Synthesis and Characterization of New Heterocyclic Compounds from 2-thioxo-4,5-imidazolidinedione Class and Their Evaluation for Antimicrobial Activity

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This paper presents the synthesis of new heterocyclic compounds from 2-thioxo-4,5-imidazolidinedione class known as thioparabanic acids and their evaluation for antimicrobial activity. The new N^1-[4-(4-X-phenylsulfonyl)benzamide]-N^3-(2-methoxyphenyl)/(3-methoxyphenyl)-2-thioxo-4,5-imidazolidinediones were synthesized by the reaction of N^1-[4-(4-X-phenylsulfonyl)benzoyl]-N^4-(2-methoxyphenyl)/(3-methoxyphenyl)-thiosemicarbazides with oxalyl chloride. Acylthiosemicarbazides were obtained from 4-(4-X-phenylsulfonyl)-benzoic acid hydrazides with 2-methoxyphenyl/3-methoxyphenyl-isothiocyanate. The structures were confirmed by elemental analysis and spectral methods: IR, UV-Vis, ^{1}H-NMR, ^{13}C-NMR, MS.

Keywords: 2-thioxo-4,5-imidazolidinedione, thioparabanic acid, acylthiosemicarbazide, oxalyl chloride

Compounds containing a 2-thioxo-4,5-imidazolidinedione heterocycle (thioparabanic acids) possess a broad range of biological properties such as: antiviral [1], anticancer [1-5], aldose reductase inhibitors [6,7], potassium channel openers [8,9], antibacterial [10,11], serum HDL-cholesterol elevating properties [12] and usefulness in treating atherosclerosis [13,14].

On the other hand diphenylsulfone derivatives possess antibacterial and antiinflamatory activity [15-18].

Therefore 2-thioxo-4,5-imidazolidinedione heterocycle subtitution with diphenylsulfone moiety could increase the biological activity of a such molecular system.

Keeping this observation in view and in continuation of our research on the synthesis of heterocyclic compounds with expected biological activity, in this paper we describe the synthesis of some new1,3-disubstitued-2-thioxo-4,5-imidazolidinediones which contain a diphenylsulfone fragment.

All synthesized compounds were tested for in vitro antimicrobial activity.

Experimental part

All reagents used in synthesis were purchased from Merck, Sigma-Aldrich and Fluka Companies. Melting points were determined on a Böetius apparatus and are uncorrected. The UV spectra were determined on a SPECORD 40 Analytik Jena spectrophotometer, using methanolic solutions ($2.5 \cdot 10^{-5}$ M). The IR spectra were recorded on a Vertex 70 Bruker spectrophotometer recorded in KBr disc. The ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Gemini 300BB spectrometer (at 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR), in DMSO-d_6 as a solvent and tetramethylsilane (TMS) as internal standard. The mass spectra were obtained with a triple quadrupole mass spectrometer Varian 1200 L/MS/MS with electrospray interface (ESI) at 20 eV collision energy and 1.5 mTorr argon, coupled with a high performance liquid chromatograph with Varian ProStar 240 SDM ternary pump. The sample solution (2 μg/mL in $CHCl_3/CH_3OH$ 1/1, v/v) was introduced in the ESI interface by direct infusion, after a tenth dilution with methanol, at a flow rate of 20 μL/min. The content of C, H, and N were done with ECS-40-10-Costeh micro-dosimeter.

Synthesis of new compounds

The most common thioparabanic acids synthesis was found to be the reaction of oxalyl chloride with thioureas [1,2,6,7,11, 13, 14, 19-24] and there are only few references in the literature where N^1-acylthiosemicarbazides are used instead of thioureas in reaction with oxalyl chloride [25-27].

This paper presents our contributions to the reaction of oxalyl chloride with N^1-[4-(4-X-phenylsulfonyl)benzoyl]-N^4-(2-methoxyphenyl)/(3-methoxyphenyl)-thiosemicarbazides (**2a-3c**).

Key intermediates (**2a-3c**) used in the synthesis of new 2-thioxo-4,5-imidazolidinediones (**4a-5c**) were obtained by nucleophilic addition of 4-(4-X-phenylsulfonyl)-benzoic acid hydrazides (**1a-c**) [28] to 2-methoxyphenyl/3-methoxyphenyl-isothiocyanate [29,30] (scheme 1).

The new thioparabanic acids derivatives were obtained by treating the acylthiosemicarbazides (**2a-3c**) with oxalyl chloride in dichloromethane at room temperature. In the yellow solution formed, petroleum ether was added and, after filtration, the solid was heated in ethanol at reflux yielding **4a-5c** (scheme 1).

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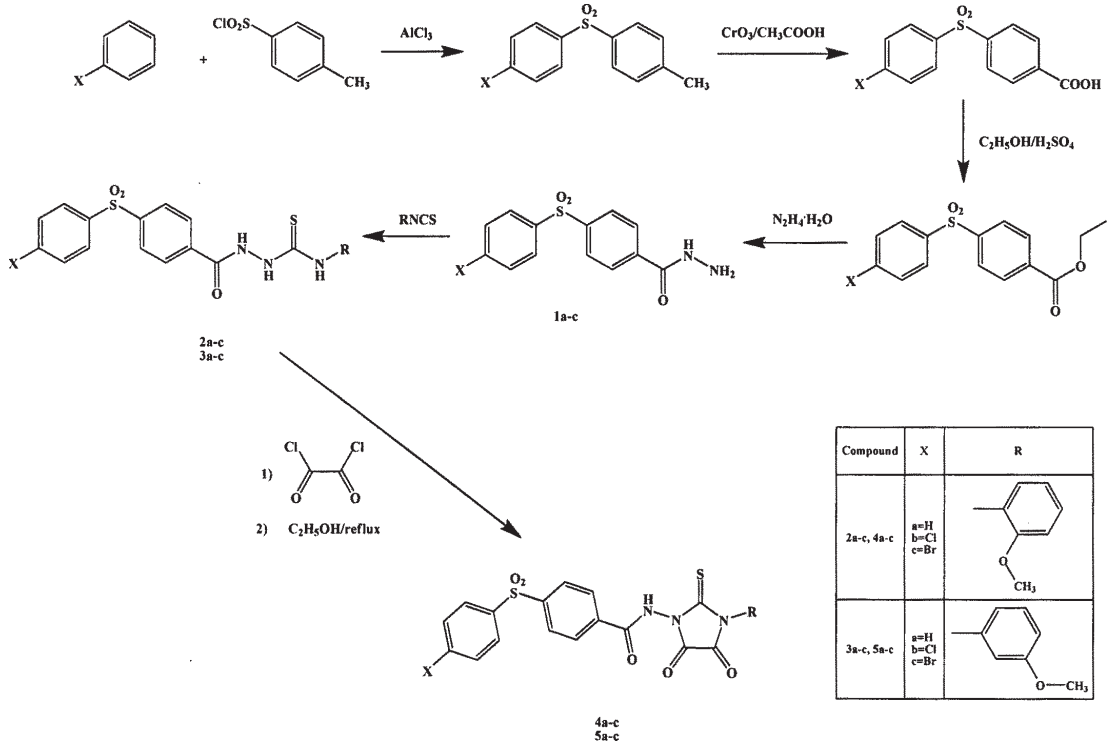


Scheme 1. Synthesis of new thioparabanic acids **4a-5c**

Synthesis of N^1 N^1-[4-(4-X-phenylsulfonyl)benzoyl]-N^4-(2-methoxyphenyl)/(3-methoxyphenyl)-thiosemicarbazides (2a-c) and (3a-c)

A mixture of acid hydrazide **1a-c** (4 mmol) and 2-methoxyphenyl/3-methoxyphenyl-isothiocyanate (4 mmol) was refluxed in anhidrous ethanol for 8 h, cooled to room temperature and the formed precipitate was filtered off and recrystalized from ethanol.

N^1-[4-(phenylsulfonyl)benzoyl]-N^4-(2-methoxyphenyl)-thiosemicarbazide (2a)

m.p. = 147-8°C, (lit. 148-9°C); yield = 91.2%

N^1-[4-(4-chlorophenylsulfonyl)benzoyl]-N^4-(2-methoxyphenyl)-thiosemicarbazide (2b)

m.p. = 173-4°C, (lit. 173-5°C). ; yield = 90.5%

N^1-[4-(4-bromophenylsulfonyl)benzoyl]-N^4-(2-methoxyphenyl)-thiosemicarbazide (2c)

m.p. = 176-7°C, (lit. 176-7°C); yield = 94.5%

N^1-[4-(phenylsulfonyl)benzoyl]-N^4-(3-methoxyphenyl)-thiosemicarbazide (3a)

m.p =189-90°C, (lit. 188-90°C); yield = 95.6%

N^1-[4-(4-chlorophenylsulfonyl)benzoyl]-N^4-(3-methoxyphenyl)-thiosemicarbazide (3b)

m.p. = 212-3°C, (lit. 212-3°C); yield = 93.7%

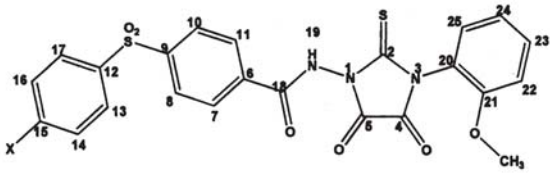
N^1-[4-(4-bromophenylsulfonyl)benzoyl]-N^4-(3-methoxyphenyl)-thiosemicarbazide (3c)

m.p. = 187-8°C, (lit. 187-8°C) ; yield = 95.4%

Synthesis of N^1-[4-(4-X-phenylsulfonyl)benzamide]-N^3-(2-methoxyphenyl)/(3-methoxyphenyl)-2-thioxo-4,5-imidazolidinediones (4a-c) and (5a-c)

A mixture of **2a-3c** (2 mmol) and oxalyl chloride (2 mmol) was stirred in dichloromethane (5 mL) at room temperature for 3 h. In the reaction mixture petroleum ether was added and the bright yellow solid formed was filtered off. The solid was dissolved in ethanol (5 mL) and heated at reflux for 2 h. The pale yellow alcoholic solution was evaporated to dryness and the residue was recrystallized from chloroform-petroleum ether (v:v=1:1).

N^1-[4-(4-X-phenylsulfonyl)benzamide]-N^3-(2-methoxyphenyl)-2-thioxo-4,5-imidazolidinediones (4a-c)



N^1-[4-(phenylsulfonyl)benzamide]-N^3-(2-methoxyphenyl)-2-thioxo-4,5-imidazolidinedione (4a)

m.p. = 138-9°C; yield = 51.3%;

IR (KBr; cm^{-1}): 3277m, 3093w, 3067w, 3005w, 2946w, 2841w, 1793vs, 1701s, 1601m, 1505s, 1467m, 1447m, 1414m, 1380s, 1341s, 1284s, 1256s, 1158vs;

^{1}H-NMR (DMSO-d$_6$, δ, ppm, *J*, Hz): 12.21 (s, 1H, H-19); 8.18 (s, 4H, H-7,H-8,H-10,H-11); 8.02 (dd, 7.5, 1.7, 2H, H-13, H-17); 7.75 (tt, 7.5,1.7, 1H, H-15); 7.66 (bt, 7.5, 2H, H-14, H-16); 7.55 (m, 1H); 7.40 (bd, 8.2, 1H); 7.26 (dd, 1.1, 8.4, 1H, H-25); 7.13 (td, 7.7, 1.1, 1H, H-24); 3.79 (s, 3H, OCH_3);

^{13}C-NMR (DMSO-d$_6$, δ, ppm): 179.07 (C-2); 164.07 (C-18); 155.07 (C-5); 153.72 (C-4); 152.60 (C-21); 144.63 (C-9); 140.30 (C-12); 135.00 (C-6); 134.09 (C-15); 131.73 (C-23); 129.87 (C-8, C-10); 129.37 (C-25); 127.89 (C-7, C-11); 127.53 (C-13, C-17); 120.70 (C-24); 120.23 (C-20); 112.76 (C-22); 56.02 (OCH_3);

UV (CH_3OH, λ_{max}(nm), lg ε): 205.3 (4.45); 246.7 (4.17);

Elemental analysis: found: C:55.84; H:3.34; N:8.57 % ; calcd. for $C_{23}H_{17}N_3O_6S_2$ (495.53 g/mol): C:55.75; H:3.46; N:8.48 %;

ESI-MS, *m/z* (abundance %): 494 (7.4) [M-H]$^-$; 317 (100, BP) [$C_6H_5SO_2C_6H_4CONHNHCOCH_2$]$^-$

N^1-[4-(4-chlorophenylsulfonyl)benzamide]-N^3-(2-methoxyphenyl)-2-thioxo-4,5-imidazolidinedione (4b)

m.p. = 143-5°C; yield = 49.4%;

IR (KBr; cm^{-1}): 3292m, 3091w, 3038w, 3009w, 2946w, 2841w, 1793vs, 1702s, 1601m, 1578s, 1505s, 1447m, 1414m, 1380s, 1341s, 1283s, 1256s, 1160s, 766s;

^{1}H-NMR (DMSO-d_6, δ, ppm, *J*, Hz): 12.23 (s, 1H, H-19); 8.20 (d, 9.0, 2H, H-7, H-11); 8.19 (d, 9.0, 2H, H-8, H-10); 8.03 (d, 8.6, 2H, H-13, H-17); 7.74 (d, 8.6, 2H, H-14, H-16); 7.54 (bt, 7.5, 1H, H-24); 7.05 (bd, 7.5, 1H, H-25); 7.26 (dd, 1.0, 7.5, 1H, H-22); 7.12 (td, 1.0, 7.5, 1H, H-24); 3.79 (s, 3H, OCH_3)

^{13}C-NMR (DMSO-d_6, δ, ppm): 179.10 (C-2); 164.05 (C-18); 155.07 (C-5); 153.77 (C-4); 152.64 (C-21); 144.17 (C-9); 139.30 (C-12); 139.12 (C-6); 135.19 (C-15); 131.77 (C-23); 130.06 (C-14, C-16); 129.83 (C-25); 129.57 (C-13, C-17); 129.48 (C-7, C-11); 128.02 (C-8, C-10); 120.74 (C-24); 120.25 (C-20); 112.79 (C-22); 56.06 (OCH_3);

UV (CH_3OH, λ_{max}(nm), lg ε): 205.3 (4.48); 251.1 (4.24);

Elemental analysis: found: C:52.19; H:2.96; N:7.98 % ; calcd. for $C_{23}H_{16}ClN_3O_6S_2$ (529.97 g/mol): C:52.12; H:3.04; N:7.93 %;

ESI-MS, *m/z* (abundance %): 528 (24.5, ^{35}Cl) [M-H]$^-$, 530 (8.3, ^{37}Cl) [M-H]$^-$, 351 (100, BP) [$^{35}ClC_6H_4SO_2C_6H_4CONHNHCOCH_2^-$], 353 (35.1) [$^{37}ClC_6H_4SO_2C_6H_4CONH NHCOCH_2^-$];

N^1-[4-(4-bromophenylsulfonyl)benzamide]-N^3-(2-methoxyphenyl)-2-thioxo-4,5-imidazolidinedione (4c)

m.p. = 146-7°C; yield = 47.9%;

IR (KBr; cm^{-1}): 3288m, 3089w, 3010w, 2928w, 2842w, 1793vs, 1702s, 1601m, 1574s, 1505s, 1468m, 1414m, 1380s, 1341s, 1283s, 1256s, 1161s, 575m;

^{1}H-NMR (DMSO-d_6, δ, ppm, *J*, Hz): 12.20 (s, 1H, H-19); 8.18 (s, 4H, 2H, H-7, H-8, H-10, H-11); 7.95 (d, 8.8, 2H, H-13, H-17); 7.87 (d, 8.8, 2H, H-14, H-16); 7.54 (bt, 1H, H-23); 7.39 (bd, 7.9, 1H, H-25); 7.12 (bt, 7.5, 1H, H-24); 3.79 (s, 3H, OCH_3)

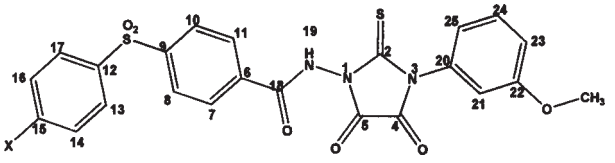
^{13}C-NMR (DMSO-d_6, δ, ppm): 179.09 (C-2); 164.05 (C-18); 155.06 (C-6); 154.20 (C-5); 153.75 (C-4); 152.63 (C-21); 144.14 (C-9); 139.55 (C-12); 135.19 (C-23); 133.07 (C-14, C-16); 131.77; 129.83 (C-25); 129.58 (C-13, C-17); 129.47; 128.42 (C-15); 128.01 (C-7, C-11); 120.74 (C-24); 120.26 (C-20); 112.80 (C-22); 56.06 (OCH_3);

UV (CH_3OH, λ_{max}(nm), lg ε): 205.3 (4.56); 254.6 (4.29);

Elemental analysis: found: C:48.15; H:2.78; N:7.36 %; calcd. for $C_{23}H_{16}BrN_3O_6S_2$ (574.42 g/mol): C:48.09; H:2.81; N:7.32 %;

ESI-MS, *m/z* (abundance %): 572 (100, BP ^{79}Br) [M-H]$^-$, 574 (89.9, ^{81}Br) [M-H]$^-$; 395 (46.5) [$^{79}BrC_6H_4SO_2C_6H_4CONHNHCOCH_2^-$], 397 (43.5) [$^{81}BrC_6H_4SO_2C_6H_4CONHNHCOCH_2^-$];

N^1-[4-(4-X-phenylsulfonyl)benzamide]-N^3-(3-methoxyphenyl)-2-thioxo-4,5-imidazolidinediones (5a-c)



N^1-[4-(phenylsulfonyl)benzamide]-N^3-(3-methoxyphenyl)-2-thioxo-4,5-imidazolidinedione (5a)

m.p. = 123-5°C; yield = 52.7%;

IR (KBr; cm^{-1}): 3277m, 3092w, 3065w, 3002w, 2940w, 2837w, 1793vs, 1702s, 1607m, 1592s, 1494m, 1447m, 1417m, 1380s, 1339s, 1289s, 1248s, 1156vs;

^{1}H-NMR (DMSO-d_6, δ, ppm, *J*, Hz): 12.12 (s, 1H, H-19), 8.19 (d, 9.0, 2H, H-8, H-10); 8.15 (d, 9.0, 2H, H-7, H-11); 8.01 (dd, 7.2, 1.5, 2H, H-13, H-17); 7.74 (tt, 7.1, 1.5, 1H, H-15), 7.66 (t, 7.1, 2H, H-14, H-16); 7.48 (t, 8.0, 1H, H-24); 7.00-7.14 (m, 3H, H-23, H-21, H-25); 3.78 (s, 3H, OCH_3);

^{13}C-NMR (DMSO-d_6, δ, ppm): 179.08 (C-2); 164.19 (C-18); 159.64 (C-5); 153.82 (C-4); 152.45 (C-22); 144.58 (C-9); 140.34 (C-12); 135.21; 134.12 (C-15); 133.11; 130.07 (C-24); 129.90 (C-14, C-16); 129.40 (C-7, C-11); 127.91 (C-8, C-10); 127.54 (C-13, C-17); 120.43 (C-23); 115.25 (C-25); 114.12 (C-21); 55.45 (OCH_3);

UV (CH_3OH, λ_{max}(nm), lg ε): 203.5 (4.39); 248.5 (4.10);

Elemental analysis: found: C:55.77; H:3.41; N:8.56 %; calcd. for $C_{23}H_{17}N_3O_6S_2$ (495.53 g/mol): C:55.75; H;3.46; N:8.48 %;

ESI-MS, *m/z* (abundance %): 494 (9.8) [M-H]$^-$; 317 (100, BP) [$C_6H_5SO_2C_6H_4CONHNHCOCH_2^-$]

N^1-[4-(4-chlorophenylsulfonyl)benzamide]-N^3-(3-methoxyphenyl)-2-thioxo-4,5-imidazolidinedione (5b)

m.p. = 225-6°C; yield = 50.4%;

IR (KBr; cm^{-1}): 3255m, 3089w, 3071w, 3001w, 2937w, 2836w, 1798vs, 1705s, 1610m, 1606s, 1519s, 1493m, 1401m, 1377s, 1341s, 1287s, 1246s, 1165s, 766s;

^{1}H-NMR (DMSO-d_6, δ, ppm, *J*, Hz): 12.14 (s, 1H, H-19); 8.17 (s, 4H, H-7, H-8, H-10, H-11); 8.03 (d, 8.8, 2H, H-13, H-17); 7.73 (d, 8.8, 2H, H-14, H-16); 7.48 (t, 7.9, 1H, H-24); 7.0-7.15 (m, 3H, H-21, H-23, H-25); 3.79 (s, 3H, OCH_3);

^{13}C-NMR (DMSO-d_6, δ, ppm): 179.08 (C-2); 164.12 (C-18); 159.64 (C-5); 153.82 (C-4); 152.45 (C-22); 144.11 (C-9); 139.28 (C-12); 139.13; 135.37 (C-15); 133.10; 130.06 (C-14, C-16); 129.55 (C-13, C-17); 129.50 (C-24); 129.47 (C-7, C-11); 128.00 (C-8, C-10); 120.43 (C-23); 115.25 (C-25); 114.12 (C-21); 55.45 (OCH_3);

UV (CH_3OH, λ_{max}(nm), lg ε): 205.3 (4.61); 252 (4.41);

Elemental analysis: found: C:52.16; H:2.98; N:7.96 %; calcd. for $C_{23}H_{16}ClN_3O_6S_2$ (529.97 g/mol): C:52.12; H:3.04; N:7.93 %;

ESI-MS, *m/z* (abundance %): 528 (100, BP, ^{35}Cl) [M-H]$^-$ 530 (38.2, ^{37}Cl) [M-H]$^-$; 351 (33.5) [$^{35}ClC_6H_4SO_2C_6H_4CONHNHCOCH_2^-$]; 353 (14.1) [$^{37}ClC_6H_4SO_2C_6H_4CONHNHCOCH_2^-$];

N^1-[4-(4-bromophenylsulfonyl)benzamide]-N^3-(3-methoxyphenyl)-2-thioxo-4,5-imidazolidinedione (5c)

m.p. = 223-4°C; yield = 53.2%;

IR (KBr; cm^{-1}): 3350m, 3089w, 3005w, 2940w, 2837w, 1782vs, 1724s, 1607m, 1592s, 1574s, 1495m, 1424m, 1379s, 1331s, 1288s, 1258s, 1155s, 572m;

^{1}H-NMR (DMSO-d_6, δ, ppm, *J*, Hz): 12.14 (s, 1H, H-19); 8.17 (s, 4H, H-7, H-8, H-10, H-11); 7.94 (d, 8.8, 2H, H-13, H-17); 7.87 (d, 8.8, 2H, H-14,H-16); 7.48 (t, 8.0, 1H, H-24); 7.02-7.15 (m, 3H, H-21, H-23, H-25); 3.79 (s, 3H, OCH_3);

^{13}C-NMR (DMSO-d_6, δ, ppm): 179.07 (C-2); 164.12 (C-18); 159.64 (C-5); 153.19 (C-4); 152.45 (C-22); 144.06 (C-9); 139.56 (C-12); 135.36 (C-15); 133.10 (C-24); 133.00; 130.07 (C-14,16); 129.56 (C-13, C-17); 129.47 (C-8, C-10); 128.41 (C-15); 127.99 (C-7, C-11); 120.43 (C-23); 115.25 (C-25); 114.12 (C-21); 55.45 (OCH_3);

UV (CH_3OH, λ_{max}(nm), lg ε): 206.2 (4.58); 257.3 (4.36);

Elemental analysis: found: C:48.17; H:2.76; N:7.38 %; calcd. for $C_{23}H_{16}BrN_3O_6S_2$ (574.42 g/mol): C:48.09; H:2.81; N:7.32 %;

ESI-MS, *m/z* (abundance %): 572 (100, BP, ^{79}Br) [M-H]$^-$; 574 (94.6, ^{81}Br) [M-H]$^-$; 395 (48.1) [$^{79}BrC_6H_4SO_2C_6H_4CONHNHCOCH_2^-$]; 397 (55.1) [$^{81}BrC_6H_4SO_2C_6H_4CONHNHCOCH_2^-$];

Antimicrobial activity

In vitro antimicrobial study was carried on Muller Hinton agar (Hi-media) plates (37 °C, 24 h) by agar diffusion cup plate method [31]. All the compounds were screened for antimicrobial activity at 2048 μg/mL concentration against the following bacterial strains: *Escherichia coli ATCC 25922, Pseudomonas aeroginosa ATCC 27853, Bacillus subtilis ATCC 6663.* Antifungal activity was tested on Sabouraud

dextrose agar (Himedia) plates (26°C, 48-72 h) by cup plate method [31] against *Candida scotti* at the concentration 2048 μg/mL. Tobramicin, Ciprofloxacin, Eritromicin were used as a standards for comparison of antibacterial activity and Nistatin for antifungal activity. DMSO was used as a solvent control for both antibacterial and antifungal activities.

Determination of MIC was made by serial dilutions in liquid broth method [32]. The materials used were well plates, suspensions of microorganism (0.5 McFarland), Muller–Hinton broth (for bacteria), and Sabouraud dextrose agar (for yeasts), solutions of the substances to be tested (2048 mg/mL in DMSO). After incubation at 37°C for 18–20 h for bacterial strains and for 48 h for *C. scotti*, the MIC for each tested substance was determined by macroscopic observation of microbial growth. It corresponds to the well with the lowest concentration of the tested substance where microbial growth was clearly inhibited. Tobramicin, Ciprofloxacin and Eritromicin for bacteria and Nistatin for the yeasts were used as standard drugs.

Results and discussions

Chemistry

Acylthiosemicarbazide moiety provides an opportunity to perform cyclocondensations as well as addition-cyclization reactions based on molecular existance of a NH exchangeable protons. They provide existence of tautomeric forms (scheme 2) that could participate on nucleophilic displacement with oxalyl chloride both nitrogen atoms and sulfur atom.

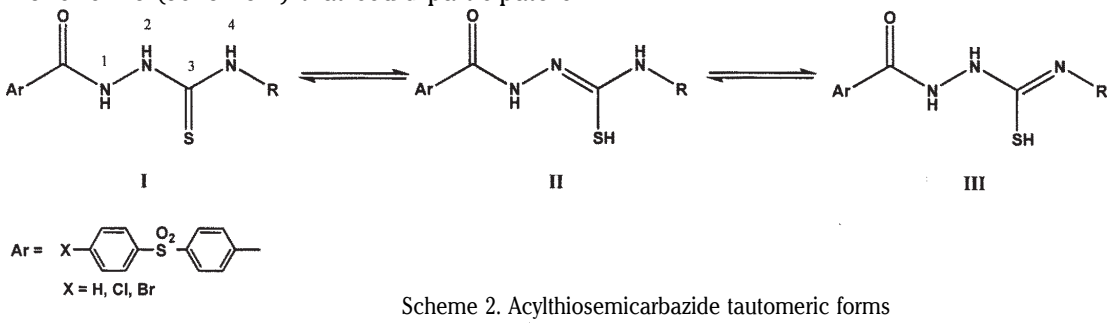
Nitrogen atom N^1 from I has an extremely low probability to participate on nucleophilic substitution because of its low nucleophilicity produced by R^1CO group through conjugation effect.

In the reaction with oxalyl chloride, the three tautomers could give three heterocycle structures: a thioparabanic acid (IV) and two imino-thiazolidinediones (V and VI, V major comparative to VI) (scheme 3).

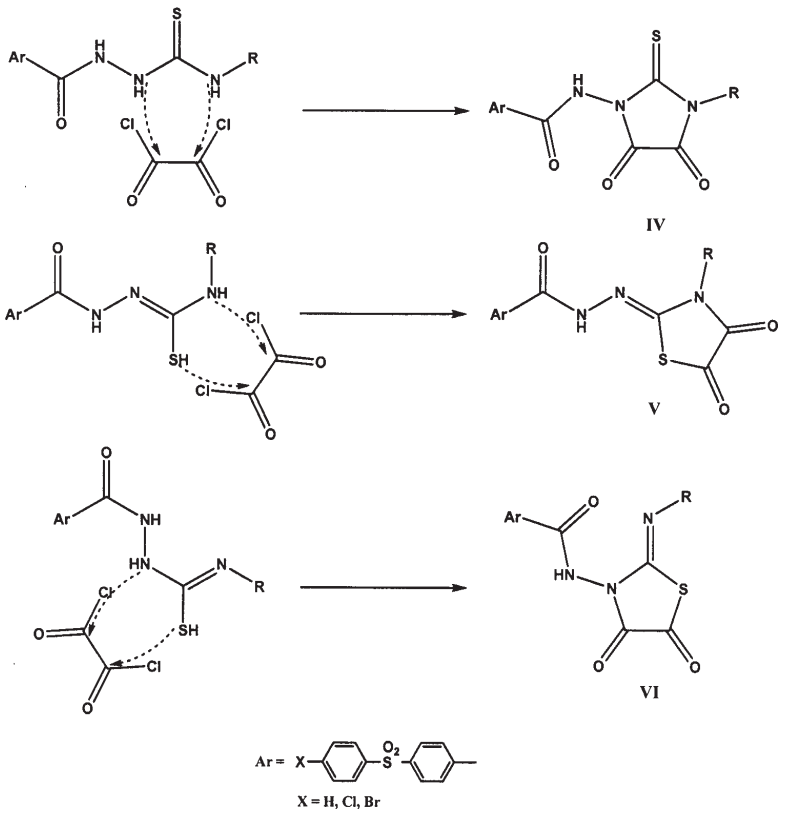
Imino-thiazolidinediones forming proceeds via nucleophilic attack by the thiosemicarbazide sulfur (after tautomeric shift to the thiol form with the hydrogen emanating from N^2 or N^4 to carbonylic carbon of oxalyl chloride. This way may afford two possible isomeric intermediates (A) and (B), which then are able to undergo different reaction routes to form one of the cyclic products (V) or (VI) (scheme 4).

Thioparabanic acid (IV) probably apears in dichloromethane at room temperature as a direct nucleophilic attack of the N^2 and N^4 to the oxalyl chloride carbon atoms or by partial isomerization of the imino-thiazolidinediones. This isomerisation is quantitative in ethanol at heating (scheme 5) [19].

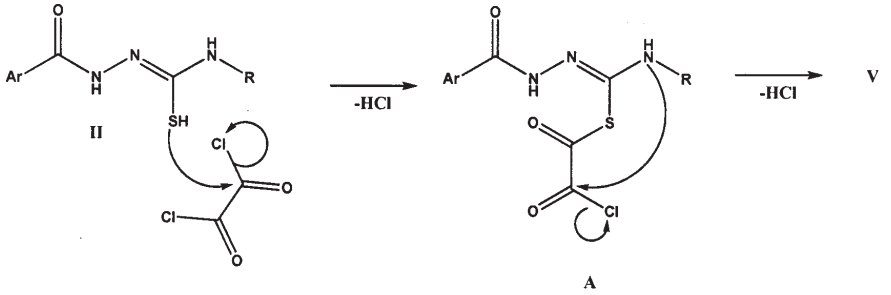
The presence of imino-thiazolidinediones together with thioparabanic acid in the reaction mixture is proven by spectral techniques (IR and NMR).



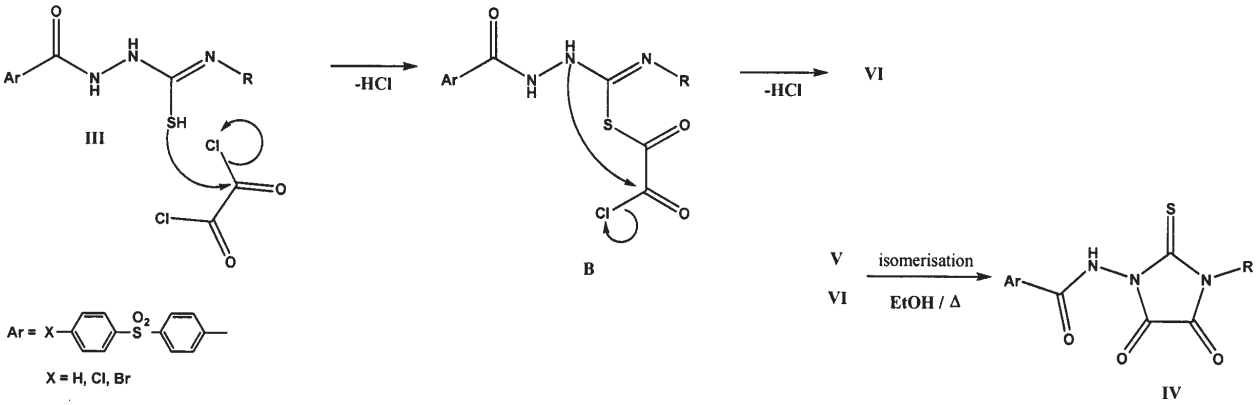
Scheme 2. Acylthiosemicarbazide tautomeric forms



Scheme 3. Acylthiosemicarbazide tautomers reaction with oxalyl chloride



Scheme 4. The probable pathways for formation of imino-thiazolidinediones V and VI



Scheme 5. Quantitative isomerisation of imino-thiazolidinediones

10μL Compund 2048 μg/L	Gram-negative bacteria				Gram-positive bacteria		Fungi	
	Escherichia coli ATCC 25922		Pseudomonas aeruginosa ATTC 27853		Baccillus subtilis ATCC 6663		Candida scotti	
	Compound	Tob 10μg	Compond	Cip 5 μg	Compound	E 15 μg	Compound	Ns 100μg
4a	5	30	1	28	3	30	1	30
4b	4	30	1	28	3	30	1	30
4c	3	30	1	28	3	30	1	30
5a	4	30	1	28	3	30	1	30
5b	4	30	1	28	3	30	1	30
5c	3	30	1	28	3	30	1	30

Table 1
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF COMPOUNDS **4a-5c.** INHIBITION ZONE DIAMETER [mm]

Tob - Tobramicin; Cip - Ciprofloxacin; E - Eritromicin; Ns - Nistatin

In IR spectra a proof for imino-thiazolidinediones is an absorption band at 1665-1680 cm^{-1} characteristic to νC=N [19], the other absorption bands can not be considered proofs because of the closer to those of thioparabanic acids.

In ^{1}H-NMR ($CDCl_3$) spectra the existence of the two forms (IV) and (V) is evidentiated by two NH singlet signals which appear at δ=9.19-10.00, also in ^{13}C-NMR ($CDCl_3$) spectra are present two closer signals around 56 ppm which can be attributed to the carbon atoms from methoxy groups present in both thioparabanic acid and imino-thiazolidinedione.

The mixture formed from two compounds which we obtained, after heating in ethanol, NMR and IR analysis indicated the presence of only one compound thioparabanic acid form (IV).

In IR spectra of new compounds **4a-5c** two absorption bands characteristic of C=O groups vibration are present, which apear at ~1700 cm^{-1} (RCONH) and ~1790 cm^{-1} respectively (corresponding of two C=O from imidazolidine ring which overlaps). Also the νC=S vibration band is present ~1250 cm^{-1}. In the region 3255-3350 cm^{-1} only one absorption band characteristic to NH group was observed. In the region 1665-1680 cm^{-1} no absorption band was found unlike the reaction mixture in which an absorption band is present in the region and is attributed to the C=N group from imino-thiazolidinedione form.

^{1}H-NMR (DMSO-d_6) spectra of new compounds **4a-5c** present only one singlet signal of one NH proton at 12.12-12.23 ppm. The signal observed at ~3.79 ppm corresponds to three protons and was assigned to OCH_3 group.

The new compounds **4a-5c** present in the ^{13}C-NMR (DMSO-d_6) spectra three characteristic signals of imidazolidine nucleus: the signals of two carbons from C=O group were observed around 153.19-153.82 ppm (for C-4) and 154.20-159.60 ppm (for C-5) respectively, while C=S signal was recorded at ~179 ppm. Also the carbon signal of OCH_3 group was observed at δ = 55-56 ppm. The signals of phenylsulfonylphenyl and phenylene fragments were recorded in ^{1}H-NMR and ^{13}C-NMR spectra at the expected chemical shifts in accordance with literature [29,30].

Antimicrobial activity

The preliminary results of antimicrobial activities indicated that the tested compounds exhibited a low activity against Gram-negative bacteria: *Escherichia coli ATCC 25922*, *Pseudomonas aeruginosa ATCC 27853*, one Gram-positive bacteria: *Bacillus subtilis ATCC 6663* and one yeast: *Candida scotti* (table 1).

Minimal inhibitory concentration (MIC) for **4a-5c** was determined to be 1024 μg/mL for all tested strains.

The obtained results indicated that the nature of the diphenylsulfone moiety (X=H, Cl, Br) and of the substituent on the N^3 from thioparabanic acid does not influence the antimicrobial activity of these compounds which is lower than reference drugs.

Conclusions

In this paper we report the synthesis and characterisation of six new compounds from 2-thioxo-4,5-imidazolidinedione class. These new compounds were obtained by the reaction of N^1-[4-(4-X-phenylsulfonyl) benzoyl]-N^4-(2-methoxyphenyl)/(3-methoxyphenyl)-thiosemicarbazides with oxalyl chloride.

The structure of new compounds was confirmed by elemental analysis and spectral methods.

All tested compounds had a low activity on growing of some gram-negative bacteria: *Escherichia coli, Pseudomonas aeroginosa,* gram-positive bacteria: *Bacillus subtilis* and fungi: *Candida scotti.*

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