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SYNTHESIS, STRUCTURAL CHARACTERIZATION AND MICROBIOLOGICAL ASSAYS OF SOME NEW 2-METHOXY-O-ACYL-OXIMINO-DIBENZ[b,e]OXEPINS

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The paper reports on the synthesis of some new 2-methoxy-O-acyl-oximino-dibenz[b,e]oxepins. The new compounds and the intermediary substances were characterized by spectroscopic data and elemental analyses. Their antibacterial activities were investigated.

INTRODUCTION

Dibenz[b,e]oxepins are known for their biological activity such as antidepressant [1-3], antipsychotic [4], antiinflammatory [5, 6], antibacterial and antifungal activity [7]. Previously we have reported the synthesis and the antidepressant activity of some new compounds derived from dibenz[b,e]oxepine [8-13]. In order to continue our work on the synthesis of new dibenz[b,e]oxepins with potential pharmacological properties, we prepared by chemical modeling some O-acyl-oximino-dibenz[b,e]oxepins substituted with a methoxy group.

RESULTS AND DISCUSSION

The target compounds were synthesized in three stages.

1. The synthesis of 2-(4-methoxyphenoxymethyl)benzoic acid (Fig. 1)

In the first stage, the 2-(4-methoxyphenoxy-methyl)benzoic acid (**1**) was prepared by treating the phtalide (**2**) with potassium *para*-methoxyphenoxide in xylene. The resulted potassium salts of 2-(4-methoxyphenoxymethyl)benzoic acid (**3**) showed a good solubility in an aqueous solution of 10% potassium hydroxide and was separated from xylene. The acid **1** was precipitated using a mineral acid solution. The potassium salt of *para*-methoxyphenol was obtained using the *para*-methoxyphenol and potassium hydroxide in xylene, the resulting water being removed by azeotropic distillation. The reactions are presented in the Fig. 1.

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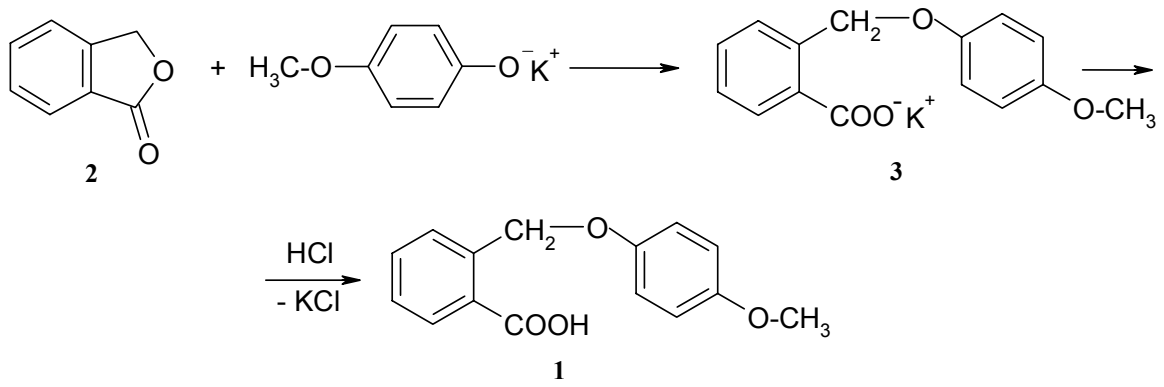


Fig. 1 – The synthesis of 2-(4-methoxyphenoxymethyl)benzoic acid.

2. The synthesis of 2-methoxy-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one (Fig. 2)

The 2-methoxy-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one (**4**) was synthesized by a Friedel-Crafts cyclization of the 2-(4-methoxyphenoxy-methyl)benzoic acid chloride (**5**) in dry 1,2-dichloroethane. The acid chloride **5** was obtained by refluxing the acid **1** with thionyl chloride in excess (the most favorable is 25%), but could also be obtained by using different anhydrous solvents as reaction medium, such as 1,2-dichloroethane. The desired ketone was also prepared directly from the acid **1** using various agents for anhydrization (e.g. polyphosphoric acid), but the yield was smaller. The acid chloride was used in the next step without further purification. The mentioned synthesis are illustrated in Fig. 2.

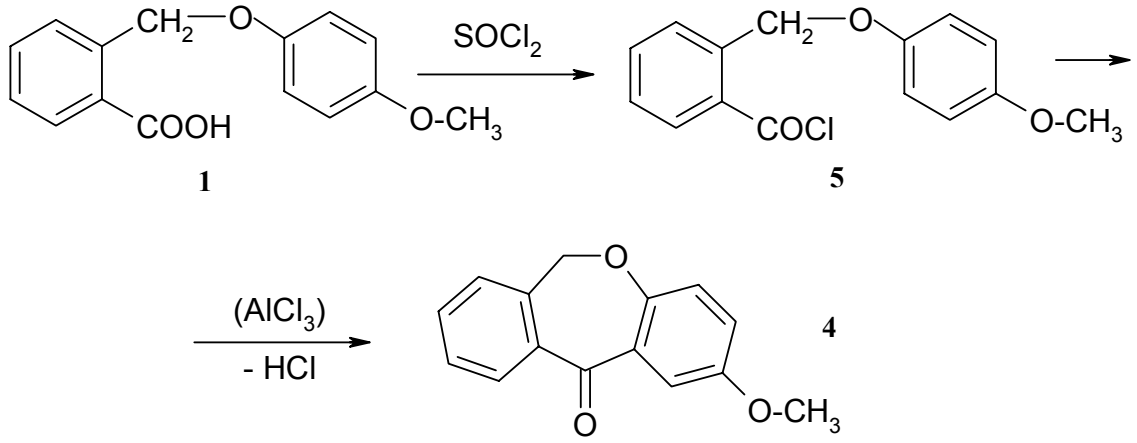


Fig. 2 – The synthesis of 2-methoxy-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one.

3. The synthesis of the new 2-methoxy-O-acyl-oximino-dibenz[b,e]oxepins (Fig. 3)

The new compounds (**6a- h**) were prepared by acylation of the 2-methoxy-11-hydroximino-6,11-dihydro-dibenz[b,e]oxepin (**7**) with different benzoic acid chlorides, in dry benzene, in the presence of anhydrous pyridine as a proton fixator. The oxime **7** was resulted by treating the ketone **4** with hydroxylamine hydrochloride in the presence of pyridine. The reactions are presented in the Fig. 3 and the structures of the new compounds (**6a-h**.) are presented in the Table 1.

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

The structure, melting point, yield and elemental analysis of the new 2-methoxy-O-acyl-oximino-dibenz[b,e]oxepins are presented in Table 1. The calculated formula provided by the elemental analysis results is in good agreement with the expected structures.

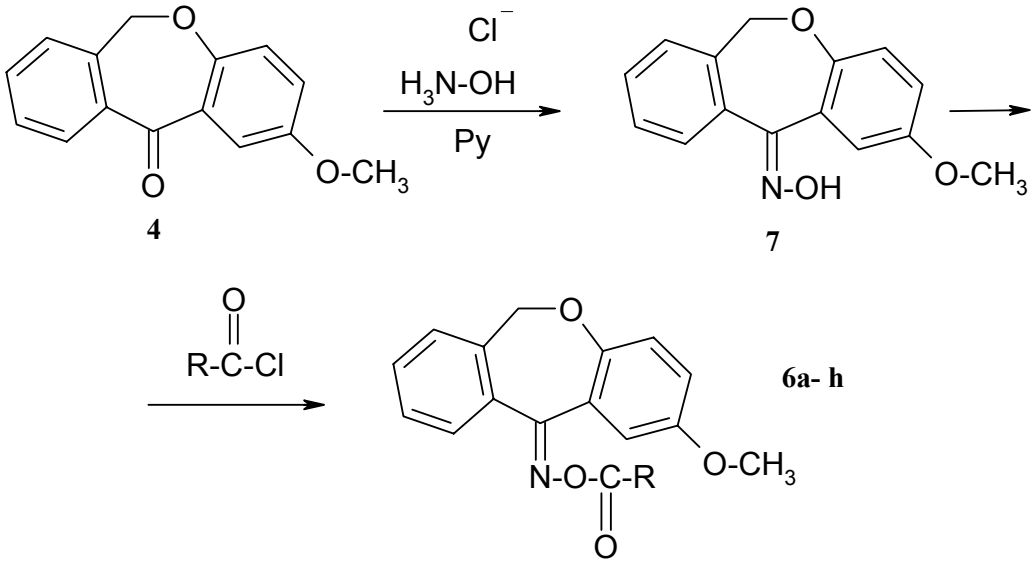
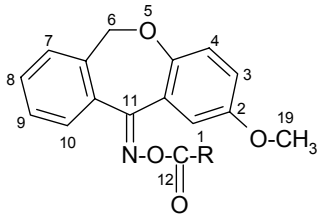
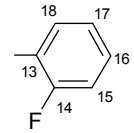
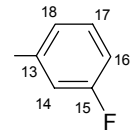
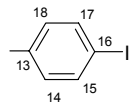
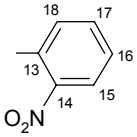
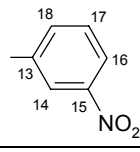


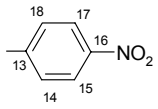
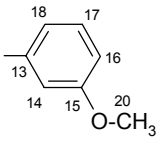
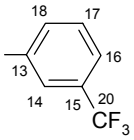
Fig. 3 – The synthesis of the new 2-methoxy-O-acyl-oximino-dibenz[b,e]oxepins.

Table 1

Data on the new compounds



No.	R	Melting point (^{0}C)	Yield (%)	C%		H%		N%	
				c.	e.	c.	e.	c.	e.
6a.		143.8-147.6	45	70.02	70.30	4.27	4.29	3.71	3.69
6b.		144.5- 148.1	50	70.02	70.28	4.27	4.26	3.71	3.74
6c.		186.2- 187.8	63	54.45	54.57	3.32	3.28	2.89	2.85
6d.		141.7- 143	58	65.35	65.51	3.99	3.99	6.93	6.91
6e.		157.0- 159.3	53	65.35	65.61	3.99	4.02	6.93	6.89

6f.		197.9- 200.4	46	65.35	65.04	3.99	3.96	6.93	6.93
6g.		154.7- 158.6	49	70.94	70.66	4.92	4.93	3.6	3.63
6h.		154.1- 155.8	80	64.64	64.38	3.77	3.74	3.28	3.31

where: c = calculated, e = experimental

Spectral data

The structures of the new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins were established through NMR and IR spectroscopy.

The new oxepins 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 chemical shifts for hydrogen and carbon atoms were established also by two dimensional H/ H and H/ C experiments.

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; dt, double triplet; t, triplet; td, triple doublet; m, multiplet), number of protons, the signals attribution presenting the major (^{M}) and minor (^{m}) signals, produced by the *sin*/ *anti* isomerism, and the coupling constants.

The ^{1}H-NMR spectra of the new dibenz[b,e]oxepins are divided into two spectra, one corresponding to the oxepinic system and another to the acyl radical attached to the oximino group. The presence of an oxygen in the 5th position makes possible the existence of *sin-anti* isomery, materialised in our spectra through the dedoublation of the protons and the carbons signals, but the difference between chemical shifts of methylene group is insignificant. In the dibenz[b,e]oxepinic system the most unscreened proton is H_{10}, and the most screened is H_4 (except the methylen group protons). The individual attribution of the H_1-H_4 protons were done using the connectivity H-H experiments (COSY). Also, for the protons H_{14}-H_{18} the complete attributions were made. The protons of the methoxy group situated in the second position of dibenz[b,e]oxepin nucleus gives a singlet signal in the range 3.85-3.61 ppm.

The ^{13}C-NMR data are reported in the following order: chemical shifts and signal/ atom attribution.

The methylene group (C_6) appears in the range of 70.6- 71.12 ppm, the differences between the chemical shifts of the two *sin-anti* isomers being unsignificant. In the oxepinic system, the carbon atom C_1 is the most screened carbon atom, and the C_{11} is the most unscreened carbon atom. The last can find in the range of 163.47- 165.45. The signal corresponding to the C_{12} atom appears in the range of 161.5- 164 ppm .

In the IR spectra the characteristic peaks intensity were designated as follows: w – weak band; m – medium band; s – intense band; vs – very intense band; sh – shoulder

The spectral data using ^{1}H-NMR, ^{13}C-NMR and FTIR spectroscopy confirmed the structure of the obtained compounds.

Antimicrobial activity results

The most efficient qualitative method proved to be the direct spotting of the tested solutions on the seeded medium, the results being very well correlated with the results of the quantitative assay results. The plates examination indicated that some compounds exhibited a bactericidal effect by comparison with the negative aspect exhibited by the solvent (DMSO).

The results of the antimicrobial activity quantitative assay of the new compounds demonstrated that the tested compounds exhibited the highest activity against *Staphylococcus aureus MRSA 1269* (MIC of 62.5 μg/mL), the majority of the tested strains being inhibited at 125 μg/mL concentration of the new chemical compounds (Table 2).

Table 2

The antimicrobial activity results of some of the new compounds (MIC, μg/mL)

Microbial Strain	**6a**	**6b**	**6e**	**6f**	**6g**	**6h**	DMSO
Escherichia coli 13147	125	125	125	62.5	125	62.5	125
Klebsiella planticola 8	125	125	125	62.5	125	62.5	125
Salmonella arizone 23	125	125	62.5	125	62.5	125	125
Proteus vulgaris 12	125	125	125	125	125	125	125
Morganella morganii 2	125	125	125	62.5	125	62.5	125
Pseudomonas aeruginosa 1246	125	125	125	125	125	62.5	125
Staphylococcus aureus MRSA1268	125	62.5	62.5	62.5	62.5	62.5	125

EXPERIMENTAL

All melting points were recorded with a SRS OptiMelt S/N: 97016 apparatus.

The elemental analysis was realized using a Perkin Elmer CHNS/ O Analyser Series II 2400 apparatus and were found within ±0.4% of the theoretical values.

The NMR spectra were recorded on a Gemini 300BB instrument, at room temperature, operating at 300MHz for ^{1}H and 75MHz for ^{13}C and an Unity Inova 400 instrument, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C.

The IR spectra were performed with a FT-IR Bruker Vertex 70 apparatus.

The synthesis of 2-(4-methoxyphenoxymethyl)benzoic acid

A solution containing freshly distilled *para*-methoxyphenol (0.05 mol) in 30 mL xylene was placed in a round-bottomed flask equipped with a Dean-Stark trap device. Subsequently, potassium hydroxide (0.055 mol) was added. The reaction mixture was refluxed while the resulting water was removed by azeotropic distillation and potassium *para*-methoxyphenoxide precipitated. Phtalide (0.05 mol) was added and the mixture was refluxed until it solidifies. The precipitate was heated for solubilisation with 10% potassium hydroxide solution and then was diluted with 50 mL of water. The aqueous phase was separated and acidulated with 1M hydrochloric acid solution until the mixture became acidic (pH 3), when 2-(4-methoxyphenoxymethyl)benzoic acid precipited. The resulting precipitate, which crystallizes from a water: isopropanol (1: 3) mixture, shows a m.p. 178- 180°C. 6.3 g Acid I (Wt 258.26) resulted (49% yield).

The synthesis of 2-(4-methoxyphenoxymethyl)-benzoyl chloride

2-(4-Methoxyphenoxymethyl)benzoic acid (0.02 mol), dry 1,2-dichloroethane (30 mL) and thionyl chloride (0.042 mol) were placed in a round-bottomed flask equipped with condenser and drying tube. The mixture was refluxed for 3 hours. The excess thionyl chloride and the solvent were removed by reduced pressure. For the next step the 2-(4-methoxyphenoxymethyl)benzoyl chloride was used in the crude status. 1,2-Dichloroethane was anhydrized over calcium chloride and distillated at normal pressure.

The synthesis of 2-methoxy-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one

Anhydrous aluminium chloride (0.02 mol) and 1,2-dichloroethane (15 mL) were placed in a round-bottomed flask equipped with stirrer, condenser and drying tube, thermometer and addition funnel. The suspension was cooled to 0°C with stirring. The 2-(4-methoxyphenoxymethyl)benzoyl chloride (0.02 mol) solubilised in 1,2-dichloroethane (25 mL), was added in portions, with the mixture maintained at 0°C to 5°C, during the addition period. After the acid chloride was added, the reaction mixture was stirred at 5°C to 20°C for one hour and then, for another hour at 20°C. The reaction mixture was poured into 5% hydrochloric acid solution and stirred until the complex aluminium chloride: ketone was decomposed. The organic and aqueous layers were then separated and the organic layer was washed once with 5% sodium hydroxide solution and twice with water, dried (anhyd. calcium chloride), treated with decolorizing charcoal and evaporated under vacuum to yield the 2-methoxy-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one (Wt 240.25), which was recrystallized from hexane (3.4 g ketone; 59% yield, m.p. 93- 94°C).

The synthesis of 2-methoxy-11-hydroximino-6,11-dihydro-dibenz[b,e]oxepin

2-Methoxy-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one (0.05 mol) and hydroxylamine hydrochloride (0.15 mol) were boiled under reflux in 100 mL of pyridine for 96 hours. The pyridine is subsequently distilled off in vacuum, the residue is triturated with water, suction-filtered, dried and recrystallized from isopropanol. 6.9 g, Wt 255.26, 54.5% yield, m.p. 215-219°C resulted.

The synthesis of the new O-acyl-oximino-dibenz[b,e]oxepins (general procedure)

2-Methoxy-11-hydroximino-6,11-dihydro-dibenz[b,e]oxepin (0.016 mol) was solubilised in anhydrous benzene by refluxing in a round-bottomed flask equipped with condenser and drying tube. To this solution was added dropwise a solution of acyl chloride (0.016 mol) in anhydrous benzene (10 mL) and dry pyridine (0.016 mol) and the mixture was refluxed two hours. After cooling and filtration, the solvent was removed by distillation and the residue was triturated with isopropanol. The resulting solid was recrystallized from isopropanol to yield the title compounds.

Compounds spectral data

O-(2-fluoro)-benzoyl-2-methoxy-11-oximino-6,11-dihydro-dibenz[b,e] oxepine (6a)

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.96(td, 1H, H-15, $J^{F\text{-}H}$=7.8 Hz, $J^{H15—H16}$=7.8 Hz, $J^{H16—H15}$=2.0 Hz); 7.72(dd, 1H, H-10, 1.4,

7.6); 7.54(m, 1H, H-16); 7.45(td, 1H, H-8, 7.6, 1.6); 7.41(td, 1H, H-9, 1.7, 7.6); 7.28(dd, 1H, H-7, 7.6, 1.6); 7.24÷7.11(m, 3H, H-1, H-17, H-18); 6.97÷6.92(m, 2H, H-4, H-3, syst. AB, J^{A-B} =12.2 Hz); 5.21(s, 2H, H-6); 3.75(s, 3H, H-19).

^{13}C-NMR($CDCl_3$, δ ppm): 163.70(C-11); 163.02(d, C-14, J^{F-C}=247 Hz); 161.92(C-12); 153.65(C-4a); 149.75(C-2); 135.82(Cq); 134.98(d, C-16, J^{F-C}=8.8 Hz); 134.91(Cq); 132.47(CH); 130.54(CH); 128.93(CH); 127.72(CH); 127.42(CH); 124.25(d, C-17, J^{F-C}=3.6 Hz); 124.40(CH); 120.09(CH); 120.00(Cq); 117.44(Cq-1a); 117.05(d, C-15 J^{F-C}=22.7 Hz); 113.72(C-1); 71.02(C-6); 55.77(C-19).

FT-IR(solid in ATR, ν cm^{-1}): 3071w; 2964w; 2885w; 2838w; 1751vs; 1729vs; 1611s; 1596m; 1571m; 1484vs; 1454s; 1419s; 1372w; 1324w; 1282vs; 1230vs; 1213vs; 1201vs; 1178m; 1146m; 1124m; 1109s; 1084m; 1034vs; 1013s; 989s; 911w; 863m; 826w; 809m; 783w; 765m; 750s; 702w; 677w; 640m; 558w.

O-(3-fluoro)-benzoyl-2-methoxy-11-oximino-6,11-dihydro-dibenz[b,e] oxepine (6b)

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.82(dt, 1H, H-14, J^{F-H}=7.8 Hz, $J^{H16—H14}$= $J^{H14—H18}$=1.4 Hz); 7.72(dd, 1H, H-10, 1.4, 7.6); 7.71(m, 1H, H-18); 7.46(td, 1H, H-8, 7.4, 1.6); 7.43(t, 1H, H-16, J^{F-H}=8.2 Hz, $J^{H16-H17}$=8.2 Hz); 7.42(td, 1H, H-9, 7.6, 1.6); 7.33÷7.26(m, 2H, H-7, H-17); 7.16(dd, 1H, H-1, 1.2, 2.0); 7.02÷6.96(m, 2H, H-4, H-3, syst. AB, J^{A-B} =12.2 Hz); 5.21(s, 2H, H-6); 3.75(s, 3H, H-19).

^{13}C-NMR($CDCl_3$, δ ppm): 163.59(C-11); 162.61(d, C-15, J^{F-C}=246.8 Hz); 162.58(C-12); 162.55(C-2); 153.78(C-4a); 149.93(Cq); 135.62(Cq); 134.92(Cq); 130.87(d, C-13, J^{F-C}= 7.3 Hz); 130.84(CH); 130.63(CH); 130.35(CH); 130.27(CH); 128.95(CH); 127.72(CH); 127.45(CH); 125.58(d, C-17, J^{F-C}= 3.0 Hz); 121.79(CH); 120.61(d, C-14, J^{F-C}=21.2 Hz); 120.03(CH); 119.87(CH); 116.75(d, C-16, J^{F-C}=22.7 Hz); 113.59(C-1); 71.12(C-6); 55.87(C-19).

FT-IR(solid in ATR, ν cm^{-1}): 3077w; 2965w; 2943w; 2911w; 2880w; 2839w; 1737vs; 1609w; 1591m; 1571m; 1484vs; 1444s; 1419s; 1374w; 1324w; 1303m; 1282m; 1253vs; 1211s; 1186s; 1149w; 1106m; 1080s; 1037m; 1015m; 994m; 925m; 886s; 815m; 772s; 741s; 702w; 665w; 642m; 608w; 554w; 524w.

O-(4-iodo)-benzoyl-2-methoxy-11-oximino-6,11-dihydro-dibenz[b,e]oxepine (6c)

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.77(d, 2H, H-14, H-18, 8.6); 7.58(d, 2H, H-15, H-17, 8.6); 7.46- 7.51(m, 4H, H-7, H-8, H-9, H-10); 7.37(d, 1H, H-1, 3.1); 6.96(dd, 1H, H-3, 9.0, 3.1); 6.84(d, 1H, H-4, 8.9); 5.14(s, 2H, H-6); 3.83(s, 3H, H-19).

^{13}C-NMR($CDCl_3$, δ ppm): 164.5(C-11); 163.1(C-12); 153.8(C-4a); 151.7(C-2); 137.9(CH-15 and CH-17); 133.9(C-7a); 133.1(C-10a); 131.0(CH-14 and CH-18); 130.5(CH-8); 128.2(CH-9); 128.1(C-13); 128.0(CH-7); 127.9(CH-10); 120.8(CH-3); 120.7(CH-4); 119.2(C-1a); 101.3(C-16); 113.0(CH-1); 70.6^{M}(C-6); 70.71^{m}(C-6); 55.9(C-19).

O-(2-nitro)-benzoyl-2-methoxy-11-oximino-6,11-dihydro-dibenz[b,e]oxepine (6d)

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.9(d, 1H, H-15, 7.6); 7.53-7.61(m, 3H, H-16, H-17, H-18); 7.19- 7.36(m, 4H, H-7, H-8, H-9, H-10); 7.14(d, 1H, H-1, 3.2); 6.86(dd, 1H, H-3, 8.9, 3.0); 6.73(d, 1H, H-4, 9.0); 5.10^{m}(s, 2H, H-6); 5.02^{M}(s, 2H, H-6); 3.75^{M}(s, 3H, H-19); 3.61^{m}(s, 3H, H-19)

^{13}C-NMR($CDCl_3$, δ ppm): 164.9(C-11); 164.0(C-12); 153.8(C-4a); 151.8(C-2); 147.6(C-14); 133.5(C-7a); 133.4(CH-17); 132.8(C-10a); 132.7(CH-16); 131.8(CH-18); 130.5(CH-8); 130.1(CH-10); 128.7(CH-9); 128.2(CH-7); 127.8(C-13); 124.0(CH-15); 121.1(CH-3); 120.9(CH-4); 119.0(C-1a); 112.7(CH-1); 70.6(C-6); 55.89(C-19).

O-(3-nitro)-benzoyl-2-methoxy-11-oximino-6,11-dihydro-dibenz[b,e]oxepine (6e)

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.67(t, 1H, H-14, 2.0); 8.40(ddd, 1H, H-16, $^{4}J^{H16-H18}$=0.9 Hz, $^{4}J^{H16-H14}$=2.0 Hz, $^{3}J^{H16-H17}$=8.2 Hz); 8.27(dt, 1H, H-18, 8.2, 1.2); 7.66(m, 1H, H-10); 7.63(t, 1H, H-17, 8.2); 7.58(td, 1H, H-9, 7.4, 1.6); 7.54(td, 1H, H-8, 7.4, 1.6); 7.48(dd, 1H, H-7, 1.6, 7.4); 7.38(d, 1H, H-1, 3.1); 6.98(dd, 1H, H-3, 3.1, 8.9); 6.85(d, 1H, H-4, 8.9); 5.15(s, 2H, H-6); 3.84(s, 3H, H-19).

^{13}C-NMR($CDCl_3$, δ ppm): 165.45(C-11); 161.50(C-12); 153.93(C-4a); 151.94(C-2); 148.30(C-15); 135.37(CH-18); 133.70(Cq); 133.22(Cq); 130.87(CH-9); 130.48(Cq); 129.89(CH-17); 128.65(CH-7); 128.57(CH-8); 127.94(CH-10); 127.75(CH-16); 124.60(CH-14); 121.21(CH-4); 120.90(CH-3); 119.08(C-1a); 113.14(CH-1); 70.74(C-6); 55.94(C-19).

FT-IR(solid in ATR, ν cm^{-1}): 3096w; 3017w; 2956w; 2834w; 1759vs; 1618w; 1591w; 1564w; 1524s; 1488s; 1452m; 1407m; 1375w; 1349s; 1321m; 1281m; 1256m; 1231s; 1217s; 1200m; 1154m; 1112m; 1094w; 1055s; 1036m; 999s; 945w; 912m; 855m; 819m; 770w; 759m; 734m; 715s; 695w; 677w; 653w; 620w; 559w.

O-(4-nitro)-benzoyl-2-methoxy-11-oximino-6,11-dihydro-dibenz[b,e]oxepine (6f)

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.25(d, 2H, H-15, H-17, 8.8); 8.04(d, 2H, H-14, H-18, 8.8); 7.58(dd, 1H, H-10, 1.8, 7.2); 7.37(d, 1H, H-1, 3.1); 6.98(dd, 1H, H-3, 3.1, 8.9); 6.85(d, 1H, H-4, 8.9); 5.15(s, 2H, H-6); 3.84(s, 3H, H-19).

^{13}C-NMR($CDCl_3$, δ ppm): 165.45(C-11); 161.80(C-12); 153.95(C-4a); 151.89(Cq); 150.73(Cq); 134.15(Cq); 133.79(Cq); 133.28(Cq); 130.84(CH); 130.78(C-15, C-17); 128.67(CH); 128.38(CH); 127.80(CH); 123.71(C-14, C-18); 121.21(CH); 120.91(CH); 119.06(C-1a); 113.11(CH-1); 70.67(C-6); 55.94(C-19).

FT-IR(solid in ATR, ν cm^{-1}): 2990w; 2941w; 2835w; 1750vs; 1594w; 1571w; 1525s; 1491vs; 1456m; 1408m; 1371w; 1347w; 1319m; 1303s; 1303m;1284m; 1231vs; 1200s; 1154s; 1104w; 1077vs; 1043s; 1000vs; 912w; 871m; 823s; 757s; 710s; 694m; 675m; 654w; 623w; 602w; 551w; 505w;.

O-(3-methoxy)-benzoyl-2-methoxy-11-oximino-6,11-dihydro-dibenz[b,e]oxepine (6g)

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.73(m, H-10); 7.64(dt, H-18, 7.6, 1.3); 7.54(dd, H-14, 1.3, 2.5); 7.50÷7.38(m, H-arom); 7.34(t, H-17, 7.9); 7.28(m, H-7); 7.21(dd, H-1, 1.6, 2.5); 7.12(ddd, H-16^{M}, 1.0, 2.5, 8.2); 7.09(ddd, H-16^{m}, 1.0, 2.5, 8.2); 7.02÷6.96(m, 2H, H-4^{M}, H-3^{m,} H-3^{M}, syst. AB, J^{A-B} =12.2 Hz); 6.84(d, H-4^{m}, 9.0); 5.21(s, H-6^{M}); 5.14(s, H-6^{m}); 3.84(s, H-20^{m}); 3.80(s, H-20^{M}); 3.77(s, H-19^{m}); 3.73(s, H-19^{M}).

^{13}C-NMR($CDCl_3$, δ ppm): 164.20(C-11^{m}); 163.47(C-11^{M}); 163.08(C-12); 159.73(C-15^{M}); 159.61(C-15^{m}); 153.90(C-4a^{m}); 153.64(C-4a^{M}); 151.77(C-2^{m}); 149.91(C-2^{M}); 135.82(Cq^{M}); 134.89(Cq^{M}); 134.19(Cq^{m}); 133.23(Cq^{m}); 130.54(CH^{M}); 130.45(CH^{m}); 129.61(CH^{M}); 129.57(CH^{m}); 129.91(Cq^{M}); 129.86(Cq^{m}); 128.95(CH^{M}); 128.48(CH^{m}); 128.25(CH^{m}); 128.16(CH^{m}); 127.72(CH^{M}); 127.44(CH^{M}); 127.33(CH^{M}); 122.17(CH^{m}); 121.69(CH^{M}); 120.16(Cq); 121.05(CH^{m}); 119.51(CH^{M}); 113.87(CH^{M}); 113.83(CH^{M}); 113.17(CH^{m}); 71.10(C-6^{M}); 70.69(C-6^{m}); 55.94(C-19^{m}); 55.79(C-19^{M}); 55.40(C-20^{m}); 55.33(C-20^{M}).

FT-IR(solid in ATR, ν cm^{-1}):3071w; 3008w; 2960w; 2836w; 1750vs; 1596w; 1487m; 1458s; 1427m; 1271s; 1205vs; 1177m; 1151m; 1059s; 1034s; 1007m; 901w; 860w; 713s; 678w; 625w.

O-(3-trifluoromethyl)-benzoyl-2-methoxy-11-oximino-6,11-dihidro-dibenz[b,e]oxepine (6h)

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.20÷8.10(m, H-10, H-14); 7.81(dq, H-16, 8.2, $^4J(3F^{20}\text{-}H^{14})$=0.6 Hz); 7.65÷7.45(m, H-7, H-8, H-9,); 7.38(d, H-1, 3.0); 6.98(dd, H-3, 3.0, 9.0); 6.85(d, H-4, 9.0); 5.15(s, H-6); 3.85(s, H-19).

^{13}C-NMR($CDCl_3$, δ ppm): 164.98(C-11); 162.24(C-12); 153.88(C-4a); 151.86(C-2); 133.82(Cq); 133.19(Cq); 132.96(CH); 131.19(q, C-15, $J(F\text{-}C^{15})$=32.8 Hz); 130.71(CH); 129.89(q, C-14, $J(F\text{-}C^{15})$=3.7 Hz); 129.51(Cq); 129.33(CH); 128.58(CH); 128.32(CH); 128.00(CH); 126.57(q, C-16, $J(F\text{-}C^{15})$=4.0 Hz); 125.31(q, C-20, $J(F\text{-}C^{20})$=271.1 Hz); 121.15(C-4); 120.84(C-3); 119.16(C-1a); 113.06(C-1); 70.70(C-6); 55.91(C-19).

FT-IR(solid in ATR, ν cm^{-1}): 3075w; 2961w; 2937w; 2892w; 2833w; 1756vs; 1596w; 1493s; 1408s; 1375vs; 1225vs; 1201s; 1175m; 1154s; 1114vs; 1068vs; 1040s; 999s; 919m; 892m; 857m; 812s; 759m; 743s; 691s; 624w.

Antimicrobial activity assay

In this study were used seven Gram negative (*Escherichia coli* 13147*, Proteus vulgaris* 12*, Morganella morganii* 2*, Salmonella arizonae* 23*, Proteus vulgaris* 12*, Klebsiella planticola* 8*, Pseudomonas aeruginosa* 1246) and one Gram positive (*Staphylococcus aureus* MRSA 1268) strain isolated from different clinical cases: one coagulase- positive methicillin resistant *Staphylococcus aureus,* one *Pseudomonas aeruginosa* strain isolated from central venous catheters and six *Enterobacteriaceae* strains 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. Bacterial suspensions of 0,5 McFarland IU density were obtained from 18 h bacterial cultures developed on solid media. The antimicrobial activity of the tested compounds was tested by classical methods, using Mueller- Hinton broth for minimal inhibitory concentration (MIC) assay and solid Mueller- Hinton agar for the screening of the antimicrobial activity using adapted disk diffusion methods. The new oxepins were previously solubilized in DMSO (1mg/ mL) and the antimicrobial activity was performed by three diffusion methods adapted from standard disk diffusion method: paper filter disk impregnation by the tested substances solutions, the distribution of tested solutions in agar wells and spotting of the tested solutions on solid medium seeded with microbial inocula.

The quantitative assay of the antimicrobial activity of the new compounds was performed by using the two fold microdilution method in liquid broth distributed in 96-multi well plates, in order to establish the minimal inhibitory concentration. Over 150 µL liquid medium distributed in each well, 150 µL of the compound solution were added, performing thereafter serial two fold dilutions from 500 µg/ mL up to 0.97 µg/ mL. Finally in each well there were added 30 µL microbial suspension of 0.5 MacFarland density. The plates were incubated 24 hrs at 37^{o}C and MICs were determined as the last concentration of the respective tested compound.

CONCLUSIONS

Following the synthesis of new compounds with potential pharmacological activity, we obtained eight new 2-methoxy-O-acyl-oximino-dibenz[b,e]oxepins. The compounds are prepared by acylating 2-methoxy-11-oximino-6,11-dihydro-dibenz[b,e]oxepin with different substituted benzoic acid chlorides. The obtained compounds have been characterized by some physical properties. The ^{1}H-NMR, ^{13}C-NMR and IR spectral parameters and the elemental analysis confirm the structure of the prepared compounds. Six of these newly synthesized compounds proved to have specific antimicrobial activity against methicillin resistant *S. aureus*, and may be regarded as potential antimicrobial agents.

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