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Influence of bulky and halogen substituents on crystal packing of pyrazolo[1,5-*a*]pyrimidines

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ABSTRACT

The crystalline structure of five 3-(R^3) and/or 5-(R^5)-substituted 7-trichloromethyl-2-methylpyrazolo[1,5-*a*]pyrimidines [where R^3, R^5 = H, Pr (**1**); Br, H (**2**); Br, Me (**3**); H, H (**4**); and H, Me (**5**)] were studied from X-ray diffractometry data. It was found that compounds presented themselves as main intermolecular interactions: Cl···Cl (**1**), Br···Cl (**2,3**); and Cl···N-pyrimidine (**4,5**). In compounds **1**–**3**, other interactions reinforce the stabilization of the crystal structure, such as C–H···N-pyrimidine (**1,2**) Cl···π-pyrazole (**1**); C–Br···π-pyrimidine (**2**); and pyrazole-π···π-pyrimidine, pyrimidine-π···π-pyrimidine (**3**). This study shows that the Cl···N-pyrimidine interactions present in compounds **4** and **5** are a typical halogen···base Lewis interaction. Geometric information of Cl···Br and Cl···Cl interactions could be explained by the σ-hole concept. In compound **2**, the chlorine atom participates with its σ-hole, while in compound **3**, the σ-hole of the interaction comes from the bromine atom. The Cl···π-pyrazole and Br···π-pyrimidine interactions have a different nature; while the Br···π-pyrimidine interaction is a strong lone pair···π interaction, the Cl···π-pyrazole is a new interaction: σ-hole···π.

1. Introduction

Pyrazolo[1,5-*a*]pyrimidines are an important class of heterocycles because they are purine analogs and have useful pharmacological properties as HMG-CoA reductase inhibitors [1] and COX-2 selective inhibitors [2]. Generally, the pharmacological activity is closely related to the molecular recognition of the active substance by the active site. Therefore, a detailed understanding of these molecular interactions is essential for the development of quantitative approaches toward molecular recognition.

Over the past two decades, our research group has worked to develop the synthesis of new trihalomethyl substituted heterocycles under conventional methods [3], as well as using ionic liquid [4], microwave [5], and ultrasound irradiation [6]. The presence of trihalomethyl groups and, both, donor and acceptor hydrogen bond groups in heterocycles, together with their aromatic character, make them interesting structures for the study of intermolecular interactions such as hydrogen bond, halogen bond, lone pair···π, and π···π interactions.

Weak nonbonding interactions may contribute to the stability, conformation, and assembly of molecules, generating interest in the determination of strengths and directional trends [7]. Hydrogen and halogen bonds are electrostatically-driven noncovalent interactions. Both, hydrogen and halogens, bonded covalently, can interact through regions of positive potential surface with a negative potential surface of other atoms, such as a lone pair of a Lewis base.

In particular, in the bonded halogen atom, the anisotropically-distributed electron density results in a negative charge concentrated in the equatorial area, and in a positive charge along the C–X bond, which is called the σ-hole [8].The halogen bond is near-linear (angles close to 180°), while the hydrogen bond is probably more nonlinear (angles less than 180°) [9]. The strengths of these two interactions are comparable and they can certainly be competitive [10].

Other intermolecular contacts that have received attention recently are the interactions involving π-aromatic systems, such as π···π and lone pair (LP)···π interactions, that appear to be of great importance for the stabilization of biological macromolecules [11]. Despite their weak electrostatic nature, LP···π interactions have been reported to be responsible for the Z-DNA stability [12], and the π···π interactions are known as dispersion forces and are auxiliary stabilizing force in the recognition process of aromatic compounds. They can, for example, direct the intercalation of drugs into DNA [13].

In connection with our recent interest in the structure of trihalomethyl substituted heterocycles [14], in this work we investigate the influence of bulky and halogen substituents on the crystal packing of pyrazolo[1,5-*a*]pyrimidines by using X-ray diffractometry

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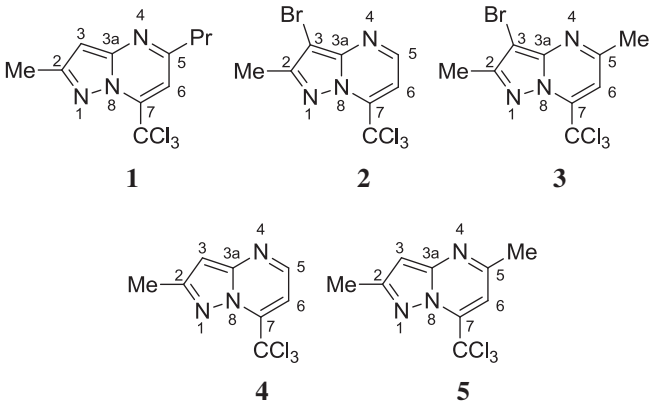

Fig. 1. Structure of pyrazolo[1,5-*a*]pyrimidines studied in this work.

data. For this purpose we selected the three structures, 7-trichloromethyl-2-methyl-5-propylpyrazolo[1,5-*a*]pyrimidine (**1**), 3-bromo-7-trichloromethyl-2-methylpyrazolo[1,5-*a*]pyrimidine (**2**), and 3-bromo-7-trichloromethyl-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (**3**), and compared them with 7-trichloromethyl-2-methylpyrazolo[1,5-*a*]pyrimidine (**4**) and 7-trichloromethyl-2,5-dimethyl pyrazolo[1,5-*a*]pyrimidine (**5**), which have been described in our previous works (Fig. 1) [14].

2. Experimental

2.1. Synthesis and physical measurements

Pyrazolo[1,5-*a*]pyrimidine **1** was synthesized from the cyclocondensation reaction of 3(5)-amino-5(3)-methyl-1*H*-pyrazole and 1,1,1-trichloro-4-methoxy-3-penten-2-one under acetic acid reflux for 16 h [15]. The products **2** and **3** were obtained from the cyclocondensation reaction of 3(5)-amino-5(3)-methyl-1*H*-pyrazole and 1,1,1-trichloro-4-methoxy-3-penten-2-one under acetic acid reflux for 16 h, followed by bromination with *N*-bromosuccinimide in THF under reflux for 20 h [15]. The complete $^{1}H/^{13}C$ NMR, mass spectra data, and elemental analysis of compounds **1**–**3** is available in the literature [15]. The crystals used for the data collection were obtained by recrystallization of compounds from hexane followed by slow evaporation at room temperature.

2.2. X-ray diffraction data

The diffraction measurements were carried out by graphite monochromatized Mo Ka radiation with $k = 0.71073$ Å on a Bruker SMART CCD diffractometer [16]. The structures were solved with direct methods using the SHELXS program [17], and refined on F^2 by full-matrix least-squares with the SHELXL [17] package. Absorption correction was performed by the Gaussian method [18]. Anisotropic displacement parameters for non-hydrogen atoms were applied. The hydrogen atoms were placed at calculated positions with 0.96 (methyl CH_3), 0.97 (methylene CH_2), 0.98 (methyne CH), 0.93 (aromatic CH), and 0.82 Å (OH) using a riding model. Hydrogen isotropic thermal parameters were kept equal to Uiso(H) = *x*Ueq (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 were set to 109.5°, and H atoms were allowed to rotate around the C–C bond. Molecular graphics were prepared using ORTEP for Windows [19]. The crystal data and details concerning data collection and structure refinement are given in Table 1 and in Supplementary material.

Table 1
General and crystal data and summary of intensity data collection and structure refinement for compounds 1–3.

Compound	**1**	**2**	**3**
Formula	$C_{11}H_{12}Cl_3N_3$	$C_8H_5BrCl_3N_3$	$C_9H_7BrCl_3N_3$
Mr	292.59	329.41	343.44
CCDC	734997	734996	751834
Temperature (K)	293(2)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	P21/c	P21	P21
Unit cell parameters			
a (Å)	11.2451(8)	7.4329(2)	9.6363(3)
b (Å)	5.8697(4)	6.7756(2)	6.9353(2)
c (Å)	20.9201(16)	11.1667(3)	9.8541(3)
α (°)	90	90	90
β (°)	104.896(5)	90.2760(10)	111.240(2)
γ (°)	90	90	90
V (Å^3)	1334.43(17)	562.37(3)	613.82(3)
Z	4	2	2
Density (calculated) (g cm^{-3})	1.456	1.945	1.858
Absorption coefficient (mm^{-1})	0.667	4.334	3.975
F (0 0 0)	600	320	336
Crystal size (mm)	0.880 × 0.328 × 0.158	0.340 × 0.337 × 0.162	0.858 × 0.295 × 0.166
θ Range for data collection (°)	1.87–28.40	2.74–28.40	2.22–28.26
h, *k*, *l* Range	$-14 \leqslant h \leqslant 14$	$-9 \leqslant h \leqslant 8$	$-12 \leqslant h \leqslant 12$
	$-7 \leqslant k \leqslant 7$	$-9 \leqslant k \leqslant 8$	$-9 \leqslant k \leqslant 9$
	$-27 \leqslant l \leqslant 27$	$-14 \leqslant l \leqslant 14$	$-12 \leqslant l \leqslant 13$
Reflections collected	13171	5503	6092
Independent reflections	3314 [*R*(int) = 0.0292]	2653 [*R*(int) = 0.0197]	2998 [*R*(int) = 0.0199]
Data/restraints/parameters	3314/0/154	2653/1/136	2998/1/145
Absorption correction	Gaussian	Gaussian	Gaussian
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0361$, $wR_2 = 0.1069$	$R_1 = 0.0362$, $wR_2 = 0.0954$	$R_1 = 0.0416$, $wR_2 = 0.1250$
R indices (all data)	$R_1 = 0.0576$, $wR_2 = 0.1361$	$R_1 = 0.0483$, $wR_2 = 0.1008$	$R_1 = 0.0579$, $wR_2 = 0.1356$
Goodness of fit on F^2	1.100	1.063	1.073
Largest diff. peak and hole (eÅ^{-3})	0.512 and −0.460	0.461 and 0.809	0.510 and −0.792

3. Results and discussion

Intramolecular interaction geometries data for compounds **1**–**5** are shown in Table 2. Intermolecular interaction geometries for synthons of compounds **1**–**5** are listed in Table 3. ORTEP of compounds **1**–**5** are shown in Fig. 2, and crystal packing of compounds **1**–**5** are depicted in Fig. 3. The intermolecular interactions observed for all structures were C–H···N-pyrimidine (**1,2**); C–Cl···Cl–C (**1**); C-Cl···N-pyrimidine (**4,5**); C–Br···Cl–C (**2,3**); C–Cl···π-pyrazole (**1**); C–Br···π-pyrimidine (**2**); and pyrazole-π···π-pyrimidine, pyrimidine-π···π-pyrimidine (**3**).

All five compounds exhibited intramolecular five-membered Cl···N contacts. The Cl···N distances (*d*) are significantly shorter than the sum of their van der Waals radii (d_0 = 3.3 Å), which is also reflected by the relatively smaller d/d_0 value (0.94). This intramolecular contact appears to exist as a consequence of the bulky effect of the chlorine atom and its fixed geometry in these compounds.

Compounds **1**–**3** and **5** relate to the monoclinic space group and compound **4** relates to the orthorhombic space group. Different from the intramolecular contacts, which were robust, appearing in all five compounds, intermolecular contacts were more sensitive to the presence of the bromine substituent. In compounds **4** and **5**, where there is no bromine substituent in the 3-position, compounds exhibited intermolecular Cl(1)···N(4) contacts, which stabilized the crystal structure, forming a zig-zag infinite chain along plane *ab*. Intermolecular contacts change from Cl(1)···N(4) in compounds **4** and **5**, to Cl(1)(2)···Br(31) in compounds **2** and **3**, which bear a bromine in the 3-position. This contact stabilizes the crystal structure forming a zig-zag infinite chain along plane *ac*. In compound **1**, despite the absence of bromine in the 3-position, the predominant intermolecular contacts were Cl(1)···Cl(2). It is reasonable to suggest that the Cl(2)···Cl(1) contacts appear in these compounds due to the bulky effect of the propyl group attached in the 5-position of pyrazolo[1,5-*a*]pyrimidine.

Table 2
Intramolecular contact geometries for crystals **1**–**5**.

Compound	Contact	Distance Cl···N (Å)	Angle C–Cl···N (°)
1	Cl(2)···N(1)	3.015(2)	69.19(8)
	Cl(3)···N(1)	3.157(2)	65.33(8)
2	Cl(2)···N(1)	3.106(7)	66.8(2)
	Cl(3)···N(1)	3.084(7)	67.4(2)
3	Cl(1)···N(1)	3.116(3)	67.43(15)
4	Cl(2)···N(1)	3.097(6)	67.1(2)
	C(3)···N(1)	3.093(6)	67.3(2)
5	Cl(1)···N(1)	3.116(3)	67.43(15)

Table 3
Intermolecular interaction geometries for synthons[a] of compounds **1**–**5**.

	Distance (Å)	Angle (°)	Symmetry code
1	Cl(1)···Cl(2) 3.3406(8)	C(71)–**Cl(2)**···Cl(1) 178.9	*x*, 1 + *y*, *z*
2	Br(31)···Cl(1) 3.4778(11)	C(71)–**Cl(1)**···Br(31) 176.5	*x*, *y*, 1 + *z*
3	Cl(2)···Br(31) 3.540(14)	C(3)–**Br(31)**···Cl(2) 160.7	1 + *x*, *y*, 1 + *z*
4	N(4)···Cl(1) 3.115(3)	C(71)–**Cl(1)**···N(4) 161.6	*x* + 1/2, −*y* + 1, *z*
5	N(4)···Cl(1) 3.174(3)	C(71)–**Cl(1)**···N(4) 170.6	−*x* + 1, *y* − 1/2, −*z* + 1/2

[a] Bold characters indicate the σ-hole atom of interaction.

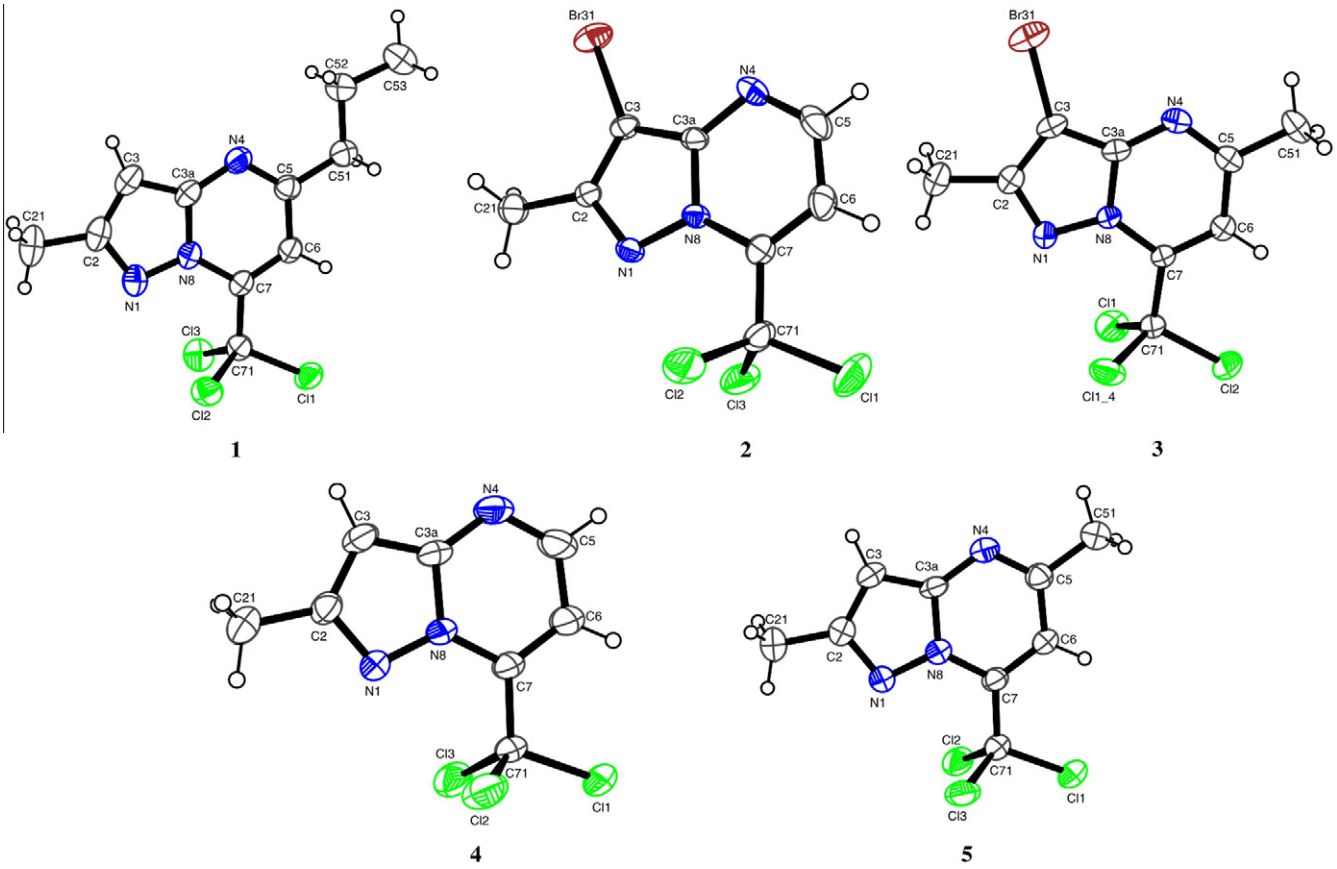

Fig. 2. ORTEP of compounds **1**–**5**.

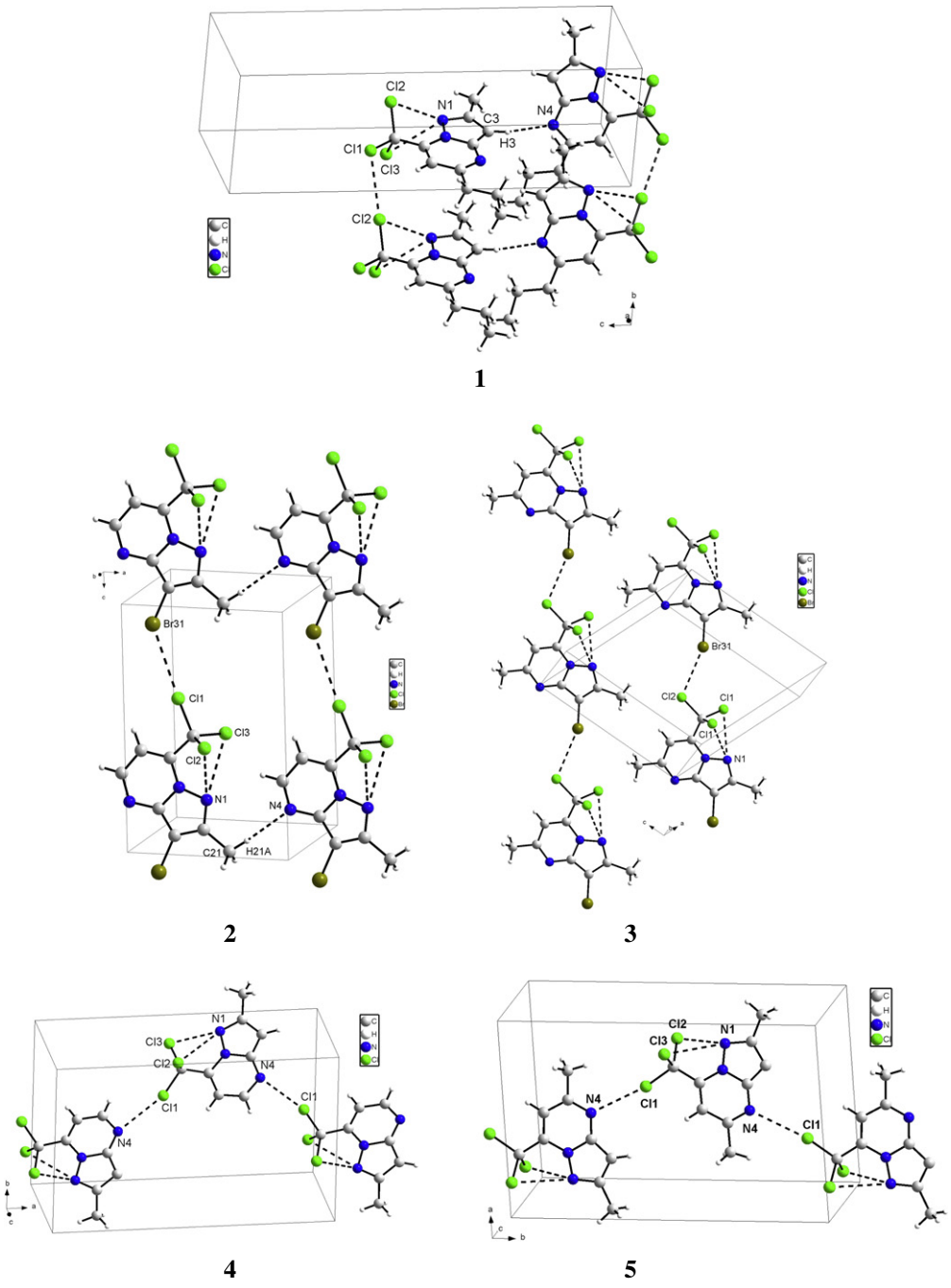

Fig. 3. Intra- and intermolecular contacts of compounds **1**–**5**.

The presence of this supramolecular bulky alkyl group in the structure obstructed the N(4)···Cl(1) interaction present in compounds **4** and **5**, which have no bulky alkyl substituent in their structures.

Regarding the geometric features of these interactions, the Cl···N distances (d) in compounds **4** and **5** and the Cl···Br distance (d) in compounds **2** and **3** are close to the sum of their van der Waals radii (d_0 = 3.3 and 3.6 Å, respectively), which is also reflected by the d/d_0 value (0.95 and 0.98 respectively). In addition, the most important contacts of the compounds studied here involve halogen atoms. This fact leads us to consider angular requirements of the interactions. Halogen atoms in covalent bonds are recognized by their non-spherical charge distribution on the potential surface. This leads to two favored geometries for contacts involving the halogen atom (Fig. 4). The first arrangement occurs when $\theta_1 = \theta_2$, called type I (where θ_1 and θ_2 are the R–X_1···X_2 and X_1···X_2–R angles, respectively). The second geometry arises when $\theta_1 = 180°$ and $\theta_2 = 90°$; the perpendicular arrangement known as type II (Fig. 4) [8–10].

We find it important to consider this information thoroughly because all five compounds discussed here present halogen contacts, and also because a correlation of the geometric data of these compounds with two preferred geometries allows us to delineate interesting observations about their behavior. Cl(2)···N(1) contacts present in compounds **4** and **5** are typical halogen···base Lewis interactions (type II), confirmed by the C(71)–Cl(1)···N(4) angle of 161.6° (**4**) and 170.6° (**5**). On the other hand, Cl···Br are considered typical halogen···halogen contacts (type II), and due to the structural similarity between compounds **2** and **3**, the angular

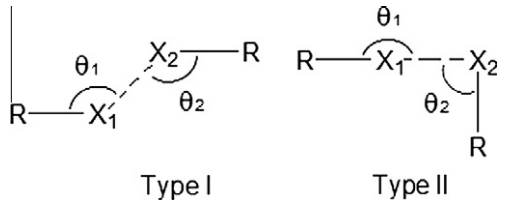

Fig. 4. The two geometries for halogen bonds (R = organic group, X = Cl, Br and I).

behavior of the interaction would be expected to be the same in both compounds. However, there is an angular inversion of this interaction and, consequently, there is a change in the atom participating in the contact with its positive potential surface (σ-hole). In the Cl···Br interaction of compound **2**, the C(71)–Cl(1)···Br(31) angle was found to be 176.5°, indicating that the chlorine atom is the participant in contact with its positive potential surface (σ-hole) and the bromine atom participates in the interaction through its negative potential surface. On the contrary, in compound **3**, the C(71)–Cl(2)···Br(31) angle was found to be 136.9°, and the C(3)–Br(31)···Cl(2) angle was found to be 160.7°, showing that, here, the bromine atom is the participant in contact with its σ-hole and the chlorine atom participates in the interaction through its negative potential surface. Finally, the Cl(2)···Cl(1) contacts, which appear only in compound **1**, are also typical halogen···halogen contacts with a strongly directionality, with a C(71)–Cl(2)···Cl(1) angle of 178.9°, where Cl(1) participates in the interaction through its negative potential surface and Cl(2) with its σ-hole.

In **1**–**3**, the action of intermolecular contacts, Cl(1)(2)···Br(31), or Cl(2)···Cl(1) is reinforced by interactions such as C–H···N-pyrimidine, C–Cl···π-pyrazole, C–Br···π-pyrimidine, or π···π between pyrazole and pyrimidine aromatic systems. C–H···N-pyrimidine contacts have a very weak electrostatic nature and appear in compounds **1** and **2**. The geometric features of contacts C–H···N are given by the C(3)···N(4) distance of 3.563 Å ($1-x$, $-1/2+y$, $1/2-z$) in compound **1** and 3.518 Å ($1+x$, y, z) in compound **2**. The Cl···π interaction arises in compound **1** between Cl(3) and the pyrazole ring of fused pyrazolo[1,5-*a*]pyrimidine($1-x$, $-y$, $1-z$), and the Br···π interaction arises in compound **2** between bromine and the pyrimidine ring ($-x$, $-1/2+y$, $2-z$). Finally, compound **3** has its crystalline structure reinforced by π···π interactions between pyrazole and the pyrimidine rings (distance between centroids of 4.164 Å, $1-x$, $-1/2+y$, $1-z$), and π···π interactions between pyrimidine rings (distance between centroids of 3.702 Å, x, y, z). All contacts that reinforced crystal stabilization of compounds **1**–**3** are illustrated in Fig. 5.

We have found further interesting behavior regarding halogen interactions with contacts with π-systems. It has been reported in the literature that halogens rich in electrons (lone pair) are attracted by electron-deficient π-systems; the interaction between the two of them is denominated lone pair···π interaction [11,12]. However, upon studying the halogen interaction in halomethyl-substituted pyrazolo[1,5-*a*]pyrimidines, we found that, in some cases, halogen atoms can attract π-systems rich in electrons by its σ-hole. The role of halogen atoms in this interaction, as in halogen···halogen contacts, may be determined by geometrical parameters, and, it has been established that a strong lone pair···π interaction is characterized by an angle (lone pair atom-centroid-plane) ranging from 75° to 90°. Therefore, in this study, we adopted as angular criteria the C–halogen···π-system angle. Thus, we found a typical lone pair···π interaction, in compound **2**, where the angle C(3)–Br(31)···pyrimidine centroid is 90.1° and the distance C(3)–Br(31)···centroid of pyrimidine is 3.427 Å. In compound **1** we found a contact between the chlorine atom and the π-system of the pyrazole ring, with an angle C(71)–Cl(3)···π-pyrazole of 177.9° and a distance

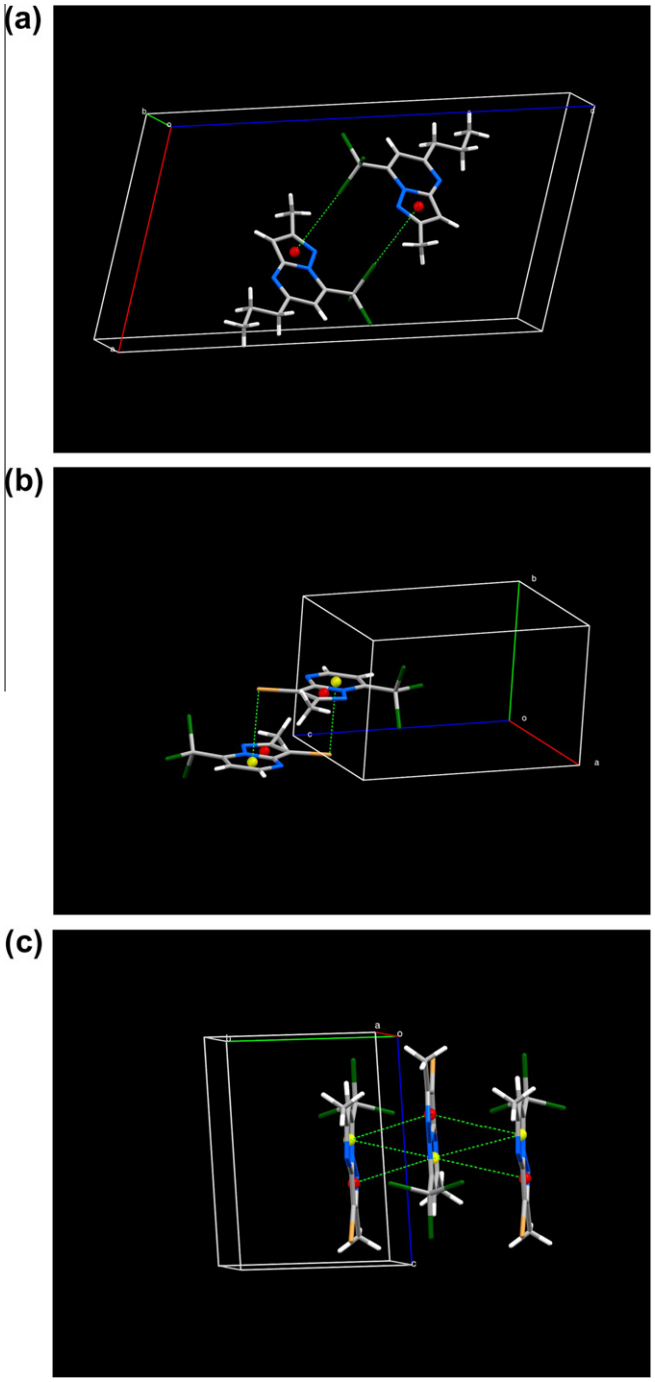

Fig. 5. (a) C(71)–Cl(3)···pyrazole ring centroid interaction of compound **1**; (b) C(3)–Br(31)···pyrimidine ring centroid interaction of compound **2**; and (c) pyrimidine-π···π-Pyrimidine, pyrazole-π···π-pyrimidine interactions of compound **3**.

C(71)–Cl(3)···centroid of pyrazole of 3.631 Å. We consider this to be a new interaction because it can be described as a σ-hole···π interaction. These facts could be expected because the pyrazolo[1,5-*a*]pyrimidine system presented a π-deficient pyrimidine ring and an electron-rich pyrazole ring; where it is expected that the favored interaction for the pyrimidine ring is a lone pair···π interaction, and, for the pyrazole ring, a σ-hole···π interaction.

4. Conclusion

In this work we have described the supramolecular synthons present in 7-trichloromethylpyrazolo[1,5-*a*]pyrimidines by using

X-ray data. Three supramolecular synthons, Cl···Cl, Cl···N, and Cl···Br, involving halogen atoms were described. The synthon Cl···N was little robust because the addition of a bulky substituent in the 5-position of 7-trichloromethylpyrazolo[1,5-*a*]pyrimidines obstructed this interaction and favored a Cl···Cl interaction. The presence of a bromine atom in the 3-positon of 7-trichloromethylpyrazolo[1,5-*a*]pyrimidines also hindered the Cl···N interactions and led to the Cl···Br interaction. These synthons were characterized by their robustness and geometric parameters, such as interatomic distances and angles between interacting groups. The formation of halogen synthons could be explained by the σ-hole concept. We observed an inversion in the atom that participated, through its σ-hole, in the Cl···Br interaction, where chlorine was the participant with its σ-hole in compound **1** and the bromine atom was the participant with its σ-hole in the same interaction in compound **2**. In addition, other contacts that stabilized the crystalline structure of 7-trichloromethylpyrazolo[1,5-*a*]pyrimidines were described. A new halogen···π interaction, also supported by the σ-hole concept, was observed, where halogen (Cl) approaches with the σ-hole to attract the π-heterocyclic system (pyrazole).

We believe that this work provides new detailed understanding of molecular interactions, which is essential for applications in the field of synthetic chemistry, material science, and bioorganic chemistry.

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Appendix A. Supplementary material

Crystallographic data for the structural analysis of the compounds have been deposited at the Cambridge Crystallographic Data Center with the deposition numbers CCDC 734997 for **1**, CCDC 734996 for **2**, and CCDC 751834 for **3**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, United Kingdom; Fax: +44 1223 336033 or deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2011.07.018.

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