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

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

Yield: 92 to 94%

ee: > 99%
Abstract:
For the last years, searching of new chiral derivatives of xanthenes (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 xanthogenic 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 xanthenes; Enantiomerically pure; HPLC; Enantioselectivity.
**INTRODUCTION**

**XANTHONES**

*From higher plants fungi, lichens, bacteria, and crude oils*  
Mainly...

- **Natural**
  - terrestrial
  - marine
  - Molecular diversity

- **Synthetic**

- Privileged structure

- Chiral derivatives of xanthones (CDXs)

*H-xanthen-9-one*

Substituent

Pharmacophoric moiety

Substituents

Pharmacophoric moiety

- Privileged structure

*Substituent*

**PHARMACOPHORIC MOIETY**

**SYNTHETIC**

- Molecular diversity

- 1st International Electronic Conference on Medicinal Chemistry  
  2-27 November 2015

INTRODUCTION

CHIRAL XANTHONES IN NATURE - SOME EXAMPLES

INTRODUCTION

CHIRAL SYNTHETIC XANTHONES – SOME EXAMPLES


\[ \text{trans} – \text{isokielcorin B} \\
\text{Hepatoprotective effect} \]

\[ \text{trans} – \text{kielcorin E} \\
\text{Antitumor} \]

\[ \text{An alkanolamine xanthone} \\
\text{Anticonvulsant activity} \]

\[ \text{Antiarrhythmic activity} \]
INTRODUCTION

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>A375-C5</th>
<th>MCF-7</th>
<th>NCI-H460</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>&gt;150</td>
<td>&gt;150</td>
<td>85.88 ± 5.30</td>
</tr>
<tr>
<td>4</td>
<td>&gt;150</td>
<td>91.91 ± 6.27</td>
<td>42.62 ± 1.77</td>
</tr>
<tr>
<td>15</td>
<td>32.15 ± 2.03</td>
<td>22.55 ± 1.99</td>
<td>14.05 ± 1.82</td>
</tr>
<tr>
<td>16</td>
<td>51.69 ± 5.77</td>
<td>36.54 ± 2.95</td>
<td>24.88 ± 1.37</td>
</tr>
<tr>
<td>31</td>
<td>&gt;150</td>
<td>&gt;150</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>130.00 ± 25.20*</td>
<td>60.30 ± 1.20*</td>
<td>19.60 ± 1.90*</td>
</tr>
</tbody>
</table>

*Results are expressed in nM

The most active

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

Structures of CDXs

GI₅₀ of enantiomeric pair of CDXs 3 and 4

RESULTS AND DISCUSSION

SYNTHESIS

Based on previous work...

<table>
<thead>
<tr>
<th>Ullmann reaction improvement</th>
<th>Time and temp.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>CuI, pyridine, K₂CO₃</td>
<td>24 h, 115 °C</td>
<td>32%²</td>
</tr>
<tr>
<td>N,N-dimethyl glycine, CuI, Cs₂CO₃, dioxane</td>
<td>14 h, 90 °C</td>
<td>54%²</td>
</tr>
<tr>
<td>CuI, K₃PO₄, Picolinic Acid, DMSO, N₂</td>
<td>24 h, 80 °C</td>
<td>96%</td>
</tr>
</tbody>
</table>

Lower reaction temperature
Higher yield

i) MeOH, H₂SO₄, reflux, 17 h; ii) CuI, K₃PO₄, Picolinic Acid, DMSO, N₂; iii) MeOH/ Tetrahydrofuran (1:1 v/v), 5M NaOH, room temp., 18 h; iv) P₂O₅, CH₃SO₃H, room temp., 22 h; v) MeOH, H₂SO₄, reflux, 19 h; vi) MeOH/ Dichloromethane (1:1 v/v), 5M NaOH, room temp., 22 h.

XANTHONIC CHEMICAL SUBSTRATE

RESULTS AND DISCUSSION

SYNTHESIS

NEW PROMISING BIOACTIVE ANALOGUES IN ENANTIOMICALLY PURE FORM

COMMERCIAL AVAILABLE CHIRAL BUILDING BLOCKS

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

SMALL LIBRARY OF CDXs
RESULTS AND DISCUSSION
SYNTHESIS

NEW SMALL LIBRARY OF CDXs

Ten CDXs
Yield: 92 to 94%
RESULT AND DISCUSSION

ENANTIOMERIC PURITY EVALUATION

Next step: evaluation of the ENANTIOMERIC PURITY

HPLC

Enantiomeric mixture of CDXs

Pump

MeOH:ACN (50:50 v/v)

Mobile phase

Detector

(S,S)-Whelk-O1® CSP

ee > 99%

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)

ee = 99.6%

ee = 99.7%

\( k_1 = 3.35 \)

\( k_2 = 7.75 \)

\( \alpha = 2.38 \)

\( R_s = 9.03 \)

(\( S,S \))-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
ACKNOWLEDGMENTS

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