SYNTHESIS AND STRUCTURE ELUCIDATION OF SOME NEW O-ACYL-OXIMINO-DIBENZO[b,e]THIEPINES AND O-ACYL-OXIMINO-DIBENZO[b,e]THIEPINE-5,5-DIOXIDES

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Abstract

The aim of the present paper was the synthesis and characterization of some new dibenzo[b,e]thiepine derivatives. *O*-acyl-oximino-dibenzo[b,e]thiepines (***3)*** were obtained by acylation of 11-hydroximino-6,11-dihydro-dibenzo[b,e]thiepine (***2)*** with various acid chlorides. *O*-acyl-oximino-dibenzo[b,e]thiepine-5,5-dioxides (***4)*** were synthesized using two different pathways. Thus, compounds ***4a-b*** have resulted by oxidation of *O*-acyl-oximino-dibenzo[b,e]thiepines ***3a-b*** and compounds ***4c-f*** have resulted following a multistage synthesis which implies transforming the 6,11-dihydrodibenzo[b,e]thiepin-11(6*H*)-one (***1)*** into the corresponding 5,5-dioxide (***5)*** and subsequently to the corresponding oxime (***6)***, the acylation taking place in the last stage. All the new products were characterized by their physical properties, and the structures were confirmed by elemental analysis and spectral analysis (^{1}H-NMR, ^{13}C-NMR, IR).

Rezumat

Lucrarea prezintă sinteza şi caracterizarea unor noi derivaţi de dibenzo[b,e]tiepină. *O*-acil-oximino-dibenzo[b,e]tiepinele (***3)*** au rezultat prin acilarea cu diverse cloruri acide a 11-hidroximino-6,11-dihidro-dibenzo-dibenzo[b,e]tiepinei (***2)***. *O*-acil-oximino-dibenzo[b,e]tiepin-5,5-dioxizii ***4*** au fost obţinuţi prin două variante de lucru. Astfel, compuşii ***4a-b*** au rezultat prin oxidarea *O*-acil-oximino-dibenzo[b,e]tiepinelor ***3a-b***, iar compuşii ***4c-f*** în urma unei sinteze în mai multe etape, care implică transformarea 6,11-dihidrodibenzo[b,e]tiepin-11(6*H*)-onei (***1)*** în 5,5-dioxidul corespunzător ***5*** şi ulterior în oxima corepunzătoare (***6)***, acilarea având loc în ultima etapă. Toţi compuşii originali, nou sintetizaţi, au fost caracterizaţi prin principalele proprietăţi fizice, iar structurile au fost confirmate prin analiză elementală şi analize spectrale (^{1}H-RMN, ^{13}C-RMN, FT-IR).

Keywords: dibenzo[b,e]thiepine, dibenzo[b,e]thiepine-5,5-dioxides, sulfones

Introduction

The present paper is a continuation of our researches [1-9] concerning the synthesis, *in silico* and *in vitro* evaluations, of new derivatives having dibenzo[b,e]thiepine scaffold.

Among the different tricyclic [6.7.6] compounds, the interest for dibenzothiepine derivatives has been heightened during the last years due to their broad spectrum of pharmacological activities: psychotropic [10, 11], analgesic, antiinflammatory [12], bacteriostatic [13], insecticidal, acaricidal, nematicidal [14]. Furthermore, dibenzo[b,e]thiepines have been shown recently [15], to be active as inhibitors of tumor necrosis factor-α (TNF- α), and therefore useful for the treatment and prevention of inflammations and, also, have demonstrated their potential use as new anti-infectious compounds, acting as DNA helicase inhibitors [16].

Motivated by these recent studies, and also by our findings, concerning antibiofilm activity of some dibenzo[b,e]thiepine compounds [6], we aimed to synthesize new *O*-acyl-oximino-dibenzo[b,e]thiepines and *O*-acyl-oximino-dibenzo[b,e]thiepine-5,5-dioxides, in order to evaluate in further studies, their antimicrobial activity against planktonic cells and adhered microbial strains.

Materials and Methods

All chemicals used were of reagent grade and were purchased from commercial sources (Sigma- Aldrich, Fluka, Merck).

Thin layer chromatography (TLC) was used to monitor the progress of the reaction .The TLC procedure was performed on silicagel 60F254 Merck plates, using as mobile phase chloroform/ ethyl acetate (10:1). The visualization was performed using an UV lamp (λ= 254nm) and iodine atmosphere.

Melting points were determined in open capillary tubes, on an Electrothermal 9100 apparatus, and are uncorrected. Elemental analyses were carried out using a Perkin Elmer CHNS/O Analyzer Series II 2400 apparatus.

FT-IR spectra were recorded using a Bruker Vertex 70 spectrometer, with horizontal device for attenuated reflectance and diamond crystal, on a spectral window ranging from 4000 to 400 cm^{-1}, at a spectral resolution of 2 cm^{-1}. The IR bands intensities are denoted as: w- weak; m- medium; s- strong; vs- very strong.

NMR spectra were recorded on a Varian INOVA 400 spectrometer operating at 9.4 Tesla, corresponding to the resonance frequency of 399.95

MHz for the ^{1}H nucleus and 100.56 MHz for the ^{13}C nucleus. As internal standard it was used the TMS (tetramethylsilane) signal both in proton and carbon spectra. All the spectra were recorded at 303K with an indirect detection probehead AS-SW and field gradients.

The ^{1}H-NMR data are reported in the following order: chemical shift (ppm), multiplicity, number of protons, assignment of the signal, coupling constant (*J*) in hertz. The splitting patterns are abbreviated as following: s, singlet; bs, broad singlet; d, doublet, bd, broad doublet, dd, double doublet, ddd, doublet of double doublets; dq, double quartet, t, triplet; td, triple doublet; sxt, sextet.

The ^{13}C-NMR data are reported in the following order: chemical shift (ppm), the signal/ atom attribution, the coupling constant (*J*) in some cases; (Cq- quaternary carbon).

The synthetic routes adopted to obtain the target compounds, *O*-acyl-oximino-dibenzo[b,e]thiepines (***3)*** and *O*-acyl-oximino-dibenzo[b,e]thiepine -5,5-dioxides (***4)*** are illustrated in figures 1 and 2.

Thus, we obtained *O*-acyl-oximino-dibenzo[b,e]thiepines (***3)*** from 6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one (***1)*** *via* 11-hydroximino-6,11-dihydro-dibenzo[b,e]thiepine (***2)***. *O*-acyl-oximino-dibenzo[b,e]thiepines (***3)*** were converted afterwards to the corresponding 5,5-dioxides by oxidation with hydrogen peroxide (Figure 1).

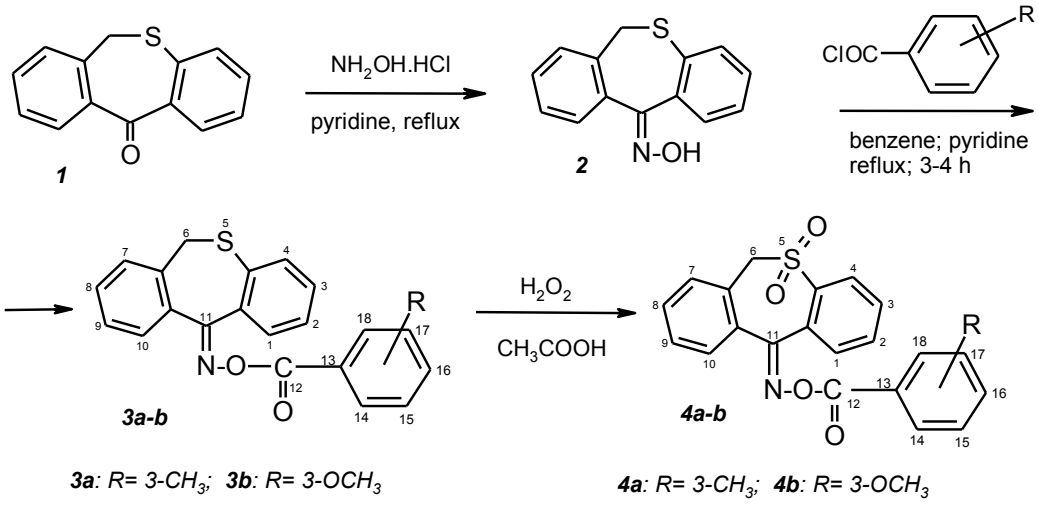


Figure 1
Synthesis of the new *O*-acyl-oximino-dibenzo[b,e]thiepines (***3***)
and of their corresponding 5,5-dioxides (***4***)

For the obtaining of some new *O*-acyl-oximino-dibenzo[b,e]thiepine-5,5-dioxides (***4)***, we also used, another synthesis pathway. This implies transforming the 6,11-dihydrodibenzo[b,e]thiepin-11(6*H*)-one (***1)*** into the corresponding 5,5-dioxide (***5)*** and subsequently to the corresponding oxime (***6)***. The acylation of oxime (***6)*** with various acid chlorides gave the new derivatives (***4)***.

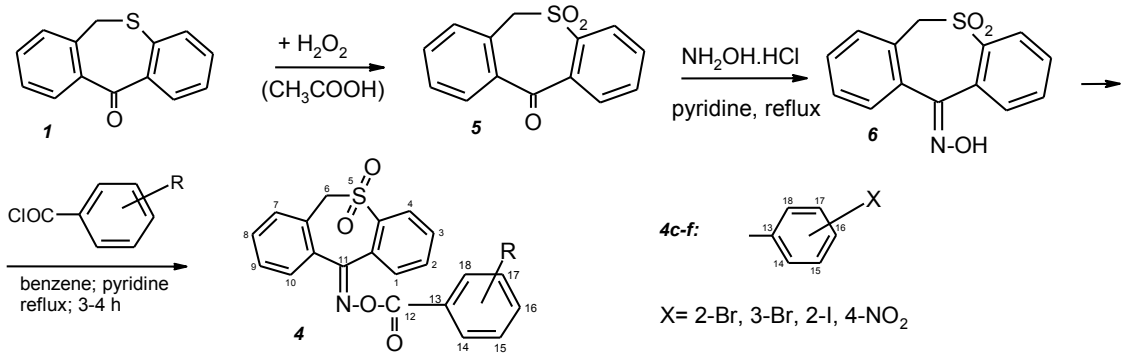


Figure 2
Synthesis pathway (pathway 2) for the new
O-acyl-oximino-dibenzo[b,e]thiepines-5,5-dioxides (***4***)

The preparation of precursor ***1***, 6,11-dihydrodibenzo[b,e]thiepin-11(6*H*)-one, was accomplished according to the previously described procedure starting from phtalide and potassium thiophenolate (Figure 3) [17].

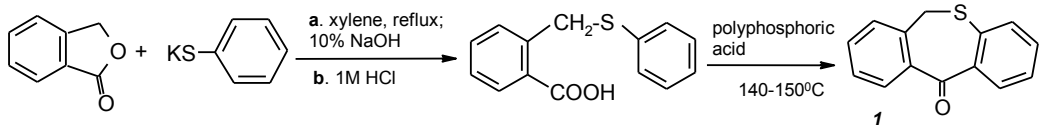


Figure 3
Synthesis of 6,11-dihydrodibenzo[b,e]thiepin-11(6*H*)-one (***1*)**

Intermediates ***2*** (11-hydroximino-6,11-dihydrodibenzo[b,e]thiepine) ***5*** (6,11-dihydrodibenzo[b,e]thiepin-11-one-5,5-dioxide) and ***6*** (11-hydroximino-6,11-dihydrodibenzo[b,e]thiepin-5,5-dioxide) were obtained in good yields, using procedures outlined in our previous works [17, 18].

*Synthesis of O-acyl-oximino-dibenzo[b,e]thiepines (**3**). General procedure.*

A solution of 11 mmol appropriated acyl chloride in 10 mL anhydrous benzene was added dropwise to a solution containing 10 mmol 11-

hydroximino-6,11-dihydrodibenzo[b,e]thiepine (***2)*** (Mol wt 241.30) and 10 mmol (0,8 mL) dry pyridine (Mol wt 79.098; d_4^{25}=0.978) in 10 mL anhydrous benzene. The reaction mixture was refluxed for 3- 4 hours, cooled, the precipitate was filtered off and the solvent was removed under reduced pressure. The resulting crude product was recrystallized from *iso*-propanol.

*Synthesis of O-acyl-oximino-dibenzo[b,e]thiepines-5,5-dioxides **(4)** (pathway 1). General procedure.*

To a solution of 10 mmol ***3a-b*** in glacial acetic acid, 2 mL of 30% aqueous hydrogen peroxide were added dropwise. The mixture was heated for 3 hours and then left overnight at room temperature. The reaction mixture was diluted with water and the compound was extracted with chloroform. The combined organic layer was dried over calcium chloride and after filtration, the solvent was removed under reduced pressure. The resulting crude product was recrystallized from an appropriate solvent (glacial acetic acid or ethanol).

*Synthesis of O-acyl-oximino-dibenzo[b,e]thiepines-5,5-dioxides **(4)** (pathway 2). General procedure.*

To a solution of 10 mmol 11-hydroxyimino-6,11-dihydrodibenzo[b,e]thiepin-5,5-dioxide ***6*** (M_r 273.31) in anhydrous benzene was added dropwise a solution of 11 mmol of appropriated acyl chloride in 10 mL anhydrous benzene and 10 mmol dry pyridine. The reaction mixture was refluxed for 2 hours, cooled, the precipitate was filtered and the solvent was removed under reduced pressure. The resulting crude product was recrystallized from an appropriate solvent (glacial acetic acid or ethanol).

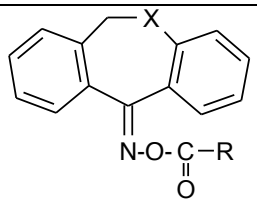
Results and Discussion

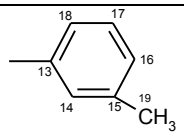
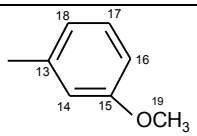
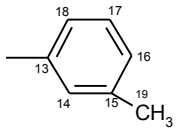
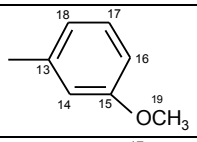
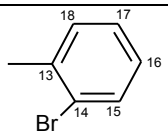
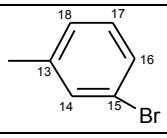
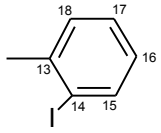
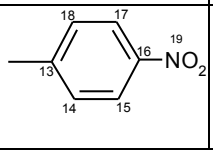
The target compounds, *O*-acyl-oximino-dibenzo[b,e]thiepines (***3a-b)*** and *O*-acyl-oximino-dibenzo[b,e]thiepine-5,5-dioxides (***4a-f***) were synthesized with good yields, following the aforementioned procedures. All the new derivatives are white or light-yellow crystalline solids, soluble at room temperature in benzene, toluene, xylene, dichloromethane, acetone, chloroform by heating in inferior alcohols, insoluble in water.

Chemical structure and some physical properties for the new compounds are presented in Table I. Melting points (M.p.) vary in a wide range, being higher for oxidized derivatives. In thin layer chromatography we found single spots, some time with tailing, with different retention factor (Rf) values for each compound. The single spots indicate that synthesized compounds are pure and contain little or no impurities.

Table I

Characterization data of the new compounds 3***a-b*** and ***4a-f***

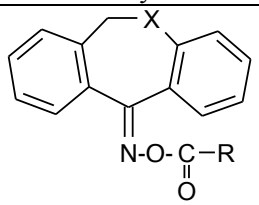


Compd.	R	X	Molecular formula	Molecular mass	M.p. (^{0}C)	Yield (%)	Rf
3a		S	$C_{22}H_{17}NO_2S$	359.43	145.9-147.8	68	0.74
3b		S	$C_{22}H_{17}NO_3S$	375.44	128.0-130.1	69	0.75
4a		SO_2	$C_{22}H_{17}NO_4S$	391.44	222.8-225.1	89	0.68
4b		SO_2	$C_{22}H_{17}NO_5S$	407.44	220.6-223.8	90	0.69
4c		SO_2	$C_{21}H_{14}BrNO_4S$	456.31	175.1-177.6	88	0.65
4d		SO_2	$C_{21}H_{14}BrNO_4S$	456.31	225.0-227.8	85	0.63
4e		SO_2	$C_{21}H_{14}INO_4S$	503.31	189.7-192.8	79	0.72
4f		SO_2	$C_{21}H_{14}N_2O_6S$	422.41	194.2-195.9	91	0.69

Elemental analysis data for the new *O*-acyl-oximino-dibenzo[b,e]thiepines (***3a-b)*** and *O*-acyl-oximino-dibenzo[b,e]thiepine-5,5-dioxides (***4a-f***) are presented in Table II. The results were within ± 0.4% of theoretical values and are in agreement with the proposed chemical structures.

Table II

The elemental analysis results for the new compounds



Compd.	R	X	Elemental analysis (calc/found)			
			C	H	N	S
3a	3-CH_3-C_6H_4	S	73.51/73.68	4.77/4.51	3.90/3.80	8.92/8.78
3b	3-OCH_3-C_6H_4	S	70.38/70.51	4.56/4.68	3.73/3.56	8.54/8.73
4a	3-CH_3-C_6H_4	SO_2	67.50/67.32	4.38/4.61	3.58/3.18	8.19/8.01
4b	3-OCH_3-C_6H_4	SO_2	64.85/64.64	4.21/4.41	3.44/3.62	7.87/7.53
4c	2-Br-C_6H_4	SO_2	55.28/55.46	3.09/3.19	3.07/3.22	7.03/6.91
4d	3-Br-C_6H_4	SO_2	55.28/55.01	3.09/2.96	3.07/3.22	7.03/7.18
4e	2-I-C_6H_4	SO_2	50.11/50.42	2.80/2.68	2.78/2.84	6.37/6.17
4f	4-NO_2-C_6H_4	SO_2	59.71/59.98	3.34/3.20	6.63/6.86	7.59/7.32

The structures of the newly synthesized compounds were elucidated by spectral data. The IR, ^{1}H-NMR and ^{13}C-NMR spectra show all the expected signals. In the following, we present the spectral data for the new *O*-acyl-oximino-dibenzo[b,e]thiepines (***3a-b***) and for the new *O*-acyl-oximino-dibenzo[b,e]thiepine-5,5-dioxides (***4a-f***).

The presence of the sulphur atom induces the asymmetry in dibenzothiepine nucleus, so, *O*-acyl-oximino-dibenzo[b,e]thiepines (***3a-b)*** and *O*-acyl-oximino-dibenzo[b,e]thiepine-5,5-dioxides (***4a-f***) may have *syn* or *anti* configuration. Therefore in some compounds (***4c, 4d***), because the two stereoisomers are present, in ^{13}C-NMR spectra the number of the carbon signals is larger than that corresponding to the raw formula, owing to the two different *syn* and *anti* configurations.

{[Dibenzo[b,e]thiepin-11(6*H*)-ylidenamino]oxy}(3-methylphenyl)methanone (***3a***)

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.85(dd, 1H, H-4, 1.4, 7.7); 7.60(t, 1H, H-14, 1.5); 7.55÷7.13(m, 10H, H-arom); 4.64(bs, 1H, H-6A); 3.48(bs, 1H, H-6B); 2.31(s, 3H, H-19).

^{13}C- NMR ($CDCl_3$, δ ppm): 167.02(C-12); 163.76(C-11); 138.43(C-15); 137.08(Cq); 135.25(Cq); 134.24(CH); 133.59(Cq); 131.90(CH); 130.67(CH); 130.47(CH); 130.41(Cq); 128.96(Cq); 128.55(Cq); 128.48(CH); 128.12(CH); 127.39(CH); 127.23(CH); 126.83(CH); 126.66(CH); 125.16(CH); 33.51(C-6); 21.34(C-19).
FT-IR (ATR in solid, ν cm^{-1}): 3067w; 3037w; 2923w; 1751vs; 1598m; 1467w; 1418m; 1317vs; 1261vs; 1201w; 1175vs; 1085s; 1067s; 1041w; 978m; 904s; 805w; 775m; 756m; 732s; 683w; 636w; 591w; 541w; 493w; 445w.
From the spectra it results that only one stereoisomer is present.

{[Dibenzo[b,e]thiepin-11(6*H*)-ylidenamino]oxy}(3-methoxylphenyl)methanone (***3b***)
^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.84(dd, 1H, H-4, 1.4, 7.7); 7.58÷7.08(m, 10H, H-arom); 7.06(ddd, 1H, H-16, 1.2, 2.7, 8.2); 4.62(bs, 1H, H-6A); 3.72(s, 3H, H-19); 3.48(bs, 1H, H-6B)
^{13}C-NMR ($CDCl_3$, δ ppm): 167.02(C-12); 163.38(C-11); 159.61(C-15); 137.07(Cq); 135.26(Cq); 133.59(Cq); 131.86(CH); 130.70(CH); 130.39(CH); 129.84(Cq); 129.63(CH); 128.85(Cq); 128.11(CH); 127.30(CH); 127.23(CH); 125.67(CH); 125.16(CH); 122.26(Cq); 120.54(C-14); 113.62(C-16); 55.47(C-19); 33.48(C-6).
FT-IR(ATR in solid, ν cm^{-1}): 3061w; 3009w; 2965w; 2936w; 2836w; 1748vs; 1594m; 1487m; 1459m; 1422m; 1323m; 1267s; 1206vs; 1178s; 1160m; 1121w; 1093m; 1054s; 980m; 916m; 887m; 831w; 808m; 774m; 742s; 728m; 681m; 636w; 594w; 571w; 476w.
From the spectra it results that only one stereoisomer is present.

{[5,5-dioxo-dibenzo[b,e]thiepin-11(6*H*)-ylidenamino]oxy}(3-methylphenyl)methanone (***4a***)
^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.05(dd, 1H, H-18, 1.4, 8.1); 7.92(dd, 1H, H-4, 1.3, 8.4); 7.60(t, 1H, H-14, 1.4); 7.75÷7.43(m, 8H, H-arom); 7.37(dt, 1H, H-16, 7.6, 1.4); 7.25(t, 1H, H-17, 7.6); 5.10(bs, 1H, H-6A); 4.40(bs, 1H, H-6B); 2.32(s, 3H, H-19).
^{13}C- NMR ($CDCl_3$, δ ppm): 164.12(C-12); 163.33(C-11); 141.94(Cq); 138.63(Cq); 135.00(Cq); 134.69(CH); 132.88(CH); 132.39(CH); 131.62(CH); 131.09(CH); 130.54(CH); 130.11(CH); 130.03(Cq); 129.03(CH); 128.63(CH); 128.08(CH); 127.85(Cq); 126.89(CH); 126.26(CH); 124.39(Cq); 58.62(C-6); 21.34(C-19).
FT-IR(ATR in solid, ν cm^{-1}): 3063w; 2962w; 2920w; 1751vs; 1593w; 1554w; 1487w; 1450w; 1415w; 1333w; 1258m; 1191s; 1158s; 1124s;

1094m; 1057vs; 983m; 920m; 898m; 881w; 812w; 778m; 734m; 684w; 637w; 607w; 586w; 551w; 521m; 481w.
From the spectra it results that only one stereoisomer is present.

{[5,5-dioxo-dibenzo[b,e]thiepin-11(6*H*)-ylidenamino]oxy}(3-methoxyphenyl)methanone (***4b***)
^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.06(dd, 1H, H-18, 1.6, 8.0); 7.92(dd, 1H, H-4, 1.3, 8.4); 7.75÷7.24(m, 6H, H-arom); 7.36(dt, 1H, H-18, 8.0, 1.4); 7.28(t, 1H, H-17, 8.0); 7.09(dddd, 1H, H-16 1.1, 2.7, 8.0); 5.10(bs, 1H, H-6A); 4.40(bs, 1H, H-6B).
^{13}C-NMR($CDCl_3$, δ ppm): 164.15(C-12); 162.98(C-11); 159.73(C-15); 141.96(Cq); 135.02(Cq); 132.90(CH); 132.43(CH); 131.64(CH); 131.09(CH); 130.09(CH); 129.96(Cq); 129.80(CH); 129.15(Cq); 129.05(CH); 128.01(CH); 126.27(CH); 124.42(Cq); 122.26(CH); 120.76(CH); 113.94(CH); 58.61(C-6); 55.50(C-19).
FT-IR(ATR in solid, ν cm^{-1}): 3078w; 3023w; 2962w; 2921w; 2832w; 1751vs; 1598w; 1556m; 1489w; 1458w; 1418w; 1332m; 1301s; 1267m; 1207vs; 1157s; 1125s; 1092m; 1056vs; 1033m; 986m; 923m; 876w; 843w; 811w; 783m; 746s; 723w; 683w; 638w; 607w; 569w; 524s.
From the spectra it results that only one stereoisomer is present.

{11(E,Z)-[5,5-dioxo-dibenzo[b,e]thiepin-11(6*H*)-ylidenamino]oxy}(2-bromophenyl)methanone (***4c***)
^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.05(dd, 1H, H-4, 1.4, 8.0); 7.91(dd, 1H, H-1, 1.6, 7.5); 7.74÷7.27(m, 10H, H-arom); 5.10(bs, 1H, H-6A); 4.40(bs, 1H, H-6B).
^{13}C-NMR($CDCl_3$, δ ppm): 164.97(C-12^{M}); 163.59(C-12^{m}); 163.27(C-11^{M}); 163.09(C-11^{m}); 141.82(Cq); 138.21(Cq); 134.81(Cq); 134.36(CH^{m});133.09(CH^{m}); 132.84(CH^{m}); 130.18(Cq);134.48(CH); 133.23(CH); 132.75(CH); 132.36(CH); 131.41(CH); 131.36(CH); 131.16(CH^{m}); 131.09(CH^{m}); 131.02(CH); 129.80(CH); 129.45(CH^{m}); 129.29(CH^{m}); 129.24(CH^{m}); 129.14(CH); 127.87(CH); 127.26(CH); 126.37(CH^{m}); 126.17(CH); 124.10(Cq); 121.85(Cq); 59.17(C-6^{m}); 58.46(C-6^{M}).
FT-IR(ATR in solid, ν cm^{-1}): 3071w; 2963w; 2912w; 1758vs; 1587m; 1565w; 1470w; 1431w; 1329m; 1306vs; 1252w; 1223vs; 1170m; 1152s; 1125s; 1074s; 1042m; 1019vs; 979vs; 893s; 868m; 788m; 755m; s; 716w; 607w; 551w; 525m.

The NMR spectra show the presence of both *syn* and *anti* stereoisomers. As to the carbon atoms data, the chemical shifts have been noted by *M* for the major, and *m* from the minor compound.

{11(E,Z)-[5,5-dioxo-dibenzo[b,e]thiepin-11(6*H*)-ylidenamino]oxy}(3-bromophenyl)methanone (***4d***)

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.06(dd, 1H, H-4, 1.4, 8.0); 7.91(dd, 1H, H-1, 1.9, 7.9); 7.86(t, 1H, H-14, 1.6); 7.84÷7.32(m, 8H, H-arom); 7.26(t, 1H, H-17, 8.0); 5.10(bs, 1H, H-6A); 4.40(bs, 1H, H-6B).

^{13}C-NMR($CDCl_3$, δ ppm): 164.69(C-12); 161.74(C-11); 141.84(Cq); 136.71(CH); 136.61(CH^m); 134.55(Cq); 132.80(CH); 132.75(CH); 132.66(CH^m); 132.42(CH); 131.61(CH); 131.37(CH^m); 131.25(CH^m); 131.17(CH); 131.13(CH^m); 130.21(CH); 129.93(CH); 129.77(Cq); 129.64(Cq); 129.55(CH^m); 129.33(CH^m); 129.07(CH^m); 129.00(CH); 128.29(CH^m); 128.22(CH); 127.80(CH); 126.62(CH^m); 126.20(CH); 124.23(Cq); 122.68(Cq); 59.16(C-6^m); 58.46(C-6^M).

FT-IR(ATR in solid, ν cm^{-1}): 3070w; 2962w; 2920w; 1752vs; 1595w; 1569w; 1472w; 1414w; 132m; 1302s; 1227vs; 1185m; 1155m; 1118m; 1086m; 1054s; 983m; 892m; 784m; 755w; 731m; 639w; 607w; 568w; 478m.

The NMR spectra show the presence of both *syn* and *anti* stereoisomers. As to the carbon atoms data, the chemical shifts have been noted by *M* for the major, and *m* from the minor compound.

{[5,5-dioxo-dibenzo[b,e]thiepin-11(6*H*)-ylidenamino]oxy}(2-iodophenyl)methanone (***4e***)

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.05(dd, 1H, H-4, 7.7, 1.4); 7.96(dd, 1H, H-1, 1.1, 8.0); 7.92(dd, 1H, H-15, 1.1, 7.7); 7.84÷7.30(m, 7H, H-arom); 7.32(td, 1H, H-17, 7.7, 1.1); 7.15(td, 1H, H-16, 7.7, 1.6); 5.12(bs, 1H, H-6A); 4.40(bs, 1H, H-6B).

^{13}C-NMR($CDCl_3$, δ ppm): 165.16(C-12); 163.53(C-11); 141.98(Cq); 141.64(CH); 134.91(Cq); 133.36(CH); 132.89(CH); 132.58(Cq); 132.51(CH); 131.58(CH); 131.20(CH); 131.05(CH); 130.01(CH); 129.94(Cq); 129.29(CH); 128.07(CH); 127.98(CH); 126.32(CH); 124.37(Cq); 94.38(C-14); 58.63(C-6).

FT-IR(ATR in solid, ν cm^{-1}): 3089w; 3059w; 2978w; 2933w; 1764vs; 1602w; 1578m; 1558m; 1455w; 1429w; 1403w; 1326m; 1304vs; 1287s; 1255m; 1218vs; 1158s; 1118s; 1062s; 1036vs; 1009s; 974vs; 896m; 861m; 777s; 728s; 679s; 633m; 606w; 585w; 550m; 529m.

From the spectra it results that only one stereoisomer is present.

{[5,5-dioxo-dibenzo[b,e]thiepin-11(6*H*)-ylidenamino]oxy}(4-nitrophenyl)methanone (***4f***)

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.24(d, 2H, H-15, H-17, 8.8); 8.06(dd, 1H, H-18, 1.6, 8.0); 7.96(d, 2H, H-14, H-18, 8.8); 7.94(dd, 1H, H-4, 1.3, 8.4); 7.75÷7.28(m, 6H, H-arom); 5.10(bs, 1H, H-6A); 4.40(bs, 1H, H-6B).

^{13}C-NMR($CDCl_3$, δ ppm): 164.29(C-12); 161.43(C-11); 150.92(C-16); 138.30(Cq); 133.67(Cq); 133.23(Cq); 132.99(CH); 131.51(CH); 131.48(CH); 131.29(CH); 130.95(CH); 130.18(Cq); 129.78(CH); 129.43(CH); 128.95(CH); 127.58(Cq); 126.88(CH); 123.85(CH); 59.32(C-6)

FT-IR(ATR in solid, ν cm^{-1}): 3262w; 3108w; 3073w; 2967w; 2926w; 1731vs; 1603m; 1524vs; 1412w; 1387w; 1350m; 1312vs; 1252vs; 1229vs; 1163m; 1127s; 1075s; 1009m; 979s; 857s; 785m; 713s; 664w; 604w; 550w; 527m; 471w; 446w.

From the spectra it results that only one stereoisomer is present.

Conclusions

In order to obtain new compounds with improved antimicrobial and antibiofilm activity, new *O*-acyl-oximino-dibenzo[b,e]thiepines and *O*-acyl-oximino-dibenzo[b,e]thiepine-5,5-dioxides were synthesized. The newly synthesized derivatives were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis.

Acknowledgements

The authors acknowledge support for this work from the Romanian Ministry of Education, Research and Youth through project PN2 41-055/2007.

References

1. Stecoza C.E., Ilie C., Căproiu M.T., Drăghici C., New 2-methyl-O-acyloximino-dibenzo[b,e]thiepins. Synthesis and structural characterization, *Rev. Chim. (Bucureşti)*, 2011, 62(6), 610- 613
2. Stecoza C.E, Rădulescu F.S., Miron D.S., Nițulescu G.M., Ciolan D., Majekova M., Integrating the values of molecular descriptors in the prediction of biopharmaceutical properties for compounds with dibenzothiepine structure, *Farmacia*, 2011, 59(6), 820- 829
3. Chifiriuc M.C., Stecoza C., Lazăr V., Drăcea O., Larion C., Israil A.M., Antimicrobial activity of some new O-acyloximino-dibenzo[b,e]thiepins and O-acyloximino-dibenzo[b,e]thiepin-5,5-dioxides against planktonic cells, *Rom. Biotech. Lett.,* 2010, 15(2), 5134-5139
4. Stecoza C.E., Chiriță I.C., Căproiu M.T., Drăghici C., Chifiriuc M.C., Ilie C., 6,11-Dihydrodibenzo[b,e]thiepine-5,5-dioxide derivatives, process for preparing the same, pharmaceutical composition containing the same and utilization thereof as antimicrobial agents, RO Patent, 123114, November 30, 2010

5. Stecoza C.E., Ciolan D., Rădulescu F.S., Nițulescu G.M., Majekova M., Miron D.S., Molecular determinants of solubility in biorelevant fluids for dibenzothiepine compounds. *Farmacia*, in press
6. Stecoza C.E., Májeková M., Májek P., Căproiu M.T., Măruțescu L., Novel dibenzothiepins with antibiofilm activity demonstrated by microbiological assays and molecular modelling, *Curr. Org. Chem*., in press
7. Stecoza C.E., Căproiu M.T., Drăghici C., Ilie C., New 6,11-dihydrodibenzo[b,e]thiepine derivatives. Note VI, *Farmacia*, 2009, 57(5), 616- 624
8. Sadek B., Limban C., Stecoza C.E., Elz S., Synthesis and Antimicrobial Evaluation of Dibenzo[b,e]oxepin-11(6H)-one O-Benzoyloxime Derivatives, *Scientia Farmaceutica*, 2011, 79, 749-761
9. Laszlo T., Stecoza C.E.,, Nițulescu G.M., Ilie C., Chifiriuc M.C., QSARs on antibacterial activity of some new, not yet synthesized, substituted dihydrodibenzothiepins, *Rev. Chim. (Bucureşti*), 2010, 61(3), 263 – 266
10. Vlase L., Achim M., Muntean D., Gal A., Cătoi C., Bodolea C., Leucuța S.E., Pharmacokinetics of intravenously and orally administered memantine in swine, *Farmacia*, 2011, 59(3), 338-346
11. Baghai T.C., Blier P., Baldwin D.S., Bauer M., Goodwin G.M., Fountoulakis K.N., Kasper S., Leonard B.E., Malt U.F., Stein D., Versiani M. Moller H.J., General and comparative effectiveness of antidepressants in acute treatment of depressive disorders: a report by the WPA section of pharmacopsychiatry, *Eur. Arch. Psy. Clin. N.,* 2011, *261*, (Suppl. 3), 207-245
12. Matsumoto M., Inoue M., Ueda H., NSAID Zaltoprofen possesses novel anti- nociceptive mechanism through blockage of B2- type bradykinin receptor in nerve endings. *Neurosci. Lett.*, 2006, 397(3), 249- 253
13. Nisa S., Blokpoel M.C.J., Robertson B.D., Tyndal J.D.A., Lun S., Bishai W.R., O'Toole R., Targeting the chromosome partitioning protein ParA in tuberculosis drug discovery, *J. Antimicrob. Chemother*., 2010**,** 65(11), 2347-2358
14. Chiarello J.F., Wood,W.W., Cultbertson D., Smith D. W., Sperry R.C., Schmidt T., Steiner G., Kordes M., von Deyn W., Gotz N., Hofmann M., Barnes K., Takasugi J., Treacy M.F., Oloumi-Sadeghi H., Diehl R., Use of substituted dibenzothiepine derivatives as insecticidal, acaricidal and nematicidal agents, WO Patent 039255, May 15, 2003
15. Lal B., Sharma S., Ghosh U., Bal-Tembe S., More T., Gagare P., Jadhav S., Patil S., Kulkarni- Almeida A., Parikh S., Panicker R., Damre A., Gupte R., Fused tricyclic compounds as inhibitors of tumor necrosis factor-α, their preparation, pharmaceutical compositions, and use in therapy, U.S. Patent 7,964,631, June 21, 2011
16. Dubaele S., Jahnke W., Schoepfer J., Fuchs J., Chene P., Inhibition of DNA helicases with DNA-competitive inhibitors, *Bioorg. Med. Chem. Lett*., 2006, 16(4), 923- 927
17. Stecoza C.E., Căproiu M.T., Drăghici C., Ilie C., Chiriță I.C., Synthesis and characterization of new dibenzo[b,e]thiepine derivatives. *Rev. Chim. (Bucureşti*) 2008, 59(12), 1348-1351
18. Stecoza C.E., Căproiu M.T., Drăghici C., Chifiriuc M.C., Drăcea N.O, Synthesis, characterization and antimicrobial activity evaluation of some new derivatives of 6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide**,** *Rev. Chim. (Bucureşti*), 2009**,** 60(2), 137-141

Manuscript received: March 8th 2012