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Theoretical study of structure, pK_a, lipophilicity, solubility, absorption, and polar surface area of some centrally acting antihypertensives

Milan Remko,[a,*] Marcel Swart[b] and F. Matthias Bickelhaupt[b]

[a]*Comenius University, Department of Pharmaceutical Chemistry, Odbojarov 10, SK-832 32 Bratislava, Slovakia*
[b]*Vrije Universiteit Amsterdam, Department of Chemistry and Pharmaceutical Sciences, Section Theoretical Chemistry, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands*

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Abstract—The methods of theoretical chemistry have been used to elucidate the molecular properties of the substituted imidazoline and oxazoline structures, a class of potent agonists and antagonists of imidazoline receptors. The geometries of various tautomers and isomers of 2-[2,6-dichlorophenylimino]imidazolidine (clonidine), 1-(*N*-dicyclopropylmethyl)amino-2-oxazoline (rilmenidine), 4-chloro-*N*-(4,5-dihydro-1*H*-imidazol-2yl)-6-methoxy-2-methyl-5-pyrimidinamine (moxonidine), *N*-(dicyclopropylmethyl)-4,5-dihydro-1*H*-pyrrol-2-amine (aminopyrroline), *N*-dicyclopropylmethyl-4,5-dihydrothiazol-2-amine (aminothiazoline), 4,5-dihydro-2-(2-methoxyphenyl)-1*H*-imidazole (compound_6), 4,5-dihydro-2-(3-methylthiophen-2-yl)-1*H*-imidazole (compound_7), *N*-(2-chloro-4-iodophenyl)-4,5-dihydro-5-methyl-3*H*-pyrrol-2-amine (LNP_911), *N*-amidino-3,5-diamino-6-chloropyrazine-carboxamide (amiloride), 2-(1,4-benzodioxan-2-yl)-2-imidazoline (idazoxan), (±)-2-(2-ethyl-2,3-dihydro-2-benzofuranyl)-2-imidazoline (efaroxan), (4-aminobutyl)guaninine (agmatine), and 1-methyl-9*H*-pyrido[3,4-*b*]indole (harmane) have been studied using Becke3-LYP/6–31+G(d,p) and BP86/TZ2P DFT methods. The optimized geometries indicate that these molecules show a distinctly non-planar configuration of the imidazoline and oxazoline moieties. In the gas-phase, rilmenidine and aminothiazoline exist in two forms (amino and imino), the amino tautomers being more stable by about 6 kJ/mol. The calculations showed, in agreement with experiments, that clonidine, moxonidine, and LNP_911 exist in a more stable imino tautomer. The tautomer containing the amino group is by about 30 kJ/mol less stable. Computations that include the effect of solvation indicated that also in water the relative stability order of individual tautomers (amino and imino forms) is preserved. The computed pK_a values varied between 6.7 and 9.0, and correlate well with the available experimental pK_a's found in the literature. Among the clinically useful antihypertensives moxonidine exhibits the lowest basicity in water. At pH = 7.4 only about 50% of this drug exists in ionized form. The available experimental partition coefficients of compounds investigated are best reproduced by the CLOGP method. The computed partition coefficients varied between −1.80 (agmatine) and 5.35 (LNP_911) (CLOGP). Clonidine, moxonidine, and rilmenidine are moderately lipophilic compounds with lipophilicities between these two extreme values. The computed solubilities (about 0.1–4 g/L) show that the imidazoline and oxazoline derivatives studied have very low water solubility. The analysis of molecular descriptors defined by Lipinski has shown that most of the compounds studied obey 'rule of five'. Amiloride and agmatine 'outlets' exhibit also the lowest absorption. Therefore, in the early stages of the design of ligands acting on imidazoline binding sites, it is becoming more important to determine the pK_a, lipophilicity, water solubility, polar surface area, absorption, and other physicochemical properties associated with a drug, before synthetic work is undertaken, with the aim of avoiding the synthesis of compounds that are predicted to have poor biopharmaceutical characteristics.

1. Introduction

Clonidine belongs to the class of centrally acting antihypertensive drugs[1,2], which are assumed to induce peripheral sympathoinhibition and reduction in elevated blood pressure as a result of the stimulation of the α_2-adrenergic receptor. Their antihypertensive efficacy is beyond doubt, but their profile of adverse reactions is considered unfavorable when compared with most other

Keywords: Centrally acting antihypertensives; Conformational analysis; Tautomerization; Solvent effect; pK_a; Lipophilicity; Solubility; Absorption; Polar surface area.
* Corresponding author. Tel.: +42 12501 17225; fax: +42 12501 17100; e-mail: remko@fpharm.uniba.sk

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antihypertensive drugs currently used.[3] However, the discovery of new binding sites specifically recognizing the imidazoline structure or similar chemical structures, both in the brain and in certain peripheral tissues including the kidney, some of which participate in the control of blood pressure,[4,5] resulted in the development of a second-generation of centrally acting antihypertensives[4–16] (moxonidine and rilmenidine). Moxonidine and rilmenidine are considered preferable over the classic α_2-adrenoreceptor stimulants because of their favorable pattern of side-effects, which may be explained on the basis of absent or weak affinity for the α_2-adrenoreceptor.[3,14] These new specific binding sites are now generally accepted as receptors (imidazoline receptors), also known as imidazoline binding sites (IBS). Pharmacological studies have allowed the characterization of two subtypes of IBS, I_1 and I_2, based on their binding affinity for different radioligands. Second-generation agents moxonidine and rilmenidine are I_1-receptor-selective ligands.[1,15]

Despite a great deal of pharmacological evidence for the imidazoline receptors at the plasma membrane, none of them have been identified using the techniques of molecular biology. The absence of experimental structural data of imidazoline receptors presents a challenge to the application of molecular modeling methods in order to obtain an insight into the recognition and binding processes. Musgrave et al.[17,18] carried out conformational analysis of clonidine and several structurally diverse imidazoline ligands using the MM+ molecular mechanics force field. Previous quantum chemical studies have been restricted to similar systems (cyclic imidazolines, oxazolines, and thiazolines), Refs. 19,20. Molecular structure and reactivity of imidazoline antihypertensive drugs (clonidine, moxonidine, and rilmenidine) have also been theoretically investigated.[21,22]

In this paper, we have used the results of large-scale theoretical calculations for the study of stable geometries of various tautomers and rotamers of clonidine (**1**), rilmenidine (**2**), moxonidine (**3**), aminopyrroline (**4**), aminothiazoline (**5**), compound_6 (**6**), compound_7 (**7**), LNP_911 (**8**), amiloride (**9**), idazoxan (**10**), efaroxan (**11**), agmatine (**12**), and harmane (**13**). All structures investigated are shown in Figure 1. Of particular interest are the molecular geometries, tautomeric equilibria, basicities, lipophilicities, and solubilities. The results of theoretical studies of compounds **1**–**13** were compared and discussed with the present theories of action of these agents.

2. Results and discussion

2.1. Geometries

An analysis at the Becke3LYP/6–31+G(d,p) level of theory optimized species revealed that these are minima since frequency analysis showed that each molecule's Hessian matrix had no negative eigenvalues, thus demonstrating that there were no imaginary frequencies.

Selected geometric parameters are listed in Table 1. Some trends are apparent:

The C(1)–N(2) and C(1)–C(5) bonds in clonidine (**1**) change only slightly upon bioisosteric substitution of nitrogen atom of imidazoline ring for oxygen, sulfur, and carbon atoms in rilmenidine (**2**), aminothiazoline (**5**), aminopyrroline (**4**), and LNP_911 (**8**), respectively. The N(2)–C(3) single bonds in most stable imino tautomers of clonidine (**1**), moxonidine (**3**), and LNP_911 (**8**) are about 0.11 Å longer than those double bonds in rilmenidine (**2**) and aminothiazoline (**5**). The C(3)–N(6) bonds and N(6)–C(7) bonds of the connecting chain are slightly shorter in imino tautomers. The sp^3 hybridized nitrogen atoms of the most stable amino tautomers of rilmenidine (**2**), aminopyrroline (**4**), and aminothiazoline (**5**) are slightly pyramidal. The arrangement of bonds about the sp^2 hybridized bridging nitrogen atoms N(6) in clonidine (**1**), moxonidine (**3**), and LNP_911 (**8**) is nearly planar. The computed N(6)–C(7) bond length of about 1.38–1.40 Å (Table 1) exhibits double bond character and indicates strong stabilizing conjugation of N(6) nitrogen atom with aromatic system of these species. All the molecules show a distinctly nonplanar configuration in the C(1)–C(5) moiety of the cyclic imidazoline, oxazoline, and thiazoline rings. These rings adopt a half-chair conformation (dihedral angle Φ[N(2)–C(1)–C(5)–N(4)]). The –X–C(NH_2)=N– (X = NH, O, and S) grouping is slightly more planar in most stable amino forms of drugs studied (rilmenidine (**2**) and aminothiazoline (**5**)). A half-chair conformation of the oxazoline ring in rilmenidine dihydrogenphosphate was also observed experimentally.[23] It is in vapor state stabilized by the favorable electrostatic interaction between partially positively charged hydrogen and partially negatively charged heteroatoms. The 2-amino substituents (N–H group) in the species studied are oriented to form an intramolecular hydrogen bond with one of the heteroatoms. The phenyl rings and imidazoline (pyrroline) moieties in the clonidine (**1**), moxonidine (**3**), and LNP_911 (**8**) are in mutual nonplanar conformation [dihedral angle C(3)–N(6)–C(7)–C(8)]. For a substantially lower value of this angle in the most stable IIA tautomer of moxonidine (**3**) the intramolecular hydrogen bond N–H···O is responsible. Its length r(H···O) = 2.12 Å is much less than the sum of the van der Waals radii of the atoms[24] (2.7 Å for H···O contact). For rilmenidine species this dihedral angle is substantially reduced due to the sp^3 hybridization on the C(7) carbon atom. The aromatic and imidazoline systems in idazoxan (**10**) are practically coplanar (Table 1) and this compound exhibits preferential affinity for I_2 sites.[25] Benzofuranyl and imidazoline rings in efaroxan (**11**) are in a mutual perpendicular arrangement (dihedral angle N(2)–C(3)–N(6)–C(7) = 85.5°). Efaroxan (**11**) is a potent I_1 ligand.[25] It is thus probable that the ligands with the highest selectivity for the I_2 receptors may assume a more or less planar conformation. Carrieri et al. also confirmed this finding in their 3D-QSAR study of derivatives of idazoxan (**10**).[26] Amiloride (**9**) computed planar most stable conformer IA is stabilized by means of two intramolecular hydrogen bonds with the lengths 2.11 Å (=N–H···O bond) and 1.95 Å (>N–H···O contact),

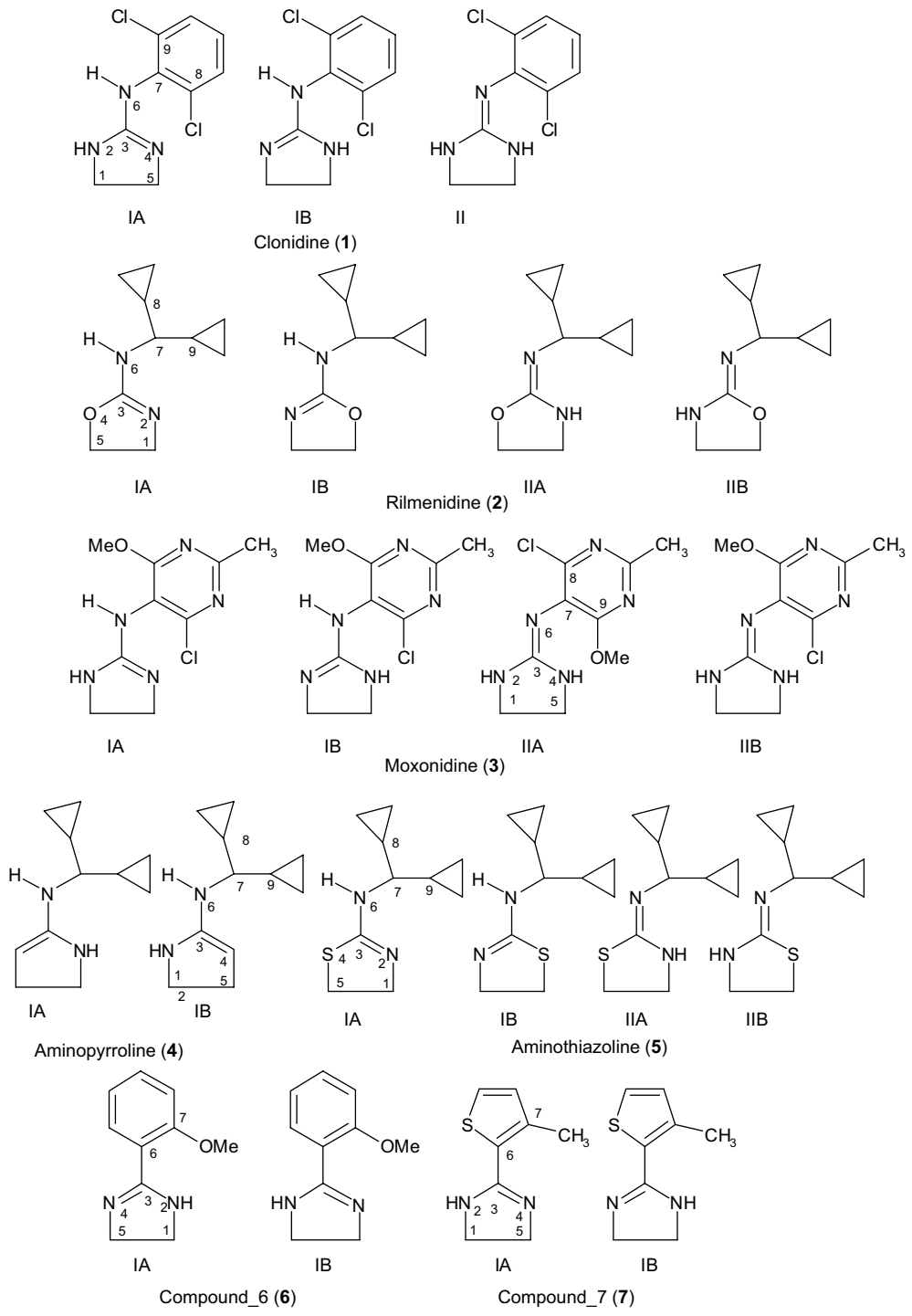

Figure 1. Structure and atom labelling in the compounds studied.

respectively. Its planar structure with intramolecular hydrogen bonds is also preserved in the solvated state. Amiloride (**9**) also displayed high affinity for imidazoline I_2 receptor.[27] The existence of planar stable conformers of amiloride salts (hydrochloride and picrate) was also confirmed experimentally.[28,29] Full geometry optimization of agmatine (**12**) resulted in the most stable all-*trans* conformation (Fig. 1).

The effect of solvent on the geometry of the compounds studied was examined using the COSMO model of solvent (water) in combination with the BP86/TZ2P method. The compounds investigated contain a small number of rotatable bonds and thus one does not expect large changes in geometry upon solvation. Selected bond lengths, bond angles, and dihedral angles of the most stable species obtained by the BP86/TZ2P method and COSMO model of solvent are presented in Table 2. The optimal geometrical parameters of molecules computed within a PCM polarizable conductor calculation model (COSMO) and solvent water do not considerably differ from those obtained for isolated molecules (Tables 1 and 2).

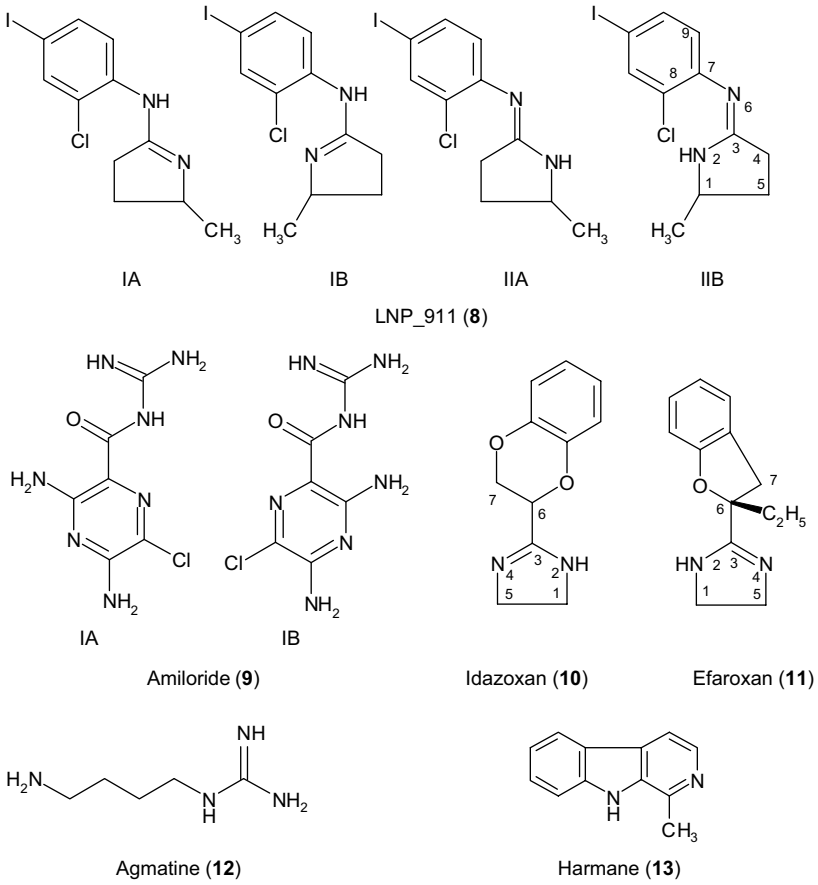

Figure 1 *(continued)*

Table 1. Selected B3LYP/6–31+G(d,p) optimized geometries of the most stable species of clonidine (**1**), rilmenidine (**2**), moxonidine (**3**), aminopyrroline (**4**), aminothiazoline (**5**), compound_6 (**6**), compound_7 (**7**), LNP_911 (**8**), idazoxan (**10**), and efaroxan (**11**)

Parameter[a]	Species									
	1, II	**2**, IA	**3**, IIA	**4**, IB	**5**, IA	**6**, IA	**7**, IA	**8**, IIB	**10**	**11**
d[C(1)–N(2)]	1.462	1.467	1.462	1.481	1.457	1.467	1.473	1.471	1.473	1.472
d[C(1)–C(5)]	1.539	1.547	1.539	1.547	1.547	1.549	1.551	1.544	1.553	1.553
d[N(2)–H]	1.010		1.011	1.016		1.010	1.013	1.014	1.012	1.012
d[N(2)–C(3)]	1.382	1.285	1.388	1.419	1.280	1.393	1.404	1.374	1.387	1.389
d[C(3)–N(4)]	1.387	1.378	1.384	1.351	1.825	1.293	1.291	1.518	1.284	1.285
d[N(4)–C(5)]	1.466	1.452	1.467	1.615	1.834	1.472	1.471	1.540	1.478	1.477
d[C(3)–N(6)]	1.286	1.366	1.289	1.392	1.364	1.485	1.461	1.287	1.505	1.513
d[N(6)–C(7)]	1.386	1.483	1.381	1.477	1.482			1.398		
d[N(6)–H]		1.010		1.014	1.009					
Θ[C(1)–N(2)–C(3)]	110.1	106.0	109.4	106.2	112.1	106.9	106.1	113.4	105.9	106.1
Θ[N(2)–C(3)–N(4)]	107.5	118.5	107.8	112.3	117.0	115.6	115.9	107.7	117.1	116.8
Θ[N(2)–C(1)–C(5)]	100.8	104.3	101.5	104.0	109.8	100.3	100.9	101.3	100.6	100.5
Θ[C(3)–N(4)–C(5)]	109.8	105.1	109.9	109.0	87.8	106.5	106.6	104.1	105.8	106.0
Θ[C(1)–C(5)–N(4)]	101.0	103.4	100.8	102.0	104.1	105.5	105.9	104.1	105.5	105.6
Θ[N(2)–C(3)–N(6)]	122.8	125.4	130.7	114.6	127.3	122.4	119.9	129.1	119.6	119.5
Θ[C(3)–N(6)–C(7)]	121.9	125.6	125.0	123.1	125.5	124.7	128.4	121.4	112.9	
Φ[C(1)–N(2)–C(3)–N(4)]	−11.9	4.7	9.0	15.5	4.7	−15.2	−14.1	−9.1	14.5	−14.4
Φ[N(2)–C(3)–N(4)–C(5)]	−10.6	6.3	13.1	0.8	12.9	−0.3	0.3	−11.1	−0.1	0.0
Φ[N(2)–C(1)–C(5)–N(4)]	−31.5	9.7	31.0	24.0	31.9	−22.2	−20.0	−30.0	21.1	−20.9
Φ[C(1)–N(2)–C(3)–N(6)]	166.3	−172.2	−174.0	−164.3	−172.3	168.4	168.2	171.2	−169.7	171.1
Φ[N(2)–C(3)–N(6)–C(7)]	176.4	−153.6	5.4	−164.8	−4.1	−20.0	−165.3	−4.0	156.2	85.5
Φ[C(3)–N(6)–C(7)–C(8)]	−75.7	−82.3	−135.9	−67.1	−75.1			−77.5		
Φ[C(3)–N(6)–C(7)–C(9)]	110.7	49.0	51.5	63.7	56.1			107.9		

Bond lengths are in angstrom, bond angles and dihedral angles in degrees.

[a] For rilmenidine species atom with number 4 is oxygen; for aminothiazoline atom with number 4 is sulfur, for compound_6 and compound_7 atom with number 6 is carbon.

Table 2. Selected structural parameters of most stable conformers of the clonidine (**1**), rilmenidine (**2**), moxonidine (**3**), aminopyrroline (**4**), aminothiazoline (**5**), compound_6 (**6**), compound_7 (**7**), LNP_911 (**8**), idazoxan (**10**), and efaroxan (**11**) computed using the COSMO BP86/TZ2P method

Parameter[a]	Species								
	1, II	**2**, IB	**2**, IA	**3**, IIA	**3**, IIB	**4**, IB	**4**, IA	**5**, IA	**5**, IB
d[C(3)–N(6)]	1.302	1.363	1.357	1.307	1.304	1.389	1.397	1.359	1.365
d[N(6)–C(7)]	1.389	1.491	1.482	1.380	1.387	1.484	1.496	1.484	1.487
Θ[C(3)–N(6)–C(7)]	121.3	125.5	126.0	124.4	121.6	123.4	121.9	126.5	127.6
Φ[N(2)–C(3)–N(6)–C(7)]	174.1	−152.9	16.7	−174.9	−172.8	−159.8	54.9	−4.6	−153.0
Φ[C(3)–N(6)–C(7)–C(8)]	111.3	−82.4	−79.8	−137.2	−118.2	−69.2	−75.5	−75.7	−76.0
Φ[C(3)–N(6)–C(7)–C(9)]	−75.5	49.0	51.3	50.9	70.1	61.7	55.5	55.4	54.7

	Species						
	6, IA	**7**, IB	**7**, IA	**8**, IIA	**8**, IIB	**9**	**10**
d[C(3)–N(6)]	1.483	1.489	1.459	1.298	1.300	1.507	1.516
d[N(6)–C(7)]				1.396	1.402		
Θ[C(3)–N(6)–C(7)]				121.6	120.6		
Φ[N(2)–C(3)–N(6)–C(7)]	−19.7	6.8	−166.1	176.0	−3.5	155.4	87.4
Φ[C(3)–N(6)–C(7)–C(8)]				−77.7	−78.4		
Φ[C(3)–N(6)–C(7)–C(9)]				109.1	107.5		

Bond lengths are in angstrom, bond angles and dihedral angles in degrees.
[a] For rilmenidine species atom with number 4 is oxygen; for aminothiazoline atom with number 4 is sulfur, for compound_6 and compound_7 atom with number 6 is carbon.

Byre et al.[30] determined the crystal structure of clonidine hydrochloride. According to this work, the imidazoline part of drug is protonated and the two nitrogen atoms of the imidazoline moiety are thus chemically equivalent. In the absence of experimental gas-phase data, the geometry of the parent drug can be compared only with X-ray data on clonidine hydrochloride (Table 3). The selected structural parameters of the experimentally determined structure of clonidine hydrochloride and computed geometries from two DFT methods are listed in Table 3. The solid-state structure of clonidine hydrochloride can be affected by so-called packing effects, which can distort the structure. Since both methods are based on different models, the general structural

Table 3. Experimental and computed geometry of clonidine hydrochloride

Parameter[a]	Clonidine hydrochloride[b]			
	X-ray[a]	B3LYP	BP86	BP86–CPCM
d[C(1)–N(2)]	1.447	1.478	1.478	1.478
d[C(1)–C(5)]	1.532	1.546	1.550	1.550
d[N(4)–Cl]	3.177	2.881	2.881	2.879
d[N(2)–C(3)]	1.321	1.373	1.388	1.387
d[C(3)–N(4)]	1.322	1.307	1.294	1.294
d[N(4)–C(5)]	1.450	1.469	1.472	1.472
d[C(3)–N(6)]	1.327	1.355	1.377	1.377
d[N(6)–C(7)]	1.418	1.423	1.412	1.411
Θ[C(1)–N(2)–C(3)]	111.4	107.7	106.5	106.5
Θ[N(2)–C(3)–N(4)]	111.7	113.3	115.7	115.7
Θ[N(2)–C(1)–C(5)]	102.6	101.8	101.9	101.7
Θ[C(3)–N(4)–C(5)]	110.6	109.6	107.8	107.8
Θ[C(1)–C(5)–N(4)]	103.5	103.9	104.9	104.9
Θ[N(2)–C(3)–N(6)]	123.1	120.2	117.0	117.2
Θ[C(3)–N(6)–C(7)]	123.0	123.9	124.8	124.4
Θ[C(3)–N(4)–Cl]	133.0	130.7	133.8	133.3
Φ[C(1)–N(2)–C(3)–N(4)]	1.0	−11.2	−11.7	−11.7
Φ[N(2)–C(3)–N(4)–C(5)]	−0.5	−2.8	0.3	0.2
Φ[N(2)–C(1)–C(5)–N(4)]	0.7	−19.9	−16.4	−16.6
Φ[C(1)–N(2)–C(3)–N(6)]	−177.3	168.8	169.8	169.4
Φ[N(2)–C(3)–N(6)–C(7)]	178.1	178.8	179.4	179.4
Φ[C(3)–N(6)–C(7)–C(8)]	−76.4	−106.6	−119.9	−118.5
Φ[C(3)–N(6)–C(7)–C(9)]	105.1	75.1	65.4	66.5
Φ[N(2)–C(3)–N(4)–Cl]	148.4	−153.4	−146.3	−145.8

Bond lengths are in angstrom, bond angles and dihedral angles in degrees.
[a] For numbering of atoms, see Figure 1.
[b] Ref. 30.

motifs of clonidine hydrochloride can be compared with results from theoretical methods only. As it is seen from Table 3 the main differences between the solid-state structure and structure computed by the DFT methods resulted from the different orientation of the imidazoline and phenyl rings. In solid-state the angle between the ring planes is −76.4°. Atoms of the phenyl ring are strictly coplanar, as are the atoms of the five-membered ring.[30] The computed structural parameters using two model chemistries are in very good agreement. The six-membered ring of clonidine (**1**) is planar and the imidazoline ring is slightly bent (Table 3). However, the deviation from planarity is lower than that found for basic imidazoline drugs (Table 1). The effect of solvent (water) on the stable structure was computed to be unimportant (Table 3). The differences found in the space orientation of pharmacophoric imidazoline and lipophilic phenolic groups of clonidine (**1**) in the solid-state and as isolated molecule indicate that clonidine (**1**) (and other imidazoline structures) may change their conformation upon binding to a protein. Thus, the conformation of these drugs observed in the single crystal may differ from that bound to the protein.

2.2. Relative energies

The relative energies, computed at the two levels of theory, of various species with respect to the most stable structures of compounds studied are reported in Table 4. Although the values of the relative energies computed by two theoretical methods in some cases differ, both methods yield the same relative stability of individual tautomers and conformers. The inclusion of solvent effect within the continuum PCM and COSMO (CPCM) models caused considerable reduction of the relative stability of individual species. Single-point PCM calculations using the Becke3LYP/6–31+G(d,p) method are in good agreement with the results of more sophisticated BP86/TZ2P calculations including geometry optimizations using the COSMO model of solvent effect (Table 4). In the case of ligands, for which the coexistence of two stable species in vapor phase is characteristic, the hydration causes a change of the stability order. However, the energy difference between two stable conformers is small and for rilmenidine (**2**), moxonidine (**3**), aminopyrroline (**4**), aminothiazoline (**5**), compound_7 (**7**), and LNP_911 (**8**) the two stable conformers may co-exist (Table 4). The superposition of these most stable conformers of rilmenidine (**2**), moxonidine (**3**), and LNP_911 (**8**) is shown in Figure 2. The imidazoline, oxazoline, and pyrroline parts of these drugs adopt the same geometry, suggesting that this part of the drug interacts with complementary binding sites of receptor via hydrogen bonding. The hydrophobic cyclopropyl and phenyl groups of rilmenidine (**2**) and LNP_911 (**8**) do not occupy common space. It is thus probable, that these two stable conformers could access different hydrophobic parts of the receptor pocket. In the case of moxonidine (**3**), the pyrimidine part is in both stable conformers (IIA and IIB) situated in the same place. It means that moxonidine (**3**) will probably interact with one defined binding site of the receptor. The computed geometric parameters of most stable solvated structures

Table 4. Relative energies (kJ/mol) of the clonidine (**1**), rilmenidine (**2**), moxonidine (**3**), aminopyrroline (**4**), aminothiazoline (**5**), compound_6 (**6**), compound_7 (**7**), LNP_911 (**8**), and amiloride (**9**) species studied (Fig. 1)

Species	ΔE[a]	ΔE_{solv}[a,b]	ΔE[c]	ΔE_{solv}[c,d]
Clonidine				
II	0	0	0	0
IB	31.5	38.9	30.6	34.1
IA	35.8	34.6	36.2	28.3
Rilmenidine				
IA	0	1.5	0	0.2
IB	5.4	0	5.9	0
IIB	14.9	6.7	13.5	6.7
IIA	28.4	15.3	25.7	9.5
Moxonidine				
IIA	0	3.1	0	0
IIB	4.0	0	2.9	1.8
IA	29.5	30.0	32.5	31.6
IB	35.8	40.0	32.4	31.3
Aminopyrroline				
IB	0	0	0	0
IA	3.1	6.8	2.4	2.1
Aminothiazoline				
IA	0	0	0	0
IB	5.9	5.1	5.6	0.1
IIB	15.3	21.5	14.8	5.5
IIA	24.6	34.2	24.0	11.3
Compound_6				
IA	0	0	0	0
IB	18.4	9.1	16.1	7.4
Compound_7				
IA	0	0	0	3.6
IB	3.5	1.9	3.9	0
LNP_911				
IIB	0		0	0.9
IIA	1.3		1.3	0
IB	27.0		28.2	15.9
IA	27.9		29.3	26.6
Amiloride				
IA	0	0	0	0
IB	63.0	41.6	64.9	37.1

[a] Becke3LYP/6–31+G(d,p) method.
[b] Single-point Becke3LYP/6–31+G(d,p)calculations using the PCM model of solvent.
[c] BP86/TZ2P calculations.
[d] Geometry optimisations using the BP86/TZ2P method and COSMO model of solvent.

(Table 2) indicate that the hydrophobic part of the drug is likely to occupy a region that is not coplanar with the plane of imidazoline, oxazoline, and pyrroline rings. It is well known[31] that especially flexible molecules change their conformation upon binding to a protein. This should be true especially in the case of rilmenidine (**2**), aminopyrroline (**4**), and aminothiazoline (**5**), which possess four rotatable bonds. In our calculations, the structures of clonidine (**1**), rilmenidine (**2**), moxonidine (**3**), aminothiazoline (**5**), and LNP_911 (**8**), respectively, were considered in two sets of tautomeric amino (I) and imino (II) structures. For imidazoline compounds (clonidine (**1**) and moxonidine (**3**), and LNP_911 (**8**))

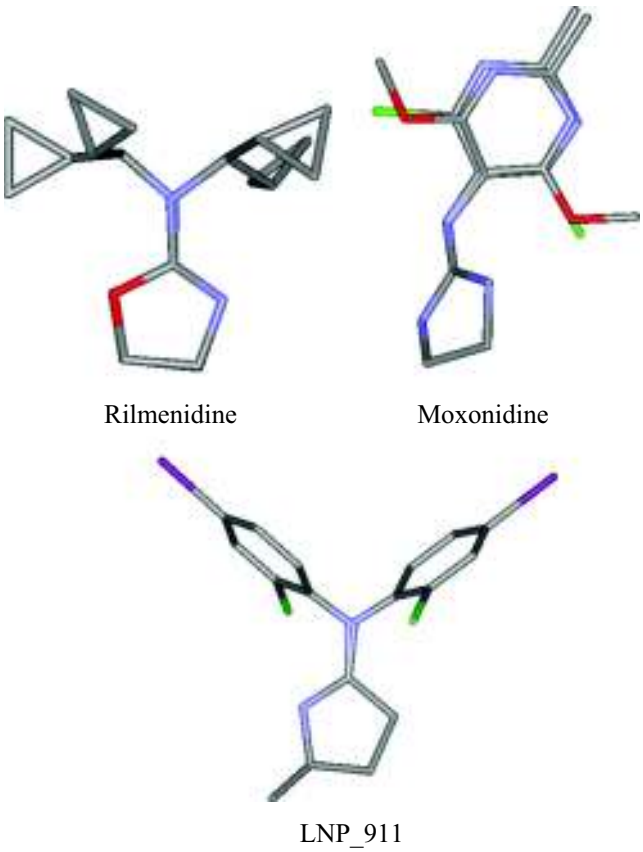

Figure 2. A molecular superimposition of the minimum energy conformations of rilmenidine (**2**) (conformers IA and IB), moxonidine (**3**) (conformers IIA and IIB), and LNP_911 (**8**) (conformes IIA and IIB). For simplicity the hydrogen atoms are omitted.

the tautomeric imino form is substantially more stable by about 15–30 kJ/mol than the amino tautomers. Spectroscopic studies reveal that, at room temperature, the imino tautomer of clonidine (**1**) is more prevalent.[32,33] The computed relative stability of the two tautomers of clonidine (**1**) and other imidazoline structures corresponds well to the conclusion reached using experimentally observed data[34] (NMR spectroscopy) that, in cyclic amidines, the predominant tautomer is the imino form. The calculations in the presence of solvent (water) have shown that water further stabilizes imino tautomers of clonidine (**1**) and moxonidine (**3**). However, in the case of oxazoline and thiazoline structures (rilmenidine (**2**) and aminothiazoline (**5**)) the imino tautomers were found, in comparison with the amino species, in vacuum by some 15 kJ/mol less stable. The solvent stabilizes imino tautomers. This stabilization is, however, not sufficient and, thus, in solution, imino tautomers of rilmenidine (**2**) and aminothiazoline (**5**) cannot exist with practically any probability (Table 4). Tautomeric equilibria are strongly dependent on the environment surrounding the tautomers. Previous theoretical studies[35] on the tautomerism of clonidine (**1**) in vacuum and in an aqueous medium using Born's theory of ion solvation have shown that the solvent does not change the relative stability of the individual tautomers of this drug. However, the results of ab initio SCF calculations of simpler model systems[20] using the SCRF formalism (2-amino-2-imidazoline, 2-amino-2-oxazoline, and 2-amino-2-thiazoline) showed that solvation causes a shift in the tautomeric equilibrium toward the species with the double bond localized out of the five-membered ring. The MD simulations of the more complex phenyl substituted derivatives (2-phenylamino-2-imidazoline, 2-phenylamino-2-oxazoline, and 2-phenylamino-2-thiazoline) have shown that the effect of water has a remarkable effect on the amino ↔ imino tautomeric equilibrium.[21] Accordingly, the presence of water results in a net stabilization of the imino species of phenyl substituted derivatives. Thus, the dehydration of imidazoline, oxazoline, and thiazoline drugs at the α_2-adrenergic and/or imidazoline receptors may lead to a stronger stabilization of the amino tautomers and yield structures that can be recognized by the receptor. Previous ab initio calculations[19] of 2-amino-2-imidazoline, 2-amino-2-oxazoline, and 2-amino-2-thiazoline have shown that the most stable structures of these compounds are stabilized via intramolecular hydrogen bonds. These hydrogen bonds are, however, weak and amino derivatives of rilmenidine (**2**), aminopyrroline (**4**), aminothiazoline (**5**), and compound_7 (**7**), respectively, may exist in two stable forms (conformers A and B, Fig. 1). Venanzi and co-workers carried out molecular dynamics calculations of amiloride.[36] Their study has shown that the relative internal energy of conformer IA was lower than that of IB, Figure 1. The solute–solvent interaction stabilized the IB conformer. However, the IA conformer was predicted to be more stable in solution than IB. This finding is in full agreement with the results of our calculations (Table 4).

2.3. Dissociation constants

Dissociation plays an important role in both partition and receptor binding processes of drug action. It is therefore important to know if drug molecules exist predominantly in the basic or protonated forms. The imidazoline and oxazoline structures studied contain both proton acceptor and proton donor groups, which may be at suitable experimental conditions ionized and/or protonated.[37–40] The ONIOM (B3LYP 6–311+G(d,p):MNDO) calculations[21,22] of gas-phase acidities and basicities of the clonidine (**1**), moxonidine (**3**), and rilmenidine (**2**) have shown that these drugs are weak acids. These calculations also showed that the primary protonation sites are the imidazoline and oxazoline parts of these drugs. However, the gas-phase basicities (Table 5) of these drugs differ only slightly. In solution, dissociation constant or the pK_a is a measure of the strength of an acid or a base. Therefore, this parameter is very useful in understanding the behavior of drug molecules at the site of action. We used software

Table 5. Gas-phase basicities of clonidine (**1**), moxonidine (**3**), and rilmenidine (**2**) (Refs. 21,22)

Compound	ΔH^{298} (kJ/mol)	ΔS^{298} (J/K/mol)	ΔG^{298} (kJ/mol)
Clonidine	−996.5	8.7	−999.1
Moxonidine	−999.5	14.0	−1003.7
Rilmenidine	−997.5	−3.0	−996.6

SPARC to compute the theoretical pK_a values of studied structures in condensed phase (water). The calculated macroscopic pK_a values are listed in Table 6. The computed pK_a values correlate well with the available experimental pK_a values found in the literature. The larger difference between calculated and experimental pK_a values was observed for rilmenidine (**2**) only. However, the experimentally determined pK_a values represent composite pK_a values of the various ionization sites and tautomers.[44] Our previous study of protonation of rilmenidine (**2**) has been shown that protonation of both amino and imino tautomers of rilmenidine (**2**) resulted in one stable structure. These studies suggested to us that ionization and tautomerization might be linked, in that ionization may provoke a shift to an alternative tautomeric form.[22] Owing to the small energy difference of amino and imino tautomers of rilmenidine (**2**) (Table 4) we computed the pK_a values for both amino (pK_a = 6.02) and imino (pK_a = 12.22) tautomers. An average pK_a of 9.12 fits very well the experimentally determined value. Matoga et al. recently determined pK_a values of eight 5-substituted 2-amino-2-oxazolines by capillary electrophoresis.[45] The pK_a values of these very poorly water-soluble compounds have been found to vary between 8.55 and 8.68. The gas-phase basicities of clonidine (**1**), moxonidine (**3**), and rilmenidine (**2**) do not correlate with the experimental (or computed) pK_a values (Tables 5 and 6), indicating that the solvation medium considerably influences the basicity of parent compounds. Of three clinically useful drugs (clonidine (**1**), rilmenidine (**2**), and moxonidine (**3**)) the moxonidine (**3**) exhibits in water lowest basicity. At pH = 7.4 only about 50% of this drug exists in ionized form. On the other hand, clonidine (**1**) and rilmenidine (**2**) at pH = 7.4 exist in prevailing ionized form. Rilmenidine (**2**) is at this pH almost completely ionized (Table 6). Since different complementary binding sites of the receptor are able to bind the neutral base or protonated imidazoline structure, it is probable that the molecular mechanism of action is not the same in the case of moxonidine (**3**) (half-ionized drug) and rilmenidine (**2**) (completely ionized species). This could be especially true in the case of imidazoline binding sites. Since biochemical studies[27] have purified various imidazoline binding proteins of 27–85 kDa, from several tissues and species, it clearly indicates the existence of a heterogeneity of imidazoline binding proteins. Thus, owing to the different basicity and structural parameters moxonidine (**3**) and rilmenidine (**2**) may interact with different imidazoline binding sites. Some trends in basicities (in water) of both imidazoline and oxazoline drugs are noticeable. Of the structures investigated the oxazoline derivative rilmenidine (**2**) is the most basic compound. Oxygen atom in cyclic oxazolines through its mesomeric effect effectively increases polarizability of the –O–C(NH_2)=N– moiety what results in the increasing of basicity at the nitrogen basic center. The increased polarizability of bases due to unsaturation results in substantially greater proton affinities in $=N\cdots H^+$ systems in comparison to the $-N\cdots H^+$ systems.[46] Aminopyrroline (**4**), pyrrolinic isostere of rilmenidine (**2**), was computed about 2.4 pK_a units less basic. For this considerable reduction of basicity of this compound substantially increased lipophilicity of aminopyrroline (**4**) (see Section 2.4) is apparently responsible. Imidazoline derivatives idazoxan (**10**), efaroxan (**11**), compound_6 (**6**), and compound_7 (**7**) with computed pK_a values from a relatively narrow interval of 7–8 pK_a units are at physiological pH = 7.4 more or less protonated (Table 6). Idazoxan (**10**) and efaroxan (**11**) are antagonists of α_2-adrenergic receptors.[47,48] On the other hand, with compound **7** its α_2-adrenergic activity was dramatically reduced.[49] Agmatine (**12**) and harmane (**13**) are endogenous ligands of imidazoline receptors. Agmatine (**12**), like clonidine (**1**), binds to the α_2-adrenergic and imidazoline binding sites.[41] Harmane (**13**) has been reported to have high affinity for I_1 sites.[25] For the different binding characteristics of these two identified endogenous ligands of IBSs different basicity and other physicochemical parameters are apparently responsible. Harmane (**13**) is a highly lipophilic, structurally rigid compound, partially ionized at the physiological pH (Table 6). Owing to high pK_a = 8.93 agmatine (**12**) is in biological tissues present in the protonated form.

Several of the compounds investigated are strong bases (pK_a > 8.5) and at pH = 7.4 will be mainly in an ionized form. The basicity (or acidity) of a drug can influence its

Table 6. The pK_a values of the compounds investigated

No.	Compound	pK_a		% Ionized form		pK$_I$, receptor[a]		
		Exp	Calcd	Exp	Calcd	α_2	I_1	I_2
1	Clonidine	8.2	8.18	86	86		7.25	6.02
2	Rilmenidine	9.0	9.12	97	98	6.90	7.22	5.96
3	Moxonidine	7.45	7.40	53	50	<5	8.37	<5
4	Aminopyrroline		6.68		16			
5	Aminothiazoline		6.47		11			
6	Compound_6		6.92		25		8.53	
7	Compound_7		7.94		78		8.37	
8	LNP_911		7.90		76		1.40[b]	
9	Amiloride		8.27		88			
10	Idazoxan	8.8	7.91	96	76		5.90	7.22
11	Efaroxan		7.92		77		7.28	<5
12	Agmatine		8.93		97	<5	7.48	<5
13	Harmane		7.16		37			

[a] Refs. 41,42.
[b] K_D value, Ref. 43.

bioavailability. Yoshida and Toplis[50] find that Bronsted acids have a better oral bioavailability than neutral species, and that Bronsted bases have lower bioavailability than neutral species. It is further shown that for strong Bronsted bases and acids, the rate constant for absorption of ionic species is close to that for absorption of the corresponding neutral species, so that to a first approximation the percentage of internal absorption can be calculated from the properties of neutral species.[51] However, human bioavailability of a drug influences also other physicochemical parameters (lipophilicity, solubility, molecular weight, counts of hydrogen bond acceptors and donors in molecule, etc.). These parameters should serve as important molecular predictors[52] of good oral bioavailability. Thus, computed and/or experimentally determined physicochemical parameters of clinically useful antihypertensives can serve as a yardstick in the design of new compounds with desired pharmacological activity and good pharmacokinetic profiles.

2.4. Lipophilicity

Poor solubility and poor permeability are among the main causes for failure during drug development.[44,53] It is therefore important to determine these physicochemical properties associated with a drug, before synthetic work is undertaken. The computed log *P* values (*P* is the partition coefficient of the molecule in the water/octanol system), together with the experimental data, are shown in Table 7. The ALOGPs and ALOGpS methods are part of the ALOGPS 2.1 program[54] used to predict lipophilicity[55] and aqueous solubility[56] of compounds. The lipophilicity calculations within this program are based on the associative neural network approach and the efficient partition algorithm. The IA LOGP and IALOGS predictors are yet other methods based on neural network algorithm[57] CLOGP is a fragment-based method.[58] The available experimental partition coefficients of hypotensives investigated are best reproduced by the CLOGP method. The neural network-based IA LOGP and ALOGPs methods perform also fairly well.

Clonidine (**1**) and chemically similar structures are often described as lipophilic drugs.[48] Due to their lipophilicity, these drugs should easily penetrate into the brain, where they could reach concentration higher than in plasma. Such a distribution patterns would support a preferential sympathoinhibitory activity.[48] Thus, the lipophilicity of a centrally acting drug is one of the important parameters, which determine its presence in the brain. Clonidine (**1**), rilmenidine (**2**), and moxonidine (**3**) reduce blood pressure by acting centrally at both α_2-adrenergic receptors and I_1 imidazoline receptors. The prevailing affinity of these drugs can be ascribed, among other factors, also to their different physicochemical parameters. Clonidine (**1**) is, according to the experimental and calculated partition coefficient, a moderately lipophilic compound. Moxonidine (**3**) and rilmenidine (**2**) derivatives possess an even lower lipophilicity. It is probable that lower lipophilicity and better solubility of rilmenidine (**2**) in comparison with those of the clonidine (**1**) are one of the important features, which regulate their affinity for imidazoline-specific binding sites. The bioisosteric replacement of the oxygen atom in rilmenidine (**2**) by the carbon atom in pyrrolinic isosteres of rilmenidine (**2**) abolished the binding affinity for α_2-adrenergic receptors, whereas the I_1-IBS affinity was hardly affected[59] LNP_911 (**8**)—high affinity I_1 receptor ligand[43] is a highly lipophilic compound. Ligands with the net preference for I_2 imidazoline receptors[25,27] (idazoxan (**10**), amiloride (**9**)) are considerably hydrophilic. Endogenous ligands agmatine (**12**) and harmane (**13**) exhibit different affinities for I_1 and I_2 IBS. Harmane (**13**) with high I_1-IBS affinity[25] is one of the most lipophilic compounds studied. Clinically useful clonidine (**1**), rilmenidine (**2**), and moxonidine (**3**) are moderately lipophilic compounds with lipophilicity between these two extreme values. It is therefore probable that lipophilicity is one of the factors that govern the I_1/I_2 selectivity of ligands.

The compounds studied exhibit pK_a values not too far from physiological pH = 7.4 and thus the ionized forms are present in equilibrium with neutral species (Table 6). For description of partition process in the body of these ionizable molecules the experimental distribution coefficient (log *D*) often provides a more meaningful description of lipophilicity. However, theoretically predicted log *D* values for ionizable drugs are not sufficiently accurate (root-mean-squared error of 1.0–1.9 log units) for practical usage.[60,61] Obviously, in the prediction of drug permeability the experimental log *D* is more reliable than

Table 7. Calculated partition coefficients of the compounds investigated

No.	Compound	Log *P* (exp)	ALOGPs	IA LOGP	CLOGP
1	Clonidine	1.59	1.92	1.95	1.43
2	Rilmenidine	1.30	1.43	1.59	1.42
3	Moxonidine		0.77	1.60	1.31
4	Aminopyrroline		1.82	2.72	2.66
5	Aminothiazoline		2.40	2.02	0.78
6	Compound_6		1.69	1.86	2.56
7	Compound_7		1.72	2.08	2.79
8	LNP_911		3.98	4.26	5.35
9	Amiloride		−0.49	−0.87	0.11
10	Idazoxan		1.01	0.90	1.81
11	Efaroxan		2.98	2.32	2.84
12	Agmatine		−1.0	0.92	−1.80
13	Harmane	3.10	3.36	3.01	3.06

the calculated values.[62] However, Raevsky et al.[63] did not find a correlation between log *D* and membrane penetration for 32 compounds. Of the compounds studied by us the experimental distribution coefficient (log *D* = 0.78) for clonidine was determined only.[62]

2.5. Solubility

Log *S*—an intrinsic solubility in neutral state is indicative of a compound's solubility (*S*). As the experimental solubilities of most compounds under study are not known, the log *S* values were calculated using ALOGpS and IA LOGS predictors. Both methods use E-state indices as descriptors and a neural network[56,57] as the modeling 'engine'. The computed solubilities are presented in Table 8. Previous calculations of chemically different biologically active compounds have shown that these methods well reproduce known experimental solubilities.[54,64,65] Drug solubility is one of the important factors, which affect the movement of a drug from a site of administration into the blood. Knowledge of drug solubility is important. It is well known that insufficient solubility of drugs can lead to poor absorption.[66] Investigation of the rate-limiting steps of human oral absorption of 238 drugs (including clonidine (**1**), moxonidine (**3**), and amiloride (**9**)) has shown[66] that the absorption of a drug is usually very low if the calculated solubility is <0.0001 mg/L. Although the imidazoline and oxazoline derivatives studied are only slightly soluble in water, their computed solubilities from the interval between 0.1 and 4 g/L are sufficient for fast adsorption. The lowest solubility is exhibited compound LNP_911 (**8**) (about 10–20 mg/L). Very high lipophilicity and low solubility of LNP_911 (**8**) are probably responsible for its high selectivity for I_1-IBSs. It is known that the different degrees of penetration of agonists and antagonists of α_2-adrenergic and imidazoline receptors may account for the differences that have been observed in whole animal preparations.[67] In the case of clinically useful antihypertensives, solubilities increase in the order: moxonidine (**3**) < clonidine (**1**) ≪ rilmenidine (**2**).

2.6. Absorption, polar surface area, and 'rule of five' properties

High oral bioavailability is an important factor for the development of bioactive molecules as therapeutic agents. Passive intestinal absorption, reduced molecular flexibility (measured by the number of rotatable bonds), low polar surface area or total hydrogen bond count (sum of donors and acceptors) are found to be important predictors of good oral bioavailability.[68,69] Properties of molecules such as bioavailability or membrane permeability have often been connected to simple molecular descriptors such as log *P* (partition coefficient), molecular weight (MW), or counts of hydrogen bond acceptors and donors in a molecule.[70] Lipinski et al.[71] has used these molecular properties in formulating his 'rule of five'. The rule states that most molecules with good membrane permeability have $\log P \leqslant 5$, molecular weight $\leqslant 500$, the number of hydrogen bond acceptors $\leqslant 10$, and the number of hydrogen bond donors $\leqslant 5$. This rule is widely used as a filter for drug-like properties. Table 9 contains a calculated percentage of absorption (%ABS), molecular polar surface area (PSA), and Lipinski parameters of the compounds investigated. Extension of absorption is expressed by the percentage of absorption. Absorption percent was calculated[66] using the expression: %ABS = 109 − 0.345 PSA. Polar surface area (PSA) was determined by the fragment-based method of Ertl et al.[72,73] Two ligands (amiloride (**9**) and agmatine (**12**)) violated 'rule of five' (too high a number of hydrogen bond donors). Since the hydrogen-bonding capacity has been identified as an important parameter for describing drug permeability[69] its violation resulted in a considerably reduced absorption of these ligands. Amiloride (**9**) exhibits medium absorption only (Table 9). High number of hydrogen bond donors and acceptors in the moxonidine (**3**) resulted in its reduced absorption in comparison with the parent clonidine (**1**). The number of hydrogen bond donors and acceptors the rest of the imidazoline and oxazoline derivatives studied is almost constant (about 1–3) and low. Thus, these compounds in their neutral state exhibit low capacity for hydrogen bonding toward proton donor and acceptor groups of the receptor. The low number of rotatable bonds in clonidine (**1**), moxonidine (**3**), compound_6 (**6**), compound_7 (**7**), LNP_911 (**8**), idazoxan (**10**), and efaroxan (**11**) indicates that these ligands upon binding to a protein change their conformation only slightly. A somewhat larger conformational change is possible with more flexible rilmenidine species. Thus, it is probable that suitable basicity, lipophilicity, solubility, and absorption are more important factors for the designing of highly active ligands selectively acting on

Table 8. Calculated solubilities of the compounds studied

No.	Compound	Log *S* (exp)	ALOGPs	IA LOGS
2	Rilmenidine		−2.13 (1.35 g/L)	−1.50 (5.70 g/L)
3	Moxonidine	−2.48 (0.8 g/L)	−3.32 (0.12 g/L)	−3.12 (0.18 g/L)
4	Aminopyrroline		−2.39 (0.73 g/L)	−2.10 (1.42 g/L)
5	Aminothiazoline		−2.39 (0.79 g/L)	−2.37 (0.84 g/L)
6	Compound_6		−2.25 (0.99 g/L)	−2.04 (1.61 g/L)
7	Compound_7		−2.70 (0.33 g/L)	−1.93 (1.95 g/L)
8	LNP_911		−4.56 (9.30 mg/L)	−4.27 (17.97 mg/L)
9	Amiloride		−2.56 (0.64 g/L)	−1.91 (2.83 g/L)
10	Idazoxan		−2.19 (1.33 g/L)	−1.69 (4.17 g/L)
11	Efaroxan		−2.49 (0.70 g/L)	−2.69 (0.44 g/L)
12	Agmatine		−1.56 (3.59 g/L)	−0.90 (16.39 g/L)
13	Harmane		−3.25 (0.10 g/L)	−3.97 (19.53 mg/L)

Table 9. Calculated absorption (%ABS), polar surface area (PSA), and Lipinski parameters of the compounds studied

No.	Compound	%ABS	PSA	NROTB	*n* ON acceptors	*n* OHNH donors	Log *P*, calcd[a]	Formula weight
1	Clonidine	96	36.42	1	3	2	1.43–1.95	230
2	Rilmenidine	97	33.63	4	3	1	1.42–1.59	180
3	Moxonidine	84	71.44	2	6	2	0.77–1.60	242
4	Aminopyrroline	100	24.05	4	2	2	1.82–2.72	178
5	Aminothiazoline	100	24.39	4	2	1	0.78–2.40	196
6	Compound_6	97	33.62	2	3	1	1.69–2.56	176
7	Compound_7	100	24.39	1	2	1	1.72–2.79	166
8	LNP_911	100	24.39	2	2	1	3.98–5.35	335
9	Amiloride	55	156.80	2	8	8, violation	−0.49 to 0.11	230
10	Idazoxan	94	42.86	1	4	1	0.90–1.81	204
11	Efaroxan	97	33.62	2	3	1	2.32–2.98	216
12	Agmatine	79	87.93	5	4	6, violation	−1.80 to 0.92	130
13	Harmane	99	28.68	0	2	1	3.01–3.16	182

[a] Range of log *P* values obtained by three theoretical methods (Table 7).

individual IBSs. One of the presently known most active I_1-IBS ligands LNP_911 (**8**) is a moderately basic compound (pK_a = 7.90), exhibiting very high lipophilicity (C log *P* = 5.35), low solubility (about 10–20 mg/L), and 100% absorption. Polar surface area is, together with lipophilicity and solubility, widely acknowledged as an important factor in transport across membranes.[74] Very high values of PSA result in worsening of the absorption of a drug. Indeed, amiloride (**9**), agmatine (**12**), and moxonidine (**3**) with PSA values between 72 and 156 belong to the compounds with reduced absorption (Table 9).

3. Conclusions

This theoretical study set out to determine stable conformations, tautomeric equilibria, solvent effect, pK_a, lipophilicity, solubility, absorption, and polar surface area of 13 ligands acting on imidazoline binding sites (IBS) for which a relatively small amount of experimental physicochemical data exist, considering its pharmacological importance. Using the theoretical methods the following conclusions can be drawn.

The optimized geometries indicate that ligands with high activity for I_1-IBS show a distinctly nonplanar configuration of the imidazoline and oxazoline moieties. In the gas-phase, the amino tautomers of rilmenidine (**2**) and aminothiazoline (**5**) are more stable by about 6 kJ/mol. The calculations showed, in agreement with experiments, that clonidine (**1**), moxonidine (**3**), and the phenyl, benzofuranyl, dicyclopropylmethyl rings, and imidazoline (pyrroline) moieties in the clonidine (**1**), moxonidine (**3**), LNP_911 (**8**), efaroxan (**11**), and rilmenidine (**2**) are in mutual nonplanar conformation. For I_2-IBS ligands idazoxan (**10**) and amiloride (**9**) the most stable conformers computed are practically planar. Clonidine (**1**), moxonidine (**3**), and LNP_911 (**8**) exist in a more stable imino tautomer. The tautomer containing the amino group is by about 30 kJ/mol less stable. Examination of the solvent effect (using the PCM and CPCM models) has shown that also in water the relative stability order of individual tautomers (amino and imino forms) is preserved.

The computed pK_a values varied between 6.7 and 9.0, and correlate well with the available experimental pK_a's found in the literature. Of the clinically useful antihypertensives the moxonidine (**3**) exhibits in water the lowest basicity. At pH = 7.4 only about 50% of this drug exists in ionized form.

The available experimental partition coefficients of IBS ligands investigated are best reproduced by the CLOGP method. The computed partition coefficients varied between −1.80 (agmatine (**12**)) and 5.35 (LNP_911 (**8**)) (CLOGP). Clonidine (**1**), rilmenidine (**2**), and moxonidine (**3**) are moderately lipophilic compounds with lipophilicity between these two extreme values. The computed solubilities (about 0.1–4 g/L) show that imidazoline and oxazoline derivatives studied are very low water soluble. The analysis of molecular descriptors defined by Lipinski has shown that most of the compounds studied obey 'rule of five'. Amiloride (**9**) and agmatine (**12**) 'outlets' exhibit also the lowest absorption.

Aminopyrroline (**4**) and aminothiazoline (**5**) represent bioisosteric derivatives of rilmenidine, which were not tested for the affinity at the α_2-adrenergic and imidazoline binding sites. The calculated absorption (%ABS), polar surface area, and Lipinski parameters for these compounds are within the general limits found for clinically useful rilmenidine. Therefore, both compounds may serve as leads in the design of new centrally active antihypertensives.

4. Computational details

The geometries of 2-[2,6-dichlorophenylimino]imidazolidine (clonidine, **1**), 1-(*N*-dicyclopropylmethyl)amino-2-oxazoline (rilmenidine, **2**), 4-chloro-*N*-(4,5-dihydro-1*H*-imidazol-2yl)-6-methoxy-2-methyl-5-pyrimidinamine (moxonidine, **3**), *N*-(dicyclopropylmethyl)-4,5-dihydro-1*H*-pyrrol-2-amine (aminopyrroline, **4**), *N*-dicyclopropylmethyl-4,5-dihydrothiazol-2-amine (aminothiazoline, **5**), 4,5-dihydro-2-(2-methoxyphenyl)-1*H*-imidazole (compound_6, **6**), 4,5-dihydro-2-(3-methylthiophen-2-yl)-1*H*-imidazole (compound_7, **7**), *N*-(2-chloro-4-iodophenyl)-4,5-dihydro-5-methyl-3*H*-pyrrol-2-amine (LNP_ 911,

8), *N*-amidino-3,5-diamino-6-chloropyrazine-carboxamide (amiloride, **9**), 2-(1,4-benzodioxan-2-yl)-2-imidazoline (idazoxan, **10**), (±)-2-(2-ethyl-2,3-dihydro-2-benzofuranyl)-2-imidazoline (efaroxan, **11**), (4-aminobutyl)guaninine (agmatine, **12**), and 1-methyl-9*H*-pyrido[3,4-*b*]indole (harmane, **13**) Figure 1 were completely optimized at Becke3LYP/6–31+G(d,p)[75–77] and BP86/TZ2P[76,78] levels of the density functional theory[79–82] (DFT) using the Gaussian 98 program,[83] and Amsterdam Density Functional Program[82,84] systems. The MOs were expanded in a large uncontracted set of Slater-type orbitals (TZ2P),[85] which is of triple-ζ quality, augmented by two sets of polarization functions (3d and 4f on C, N, O; 2p and 3d on H); the core electrons (e.g., 1s for 2nd row, 1s2s2p for 3rd row, etc.) were treated by the frozen core (FC) approximation.[77] An auxiliary set of s, p, d, f, and g STOs was used to fit the molecular density and to represent the Coulomb and exchange potentials accurately in each SCF cycle. Energies and gradients were calculated using the local density approximation (LDA; Slater exchange and VWN[86] correlation) with nonlocal corrections due to Becke[75] (exchange) and Perdew[78](correlation) added self-consistently. This xc-functional is one of the three best DFT functionals for the accuracy of geometries,[87] with an estimated unsigned error of 0.009 Å in combination with the TZ2P basis set.

For evaluation of the solvent effects on the species studied the Polarizable Continuum (overlapping spheres) Model (PCM) of Tomasi and co-workers[88,89] was used in connection with the single-point calculations using the Becke3LYP/6–31+G(d,p) method. In this approach, the solvent is described as a dielectric continuum medium, polarized due to the presence of the solute. A cavity is opened in this dielectric continuum, built from interlocking spheres centered on the nuclei of the solute atoms. Within the BP86/TZ2P method the solvent effect was also evaluated by means of the CPCM model[90–92] (a PCM calculation using the polarizable calculation model COSMO). In these calculations, the full geometry optimizations were also performed for solvated molecules. Lipophilicity and water solubility calculations were carried out using web-based tools.[93] Calculations of macroscopic pK_a were performed using the program SPARC.[94] The computer program SPARC, developed by Carreira et al.[95,96] uses computational algorithms based on the fundamental chemical structure theory to estimate a variety of chemical reactivity parameters (such as ionization pK_a, kinetics, heat of vaporization, boiling point, diffusion coefficient, etc.). SPARC costs the user only a few minutes of computer time and provides greater accuracy than is possible with other conventional methods.[97] For calculations of molecular polar surface areas the fragment-based method of Ertl et al.[72,73] was used.

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