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Synthesis of 1-aroyl(1-arylsulfonyl)-4-*bis*(trifluoromethyl)alkyl semicarbazides as potential physiologically active compounds

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ABSTRACT

1,1-*Bis*(trifluoromethyl)alkyl isocyanates obtained from perfluoroisobutene (PFIB) react with aroyl(arylsulfonyl)hydrazines. Twenty eight prospective biologically active polyfluorinated 1,4-substituted semicarbazides were synthesized. The structure of each new product was confirmed by analytical and spectroscopic methods. The Lipinski's and Gelovani's parameters were then calculated. Two adjustments to the Lipinski rules of five are suggested for fluorinated drug candidates.

1. Introduction

The current communication is an extension of our publications united by a common idea of developing new physiologically active fluorinated compounds from perfluoroisobutene (**1**), a toxic by-product of tetrafluoroethene and hexafluoropropene manufacturing [1,2]. Our work covering the development of new synthetic methods for preparing *mono*-, *bis*- and *tris*-trifluoromethyl(alkyl)-containing compounds and their precursors has spanned nearly 20 years [3–13]. Among these methods is the preparative syntheses of *bis*(trifluoromethyl)methyl-, ethyl- (**2**) or propyl- (**3**) isocyanates (Scheme 1 [3,6]), which are precursors of polyfluorinated substituted ureas, carbamates and other derivatives [3,6].

Fluorinated organic molecules are known to perform a wide range of biological functions [14–24] and fluorinated agents have become a focus in the development of new therapies for cancer and other diseases. In fact, approximately 20% of all currently approved drugs contain at least one fluorine atom [21,25]. Fluorine can have direct effects on the drug binding to the target site in the body, as it is able to form strong interactions with hydrogen bond donors and lipophilic sidechains, including aromatic groups [20,22,23]. The trifluoromethyl group is one of the most lipophilic functional groups known. Its electronegative nature also has dramatic effects on the drug molecule's electronic character and adds more bulk than a normal methyl group [26,27]. Our recent studies suggest that the anticancer properties of several polyfluoroalkyl-substituted ureas are due to the presence of *bis*(trifluoromethyl)ethyl or -propyl groups [3–5]. Ureas are more resistant to enzymatic hydrolytic cleavage than amides. This fact makes substituted ureas promising drug candidates [28,29]. That is why we have recently focused on the synthesis of new fluoro-substituted compounds containing the moiety –N–C(O)–N– [3–6]. Recently it was reported that trifluoromethyl groups bring anticancer activity to substituted ureas [30].

It has long been known that hydrazides are biologically active compounds. For example isoniazid (isonicotinic acid hydrazide, INH) [31] has been used for more than 50 years as the most effective anti-tuberculous drug. Many semicarbazide compounds containing sulfonyl moieties were found to be enzyme inhibitors [32–34], showing antibacterial [35,36] and antiviral activity [37,38]. In addition, several 1,4-disubstituted (non-fluorinated) semicarbazides have demonstrated anticancer activity [39–49].

Here we present the synthesis of novel compounds which combine the above-mentioned moieties in a single structure.

2. Results and discussion

This report presents the preparation of 1-aroyl(1-arylsulfonyl)-4-[1,1-*bis*(trifluoromethyl)alkyl] semicarbazides which, as single structures or as fragments, may be biologically active with anticancer activity or other cellular targets.

We obtained isocyanates **2**, **3** from isobutene **1** as described in our previous publications [3,6] (Scheme 1). The preparation of

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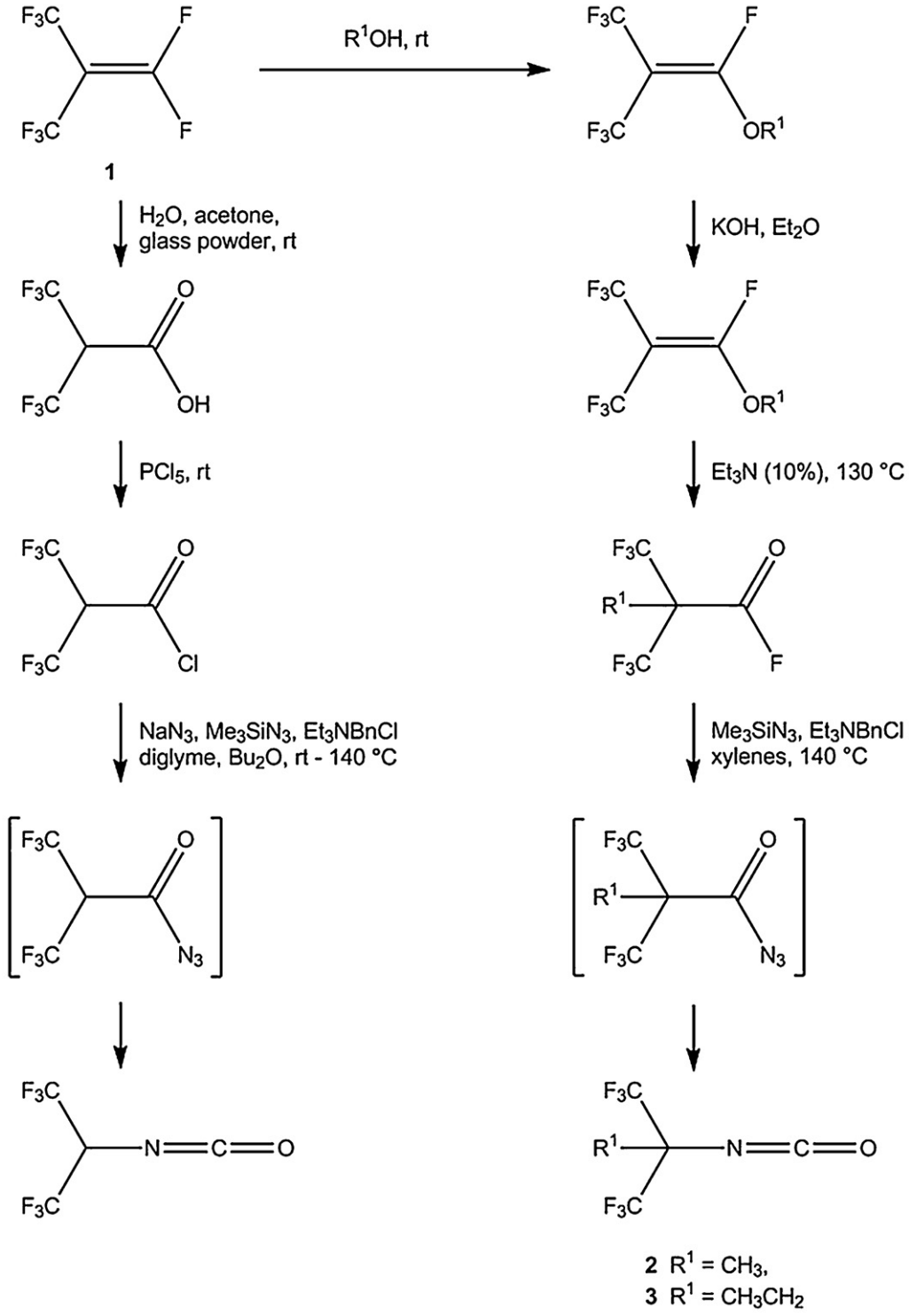
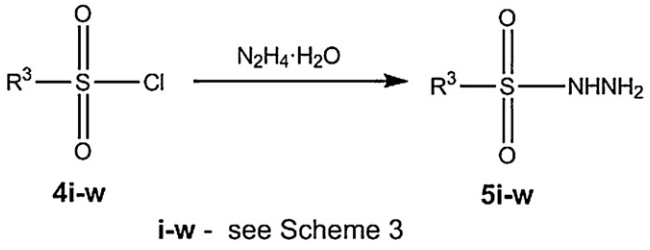


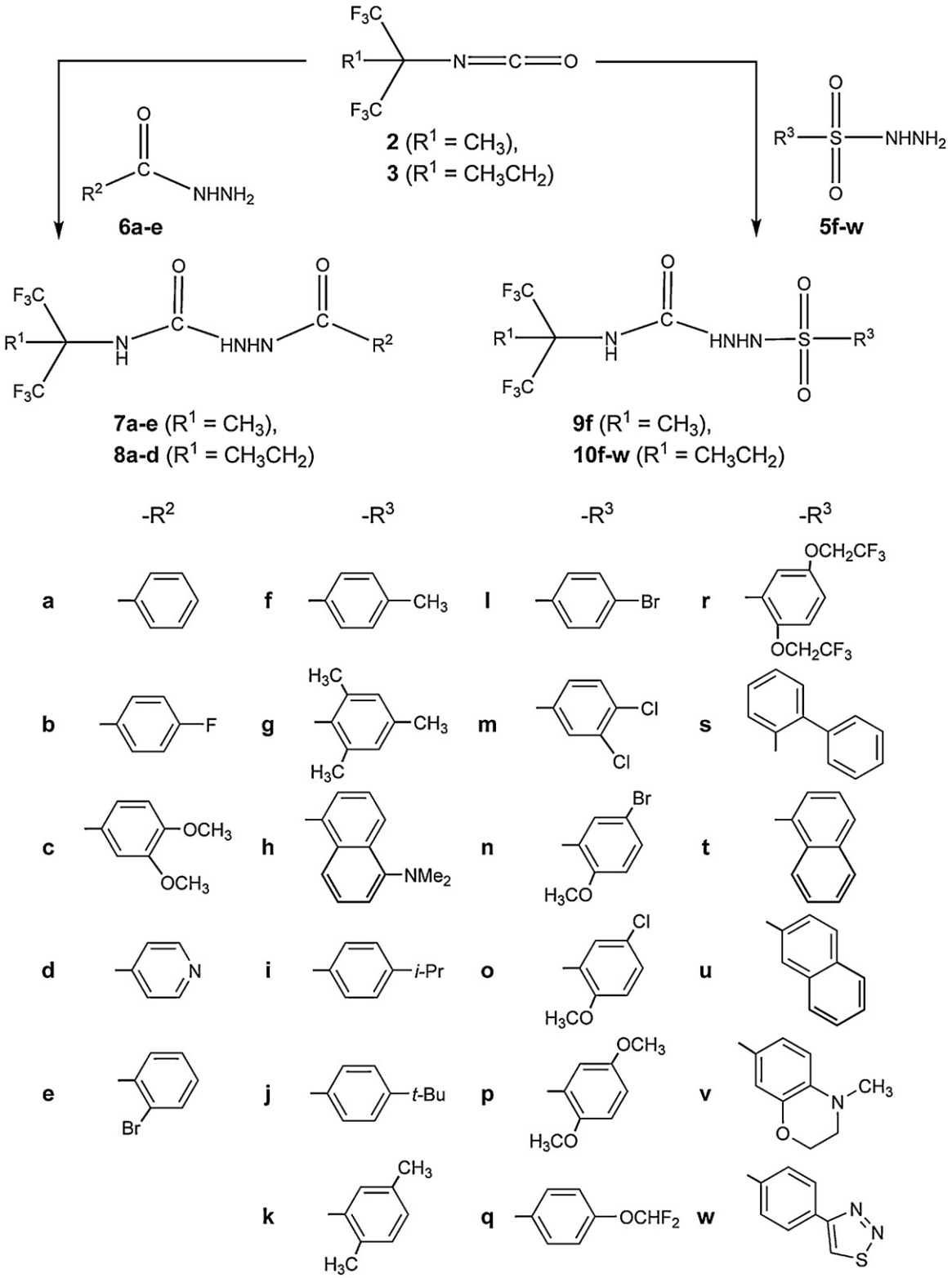
Scheme 1. Preparation of *bis*(trifluoromethyl)alkyl isocyanates from perfluoroisobutene **1**.

novel arylsulfonehydrazides **5i**–**w** is shown in Scheme 2. All these novel hydrazides are white crystalline substances. The yields are from moderate to high, namely: **5v**, **k** – 60–67%; **5q**, **p** – 75–78%; **5l**, **w**, **i** – 84–89%; and **5o**, **t**, **r**, **h**, **j**, **s** – 90–99%. Scheme 3 represents synthesis of 1-aroyl-4-[1,1-*bis*(trifluoromethyl)alkyl] semicarbazides **7a**–**e**, **8a**–**d** and 1-arylsulfonyl-4-[1,1-*bis*(trifluoromethyl)alkyl] semicarbazides **9f**, **10f**–**w**.

All 28 synthesized polyfluorinated compounds **7a**–**e**, **8a**–**d** and **9f**, **10f**–**w** are white crystals, stable at rt for more than 1 year without noticeable changes. 1-Aroyl-substitudes semicarbazides



Scheme 2. Synthesis of arylsulfonehydrazides **5i**–**w**.



Scheme 3. Synthesis of 1-aroyl-4-*bis*(trifluoromethyl)alkyl semicarbazides **7a**–**e**, **8a**–**d** and 1-arylsylfonyl-4-*bis*(trifluoromethyl)alkyl semicarbazides **9f**, **10f**–**w**.

were obtained with high yields: **7b**, **e** – 75–78%; **8b**, **c**, **7c** – 83–85%; and **7d**, **8d**, **7a**, **8a** – 90–98%. Yields of 1-arylsulfonyl-substitited semicarbazides differ from relatively low to high: **10k**, **l**, **j** – 31–40%; **10q**, **v**, **w**, **r** – 54–57%; **10j**, **i**, **m**, **u** – 60–67%; **10t**, **n**, **s**, **o** – 73–75%; and **10f**, **9f** – 95–96%.

Lipinski's rule of five can be used to predict the "drug-likeness" of potential molecular targets [50,51]. This rule defines ranges for various molecular parameters including MW, number of H-bond donors and acceptors, and hydrophobicity in order to maximize the likelihood that compounds have acceptable absorption, distribution, metabolism and excretion (ADME) properties. The calculated parameters for the new potential drug candidates (Table 1) are in agreement with the Lipinski rules of five [50,51] (MW $\leq$ 500; CLogP $\leq$ 5; number of H-bond donors $\leq$ 5; number of

Table 1
Properties of the compounds **7a–e**, **8a–d** and **9f**, **10f–w** calculated with ChemBioDraw Ultra, v.13. The Lipinski's and Gelovani's parameters.

Compound	MW	CLogP	H-bond donor	H-bond acceptor	Lipinski score of 4	MR (cm^3/mol)	Molecular formula (number of atoms)	PSA ($Å^2$)
7a	343.23	1.748	3	8	4	66.41	$C_{12}H_{11}F_6N_3O_2$ (34)	70.23
7b	361.22	1.891	3	9	4	66.82	$C_{12}H_{10}F_7N_3O_2$ (34)	70.23
7c	403.28	1.406	3	10	4	80.91	$C_{14}H_{15}F_6N_3O_4$ (42)	88.69
7d	344.22	0.251	3	9	4	64.88	$C_{11}H_{10}F_6N_4O_2$ (33)	82.59
7e	422.13	2.611	3	8	4	74.1	$C_{12}H_{10}BrF_6N_3O_2$ (34)	70.23
8a	357.26	2.277	3	8	4	71.01	$C_{13}H_{13}F_6N_3O_2$ (37)	70.23
8b	375.25	2.42	3	9	4	71.41	$C_{13}H_{12}F_7N_3O_2$ (37)	70.23
8c	417.31	1.935	3	10	4	85.51	$C_{15}H_{17}F_6N_3O_4$ (45)	88.69
8d	358.24	0.78	3	9	4	69.48	$C_{12}H_{12}F_6N_4O_2$ (36)	82.59
9f	393.30	2.069	3	9	4	75.787	$C_{12}H_{13}F_6N_3O_3S$ (38)	87.3
10f	407.33	2.598	3	9	4	80.425	$C_{13}H_{15}F_6N_3O_3S$ (41)	87.3
10g	435.39	3.596	3	9	4	89.701	$C_{15}H_{19}F_6N_3O_3S$ (47)	87.3
10h	486.43	3.438	3	10	4	105.63	$C_{18}H_{20}F_6N_4O_3S$ (52)	90.54
10i	435.39	3.526	3	9	4	89.701	$C_{15}H_{19}F_6N_3O_3S$ (47)	87.3
10j	449.41	3.925	3	9	4	94.339	$C_{16}H_{21}F_6N_3O_3S$ (50)	87.3
10k	421.36	3.097	3	9	4	85.063	$C_{14}H_{17}F_6N_3O_3S$ (44)	87.3
10l	472.20	2.962	3	9	4	85.557	$C_{12}H_{12}BrF_6N_3O_3S$ (38)	87.3
10m	462.19	3.405	3	9	3	85.615	$C_{12}H_{11}Cl_2F_6N_3O_3S$ (38)	87.3
10n	457.77	2.871	3	10	3	86.87	$C_{13}H_{14}ClF_6N_3O_4S$ (42)	96.53
10o	502.23	3.021	3	10	3	89.726	$C_{13}H_{14}BrF_6N_3O_4S$ (42)	96.53
10p	453.36	2.107	3	11	3	88.125	$C_{14}H_{17}F_6N_3O_5S$ (46)	105.76
10q	459.31	2.464	3	12	3	82.266	$C_{13}H_{13}F_8N_3O_4S$ (42)	96.53
10r	589.35	3.693	3	17	2	98.331	$C_{16}H_{15}F_{12}N_3O_5S$ (52)	105.76
10s	469.40	3.987	3	9	3	100.899	$C_{18}H_{17}F_6N_3O_3S$ (48)	87.3
10t	443.36	3.273	3	9	3	92.667	$C_{16}H_{15}F_6N_3O_3S$ (44)	87.3
10u	443.36	3.273	3	9	3	92.667	$C_{16}H_{15}F_6N_3O_3S$ (44)	87.3
10v	464.38	2.3227	3	11	3	93.145	$C_{15}H_{18}F_6N_4O_4S$ (48)	99.77
10w	477.40	1.879	3	11	3	94.768	$C_{14}H_{13}F_6N_5O_3S_2$ (43)	112.02

H-bond acceptors $\leq$ 10). The Lipinski rule states that, in general, an orally active drug has no more than one violation of the above criteria. Only one compound **10r** violates 2 Lipinski rules (score of 4, Table 1), although the applicability of these rules to polyfluorinated drug candidates, in our humble opinion, is questionable. At least 2 corrections/adjustments have to apply for polyfluorinated and especially trifluoromethyl-containing small molecules. First, the rule MW $\leq$ 500 dramatically reduces the number of polyfluorinated (especially polytrifluoromethylated) candidates. The fluorine atom is a classic bioisostere of the hydrogen atom [52]. For this reason, we suggest treating fluorine atoms as hydrogens for molecular weight calculation in the rules of five.

Second, the number of H-bond acceptors, calculated using the tools incorporated into the structure-drawing programs, was overcalculated in each of the products listed in Table 1. This miscalculation "makes" trifluoromethyl-containing lipophilic molecules "highly hydrophilic", thus misleading those less-familiar with the field of fluorine organic chemistry. It is reported that one trifluoromethyl group can form only one H-bond [53], so we suggest considering one trifluoromethyl group as one H-bond acceptor in the Lipinski rules. The use of these corrections will dramatically increase the number of fluorinated drug candidates.

The difficulties mentioned above have led us to pay attention to other calculated parameters that can be used to evaluate polyfluorinated small molecules as potential drug candidates. Recently, J.G. Gelovani formulated rules for potential small molecule drug candidates [54] and granted us permission to use his rules in publications [5]. His rules concerning the properties of prospective small molecule drugs are (1) molecular polar surface area (PSA) [55–59] <140 $Å^2$; (2) molar refractivity (MR) [60–64] within the range of 40–130 cm^3/mol; (3) the number of atoms in the molecule 20–70 (Table 1). One can now see that all 1,4-disubstituted semicarbazides **7a–e**, **8a–d** and **9f**, **10f–w** are in agreement with the Gelovani rules. We believe that these criteria will help medicinal chemists to better evaluate pharmacological potency of polyfluoro organic compounds.

3. Conclusion

We demonstrated a simple approach to synthesize compounds with potential biological activity. We showed, specifically, that the interaction of *bis*(trifluoromethyl)alkyl isocyanates with aroyl- or arylsulfonyl-hydrazines leads to variable 1-aroyl(or arylsulfonyl)-4-[1,1-*bis*(trifluoromethyl)alkyl] semicarbazides, which were obtained starting from perfluoroisobutene, a toxic industrial by-product. Applicability of the Lipinski and Gelovani rules for polyfluorinated small molecule drug candidates is discussed.

4. Experimental

4.1. General methods

The ^1H and ^{19}F NMR spectra were recorded on Bruker DXP at 200 and 188 MHz, respectively, in $CDCl_3$, DMSO-d_6, acetone-d_6 using tetramethylsilane (TMS) as an internal standard and CF_3COOH as an external standard. Chemical shifts are reported in ppm units with the use of δ scale. Mass-spectra were recorded on a Finnigan 4021 spectrometer. The elemental analyses (C, H, F, N) were performed in the laboratory of analytical chemistry of IPAC RAS. Melting points were measured in open capillary tubes and are uncorrected. HPLC analysis was performed as described elsewhere [65]. The starting materials isocyanates **2** and **3** were prepared by the Curtius reaction [3,6]. The starting sulfonohydrazides **5f–h** and hydrazides **6a–e** are commercial and were used without additional treatment. The products are named with ChemBioDraw Ultra, v.13 [66].

4.1.1. General procedure for the synthesis of compounds *7a–e* and *8a–d*

To a solution of 1 mmol of hydrazide **6a–e** in 10 ml of dry diethyl ether or dry benzene was added 1 mmol of isocyanate **2**, **3**. The mixture was stirred for 4 h at rt and left overnight. The resulting precipitate was filtered and recrystallized from benzene,

or in some cases, solvent was evaporated and the residue was crystallized from hexane.

*4.1.1.1. 2-Benzoyl-N-(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)hydrazine-1-carboxamide (**7a**).* Yield 95%, m.p. 190–191 °C. ^{1}H NMR (DMSO-d_6): δ 1.96 (s, 3H, CH_3), 7.22 (s, 1H, NH), 7.40–7.60 (m, 3H, CH_{Ar}), 7.86 (d, 2H, CH_{Ar}, J_{HH} = 7.0 Hz), 8.26 (s, 1H, NH), 10.22 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.64 s. EI-MS (*m*/*z*): 343 $[M]^+$. Anal. calcd. for $C_{12}H_{11}F_6N_3O_2$: C, 41.99; H, 3.23; F, 33.21; N, 12.24; O, 9.32; found: C, 42.12; H, 3.12; F, 33.45; N, 12.42.

*4.1.1.2. 2-(4-Fluorobenzoyl)-N-(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)hydrazine-1-carboxamide (**7b**).* Yield 75%, m.p. 191–193 °C. ^{1}H NMR (DMSO-d_6): δ 1.98 (s, 3H, CH_3), 7.30 (m, 3H, NH + CH_{Ar}), 8.00 (m, 2H, CH_{Ar}), 8.32 (s, 1H, NH), 10.42 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.04 (s, 6F, CF_3); 36.96 (m, 1F, CF_{Ar}). EI-MS (*m*/*z*): 361 $[M]^+$. Anal. calcd. for $C_{12}H_{10}F_7N_3O_2$: C, 39.90; H, 2.79; F, 36.82; N, 11.63; O, 8.86; found: C, 40.02; H, 2.64; F, 36.90; N, 11.68.

*4.1.1.3. 2-(3,4-Dimethoxybenzoyl)-N-(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)hydrazine-1-carboxamide (**7c**).* Yield 82%, m.p. 184–186 °C. ^{1}H NMR (acetone-d_6): δ 1.92 (s, 3H, CH_3), 3.88 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 7.08 (d, 1H, CH_{Ar}, *J* = 7.1 Hz), 7.45 (s, 1H, NH), 7.58 (s, 1H, CH_{Ar}), 7.60 (d, 1H, CH_{Ar}, *J* = 7.1 Hz), 8.32 (s, 1H, NH), 10.30 (s, 1H, NH). ^{19}F NMR (acetone-d_6): δ 6.04 s. EI-MS (*m*/*z*): 403 $[M]^+$. Anal. calcd. for $C_{14}H_{15}F_6N_3O_4$: C, 41.70; H, 3.75; F, 28.27; N, 10.42; O, 15.87; found: C, 41.86; H, 3.74; F, 28.36; N, 10.44.

*4.1.1.4. N-(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)-2-isonicotinoylhydrazine-1-carboxamide (**7d**).* Yield 90%, m.p. 192–194 °C. ^{1}H NMR (DMSO-d_6): δ 1.92 (s, 3H, CH_3), 7.77 (s, 1H, NH), 7.72 (d, 2H, CH_{Ar}, J_{HH} = 7.1 Hz), 8.38 (s, 1H, NH), 8.68 (d, 2H, CH_{Ar}, J_{HH} = 7.1 Hz), 10.68 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.66 s. EI-MS (*m*/*z*): 345 $[M+1]^+$. Anal. calcd. for $C_{11}H_{10}F_6N_4O_2$: C, 38.38; H, 2.93; F, 33.12; N, 16.28; O, 9.30; found: C, 38.48; H, 2.84; F, 33.35; N, 16.02.

*4.1.1.5. 2-(2-Bromobenzoyl)-N-(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)hydrazine-1-carboxamide (**7e**).* Yield 77%, m.p. 148–150 °C. ^{1}H NMR (DMSO-d_6): δ 1.94 (s, 3H, CH_3), 7.25 (s, 1H, NH), 7.30–7.50 (m, 3H, CH_{Ar}), 7.76 (d, 1H, CH_{Ar}, J_{HH} = 7.0 Hz), 8.42 (s, 1H, NH), 10.26 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.76 s. EI-MS (*m*/*z*): 423 $[M+1]^+$. Anal. calcd. for $C_{12}H_{10}BrF_6N_3O_2$: C, 34.14; H, 2.39; Br, 18.93; F, 27.00; N, 9.95; O, 7.58; found: C, 34.32; H, 2.48; F, 26.92; N, 10.04.

*4.1.1.6. 2-Benzoyl-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**8a**).* Yield 98%, m.p. 193–195 °C. ^{1}H NMR (DMSO-d_6): δ 1.06 (t, 3H, CH_3, J_{HH} = 7.0 Hz), 2.48 (q, 2H, CH_2, J_{HH} = 7.0 Hz) 7.18 (s, 1H, NH), 7.40–7.60 (m, 3H, CH_{Ar}), 7.90 (d, 2H, CH_{Ar}, J_{HH} = 7.0 Hz), 8.20 (s, 1H, NH), 10.26 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.84 s. EI-MS (*m*/*z*): 357 $[M]^+$. Anal. calcd. for $C_{13}H_{13}F_6N_3O_2$: C, 43.71; H, 3.67; F, 31.91; N, 11.76; O, 8.96; found: C, 43.82; H, 3.75; F, 32.05; N, 11.84.

*4.1.1.7. 2-(4-Fluorobenzoyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)-butan-2-yl)hydrazine-1-carboxamide (**8b**).* Yield 83%, m.p. 188–190 °C. ^{1}H NMR (DMSO-d_6): δ 0.99 (t, 3H, CH_3, J_{HH} = 7.0), 2.32 (q, 2H, CH_2, J_{HH} = 7.0 Hz) 6.92 (s, 1H, NH), 7.30 (m, 2H, CH_{Ar}), 7.94 (s, 1H, NH), 8.04 (m, 2H, CH_{Ar}), 9.60 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.74 (s, 6F, CF_3); 36.64 (m, 1F, CF_{Ar}). EI-MS (*m*/*z*): 376 $[M+1]^+$. Anal. calcd. for $C_{13}H_{12}F_7N_3O_2$: C, 41.61; H, 3.22; F, 35.44; N, 11.20; O, 8.53; found: C, 41.75; H, 3.16; F, 35,26; N, 11.32.

*4.1.1.8. 2-(3,4-Dimethoxybenzoyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**8c**).* Yield 85%, m.p. 187–189 °C. ^{1}H NMR (DMSO-d_6): δ 0.99 (t, 3H, CH_3, J_{HH} = 7.0 Hz), 2.32 (q, 2H, CH_2, J_{HH} = 7.0 Hz), 3.90 (s, 6H, CH_3O), 7.02 (d, 1H, CH_{Ar}, *J* = 7.0 Hz), 7.46 (s, 1H, CH_{Ar}), 7.50 s (1H, NH), 7.65 (d, 1H, CH_{Ar}, *J* = 7.0 Hz), 8.12 (s, 1H, NH), 10.30 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 6.04 s. EI-MS (*m*/*z*): 418 $[M+1]^+$. Anal. calcd. for $C_{15}H_{17}F_6N_3O_4$: C, 43.17; H, 4.11; F, 27.32; N, 10.07; O, 15.34; found: C, 43.32; H, 4.03; F, 27.50; N, 9.98.

*4.1.1.9. 2-Isonicotinoyl-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**8d**).* Yield 91%, m.p. 198–200 °C. ^{1}H NMR (DMSO-d_6): δ 1.07 (t, 3H, CH_3, J_{HH} = 7.0 Hz), 2.40 (q, 2H, CH_2, J_{HH} = 7.0 Hz), 7.27 (s, 1H, NH), 7.92 (d, 2H, CH_{Ar}, J_{HH} = 7.1 Hz), 8.32 (s, 1H, NH), 8.72 (d, 2H, CH_{Ar}, J_{HH} = 7.1 Hz), 10.55 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 6.02 s. EI-MS (*m*/*z*): 359 $[M+1]^+$. Anal. calcd. for $C_{12}H_{12}F_6N_4O_2$: C, 40.23; H, 3.38; F, 31.82; N, 15.64; O, 8.93; found: C, 40.17; H, 3,52; F, 32.02; N, 15,42.

*4.1.2. General procedure for the synthesis of compounds **5i**–**w***

To solution of 1 mmol of arylsulfonyl chloride **4i**–**w** in 10 ml of THF, 1.1 mmol of hydrazine-hydrate in 10 ml THF were added drop wise at 0–5 °C with stirring. After stirring 1–2 h at rt 20 ml of water were added, the precipitate was filtered, dried and crystallized from benzene or hexane. HPLC analysis revealed single peaks for all tested compounds.

*4.1.2.1. 4-Isopropylbenzenesulfonohydrazide (**5i**).* Yield 89%, m.p. 48–51 °C. ^{1}H NMR (DMSO-d_6): δ 1.30 (d, 6H, J_{HH} = 7.2 Hz, $\underline{CH_3}CH$), 3.02 (septet, 6H, J_{HH} = 7.2 Hz, $CH_3C\underline{H}$), 7.42 (d, 2H, J_{HH} = 7.9 Hz, H_{Ar}), 7.78 (d, 2H J_{HH} = 7.9 Hz, CH_{Ar}), 8.13 (s, 1H, NH). EI-MS (*m*/*z*): 215 $[M+1]^+$. Anal. calcd. for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.59; N, 13.07; O, 14.93; S, 14.96; found: C, 50.64; H, 6,72; N, 13.02.

*4.1.2.2. 4-(tert-Butyl)benzenesulfonohydrazide (**5j**).* Yield 97%, m.p. 72–75 °C. ^{1}H NMR (DMSO-d_6): δ 1.34 (s, 9H, $\underline{CH_3}C$), 7.60 (d, 1H, J_{HH} = 8.6 Hz, H_{Ar}), 7.84 (d, 1H, J_{HH} = 8.6 Hz, H_{Ar}), 8.50 (s, 1H, NH). EI-MS (*m*/*z*): 229 $[M+1]^+$. Anal. calcd. for $C_{10}H_{16}N_2O_2S$: C, 52.61; H, 7.06; N, 12.27; O, 14.02; S, 14.04; found: C, 52.82; H, 6.96; N, 12.38.

*4.1.2.3. 3,5-Dimethylbenzenesulfonohydrazide (**5k**).* Yield 67%, m.p. 82–84 °C. ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 6H, CH_3), 6.75 (s, 1H, H_{Ar}), 7.54 s (2H, H_{Ar}), 8.30 (s, 1H, NH). EI-MS (*m*/*z*): 201 $[M+1]^+$. Anal. calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99; O, 5.98; S, 16.01; found: C, 48.05; H, 6.18; N, 14.10.

*4.1.2.4. 4-Bromobenzenesulfonohydrazide (**5l**).* Yield 84%, m.p. 87–89 °C. ^{1}H NMR (DMSO-d_6): δ 7.69 (d, 1H, J_{HH} = 8.8 Hz, H_{Ar}), 7.75 (d, 1H, J_{HH} = 8.8 Hz, H_{Ar}), 8.30 (s, 1H, NH). EI-MS (*m*/*z*): 252 $[M+1]^+$. Anal. calcd. for $C_6H_7BrN_2O_2S$: C, 28.70; H, 2.81; Br, 31.82; N, 11.16; O, 12.74; S, 12.77; found: C, 28.66; H, 2.93; N, 11.02.

*4.1.2.5. 3,4-Dichlorobenzenesulfonohydrazide (**5m**).* Yield 98%, m.p. 107–109 °C. ^{1}H NMR (DMSO-d_6): δ 7.66 (d, 1H, J_{HH} = 8.2 Hz, H_{Ar}), 7.74 (dd, 1H, J_{HH} = 8.2, 1.8 Hz, H_{Ar}), 7.78 (s, 1H, NH), 7.92 (d, 1H, J_{HH} = 1.8 Hz, H_{Ar},). EI-MS (*m*/*z*): 241 $[M]^+$. Anal. calcd. for $C_6H_6Cl_2N_2O_2S$: C, 29.89; H, 2.51; Cl, 29.41; N, 11.62; O, 13.27; S, 13.30; found: C, 30.02; H, 2.36; N, 11.78.

*4.1.2.6. 5-Chloro-2-methoxybenzenesulfonohydrazide (**5n**).* Yield 97%, m.p. 110–112 °C. ^{1}H NMR (DMSO-d_6): δ 3.95 (s, 3H, CH_3O), 7.19 (d, 1H, J_{HH} = 8.8 Hz, H_{Ar}), 7.52 (dd, 1H, J_{HH} = 8.8, 2.8 Hz, H_{Ar}), 7.72 (d, 1H, J_{HH} = 2.8 Hz, H_{Ar}), 7.95 (s, 1H, NH). EI-MS (*m*/*z*): 237 $[M+1]^+$. Anal. calcd. for $C_7H_9ClN_2O_3S$: C, 35.52; H, 3.83; Cl, 14.98; N, 11.84; O, 20.28; S, 13.55; found: C, 35.68; H, 3.72; N, 11.88.

*4.1.2.7. 5-Bromo-2-methoxybenzenesulfonohydrazide (**5o**).* Yield 90%, m.p. 136–138 °C (dec). ^{1}H NMR (DMSO-d_6): δ 3.93 (s, 3H, CH_3O), 7.11 (d, 1H, J_{HH} = 8.8 Hz, H_{Ar}), 7.67 (dd, 1H, J_{HH} = 8.8, 2.0 Hz,

H_{Ar}), 7.82 (d, 1H, J_{HH} = 2.0 Hz, H_{Ar}). EI-MS (*m*/*z*): 281 $[M]^+$. Anal. calcd. for $C_7H_9BrN_2O_3S$: C, 29.91; H, 3.23; Br, 28.42; N, 9.96; O, 17.07; S, 11.41; found: C, 30.02; H, 3.38; N, 10.12.

*4.1.2.8. 2,5-Dimethoxybenzenesulfonohydrazide (**5p**).* Yield 78%, m.p. 98–100 °C. ^{1}H NMR (DMSO-d_6): δ 3.82 (s, 3H, CH_3O), 3.90 (s, 3H, CH_3O), 7.22 (m, 2H, H_{Ar}), 7.31 (d, 1H, J_{HH} = 2.6 Hz, H_{Ar}), 7.74 (s, 1H, NH). EI-MS (*m*/*z*): 233 $[M+1]^+$. Anal. calcd. for $C_8H_{12}N_2O_4S$: C, 41.37; H, 5.21; N, 12.06; O, 27.55; S, 13.81; found: C, 41.52; H, 5.38; N, 12.29.

*4.1.2.9. 4-(Difluoromethoxy)benzenesulfonohydrazide (**5q**).* Yield 75%, m.p. 72–74 °C. ^{1}H NMR (DMSO-d_6): δ 3.83 (s, 2H, NH_2), 7.16 (t, 1H, J_{HF} = 73.3 Hz, CHF_2), 7.28 (d, 2H, J_{HH} = 7.0 Hz, H_{Ar}), 7.86 (d, 2H, J_{HH} = 7.0 Hz, H_{Ar}), 8.22 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ −5.71 (d, 2F, J_{FH} = 73.3 Hz, CF_2). EI-MS (*m*/*z*): 239 $[M+1]^+$. Anal. calcd. for $C_7H_8F_2N_2O_3S$: C, 35.29; H, 3.39; F, 15.95; N, 11.76; O, 20.15; S, 13.46; found: C, 35.46; H, 3.51; F, 16.12; N, 11.94.

*4.1.2.10. 2,5-bis(2,2,2-Trifluoroethoxy)benzenesulfonohydrazide (**5r**).* Yield 94%, m.p. 118–120 °C. ^{1}H NMR (DMSO-d_6): δ 4.62 (q, 2H, J_{HF} = 8.6 Hz, CH_2O), 4.72 (q, 2H, J_{HF} = 8.6 Hz, CH_2O), 7.28 (m, 2H, H_{Ar}), 7.42 (s, 1H, H_{Ar}). ^{19}F NMR (DMSO-d_6): δ 4.30 (t, 3F, J_{FH} = 8.6, CF_3CH_2), 5.01 (t, 3F, CF_3CH_2, J_{FH} = 8.6 Hz). EI-MS (*m*/*z*): 383 $[M+1]^+$. Anal. calcd. for: $C_{10}H_{10}F_6N_2O_4S$: C, 34.56; H, 3.16; F, 29.82; N, 7.33; O, 16.74; S, 8.39; found: C, 32.48; H, 2.92; F, 31.05; N, 7.73.

*4.1.2.11. [1,1′-Biphenyl]-2-sulfonohydrazide (**5s**).* Yield 99%, m.p. 84–86 °C. ^{1}H NMR (DMSO-d_6): δ 3.79 (br. s, 2H, NH_2), 7.27–7.47 (m, 6H, H_{Ar}), 7.48–7.67 (m, 2H, H_{Ar}), 8.00 (dd, 1H, J_{HH} = 7.4, 1.6 Hz, H_{Ar}). EI-MS (*m*/*z*): 249 $[M+1]^+$. Anal. calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28; O, 12.89; S, 12.91; found: C, 58.17; H, 4.98; N, 11.36.

*4.1.2.12. Naphthalene-1-sulfonohydrazide (**5t**).* Yield 92%, m.p. 108–110 °C. ^{1}H NMR (DMSO-d_6): δ 7.51–7.70 (m, 4H, H_{Ar}), 7.97 (d, 1H, J_{HH} = 7.8 Hz, H_{Ar}), 8.15 (m, 2H, H_{Ar}), 8.51 (s, 1H, NH), 8.69 (d, 1H, J_{HH} = 8.2 Hz, H_{Ar}). EI-MS (*m*/*z*): 223 $[M+1]^+$. Anal. calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60; O, 14.40; S, 14.43; found: C, 54.18; H, 4,66; N, 12.34.

*4.1.2.13. Naphthalene-2-sulfonohydrazide (**5u**).* Yield 94%, m.p. 134–136 °C. ^{1}H NMR (DMSO-d_6): δ 3.80 (br s, 2H, NH_2), 7.64 (m, 2H, CH_{Ar}), 7.84–8.14 (m, 4H, CH_{Ar}), 8.33 (s, 1H, CH_{Ar}), 8.46 (s, 1H, NH). EI-MS (*m*/*z*): 223 $[M+1]^+$. Anal. calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60; O, 14.40; S, 14.43; found: C, 53.94; H, 4.44; N, 12.36.

*4.1.2.14. 4-Methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-sulfonohydrazide (**5v**).* Yield 59(60) %, m.p. 116–118 °C. ^{1}H NMR (DMSO-d_6): δ 2.94 (s, 3H, CH_3N), 3.32 (m, 2H, CH_2N), 4.31 (m, 2H, CH_2O), 6.75 (d, 1H, J_{HH} = 8.3 Hz, H_{Ar}), 7.04 (m, 2H, H_{Ar}), 7.94 (s, 1H, NH). EI-MS (*m*/*z*): 244 $[M+1]^+$. Anal. calcd. for $C_9H_{13}N_3O_3S$: C, 44.43; H, 5.39; N, 17.27; O, 19.73; S, 13.18; found: C, 44.56; H, 5.48; N, 17.32.

*4.1.2.15. 4-(1,2,3-Thiadiazol-4-yl)benzenesulfonohydrazide (**5w**).* Yield 87%, m.p. 156–158 °C. ^{1}H NMR (DMSO-d_6): δ 7.97 (d, 2H, J_{HH} = 8.2 Hz, H_{Ar}), 8.34 (d, 3H, J_{HH} = 8.2 Hz, NH + H_{Ar}), 9.66 (s, 1H, H_{Ar}). EI-MS (*m*/*z*): 257 $[M+1]^+$. Anal. calcd. for $C_8H_8N_4O_2S_2$: C, 37.49; H, 3.15; N, 21.86; O, 12.48; S, 25.02; found: C, 37.69; H, 3.01; N, 21.59.

*4.1.3. General procedure for the synthesis of compounds **9f** and **10f–w***

To the stirred solution of 1 mmol of sulfonohydrazide **5f–v** in 5 ml dry benzene, 1.1 mmol of isocyanate **2** or **3** in 5 ml benzene was added drop wise and stirred at rt during 1 h. The volatile were evaporated and residue was crystallized from petroleum ether:-benzene 1:1 (v/v). HPLC analysis revealed single peaks for all tested compounds.

*4.1.3.1. N-(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)-2-tosylhydrazine-1-carboxamide (**9f**).* Yield 96%, m.p. 144–145 °C. ^{1}H NMR (acetone-d_6): δ 1.90 (s, 3H, $\underline{CH_3}CCF_3$), 2.50 (s, 3H, CH_3Ar), 6.61 (s, 1H, NH), 7.40 (m, 2H, CH_{Ar}), 7.80 (m, 2H, CH_{Ar}), 8.10 (s, 1H, NH), 8.40 (br. s, 1H, NH). ^{19}F NMR (acetone–d_6): δ 1.00 s. EI-MS (*m*/*z*): 394 $[M+1]^+$. Anal. calcd. for $C_{12}H_{13}F_6N_3O_3S$: C, 36.67; H, 3.34; F, 27.86; N, 10.49; O, 13.77; S, 7.87; found: C, 36.65; H, 3.33; F, 28.98; N, 10.68.

*4.1.3.2. 2-Tosyl-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10f**).* Yield 95%, m.p. 90–92 °C. ^{1}H NMR (DMSO-d_6): δ 0.87 (t, 3H, CH_3, J_{HH} = 7.0 Hz), 2.24 (q, 2H, CH_2, J_{HH} = 7.0 Hz), 2.42 (s, 3H, CH_3C_{Ar}), 6.70 (s, 1H, NH), 7.26 (d, 2H, CH_{Ar}, J_{HH} = 7.0 Hz), 7.67 (d, 2H, CH_{Ar}, J_{HH} = 7.0 Hz), 8.26 (s, 1H, NH), 9.44 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 4.03 s. EI-MS (*m*/*z*): 408 $[M+1]^+$. Anal. calcd. for $C_{13}H_{15}F_6N_3O_3S$: C, 38.33; H, 3.71; F, 27.98; N, 10.32; O, 11.78; S, 7.87; found: C, 38.42; H, 3.63; F, 27.86; N, 10.44.

*4.1.3.3. 2-(Mesitylsulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10g**).* Yield 40%, m.p. 116–117 °C. ^{1}H NMR (DMSO-d_6): δ 0.76 (t, 3H, J_{HH} = 7.2 Hz, $\underline{CH_3}CH_2$), 2.26 (q, 2H, J_{HH} = 7.2 Hz, CH_2), 2.30 (s, 3H, CH_3), 2.60 (s, 6H, CH_3), 6.62 (s, 1H, NH), 6.91 (s, 2H, H_{Ar}), 8.32 (s, 1H, NH), 9.20 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.08 s. EI-MS (*m*/*z*): 436 $[M+1]^+$. Anal. calcd. for $C_{15}H_{19}F_6N_3O_3S$: C, 41.38; H, 4.40; F, 26.18; N, 9.65; O, 11.02; S, 7.36; found: C, 41.32; H, 4.50; F, 26.22; N, 9.71.

*4.1.3.4. 2-((5-(Dimethylamino)naphthalen-1-yl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10h**).* Yield 68%, m.p. 141–143 °C. ^{1}H NMR ($CDCl_3$): δ 0.74 (t, 3H, J_{HH} = 7.0 Hz, CH_3,), 2.16 (q, 2H, J_{HH} = 7.0 Hz, CH,), 2.89 (s, 6H, CH_3N), 5.64 (s, 1H, NH), 6.53 (s, 1H, NH), 6.94 (s, 1H, NH), 7.22 (d, 1H, J_{HH} = 7.4 Hz, H_{Ar}), 7.50–7.69 (m, 2H, H_{Ar}), 8.28 (m, 2H, H_{Ar}), 8.65 (d, 1H, J_{HH} = 8.4 Hz, H_{Ar}). ^{19}F NMR ($CDCl_3$): δ 5.08 s. EI-MS (*m*/*z*): 487 $[M+1]^+$. Anal. calcd. for $C_{18}H_{20}F_6N_4O_3S$: C, 44.45; H, 4.14; F, 23.43; N, 11.52; O, 9.87; S, 6.59; found: C, 44.60; H, 4.02; F, 23.54; N, 11.38.

*4.1.3.5. 2-((4-Isopropylphenyl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10i**).* Yield 66%, m.p. 126–128 °C. ^{1}H NMR (DMSO-d_6): δ 0.82 (t, 3H, J_{HH} = 7.2 Hz, $\underline{CH_3}CH_2$,), 1.29 (d, 6H, J_{HH} = 7.0 Hz, $\underline{CH_3}$CH), 2.28 (q, 2H, J_{HH} = 7.2 Hz, CH_2), 3.02 (sept, 6H, J_{HH} = 7.0 Hz, $CH_3C\underline{H}$), 6.72 (s, 1H, NH), 7.40 (d, 2H, J_{HH} = 7.9 Hz, H_{Ar}), 7.78 (d, 2H, J_{HH} = 7.9 Hz, H_{Ar}), 8.39 (br. s, 1H, NH), 9.43 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.10 s. EI-MS (*m*/*z*): 436 $[M+1]^+$. Anal. calcd. for $C_{15}H_{19}F_6N_3O_3S$: C, 41.38; H, 4.40; F, 26.18; N, 9.65; O, 11.02; S, 7.36; found: C, 41.46; H, 4.52; F, 26.04; N, 9.74.

*4.1.3.6. 2-((4-(tert-Butyl)phenyl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10j**).* Yield 60%, m.p. 148–150 °C. ^{1}H NMR (DMSO-d_6): δ 0.89 (t, 3H, J_{HH} = 7.2 Hz, $\underline{CH_3}CH_2$), 1.32 (s, 9H, $\underline{CH_3}$C), 2.34 (q, 2H, J_{HH} = 7.2 Hz, CH_2), 5.92 (s, 1H, NH), 6.89 (br. s, 1H, NH), 6.97 (s, 1H, NH), 7.57 (s, 2H, J_{HH} = 8.6 Hz, H_{Ar}), 7.82 (d, 2H, J_{HH} = 8.6 Hz, CH_{Ar}). ^{19}F NMR (DMSO-d_6): δ 5.04 s. EI-MS (*m*/*z*): 450 $[M+1]^+$. Anal. calcd. for $C_{16}H_{21}F_6N_3O_3S$: C, 42.76; H, 4.71; F, 25.36; N, 9.35; O, 10.68; S, 7.13; found: C, 42.68; H, 4.82; F, 25.52; N, 9.44.

*4.1.3.7. 2-((3,5-Dimethylphenyl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10k**).* Yield 31%, m.p. 121–123 °C. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, J_{HH} = 7.2 Hz, $\underline{CH_3}CH_2$), 2.36 (q, 2H, J_{HH} = 7.2 Hz, CH_2), 2.39 (s, 6H, CH_3), 5.90 (s, 1H, NH), 6.60 (s, 1H, NH), 6.74 (s, 1H, H_{Ar}), 7.30 (s, 1H, NH), 7.52 (s, 2H, H_{Ar}). ^{19}F NMR ($CDCl_3$): δ 5.12 s. EI-MS (*m*/*z*): 422 $[M+1]^+$. Anal.

calcd. for $C_{14}H_{17}F_6N_3O_3S$: C, 39.91; H, 4.07; F, 27.05; N, 9.9; O, 11.39; S, 7.61; found: C, 40.02; H, 4. 12; F, 27.18; N, 10.04.

*4.1.3.8. 2-((4-Bromophenyl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10l**).* Yield 32%, m.p. 59–61 °C. ^{1}H NMR (DMSO-d_6): δ 0.86 (t, 3H, J_{HH} = 7.2 Hz, $\underline{CH_3}CH_2$), 2.32 (q, 2H, J_{HH} = 7.2 Hz, CH_2,), 6.76 (s, 1H, NH), 7.65 (d, 2H, J_{HH} = 8.6 Hz, H_{Ar}), 7.75 (d, 2H, J_{HH} = 8.6 Hz, H_{Ar}), 8.40 (s, 1H, NH), 9.69 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.10 s. EI-MS (*m*/*z*): 473 $[M+1]^+$. Anal. calcd. for $C_{12}H_{12}BrF_6N_3O_3S$: C, 30.52; H, 2.56; Br, 16.92; F, 24.14; N, 8.90; O, 10.16; S, 6.79; found: C, 30.48; H, 2.48, F, 24.24; N, 7.02.

*4.1.3.9. 2-((3,4-Dichlorophenyl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10m**).* Yield 66%, m.p. 62–64 °C. ^{1}H NMR (DMSO-d_6): δ 0.82 (t, 3H, J_{HH} = 7.2 Hz, $\underline{CH_3}CH_2$), 2.26 (q, 2H, J_{HH} = 7.2 Hz, CH_2), 6.78 (s, 1H, NH), 7.62 (d, 1H, J_{HH} = 8.4 Hz, H_{Ar}), 7.72 (dd, 1H, J_{HH} = 8.6, 1.9 Hz, H_{Ar}), 7.89 (d, 1H, J_{HH} = 1.9 Hz, H_{Ar}), 8.42 (d, 1H, J_{HH} = 2.6 Hz, NH), 9.84 (d, 1H, J_{HH} = 2.6 Hz, NH). ^{19}F NMR (DMSO-d_6): δ 5.06 s. EI-MS (*m*/*z*): 463 $[M+1]^+$. Anal. calcd. for $C_{12}H_{11}Cl_2F_6N_3O_3S$: C, 31.18; H, 2.40; Cl, 15.34; F, 24.66; N, 9.09; O, 10.38; S, 6.94; found: C, 31.02; H, 2.56; F, 24.43; N, 9.28.

*4.1.3.10. 2-((5-Chloro-2-methoxyphenyl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10n**).* Yield 74%, m.p. 162–164 °C. ^{1}H NMR (DMSO-d_6): δ 0.86 (t, 3H, J_{HH} = 7.2 Hz, $\underline{CH_3}CH_2$), 2.32 (q, 2H, J_{HH} = 7.2 Hz, CH_2), 4.00 (s, 3H, CH_3O), 6.71 (br. s, 1H, NH), 7.10 (d, 1H, J_{HH} = 9.1 Hz, H_{Ar}), 7.52 (dd, 1H, J_{HH} = 9.1, 2.6 Hz, H_{Ar}), 7.70 (d, 1H, J_{HH} = 2.6 Hz, H_{Ar}), 8.42 (s, 1H, NH), 9.12 (br. s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.10 (s, 6F, CF_3C). EI-MS (*m*/*z*): 458 $[M+1]^+$. Anal. calcd. for $C_{13}H_{14}ClF_6N_3O_4S$: C, 34.11; H, 3.08; Cl, 7.74; F, 24.90; N, 9.18; O, 13.98; S, 7.00; found: C, 34.25; H, 2.96; F, 24.96; N, 9.32.

*4.1.3.11. 2-((5-Bromo-2-methoxyphenyl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10o**).* Yield 75%, m.p. 178–180 °C. ^{1}H NMR (DMSO-d_6): δ 0.87 (t, 3H, J_{HH} = 7.2 Hz, $\underline{CH_3}CH_2$), 2.29 (q, 2H, J_{HH} = 7.2 Hz, CH_2), 3.96 (s, 3H, CH_3O), 6.70 (br. s, 1H, NH), 7.04 (d, 1H, J_{HH} = 9.1 Hz, H_{Ar}), 7.64 (dd, 1H, J_{HH} = 9.1, 2.3 Hz, H_{Ar}), 7.66 (d, 1H, J_{HH} = 2.3 Hz, CH_{Ar}), 8.38 (s, 1H, NH), 9.17 (br. s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.5 s. EI-MS (*m*/*z*): 503 $[M+1]^+$. Anal. calcd. for $C_{13}H_{14}BrF_6N_3O_4S$: C, 31.09; H, 2.81; Br, 15.91; F, 22.70; N, 8.37; O, 12.74; S, 6.38; found: C, 31.22; H, 2.91; F, 22.64; N, 8.24.

*4.1.3.12. 2-((2,5-Dimethoxyphenyl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10p**).* Yield 79%, m.p. 147–149 °C. ^{1}H NMR (DMSO-d_6): δ 0.87 (t, 3H, J_{HH} = 7.2 Hz, $\underline{CH_3}CH_2$), 2.26 (q, 2H, J_{HH} = 7.2 Hz, CH_2), 3.80 (s, 3H, CH_3O), 3.94 (s, 3H, CH_3O), 6.71 (br. s, 1H, NH), 7.02 (d, 1H, J_{HH} = 9.1 Hz, H_{Ar}), 7.11 (dd, 1H, J_{HH} = 9.1, 2.8 Hz, H_{Ar}), 7.28 (d, 1H, J_{HH} = 2.8 Hz, H_{Ar}), 8.36 (s, 1H, NH), 8.90 (br. s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.08 s. EI-MS (*m*/*z*): 454 $[M+1]^+$. Anal. calcd. for $C_{14}H_{17}F_6N_3O_5S$: C, 37.09; H, 3.78; F, 25.14; N, 9.27; O, 17.65; S, 7.07; found: C, 36.94; H, 3.87; F, 25.31; N, 9.42.

*4.1.3.13. 2-((4-(Difluoromethoxy)phenyl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10q**).* Yield 54%, m.p. 44–46 °C. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 3H, J_{HH} = 7.2 Hz, CH_3), 2.31 (q, 2H, J_{HH} = 7.2 Hz, CH_2), 5.91 (s, 1H, NH), 6.61 (t, 1H, J_{HF} = 72.2 Hz, CHF_2), 7.17 (s, 1H, NH), 7.26 (d + s, 3H, J_{HH} = 8.8 Hz, H_{Ar} + NH), 7.91 (d, 2H, J_{HH} = 8.8 Hz, H_{Ar}). ^{19}F NMR ($CDCl_3$): δ-6.00 (d, 2F, J_{FH} = 72.2 Hz, CF_2), 5.07 (s, 6F, CF_3C). EI-MS (*m*/*z*): 460 $[M+1]^+$. Anal. calcd. for $C_{13}H_{13}F_8N_3O_4S$: C, 34.00; H, 2.85; F, 33.09; N, 9.15; O, 13.93; S, 6.98; found: C, 34.12; H, 3.01; F, 32.98; N, 9.20.

*4.1.3.14. 2-((2,5-bis(2,2,2-Trifluoroethoxy)phenyl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10r**).* Yield 57%, m.p. 58–60 °C. ^{1}H NMR (DMSO-d_6): δ 0.77 (t, 3H, J_{HH} = 7.0 Hz, CH_3), 2.23 (q, 2H, J_{HH} = 7.0 Hz, CH_2), 4.54 (q, 2H, J_{HF} = 8.6 Hz, CH_2O), 4.72 (q, 2H, J_{HF} = 8.8 Hz, CH_2O), 6.80 (br. s, 1H, NH), 7.23 (m, 2H, H_{Ar}), 7.43 (d, 1H, J_{HH} = 2.6 Hz, H_{Ar}), 8.45 (s, 1H, NH), 8.97 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 4.29 (t, 3F, J_{FH} = 8.6 Hz, CF_3CH_2), 4.99 (t, 3F, CF_3CH_2, J_{FH} = 8.8 Hz), 5.03 (s, 6F, CF_3C). EI-MS (*m*/*z*): 590 $[M+1]^+$. Anal. calcd. for $C_{16}H_{15}F_{12}N_3O_5S$: C, 32.61; H, 2.57; F, 38.68; N, 7.13; O, 13.57; S, 5.44; found: C, 32.70; H, 2.62; F, 38.54; N, 7.01.

*4.1.3.15. 2-([1,1′-Biphenyl]-2-ylsulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10s**).* Yield 74%, m.p. 164–166 °C. ^{1}H NMR (DMSO-d_6): δ 0.83 (t, 3H, J_{HH} = 7.4 Hz, CH_3), 2.30 (q, 2H, J_{HH} = 7.4 Hz, CH_2), 6.74 (br. s, 1H, NH), 7.21–7.41 (m, 4H, H_{Ar}), 7.42–7.62 (m, 4H, H_{Ar}), 8.00 (d, 1H, J_{HH} = 7.7 Hz, H_{Ar}), 8.33 (s, 1H, NH), 8.77 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.11 s. EI-MS (*m*/*z*): 470 $[M+1]^+$. Anal. calcd. for $C_{18}H_{17}F_6N_3O_3S$: C, 46.06; H, 3.65; F, 24.28; N, 8.95; O, 10.23; S, 6.83; found: C, 46.22; H, 3.54; F, 24.42; N, 9.03.

*4.1.3.16. 2-(Naphthalen-1-ylsulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10t**).* Yield 73%, m.p. 104–106 °C. ^{1}H NMR (DMSO-d_6): δ 0.70 (t, 3H, J_{HH} = 7.0 Hz, CH_3), 2.15 (q, 2H, J_{HH} = 7.0 Hz, CH_2), 6.55 (br. s, 1H, NH), 7.48–7.73 м (3H, H_{Ar}), 7.95 (d, 1H, J_{HH} = 7.7 Hz, H_{Ar}), 8.10 (d, 1H, J_{HH} = 8.1 Hz, H_{Ar}), 8.18 (d, 1H, J_{HH} = 7.4 Hz, H_{Ar}), 8.35 (s, 1H, NH), 8.70 (d, 1H, J_{HH} = 8.1 Hz, H_{Ar}), 9.78 (s, 1H, NH). ^{19}F NMR (DMSO-d_6): δ 5.02 s. EI-MS (*m*/*z*): 444 $[M+1]^+$. Anal. calcd. for $C_{16}H_{15}F_6N_3O_3S$: C, 43.34; H, 3.41; F, 25.71; N, 9.48; O, 10.83; S, 7.23; found: C, 43.52; H, 3.52; F, 25.63; N, 9.44.

*4.1.3.17. 2-(Naphthalene-2-ylsulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10u**).* Yield 67%, m.p. 110–112 °C. ^{1}H NMR ($CDCl_3$): δ 0.71 (t, 3H, J_{HH} = 7.0 Hz, CH_3), 2.20 (q, 2H, J_{HH} = 7.0 Hz, CH_2), 5.93 (s, 1H, NH), 6.90 (s, 1H, NH), 7.02 (s, 1H, H_{Ar}), 7.55–7.73 (m, 2H, H_{Ar}), 7.76–8.03 (m, 4H, H_{Ar}), 8.46 (s, 1H, NH). ^{19}F NMR ($CDCl_3$): δ 5.06 s. EI-MS (*m*/*z*): 444 $[M+1]^+$. Anal. calcd. for $C_{16}H_{15}F_6N_3O_3S$: C, 43.34; H, 3.41; F, 25.71; N, 9.48; O, 10.83; S, 7.23; found: C, 43.42; H, 3,26; F, 25.64; N, 9.55.

*4.1.3.18. 2-((4-Methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10v**).* Yield 55%, m.p. 72–74 °C. ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H, J_{HH} = 7.4 Hz, CH_3), 2.38 (q, 2H, J_{HH} = 7.4 Hz, CH_2), 2.92 (s, 3H, CH_3N), 3.31 (m, 2H, CH_2N), 4.33 (m, 2H, CH_2O), 5.95 (s, 1H, NH), 6.63 (s, 1H, NH), 6.74 (s, 1H, NH), 6.83 (d, 1H, J_{HH} = 8.4 Hz, H_{Ar},), 7.05 (d, 1H, J_{HH} = 2.1 Hz, H_{Ar},), 6.83 (d, 1H, J_{HH} = 8.4, 2.1 Hz, H_{Ar},). ^{19}F NMR ($CDCl_3$): δ 5.04 s. EI-MS (*m*/*z*): 465 $[M+1]^+$. Anal. calcd. for $C_{15}H_{18}F_6N_4O_4S$: C, 38.80; H, 3.91; F, 24.55; N, 12.07; O, 13.78; S, 6.90; found: C, 38.72; H, 3.86; F, 24.72; N, 11.99.

*4.1.4. Procedure for the synthesis of compound **10w***

1 mmol of hydrazide **5w** and 1.2 mmol of isocyanate **3** in 10 ml of benzene were heated in a sealed ampoule during 3 h at 90 °C. The ampoule was opened and volatiles were evaporated. The residue was crystallized from benzene. HPLC analysis revealed a single peak.

*4.1.4.1. 2-((4-(1,2,3-Thiadiazol-4-yl)phenyl)sulfonyl)-N-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)hydrazine-1-carboxamide (**10w**).* Yield 55%, m.p. 170–172 °C. ^{1}H NMR (DMSO-d_6): δ 0.88 (t, 3H, J_{HH} = 7.4 Hz, CH_3), 2.32 (q, 2H, J_{HH} = 7.4 Hz, CH_2), 6.65 (s, 1H, NH), 8.01 (d, 2H, J_{HH} = 7.9 Hz, CH_{Ar}), 8.30 (d, 2H, J_{HH} = 7.9 Hz, H_{Ar}), 8.39 (s, 1H, NH), 9.30 (s, 1H, NH), 9.40 (s, 1H, H_{Ar}). ^{19}F NMR (DMSO-d_6): δ 5.02 s. EI-MS (*m*/*z*): 478 $[M+1]^+$. Anal. calcd. for

$C_{14}H_{13}F_6N_5O_3S_2$: C, 35.22; H, 2.74; F, 23.88; N, 14.67; O, 10.05; S, 13.43; found: C, 35.38; H, 2.89; F, 23.67; N, 14.80.

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