Immuno-biological activity of izatizon and its connection with structurally conformational properties of the metisazone molecule

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Unification of achievements in biological, chemical and physical spheres of science promotes the progress of chemotherapeutical researches, directed to improve the existing and to develop new effective preparations with antiviral action. The arsenal of these preparations increases from year to year. At the same time, quick growth of infectious diseases that have already considered as the deleted ones is observed on all continents of our planet. Also appear new ones, among which viral diseases occupy the main place. Elaboration of structural-directed preparations has become an integral part of modern search of medications and molecular identification researches among three-dimensional structural targets.

Character of viruses as a class of obligate intracellular and even genetic parasites determined main difficulties in creation of effective chemotherapeutical preparations for the treatment and prevention of viral infections. Main target for viral infections chemotherapy is to create effective antiviral preparations on the base of components that selectively and specifically inhibit viral reproduction and do not harm the vital activity of cell and the whole organism. Izatizon is one of such home complex preparations with antiviral, antibacterial and antitumoral activities and with immunomotropical qualities. It is a 2% solution of 1-metyl-izatin β-tiosemicarbazon in the universal solvent.

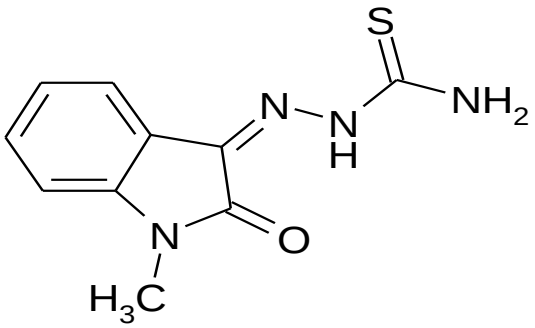


Image 1: It is a structural formula of metisazon molecule.

It is determined that izatizon increases the number of cells that express CD 69 antigen, induces T- and B-lymphocytes proliferation, stimulates pre-T-lymphocytes differentiation, enhances T-lymphocytes functional activity, including their capability to

product lymphokines. It also stimulates natural killers' activity, metabolic and phagocytic activity of macrophages and IL-1 synthesis, increases bactericidal action of blood serum. This means that it enhances nonspecific factors of the immune system.

Structural-conformational characteristics of izatizon were analyzed for better understanding of mechanisms of its action and particularly its active molecule - metisazone. Calculations of structural-dynamic molecule characteristics were performed by half-empirical quantum chemical methods AM1 and MNDO/H.

Qualitative stereo-chemical analysis of izatin, that is a base substance for receipt the metisazone molecule, which is a main part of izatizon shows us that it has five molecular prototropical tautomers (image 2). Prototropical tautomerism can be considered as a functionally important form of structural mutability that unconditionally used by nature for various functional needs. Among all prototropical izatin tautomers imine diketoform 1 is one of the most efficient, because it has big energetic abruption (>16 cal/mol) from the most efficien enol tautomers. It is logically to think that diketoform 1 must be observed in the polar medium because it has a considerable dipole moment (5,1D). We have to mention that izatin molecule is quite "labile" in relation to its nonplanar deformation.

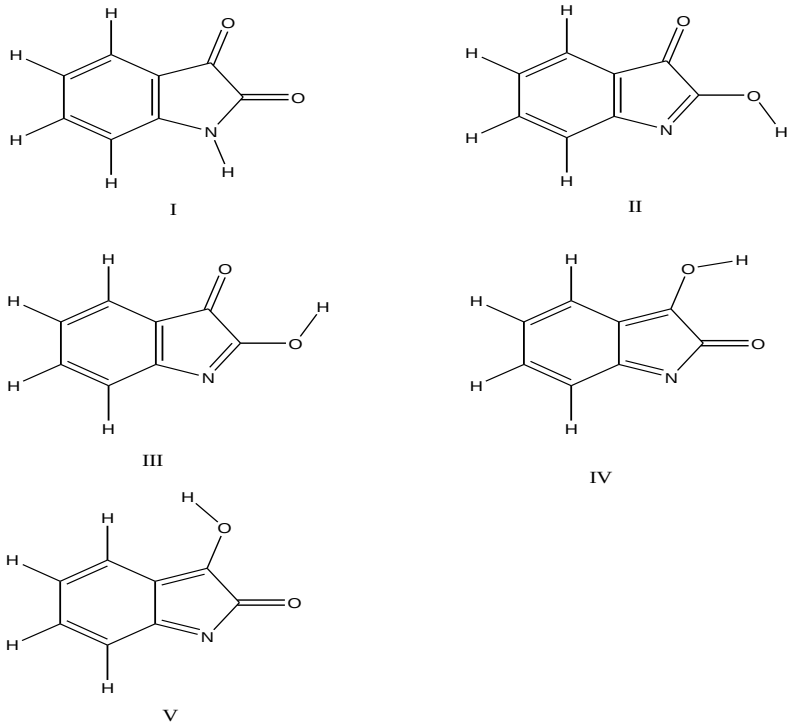


Image 2: It is the whole family of molecular-prototropical izatin tautomers.

Significances of izatin protonation and deprotonation energies were calculated (image 3). Capability to attach or detach proton is a very important physicochemical characteristic that has direct attitude to the functional activity.

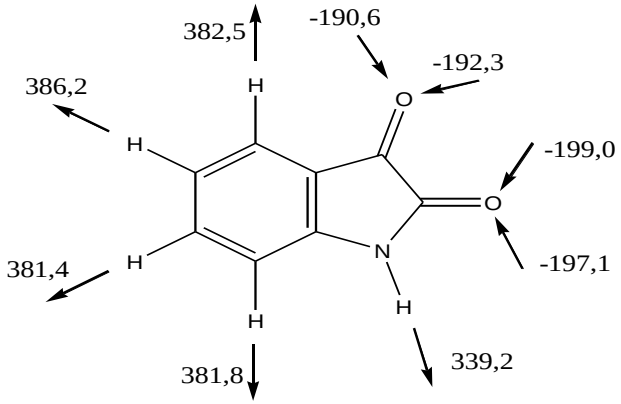
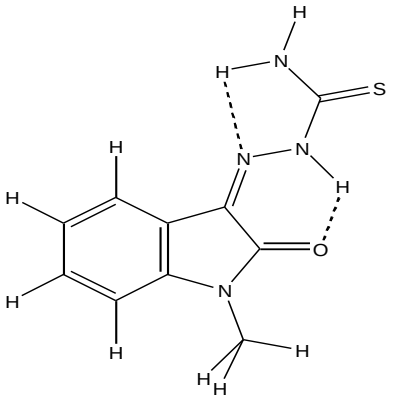


Image 3: It is protonodonors-protonoacceptorical qualities of the main izatin molecule tautomerical form according to the data of AM1 method. Places of protonation and deprotonation are pointed with arrows; appropriate protonation and deprotonation energies are given in cal/mol.

It is determined for the first time that hyper-surface of metisazon molecule potential energy has 8 minimums – one global and seven local. Four planar conformations (one of them is the principal) and two pairs of reflection symmetric conformations correspond them. The most polar among them is the principal 1 (6,8D) and the VIII conformation is the sloppiest energetically (image 4). We have determined the ways and energy of creation of high energetic metisazon molecule conformations from the main one.

Typical feature of the principal conformation 1 is that it, unlike the others, gets stabilized with two intermolecular H-connections NH…O and NH…N with 2,4 and 2,7 cal/mol energy respectively. Energetically the weakest VIII conformation has no intermolecular H-connections but destabilizing elements such as repulsions of free electronic pears of contiguous nitrogen, oxygen and sulfur atoms completely presented in it.

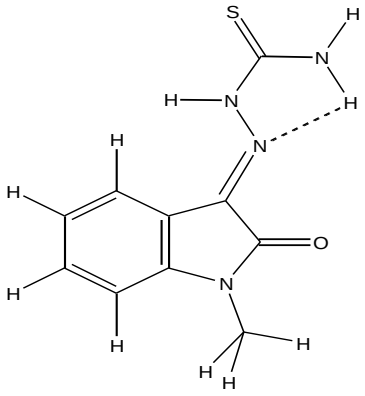
Its comparatively high energy (14,7 cal/mol) is explained by the factor that destabilizing factors are broadly presented in it.



I

ΔE = 0

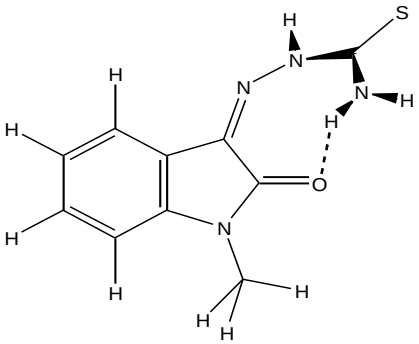
d = 6,8



II

ΔE = 2,9

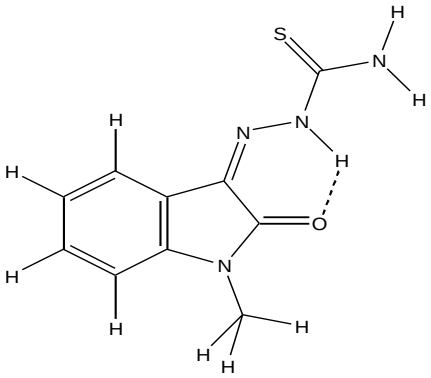
d = 4,2



III, IV

ΔE = 5,7

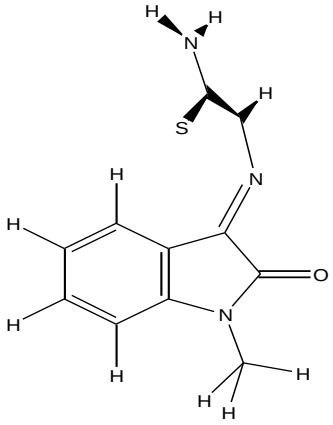
d = 7,5



V

ΔE = 7,4

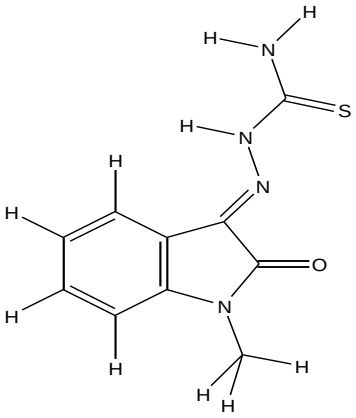
d = 4,7



VI,VII

ΔE= 14,2

d = 4,5



VIII

ΔE = 14,7

d = 8,5

Image 4: It is metisazon molecule conformations according to data of half-empirical quantum-chemical method AM1. Intermolecular H-connections are shown with dotted lines. Only one conformation is given for reflection symmetric couples III, IV and VI, VII. Symbols: ▲E – comparative energy, cal/mol; d – dipole moment.

So, the structure of molecule provides the changeability during their interactions. That's why the preparation has different effect and wide spectrum of biological activity. This structure can obtain different conformations depending on microenvironment and solvent character that assures its cell penetration.