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Acetylcholinesterase and Antioxidant Evaluation of C18-functionalized Ferruginol Analogues

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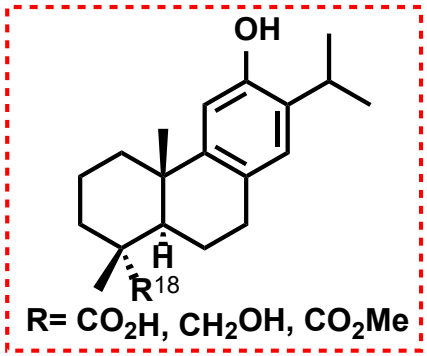
Acetylcholinesterase and Antioxidant Evaluation of C18-functionalized Ferruginol Analogues

Graphical Abstract



C18-Ferruginol Analogues

AChE inhibition (%,10 μg/mL) = 1.5-49.3%
DPPH inhibition (%, 2 mM) = 44.8-59.8%
IC_{50} (DPPH)= 405-795 μM

Abstract: One slide, Max 200 words

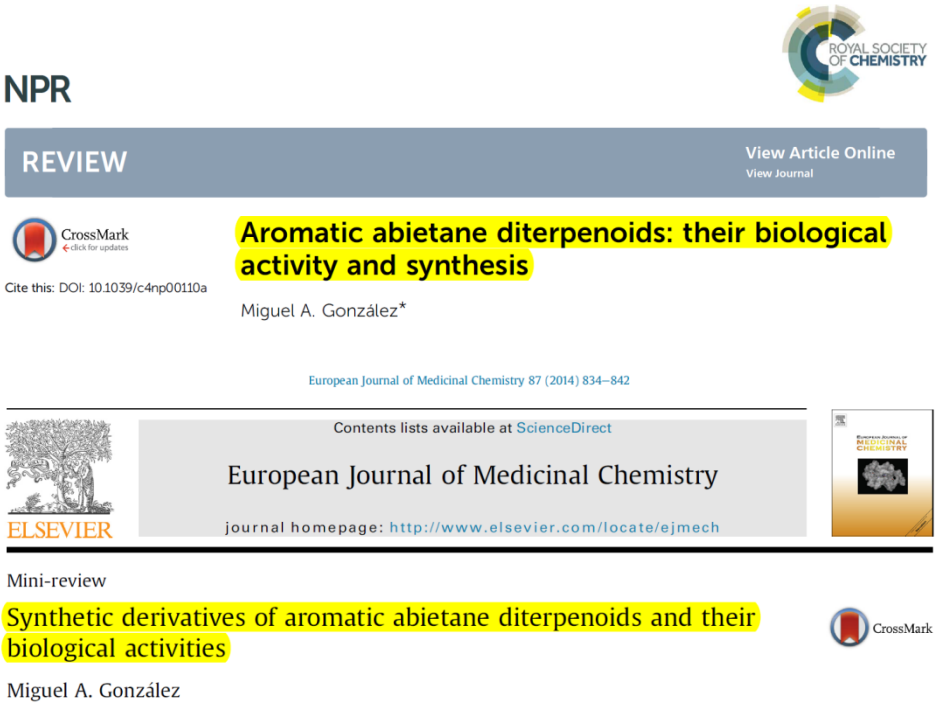
The abietane-type diterpenoids are characterized by a tricyclic ring system and have shown a wide range of chemical diversity and biological activity. Medicinal chemists have studied derivatives of two readily available materials such as dehydroabietic acid and dehydroabietylamine. To date, there is only one commercial drug, Ecabet® [ecabet sodium], based on abietanes, which is used for the treatment of reflux esophagitis and peptic ulcer disease. The simplest phenolic abietane, ferruginol, exhibits anticancer effects in human ovarian cancer and inhibition of cancer cell migration. It also has shown interesting properties in different models of Alzheimer's disease, researchers have reported neuroprotective effects of ferruginol against amyloid-b (Aβ) oligomers-induced neurodegenerative alterations and butyrylcholinesterase inhibition.

In this communication, we present the results of an investigation of several C18-ferruginol analogues on anti-acetylcholinesterase activity and antioxidant agents.

Keywords: Alzheimer; acetylcholinesterase; antioxidant; semisynthesis; diterpenoid; abietane

Introduction

Privileged structure


NPR

REVIEW View Article Online View Journal

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Cite this: DOI: 10.1039/c4np00110a

Aromatic abietane diterpenoids: their biological activity and synthesis

Miguel A. González*

European Journal of Medicinal Chemistry 87 (2014) 834–842

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Mini-review

Synthetic derivatives of aromatic abietane diterpenoids and their biological activities

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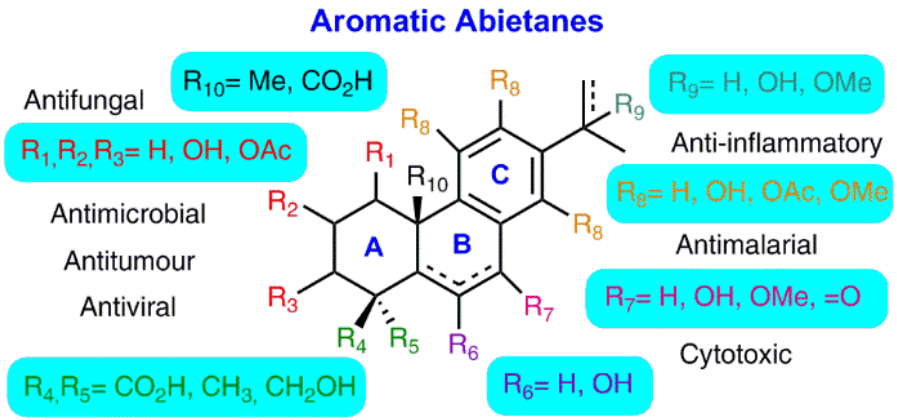
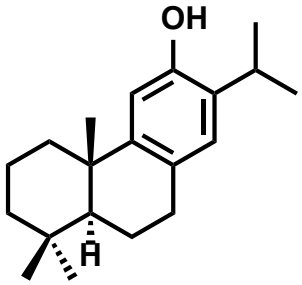
Miguel A. González



After a large number of scientific evidence (~250 references), the tricyclic system of the abietane skeleton with an aromatic C ring can be considered a privileged structure able to interact with a number of biological targets.

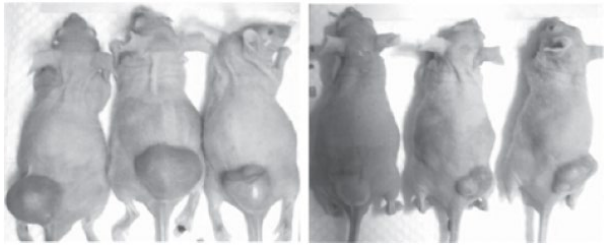
Introduction

Background: Ferruginol and analogues

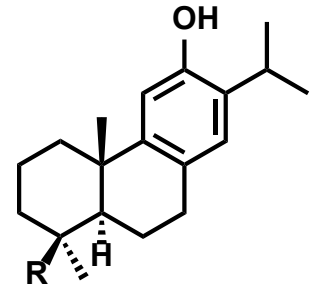


(+)-Ferruginol

Antitumor activity *in vitro* in prostate cancer, pancreas and leukemia (apoptosis).
Antitumor activity *in vivo* in lung cancer xenografts in mouse.

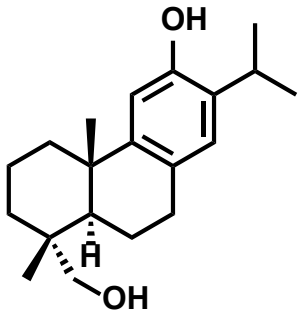


Control Ferruginol



R= CH_2OH, CO_2Me

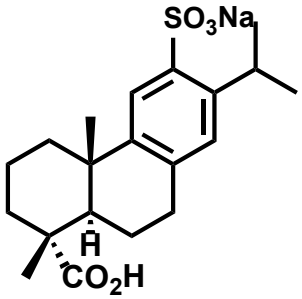
Antileishmania activity *in vitro* (ferruginol and C-19 derivatives)



Antiviral activity *in vitro* against SARS-CoV coronavirus

Introduction

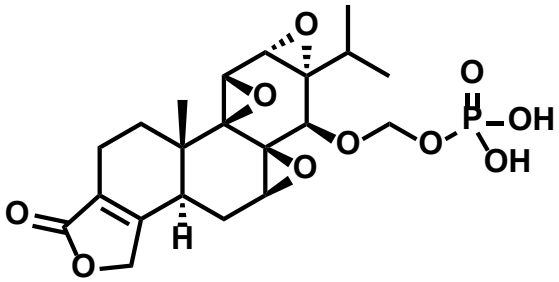
Background: Drugs based on Abietane diterpenoids



Ecabet®

Sodium Ecabet is commercially available in Japan and China for the treatment of reflux oesophagitis and peptic ulcer disease.

Antibacterial against *Helicobacter pylori*

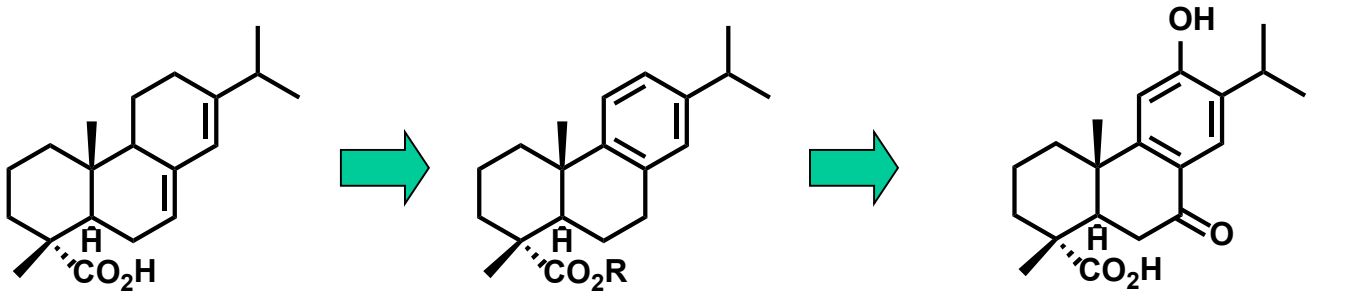


Minnelide™

In Clinical development for anticancer agent for pancreas carcinoma.

Results and discussion

Semisynthesis of Liquiditerpenoic acid A or Abietopinoic acid: from Abietic acid: C18-Ferruginol Analogues



(-)-Abietic acid

R= H (+)-Dehydroabietic acid
R= Me methyl dehydroabietate

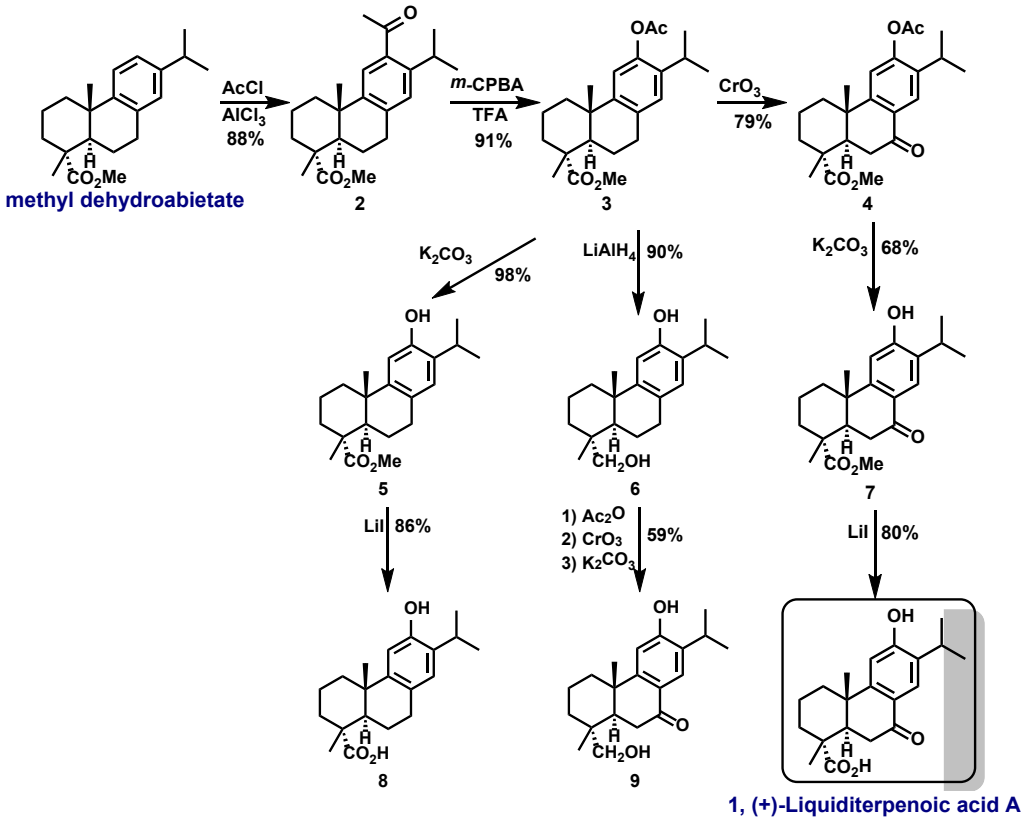
(+)-Liquiditerpenoic acid A

González, M. A. *et al.*
Eur. J. Med. Chem. **2010**, *45*, 811-816.

Hamulic, D.; Padrón, J. M.; González-Cardenete, M. A. et al. *J. Nat. Prod.* **2019**, *82*, 823-831

Results and discussion

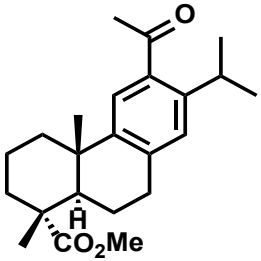
Semisynthesis of C18-Ferruginol analogues



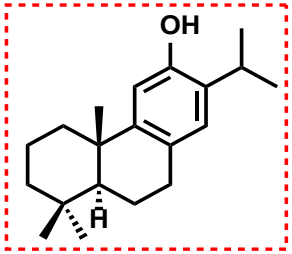
Hamulic, D.; Padrón, J. M.; González-Cardenete, M. A. et al. *J. Nat. Prod.* **2019**, *82*, 823-831

Results and discussion

Biological activity of C18-Ferruginol analogues: Anticholinesterase and Antioxidant

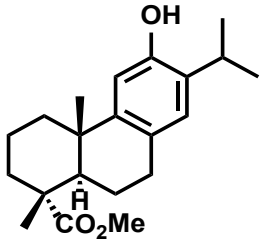


AChE inhibition (%,10 μg/mL) = 14.7%
DPPH inhibition (%, 2 mM) = not active

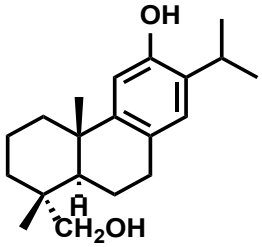


(+)-Ferruginol

AChE inhibition (%,10 μg/mL) = 49.3%
DPPH inhibition (%, 2 mM) = 45.1%
IC_{50} (DPPH)= 795 μM



AChE inhibition (%,10 μg/mL) = 1.5%
DPPH inhibition (%, 2 mM) = 44.8%
IC_{50} (DPPH)= 446 μM



18-hydroxyferruginol

AChE inhibition (%,10 μg/mL) = 2.0%
DPPH inhibition (%, 2 mM) = 59.8%
IC_{50} (DPPH)= 405 μM

Conclusions

The combined findings indicate that:

- abietane-diterpenoid natural product analogs:
  source of novel bioactive molecules with promising pharmacological properties.
- Funtionalization at C18 with the tested functional groups led to:
  1. little inhibition of AChE in comparison with the parent molecule (+)-ferruginol
  2. potentiated the antioxidant activity.

Acknowledgments

INSTITUTO DE TECNOLOGÍA QUÍMICA
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Universitat de València
Universidade Lusófona
U Lisboa Universidade de Lisboa

Thank you for your attention!

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