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Synthesis and anticancer activity of quinopimaric and maleopimaric acids' derivatives

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ABSTRACT

A series of quinopimaric and maleopimaric acids' derivatives modified in the E-ring, at the carbonyl- and carboxyl-groups were synthesized and their in vitro cytotoxic activity was evaluated at the National Cancer Institute, USA. Methyl esters of dihydroquinopimaric, 1a,4a-dehydroquinopimaric, 2,3-epoxyquinopimaric, 1-ethylenketal-dihydroquinopimaric, 1-ethylenketal-4-hydroxyiminodihydroquinopimaric acids displayed an activity on renal cancer, leukemia, colon cancer and breast cancer cell lines in concentration 10^{-5} M. Methyl 1,4-dihydroxyiminodihydroquinopimarate showed both a potent and broad spectrum of cytotoxic activity against NSC lung cancer, colon cancer, breast cancer, renal cancer and leukemia and revealed in vivo antineoplastic activity towards mouse solid transplantable mammary carcinoma Ca755 and colon adenocarcinoma AKATOL. The information about antineoplastic activity of the studied quinopimaric and maleopimaric acids' derivatives will be used for hit to lead optimization in these chemical series.

1. Introduction

Abietane diterpenoids, especially abietic acid, are interesting metabolites due to the wide range of valuable biological activity exhibited by some of them. Abietic, dehydroabietic and levopimaric acids possess different types of pharmacological activities such as hypocholesteromic,[1] antigastric ulcer,[2] blood glucose lowering effect,[3] and macrocyte clumping activity.[4] Many intensive studies were focused on the antibacterial activity of abietic and levopimaric acids, especially on the interaction of abietic acid with zinc oxide, rosin and other resin acids and their combination.[5] In vivo experiments have shown that diene adducts of levopimaric acid and its derivatives possess an anti-inflammatory,[6] antiulcer,[7] and antiviral activities.[8] Abietic and levopimaric acids are the major components of rosin (colophony) and can be extracted from *Pinus* rosin or commercial disproportionate rosin.

Abietic acid and derivatives thereof are capable to inhibit the growth of cancer cells, to treat nude mice with human MCF-7 breast cancer, to modulate the permeability of a cell plasma membrane, or improve the therapeutic effect of an anti-cancer agent.[9] Natural derivatives of abietic acid exhibited the anti-tumor promoting activity in two-stage mouse skin carcinogenesis test.[10] The cytotoxic activity of abietic acid towards HeLa cervical cancer and HepG2 hepatocellular carcinoma cells was described in the patent.[11] *seco*-Abietane diterpenoids from *Salvia prionitis* exhibited cytotoxic activities against HL-60 human leukemia and the SGC-7901 and MKN-28 stomach cancer cell lines with IC_{50} values of 4.6, 0.2, and 0.3 μM, respectively.[12] Abietane-type compounds having both ester group and *o*-quinone fragment in the C-ring were shown to be the most active against P388 murine leukemia cells (IC_{50} values of 0.27 and 0.22 μM).[13] The results of the study of the abietane diterpenoid ferruginol effects molecular mechanisms on the human prostate cancer cells PC3 indicate that it may act as a potential agent to prevent and treat prostate cancer.[14] Abietic acid is able to inhibit the transmembrane efflux of substances from the cells mediated by protein-transporters P-gp[15] and MRP-2,[16] which may cause the multidrug resistance of cancer cells to anticancer agents. Therefore, abietane diterpenoids are considered to be able to reduce the resistance of tumor cells to chemotherapy.

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The diterpenoids ability to induce apoptosis in different tumor cells is shown.[17,18]

As a part of our program to investigate the plant terpenoids pharmacological potency,[6–8,19–23] especially to find cytotoxic agents among the levopimaric acid derivatives, we have realized the chemical transformations of levopimaric acid diene adducts with *p*-benzoquinone and maleic anhydride, resulting in more than twenty derivatives of quinopimaric and maleopimaric acids' with different double bonds, types of the E-ring and modification of the carbonyl-groups.

2. Results and discussion

2.1. Chemistry

The starting materials: quinopimaric **2a**,[24] maleopimaric **3**[25] and dihydroquinopimaric acids **4a**,[26] methyl dihydroquinopimarate **4b**,[26] methyl 1a,4a-dehydroquinopimarate **5**[27] and methyl 2,3-epoxyquinopimarate **6**[26] as well as dimethyl cyclopentenonepimarate **7**[26] were obtained using pine resin *Pinus sylvestris* as starting material by procedures described before (Scheme 1).

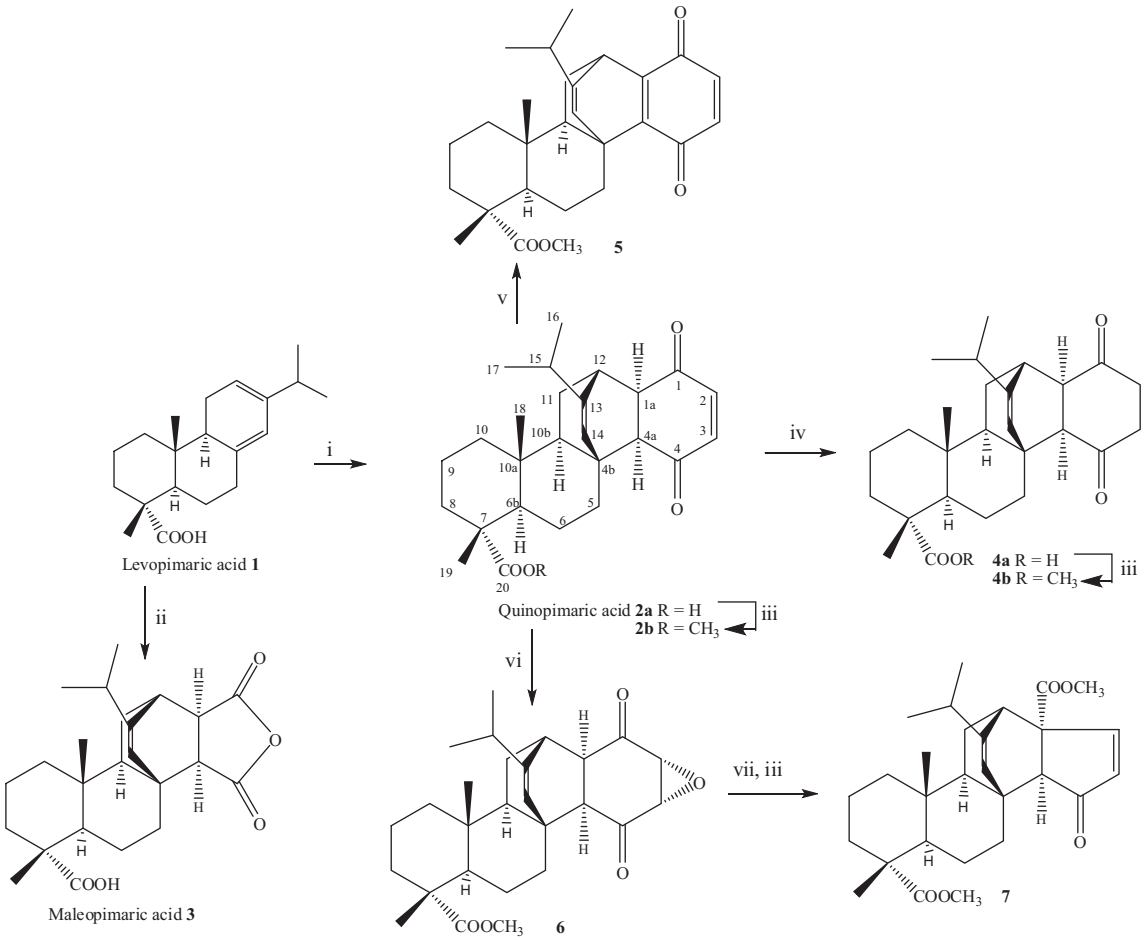
Functionalization of the carboxylic group of maleopimaric and dihydroquinopimaric acids was performed by chloride method to yield amides **8**–**10**[10,28] as well as *N*-methylpiperazinylamide **11**. The introduction of hemisuccinyl fragment into the structure of **10** in two steps yielded amide **12**[28] with better water solubility. Reduction of compound **9** resulted in 1β-hydroxy derivative **13**[28] (Scheme 2).

To get oximes and their subsequent transformations we used the reaction of ketones **4b**[26] **17**,[22] **21**,[29] **24**[30] with hydroxylamine hydrochloride. Bisoxime **14** was synthesized as a mixture of four isomers separated by column chromatography followed by crystallization of the individual *E*-oxime from CH_2Cl_2. Oximes **15**,[6] **18**[31] and **22**[32] were obtained as *E*/*Z* mixtures in ratios 3:1, 4:1 and 1:1, respectively, (Scheme 3). Individual *E*-oximes **15**, **18**, **22** from crude mixtures were crystallized from MeOH.

To obtain seven-membered caprolactams we used the Beckmann rearrangement. The interaction of the *E*-oximes **15**, **22**, **25** with PCl_5 in ether led to 5′-caprolactams **16**,[6] **23**,[33] and **26**. The rearrangement of oxime **18** in similar conditions led to 5′-caprolactam **19** and non-expected derivative **20** with yields of 62% and 24%, respectively. We propose that the formation of **20** could be explained by the 1,2-sigmatropic hydride shift of the double bond at C13(14) to C13(15) with the subsequent removal of ethyleneketal protective group.

The synthesis of some annellated with the E-ring heterocycles is presented at the Scheme 4. Indoles **27**, **29**, substituted pyrazoles **30**, **31** and mercaptopyrimidine **33** were synthesized previously[34] and indole **28** was obtained for the first time by the interaction of the ketone **17** with phenylhydrazine in Fischer's reaction.

Thus, we have performed various chemical modifications of the quinopimaric acid comprising of double bond reduction at C2 and C3, double bond introduction into C1a–C4a as well as C2–C3 double bond epoxidation with the subsequent contraction of cycle E to pentacyclic. The functionalization of carboxyl-groups of levopimaric acid diene adducts (quinopimaric and maleopimaric acids)



Scheme 1. Reagents and conditions: (i) 1,4-benzoquinone, $CHCl_3$–CH_3CN (1:4), 7 days, rt (ii) maleic anhydride, 200 °C (iii) CH_2N_2/Et_2O, EtOH, 0 °C (iv) Zn/AcOH, 100 °C (v) $((NH_4)_2Ce(NO_3)_6)$, CH_3CN, rt (vi) 35% H_2O_2, 6 M NaOH/MeOH, Et_2O, 0 °C (vii) 10% NaOH, EtOH, rt.