# Synthesis, Characterization and Antimicrobial Activity Evaluation of Some New Derivatives of 6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide

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*The aim of the present study was the synthesis, physico-chemical characterization and in vitro antimicrobial activity evaluation of some new derivatives of 6,11-dihydrodibenzo[b,e]thiepine-5,5-dioxide. The synthesis of the new compounds was performed in several stages. Thus, by reaction of phtalide with thiophenol potassium salt, we obtained the 2-(phenylthiomethyl)benzoic acid. The acid was cyclized with polyphosphoric acid to the desired 6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one, converted afterwards to the corresponding 5,5-dioxide and subsequently to the corresponding oxime, 11-hydroxyimino-6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide. The acylation of this oxime with various acid chlorides afforded the new derivatives of 6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide. The new compounds were characterized by their physico-chemical properties and their chemical structures and purity were confirmed by elemental analysis and spectral analysis (IR, $^{1}$H-NMR, $^{13}$C-NMR). The original compounds were screened for their in vitro antibacterial activity against Gram –positive strains, Gram –negative bacteria and fungal strains, using both reference and clinical, multidrug resistant strains. The qualitative screening of the susceptibility spectra of various microbial strains to these compounds was performed by three adaptated diffusion methods: paper filter disk impregnation with tested substances solutions, the disposal of tested solutions in agar wells and the spotting of the tested solutions on solid medium seeded with microbial inoculums. The quantitative assay of the antimicrobial activity was performed by nutrient broth microdilution method in order to establish the minimal inhibitory concentration (MIC). The new sulfones exhibited a significant antimicrobial activity with MICs ranging from 15.6 μg/mL to 250 μg/mL.*

*Keywords: dibenzo[b,e]thiepine, sulfones, antimicrobial activity, NMR spectroscopy*

Dibenzo[b,e]thiepin system has proved to be a useful structural basis of many compounds with different biological properties [1] like antidepressant, antihistaminic, anti-inflammatory etc. In preceding communications [2-10] we reported the synthesis and characterization of some new dibenzo[b,e]thiepine derivatives.

The present work is a continuation-in-part of our researches, and presents the synthesis, structure confirmation and antimicrobial activity evaluation of some new derivatives of 6,11-dihydrodibenzo[b,e]thiepine-5,5-dioxide. It was considered worthwhile to investigate the antimicrobial activity for the new sulfones, being known that sulfone functionality in the molecule may be advantageous for antimicrobial activity.

## Experimental part

All reagents were obtained from commercial suppliers and used without further purification unless otherwise specified.

Melting points were determined using an Electrothermal 9100 apparatus without being corrected.

The NMR spectra were registered with a Varian Gemini 300BB apparatus, at 300 MHz for $^{1}$H-NMR and 75 MHz for $^{13}$C-NMR and an Unity-Inova 400 operating at 400 MHz in proton and 100 MHz in carbon. Dimethylsulfoxide-$d_6$ and chloroform-$d_1$ were used as solvents and tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in δppm values and the coupling constants are in Hertz. The spectra are recorded at room temperature in usual conditions and sometimes Apt and Cosy sequences are used.

The IR spectra were registered in potassium bromide pellets with a Fourier transform infrared spectrophotometer FTS-135 BIORAD and by ATR technique with an FT-IR Bruker instrument Vertex 70.

The elemental analysis was performed on a Perkin-Elmer 2400 Series II CHNS/O Analyser.

*2-Phenylthiomethyl-benzoic acid (3) and 6,11-dihydro/dibenzo[b,e]thiepin-11(6H)-one (4)* were synthesized according to the methods described previously [5, 10].

*Synthesis of 6,11-dihydrodibenzo[b,e]thiepin-11-one 5,5-dioxide (**5**)*

To a solution of 2.26 g (0.01 mol) 6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one in 15 mL glacial acetic acid were added drop wise 4 mL 30% hydrogen peroxide, the mixture was heated for 3 hours and left overnight at room temperature. The reaction mixture was diluted with water and the compound was extracted with chloroform. The organic layer was dried over calcium chloride and the solvent was removed under reduced pressure. The resulting crude product was recrystallized from ethanol (m.p. 126.8- 127.5$^{0}$C; yield 97.5%; lit. [11] m.p.= 127- 128$^{0}$C).

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*Synthesis of 11-hydroxyimino-6,11-dihydrodibenzo[b,e] thiepin 5,5-dioxide (**6**)*

2.58 g (0.01 mol) of 6,11-Dihydrodibenzo[b,e]thiepin-11-one 5,5-dioxide (Mol wt 258.29) and 2.08 g (0.03 mol) of hydroxylamine hydrochloride (Mol wt 69.49) were boiled under reflux in 40 mL of pyridine for 24 h. The pyridine was subsequently distilled off in a *vacuum*, the residue was triturated with water, suction-filtered, dried and recrystallized from toluene (m.p. 204.3- 206.2$^0$C; yield 90.1%).

*Synthesis of O-acyl-oximino-dibenzo[b,e]thiepin 5,5-dioxides (**7**). General procedure*

To a solution of 2.73 g (0.01 mol) 11-hydroxyimino-6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide ($M_r$ 273.31) in anhydrous benzene was added drop wise a solution of 0.01 mol of appropriated acylchloride in 10 mL anhydrous benzene and 0.79 g (0.8 mL; 0.01 mol) dry pyridine (Mol wt 79.098; $d_4^{25}$=0.978). The reaction mixture was refluxed for two hours, afterwards was cooled, the precipitate was filtered and the solvent was removed under reduced pressure. The resulting crude product was recrystallized from an appropriate solvent.

Analytical and spectral data of the new compounds, 11-hydroxyimino-6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide (***6***) and sulfones ***(7)***, are given below.

*11-hydroxyimino-6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide **(6)***

$C_{14}H_{11}NO_3S$ (273.31); colorless crystals, m.p. 204.3-206.2$^0$C (toluene); yield 91.1%

Elemental analysis. Calcd. C: 61.53; H: 4.06; N: 5.12; S: 11.72. Found: C: 61.71; H: 3.95; N: 5.20; S: 11.50.

**FT-IR** (ATR in solid, ν cm$^{-1}$): 3607m; 3514m; 3163m; 3028s; 2928s; 1601s; 1481s; 1434m; 1322s; 1287vs; 1155m; 933m; 753m

**$^1$H-NMR** ($CDCl_3$, δ ppm, J Hz): 4.71 (s, 2H, H-6); 7.35÷7.70 (m, 7H, Ar-H); 8.00 (dd, 1H, H-4, 1.9, 7.4); 8.92 (s, 1H, H-12, deuterable)

**$^{13}$C-NMR** ($CDCl_3$, δ ppm): 59.04 (C-6); 124.88 (Cq); 126.25 (CH); 128.93 (CH); 129.25 (CH); 129.53 (CH); 130.70 (CH); 131.39 (CH); 131.51 (CH); 131.93 (Cq); 132.83 (CH); 135.35 (Cq); 141.69 (Cq); 156.00 (C-11).

*11-[O-(2,3-Dimethoxy-benzoyl)-oximino]-6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide **(7a)***

$C_{23}H_{19}NO_6S$ (437.47); colorless crystals, m.p. 188.3-190.1$^0$C (ethanol); yield 70.6%

Elemental analysis. Calcd. C: 63.15; H: 4.38; N: 3.20; S: 7.33. Found: C: 63.48; H: 4.24; N: 3.61; S: 7.49.

**FT-IR** (ATR in solid, ν cm$^{-1}$): 3063w; 2964w; 2937w; 2922w; 2829w; 1750vs; 1582s; 1479s; 1271s; 1170s; 1036m; 748m.

**$^1$H-NMR** ($CDCl_3$, δ, ppm, J, Hz): 3.63 (s, 3H, -$OCH_3$), 3.85 (s, 3H, -$OCH_3$), 4.37 (bs, 1H, sist AB, H-6A); 5.18 (bs, 1H, sist AB, H-6B); 7.00 ÷ 7.18 (m, 3H, Ar-H); 7.38 - 7.56 (m, 4H, Ar-H); 7.64 (td, 1H, H-2, 7.4, 1.7); 7.70 (td, 1H, H-3, 7.4, 1.7); 7.91 (dd, 1H, H-1, 7.5, 1.7); 8.04 (dd, 1H, H-4, 7.4, 1.8).

**$^{13}$C-NMR** ($CDCl_3$, δ, ppm): 56.07 (-$OCH_3$); 58.44 (C-6); 61.38 (-$OCH_3$); 116.58 (CH); 122.20(CH); 123.54 (Cq); 123.97 (CH); 124.12 (Cq); 126.11 (CH); 127.99 (CH); 129.22 (CH); 129.96 (CH); 130.13 (Cq); 130.92 (CH); 131.33 (CH); 132.24 (CH); 132.77 (CH); 135.06 (Cq); 141.73 (Cq); 149.54 (Cq); 153.56 (Cq); 163.05 (C-11); 163.95 (C-12).

*11-[O-(2,4-Dimethoxy-benzoyl)-oximino]-6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide **(7b)***

$C_{23}H_{19}NO_6S$ (437.47); colorless crystals, m.p. 211.5-213.1$^0$C (ethanol); yield 70.9%.

Elemental analysis. Calcd. C: 63.15; H: 4.38; N: 3.20; S: 7.33. Found: C: 63.05; H: 4.58; N: 3.49; S: 7.63.

**FT-IR** (ATR in solid, ν cm$^{-1}$): 3039vw; 2967w; 2915vw; 2842vw; 1739vs; 1604s; 1478m; 1328m; 1172m; 745m.

**$^1$H-NMR** ($CDCl_3$, δ, ppm, J, Hz): 3.65 (s, 3H, -$OCH_3$), 3.81 (s, 3H, -$OCH_3$), 4.38 (bs, 1H, sist AB, H-6A); 5.20 (bs, 1H, sist AB, H-6B); 6.39 (d, 1H, H-15, 2.2); 6.42 (dd, 1H, H-17, 8.7, 2.2); 7.40 ÷ 7.55 (m, 4H, Ar-H); 7.62 (d, 1H, H-18, 8.7); 7.62 (td, 1H, H-2, 7.4, 1.7); 7.68 (td, 1H, H-3, 7.4, 1.7); 7.89 (dd, 1H, H-1, 7.4, 1.7); 8.02 (dd, 1H, H-4, 7.5, 1.7).

**$^{13}$C-NMR** ($CDCl_3$, δ, ppm): 55.50 (-$OCH_3$); 55.59 (-$OCH_3$); 58.41 (C-6); 98.79 (CH); 104.85 (CH); 109.61 (Cq); 124.09 (Cq); 125.92 (CH); 128.14 (CH); 128.75 (CH); 130.55 (CH); 130.55 (CH); 131.96 (CH); 131.96 (Cq); 131.11 (CH); 132.62 (CH); 134.15 (CH); 135.46 (Cq); 141.61 (Cq); 153.20 (Cq); 161.60 (Cq); 162.76 (C-11); 164.99 (C-12)

*11-[O-(3,4-Dimethoxy-benzoyl)-oximino]-6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide **(7c)***

$C_{23}H_{19}NO_6S$ (437.47); colorless crystals, m.p. 228.1-230.1$^0$C (ethanol); yield 77.8%.

Elemental analysis. Calcd. C: 63.15; H: 4.38; N: 3.20; S: 7.33. Found: C: 63.45; H: 4.59; N: 3.51; S: 7.48.

**FT-IR** (ATR in solid, ν cm$^{-1}$): 3066vw; 3002vw; 2973vw; 2931w; 2839w; 1755vs; 1600m; 1332s; 1269s; 1170s; 1057s; 745m.

**$^1$H-NMR** ($CDCl_3$, δ, ppm, J, Hz): 3.77 (s, 3H, -$OCH_3$); 3.91 (s, 3H, -$OCH_3$); 4.39 (bs, 1H, sist AB, H-6A); 5.18 (bs, 1H, sist AB, H-6B); 6.83 (d, 1H, H-17, 8.5); 7.22 (d, 1H, H-14, 2.0); 7.42 (dd, 1H, H-18, 8.5, 2.0); 7.45 ÷ 7.60 (m, 4H, Ar-H); 7.66 (td, 1H, H-2, 7.3, 1.7,); 7.71 (td, 1H, H-3, 7.3, 1.7,); 7.92 (dd, 1H, H-1, 7.3, 1.7); 8.05 (dd, 1H, H-4, 7.7, 1.7).

**$^{13}$C-NMR** ($CDCl_3$, δ, ppm): 55.91 (-$OCH_3$); 56.11 (-$OCH_3$); 58.52 (C-6); 110.49 (CH); 111.77 (CH); 119.93 (Cq); 124.44 (Cq); 124.13 (CH); 126.12 (CH); 127.97 (CH); 128.83 (CH); 129.89 (Cq); 130.00 (CH); 130.87 (CH); 131.55 (CH); 132.28 (CH); 132.81 (CH); 135.11 (Cq); 141.81 (Cq); 148.71 (Cq); 153.69 (Cq); 162.68 (C-11); 163.40 (C-12);

*11-(O-Propionyl-oximino)- 6,11-dihydrodibenzo[b,e] thiepin 5,5-dioxide **(7d)***

$C_{17}H_{15}NO_4S$ (329.38); colorless crystals, m.p. 130.1-132.8$^0$C (ethanol); yield 81.1%.

Elemental analysis. Calcd. C: 61.99; H: 4.59; N: 4.25; S: 9.73. Found: C: 61.68; H: 4.41; N: 4.46; S: 9.87

**FT-IR** (ATR in solid,ν cm$^{-1}$): 3066vw; 2990vw; 2963vw; 2918vw; 2880vw; 1768vs; 1602w; 1308m; 1122s; 1061s; 785m; 753w.

**$^1$H-NMR** (dmso-d6, δ ppm, J, Hz): 1.13 (t, 3H, H-14, 7.5); 2.38 (q, 2H, H-13, 7.5); 4.63 (bs, 1H, sist AB, H-6A); 4.95 (bs, 1H, sist. AB, H-6B); 7.30 (dd, 1H, H-7, 1.1, 7.9); 7.41÷7.72 (m, 5H, Ar-H); 7.82 (dd, 1H, H-1, 1.6, 7.3); 8.03 (dd, 1H, H-4, 1.3, 7.8).

**$^{13}$C-NMR** (dmso-d6, δ, ppm): 8.87 (C-14); 26.31 (C-13); 58.60 (C-6); 124.29 (Cq); 126.24 (CH); 127.92(CH); 129.08 (CH); 129.94 (CH); 130.94 (CH); 131.48 (CH); 132.26 (CH); 132.79(CH); 134.28 (Cq); 135.69 (Cq); 171.24 (C-12)

*11-[O-(α-Thenoyl)-oximino]-6,11-dihydrodibenzo[b,e] thiepin 5,5-dioxide **(7e)***

$C_{19}H_{13}NO_4S_2$ (383.45); colorless crystals, m.p. 222.3-224.1$^0$C (glacial acetic acid); yield 78.3%.

Elemental analysis. Calcd. C: 59.52; H: 3.42; N: 3.65; S: 16.72. Found: C: 59.28; H: 3.43; N: 3.75; S: 16.98

**FT-IR** (ATR in solid, ν cm$^{-1}$): 3095w; 2961w; 2920vw; 1751vs; 1741m; 1603w; 1359vs; 1156s; 889m.

**$^1$H-NMR** (dmso-d6, δ ppm, J, Hz): 4.45 (bs, 1H, sist. AB, H-6A). 4.98 (bs, 1H, sist. AB, H-6B); 7.09 (dd, 1H, H-15, 3.8, 4.9); 7.40 ÷ 7.70 (m, 8H); 7.89 (dd, 1H, H-1, 1.6, 7.4); 8.03 (dd, 1H, H-4, 1.5, 7.7).

**$^{13}$C-NMR** (dmso-d6, δ, ppm): 58.65 (C-6); 124.39 (Cq); 126.25 (CH); 128.14 (CH); 128.18 (CH); 129.06 (CH); 130.08 (CH); 131.07 (CH); 131.51 (CH); 132.37 (CH); 132.81 (CH); 133.87 (CH); 134.77 (CH); 142.05 (Cq); 158.82 (C-11); 164.05 (C-12).

Antimicrobial activity assay

The antimicrobial properties of the new compounds were tested against reference strains (Klebsiella pneumoniae IC 13420, Escherichia coli IC 13529, Staphylococcus aureus IC13204, Pseudomonas aeruginosa IC 13202, Bacillus subtilis IC12488, Candida albicans IC249, Aspergillus niger IC 13534) and also against bacterial and fungal strains recently isolated from clinical samples (Staphylococcus aureus 1263, Klebsiella pneumoniae 1204, Escherichia coli 13147, Pseudomonas aeruginosa 1246, Candida albicancs 101404).

The microbial strains were identified by aid of VITEK I automatic system. VITEK cards for identification and susceptibility testing for antibiotics (GNS-522) were inoculated and incubated according to the manufacturer's recommendations. The results were interpreted using software version AMS R09.1.

We used in our experiments bacterial suspensions of 0.5 MacFarland density (corresponding to 1-3 . $10^8$ CFU/mL) obtained from 15-18h bacterial cultures grown on solid media. The antimicrobial activity was tested on Mueller-Hinton medium recommended for the bacterial strains and Yeast Peptone Glucose (YPG) medium for *Candida albicans*. We solubilized the tested compounds in DMF (dimethylformamide) and stock solutions of 1000 mg/mL concentration were obtained.

Qualitative screening of the antimicrobial properties of the tested compounds

The *qualitative screening* of the tested sulfones was performed by three adapted diffusion methods: paper filter disk impregnation with the tested substances solutions, the disposal of the tested solutions in agar wells and the spotting of the tested solutions on solid medium seeded with microbial inoculums [12- 15].

In the 1st method, Petri dishes containing Mueller-Hinton/ YPG medium were seeded with bacterial inoculums as for the classical antibiotic susceptibility testing disk diffusion method (Kirby-Bauer); 5 mm diameter paper filter disk were placed on the seeded medium, at 30 mm distance to each other. Subsequently, the disks were impregnated with 5μL of the tested compounds solution.

In the 2nd method, 5 μL of the tested compounds solution were placed in the agar wells cut in the solidified culture medium seeded with the microbial inoculum.

In the 3rd method, 5ìL of the compounds solution were spotted on Petri dishes seeded with bacterial/ yeast inoculum.

In all three variants, the Petri dishes were left at room temperature to ensure the homogenous diffusion of the compound in the culture medium or to allow the drop of the solution to be absorbed in the medium and afterwards the dishes were incubated at 37$^0$C for 24 h. The solvent (dimethylformamide) was equally tested to evaluate its intrinsic antimicrobial activity.

Quantitative assay of the antimicrobial activity

Quantitative assay of the antimicrobial activity was performed by the binary microdilution method in 96 multi-well plates, in order to establish the minimal inhibitory concentration (MIC) [16, 17].

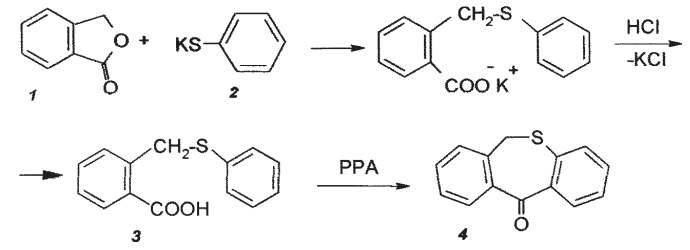
Binary serial dilutions of the tested compound in DMF (ranging between 1000 mg/mL and 0.97 mg/mL) were performed in a 200 μL volume of nutrient broth and subsequently each well was seeded with 50 μL microbial suspension of 0.5 MacFarland density.

In each test a microbial culture control (a series of wells containing exclusively culture medium with microbial suspension) and a sterility control (a series of wells containing exclusively culture medium) were performed. The plates were incubated for 24 h at 37$^0$C.

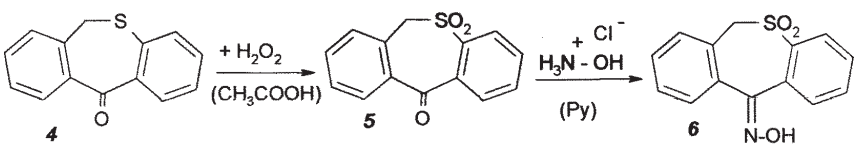
**Results and discussions**

The synthesis of the new compounds was performed in several stages.

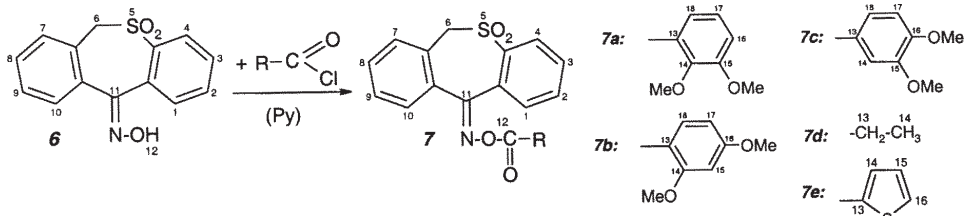
The preparation of the starting materials, 2-phenylthiomethyl-benzoic acid (***3***) and 6,11-dihydrodibenzo [b,e]thiepin-11(6H)-one (***4***), was accomplished by the synthetic sequences as previously reported [5, 10]. Thus, by reaction of phtalide (***1***) with thiophenol potassium salt (***2***), we obtained the acid (***3***). Ketone (***4***) was synthesized by cyclodehydration of acid (***3***) in the presence of polyphosphoric acid (PPA). The reactions are presented in scheme 1.The ketone (***4***) was converted to the corresponding 5,5-dioxide (***5***) by oxidation with hydrogen peroxide (30%) in glacial acetic acid medium under reflux, as is mentioned in literature [11, 18, 19] and subsequently to the corresponding oxime (***6***), by treating with hydroxylamine hydrochloride, in the presence of pyridine. The reactions are presented in scheme 2.



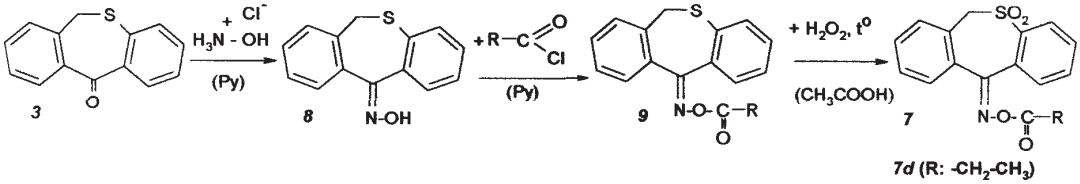

Scheme 1. Synthesis of 2-phenylthiomethyl-benzoic acid (***3***) and 6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one (***4***)




Scheme 2. Synthesis of 6,11-dihydrodibenzo[b,e]thiepin-11-one 5,5-dioxide (***5***) and 11-hydroxyimino-6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide (***6***)



Scheme 3. The synthesis of the new sulfones (**7**)



Scheme 4. The synthesis pathway for the sulfones (**7**)

**Table 1**
THE RESULTS OF THE ANTIMICROBIAL ACTIVITY OF THE NEW SULFONES; MIC VALUES (μg/mL)

| Compound / Microbial strain | 7a MIC (μg/mL) | 7b MIC (μg/mL) | 7c MIC (μg/mL) | 7d MIC (μg/mL) | 7e MIC (μg/mL) |
|---|---|---|---|---|---|
| *K. pneumoniae* 1204 | 62.5 | 62.5 | 125 | 62.5 | 62.5 |
| *K. pneumoniae* IC 13420 | 62.5 | 125 | 250 | 62.5 | 62.5 |
| *E. coli* 13147 | 62.5 | 125 | 250 | 62.5 | 62.5 |
| *E. coli* IC 13529 | 62.5 | 125 | 250 | 62.5 | 62.5 |
| *S. aureus* 1263 | 250 | 250 | 250 | 125 | 125 |
| *S. aureus* IC 13204 | 125 | 125 | 125 | 125 | 125 |
| *P. aeruginosa* 1246 | 62.5 | 62.5 | 62.5 | 62.5 | 62.5 |
| *P. aeruginosa* IC 13202 | 62.5 | 62.5 | 62.5 | 62.5 | 62.5 |
| *B. subtilis* IC 12488 | 125 | 125 | 125 | 125 | 125 |
| *C. albicans* 101404 | 62.5 | 62.5 | 125 | 62.5 | 62.5 |
| *C. albicans* IC 249 | 62.5 | 62.5 | 125 | 62.5 | 62.5 |
| *A. niger* IC 13534 | 31.25 | 31.25 | 31.25 | 15.6 | 31.25 |

The acylation of the oxime (***6***) with various acid chlorides, in dry benzene or toluene, in the presence of anhydrous pyridine as proton acceptor, gave the new sulfones (***7***). The reaction is presented in scheme 3.

Our attempt to obtain 11-(O-propionyl-oximino)-6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide (***7d***; R=-$CH_2$-$CH_3$) following the synthesis pathway presented in our previous communications [5, 6, 10] (scheme 4), *via* oxime (***8***) and O-acyloximino-dibenzo[b,e]thiepine (***9***), was not successful. In the last stage, under the reaction condition 11-(O-propionyl-oximino)-6,11-dihydrodibenzo[b,e] thiepine ***9*** (R=-$CH_2$-$CH_3$) was cleaved, affording the oxidation product, oxime ***6.***

All the new sulfones are solid, crystallized, white, soluble at room temperature in acetone, chloroform, benzene, toluene, xylene, dichloromethane, by heating in inferior alcohols, insoluble in water.

Their structures were elucidated by elemental analysis and spectral analysis. The IR, $^1$H-NMR and $^{13}$C-NMR spectra show all the expected signals. All elemental analyses results were within ±0.4% of the theoretical values.

*Qualitative antimicrobial activity screening*

For the qualitative testing the reading of the results was performed by measuring the microbial growth inhibition zones around the filter disks impregnated with the testing sulfones / around the wells / on the spot of solution drop, respectively.

The qualitative screening emphasized that the most appropriate method for the antimicrobial assay were the disk diffusion method and the method of spot solution disposal, the results being well correlated with those of the quantitative antimicrobial assays.

*Quantitative antimicrobial activity assay by microdilution method*

In the quantitative assay the minimal inhibitory concentration was read by wells observations. In the first wells containing high concentrations of compounds the culture growth was not visible, the microbial cells being killed or inhibited by the tested compound. The lowest concentration which inhibited the visible microbial growth represents the MIC (μg/mL) value for the tested compound.

The quantitative assay results for the antimicrobial activity of the new sulfones are presented in table 1; based on literature data, we considered a very strong antimicrobial activity for MICs ranging between 15.6 μg/mL and 125 μg/mL, while a MIC of 250 μg/mL concentration represented a moderate effect.

All tested sulfones **7a-e** exhibit both antibacterial and antifungal activity against reference, but also clinical strains. The compounds presented broad spectrum antimicrobial activity, being active at low concentrations both on Gram-positive, Gram-negative bacteria and fungi. The MIC values ranged between 250 μg/mL and 15.6 μg/mL.

All the tested compounds were highly active against *A. niger* (MIC 15.6 μg/mL to 31.25 μg/mL), demonstrating the potential use of these compounds for the selection of new therapeutical options for the treatment of the fungal infections.

## Conclusions

We have synthesized some original compounds, 11-hydroxyimino-6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide and five new derivatives of 6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide.

We have developed a new pathway for O-acyl-oximino-dibenzo[b,e]thiepin-5,5-dioxides synthesis, which assume S-oxidation of the 6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one to the corresponding 5,5-dioxide, obtaining of the 11-hydroxyimino-6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide, the acylation with various acid chlorides being performed in the final stage.

All the compounds were characterized by their main physical properties. The structures were confirmed by spectral analysis ($^{1}$H-NMR, $^{13}$C-NMR, IR) and elemental analysis.

The new sulfones were screened for their *in vitro* antibacterial activity against Gram- positive strains, Gram-negative bacteria and fungal strains, using both reference and clinical, multidrug resistant strains.

The *in vitro* qualitative and quantitative antimicrobial activity assay showed that all the new compounds exhibited significant antimicrobial activity, with MICs values ranging from 15.6 μg/mL to 250 μg/mL that could lead to the selection and use of these compounds as new efficient antimicrobial agents.

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