New Potential Antimicrobial Agents from 2-methoxy-)-*O*-acyl-oximino-dibenz[b,e]oxepin Class

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In this paper we report the synthesis of new 2-methoxy-O-acyl-oximino-dibenz[b,e]oxepins, ({[11E,Z)-2-methoxydibenzo[b,e]oxepin-11(6H)-ylidene]amino}oxy)(mono- or disubstituted-phenyl)metanona derivatives, by acylation of the 11-hydroximino-2-methyl-6,11-dihydro-dibenz[b,e]oxepin with various acid chlorides. The structures of the synthesized compounds were confirmed by IR, ^{1}H-NMR and ^{13}C-NMR spectral data and by elemental analyses.

Keywords: dibenz[b,e]oxepin, metanona derivatives , ^{1}H-NMR, ^{13}C-NMR

The tricyclic structure of dibenz[b,e]oxepin constitutes the fundamental structure of many compounds with biological activity, the best known representative being doxepin [1, 2] which is used for its antidepressant, anxiolytic, anticholinergic and antihistamine properties. Pinoxepin [3] shows potent antipsychotic activity, oxepinac [4] and isoxepac [5] are analgesic, antipyretic and anti-inflammatory agents, olopatadine [6] inhibits phospholipase A2, and spiroxepin [7] shows interest for treatment of depressive disorders. A series of new imidazole derivatives of 6,11-dihydrodibenz[b,e]oxepines [8] are useful as antifungal and antibacterial agents.

Previously we have reported the synthesis of some new compounds derived from dibenz[b,e]oxepine [9, 10].

The aim of this study was to synthesize the hybrid molecules through the combination of different pharmacophores in one structure. We synthesized new dibenz[b,e]oxepin derivatives carring oximinic group at 11 position in order to investigate their biological activities.

Experimental part

The chemicals were purchased from several different companies (Merck, Fluka, Sigma- Aldrich) and used as received, except 1,2-dichloroethane which was anhydrized over calcium chloride and distilled at normal pressure, pyridine which was stored over potassium hydroxide and then distilled, and benzene which was kept over night with sodium and then distilled.

The reaction progress was observed by thin layer chromatography performed on silica gel 60 F_{254} (0.2 mm thickness) plates (Merck, Germany) using ethylacetate/cyclohexane (φr = 4 : 6; system 1) and chloroform/ethyl acetate (φr = 10 : 1; system 2) as a mobile phase with visualisation by ultraviolet light; R_f values are presented in table 1.

Melting points (m.p.) were determined in open capillary tubes on digital Electrothermal 9100 apparatus 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.

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

^{1}H-NMR and ^{13}C-NMR in deuterated chloroform ($CDCl_3$) spectra were recorded on a Varian Gemini 300BB instrument operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C, and a Varian Unity Inova 400 instrument operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C.

The intermediary derivatives 2-(4-methoxyphenoxymethyl)benzoic acid (**1**), 2-methoxy-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one (**4**) and new 2-methoxy-O-acyl-oximino-dibenz[b,e]oxepins (**6a-g**) were synthesized following the methods described in a previous paper [11].

Results and discussions

The synthetic route to get the target compounds is shown in scheme 1.

The 2-(4-methoxyphenoxymethyl)benzoic acid (**1**) was prepared by heating phtalide (**2**) with potassium 4-methoxyphenoxyde in xylene. The resulting 2-(4-methoxyphenoxymethyl)benzoic acid potassium salt (**3**) has a good solubility in an aqueous potassium hydroxide solution, allowing its facile separation from xylene. The acide (**1**) was precipitated using a mineral acid solution. The potassium 4-methoxyphenoxide was obtained through the reaction of 4-methoxyphenol with potassium hydroxide in xylene. The resulting water was removed by azeotropic distillation.

The 2-methoxy-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one (**4**) was obtained by Friedel- Crafts cyclization of the 2-(4-methoxyphenoxymethyl)benzoic acid chloride (5) in dry 1,2-dichloroethane. The acid chloride was synthesized by refluxing the acid (**1**) with thionyl chloride and 1,2-dichloroethane as reaction medium.

The new compounds (**6a- g**) were prepared by acylation of the 2-methoxy-11-hydroximino-6,11-dihydro-dibenz[b,e] oxepin (**7**) with various substituted benzoic acid chlorides, in dry benzene, using anhydrous pyridine as a proton fixator. The oxime (**7**) was synthesized by treating the 2-methoxy-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one (**4**) with hydroxylamine hydrochloride in pyridine as reaction medium.

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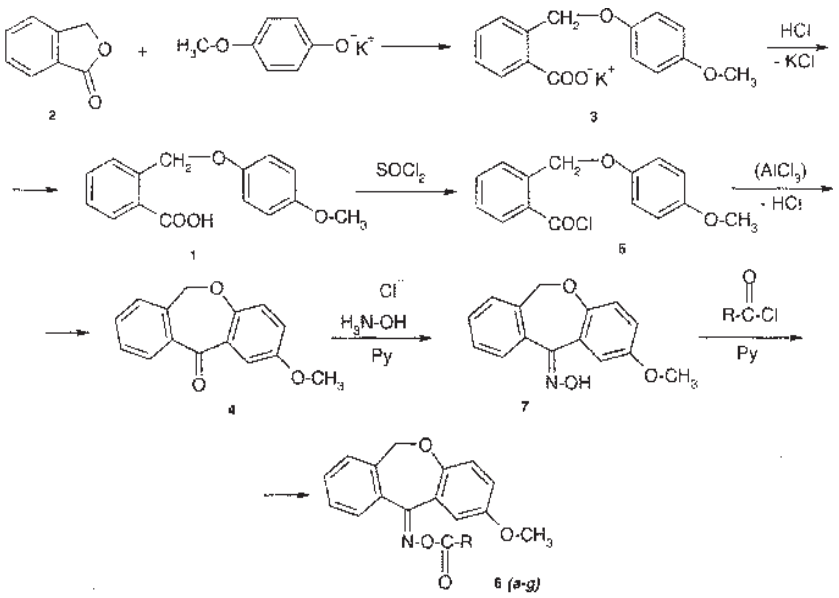
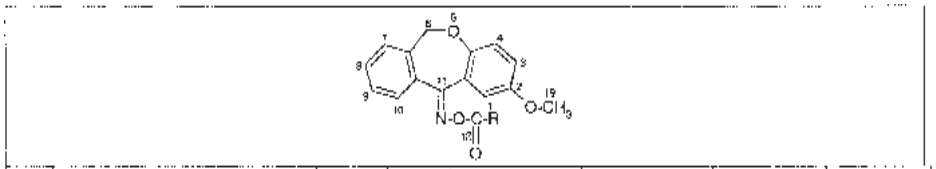
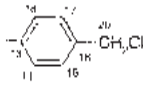
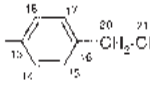
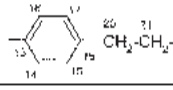
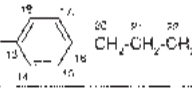
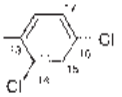
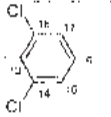
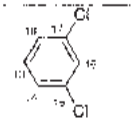


Scheme 1. Synthesis of new dibenz[b,e]oxepins

R= -C_6H_4-CH_2Cl (4) (**6a**), -C_6H_4-C_2H_5 (4) (**6b**), -C_6H_4-C_3H_7-n (4) (**6c**), -C_6H_4-C_4H_9-n (4) (**6d**), -C_6H_4-Cl_2 (2,4) (**6e**), -C_6H_4-Cl_2 (2,6) (**6f**), -C_6H_2-Cl_2 (3,5) (**6g**)



No.	R	m. p. (°C)	yield (%)	R_f sys. 1	R_f sys. 2	C% c.	C% e.	H% c.	H% e.	N% c.	N% e.
6a.		108.2-110.1	62	0.65	0.85	67.73	68.07	4.45	4.38	3.43	3.45
6b.		125.3-127.8	55	0.63	0.84	74.40	74.61	5.46	5.37	3.62	3.56
6c.		116.3-118.2	67	0.62	0.80	74.80	74.59	5.77	5.81	3.49	3.41
6d.		117.9-119.6	72	0.60	0.82	75.16	74.92	6.06	5.98	3.37	3.41
6e.		128.2-129.7	75	0.82	0.95	61.70	61.99	3.53	3.46	3.27	3.28
6f.		138.5-140.3	82	0.64	0.86	61.70	61.47	3.53	3.64	3.27	3.31
6g.		167.8 170.1	69	0.85	0.88	61.70	61.43	3.53	3.62	3.27	3.32

where: c = calculated, e = experimental

Table 1
DATA ON THE NEW COMPOUNDS

The structure, melting point, yield and the results of the 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.

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

Spectral data

The chemical shifts values, expressed in ppm, were referenced downfield to tetramethylsilane. Coupling constants (J) were given 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 following order: chemical shifts, multiplicity (s, singlet; d, doublet; dd, double doublet; dt, double triplet; bd, broad doublet, t, triplet; q, quartet, sex, sextet, 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 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.

All spectroscopic methods confirm the proposed structures of the new compounds.

*({[11E,Z)-2-methoxydibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)(4-chloromethylphenyl)metanona (**6a**)*

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.88 (d, 2H, H-14, H-18, 8.4); 7.60 (m, 1H, H-10); 7.52-7.44 (m, 3H, H-9, H-8, H-7); 7.43 (dt, 2H, H-15, H-17, 8.4, 0.6); 7.39 (d, 1H, H-1, 3.0); 6.96 (dd, 1H, H-3, 3.0, 9.0); 6.84 (d, 1H, H-4, 9.0); 5.15 (s, 2H, H-6); 3.84 (s, 3H, H-19).

^{13}C-NMR ($CDCl_3$, δ ppm): 164.44 (C-11); 163.13 (C-12); 153.86 (C-2); 151.76 (C-4a); 142.75 (C-16); 134.05 (C-10a); 133.16 (C-13); 130.55 (C-8 or C-9); 130.15 (C-14, C-18); 128.65; 128.55 (C-7a); 128.48 (C-8 or C-9); 128.32 (C-7); 128.05 (C-10); 121.07 (C-4); 120.75 (C-3); 119.39 (C-1a); 113.08 (C-1); 70.67 (C-6); 55.93 (C-19); 45.24 (C-20).

FT-IR (solid in ATR, ν cm^{-1}): 3073w; 2990w; 2933w; 2903w; 2828w; 1740vs; 1603m; 1578w; 1491vs; 1460m; 1409s; 1375w; 1340w; 1302m; 1251vs; 1211vs; 1179s; 1153s; 1107w; 1066s; 1042s; 995vs; 912m; 858s; 824s; 758vs; 701s; 666m; 625w.

*({[11E,Z)-2-methoxydibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)(4-ethylphenyl)metanona (**6b**)*

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.80 (d, 2H, H-14, H-18, 8.2); 7.61 (m, 1H, H-10); 7.51-7.44 (m, 3H, H-9, H-8, H-7); 7.40 (d, 1H, H-1, 3.0); 7.22 (d, 2H, H-15, H-17, 8.2) ; 6.95(dd, 1H, H-3, 3.0, 9.0); 6.83 (d, 1H, H-4, 9.0); 5.14 (s, 2H, H-6); 3.84 (s, 3H, H-19); 2.68 (q, 2H, H-20, 7.6); 1.23 (t, 3H, H-21, 7.6).

^{13}C-NMR ($CDCl_3$, δ ppm): 163.97 (C-11); 163.72 (C-12); 153.90 (C-2); 151.75 (C-4a); 150.36 (C-16); 134.23 (C-10a); 133.19 (C-13); 130.43 (C-8 or C-9); 129.88 (C-14, C-18); 128.41 (C-8 or C-9); 128.30 (C-7); 128.20 (C-10); 128.09 (C-15, C-17); 126.04 (C-7a); 121.02 (C-4); 120.65 (C-3); 119.62 (C-1a); 113.20 (C-1); 70.69 (C-6); 55.96 (C-19); 28.99 (C-20); 15.12 (C-21).

FT-IR (solid in ATR, ν cm^{-1}): 3036m; 2964m; 2933m; 2873w; 2836w; 1750vs; 1603m; 1574w; 1490s; 1455s; 1371w; 1338w; 1304m; 1244vs; 1210s; 1182s; 1152m; 1106w; 1070vs; 1040s; 997vs; 920m; 858m; 820m; 753m; 697m.

*({[11E,Z)-2-methoxydibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)(4-propylphenyl)metanona (**6c**)*

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.80 (d, 2H, H-14, H-18, 8.2); 7.61 (m, 1H, H-10); 7.51- 7.44 (m, 3H, H-9, H-8, H-7); 7.40 (d, 1H, H-1, 3.0); 7.20 (d, 2H, H-15, H-17, 8.2); 6.95 (dd, 1H, H-3, 3.0, 9.0); 6.83 (d, 1H, H-4, 9.0); 5.14 (s, 2H, H-6); 3.84 (s, 3H, H-19); 2.61 (t, 2H, H-20, 7.4); 1.64 (sex, 2H, H-21, 7.4); 0.92 (t, 3H, H-22, 7.4).

^{13}C-NMR ($CDCl_3$, δ ppm): 163.94 (C-11); 163.72 (C-12); 153.88 (C-2); 151.74 (C-4a); 148.85(C-16); 134.23 (C-10a); 133.19 (C-13); 130.42 (C-8 or C-9); 129.77 (C-14, C-18); 128.68 (C-15, C-17); 128.41 (C-8 or C-9); 128.30 (C-7); 128.20 (C-10); 126.05 (C-7a); 121.01 (C-4); 120.64 (C-3); 119.63 (C-1a); 113.20 (C-1); 70.69 (C-6); 55.94 (C-19); 38.07 (C-20); 24.15 (C-21); 13.71 (C-22).

FT-IR (solid in ATR, ν cm^{-1}): 2962m; 2933m; 2869w; 2838w; 1750vs; 1603m; 1573w; 1490s; 1456m; 1371w; 1303m; 1244vs; 1210s; 1180m; 1152m; 1106w; 1068s; 1037s; 997vs; 920m; 859m; 753m; 701w; 623w.

*({[11E,Z)-2-methoxydibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)(4-butylphenyl)metanona (**6d**)*

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.80 (d, 2H, H-14, H-18, 8.2); 7.61 (m, 1H, H-10); 7.51-7.44 (m, 3H, H-9, H-8, H-7); 7.40 (d, 1H, H-1, 3.0); 7.20 (d, 2H, H-15, H-17, 8.2); 6.95 (dd, 1H, H-3, 3.0, 9.0); 6.83 (d, 1H, H-4, 9.0); 5.14 (s, 2H, H-6); 3.84 (s, 3H, H-19); 2.64 (t, 2H, H-20, 7.4); 1.59 (q, 2H, H-21, 7.4); 1.34 (sex, 2H, H-22, 7.4); 0.91 (t, 3H, H-23, 7.4).

^{13}C-NMR ($CDCl_3$, δ ppm): 163.94 (C-11); 163.73 (C-12); 153.90 (C-2); 151.75 (C-4a); 149.12 (C-16); 134.23 (C-10a); 133.19 (C-13); 130.43 (C-8 or C-9); 129.80 (C-14, C-18); 128.64 (C-15, C-17); 128.41 (C-8 or C-9); 128.30 (C-7); 128.21 (C-10); 126.00 (C-7a); 121.02 (C-4); 120.64 (C-3); 119.64 (C-1a); 113.21 (C-1); 70.69 (C-6); 55.95 (C-19); 35.74 (C-20); 33.18 (C-21); 22.29 (C-22); 13.87 (C-23).

FT-IR (solid in ATR, ν cm^{-1}): 3068w; 2992w; 2930m; 2852m; 1753vs; 1604m; 1491s; 1458m; 1410m; 1378w; 1303m; 1234vs; 1205s; 1179m; 1152m; 1061s; 998vs; 920m; 858m; 754s; 698w; 624w.

*({[11E,Z)-2-methoxydibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)(2,4-dichlorophenyl)metanona (**6e**)*

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.58 (d, 1H, H-18, 8.4); 7.53 (bd, 1H, H-10, 7.4); 7.50-7.37 (m, 3H, H-9, H-8, H-7); 7.38 (d, 1H, H-1, 3.0); 7.26 (d, 1H, H-15, 2.0); 7.25 (dd, 1H, H-17, 2.0, 8.4); 6.95 (dd, 1H, H-3, 3.0, 9.0); 6.83 (d, 1H, H-4, 9.0); 5.14 (s, 2H, H-6); 3.84 (s, 3H, H-19).

^{13}C-NMR ($CDCl_3$, δ ppm): 165.27 (C-11); 162.22 (C-12); 153.91 (C-2); 151.84 (C-4a); 138.74 (C-14); 135.06 (C-16); 133.93 (C-10a); 133.04 (C-13); 132.31 (C-18); 131.09 (C-8 or C-9); 130.58; 128.42; 128.36 (C-8 or C-9); 128.09 (C-7); 127.23 (C-7a); 127.12 (C-10); 121.15 (C-4); 120.88 (C-3); 119.21 (C-1a); 113.00 (C-1); 70.67 (C-6); 55.95 (C-19).

FT-IR (solid in ATR, ν cm^{-1}): 3066w; 3024w; 2942w; 2904w; 2834w; 1765vs; 1582m; 1493s; 1464m; 1409m; 1372w; 1305w; 1257m; 1214vs; 1154s; 1110s; 1036s;

*({[11E,Z)-2-methoxydibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)(2,6-dichlorophenyl)metanona (**6f**)*

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.55 (bd, 1H, H-10, 7.4); 7.46- 7.24(m, 7H, H-arom.); 6.94 (dd, 1H, H-3, 3.0, 9.0); 6.82 (d, 1H, H-4, 9.0); 5.19 (s, 2H, H-6^{m}); 5.12 (s, 2H, H-6^{M}); 3.80 (s, 3H, H-19^{M}); 3.68 (s, 3H, H-19^{m}).

^{13}C-NMR ($CDCl_3$, δ ppm): 165.26 (C-11); 164.03 (C-12); 153.80 (C-2); 151.90 (C-4a); 134.94; 133.58; 132.89; 132.31; 131.22; 130.57; 128.57; 128.36; 128.23; 127.86; 121.50 (C-4^{m}); 121.18 (C-4^{M}); 120.94 (C-3^{M}); 120.23 (C-3^{m}); 113.55 (C-1^{m}); 112.84 (C-1^{M}); 71.01 (C-6^{m}); 70.68 (C-6^{M}); 55.88 (C-19^{M}); 55.85 (C-19^{m}).

FT-IR (solid in ATR, ν cm^{-1}): 3076w; 3028w; 2972w; 2940w; 2866w; 1759vs; 1583m; 1564m; 1488s; 1459m; 1432m; 1406m; 1374w; 1307m; 1281m; 1249vs; 1210s; 1150m; 1121s; 1076m; 1040s; 992s; 912w; 861w; 820m; 774s; 734m; 681w; 621w.

*({[11E,Z)-2-methoxydibenz[b,e]oxepin-11(6H)-ylidene]amino}oxy)(3,5-dichlorophenyl)metanona (**6g**)*

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.74 (d, 2H, H-14, H-18, 2.0); 7.60-7.46 (m, 4H, H-7, H-8, H-9, H-10); 7.53 (d, 1H, H-16, 2.0); 7.36 (d, 1H, H-1, 3.0); 6.97 (dd, 1H, H-3, 3.0, 9.0); 6.85 (d, 1H, H-4, 9.0); 5.14 (s, 2H, H-6); 3.84 (s, 3H, H-19).

^{13}C-NMR ($CDCl_3$, δ ppm): 165.32 (C-11); 161.33 (C-12); 153.94 (C-2); 151.92 (C-4a); 135.52 (C-10a); 133.75 (C-13); 133.26 (C-15, C-17); 133.19 (C-16); 131.52 (C-7a); 130.81 (C-8 or C-9); 128.63 (C-8 or C-9); 128.34 (C-7) 128.11 (C-14, C-18); 127.94 (C-10); 121.18 (C-4); 120.91 (C-3); 119.09 (C-1a); 113.11 (C-1); 70.72 (C-6); 55.95 (C-19).

FT-IR (solid in ATR, δν cm^{-1}): 3078s; 3000w; 2966w; 2838w; 1796vs; 1598w; 1569m; 1489s; 1435w; 1410s; 1375w; 1304w; 1282m; 1236vs; 1154m; 1128m; 1094m; 1038m; 1004m; 1004s; 897s; 824m; 801m; 767m; 745m; 698w; 657w; 623w.

Conclusions

This work describes an efficient way to obtain new 2-methoxy-O-acyl-oximino-dibenz[b,e]oxepin derivatives as potential new antimicrobial agents.

The synthesized compounds have been characterized by some physical properties and their chemical structures were confirmed by FT-IR and NMR spectral data and by elemental analysis.

These dibenzoxepins are in course of testing in order to establish their antimicrobial activity.

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