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Synthesis and Characterization of Novel Isoxazolidine-Thiosemicarbazone Hybrid Derivatives as Precursor of Unnatural Amino acids

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Abstract

Novel sixteen enantiopure isoxazolidine-(thio)semicarbazone hybrid derivatives were synthesized by condensation of isoxazolidines based on benzaldehyde derivatives with (thio)semicarbazide in good yield. The analysis of the 1D NMR and NOESY spectra of all compounds unambiguously confirms the *E*-stereochemistry of the synthesized (thio)semicarbazones.

Keywords: isoxazolidine, semicarbazone, thiosemicarbazone, enantiopure, stereochemistry

1. Introduction

(Thio)semicarbazones (TSCs, SCs), derived from thiourea and urea, are organic compounds which can be obtained by condensation of (thio)semicarbazide with appropriate carbonyl compounds (aldehydes or ketones). For several decades, considerable interest has been focused on the synthesis of derivatives of TSCs and CSs due to their diverse biological activities, such as anticancer [1-5], antibacterial [6], antimicrobial [7], anticarcinogenic [8], antiparasitic [9], anti-HIV [10], antimalarials, [11] antidepressants, [12] antiprotozoa, [13,14] antivirals, [15] antifungals [16] antioxidants, [16] antidiabetic [17] etc… TSCs are considered a high effective pharmacophore in the molecular design of drugs. Also, this type of compounds has been used as a precursor of thiadiazoles, [18] oxadiazoles [19] and thiazolidinones [20] known as good inhibitors of the HCV NS5B polymerase. [21] In addition, TSCs have been used to access complexes with marked and diverse biological applications [22-28].

In addition, our research group has been worked for years on the synthesis of enantiopure isoxazolidine derivatives [29-38]. Some analogues show antimicrobial [31], antioxidant [32] and anti-diabetic [39,40] activities. Likewise, certain derivatives have been used for access to natural and unnatural amino acids [33,36] such as 4-hydroxyisoleucine [41,42] and 4(S)-4-hydroxy-L-ornithine [43].

Based on the data mentioned above on the biological properties of TSCs, CSs and isoxazolidine derivatives, and continuing our previous studies, we report herein the synthesis of novel isoxazolidine-(thio)semicarbazone hybrids that may be of interest as unprecedented unnatural amino acid precursors.

2. Experimental

General methods

Reagents and aldehydes **3a-i** were used as purchased from Aldrich. Thin-layer chromatography (TLC) was performed on Silica Gel 60 F254 (Merck). The plates were visualized under UV light, or by gentle heating, Optical rotations were determined with a Perkin–Elmer model 241 polarimeter in a 1 dm cell. Melting points were measured with a Büchi apparatus (values were uncorrected). ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DRX400 spectrometer. Chemical shifts are quoted in parts per million,

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referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quadruplet; quin, quintuplet; m, multiplet; br, broad. Coupling constants are reported in Hertz (Hz). HRMS (LSIMS) data were recorded in the positive mode (unless stated otherwise) using a Thermo Finnigan Mat 95 XL spectrometer. MS (ESI) data were recorded in the positive mode using a Thermo Finnigan LCQ spectrometer.

Procedure for the synthesis of (thio)semicarbazones **6a-i** and **7a-g.**

A solution of thiosemicarbazide **4** or **5** (1 eq) in ethanol was added to a solution of **3a-i** (1 eq) in ethanol and glacial AcOH. The reaction was heated under ethanol reflux for 32 h (25°C for semicarbazide **5**). After complete disappearance of the starting materials, the reaction crude was purified by column chromatography (EtOAc / PE 1/1) to give the thiosemicarbazones **6a-i** and **7a-g**.

Procedure for the synthesis of (thio)semicarbazones **6a-i** and **7a-g.**

A solution of thiosemicarbazide **4** or **5** (1 eq) in ethanol was added to a solution of **3a-i** (1 eq) in ethanol and glacial AcOH. The reaction was heated under ethanol reflux for 32 h (25°C for semicarbazide **5**). After complete disappearance of the starting materials, the reaction crude was purified by column chromatography (EtOAc / PE 1/1) to give the thiosemicarbazones **6a-i** and **7a-g**.

According to the general procedure, thiosemicarbazide **5** (0.55 mmol, 50 mg, 1 eq) reacts with **3a** (0.55 mmol 1 eq) to prepare the desired product **6a** (182 mg, 70%).

White solid, m.p. 216-218°C. $[\alpha]_D^{24}$ = +23 (c = 1, DMSO) ; 1H NMR (300 MHz, DMSO-*d6*) δ 0.77 (d, 3H, *J* = 6.6 Hz, CH_3), 0.79 (d, 3H, *J* = 6.3 Hz, CH_3), 0.83 (d, 3H, *J* = 6.9 Hz, CH_3), 0.91 (m, 1H), 1.25 (m, 1H), 1.33 (m, 1H), 1.42 (m, 1H), 1.52 (m, 2H), 1.65 (d, 1H, *J* = 11.4 Hz), 1.79 (m, 1H), 1.92 (d, 1H, *J* = 12.3 Hz), 2.41 (m, 1H), 2.5 (m, 1H), 2.65 (s, 3H, *N*CH_3), 3.93 (d, 1H, *J* = 8.4 Hz), 4.15 (m, 3H), 6.95 (t, 1H, *J* = 7.5 Hz), 7.08 (d, 1H, *J* = 8.1 Hz), 7.33 (m, 1H), 7.91 (s, 1H), 8.07 (dd, 1H, *J* = 7.8 Hz, J = 1.5 Hz), 8.12 (s, 1H), 8.43 (s, 1H, CH=N), 11.45 (s, 1H, NH); 13C NMR (75 MHz, DMSO-*d6*) δ 18.6; 22.2; 22.3; 24.0; 24.2; 25.8; 29.1; 34.1; 34.6; 47.1; 65.1; 68.3; 74.8; 88.5; 113.2; 121.0; 122.8; 126.3; 131.3; 138.3; 157.1; 172.1; 177.9. HRMS (ESI) calcd $C_{24}H_{35}N_5NaO_3S$ $[M+Na]^+$: 496.2354, found 496.2353.

According to the general procedure, thiosemicarbazide **5** (0.55 mmol, 50 mg, 1 eq) reacts with **3b** (0.55 mmol 1 eq) to prepare the desired product **6b** (180 mg, 69%).

White solid, m.p. 186-188 °C. $[\alpha]_D^{24}$ = +18,1 (c = 1, DMSO). 1H NMR (300 MHz, DMSO-*d6*) δ 0.77 (d, 3H, *J* = 6.9 Hz, CH_3), 0.80 (d, 3H, *J* = 6.3 Hz, CH_3), 0.82 (d, 3H, *J* = 6.6 Hz, CH_3), 0.90 (m, 1H), 1.20 (m, 1H), 1.28 (m, 1H), 1.38 (m, 1H), 1.52 (m, 2H), 1.65 (d, 1H, *J* = 12 Hz), 1.81 (m, 1H), 1.89 (d, 1H, *J* = 12.3 Hz), 2.32 (m, 1H), 2.47 (m, 1H), 2.64 (s, 3H, *N*CH_3), 3.89 (d, 1H, *J* = 8.4 Hz), 4.13 (m, 3H), 6.95 (dt, 1H, *J* = 6.3 Hz, *J* = 2.4 Hz), 7.28 (m, 2H), 7.44 (d, 1H, *J* = 1.5 Hz), 8.00 (s, 1H, CH=N), 8.04 (s, 1H), 8.21 (s, 1H), 11.42 (s, 1H, NH). 13C NMR (75 MHz, DMSO-*d6*) δ 18.6; 22.2; 22.4; 24.0; 24.2; 25.8; 29.1; 34.1; 34.6; 47.1; 65.0; 67.8; 75.0; 88.6; 112.0; 117.0; 121.0; 121.0; 129.9; 135.8; 142.3; 158.9; 172.1; 178.2. **HRMS** (ESI) calcd $C_{24}H_{35}N_5NaO_3S$ $[M+Na]^+$: 496.2355, found 496.2353.

According to the general procedure, thiosemicarbazide **5** (0.55 mmol, 50 mg, 1 eq) reacts with **3c** (0.55 mmol 1 eq) to prepare the desired product **6c** (175 mg, 67%).

White solid, m.p. 198-200 °C (Cyclohexane). $[\alpha]_D^{24}$ = +34 (c = 1, DMSO). 1H NMR (300 MHz, DMSO-*d6*) δ 0.79 (d, 3H, *J* = 6 Hz, CH_3), 0.80 (d, 3H, *J* = 5.7 Hz, CH_3), 0.83 (d, 3H, *J* = 5.4 Hz, CH_3), 0.91 (m, 1H), 1.29 (dd, 1H, *J* = 9.9 Hz, *J* = 5.1 Hz), 1.34 (d, 1H, *J* = 9.3 Hz), 1.41 (m, 1H), 1.54 (m, 2H), 1.67 (d, 1H, *J* = 9 Hz), 1.83 (m, 1H), 1.89 (d, 1H, *J* = 9.3 Hz), 2.31 (m, 1H), 2.47 (m, 1H), 2.64 (s, 3H, *N*CH_3), 3.90 (d, 1H, *J* = 6.6 Hz), 4.10 (m, 3H), 6.96 (d, 2H, *J* = 6.6 Hz), 7.72 (d, 2H, *J* = 6.6 Hz), 7.91 (s, 1H), 7.99 (s, 1H, CH=N), 8.10 (s, 1H), 11.30 (s, 1H, NH); 13C NMR (75 MHz, DMSO-*d6*) δ 18.5; 22.2; 22.3; 23.9; 24.2; 25.7; 29.1; 34.1; 34.6; 47.1; 64.9; 67.9; 74.9; 88.5; 115.0; 127.1; 129.0; 142.3; 159.9; 172.0; 177.8. HRMS (ESI) calcud $C_{24}H_{35}N_5NaO_3S$ $[M+Na]^+$: 496.2337, found 496.2353.

According to the general procedure, thiosemicarbazide **5** (0.55 mmol, 50 mg, 1 eq) reacts with **3d** (0.55 mmol 1 eq) to prepare the desired product **6d** (205 mg, 74%).

Yellow oil, $[\alpha]_D^{24}$ = +8.6 (c = 1, DMSO). 1H NMR (300 MHz, DMSO-*d6*) δ 0.78 (d, 3H, *J* = 6 Hz, CH_3), 0.8 (d, 3H, *J* = 6 Hz, CH_3), 0.83 (d, 3H, *J* = 4.2 Hz, CH_3), 0.89 (m, 1H), 1.26 (m, 1H), 1.33 (m, 1H), 1.4 (t, 1H, *J* = 4.2 Hz), 1.52 (m, 2H), 1.65 (d, 1H, *J* = 7.2 Hz), 1.76 (m, 1H), 1.91 (d, 1H, *J* = 7.5 Hz), 2.38 (m, 1H), 2.54 (m, 1H), 2.65 (s, 3H, *N*CH_3), 3.75 (s, 3H, OCH_3), 3.91 (d, 1H, *J* = 5.1 Hz), 4.04 (dd, 1H, *J* = 8.7 Hz, *J* = 2.4 Hz), 4.08 (dd, 1H, *J* = 6.3 Hz, *J* = 3.6 Hz), 4.14 (m, 1H), 6.91 (dd, 1H, *J* = 5.4 Hz, *J* = 1.8 Hz), 7.02 (d, 1H, *J* = 5.4 Hz), 7.61 (d, 1H, *J* = 1.8 Hz), 8.02 (s, 1H), 8.13 (s, 1H), 8.40 (s, 1H, CH=N), 11.42 (s, 1H, NH); 13C NMR (75 MHz, DMSO-*d6*) δ 18.5; 22.1; 22.3; 23.9; 24.2; 25.8; 29.0; 34.1; 34.6; 40.0; 47.1; 55.8; 65.0; 69.2; 74.9; 88.5; 109.9; 115.0;

117.6; 123.6; 138.2; 151.7; 153.8; 172.1; 177.9. HRMS (ESI) calcud $C_{25}H_{37}N_5NaO_4S$ $[M+Na]^+$: 526.2468, found 526.2458.

According to the general procedure, thiosemicarbazide **5** (0.55 mmol, 50 mg, 1 eq) reacts with **3e** (0.55 mmol 1 eq) to prepare the desired product **6e** (202 mg, 73%).

White solid, m.p. 230-232 °C, $[\alpha]_D^{24}$ = +6.4 (c = 1, DMSO). 1H NMR (300 MHz, DMSO-*d6*) δ 0.78 (d, 3H, *J* = 6.6 Hz, CH_3), 0.82 (d, 3H, *J* = 6.6 Hz, CH_3), 0.83 (d, 3H, *J* = 6.9 Hz, CH_3), 0.92 (m, 1H), 1.28 (m, 2H), 1.40 (m, 1H), 1.54 (m, 2H), 1.67 (d, 1H, *J* = 11.4 Hz), 1.83 (m, 1H), 1.90 (d, 1H, *J* = 12 Hz), 2.28 (m, 1H), 2.47 (m, 1H), 2.64 (s, 3H, *N*CH_3), 3.81 (s, 3H, OCH_3), 3.89 (d, 1H, *J* = 8.4 Hz), 4.06 (m, 3H), 6.98 (d, 1H, *J* = 8.4 Hz), 7.11 (dd, 1H, *J* = 8.4 Hz, *J* = 1.8 Hz), 7.51 (d, 1H, *J* = 1.8 Hz), 7.96 (s, 1H, CH=N), 8.01 (s, 1H), 8.15 (s, 1H), 11.31 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 18.5; 22.2; 22.2; 24.0; 24.2; 25.8; 29.1; 34.1; 34.7; 39.9; 47.1; 56.0; 64.9; 68.5 ; 74.9; 88.5; 109.3; 113.1; 122.2; 127.5; 142.6; 149.5; 149.8; 172.0; 177.7. HRMS (ESI) calcd $C_{25}H_{37}N_5NaO_4S$ $[M+Na]^+$: 526.2460, found 526.2458.

According to the general procedure, thiosemicarbazide **5** (0.55 mmol, 50 mg, 1 eq) reacts with **3f** (0.55 mmol 1 eq) to prepare the desired product **6f** (224 mg, 81%).

White solid, m.p. 202-204 °C, $[\alpha]_D^{24}$ = +15.9 (c = 1, DMSO). 1H NMR (300 MHz, DMSO-*d6*) *δ* 0.79 (d, 3H, *J* = 6.6 Hz, CH_3), 0.80 (d, 3H, *J* = 9.3 Hz, CH_3), 0.83 (d, 3H, *J* = 6.3 Hz, CH_3), 0.91 (m, 1H), 1.28 (m, 2H), 1.40 (m, 1H), 1.52 (m, 2H), 1.65 (d, 1H, *J* = 11.7 Hz), 1.84 (m, 1H), 1.91 (d, 1H, *J* = 12.9 Hz), 2.31 (m, 1H), 2.47 (m, 1H), 2.65 (s, 3H, *N*CH_3), 3.78 (s, 3H, OCH_3), 3.89 (d, 1H, *J* = 8.4 Hz), 4.08 (m, 3H), 6.96 (d, 1H, *J* = 8.4 Hz), 7.17 (dd, 1H, *J* = 8.4 Hz, *J* = 1.8 Hz), 7.51 (d, 1H, *J* = 1.8 Hz), 7.95 (s, 1H, CH=N), 7.99 (s, 1H), 8.16 (s, 1H), 11.32 (s, 1H); 13C NMR (75 MHz, DMSO-*d6*): δ 18.5; 22.1; 22.3; 24.0; 24.2; 25.8; 29.1; 34.1; 34.8; 47.1; 55.8; 65.0; 68.4; 75.1; 88.6; 110.3; 111.9; 122.5; 127.1; 142.6; 148.4; 150.9; 172.0; 177.7. HRMS (ESI) calcd $C_{25}H_{37}N_5NaO_4S$ $[M+Na]^+$: 526.2467, found 526.2458.

According to the general procedure, thiosemicarbazide **5** (0.55 mmol, 50 mg, 1 eq) reacts with **3g** (0.55 mmol 1 eq) to prepare the desired product **6g** (225 mg, 79%).

White solid, m.p. 191-193 °C. $[\alpha]_D^{24}$ = +11.7 (c = 1, DMSO). 1H NMR (300 MHz, DMSO-*d6*) *δ* 0.77 (d, 3H, *J* = 6.6 Hz, CH_3), 0.81 (d, 3H, *J* = 6.3 Hz, CH_3), 0.82 (d, 3H, *J* = 6.6 Hz, CH_3), 0.90 (m, 1H), 1.24 (m, 1H), 1.35 (m, 4H), 1.39 (m, 1H), 1.53 (m, 2H), 1.66 (d, 1H, *J* = 11.7 Hz), 1.83 (m, 1H), 1.89 (d, 1H, *J* = 12.3 Hz), 2.28 (m, 1H), 2.48 (m, 1H), 2.63 (s, 3H, *N*CH_3), 3.88 (d, 1H, *J* = 8.4 Hz), 4.01 (m, 1H), 4.09 (m, 4H), 6.98 (d, 1H, *J* = 8.4 Hz), 7.11 (dd, 1H, *J* = 8.4 Hz, *J* = 1.8 Hz), 7.50 (d, 1H, *J* = 1.8 Hz), 7.95 (s, 1H, CH=N), 7.99 (s, 1H), 8.14 (s, 1H), 11.30 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*): δ14.9; 18.5; 22.2; 22.3; 23.9; 24.2; 25.8; 29.1; 34.1; 34.7; 47.1; 64.2; 64.9; 68.8; 75.0; 88.5; 110.8; 113.6; 122.2; 127.6; 142.6; 148.8; 150.1; 172.1; 177.8. HRMS (ESI) calcd $C_{24}H_{41}N_5NaO_4S$ $[M+Na]^+$: 518.2781, found 518.2771.

According to the general procedure, thiosemicarbazide **5** (0.55 mmol, 50 mg, 1 eq) reacts with **3h** (0.55 mmol 1 eq) to prepare the desired product **6h** (205 mg, 76%).

Beige paste, $[\alpha]_D^{24}$ = +21.9 (c = 1, DMSO). 1H NMR (300 MHz, DMSO-*d6*) *δ* 0.78 (d, 3H, *J* = 6.6 Hz, CH_3), 0.82 (d, 3H, *J* = 6.6 Hz, CH_3), 0.82 (d, 3H, *J* = 6.9 Hz, CH_3), 0.91 (m, 1H), 1.27 (m, 2H), 1.40 (m, 1H), 1.54 (m, 2H), 1.67 (d, 1H, *J* = 12 Hz), 1.86 (m, 2H), 2.29 (m, 1H), 2.47 (m, 1H), 2.64 (s, 3H, *N*CH_3), 3.89 (d, 1H, *J* = 8.4 Hz), 4.06 (m, 3H), 6.40 (d, 1H, *J* = 2.4 Hz), 6.43 (dd, 1H, *J* = 8.4 Hz, *J* = 2.4 Hz), 7.78 (d, 1H, *J* = 8.7 Hz), 7.82 (s, 1H), 8.00 (s, 1H), 8.27 (s, 1H, CH=N), 9.91 (s, 1H, OH), 11.24 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 18.5; 22.2; 22.3; 23.9; 24.2; 25.7; 29.2; 34.1; 34.6; 47.1; 64.9; 67.7; 74.8; 88.5; 101.8; 106.8; 113.7; 128.4; 140.3; 158.0; 161.0; 172.0; 177.4. HRMS (ESI) calcd $C_{24}H_{35}N_5NaO_4S$ $[M+Na]^+$: 512.2299, found 512.2302.

According to the general procedure, thiosemicarbazide **5** (0.55 mmol, 50 mg, 1 eq) reacts with **3i** (0.55 mmol 1 eq) to prepare the desired product **6i** (194 mg, 72%).

Beige paste, $[\alpha]_D^{24}$ = +32.4 (c = 1, DMSO). 1H NMR (300 MHz, DMSO-*d6*) *δ* 0.77 (d, 3H, *J* = 6.6 Hz, CH_3), 0.80 (d, 3H, *J* = 6.9 Hz, CH_3), 0.83 (d, 3H, *J* = 6.9 Hz, CH_3), 0.92 (m, 1H), 1.28 (m, 2H), 1.40 (m, 1H), 1.53 (m, 2H), 1.67 (d, 1H, *J* = 11.7 Hz), 1.79 (m, 1H), 1.91 (d, 1H, *J* = 12.6 Hz), 2.37 (m, 1H), 2.55 (ddd, 1H, *J* = 12.6 Hz, *J* = 5.7 Hz, *J* = 1.5 Hz), 2.65 (s, 3H, *N*CH_3), 3.91 (d, 1H, *J* = 8.4 Hz), 4.01 (m, 2H), 4.12 (m, 1H), 6.76 (dd, 1H, *J* = 9 Hz, *J* = 3 Hz), 6.90 (d, 1H, *J* = 9 Hz), 7.40 (d, 1H, *J* = 3 Hz), 7.79 (s, 1H), 8.09 (s,1H), 8.36 (s, 1H, CH=N), 9.03 (s, 1H, OH), 11.42 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 18.6; 22.1; 22.3; 23.9; 24.2; 25.8; 29.1; 34.1; 34.7; 47.1; 65.0; 69.2; 74.9; 88.5; 111.9; 114.9; 118.2; 123.6; 138.7; 150.7; 151.6; 172.1; 177.9. HRMS (ESI) calcd $C_{24}H_{35}N_5NaO_4S$ $[M+Na]^+$: 512.2298, found 512.2302.

According to the general procedure, thiosemicarbazide **4** (0.45 mmol, 50 mg, 1 eq) reacts with **3a** (0.45 mmol 1 eq) to prepare the desired product **7a** (169 mg, 82%).

Yellow paste, $[\alpha]_D^{24}$ = +33.6 (c = 1, DMSO). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 0.78 (d, 3H, *J* = 6.3

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Hz, CH_3), 0.80 (d, 3H, *J* = 6.6 Hz, CH_3), 0.83 (d, 3H, *J* = 6.9 Hz, CH_3), 0.92 (m, 1H), 1.28 (m, 2H), 1.41 (m, 1H), 1.53 (m, 2H), 1.66 (d, 1H, *J* = 11.4 Hz), 1.80 (m, 1H), 1.91 (d, 1H, *J* = 12.3 Hz), 2.35 (m, 1H), 2.57 (m, 1H), 2.65 (s, 3H, *N*CH_3), 3.92 (d, 1H, *J* = 8.1 Hz), 4.14 (m, 3H), 6.42 (s, 2H, NH_2), 6.95 (m, 1H) , 7.07 (m, 1H), 7.26 (m, 1H), 7.97 (dd, 1H, *J* = 7.8 Hz, *J* = 1.8 Hz), 8.19 (s, 1H, CH=N), 10.26 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 18.5; 22.1, 22.3; 23.9; 24.2; 25.8; 29.1; 34.1; 34.6; 47.1; 65.0; 68.2; 74.8; 88.5; 113.0; 120.9; 123.3; 125.7; 130.3; 135.0; 156.3; 156.9; 172.0. HRMS, (ESI) calcd $C_{24}H_{35}N_5NaO_4$ $[M+Na]^+$: 480.2573, found 480.2581.

According to the general procedure, thiosemicarbazide **4** (0.45 mmol, 50 mg, 1 eq) reacts with **3b** (0.45 mmol 1 eq) to prepare the desired product **7b** (159 mg, 77%).

White solid, m.p. 213-215 °C, $[\alpha]_D^{24}$ = +29,4 (c = 1, DMSO). ^{1}H NMR (300 MHz, DMSO-*d6*) *δ* 0.78 (d, 3H, *J* = 6.6 Hz, CH_3), 0.81 (d, 3H, *J* = 6.3 Hz, CH_3), 0.82 (d, 3H, *J* = 6.9 Hz, CH_3), 0.91 (m, 1H), 1.30 (m, 2H), 1.38 (m, 1H), 1.52 (m, 2H), 1.66 (d, 1H, *J* = 11.4 Hz), 1.89 (m, 2H), 2.32 (m, 1H), 2.48 (m, 1H), 2.64 (s, 3H, *N*CH_3), 3.89 (d, 1H, *J* = 8.4 Hz), 4.07 (m, 3H), 6.53 (s, 2H, NH_2), 6.90 (dq, 1H, *J* = 7.8 Hz, *J* = 1.5 Hz), 7.21 (m, 1H), 7.26 (q, 1H, *J* = 7.8 Hz), 7.34 (m, 1H), 7.80 (s, 1H, CH=N), 10.27 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 18.5; 22.1; 22.3; 23.9; 24.2; 25.7; 29.1; 34.1; 34.6; 47.1; 65.0; 67.8; 75.0; 88.5; 111.6; 116.1; 120.0; 129.8; 136.4; 139.2; 157.0; 158.9; 172.1. HRMS (ESI) calcd $C_{24}H_{35}N_5NaO_4$ $[M+Na]^+$: 480.2579, found 480.2581.

According to the general procedure, thiosemicarbazide **4** (0.45 mmol, 50 mg, 1 eq) reacts with **3c** (0.45 mmol 1 eq) to prepare the desired product **7c** (144 mg, 70%).

White solid, m.p. 188-190 °C, $[\alpha]_D^{24}$ = +9.2 (c = 1, DMSO). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 0.79 (d, 3H, *J* = 6.9 Hz, CH_3), 0.81 (d, 3H, *J* = 6.9 Hz, CH_3), 0.85 (d, 3H, *J* = 6.6 Hz, CH_3), 0.91 (m, 1H), 1.28 (m, 2H), 1.40 (m, 1H), 1.54 (m, 2H), 1.67 (d, 1H, *J* = 12.9 Hz), 1.79 (m, 1H), 1,89 (d, 1H, *J* = 12.6 Hz), 2.30 (m, 1H), 2.46 (m, 1H), 2.64 (s, 3H, *N*CH_3), 3.90 (d, 1H, *J* = 8.7 Hz), 4.06 (m, 3H), 6.41 (s, 2H), 6.94 (d, 2H, *J* = 8.7 Hz), 7.63 (d, 2H, *J* = 9 Hz), 7.77 (s, 1H, CH=N), 10.10 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 18.5; 22.2; 22.3; 24.0; 24.2; 25.7; 29.1; 34.1; 34.6; 47.1; 64.9; 67.8; 74.9; 88.5; 114.9; 127.8; 128.2; 139.2; 157.0; 159.3; 172.0. HRMS, (ESI) calcd $C_{24}H_{35}N_5NaO_4$ $[M+Na]^+$: 480.2578, found 480.2581.

According to the general procedure, thiosemicarbazide **4** (0.45 mmol, 50 mg, 1 eq) reacts with **3d** (0.45 mmol 1 eq) to prepare the desired product **7d** (147 mg, 67%).

White paste, $[\alpha]_D^{24}$ = +19.1 (c = 1, DMSO). ^{1}H NMR (300 MHz, DMSO-*d6*) *δ* 0.76 (d, 3H, *J* = 6 Hz, CH_3), 0.78 (d, 3H, *J* = 5.7 Hz, CH_3), 0.82 (d, 3H, *J* = 6.9 Hz, CH_3), 0.90 (m, 1H), 1.26 (m, 2H), 1.38 (m, 1H), 1.51 (m, 2H), 1.64 (d, 1H, *J* = 7.8 Hz), 1.90 (m, 2H), 2.32 (m, 1H), 2.54 (m, 1H), 2.63 (s, 3H, *N*CH_3), 3.73 (s, 3H, OCH_3), 3.89 (d, 1H, *J* = 8.7 Hz), 4.08 (m, 3H), 6.82 (s, 2H), 6.85 (dd, 1H, *J* = 9 Hz, J = 3 Hz), 7.00 (d, 1H, *J* = 9 Hz), 7.50 (d, 1H, *J* = 3.3 Hz), 8.16 (s, 1H, CH=N), 10.30 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 18.6; 22.2; 22.3; 24.0; 24.2 ; 25.8; 29.1; 34.2; 34.6; 47.1; 55.7; 65.0; 69.1; 74.9; 88.5; 109.7; 114.9; 116.5; 124.2; 135.1; 146.9; 150.9; 157.6; 172.2. HRMS (ESI) calcd $C_{25}H_{37}N_5NaO_5$ $[M+Na]^+$: 510.2696, found 510.2687.

According to the general procedure, thiosemicarbazide **4** (0.45 mmol, 50 mg, 1 eq) reacts with **3e** (0.45 mmol 1 eq) to prepare the desired product **7e** (182 mg, 83%).

White solid, m.p. 197-199 °C, $[\alpha]_D^{24}$ = +22 (c = 1, DMSO). ^{1}H NMR (300 MHz, DMSO-*d6*) *δ* 0.78 (d, 3H, *J* = 6.9 Hz, CH_3), 0.80 (d, 3H, *J* = 6.9 Hz, CH_3), 0.83 (d, 3H, *J* = 6.6 Hz, CH_3), 0.92 (m, 1H), 1.28 (td, 2H, *J* = 11.1 Hz, *J* = 3.6 Hz), 1.40 (m, 1H), 1.54 (m, 2H), 1.67 (m, 1H), 1.81 (m, 1H), 1.90 (d, 1H, *J* = 12.9 Hz), 2.28 (m, 1H), 2.47 (m, 1H), 2.64 (s, 3H, *N*CH_3), 3.80 (s, 3H, OCH_3), 3.89 (d, 1H, *J* = 8.4 Hz), 4.02 (dd, 1H, *J* = 11.1 Hz, *J* = 7.2 Hz), 4.11 (m, 2H), 6.50 (s, 2H), 6.96 (d, 1H, *J* = 8.4 Hz), 7.05 (dd, 1H, *J* = 8.4 Hz, *J* = 1.8 Hz), 7.42 (d, 1H, *J* = 1.8 Hz), 7.75 (s, 1H, CH=N), 10.14 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 18.5; 22.2; 22.2; 24.0; 24.2; 25.8; 29.1; 34.1; 34.7; 39.9; 47.1; 55.9; 64.9; 68.5; 75.0; 88.5; 109.0; 113.2; 120.8; 128.3; 139.5; 149.1; 149.5; 157.0; 172.0. HRMS (ESI) calcd $C_{25}H_{37}N_5NaO_5$ $[M+Na]^+$: 510.2680, found 510.2687.

According to the general procedure, thiosemicarbazide **4** (0.45 mmol, 50 mg, 1 eq) reacts with **3f** (0.45 mmol 1 eq) to prepare the desired product **7f** (178 mg, 81%).

Beige solid, m.p. 224-226 °C, $[\alpha]_D^{24}$ = +13,2 (c = 1, DMSO). ^{1}H NMR (300 MHz, DMSO-*d6*) *δ* 0.78 (d, 3H, *J* = 6.6 Hz, CH_3), 0.82 (d, 3H, *J* = 6.9 Hz, CH_3), 0.83 (d, 3H, *J* = 6 Hz, CH_3), 0.90 (m, 1H), 1.25 (m, 1H), 1.35 (m, 2H), 1.52 (m, 2H), 1.66 (d, 1H, *J* = 12 Hz), 1.84 (m, 1H), 1.92 (d, 1H, *J* = 12 Hz), 2.31 (m, 1H), 2.47 (m, 1H), 2.64 (s, 3H, *N*CH_3), 3.76 (s, 3H, OCH_3), 3.89 (d, 1H, *J* = 8.7 Hz), 4.11 (m, 3H), 6.49 (s, 2H), 6.94 (d, 1H, *J* = 8.4 Hz), 7.10 (dd, 1H, *J* = 8.4 Hz, *J* = 1.5 Hz), 7.41 (d, 1H, *J* = 1.8 Hz), 7.74 (s, 1H, CH=N), 10.14 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 18.5; 22.2; 22.2; 24.0; 24.2; 25.8; 29.1; 34.1; 34.8; 47.1; 55.8; 65.0; 68.5; 75.1; 88.6; 110.1; 112.0; 121.2; 127.9; 139.5; 148.3; 150.2; 157.1; 172.0. HRMS (ESI) calcd $C_{25}H_{37}N_5NaO_5$ $[M+Na]^+$: 510.2680, found 510.2687.

According to the general procedure, thiosemicarbazide **4** (0.45 mmol, 50 mg, 1 eq) reacts with **3g** (0.45 mmol 1 eq) to prepare the desired product **7g** (190 mg, 84%).

White paste, $[\alpha]_D^{24}$ = +27,3 (c = 1, DMSO). **^{1}H NMR** (300 MHz, DMSO-*d6*) δ 0.76 (d, 3H, *J* = 4.8 Hz, CH_3), 0.80 (d, 3H, *J* = 4.5 Hz, CH_3), 0.81 (d, 3H, *J* = 5.1 Hz, CH_3), 0.89 (m, 1H), 1.26 (t, 1H, *J* = 5.4 Hz), 1.31 (m, 4H), 1.38 (m, 1H), 1.52 (m, 2H), 1.65 (d, 1H, *J* = 8.7 Hz), 1.80 (d, 1H, *J* = 6.6 Hz), 1.88 (m, 1H), 2.27 (m, 1H), 2.47 (ddd, 1H, *J* = 9.6 Hz, *J* = 5.1 Hz, *J* = 1.2 Hz), 2.63 (s, 3H, *N*CH_3), 3.87 (d, 1H, *J* = 6.3 Hz), 4.07 (m, 5H), 6.50 (s, 2H), 6.96 (d, 1H, *J* = 6.3 Hz), 7.05 (dd, 1H, *J* = 6.6 Hz, *J* = 1.5 Hz), 7.39 (d, 1H, *J* = 1.2 Hz), 7.78 (s, 1H, CH=N), 10.21 (s, 1H, NH); **^{13}C NMR** (75 MHz, DMSO-*d6*) δ 15.0; 18.6; 22.2; 22.4; 24.0; 24.2; 25.8; 29.1; 34.1; 34.8; 47.1; 64.2; 64.9; 68.9; 75.1; 88.6; 110.6; 113.8; 120.9; 128.4; 139.7; 148.8; 149.4; 157.1; 172.1. **HRMS** (ESI) calcd $C_{26}H_{39}N_5NaO_5$ $[M+Na]^+$: 524.2838, found 524.2843.

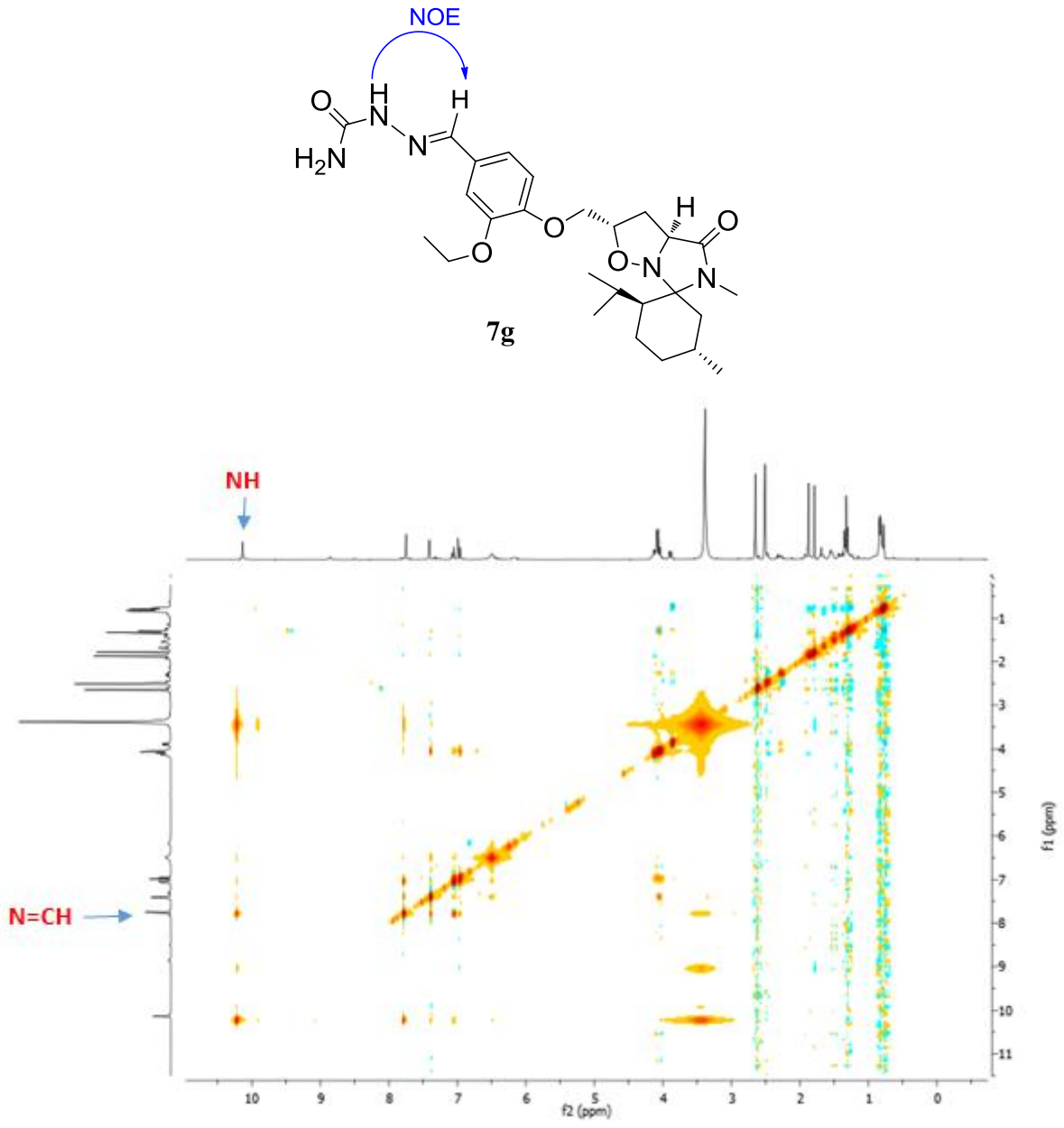

Figure 1. NOESY spectrum of **7g** recorded at 300 MHz in DMSO

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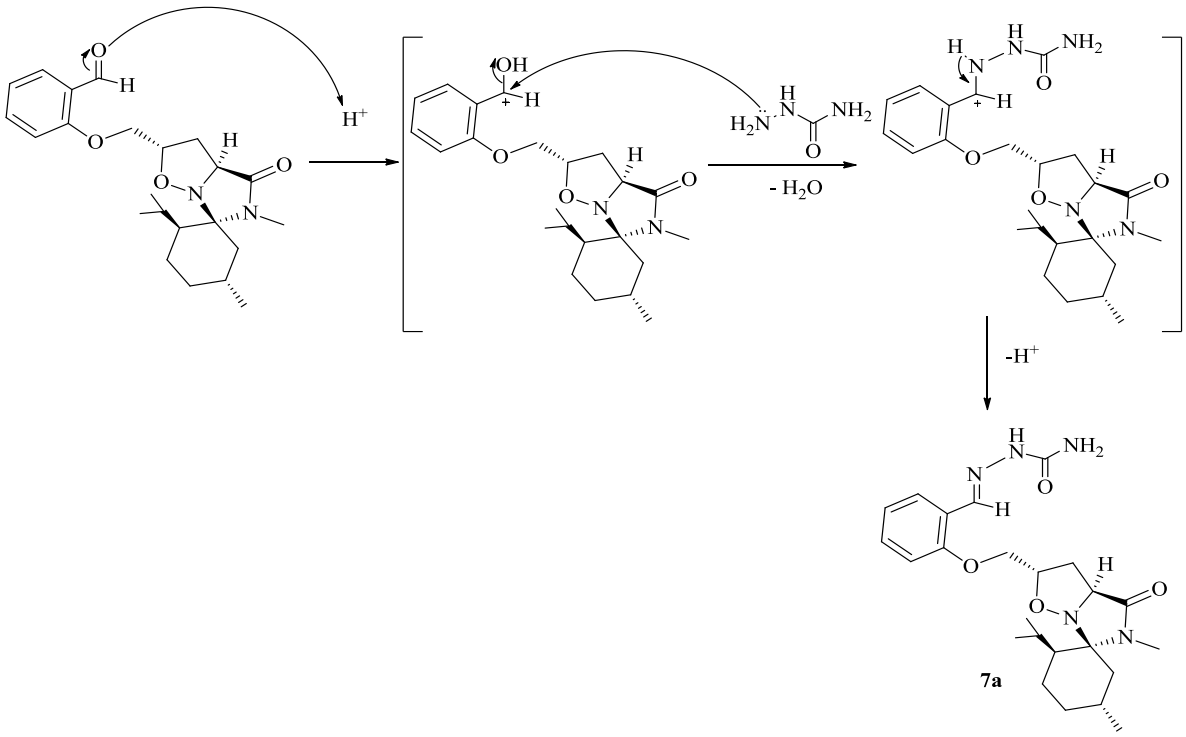
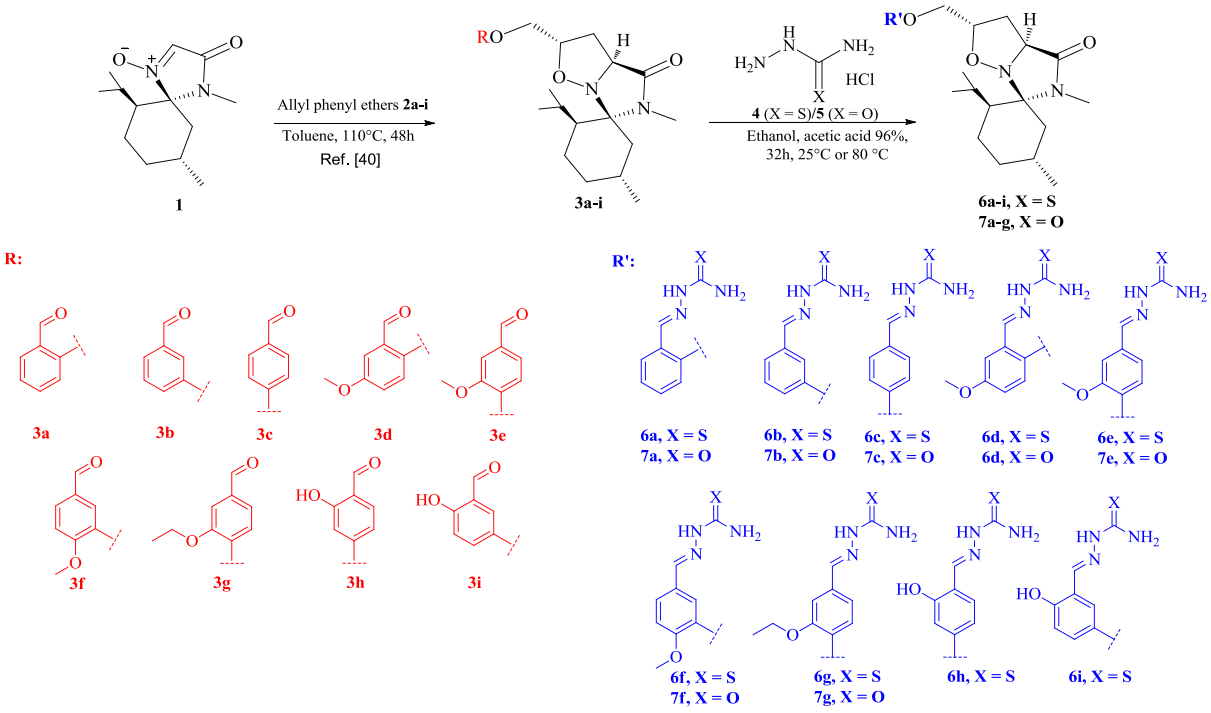


Figure 2. Proposed mechanism of the reaction of **2a** with **7a**.



Scheme 1. Synthesis of isoxazolidine-(thio)semicarbazone hybrids **6a-i** and **7-g**.

3- Results and discussion

Compounds **3a-i** were synthesized by 1,3-dipolar cycloaddition between a menthone-based nitrone **1** and allyl phenyl ethers **2a-i** as described in our recently published work [40]. The condensation reaction of (thio)semicarbazide hydrochloride **4** and **5** with compounds **3a-i** in the presence of ethanol and sodium acetate gives (thio)semicarbazones **6a-g** and **7a-i**, respectively (scheme 1).

The stereochemistry of compounds **3a-i** has been studied in detail in a recently published work [40]. To determine the E/Z geometry of the synthesized (thio)semicarbazones we used 1D and 2D NMR. Indeed, the analysis of the NMR spectra of compounds **6a-i** and **7a-g** shows the appearance of the characteristic signals, of the (thio)semicarbazone fragment, attributable to the protons NH, NH_2 and CH = N (see experimental part).

For (thio)semicarbazones **6a-i** and **7a-g**, the proton of the CH = N group appears in the range 7.95-8.43 ppm and 7.74-8.19 ppm and the proton of the NH group appears at 11.24-11.45 ppm and 10.10-10.30 ppm, respectively. Also, the interpretation of the 1H NMR spectra of compounds **6a-i** shows that the latter are in the thione form due to the absence of the signal corresponds to the SH proton which generally appears at 4.0 ppm. In addition, data from the literature have shown that for *Z*-configuration (thio)semicarbazones, the NH group proton appears in the range 14-15 ppm for CSs and 12 ppm for TCSs [44,45]. All of these results are then in favor of the *E*-stereochemistry for (thio)semicarbazones **6a-i** and **7a-g**.

The ^{13}C NMR spectra shows two characteristic signals: (i) a signal appears approximately around 177.8 ppm (C=S) for thiosemicarbazones **6a-i** and around 157 ppm (C=O) for semicarbazones **7a-g**, (ii) a second signal attributable to imine group (C=N) which appears at 138.3-142.6 ppm for thiosemicarbazones and between 135-139.7 ppm for semicarbazones. In order to further confirm the stereochemistry of the (thio) semicarbazones obtained, we used the NOESY experiment. Indeed, the analysis of the NOESY spectrum of compound **7g** shows an NOE effect between the proton of the –N-NH- group (δ = 10.21 ppm) and that of the -CH=N- group (δ = 7.78 ppm) which unambiguously confirms the E-stereochemistry of the synthesized (thio)semicarbazones (Figure 1).

The proposed mechanism of the reaction of semicarbazide **5** with the benzaldehyde derivative **2a** to form semicarbazone **7a** is illustrated in figure 2.

4. Conclusion

A new class of sixteen isoxazolidine-(thio)semicarbazone hybrid derivatives has been synthesized *via* a condensation reaction of isoxazolidines based on benzaldehyde derivatives with (thio)semicarbazide hydrochloride. The access to amino acids by isoxazolidine ring-opening is well documented, further studies of this strategy to lead to unnatural (thio)semicarbazones-based amino acids are currently under investigation.

5. Conflicts of interest

There are no conflicts to declare.

6. Formatting of funding sources

Not funding sources

7. References

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