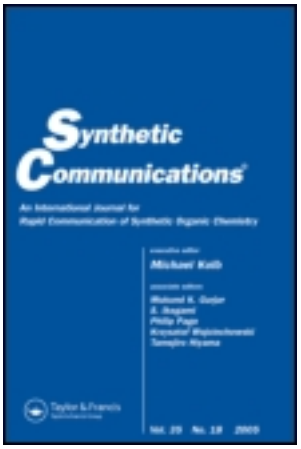

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Synthesis of New Perfluoroalkylated 1,3,4-Oxadiazoles and 1,2,4-Triazoles Starting from 2-(Perfluoroalkyl)ethane Thiols

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SYNTHESIS OF NEW PERFLUOROALKYLATED 1,3,4-OXADIAZOLES AND 1,2,4-TRIAZOLES STARTING FROM 2-(PERFLUOROALKYL)ETHANE THIOLS

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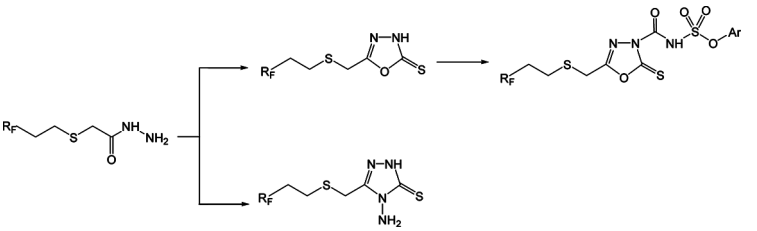
GRAPHICAL ABSTRACT



Abstract *5-{[2-(Perfluoroalkyl)ethylthio]methyl}-1,3,4-oxadiazole-2-thiones* ***4a, b*** *and 4-amino-5-{[2-(perfluoroalkyl)ethylthio]methyl}-4*H*-1,2,4-triazole-3-thiones* ***5a, b*** *have been prepared from 2-(perfluoroalkyl)ethane thiols* ***1a, b*** *through a multistep reaction sequence. Compounds* ***4a, b*** *were further reacted with aryloxysulfonylisocyanates to give the corresponding 5-{[2-(perfluoroalkyl)ethylthio]methyl}-*N*-(aryloxysulfonyl)-2-thioxo-1,3,4-oxadiazole-3(2*H*)-carboxamide* ***6a–d****. The new products were obtained in good to moderate yields, and their structures were established on the basis of their infrared, NMR, and mass spectral data.*

Keywords Aryloxysulfonylisocyanates; carbon disulfide; 1,3,4-oxadiazole; 2-(perfluoroalkyl)ethane thiols; 1,2,4-triazole

INTRODUCTION

Heterocycles containing a 1,2,4-triazole or 1,3,4-oxadiazole moiety constitute a class of compounds that possess a wide spectrum of biological activities such as anti-inflammatory, antiviral, antimicrobial, and antitumoral properties.[1–4] For instance, some azole derivatives were developed as new antimicrobial agents, such as linezolid and eperezolid, which are currently used for the treatment of multidrug-resistant Gram-positive infections.[5–7] It was also shown that derivatization of the carboxylate function of representative nonsteroidal anti-inflammatory

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drugs with less acidic azoles (viz., 1,3,4-oxadiazole, 1,2,4-triazole, etc.) resulted in an increased anti-inflammatory activity with reduced ulcerogenicity.[8–10] 1,3,4-Oxadiazole-containing molecules have also interesting optical properties. They have been recently incorporated into polymers and small molecules in new optoelectronic materials to increase external quantum efficiencies and overall device performance.[11]

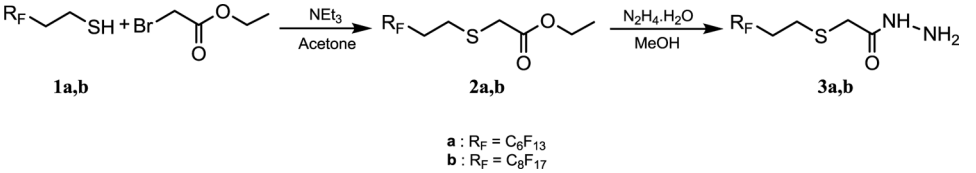
On the other hand, fluorinated heterocycles are widely used in pharmaceuticals, agrochemicals, and new materials, and their synthesis constitutes an increasingly valuable research area.[12–15]

Recently, we have reported the synthesis of perfluoroalkyl tertazol-5-ones[16] and dioxalanones[17] starting from fluorinated azides and α-hydroxy acids, respectively. Following our interest in the study of fluorine-containing compounds, we report herein the synthesis of hybrid compounds that contain both a perfluoroalkyl group and oxadiazole or triazole ring systems. These perfluoroalkylated oxadiazoles and triazoles have been characterized by NMR, infrared (IR) and mass (MS) spectroscsopic techniques. As for some other oxadiazole- and triazole-containing compounds, the new fluorinated heterocycles may have important anti-inflammatory properties and would show the effect of such hybridization on the anticipated biological properties.

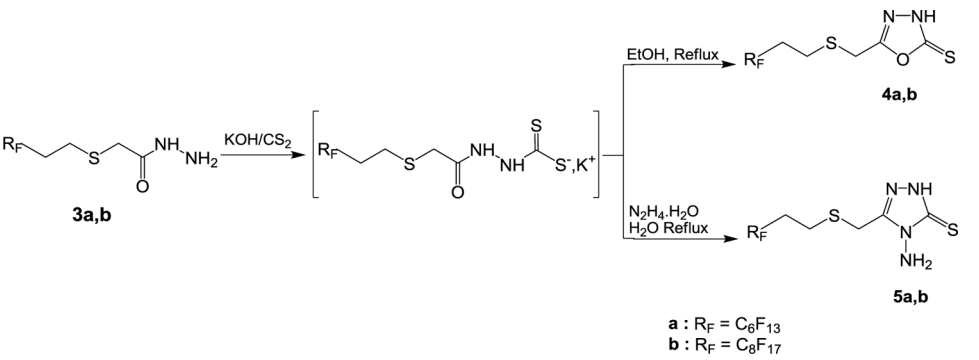
RESULTS AND DISCUSSION

2-(Perfluoroalkyl)ethane thiols **1** were easily converted into 2-(perfluoroalkyl) ethylthioacetates **2** in the presence of triethylamine and ethyl bromoacetate in anhydrous acetone. The reaction of hydrazine hydrate with acetates **2** in refluxing methanol afforded 2-(perfluoroalkyl)ethylthioacetohydrazide **3** in good yields (Scheme 1). In the IR spectra of compounds **3**, broad stretching bands at 3211 and 3328 cm^{-1} were due to amine /amide, NH whereas a strong stretching band at ~1660 cm^{-1} was attributed to amide carbonyl. ^1H NMR spectra showed singlets at ~4.11 and 9.10 ppm, which were assigned to NH_2 and NH groups.

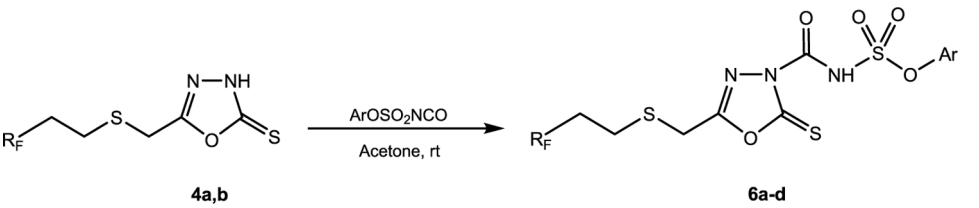
Hydrazides **3** react with carbon disulfide in the presence of potassium hydroxide to give the intermediate potassium dithiocarbazate salts, which on refluxing in ethanol yield 1,3,4-oxadiazoles **4**, and their treatment with hydrazine hydrate led to formation of the corresponding 1,2,4-triazoles **5** as shown in Scheme 2. The new products **4** and **5** were characterized by their IR, NMR, and MS spectra. The lack of ^1H NMR resonances observed with NH and NH_2 groups in the ^1H NMR spectra of **4** proved that ring closure starting from **3** resulted in the formation of an 1,3,4-oxadiazole ring. This was further confirmed by the ^{13}C NMR data of **4,** which showed peaks at ~162 and 180 ppm due to C_5 and C_2 of oxadiazole. Mass spectra of **4a** and **4b** displayed molecular ion base peaks at m/z 479 and 579,



Scheme 1. Synthetic pathway for the preparation of 2-(perfluoroalkyl) ethylthioacetohydrazides **3a, b**.



Scheme 2. Synthetic pathway for the preparation of oxadiazoles **4a, b** and triazoles **5a, b**.



Scheme 3. Synthetic pathway for the preparation of oxadiazoles **6a–d**.

respectively, which confirmed their molecular weights. The IR spectra of **5** show stretching bands at about 3320 and 3115 cm^{-1} due to NH/NH_2. ^1H NMR spectra of this sample displayed singlets at 13.57 and 5.50 ppm, assigned to NH and NH_2, respectively, which disappeared on D_2O exchange. ^{13}C NMR spectra of **5** showed signals at 168 and 149 ppm due to C=S and C_5 carbons of the triazole ring. Mass spectra of **5a** and **5b** displayed molecular ion base peaks at m/z 507 and 607, respectively, which confirmed their molecular weights.

In continuation of our research work on the reactivity of isocyanates,[18–22] 1,3,4-oxadiazoles **6** were obtained via reaction of 1,3,4-oxadiazoles **4** with aryloxysulfonylisocyanate in anhydrous acetone at room temperature (see Scheme 3). The *N*-alkylation of oxadiazoles **4** was further confirmed by the presence of a C=S stretching vibration at 1560–1575 cm^{-1} in the IR spectra of oxadiazoles **6,** together with absorption bands in the range 3220–3230 and 1690–1700 cm^{-1} due to NH and C=O, respectively. Interestingly, the ^1H NMR spectra of products **6** show the lack of NH resonance of the starting oxadiazole and the appearance of a new broad signal at 9.50 ppm, assigned to amide proton. This is in good agreement with results obtained for unfluorinated analogs.[23]

CONCLUSION

New fluorinated oxadiazoles and triazoles were prepared from the readily available 2-(perfluoroalkyl)ethane thiols. These compounds could present versatile

intermediates for the preparation of various oxadiazole- and triazole-containing heterocycles. The study related to the application of these new oxadiazoles and triazoles in biological and industrial field is ongoing.

EXPERIMENTAL

IR spectra were obtained using a Perkin-Elmer Fourier transform (FT) Pragon 1000 PC. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Brucker AC 300 spectrometer at 300, 75, and 282 MHz, respectively. Chemical shifts were reported in parts per million (ppm) from external C_6F_6 for ^{19}F and internal tetramethylsilane (TMS) for ^{1}H and ^{13}C. The mass spectra were recorded on a Quattro microinstrument (micromass, UK Manchester; capillary voltage: 3.2 kV; cone voltage: 25 V; source temperature: 120 °C; desolvation temperature: 400 °C; desolvation gaz flow: 500 L/h; neublization: 7 psi) with negative electrospray ionization mode. Melting points were determined using an Electrothermal IA 9000 series II instrument and are uncorrected. 2-(Perfluoroalkyl)ethane thiols were supplied by AtoFina and used as received. The aryloxysulfonyisocyanates were prepared from phenols and sulfonylisocyanate chloride as previously described.[24,25]

Synthesis of 2-(Perfluoroalkyl)ethylthioacetates (2a, b)

To a solution of 2-(perfluorohexyl)ethane thiol **1a** (3.8 g, 10 mmol) and triethylamine (1.2 g, 12 mmol) in 10 ml of dry acetone was added ethyl bromoacetate (2.0 g, 12 mmol). The reaction mixture was stirred at room temperature for 10 min. The filtrate was concentrated in vacuo and the residue was distilled under reduced pressure.

Synthesis of 2-(Perfluoroalkyl)ethylthioacetohydrazides (3a, b)

A mixture of 2-(perfluorohexyl)ethylthioacetate **2a** (4.52 g, 10 mmol) and hydrazine hydrate (1.0 g, 20 mmol) in 10 ml of methanol was heated under reflux for 5–6 h. The reaction mixture was left overnight at room temperature. The solid separated was collected by filtration, washed with methanol, dried, and recrystallized from benzene.

Synthesis of 5-{[2-(Perfluoroalkyl)ethylthio]methyl}-1,3,4-oxadiazole-2-thiones (4a, b)

2-(Perfluorooctyl)ethylthioacetohydrazide **3b** (1.65 g, 3 mmol) was dissolved in a solution of potassium hydroxide (0.34 g, 6 mmol) in water (2 ml) and ethanol (20 ml). Carbon disulfide (2.51 g, 33 mmol) was then added while stirring, and the reaction mixture was heated under reflux for 8 h. The solvents were removed under reduced pressure; the residue was treated with water and then filtered. The filtrate was cooled and neutralized to pH 6 using dilute hydrochloric acid, and the separated solid was filtered, washed with water, dried, and recrystallized from carbon tetrachloride.

Synthesis of 4-Amino-5-{[2-(perfluoroalkyl)ethylthio]methyl}-4*H*-1,2,4-triazole-3-thiones (5a, b)

2-(Perfluorooctyl)ethylthioacetohydrazide **3b** (1.65 g, 3 mmol) and carbon disulfide (0.46 g, 6 mmol) were added to a solution of potassium hydroxide (0.37 g, 6.6 mmol) in absolute ethanol (30 ml), and the mixture was stirred at room temperature for 16 h. Anhydrous ether was added to the resulting solution, and the precipitated potassium dithiocarbazate salt was collected by filtration, washed with ether, and dried under vacuum. This salt was obtained in quantitative yield and was used in the next step without further purification.

A mixture of the potassium salt (4 g, 6 mmol), hydrazine hydrate (0.3 g, 6 mmol), and water (1 ml) was heated under reflux for 5 h. Hydrogen sulfide evolved, the homogenous solution obtained was diluted with 50 ml water, and subsequent acidification with dilute acetic acid gave a white precipitate, which was filtered, washed with water, and recrystallized from hexane.

Synthesis of *5*-{[2-(Perfluoroalkyl)ethylthio]methyl}-*N*-(aryloxysulfonyl)-2-thioxo-1,3,4-oxadiazole-3(2*H*)-carboxamides (6a–c)

2,4,6-Trimethylaryloxysulfonylisocyanate (0.24 g, 1 mmol) was added to a solution of 5-{[2-(perfluorohexyl)ethylthio]methyl}-1,3,4-oxadiazole-2-thione **4a** (0.49 g, 1 mmol) in dry acetone (10 ml) while stirring. The reaction mixture was stirred at room temperature for 15 min, the solvent was evaporated, and the residue was recrystallized from benzene.

Selected Data

Ethyl 2-(perfluorohexyl)ethylthioacetate (2a). Yield: 96%, colorless liquid, bp: 108–110 °C / 15 mmHg. IR (CH_3Cl, ν, cm^{-1}): 1743 (C=O). ^1H NMR ($CDCl_3$): 1.29 (t, 3H, CH_3, $^3J_{HH} = 7.20$), 2.45 (m, 2H, CH_2-CF_2), 2.87 (t, 2H, CH_2-S, $^3J_{HH} = 6.93$), 3.26 (s, 2H, CH_2-CO), 4.22 (q, CH_2-O, $^3J_{HH} = 7.20$). ^{13}C NMR ($CDCl_3$): 14.1 (s, $\underline{C}H_3$-CH_2-), 23.3 (s, CH_2-$\underline{C}H_2$-S), 31.6 (t, $\underline{C}H_2$-CH_2-S, $^2J_{CF} =$ 21.38), 33.7 (s, S-$\underline{C}H_2$-CO), 61.8 (s, O-$\underline{C}H_2$-CH_3), 104–122 (m, $\underline{C}_6F_{13}$), 170.1 (s, CO). ^{19}F NMR ($CDCl_3$): 35.33 (m, 2 F, $CF_{2\alpha}$), 38.16 (m, 2 F, $CF_{2\beta}$), 38.68 (m, 2 F, $CF_{2\gamma}$), 39.80 (m, 2 F, $CF_{2\delta}$), 48.72–48.19 (m, 2 F, $CF_{2\omega}$), 80.56 (m, 3 F, CF_3).

Ethyl 2-(perfluorooctyl)ethylthioacetate (2b). Yield: 94%, colorless liquid, bp: 165–167 °C / 15 mmHg. IR (CH_3Cl, ν, cm^{-1}): 1749 (C=O). ^1H NMR ($CDCl_3$): 1.26 (t, 3H, CH_3, $^3J_{HH} = 7.21$), 2.47 (m, 2H, CH_2-CF_2), 2.88 (t, 2H, CH_2-S, $^3J_{HH} = 6.92$), 3.25 (s, 2H, CH_2-CO), 4.21 (q, 2H, CH_2-O, $^3J_{HH} = 7.21$). ^{13}C NMR ($CDCl_3$): 13.9 (s, $\underline{C}H_3$-CH_2-O), 23.1 (s, CH_2-$\underline{C}H_2$-S), 31.5 (t, $\underline{C}H_2$-CH_2-S, $^2J_{CF} = 21.40$), 33.8 (s, S-$\underline{C}H_2$-CO), 61.9 (s, O-$\underline{C}H_2$-CH_3), 105–122 (m, $\underline{C}_8F_{17}$), 169.8 (s, CO). ^{19}F NMR ($CDCl_3$): 35.32 (m, 2 F, $CF_{2\alpha}$), 35.43 (m, 2 F, $CF_{2\beta}$), 38.21 (m, 2 F, $CF_{2\gamma}$), 38.69 (m, 2 F, $CF_{2\delta}$), 38.85 (m, 2 F, $CF_{2\omega}$), 38.95 (m, 4 F, $2CF_{2\epsilon}$), 80.56 (m, 3 F, CF_3).

2-(Perfluorohexyl)ethylthioacetohydrazide (3a). Yield: 90%, white solid, mp: 58 °C. IR (KBr, ν, cm^{-1}): 3328 (NH), 3211 (NH_2), 1660 (C=O). ^1H NMR (acetone-d_6): 2.44 (m, 2H, CH_2-CF_2), 2.89 (t, 2H, CH_2-S, $^3J_{HH} = 6.89$), 3.28 (s, 2H, CH_2-CO), 4.11 (br, 2H, NH_2), 9.10 (br, 1H, NH-CO). ^{13}C NMR (acetone-d_6): 23.7 (s, CH_2-$\underline{C}H_2$-S), 31.2 (t, $\underline{C}H_2$-CH_2-S, $^2J_{CF} = 21.45$), 34.1 (s, S-$\underline{C}H_2$-CO), 105–122 (m, $\underline{C}_6F_{13}$), 173.8 (s, CO). ^{19}F NMR (acetone-d_6): 35.35 (m, 2 F, $CF_{2\alpha}$), 38.14 (m, 2 F, $CF_{2\beta}$), 38.65 (m, 2 F, $CF_{2\gamma}$), 39.82 (m, 2 F, $CF_{2\delta}$), 48.70–48.17 (m, 2 F, $CF_{2\omega}$), 80.57 (m, 3 F, CF_3). MS: $m/z = 451$ $(M - H)^-$.

2-(Perfluorooctyl)ethylthioacetohydrazide (3b). Yield: 93%, white solid, mp: 111 °C. IR (KBr, ν, cm^{-1}): 3327 (NH), 3210 (NH_2), 1663 (C=O). ^1H NMR (acetone-d_6): 2.52 (m, 2H, CH_2-CF_2), 2.91 (t, 2H, CH_2-S, $^3J_{HH} = 6.90$), 3.24 (s, 2H, CH_2-CO), 4.09 (br, 2H, NH_2), 9.11 (br, 1H, NH-CO). ^{13}C NMR (acetone-d_6): 24.6 (s, CH_2-$\underline{C}H_2$-S), 30.6 (t, $\underline{C}H_2$-CH_2-S, $^2J_{CF} = 21.43$), 32.9 (s, S-$\underline{C}H_2$-CO), 105–122 (m, $\underline{C}_8F_{17}$), 172.9 (s, CO). ^{19}F NMR (acetone-d_6): 35.33 (m, 2 F, $CF_{2\alpha}$), 35.45 (m, 2 F, $CF_{2\beta}$), 38.24 (m, 2 F, $CF_{2\gamma}$), 38.71 (m, 2 F, $CF_{2\delta}$), 38.88 (m, 2 F, $CF_{2\omega}$), 38.96 (m, 4 F, $2CF_{2\epsilon}$), 80.58 (m, 3 F, CF_3). MS: $m/z = 551$ $(M - H)^-$.

5-{[2-(Perfluorohexyl)ethylthio]methyl}-1,3,4-oxadiazole-2-thione (4a). Yield: 54%, white solid, mp: 93 °C. IR (KBr, ν, cm^{-1}): 3347 (NH), 1629 (C=N), 1567 (C=S), and 1123 (=C-O-C=). ^1H NMR (DMSO-d_6): 2.49 (m, 2H, CH_2-CF_2), 2.82 (t, 2H, CH_2-$C\underline{H}_2$-S, $^3J_{HH} = 6.92$), 3.85 [s, 2H, CH_2-C(O)(N)], 14.4 (br, NH). ^{13}C NMR (DMSO-d_6): 22.1 (s, CH_2-$\underline{C}H_2$-S), 24.3 [s, $\underline{C}H_2$-C(O)=N], 30.4 (t, $\underline{C}H_2$-CH_2-S, $^2J_{CF} = 21.63$), 107–122 (m, $\underline{C}_6F_{13}$), 161.8 [s, CH_2-$\underline{C}$(O)=N], 177.9 (s, C=S). ^{19}F NMR (DMSO-d_6): 35.33 (m, 2 F, $CF_{2\alpha}$), 38.16 (m, 2 F, $CF_{2\beta}$), 38.64 (m, 2 F, $CF_{2\gamma}$), 39.83 (m, 2 F, $CF_{2\delta}$), 48.71–48.19 (m, 2 F, $CF_{2\omega}$), 80.54 (m, 3 F, CF_3). MS: $m/z = 479$ $(M - H)^-$, $MS2_{(m/z=479)}$: $m/z = 147$ $(M\text{-}H\text{-}CH_2=CH\text{-}C_6F_{13})^-$ AR = 100%.

5-{[2-(Perfluorooctyl)ethylthio]methyl}-1,3,4-oxadiazole-2-thione (4b). Yield: 61%, white solid, mp: 110 °C. IR (KBr, ν, cm^{-1}): 3345 (NH), 1622 (C=N), 1565 (C=S) and 1128 (=C-O-C=). ^1H NMR (DMSO-d_6): 2.51 (m, 2H, CH_2-CF_2), 2.85 (t, 2H, CH_2-$C\underline{H}_2$-S, $^3J_{HH} = 6.93$), 3.86 [s, 2H, CH_2-C(O)(N)], 14.5 (br, NH). ^{13}C NMR (DMSO-d_6): 23.4 (s, CH_2-$\underline{C}H_2$-S), 25.8 [s, $\underline{C}H_2$-C(O)=N], 32.3 (t, $\underline{C}H_2$-CH_2-S, $^2J_{CF} = 21.65$), 108–122 (m, $\underline{C}_8F_{17}$), 162.2 [s, CH_2-$\underline{C}$(O)=N], 179.8 (s, C=S). ^{19}F NMR (DMSO-d_6): 35.34 (m, 2 F, $CF_{2\alpha}$), 35.46 (m, 2 F, $CF_{2\beta}$), 38.28 (m, 2 F, $CF_{2\gamma}$), 38.71 (m, 2 F, $CF_{2\delta}$), 38.88 (m, 2 F, $CF_{2\omega}$), 38.90 (m, 4 F, $2CF_{2\epsilon}$), 80.56 (m, 3 F, CF_3). MS: $m/z = 579$ $(M - H)^-$, $MS2_{(m/z=579)}$: $m/z = 147$ $(M\text{-}H\text{-}CH_2=CH\text{-}C_8F_{17})^-$ AR = 100%.

4-Amino-5-{[2-(perfluorohexyl)ethylthio]methyl}-4*H*-1,2,4-triazole-3-thione (5a). Yield: 49%, white solid, mp: 90 °C. IR (KBr, ν, cm^{-1}): 3320 (NH), 3115 (NH_2), 1570 (C=S), and 1621 (C=N). ^1H NMR (DMSO-d_6): 2.63 (m, 2H, CH_2-CF_2), 2.98 (t, 2H, CH_2-$C\underline{H}_2$-S, $^3J_{HH} = 6.92$), 3.38 [s, 2H, CH_2-C(N)(N)], 5.50 (br, NH_2), 13.57 (br, NH). ^{13}C NMR (DMSO-d_6): 24.4 (s, CH_2-$\underline{C}H_2$-S), 32.5 (t, $\underline{C}H_2$-CH_2-S, $^2J_{CF} = 21.55$), 33.7 (s, $\underline{C}H_2$-C(N)=N), 111–122 (m, $\underline{C}_6F_{13}$), 149.0 [s, CH_2-$\underline{C}$(N)=N], 167.8 (s, C=S). ^{19}F NMR (DMSO-d_6): 35.36 (m, 2 F, $CF_{2\alpha}$), 38.14 (m, 2 F, $CF_{2\beta}$), 38.66 (m, 2 F, $CF_{2\gamma}$), 39.88 (m, 2 F, $CF_{2\delta}$), 48.67–48.15

(m, 2 F, $CF_{2\omega}$), 80.55 (m, 3 F, CF_3). MS: $m/z = 507$ $(M - H)^-$, $MS2_{(m/z=507)}$: $m/z = 161$ $(M\text{-}H\text{-}CH_2 = CH\text{-}C_6F_{13})^-$ AR = 100%.

4-Amino-5-{[2-(perfluorooctyl)ethylthio]methyl}-4*H*-1,2,4-triazole-3-thione (5b). Yield: 57%, white solid, mp: 113 °C. IR (KBr, ν, cm^{-1}): 3219 (NH), 3113 (NH_2), 1571 (C=S) and 1623 (C=N).^{1}H NMR (DMSO-d_6): 2.61 (m, 2H, CH_2-CF_2), 2.97 (t, 2H, CH_2-C<u>H</u>$_2$-S, $^3J_{HH} = 6.91$), 3.36 [s, 2H, CH_2-C(N)(N)], 5.52 (br, NH_2), 13.58 (br, NH). ^{13}C NMR (DMSO-d_6): 24.5 (s, CH_2-<u>C</u>H_2-S), 32.6 (t, <u>C</u>H_2-CH_2-S, $^2J_{CF} = 21.54$), 33.7 [s, <u>C</u>H_2-C(N) = N], 110–122 (m, <u>C</u>$_8F_{17}$), 149.1 [s, CH_2-<u>C</u>(N) = N], 167.9 (s, C=S). ^{19}F NMR (DMSO-d_6): 35.31 (m, 2 F, $CF_{2\alpha}$), 35.44 (m, 2 F, $CF_{2\beta}$), 38.27 (m, 2 F, $CF_{2\gamma}$), 38.73 (m, 2 F, $CF_{2\delta}$), 38.89 (m, 2 F, $CF_{2\omega}$), 38.92 (m, 4 F, $2CF_{2\epsilon}$), 80.52 (m, 3 F, CF_3). MS: $m/z = 607$ $(M - H)^-$, $MS2_{(m/z=607)}$: $m/z = 161$ $(M\text{-}H\text{-}CH_2 = CH\text{-}C_8F_{17})^-$ AR = 100%.

***5*-{[2-(Perfluorohexyl)ethylthio]methyl}-*N*-(2,4,6-trimethylphenyloxysulfonyl)-2-thioxo-1,3,4-oxadiazole-3(2*H*)-carboxamide (6a).** Yield: 91%, white solid, mp: 96 °C. IR (KBr, ν, cm^{-1}): 3221 (NH), 1698 (C=O), 1563 (C=S), 1399, 1174 (SO_2 sym., asym. stretching), and 1123 (= C-O-C =). ^{1}H NMR (DMSO-d_6): 2.10 (s, 3H, CH_{3arom}), 2.19 (s, 6H, $2CH_{3arom}$), 2.65 (m, 2H, CH_2-CF_2), 2.97 (t, 2H, CH_2-C<u>H</u>$_2$-S, $^3J_{HH} = 6.90$), 3.36 (s, 2H, CH_2-CH_2-S-C<u>H</u>$_2$), 6.94 (s, 2H, H_{arom}), 9.21 (br, 1H, NH-CO). ^{13}C NMR (DMSO-d_6): 23.4 (s, CH_2-<u>C</u>H_2-S), 25.8 (s, S-<u>C</u>H_2-CO) 32.6 (t, <u>C</u>H_2-CH_2-S, $^2J_{CF} = 21.63$), 107–122 (m, <u>C</u>$_6F_{13}$), 129–144 (C_{arom}), 148.4 (s, CO), 160.2 [s, CH_2-<u>C</u>(O) = N], 176.8 (s, C=S). ^{19}F NMR (DMSO-d_6): 35.36 (m, 2 F, $CF_{2\alpha}$), 38.19 (m, 2 F, $CF_{2\beta}$), 38.67 (m, 2 F, $CF_{2\gamma}$), 39.84 (m, 2 F, $CF_{2\delta}$), 48.73–48.21 (m, 2 F, $CF_{2\omega}$), 80.61 (m, 3 F, CF_3). MS: $m/z = 762$ $(M\text{-}H + CH_3CN)^-$, $MS2_{(m/z=762)}$: $m/z = 197$ $[HS\text{-}CO\text{-}NH\text{-}SO_3 + CH_3CN]^-$ AR = 100%.

***5*-{[2-(Perfluorohexyl)ethylthio]methyl}-*N*-(2,4,6-trichlorophenyloxysulfonyl)-2-thioxo-1,3,4-oxadiazole-3(2*H*)-carboxamide (6b).** Yield: 88%, white solid, mp: 117 °C. IR (KBr, ν, cm^{-1}): 3229 (NH), 1691 (C=O), 1575 (C=S), 1409, 1178 (SO_2 sym., asym. stretching), and 1125 (= C-O-C =). ^{1}H NMR (DMSO-d_6): 2.63 (m, 2H, CH_2-CF_2), 2.91 (t, 2H, CH_2-C<u>H</u>$_2$-S, $^3J_{HH} = 6.89$), 3.35 (s, 2H, CH_2-CH_2-S-C<u>H</u>$_2$), 7.49 (s, 2H, H_{arom}), 9.50 (br, 1H, NH-CO). ^{13}C NMR (DMSO-d_6): 24.4 (s, CH_2-<u>C</u>H_2-S), 27.1 (s, S-<u>C</u>H_2-CO), 33.9 (t, <u>C</u>H_2-CH_2-S, $^2J_{CF} = 21.64$), 105–122 (m, <u>C</u>$_6F_{13}$), 125–149 (C_{arom}), 149.8 (s, CO), 160.9 [s, CH_2-<u>C</u>(O) = N], 177.0 (s, C=S). ^{19}F NMR (DMSO-d_6): 35.38 (m, 2 F, $CF_{2\alpha}$), 38.22 (m, 2 F, $CF_{2\beta}$), 38.68 (m, 2 F, $CF_{2\gamma}$), 39.85 (m, 2 F, $CF_{2\delta}$), 48.75–48.22 (m, 2 F, $CF_{2\omega}$), 80.63 (m, 3 F, CF_3). MS: $m/z = 836$ $(M - H + CH_3CN)^-$, $MS2_{(m/z=836)}$: $m/z = 197$ $[HS\text{-}CO\text{-}NH\text{-}SO_3 + CH_3CN]^-$ AR = 100%.

***5*-{[2-(Perfluorooctyl)ethylthio]methyl}-*N*-(2,4,6-trimethylphenyloxysulfonyl)-2-thioxo-1,3,4-oxadiazole-3(2*H*)-carboxamide (6c).** Yield: 89%, white solid, mp: 124 °C. IR (KBr, ν, cm^{-1}) 3220 (NH), 1697 (C=O), 1561 (C=S), 1400, 1175 (SO_2 sym., asym. stretching), and 1121 (= C-O-C =). ^{1}H NMR (DMSO-d_6): 2.11 (s, 3H, CH_{3arom}), 2.20 (s, 6H, $2CH_{3arom}$), 2.64 (m, 2H, CH_2-CF_2), 3.01 (t, 2H, CH_2-C<u>H</u>$_2$-S, $^3J_{HH} = 6.91$), 3.35 (s, 2H, CH_2-CH_2-S-C<u>H</u>$_2$), 6.97 (s, 2H, H_{arom}), 9.25 (br, 1H, NH-CO). ^{13}C NMR (DMSO-d_6): 23.3 (s, CH_2-<u>C</u>H_2-S), 25.7 (s, S-<u>C</u>H_2-CO) 32.5 (t, <u>C</u>H_2-CH_2-S, $^2J_{CF} = 21.64$), 105–122 (m, <u>C</u>$_8F_{17}$), 129–144 (C_{arom}), 148.5 (s, CO), 159.9 [s, CH_2-<u>C</u>(O) = N], 178.1 (s, C=S). ^{19}F NMR (DMSO-d_6): 35.32

(m, 2 F, $CF_{2\alpha}$), 35.44 (m, 2 F, $CF_{2\beta}$), 38.25 (m, 2 F, $CF_{2\gamma}$), 38.68 (m, 2 F, $CF_{2\delta}$), 38.86 (m, 2 F, $CF_{2\omega}$), 38.89 (m, 4 F, $2CF_{2\epsilon}$), 80.55 (m, 3 F, CF_3). MS: $m/z = 862$ (M-H + $CH_3CN)^-$, $MS2_{(m/z=862)}$: $m/z = 197$ [HS-CO-NH-SO_3 + $CH_3CN]^-$ AR = 100%.

***5*-{[2-(Perfluorooctyl)ethylthio]methyl}-*N*-(2,4,6-trichlorophenyloxysulfonyl)-2-thioxo-1,3,4-oxadiazole-3(2*H*)-carboxamide (6d).** Yield: 84%, white solid, mp: 101 °C. IR (KBr, ν, cm^{-1}): 3230 (NH), 1693 (C=O), 1574 (C=S), 1408, 1177 (SO_2 sym., asym. stretching) and 1119 (= C-O-C=). ^1H NMR (DMSO-d_6): 2.65 (m, 2H, CH_2-CF_2), 2.92 (t, 2H, CH_2-C$\underline{H}_2$-S, $^3J_{HH} = 6.92$), 3.36 (s, 2H, CH_2-CH_2-S-C$\underline{H}_2$), 7.48 (s, 2H, H_{arom}), 9.54 (br, 1H, NH-CO). ^{13}C NMR (DMSO-d_6): 24.6 (s, CH_2-$\underline{C}H_2$-S), 26.9 [s, $\underline{C}H_2$-C(O)=N], 33.8 (t, $\underline{C}H_2$-CH_2-S, $^2J_{CF} = 21.63$), 105–122 (m, $\underline{C}_8F_{17}$), 125–149 (C_{arom}), 149.9 (s, CO), 159.8 [s, CH_2-$\underline{C}$(O) = N], 177.5 (s, C=S). ^{19}F NMR (DMSO-d_6): 35.33 (m, 2 F, $CF_{2\alpha}$), 35.43 (m, 2 F, $CF_{2\beta}$), 38.26 (m, 2 F, $CF_{2\gamma}$), 38.69 (m, 2 F, $CF_{2\delta}$), 38.86 (m, 2 F, $CF_{2\omega}$), 38.90 (m, 4 F, $2CF_{2\epsilon}$), 80.56 (m, 3 F, CF_3). MS: $m/z = 936$ $(M\text{-}H + CH_3CN)^-$, $MS2_{(m/z=936)}$: $m/z = 197$ [HS-CO-NH-SO_3 + $CH_3CN]^-$ AR = 100%.

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