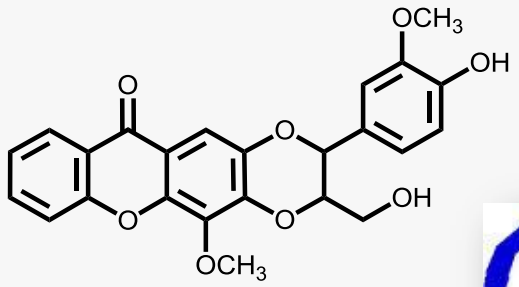
(caged xanthones)

- *Chem. Rev.*, **2012**, *112* (7), 3717- 3776; *Chemistry,* **2010,** *16*(33), 944 – 962; *Mol. Cancer .Ther .*, **2008**, *7,* 617-*3623.*

INTRODUTION

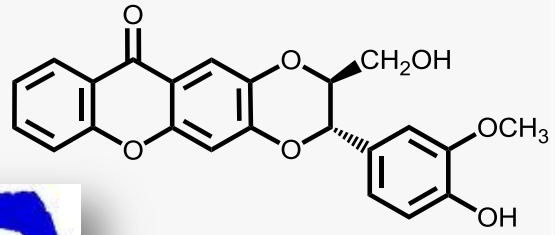
CHIRAL SYNTHETIC XANTHONES – SOME EXAMPLES





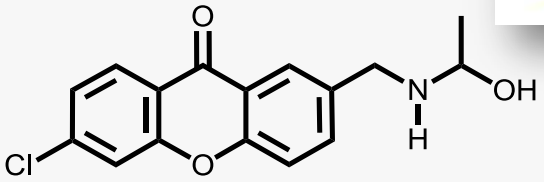
trans – isokielcorin B

Hepatoprotective effect



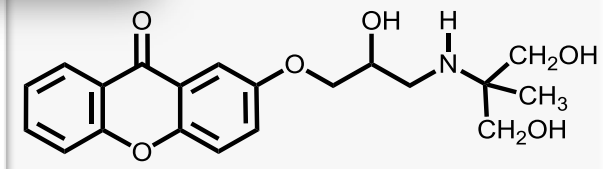
trans – kielcorin E

Antitumor



An alkanolamine xanthone

Anticonvulsant activity



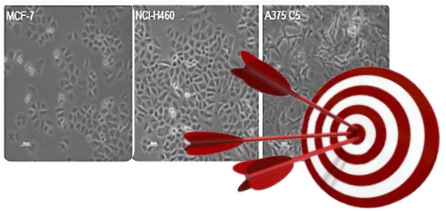
Antiarrhythmic activity

Few examples...

-*Pharmaceutical Reseach*, **1995,** *12* , 1756 – 1760; *Bioorg. Med.Chem.*, **2008,** *16* , 7234 -7244; *Helv. Chim. Acta* , **2002,** *85* , 2862; *Bioorg. Med.Chem.*, **2009,** *17*, 1345 – 1352.

INTRODUTION

CHIRAL DERIVATIVES OF XANTHONES: ENANTIOSELECTIVITY STUDY AS INHIBITORS OF GROWTH OF HUMAN TUMOR CELL LINES



Recently ,
we have described...

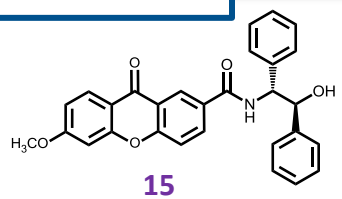
INHIBITION OF GROWTH OF HUMAN TUMOR CELL LINES

		GI_{50} (μM)		
	Compound	A375-C5	MCF-7	NCI-H460
	3	>150	>150	85.88 ± 5.30
	4	>150	91.91 ± 6.27	42.62 ± 1.77
THE MOST ACTIVE	15	32.15 ± 2.03	22.55 ± 1.99	14.05 ± 1.82
	16	51.69 ± 5.77	36.54 ± 2.95	24.88 ± 1.37
	31	>150	>150	>150
	Doxorubicin	130.00 ± 25.20*	60.30 ± 1.20*	19.60 ± 1.90*

*Results are expressed in nM

A375-C5 (melanoma),
MCF-7 (breast adenocarcinoma)
NCI-H460 (non-small cell lung cancer)

Structures of CDXs



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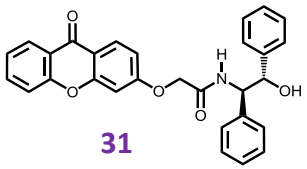

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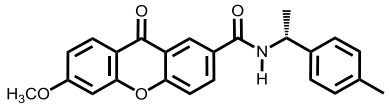

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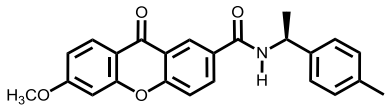
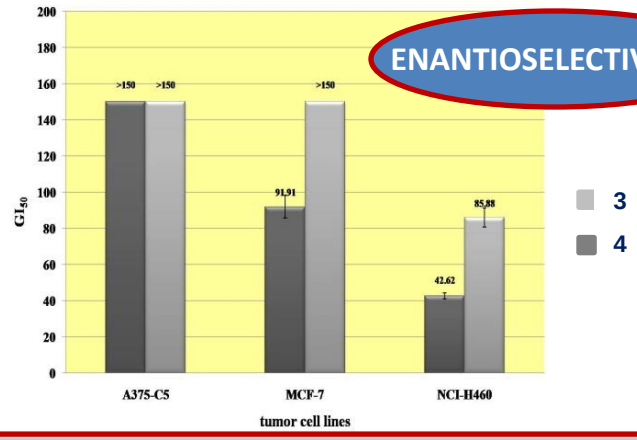


4

GI_{50} of enantiomeric pair of CDXs 3 and 4



-Fernandes C.; Masawang K.; Tiritan M. E.; Sousa E.; Lima V.; Afonso C.; Bousbaa H.; Sudprasert W.; Pedro M.; Pinto M. M. *Bioorgan. Med. Chem*. **2014**, 22, *1049*.

Results and Discussion

Synthesis

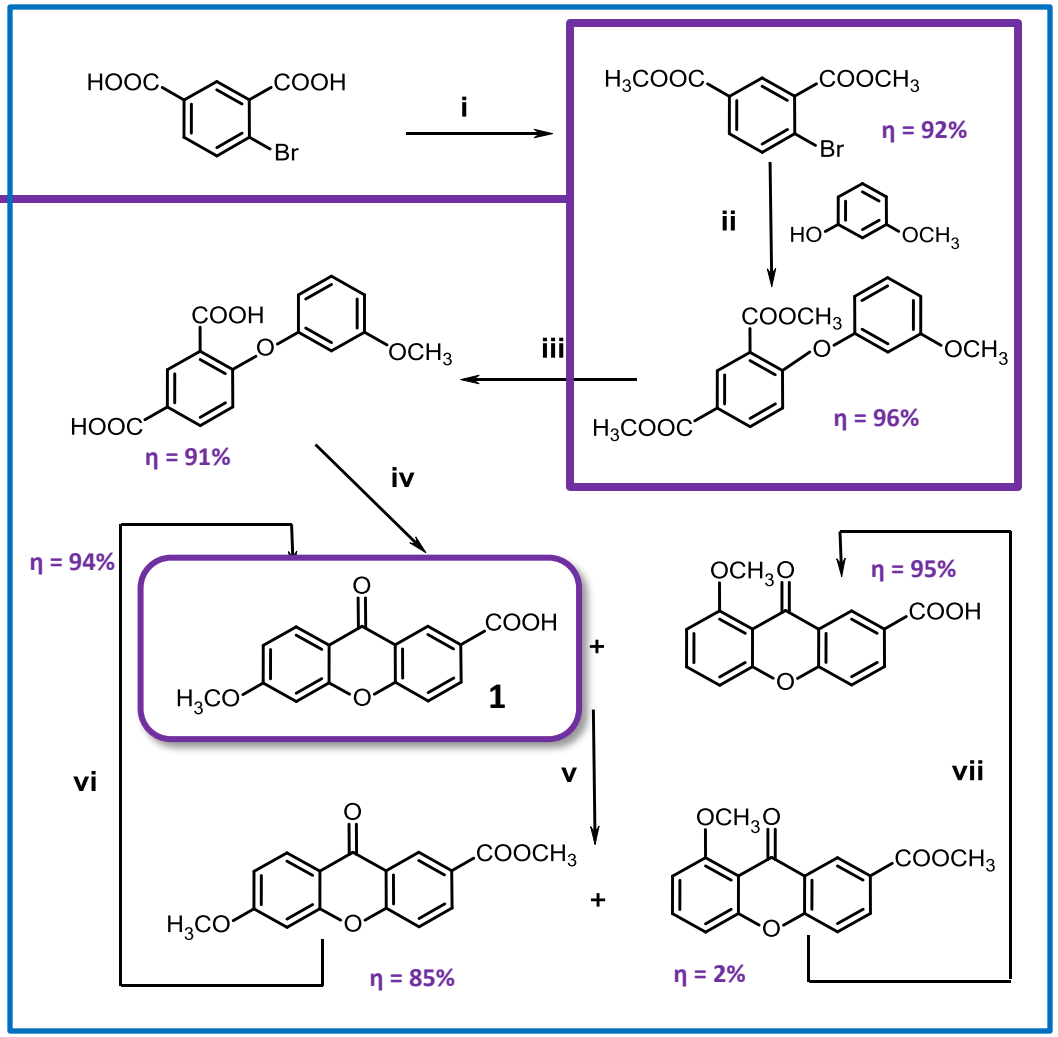
Based on previous work...

Ullmann reaction improvement		
Reagents	**Time and temp.**	**Yield**
CuI, pyridine, K_2CO_3	24 h, 115 ^{0}C	32%[1]
N,*N*-dimethyl glycine, CuI, Cs_2CO_3, dioxane	14 h, 90 ^{0}C	54% [2]
CuI, K_3PO_4, Picolinic Acid, DMSO, N_2	24 h, 80 ^{0}C	96%

Lower reaction temperature
Higher yield

i) MeOH, H_2SO_4, reflux, 17 h; **ii)** CuI, K_3PO_4, Picolinic Acid, DMSO, N_2; **iii)** MeOH/ Tetrahydrofuran (1:1 v/v), 5M NaOH, room temp., 18 h; **iv)** P_2O_5, CH_3SO_3H, room temp., 22 h; **v)** MeOH, H_2SO_4, reflux, 19 h; **vi)** e **vii)** MeOH/ Dichloromethane (1:1 v/v), 5M NaOH, room temp., 22 h.

Optimization of the synthetic pathways to obtain the xanthonic derivative (1) used as chemical substrate for synthesis of CDXs



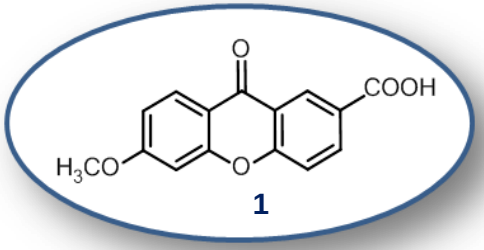
- [1]Jackson, W.T. *et al.*,*J. Med. Chem.*, **1993**, *36*, 1726
- [2]Fernandes, C. *et al.*, *Eur. J. Med. Chem.*, **2012**, *55*, 1

RESULTS AND DISCUSSION

SYNTHESIS

NEW PROMISING BIOACTIVE ANALOGUES IN ENANTIOMERICALLY PURE FORM

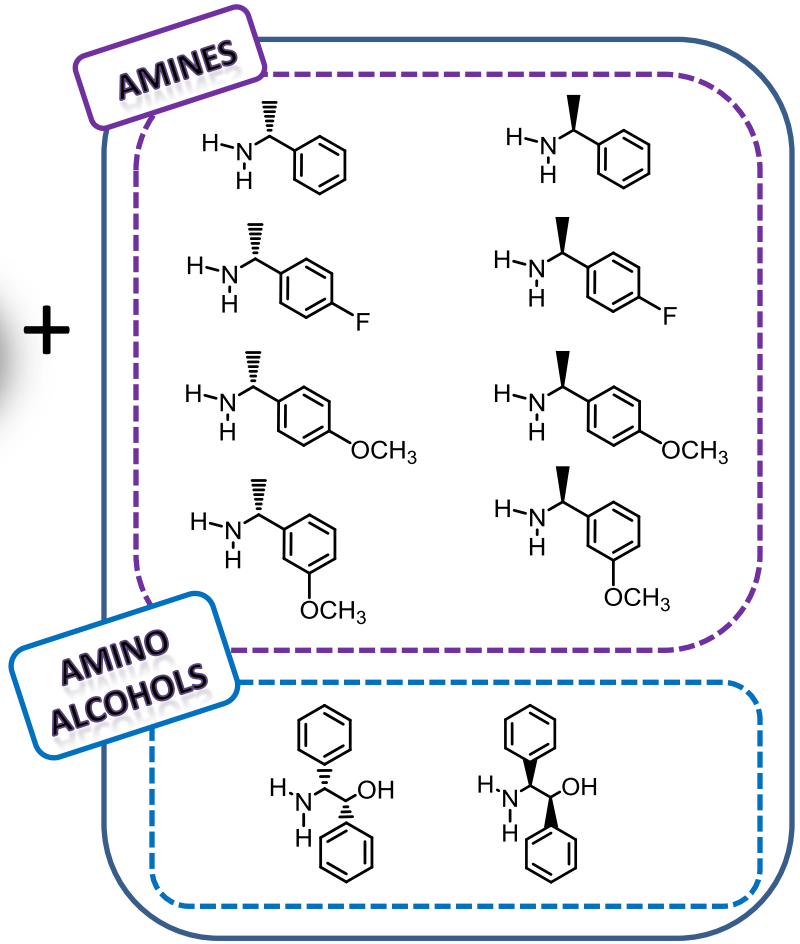
XANTHONIC CHEMICAL SUBSTRATE

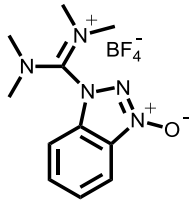


1

+

COMMERCIALLY AVAILABLE CHIRAL BUILDING BLOCKS





TBTU (1.0 equiv)

TEA (2.0 equiv)
anhydrous THF, rt

0.5 to 5h

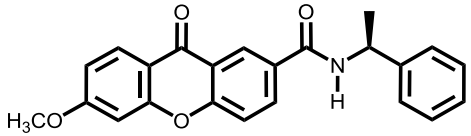
SMALL LIBRARY OF CDXs

TEA: Triethylamine;
THF: Tetrahydrofuran;
TBTU: *O*-(Benzotriazol-1-yl)-*N*-*N*-*N'*-*N'*-tetramethyluronium tetrafluoroborate.

RESULTS AND DISCUSSION

SYNTHESIS

NEW SMALL LIBRARY OF CDXS



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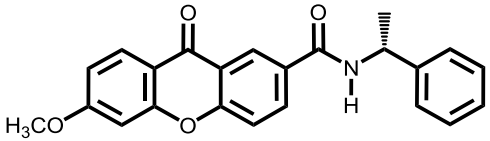

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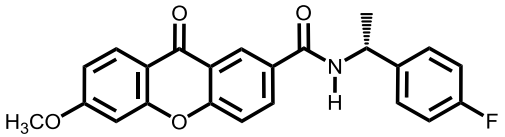

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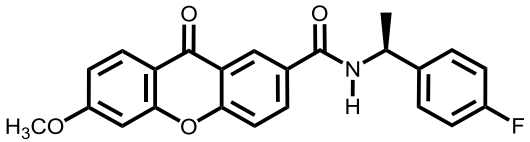
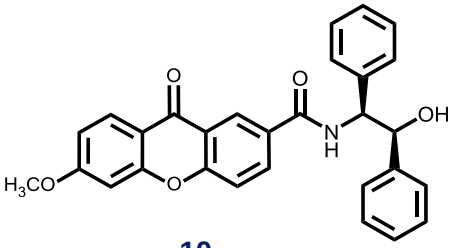


4

Ten CDXs
Yield: 92 to 94%



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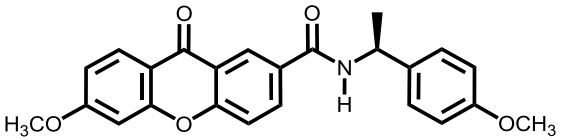

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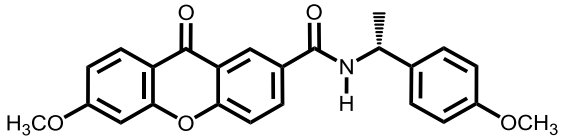

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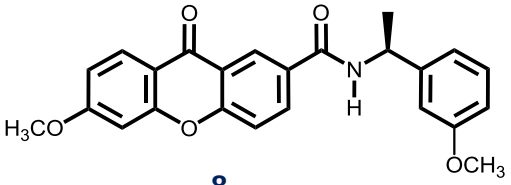

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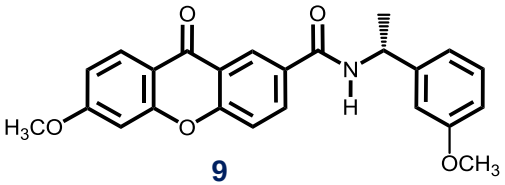

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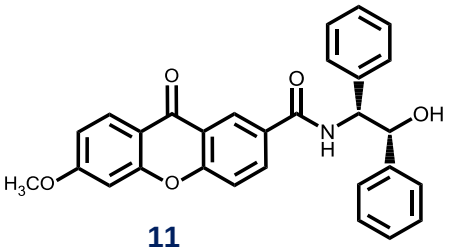
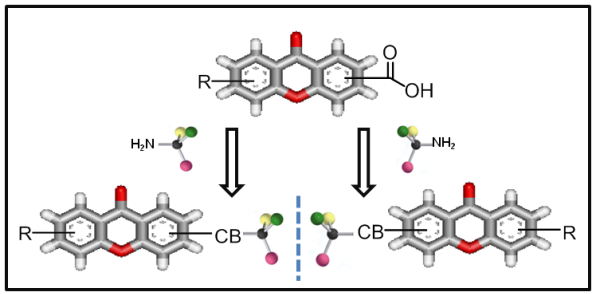


11

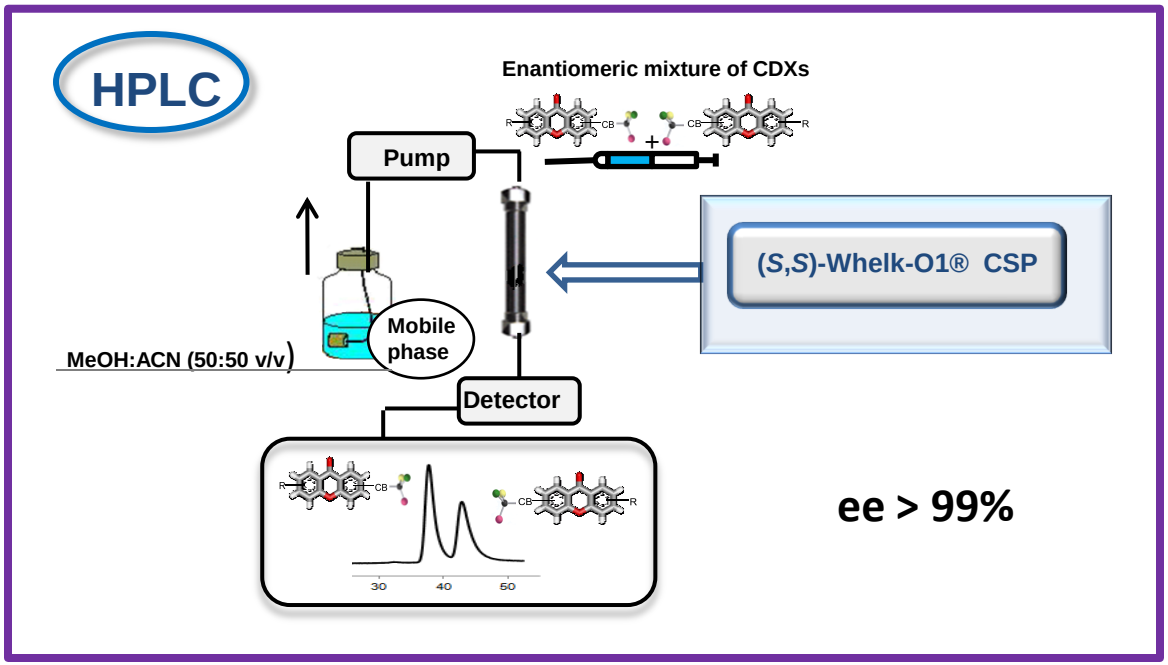
RESULTS AND DISCUSSION

ENANTIOMERIC PURITY EVALUATION



Next step: evaluation of the

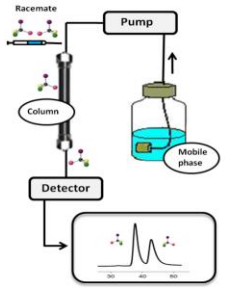
ENANTIOMERIC PURITY



CSP = Chiral stationary phase
ee = enantiomeric excess

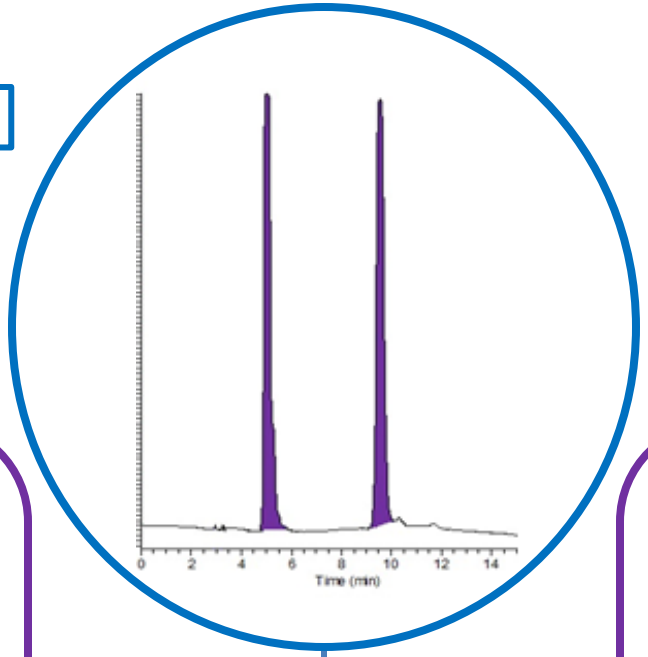
RESULTS AND DISCUSSION

ENANTIOMERIC PURITY EVALUATION

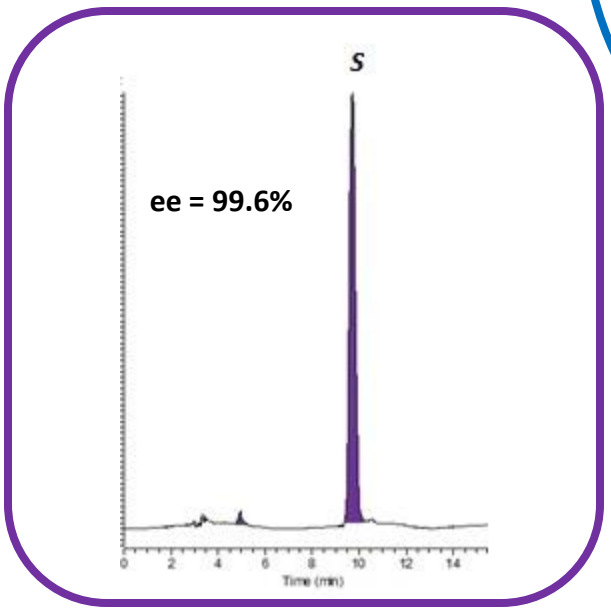


EXAMPLE

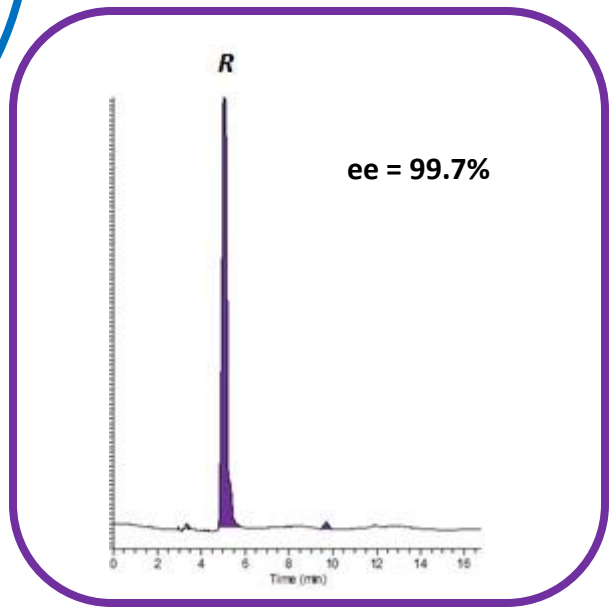
Chromatogram of enantiomeric mixture of CDX2 and CDX3



Chromatogram of CDX2 (*S*-enantiomer)



Chromatogram of CDX3 (*R*-enantiomer)



k_1	= 3.35
k_2	= 7.75
α	= 2.38
R_S	= 9.03

(*S*,*S*)-Whelk-O1 CSP; ACN:MeOH (50:50 v/v); flow rate 1.0 mL/min; detection wavelength 254 nm.

CONCLUSIONS

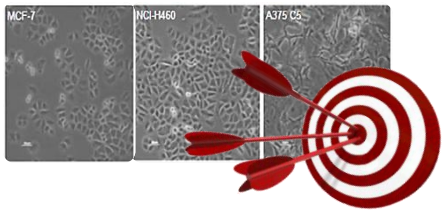
Ten new promising bioactive CDXs were synthesized with good yields, short reaction time and no racemization.

The optimization of the synthetic pathways to obtain the xanthonic derivative used as chemical substrate was successfully applied.

The ee for all synthesized CDXs were measured by HPLC on (*S*,*S*)-Whelk-O1® CSP under polar-organic elution conditions, achieving values higher than 99%.

Evaluation of growth inhibitory activity on human tumor cell lines of the synthesized CDXs

IN PROGRESS



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