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Characterization and comparison of perezone with some analogues. Experimental and theoretical study

Rene Gerardo Escobedo-González [a], Luis Bahena [c], José Luis Arias Tellez [a], Jaime Hinojosa Torres [b], Rene Miranda Ruvalcaba [a], Juan Manuel Aceves-Hernández [a,*]

[a] Departamento de Ciencias Químicas, Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de México, Av. 1 de Mayo s/n, Cuautitlán Izcalli, Mexico
[b] Centro de Asimilación Tecnológica, Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de México, Av. Jorge Jiménez Cantú s/n, Cuautitlán Izcalli CP 54729, Mexico
[c] Departamento de Ciencias Químicas, Universidad de Guanajuato, Noria Alta s/n, CP 36010 Guanajuato, Gto, Mexico

HIGHLIGHTS

- Perezone presents inhibitory properties against leukemia cell line K-562.
- Perezone is more potent inhibitor than its analogue isoperezone.
- Molecular docking results corroborates cancer inhibitory results.
- Theoretical calculations and experimental results are in good agreement.
- Perezone and analogues present properties ascribed to cancer inhibitors.

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ABSTRACT

Perezone had been used for centuries in the traditional Mexican medicine, it is useful and a handful of illness. Perezone and other derivatives also present activity against certain lines of cancer, such as the myeloblastoid leukemia cell line K-562 and carcinoma cell lines (PC-3 and SKLU-1) with IC50 <10 μM. Perezone and isoperezone have shown the major cytotoxic potency. Characterization of perezone was carried out by UV–Visible, IR, DSC, TGA and powder X-ray diffraction, as well as docking studies using caspase-3 structures as receptors. Theoretical studies for optimizing the geometry of perezone were carried out and the results compared with values of single crystal X-ray diffraction. The experimental values of atomic distances, angles and dihedral angles are in good agreement with the theoretical values. Interaction of perezone with the cysteine catalytic site with the caspase-3 was found in the docking studies. A docking study of perezone, with horminone, thymoquinone and isoperezone as ligands and the protein apoptein, caspase-3 as receptor, was carried to demonstrate that the hindrance steric factor, chemical structure and the functional groups are important in the biological activity of these natural products. The docking score energetic values are in good agreement with the experimental cytotoxic results obtained from the experiments when perezone and analogues were studied in different types of cancer.

Introduction

Perezone, (2-(1,5-dimethyl-4-hexenyl)-3-hydroxymethyl-p-benzoquinone) a sesquiterpene quinone, molecular weight 248.3 Dalton, is a secondary metabolite from the genus Perezia and recently renamed 'Acourtia'. Perezone (**1**) was first reported in 1852 by Leopoldo Río de la Loza [1]. This natural product was isolated for the first time from the root of Perezia adnata. It has been studied in order to know the effect of its structure on its biological properties [2–5].

The structure of **1** was determined by using NMR spectroscopic methods [6–8] and its crystal structure was reported in 1986 [9]. Synthetic methods have been developed to obtain **1** in racemic form and related compounds [10–12]. In the Mexican traditional medicine the roots of perezia is used in laxative drinks, and for diuretic, regenerative and analgesic purposes. Perezone has interesting biological activities, such as the hypoglycemic effect, [13] inhibition of platelet aggregation [14], it increases the release of mitochondrial Ca^{2+} maintaining ATP production during reperfusion

* Corresponding author.

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[15], also it relaxes the basal tonus of the smooth muscle [16] and blocks the contractile response induced by Ach, K^+ and Ba^{2+} [17]. Perezone acts as an electron sink in electron transport in the mitochondria [18] and it is considered to be a cardio protective agent [19]. Anti-feedant effects and phytotoxic activity [20] have been studied as well as the cytotoxic effect against several cancer cell lines [20]. In the present work we studied the properties of perezone in the caspase mechanism of some cancer cell lines, since some research the cytotoxic effect of ten derivative compounds including perezone and isoperezone, [NSC697124] was determined on the K-562 leukemia cell line and other cancer cell lines. Perezone and isoperezone have shown the major cytotoxic potency.

It was shown that perezone has greater cytotoxic effect than isoperezone [21]. Besides, perezone was part of the screening of compounds that induce apoptosis of cancer cell lines [22] and for the screening of agents against neuroblastoma [23].

Isolation of perezone and its isomerization to isoperezone

Perezone was isolated from dry roots of *Acourtia cuernavacana* spp. and extracted three times by using maceration with hexane at room temperature. As a result orange crystals were obtained. The yield was 2%, after purification 1% was achieved by recrystallization with acetone–hexane (1% yield). The non-natural derivative isoperezone **2** was prepared according to the protocol previously described with specific modifications [29].

Synthesis of other derivatives was described previously [1]. However, to our knowledge it is the first time that an explanation of mode of action of perezone in the catalytic site of a caspase 3 is given.

Cytotoxic activity in human tumor cell lines

The new derivatives of perezone reported in the literature [24] are a set of molecules with potential cytotoxic activities. After the cytotoxic test it is found that those compounds were less cytotoxic than Adriamycin, all of them exhibited high cytotoxicity predominantly on leukemia cell line K-562. Perezone and its isomer isoperezone can be considered as high cytotoxic agents for the myeloblastoid leukemia cell line K-562 and for carcinoma cell lines (PC-3 and SKLU-1) with IC50 <10 μM.

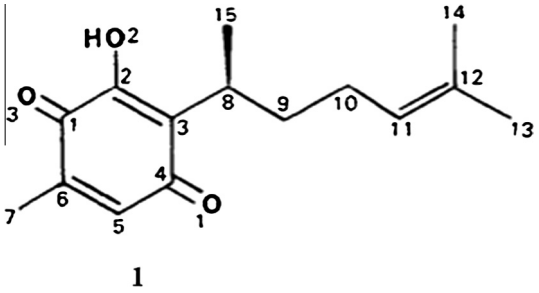

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Fig. 1. Chemical structure of perezone.

There are other studies of perezone in the death induction on the K-562 human leukemia cell line [25]. In order to understand the action mechanism in the present report, a docking study of perezone as ligand and caspase 3, PDB code 1PAU as receptor, was carried out. The main objective is to explore the possibility to show that there is a specific site in this protein that interacts with the active compound perezone and some analogues.

Materials and methods

X-ray diffraction

Perezone was extracted and purified as reported previously from the root of Perezia adnata. A diffractometer made by SIEMENS model D-5000 Kristalloflex with a scanning rate of 1°/min and 2 h ranging from 3° to 70° was used at room temperature (25 °C). Cu Kα radiation with nickel filter and the powder method was employed to obtain the X-ray pattern. Experimental values from the X-ray diffraction analysis were compared with the corresponding calculated values using theoretical methods.

Differential scanning calorimetry and thermogravimetric analysis

A TA-Instruments-DSC-2060-Differential-Scanning-Calorimeter was employed with Indium (In) as reference for calibration. The

Table 1
Experimental[a] X-ray diffraction values of bond lengths in Å, angles (e.s.d.), and dihedral angles (e.s.d.); in **bold**, the calculated equilibrium values using B3LYP, 6-31G(d,p), 6-311G, and 6-311G(d,p) basis sets.

Bond lengths Å from X-ray pattern (e.s.d.) and **theoretical values**			
O(1)—C(4) 1.226 (7) **1.226**	O(2)—C(2) 1.347 (7) **1.386**	O(3)—C(1) 1.220 (8) **1.228**	C(1)—C(2) 1.498 (8) **1.490**
C(1)—C(6) 1.472 (9) **1.478**	C(2)—C(3) 1.334 (8) **1.344**	C(3)—C(4) 1.469 (9) **1.492**	C(3)—C(8) 1.499 (7) **1.525**
C(4)—C(5) 1.469 (9) **1.477**	C(5)—C(6) 1.332 **1.337**	C(6)—C(7) 1.507 (8) **1.495**	C(8)—C(9) 1.535 (7) **1.544**
C(8)—C(15) 1.523 (8) **1.535**	C(9)—C(10) 1.509 (8) **1.532**	C(10)—C(11) 1.512 (9) **1.505**	C(11)—C(12) 1.312 (8) **1.347**
C(12)—C(13) 1.478 (10) **1.506**	C(12)—C(14) 1.495 (11) **1.504**		
Angles (°) experimental (e.s.d.) and **theoretical values**			
O(3)—C(1)—C(2) 119.3 (5) **119.2**	O(3)—C(1)—C(6) 122.0 (5) **122.67**	C(2)—C(1)—C(6) 118.6 (5) **118.5**	
O(2)—C(2)—C(1) 115.0 (1) **114.8**	O(2)—C(2)—C(3) 121.4 (5) **121.2**	C(1)—C(2)—C(3) 123.6 (5) **123.4**	
C(2)—C(3)—C(4) 116.6 (5) **116.3**	C(2)—C(3)—C(8) 124.5 (5) **124.7**	C(4)—C(3)—C(8) 118.9 (5) **118.7**	
O(1)—C(4)—C(3) 120.4 (5) **120.2**	O(1)—C(4)—C(5) 119.3 (6) **119.2**	C(3)—C(4)—C(5) 120.3 (6) **120.5**	
C(4)—C(5)—C(6) 123.4 (6) **123.2**	C(1)—C(6)—C(5) 117.5 (5) **117.3**	C(1)—C(6)—C(7) 117.5 (6) **117.6**	
C(5)—C(6)—C(7) 124.8 (6) **124.6**	C(3)—C(8)—C(9) 112.5 (5) **112.2**	C(3)—C(8)—C(15) 110.9 (4) **111.2**	
C(9)—C(8)—C(15) 111.9 (5) **111.7**	C(8)—C(9)—C(10) 114.3 (5) **114.6**	C(9)—C(10)—C(11) 113.6 (6) **113.8**	
C(10)—C(11)—C(12) 127.2 (6) **126.9**	C(11)—C(12)—C(13) 122.7 (6) **122.5**	C(11)—C(12)—C14) 122.6 (6) **122.3**	
C(13)—C(12)—C(14) 114.7 (5) **114.3**			
Dihedral angles (°) experimental (e.s.d.) and **theoretical values**			
C(2)—C(3)—C(8)—C(15) 63.8 (7) **71.30**	C(4)—C(3)—C(8)—C(15)—114.7 (6) **−113.8**	O(3)—C(1)—C(6)—C(7) 0.3 (8) **0.43**	
C(3)—C(8)—C(9)—C(10) −116.4 (5) **−115.80**	O(2)—C(2)—C(3)—C(8) 1.0 (8) **0.94**	C(8)—C(9)—C(10)—C(11) −179.9 (6) **174.66**	
C(8)—C(3)—C(4)—O(1) 0.3 (8) **1.08**	C(10)—C(11)—C(12)—C(14) −2.5 (12) **2.33**	C(10)—C(11)—C(12)—C(13) 176.0 (7) **178.39**	
O(3)—C(1)—C(2)—O(2) −0.1 (7) **−0.48**			

[a] Experimental values from Ref. [9], CCDC code DIPVON SUP 42582.SUP.