Synthesis, Structure Elucidation, and Microbiological Screening of Some New Dibenz[b,e]Oxepin Derivatives

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New O-acyl-oximino-dibenz[b,e]oxepins, ({[(E,Z)-11-dibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy) (substituted-phenyl)methanone derivatives have been prepared, in order to search for new antibacterial compounds, as response to the overwhelming problem of multiple drug resistance emergence in clinical microbial strains. The structure of these compounds has been investigated by using elemental analysis and spectral measurements. The new compounds proved a good antimicrobial activity with low MIC values on Gram- negative, enterobacterial strains and Pseudomonas aeruginosa.

Keywords: dibenz[b,e]oxepin, methanone derivatives, antimicrobial activity, Escherichia coli, Proteus vulgaris, Moganella morganii, Pseudomonas aeruginosa

Several reports revealed that dibenz[b,e]oxepin derivatives possess significant biological activities, such as antidepressant, anxiolytic, anticholinergic and antihistaminic properties, as well as antipsychotic, analgesic, antipyretic and anti-inflammatory activities [1-5].

Over the last few years, the dibenz[b,e]oxepin nucleus has been of interest to design molecules designed as antitumoral agents. The 8-(11-Oxo-6,11-dihydro-dibenz[b,e]oxepin-2-yloxy)-octanoic acid hydroxyamide has histone deacetylase (HDAC) inhibitory activity, inhibiting cell proliferation and being promissing reagents for cancer therapy as effective inducers of apoptosis [6].

Researchers have also reported that some new imidazole derivatives of 6,11-dihydro-dibenz[b,e]oxepines are useful as antifungal and antibacterial agents [7].

The last years have been dominated by an incessant need for the development of new antimicrobial agents, in response to the overwhelming problem of multiple drug resistance emergence in clinical microbial strains.

Leptosphaerin D with dibenz[b,e]oxepin structure, is a new polyketide isolated from solid cultures of the ascomycete fungus *Leptosphaeria* sp. This compound, an analogue of Arugosin F, showed antimicrobial and antifungal effects against the plant pathogens *Fusarium nivale* and *Piricularia oryzae* [8].

The purpose of the present paper was to investigate new opportunities for developing new antimicrobial compounds, by the synthesis of new ({[(E,Z)-11-dibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy) (substituted-phenyl)methanone derivatives from the reaction of the 11-hydroximino-6,11-dihydro-dibenz[b,e] oxepin with various acid chlorides. The assignnement of new compounds structures is based on their analytical and spectroscopic data.

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Experimental part

All chemicals used for the preparation of the compounds were of reagent grade quality and purchased from Fluka, Merck and Sigma- Aldrich.

Melting points were estimated with an Electrothermal 9100 apparatus in open capillary tubes and are uncorrected.

Elemental analyses were done on a Perkin Elmer CHNS/O Analyser Series II 2400 apparatus and all the values were within ± 0.4 % of the calculated compositions.

IR spectra were recorded on a FT- IR Bruker Vertex 70 spectrophotometer.

NMR spectra were recorded on a Varian Unity Inova 400 instrument operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C.

New dibenz[b,e]oxepins were synthesized according to previously described procedures [9].

The synthesis of the new compounds (general procedure)

An amount of 0.016 mol of 11-hydroximino-6,11-dihydro-dibenz[b,e]oxepin was solubilised in anhydrous benzene by refluxing in a round-bottom flask equipped with condenser and drying tube. To this solution it was added dropwise a solution of 0.016 mol of dry pyridine and 0.016 mol of acyl chloride in 10 mL anhydrous benzene, the resulted mixture being refluxed two hours.

After the reaction was completed (monitored by TLC), the mixture was filtered and the organic layer was removed under reduced pressure and the residue was triturated with isopropanol. The resulting solid was recrystallized from isopropanol to yield the new O-acyl-oximino-dibenz[b,e] oxepins.

Antimicrobial activity

Microbial strains

The antimicrobial activity of the investigated compounds was tested against the following Gram- positive (coagulase- positive, methicillin resistant *Staphylococcus*

aureus 1268) and Gram- negative (*Morganella morganii 2*, *Pseu*domonas aeruginosa 1246, Salmonella arizonae 23, Proteus vulgaris 12, Klebsiella planticola 8, Escherichia coli 13147) strains.

The coagulase- positive, methicillin resistant Staphylococcus aureus and one Pseudomonas aeruginosa strain were recently isolated from central venous catheters associated infections and the Enterobacteriaceae strains were isolated from different cases of acute diffuse peritonitis.

The Enterobacteriaceae strains were identified by API 20E biochemical tests, while Pseudomonas aeruginosa and Staphylococcus aureus were identified by VITEK I automatic system.VITEK cards for identification and susceptibility testing (GNS- 522) were inoculated and incubated according to the manufacturer's recommendations. The results were interpreted by using software version AMS R091. Bacterial suspensions of 0.5 McFarland UI density obtained from 18 h bacterial cultures developed on solid media were used in the experiments. The antimicrobial activity was tested on Mueller- Hinton medium.

Stock solutions

The tested compounds were solubilised in DMSO and used for the antimicrobial activity screening at 1mg/ mL concentration.

Quantitative assay of the antimicrobial activity

It was performed by binary micro dilution method, in 96 multi-well plates, in order to establish the MIC [10].

For this purpose, serial binary dilutions of the tested compounds were performed in a 150 mL volume of Muller Hinton nutrient broth (from 1000 μg/mL to 7.8 μg/mL) and each well was seeded with 30 mL of microbial inoculum. The plates were incubated for 24 h at 37°C, and MICs were read as the last concentration of the compound which inhibited the visual microbial growth.

Results and discussion

Chemistry

The new compounds were obtained in satisfactory yields, and the synthetic pathways to obtain the targets are described in the scheme 1.

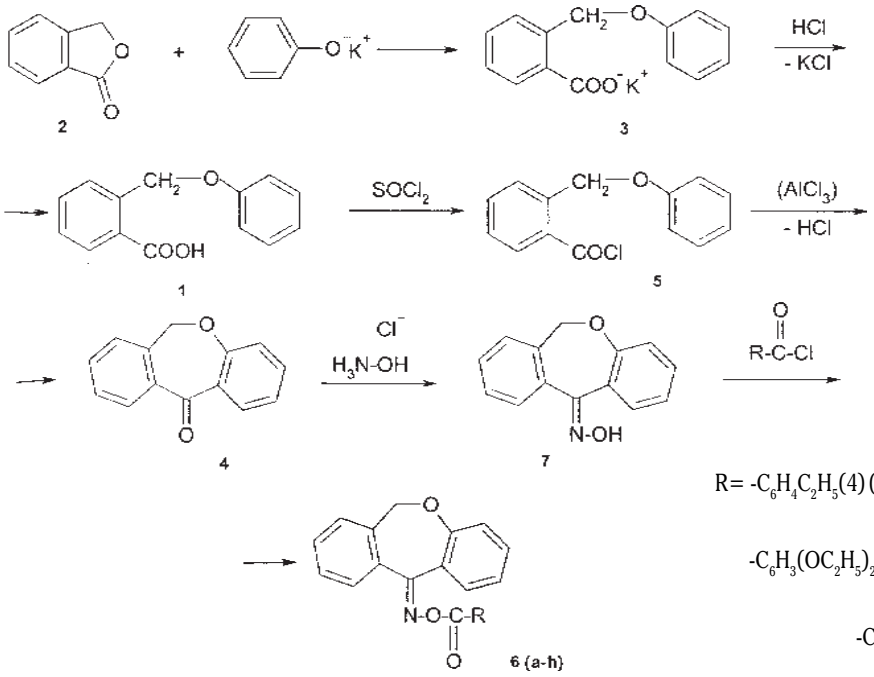
Synthesis of the new compounds was accomplished in three steps.

In the first stage, the 2-phenoxymethylbenzoic acid (**1**) was prepared by treating the phtalide (**2**) with potassium phenoxyde in xylene. The resulting 2-phenoxymethylbenzoic acid potassium salt (**3**) shows a good solubility in a potassium hydroxide aqueous solution and thus was separated from xylene. The aforementioned acid was precipitated using a mineral acid solution. The potassium salt of phenol was obtained using phenol and potassium hydroxide in xylene, the resulting water being removed by azeotropic distillation.

The 6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one (**4**) was synthesized in the second stage by a Friedel-Crafts cyclization of the 2-phenoxymethylbenzoic acid chloride (**5**) in dry 1,2-dichloroethane. The acid chloride was obtained by refluxing the coresponding acid with thionyl chloride in excess, but it could also be obtained using different anhydrous solvents as reaction medium, such as 1,2-dichloroethane. The desired ketone was also prepared directly from the 2-phenoxymethylbenzoic acid by using various agents for anhydrization (e.g. poliphosporic acid), but the yields were smaller.

The new compounds (**6**) were prepared by acylation of the 11-hydroximino-6,11-dihydro-dibenz[b,e]oxepin (**7**) with various substituted benzoic acid chlorides, in dry benzene and in the presence of anhydrous pyridine as a proton fixator. The oxime was obtained by treating the 6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one with hydroxylamine hydrochloride in the presence of pyridine.

The new compounds are solid, crystallized, white or light yellow, soluble at normal temperature in acetone, benzene, toluene, xylene, chloroform, dichloromethane and dichloroethane, by heating in inferior alcohols, insoluble in water.



R= -$C_6H_4C_2H_5$(4) (**6a**), -$C_6H_4OC_2H_5$(2) (**6b**), -$C_6H_3(OC_2H_5)_2$(2,5) (**6c**),

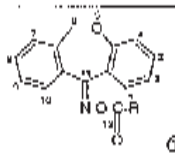
-$C_6H_3(OC_2H_5)_2$(3,5) (**6d**), -$C_6H_4CF_3$(2) (**6e**), -$C_6H_4CF_3$(3) (**6f**),

-$C_6H_4CF_3$(4) (**6g**), -$C_6H_4OCF_3$(4) (**6h**)

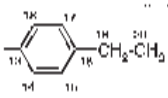
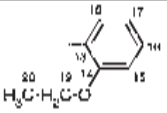
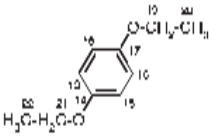
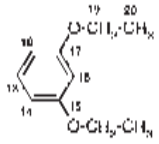
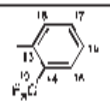
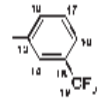
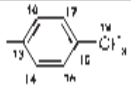
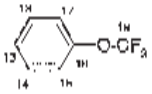
Scheme 1. The pathway for the synthesis of the new dibenz[b,e]oxepins

Table 1

DATA ON THE NEW COMPOUNDS



6(a- h)

No.	R	m. p. (°C)	yield (%)	M_r	C%		H%		N%	
					c.	e.	c.	e.	c.	e.
6a.		96-98	71	357.4	77.29	77.51	5.36	5.40	3.92	3.87
6b.		144-146.9	69	374.4	74.98	73.67	5.13	5.05	3.75	3.69
6c.		141.2 144.1	83	417.46	71.93	72.21	5.55	5.47	3.36	3.36
6d.		171.2 173.2	79	417.46	71.93	71.69	5.55	5.59	3.36	3.39
6e.		142.9-144.5	64	397.35	66.50	66.33	3.55	3.59	3.53	3.52
6f.		132.3 134.8	65	397.35	66.50	66.29	3.55	3.54	3.52	3.50
6g.		101.9 103.6	77	397.35	66.50	66.87	3.55	3.49	3.52	3.51
6h.		86.2-87.3	76	413.35	63.93	64.21	3.41	3.44	3.39	3.43

where: c = calculated, e = experimental

The structure, melting point, synthesis yield, molecular weight, and elemental analysis are presented in the table 1.

Also, structural elucidation of these compounds was performed by IR, NMR spectra.

The IR spectra are given as w – weak band; m – medium band; s – intense band; vs – very intense band and were obtained using the ATR technique.

In the IR spectra some significant stretching bands due to νC=N and νN-O were observed at 1595- 1610 cm^{-1} and 974- 1005 cm^{-1}, respectively.

The caracteristic bands for the $-CH_2-O-$ moiety are: νCH_2 sym: 2869- 2890 cm^{-1}; νCH_2 asym: 2941- 2990 cm^{-1}; δCH_2 sym: 1297-1311 cm^{-1}; δCH_2 asym: 1472- 1483 cm^{-1}; νC-O-C sym: 947- 980 cm^{-1}; νC-O-C asym: 1103- 1112 cm^{-1}.

The IR spectra revealed the presence of -O-C=O absorption bands as νC=O in the region 1746- 1764 cm^{-1} and the νC-O at about 1204- 1254 cm^{-1}.

The aromatic rings appeared as ν=C-H in the region 3059- 3077 cm^{-1}. Halogen presence, in the molecules of new compounds, is proved by stretching bands situated at 1008- 1049 cm^{-1} (for νC_{ar}-F).

The structure of the new compounds is also supported by NMR spectra. The new dibenzoxepins were dissolved in $CDCl_3$ and the chemical shifts were recorded as δ values presented in parts per million (ppm) relative to tetramethylsilane used as internal standard. The coupling constants (J) values are reported in Hertz.

The ^{1}H-NMR data are reported in the order: chemical shifts, multiplicity (s, singlet; d, doublet; dd, double doublet; ddd, doublet of double doublets; td, triple doublet; t, triplet;

q, quartet, m, multiplet; b, broad), coupling constants, number of protons and the signal/ atom attribution, the signals attribution presenting the major (^{M}) and minor (^{m}) signals, produced by the *E*/ *Z* isomerism.

The presence of an oxygen in the 5th position makes possible the existence of *E*/ *Z* isomery, materialised in our spectra through the dedoublation of the protons and the carbons signals.

Analyzing the chemical shifts of the dibenz[b,e]oxepin scaffold in the ^{1}H-NMR spectra, CH_2O protons appeared as a singlet at 5.23- 5.27 ppm as minor signal and 5.18- 5.25 ppm as major signal.

Also, the ^{13}C-NMR spectra displayed the characteristic signal of the suggested structures. The signal at about 163.68- 165.37 ppm as major signal and 163.33- 164.40 ppm as minor signal, is attributed to C-11, the most unscreened carbon atom. The signal of the carbonyl carbon appears in the range of 162.26- 164.48 ppm as major signal and 162.43- 163.15 ppm as minor signal. The methylene group (C-6) appears in the range of 70.48- 70.61 ppm as major signal and 70.36- 70.54 ppm as minor signal the differences between the chemical shifts of the two *E*/ *Z* isomers being unsignificant.

({[(E,Z)-11-dibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)(4-ethyl-phenyl)methanone (**6a**)

(*E*/ *Z* isomers mixture in ratio 1: 2.65 estimated by ^{1}H-NMR)

^{1}H-NMR ($CDCl_3$): δ 8.22- 7.90 (m, 2H, H-arom), 7.81 (d, *J*= 7.8 Hz, 2H, H-14, H-18), 7.34 (t, *J* = 8.4 Hz, 1H, H-3), 7.76- 7.21 (m, H-arom), 7.22 (d, *J* = 7.8 Hz, 2H, H-15, H-17), 7.01 (t, *J* = 8.4 Hz, 1H, H-2), 6.90 (d, *J* = 8.4 Hz, 1H, H-4), 5.23 (s, H-6^{m}), 5.20 (s, H-6^{M}), 2.70 (q, *J* = 7.4 HZ, CH_2^{19m}), 2.68 (q, *J* = 7.4 Hz, CH_2^{19M}), 1.25 (t, *J* = 7.4 Hz, CH_3^{20m}), 1.23 (t, , *J* = 7.4 Hz, CH_3^{20M}).

^{13}C-NMR ($CDCl_3$): δ 163.91 (C-11^{M}), 163.85 (C-11^{m}), 163.73 (C-12^{M}), 162.93 (C-12^{m}), 157.45 (C-4a^{M}), 155.85 (C-4a^{m}), 150.43 (C-10a^{m}), 150.35 (C-10a^{M}), 137.32^{m}, 134.70^{M}, 134.07^{m}, 132.94^{M}, 132.60^{m}, 132.43^{M}, 131.01^{M}, 130.83^{m}, 130.40^{M}, 130.04^{m}, 128.88 (C-14, C-18), 129.34^{m}, 128.49^{M}, 128.40^{M}, 128.15^{m}, 128.08 (C-15, C-17), 127.80^{m}, 127.25^{M}, 126.11^{m}, 126.04^{M}, 121.45^{M}, 120.68^{m}, 120.60^{m}, 119.87^{M}, 119.81 (C-1a^{M}), 1189.43 (C-1a^{m}), 70.57 (C-6^{M}), 70.43 (C-6^{m}), 28.99 (C-19), 15.12 (C-20).

FT-IR (solid in ATR, ν cm^{-1}): 3062w, 2963m, 2927w, 2869w, 1746vs, 1607s, 1572m, 1478m, 1460w, 1439s, 1416w, 1330m, 1300s, 1249vs, 1204s, 1181s, 1150m, 1109w, 1065vs, 1044vs, 1007s, 976vs, 889s, 851m, 797w, 744s, 695m, 630m, 547w.

({[(E,Z)-11-dibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)(2-ethoxy-phenyl)methanone (**6b**)

(*E*/ *Z* isomers mixture in ratio 2.5: 1 estimated by ^{1}H-NMR)

^{1}H-NMR ($CDCl_3$): δ 7.91 (dd, *J*= 1.6, 8.0 Hz, H-10^{m}), 7.76 (dd, *J*= 1.8, 8.2 Hz, 1H, H-1), 7.74 (dd, *J*= 1.6, 8.0 Hz, H-10^{M}), 7.67 (m, 1H, H-18), 7.58 (m, 1H, H-7), 7.48- 7.27 (m, 3H, H-8, H-9, H-16), 7.03- 6.88 (m, 5H, H-2, H-3, H-4, H-15, H-17), 5.25 (s, H-6^{M}), 5.20 (s, H-6^{m}), 4.08 (q, *J*= 7.0 Hz, CH_2^{19M}), 4.04 (q, *J*= 7.0 Hz, CH_2^{19m}), 1.34 (t, *J*= 7.0 Hz, $CH3^{20M}$), 1.32(t, *J*= 7.0 Hz, CH_3^{20m}).

^{13}C-NMR ($CDCl_3$): δ 164.05 (C-11), 162.49 (C-12), 158.59 (C-14), 155.79 (C-4a), 137.57, 133.97, 133.71^{M}, 133.64^{m}, 132.49^{m}, 132.29^{M}, 131.65^{M}, 131.42^{m}, 131.22^{M}, 131.09^{m}, 130.33^{M}, 130.24^{m}, 129.34^{M}, 128.35^{m}, 128.33^{m}, 128.30^{m}, 127.77^{M}, 127.24^{M}, 121.38, 120.44^{M}, 120.27^{M}, 120.11^{M}, 120.01^{m}, 119.79, 119.15^{m}, 118.19^{m}, 113.10 (C-15), 70.48 (C-6^{m}), 70.29 (C-6^{M}), 64.49 (C-19), 14.51 (C-20).

FT-IR (solid in ATR, ν cm^{-1}): 3077w, 2980w, 2939w, 2890w, 1760vs, 1597m, 1491m, 1477m, 1446m, 1392w, 1252s, 1224s, 1107w, 10028s, 1005m, 969s, 920w, 750s, 645w.

({[(E,Z)-11-dibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)(2,5-diethoxy-phenyl)methanone (**6c**)

(*E*/ *Z* isomers mixture in ratio 1: 2.5 estimated by ^{1}H-NMR)

^{1}H-NMR ($CDCl_3$): δ 7.91 (dd, *J*= 1.7, 7.8 Hz, H-1^{M}), 7.76 (dd, *J*= 1.7, 7.8 Hz, H-1^{m}), 7.67 (m, H-10^{M}), 7.59 (m, H-10^{m}), 7.46- 7.25 (m, 3H, H-7, H-8, H-9), 7.10 (d, *J*= 3.1 Hz, 1H, H-18), 7.02- 6.88 (m, 4H, H-2, H-3, H-4, H-16), 6.86 (d, *J*= 9.1 Hz, 1H, H-15), 5.24 (s, H-6^{m}), 5.18 (s, H-6^{M}), 3.96 (q, *J*= 7.0 Hz, 2H, CH_2^{21M+m}), 3.88 (q, *J*= 7.0 Hz, 2H, CH_2^{19M+m}), 1.35 (t, *J*= 7.0 Hz, 3H, CH_3^{20M+m}), 1.28 (t, *J*= 7.0 Hz, 3H, CH_3^{22M+m}).

^{13}C-NMR ($CDCl_3$): δ 163.68 (C-11^{M}), 163.62 (C-11^{m}), 163.33 (C-12^{M}), 162.68 (C-12^{m}), 157.40 (C-4a), 153.06 (C-14^{M}), 153.02 (C-14^{m}), 152.45 (C-17^{m}), 152.36 (C-17^{M}), 134.86^{M}, 134.05^{m}, 132.84, 132.51^{M}, 132.24^{m}, 131.17^{m}, 131.05^{M}, 130.34^{m}, 130.16^{M}, 129.30^{m}, 128.35^{M}, 128.30^{M}, 127.76^{m}, 127.25^{m}, 121.39^{M}, 120.96^{m}, 120.93^{M}, 120.49^{m}, 120.36^{M}, 119.90, 119.82, 119.60 (C-1a), 116.23^{m}, 116.01^{M}, 115.74^{M}, 115.63^{m}, 70.49 (C-6^{M}), 70.36 (C-6^{m}), 65.63 (C-19^{M+m}), 64.17 (C-21^{m}), 64.12 (C-21^{M}), 14.81 (C-20^{m}), 14.79 (C-20^{M}), 14.74 (C-22^{M}), 14.71 (C-22^{m}).

FT-IR (solid in ATR, ν cm^{-1}): 3065w, 2979w, 2944w, 2873w, 2835w, 1764s, 1604w, 1500m, 1472m, 1441w, 1392w, 1304w, 1271w, 1236m, 1188vs, 1108m, 1028s, 987m, 950m, 895m, 805w, 753m, 691w, 635w, 552w.

({[(E,Z)-11-dibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)(3,5-diethoxy-phenyl)methanone (**6d**)

(*sin-anti* isomers mixture in ratio 1: 3 estimated by ^{1}H-NMR)

^{1}H-NMR($CDCl_3$): δ 7.91 (dd, *J*= 1.7, 7.8 Hz, H-1^{M}), 7.74 (dd, *J*= 1.7, 7.8 Hz, H-1^{m}), 7.68 (m, H-10^{M}), 7.62 (m, H-10^{m}), 7.51- 7.32 (m, 3H, H-7, H-8, H-9), 7.14 (d, *J*= 2.3 Hz, 2H, H-14, H-18), 7.05- 6.99 (m, 2H, H-2, H-3), 6.90 (dd, *J*= 1.1, 8.2 Hz, 1H, H-4), 6.65 (t, *J*= 2.3 Hz, H-16^{m}), 6.61 (t, *J*= 2.3 Hz, H-16^{M}), 5.25 (s, H-6^{m}), 5.20 (s, H-6^{M}), 4.00 (q, *J*= 7.0 Hz, CH_2^{19M}), 3.96 (q, *J*= 7.0 Hz, CH_2^{19m}), 1.39 (t, *J*= 7.0 Hz, CH_3^{20m}), 1.38 (t, *J*= 7.0 Hz, CH_3^{20M}).

^{13}C-NMR ($CDCl_3$): δ 164.08 (C-11^{M}), 163.50 (C-11^{m}), 163.36 (C-12^{M}), 163.15 (C-12^{m}), 160.07 (C-15^{m}, C-17^{m}), 159.99 (C-15^{M}, C-17^{M}), 157.48 (C-4a), 134.76^{M}, 134.07^{m}, 133.04, 132.67^{M}, 132.36^{m}, 130.95^{M}, 130.80^{m}, 130.48^{m}, 130.29^{M}, 130.24^{M}, 129.34^{m}, 128.57, 128.27, 128.13, 127.81, 127.24^{m}, 121.48^{M}, 120.69, 120.55, 119.89 (C-4), 119.66 (C-1a), 107.81 (C-1^{m}), 107.67 (C-1^{M}), 107.58 (C-16^{m}), 107.49 (C-16^{M}), 70.57 (C-6^{M}), 70.46 (C-6^{m}), 63.82 (C-19^{m}), 63.78 (C-19^{M}), 14.70 (C-20).

FT-IR (solid in ATR, ν cm^{-1}): 3071w, 2979m, 2938w, 2881m, 1753vs, 1595vs, 1477m, 1443s, 1390m, 1348s, 1297vs, 1250m, 1197vs, 1171vs, 1112s, 1090m, 1049vs, 1005m, 947vs, 891m, 817m, 752s, 679w, 634m, 591w, 550w.

({[(E,Z)-11-dibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)[2-(trifluoromethyl)-phenyl]methanone (**6e**)

(*E*/ *Z* isomers mixture in ratio 1: 2 estimated by ^{1}H-NMR)

^{1}H-NMR ($CDCl_3$): δ 7.89 (dd, *J*= 1.6, 7.8 Hz, 1H, H-1), 7.78- 7.53 (m, H-arom), 7.48- 7.27 (m, H-arom), 7.01 (ddd, *J*= 1.2, 7.8, 8.4 Hz, H-2^{M}), 6.96 (dd, *J*= 1.2, 8.4 Hz, H-4^{m}), 6.92 (ddd, *J*= 1.2, 7.8, 8.4 Hz, H-2^{m}), 6.90 (dd, *J*= 1.2, 8.4 Hz, H-4^{M}), 5.25 (s, H-6^{m}), 5.20 (s, H-6^{M}).

^{13}C-NMR ($CDCl_3$): δ 165.37 (C-11^M), 164.40 (C-11^m), 164.10 (C-12), 157.49 (C-4a^M), 157.73 (C-4a^m), 136.88, 134.37, 134.21 (q, $J_{(F-C-14)}$= 28.6.0 Hz, C-14), 123.13 (q, $J_{(F-C-19)}$= 272.4 Hz, C-19), 132.80, 132.62, 131.74, 131.43, 130.82, 130.43, 130.10, 129.51 (q, $J_{(F-C-13)}$= 2.4 Hz, C-13), 128.52^M, 128.34^m, 127.82, 126.81 (q, $J_{(F-C-15)}$= 5.1 Hz, C-15), 121.44 (C-2^M), 120.78 (C-2^m), 120.43 (C-4^m), 119.95 (C-4^M), 119.44 (C-1a), 70.48 (C-6^M), 70.39 (C-6^m).

FT-IR (solid in ATR, ν cm^{-1}): 3072w, 2990w, 2890w, 1761vs, 1601m, 1483m, 1445m, 1311vs, 1282m, 1242s, 1163s, 1153s, 1125vs, 1114s, 1033s, 1008m, 974s, 867m, 751s, 725m, 686w, 640w, 594w.

({[(E,Z)-11-dibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)[3-(trifluoromethyl)-phenyl]methanone (**6f**)

(*E*/ *Z* isomers mixture in ratio 1: 2.7 estimated by ^{1}H-NMR)

^{1}H-NMR ($CDCl_3$): δ 8.28 (bs, H-14^m), 8.22 (bd, *J*= 8.0 Hz, H-16^m), 8.12 (bd, *J*= 8.0 Hz, H-16^M) 8.11 (bs, H-14^M), 7.90 (dd, *J*= 1.6, 8.4 Hz, 1H, H-1), 7.82 (m, 1H, H-10), 7.74-7.33 (m, 5H, H-7, H-8, H-9, H-17, H-18), 7.08 (td, *J*= 8.4, 1.2 Hz, H-2^m), 7.03 (td, *J*= 8.4, 1.2 Hz, H-2^M), 6.92 (dd, *J*= 1.2, 8.4 Hz, 1H, H-4), 5.27 (s, H-6^m), 5.20 (s, H-6^M).

^{13}C-NMR ($CDCl_3$): δ 164.98 (C-11^M), 164.08 (C-11^m), 162.43 (C-12^m), 162.26 (C-12^M), 157.60 (C-4a^M), 155.90 (C-4a^m), 134.35^M, 134.15^m, 134.00, 132.96, 132.89, 131.22 (q, $J_{(F-C-15)}$= 33.0 Hz, C-15), 130.90, 130.69, 129.84 (q, $J_{(F-C-14)}$= 14.7 Hz, C-14), 129.66^m, 129.59^M, 129.36^m, 129.31^M, 128.66^M, 128.42^m, 1278.96^M, 127.86^m, 126.78 (q, $J_{(F-C-16)}$= 5.9 Hz, C-16^M), 126.58 (q, $J_{(F-C-16)}$= 5.9 Hz, C-16^M), 123.53 (q, $J_{(F-C-19)}$= 270.9 Hz, C-19), 121.54 (C-2), 120.86^M, 120.80^m, 120.01 (C-4), 119.41 (C-1a), 70.61 (C-6^M), 70.54 (C-6^m).

FT-IR (solid in ATR, ν cm^{-1}): 3074w, 2941w, 2885w, 1755vs, 1610m, 1481m, 1442m, 1334vs, 1306s, 1223vs, 1163s, 1103vs, 1063vs, 1049vs, 980s, 885m, 745s, 678m, 629w.

({[(E,Z)-11-dibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)[4-(trifluoromethyl)-phenyl]methanone (**6g**)

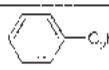
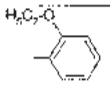
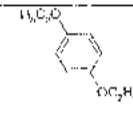
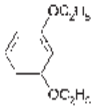
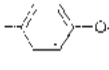
(*E*/ *Z* isomers mixture in ratio 1: 5.4 estimated by ^{1}H-NMR)

^{1}H-NMR ($CDCl_3$): δ 8.13 (d, *J*= 9.0 Hz, H-14^m, H-18^m), 8.00 (d, *J*= 9.0 Hz, H-14^M, H-18^M), 7.90 (dd, *J*= 1.6, 8.4 Hz, 1H, H-1), 7.72 (d, *J*= 9.0 Hz, H-15^m, H-17^m), 7.68 (d, *J*= 9.0 Hz, H-15^M, H-17^M), 7.59 (m, 1H, H-10), 7.55- 7.41 (m, 3H, H-7, H-8, H-9), 7.36 (td, *J*= 8.4, 1.6 Hz, 1H, H-3), 7.07 (td, *J*= 8.4, 1.2 Hz, H-2^m), 7.03 (td, *J*= 8.4, 1.2 Hz, H-2^M), 6.92 (dd, *J*= 1.2, 8.4 Hz, 1H, H-4), 5.27 (s, H-6^m), 5.21 (s, H-6^M).

^{13}C-NMR ($CDCl_3$): δ 164.99 (C-11), 162.48 (C-12), 157.57 (C-4a), 134.83 (q, $J_{(F-C-16)}$= 32.3 Hz, C-16), 134.41, 133.00, 132.89 (C-3), 131.99, 130.89 (C-1), 130.69, 130.10 (C-14, C-18), 128.68, 128.46, 127.88, 125.62 (q, $J_{(F-C-17)}$= 3.7 Hz, C-15, C-17), 121.54 (C-2), 120.01 (C-4), 119.42 (C-1a), 70.56 (C-6).

FT-IR (solid in ATR, ν cm^{-1}): 3059w, 2995w, 2887w, 1756vs, 1610w, 1598w, 1481m, 1463w, 1442m, 1410w,

Table 2
THE RESULTS OF THE QUANTITATIVE ANALYSIS OF THE ANTIMICROBIAL ACTIVITY, EXPRESSED IN MIC VALUES (μg/ mL)

No.	R	*Escherichia coli* 1114/	*Klebsiella planticola* 8	*Salmonella arizonae* 23	*Proteus vulgaris* 12	*Morganella morganii* 2	*Pseudomonas aeruginosa* 1246	*Staphylococcus aureus MRSA* 1268
6a.		125	125	125	125	125	125	125
6b.		**62.5**	125	125	**62.5**	125	125	125
6c.		125	125	125	125	125	125	125
6d.		125	125	125	125	125	125	125
6e.		125	125	125	125	**62.5**	**62.5**	125
6f.		125	125	125	125	125	125	125
6g.		125	125	125	125	125	125	125
6h.		125	125	125	125	125	**62.5**	125
	DMSO (solvent)	125	125	125	125	125	125	125

1332vs, 1302m, 1254s, 1181s, 1139w, 1110s, 1069vs, 1041m, 1015m, 994m, 973s, 883m, 855m, 758s, 693m, 591w.

({[(E,Z)-11-dibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)[4-(trifluoromethoxy)-phenyl]methanone (**6h**)

(*E*/ *Z* isomers mixture in ratio 1: 2.65 estimated by ^{1}H-NMR)

^{1}H-NMR ($CDCl_3$): δ 8.06 (d, *J*= 9.0 Hz, H-14^{m}, H-18^{m}), 7.93 (d, *J*= 8.8 Hz, H-14^{M}, H-18^{M}), 7.90 (dd, *J*= 8.4, 1.6 Hz, 1H, H-1), 7.69 (ddd, *J*= 1.6, 6.8, 7.8 Hz, 1H, H-9), 7.59 (m, 1H, H-10), 7.54- 7.32 (m, H-arom), 7.23 (d, *J*= 8.8 Hz, H-15^{M}, H-17^{M}), 7.27 (d, *J*= 9.0 Hz, H-15^{m}, H-17^{m}), 7.36 (td, *J*= 8.4, 1.6 Hz, 1H, H-3), 7.07 (td, *J*= 8.4, 1.2 Hz, H-2^{m}), 7.03 (td, *J*= 8.4, 1.2 Hz, H-2^{M}), 6.91 (dd, *J*= 1.0, 8.4 Hz, 1H, H-4), 5.26 (s, H-6^{m}), 5.20 (s, H-6^{M}).

^{13}C-NMR ($CDCl_3$): δ 164.60 (C-11^{M}), 163.69 (C-11^{m}), 162.62 (C-12^{m}), 162.49 (C-12^{M}), 157.52 (C-4a), 155.91 (C-16), 152.90, 134.50, 132.98, 132.81, 131.72 (C-14, C-18), 130.91, 130.62, 128.64, 128.45, 127.91, 127.04, 121.52 (C-2), 120.41 (C-15, C-17), 119.97 (C-4), 119.52 (C-1a), 70.54 (C-6^{M}), 70.47 (C-6^{m}).

FT-IR (solid in ATR, ν cm^{-1}): 3070w, 2988w, 2875w, 1755vs, 1605m, 1480w, 1463w, 1441w, 1304m, 1275m, 1243s, 1204vs, 1152vs, 1110m, 1070s, 1042s, 1015m, 975s, 926w, 885m, 861m, 754s, 630w.

Microbiological assay results

In a previous paper [11] were studied some new potential antimicrobial agents from dibenz[b,e]oxepin class.

The results of the quantitative assay of the antimicrobial activity (expressed by Minimal Inhibitory Concentration values) of the new thioureides are summarized in table 2.

Concerning the antimicrobial activity of these compounds, only three of the tested compounds exhibited good antimicrobial activity, with MIC values lower than DMSO, i.e. one against two enterobacterial strains (*Escherichia coli* and *Proteus vulgaris*), one against one enterobacterial (*Morganella morganii*) and *Ps. aeruginosa* strains and one against *Ps. aeruginosa*.

The good antimicrobial activity against the enterobacterial strains was correlated with the compounds *orto*- substituted with the etoxi and trifluoromethyl groups.

The anti-*Pseudomonas* activity was improved by the same *orto*-substitution with trifluoromethyl group as well as by the *para*- substitution with trifluoromethoxi group.

The *orto*-substitution with trifluoromethyl group conferred to the respective compound good antimicrobial properties against both enterobacterial strains (*M. morganii*) and pseudomonads (*Ps. aeruginosa*).

None of the tested compound exhibited antimicrobial activity against the Gram-positive, methicillin resistant *Staphylococcus aureus*.

The substitution with two etoxi groups and the substitution with ethyl group in *para*-position and with trifluoromethyl group in *meta* or *para* position was accompanied by a low antimicrobial activity, similar to that exhibited by DMSO solvent.

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