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ORIGINAL PAPER

Structures of two *N*-{2-([(5-amino-1,3,4-thiadiazol-2-yl) difluoromethyl]-4-halophenyl}acetamides

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Abstract The compounds, *N*-{2-[(5-amino-1,3,4-thiadiazol-2-yl)difluoromethyl]-4-chlorophenyl}acetamide (**1**: X = Cl) and *N*-{2([(5-amino-1,3,4-thiadiazol-2-yl)difluoromethyl]-4-bromo-phenyl}acetamide (**1**: X = Br), are isostructural. The molecules are near ''V'' shaped with the angles between the two aromatic planes *ca*. 84° in each case. The various intermolecular interactions, namely N–H···O, N–H···N, N–H···F, and C–H···N hydrogen bonds and C–H···π, C–Cl···π and C–O···π interactions, generate 3-D arrays. Compound (**1**: X = Cl) crystallizes in the monoclinic space group P21/c with a = 16.9032(7) Å, 10.2193(4) Å, c = 7.5227(4) Å, β = 100.179(3)° and Z = 4. Compound (**1**: X = Br) crystallizes in the monoclinic space group P21/c with a = 17.2119(4) Å, 10.2167(2) Å, c = 7.5677(2) Å, β = 100.326(2)° and Z = 4.

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Introduction

Interests of the Boechat group during the past few years have been concerned with the synthesis, structures and biological activities of compounds bearing fluoro substituents [1–9], and on small ring heterocycles, including triazoles and thiadiazoles [10–15]. Recently we reported on the usefulness of *N*-acyl-3,3-difluoro-2-oxoindoles as precursors of 1-(2-acetamidophenyl)-2,2-difluoroacetic acid derivatives, 1-(2-(2-acetamidophenyl)-2,2-difluoroacetyl)thiosemi-carbazides and *N*-(2-((5-amino-1,3,4-thiadiazol-2-yl)difluoromethyl)-4-phenyl)acetamides [9].

We now wish to report on two isostructural *N*-{2-[(5-amino-1,3,4-thiadiazol-2-yl)difluoromethyl]-4-halophenyl} acetamides (**1**: X = Cl and Br) prepared from *N*-acyl-3,3-difluoro-2-oxoindoles, see Fig. 1.

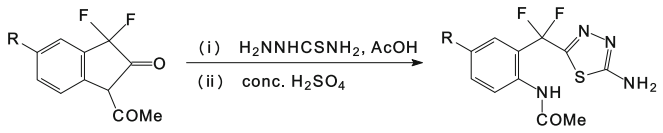
Experimental

The compounds were prepared as reported [9].

X-ray Crystallography

Data for compounds (**1:** X = Cl and Br) were obtained at 120(2) K with Mo-Kα radiation by means of the Bruker-Nonius 95 mm CCD camera on \k-goniostat of the EPSRC crystallographic service, based at the University of Southampton. Data collection was carried out under the control of the program COLLECT [16] and data reduction and unit cell refinement were achieved with the COLLECT and DENZO [17] programs. No correction for absorption

Fig. 1 Formation of **1** and structure of compound **3**



(**1**: **R = Cl or Br**) **3**

Table 1 Crystal data and structure refinement

Identification code	(**1**: X = Cl)	(**1**: X = Br)
Empirical formula	$C_{11}H_9ClF_2N_4OS$	$C_{11}H_9BrF_2N_4OS$
Formula weight	318.73	363.19
Temperature (K)	120(2)	120(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Unit cell dimensions:		
a (Å)	16.9032(7)	17.2119(4)
b (Å)	10.2193(4)	10.2167(2)
c (Å)	7.5227(4)	7.5677(2)
((^{o})	100.179(3)	100.326(2)
Volume ($Å^3$)	1279.01(10)	1309.22(5)
Z	4	4
Density (calculated) (Mg/m^3)	1.655	1.843
Absorption coefficient (mm^{-1})	0.487	3.324
F(000)	648	720
Crystal size (mm)	0.38 × 0.28 × 0.03	0.44 × 0.20 × 0.08
Theta range for data collection (°)	2.9 to 27.5	3.1 to 27.5
Index ranges	$-21 \le h \le 21$; $-13 \le k \le 13$; $-9 \le l \le 9$	$-22 \le h \le 22$; $-13 \le k \le 13$; $-9 \le l \le 9$
Reflections collected	16918	5796
Independent reflections	2934 [R(int) = 0.073]	2988 [R(int) = 0.021]
Reflections observed ($>\sigma$)	2183	2668
Data completeness	0.999	0.997
Absorption correction	Multi-scan	Multi-scan
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2934/0/191	2988/0/191
Goodness-of-fit on F^2	1.04	1.04
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.042$	$R_1 = 0.027$
	$wR_2 = 0.094$	$wR_2 = 0.064$
R indices (all data)	$R_1 = 0.068$	$R_1 = 0.033$
	$wR_2 = 0.104$	$wR_2 = 0.067$
Largest diff. peak and hole, $eÅ^{-3}$	0.33 and −0.33	0.40 and −0.64

was applied. The programs ORTEP-3 for Windows [18] and MERCURY [19] were used in the preparation of the figures. SHELXL97 [20] and PLATON [21] were used in the calculation of molecular geometry.

The structures were solved by direct methods using SHELXS-97 [22] and fully refined by means of the program SHELXL-97 [20]. Difference map peaks provided positions for the hydrogen atoms of the NH groups for which the coordinates, along with isotropic displacement parameters, were fully refined. All other hydrogen atoms were placed in calculated positions. Crystal data and structure refinement details are listed in Table 1.

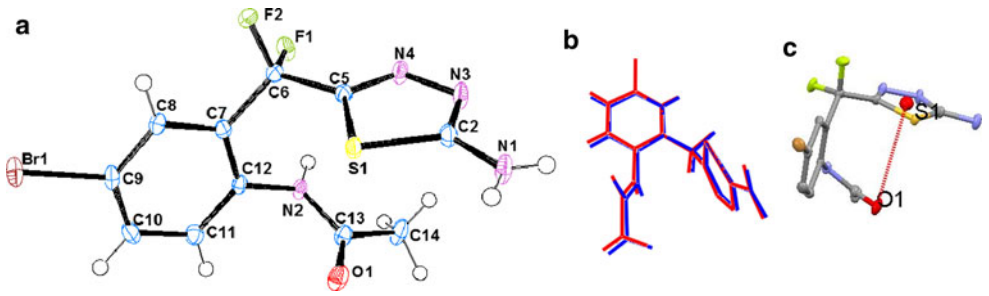


Fig. 2 **a** Atom numbering scheme and atom arrangement for (**1**: X = Br). Numbering for (**1**: X = Cl), Cl1 replaces Br1. Probability ellipsoids are drawn at the 50% level and hydrogen atoms are drawn as spheres of arbitrary radii; **b** overlay of molecules (**1**: X = Cl), and (**1**: X = Br); **c** View of the conformation of **1**: X = Br) with the C–O–$\pi_{thiadiazole}$ shown as a dashed red line: hydrogen atoms have been omitted for clarity

Results and Discussion

Molecular Structures

Compounds (**1**: X = Cl) and (**1**: X = Br) crystallize in the monoclinic space group P21/c, and have similar cell dimensions. Figure 2a shows the atom numbering system and atom arrangements for (**1**: X = Br): the notation used for (**1**: X = Cl) is similar except with Cl1 replacing Br1. As shown in Fig. 2b, there is a very close overlay involving the two molecular structures. Indeed the two isometric compounds satisfy the criteria proposed by Kalman and co-workers [23] for isotructural compounds, e.g., in terms of orthogonized lattice parameters and isostructurality index.

Selected bond lengths and angles are listed in Table 2. The data relating to the thiadiazole unit are in the ranges generally found for 5-*R*-2-H_2N-1,3,4-thiadiazoles (**2**: *R* = alkyl or aryl) [24–33]. Weak intramolecular C6–H6···F2 hydrogen bonds are present in **1**, see Table 2.

The essentially planar 1,3,4-thiadiazole and the aryl rings are nearly orthogonal as shown by the angles between the best planes though the aromatic rings of 83.7(3) and 83.8(3)° in (**1**: X = Cl) and (**1**: X = Br), respectively. A twist between the aromatic group planes is indicated by the S1–C5–C6–C7 torsion angle of 44.4 (3)° in each molecule. The orientation of the thiadiazole and phenyl rings has the S atom of the thiadiazole ring and the acetamido substituent of the phenyl ring placed on the same side of the molecule, see Fig. 2c. This allows weak C(13)–O(1)···$\pi_{(thiadiazole)}$ intramolecular interactions with O–$Cg_{(thiadiazole)}$ distances of 3.781(2) and 3.8045(17) Å, respectively for (**1**: X = Cl) and (**1**: X = Br).

A slightly smaller dihedral angle, 73.92(8)°, between the thiadiazole and phenyl rings was earlier reported by us for another substituted benzylated thiadiazole derivative, namely 5-(3-nitrobenzyl)-1,3,4-thiadiazol-2-amine, **3**. Of interest, the thiadiazole S atom in **3** is also directed towards the phenyl ring [23].

Crystal Structures

The supramolecular arrangements in each case is generated from a combination of hydrogen bonds, N1–H1A···O1, N1–H1B···N3, N2–H2···N4, N2–H2···F1 and C14–H14B···N4, and C–Y···π interactions, namely C11–H11···Cg(1), and C9–Cl1··Cg(2): symmetry operations are listed in Table 3. The amino groups act as double donors in N–H···N and N–H···O hydrogen bonds, while the NH of the amido group

Table 2 Selected geometric parameters

	(**1**: X = Cl)	(**1**: X = Br)		(**1**: X = Cl)	(**1**: X = Br)
S1–C2	1.750(2)	1.748(2)	C5–S1–C2	85.94(10)	85.98(10)
N3–C2	1.322(3)	1.323(3)	S1–C2–N3	114.31(16)	114.21(15)
N3–N4	1.386(3)	1.382(2)	C2–N3–N4	111.37(18)	111.53(17)
N4–C5	1.290(3)	1.291(3)	N3–N4–C5	113.09(18)	113.09(16)
S1–C5	1.734(2)	1.734(2)	N4–C5–S1	115.29(17)	115.19(16)

Intramolecular hydrogen bonds

Compound	D–H···A	D–H	H···A	D–A	D–H···A
(**1**: X = Cl)	C8–H8–F2	0.95	2.34	2.680(3)	101
(**1**: X = Br)	C8–H8–F2	0.95	2.33	2.675(2)	101

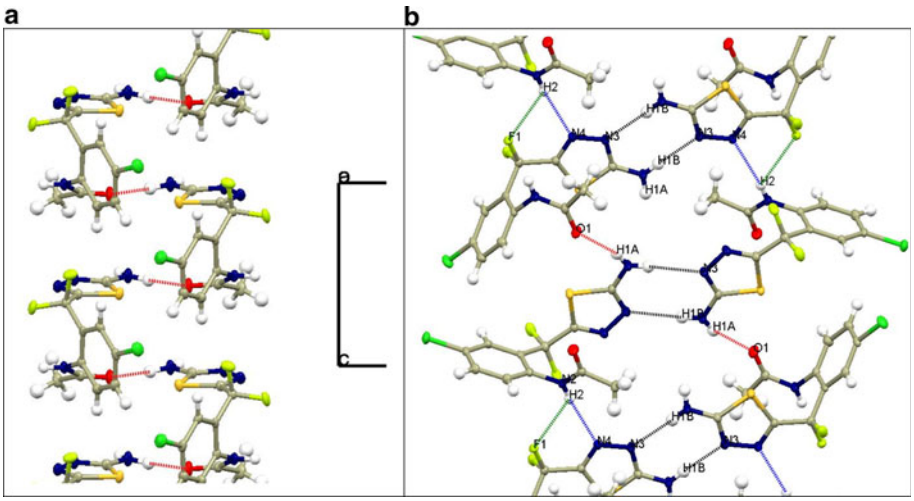


Fig. 3 **a** A zig-zag chain of molecules, [C(11)], of (**1**: X = Cl), formed from N1–H1A–O1 hydrogen bonds aligned along *c*; **b** Network of molecules formed from N1–H1A–O1, (*red dash line*), N1–H1B–N3 (*black*), N2–H2–N4 (*blue*) and N2–H2–F1 (*green*): symmetry codes are listed in Table 3. Chlorine, fluorine, oxygen, sulfur, nitrogen, carbon and hydrogen atoms are coloured bright *green*, *lime green*, *red*, *yellow*, *blue*, *grey* and *white*, respectively (Color figure online)

Table 3 Parameters (Å, °) for intermolecular contacts

(a) Intermolecular Hydrogen-bonds

Compound	D–H···A	D–H	H···A	D–A	D–H···A
(**1**: X = Cl)	N1–H1A···O1^{i}	0.89(3)	1.97(3)	2.801(3)	156(2)
(**1**: X = Br)	N1–H1A···O1^{i}	0.79(3)	2.06(3)	2.799(2)	156(3)
(**1**: X = Cl)	N6–H1B···N3^{ii}	0.85(3)	2.32(3)	3.147(3)	173(3)
(**1**: X = Br)	N6–H1B···N3^{ii}	0.77(3)	2.39(3)	3.149(3)	168(3)
(**1**: X = Cl)	N2–H2···F1^{iii}	0.83(3)	2.52(3)	3.021(2)	119(2)
(**1**: X = Br)	N2–H2···F1^{iii}	0.83(3)	2.56(3)	3.034(2)	118(2)
(**1**: X = Cl)	N2–H2···N4^{iii}	0.85(3)	2.33(3)	3.156(3)	164(2)
(**1**: X = Br)	N2–H2···N4^{iii}	0.83(3)	2.32(3)	3.149(3)	165(2)
(**1**: X = Cl)	C14–H14B···N4^{iii}	0.98	2.58	3.358(3)	137
(**1**: X = Br)	C14–H14B···N4^{iii}	0.98	2.59	3.358(3)	135

(b) X–Y–π interactions

Compound	C–H···Cg	H···Cg	H_{perp}	γ	C–H···Cg	C···Cg	C–H, π
(1: X = Cl)	C11–H11···Cg(1^{i})	2.82	2.73	14.75	173	3.768(2)	80
(1: X = Br)	C11–H11···Cg(1^{i})	2.84	2.76	14.04	173	3.789(2)	80
(1: X = Cl)	C9–Cl1···Cg(2^{ii})	3.5999(11)	3.549	9.66	98.17(8)	4.213(3)	0.36
(1: X = Br)	C9–Cl1···Cg(2^{iii})	3.7267(9)	3.652	11.48	100.95(6)	4.490(2)	0.44
(1: X = Cl)	C13–O1···Cg(1^{iii})	3.781(2)	3.444	24.36	71.93(14)	3.595(2)	1.86
(1: X = Br)	C13–O1···Cg(1^{iii})	3.8024(17)	3.457	24.61	71.90(12)	3.615(2)	1.91

(a) Intermolecular Hydrogen-bonds: symmetry codes: (i) x, $3/2 - y$, $1/2 + z$ (ii) $1 - x$, $-1 - y$, $2 - z$; (iii) x, $1/2 - y$, $-1/2 + z$

(b) X–Y–π interactions: Cg(1) and Cg(2) are the centroids of the thiadiazole and phenyl rings, respectively. Gamma is the angle at H between the vectors H–Cg and H_{perp}. C–H, π is an estimate of the significance of the interaction. Symmetry codes: (i) x, y, $-1 + z$; (ii) $2 - x$, $1 - y$, $1 - z$; (iii) x, y, z

acts as a donor in N–H···N hydrogen bonds, as well as in weaker N–H···F hydrogen bonds. The acetamido oxygen, as well as the two nitrogen atoms in the thiadiazole ring, act as strong acceptors.

The discussion of intermolecular interactions will consider just the chloro compound, as the arrangement for (**1**: X = Br) is essentially the same. The N1–H1A···O1 hydrogen bonds lead to zig-zag chains, [C(11)], of molecules aligned along the *c* axis, see Fig. 3a. Centrosymmetic $R_2^2(8)$ dimers [14], are generated by paired N1–H1B···N3 hydrogen bonds. The combination of the N2–H2···N4 and N2–H2···F1 hydrogen bonds result in the formation of $R_2^1 5$ rings. In addition, the combination of N1–H1A···O1, N1–H1B···N3 [2 of these], and N2–H2···N4 hydrogen

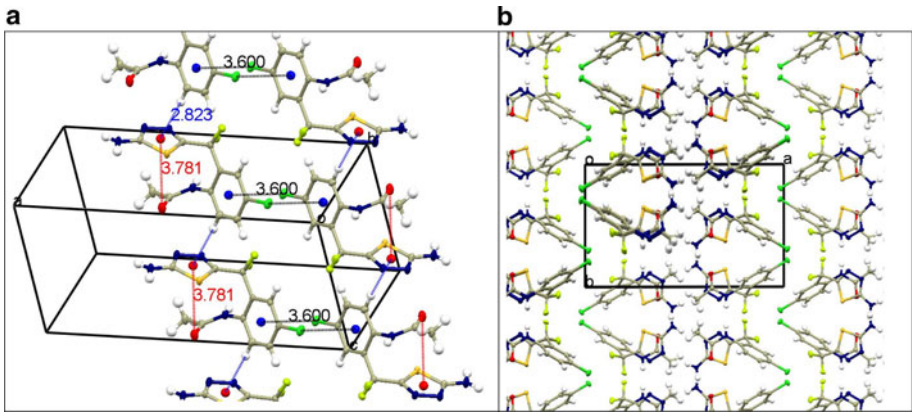


Fig. 4 **a** Intermolecular connections involving X–Y–π interactions, illustrated for (**1**: X = Cl). *Blue*, *red* and *black dash lines* represent C11–H11–Cg(1), C13–O1–Cg(1) and C9–Cl1–Cg(2), respectively: symmetry codes are listed in Table 3. Values, in Å, without esds, are those calculated using the Y–Cg distances. Red and blue spheres are centroids of the thiadiazole {Cg(1)} and phenyl [C7–C12] {Cg(2)} rings; **b** Packing arrangement illustrated for (**1**: X = Cl). Chlorine, fluorine, oxygen, sulfur, nitrogen, carbon and hydrogen atoms are coloured *bright green*, *lime green*, *red*, *yellow*, *blue*, *grey* and *white*, respectively (Color figure online)

bonds result in formation of $[R_4^4(18)]$ rings. The network formed from these interactions is illustrated in Fig. 3b. A PLATON analysis also recognized a weak C14–H14B···N4 hydrogen bond, which utilises a hydrogen of the methyl group: this is not indicated but, if significant, would further cement the network shown in Fig. 3b.

There are two intermolecular C–Y···π interactions, namely C11–H11···π_{phenyl} and C9–Cl1···π_{phenyl}, in addition to the intramolecular C13–O1···$\pi_{(thiadiazole)}$ intramolecular interaction mentioned earlier. Chains of molecules are formed by alternating C11–H11···π_{phenyl} and C13–O1···$\pi_{thiadizole}$ interactions. Such chains are linked by symmetry related C9–Cl1···π_{phenyl} interactions into double columns. The combination of the three C–Y···π interactions is illustrated in Fig. 4a: $Cg(2)_{phenyl}$ $Cg(1)_{thiadiazole}$ are the centroids of the phenyl and thiadiazole rings respectively.

Altogether, all the intermolecular interactions result in a 3-D array: Fig. 4b shows the packing arrangement.

Comparisons with Other Thiadiazoles

Generally for compounds **2** having simple alkyl groups, e.g., R = Me [25], Et [25], Pr [26], CF_3 [1], and aryl groups with no or poor donor/acceptor groups, e.g., R = Ph [27], 4-MeC_6H_4 [28], 3-MeC_6H_4 [29], 2-MeC_6H_4 [30], 4-PeC_6H_4 [31], 4-FC_6H_4 [32] and 2-BrC_6H_4 [33], the supramolecular arrangements simply involve N–H–N interactions. A common motive is the centrosymmetric dimer generated from two intermolecular N–H–N hydrogen bonds: additionally other motives can also be generated from the N–H–N hydrogen bonds, e.g., [1]. For compounds 2 having additional donor groups, other types of intermolecular interactions arise as well as the N–H–N hydrogen bonds, e.g., the π–π stacking interactions as found in **2**: R = 3-py) [34] and **2**: R = 3-py) [35], and the C–H–O hydrogen bonds detected in both 2: R = 2-F-4-$O_2NC_6H_3$) [36] and in **3** [24].

In compounds **1**, while the hydrogen bonds involving the amido O atom contribute significantly to the supramolecular arrangements, the centrosymmetric dimers generated from intermolecular N–H–N hydrogen bonds remain major features.

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