A PRELIMINARY INVESTIGATION OF THE ELECTRONIC STRUCTURE OF ANTITUMOR DRUG ELLIPTICINE AND THEIR DERIVATIVES

por

S.O. Dantas , F.C. Lavarda[+], D.A. dos Santos, D.S. Galvão and B. Laks

ABSTRACT – Ellipticine and their derivatives are a class of molecules that shows antitumor and cytotoxic activity, with multimodal mechanism of action. In this work we report a preliminary study of the electronic structure of Ellipticine and some molecules derived from it. We have shown that a relationship between charge density distribution and the biological selectivity exists in these molecules. A mechanism to improve the antitumor activity is proposed.

INTRODUCTION

Ellipticine is a molecule derived from the natural extract 'ochrosia elliptica' (Courseille et al., 1974). Ellipticine and their derivatives are highly cytotoxic on malignant cell (Sizum et al., 1988) and have been used in the treatment of human cancer (Auclair, 1987). Ellipticines are specially interesting for chemical purposes due to their limited toxic side effects and their complete lack of hematological toxicity (Sizum et al., 1988).

Most cytotoxic anticancer agents interact directly or indirectly with nuclear DNA, the ultimate target for this class of compounds. The ellipticines series present multimodal mechanism of action: they may bind to DNA through intercalation, covalent bonding, generation of oxidizing species and interference with the catalytic activity of topoisomerase II (Sizum et al., 1988; Auclair, 1987). It is not clear the relative contribution of each of these mechanisms. The major challenge in molecular pharmacology is to determine the degree to which each individual event contributes to the cytotoxic activity of drugs (Sizum et al., 1988; Auclair, 1987).

In this work we report a preliminary study on the electronic structure of ellipticine and some derived molecules. We also discuss the relationship between electronic and biological activity.

Instituto de Física, UNICAMP, CP 6165, Campinas, SP, Brasil

[+]-Permanent Address: Depto. Física, UNESP, Bauru, SP, Brasil

In next section we present a brief summary of the techniques used; our results are presented and discussed in section 3.

METHOD

Due to the lack of geometrical data for all the molecules of ellipticine series, we have used the Austin Method One (Dewar et al., 1985) (AM1) to perform geometrical optimization. The AM1 is a very sophisticated semiempirical method that has been developed in an attempt to correct some of the weaknesses present in the Modified Neglect of Differential Overlap (Higgins et al., 1988) (MNDO), which was largely used in the polymer optimization in the last years. In AM1, for instance, the tendency of MNDO to overestimate the repulsion between atoms has been corrected by a suitable modification of the core repulsion functions. We have use the charge population obtained from the AM1 calculations to generate the equipotential curves for charge density.

RESULTS AND DISCUSSIONS

In Table I we show the ellipticine and their derivatives considered in this work. In Table II we present a brief summary from the AM1 calculations which displays the values for: Heat formation (Kcal), Ionization potential (ev)(this gives an idea of the required energy to ionize the molecule), Dipole momentum (Debyes), the difference LUMO (Lowest Occupied Molecular Orbital)- HOMO (Highest Occupied Molecular Orbital). The value for Apparent Affinity (K_{app}) for DNA (Sizum et al., 1988) is also indicated in this table. K_{app} values higher than $10^5 M^{-1}$, indicating a high affinity to DNA, is a necessary but not sufficient condition for antitumor activity or citotoxic action on L1210 Leukemia cells (Sizum et al., 1988; Auclair, 1987).

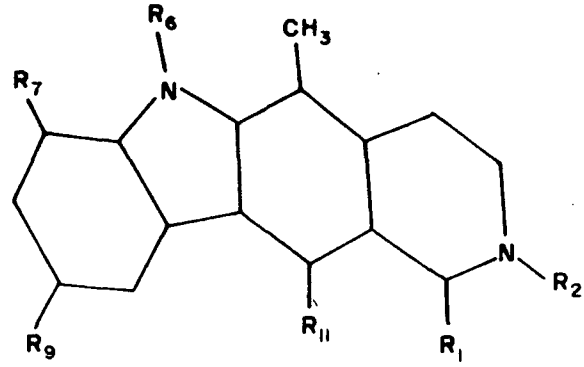
The analysis of data from AM1 calculations has shown the existence of two very similar electronic behaviors (related to the existence of molecules with an odd and even number of electrons). This means that, with regard to optical response, the molecules are practically indistinguishable and thus their selective action in terms of antitumor or citotoxic activity can not be explained only in terms of the electronic density of states.

It is a well known (Courseille et al., 1974) that the selective interaction of ellipticines with DNA are strongly dependent on the electrostatic fields generated in the process. Based on that we have performed a careful calculation of the equipotential charge density for these molecules.

Our results have shown (see fig. 1 and 2) that a high K_{app} (and consequently a better efficient antitumor activity) is directly related to a conjugated high charge density on the sites N_2

and C_7. For the first time a correlation involving theoretically electronic indices and the biological

Table I
Structures of the main ellipticines derivatives



	R_1	R_2	R_6	R_7	R_8	R_9	Abbrev.
Ellipticine	H	-	H	H	H	H	E
9-Aminoellipticine	H	-	H	H	H	NH_2	9-NH_2-E
9-Hydroxyellipticine	H	-	H	H	H	OH	9-OH-E
8-Hydroxyellipticine	H	-	H	H	OH	H	8-OH-E
Ellipticinium	H	CH_3	H	H	H	H	NME
2N-Methyl-9-Hydroxy-ellipticinium	H	CH_3	H	H	H	OH	NMHE

Table II
Summary AM1 calculations

	E	9-NH_2-E	9-OH-E	8-OH-E	NME	NMHE
Heat of form.	92.54	92.47	49.39	48.11	109.05	65.55
Ionizat. Pot.	8.06	7.77	7.97	8.09	6.06	6.10
Dipole	3.44	3.90	2.40	2.54	3.72	4.99
(LUMO-HOMO)	7.31	7.04	7.14	7.33	3.10	3.05
$K_{app}(10^6M^{-1})$	0.15	---	2.00	---	0.40	1.10

selectivity is reported for these compounds. Although our results are preliminary and restrict to a few molecules of the series of ellipticines, they suggest that it is possible to improve on the antitumor and cytotoxic efficiency of ellipticines by structural modifications, which should increase the charge density at the sites N_2 and C_7. Further studies in these directions are under investigation.

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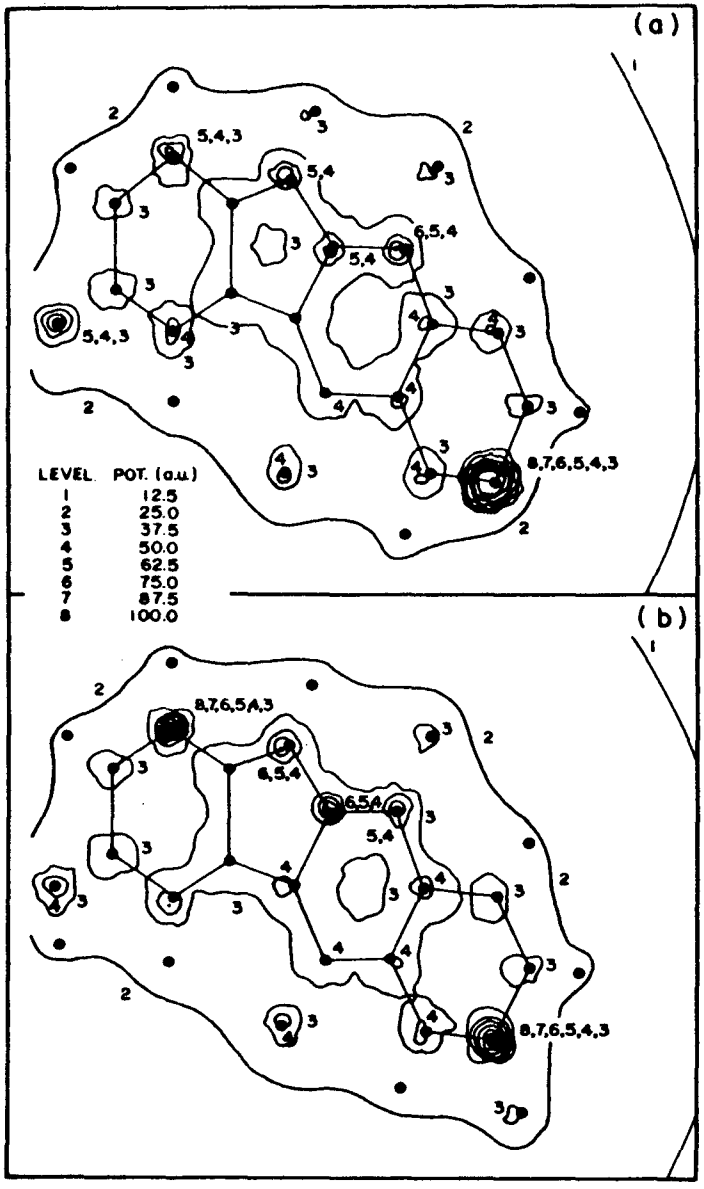

Fig. 1 - Equipotentials for (a) 9-Hydroxyellipticine
(b) 2N-Methyl-9-Hydroxyellipticinium

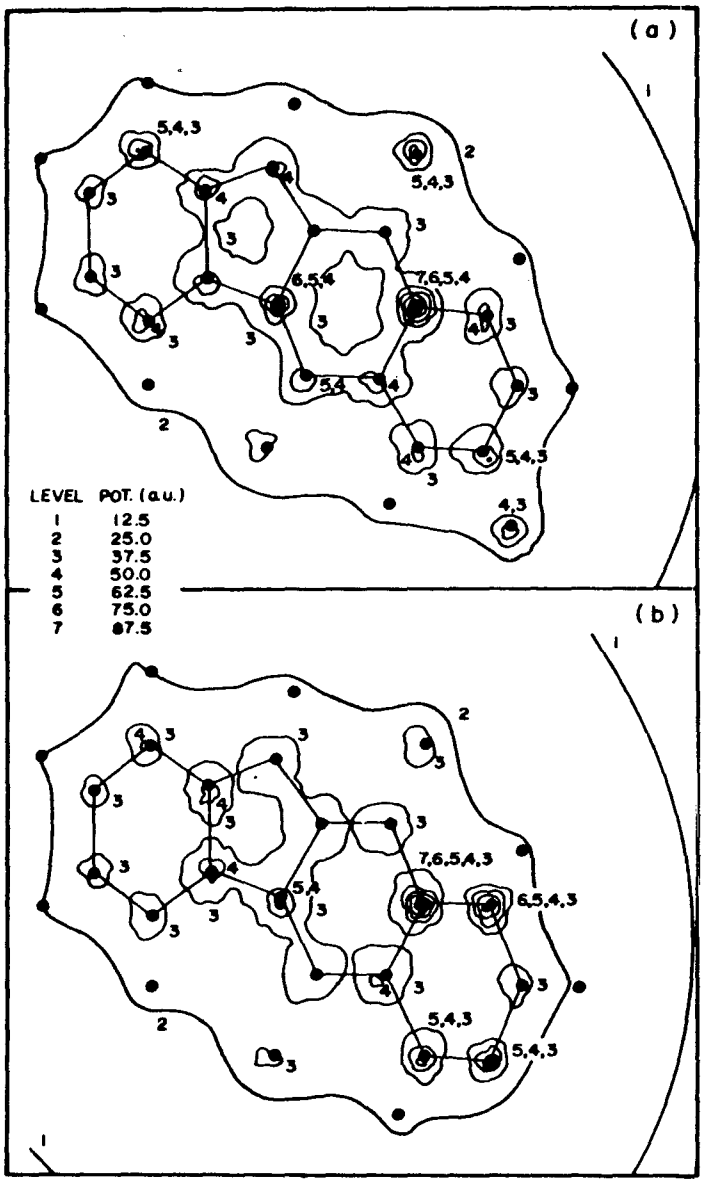

Fig. 2 - Equipotentials for (a) Ellipticinium
(b) Ellipticine