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PAPER

Intramolecular hypervalent C=O···S interactions in a series of 1,3-benzothiazole derivatives†

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Seven compounds derived from 2-(4-chlorophenoxy)-2-methylpropionic acid and 2-aminobenzothiazole, 2-amino-6-methylbenzothiazole, 2-amino-6-methoxybenzothiazole, 2-amino-6-ethoxybenzothiazole, 2-amino-6-chlorobenzothiazole, 2-amino-6-nitrobenzothiazole, and 2-amino-6-(methylsulfonyl) benzothiazole have been prepared and structurally characterized. This set of 1,3-benzothiazole derivatives (**1–7**) has been studied by means of elemental analysis, mass spectrometry, IR, NMR (^{1}H, ^{13}C) spectroscopy, and single-crystal X-ray diffraction analysis. This work focuses on the description of the hypervalent contacts (C=O···S, S···S), hydrogen bonds Y–H···X (Y = O, N, C; X = O, N, Cl, π) and van der Waals contacts (Cl···π, S···π, H···H) that are found to be the driving forces for the supramolecular arrangements present in the crystal structures.

1. Introduction

The aim of crystal engineering is to establish connections between molecular and supramolecular structure on the basis of non-covalent intra- and intermolecular interactions. The forces resulting from these interactions range from very weak to strong and depend on several properties of the interacting individual molecules. In most cases they are cooperative, thus their combined effect on the crystal structure is hard to evaluate from each single interaction present in the system. It would be very convenient to identify substructural units (*supramolecular synthons*) in a target supramolecule and assemble it from logically chosen precursor molecules.[1] However, the final outcome of multiple interactions in a system has proven to be difficult to anticipate due to the subtleties governing non-covalent interactions.

Hydrogen bonding is a classical example of a strong or moderate, but generally specific and highly directional, intermolecular interaction. Being specific and highly directional, hydrogen bonds promote the optimal geometrical arrangement of the different synthons found in crystal structures. In recent times weak interactions such as C–H···X (X = O, N, S, F, Cl, Br, I), C–H···π and π···π contacts have been identified as an important driving force on the stabilization of molecular solids.[2] In the same way, hypervalent interactions, X···X or X···Y, may form robust supramolecular synthons with many features in common with organic hydrogen bonds, including the ability to form polymeric networks in the solid state.[3] Additionally, C–H···X hydrogen bonds have great importance for molecular recognition processes,[4] the reactivity and structure of biomolecular species,[5] the stabilization of inclusion complexes,[6] conformational isomerism[7] and the properties of ionic liquids.[8]

The seven molecules studied here are hybrid amides from clofibric acid and 1,3-benzothiazole pharmacophore, related to antidiabetic activity.[9] Fibrates (phenoxyisobutyrates) such as bezafibrate, clofibrate and fenofibrate are used as therapeutic agents in the treatment of dyslipidemia, heart disease and diabetic complications in humans. The fibrates are a widely used class of lipid-modifying agents that decrease plasma triglycerides.[10] The fibrate pharmacophore has been of interest to medicinal chemists ever since the initial discovery that ethyl chlorophenoxyisobutyrate (clofibrate, a prodrug, that is biotransformed into clofibric acid) possessed hypolipidemic properties.[11]

In order to assist our knowledge about the electronic and steric requirements from these kinds of molecules to show anti-hyperlipidemic activity, we have designed, synthesized and

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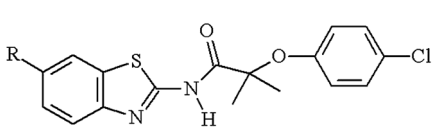

1 R = H
2 R = CH_3
3 R = OCH_3
4 R = OCH_2CH_3
5 R = Cl
6 R = NO_2
7 R = SO_2CH_3

Scheme 1 Molecular structures of compounds **1–7**.

determined the crystal structures of a series of 1,3-benzothiazole derivatives **1–7** (Scheme 1).

The structural differences found in this family of compounds emphasize the influence that small chemical and electronic modifications on the molecular level have on the 3D arrangement in the solids. In this respect it is interesting to note that these seven crystal structures share only two kinds of cooperative intramolecular interactions: an intramolecular hydrogen bond N–H···O–C that can be described by the graph S(5), and an intramolecular hypervalent C═O···S contact. These interactions govern the molecular conformation and lead to six different synthons.

2. Results and discussion

2.1 Syntheses and spectroscopic characterization

Compounds **1–7** were obtained in yields ranging from 25 to 60% by combination of 2-(*p*-chlorophenoxy)-2-methyl-propionic acid with 2-aminobenzothiazole, 2-amino-6-methyl-benzothiazole, 2-amino-6-methoxybenzothiazole, 2-amino-6-ethoxybenzothiazole, 2-amino-6-chlorobenzothiazole, 2-amino-6-nitrobenzothiazole, and 2-amino-6-(methylsulfonyl)benzo-thiazole in dichloromethane as solvent. The compounds **1–7** have been characterized by means of elemental analysis, mass spectrometry, IR, and NMR (^{1}H, ^{13}C) spectroscopy, and single-crystal X-ray diffraction.

The formation of the compounds **1–7** could be evidenced directly from the IR and ^{13}C NMR spectra. The IR spectra showed bands in the range from 1617 to 1697 cm^{-1} and 1574 to 1604 cm^{-1} that are typical for the vibrations of the N–C═O and C═N groups, respectively.[12] The ^{13}C NMR signals of the amide and imine carbon atoms (NC═O, N═C) are found in the range of δ_C 173.0–173.8 and 156.5–161.8 ppm, respectively.[13] The chemical shifts of the carbon atoms in the 6-substituted-2-amino-benzothiazole moieties were modulated by the inductive effect of the substituent on C6 (see the Experimental part).

The ^{1}H NMR signals of the amide hydrogen atoms (N–H) were found in the range of δ_H 9.90 to 10.34 ppm. The mass spectra (FAB$^+$) showed the peak for the molecular ions at *m*/*z* 347 (70%) for compound **1**, 361 (100%) for compound **2**, 377 (70%) for compound **3**, 391 (100%) for compound **4**, 381 (70%) for compound **5**, 392 (20%) for compound **6**, and 425 (100%) for compound **7**.

2.2 X-Ray crystal structures

Single crystals were grown at room temperature; **1**, **2**, **3**, **5** from methanol solution; **4**, **7** from ethanol solution and **6** from an acetone–water (2 : 1) mixture.‡ Selected bond lengths, torsion angles, and intramolecular hypervalent contacts are given in Table 1 and hydrogen bonding parameters are given in Table 2.

The seven independent molecular systems have some common features. All crystal structures showed two kinds of intra-molecular interactions: one N–H···O–C hydrogen-bond that can be described by the graph set S(5)[14] and an hypervalent C═O···S contact (Tables 1 and 2).[15]

This presumably sets the stage for the intermolecular interactions observed in the crystal networks. These intramolecular cooperative interactions provide essentially planar 1,3-benzothiazole moieties, with the N1–C8–C7 side chain deviating only slightly from the plane of the benzothiazole group; the C11–N1–C8–C7 torsion angle values are in the range of 169.1(2)–177.9 (2)°. The 4-chlorophenyl rings are synclinal to the C═O groups in compounds **1** and **2** with C8–C7–O1–C1 torsion angles of 73.5 (3) and 74.0(3)°, respectively, and antiperiplanar in compounds **3–7**; the C8–C7–O1–C1 torsion angle values are in the range of 156.2(2)–179.2(1)°. The N1–C8 and N1–C11 bond lengths are intermediate between single and double bond length, indicative of electronic delocalization in the O2–C8–N1–C11 region. However, the O2–C8 distances are not significantly longer than the expected distances for C═O bonds (Table 1).[16]

The hypervalent C═O···S contacts in all systems are within the 2.648(1)–2.788(2) Å range, considerably smaller than the sum of the van der Waals radii (3.32 Å); the C13–S1···O2 and C8–O2···S1 angles are in the 157–162° and 95–98° range, respectively, consistent with hypervalent interactions (Table 1).[15]

In all compounds was observed the formation of N–H···X (**1**, **2**, **3** and **5**, X = O; **4** and **6**, X = Cl; **7**, X = N) hydrogen bond

‡ Crystal data for **1–7**: $C_{17}H_{15}ClN_2O_2S$ **1**, M = 346.82, orthorhombic, space group *Pbca*, a = 12.097(3), b = 10.088(2), c = 26.807(6) Å, α = β = γ = 90°, V = 3271.3(13) Å^3, T = 100 K, Z = 8. 27083 reflections measured, 2868 unique (R_{int} = 0.054) and 2830 with $I > 2\sigma(I)$. The final R values were R_1 = 0.053 and wR_2 (all data) = 0.103. CCDC 827868. $C_{18}H_{17}ClN_2O_2S$ **2**, M = 360.85, orthorhombic, space group *Pbca*, a = 14.1449(13), b = 9.9181(9), c = 25.167(2) Å, α = β = γ = 90°, V = 3530.7(6) Å^3, T = 100 K, Z = 8. 23225 reflections measured, 3109 unique (R_{int} = 0.044), 3035 with $I > 2\sigma(I)$. The final R values were R_1 = 0.062 and wR_2 (all data) = 0.12. CCDC 827869. $C_{19}H_{21}ClN_2O_4S$ **3**, M = 408.89, monoclinic, space group *P*2(1)/*n*, a = 14.9642(18), b = 7.7170 (9) c = 17.958(2) Å, β = 111.457(2)°, V = 1930.1 (4) Å^3, T = 173 K, Z = 4. 17913 reflections measured, 3394 unique (R_{int} = 0.040), 2816 with $I > 2\sigma(I)$. The final R values were R_1 = 0.037 and wR_2 (all data) = 0.102. CCDC 827870. $C_{19}H_{19}ClN_2O_3S$ **4**, M = 390.87, monoclinic, space group *P*2(1)/*c*, a = 23.731(2), b = 13.7198 (14), c = 17.4841(18) Å, β = 102.160(2)°, V = 5564.7 (10) Å^3, T = 100 K, Z = 12. 53185 reflections measured, 9817 unique (R_{int} = 0.055), 8003 with $I > 2\sigma(I)$. The final R values were R_1 = 0.041 and wR_2 (all data) = 0.099. CCDC 827871. $C_{18}H_{18}Cl_2N_2O_3S$ **5**, M = 413.30, triclinic, space group $P\bar{1}$, a = 7.2962(7), b = 9.8387(10), c = 13.9567(14) Å, α = 77.188(2), β = 84.710(2), γ = 76.498(2)°, V = 949.08(16) Å^3, T = 173 K, Z = 2. 9171 reflections measured, 3333 unique (R_{int} = 0.032), 3093 with $I > 2\sigma(I)$. The final R values were R_1 = 0.031 and wR_2 (all data) = 0.085. CCDC 827872. $C_{17}H_{14}ClN_3O_4S$ **6**, M = 391.82, triclinic, space group $P\bar{1}$, a = 7.395(2), b = 7.653(2), c = 15.958(4) Å, α = 90.156(5), β = 96.693(4), γ = 99.998(4)°, V = 883.0 (4) Å^3, T = 294 K, Z = 2. 8330 reflections measured, 3097 unique (R_{int} = 0.030), 2344 with $I > 2\sigma(I)$. The final R values were R_1 = 0.042 and wR_2 (all data) = 0.133. CCDC 827873. $C_{18}H_{17}ClN_2O_4S_2$ **7**, M = 424.91, monoclinic, space group *C*2/*c*, a = 29.002(3), b = 8.6295(9), c = 16.5593(18) Å, β = 113.948(2)°, V = 3787.5(7) Å^3, T = 294 K, Z = 8. 17796 reflections measured, 3338 unique (R_{int} = 0.038), 2688 with $I > 2\sigma(I)$. The final R values were R_1 = 0.039 and wR_2 (all data) = 0.12. CCDC 827874.

Table 1 Selected bond lengths, torsion angles, and intramolecular hypervalent contacts for compounds **1–7**

Compound	C8═O2/Å	N1–C8/Å	N1–C11/Å	C7–C8–N1–C11/°	C8–C7–O1–C1/°	S1···O2/Å	C13–S1···O2/°	S1···O2═C8/°
1	1.219(3)	1.359(3)	1.384(3)	169.1(2)	73.5(3)	2.696	159.4	97.5
2	1.229(4)	1.356(4)	1.385(4)	176.3(3)	74.0(3)	2.758	161.2	96.2
3	1.218(2)	1.358(3)	1.383(3)	173.4(2)	177.4(2)	2.709	161.6	97.1
4a	1.218(3)	1.350(3)	1.382(3)	−177.9(2)	171.2(2)	2.774	161.1	95.0
4b[a]	1.217(2)	1.356(3)	1.381(3)	−174.5(2)	171.3(2)	2.787	161.3	94.8
4c[b]	1.223(3)	1.354(3)	1.382(3)	−174.4(2)	178.5(2)	2.788	161.1	94.8
5	1.220(2)	1.367(2)	1.378(2)	−171.1(1)	−179.2(1)	2.648	162.8	98.1
6	1.210(3)	1.354(3)	1.384(3)	−175.0(2)	−156.2(2)	2.745	160.6	96.0
7	1.218(3)	1.355(3)	1.385(3)	−169.9(2)	−161.1(2)	2.778	157.3	95.7

[a] Data belong to: C27═O5, C27–N3, C30–N3, C26–C27–N3–C30, C27–C26–O4–C20, S2···O5, C32–S2···O5, S2···O5═C27. [b] Data belong to: C46═O8, C46–N5, C49–N5, C45–C46–N5–C49, C46–C45–O7–C39, S3···O8, C51–S3···O8, S3···O8═C46.

that, in addition to being an intramolecular organizer, acts as a three center or bifurcated interaction.[17] In addition to the intermolecular N–H···X bond, other hydrogen bonds Y–H···X (Y = O, C; X = O, N, Cl, π) and van der Waals contacts (Cl···π, S···π, H···H) are found as the contributing forces for the supramolecular arrangements in the crystal structures.

Table 2 Hydrogen-bond geometries (Å, °) for compounds **1–7**

D–H···A	D–H	H···A	D···A	D–H···A	Symmetry codes
Compound **1**					
N1–H1···O1	0.86	2.37	2.714(3)	104	
N1–H1···O2	0.86	2.09	2.918(3)	163	$^1/_2 - x, -^1/_2 + y, z$
C10–H10B···N2	0.98	2.59	3.524(4)	159	$^1/_2 - x, ^1/_2 + y, z$
C14–H14···C16	0.95	2.79	3.557(4)	137	$-^1/_2 - x, ^1/_2 + y, z$
Compound **2**					
N1–H1···O1	0.86	2.45	2.740(3)	100	
N1–H1···O2	0.86	2.07	2.909(4)	165	$^1/_2 - x, -^1/_2 + y, z$
C14–H14···Cl1	0.95	2.91	3.682(3)	139	$-x, 1 - y, -z$
C17–H17···Cl1	0.95	2.84	3.697(3)	151	$-x, -y, -z$
C4–Cl1···π	1.75	3.36	5.11	178	$x, ^1/_2 - y, -^1/_2 + z$
Compound **3**					
N1–H1···O1	0.86	2.14	2.516(2)	106	
N1–H1···O4	0.86	2.04	2.874(2)	162	$1 - x, 1 - y, 1 - z$
O4–H6A···N2	0.84	2.13	2.888(2)	151	
C3–H3···O3	0.95	2.62	3.261(2)	125	$1 + x, y, z$
C14–H14···O3	0.95	2.71	3.406(3)	131	$-x, -^1/_2 + y, ^1/_2 - z$
C9–H9A···O2	0.98	2.47	3.448(3)	175	$1 - x, ^1/_2 + y, ^1/_2 - z$
C16–H16···π	0.95	3.14	3.78	127	$1 - x, 1 - y, 1 - z$
C18–H18C···π	0.98	2.78	3.43	124	$-x, -^1/_2 + y, ^1/_2 - z$
Compound **4**					
N1–H1A···O1	0.86	2.07	2.511(2)	111	
N3–H3A···O4	0.86	2.01	2.492(2)	114	
N5–H5A···O7	0.86	2.03	2.498(2)	113	
C14–H14···O5	0.95	2.57	3.409(3)	148	
N3–H3A···Cl2	0.86	2.72	3.464(2)	146	$-x, -y, 1 - z$
N5–H5A···Cl1	0.86	2.74	3.441(2)	140	$1 - x, 1 - y, -z$
C16–H16···Cl2	0.95	2.77	3.599(2)	146	$-x, 1 - y, 1 - z$
C19–H19C···π	0.98	3.03	3.61	119	$-x, 1 - y, 1 - z$
Compound **5**					
N1–H1···O1	0.86	2.14	2.542(2)	110	
N1–H1···O3	0.86	2.04	2.873(2)	161	$1 - x, -y, 1 - z$
O3–H3A···N2	0.84	2.11	2.874(2)	152	$1 + x, y, z$
C9–H9C···Cl1	0.98	2.94	3.856(2)	157	$1 - x, -1 - y, 2 - z$
C14–H14···O2	0.95	2.52	3.263(2)	135	$1 - x, 1 - y, 1 - z$
C16–H16···π	0.95	3.24	3.87	125	$-x, -y, 1 - z$
Compound **6**					
N1–H1A···O1	0.86	2.04	2.508(3)	113	
N1–H1A···Cl1	0.86	2.83	3.602(2)	151	$-x, 2 - y, -z$
C14–H14···O2	0.93	2.59	3.361(3)	140	$-x, 1 - y, 1 - z$
Compound **7**					
N1–H1···O1	0.86	2.14	2.553(3)	109	
N1–H1···N2	0.86	2.25	3.073(3)	159	$2 - x, y, 3/2 - z$
C10–H10A···O4	0.96	2.58	3.400(3)	144	$2 - x, 1 - y, 1 - z$
C17–H17···O3	0.93	2.67	3.487(3)	147	$x, 1 - y, 1/2 + z$

In the packing of compounds **1** and **2** the intermolecular hydrogen bonds N–H···O═C link molecules into chains running along the *b* axis. This bond is shorter than the intramolecular one (Fig. 1 and Table 2).

The adjacent chains in **1** are connected through C–H···π and C–H···N interactions. It is possible to see that these latter lead to a 2D undulating network parallel to plane *ab* (Table 2 and Fig. 2a and b). In the C–H···π van der Waals contact the distance C14···*Cg* (C12–C17) is 4.52 Å, and the shortest carbon–carbon distance is 3.547(4) Å.[18b,e,f]

In the crystal structure of **2**, in addition to the aforementioned interactions, the neighboring chains also are associated through two weak C–H···Cl hydrogen bonds and Cl···π contacts leading to an overall 3D network (Table 2).[19] Of these, the C–H···Cl distance between the ring centroid *Cg* (C12–C17) and the Cl(1) atom is 3.362 Å (Fig. 3).[19e] Of these, the C–H···Cl interactions link three neighboring molecules forming cyclic motifs (**I** and **II**) that belong to the graph set $R_2^2(28)$ (Fig. 3).[14] Additionally, the packing is stabilized by Cl···π contacts. The distance between the ring centroid *Cg* (C12–C17) and the Cl(1) atom is 3.362 Å (Fig. 3).[19e]

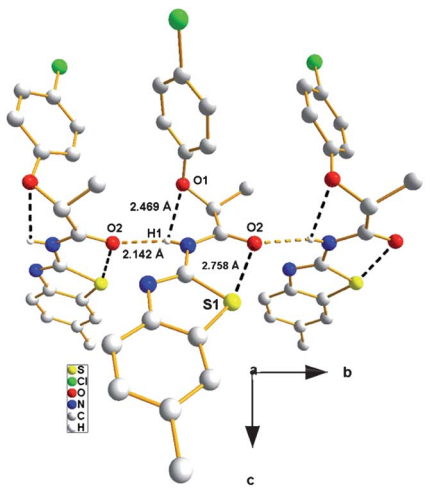

Fig. 1 View of the bifurcated hydrogen bonds (N–H···O) and hypervalent contacts (C═O···S)—dashed lines—generating chains along the *b* axis in compound **2**. For clarity, methyl groups and hydrogen atoms not involved in the hydrogen-bonding interactions were omitted.

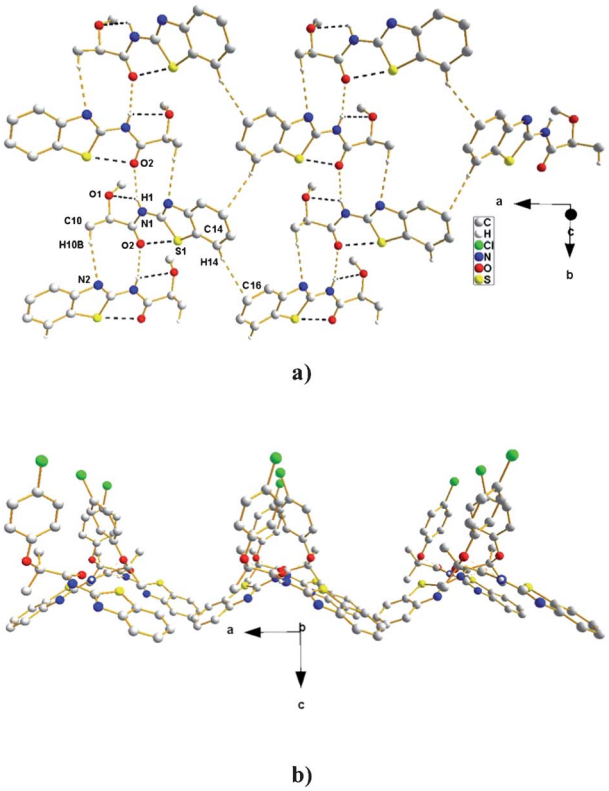

Fig. 2 (**a**) View of two adjacent chains in the crystal structure of **1**, showing the 2D undulating network parallel to the plane *ab* and their association with C–H···N and C–H···π hydrogen-bonding; methyl and chlorophenyl groups, and hydrogen atoms not involved in the hydrogen-bonding interactions were omitted for clarity. (**b**) Lateral view of the 2D undulated network.

Solvent forms part of the crystal structure of compounds **3** and **5** in which the asymmetric units contain one molecule of methanol acting both as donor and acceptor of H-bonds (Table 2). The crystal structures of **3** and **5** show that neighboring molecules are coupled through N–H···OM–H···N links (OM is the oxygen atom of the methanol molecule) and C–H···π interactions, thus generating the supramolecular synthons **3a** and **5a** that possess crystallographic inversion symmetry (Fig. 4).[17,18,20]

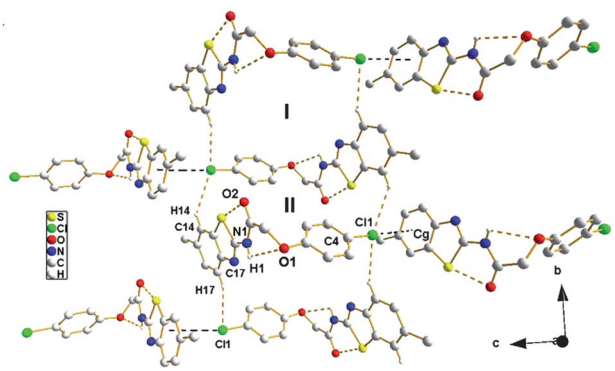

Fig. 3 Fragment of the 3D hydrogen-bonded network for compound **2**, showing the Cl···π contacts and cyclic motifs **I** and **II** generated by C–H···Cl interactions. Methyl groups and hydrogen atoms not involved in the hydrogen-bonding interactions were omitted for clarity.

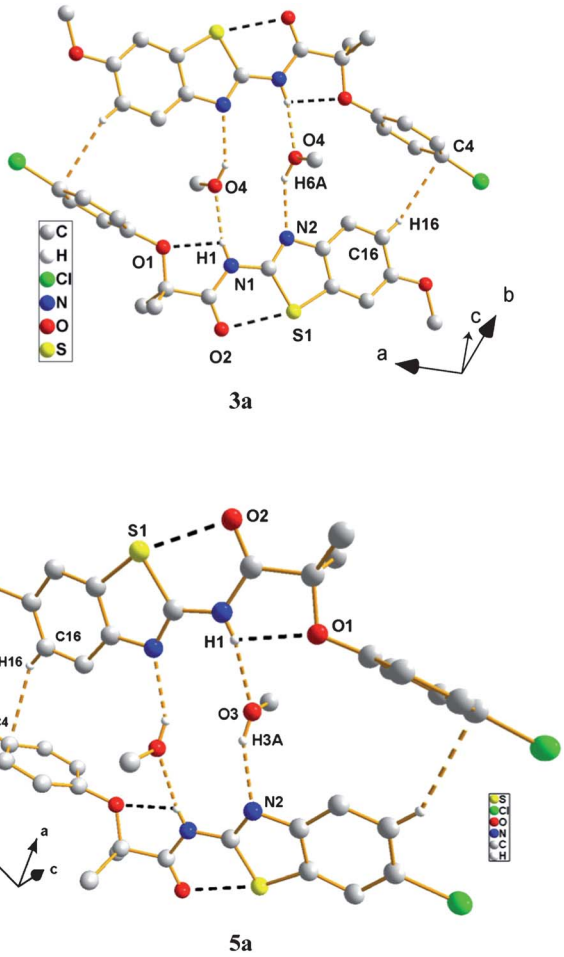

Fig. 4 Supramolecular synthons **3a** and **5a**, showing their association with N–H···O–H···N and C–H···π interactions. Hydrogen atoms not involved in the hydrogen-bonding interactions were omitted for clarity.

The 3D and 2D networks observed in the packing of these synthons suggest that some stereoelectronic effects of the substituents on C15 (CH_3–O for compound **3** and Cl for compound **5**) might play a role in modulating the final packing.

In the crystal packing of **3**, the adjacent synthons **3a** are connected together by C–H···O and C–H···π hydrogen bonds inducing an overall 3D network (Fig. 5).

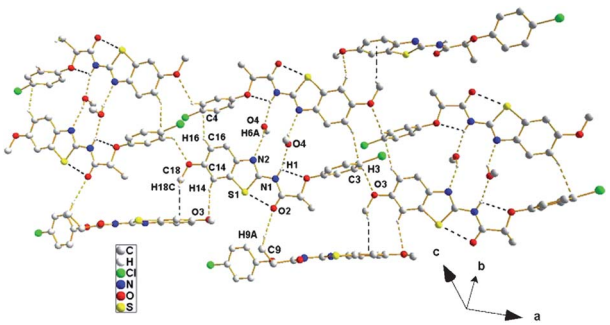

Fig. 5 Fragment of the crystal packing of **3**, showing the 3D network generated by C–H···O and C–H···π interactions between the **3a** synthons. Methyl groups and hydrogen atoms not involved in the hydrogen-bonding interactions were omitted for clarity.

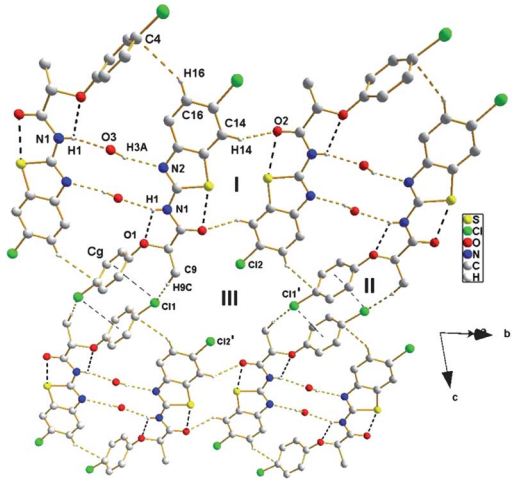

Fig. 6 Fragment of the crystal structure of compound **5**, showing the 2D network generated by C–H···Cl, C–H···O and Cl···π interactions between the **5a** synthons. Methyl groups and hydrogen atoms not involved in the hydrogen-bonding interactions were omitted for clarity.

The oxygen atom of the methoxy group (CH_3–O–Ar) is an acceptor of two H atoms. These H atoms are donated by the carbon atoms C3 and C14. Thus, the C3–H3···O3 contacts generate chains that run along the *a* axis. These chains are connected by C14–H14···O3, C9–H9A···O2 contacts and facial hydrogen bonds ($ArOCH_3$···π) producing the overall 3D network. The separation of the methyl group (C18) and the aryl centroid *Cg* (C12–C17) is 3.433 Å (Fig. 5 and Table 2).[18]

The crystal packing of **5** shows that the adjacent synthons **5a** are interconnected by weak hydrogen bonds C14–H14···O2, C9–H9C···Cl1 and Cl···π contacts generating a 2D network, in which it is possible to observe the chlorine atom bonded to the aryl group (Cl1) being a better donor/acceptor than the chlorine atom attached to the benzothiazole group (Cl2).[18,19] The motifs $R_2^2(16)$, $R_2^2(18)$ and $R_6^6(24)$ (**I–III**) can be identified (Fig. 6).

The motifs $R_2^2(16)$ and $R_2^2(18)$ are further stabilized by intramolecular hypervalent S···O interactions and van der Waals Cl···π contacts, respectively. The distance between the ring centroid *Cg* and the Cl(1) atom is 3.546 Å. On the other hand, the transannular Cl1···Cl1′ and Cl2···Cl2′ distances in the motif $R_6^6(24)$ are 8.842(1) and 5.937(1) Å, respectively.

Fig. 7 shows the crystal packing of compound **4**. The asymmetric unit contains three independent molecules (**4a**, **4b**, **4c**). From the hydrogen-bond pattern, the supramolecular synthons **I** and **II** that possess crystallographic inversion symmetry can be distinguished. The synthon **I** is generated by coupling of two adjacent **4b** molecules through N–H···Cl hydrogen bonds; the N–H group is also involved in the previously described intramolecular bifurcated H-bond. **I** is further stabilized by offset π··· π interactions, with a distance between the ring centroids *Cg*2 and *Cg*2′ (centroids of the 4-chlorophenoxy groups) of 3.66 Å. The synthon **II** is generated by the C–H···O hydrogen bonds between two **4c** molecules in which the acceptor oxygen atom is also involved in the intramolecular hypervalent O···S contact.

Synthons **I** and **II** are further interconnected by the molecule **4a** through C–H···O, C–H···Cl, N–H···Cl, C–H···π and offset π···π interactions to give an overall 2D network (Table 1).[18,19]

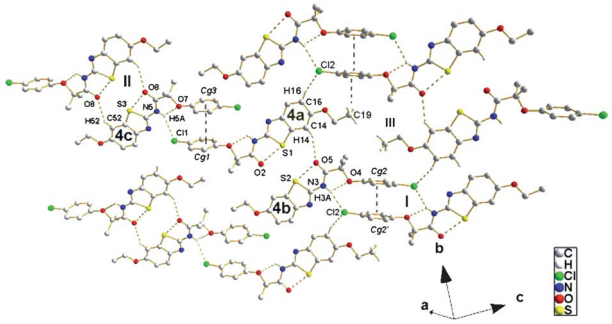

Fig. 7 Fragment of the crystal structure of compound **4**, showing the assembly of the synthons **I–III** through cooperative C–H···O, C–H···Cl, N–H···Cl, C–H···π and offset π···π interactions. H atoms not involved in the hydrogen-bonding interactions were omitted for clarity.

Synthons **II** assemble using C–H···O and C–H···Cl interactions involving the 6-ethoxybenzothiazole H atoms on C14 and C16 of molecule **4a**. These interactions lead to synthon **III**, described by the graph set $R_4^4(28)$. Due to the distance found between the methyl H atoms on C19 of molecule **4a** and the 4-chlorophenoxy group of molecule **4b**, 3.62 Å, it is possible that the packing is further stabilized by these C–H···π interactions. The N–H···Cl hydrogen bond between molecules **4c** and **4a** is further stabilized by an offset π···π interaction between **4a** and **4c**, with a distance between the ring centroids *Cg*1 and *Cg*3 (centroids of adjacent 4-chlorophenoxy groups in molecules **4a** and **4c**) of 3.76 Å.

Compound **6** has a singular interaction pattern that differentiates it from the other six members of the family. The crystal structure shows that two adjacent molecules are interconnected through C–H···O interactions and O···S···S trifurcated hypervalent contacts that generate the synthon **I** with crystallographic inversion symmetry.[15h] In this intermolecular hypervalent interaction the O···S and S···S distances are 3.298(2) and 3.494(1) Å, respectively, the former being only slightly smaller than the sum of the van der Waals radii of these centers (O···S = 3.32 Å, S···S = 3.6 Å) suggesting that its role in the stability of this synthon is only marginal but probably contributing through cooperative effects.[15]

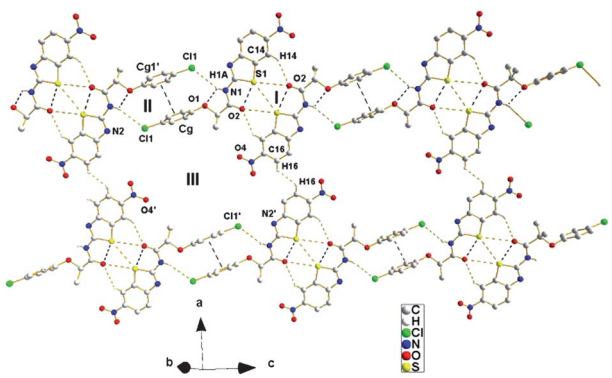

Fig. 8 Fragment of the crystal structure of compound **6**, showing the motifs **I–III** generated by N–H···Cl hydrogen bonds, π···π interactions and H···H van der Waals contacts. Methyl groups and hydrogen atoms not involved in the hydrogen-bonding interactions were omitted for clarity.

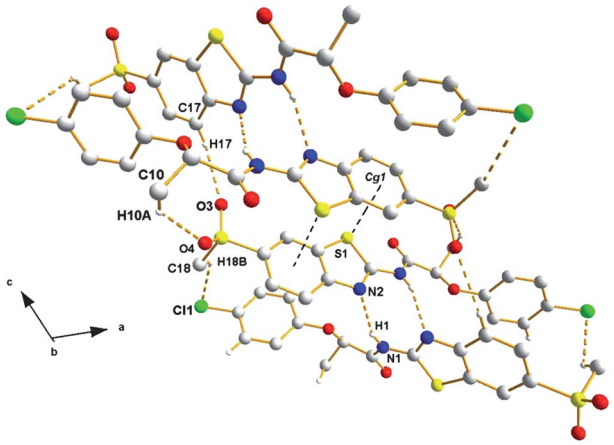

Fig. 9 Packing of compound **7**, showing N–H···N, C–H···Cl, C–H···O and S···π interactions. Methyl groups and H atoms not involved in the hydrogen-bonding interactions were omitted for clarity.

These synthons are connected through N–H···Cl and π···π interactions, thus generating supramolecular chains which are further interconnected through H···H van der Waals contacts (distance H···*H* = 2.2 Å)[21] to give an overall 2D network (Fig. 8 and Table 2). The motifs **II** and **III** with graph sets $R_2^2(14)$ and $R_4^4(44)$ can be distinguished. The distance between centroids of the chlorophenoxy rings (*Cg*···*Cg*′) is 3.77 Å. The largest motif (**III**) is characterized by transannular Cl1···Cl1′, O4···O4′ and N2···N2′ distances of 12.655(2), 9.786(3) and 17.693(4) Å, respectively.

The crystal structure of compound **7** shows neighboring molecules linked by N–H···N and C–H···Cl hydrogen bonds, forming dimers. These dimers are interconnected through C–H···O and S···π interactions, thus generating supramolecular zig-zag ribbons running along the *c* axis (Fig. 9 and Table 2). The *Cg*1···S1 (*Cg*1 is the centroid of the aryl ring in the benzothiazole moiety) distance is 3.72 Å.[18,19]

Conclusions

The present paper demonstrated that the molecular self-assembly in the seven crystal structures of the benzothiazole derivatives is modulated by the cooperative nature of hypervalent and hydrogen bonding interactions. It is interesting that the full range of intermolecular interactions found are somehow induced by the hypervalent intramolecular C═O···S contact. In particular, due to their cooperative nature, the hydrogen bonds Y–H···X (Y = O, N, C; X = O, N, Cl, π) and van der Waals contacts (Cl···π, S···π, H···H) induce different 2D or 3D patterns. The bifurcated hypervalent contacts found in compound **6** are partly favoured by the NO_2 group in the benzothiazole moiety. The variability of the supramolecular synthons found for this family of compounds suggests that even subtle structural modifications might lead to significant modifications in bi- or tridimensional molecular arrangements.

3 Experimental

3.1 General details

Instrumental: NMR studies were carried out with a Varian Inova 400 instrument. Chemical shifts (δ_H, δ_C) and *J* values are given in ppm and Hz, respectively. Standard reference was used: TMS (δ_H = 0 and δ_C = 0). IR spectra have been recorded on a Bruker Vector 22 FT spectrophotometer. Mass spectra were obtained on a Jeol JMS 700 mass spectrometer. Elemental analyses have been carried out on an Elementar Vario ELIII instrument.

3.2 Synthesis

Compounds 1–7

General method. A mixture of 2-(4-chlorophenoxy)-2-methylpropionic acid (0.50 g, 2.35 mmol) and the corresponding aminobenzothiazole (2.53 mmol) was dissolved in dichloromethane (5 mL) at 0.5 °C. A catalytic amount of dimethylaminopyridine was added. After that, a solution of dicyclohexylcarbodiimide (3.52 mmol) in dichloromethane (1 mL) was added to the reaction mixture. The ice bath was removed, and the mixture was stirred at room temperature between 2 and 24 h for each case. After the reaction was complete, the mixture was filtered off through celite, the mother liquors were removed *in vacuo*, and the solid residue was dissolved in acetone and filtered again. Acetone was removed *in vacuo* to give a solid color (white, yellow or orange, for each case). The crystals were obtained from methanol, ethanol or acetone for each case.

2-(4-Chlorophenoxy)-2-methyl-N-*(1,3-benzothiazol-2-yl)propanamide* ***1***. Crystals suitable for X-ray crystallography were grown from a solution of **1** in methanol (yield 47%). Mp: 135 °C. Elemental analysis (found: C, 58.85; H, 4.52; N, 7.46; calc. for $C_{17}H_{15}ClN_2O_2S$: C, 58.87; H, 4.36; N, 8.08%). IR (KBr): $\tilde{\nu}_{max}$ cm^{-1} 3445 (N–H), 1617 (C═O), 1597 (N═C). δ_H (400 MHz; $CDCl_3$; Me_4Si): 1.58 (6H, s, C(CH_3)$_2$), 6.85 (2H$_o$, d, ^3J = 8.8 Hz, C_6H_4ClO), 7.23 (2H$_m$, d, ^3J = 8.8 Hz, C_6H_4ClO), 7.31 (1H$_6$, dd, ^3J = 8.0, ^3J = 7.2 Hz, C_6H_4NS), 7.43 (1H$_7$, dd, ^3J = 8.0, ^3J = 7.2 Hz, C_6H_4NS), 7.77 (1H$_5$, d, ^3J = 8.0 Hz, C_6H_4NS), 7.82 (1H$_8$, d, ^3J = 8.0, C_6H_4NS), 10.13 (1H, s, N–H). δ_C (100 MHz, $CDCl_3$, Me_4Si): 24.9 (C(CH_3)$_2$), 82.0 (*C*(CH_3)$_2$), 123.5, 129.7, 129.8, 152.0 (*C*$_6$H$_4$*ClO*), 121.4, 121.6, 124.4, 126.5, 132.4, 148.7 (*C*$_6$H$_4$*NS*), 157.4 (*C*═*N*), 173.3 (C═O). MS (FAB$^+$): *m*/*z* (%) 347 ([$C_{17}H_{16}ClN_2O_2S$]$^+$, 70).

2-(4-Chlorophenoxy)-2-methyl-N-*(6-methyl-1,3-benzothiazol-2-yl)propanamide* ***2***. Crystals suitable for X-ray crystallography were grown from a solution of **2** in methanol (yield 25%). Mp: 127 °C. Elemental analysis (found: C, 58.85; H, 4.52; N, 7.46; calc. for $C_{18}H_{17}ClN_2O_2S{\cdot}0.5CH_3OH$: C, 59.04; H, 4.95; N, 7.44%). IR (KBr): $\tilde{\nu}_{max}$ cm^{-1} 3395 (N–H), 1677 (C═O), 1604 (N═C). δ_H (400 MHz; $CDCl_3$; Me_4Si): 1.57 (6H, s, C(CH_3)$_2$), 2.45 (3H, s, CH_3), 6.84 (2H$_o$, d, ^3J = 8.8 Hz, C_6H_4ClO), 7.23 (2H$_m$, d, ^3J = 8.8 Hz, C_6H_4ClO), 7.61 (1H$_5$, s, C_6H_3NS), 7.62 (1H$_7$, d, ^3J = 8.4 Hz, C_6H_3NS), 7.64 (1H$_8$, d, ^3J = 8.4 Hz, C_6H_3NS), 10.12 (1H, s, N–H). δ_C (100 MHz, $CDCl_3$, Me_4Si): 21.7 (CH_3), 24.9 (C(CH_3)$_2$), 81.9 (*C*(CH_3)$_2$), 123.5, 129.8, 129.8, 152.0 (*C*$_6$H$_4$*ClO*), 121.0, 121.4, 128.0, 132.6, 134.4, 146.6 (*C*$_6$H$_3$*NS*), 156.6 (*C*═*N*), 173.2 (C═O). MS (FAB$^+$): *m*/*z* (%) 361 ([$C_{18}H_{18}ClN_2O_2S$]$^+$, 100).

2-(4-Chlorophenoxy)-2-methyl-N-*(6-methoxy-1,3-benzothiazol-2-yl)propanamide* ***3***. Crystals suitable for X-ray crystallography were grown from a solution of **3** in methanol (yield 50%).

Mp: 94 °C. Elemental analysis (found: C, 57.27; H, 4.22; N, 7.59; calc. for $C_{18}H_{17}ClN_2O_3S$: C, 57.37; H, 4.55; N, 7.43%). IR (KBr): $\tilde{\nu}_{max}$ cm^{-1} 3365 (N–H), 1693 (C═O), 1603 (N═C). δ_H (400 MHz; $CDCl_3$; Me_4Si): 1.57 (6H, s, C(CH_3)$_2$), 3.85 (3H, s, CH_3O), 6.83 (2H$_o$, d, ^3J = 8.8 Hz, C_6H_4ClO), 7.22 (2H$_m$, d, ^3J = 8.8 Hz, C_6H_4ClO), 7.01 (1H$_7$, dd, ^3J = 8.8, ^4J = 2.4 Hz, C_6H_3NS), 7.28 (1H$_5$, d, ^4J = 2.4 Hz, C_6H_4NS), 7.64 (1H$_8$, d, ^3J = 8.8 Hz, C_6H_3NS), 10.08 (1H, s, N–H). δ_C (100 MHz, $CDCl_3$, Me_4Si): 24.9 (C(CH_3)$_2$), 56.0 (OCH_3), 81.9 (C(CH$_3$)$_2$), 123.5, 129.7, 129.7, 152.0 (C_6H_4ClO), 104.3, 115.6, 122.0, 133.7, 142.9, 155.4 (C_6H_3NS), 157.2 (C═N), 173.1 (C═O). MS (FAB$^+$): m/z (%) 377 ([$C_{18}H_{18}ClN_2O_3S$]$^+$, 70).

2-(4-Chlorophenoxy)-2-methyl-N-*(6-ethoxy-1,3-benzothiazol-2-yl)propanamide* ***4***. Crystals suitable for X-ray crystallography were grown from a solution of **4** in methanol (yield 51%). Mp: 152 °C. Elemental analysis (found: C, 56.11; H, 4.82; N, 6.72; calc. for $C_{19}H_{19}ClN_2O_3S{\cdot}CH_3OH$: C, 56.80; H, 5.48; N, 6.62%). IR (KBr): $\tilde{\nu}_{max}$ cm^{-1} 3156 (N–H), 1693 (C═O), 1597 (N═C). δ_H (400 MHz; $CDCl_3$; Me_4Si): 1.46 (3H, t, ^3J = 6.8 Hz, CH_3CH_2O), 4.10 (2H, q, ^3J = 6.8 Hz, CH_3–CH_2O), 1.60 (6H, s, C(CH_3)$_2$), 6.89 (2H$_o$, d, ^3J = 8.8 Hz, C_6H_4ClO), 7.26 (2H$_m$, d, ^3J = 8.8 Hz, C_6H_4ClO), 7.04 (1H$_7$, dd, ^3J = 9.2, ^4J = 2.4 Hz, C_6H_3NS), 7.30 (1H$_5$, d, ^4J = 2.4 Hz, C_6H_4NS), 7.66 (1H$_8$, d, ^3J = 9.2 Hz, C_6H_3NS), 10.0 (1H, s, N–H). δ_C (100 MHz, $CDCl_3$, Me_4Si): 15.0 (CH_3CH_2O), 64.3 (CH_3CH_2O), 24.9 (C(CH_3)$_2$), 81.9 (C(CH$_3$)$_2$), 123.5, 129.7, 129.8, 152.0 (C_6H_4ClO), 105.1, 116.0, 122.0, 133.6, 142.8, 155.2 (C_6H_3NS), 156.5 (C═N), 173.0 (C═O). MS (FAB$^+$): m/z (%) 391 ([$C_{19}H_{20}ClN_2O_3S$]$^+$, 100).

2-(4-Chlorophenoxy)-2-methyl-N-*(6-chloro-1,3-benzothiazol-2-yl)propanamide* ***5***. Crystals suitable for X-ray crystallography were grown from a solution of **5** in methanol (yield 51%). Mp: 146 °C. Elemental analysis (found: C, 53.0; H, 3.47; N, 7.14; calc. for $C_{17}H_{14}Cl_2N_2O_2S$: C, 53.55; H, 3.70; N, 7.35%). IR (KBr): $\tilde{\nu}_{max}$ cm^{-1} 3339 (N–H), 1683 (C═O), 1604 (N═C). δ_H (400 MHz; $CDCl_3$; Me_4Si): 1.60 (6H, s, C(CH_3)$_2$), 6.89 (2H$_o$, d, ^3J = 8.8 Hz, C_6H_4ClO), 7.27 (2H$_m$, d, ^3J = 8.8 Hz, C_6H_4ClO), 7.41 (1H$_7$, dd, ^3J = 8.6, ^4J = 2.0 Hz, C_6H_3NS), 7.67 (1H$_8$, d, ^3J = 8.6 Hz, C_6H_4NS), 7.82 (1H$_5$, d, ^4J = 2.0 Hz, C_6H_3NS), 10.1 (1H, s, N–H). δ_C (100 MHz, $CDCl_3$, Me_4Si): 24.9 (C(CH_3)$_2$), 81.9 (C(CH$_3$)$_2$), 123.5, 129.7, 129.9, 151.9 (C_6H_4ClO), 121.2, 122.1, 127.2, 129.9, 133.7, 147.3 (C_6H_3NS), 157.7 (C═N), 173.4 (C═O). MS (FAB$^+$): m/z (%) 381 ([$C_{17}H_{15}Cl_2N_2O_2S$]$^+$, 70).

2-(4-Chlorophenoxy)-2-methyl-N-*(6-nitro-1,3-benzothiazol-2-yl)propanamide* ***6***. Crystals suitable for X-ray crystallography were grown from a solution of **6** in methanol/water (yield 43%). Mp: 188–189 °C. Elemental analysis (found: C, 50.20; H, 3.58; N, 10.01; calc. for $C_{17}H_{14}ClN_3O_4S{\cdot}H_2O$: C, 49.82; H, 3.93; N, 10.25%). IR (KBr): $\tilde{\nu}_{max}$ cm^{-1} 3348 (N–H), 1697 (C═O), 1588 (N═C). δ_H (400 MHz, $CDCl_3$, Me_4Si): 1.62 (6H, s, C(CH_3)$_2$), 6.93 (2H$_o$, d, ^3J = 8.6 Hz, C_6H_4ClO), 7.30 (2H$_m$, d, ^3J = 8.6 Hz, C_6H_4ClO), 7.85 (1H$_8$, d, ^3J = 8.8 Hz, C_6H_3NS), 8.34 (1H$_7$, dd, ^3J = 8.8, J = 2.4 Hz, NO_2Ph), 8.80 (1H$_5$, d, ^4J = 2.4 Hz, C_6H_3NS), 10.23 (1H, s, N–H). δ_C (100 MHz, $CDCl_3$, Me_4Si): 24.9 (C(CH_3)$_2$), 82.1 (C(CH$_3$)$_2$), 123.7, 129.9, 130.3, 151.7 (C_6H_4ClO), 118.4, 121.4, 122.3, 132.8, 144.4, 153.2 (C_6H_3NS), 161.8 (C2), 173.8 (C═O). MS (FAB$^+$): m/z (%) 392 ([$C_{17}H_{15}ClN_3O_4S$]$^+$, 20).

2-(4-Chlorophenoxy)-N-*(6-methanesulfonyl-1,3-benzothiazol-2-yl)-2-methylpropanamide* ***7***. Crystals suitable for X-ray crystallography were grown from a solution of **7** in ethanol (yield 43%). Mp: 220 °C. Elemental analysis (found: C, 51.03; H, 4.31; N, 6.85; calc. for $C_{18}H_{17}ClN_2O_4S_2$: C, 50.88; H, 4.03; N, 6.59%). IR (KBr): $\tilde{\nu}_{max}$ cm^{-1} 3297 (N–H), 1690 (C═O), 1588 (N═C). δ_H (400 MHz, $CDCl_3$, Me_4Si): 1.68 (6H, s, C(CH_3)$_2$), 3.18 (3H, s, CH_3–S), 6.96 (2H$_o$, d, ^3J = 8.6 Hz, C_6H_4ClO), 7.33 (2H$_m$, d, ^3J = 8.6 Hz, C_6H_4ClO), 7.95 (1H$_7$, d, ^3J = 8.8 Hz, C_6H_3NS), 8.04 (1H$_8$, d, ^3J = 8.8 Hz, C_6H_3NS), 8.53 (1H$_5$, s, C_6H_3NS), 10.34 (1H, s, N–H). δ_C (100 MHz, $CDCl_3$, Me_4Si): 24.2 (C(CH_3)$_2$), 80.7 (C(CH$_3$)$_2$), 123.4, 129.7, 130.0, 152.3 (C_6H_4ClO), 121.9, 121.9, 125.3, 132.9, 136.0, 151.7 (C_6H_3NS), 161.1 (C2), 173.08 (C═O). MS (FAB$^+$): m/z (%) 425 ([$C_{18}H_{18}ClN_2O_4S_2$]$^+$, 100).

3.3 X-Ray crystallography

X-Ray diffraction studies were performed on a Bruker-APEX diffractometer with a CCD area detector ($\lambda_{Mok\alpha}$ = 0.71073 Å, monochromator: graphite). Frames were collected at T = 100 K (compounds **1**, **2**, **4**), T = 173 K (compounds **3** and **5**) and T = 294 K (compounds **6** and **7**) *via* ω/ϕ-rotation at 10 s per frame (SMART).[22a] The measured intensities were reduced to F^2 and corrected for absorption with SADABS (SAINT-NT).[22b] Corrections were made for Lorentz and polarization effects. Structure solution, refinement and data output were carried out with the SHELXTL-NT program package.[22c,d] Non-hydrogen atoms were refined anisotropically. C–H hydrogen atoms were placed in geometrically calculated positions using a riding model. O–H and N–H hydrogen atoms were localized by difference Fourier maps and refined fixing the bond lengths to 0.840(1) and 0.860(1) Å, respectively; the corresponding isotropic temperature factors have been fixed to a value 1.5 times that of the corresponding oxygen/nitrogen atoms. Hydrogen-bonding interactions in the crystal lattice were calculated with the PLATON program package.[22e] In the final electron density map of compound **2** there are peaks with maximum residual electron densities of $\Delta\rho$ = 0.42 (Q1) and 0.41 (Q2), which are located in the proximity of the chlorine and sulfur atoms. The distances between Q1···S1 and Q2···Cl1 were 0.93 and 0.96 Å, respectively; the residual void was verified with PLATON/SQUEEZE (volume 147.5 Å^3 per unit cell volume 3530.7 Å^3 [4.2%]).

Figures were drawn with DIAMOND using spheres of arbitrary radius.[22f]

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References

1 (*a*) J. de Mendoza, *Chem.–Eur. J.*, 1998, **4**, 1373–1377; (*b*) M. Fujita, *Chem. Soc. Rev.*, 1998, **27**, 417–425; (*c*) C. J. Jones, *Chem. Soc. Rev.*, 1998, **27**, 289–299; (*d*) L. R. MacGillivray and J. L. Atwood, *Angew. Chem., Int. Ed.*, 1999, **38**, 1018–1033; (*e*) D. L. Caulder and K. N. Raymond, *J. Chem. Soc., Dalton Trans.*, 1999, 1185–1200; (*f*) A. Jasat and J. C. Sherman, *Chem. Rev.*, 1999, **99**, 931–968; (*g*) J. W. Steed and J. L. Atwood, *Supramolecular Chemistry*, John Wiley & Sons, Ltd., UK, 2000; (*h*) F. Hof, S. L. Craig, C. Nuckolls

and J. Rebek, Jr, *Angew. Chem., Int. Ed.*, 2002, **41**, 1488–1508; (*i*) C. Schmuck, *Angew. Chem., Int. Ed.*, 2007, **46**, 5830–5833; (*j*) C. Pariya, C. R. Sparrow, C.-K. Back, G. Sandí, F. R. Fronczek and A. W. Maverick, *Angew. Chem., Int. Ed.*, 2007, **46**, 6305–6308; (*k*) Q.-R. Fang, G.-S. Zhu, Z. Jin, Y.-Y. Ji, J.-W. Ye, M. Xue, H. Yang, Y. Wang and S.-L. Qiu, *Angew. Chem., Int. Ed.*, 2007, **46**, 6638–6642; (*l*) K. Uemura, Y. Yamasaki, Y. Komagawa, K. Tanaka and H. Kita, *Angew. Chem., Int. Ed.*, 2007, **46**, 6662–6665; (*m*) J. A. R. P. Sarma and G. R. Desiraju, *Acc. Chem. Res.*, 1986, **19**, 222–228.

2 (*a*) J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1304–1319; (*b*) G. A. Jeffrey and W. Saenger, *Hydrogen Bonding in Biological Structures*, Springer, Berlin, 1991; (*c*) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, New York, 1995; (*d*) J.-M. Lehn, J. L. Atwood, J. E. D. Davies, D. D. MacNicol and F. Vögtle, *Comprehensive Supramolecular Chemistry*, Pergamon, Oxford, 1996; (*e*) M. M. Conn and J. Rebek, Jr, *Chem. Rev.*, 1997, **97**, 1647–1668; (*f*) G. Desiraju and T. Steiner, *The Weak Hydrogen Bond in Structural Chemistry and Biology*, Oxford University Press, New York, 1999; (*g*) K. Müller-Dethlefts and P. Hobza, *Chem. Rev.*, 2000, **100**, 143–167; (*h*) S. Leininger, B. Olenyuk and P. J. Stang, *Chem. Rev.*, 2000, **100**, 853–908; (*i*) M. J. Calhorda, *Chem. Commun.*, 2000, 801–809; (*j*) G. R. Desiraju, *Acc. Chem. Res.*, 2002, **35**, 565–573; (*k*) T. Steiner, *Angew. Chem., Int. Ed.*, 2002, **41**, 48–76; (*l*) M. A. Buntine, F. J. Kosovel and E. R. T. Tiekink, *CrystEngComm*, 2003, **5**, 331–336.

3 (*a*) J. Starbuck, N. C. Norman and A. G. Orpen, *New J. Chem.*, 1999, **23**, 969–972; (*b*) V. I. Minkin and R. M. Minyaev, *Chem. Rev.*, 2001, **101**, 1247–1265; (*c*) F. Iwasaki, N. Toyoda and N. Yamazaki, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1989, **45**, 1914–1917; (*d*) J. G. Ángyán, R. A. Poirier, Á. Kucsman and I. G. Csizmadia, *J. Am. Chem. Soc.*, 1987, **109**, 2237–2245; (*e*) T. Atsumi, T. Abe, K. Akiba and H. Nakai, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 892–899; (*f*) J. I. Arenas-García, D. Herrera-Ruiz, K. Mondragón-Vásquez, H. Morales-Rojas and H. Höpfl, *Cryst. Growth Des.*, 2010, **10**, 3732–3742.

4 (*a*) L. J. W. Shimon, M. Vaida, L. Addadi, M. Lahav and L. Leiserowitz, *J. Am. Chem. Soc.*, 1990, **112**, 6215–6220; (*b*) E. M. D. Keegstra, A. L. Spek, J. W. Zwikker and L. W. Jenneskens, *J. Chem. Soc., Chem. Commun.*, 1994, 1633–1634; (*c*) G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311–2327.

5 (*a*) Z. S. Derewenda, U. Derewenda and P. M. Kobos, *J. Mol. Biol.*, 1994, **241**, 83–93; (*b*) Z. S. Derewenda, L. Lee and U. Derewenda, *J. Mol. Biol.*, 1995, **252**, 248–262.

6 (*a*) T. Steiner and W. Saenger, *J. Chem. Soc., Chem. Commun.*, 1995, 2087–2088; (*b*) D. Braga, F. Grepioni, J. J. Byrne and A. Wolf, *J. Chem. Soc., Chem. Commun.*, 1995, 1023–1024.

7 G. Müller, M. Lutz and S. Harder, *Acta Crystallogr., Sect. B: Struct. Sci.*, 1996, **52**, 1014–1022.

8 (*a*) A. K. Abdul-Sada, A. M. Greenway, P. B. Hitchcock, T. J. Mohammed, K. R. Seddon and J. A. Zora, *J. Chem. Soc., Chem. Commun.*, 1986, 1753–1754; (*b*) A. G. Avent, P. A. Chaloner, M. P. Day, K. R. Seddon and T. Welton, *J. Chem. Soc., Dalton Trans.*, 1994, 3405–3413.

9 (*a*) G. Navarrete-Vazquez, P. Paoli, I. León-Rivera, R. Villalobos-Molina, J. L. Medina-Franco, R. Ortiz-Andrade, S. Estrada-Soto, G. Camici, D. Diaz-Coutiño, I. Gallardo-Ortiz, K. Martinez-Mayorga and H. Moreno-Díaz, *Bioorg. Med. Chem.*, 2009, **17**, 3332–3341; (*b*) H. Moreno-Díaz, R. Villalobos-Molina, R. Ortiz-Andrade, D. Díaz-Coutiño, J. L. Medina-Franco, S. P. Webster, M. Binnie, S. Estrada-Soto, M. Ibarra-Barajas, I. León-Rivera and G. Navarrete-Vázquez, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2871–2877.

10 (*a*) J. M. Thorp, *Lancet*, 1962, **1**, 1323–1326; (*b*) D. B. Miller and J. D. Spence, *Clin. Pharmacokinet.*, 1998, **34**, 155–162; (*c*) F. Forcheron, A. Cachefo, S. Thevenon, C. Pinteur and M. Beylot, *Diabetes*, 2002, **51**, 3486–3491.

11 J. M. Thorp and W. S. Waring, *Nature*, 1962, **194**, 948–949.

12 G. Jayanthi, S. Muthusamy, R. Paramasivam, V. T. Ramakrishnan, N. K. Ramasamy and P. Ramamurthy, *J. Org. Chem.*, 1997, **62**, 5766–5770.

13 I. Caleta, D. Cincic, G. Karminsky-Zamola and B. Kaitner, *J. Chem. Crystallogr.*, 2008, **38**, 775–780.

14 J. Bernstein, R. E. Davis, L. Shimoni and N.-L. Chang, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1555–1573.

15 (*a*) R. E. Rosenfield, R. Parthasarathy and J. D. Dunitz, *J. Am. Chem. Soc.*, 1977, **99**, 4860–4862; (*b*) C. Cohen-Addad, M. S. Lehmann, P. Becker, L. Párkányi and A. Kálmán, *J. Chem. Soc., Perkin Trans. 2*, 1984, 191–196; (*c*) N. Pandya, A. J. Basile, A. K. Gupta, P. Hand, C. L. MacLaurin, T. Mohammad, E. S. Ratemi, M. S. Gibson and M. F. Richardson, *Can. J. Chem.*, 1993, **71**, 561–571; (*d*) J. G. Ángyán, R. A. Poirier, A. Kucsman and I. G. Csizmadia, *J. Am. Chem. Soc.*, 1987, **109**, 2237–2245; (*e*) A. Esparza-Ruiz, A. Peña-Hueso, J. Hernández-Díaz, A. Flores-Parra and R. Contreras, *Cryst. Growth Des.*, 2007, **7**, 2031–2040; (*f*) F. Tellez, A. Cruz, H. López-Sandoval, I. Ramos-García, M. Gayosso, R. N. Castillo Sierra, B. Paz-Michel, H. Nöth, A. Flores Parra and R. Contreras, *Eur. J. Org. Chem.*, 2004, 4203–4214; (*g*) Z. García-Hernández, A. Flores Parra, J. M. Grevy, A. Ramos-Organillo and R. Contreras, *Polyhedron*, 2006, **25**, 1662–1672; (*h*) K. Lekin, S. M. Winter, L. E. Downie, X. Bao, J. S. Tse, S. Desgreniers, R. A. Secco, P. A. Dube and R. T. Oakley, *J. Am. Chem. Soc.*, 2010, **132**, 16212–16224.

16 F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1.

17 (*a*) R. Taylor, O. Kennard and W. Versichel, *J. Am. Chem. Soc.*, 1983, **105**, 5761–5766; (*b*) R. Taylor, O. Kennard and W. Versichel, *J. Am. Chem. Soc.*, 1984, **106**, 244–248.

18 (*a*) L. R. Hanton, C. A. Hunter and D. H. Purvis, *J. Chem. Soc., Chem. Commun.*, 1992, 1134–1136; (*b*) H. Adams, F. J. Carver, C. A. Hunter, J. C. Morales and E. M. Seward, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1542–1544; (*c*) P. Munshi and T. N. G. Row, *CrystEngComm*, 2005, **7**, 608–611; (*d*) J.-A. van den Berg and K. R. Seddon, *Cryst. Growth Des.*, 2003, **3**, 643–661; (*e*) J. G. Planas, C. Masalles, R. Sillanpää, R. Kivekäs, F. Teixidor and C. Viñas, *CrystEngComm*, 2006, **8**, 75–83; (*f*) A. K. Tewari and R. Dubey, *ARKIVOC (Gainesville, FL, U. S.)*, 2009, 283–291.

19 (*a*) P. K. Thallapally and A. Nangia, *CrystEngComm*, 2001, **27**, 1–6; (*b*) M. Freytag and P. G. Jones, *Chem. Commun.*, 2000, 277–278; (*c*) C. B. Aakeröy, T. A. Evans, K. R. Seddon and I. Pálinkó, *New J. Chem.*, 1999, **23**, 145–152; (*d*) R. G. Gonnade, M. S. Shashidhar and M. M. Bhadbhade, *J. Indian Inst. Sci.*, 2007, **87**, 149–164; (*e*) I. Csöregh, E. Weber, T. Hens and M. Czugler, *J. Chem. Soc., Perkin Trans. 2*, 1996, 2733–2739; (*f*) G. Aullón, D. Bellamy, L. Brammer, E. A. Bruton and A. G. Orpen, *Chem. Commun.*, 1998, 653–654.

20 (*a*) G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311–2327; (*b*) I. Caleta, D. Cincic and G. Karminski-Zamola, *J. Chem. Crystallogr.*, 2008, **38**, 775–780.

21 (*a*) M. A. Spackman and J. J. McKinnon, *CrystEngComm*, 2002, **4**, 378–392; (*b*) R. S. Rowland and R. Taylor, *J. Phys. Chem.*, 1996, **100**, 7384–7391; (*c*) J. D. Dunitz and A. Gavezzotti, *Acc. Chem. Res.*, 1999, **32**, 677–684; (*d*) T. Steiner and G. R. Desiraju, *Chem. Commun.*, 1998, 891–892.

22 (*a*) Bruker Analytical X-ray Systems, *SMART: Bruker Molecular Analysis Research Tool, Versions 5.057 and 5.618*, 1997 and 2000; (*b*) Bruker Analytical X-ray Systems, *SAINT + NT, Versions 6.01 and 6.04*, 1999 and 2001; (*c*) G. M. Sheldrick, *SHELX86, Program for Crystal Structure Solution*, University of Göttingen, Germany, 1986; (*d*) Bruker Analytical X-ray Systems, *SHELXTL-NT Versions 5.10 and 6.10*, 1999 and 2000; (*e*) A. L. Spek, *J. Appl. Crystallogr.*, 2003, **36**, 7–13; (*f*) DIAMOND, *Visual Crystal Structure Information System, Version 3.1, CRYSTAL IMPACT, Postfach 1251, D-53002*, Bonn, Germany, 2006.