DESIGN, SYNTHESIS AND MOLECULAR MODELLING OF NEW THIAZOLIDINES 2,3-DISUBSTITUTED WITH ANTITUMORAL ACTIVITY.

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New thiazolidine 2,3 disubstituted derivatives of 1'-acetamidyl-5'-nitroindazole with antitumoral activity against the Walker Carcinosarcoma and Jensen Sarcoma were designed and synthesized. The structural features of new compounds have been established by chemical elemental and spectral (^{1}HNMR and IR) analyses. The optimized molecular geometry, the length of the covalent bonds, the atomic charges and some electro-optical parameters influencing the bioactivity of the new compounds were established by using HyperChem 5.0 programs. The determined values of the 1,3-thiazolidines toxicity are in the limits of the laboratory screening. The new compounds prove inhibition activity when they were tested on experimental tumors, the most active being 4-oxo-1,3-thiazolidine (VI) with ortho-hydroxy-phenyl.

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1. Introduction

Correlations between the chemical structure and biological activity are in the attention of many researchers in order to discover the factors responsible for biological effects of substances. The thiazolidines derivatives have antimicrobial [1], anticancerous [2], antituberculous [3], antiviral [4] activities, that the presence of indazol ring in various chemical structures provide them antitumoral [5,6], antiinflamatory [7], antibacterian [8,9], bactericidal [10], anti-HIV [11] and respectively antimalarial [12] activities.

A series of new 2,3-disubstitued- 4 oxo-thiazolidine with 5-nitroindazole as support was synthesized and characterized in terms of physical-chemical and biological activity. Further study of biological activity of new compounds containing both 4-oxo-thiazolidine and 5-nitroindazole rings, will allow identification of the reciprocal influence of the two components present in the same molecules, as well as their contribution to the overall biological activity of the active principle.

The characterization of new thiazolidines by HyperChem-5.0 program emphasized very important information on the molecular optimized geometry, the length of the covalent bonds and the charge distribution near the molecular atoms.

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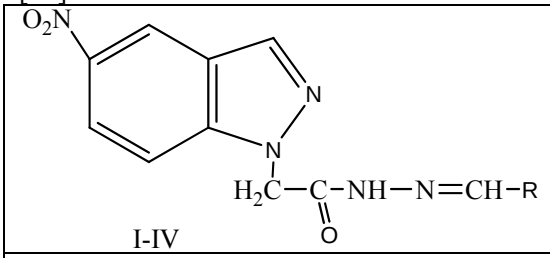
2. Experimental part and molecular modelling

2.1. Synthesis of new thiazolidines

Synthesis of new chemical compounds with potential antitumor activity was done by cyclization reaction of the hydrazones derived from 5-nitroindazole with thioglycolic acid.

The hydrazones were prepared by condensation of 5-nitroindazole-1-il-acethydrazides with benzoic aldehyde, o- and p-nitrobenzoic aldehyde, salicylic aldehyde with following structure [13]:

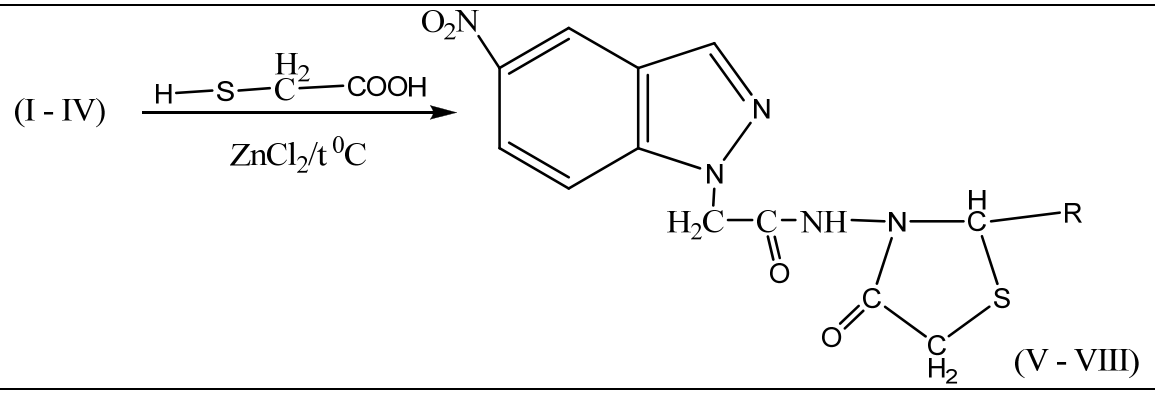


I-IV

(I) R = $-C_6H_5$;
(II) (II) R = $-C_6H_4$ – OH(orto);
(III) (III) R = $-C_6H_4 - NO_2$ (orto);
(IV) R = $-C_6H_4-NO_2$ (para).

Scheme 1 N-acyl-hidrazones structure

The hydrazones (I – IV) and the thioglycolic acid were heated in anhydrous dioxane, in the presence of $ZnCl_2$ for 6 hours, until reaching the intramolecular cyclization with the formation of thiazolidines (V – VIII) and the elimination of water molecules.



(I, V) R = $-C_6H_5$; (II, VI) R = $-C_6H_4$ – OH(orto); (III, VII) R = $-C_6H_4 - NO_2$ (orto);
(IV, VIII) R = $-C_6H_4-NO_2$ (para).

Scheme 2 Obtaining scheme of the studied thiazolidines (V – VIII)

The cyclization process took place with the formation, in the initial step, of the thioacid hydrazone converted to 2, 3-disubstituted thiazolidine by eliminating one molecule of water, together with the nucleophilic attack of the nitrogen upon the carbon in the carbonyl group (thioacid pending group). 1, 3-Thiazolidine derivatives (V - VIII) were purified by repeated recrystallizations from ethanol. A formal purification was done on alumina column. The solvent was dichlormethane (CH_2Cl_2) and eluent was a mixture of CH_2Cl_2- isopropanol [$(CH_3)_2CH$ - OH] 9:1 (V/V).

The structure of new compounds inferred by the synthesis was checked by determining the melting point and also by elemental and spectral (FT-IR and ^{1}H-NMR) analyses.

All reagents were used as purchased (Sigma-Aldrich, Fluka, Merck, S.C. Chemical Company S.A.). FT-IR spectra were registered using a FTIR spectrophotometer (ATR) Brucker Tensor-27; ^{1}H-NMR analysis was performed on a Brucker ARX 400 spectrometer (5mm QNP probe;^{1}H/^{13}C/^{31}P/^{19}F) and elemental analysis was made using Exeter Analytical CE 440 elemental analyser. The melting points of the obtained compounds were determined with a Mel-Temp melting point module, provided with digital thermometer.

2.2. HyperChem calculations

Some physical-chemical properties of the new molecules were established by using one of the most complete molecular modeling software – HyperChem 5.0 [14]. The semi-empirical method used here was AM1 which is generally the most accurate computational method included in HyperChem [14-17] and considered the best for collecting quantitative information [18].
The ionization potential I along with the electron affinity A, is related with the chemical hardness η and electronegativity χ of the molecule through the next equations [19]:

$$\eta = \frac{I - A}{2} \tag{1}$$

and

$$\chi = \frac{I + A}{2} \tag{2}$$

From the Koopmans theorem [20] one can consider:

$$I = -\varepsilon_{HOMO} \tag{3}$$

and

$$A = -\varepsilon_{LUMO} \tag{4}$$

The chemical behavior can be also correlated with the visible-UV spectra. A small energy gap means that absorption bands are shifted toward the visible. Generally, the spectroscopic excitation energy is about the chemical hardness (one half of I – A).

3. Results and discussions

By using the molecular modeling software, the main physical-chemical characteristics of the new tiazolidine 2, 3 disubstituted were calculated. The atoms'notations in structural formula of compounds $V - VIII$ are given in Fig. 1

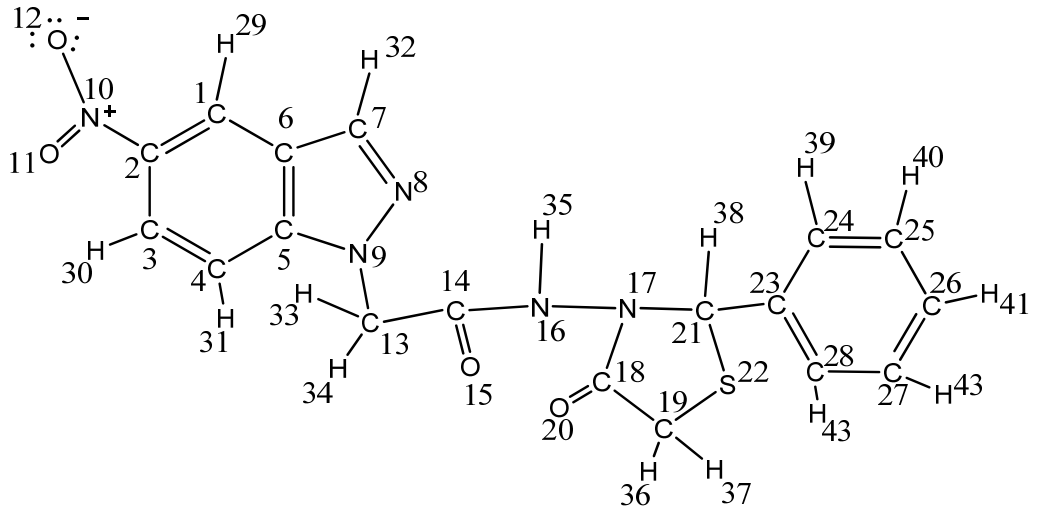


Figure 1 Notations of atoms in V *;* H_{39} *is replaced by* $O_{39} - H_{44}$ *in* VI *;* H_{39} *is replaced by* $N_{39}(O_{44};O_{45})$ *in VII and* H_{41} *is replaced by* $N_{41}(O_{44};O_{45})$ *in VIII .*

In Table 1 are given the lengths (in Å) of some covalent bonds directly influenced by structural changes when passes from V to $VIII$.

The lengths of the chemical bonds in nitro group are comparable for $N_{10}O_{11}O_{12}$ and $N_{41}O_{44}O_{45}$ (when nitro group is substituted in para position of phenyl cycle in compound $VIII$). Some modifications in the lengths of covalent bonds are induced by substitutions in ortho and in

para positions of the phenyl cycle (see the lengths of $C_4 - H_{31}$; $C_6 - C_7$; $C_7 - N_8$; $N_8 - N_9$ in Table 1).

The length of $C_{21} - H_{38}$ is higher in compounds *VI* and *VII* in which intramolecular hydrogen bond is realized (between H_{38} and O_{39} in *VI*, or between H_{38} and O_{45} in *VII*).

Table 1 Bond lengths (Å) of some covalent bonds in the structures $V - VIII$.

Bond	*V*	*VI*	*VII*	*VIII*
$C_4 - H_{31}$	**4.1030**	**4.0486**	**1.1122**	**3.3013**
$C_6 - C_7$	**1.5029**	**1.4972**	**2.3713**	**1.4774**
$C_7 - N_8$	**1.4757**	**1.4392**	**1.278**	**1.4821**
$N_8 - N_9$	**2.4874**	**3.1853**	**4.1496**	**2.9501**
$C_5 - N_9$	2.5294	2.5018	2.4151	2.5232
$N_9 - C_{13}$	1.4627	1.4791	1.4487	1.4790
$N_{17} - C_{21}$	**1.4810**	**1.4371**	**1.3395**	**1.4436**
$C_{14} - O_{15}$ (amide)	1.2178	1.2173	1.2154	1.2123
$C_{18} - O_{20}$ (cyclic)	1.2149	1.2149	1.2031	1.2064
$C_{21} - H_{38}$	**2.0733**	**3.2242**	**6.3363**	**2.1555**
$C_{21} - S_{22}$	**3.2762**	**3.1942**	**1.6796**	**2.0087**
$C_{24} - O_{39}$	-	1.356	-	-
$O_{39} - H_{44}$	-	0.9499	-	-
$C_{24} - N_{39}$	-	-	1.4985	-
$N_{39} - O_{44}$	-	-	**1.1721**	-
$N_{39} - O_{45}$	-	-	**3.5748**	-
$C_{24} - N_{39}$	-	-	-	1.4316
$N_{41} - O_{44}$	-	-	-	1.2300
$N_{41} - O_{45}$	-	-	-	1.2293

The substitution of H_{39} from *V* by $O_{39}H_{44}$ in *VII*, by $N_{39}O_{44}O_{45}$ (nitro group in ortho position) in *VII* or the substitution of H_{41} from *V* by $N_{41}O_{44}O_{45}$ in *VIII* induce modifications in the lenghts of chemical bonds. For example, the lenght of the covalent bond $C_4 - H_{31}$ is shortened when the nitro group is substituted in compounds *VII* and *VIII*. It also results that the length of the covalent bond $N_{17} - C_{21}$ depends on the chemical nature of the substitutes in compounds $V - VIII$. The length of the chemical bonds in the heterocycle containing sulfur are also influenced when passes from *V* to *VIII*.

Table 2. Some atomic charges for compounds $V - VIII$ (with notation from Fig. 1)

Atom	*V*	*VI*	*VII*	*VIII*
O_{11}	-0.588	-0.591	-0.592	0.586
N_{10}	1.308	1.315	1,302	1.320
O_{12}	-0.602	-0.604	-0.598	-0.608
N_8	**-0.014**	**-0.189**	**-0.131**	**-0.108**
N_9	-0.096	-0.074	-0.098	-0.096
C_{13}	-0.075	-0.106	-0.061	-0.102
C_{14}	**0.230**	**0.222**	**0.232**	**0.271**
O_{15}	**-0.327**	**-0.323**	**-0.309**	**-0.300**
C_{18}	**0.284**	**0.292**	**0.244**	**0.269**
O_{20}	**-0.309**	**-0.320**	**-0.236**	**-0.244**
N_{16}	-0.046	-0.049	-0.026	-0.068
N_{17}	**-0.055**	**-0.015**	**+ 0.116**	**+0.011**
C_{19}	**-0.188**	**-0.161**	**-0.303**	**-0.264**
C_{21}	**-0.060**	**-0.028**	**-0.398**	**+0.018**
C_{24}	**-0.115**	**0.059**	**-0.133**	**0.102**
C_{25}	**0.033**	**0.038**	**-0.111**	**0.213**
C_{26}	**-0.127**	**-0.137**	**-0.097**	**-0.832**
S_{22}	**-0.013**	**-0.038**	**+0.229**	**+0.373**
H_{38}	**0.090**	**0.086**	**0.091**	**0.132**
H_{39}	0.152			0.146
O_{39}		-0.200		
H_{44}		0.216		
N_{39}			0.292	
O_{44}			-0.225	
O_{45}			-0.149	
N_{41}				**1.367**
O_{44}				**-0.689**
O_{45}				**-0.685**

The most important modification by substitution is evidenced by the variation in the length of the chemical bond $C_{21} - H_{38}$ which becomes longer in the case of ortho- substituted compounds *VI* and *VII* , proving the possibility of hydrogen bond formation between the free electronic orbital of atom O_{39} and the proton of the bond $C_{21} - H_{38}$ in *VI* , or between the oxygen of the $N_{39}O_2$ nitro group and the proton of the bond $C_{21} - H_{38}$. By comparing the lengths of the covalent bonds in $N_{39}O_2$ nitro group (able to be involved in hydrogen bond) and of

the covalent bonds of $N_{41}O_2$ nitro group (uninvolved in hydrogen bond), one can observe that the last atomic group is characterized by normal lengths; it can not be involved in hydrogen bonds because it is substituted in para position of the cycle. In compound VII, H_{39} is substituted in ortho position by $N_{39}(O_{44};O_{45})$ and the length of the chemical bond $N_{39}-O_{45}$ is longer than the length of the $N_{39}-O_{44}$. This certifies the possibility of hydrogen bond formation between H_{38} and O_{45}. For comparison, one can observe that the lengths of the chemical bonds $N_{41}-O_{44}$ and $N_{41}-O_{45}$ are comparable and have normal values, of about 1.229 Å, in the compound $VIII$.

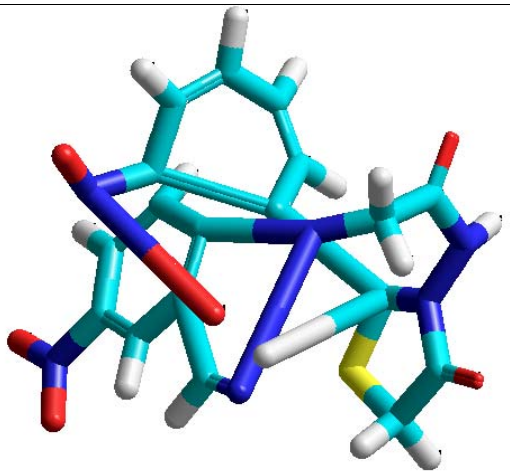


Fig. 2 Optimized geometry of the bulk conformers of the compound VII ; C-vert; N-blue; H-white; S-yelow; O-red.

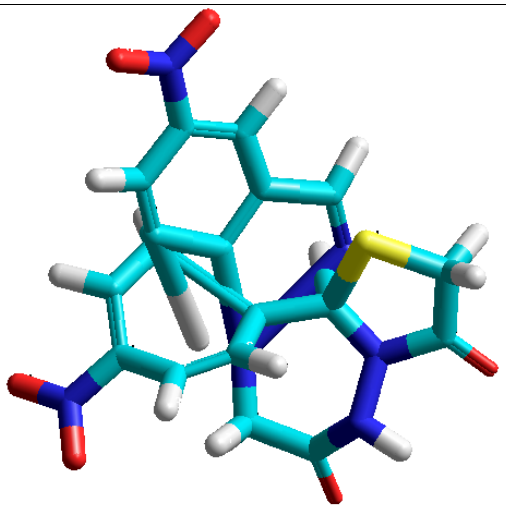


Fig. 3 Optimized geometry of the bulk conformers of the compound VIII ; C-vert; N-blue; H-white; S-yelow; O-red.

Some atomic charges computed for compounds $V-VIII$ are listed in Table 2.

The atomic charges on $-NO_2$ $(N_{10}O_{11}O_{12})$ nitro group are comparable in the studied compounds. The charges written in bold in Table 2 are considerably influenced by the substitutions in $V-VIII$ compounds. So, the atoms N_{17} and S_{22} are negatively charged in V and VI, while they are positively charged in VII and $VIII$ compounds, containing nitro groups (see Table 2). The C_{21} atom also changes dramatically its charge when passing from V to $VIII$.

There is a great separation of the charges in $(N_{41}O_{44}O_{45})$ nitro group of compound $VIII$, determining the highest dipole moment of this compound. In the second $-NO_2$ group of compounds VII and $VIII$ there are differences between atomic charges distribution. The nitro group in ortho position of phenyl cycle in VII has smaller charges on the component atoms compared with $VIII$.

In VII the charges on the oxygen atoms O_{44} and O_{45} are more different, due to the possibility of one $-NO$ $(N_{39}O_{44})$ chemical bond to be involved in a hydrogen bond with the hydrogen atom of the group $C_{21}-H_{38}$. From Table 2 it also results that some of the electronic charge is delocalized on C_{21} in compound VII.

The charge of N_{17} atom is also modified by the presence of nitro group in VII and $VIII$. This atom is positive in VII and $VIII$ compounds and negative in V and VI compounds.

The lengths of the covalent bonds and the charges near the molecular atoms are strongly correlated with the most stable conformers of the compounds, wich are bulk chemical structures. In Fig.2 the computed optimized nanometric structures for *VII* and *VIII* are illustrated for comparison.

Some molecular parameters computed by AMI Hyperchem 5.0 are listed in Table 3. The data from Table 3 evidence the high molecular volume of the studied compounds, the high values of their polarizability and of their dipole moments.

Table 3 Some molecular parameters computed by AM1 HyperChem

Nr.		*V*	*VI*	*VII*	*VIII*
1	Surface (A)	484.68	382.30	422.33	381.16
2	Volume ($Å^3$)	931.32	943.01	1059.63	972.63
3	Polarizability ($Å^3$)	39.56	40.19	41.40	41.40
4	Dipole Moment (D)	4.691	4.422	4.525	16.4
5	Total energy (kcal/mol)	-104383	-111136	-121242	-121186
6	LUMO (eV)	-1,629744	-1.582825	-1.391322	-3.542343
7	HOMO (eV)	-9.820712	-9.574428	-9.58033	-7.750544
8	χ (eV)	5.725228	5.5786265	5.485826	5.6464435
9	η (eV)	4.095484	3.9958015	4.094504	2.1041005
10	Hydration energy (kcal/mol)	-12.22	-15.35	-18.23	-14.77
11	Log P	-1.18	-2.21	-2.00	2.00

A relative great dipole moment was obtained for *VIII* , in which the second nitro group is not involved in hydrogen bond. The dipole moments of the *V* , *VI* and *VII* compounds are smaller than the dipole moment of *VIII* . The smaller dipole moment of *VII* compared to that of *VIII* certifies the formation of an intramolecular hydrogen bond in the first molecule.

The stability of the studied molecular structures is given by their high values of negative total energy. The modulus of the total energy is higher for the compounds *VII* and *VIII* , compared to that of the compounds *V* and *VI* which do not contain the second nitro group in their molecule. The compounds *VII* and *VIII* are also characterized by a higher polarizability compared with *V* and *VI* .

The biological activity was estimated from the difference between HOMO and LUMO levels. Hydration energy is defined as the energy absorbed when a substance is dissolved in water [19, 21]. LogP (the octanol/water partition coefficient) and molar refractivity are considered molecular descriptors [22, 23] that can be used related to one structure for observing its chemical behavior. LogP plays an important role for biochemical interactions [19] and it is related to the hydrophobic character of the molecule.

The new synthesized molecules are polarizable and less hydrophobic due to their high values of the hydration energy (see Table 3).

The difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), called the HOMO – LUMO gap, gives a measure of the biological activity (Table3).

Some wavenumbers in the maximum of the bands measured in IR spectra of compounds $V - VIII$ are listed in Table 4.

The IR spectra of the compounds $V - VIII$ are in accordance with the distances between the atoms and the atomic charges in the ground electronic state of the most stable conformers,

computed by HyperChem. The hydrogen bond formation is reflected in IR spectrum of compound *VII* by spectral shift of deformation vibration of the $N-CH-S$ atomic group (see Table 3).

Table 4. Wavenumbers (cm^{-1}) in the maximum of IR spectra of $V-VIII$ compounds.

	V	*VI*	*VII*	*VIII*
$C-H$	3179	3140	3120	3084
$N-CH-S$	2977	2977	2959	2970
CO (cycle)	1710	1710	1702	1700
CO (amide)	1660	1675	1677	1684
$N=CH$ (cycle)	1615	1617	1658	1614
NO_2 (symmetric)	1340	1346	1384	1338
NO_2 (asymmetric)	1518	1515	1520	1587
$N-CH_2$	1455	1421	1497	1495
$C-S-C$	751	664	751	689

By passing from *V* to *VIII* , a decrease in the wavenumber in the maximum of the $C_{14}-O_{15}$ (amide) valence vibration band can be observed when the second nitro group is substituted in *V* to obtain *VII* and *VIII* compounds. The tendency of the wavenumber in the maximum IR band corresponding to valence vibration of the lenght $C_{14}-O_{15}$ to decrease when the bong length increases can be evidenced from the data of Tables 1 and 4.

Table 5 NMR spectra $\delta(ppm)$ ($DMSO-d_6$, 400Hz) of $V-VIII$ compounds.

	V	*VI*	*VII*	*VIII*
(s, 2H, CH2)	5.33	5.39	5.30	5.35
(s, 2H, CH2)	5.85	5.80	5.78	5.85
(s, 1H, CH)	6.78	6.84	6.82	6.74
(d, 2H, Ar)	6.96-7.00	6.90-6.92	6.93-6.95	6.94-6.98
(d, 1H, Ar)	7.18-7.22	7.24-7.26	7.21-7.24	7.20-7.24
(d, 1H, Ar)	7.60-7.62	7.55-7.57	7.51-7.54	7.59-7.61
(d, 2H, Ar)	7.72-7.74	7.75-7.77	7.76-7.78	7.75-7.80
(s, 1H, Ar)	8.40	8.37	8.33	8.44
(s, 1H, Ar)	8.50	8.48	8.45	8.51
(s, 1H, NH)	8.92	8.84	8.83	8.96
(s, 1H, OH)		11.70		

Important increase in the electronic charges on the atomic group $C_{19}-S_{22}-C_{21}$ in *VIII* , compared with *VII* determines a decrease in the wavenumber of the deformation vibration band of this atomic group in *VIII* as compared to *VII* (see Table 4).

The principal signals from NMR spectrum of the studied compounds are listed in Table 5. The chemical shifts from the ^{1}H NMR spectra of 4-oxo-thioazolidines 2,3-disubstituted (V-VIII) are characterized by the signals of the aromatic protons in the range 8.51-6.90 ppm. In the alifatic zone one can see, as singlets, the signals of the $-CH_2$ group between 5.39-5,30 ppm (2H) and of $-NH$ at 8.96-8.83 ppm (1H) .

The two protons of the group $-CH_2$ from the tiazolidinic cycle appear as singlet between 5.85-5.78 ppm (2H). The signal of the proton from the $-OH$ group appears as a singlet at 11.70 ppm (1H) in the ^{1}H NMR spectra of compound VI , certifying the participation of Oxygen from hydroxy group to a hydrogen bond with H_{38}. The NMR signal for H_{35} is very sensitive to the substituents of the phenyl cycle; this fact is also confirmed by the values of the charges near the carbon atoms of this cycle (See Table 2).

4. Antitumoral activity

4.1 Determination of acute toxicity

The acute toxicity (LD_{50}) of the synthesized thiazolidines has been determined, using the indications of Karber's method [24]. The compounds have been administered intraperitoneally as suspensions in Tween80 to groups of 10 mice of either gender and weighing of 20±2 g. The mortality (LD_{50}) has been registered after 24 hours, 48 hours and 7 days. The obtained results are presented in Tabel I

Table 6 Acute toxicity of thiazolidines V, VI, VII, VIII.

Compound	LD50 (mg/Kg body)			
	24 hours	48 hours	7 days	Average
V	1310	1310	1295	1305
VI	1585	1585	1542	1570
VII	1120	1120	1105	1115
VIII	1100	1100	1090	1096

The values of LD_{50} for the synthesized compounds were compared with the acute toxicity of the starting, reference compound, 5-nitroindazole. Although, the compounds V-VIII present a slightly higher toxicity than 5-nitroindazole (LD_{50} = 1670 mg/Kg body), LD 50 values are within admissible limits (Table I), recommending them for further laboratory screening.

4.2 Antitumoral activity

The cytostatic effect of the synthesized compounds was evaluated on the development of two experimental tumors: Walker 256 carcinosarcoma and Jensen sarcoma implanted into Wistar rats of 100-130 g (±15 g) each, provided by "Prof.dr. Ion Chiricuta" Institute of Oncology from Cluj-Napoca. The solid tumors were transplanted subcutaneously to rats from donors with 21 days old tumors. Considering the difficulties of solving the studied compounds (V - VIII), they were administered intraperitoneally as suspensions in methylcellulose (1%, w/w). Methylcellulose is usually used in testing of biologic activity of various biomaterials, as it is chemically inert and inactive when in contact with animal tissue [25]. 14 days after tumor transplantation, the thiazolidines were administered in unique shots of 400, 200 and 40 mg/Kg body at 20 rats for each drug concentration. The two control batches were formed of 10 rats each, implanted with the Walker and Jensen tumors, respectively.

The inhibition of the two tumors development, exerted by the thiazolidines was calculated 14 days after drug administration, using a method indicated in literature [26, 27].

The tumors inhibition capacity of the 1,3-thiazolidines and of 5-nitroindazole as it was evaluated on two experimental malignant tumors is presented in Table II.

Table II shows that compounds V - VIII present a higher inhibition capacity on the development of Walker carcinosarcoma than on Jensen sarcoma.

Table 7 Tumor inhibition (%) exerted by 5-nitroindazole and the newly synthesized 2,3-disubtituted 1,3-thiazolidines.

Compound	Tumor Inhibition, %					
	Walker carcinosarcoma			Jensen sarcoma		
	(mg/Kg body)					
	400	200	40	400	200	40
5-nitroindazole	35	26	19	31	22	17
V	45	40	34	41	36	31
VI	54	44	40	50	45	40
VII	44	39	35	42	37	33
VIII	50	42	34	41	37	32

Also, it has been shown that 3-[(5'-nitroindazole-1'-acetamidyl)]-2-(o-hydroxyphenyl)-4-oxo-1,3-thiazolidine (VI) has the highest inhibition of tumor growth, probably, due to o-hydroxyphenyl as pendant group, that favors and enhances the cytostatic action.

5. Conclusions

The bulk molecules with a volume of a nanometer to cube are active from the antitumoral point of view. The sequence of some simple covalent bonds and also the possible hydrogen bonds from the new compounds is responsible for spatial distribution of the atoms in the optimized molecular geometries. The computed parameters of these molecules are in accordance with their antitumoral activity. The most active compound is VI with the lowest electric dipole moment.

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