Crystal Structure, Aromatic Character and AM1 Calculations of 2-(*N*'-Benzylidenehydrazino)-4-trifluoromethyl-pyrimidine and 2-(*N*'-2-Methyl-benzylidenehydrazino)-5-methyl-4-trifluoromethyl-pyrimidine

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Abstract: The structure of two novel 2-(*N*'-benzylidenehydrazino)-4-trifluoromethyl-pyrimidines has been determined by X-ray crystallography and their energy-minimized structures were stablished by molecular orbital calculations (AM1) by means of comparison. Additionally, the bond lengths of the compounds were analyzed in order to verify the occurance of electronic resonance. Bond lengths and bond angles in the pyrimidine ring and the benzylidene portion compare well with those found in similar compounds. 2-(*N*'-benzylidenehydrazino)-4-trifluoromethyl-pyrimidine, crystallized in the triclinic space group P-1 solvated with a molecule of water, while 2-(*N*'-2-methyl-benzylidenehydrazino)-5-methyl-4-trifluoromethyl-pyrimidine crystallized in the tetragonal space group P41. The azomethine moieties showed a *trans*-planar conformation. The energy-minimized structures of both compounds are in good agreement with their X-ray crystal structures. Nevertheless, a significant difference between calculated and experimental data regarding to the ring planarity was observed due to relevant intermolecular interactions in the real structures. Finally, aromaticities of both pyrimidines and phenyl rings were determined using HOMA calculations.

Keywords: X-ray, HOMA, AM1, trifluoromethylpyrimidines.

INTRODUCTION

Pyrimidines are an important class of heterocyclic compounds. They have been widely used in areas of great importance such as the agricultural [1], microbiology [2] and medicine fields [3]. In particular, *N*-benzylidenehydrazino pyrimidines have been associated with antitumor, antimicrobial, anti-inflammatory, anti-HIV and analgesic activities [4-6]. Additionally, since these compounds present donor atoms on their structures they are also very appealing ligands for the synthesis of coordination compounds [7].

We have recently described the synthesis, evaluated the cruzain inhibitory activity and proposed a binding model based on docking protocols of novel 2-(*N*'-benzylidenehydrazino)-4-trifluoromethyl-pyrimidines [8]. In order to further advance our knowledge as to how these compounds bind to the *T. cruzi* enzyme and to ultimately improve the potency of these inhibitors definitive structural and electronical data are required.

There are some reports about the characterization of general pyrimidinic compounds based on NMR spectroscopy [9, 10] and X-ray scattering of crystallin supramolecular structures techniques [11-13]. There are very few reports, however, dedicated to the structural assignement of pyrimidines based on X-ray crystallography associated with theoretical calculations or to the aromatic character quantification of such heterocycles [14-16] and, to the best of our knowledge, there are no studies of this nature dealing with *N*'-benzylidenehydrazino pyrimidines.

In this context, we now wish to present the detailed crystal structures based on X-ray experiments combined with theoretical studies by means of semi-empirical molecular orbital calculations (AM1) and a quantitative description of aromaticity based on geometrical indices by means of harmonic oscillator model of aromaticity (HOMA) of two *N*-benzylidenehydrazino pyrimidine derivatives.

MATERIALS AND METHODOLOGY

General Synthetic Procedure

Both 2-(*N*'-benzylidenehydrazino)-4-trifluoromethyl-pyrimidines **I** and **II** (Fig. (**1**)) were prepared from the cyclo-condensation reaction between the related *N*-guanidino-benzylimines and β-alkoxyvinyl trifluoromethyl ketones in excellent yields [8]. Crystals suitable for X-ray diffraction were obtained by slow evaporation of dichloromethane/ methanol solutions of compounds **I** and **II**.

X-Ray Crystallographic Studies

The diffraction measurements were carried out by graphite-monochromatized Mo Kα radiation with λ = 0.71073 Å on a Bruker SMART CCD diffractometer [17]. The structures were solved with direct methods using the SHELXL97 package [18], and refined on F^2 by full-matrix least-squares by SHELXL97 package [18]. The absorption correction was performed by Gaussian methods [19]. The anisotropic

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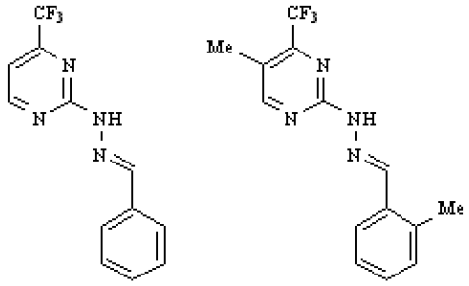
displacement parameters for non-hydrogen atoms were applied. The hydrogen atoms were placed at calculated positions with 0.96 Å (methyl CH_3), 0.97 Å (methylene CH_2), 0.98 Å (methine CH), 0.93 Å (aromatic CH) and 0.86 Å (NH) using a riding model. The hydrogen isotropic thermal parameters were kept equal to *U*iso(H) = *xU*eq (carrier C atom), with *x* = 1.5 for methyl groups and *x* = 1.2 otherwise. The valence angles C–C–H and H–C–H of methyl groups set to 109.5° and H atoms were allowed to rotate around the C–C bond. Molecular graphics were prepared using ORTEP3 for Windows [20].



I **II**

Fig. (1). Chemical scheme of the 2-(*N'*-Benzylidenehydrazino)-4-trifluoromethyl-pyrimidines **I** and **II**.

Semi-Empirical Molecular Orbital Calculations (AM1)

The geometry of compounds were optimized using semi-empirical SCF, AM1 [21] method implemented in the HyperChem 7.52 package (2002) [22]. The structures were fully optimized without fixing any parameter, thus bringing all geometric variables to their equilibrium values. The energy minimization protocol employed the Polak-Ribiere conjugated gradient algorithm. Convergence to a local minimum was achieved when the energy gradient was $\leq$ 0.01 kcal·mol^{-1}. The RHF method was used in the spin pairing for the two semi-empirical tools.

Harmonic Oscillator Model of Aromaticity (HOMA) Calculations

Cyclic compounds with alternating single and double bounds tend to present intermediate bond lengths between those compounds with isolated single and/or double bonds. This property is a cooperative effect of both the σ and π orbitals. The harmonic oscillator model of aromacity (HOMA model) is a quantitative descriptor of this effect (geometric criterion) that allows a quantitative measure of the aromaticity of organic compounds. HOMA is defined as a normalized sum of squared deviations of the individual experimental (or calculated) bond lengths and an optimal bond length, which corresponds to full π -electron delocalization

Eq. 1. $HOMA = 1 - \alpha/n \sum (R_{opt} - R_i)^2$

where *n* is the number of bonds taken into the summation; α is a normalization constant (for CC bonds α = 257.7; for CN bonds α = 93.52 for NN bonds α = 130.33) fixed to give HOMA = 0 for a model nonaromatic system (e.g. the Kekulé structure of benzene) [23] and HOMA = 1 for the system with all bonds equal to the optimal value R_{opt} (e.g. a full aromatic system - for CC bonds R_{opt} is equal to 1.388 Å; for CN bonds R_{opt} is equal to 1.334 Å, for NN bonds R_{opt} is equal to 1.309 Å); R_i stands for a running bond length.

The very last modification of HOMA index [24-26], applied also for rings containing heteroatoms, states that the decrease in aromatic character of the π-electron system may be realized in two different ways: (i) by the increase of the bond length alternation and (ii) by the extension of the mean bond length (bond elongation) of the system in question [27]. In general, aromaticity decreases with an increase in heteroatom electronegativity [28]. An important advantage of using bond lengths as a criterion of aromaticity is the routine X-ray measurement of molecular geometries and the wealth of experimental data available.

RESULTS AND DISCUSSION

X-Ray Crystallographic Studies

Compound **I**, crystallized in the triclinic space group P-1 solvated with a molecule of water, while compound **II** crystallized in the tetragonal space group P41. The crystal data and details concerning data collection and structure refinement are given in Table **1** and bond lengths and bond angles are given in Table **2**.

Bond lengths in the pyrimidine rings are between 1.375-1.383 and 1.377-1.379 Å for C-C bonds and between 1.322-1.353 and 1.329-1.344 Å for C-N bonds of compounds **I** and **II**, respectively (Table **2**). These results are in agreement with the available data for pyrimidine rings [28, 29] clearly indicating that there is no influence of the methyl group on the aromaticity character of the heterocycles (compound **II**). The length of the N8=C9 bond is 1.2700(14) Å in compound **I** and 1.299(4) Å in compound **II**, suggesting a small elongation of the double bond in the latter compound which have been previously described to be around 1.279 Å [30, 31]. Additionally, the C9-C91 bond length is 1.4646(15) and 1.449(5) Å for **I** and **II**, respectively, indicating a shortening of the σ bond for compound **II**, which have been described to be 1.478 Å on average [30, 31]. These unusual pattern of bond lengths may be associated with the small electronic resonance involving the phenyl group and the N8=C9-C91 fragment in compound **II**. Such electron delocalization was not observed in compound **I** since its N8=C9 bond is located. The mean values for N7-N8 bond lengths are 1.3723(12) and 1.370(4) for **I** and **II**, respectively. These results are slightly deviated from those normally obtained for structurally related compounds (1.420 Å, on average) [30, 31]. The C2-N7 bond length is 1.342 Å for compound **I** and 1.380 Å for compound **II**. Since the reported values for bonds of this type are on average 1.423 Å, a shortening of the simple bond in compound **I** is evident [30, 31]. These differences in bond lengths may be attributed to a more expressive electronic resonance between the pyrimidine ring and the C2-N7-N8 fragment in compound **I**.

Finally, the ultimate analysis of the bond lengths (Table **2**) reveals that no electronic delocalization is taking place between the two rings of compound **I** since a localized N8=C9 bond is clearly depicted from its crystal structure. Conversely, shorter simple bonds associated with longer double bonds in the N7-N8=C9-C91 fragment of compound **II** suggests an electronic resonance in the molecule.

In each molecule, the pyrimidine ring is planar, with r.m.s. deviations from the plane of 0.0079 and 0.0031 Å in compound **I** and **II**, respectively. C6 atom is displaced by 0.011 Å from the plane defined by the atoms N1/C2/N3/C4/

Table 1. Crystal Data and Details Concerning Data Collection and Structure Refinement for Compounds I and II

Compound	I	II
Formula	C_{12} H_{11} F_3 N_4 O	C_{14} H_{13} F_3 N_4
Mr	284.25	294.28
CCDC	683536	683535
Temperature (K)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Triclinic	Tetragonal
Space Group	P-1	P41
Unit cell parameters		
a (Å)	6.6175(4)	9.46570(10)
b (Å)	8.7952(5)	9.46570(10)
c (Å)	11.8760(6)	16.3543(3)
α (°)	70.062(3)	90
β (°)	86.135(3)	90
γ (°)	79.645(3)	90
V ($Å^3$)	639.18(6)	1465.34(3)
Z	2	4
Density (calculated) (g cm^{-3})	1.477	1.334
Absorption coefficient (mm^{-1})	0.128	0.110
F (000)	292	608
Crystal size (mm)	0.3 x 0.3 x 0.2	0.222 x 0.168 x 0.101
θ range for data collection (°)	3.13 to 30.14	3.04 to 25.70
h,k,l range	$-9 \le h \le 9$ $-12 \le k \le 12$ $-16 \le l \le 16$	$-11 \le h \le 11$ $-11 \le k \le 11$ $-19 \le l \le 19$
Reflections collected	13100	12191
Independent reflections	3721 [R(int) = 0.0231]	2497 [R(int) = 0.0566]
Data/ restraints/ parameters	3721 / 0 / 189	2497 / 1 / 186
Absorption correction	Gaussian	Gaussian
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Final R indices [I>2σ(I)]	R1 = 0.0408, wR2 = 0.1220	R1 = 0.0868, wR2 = 0.2309
R indices (all data)	R1 = 0.0675, wR2 = 0.1328	R1 = 0.1282, wR2 = 0.2534
Goodness of fit on F^2	1.070	0.964
Largest diff. peak and hole ($eÅ^{-3}$)	0.196 and -0.211	0.498 and -0.407

C5 for compound **I**, and N3 atom is displaced by -0.005 Å from the plane defined by the atoms C2/N1/C6/C5/C4 for compound **II**. In these molecules, the azomethine group is invariably in the *trans*-planar conformation with torsion angle magnitudes for N7-N8-C9-C91 in the range of -178.8(9) and 178.0(3)º for compound **I** and **II**, respectively (Fig. (**2**)). The pyrimidine ring is approximately coplanar with the benzene ring (the interplanar angles are 8.43(6) and 10.27(19)º for **I** and **II**). The orientation of the heterocyclic ring attached to the azomethine group and the azomethine group attached to the phenyl ring in both molecules is similar. The torsion angles for N8-N7-C2-N1 are 2.70(15) and -10.2(4)º, and the torsion angles for N8-C9-C91-C96 are 8.41(18) and 4.8(5) in **I** and **II**, respectively. The planarity of the rings (pyrimidine and phenyl rings) in the *N*-benzylidenehydrazino pyrimidines strongly indicates that there is an electronic resonance between the rings and the exocyclic frangments.

The crystal structures of **I** and **II** are mainly stabilized by intermolecular hydrogen bonds (Table **3**). As mentioned previously, compound **I** is solvated by a molecule of water. There are four intermolecular hydrogen bonds between the title compound and the water molecule (Fig. (**3**)). Water atom O1w acts as a hydrogen-bond acceptor to N7-H7···O1w in the azomethine portion of compound **I**. This interaction

Table 2. Experimental and Calculated Bond Lengths [Å] and Angles [°] for Compound I and II

Compound I					
Bond Lengths [Å]					
	X-ray	**AM1**		**X-ray**	**AM1**
C2-N7	1.3421(14)	1.423	N7-N8	1.3723(12)	1.327
C2-N1	1.3471(14)	1.388	C4-C41	1.5062(16)	1.547
C2-N3	1.3525(13)	1.393	N8-C9	1.2700(14)	1.304
F1-C41	1.3165(14)	1.369	C9-C91	1.4646(15)	1.469
N3-C4	1.3244(14)	1.345	C91-C92	1.3847(18)	1.404
C6-N1	1.3217(15)	1.340	C92-C93	1.3861(19)	1.392
C6-C5	1.3832(18)	1.409	C91-C96	1.386(2)	1.401
F2-C41	1.3302(16)	1.370	C93-C94	1.361(3)	1.396
C5-C4	1.3749(18)	1.402	C94-C95	1.384(2)	1.394
F3-C41	1.3310(14)	1.372	C95-C96	1.3902(19)	1.395
Bond Angles [°]					
N7-C2-N1	119.17(9)	120.05	C92-C91-C96	119.21(11)	119.44
N7-C2-N3	115.36(9)	115.61	C92-C91-C9	118.83(11)	117.89
N1-C2-N3	125.47(10)	124.25	C96-C91-C9	121.94(11)	122.67
C4-N3-C2	115.39(9)	116.12	C91-C92-C93	120.65(15)	120.21
N1-C6-C5	123.74(11)	123.49	C94-C93-C92	120.02(15)	120.14
C6-N1-C2	115.97(10)	116.53	C93-C94-C95	120.26(13)	119.88
C4-C5-C6	115.08(11)	115.92	C94-C95-C96	120.10(15)	120.35
C2-N7-N8	120.35(9)	129.46	C91-C96-C95	119.76(14)	119.99
N3-C4-C5	124.30(11)	123.68	F1-C41-F2	107.30(11)	104.57
N3-C4-C41	114.42(10)	116.75	F1-C41-F3	107.21(10)	104.59
C5-C4-C41	121.22(11)	119.57	F2-C41-F3	105.35(11)	105.26
C9-N8-N7	115.66(9)	127.33	F1-C41-C4	112.86(11)	113.52
N8-C9-C91	121.60(10)	120.77	F2-C41-C4	112.88(10)	113.93
			F3-C41-C4	110.80(10)	113.96
Compound II					
	X-ray	AM1		X-ray	AM1
N7-N8	1.370(4)	1.342	C92-C91	1.413(5)	1.409
N7-C2	1.379(4)	1.432	C92-C921	1.468(6)	1.482
N1-C6	1.339(4)	1.336	F3-C41	1.237(6)	1.369
N1-C2	1.345(4)	1.390	C4-C5	1.379(5)	1.409
N3-C4	1.329(5)	1.348	C4-C41	1.489(6)	1.549
N3-C2	1.337(4)	1.385	C6-C5	1.377(5)	1.419
C9-N8	1.299(4)	1.300	C5-C51	1.494(5)	1.473
C9-C91	1.449(5)	1.466	C91-C96	1.404(5)	1.401
F1-C41	1.337(7)	1.369	C94-C93	1.355(7)	1.393
F2-C41	1.324(6)	1.373	C94-C95	1.367(7)	1.394
C92-C93	1.394(6)	1.399	C95-C96	1.380(6)	1.394

Table 2. contd….

Bond Angles [°]					
N8-N7-C2	120.1(3)	119.03	C93-C92-C91	117.6(4)	119.115
C6-N1-C2	114.1(3)	116.00	C93-C92-C921	118.4(4)	119.553
C4-N3-C2	115.7(3)	116.71	C91-C92-C921	123.9(3)	121.331
N8-C9-C91	122.2(3)	130.69	C96-C91-C92	118.8(3)	119.822
C9-N8-N7	114.8(3)	122.12	C96-C91-C9	121.6(3)	120.961
N3-C4-C5	124.8(3)	123.28	C92-C91-C9	119.6(3)	119.209
N3-C4-C41	113.8(4)	117.21	C93-C94-C95	119.6(4)	119.957
C5-C4-C41	121.3(4)	119.49	C94-C95-C96	120.4(4)	119.996
N3-C2-N1	126.3(3)	124.44	C95-C96-C91	120.6(4)	120.331
N3-C2-N7	115.6(3)	115.43	C94-C93-C92	122.9(4)	120.778
N1-C2-N7	118.1(3)	119.99	F3-C41-F2	108.9(4)	104.830
N1-C6-C5	125.9(3)	124.21	F3-C41-F1	106.0(5)	103.962
C6-C5-C4	113.2(3)	115.33	F2-C41-F1	101.5(4)	104.437
C6-C5-C51	121.0(4)	120.86	F3-C41-C4	114.2(5)	113.239
C4-C5-C51	125.7(4)	123.81	F2-C41-C4	112.0(4)	112.676
			F1-C41-C4	113.3(4)	116.533

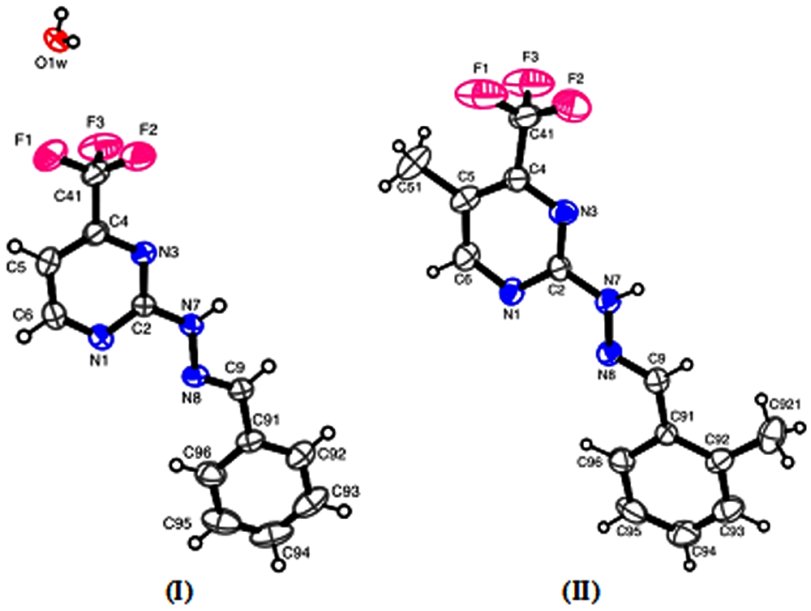


Fig. (2). ORTEP drawing of the molecular structure of **I** and **II** indicating atom numbering scheme with 50% of probability.

presents an interatomic distance of 2.8245(13) Å for N7···O1w (x, y, z-1). When acting as a hydrogen-bond donor, the water molecule shows a O1w-H1w···N1 interaction with the pyrimidine ring and a O1w-H1···N8 interaction with the *N*-benzyliminic portion of compound **I**. The interatomic distances observed are 2.9118(15) Å for O1w···N1 and 3.2278(14) Å for O1w···N8 (x+1, y, z+1) forming a pseudo 5 membered ring. The third hydrogen bond where the water acts as a hydrogen-bond donor is the O1w-H2w···N3 with interatomic distance of 3.1079(15) Å for O1w···N3 (-x+1, -y, -z+1). In compound **II** the crystaline packing generates an infinite chain along of plane *ac* (Fig. (**3**)) through intermolecular hydrogen bond N7-H7···N1 with interatomic distance of 2.985(4) Å (y, -x, z-1/4) for N7···N1. Whole interatomic distances are lower than the sum of the acceptor and donor atoms (D···A) van der Waals radii involved in the interaction [32]. The symmetry codes for intermolecular hydrogen bonds are depicted in Table **3**. Due to the presence of the water molecule in the unit cell of **I** it was impossible to determine the effect of the methyl group in the crystal packing of compounds **I** and **II**. It became clear, however, that the water molecule is a stronger hydrogen donor than the NH group of the azomethine fragment.

Table 3. Hydrogen Bonding Geometry in Structures I and II [Å, °]

Compound	D-H···A	D-H	H···A	D···A	D-H···A	Symmetry Codes
I	N7-H7···O1w	0.860	1.981	2.825	167	x, y, z-1
	O1w-H1w··· N1	0.812	2.133	2.912	161	x+1, y, z+1
	O1w-H1w···N8	0.812	2.668	3.228	128	x+1, y, z+1
	O1w-H2w···N3	0.808	2.331	3.108	162	-x+1, -y, -z+1
II	N7-H7···N1	0.860	2.279	2.985	139	y, -x, z-1/4

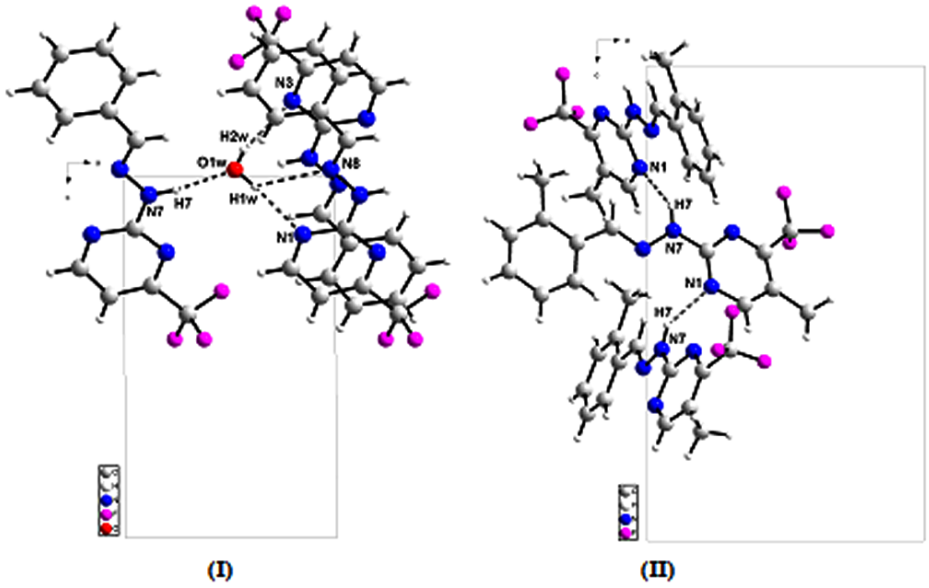


Fig. (3). A part of the crystal structure of compound **I** and **II**, showing the formation of intermolecular hydrogen-bonded chains along of the plane *ac* in crystalline packing.

Semi-Empirical Molecular Orbital Calculations (AM1)

The selected bond lengths and angles for compounds **I** and **II** obtained from semi-empirical calculations and X-ray diffraction are presented in Table **2**. Although it is expected that the intermolecular interactions observed in the crystal structures of the compounds will affect its molecular geometry for the most geometrical parameters there is an excellent correspondence between experimental and calculated data.

The simple linear regression analysis applied to quantify the strength of the relationship between bond lengths and bond angles acquired from X-ray experiments against theoretical values (AM1) showed good and similar correlation coefficients. For instance, the correlation coefficients between crystal bond lengths and calculated bond lengths are r = 0.887 and 0.837 which represent a 78.7% and a 70.1% of agreement between observed and modeled bond lengths of pyrimidines **I** and **II**, respectively. The correlation coefficients between experimental and calculated data for bond angles are r = 0.991 and 0.994 that show a 98.3 and 98.9% of agreement between observed and modeled bond angles of pyrimidines **I** and **II**, respectively.

It is important to notice however, that although the experimental data indicates the existence of electronic resonance between the pyrimidine ring and the azomethine fragment in **I** and **II**, the theoretical values of the bond lengths of C2-N7 show typical values (1.423 Å) of bonds between an aromatic carbon atom and a nitrogen atom with sp^3 hybridization (1.423 for **I** and 1.432 Å for **II**) [31]. Additionally, the calculated values for N7-N8 are 1.327 for **I** and 1340 Å for **II** therefore, lower than the standard value (1.420 Å). The values for N8-C9 are higher than the expected (1.279 Å), being 1.304 for **I** and 1.300 Å for **II**. Finally, the calculated bond lengths for C9-C91 are 1.469 and 1.465 for **I** and **II**, respectively, resembling the bond lengths of double bonds in conjugated systems (1.470 Å) [31]. These values indicate the existence of an electronic resonance between the azomethine fragment and the phenyl ring.

Remarkable differences between the experimental and the optimized data regarding to the configuration of the exocyclic double bond and ring planarities of compounds **I** and **II** were also noticed. From AM1 calculations, the exocyclic double bond of compound **I** preferably shows an *E*-configuration while the *Z*-configuration is preferably adopted by compound **II**. Compound **I** presented a N1-C2-N7-N8 dihedral angle of 2.70(15)° and a N8-C9-C91-C96 dihedral angle of 8.41(18)º while its optimized structure showed values of 24.09° for N1-C2-N7-N8 and -14.82º for N8-C9-C91-C96. The same dihedral angles found in compound **II** are -10.2(4)º and 4.8(5)º and its optimized structure showed val-

ues of -29.35º and 49.42º, respectively. The contrast of such results can be attributed to the relevant intermolecular interactions observed in the real structures which are not taken under consideration in the theoretical AM1 approach.

Aromaticity

After determining the ring planarity, and the endocyclic and exocyclic bond lengths of pyrimidines **I** and **II** from X-ray experiments, we aimed to perform HOMA calculations to quantitatively measure their aromaticities. Geometry parameters of the ring (CC, CN and NN bond lengths) were used to estimate the so-called geometrical indices of aromaticity based on the harmonic oscillator model of aromaticity (HOMA model, Eq. **1**) [33, 34].

The HOMA calculations furnished aromaticity indices of 0.979 and 0.989 for the pyrimidine rings of compounds **I** and **II**. These values are very close to the ideal aromaticity index (HOMA = 1,0) stated by the HOMA model and indicate that the referred pyrimidine rings show: *(i)* little alternation in bond lengths and *(ii)* average bond length values (R_{av}) near optimal (R_{opt}). Therefore, as the methyl group does not cause significant distortions in the heterocyclic ring of compound **II**, it shows no appreciable effect in its aromaticity as well. Interestingly, these results are better than the aromaticity indices of the optimized molecules of compounds **I** and **II** (0.870 for **I** and 0.847 for **II**) and are in agreement with previously stated results for the crystalline structures of heterocycles.

Unlike the pyrimidine ring, the aromaticity of the phenyl group was deeply affected by the methyl group. The presence of such group ultimately caused a reduction of 0.078 in the aromaticity index of compound **II** (0.967 for **I** and 0.889 for **II**). According to the HOMA model, the small deformation of the 2-methyl-phenyl ring (deviations of the r.m.s. of 0.0061 Å for **II** and 0.0028 Å for **I**) accounts for the decrease of the aromaticity since there is a clear deviation from the pre-stated optimal values for bond lengths of aromatic compounds.

CONCLUSION

Structure-based approaches have become a vital part on modern drug design. The understanding of protein–ligand interactions is essential for the design of new inhibitors with improved potency. We have recently described the convergent synthesis and the *T. cruzi* cruzain inhibitory activity of novel 2-(*N*'-benzylidenehydrazino)-4-trifluoromethyl-pyrimidines. In order to advance our knowledge as to how these compounds bind to the cruzain enzyme definitive structural and electronical data are required. In this work, we presented the structures of two novel 2-(*N*'-benzylidenehydrazino)-4-trifluoromethyl-pyrimidines (**I** and **II**) by means of single-crystal X-ray analysis. Furthermore, optimal molecular geometries were calculated by means of the semi-empirical quantum-chemical method (AM1) and the structures were compared. Crystallographic data showed that the 2-(*N*'-benzylidenehydrazino)-4-trifluoromethyl-pyrimidine crystals (compound **I**) are triclinic (space group P-1) and are solvated by a water molecule. On its turn, the 2-(*N*'-2-methyl-benzylidenehydrazino)-4-trifluoromethyl-pyrimidine molecules (compound **II**) crystallized in the tetragonal space group P41. The azomethine moiety of both compounds showed a *trans*-planar conformation and a small electronic resonance in **II**. The crystal structures were stabilized by intermolecular hydrogen bonds of the type N-H···N in **I** and N-H···O and O-H···N in **II** due to the presence of water in the asymmetric unit. The planarity found in the molecules is directly associated with the electronic resonance between the rings and the exocyclic fragments. The energy-minimized structures of the compounds compare well with those determined using X-ray crystallography. However, a remarkable difference between experimental and calculated data regarding to the molecule planarity were observed. These results can be explained in terms of the relevant intermolecular interactions that are present in the real structures which are not taken under consideration in the theoretical experiments. Finally, aromaticities of the pyrimidine and the phenyl rings of the compounds were calculated by the harmonic oscillator model of aromaticity (HOMA) and showed a high aromatic character for both. The aromaticity of the phenyl group was calculated and as the phenyl ring was slightly deformed in compound **II** its geometrical index of aromaticity was diminished.

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