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Review article

Synthesis and antiviral activity of maleopimaric and quinopimaric acids' derivatives



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ABSTRACT

A series of maleopimaric and quinopimaric acids' derivatives modified in the E-ring, at the carbonyl- and carboxyl-groups were synthesized and evaluated for their activity in vitro against respiratory viruses (influenza; rhinovirus; adenovirus; and SARS), papilloma virus, and hepatitis B and C viruses. The antiviral screening of levopimaric acid diene adducts derivatives was carried out with minimal effect on SARS and influenza type B viruses. Excellent antiviral activity of the ozonolysis product of maleopimaric acid and dihydroquinopimaric methyl-(2-methoxycarbonyl)ethylene amide was found toward papilloma virus (HPV-11 strain) with the selectivity index of SI 30 and 20, respectively. Methyl (2-methoxycarbonyl)ethylene-, 1β -hydroxy-5'-kaprolaktamo- and 4β -hydroxy- 4α , 14α -epoxy-13(15)-ene-dihydroquinopimaric acid derivatives have also shown activity against replication of HCV nucleic acid and low toxicity.

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1. Introduction

Tricyclic diterpenoids of abietane series is one of the important groups of the secondary metabolites, which are widespread in nature.¹ Their natural and synthetic derivatives exhibit a broad spectrum of biological activities for example, antimicrobial,² antiviral,^{3,4} antimalaria,⁵ antiulcer,⁶ antileishmaniasis,⁷ antioxidant,^{8,9} and others. Abietane diterpenoids exhibited the antitumor promoting activity^{10,11} and they are inhibitors of viruses reproduction^{12,13} such as the herpes simplex virus type 1 (HSV-1),¹⁴ cytomegalovirus (CMV),¹⁵ varicella-zoster virus (VZV)¹⁵ and Epstein-Barr virus.¹⁶

Abietane acids', such as abietic and levopimaric acids', readily available from an oleoresin produced by *Pinus* or commercial disproportionate rosin and easily reacts with dienophiles giving the Diels–Alder adducts in high yields. ^{17–19} Diterpene derivatives obtained by the diene synthesis and their synthetic derivatives have diverse pharmacological activity, including anti-inflammatory, ^{20–22} antiulcer, ²³ anticancer ²⁴ and antitumor. ²⁵ Despite the variety of biological properties of this compounds family, there are few data on the antiviral activity study of their derivatives. So, for dihydroquinopimaric acid amides ²⁶ and some frame derivatives of quinopimaric acid ²⁷ was set a moderately antiviral activity against influenza A virus. Dihydroquinopimaric acid and its non-

trivial product of dimethyldioxirane oxidation proved to be effective inhibitors of papillomavirus (HPV).²⁸

The present work is an extension of our ongoing efforts toward developing promising biologically active agents among the levopimaric acid diene adducts derivatives. ^{20–24,26,28–30} We have realized the chemical transformations of levopimaric acid diene adducts with maleic anhydride and *p*-benzoquinone, resulting in more than thirty derivatives of maleopimaric and quinopimaric acids' modified in the E-ring, at the carbonyl- and carboxyl-groups were synthesized and their in vitro antiviral activity was evaluated.

2. Results and discussion

2.1. Chemistry

For the synthesis of maleopimaric acid **1**³¹ and quinopimaric acid **3**³² pine resin *Pinus silvestris* containing about 25% levopimaric acid was used. Dihydroquinopimaric acid **5**,³³ trimethyl fumaropimarate **2**,³⁴ and methyl 2,3-epoxyquinopimarate **6**,³³ as well as dimethyl cyclopentenonepimarate **7**³³ and dimethyl cyclopentanonepimarate **8**,³³ were obtained by procedures described before (Scheme 1).

The reaction of the diester **7** with sodium borohydride in refluxing methanol showed recovery not only of the carbonyl group, but

Scheme 1. Reagents and conditions: (i) maleic anhydride, 200 °C (ii) 1,4-benzoquinone, CHCl₃-CH₃CN (1:4), 7 days, rt (iii) 15% KOH/MeOH, reflux, 2 h. (iv) CH₂N₂/Et₂O, EtOH, 0 °C (v) Zn/AcOH, 100 °C (vi) 35% H₂O₂, 6 M NaOH/MeOH, Et₂O, 0 °C (vii) 10% NaOH, EtOH, rt (viii) H₂, 20% Ni/Raney, MeOH (ix) NaBH₄, MeOH, reflux.

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