

## Quantum Chemistry Study of 1,3-Diazaspiro[4,5/4]dec/non-1-en-4-one Derivatives

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The geometry structures of the title compounds were optimized by means of the self-consistent *ab initio* restricted Hartree-Fock (RHF) level with 3-21G basis set. The quantitative structure-activity relationship of the title compounds was systematically investigated based on Hansch-Fujita approach. A correlative equation between  $IC_{50}$  and  $E_{LUMO}$ ,  $C \log P$  and MR was well established. The correlation coefficient  $r$  is 0.9647 and

$$pIC_{50} = 11.5137 - 116.9688E_{LUMO} - 0.1959C \log P + 0.2820MR$$

$n = 14, R = 0.9647, F = 44.69$

shows that the introduction of electron-withdrawing groups on to the  $R^2$ -position would be favourable to the activity of the compounds.  $C \log P$  was influenced by the number of carbons on the spiro. Reducing of  $C \log P$  and building up the polarization of the compounds would be favourable to the activity.

**Key Words:** 1,3-Diazaspiro[4,5/4]dec/non-1-en-4-one, QSAR, *ab initio*, Hansch-Fujita.

### INTRODUCTION

The rennin-angiotensin-aldosterone system (RAAS) has important functions in adjusting the blood pressure and the balance between the body fluid and electrolyte<sup>1-3</sup>. The activity hormone II(AII) of RAAS has a function in stimulating the blood vessel to shrink, but its abnormal activation can induce such diseases as hypertension and heart failure. Losartan is a kind of non-peptide AII receptor antagonist, it has high potency on AII receptor<sup>4, 5</sup>. In recent years, there has been taken increasing interest in this field. Most synthesized compounds are based on losartan with the imidazole ring replaced by the aryl ring. 1,3-Diazaspiro[4,5/4]dec/non-1-en-4-one was found to be a good substitute of imidazole ring<sup>6</sup>. Xu *et al.*<sup>7</sup> have synthesized fourteen 1,3-diazaspiro[4,5/4]dec/non-1-en-4-one derivatives and reported their biological activities.

In order to investigate the quantitative structure-activity relationship (QSAR) of this series of compounds, the conformation analysis of the title compounds by using molecular mechanics is performed. The geometry structures of the fourteen derivatives were optimized by means of the self-consistent *ab initio* method. The QSAR of these compounds was discussed based on Hansch-Fujita approach to

establish the foundation for designing novel non-peptide AII receptor antagonists with high potency.

### Calculation Methods

The synthesis and activities of the title compounds were reported in literature<sup>7</sup>. Because the crystal structures of the title compounds (Fig. 1) were still not

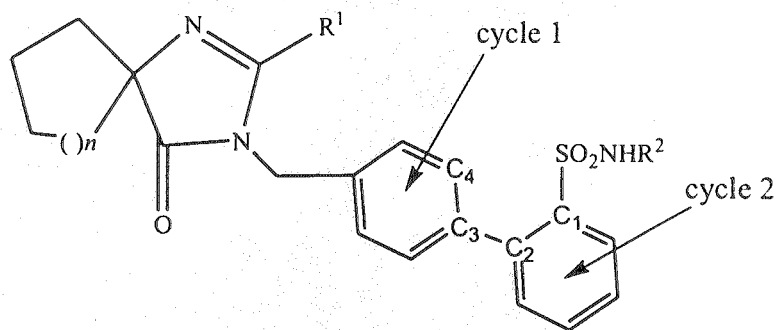


Fig. 1. Structures of 1,3-diazaspiro[4,5/4]dec/non-1-en-4-one derivatives ( $R^1 = n\text{-Bu}, n\text{-Pr}; R^2 = t\text{-Bu}, \text{H}, \text{CO}_2\text{Et}, \text{CO}_2\text{Me}, n = 1, 2$ )

measured, the three-dimensional structures of the compounds were built by the Chem3D package and the MM2 force field was applied to search for the low energy conformations for each molecule<sup>8</sup>. The step interval is 2.0 fs and the frame interval is 10 fs, the terminative step is 10000, the heating/cooling rate is 4.18 kJ (atom ps) and the target temperature is 300 K.

Computational practice shows that the *ab initio* method is suitable for the situation with scarce experimental structure data. The *ab initio* method was performed to optimize the low energy conformation of the compounds at RHF/3-21G level. All of the quantum chemistry calculations was performed by using Gaussian98 package on Pentium-IV PC.

## RESULTS AND DISCUSSION

### Conformational analysis

The couple of conformational isomers for each molecule can be obtained after using MM2 force field to search for the low energy conformations of this series of derivatives. The greatest difference among these conformations is the dihedral angle of C1-C2-C3-C4 (Fig. 1). The compound **IIIa** has higher activity than the other derivatives<sup>7</sup>, so the different conformational isomers of **IIIa** are shown in Fig. 2 and the energies and the total energy of **IIIa** calculated by MM2 force field are listed in Table-1.

The total energy of conformation 3 is the minimum compared with others (Table-1). So the conformation 3 can be assumed as the active conformation of **IIIa**. The quantum chemistry *ab initio* calculation of **IIIa** was based on the conformation 3. The conformation analysis of other derivatives has been done in the same way.

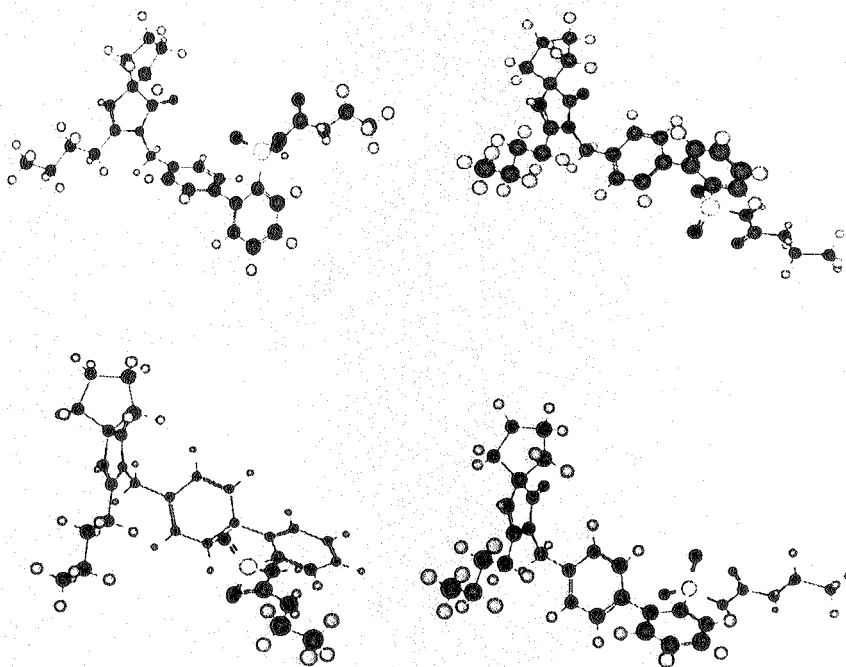


Fig. 2. Different conformations of compound 1

TABLE-1  
ENERGY OF DIFFERENT CONFORMATIONS OF COMPOUND C BASED ON MM2  
FORCE FIELD (kJ/mol)

Energy	Conformation 1	Conformation 2	Conformation 3	Conformation 4
Stretch	1.8478	1.7325	1.7363	1.7820
Bend	20.6995	19.5509	20.0791	19.8934
Stretch bend	-0.0661	-0.0059	-0.0393	-0.0241
Torsion	-6.0025	-5.7886	-5.8099	-6.0102
Non-1,4-VDW	-10.3844	-10.0641	-10.7179	-10.0496
1,4-VDW	14.6640	15.2247	14.8953	15.0565
Dipole	0.5953	-0.1766	-0.1959	0.1385
Total	21.3536	20.4730	19.9477	20.7864

### QSAR study of the 1,3-diazaspiro[4,5]dec/non-1-en-4-one derivatives

Based on the lowest energy conformations calculated by MM2 force field, the title compound's geometry structures were optimized by means of the self-consistent *ab initio* restricted Hartree-Focks (RHF) level with 3-21G basis set and frequency calculations for each derivative molecule were carried out at 298.15 K and 1 atmosphere pressure based on the optimized geometries calculated *ab initio*. There were no imaginary frequencies produced. A large variety of the quantum chemical parameters were taken from the calculation results, such as the

highest occupied molecular energy ( $E_{\text{HOMO}}$ ), the lowest unoccupied molecular orbital energy ( $E_{\text{LUMO}}$ ), the molecular molar volume ( $V_m$ ), etc. The *n*-octanol/water partition coefficient ( $C \log P$ ) and the molar refractivity (MR) were calculated by using thermodynamic theory. Selected parameters and the activities of the title compounds were included in Table-2.

TABLE-2  
DATA OF THE QUANTUM CHEMICAL PARAMETERS AND ACTIVITY

No.	<i>n</i>	R <sup>1</sup>	R <sup>2</sup>	$E_{\text{HOMO}}$ (Hartree)	$E_{\text{LUMO}}$ (Hartree)	$V_m$ (cm <sup>3</sup> mol <sup>-1</sup> )	C log P	MR	pIC <sub>50</sub>
Ia	1	<i>n</i> -Bu	<i>t</i> -Bu	-0.32567	0.08916	315.282	6.3488	12.28	3.20
Ib	2	<i>n</i> -Bu	<i>t</i> -Bu	-0.32730	0.09105	378.331	6.9078	12.74	3.28
Ic	1	<i>n</i> -Pr	<i>t</i> -Bu	-0.32538	0.08923	351.137	5.8198	12.82	3.62
Id	2	<i>n</i> -Pr	<i>t</i> -Bu	-0.32623	0.08911	386.443	6.3788	12.28	3.10
IIa	1	<i>n</i> -Bu	H	-0.32708	0.08451	284.869	4.4958	13.42	4.56
IIb	2	<i>n</i> -Bu	H	-0.32776	0.08433	340.678	5.0548	13.89	4.32
IIc	1	<i>n</i> -Pr	H	-0.32770	0.08730	291.845	3.9668	13.96	4.41
IId	2	<i>n</i> -Pr	H	-0.32883	0.08713	318.611	4.5258	12.42	4.09
IIIa	1	<i>n</i> -Bu	CO <sub>2</sub> Et	-0.32683	0.08207	351.311	5.3908	14.00	5.14
IIIb	2	<i>n</i> -Bu	CO <sub>2</sub> Et	-0.32906	0.08165	416.043	5.9498	14.47	5.04
IIIc	1	<i>n</i> -Pr	CO <sub>2</sub> Me	-0.32720	0.08139	337.168	4.3328	13.08	5.00
IIId	2	<i>n</i> -Pr	CO <sub>2</sub> Me	-0.32953	0.08076	326.754	4.8918	13.54	4.82
IIIe	1	<i>n</i> -Pr	CO <sub>2</sub> Et	-0.32679	0.08210	358.720	4.8618	13.54	4.70
IIIf	2	<i>n</i> -Pr	CO <sub>2</sub> Et	-0.32897	0.08168	352.445	5.4208	14.00	4.55

If the organic metabolism processes in the body are ignored, the activities of compounds are the linearity functions of the electronic effect, the volume effect and the hydrophobic effect<sup>9,10</sup>. The front molecular orbital energies ( $E_{\text{HOMO}}$  and  $E_{\text{LUMO}}$ ) have very important effect on the compound's activity; the reaction between the compound and the receptor is influenced by  $E_{\text{HOMO}}$  or  $E_{\text{LUMO}}$ . If the compound works as electron donor in the reaction with the receptor, higher  $E_{\text{HOMO}}$  means it is easy to donate electrons. So the compound has higher activity accordingly. And if the compound works as electron acceptor in the reaction with the receptor, lower  $E_{\text{LUMO}}$  means it is easy to accept electrons and its activity should be higher. Based on the quantum chemical parameters calculated *ab initio* (Table-2), IIIa-f have higher activities compared with Ia-d and IIa-d and the  $E_{\text{LUMO}}$  of IIIa-f is lower than others. So, we can forecast this series of derivatives reacting with the AII receptor as an electron acceptor.

The molecular mole volume ( $V_m$ ) has no distinct relationship with the activity as listed in Table-2 and the reason why  $V_m$  changes abnormally may be the different replacements and changes on the molecular matrix of these derivatives.

It shows that  $V_m$  is not the main factor that affects the activity of the compound. In addition, the molar refractivity (MR) can be regarded as the volume effect<sup>11</sup>; so it was considered.

To sum up, the stepwise multiple regression (SMR) was used to build a quantitative structure-activity relationship model based on Hansch-Fujita approach and the QSAR equation was built as eqn. (1).

$$\begin{aligned} \text{pIC}_{50} &= 11.5137 - 116.9688E_{\text{LUMO}} - 0.1959C \log P + 0.2820\text{MR} \\ n &= 14, \quad R = 0.9647, \quad F = 44.69 \end{aligned} \quad (1)$$

Eqn. (1) showed that the correlation coefficient  $r$  was 0.9647 and F-test value was 44.69. The QSAR model had good predictability and  $E_{\text{LUMO}}$  was a negative correlation to  $\text{pIC}_{50}$ . So the lower  $E_{\text{LUMO}}$  means higher antagonistic ability. This

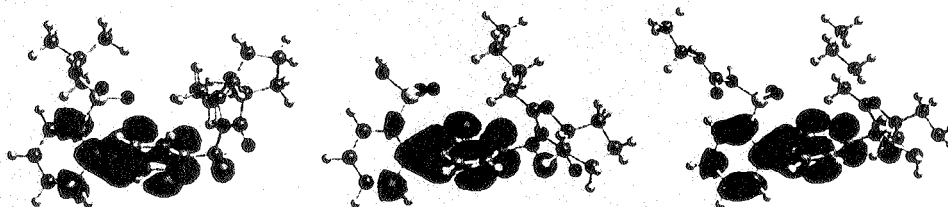


Fig. 3. The stereographs of the front molecular orbitals LUMO of Ia, IIa and IIIa

conclusion accords with our forecasting. Chem3D package was used to perform orbital analysis based on the optimized geometries<sup>12</sup>. The stereographs of the frontier molecular orbitals LUMO of Ia, IIa and IIIa were depicted in Fig.3.

By studying the front molecular orbits, it has been found that LUMO in these molecules is mainly distributed on the biphenyl rings (Fig. 3). The reaction between the active molecules and the receptor mainly happened on the frontier molecular orbitals and near orbital LUMO accepted the electrons, which came from the receptor. So the biphenyl rings in these active molecules work as the electronic acceptors. Decreasing the electronic densities on the biphenyl rings would be favourable to making the active molecule accepting electrons more easily. Accordingly, it made the compound highly active. IIIa-f (Table-2) were introduced as the electron-withdrawing groups ( $\text{CO}_2\text{Et}$ ,  $\text{CO}_2\text{Me}$ ) on to the  $\text{R}^2$ -position and the electron-withdrawing effect of these substitute groups made the electronic densities of the biphenyl rings decreasing. The LUMO energies ( $E_{\text{LUMO}}$ ) of IIIa-f were lower than other compounds in Table -2. So the activities of IIIa-f were higher than Ia-d. On the other hand, Ia-d were introduced as the electron donor group ( $t\text{-Bu}$ ) on to  $\text{R}^2$ -position. The electronic densities of the biphenyl rings in these molecules increased; it made the  $E_{\text{LUMO}}$  increasing accordingly. So the activities of Ia-d were lower than other compounds.

The deeply linear analysis for  $\text{pIC}_{50}$  and  $E_{\text{LUMO}}$  was shown in Fig. 4 and a linear equation was built.

$$\begin{aligned} 6\text{pIC}_{50} &= 19.6120 - 180.2298E_{\text{LUMO}} \\ n &= 14, \quad r = -0.9196, \quad \text{SD} = 0.2892 \end{aligned} \quad (2)$$

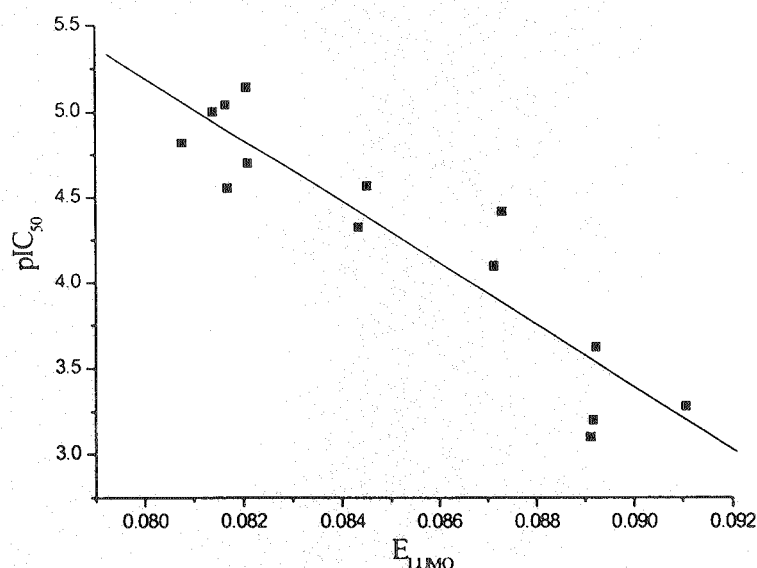


Fig. 4. The linear analysis for  $pIC_{50}$  and  $E_{LUMO}$

Eqn. (2) showed that the correlation coefficient  $r$  was  $-0.9196$  and the standard deviation  $SD$  was  $0.2992$ . So, one can draw the conclusion that introducing the electron-withdrawing groups on to the biphenyl rings should be favourable to the activities of these series of derivatives.

The hydrophobic parameter ( $C \log P$ ) is another important factor that would affect the activities ( $IC_{50}$ ) of the compounds. The hydrophobic effect was positive to the proportion of the hydrophobic groups in the molecule<sup>13</sup>. The coefficient of  $C \log P$  was  $-0.1959$  in eqn. (1). It indicated that  $C \log P$  was in negative correlation with the activity. Ignoring the changes in the substituent groups, the value of  $C \log P$  is smaller when  $n$  is 1 than the situation that  $n$  is 2. Table-2 gives the changing disciplinarian that  $C \log P$  were  $Ia < Ib$ ,  $Ic < Id$ ,  $IIa < IIb$ ,  $IIc < IIId$ ,  $IIIa < IIIb$ ,  $IIIc < IIIId$ ,  $IIIe < IIIIf$  and the activities of the title compounds were  $Ic > Id$ ,  $IIa > IIb$ ,  $IIc > IIId$ ,  $IIIa > IIIb$ ,  $IIIc > IIIId$ ,  $IIIe > IIIIf$ . It showed that  $C \log P$  was mostly affected by the number of C atoms in spiro. The activities of  $Ia$  and  $Ib$  may be affected by other factors, so they did not abide by this orderliness. So if we ignore the changes in substituent groups, the 5-member ring spiro should be a better choice than the 6-member ring spiro when the novel non-peptide AII receptor antagonists are designed.

The molecular refractivity ( $MR$ ) is influenced by the atomic type and the atomic number of molecules. And the molecular interaction also has effect on  $MR$  in some degree. Compared to the atoms of alkyl, the 6 carbon atoms of phenyl are located in a plane as a whole, so the steric stentening degree of freedom of each atom is restricted and this restriction must have effects on  $MR$ . Investigation showed that if the substituents on the phenyl were located in the ortho position, the interaction between the substituents also had remarkable effects on  $MR$ <sup>14</sup>. Fig. 1 shows that the sulfonamide was located in the ortho position of cycle I; so the interaction between them influenced  $MR$  in some degree. Eqn. (1) shows that  $MR$  was in positive correlation with the activity and the coefficient was  $0.2820$ .  $IIIa-f$

were introduced as the electron-withdrawing groups (CO<sub>2</sub>Et, CO<sub>2</sub>Me) on to the R<sup>2</sup>-position; it made the polarity of these molecules increasing. And the increasing in polarity induced the molecular interaction of IIIa-f to strengthen. So, MR of IIIa-f increased accordingly and the activities of IIIa-f are higher than Ia-d and IIa-d (Table-2).

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### REFERENCES

1. C.R. Hong and H.L. Zhang, *J. QingHai Medical College*, **25**, 182 (2004).
2. H. Urata, B. Healy, R.W. Stewart, S.M. Bumpus and A. Husain, *Circ. Res.*, **66**, 883 (1990).
3. H. Hirakata, F.M. Fouad-Tarazi, F.M. Bumpus, M. Khosla, B. Healy, A. Husain, H. Urata and H. Kumagai, *Circ. Res.*, **66**, 891 (1990).
4. J.V. Duncia, A.T. Chiu and D.J. Carin, *J. Med. Chem.*, **33**, 1312 (1990).
5. R. Andrew and G. Houghton, *Drugs*, **62**, 1433 (2002).
6. C.A. Bernhart, P.M. Perreaut and Y.A. Maneaux, *J. Med. Chem.*, **36**, 3371 (1993).
7. J.Y. Xu, N.G. Li and X.M. Wu, *Chinese J. Med. Chem.*, **13**, 311 (2003).
8. L.S. Xu, Y.P. He and Z.H. Li, *Acta Chim. Sinica*, **60**, 1784 (2002).
9. C. Hansch, *Structure-Activity Relationships*, Dergmon Elmsford, New York (1973).
10. C. Hansch and A. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, New York (1979).
11. G.F. Yang, Y. Ding and H.Z. Yang, *Chem. J. Chinese Univ.*, **25**, 71 (2004).
12. H.A. Geng, X.W. Wei and L.J. Yang, *Comput. Appl. Chem.*, **21**, 508 (2004).
13. E. Creighton, *Protein-Structures and Molecular Properties*, Freeman, New York (1993).
14. K.Q. Wang, *J. Sichuan Teachers College*, **15**, 325 (1994).

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