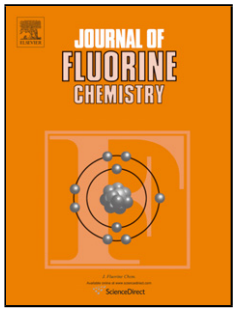

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ortho-Fluorobenzanilides and *ortho*-fluorothiobenzanilides: molecular conformations and crystal packing

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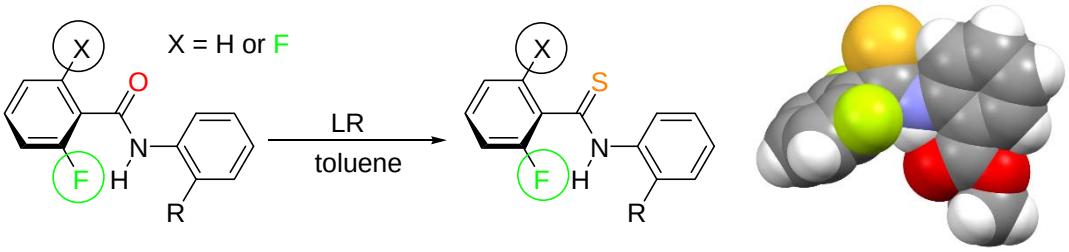
Graphical abstract



Highlights

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- Role of *ortho* fluorine substituent in the crystal structures of *o*-fluorobenzanilides.
- Synthesis of two new 2,6-difluoro(*N*-phenyl)thiobenzanilides was performed.
- Weak C_{Ar}–$F\cdots H$–C_{Ar} or C_{Ar}–$F\cdots F$–C_{Ar} interactions are observed in the molecular self-assembly in the crystals lattices.

ABSTRACT

Series of 2-fluoro and 2,6-difluoro(*N*-phenyl)benzanilides and their thiobenzanilide analogs have been synthesized to investigate the influence of the fluorine atom on their crystal structures and self-assembly in the crystal lattice. The X-ray analysis of the single crystal revealed that the synthesized molecules adopt a geometry being deflected from planarity.

The deflection was investigated by analysis of dihedral angles between mean planes of benzoyl, amide and aniline residues. Molecular conformation depends mainly on strong N–H···O bonds, although operation of N–H···F hydrogen bonding was observed in one case. Crystal packing is controlled mainly by interactions of the C–H···O type, also by π–π stacking and in one difluorosubstituted case by operation of weak C_{Ar}–F...F–C_{Ar} halogen bonding.

Fluorine substitution in *ortho* position in benzoyl subunit of benzanilides and thiobenzanilides is not without significance of their molecular conformations and crystal packing.

Keywords: *o*-fluorobenzanilides, *o*-fluorothiobenzanilides, fluorinated benzanilides, crystal structures, self-assembly.

1. Introduction

Secondary amide linkage [1] $RC(O)HNR_1$, as a key element of polypeptide chains, is the fundamental structural unit in living organisms and one of the most important functional group in contemporary organic chemistry [2] present in many natural products, polymers, and pharmaceuticals [3]. Due to the ability to form highly directional hydrogen bonds, the amide group is also an extremely useful building block in supramolecular chemistry and crystal engineering [4].

The detailed structural parameters of the secondary amide linkage $RC(O)HNR_1$ such as CO and CN bonds length and orders, or planarity of the amide unit are determined by the size and electron-releasing or electron-withdrawing character of the substituents R and R_1. Restricted rotation about C–N bond in amide group results in the existence of the *cis*-*trans* configurational isomers. The *trans* isomer is generally more stable over the *cis* one [5] and demonstrates preferences to form intermolecular hydrogen bonding patterns (chain or polymeric structures), whereas the other one tends to create dimers.

Benzanilides with two aromatic substituents constitute a special group of amides, which due to the wide range of biological activities have been extensively studied both theoretically and experimentally [6]. In particular, their fluorinated derivatives have gained much attention as drugs intermediates, potential drug candidates [7a-e], herbicides [7f], and useful model for observation of intra- and intermolecular interactions associated with the presence of fluorine atom and strong hydrogen bonds in crystal lattices [8].

It is known that the molecule of benzanilide having two unsubstituted phenyl rings $R=R_1=Ph$, in crystal lattice assumes the conformation in which the central C–C(O)–N(H)–C fragment of benzanilide molecule is essentially planar, with the phenyl rings twisted about 30 degrees from this plane in opposite directions [9]. Additionally, the results of DFT calculations

indicate that the non-planar *trans* conformer is the most stable structure for benzanilide molecule [10].

Introduction of an *ortho* substituent at either C–phenyl or *N*–phenyl ring in benzanilide, in close proximity to the amide bonding, should strongly affect molecular conformation of the molecule. Moreover, through interaction with the amide unit they could also affect ability of the molecule to form hydrogen bonds.

2. Results and discussion

An analysis of the Cambridge Structural Database for molecular geometry of benzanilides having *ortho* substituent on either of the C–phenyl or *N*–phenyl ring resulted in 316 hits. The search was restricted to the compounds neither involved in metal complexes structures nor in cyclic di- or triantranilides. Examination of the selected structures brings out a few general conformational features. First of all, amide bond C–C(O)–N(H)–C linking the two phenyl rings is essentially planar, with CO–NH torsion angle of 180 deg. apart from the cyclic molecules the torsion is close to zero (see ESI Fig. 1S).

In order to examine intramolecular hydrogen bond interactions we defined three planes: R1, R2 and R3. R1 is the mean least squares plane defined by the six carbon atoms of the benzoyl ring, R2 is the mean plane of amide residue, defined by C–N(CO)–C atoms and R3 is defined by the six atoms of the anilide ring. Since strong hydrogen bonding requires coplanarity of residues bearing donor NH and acceptor group, dihedral angles between R2 and R1 or R3 can be used to indicate the strengths of intramolecular hydrogen bond. Low values of ANG1= $\angle(R_1, R_2)$ or ANG2 = $\angle(R_2, R_3)$ (see ESI Fig. 2S) can be interpreted as result of strong bonding to an acceptor attached to the benzoyl or anilide ring, respectively.

Furthermore, the studied molecules tend to have their phenyl rings coplanar when both of the *ortho* substituents are halogens (not able to participate in hydrogen bond formation). In such

cases chains of intermolecular N–H···O interactions define the crystal packing and molecular conformation. The presence of substituent (-NH_2, -COOH, -OH) capable to form intermolecular hydrogen bond with amide group lead to the conformation in which the amide bond and the C–phenyl or *N*–phenyl ring bearing the *ortho* substituent are coplanar and the remaining phenyl ring is out of this plane.

To the best of our knowledge, no systematic studies were carried out to evaluate the influence of substituents in *ortho* position on the central amide moiety in benzanilide molecule and subsequently the changes in its molecular conformation and crystal packing. In this context we have focused our attention on 2-fluoro-*N*-phenylbenzamide (**I**) with defined crystal structure and have decided to investigate the influence of the *ortho* substituent on molecular conformation of *ortho*-fluoro(*N*-phenyl)benzamides **1-2** and *ortho*-fluoro(*N*-phenyl)thiobenzamides **3** analogs, including 2,6-difluoro substitution in benzamide rings.

Fluorine atom present in *ortho* position in our base structure of 2-fluoro-*N*-phenylbenzamide (**I**) is similar in size to hydrogen, however it has a different chemical nature [11]. Due to the high electronegativity and low polarizability [11a] its presence in close proximity to amide unit alters molecular conformation and crystal packing of molecule (**I**) comparing to benzanilide. As reported by Chopra and Row, the structure of 2-fluoro-*N*-phenylbenzamide (**I**) lacking additional functional groups, assumed in crystal a non-planar conformation stabilized by strong *N–H···F* hydrogen bond (*NH···F* distance: 2.16 Å) and *C–H···O=C* hydrogen bonds [12]. It is worth noting that the *N–H···F* hydrogen bonds are not common interactions in crystal lattice, as organic fluorine is a weak hydrogen bond acceptor in contrast to fluorine ion which is a very strong proton acceptor [13]. The molecules of compound (**I**) are held together by an intermolecular *N–H···O* hydrogen bonds and weak *C–H···F* and *C–H···π* intermolecular interactions generating a ‘‘molecular staircase”.

Thus, introduction of the second fluorine atom at *ortho* position in benzoyl ring in molecules **2a-3b** should lead to considerable changes in their conformations, particularly in terms of the arrangement of amide group relative to the phenyl rings.

To assure crystallinity of designed molecules as well as the formation of highly favorable intramolecular bonding, the $-NO_2$ or $-COOCH_3$ group was incorporated into (**I**). Both of them being in close proximity of amide unit should prevent formation of intermolecular hydrogen bonding through blocking access to -NH- of the amide group and thus facilitating the observation of conformational effects associated with presence of organic fluorine atom(s) in molecules **1a-3b**.

The sequence of reactions leading to the formation of aromatic amides **1a-2b** and thionoamides **3a**,**b** is outlined in Scheme 1. Commercially available 2-nitroaniline **4a** and methyl 2-aminobenzoate **4b** were used as substrates that were treated with acid chloride **5a** or **5b** in dichloromethane in the presence of triethylamine to give amides **1a**,**b** or **2a**,**b**, respectively. Resulting compounds **2a**,**b** were converted to thionoamide **3a**,**b** with the Lawesson's reagents [14] in boiling toluene. Crystals of compounds suitable for X-ray analysis were grown from toluene/hexane mixture by slow evaporation.

We expected that introduction of electronegative substituent to the basic structure (**I**), which is better hydrogen acceptor comparing to the covalently bound fluorine atom, should lead to formation of intramolecular hydrogen bonds between an oxygen atom from the substituted group and the amide NH group.

The ^{1}H NMR spectra of compounds **1a-3b** taken in $CDCl_3$ confirmed the existence of intramolecular H-bonding in solution. Its presence is manifested by the chemical shift of the amide proton that appears in the range of 11.83 (**1b**) to 10.89 (**2a**) ppm and is significantly shifted downfield in comparison to the amide proton of *N*-phenylbenzamide, that cannot form intramolecular H-bonding and shows up between 7.91-7.88 ppm [15]. The signal of the amide

proton NH in molecules **1a-3b** is also downfield shifted in respect to 2-fluoro-*N*-phenylbenzamide (NH at 8.56-8.31 ppm) in structure of which only weak intramolecular C_{Ar}–$F\cdots H$–$N(CO)$ bonding was reported [16]. Moreover, the signals are in a good agreement with the amide proton shift of *N*-(2-nitrophenyl)benzanilide 11.37 ppm [17] or methyl-2-(benzamido)benzoate 12.07 ppm [15], in which structures strong intramolecular H-bonding are observed.

Table 1 lists the relevant crystallographic data for all synthesized compounds **1a-3b**.

In the crystal structures of all *ortho*-fluorosubstituted compounds **1a-3b**, formation of a strong six-membered intramolecular hydrogen bond, between the amide NH group and the nitro group $N{-}H\cdots O_2N$ in molecules **1a-3a** or the $COOCH_3$ group $N{-}H\cdots OCCOCH_3$ in molecules **1b-3b** is observed. All they show the same graph set motif S(6). Additionally, the bifurcated hydrogen bonding pattern involving fluorine atom as the additional acceptor is present in **1a**. Geometrical parameters of selected intra- and intermolecular interactions for all investigated compounds are listed in Table 2 and Table 3. In each of the compounds **1a-3a,** hydrogen bonds motifs are the main factors responsible for stabilization of molecule conformation as well as for inhibition of the intermolecular hydrogen bonding formation in the crystal lattices. It affects also the *trans* amide group. Owing to the steric effect of the *ortho* substitution, the nitro groups attached to C2 of aniline subunits are not co-planar with the benzene ring. The dihedral angles (O2−N2−C2−C1 in **1a**, **2a** or O1−N2−C2−C1 in **3a**) are equal to -22.04° in compound **2a**, -29.05° in **3a** and -21.17° in **1a**, respectively. Similar behavior is observed for $COOCH_3$ groups, attached to C2, in molecules **1b-3b**. However, the dihedral angles between the substituent's mean plane and the aromatic ring plane are much smaller:

(O2−C14−C2−C1) equals 4.41° in compound **1b**, (O2−C14−C2−C1) -7.78° in **2b**, and (O1−C14−C2−C1) -7.44° in **3b**.

Compound **1a** crystallizes in the monoclinic system in the space group $P2_1/n$ with four molecules in the unit cell. The crystal structure revealed a well-defined coplanar orientation of both phenyl rings of the molecule (Table 3) with the amide unit twisted by dihedral angle of ca 15°. An additional intramolecular *N1−H1···F1* hydrogen bond, with H···F separation of 2.04 (2) Å can be observed. The packing motif in the crystal structure comprises of an infinite stack of alternating molecules (Fig. 1.) which are related by the inversion centers.

In the stack, adjacent phenyl rings, fluoro- and nitro- substituted, contact face-to-face with the centroids separation of 3.624 and 3.706 Å. The electrostatic attraction of the aromatic rings is enhanced vertically by amide groups interactions which are oriented in the opposite direction in the alternating molecules in columns with the contact distances (N1H1···O1=C7) of 3.49 and 4.02Å alternately. The packing motif is similar to that found in some arene-perfluoroarene complexes showing a stacked structure with the alternate sequence of molecules and can be attributed to $C_{Ar}–H···O_2N–C_{Ar}$ and $C_{Ar}–H···O=C$ (C10−H10···O2−N2 and C5−H5···O1=C7) interactions between neighboring rings in layer. Due to the numerous weak interactions between molecules in neighboring columns, they are assembled into regular slipped stacks.

Compound **1b** (Fig. 2.), bearing the methoxycarbonyl functionality at *ortho* position of anilide aromatic subunit which is, similarly to NO_2, an electron withdrawing group, crystallizes in the $P\bar{1}$ space group. In contrast to compound **1a,** structure of which is almost planar (with the dihedral angle of 2.41º) two aromatic subunits in molecule **1b** are twisted by 49.47° (dihedral angle between mean planes of aromatic rings), see Table 3. Stacking interactions between fluorinated phenyl rings (centroid···centroid distance 3.767 Å), supported with *C–H···O*

hydrogen bonds formed between phenyl rings and carbonyl O atoms of $COOCH_3$ groups, join molecules into centrosymmetric dimmers. In the crystal structure those dimmers are arranged into stacks along **a** axis, but fluorinated phenyl rings within columns do not overlap, only theirs F atoms are located directly above (or below) of the center of the adjacent dimmers (centroid···F distance 3.368 Å).

Both of the structures **1a**,**b** are similar to those of 2-(2-fluorobenzylamino)benzoic acid in which the NH donor group, located in a sterically hindered position, does not participate in any intermolecular hydrogen-bonding interactions [18].

Introduction of the second fluorine atom in the *ortho* position in compounds **2a**,**b** does not considerably enlarge the molecular volume (see Table 1) due to the similarity in van der Waals radii between H and F. On the other hand, this kind of modification changes significantly the charge distribution in the molecules as well as the attractive and repulsive forces between adjacent aromatic subunits. It is noteworthy that due to the presence of a second fluorine atom in *ortho* position of benzoyl subunits in **2a**,**b** the coplanar assemble of amide group and benzoyl ring is hampered (Table 3, second column). Negative charge on the fluorine atom disfavors the approach of the carbonyl oxygen atom to the plane formed by 2,6-difluoro substituted benzoyl ring. Dihedral angles between mean planes defined by aromatic subunits in molecules **2a**,**b** are 31.63° and 82. 06°, respectively (Table 3).

The molecules of **2a** (Fig. 3.) crystallize in the orthorhombic non-centrosymmetric space group $Pca2_1$ with $Z = 4$, having an intramolecular *N1−H1···O2* hydrogen bond which causes coplanar orientation of nitrosubstitued ring and N–H amide group. As in **1a**, in **2a** columns

formed through stacking interactions of both benzanilide phenyl rings are observed. However, in **1a** the nitro-substituted rings interact with fluoro-substituted rings, while in **2a** nitro-substituted rings interact with nitro-substituted rings and difluoro substituted rings with other fluorinated rings. Molecules in those columns are related by translation along **b** axis (centroid ⋯centroid distance 3.72 Å). Neighboring 1D motifs are connected *via* weak *C–H⋯O* hydrogen bonds (Table 2).

The inspection of the crystal structure of compound **2b** (triclinic, space group $P\bar{1}$) reveals again stacks of fluorinated phenyl rings, along the **b** axis, in antiparallel positions, separated by local symmetry centers. Moreover, short contacts *C5−H5⋯O1* form links between the molecules from the stacks held by $\pi-\pi$ interactions (Fig. 4.). Such chains are further supported by weak *C9−F1⋯F2* interactions between neighboring aromatic subunits. In addition, homo-halogen F1⋯F2 directional contacts (letter L arrangement of atoms or Type II, according to geometrical classification of halogen⋯halogen interactions) enhanced the stability of packing.The double bond in thiocarbonyl group is longer than that in the carbonyl group due to the larger size of sulfur atom, its higher polarizability and lower electronegativity. So that it was expected that introduction of sulfur atom in lieu of oxygen in thiobenzanilides **3a**,**b** that is localized between two *ortho* fluorine atoms in space will enhance weak interactions related with the presence of fluorine atoms in their crystal lattices. Thiobenzanilides **3a**,**b** have been synthesized for the first time.Both **3a** and **3b** crystallized in the monoclinic system in space-group type No. 14. Structure **3a** was solved and refined in $P2_1/c$ space group while symmetry of **3b** was analyzed using different setting, i.e. $P2_1/n$. Packing in both structures are dominated by $\pi-\pi$ stacking interactions. In **3a** difluorinated rings C8−C13 stack run in direction parallel to the **c** axis Fig. 5, with separation between centroids of 3.857(2) Å, while nitro-substituted rings C1−C6 have their centroids separated

by 3.916(2) Å. Either of the interacting rings in **3a** are related by glide planes *c*. Interestingly, 2,6-difluorobenzene rings are not antiparallel, but are rotated ca 120º to one another. Also the positions of nitro substituents in interacting rings form an angle smaller than 180 degree. On the other hand, the dihedral angle between the mean planes of the two rings, defined by carbon atoms, is small (12.39º) indicating they are almost parallel.

Packing in structure **3b** is mainly dictated by π-π stacking interactions of 2,6-difluorinated rings related by the symmetry center with distance of centroids of 3.7169(15) Å (naturally strictly parallel) Fig. 6. Other rings have their centroids distant more than 5.2 Å, so those interactions can be neglected. Such antiparallel position ensures the resultant electric dipole moments of both rings are in the energetically preferred configuration. Since stacking of the other rings is not operating the two kinds of rings are almost mutually perpendicular – the dihedral angle between mean planes is equal to 80.99º.

It is observed that thioamide bonds C(S)−NH have a partial double bond character in both structures **3a** and **3b**. Moreover, the geometric parameters such as bond lengths and bond angles determined for the central thioamide group in *ortho*-fluoro(*N*-phenyl)thiobenzamides **3a**,**b** remain in a good agreement with the values reported by Saeed et al. [19] for fluoro-substituted thiourea derivatives containing the thioamide moiety.

To sum up, crystallographic investigation of benzanilides **1a-3b** revealed that intramolecular hydrogen bonding between amide hydrogen NH and oxygen of -NO_2 or carbonyl oxygen of -$COOCH_3$ group in *ortho* position of anilide subunits are the main factors responsible for molecular conformation of investigated structures. They exist in both solid state as well as in the solution that was confirmed by the ^{1}H NMR spectroscopy.

Apart from compound **1a** in which three centered, bifurcated hydrogen bonding pattern C_{Ar}–$F\cdots H$–$N(CO)\cdots O_2N$ rigidified the structure, molecules **1b-3a**,**b** adopt geometry being

more or less disturbed from planarity which is related with the presence of fluorine atom(s) in *ortho* position of benzoyl ring. Theirs close proximity to amide/thioamide group results in deflection out of the benzoyl ring plane the amide/thioamide group due to the weak interaction C_{Ar}–$F\cdots H$–$N(CO)$ or/and mutual repulsive forces between the C_{Ar}–F and carbonyl oxygen C=O (or C=S) dipoles. The small deviation of the amide group from the benzoyl ring plane was found in crystal structure of compound **1b** whereas two fluorine atoms in *ortho* position of benzanilide/thiobenzanilide framework in molecules **2-3a**,**b** enhanced the deviation of the amide/thioamide group effect.

Intermolecular $\pi-\pi$ stacking together with weak hydrogen bonds are mainly responsible for the molecular self-assembly in the crystal structure; $NO_2\cdots H-C_{Ar}$, $C_{Ar}-H\cdots O=C$ in the compounds **1a-3a**, $CO_2CH_3(C=O)\cdots H-C$, $C_{Ar}-H\cdots O=C(CO_2CH_3)$ in **1b** and $C_{Ar}-H\cdots O=C(CONH)$ in **2b**. They are generating corrugated layers or infinite molecular chains which are main building blocks in the discussed crystals. Stability of crystal packing in compounds **2a**,**b** is enhanced through weak C_{Ar}–$F\cdots H$–C_{Ar} or C_{Ar}–$F\cdots F$–C_{Ar} interactions, respectively. In compound **3b** $\pi-\pi$ stacking and weak C_{Ar}–$F\cdots H$–C_{Ar} interactions dominate in the molecular self-assembly in the crystal.

3. Conclusion

In conclusion, strong hydrogen bondings related to the presence of $-NO_2$ or $-COOCH_3$ groups play the major role in the adopted molecular conformations of the studied *ortho* substituted fluorobenzanilides and their thiobenzanilide analogs as well as their self-assembly. However, week interactions C_{Ar}–$F...F$–C_{Ar}, C_{Ar}–$F\cdots H$–C_{Ar} or N–$H\cdots F$–C_{Ar} involving fluorine atom(s) are still noticeable in stabilizing their conformations and formation of supramolecular structures. Due to the electronic effects of the *orto*-substituted phenyl rings and the nature of the amide or thioamide central linkage the synthesized molecules adopt a geometry being

deflected from planarity. The presence of sulfur atom in the central thioamide linkage of *ortho*-fluoro(*N*-phenyl)thiobenzamides decreases their ability of formation intermolecular hydrogen bonds and therefore lead to crystal packing controlled mainly by week π–π stacking type interactions.

4. Experimental

All solvents and reagents were used as obtained from commercial source. ^{1}H NMR,^{13}C NMR and ^{19}F NMR spectra were obtained at 500, 125 and 470 MHz (Varian Unity Plus), respectively, and the deuterated solvents were used as internal lock. Melting points were determined on a melting point apparatus equipped with thermometer and were uncorrected. Column chromatography was carried out in silica gel 0.040-0.063 mm. The mass spectra analyses were carried out using the Aqilent Technologies 6540 UHD Accurate – Mass Q-TOF LC/MS mass spectrometer.

*4.1 Fluorobenzanilide (**1**, **2**)* – general procedure

To a solution of *o*-substituted aniline (2.7 mmol) in dichloromethane (10 mL), fluorobenzoyl chloride (2.5 mmol) and triethylamine (0.37 mL, 2.7 mmol) were added and the mixture was kept at room temperature overnight. The reaction mixture was washed with water, dilute hydrochloric acid, and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and then evaporated at reduced pressure. The resulting solid was recrystallized to obtain the product.

*4.1.1 2-Fluoro-N-(2-nitrophenyl)benzamide (**1a**)*

Compound **1a** was obtained as ecru crystals 600 mg (92 %); mp 117-118 ºC (EtOH); ^{1}H NMR (DMSO-d_6) δ: 10.89 (s, 1H, NH); 8.18 (dd, *J*=1.1 and 8.2 Hz, 1H); 7.93 (d, *J*=7.9 Hz,

1H); 7.79 (dt, *J*=1.4 and 7.7 Hz, 1H); 7.70 (dt, *J*=1.4 and 7.7 Hz, 1H); 7.50 (m, 3H); ^{13}C NMR (DMSO-*d*$_6$) δ: 163.1; 160.1 (d, *J*=251.0 Hz); 142.5; 135.1; 134.5 (d, *J*=8.9 Hz); 132.0; 131.2; 126.2; 125.9; 125.8; 125.6; 123.3 (d, *J*=13.0 Hz); 117.2 (d, *J*=22.0 Hz); ^{19}F NMR (DMSO-*d*$_6$) δ: -113.84; MS (ESI) calcd *m/z* for $C_{13}H_9FN_2O_3$ 260.0597; found *m/z* 261.0601 [M+1].

*4.1.2 Methyl 2-(2-Fluorobenzamido)benzoate (**1b**)*

Crude product **1b** was purified by chromatography on silica gel with chloroform as an eluent and recrystallized from toluene–hexane. Compound **1b** was obtained as white crystals 510 mg (75%); mp 83-84ºC; ^{1}H NMR (DMSO-*d*$_6$) δ: 11.49 (d, *J*=5.5 Hz, 1H, NH); 8.56 (d, *J*= 8.4 Hz, 1H); 7.96 (d, *J*=7.5 Hz, 1H); 7.90 (dt, *J*=1.5 and 7.7 Hz, 1H); 7.65 (m, 2H); 7.39 (m, 2H); 7.23 (t, *J*=7.5 Hz, 1H); 3.85 (s, 3H, CH_3O); ^{13}C NMR (DMSO-*d*$_6$) δ: 168.2; 162.4; 160.0 (d, *J*=249.0 Hz); 140.4; 134.9; 134.7 (d, *J*=9.0 Hz); 131.5; 131.4; 125.8 (d, *J*=4.0 Hz); 124.3; 123.3 (d, *J*=12.0 Hz); 121.8; 117.8; 117.2 (d, *J*=23.0 Hz); 53.2; ^{19}F NMR (DMSO-*d*$_6$) δ: -113.34; MS (ESI) calcd *m/z* for $C_{15}H_{12}FNO_3$ 273.0801; found *m/z* 272.0805 [M+1].

*4.1.3 2,6-Difluoro-N-(2-nitrophenyl)benzamide (**2a**)*

Compound **2a** was obtained as white crystals 675 mg (97%); mp 146-147ºC (EtOH); ^{1}H NMR (DMSO-*d*$_6$) δ: 11.15 (s, 1H, NH); 8.00 (dd, *J*=1.1 and 8.2 Hz, 1H); 7.75 (t, *J*=7.4 Hz, 1H); 7.61 (m, 2H); 7.46 (dt, *J*=1.1 and 7.7 Hz, 1H); 7.25 (t, *J*=8.1 Hz, 2H); ^{13}C NMR (DMSO-*d*$_6$) δ: 159.4; 159.7 (dd, *J*=7.0 and 250.0 Hz); 144.0; 134.7; 133.4 (t, *J*=10.0 Hz); 130.4; 127.1; 126.6; 125.7; 114.9; 112.9 (dd, *J*=4.5 and 25.0 Hz); ^{19}F NMR (DMSO-*d*$_6$) δ: -113.61 (t, *J*=7.3 Hz); MS (ESI) calcd *m/z* for $C_{13}H_8F_2N_2O_3$ 278.0503; found *m/z* 279.0501 [M+1].

*4.1.4 Methyl 2-(2,6-difluorobenzamido)benzoate (**2b**)*

Compound **2b** was obtained as white crystals 640 mg (88%); mp 129-130ºC (toluene); ^{1}H NMR (DMSO-*d*$_6$) δ: 11.20 (s, 1H, NH); 8.18 (d, *J*=8.2 Hz, 1H); 7.91 (d, *J*=7.7 Hz, 1H); 7.62 (t, *J*=7.8 Hz, 1H); 7.62 (m, 1H); 7.28 (m, 3H); 3.80 (s, 3H, CH_3O); ^{13}C NMR (DMSO-*d*$_6$) δ: 168.1; 159.6 (dd, *J*=7.0 and 250.0 Hz); 158.9; 138.6; 134.5; 133.5 (t, *J*=10.0 Hz); 131.3; 125.3; 122.6; 120.5; 115.3; 113.0 (dd, *J*=4.0 and 20.0 Hz); 53.1; ^{19}F NMR (DMSO-*d*$_6$) δ: -113.84 (t, *J*=7.2 Hz); MS (ESI) calcd *m/z* for $C_{15}H_{11}F_2NO_3$ 291.0707; found *m/z* 292.0705 [M+1].

*4.2 Fluorothiobenzanilide (**3**) – general procedure*

To the solution of benzamide **2** (1.8 mmol) in toluene (10 ml) was added the Lawesson's reagents (0.9 mmol) and the reaction mixture was heated to maintain a gentle reflux for 40 h. Then the reaction mixture was allowed to cooled to room temperature and the solvent was evaporated *in vacuo*. The residue was treated with methanol (10 ml) and immediately a solid precipitated which was filtered off. The residue was concentrated and purified by chromatography on a silica gel column eluted with 1:9 (v/v) ethyl acetate in petroleum ether to give the product **3**.

*4.2.1 2,6-Difluoro-N-(2-nitrophenyl)thiobenzamide (**3a**)*

Compound **3a** was obtained as yellow orange solid 320 mg (60 %); mp 101-105ºC; ^{1}H NMR (DMSO-*d*$_6$) δ: 12.58 (s, 1H, NH); 8.10 (dd, *J*=1.0 and 8.3 Hz, 1H); 7.85 (t, *J*=7.8 Hz, 1H); 7.64 (m, 2H); 7.46 (m, 1H); 7.22 (t, *J*=7.8 Hz, 2H); ^{13}C NMR (DMSO-*d*$_6$) δ: 188.8; 159.1; 157.1 (d, *J*=6.0 Hz); 145.9; 135.2; 132.1; 131.8 (t, *J*=10.0 Hz); 129.8 (d, *J*=2.0 Hz); 125.9; 112.7 (d, *J*=24.5 Hz); ^{19}F NMR (DMSO-*d*$_6$) δ: -115.03 (t, *J*=6.6 Hz); MS (ESI) calcd *m/z* for $C_{13}H_8F_2N_2O_2S$ 294.0275; found *m/z* 295.02698 [M+1].

*4.2.2 Methyl 2-(2,6-difluorothiobenzamido)benzoate (**3b**)*

Compound **3b** was obtained as yellow solid 126 mg (12 %); mp 117-120ºC; ^{1}H NMR (DMSO-d_6) δ: 12.37 (s, 1H, NH); 7.92 (dd, *J*=1.0 and 8.0 Hz, 1H); 7.70 (m, 2H); 7.49 (m, 2H); 7.21 (t, *J*=7.4 Hz, 2H); 3.78 (s, 3H, CH_3O); ^{13}C NMR (DMSO-d_6) δ: 187.5; 166.6; 159.0 (d, *J*=6.2 Hz); 157.0 (d, *J*=6.5 Hz); 138.3; 133.7; 131.4 (t, *J*=10.0 Hz); 128.4; 128.1; 127.5; 112.7 (dd, *J*=4.0 and 20.0 Hz); 53.1; ^{19}F NMR (DMSO-d_6) δ: -115.48 (t, *J*=7.0 Hz); MS (ESI) calcd *m/z* for $C_{15}H_{11}F_2NO_2S$ 307.0479; found *m/z* 308.04705 [M+1].

4.3 X-ray crystal structure analyses

Reflection intensities were determined with: Oxford Diffraction SuperNova (**1**, **2a**), Oxford Diffraction Xcalibur E (**2b**) or Oxford Diffraction KM4CCD (**3**) diffractometers. Measurements for all but two crystals were performed at room temperature. Experiments for **1a** and **2a** were conducted at 130 K. Data were processed with the CrysAlis PRO [20] software, the structures were solved by direct methods using SIR2004 [21] (1, 2) or SHELXS [22] (**3**) and refined by full matrix least-squares based on F^2 (SHELXL-2014) [22]. C-bound hydrogen atoms were placed at idealized positions and refined as riding on their carriers with $U_{iso}(H)=1.2_{eq}$ (CH) and $U_{iso}(H)=1.2_{eq}$ (CH_3). Amide H atoms were located in difference electron-density maps and, expect this from **2a**, were freely refined. Because of significant contraction of N–H bond in **2a** (0.75 (5) Å) AFIX43 was used during refining. U_{iso} parameters for all amide H were refined.

Crystal data for **1a** ($C_{13}H_9FN_2O_3$, *M* =260.22 g/mol): monoclinic, space group $P2_1/n$ (no. 14), *a* = 7.1448(2) Å, *b* = 7.43040(10) Å, *c* = 20.9781(5) Å, *β* = 90.060(2)°, *V* = 1113.70(4) Å^3, *Z* = 4, *T* = 130(2) K, μ(CuKα) = 1.053 mm^{-1}, *Dcalc* = 1.552 g/cm^3, 6479 reflections were measured up to θ_{max} = 68.24° (R_{int} = 0.0124, R_{sigma} = 0.0112). The final *R*

indices for 1894 reflections with I > 2σ(I) and 176 refined parameters are R_1= 0.0310, wR_2 = 0.0852 (R_1= 0.0327, wR_2 = 0.0869 for all 2028 data). (CCDC no. 1474679)

Crystal data for **1b** ($C_{15}H_{12}FNO_3$, M =273.26 g/mol): triclinic, space group P-1 (no. 2), a = 7.8406(8) Å, b = 8.4026(6) Å, c = 10.8252(12) Å, α = 74.041(8)°, β = 73.372(10)°, γ = 76.291(8)°, V = 647.25(12) Å^3, Z = 2, T = 295(2) K, μ(CuKα) = 0.908 mm^{-1}, *Dcalc* = 1.402 g/cm^3, 6837 reflections were measured up to θ_{max} = 68.24° (R_{int} = 0.0131, R_{sigma} = 0.0118). The final R indices for 2131 reflections with I > 2σ(I) and 186 refined parameters are R_1= 0.0382, wR_2 = 0.1050 (R_1= 0.0413, wR_2 = 0.1092 for all 2368 data). (CCDC no. 1474680)

Crystal data for **2a** ($C_{13}H_8F_2N_2O_3$, M =278.21 g/mol): orthorhombic, space group $Pca2_1$ (no. 29), a = 22.7758(5) Å, b = 3.7202(7) Å, c = 13.4022(3) Å, V = 1135.6(2) Å^3, Z = 4, T = 130(2) K, μ(CuKα) = 1.207 mm^{-1}, *Dcalc* = 1.627 g/cm^3, 2333 reflections were measured up to θ_{max} = 68.24° (R_{int} = 0.0122, R_{sigma} = 0.0143). The final R indices for 1519 reflections with I > 2σ(I) and 182 refined parameters are R_1= 0.0444, wR_2 = 0.1070 (R_1= 0.0446, wR_2 = 0.1075 for all 1534 data). (CCDC no. 1474681)

Crystal data for **2b** ($C_{15}H_{11}F_2NO_3$, M =291.25 g/mol): triclinic, space group P-1 (no. 2), a = 7.1277(8) Å, b = 8.0841(10) Å, c = 12.2305(14) Å, α = 88.375(9)°, β = 82.483(9)°, γ = 79.298(10)°, V = 686.52(14) Å^3, Z = 2, T = 295(2) K, μ(MoKα) = 0.116 mm^{-1}, *Dcalc* = 1.409 g/cm^3, 8040 reflections were measured up to θ_{max} = 25.35° (R_{int} = 0.0206, R_{sigma} = 0.0222). The final R indices for 1833 reflections with I > 2σ(I) and 182 refined parameters are R_1= 0.0502, wR_2 = 0.1309 (R_1= 0.0683, wR_2 = 0.1457 for all 2514 data). (CCDC no. 1474682)

Crystal data for **3a** ($C_{13}H_8F_2N_2O_2S$, M =294.27 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 19.1987(10) Å, b = 8.5469(5) Å, c = 7.7029(6) Å, β = 91.885(5) , V = 1263.28(14) Å^3, Z = 4, T = 293(2) K, μ(MoKα) = 0.283 mm^{-1}, *Dcalc* = 1.547 g/cm^3, 7570 reflections were measured up to θ_{max} = 25.49° (R_{int} = 0.0297, R_{sigma} = 0.0263). The final R

indices for 1991 reflections with I > 2σ(I) and 185 refined parameters are R1= 0.0521, wR2 = 0.1284 (R1= 0.0605, wR2 = 0.1344 for all 2353 data). (CCDC no. 1474683)

Crystal data for **3b** ($C_{15}H_{11}F_2NO_2S$, M =307.31 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 7.3218(8) Å, b = 23.3328(16) Å, c = 8.4995(6) Å, β = 98.986(8)°, V = 1434.2(2) Å^3, Z = 4, T = 293(2) K, μ(MoKα) = 0.251 mm^{-1}, *Dcalc* = 1.423 g/cm^3, 5117 reflections were measured up to θ_{max} = 25.99° (R_{int} = 0.0234, R_{sigma} = 0.0353). The final R indices for 1976 reflections with I > 2σ(I) and 194 refined parameters are R1= 0.0524, wR2 = 0.1248 (R1= 0.0775, wR2 = 0.1453 for all 2823 data). (CCDC no. 1474684)

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1474679-1474684. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk)

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a) b)

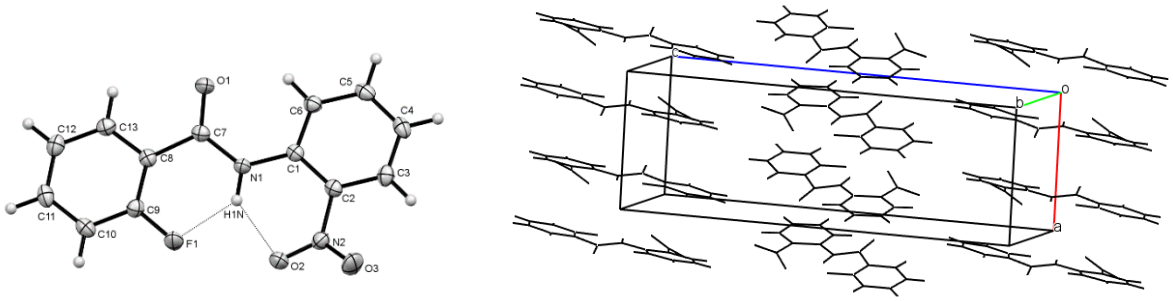


Fig. **1**. (a) Atom labeling in the asymmetric unit, bifurcated hydrogen bonding depicted by dotted line (b) molecular stacking in the structure of **1a**.

a) b)

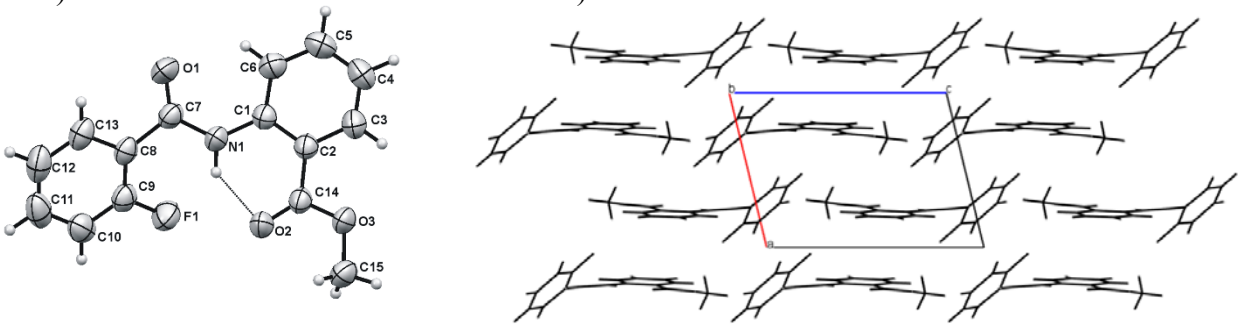


Fig. **2**. (a) Atom numbering scheme and intramolecular interaction depicted by dotted line (b) crystal packing, view along the b-axis in the structure of **1b**.

a) b)

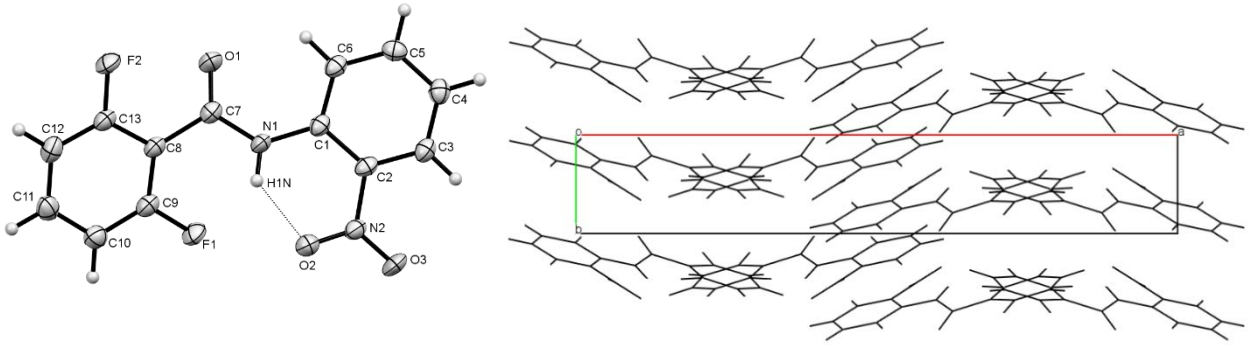


Fig. **3**. (a) Atom labeling in the asymmetric unit, intramolecular interaction depicted by dotted line (b) crystal packing, view along the **c**-axis in the crystal structures of **2a**.

a) b)

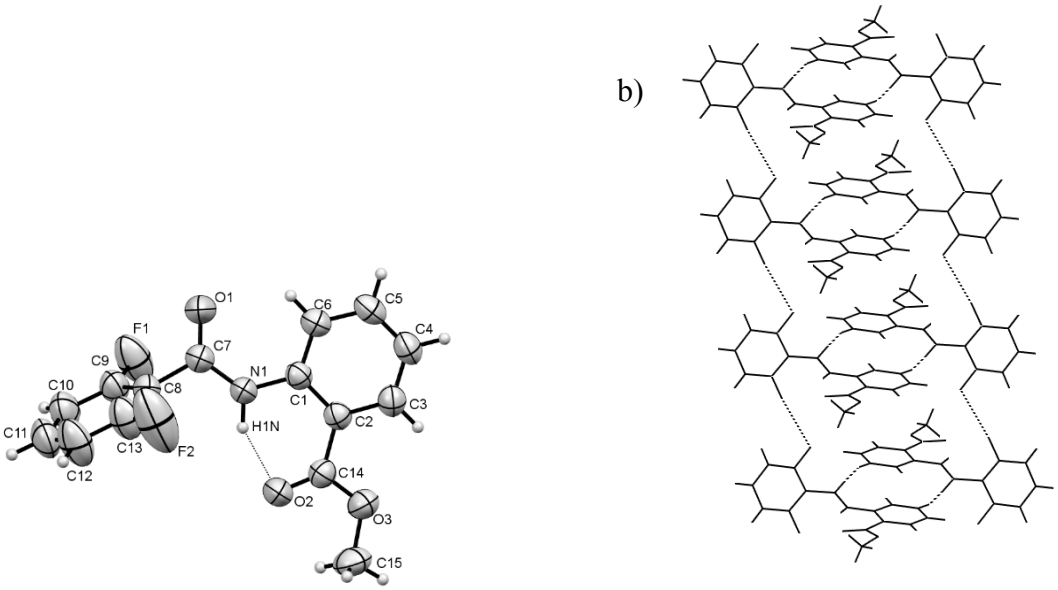


Fig. **4**. (a) Atom labeling in the asymmetric unit with intramolecular interaction depicted by a dotted line (b) crystal packing viewed along the b-axis showing C5−H5···O1 hydrogen bonds and C9−F1···F2 interactions in **2b**.

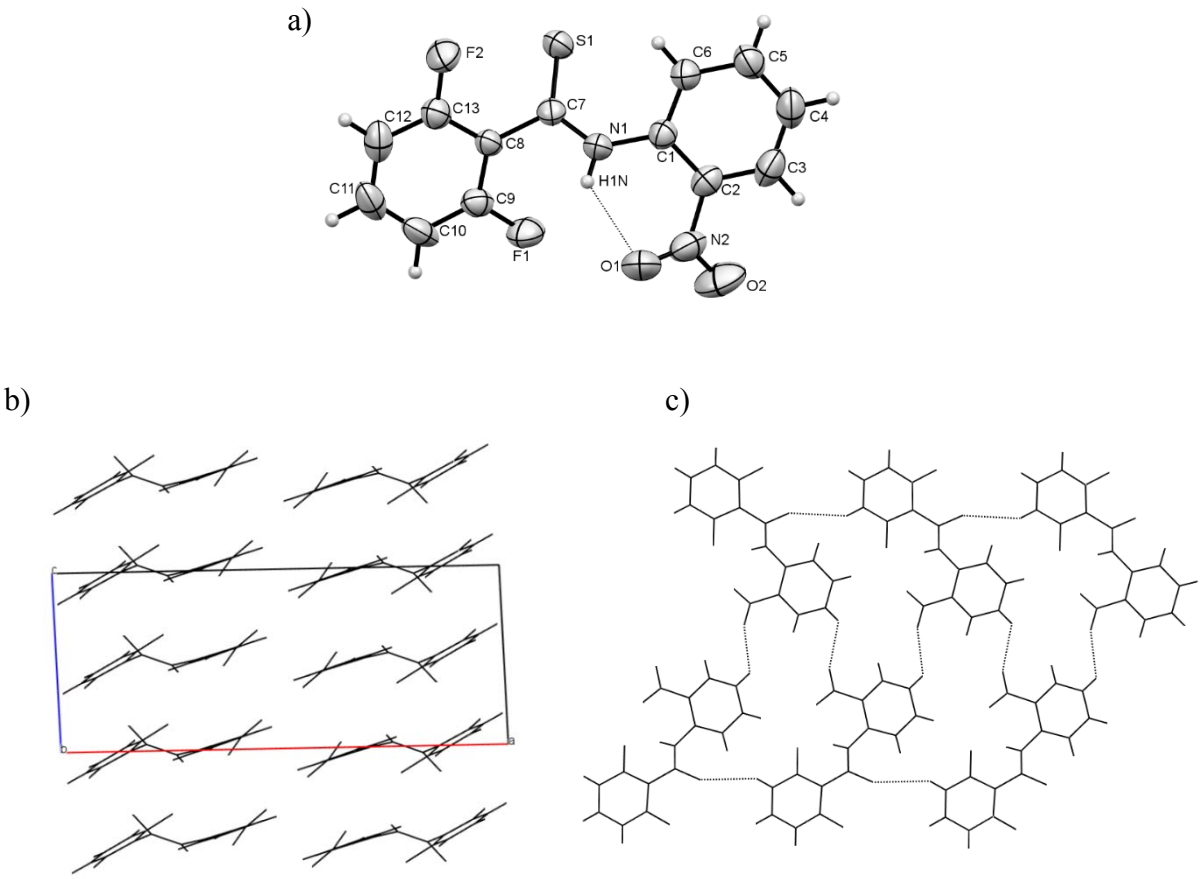


Fig. **5**. (a) Atom labeling in the asymmetric unit, intramolecular interaction depicted by dotted line (b) crystal packing, viewed along the b-axis c) C4−H4···O2 and C10−H10···S1 hydrogen bonding in structure of **3a**.

a) b)

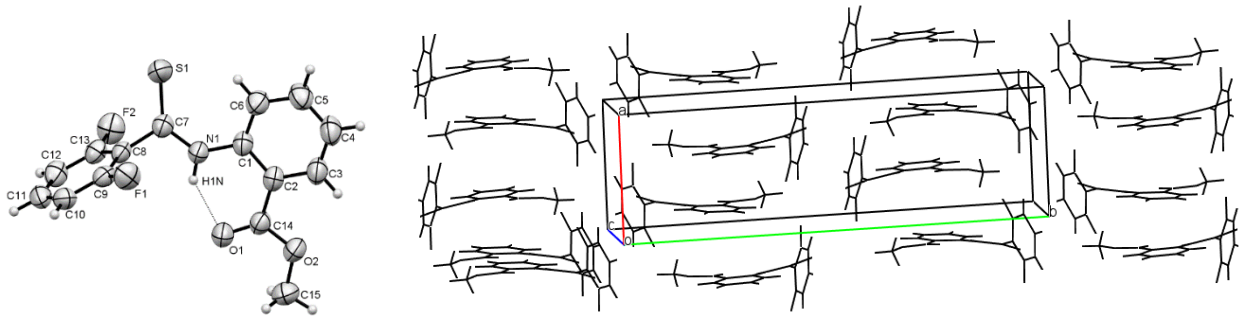
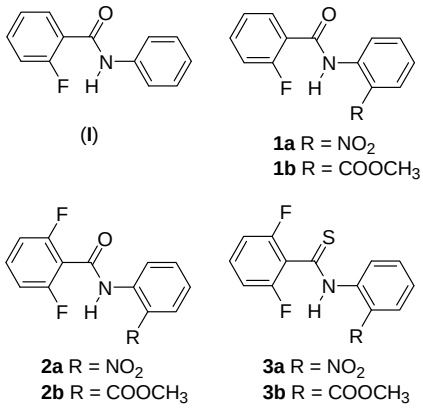
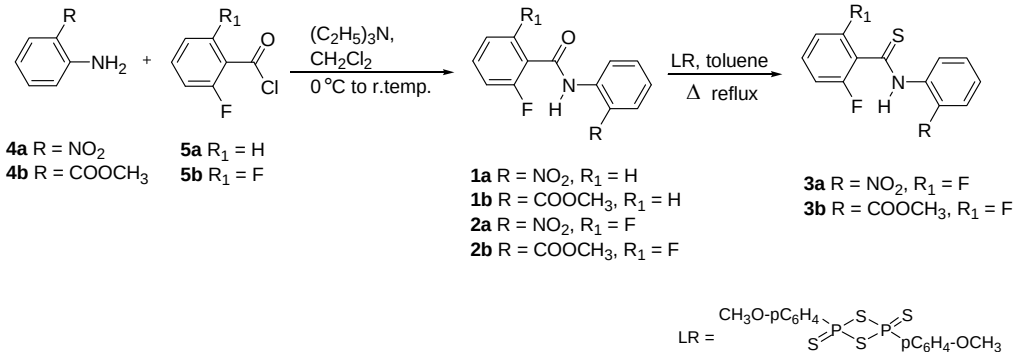


Fig. **6**. (a) Atom labeling in the asymmetric unit, intramolecular interaction depicted by a dotted line (b) crystal packing in **3b**.



Scheme 1: . Chemical structures of ortho-fluorobenzanilides 1-2 and ortho-fluorothiobenzanilides 3.



Scheme 2. Synthesis of ortho-fluorobenzanilides 1-2 and ortho-fluorothiobenzanilides 3.

Table 1 Crystallographic data and structure parameters for compounds **1a-3b**.

Compound	**1a**	**1b**	**2a**	**2b**	**3a**	**3b**
Formula	$C_{13}H_9FN_2O_3$	$C_{15}H_{12}FNO_3$	$C_{13}H_8F_2N_2O_3$	$C_{15}H_{11}F_2NO_3$	$C_{13}H_8F_2N_2O_2S$	$C_{15}H_{11}F_2NO_2S$
MW	260.22	273.26	278.21	291.25	294.28	307.31
Crystal system	monoclinic	Triclinic	orthorhombic	triclinic	monoclinic	monoclinic
Space group	$P2_1/n$	$P\bar{1}$	$Pca2_1$	$P\bar{1}$	$P2_1/c$	$P2_1/n$
a/Å	7.1448(2)	7.8399(3)	22.7758(5)	7.1277(8)	19.1987(10)	7.3218(8)
b/Å	7.43040(10)	8.4111(4)	3.7202(7)	8.0841(10)	8.5469(5)	23.3328(16)
c/Å	20.9781(5)	10.8184(5)	13.4022(3)	12.2305(14)	7.7029(6)	8.4995(6)
α/°	90.00	73.991(4)	90.00	88.375(9)	90	90
β/°	90.060(2)	73.336(4)	90.00	82.483(9)	91.885(5)	98.986(8)
γ/°	90.00	76.244(4)	90.00	79.298(10)	90	90
V/Å^3	1113.7	647.094	1135.58	686.519	1263.28	1434.22
Z	4	2	4	2	4	4

Table 2 Geometrical parameters of intra- and intermolecular interactions for compounds **1a-3b**.

Compound	*D*—H···*A*	*D*—H (Å)	*D*···*A* (Å)	H···*A*(Å)	*D*—H···*A* (deg)
1a	N1—H1*N*···O2	0.85 (2)	2.660 (1)	1.98 (2)	135.4 (1)
	N1—H1*N*···F1	0.85 (2)	2.716 (1)	2.04 (2)	135.5 (1)
	C3—H3···O3^{i}	0.95	3.233 (1)	2.60	124
	C5—H5···O1^{ii}	0.95	3.415 (1)	2.53	156

	C10—H10···O2^{iii}	0.95	3.480 (1)	2.60	155

Symmetry codes: (i) −x+3/2, y+1/2, −z+1/2; (ii) −x+2, −y+2, −z+1; (iii) −x+1, −y, −z+1.

2a	N1—H1*N*···O2	0.88	2.647 (3)	1.96	134
	N1—H1*N*···F1	0.88	2.787 (3)	2.35	111
	C12—H12···O2^{i}	0.95	3.316 (3)	2.65	127
	C11—H11···O3^{i}	0.95	3.440 (3)	2.63	143
	C3—H3···O1^{ii}	0.95	3.146 (3)	2.46	129

Symmetry codes: (i) −x+3/2, y, z−1/2; (ii) −x+1, −y+2, z+1/2.

3a	N1−H1···O1	0.83(3)	2.713(3)	2.14(3)	126(3)
	C6−H6···S1	0.93	3.211(3)	2.79	108

1b	N1—H1*N*···O2	0.89 (2)	2.690 (1)	1.96 (2)	139.1 (1)
	N1—H1*N*···F1	0.89 (2)	2.821 (1)	2.38 (2)	110.6 (1)
	C12—H12···O2^{ii}	0.93	3.548 (2)	2.68	156

Symmetry codes: (i) x, y, z+1; (ii) −x+1, −y+2, −z.

2b	N1—H1*N*···O2	0.92 (3)	2.656 (2)	1.89 (3)	140 (2)
	C5—H5···O1^{i}	0.93	3.311 (3)	2.44	157
	C9−F1···F2^{ii}		2.897(3)		

Symmetry codes: (i) 1-x, 1-y, -z; (ii) -1+x, y, z.

3b	N1−H1N···O1	0.86(2)	2.672(2)	1.94(2)	141(2)
	C3−H3···O2	0.93	2.706(3)	2.36	102

C6−H6···S1	0.93	3.247(3)	2.58	129
C10−H10···F2^{i}	0.93	3.348(3)	2.51	149

Symmetry code: (i) -1+x, y, z.

Table 3 Selected dihedral angles (°) in structures **1a-3b**.

Compound	∠ (R_1, R_2)	∠ (R_1, R_3)	∠ (R_2, R_3)
1a	16.62 (5)	15.51 (5)	2.41 (4)
2a	11.16 (13)	42.73 (8)	31.63 (7)
3a	42.8(15)	54.71(15)	12.39(14)
1b	8.54 (7)	41.26 (4)	49.47 (4)
2b	14.02 (9)	68.10 (10)	82.06 (9)
3b	17.42(13)	66.72(12)	80.89(12)

R_1 = mean plane of amide group (C1, N1, C7, C8, O1 (S1)), R_2 = mean plane of C1-C6 (aniline) ring, R_3 = mean plane of C8-C13 (benzoyl) ring.