STRUCTURE-ACTIVITY RELATIONSHIP OF IMIDAZO-BENZODIAZEPINES, AN AM1 SEMI-EMPIRICAL QUANTUM MECHANICS STUDY

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ABSTRACT: *Conformations and electronic properties of a series of imidazo-benzodiazepines are investigated by AM1 semi-empirical quantum mechanics method. It is shown that substitution of Cl in position 7 instead of 8, changes the geometry of the seven membered lactam ring; this may put the N5 nitrogen in a better position to act as a hydrogen bond acceptor, and the phenyl ring in position 6 is probably more adapted for hydrphobic pocket of the receptor binding site.*

KEY WORDS: *AM1 semi-empirical quantum mechanics, Structure-activity, Imidazobenzodiazepine, Benzodiazepines*

INTRODUCTION

The benzodiazepines (BZDS) are widely used in the treatment of anxiety, status epilepticis, and convulsive and emotional disorders [1]. It is established that BZDS interact with a specific and high affinity receptor "the benzodiazepine receptor" [2,3]. This receptor is closely associated with a neuro-inhibitory, postsynaptic $GABA_A$ receptor and a chloride ionophore channel [4,5]. The binding sites appear to be distributed unevenly throughout the brain. The existence of two different subtypes of BZD-receptor (BDZ-R_1 and BDZ-R_2) have been proposed [6]. Ligands that bind to BZD-receptor have three possible effects. The ligand can be an agonist that reduces anxiety, an antagonist which binds to the receptor but has no biological effect, or an inverse agonist that promotes convulsion. Superposition of typical agonists and antagonists leads to a model with conformationally mobile binding points [7]. Inverse agonists are distinguished from antagonists by the length of the hydrophobic side chain [7]. Antagonists are distinguished from agonists in part by the lack of a binding feature similar to imin-N atom of

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the diazepam ring [7]. However, classical full agonists such as diazepam and nitrazepam show anxiolytic, anticonvulsant, sedative and muscle relaxant effects. These latter two properties are believed to be unwanted side effects which appear because of the high level of receptor stimulation achieved by full agonists. Partial agonists are desirable for stimulating one of the effects like anxiolysis [8]. Some ester derivatives such as imidazobenzodiazepines and oxadiazolylimidazo-benzodiazepines have been reported to act as partial agonists at the benzodiazepine receptor [9,10]. In the imidazobenzodiazepin-3-carboxylic acid ester series, there is a wide tolerance in the size of the alkyl group that is acceptable with little or no effect on binding [11]. In the oxadiazol system, which is an isoesteric replacement for the ester linkage, variation of the 3- or 5-alkyl substituent only marginally altered the affinity of the ligand for the receptor, had a significant effect on its efficasy [10]. The most surprising effect has been found in the changing of the chloro substituent from position 8 to 7. Shifting the chlorine atom to position 8 reduced the affinity by 2-fold [10], in clear contrast to the rules observed for classical agonists such as diazepam [7, 12,13,14]. In this paper a model is presented which could account for the better affinity of imidazobenzodiazepine compounds with chlorine at position 7.

RESULTS AND DISCUSSION

Sixteen oxadiazolylimidazo-benzodiazepines with phenyl ring at position 5 were considered which differ in alkyl group substitution at positions 3′ and 5′ of the oxadiazol ring and chlorine atom at either 7 or position 8 of the fused seven membered phenyl ring. Their IC_{50} values [10] for [3H]-oxadiazolylimidazo-BDZ binding are shown in Table 1. The general structure and numbering used in the present discussion are shown in Fig. 1. These compounds have been selected from the work of *Watjen* et al. [10]. The results of AM1 calculations for important geometry and electronic parameters are shown in Tables 2 and 3.

Stereoview of the superimposition of the 7- and 8-chloro substituted oxadiazolylimidazo-BDZ is shown in Fig. 2. Inspection of Tables 2 and 3, and Fig. 2 suggests that the difference in affinity of oxadiazolylimidazo-BDZ toward the receptor could be either due to different localized charges or difference in stereochemistry of the 7-membered ring, or both. The very small difference of N-5 and N-2 atomic charges in these two families could not be taken into account for such a different IC_{50} values (Table 1). The difference in stereochemistry of the 7-membered rings should be the main reason. There are a number of reports which indicate that slight changes of lactam ring geometry are probably very critical to reactivity [15,16]. The most important change occurs for imino N-5 and phenyl at the 6 position as other parts of the

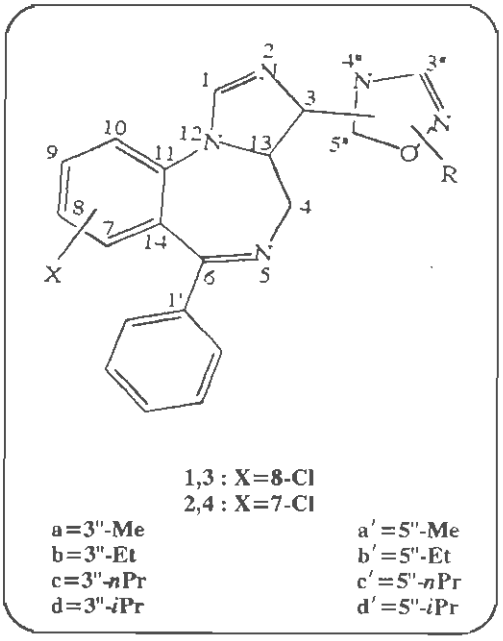

Fig. 1: Structure and numbering of the oxadiazolylimidazo-BDZ

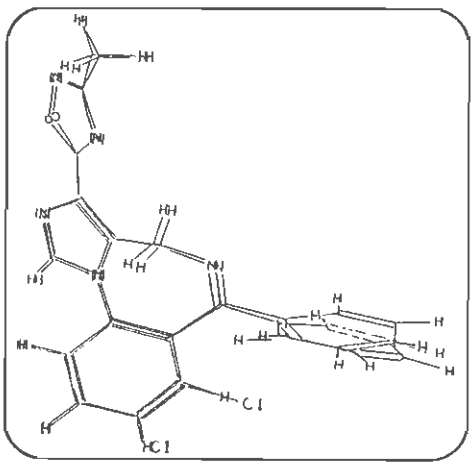

Fig. 2: Superimposition of the 7-chloro (upper) and the 8-chloro substituted imidazobenzodiazepine.

Table 1: In vitro binding data for oxadiazolylimidazo-BDZ. For numbering see Fig. 1.

No.	X	R	IC_{50} , nM(SEM)
1a	8-Cl	3"-CH_3	180
1b	8-Cl	3"-C_2H_5	160
1c	8-Cl	3"-*n*-C_3H_7	120
1d	8-Cl	3"-*i*-C_3H_7	120
2a	7-Cl	3"-CH_3	3.4±0.1
2b	7-Cl	3"-C_2H_5	4.1±0.4
2c	7-Cl	3"-*n*-C_3H_7	5.2±0.5
2d	7-Cl	3"-*i*-C_3H_7	6.9±2.7
3a'	8-Cl	5"-CH_3	71
3b'	8-Cl	5"-C_2H_5	44
3c'	8-Cl	5"-*n*-C_3H_7	45
3d'	8-cl	5"-*i*-C_3H_7	53
4a'	7-Cl	5"-CH_3	1.3±0.2
4b'	7-Cl	5"-C_2H_5	2.8±0.4

IC_{50} = Binding affinities in rat cortical membranes; see ref. 10 for the details about the binding data.

molecules are superimposed on each other. The imino N-5 of the lactam ring is probably involved in binding to the receptor via a hyrogen bond [7]. Changing the lactam ring geometry in the N-5 imino position of the 7-chloro derivative, could facilitate a better hydrogen bonding to the receptor.

Oxadiazolylimidazo-BDZ having carboxyl group at position 6 instead of phenyl ring with chlorine at position 7 and 8 differ in reactivity. In the more potent subsets having a 7-substitutent, the 6-aryl derivatives are up to 5-fold more potent and more efficatious than the 6-oxo counterparts. This might be due to the binding of phenyl ring at position 6 to a hydrophobic cleft of the receptor. Both series of compounds with phenyl at position 6 are partial agonists. The phenyl group should therefore contribute to the binding to the receptor. Change of chlorine position from 8 to 7 causes phenyl ring at the position 6 displaces up; this may lead to a better binding to the hydrophobic pocket of the receptor binding site.

In conclusion, substitution of chlorine atom at position 7 will probably put the imino nitrogen in closer proximity to the hydrogen donor position and also place the phenyl ring in a better position for hydrophobic interaction. This phenomenon which is observed only in the oxadiazolylimidazo-BDZ, is probably due to a fixed position for the oxadiazol, imidazo and substituted phenyl ring in the position 7 or

Table 2: Heats of formation (kJ/mol) and selected parameters (bond lengths, r, (Angstrom), bond angles, (θ), and dihedral angles (ϕ), in degrees; l, distances (Angstrom) for compounds 7-cl and 8-Cl-Imidazo- BZD and the transition state for ring inversion. For the numbering see Fig. 1.

	7-Cl	8-Cl	TS(7-Cl)	TS(8-Cl)
H_f	804.4	786.5	1160.1	1228.7
(r)				
4-5	1.44	1.44	1.41	1.40
5-6	1.29	1.29	1.29	1.29
6-14	1.49	1.49	1.48	1.49
14-11	1.42	1.41	1.43	1.42
11-12	1.41	1.41	1.41	1.41
12-13	1.41	1.40	1.39	1.39
13-14	1.49	1.49	1.48	1.48
(θ)				
4-5-6	122	123	134	135
5-6-14	126	128	129	128
6-14-11	121	123	122	124
14-11-12	121	122	124	125
11-12-13	125	126	131	131
12-13-4	122	123	126	127
13-4-5	112	114	122	122
(ϕ)				
4-5-6-14	-4	-3	10	12
5-6-14-11	48	38	12	10
6-14-11-12	-7	-1	-34	-29
14-11-12-13	-40	-39	28	22
11-12-13-4	15	10	1	0.5
12-13-4-5	51	50	-12	-5
13-4-5-6	-58	-54	-3	-9
14-6-1'-2'	45	55	44	29
13-3-5"-4"	13	-15	-8	-5
(l)				
Cl-N_{12}	5.16	5.91	5.09	5.85
Cl-N_5	4.08	6.27	4.44	6.39
Cl-N_2	7.43	8.06	7.19	7.84

Table 3: Calculated charge density, by AM1 method, for the 7-chloro and 8-chloro compounds. For the numbering see Fig.1.

Atom no./charge density	7-Chloro	8-Chloro
5	-0.154	-0.155
6	0.078	0.073
14	-0.098	-0.091
11	0.078	0.072
7	-0.019	-0.081
12	-0.127	-0.125
10	-0.149	-0.141
8	-0.134	-0.072
13	-0.023	-0.026
1	-0.076	-0.077
9	-0.092	-0.095
4	-0.049	-0.047
3	-0.084	-0.086
2	-0.084	-0.083
5"	0.106	0.106
4"	-0.176	-0.177
3"	-0.088	-0.088
1'	-0.054	-0.063
X(Cl)	0.021	0.008

8. The barrier to ring inversion in one of the 7- and 8-chloro compounds was estimated to be lower for the 7-chloro compound. The results of AM1 calculations are shown in Table 2.

CALCULATIONS

Molecular mechanics calculations were performed by MMX-force field implemented in PCMODEL software [17]. For the superimposition of AM1 optimized structures, PCMODEL and MOLBUILD [18] softwares were used. The AM1 [19] calculations were run on a VAX-4000 by using MOPAC 6.0 [20] program. The input files for the AM1 calculations were the optimized geometry of the MMX force field. All the structures were characterized as stationary points and true minima on the potential energy surface in the AM1 calculations using the key word FORCE. A stationary point is described if the first derivatives of the energy with respect to change in the geometry are zero. The criteria for a minimum is that all eigenvalues of the Hessian matrix are positive [21]. The barrier to ring inversion by AM1 was searched by SADDLE key word.

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