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ORIGINAL PAPER

A theoretical investigation of cytotoxic activity of celastroid triterpenoids

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Abstract Quantum chemical calculations at the B3LYP/6-31G* level of theory have been carried out on 20 celastroid triterpenoids to obtain a set of molecular electronic properties and to correlate these with cytotoxic activities. The cytotoxic activities of these compounds can be roughly correlated with electronic effects related to nucleophilic addition to C(6) of the compounds: The energies of the frontier molecular orbitals (E_{HOMO} and E_{LUMO}), the HOMO-LUMO energy gap, the dipole moment, the charge on C(6), and the electrophilicity on C(6).

Keywords Cytotoxicity · Density functional theory · Quinone-methide triterpenoids

Introduction

Celastroids are a small group of oxygenated and unsaturated 14-nor-D:A-*friedo*-oleanane triterpenoids (see Fig. 1), restricted to the Celastraceae and Hippocrateaceae plant families [1]. These compounds, as a class, have shown notable antimicrobial and antineoplastic activities [1–3]. This work presents an analysis of the electronic properties that correlate with cytotoxic activity of celastroid triterpenoids (see Fig. 2).

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Computational studies

All quantum chemical calculations have been carried out using the Spartan'06 program package [4]. The ground-state geometries and electronic properties of the triterpenoids were determined at the B3LYP/6-31G* level of computation.

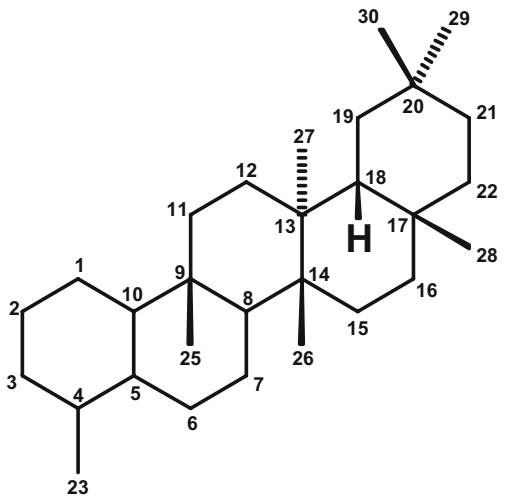


Fig. 1 Basic structure of celastroid triterpenoids

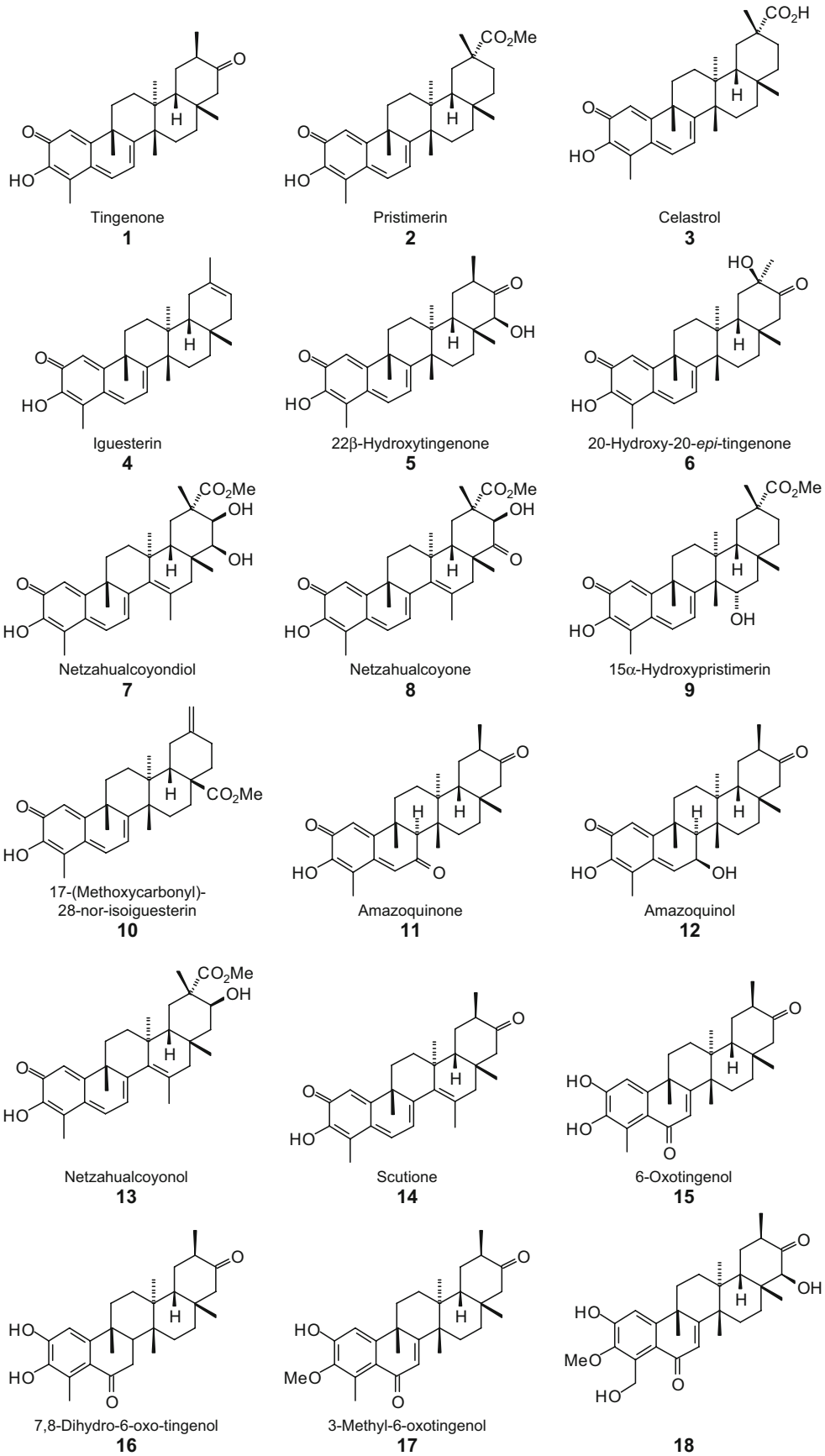
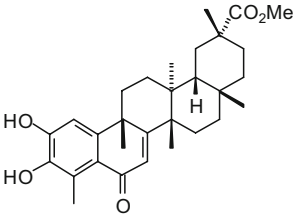
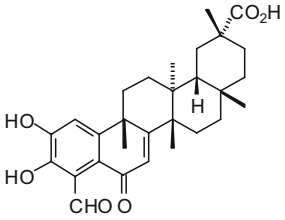


Fig. 2 Cytotoxic celastroid triterpenoids discussed in this work



6-Oxopristimerol
19



Demethylzeylasteral
20

Fig. 2 (continued)

Calculated octanol-water partition coefficients (C log *P*) were determined using ACD/ChemSketch, version 11.01 [5]. Numerical cluster analysis was carried out using NTSYSpc software, version 2.2 [6]. The 20 triterpenoids were treated as operational units and correlation of selected electronic properties was used to determine similarity. The unweighted pair-group method with arithmetic average (UPGMA) was used for cluster definition.

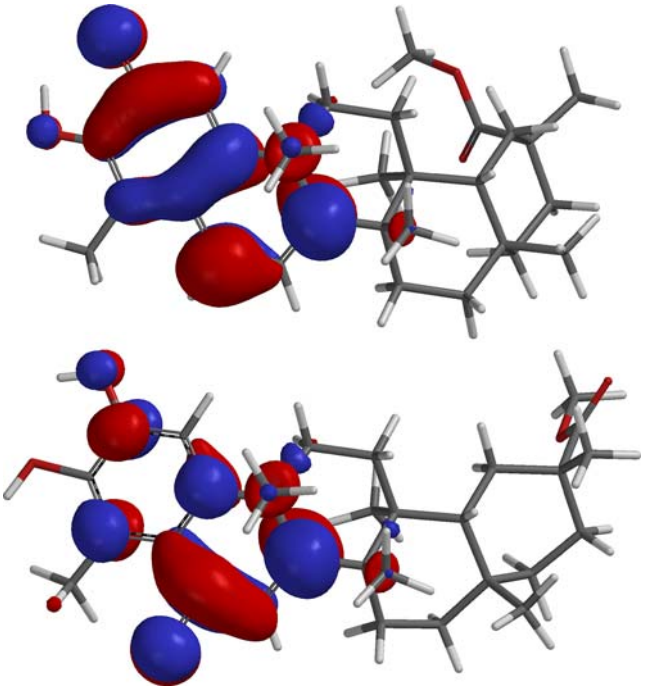


Fig. 3 Lowest unoccupied molecular orbitals (LUMOs) for pristimerin (above) and 6-oxopristimerol (below)

Results and discussion

Selected electronic properties for the celastroid triterpenoids are summarized in Table 1 along with the average values for cytotoxic activities [2]. Quinone-methide triterpenoids have been shown to undergo nucleophilic attack at C(6) [7, 8], and this likely accounts for the biological activity of this class of cytotoxic agents. Pristimerin (**2**), for example, targets the proteasome of prostate tumor cells where it undergoes nucleophilic attack at C(6) by the hydroxyl

Table 1 Cytotoxic activities and selected molecular electronic properties of celastroid triterpenoids

Compound Number	IC_{50} (μM)[a]	$E_{(HOMO)}$ (eV)	$E_{(LUMO)}$ (eV)	Δ *E* (LUMO-HOMO)	$q_{C(6)}$[b]	$2\Sigma c^2_{LUMO}$ C(6)	dipole (*D*)	Vol (Å^3)	C log *P*
1	1.03	−5.46	−2.54	2.92	−0.23	0.37	4.46	450.23	6.02
2	0.74	−5.34	−2.41	2.93	−0.23	0.38	5.60	494.59	7.54
3	2.72	−5.34	−2.42	2.93	−0.23	0.38	6.04	474.28	7.08
4	1.50	−5.33	−2.41	2.92	−0.23	0.38	5.95	443.29	8.23
5	0.27	−5.45	−2.53	2.92	−0.23	0.37	3.79	456.98	4.65
6	2.80	−5.48	−2.56	2.92	−0.23	0.37	4.91	457.07	4.70
7	2.00	−5.28	−2.45	2.83	−0.24	0.37	6.76	487.30	4.81
8	0.20	−5.26	−2.51	2.76	−0.24	0.35	4.93	482.41	4.36
9	1.55	−5.40	−2.48	2.92	−0.23	0.37	4.32	501.77	5.58
10	5.31	−5.36	−2.44	2.92	−0.23	0.38	5.32	491.02	5.06
11	10.05	−6.36	−3.24	3.12	−0.28	0.31	2.42	456.82	4.36
12	11.4	−5.98	−2.54	3.44	−0.26	0.45	3.90	461.63	4.71
13	1.59	−5.23	−2.47	2.75	−0.24	0.35	6.20	480.16	5.65
14	14.10	−5.41	−2.56	2.85	−0.24	0.37	3.53	447.81	5.81
15	29.60	−5.88	−1.48	4.40	0.37	0.33	3.19	457.08	5.83
16	17.10	−5.95	−1.24	4.71	0.38	0.39	3.42	460.93	7.12
17	24.40	−6.08	−1.47	4.61	0.38	0.32	3.98	477.63	6.05
18	8.90	−6.20	−1.79	4.41	0.38	0.36	5.19	490.90	3.04
19	4.90	−5.82	−1.40	4.42	0.37	0.33	0.99	502.18	7.35
20	20.80	−6.07	−2.22	3.85	0.39	0.15	5.94	483.31	6.90

[a] Average cytotoxicities [2].
[b] Mulliken charges on C(6).

Table 2 Correlation matrix of cytotoxicity and molecular descriptors for celastroid triterpenoids

	log IC_{50}	$E_{(HOMO)}$	$E_{(LUMO)}$	ΔE	$q_{C(6)}$	$2\Sigma c^2_{LUMO}$ C(6)	dipole (D)	Vol (Å^3)	C log P
log IC_{50}	1.000	−0.722	0.455	0.687	0.624	−0.294	−0.319	−0.111	0.063
$E_{(HOMO)}$	−0.722	1.000	−0.343	−0.748	−0.650	0.364	0.507	0.053	0.194
$E_{(LUMO)}$	0.455	−0.343	1.000	0.880	0.878	−0.087	−0.307	0.220	0.304
ΔE	0.687	−0.748	0.880	1.000	0.949	−0.246	−0.473	0.128	0.117
$q_{C(6)}$	0.624	−0.650	0.878	0.949	1.000	−0.468	−0.331	0.218	0.170
$2\Sigma c^2_{LUMO}$ C(6)	−0.294	0.364	−0.087	−0.246	−0.468	1.000	−0.035	−0.177	−0.148
dipole (D)	−0.319	0.507	−0.307	−0.473	−0.331	−0.035	1.000	0.134	0.010
Vol (Å^3)	−0.111	0.053	0.220	0.128	0.218	−0.177	0.134	1.000	−0.050
C log P	0.063	0.194	0.304	0.117	0.170	−0.148	0.010	−0.050	1.000

group of the *N*-terminal threonine of proteasomal chymotrypsin [9]. The LUMOs of celastroid triterpenoids (e.g., Fig. 3) are consistent with the observed reactivity; there is a large coefficient at C(6). The electronic properties that showed correlation with cytotoxic activity (log IC_{50}) (see Table 2) were the energy levels of the frontier molecular orbitals, E_{HOMO} (negatively correlated) and E_{LUMO} (positively correlated), the HOMO-LUMO energy gap (positively correlated), the dipole moment (positively correlated, the Mulliken charge on C(6) (positively correlated), the electrophilicity of C(6) [calculated as 2× the sum of the squares of the coefficients of the LUMO on C(6)] (weakly negatively correlated), and the dipole moment (weakly negatively correlated), and these were used to correlate electronic properties of the triterpenoids with cytotoxic activity. Interestingly, neither molecular volume (as a measure of steric effects) nor C log P (as a measure of hydrophobicity) showed any correlation with cytotoxic activity ($R^2 \leq 0.01$). The cluster analysis, based on the electronic properties above, is shown in Fig. 4. With the exception of two anomalous compounds (scutione, **14**, and 6-oxopristimerol, **19**), there are two clusters, one cluster that can be defined as very active ($IC_{50} \leq 5$ μM) and a less-active cluster ($IC_{50} \geq 9$ μM). There is another cluster (compounds **15–20**) that makes up an aromatic A-ring/6-keto cluster; electronically distinct from the quinone-methide (compounds **1–14**) cluster. The anomalously high activity of 6-oxopristimerol (**19**) may suggest a mechanism of activity that does not correlate with the electronic properties above. That is, the activity of **19** may not be due to nucleophilic attack at C(6). It is not clear why scutione (**14**) is not so active. It may be that that compound just needs to be screened against additional tumor cell lines.

Summary

Celastroid triterpenoids are generally cytotoxic compounds and the cytotoxic activities can be roughly correlated with electronic effects related to nucleophilic addition to C(6) of the compounds: The energies of the frontier molecular orbitals (E_{HOMO} and E_{LUMO}), the HOMO-LUMO energy gap, the dipole moment, the charge on C(6), and the electrophilicity on C(6).

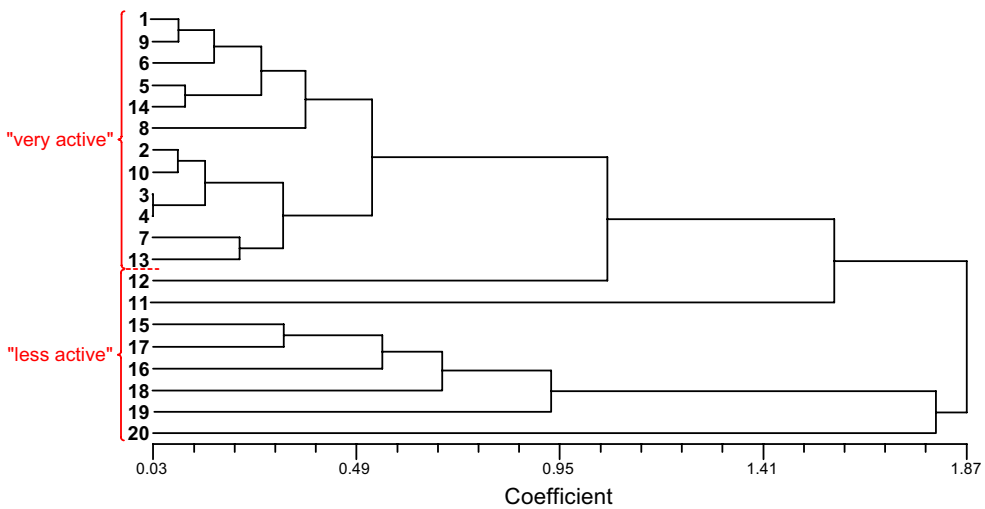


Fig. 4 Dendrogram obtained by cluster analysis of electronic properties of the celastroid based on correlation and using the unweighted pair-group method with arithmetic average (UPGMA)

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