Hydrazinecarbothioamides and 1,3,4-Thia/Oxadiazoles
Derivatives with Potential Biological Activity
Synthesis and Spectral Characterization

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This paper presents synthesis of some compounds containing the arylsulfonylphenyl and 4-trifluoromethylphenyl moieties. The hydrazinecarbothioamides were synthesized using 4-(4-X-phenylsulfonyl)benzoic acid hydrazides in reaction with the (4-trifluoromethyl)phenyl isothiocyanate. The 1,3,4-thiadiazoles were obtained from hydrazinecarbothioamides in acidic media and 1,3,4-oxadiazoles by treating of same acyclic compounds with mercury oxide. The synthesized compounds structures were elucidated by spectral data and elemental analysis.

Keywords: 1,3,4-thiadiazole, 1,3,4-oxadiazole, hydrazinecarbothioamide, cyclization

Hydrazinecarbothioamides are building blocks for the construction of a wide variety of molecules especially heterocyclic compounds including thiadiazoles and oxadiazoles [1].

A large number of heterocyclic compounds from 1,3,4-thiadiazole and 1,3,4-oxadiazole class derivatives have been prepared using hydrazinecarbothioamides as raw material by different methods [1-5] and many of these have shown a broad spectrum of biological properties including, anti-inflammatory [3,6,7], antiviral [8,9], antidepressant [10], antitumoral [11-16], analgesic [3,5,16,17], antibacterial, antifungal [18-21], etc.

Also, from the literature it is known that the introduction of a trifluoromethyl group into bioactive molecules, especially in the positions responsible for their physiological profile, has become an important aspect of pharmaceutical research owing to the unique physical and biological properties of fluorine and can have unexpected results on reactivity and biological activity of the fluorinated derivatives [22].

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Having regard to our experience in the field of heterocyclic compounds, especially those mentioned above, obtained from hydrazinecarbothioamides having an arylsulfonylphenyl moiety [23-28], we proposed to continue our researches in these classes in order to obtain new derivatives containing additionally in the molecule the (4-trifluoromethyl)phenyl moiety.

Experimental part
Melting points were determined with a Böetius apparatus and are uncorrected. The IR spectra were recorded in KBr disc on a Vertex 70 Bruker spectrometer. The NMR spectra were recorded on a Varian Gemini 300BB spectrometer in DMSO-d$_6$ at 300 MHz for 1H-NMR and at 75 MHz for 13C-NMR using TMS as internal standard. The 1H-NMR and 13C-NMR spectral data of compounds obtained summarized in table 1 and table 2. The content of C, H, and N was assayed using a ECS-40-10-Costech microdosimeter. The mass spectra of compounds were recorded with a triple quadrupole mass spectrometer Varian 1200 L/MS/MS with electrospray interface (ESI), coupled with a high performance liquid chromatograph with Varian ProStar 240 SDM ternar pump and automatic injector Varian Prostar 410. The sample solution (2µg/mL in CH$_3$OH) was introduced in the ESI interface by direct infusion, after a tenth dilution with methanol/water 0.1 % ammonia 4/L, at a flow rate of 20µL/min. The instrument was operated in positive ions or negative ions mode.

Synthesis of compounds
The reaction of 4-(4-X-phenylsulfonyl)benzoic acid hydrazides 1a-c [29] with (4-trifluoromethyl)phenyl isothiocyanate occurred with obtaining the corresponding hydrazinecarbothioamides, type of 2-(4-(4-X-phenylsulfonyl)benzoyl)-N-(4-(trifluoromethyl)phenyl)-hydrazinecarbothioamides 2a-c. By treatment of hydrazinecarbothioamides with sulfuric acid, the dehydration cyclization took place obtaining the 5-(4-(4-X-phenylsulfonyl)phenyl)-N-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-amines 3a-c and by refluxing of same acyclic compounds with mercury oxide, the desulfurative cyclization took place obtaining the 5-(4-(4-X-phenylsulfonyl)phenyl)-N-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-amines 4a-c.

Synthesis of 2-(4-(4-X-phenylsulfonyl)benzoyl)-N-(4-(trifluoromethyl)phenyl)hydrazinecarbothioamides 2a-c
Synthesis of compounds was realized similarly with literature data [24, 27, 28].
An equimolecular mixture formed by hydrazide 1 and isothiocyanate (4mmol), in ethanol, was refluxed for ca 12h. The product obtained was filtered off, dried and recrystallized from ethanol.

2-(4-(Phenylsulfonyl)benzoyl)-N-(4-(trifluoromethyl)phenyl)hydrazinecarbothioamide 2a

m.p. 186-187 °C; yield: 79 %;
Elemental analysis: anal. calcd for C_{21}H_{15}BrF_{3}N_{3}O_{3}S_{2} (558.39): C, 45.17; H, 2.71; N, 7.53. Found: C, 45.21; H, 2.64; N, 7.49%.
ESI-MS, m/z: 558 [^{79}Br M+H]+; 560 [^{81}Br M+H]+; 397 [^{79}Br H+H]+; 399 [^{81}Br H+H]+; 355 [^{79}Br_{2}C_{6}H_{4}SO_{2}C_{6}H_{4}CONHNH_{2}H]+; 357 [^{81}Br_{2}C_{6}H_{4}SO_{2}C_{6}H_{4}CONHNH_{2}H]+.
IR (KBr, cm⁻¹): 3344 s, 3090 w, 3061 w, 1614 m, 1573 m, 1524 m, 1485 m, 1321 m, 1290 m, 1246 m, 1214 m, 1167 m, 1106 m, 1069 m, 844 m, 570 s.

5-(4-(4-X-phenylsulfonyl)phenyl)-N-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-amine 3a-c

Synthesis of compounds was realized similarly with literature data [23,27].

A mixture formed by the hydrazinecarbothioamide 2 (2mmol) and phosphorous oxychloride (10 mL) was refluxed for 5h. The residue obtained by distillation under reduced pressure was put into water and ice. To the precipitate was added a diluted aqueous solution of NaHCO₃ until slightly basic pH. The product was filtered off, washed with water, dried and purified from chloroform/petroleum ether (~1:2, v/v).

2-(4-(Chlorophenylsulfonyl)benzoyl)-N-(4-(trifluoromethyl)phenyl)hydrazinecarbothioamide 2b

m.p. 194-196 °C; yield: 72 %;
Elemental analysis: anal. calcd for C_{21}H_{15}ClF_{3}N_{3}O_{3}S_{2} (495.93): C, 49.08; H, 2.94; N, 8.18. Found: C, 49.15; H, 2.87; N, 8.13%.
ESI-MS, m/z: 514 [^{35}Cl M+H]+, 516 [^{37}Cl M+H]+; 353 [^{35}ClH+H]+; 355 [^{37}ClH+H]+; 311 [^{35}ClH_{2}O_{2}C_{6}H_{4}CONHNH_{2}H]+; 313 [^{37}ClH_{2}O_{2}C_{6}H_{4}CONHNH_{2}H]+.
IR (KBr, cm⁻¹): 3330 m, 3061 w, 3006 w, 1615 m, 1573 w, 1553 m, 1492 m, 1326 m, 1290 m, 1246 m, 1214 m, 1167 m, 1106 m, 1069 m, 837 m, 765 m.

5-(4-(Chlorophenylsulfonyl)phenyl)-N-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-amine 3b

m.p. 204-206 °C; yield: 87 %;
Elemental analysis: anal. calcd for C_{21}H_{13}ClF_{3}N_{3}O_{2}S_{2} (461.48): C, 50.86; H, 2.42; N, 7.78. Found: C, 50.70; H, 2.76; N, 8.38%.
ESI-MS, m/z: 494 [^{35}Cl M-H]-; 496 [^{37}Cl M-H]-; 498 [^{39}Cl M-H]-; 321 [^{35}ClH_{2}O_{2}C_{6}H_{4}CONHNH_{2}H]-; 185 [^{37}ClH_{2}O_{2}C_{6}H_{4}CONHNH_{2}H]-.
IR (KBr, cm⁻¹): 3383 m, 3090 w, 3061 w, 1615 m, 1573 m, 1550 m, 1493 m, 1326 m, 1290 m, 1157 m, 1108 m, 1084 m, 841 m.

2-(4-(Bromophenylsulfonyl)benzoyl)-N-(4-(trifluoromethyl)phenyl)hydrazinecarbothioamide 2c

m.p. 259 °C (dec.); yield: 79 %;
Elemental analysis: anal. calcd for C_{21}H_{13}BrF_{3}N_{3}O_{2}S_{2} (540.38): C, 46.68; H, 2.42; N, 7.78. Found: C, 46.51; H, 2.31; N, 7.70%.
ESI-MS, m/z: 520 [^{79}Br M+H]+; 522 [^{81}Br M+H]+; 321 [^{79}Br_{2}C_{6}H_{4}SO_{2}C_{6}H_{4}CONHNH_{2}H]+; 323 [^{81}Br_{2}C_{6}H_{4}SO_{2}C_{6}H_{4}CONHNH_{2}H]+.
IR (KBr, cm⁻¹): 3344 m, 3094 w, 3061 w, 1615 m, 1551 m, 1491 m, 1326 m, 1280 m, 1158 s, 1108 m, 1084 m, 839 m, 764 m.

5-(4-(Bromophenylsulfonyl)phenyl)-N-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-amine 3c

m.p. 239 °C (dec.); yield: 79 %;
Elemental analysis: anal. calcd for C_{21}H_{15}BrF_{3}N_{3}O_{2}S_{2} (504.38): C, 46.68; H, 2.42; N, 7.78. Found: C, 46.51; H, 2.31; N, 7.70%.
ESI-MS, m/z: 540 [^{79}Br M+H]+; 542 [^{81}Br M+H]+; 321 [^{79}Br_{2}C_{6}H_{4}SO_{2}C_{6}H_{4}CONHNH_{2}]+; 323 [^{81}Br_{2}C_{6}H_{4}SO_{2}C_{6}H_{4}CONHNH_{2}]+.
IR (KBr, cm⁻¹): 3327 m, 3090 w, 3061 w, 1614 m, 1573 m, 1553 m, 1492 m, 1325 m, 1291 m, 1158 s, 1118 m, 1105 m, 1069 s, 840 m, 571 m.
Synthesis of 5-(4-(4-X-phenylsulfonyl)phenyl)-N-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-amines 4a-c

Synthesis of compounds was realized similarly with literature data [23,24]. To a solution of hydrazinecarbothioamide 2 (2mmol) in ethanol the mercury oxide (4 mmol) was added and the mixture was refluxed for 10h. The mixture obtained was filtered off for removing the mercury sulfide obtained. The precipitate obtained by concentration of the filtrate was filtered off, dried and recrystallized from ethanol.

5-(4-(4-Chlorophenylsulfonyl)phenyl)-N-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-amine 4b

m.p. 275-278°C; yield: 33 %
Elemental analysis: anal. calcld for C_{21}H_{13}ClF_{3}N_{3}O_{3}S (479.86): C, 52.56; H, 2.73; N, 8.76. Found: C, 52.50; H, 2.64; N, 8.71%.

ESI-MS, m/z: 480 [^{35}Cl M+H]^+, 482 [^{37}Cl M+H]^+; 319 [M+H+CF,C_{6}H_{4}NH]^+; 321 [M+H+CF,C_{6}H_{4}NH]^+.

IR (KBr, cm⁻¹): 3301m, 3086m, 3071m, 3032w, 1615s, 1594s, 1578s, 1552m, 1335vs, 1310m, 1292m, 1158s, 1119s, 1071s, 840s, 767s.

5-(4-(4-Bromophenylsulfonyl)phenyl)-N-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-amine 4c

m.p. 292-294°C; yield: 39 %
Elemental analysis: anal. calcld for C_{21}H_{13}BrF_{3}N_{3}O_{3}S (524.31): C, 48.11; H, 2.50; N, 8.01. Found: C, 48.19; H, 2.45; N, 7.94%.

Table 1

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Table 2

<p>| Table 2 THE 1H-NMR SPECTRAL DATA OF COMPOUNDS 2a-c - 4a-c (DMSO-d₆, δ ppm, J Hz) |</p>
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IR (KBr, cm⁻¹): 3287m, 3067m, 3032m, 1616s, 1594s, 1578s, 1552m, 1335vs, 1310m, 1292m, 1158s, 1121s, 1072m, 839s.


IR (KBr, ν cm⁻¹): 3297n, 3083n, 3031w, 1617s, 1594s, 1578s, 1552m, 1334s, 1292m, 1159s, 1135m, 1118m, 1071s, 840s, 570m.

Results and discussions

Acyclic compounds 2a-c showed the characteristic stretching absorption bands due to NH (three bands), C=O and C=S functions present in the following intervals in their IR spectra: at 3105-3332 cm⁻¹, 1681-1692 cm⁻¹ and 1224-1228 cm⁻¹ respectively. The 1H-NMR spectra showed the characteristic singlet signals of NH groups with chemical shift δ in region 9.90-10.90 ppm. On the other hand, the 13C-NMR spectra showed the characteristic signals of C=O and C=S at 164.19-164.61 ppm and 180.87-180.94 ppm, respectively. The CF carbon signal appeared as quartet at δ = 124 ppm with coupling constants J = 270.1-272.0 Hz.

The main proof of heterocyclisation of hydrazinecarbothioamides 2a-c is disappearance from IR spectra of compounds 3 and 4 of absorption bands due to stretching vibrations of the C=O and C=S groups. Also, comparatively with acyclic compounds 2, the IR spectra of compounds 3 and 4 showed a single band at 3327-3344 cm⁻¹ for 3a-c and at 3287-3301 cm⁻¹ for 4a-c characteristic to NH group.

The stretching vibration bands of SO group appeared in the IR spectra of all compounds at 1322-1335 cm⁻¹ (νs, SO) and 1157-1161 cm⁻¹ (νas, SO), respectively. Unlike the hydrazinecarbothioamides, the 1H-NMR spectra presented a single singlet signal at 11.08-11.10 ppm for 3a-c and at 11.30-11.32 ppm for 4a-c for proton of NH group, more deshielded than those of compounds 2. In the 13C-NMR spectra of these compounds, the signal from C=O and C=S disappeared. Instead, new isotope contribution in molecular ions. The compounds obtained have similar fragmentation. In case of hydrazinecarbothioamide 2a the main fragments are summarized in Scheme 3:

Using fragmentations both in positive and in negative mode for molecules that posses both acidic and basic center we can obtain supplementary structural information for a better assignment of synthons in molecule.

Conclusions

The aim of the present study was the synthesis and characterization of some compounds containing 4-trifluoromethylphenyl and arylsulfonylphenyl moieties. The structure of hydrazinecarbothioamides which were synthesized by treatment of some arylsulfonylbenzoic acid hydrazides with an aromatic isothiocyanate having a trifluoromethyl radical in para-position on the phenyl moiety and the structure of 1,3,4-thiadiazoles/1,3,4-oxadiazoles obtained by dehydrative/desulfurative cyclization of these acyclic compounds was confirmed by spectroscopic techniques.

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