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Fluorine hydrogen short contacts and hydrogen bonds in substituted benzamides

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ABSTRACT

A series of fluorine substituted benzamides **1–10** was synthesised and investigated by spectroscopic methods (NMR, IR, MS) and X-ray structure analysis. The configuration of these compounds strongly depends on solvent, temperature and substitution pattern. Unexpectedly, some of these compounds form weak intramolecular hydrogen bonds/short N–H···F–C contacts in $CDCl_3$ solution and in the solid state.

1. Introduction

It is well-known that anionic fluorine forms very strong hydrogen bonds, but in organic molecules F···H interactions are very rare [1]. Such interactions are traditionally indicated as hydrogen bonds or characterised as non-conventional H-bonds, weak hydrogen bonds (1.5–2.5 kcal mol^{-1}) or short contacts to distinguish them from classical hydrogen bonds (5–10 kcal mol^{-1}) [2,3]. A CSD analysis showed:

(a) Only 40 out of 1163 organic F atoms possibly accept a hydrogen bond from OH or NH using a distance cut-off $d < 2.35$ Å (3.4%). 25 out of these 40 are intramolecular interactions [3].
(b) From 5947 C–F bonds in crystal structures with at least one potential OH or NH donor only 37 are involved in possible O/N–H···F hydrogen bonds with distances $d < 2.3$ Å, i.e. 0.6% of the potential F–C acceptors [4].

On investigation of fluorine substituted benzamides we now found that these compounds represent a very sensitive system concerning the formation of hydrogen bonds and/or short contacts.

2. Results and discussion

A series of benzamide derivatives was synthesised by reaction of substituted benzoyl chlorides with KSCN and secondary amines (diethylamine, diisopropylamine, morpholine, diethanol amine) in acetone (Scheme 1).

Analogously to **1** [7] the fluorine substituted compounds **2, 3, 5, 6,** and **7** exist as NH tautomers in E/Z′ configuration with a partially hindered rotation of the C(S)–N(R^4)$_2$ bond (Scheme 2). Temperature depending NMR measurements in DMSO-d_6 showed that the activation barrier of the fluorine substituted compounds is marginally lower (e.g., **1**: T_c = 345 K, $\Delta G^{\neq}$ = 69.7 kJ mol^{-1}; **2**: T_c = 336 K, $\Delta G^{\neq}$ = 68.2 kJ mol^{-1}). By contrast compounds **4** and **8–10** have a Z,Z′ configuration (see below).

Surprisingly, the ^{1}H NMR spectra of the investigated compounds **2**, **3**, and **7** are completely different concerning the NH signal in DMSO-d_6 and $CDCl_3$ at room temperature. Whereas the NH in DMSO-d_6 appears as a singlet in the range from 10.5 to 11 ppm, the NH signal in $CDCl_3$ gives a doublet with coupling constants ranging from 9 to 12.2 Hz, and additionally the signal is shifted to approximately 8.5 ppm (Table 1).

A five bond H–F coupling with such large coupling constants is unusual. Normally a proton–fluorine coupling via 5 bonds is less than 1 Hz. Therefore, the large coupling should be caused by coupling 'through space'. This unexpected behaviour was already observed in 2-fluoro-benzamides earlier. The solvent dependence

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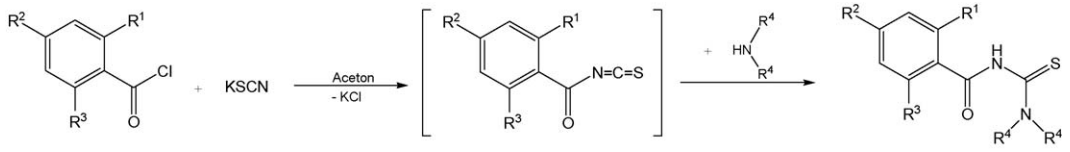


Nr.	R^1	R^2	R^3	R^4	
1	H	H	H	C_2H_5	[5]
2	F	H	H	C_2H_5	
3	F	F	H	C_2H_5	
4	F	H	F	C_2H_5	
5	H	F	H	C_2H_5	
6	F	H	H	$CH(CH_3)_2$	
7	F	H	H	$-CH_2-CH_2-O-CH_2-CH_2-$	
8	H	H	H	CH_2-CH_2-OH	[6]
9	F	H	H	CH_2-CH_2-OH	
10	H	F	H	CH_2-CH_2-OH	

Scheme 1.

Scheme 2.

Table 1
NH chemical shifts of **1–10** in DMSO-d_6 and $CDCl_3$.

Nr.	NH	
	DMSO-d_6	$CDCl_3$
1	10.52	8.44 s (br)
2	10.64	8.61 d (J = 10.6 Hz)
3	10.68	8.51 d (J = 9.0 Hz)
4	11.08	not observed (H-D exchange)
5	10.58	8.59 s (br)
6	8.45(br)	8.38 s (br)
7	10.95	8.84 d (J = 12.2 Hz)
8	10.88	(not enough soluble)
9	10.86	9.42 (br) (limited solubility)
10	10.86	(not enough soluble)

and the large 'through space' hydrogen–fluorine coupling were explained with transmission of nuclear spin information via hydrogen bonds [8]. This was supported by NMR investigations of ^{15}N labelled 2-fluoro-benzamide and the detection of the negative sign of the H···F and N···F coupling constant [9]. Only much later it was found that in intermolecular N···H···F systems such couplings reflect the strength of the NHF hydrogen bond [10]. Recently F···H–N interactions in solution were used to control the conformation in the synthesis of new foldamers [11].

Obviously, the weak intramolecular F···H–N interaction in $CDCl_3$ is replaced in DMSO-d_6 by formation of an intermolecular hydrogen bond from NH to the solvent. This was confirmed by NMR spectra of **5** and **9** in $CDCl_3$. As expected no F···H–N interaction was observed for the 4-fluorine substituted product **5** (NH as a broad singlet at 8.59 ppm). The NH of **9** appears as a broadened singlet which is shifted to 9.42 ppm. This means that already the introduction of polar hydroxy groups prevents the F···H short contact.

The F···N–H interaction in $CDCl_3$ could additionally be confirmed by ^{19}F NMR spectra and decoupling experiments. The ^{19}F signal of **7** in $CDCl_3$ shows a stronger coupling (−111.7 ppm; coupling with aromatic protons and NH) than in DMSO-d_6 (−113.9 ppm; only coupling with aromatic protons) (Fig. 1).

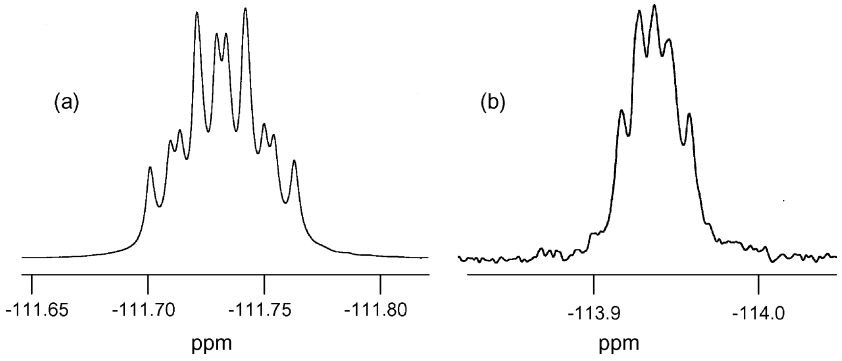


Fig. 1. ^{19}F NMR spectra of **7** in $CDCl_3$ (a) and DMSO-d_6 (b).

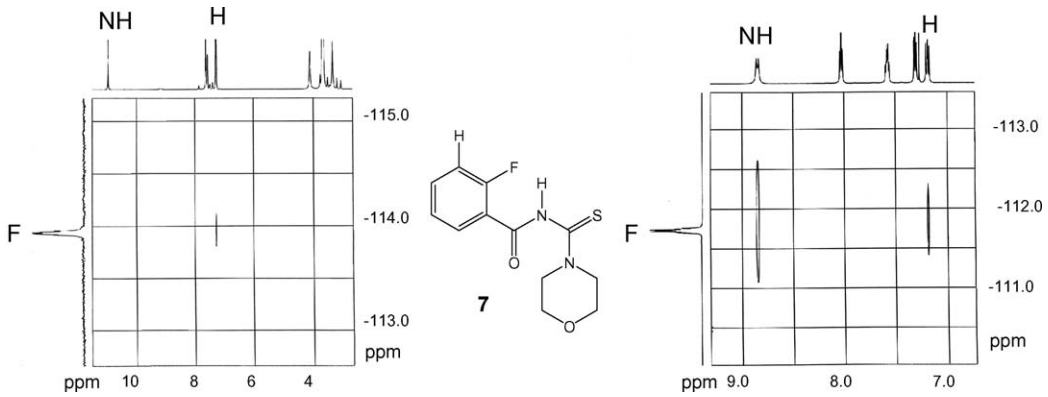


Fig. 2. $^{1}H,^{19}F$-HOESY spectra of **7** in DMSO-d_6 (left) and $CDCl_3$ (right).

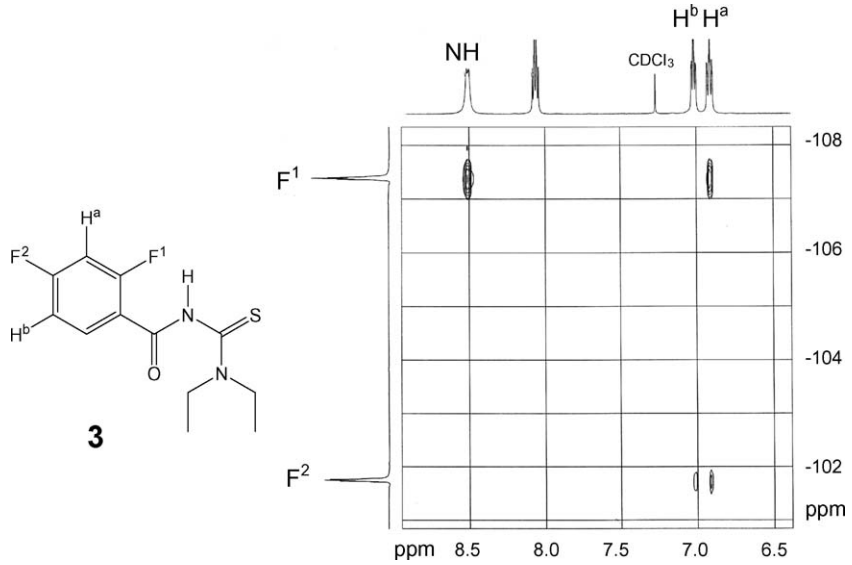
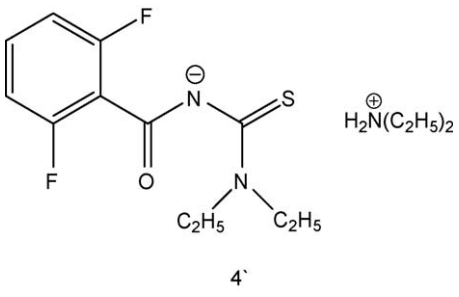


Fig. 3. $^{1}H,^{19}F$ HOESY spectrum of **3** in $CDCl_3$.

Proton decoupling leads to a simplification of the ^{19}F NMR signal. Vice versa, fluorine decoupling furnishes in the ^{1}H spectrum only a singlet for the NH proton.

Moreover, the measurement of two dimensional $^{1}H,^{19}F$ HOESY spectra (fluorine-proton correlation depending on their spatial distance) is a powerful tool for the detection of F···H–N short contacts in solution. E.g., while only one correlation cross peak between fluorine (−113.9 ppm) and the aromatic proton in 3-position of the phenyl substituent (7.29 ppm) was found for **7** in DMSO-d_6, two cross peaks were observed in $CDCl_3$. Here additionally a cross peak between fluorine (−111.7 ppm) and NH (8.84 ppm) appears (Fig. 2).

Hence, a short contact/weak hydrogen bond between fluorine and NH exits in $CDCl_3$ which is not the case in DMSO-d_6. This is due to a stronger intermolecular hydrogen bond formation from NH to the solvent (DMSO).



Scheme 3.

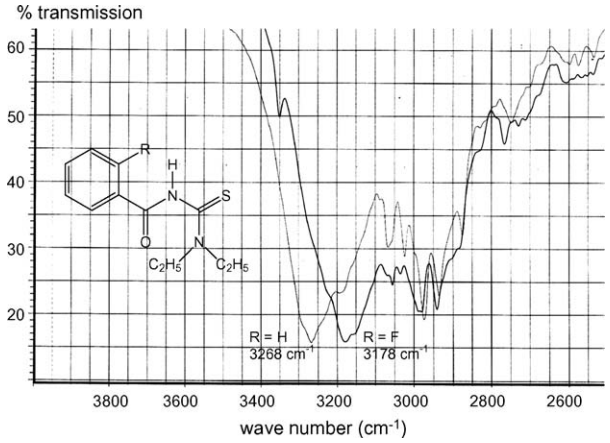


Fig. 4. NH signal in the IR spectrum of **1** and **2** in KBr.

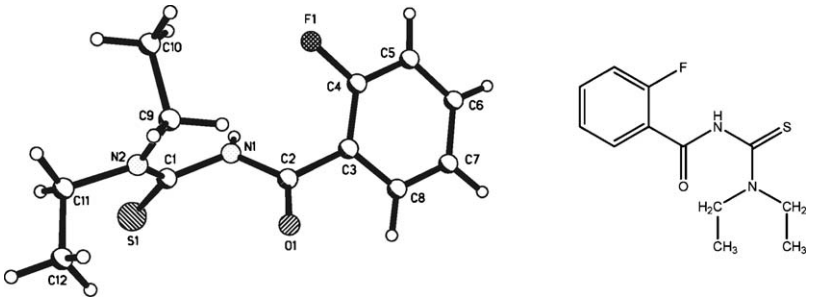


Fig. 5. Molecular structure of **2**.
Selected bond lengths (Å):
S1-C1 1.664(3), O1-C2 1.210(3), N1-C1 1.421(3), N1-C2 1.370(3), N2-C1 1.322(3), C2-C3 1.500(3), F1-C4 1.349(3).

Table 2
Bond lengths (Å) and angles (°) for possible intramolecular F···H–N hydrogen bridges/short contacts.

	2	4	6	7	10
N–H	0.84(3)	0.82(2)	0.80(2)	0.84(2)	0.87(2)
H···F	2.69(3)	2.83(2)	2.26(2)	2.42(2)	3.36(2)[#]
N···F	2.820(3)	3.037(2)	2.723(2)	2.696(2)	3.668(2)[#]
N–H···F	90(2)	97(2)	117(2)	100(2)	104(2)[#]
C3–C8/O1N1C2	46.3(1)	64.8(1)	16.2(2)	29.3(1)	24.5(2)

[#] Shortest intermolecular contact.

The usefulness of the HOESY method was also demonstrated with compound **3** which contains two fluorine atoms in 2- and 4-position of the phenyl ring, respectively. In the proton spectrum we observed three different signals for the aromatic protons (6.91, 7.02 and 8.04 ppm) and two signals in the fluorine spectrum (−107.4 and −101.8 ppm). The NH at 8.51 ppm furnished a doublet with a coupling constant of 9 Hz caused by interaction of F^1 and NH. This interaction was again detected in the 2D-HOESY spectrum (among another contact of F^1 to H^a). From the second fluorine atom F^2 only contacts to H^a and H^b were found (Fig. 3).

In further studies the 2,6-bis-fluorinated compound **4** was investigated. Nearly no absorption for the NH was observed in the $CDCl_3$ NMR spectrum of **4** because H-D exchange with the solvent occurs. Otherwise, in DMSO-d_6 the expected singlet appears at 11.08 ppm. In the fluorine spectra only one signal was found (DMSO-d_6: −114.4 ppm; $CDCl_3$: −111.7 ppm). As a consequence the introduction of the second fluorine in ortho-position prevents the F···H–N contact for electronic and steric reasons.

Remarkably, already the synthesis of **4** differs in comparison to the other compounds. The introduction of a second fluorine atom in ortho-position results in the preferred formation of diethyl ammonium salt **4′** (Scheme 3).

The IR spectra of the fluorine and non-fluorine substituted compounds are almost identical. However, a closer look at the NH absorption (e.g., in comparison of **1** and **2**) shows a significant red shift (90 cm^{-1}) of the non-fluorinated compound (Fig. 4). This phenomenon is well-known in IR spectroscopy and characteristic for hydrogen bond formation [12].

An evidence for the existence of hydrogen bonds/short contacts in solid state is the distance of the relevant atoms which should be less than the sum of the van der Waals radii. In case of H···F this would be a distance less than 2.70 Å. A scatter plot of potential hydrogen bonds summarising F···H–N angle versus F···H distance shows that at sp^2 carbons the distance is 2.2–2.4 Å in the most cases and the angle varies between 90° and 170°. The angle of intramolecular contacts is smaller (mainly between 100° and 120°) than that of intermolecular interactions (mainly 130–170°) [3].

X-ray structure determinations were performed with the fluorine substituted benzamides **2**, **4**, **6**, **7** and **10**. The molecular structures of these five compounds are shown in Figs. 5–9.

The parameters important for possible F···H bridges/short contacts are summarised in Table 2.

The distance F···H is much smaller than the sum of the van der Waals radii in **6** (2.26 Å) and **7** (2.42 Å), equals this sum in **2** (2.69 Å) and exceeds it in **4** (2.84 Å). In **10** intramolecular interactions between N1 and F1 are not possible. The F···H–N angles are in agreement with the formulated criteria for **6** and **7** and are slightly smaller for **2** and **4**.

In this respect the criteria for the formation of weak intramolecular interactions between C–F···H–N in the solid state [1,3,4] are fulfilled by **6** and **7**, possibly also by **2**. In **4** the distance F···H exceeds 2.70 Å considerably (2.83 Å) because the bis-fluorinated phenyl ring is strongly twisted against the plane O1N1C2 (64.8°). Hence, the introduction of the second fluorine in ortho-position also prevents the F···H–N contact in solid state for steric reasons.

Most remarkably, the introduction of hydroxy groups in the amine part of the molecule by using diethanol amine in the synthesis of **8–10** changes the stereochemistry from the E,Z′ configuration of **1–3** and **5–7** to a Z,Z′ configuration with formation of an intramolecular N–H···O hydrogen bond [6b,13].

Obviously, this intramolecular hydrogen bond formation dominates in comparison to the intramolecular F···H–N interaction possible for **9**. In **10** an intramolecular F···H–N bridge formation is not possible and no intermolecular F···H–N bridges were found in the crystal structure.

In spite of the possibly different behaviour in solution and in solid state the results of the X-ray determinations do not oppose the results of the NMR investigations and also give indication at H···F hydrogen bridges/short contacts in some of these compounds.

Unexpectedly, the hydroxyethyl substituted compound **8** can be oxidised easily to give an oxathiazine derivative **11** [14].

3. Conclusions

Fluorine takes more and more a leading part as a substituent in organic compounds and especially in biologically active substances. It is known that fluorine atoms form short contacts or weak hydrogen bonds in rare cases. We found with fluorine substituted benzamides a system which is very sensitive concerning hydrogen bond formation and F···H–N short contacts. The ability to measure these interactions by X-ray, NMR, and IR may be important in structure-activity investigations of fluorine substituted active compounds [15].

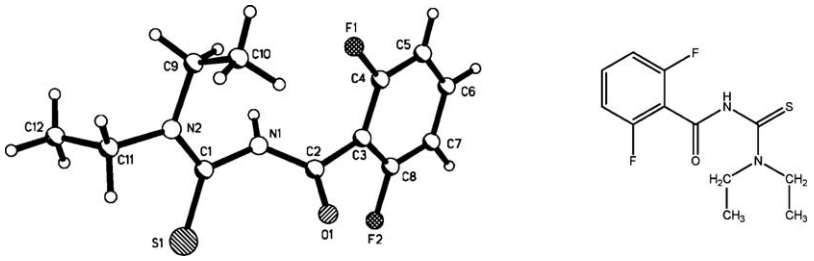


Fig. 6. Molecular structure of **4**.
Selected bond lengths (Å):
S1-C1 1.656(2), O1-C2 1.224(2), N1-C1 1.426(2), N1-C2 1.344(2), N2-C1 1.323(2), C2-C3 1.504(2), F1-C4 1.350(2), F2-C8 1.348(2).

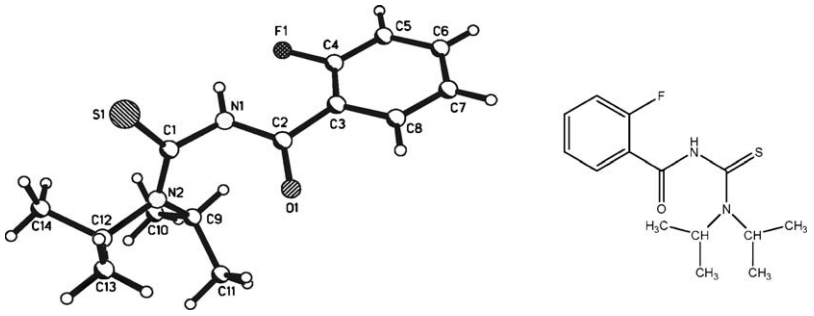


Fig. 7. Molecular structure of **6**.
Selected bond lengths (Å):
S1-C1 1.667(1), O1-C2 1.218(2), N1-C1 1.434(1), N1-C2 1.362(2), N2-C1 1.324(2), C2-C3 1.498(2), F1-C4 1.351(2).

4. Experimental

Melting points were determined on Boetius micro-melting-point apparatus and are corrected. NMR spectra were recorded with Varian Gemini 2000, Varian Mercury Plus 300, Varian Mercury Plus 400 and Bruker DRX-600 spectrometers. Residual solvent signals were used as internal chemical shift references for proton (DMSO-d_6: δ 2.50 ppm; $CDCl_3$: δ 7.26 ppm) and carbon (DMSO-d_6: δ 39.52 ppm; $CDCl_3$: δ 77.16 ppm), fluorine spectra were referenced to CCl_3F (δ 0 ppm). Mass spectra were measured on a VG ZAB-HSQ (VG Analytics) and HRMS spectra in positive mode on a FT-ICR-MS APEX II (Bruker Daltonics) spectrometer. IR spectra were recorded with an AVATAR 360 FT-IR spectrometer (Thermo Nicolet). Elemental analyses were performed on a Heraeus CHNO Rapid Analyzer.

The data for the crystal structure determinations were collected on a Bruker SMART CCD area-detector diffractometer with Mo Kα radiation (λ = 0.71073 Å) at temperature of 220 K. The intensities were corrected for Lorentz and polarization effects and for absorption using SADABS.

The structures were solved by direct methods and refined by least-squares on weighted F^2 values for all reflections. All non-hydrogen atoms were refined with anisotropic displacement parameters [16]. In **7** the atom F1 is disordered by bonding to C4 (91%) and C8 (9%).

The positions of most of the hydrogen atoms were taken from difference syntheses and refined with isotropic displacement parameters. Calculated hydrogen positions without refinement were only used in **2** (H at the diethyl groups) and in **7** (H at the disorder positions at C4 and C8).

CCDC-708959 (**2**), CCDC-708960 (**4**), CCDC-708961 (**6**), CCDC-708962 (**7**) and CCDC-708963 (**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

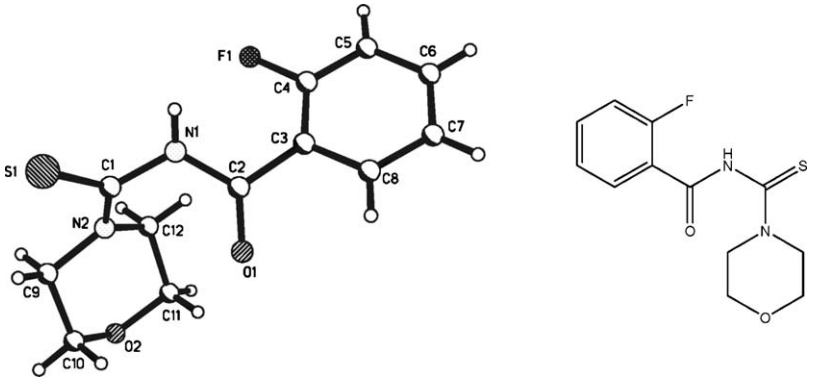


Fig. 8. Molecular structure of **7**.
Selected bond lengths (Å):
S1-C1 1.669(1), O1-C2 1.216(2), N1-C1 1.410(2), N1-C2 1.379(2), N2-C1 1.331(2), C2-C3 1.495(2), F1-C4 1.342(2).

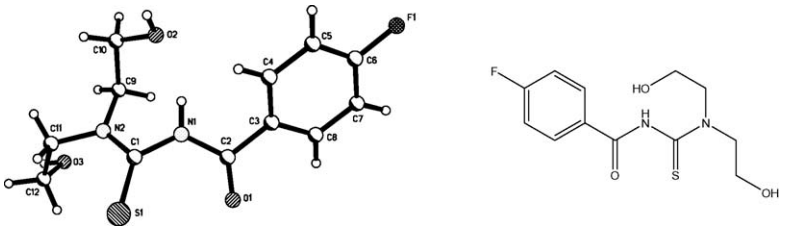


Fig. 9. Molecular structure of **10**.
Selected bond lengths (Å):
S1-C1 1.678(2), O1-C2 1.214(2), N1-C1 1.392(2), N1-C2 1.379(2), N2-C1 1.337(2), C2-C3 1.497(2), F1-C6 1.362(2).

4.1. General procedure for the synthesis of 1–10

A modified method of [17] has been used for the preparation of the benzamides:

To 0.05 mol KSCN in 100 ml of boiling dry acetone 0.05 mol of the corresponding benzoyl chloride were added dropwise. The mixture was kept at 50 °C for 2 h, and then 0.075 mol amine in a solution of hot acetone were added. After the reaction was completed the mixture was cooled to room temperature and stored in the refrigerator. The separated precipitate was collected and crystallized from acetone (**1**, **4′**, **6**, **7**, **9**, **10**), a mixture of acetone/ethanol 1:1 (**2**, **3**, **5**) or methanol (**8**). In case of **4** conc. HCl was added before storing in the refrigerator, and the product was crystallized from ethanol.

4.2. N-(Diethylcarbamothioyl)benzamide (1) [5]

Colorless crystals, mp 98–99 °C;

^{1}H NMR (200.14 MHz, $CDCl_3$): δ 1.31 (br, 6H, CH_3), 3.59 (br, 2H, CH_2), 3.99 (br, 2H, CH_2), 7.81 (2H, H-2,6-Phenyl), 7.40–7.60 (3H, H-3,4,5-Phenyl), 8.44 (br, 1H, NH);

(600.13 MHz, DMSO-d_6): δ 1.18 (t, 3H, CH_3), 1.25 (t, 3H, CH_3), 3.52 (q, 2H, CH_2), 3.95 (q, 2H, CH_2), 7.50 (t, 2H, H-3,5-Phenyl) 7.59 (t, 1H, H-4-Phenyl), 7.92 (d, 2H, H-2,6-Phenyl), 10.52 (s, 1H, NH);

^{13}C (50.33 MHz, $CDCl_3$): δ 11.60 (CH_3), 13.33 (CH_3), 47.86 (2xCH_2), 128.07 (C-3,5-Phenyl), 129.05 (C-2,6-Phenyl), 132.87 (C-1-Phenyl), 132.97 (C-4-Phenyl), 163.84 (CO), 179.45 (CS).

4.3. N-(Diethylcarbamothioyl)-2-fluorobenzamide (2)

Colorless crystals, mp 93–94 °C;

^{1}H NMR (200.14 MHz, $CDCl_3$): δ 1.26 (br, 6H, CH_3), 3.57 (br, 2H, CH_2), 3.94 (br, 2H, CH_2), 7.10 (m, 1H, H-3-Phenyl), 7.21 (m, 1H, H-5-Phenyl), 7.45 (m, 1H, H-4-Phenyl), 7.92 (m, 1H, H-6-Phenyl), 8.61 (d, 1H, NH, J = 10.6 Hz);

(200.14 MHz, DMSO-d_6): δ 1.25 (br, 3H, CH_3), 1.32 (br, 3H, CH_3), 3.63 (br, 2H, CH_2), 4.03 (br, 2H, CH_2), 7.22–7.34 (m, 2H, Phenyl), 7.51–7.64 (m, 2H, Phenyl), 10.64 (s, 1H, NH);

^{13}C (50.33 MHz, $CDCl_3$): δ 11.52 (CH_3), 13.35 (CH_3), 47.91 (2xCH_2), 116.51 (d, $^2J_{C,F}$ = 24.0 Hz, C-3-Phenyl), 120.09 (d, $^2J_{C,F}$ = 11.1 Hz, C-1-Phenyl), 125.16 (d, $^4J_{C,F}$ = 3.4 Hz, C-5-Phenyl), 132.33 (d, $^3J_{C,F}$ = 1.5 Hz, C-6-Phenyl), 134.81 (d, $^3J_{C,F}$ = 9.5 Hz, C-4-Phenyl), 159.87 (d, $^3J_{C,F}$ = 3.4 Hz, CO), 160.68 (d, $^1J_{C,F}$ = 249.9 Hz, C-2-Phenyl), 178.50 (CS);

^{19}F NMR (188.32 MHz, $CDCl_3$): δ −112.0;

HRMS (ESI) m/z calcd. for $C_{12}H_{15}FN_2OS$: 255.0962 $(M+H)^+$, found: 255.0961.

4.4. N-(Diethylcarbamothioyl)-2,4-difluorobenzamide (3)

Colorless crystals, mp 71–72 °C;

^{1}H NMR (300.06 MHz, $CDCl_3$): δ 1.32 (br, 6H, CH_3), 3.60 (br, 2H, CH_2), 4.00 (br, 2H, CH_2), 6.91 (m, 1H, H-3-Phenyl), 7.02 (m, 1H, H-5-Phenyl), 8.04 (m, 1H, H-6-Phenyl), 8.51 (d, 1H, NH, J = 9.0 Hz);

(400.02 MHz, DMSO-d_6): δ 1.21 (br, 6H, CH_3), 3.58 (q, 2H, CH_2), 3.91 (q, 2H, CH_2), 7.19 (m, 1H, H-3-Phenyl), 7.36 (m, 1H, H-5-Phenyl), 7.68 (m, 1H, H-6-Phenyl), 10.68 (s, 1H, NH);

^{13}C (75.45 MHz, $CDCl_3$): δ 11.47 (CH_3), 13.33 (CH_3), 47.84 (CH_2), 48.03 (CH_2), 104.80 (dd, $^2J_{C,F}$ = 28.1 Hz, $^2J_{C,F}$ = 25.8 Hz, C-3-Phenyl), 112.92 (dd, $^2J_{C,F}$ = 21.2 Hz, $^4J_{C,F}$ = 3.4 Hz, C-5-Phenyl), 116.68 (dd,, $^2J_{C,F}$ = 11.5 Hz, $^4J_{C,F}$ = 4.0 Hz, C-1-Phenyl), 134.24 (dd, $^3J_{C,F}$ = 10.3 Hz, $^3J_{C,F}$ = 3.4 Hz, C-6-Phenyl), 159.07 (d, $^3J_{C,F}$ = 4.0 Hz, CO), 161.19 (d, $^1J_{C,F}$ = 251.8 Hz, $^3J_{C,F}$ = 12.6 Hz, C-2-Phenyl), 165.74 (d, $^1J_{C,F}$ = 257.3 Hz, $^3J_{C,F}$ = 12.6 Hz, C-4-Phenyl), 178.38 (CS);

^{19}F NMR (282.34 MHz, $CDCl_3$): δ −101.8, −107.2;

HRMS (ESI) m/z calcd. for $C_{12}H_{14}F_2N_2OS$: 273.0868 $(M+H)^+$, found 273.0864.

4.5. N-(Diethylcarbamothioyl)-2,6-difluorobenzamide (4)

^{1}H NMR (400.02 MHz, $CDCl_3$): δ 1.33 (t, 6H, CH_3), 3.67 (br, 2H, CH_2), 3.96 (br, 2H, CH_2), 6.97 (t, 2H, H-3,5-Phenyl), 7.42 (m, 1H, H-4-Phenyl);

(400.02 MHz, DMSO-d_6): δ 1.21 (t, 6H, CH_3), 3.62 (q, 2H, CH_2), 3.90 (q, 2H, CH_2), 7.18 (t, 2H, H-3,5-Phenyl) 7.55 (m, 1H, H-4-Phenyl), 11.08 (s, 1H, NH);

Anal Calc. for $C_{12}H_{14}F_2N_2OS$: C, 52.9; H, 5.1; N, 10.3; S 11.8. Found: C, 53.0; H, 5.2; N, 10.0; S, 12.0.

Diethyl ammonium salt **4′**,

$C_{16}H_{25}F_2N_3OS$ (345.46); mp108–110 °C;

^{1}H NMR (200.14 MHz, DMSO-d_6): δ 1.13 (t, 6H, CH_3-salt), 1.21 (br, 3H, CH_3), 1.23 (br, 3H, CH_3), 2.58 (q, 4H, NCH_2-salt), 3.64 (br, 2H, CH_2), 3.91 (br, 2H, CH_2), 6.59 (br, 2H, NH_2-salt), 6.88 (t, 2H, H-3,5-Phenyl), 7.25 (m, 1H, H-4-Phenyl);

^{13}C (50.33 MHz, $CDCl_3$): δ 11.90 (CH_3), 12.81 (CH_3-salt), 13.56 (CH_3), 43.69 (NCH_2-salt), 45.71 (CH_2), 46.77 (CH_2), 111.76 (m, AXX', C-3,5-Phenyl), 117.97 (t, $^2J_{C,F}$ = 21.9 Hz, C-1-Phenyl), 130.22 (t, $^3J_{C,F}$ = 9.9 Hz, C-4-Phenyl), 157.81 (br, CO), 159.86 (dd, $^1J_{C,F}$ = 249.8 Hz, $^3J_{C,F}$ = 8.0 Hz, C-2,6-Phenyl), 185.99 (CS);

^{19}F NMR (376.39 MHz, $CDCl_3$): δ −111.7, (DMSO-d6): δ −114.4.

Anal Calc. for $C_{16}H_{25}F_2N_3OS$: C, 55.6; H, 7.3; N, 12.2; S 9.3. Found: C, 55.6; H, 7.1; N, 11.9; S, 8.8.

4.6. N-(Diethylcarbamothioyl)-4-fluorobenzamide (5)

Colorless crystals, mp 133–135 °C;

^{1}H NMR (200.14 MHz, $CDCl_3$): δ 1.31 (br, 6H, CH_3), 3.59 (br, 2H, CH_2), 3.99 (br, 2H, CH_2), 7.11 (t, 2H, H-3,5-Phenyl), 7.84 (t, 2H, H-2,6-Phenyl), 8.59 (br, 1H, NH);

(300.06 MHz, DMSO-d_6): δ 1.20 (t, 3H, CH_3), 1.22 (t, 3H, CH_3), 3.51 (q, 2H, CH_2), 3.94 (q, 2H, CH_2), 7.33 (t, 2H, Phenyl), 8.00 (dd, 2H, Phenyl), 10.58 (s, 1H, NH);

^{13}C (50.33 MHz, $CDCl_3$): δ 11.56 (CH_3), 13.37 (CH_3), 47.73 (CH_2), 48.00 (CH_2), 116.01 (d, $^2J_{C,F}$ = 22.2 Hz, C-3,5-Phenyl), 128.84 (d, $^4J_{C,F}$ = 2.5 Hz, C-1-Phenyl), 130.59 (d, $^3J_{C,F}$ = 9.5 Hz, C-2,6-Phenyl), 163.01 (CO), 165.59 (d, $^1J_{C,F}$ = 254.5 Hz, C-4-Phenyl), 179.36 (CS);

^{19}F NMR (188.32 MHz, $CDCl_3$): δ −105.9;

HRMS (ESI) *m*/*z* calcd. for $C_{12}H_{15}FN_2OS$: 255.0962 $(M+H)^+$, found 255.0959.

4.7. N-(Diisopropylcarbamothioyl)-2-fluorobenzamide (6)

Colorless crystals, mp 100–101 °C;

^{1}H NMR (200.14 MHz, $CDCl_3$): δ 1.47 (br, 12H, CH_3), 4.37 (br, 2H, CH), 7.14 (m, 1H, H-3-Phenyl), 7.26 (m, 1H, H-5-Phenyl), 7.48 (m, 1H, H-4-Phenyl), 8.03 (m, 1H, H-6-Phenyl), 8.38 (br, 1H, NH);

(300.05 MHz, DMSO-d_6): δ 1.20 (d, 12H, CH_3), 3.32 (sep, 2H, CH), 7.04 (m, 1H, H-3-Phenyl), 7.13 (m, 1H, H-5-Phenyl), 7.39 (m, 1H, H-4-Phenyl), 7.84 (m, 1H, H-6-Phenyl), 8.45 (br, 1H, NH);

^{13}C (50.33 MHz, $CDCl_3$): δ 19.96 (br, CH_3), 52.21 (br, CH), 116.40 (d, $^2J_{C,F}$ = 24.4 Hz, C-3-Phenyl), 120.41 (d, $^2J_{C,F}$ = 11.1 Hz, C-1-Phenyl), 125.07 (d, $^4J_{C,F}$ = 3.4 Hz, C-5-Phenyl), 132.335 (d, $^3J_{C,F}$ = 1.5 Hz, C-6-Phenyl), 134.56 (d, $^3J_{C,F}$ = 9.5 Hz, C-4-Phenyl), 160.64 (br, CO), 160.66 (d, $^1J_{C,F}$ = 249.5 Hz, C-2-Phenyl), 177.76 (br, CS);

^{19}F NMR (564.62 MHz, $CDCl_3$): δ −112.1;

MS: *m*/*z* 282 $[M]^+$ (44), 123 (100);

Anal. Calc for $C_{14}H_{19}FN_2OS$: C, 59.6; H, 6.8; N, 9.9; S 11.4. Found: C, 59.2; H, 6.7; N, 9.9; S, 11.4.

4.8. 2-Fluoro-N-(morpholine-4-carbamothioyl)benzamide (7)

Colorless crystals, mp 141–142 °C;

^{1}H NMR (600.13 MHz, $CDCl_3$): δ 3.68 (br, 2H, NCH_2), 3.84 (br, 2H, OCH_2), 3.84 (br, 2H, NCH_2), 4.23 (br, 2H, OCH_2), 7.18 (m, 1H, H-3-Phenyl), 7.29 (m, 1H, H-5-Phenyl), 7.56 (m, 1H, H-4-Phenyl), 8.02 (m, 1H, H-6-Phenyl), 8.84 (d, 1H, NH, *J* = 12.2 Hz);

(600.13 MHz, H,H-COSY, HMQC, HMBC, DMSO-d_6): δ 3.67 (br, 2H, NCH_2), 3.68 (br, 2H, OCH_2), 3.71 (br, 2H, OCH_2), 4.13 (br, 2H, OCH_2), 7.29 (m, 1H, H-3-Phenyl), 7.30 (m, 1H, H-5-Phenyl), 7.58 (m, 1H, H-4-Phenyl), 7.64 (m, 1H, H-6-Phenyl), 10.95 (s, 1H, NH);

^{13}C (150.90 MHz, HMQC, HMBC, DMSO-d_6): δ 50.28 (br, NCH_2), 51.07 (br, NCH_2), 65.62 (2xOCH_2), 116.16 (d, $^2J_{C,F}$ = 21.8 Hz, C-3-Phenyl), 122.99 (d, $^2J_{C,F}$ = 13.7 Hz, C-1-Phenyl), 124.42 (d, $^4J_{C,F}$ = 3.8 Hz, C-5-Phenyl), 130.24 (d, $^3J_{C,F}$ = 2.3 Hz, C-6-Phenyl), 133.41 (d, $^3J_{C,F}$ = 8.4 Hz, C-4-Phenyl), 159.37 (d, $^1J_{C,F}$ = 251.0 Hz, C-2-Phenyl), 161.82 (d, $^3J_{C,F}$ = 1.1 Hz, CO), 178.90 (CS);

^{19}F NMR (564.62 MHz, $CDCl_3$): δ −111.7, (DMSO-d_6): δ −113.9;

MS: *m*/*z* 268 $[M]^+$ (33), 123 (100);

Anal. Calc for $C_{12}H_{13}FN_2O_2S$: C, 53.7; H, 4.9; N, 10.4; S 12.0. Found: C, 53.7; H, 5.3; N, 10.3; S, 12.1.

4.9. N-[Bis(2-hydroxyethyl)carbamothioyl]benzamide (8) [6]

Colorless crystals, mp 118–120 °C;

^{1}H NMR (600.13 MHz, H,H-COSY, HMQC, HMBC, DMSO-d_6): δ 3.70 (br, 2H, OCH_2), 3.72 (br, 2H, NCH_2), 3.77 (br, 2H, OCH_2), 3.99 (br, 2H, NCH_2), 4.87 (t, 1H, OH), 5.65 (br, 1H, OH), 7.51 (t, 2H, H-3,5-Phenyl), 7.60 (t, 1H, H-4-Phenyl), 7.86 (d, 2H, H-2,6-Phenyl), 10.88 (s, 1H, NH);

^{13}C (150.90 MHz, HMQC, HMBC, DMSO-d_6): δ 54.98 (NCH_2), 55.09 (NCH_2), 57.58 (OCH_2), 59.23 (OCH_2), 127.86 (C-2,6-Phenyl), 128.60 (C-3,5-Phenyl), 132.36 (C-4-Phenyl), 133.52 (C-1-Phenyl), 164.53 (CO), 181.15 (CS).

4.10. N-[Bis(2-hydroxyethyl)carbamothioyl]-2-fluorobenzamide (9)

Colorless crystals, mp 110–112 °C;

^{1}H NMR (600.13 MHz, H,H-COSY, HMQC, HMBC, DMSO-d_6): δ 3.71 (m, 2H, OCH_2), 3.74 (m, 2H, OCH_2), 3.79 (t, 2H, NCH_2), 3.94 (t, 2H, NCH_2), 4.89 (t, 1H, OH), 5.71 (br, 1H, OH), 7.28 (m, 1H, H-3-Phenyl), 7.29 (m, 1H, H-5-Phenyl), 7.56 (m, 1H, H-4-Phenyl), 7.62 (m, 1H, H-6-Phenyl), 10.86 (s, 1H, NH);

(600.13 MHz, $CDCl_3$): δ 3.48 (br, 1H, OH), 3.76 (br, 1H, OH), 3.88–3.94 (br, 4H, NCH_2/OCH_2), 4.08–4.14 (br, 4H, NCH_2/OCH_2), 7.17 (m, 1H, H-3-Phenyl), 7.28 (m, 1H, H-5-Phenyl), 7.55 (m, 1H, H-4-Phenyl), 7.98 (m, 1H, H-6-Phenyl), 9.42 (br, 1H, NH);

^{13}C (150.90 MHz, HMQC, HMBC, DMSO-d_6): δ 54.92 (NCH_2), 55.02 (NCH_2), 57.62 (OCH_2), 59.22 (OCH_2), 116.19 (d, $^2J_{C,F}$ = 21.7 Hz, C-3-Phenyl), 123.47 (d, $^2J_{C,F}$ = 13.4 Hz, C-1-Phenyl), 124.58 (d, $^4J_{C,F}$ = 3.4 Hz, C-5-Phenyl), 130.26 (d, $^3J_{C,F}$ = 2.7 Hz, C-6-Phenyl), 133.33 (d, $^3J_{C,F}$ = 8.8 Hz, C-4-Phenyl), 163.02 (d, $^3J_{C,F}$ = 1.3 Hz, CO), 159.24 (d, $^1J_{C,F}$ = 250.3 Hz, C-2-Phenyl), 180.44 (CS);

^{19}F NMR (564.62 MHz, DMSO-d_6): δ −112.3;

MS: *m*/*z* 286 $[M]^+$ (2), 123 (100);

Anal. Calc for $C_{12}H_{15}FN_2O_3S$: C, 50.3; H, 5.3; N, 9.8; S 11.2. Found: C, 50.1; H, 5.7; N, 9.7; S, 11.6.

4.11. N-[Bis(2-hydroxyethyl)carbamothioyl]-4-fluorobenzamide (10)

Colorless crystals, mp 154–156 °C;

^{1}H NMR (600.13 MHz, H,H-COSY, HMQC, HMBC, DMSO-d_6): δ 3.69 (br, 2H, OCH_2), 3.71 (br, 2H, NCH_2), 3.76 (m, 2H, OCH_2), 3.99 (t, 2H, NCH_2), 4.85 (t, 1H, OH), 5.56 (br, 1H, OH), 7.33 (m, 2H, H-3,5-Phenyl), 7.93 (m, 2H, H-2,6-Phenyl), 10.86 (s, 1H, NH);

^{13}C (150.90 MHz, HMQC, HMBC, DMSO-d_6): δ 55.05 (NCH_2), 55.09 (NCH_2), 57.51 (OCH_2), 59.17 (OCH_2), 115.57 (d, $^2J_{C,F}$ = 22.1 Hz, C-3,5-Phenyl), 130.01 (d, $^4J_{C,F}$ = 3.1 Hz, C-1-Phenyl), 130.70 (d, $^3J_{C,F}$ = 9.5 Hz, C-2,6-Phenyl), 163.50 (CO), 164.47 (d, $^1J_{C,F}$ = 250.3 Hz, C-4-Phenyl), 181.09 (CS);

^{19}F NMR (564.62 MHz, DMSO-d_6): δ −108.0;

MS: *m*/*z* 286 $[M]^+$ (24), 154 (100);

Anal. Calc for $C_{12}H_{15}FN_2O_3S$: C, 50.3; H, 5.3; N, 9.8; S 11.2. Found: C, 50.3; H, 5.4; N, 9.4; S, 11.4.

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