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Synthesis, *in vitro* and *in vivo* antitumoral effect against oral squamous cell carcinoma of new dithioethers based on catalyst-free Michael addition of thiols to α-xyloidone

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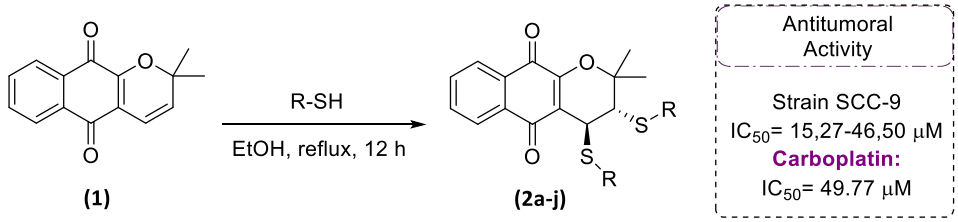
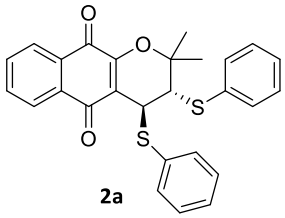
ABSTRACT

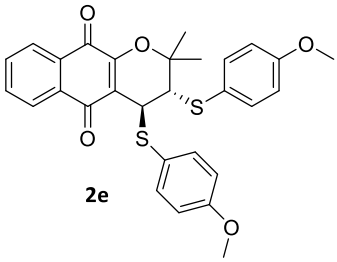
The Michael addition of thiols to α-xyloidone **(1)** led to the formation of ten dithioethers **(2a-j)** with yields between 36-73%. An initial screening against human tongue squamous cell carcinoma (SCC-9) showed an IC_{50} range between 15.27 and 46.50 μM (reference: carboplatin, IC_{50}= 49.77 μM). Dithioethers **2a** and **2e**, qualified in initial tests after evaluation in three different oral squamous cell carcinoma strains, were able to inhibit SCC-9 cell migration by 71.7 and 45.3%, respectively. **2a** showed a promise candidate for antimigratory agent, indicating a lower risk of metastatic cancer. In hemolysis assays, **2a** presented a rate of 1.06%, lower than carboplatin (1.34%). The mechanism of action of these dithioethers showed an induction of cell death by apoptosis and significant formation of reactive oxygen species. The relevant results show the potential of this molecules, obtained in this work in a single step from α-xyloidone for the first time in the literature.[1,2]



2a: R= Ph, 60 %; **2b:** R= 2-MePh, 53 %; **2c:** R= 3-MePh, 40 %; **2d:** R= 4-MePh; 60 %; **2e:** R= 4-OMePh, 61 %; **2f:** R= 4-FPh, 37 %; **2g:** R= 4-SMePh, 73 %;**2h:** R= 4-ClPh, 36 %; **2i:** R= 4-OHPh, 64 %; **2j:** R= 2-Naph, 67 %

Selected Derivatives





- qualified to in vivo assays
- **2a:** promise candidate for antimigratory agent
- lower hemolysis rate
- mechanism of action: cell death by apoptosis
- relevant ROS formation

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FAPERJ, CAPES, CNPq

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[2] Lee, Y.; Choi, J.; Trinh, D.; Kim, N. *Synthesis* **2005**, 18, 3026-3034.