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# Intramolecular N–H...X (X = F, Cl, Br, I, and S) Hydrogen Bonding in Aromatic Amide Derivatives - The X-Ray Crystallographic Investigation

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## 1. Introduction

Hydrogen bonding (H-bonding) has recently been defined by IUPAC as “an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation”. In most cases, the strength of an H-bond increases with the increase of the electronegativity value of the acceptor atom (Pauling, 1960). This is exactly the case for oxygen and nitrogen atoms. The H-bonds formed between them and the NH and OH groups are usually strong, which play essential roles in studies in supramolecular, crystal engineering, materials, and life sciences (Scheiner, 1997; Jeffrey, 1997). As a result of their growing applications in supramolecular chemistry and crystal engineering, in the past two decades, the critical assessment of the weaker H-bonds has also become an important topic (Desiraju & Steiner, 2001). In this context, organic halogen and sulfur atoms, C–X (X = F, Cl, Br, I, S), have all been demonstrated to be weak H-bonding acceptors (Dunitz & Taylor, 1997), although their electronegativities (Pauling scale: 3.98, 3.16, 2.96, 2.66, and 2.58, respectively) are all higher than that of hydrogen (2.20). Indeed, over years it has been accepted that organic fluorine “hardly ever accepts hydrogen bonds (Dunitz, 2004),” presumably due to its low polarizability and tightly contracted lone pairs. For other organic heteroatoms, the increased van der Waals radius and decreased electronegativities may also weaken their capacity of forming the intramolecular electrostatic interaction, i.e., H-bonding, with the amide hydrogen and lose the competition with the amide oxygen of another molecule which forms the intermolecular N–H...O=C H-bonding. In contrast, the halogen anions are capable of forming strong intermolecular H-bonding with NH, OH or even CH protons (Harrell & McDaniel, 1964; Simonov et al., 1996; Del Bene & Jordan, 2001).

This chapter summarizes recent progresses in the assessment of the weak intramolecular six- and five-membered H-bonding patterns formed by aromatic amides bearing the above five atoms. Theoretical investigations show that similar intermolecular H-bonding patterns can be formed by fluorine in DNA or RNA base analogues (Frey et al., 2006; Koller et al., 2010; Manjunatha et al., 2010), although they are difficult to be confirmed in solution

experimentally. The crystal structures of many organic halogen or sulfur (ether) compounds exhibit such intermolecular short contacts, which may be mainly driven by the intrinsic preference of these atoms in forming the H-bonding or formed due to the assistance of the intermolecular stacking and van der Waals force (Toth et al., 2007) and other intra- and intermolecular interactions.

Due to the increased conformational flexibility of the backbones and the decreased acidity of the amide proton, the H-bonding in aliphatic amide derivatives is expected to be even weaker. However, five-membered intramolecular N–H...F (F: Hughes & Small, 1972; O'Hagan et al., 2006), N–H...Cl (de Sousa et al., 2007; Kalyanaraman et al., 1978) and N–H...I (Savinkina et al., 2008) H-bonding patterns have been observed in aliphatic amides. To the best of our knowledge, the six-membered one is not available yet in simple organic molecules.

One consideration for exploiting the intramolecular N–H...X (X = F, Cl, Br, I, S) H-bonding of the aromatic amides is that the new patterns may find applications in designing new preorganized building blocks for crystal and supramolecular engineering (Biradha, 2003; Desiraju, 2005). Furthermore, new H-bonding motifs may also be useful in building foldamers (Zhu et al., 2011; Zhao & Li, 2010; Saraogi & Hamilton, 2009; Li et al., 2008; Li et al., 2006; Huc, 2004; Sanford & Gong, 2003), the artificial secondary structures, and for designing biologically or medicinally useful structures (Tew et al., 2010; Li et al., 2008; Bautista et al., 2007). For doing this, the more competitive intermolecular N–H...O=C H-bonding of the amide unit has to be suppressed. There are two approaches for realizing this purpose. The first one concerns the introduction of a strong intramolecular H-bond to "lock" the amide proton. The second one is to introduce one or more bulky groups to impede the contact of the amides. In these ways, the very weak intramolecular N–H...I hydrogen bonding can be observed. There are several techniques for investigating the formation of the weak intramolecular H-bonding. The NMR spectroscopy is promising for studies in solution (Manjunatha et al., 2010), and the infrared spectroscopy can be used to detect samples in both the solution and solid state (Legon, 1990), while the computational modeling can provide useful information about the effects of discrete factors on the stability of the H-bonds (Dunitz, 2004; Liu et al., 2009), which are particularly valuable when experimental evidences are not available. In view of the feature of this book, we will focus on the investigations by the X-ray crystallography.

The crystal structure of an aromatic amide molecule is affected by many factors, including the stacking pattern, van der Waals force, intra- and intermolecular hydrogen and halogen bonding, and shape matching of the molecule. The entrapped solvent molecules, particularly those containing heteroatoms, may also play an important role because they are able to form hydrogen or halogen bonding with the molecule and thus affect the stacking pattern to suppress or promote the formation of the intramolecular H-bonding. Concerning the criterion for the formation of the weak intramolecular H-bonding, we simply check the distance between the heteroatom and the amide hydrogen in the crystal structure. If it is shorter than the sum of the radius of the two atoms, we consider that an H-bonding is formed (Desiraju & Steiner, 2001). Although in X-ray structures the proton/hydrogen is not located accurately and may bend toward or away from the acceptor, for clarity we simply use the reported distances between the two concerned atoms as the criteria.

## 2. N–H...F Hydrogen bonding

Fluorine atom has the highest electronegativity. In 1996, Howard et al. carried out a review on the short F...H contacts from all of the organofluorine compounds deposited in the

Cambridge Structural Database System (CSDS) and concluded that organic fluorine is at best only a weak H-bonding acceptor (Howard et al., 1996). In 1997, Dunitz and Taylor also executed an intensive search of the CSDS and confirmed that organic fluorine accepts hydrogen bonds only in the absence of a better acceptor (Dunitz & Taylor, 1997). They also examined the evidence for H-bonding to organic fluorine in protein-ligand complexes and found that it is unconvincing. They thus proposed that, due to its low polarizability and tightly contracted lone pairs, organic fluorine does not compete with stronger H-bond acceptors such as oxygen or nitrogen, and only when other better acceptor atoms are sterically hindered that the O–H···F or N–H···F H-bonding can be formed (Barbarich et al., 1999).

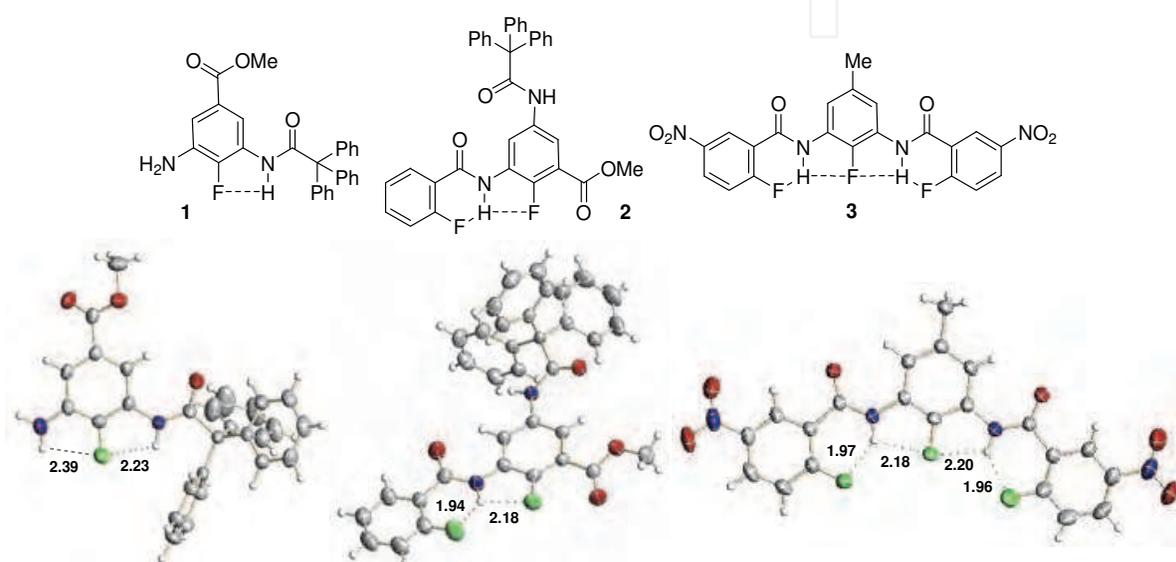


Fig. 1. Compounds 1-3 and their crystal structures.

In 1982, Kato et al. reported the crystal structure of 2-fluorobenzamide (Kato & Sakurai, 1982). Although the positions of hydrogen atoms were not determined, the N···F distance is 2.80 Å, which corresponded to an NH···F distance of 2.15 Å by molecular modeling. Clearly, an intramolecular six-membered N–H···F hydrogen bond exists in the crystal. In 2003, Li et al. found that 2-fluorobenzamide derivatives might promote the stability of hydrazide-based quadruply hydrogen-bonded heterodimers by forming six-membered intramolecular N–H···F hydrogen bonding (Zhao et al, 2003). A number of model compounds were then designed and prepared (Li et al., 2005). The crystal structures of compounds **1-3**, which bear one triphenylmethyl or two nitro groups to increase their crystallinity (Corbin et al, 2003; Yin et al., 2003), were obtained (Figure 1). All the three compounds adopt a well-defined planar conformation rigidified by the intramolecular N–H···F H-bonds. The F···H (amide) distance of compound **1** is 2.23 Å, and the N–H···F angle is 106°. The fluorine atoms of both **2** and **3** are located to the proximity of the amide hydrogen due to the formation of the three-centered H-bonds, which is common for similar alkoxy-substituted aromatic amide (Gong, 2001). The F···H (amide) distance of the six- and five-membered H-bonds is 1.94 and 2.18 Å in **2**, and 1.97 and 2.18 Å in **3**, respectively. The corresponding F···H–N angle is 136 and 108° for **2**, and 136 and 111° for **3**. All these values fall into the range of the criterion for the judgment of a F···H–N H-bond—the F···HN distance < 2.3 Å and the N–H···F angle > 90°

proposed by Dunitz and Taylor (Dunitz & Taylor, 1997). The  $NH\cdots F$  distance of the amino group of **1** is 2.39 Å, which is larger than that of the amide, also reflecting the preference of the amide proton to form the intramolecular hydrogen bond.  $^1H$  NMR experiments also support that the five- and six-membered and three-center H-bonds are formed in solution. Recently, the crystal structures of more *N*-aryl 2-fluorobenzamides have been reported, most of which display the six-membered  $N-H\cdots F$  H-bonding motif. The structures of compounds **4** and **5** are shown in Figure 2 as examples (Chopra & Row, 2008, 2005). The crystal structures of many *N*-(2-fluorophenyl)amides are also available, which usually exhibit the intramolecular five-membered  $N-H\cdots F$  H-bonding. As examples, the structures of **6** and **7** are provided in Figure 2 (Chopra & Row, 2005; Buyukgungor & Odabasoglu, 2008). It is worthy to note that no intramolecular  $N-H\cdots F$  H-bonding is generated by the 2-fluorobenzamine cation of **7**. Its three ammonium protons only form intermolecular H-bonding with the oxygen atoms of the anion, reflecting that organic fluorine is weaker than oxygen as proton acceptor.

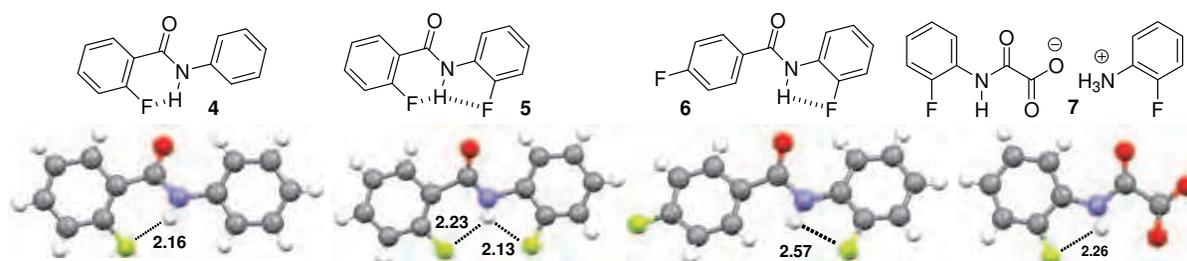


Fig. 2. Compounds 4-7 and their crystal structures.

Generally, 2-fluorobenzamides have a large preference of forming the six-membered  $N-H\cdots F$  H-bonding. When there exist other strong competitive interactions, this H-bonding may be suppressed. This occurs for selenourea derivative **8** (Kampf et al., 2004). This compound forms a dimeric pattern in the crystal stabilized by two strong  $N-H\cdots Se=C$  H-bonds (Figure 3), which causes a large torsion ( $51^\circ$ ) of the amide unit from the benzene plane. As a result, the intramolecular  $N-H\cdots F$  H-bonding is not formed. For *N*-(2-fluorophenyl)amides, the five-membered  $N-H\cdots F$  H-bonding may also be suppressed, as revealed in the crystal structure of **9** (Lewis et al., R. J.; 1991). This compound exists in two conformations in the crystal structure. One of them forms the intramolecular five-membered H-bonding, while another one displays an intramolecular  $F\cdots O=C$  contact (Figure 3). These observations indicate that, although fluorine is quite strong to form the five- and six-membered H-bonds, in the presence of other strong interactions, they may still be inhibited.

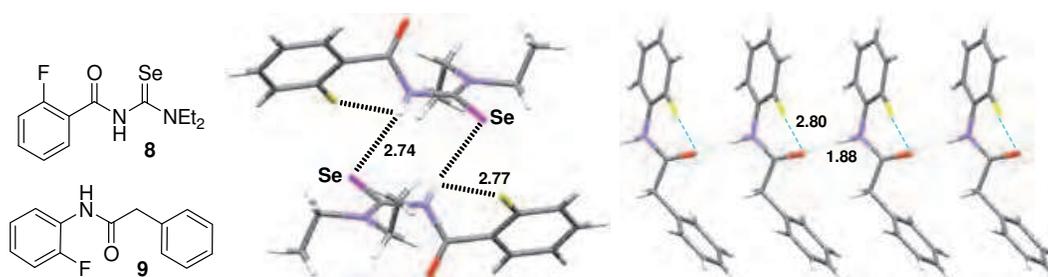


Fig. 3. Compounds 8 and 9 and their crystal structures.

To compare with their methoxyl-bearing analogues that form the N-H...OMe H-bonding, Li et al. also prepared compounds 10-12 (Zhu et al., 2007). The fluorine atoms in these compounds all form the intramolecular six- and five-membered N-H...F H-bonds (Figure 4). This three-center H-bonding pattern has been revealed for many alkoxy-substituted linear aromatic amides (Li et al., 2006). The amide protons in these fluorine-bearing compounds further form intermolecular N-H...O=C H-bonding with the carbonyl oxygen. Similar intermolecular H-bonding is not displayed for the methoxyl-substituted analogues. Two factors are proposed to cause this difference. The first is that the intramolecular N-H...OMe H-bonding is strong and reduces the ability of the amide proton to form other H-bonding. The second is that methoxyl group is larger than fluorine and thus has a larger steric hindrance to suppress the formation of additional intermolecular H-bonding. The three-center H-bonding pattern is also observed for 13 (Chisholm et al., 2002), the 3-oxobutanamide unit of which forms a strong six-membered N-H...O=C H-bond. We may expect that the two H-bonds stabilize each other by co-inhibiting the intermolecular N-H...O=C H-bond.

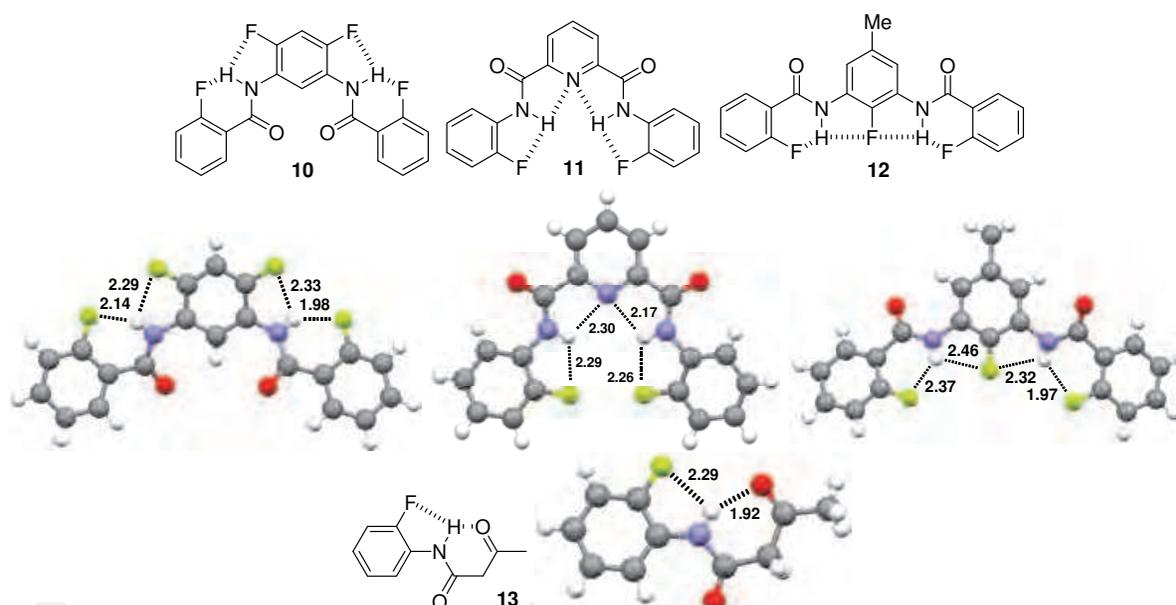


Fig. 4. Compounds 10-13 and their crystal structures.

The three-center H-bonding pattern does not always survive. For example, obviously due to the rigidity of the macrocyclic skeleton, the 2-fluoroisophthalamide units of macrocycle **14** form only one six-membered N-H...F H-bond (Figure 5) (Zhu et al., 2009). In the crystal structure of compound 15 (Guo et al., 2009), the molecules form a dimer which is stabilized by two N-H...O=C H-bonds between the carboxylic and amide units (Figure 5). The two H-bonds strengthen the torsion of the amide units from the two benzene planes. As a result, it only exhibits one weak six-membered N-H...F H-bond, and the 2-F of the aniline does not form the expected five-membered N-H...F H-bond. Instead, it displays an intermolecular F...OH contact (the distance: 2.81 Å). This compound contains several fluorine atoms and a carboxylic acid group and thus can produce discrete weak interactions. This result again reflects that the molecular conformation formed in the crystal is the outcome of the competition of different intra- and intermolecular interactions.

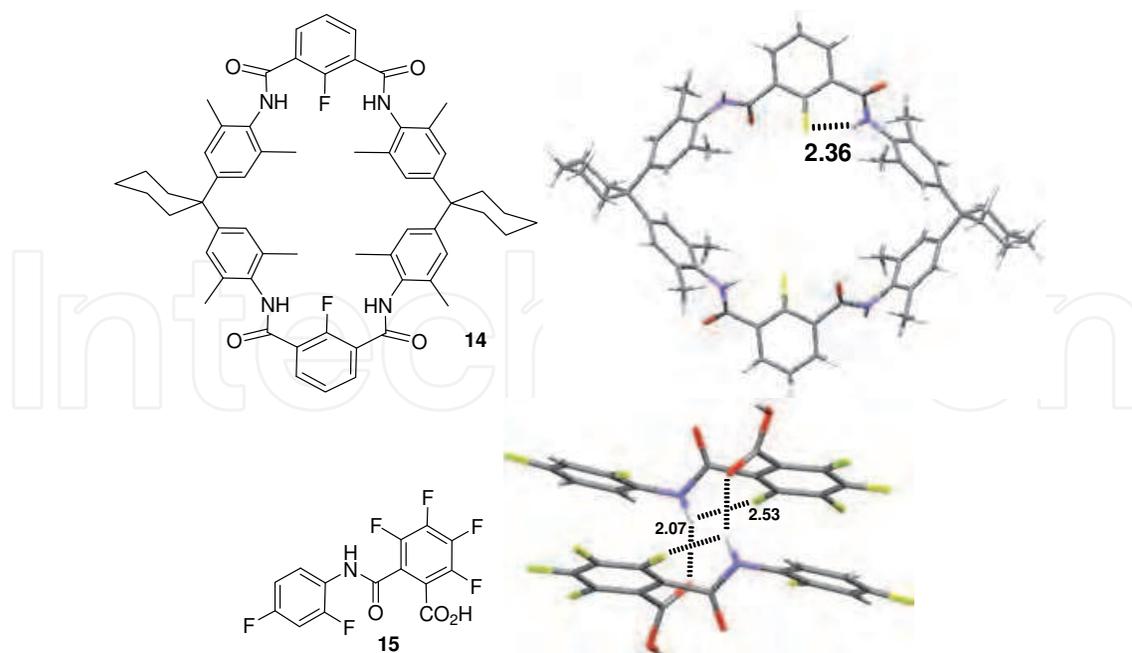


Fig. 5. Compounds 14 and 15 and their crystal structures.

### 3. N–H...Cl hydrogen bonding

In 1974, Kato et al. reported the crystal structure of 2-chlorobenzamide (Kato et al., 1974), which exhibits a dimeric structure stabilized by the intermolecular eight-membered N–H...O=C H-bonding (Etter, 1990). The amide units further form a chain of the N–H...O=C H-bonding, which is typical for benzamides, but no six-membered N–H...Cl H-bonding is displayed. In recent years, the crystal structures of many 2-chloro-*N*-phenylbenzamide derivatives have been reported. Most of them do not form the intramolecular six-membered N–H...Cl H-bonding. However, compounds 16a-c (Arslan et al., 2007; Binzet et al., 2006; Binzet et al., 2004), 17 (Caleta et al., 2008) and 18 (Zhu et al., 2008) do form this weak H-bonding (Figure 6). The thiourea unit in 16a-c and the benzothiazole unit in 17 should increase the acidity of the amide protons, which, together with the possible steric effect, may facilitate the formation of the intramolecular six-membered N–H...Cl H-bonding. For 18, the large trityl group suppresses the intermolecular N–H...O=C H-bonding. Thus, the weak N–H...Cl H-bonding can be formed. When the trityl group is replaced with an adamantyl group, the resulting amide do not give rise to the N–H...Cl H-bonding in the crystal structure. Although  $^1\text{H}$  NMR experiments in chloroform-*d* reveal that the intramolecular six-membered N–H...Cl H-bonding is generated in solution (Zhu et al., 2008), in the crystal structure, the amide units are only engaged in intermolecular N–H...O=C H-bonding.

*N*-(2-chlorophenyl)acetamide 19a forms a five-membered N–H...Cl H-bond (Figure 7) (Wan et al., 2006). The crystal structures of a number of its analogues are also available. In most cases, for example, for 19b (Gowda et al., 2007d), 19c (Zhu et al., 2008), 19d (Gowda et al., 2007a), 19e (Gowda et al., 2001), 19f (Gowda et al., 2000), 19g (Gowda et al., 2009), and 19h (Gowda et al., 2010), the intramolecular N–H...Cl H-bonding is formed (Figure 7). The intermolecular N–H...O=C H-bonding is also formed for all the compounds. Thus, we may consider that their strengths are comparable. The Cl and Br atoms on the methyl groups of

19d-h do not form the similar five-membered H-bonding. The crystal structure of methacrylamide derivative 19i does not display the five-membered H-bonding (Figure 7) (Kashino et al., 1994). Instead, a weak intermolecular C=C-H... $\pi$  contact, together with the strong intermolecular N-H...O=C H-bonding, is observed, indicating that the existence of other additional intermolecular interaction may also be able to suppress this intramolecular five-membered N-H...Cl H-bonding.

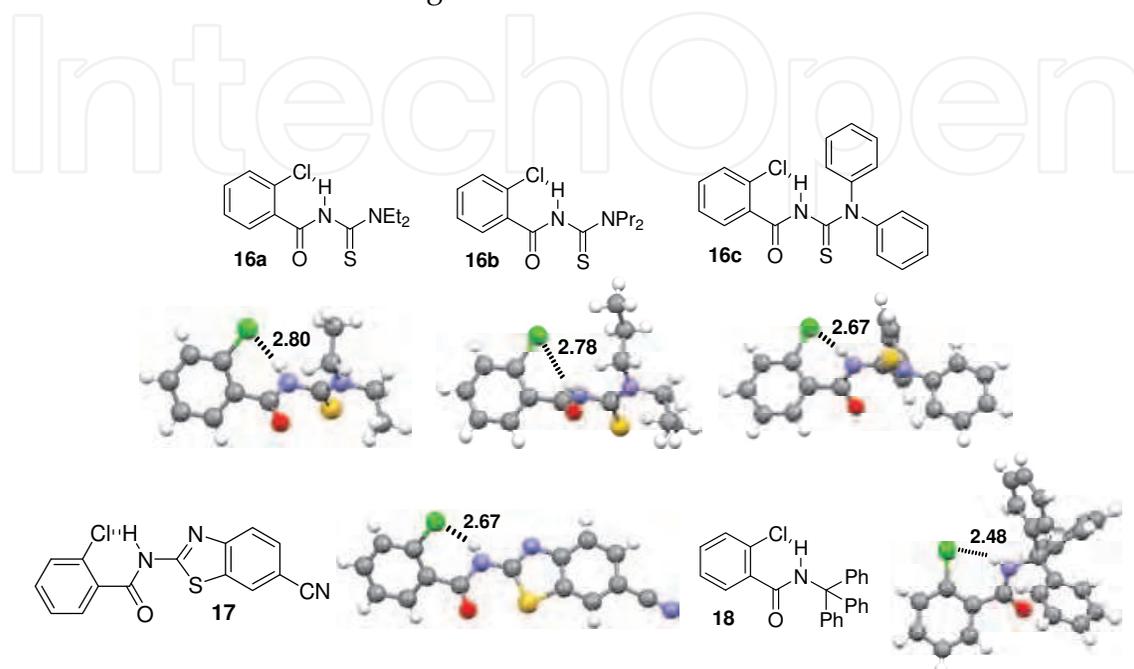


Fig. 6. Compounds 16a-c, 17 and 18 and their crystal structures.

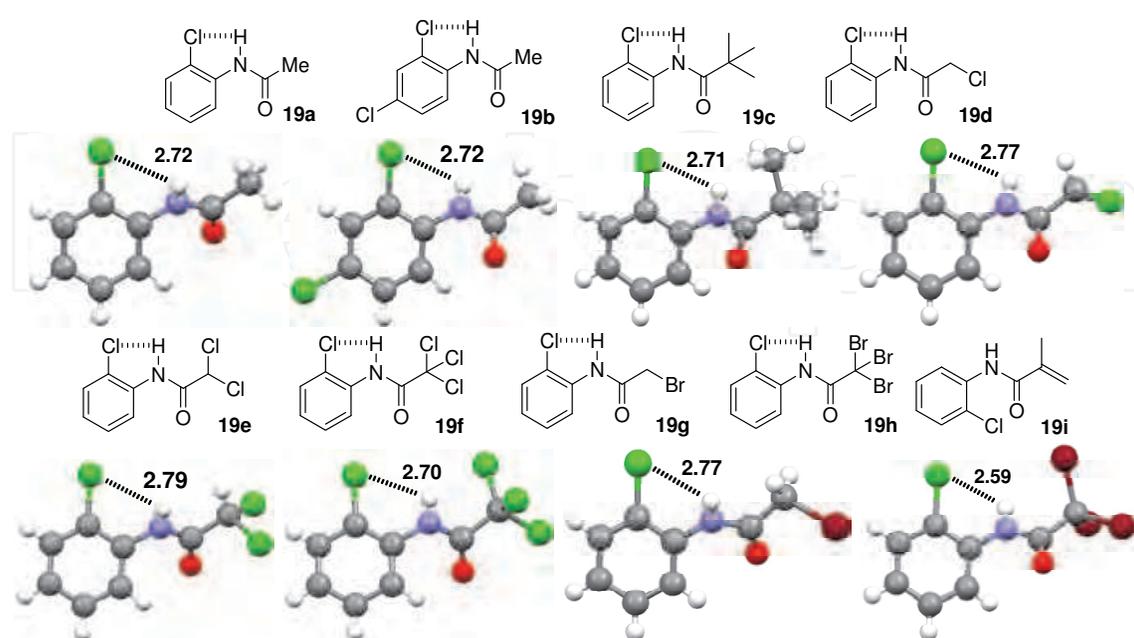


Fig. 7. Compounds 19a-i and the crystal structures of 19a-h.

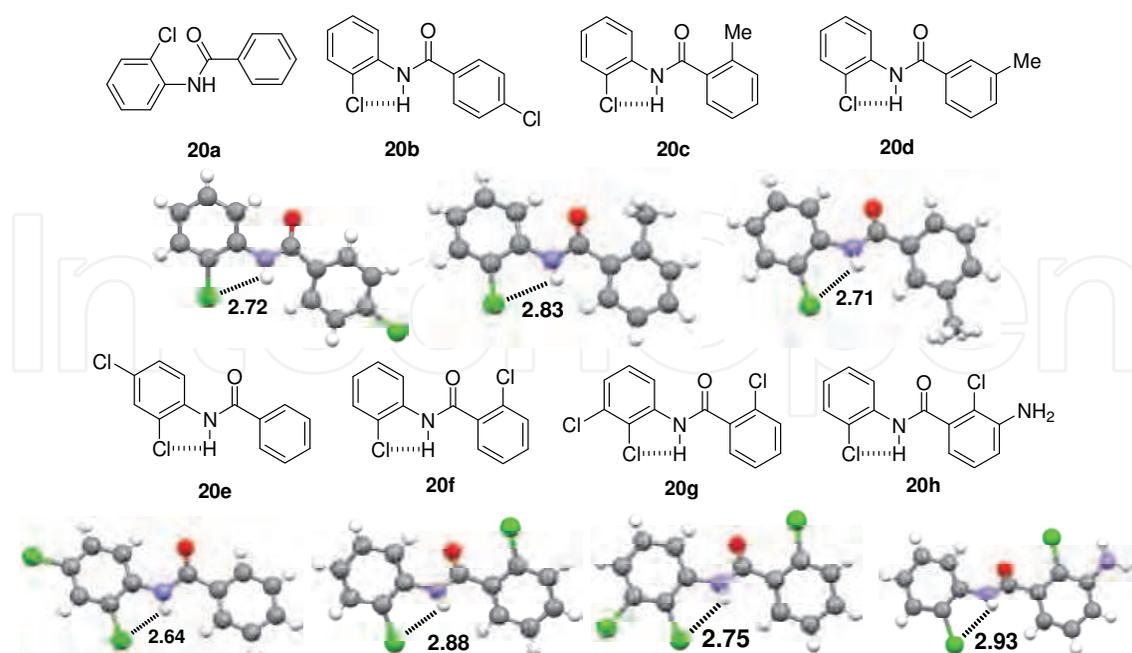


Fig. 8. Compounds 20a-h and the crystal structures of 20b-h.

Concerning the *N*-phenyl benzamide backbone, the crystal structure of *N*-(2-chlorophenyl)-benzamide 20a does not form the five-membered N-H...Cl H-bonding (Gowda et al., 2007c), because its amide unit is distorted too much ( $65^\circ$ ) from the 2-chlorobenzene plane due to the competition of the strong intermolecular N-H...O=C H-bonding. However, the five-membered H-bonding is observed in the crystal structures of its derivatives 20b (Saeed et al., 2008), 20c (Gowda et al., 2008b), 20d (Rodrigues et al., 2010), 20e (Gowda, B. T. Et al, 2008c), 20f (Gowda, B. T. et al., 2007b), 20g (Gowda, B. T. et al., 2008a), and 20h (Zhu et al., 2008) (Figure 8). The increase of the molecular size might be one of the factors that favor the formation of the bonding. Different from the fluorine-bearing analogues, compounds 20g-i do not form the six-membered N-H...Cl H-bonding on the benzoyl side because of a large torsion of the amide unit from the benzene ring which favors the intermolecular N-H...O=C H-bonding.

Although the intramolecular six-membered N-H...Cl H-bonding is not observed in the crystal structures of compound 20e-h, it occurs in the crystal structures of compounds 21 and 22 (Figure 9) (Sindt & Mackay, 1979; Khan et al., 2007). Compound 21 forms the shortest NH...Cl contact (2.23 Å) (Sindt & Mackay, 1979). Another three intramolecular H-bonds formed by the two hydroxyl groups should remarkably facilitate its formation because they not only inhibit the intermolecular N-H...O=C H-bonding, but also promote the co-planarity of the benzamide unit. The intramolecular six-membered N-H...O=C H-bonding in 22 should also help the formation of its six-membered N-H...Cl H-bonding, because it prevents the amide proton from forming the intermolecular N-H...O=C H-bonding (Khan et al., 2007). The hydroxyl group also forms a strong intermolecular H-bond (the OH...O=C distance: 1.79 Å) with the amide oxygen of another molecule, which might further facilitates the formation of the N-H...Cl H-bonding by enhancing the planarity of the benzamide unit.

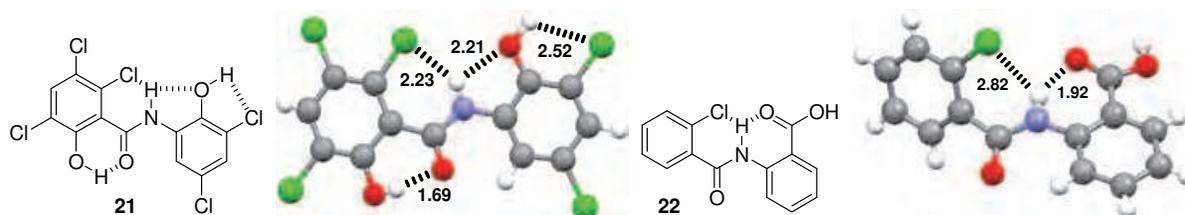


Fig. 9. Compounds 21 and 22 and their crystal structures.

#### 4. N–H...Br hydrogen bonding

In 1972, Izumi reported the crystal structure of 2-bromobenzamide (Izumi & Okamoto, 1972), which displays a stacking pattern similar to that of 2-chlorobenzamide, with no six-membered N–H...Br H-bonding being formed (Kato et al., 1974). *N*-substituted derivatives 23a-c also do not form this H-bonding in the crystal structures (Figure 10) (Zhu et al., 2008, 2009), even though they bear the bulky trityl group, which helps to promote the formation of the intramolecular H-bonding for 18 (Zhu et al., 2008). The amide unit of 23a is distorted to be nearly perpendicular ( $89^\circ$ ) to the benzamide plane to form the continued intermolecular N–H...O=C H-bonding (Zhu et al., 2008). This continued intermolecular H-bonding is not observed in the crystal structures of 23b and 23c (Zhu et al., 2009). The Br atom of 23b chooses to form weak intermolecular trifurcate Br...O<sub>2</sub>N contacts (the distance: 2.80 Å), while the benzamide carbonyl oxygen forms an H-bond with the proton of another amide of the neighboring molecule. These results confirm that the 2-Br atom of benzamide is even weaker than Cl at the same position as the H-bonding acceptor. To verify if this weak H-bonding occurs, Zhu et al. prepared compounds 24a and 24b (Zhu et al., 2009). The crystal structures of both compounds show the formation of the intramolecular six-membered N–H...Br H-bonding (Figure 10). Compound 24a displays a dimeric motif stabilized by two intermolecular N–H...O=C (amino) H-bonds, which also prevent the amide from forming the intermolecular N–H...O=C H-bonding. This dimeric structure should also promote the co-planarity of the benzamide unit and thus facilitate the bromine atom to approach the amide proton to form the N–H...Br H-bonding. The Br...HN distance is 2.70 Å, which is pronouncedly shorter than the sum of the van der Waals radii of bromine and hydrogen (3.05 Å). The two trityl groups of 24b provide large enough steric hindrance to suppress the intermolecular N–H...O=C H-bonding. They also create a cavity seized by an ethyl acetate molecule, the C=O oxygen of which is H-bonded to acetamide proton, which may also facilitate the formation of the N–H...Br H-bonding by weakening the capacity of the molecule to interact intermolecularly. The Br...HN distance is 2.84 Å, indicating that this H-bonding is weaker than that in 24a. Compound 24c adopts two conformations in the crystal structure (Narayana et al., 2007). One of them forms the intramolecular N–H...Br H-bonding. Both the amide O and H are H-bonded to water trapped in the crystal and thus no intermolecular N–H...O=C H-bonding is formed, which may play a key role in promoting the formation of the N–H...Br H-bonding. Another conformation does not form the N–H...Br H-bonding. Its Br atom is engaged in a very weak intermolecular C=N...Br contact (the distance: 3.39 Å). The amino, triphenylacetamido and methoxyl groups in 24a-c are all electron donors. This feature may also make a contribution for the formation of the six-membered H-bonding.

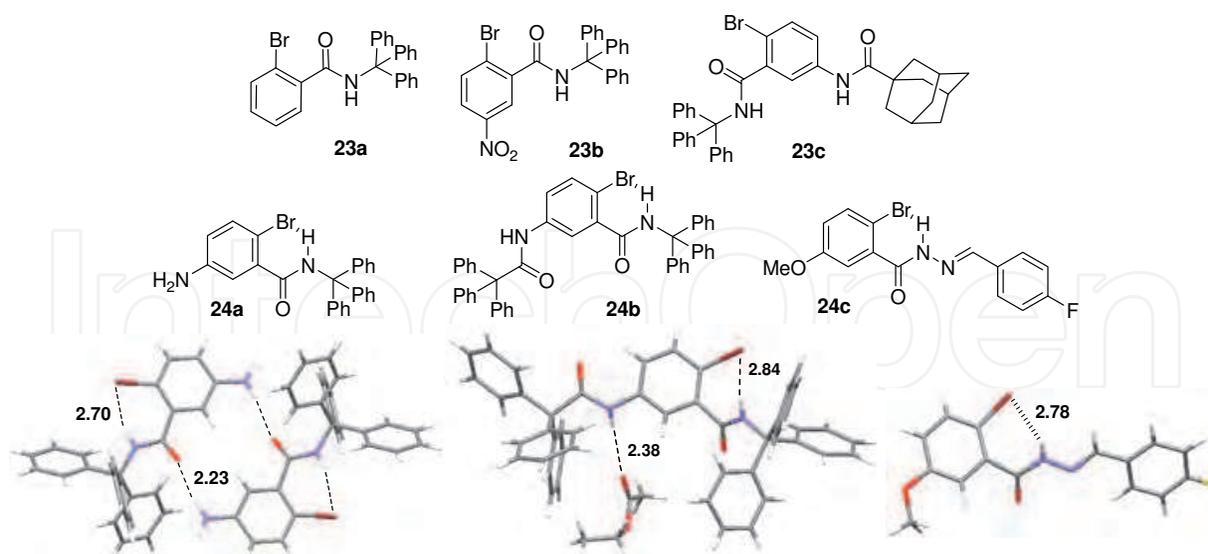


Fig. 10. Compounds 23a-c and 24a-c and the crystal structures of 24a-c.

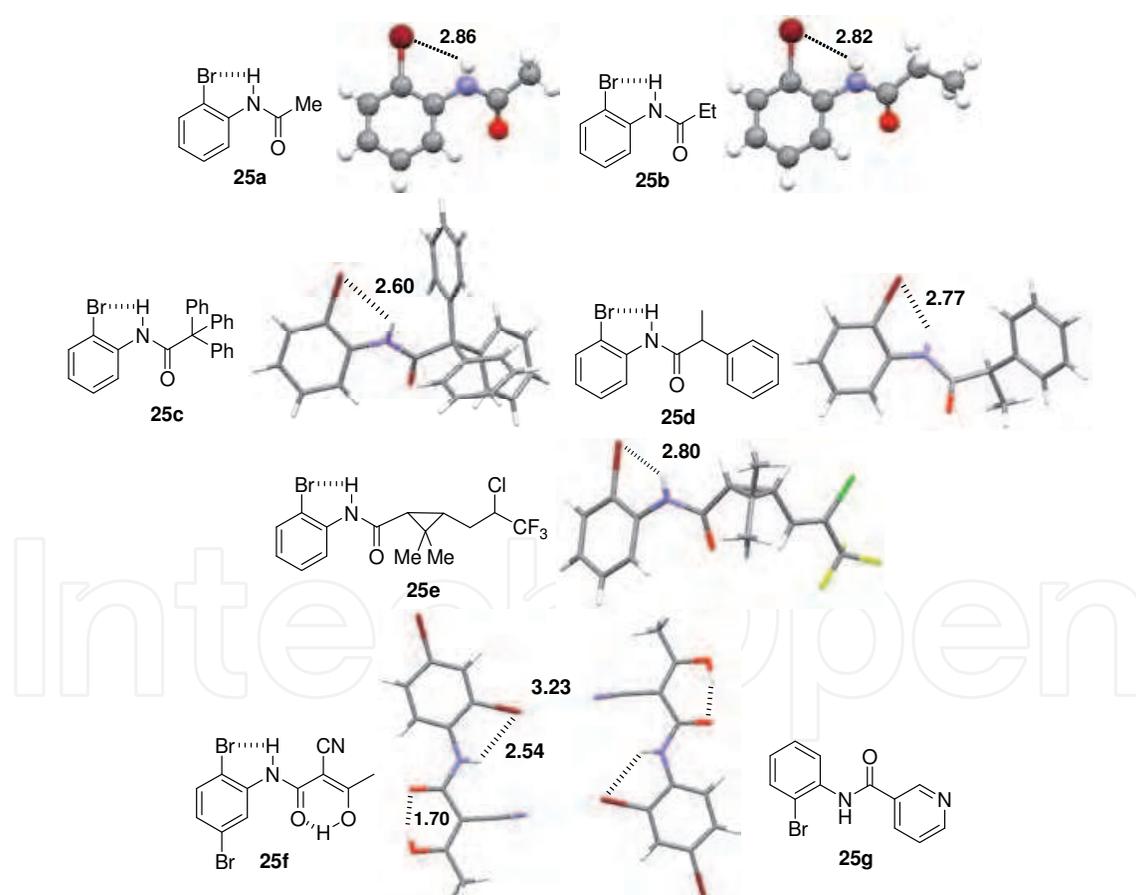


Fig. 11. Compounds 25a-g and the crystal structures of 25a-f.

In 2005, Ronaldson et al. reported the crystal structures of compounds 25a and 25b (Ronaldson et al., 2005a, 2005b). Both compounds form a five-membered N-H...Br H-bond (Figure 11) and the amide units also form strong intermolecular N-H...O=C H-bonding,

which is similar to that observed for 19a. The crystal structures of compounds 25c (Zhu et al., 2008), 25d (Huang & Xu, 2006), 25e (Liu & Yan, 2007), 25f (Venkatachalam et al., 2005), 25g (Percival et al., 2007) are also available (Figure 11). Only compound 25g does not form the intramolecular N–H...Br H-bonding. The Br...HN distance of 25c is pronouncedly shorter than that of 25d and 25e, which may be attributed to the bulky trityl group in 25c which prevents it from forming the intermolecular N–H...O=C H-bonding. By contrast, both 25d and 25e form the intermolecular N–H...O=C H-bonding, which causes a large torsion of the amide unit from the attached benzene ring. Compound 25f displays the shortest Br...HN contact (2.54 Å), together with a strong intramolecular OH...O=C H-bond. It also exists as a dimer in the crystal stabilized by two intermolecular Br...N≡C bonds. These two bonds should remarkably promote the co-planarity of the benzamide unit and consequently the formation of the N–H...Br H-bonding because the benzamide unit displays a very small torsion (2°). Compound 25g does not form the N–H...Br H-bonding, because the strong intermolecular N–H...O=C H-bonding induces a large torsion (64°) of the amide unit from the benzene ring.

## 5. N–H...I hydrogen bonding

The crystal structures of 2-iodobenzamide 26a (Nakata et al., 1976) and its derivatives 26b (Balavoine et al., 1999), 26c (Wardell et al., 2005), 26d (Garden et al., 2005), and 26e (Zhu et al., 2008), have been reported. All these compounds do not form the intramolecular six-membered N–H...I H-bonding, but give rise to the intermolecular N–H...O=C H-bonding, which causes the amide unit to distort greatly from the attached benzene ring. For compound 26e which bears a bulky trityl group, the torsion angle is as high as 80° for the formation of the intermolecular N–H...O=C H-bonding (the NH...O distance: 2.39 Å). Even so, the intramolecular N–H...I H-bonding can not compete with this intermolecular H-bonding. However, the crystal structure of compound 26f does display this weak six-membered N–H...I H-bonding (Figure 12) (Zhu et al., 2009). Similar to 24a, 26f also exists as a dimer stabilized by two intermolecular C=O...H(NH) H-bonds. Such a dimeric stacking pattern remarkably enhances the co-planarity of the benzamide unit. As a result, the benzamide has a relatively small torsion of 39°, enabling the formation of the N–H...I H-bonding.

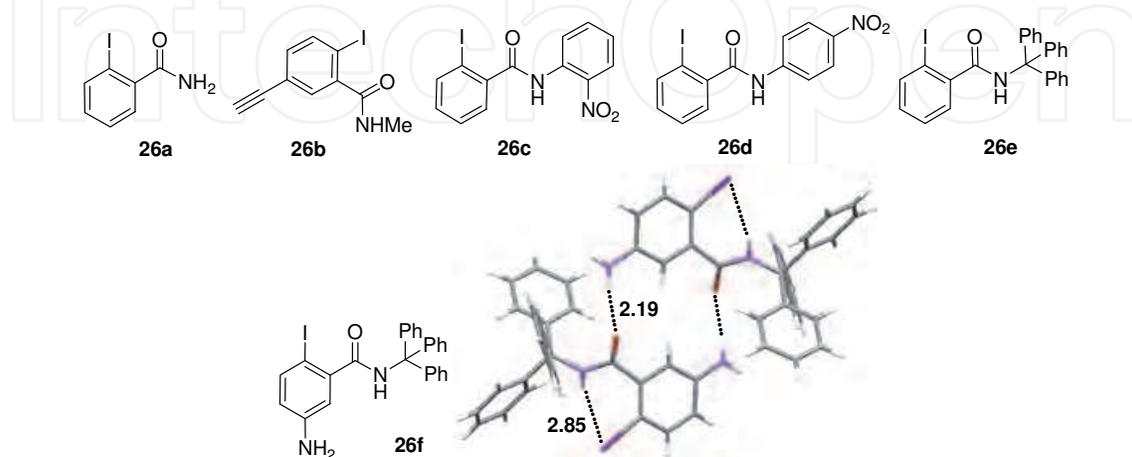


Fig. 12. Compounds 26a-f and the crystal structures of 26f.

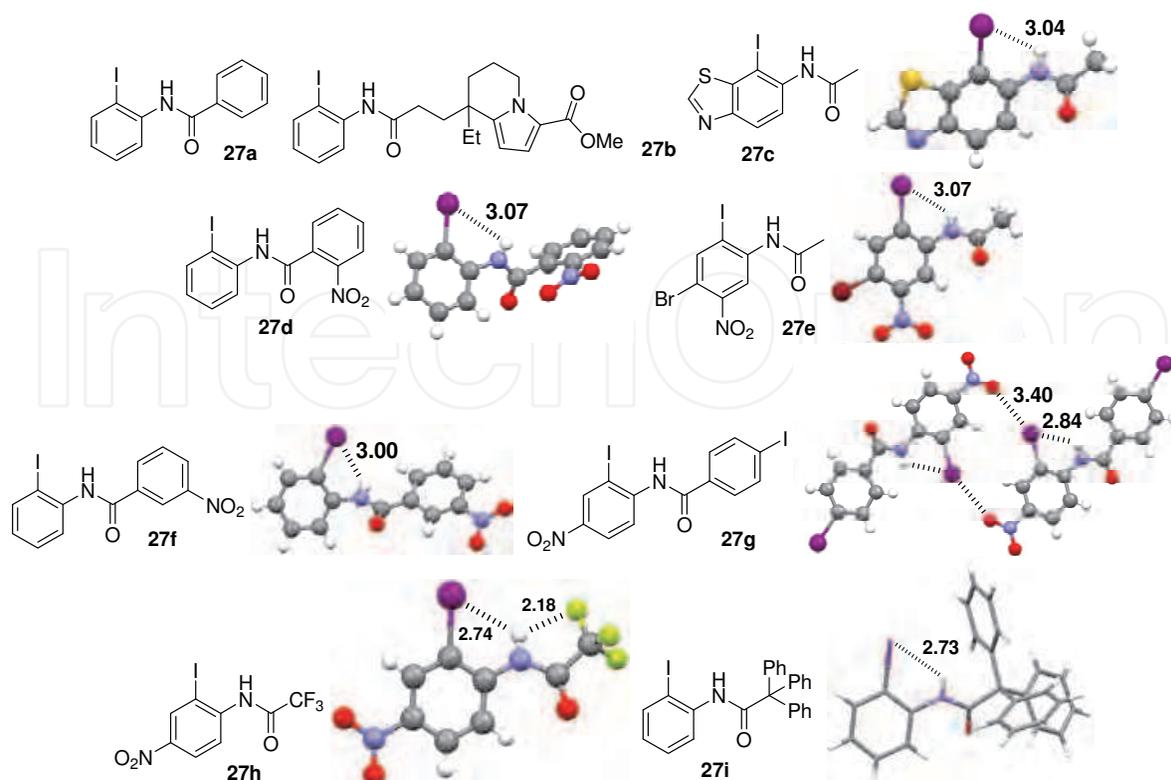


Fig. 13. Compounds 27a-i and the crystal structures of 27c-i.

The crystal structures of compounds 27a (Zhu et al., 2008), 27b (Bowie et al., 2005), 27c (Cicak et al., 2010), 27d (Wardell et al., 2005), 27e (Demartin et al., 2004), 27f (Wardell et al., 2006), 27g (Glidewell et al., 2003), 27h (Garden et al., 2006) and 27i (Zhu et al., 2008), are also available (Figure 13). No intramolecular five-membered N-H...I H-bonding is observed for 27a and 27b. However, this weak H-bonding is formed in the crystals of 27c-i. The intermolecular C=O...H-N H-bonding is also observed for 27c-h. However, this H-bonding is very weak for 27h (the O...H distance: 2.67 Å). As a result, its NH...I distance is shorter than that of 27d-g. The amide proton of 27h is also H-bonded to one of the F atom on the CF<sub>3</sub> group, which may also help to strengthen the N-H...I H-bonding by weakening the intermolecular N-H...O=C H-bonding. All the I atoms in the nitro derivatives also produce the intermolecular I...O(NO) contact. However, only 27g forms a dimeric structure. Compound 27i exhibits the shortest I...HN contact. As observed for 25c, its bulky trityl group completely suppresses the intermolecular N-H...O=C H-bonding. Clearly, without the competition of this stronger H-bonding, the weak N-H...I H-bonding can be formed more easily.

## 6. N-H...S hydrogen bonding

In 2009, Du et al. reported the crystal structures of compounds 28a-c (Figure 14) (Du et al., 2009). Compound 28a does not give rise to the intramolecular six-membered N-H...S H-bonding. However, compounds 28b and 28c do. The introduction of the bulky trityl group inhibits the formation of the intermolecular N-H...O=C H-bonding for both compounds. Compound 28b also forms two intermolecular (3,4)C-H...O=C contacts (2.58 and 2.64 Å) with one benzene of another molecule, which might also strengthen the torsion of the amide

unit from the attached benzene ring and weaken its intramolecular N–H···S H-bonding. Thus, its NH···S distance is larger than that of 28c.

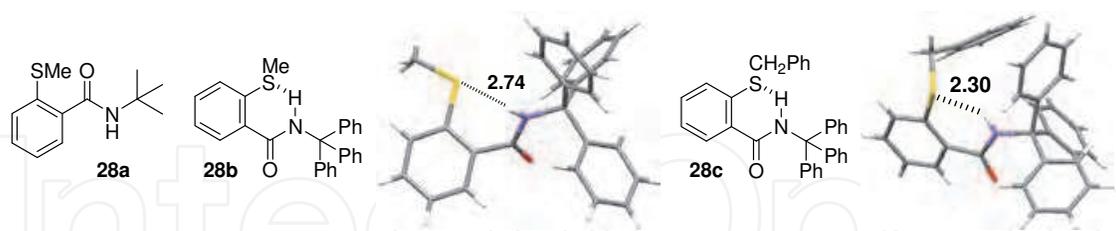


Fig. 14. Compounds 28a-c and the crystal structures of 28b and 28c.

In 1980, Rahman et al. reported that compound 29 formed a weak intramolecular five-membered N–H···S H-bonding (the S···H distance: 2.92 Å) in the crystal structure (Figure 15) (Rahman & van der Helm, 1980). The two amide units form two intermolecular N–H···O=C H-bonds, which lead to a dimeric binding pattern. Because the two molecules do not come from one stacking layer, the formation of the dimeric pattern causes a large torsion of the amide unit from the MeS-substituted benzene ring. In contrast, compound 30 did not form the intramolecular N–H···S H-bonding (Du et al., 2009). Its amide unit is greatly distorted from the benzene ring to form the intermolecular N–H···O=C H-bonding. In 2004, Liu et al. reported that 31 formed stronger intramolecular five-membered N–H···S H-bonds (Figure 15) (Liu et al., 2004). The two amide units are also engaged in five-membered (Py)N···H–N H-bonding, which inhibits the intermolecular C=O···H–N H-bonding and thus facilitates the formation of the neighboring N–H···S H-bonding. The similar three-center H-bonding is also generated in the crystal structure of compound 32 (Figure 15) (Choi et al., 2009). In this compound, two ether O atoms act as H-bonding acceptors to form two additional intramolecular six-membered N–H···O H-bonds, which prevent the amides from forming the intermolecular C=O···H–N H-bonding. Similar three-center hydrogen bonding pattern is not observed in the crystal structure of 33 (Du et al., 2009). (Figure 15), reflecting the weakness of the six-membered S···H–N H-bonding.

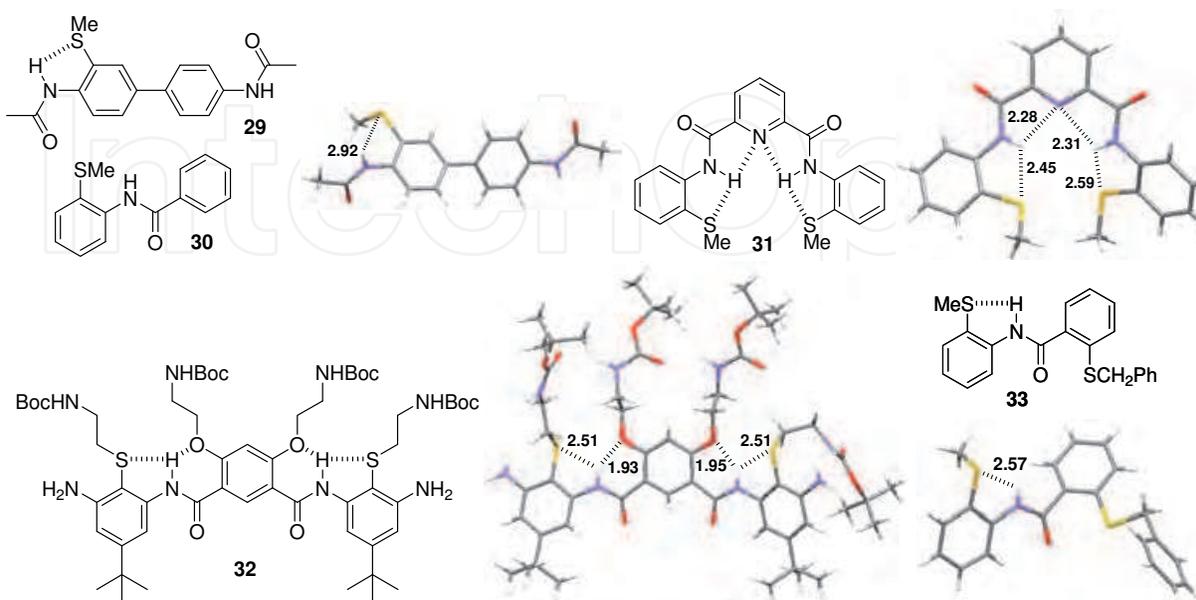


Fig. 15. Compounds 29-33 and the crystal structures of 29 and 31-33.

## 7. Conclusion

This chapter summarizes the crystal structures of aromatic amide derivatives that bear one halogen or sulfur atom at the ortho position of the amide unit to observe the possibility of forming the weak intramolecular N–H···X (X = F, Cl, Br, I, S) H-bonds. Generally, the five-membered H-bonds are easier to form than the six-membered ones for the identical aromatic backbone. Considering the difference of the chemical, steric and electronic environments of the heteroatom at the two different positions, this observation does not lead to conclusion that the former H-bonds are stronger than the latter ones. One straightforward reason for this difference is that the formation of the six-membered H-bonding requires to confine the rotation of three single bonds, while the five-membered one just needs to confine two. Since many complicated factors may affect the formation and stability of these intramolecular H-bonds, it is still difficult to predict whether or not a compound forms such H-bonding in the crystal. However, in most cases, if the competition of the intermolecular C=O···H–N H-bonding is suppressed, there will be a good chance of observing them, and for the halogen derivatives of the same backbone, it is obvious that their capacity of accepting the amide proton is in the order of F>Cl>Br>I, which is in the same order as electronegativity but reverse of atomic size and polarizability.

The fact that a compound does not form the above intramolecular H-bonding in crystal does not mean that it does not form the intramolecular H-bonding in solution. In crystal, the compound usually has one or two conformations, while in solution it generally exists as a dynamic mixture of several conformers of low energy and their distribution ratios will be affected by strong and weak interactions. In crystal, the structure and conformation of a compound is affected remarkably by intermolecular interactions, while in solution, the intermolecular interactions are highly concentration- and solvent-dependent. In a solvent of high polarity, the intermolecular interactions are broken by the solvent molecules, and the intramolecular H-bonding may also be weakened by the solvent to the extent that it is difficult to be detected. However, in a solvent of low polarity, a compound of low concentration should have a good chance to form the above intramolecular H-bonding.

In the past decades, the conventional, strong N–H···O and N–H···N H-bonds of amide derivatives have been the “protagonists” in studies in molecular recognition, crystal engineering, materials and biological sciences. In recent years, the above relatively weak H-bonding patterns have been used in discrete research areas. For example, the N–H···F and N–H···Cl H-bonds have been utilized to construct artificial secondary structures (Li et al., 2005; Gan et al., 2010, 2011a, 2011b), and the N–H···S H-bond has been used to create antimicrobial agents by restraining their conformations (Tew et al., 2010; Choi et al., 2009). We may expect that they will find more applications in the future, in particular in crystal engineering and supramolecular chemistry.

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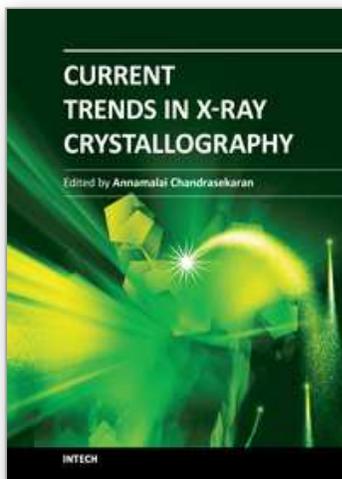
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