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Review article

Synthesis and antiviral activity of maleopimaric and quinopimaric acids' derivatives

Elena V. Tretyakova [a,*], Irina E. Smirnova [b], Elena V. Salimova [a], Victor N. Odinokov [a]

[a] Institute of Petrochemistry and Catalysis of the Russian Academy of Sciences, 141 Prospect Oktyabrya, 450075 Ufa, Russian Federation
[b] Ufa Institute of Chemistry of the Russian Academy of Science, 71 Prospect Oktyabrya, 450054 Ufa, Russian Federation

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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.

Contents

* Corresponding author. Fax: +7 (347) 2842750.
E-mail address: tretyakovaelv@gmail.com (E.V. Tretyakova).

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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]

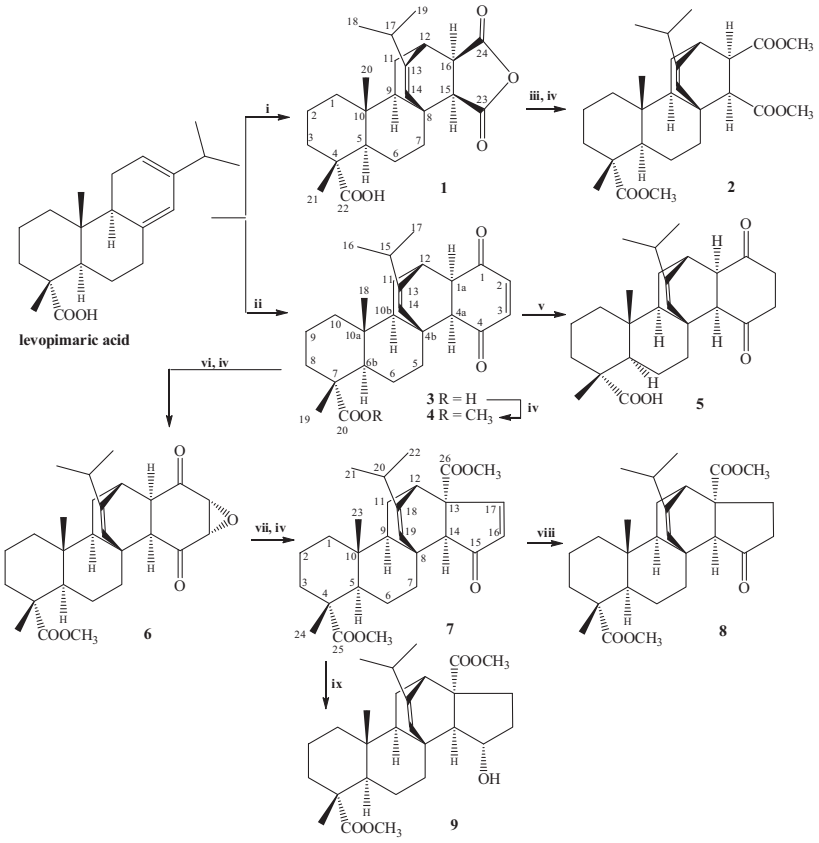
The present work is an extension of our ongoing efforts toward developing promising biologically active agents among the levopimaric acid diene adducts derivatives.[20–24,26,28–30] We have realized the chemical transformations of levopimaric acid diene adducts with maleic anhydride and *p*-benzoquinone, 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, $CHCl_3$–CH_3CN (1:4), 7 days, rt (iii) 15% KOH/MeOH, reflux, 2 h. (iv) CH_2N_2/Et_2O, EtOH, 0 °C (v) Zn/AcOH, 100 °C (vi) 35% H_2O_2, 6 M NaOH/MeOH, Et_2O, 0 °C (vii) 10% NaOH, EtOH, rt (viii) H_2, 20% Ni/Raney, MeOH (ix) $NaBH_4$, MeOH, reflux.