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SYNTHESIS AND CHARACTERIZATION OF SOME NEW ACYL-OXIMINES DERIVATIVES

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ABSTRACT. This paper presents the synthesis of some new substances with heterocyclic structures which might become new compounds with pharmacological properties similar with the tricyclic antidepressants. These new substances are acyl-oximines derivatives with 10,11-dihydro-5H-dibenzo[a,d]-cycloheptadienic structure. A structural analysis of the synthesized compounds was performed by elemental analysis, infrared and NMR spectra, confirming the structures of these new compounds.

Keywords: 11-dihydro-5H-dibenzo[a,d]-cylcoheptene, oximes, oximines, acylation, dibenzocycloheptadienes, 5-oximino-10

INTRODUCTION

Several medicinal chemistry and pharmacological experimental research revealed the importance of dibenzocycloheptadienes derivatives such as amitriptyline [1, 2], nortriptyline [3], noxiptyline [4] or doxepin [5]. These substances are all used for clinical purpose due to their antidepressant effect [6]. As well as reducing depressive symptoms, these types of tricyclic derivatives also ease migraines, tension headaches, anxiety, attacks and some schizophrenic symptoms. They are also known to reduce aggression and violent behavior and they have a positive influence on eating disorders. [7]

These tricyclic antidepressants block the reuptake of norepinephrine and serotonin. [1] Recent studies show pro-inflammatory cytokine processes taking place during clinical depression, maniac and bipolar disorders and it is possible that symptoms of these conditions are attenuated by the pharmacological effect of antidepressants on the immune system. [8, 9] Antidepressants have also shown important analgesic properties. [10]

For all these reasons we decided to synthesis some new acyl-oximines derivatives with potential antidepressant, analgesic or anti-inflammatory effects with 10,11-dihydro-5H-dibenzo[a,d]-cycloheptadiene structure.

MATERIALS AND METHODS

We decided to try the acylation reaction of some dibenzocycloheptaatomic oximes with some acid chlorides, thinking that the combined molecular structures will improve the biological action of the future substances.

All starting materials and solvents were purchased from common commercial suppliers and used without purification unless otherwise noted.

Intermediate synthesis

The intermediate compound was obtained using a condensation reaction. Dibenzosuberone (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-one) (VIII) was condensed with hydroxylamine hydrochloride to obtain 5-oximino-10,11-dihydro-5H- dibenzo[a,d]-cycloheptene (VII). The condensation reaction is presented in Figure 1.

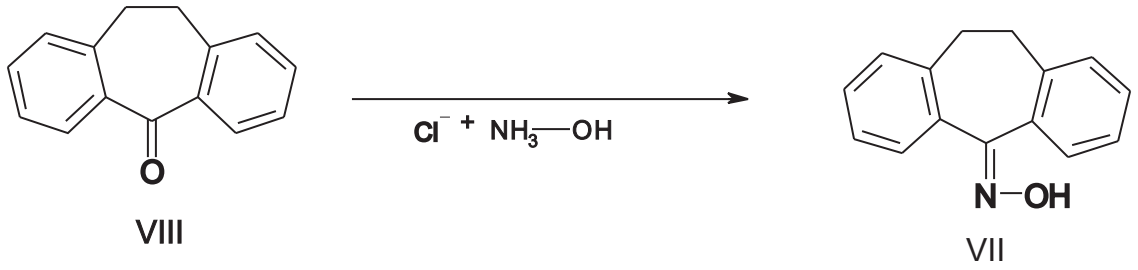

Fig. 1 The synthesis of the intermediate compound (VII)

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In a round-bottom flask equipped with condenser, stirrer and dropping funnel are added 65 mL methanol, 25g dibenzosuberone (0.12 mol) and 28.75g of sodium hydroxide (0.718 mol). The mixture is stirred until the complete dissolution of the compounds. A solution of 12.5g hydroxylamine (0.179 mol) and 70 mL methanol is added dropwise. The mixture is refluxed for 5 hours. After the mixture returns to room temperature we add a solution of 62 mL concentrated hydrochloride acid and 137.5 mL water. While this part of the reaction takes place, we have to keep the temperature under 25°C. We obtain a precipitate which is filtered, washed with water and then dry at 70°C. Results 24.5g of crude oxime with a melting point of 166-167°C and an yield of 91.4%. The compound is purified from toluene. [11]

Final compounds synthesis

The acylation reaction parameters were tested by obtaining some original O-acyl-oximines. These oximines were obtained by treating the tricyclic oximes with substituted aromatic acid chlorides in anhydrous benzene and in the presence of anhydrous pyridine as a proton fixator. [12-14]

The new O-acyl-oximines were obtained like in the following general procedure described in Figure 2:

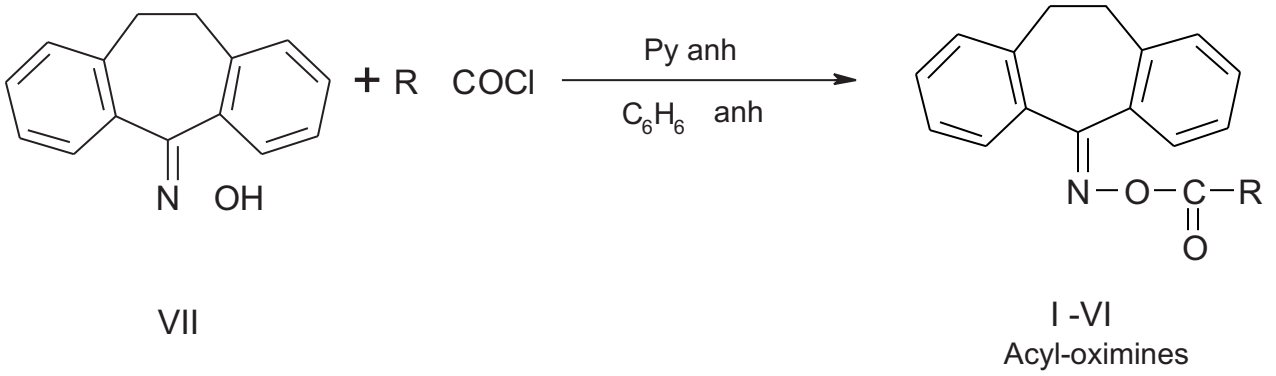
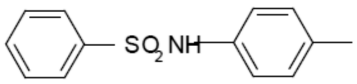
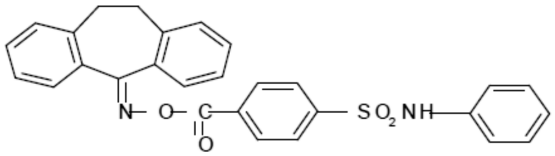
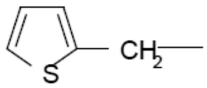
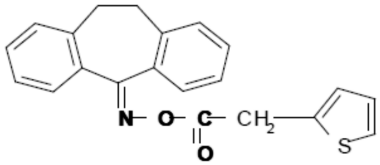
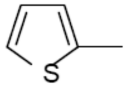
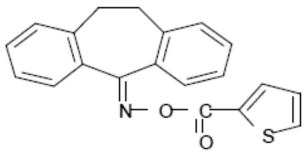


Fig. 2 The synthesis of the new acyl-oximines

Tabel 1

Nr. Crt.	R	Final Compound	Melting points °C
I		 O-(4-Phenylsulfonamidobenzoyl)-5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene	95-96
II		 O-(2-Thienyl-acetyl)-5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene	128-129
III		 O-(2-Tenoyl)-5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene	103-104

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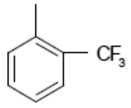
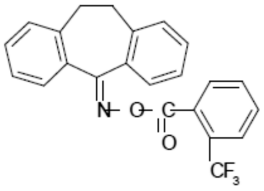
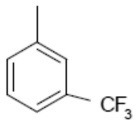
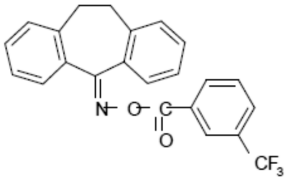
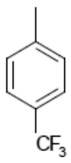
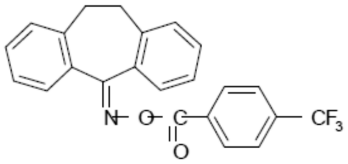
IV		 O-(2-Trifluoromethyl-benzoyl)-5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene	127-128
V		 O-(3-Trifluoromethyl-benzoyl)-5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene	114-115
VI		 O-(4-Trifluoromethyl-benzoyl)-5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene	118-119

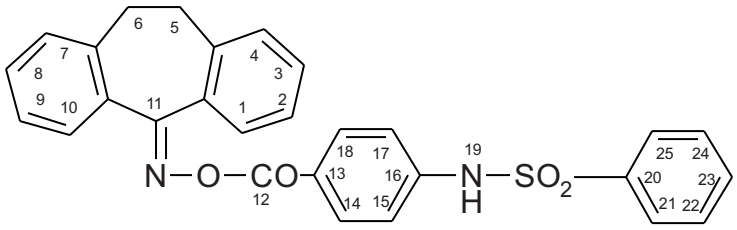
In 15 mL anhydrous benzene there are dissolved 0.58g of 5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene (0.0026 mol). There are gradually added 0.0026 mol of each coresponding acid chlorides in 15mL anhydrous benzene and 0.21mL anhydrous pyridine (0.0026 mol). Immediatelly it appears a white precipitate (pyridinium hydrochloride). The mixture is refluxed for 3 hours and then is filtered. The organic phase is evaporated to dryness at room temperature to give the final crude compound. The new acyl-oximines are recrystallised from isopropanol.

Melting points were measured in open capillary tubes on an Electrothermal apparatus and were not corrected. The elemental analysis was performed on a Perkin Elmer CHNS/O Analyser Series II 2400 apparatus. Infrared spectra were recorded on a FT/IR – solid in ATR spectrometer. The NMR spectra were recorded on a Gemini 300BB instrument at room temperature, operating at 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR. The chemical shifts were reported in δ units (ppm) relative to residual peak of the deuterated solvent ($CDCl_3$ and DMSO-d_6).

RESULTS AND DISCUSSIONS

Following the acylation reaction between 5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene and the chlorides of different carboxylic acids we obtained six new acyl-oximines. We used anhydrous reaction conditions in the presence of anhydrous pyridine as a proton fixator. These new acyl-oximines are solid, crystalline, white compounds and their structures were confirmed by elemental analysis, IR and NMR spectra. In the following are presented spectral data for compounds I-VI.

O-(-4-Phenylsulfonamido-benzoyl)-5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene

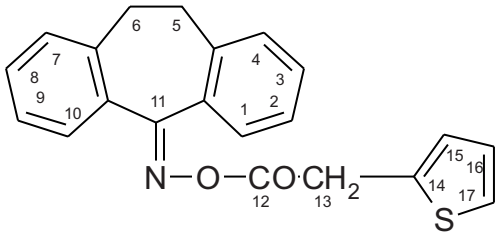


$C_{28}H_{22}N_2O_4S$: ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T=298K): 8.92(d, 1H, H-1, 5.2); 8.37(t, 1H, H-3, 7.7); 8.16 (s, 1H, H-19, deuterable); 7.89 (m, 1H, H-2); 7.86 (dd, 2H, H-21 H-25, 1.7, 7.7); 7.75 (dd, 1H, H-10, 1.5, 7.4); 7.70 (d, 2H, H-14, H-18, 8.8); 7.53 (tt, 1H, H-23, 1.7, 7.2); 7.43 (dd, 2H, H-22, H-24, 7.2, 7.7); 7.42÷7.12 (m, 4H, H-4, H-7, H-8, H-9); 7.15 (d, 2H, H-15, H-17, 8.8); 3.18 (bs, 4H, H-5, H-6).

^{13}C-NMR ($CDCl_3$, δ ppm, T=298K): 167.22 (Cq); 163.21 (Cq); 142.26 (Cq); 141.52 (Cq); 139.18 (Cq); 137.97 (Cq); 133.99 (Cq); 133.29 (CH); 132.85 (Cq); 131.20 (2CH); 130.56 (CH); 130.32 (CH); 129.95 (CH); 129.53 (CH); 129.20 (2CH); 128.42 (CH); 127.60 (CH); 127.19 (2CH); 127.36 (CH); 125.80 (CH); 124.50 (Cq); 119.08 (2CH); 33.44 (C-5 or C-6); 31.85 (C-6 or C-5).

FT-IR (solid in ATR, ν cm^{-1}): 3220w; 3065m; 2967m; 2920m; 2858m; 1735s; 1604vs; 1510m; 1485m; 1447m; 1404w; 1330s; 1257s; 1237s; 1155vs; 1071s; 982m; 914m; 855m; 751w; 718m; 685m; 645w.

O-(2-Thienyl-acetyl)-5oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene

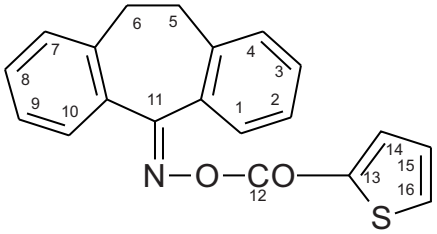


$C_{21}H_{17}NO_2S$: ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T=298K): 7.69 (dd, 1H, H-1, 1.7, 7.7); 7.36÷7.08 (m, 8H, H-2, H-3, H-4, H-7, H-8, H-9, H-10, H-17); 6.92 (dd, 1H, H-16, $^3J(H^{15}\text{-}H^{16})$=3.6Hz, $^3J(H^{17}\text{-}H^{16})$=4.4Hz); 6.85 (dq, 1H, H-15, $^3J(H^{16}\text{-}H^{15})$ = 3.6 Hz, $^4J(2H^{13}\text{-}H^{15})$=1.1 Hz); 3.86 (d, 2H, H-13, $^4J(H^{15}\text{-}H^{13})$=1.1Hz); 3.16 (bs, 4H, H-5, H-6).

^{13}C-NMR ($CDCl_3$, δ ppm, T=298K): 167.90 (Cq); 167.63(Cq); 133.31 (Cq); 137.88(Cq); 134.22(Cq); 133.81(Cq); 132.94(Cq); 130.68(CH); 130.44(CH); 129.88(CH); 129.55(CH); 128.35(CH); 127.76(CH); 127.28(CH); 127.00(CH); 126.47(CH); 126.03(CH); 125.20(CH); 33.46(C-5 or C-6); 33.53(C-13); 31.92(C-6 or C-5).

FT-IR (solid in ATR, ν cm^{-1}): 3093w; 3067w; 3024w; 2909w; 2857w; 1771vs; 1606w; 1484w; 1442w; 1424w; 1395w; 1362w; 1323m; 1254w; 1200w; 1137w; 1100vs; 1037w; 995w; 921m; 909m; 876m; 804w; 777m; 761m; 743m; 709m; 693s; 639w.

O-(2-Tenoyl)-5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene



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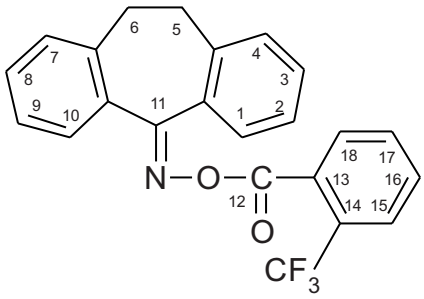
$C_{20}H_{15}NO_2S$: ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T=298K): 7.78 (dd, 1H, H-1, 1.1, 7.4); 7.69(dd, 1H, H-14, 1.1, 3.9); 7.53 (dd, 1H, H-16, 1.1, 4.9); 7.47÷7.22 (m, 6H, H-arom); 7.16 (bd, 1H, H-arom, 7.7); 7.06 (dd, 1H, H-15, 3.9, 4.9); 3.19 (bs, 4H, H-5, H-6).

^{13}C-NMR ($CDCl_3$, δ ppm, T=298K): 167.30 (Cq); 159.64(Cq); 139.39(Cq); 138.11(Cq); 134.23(CH); 134.02(Cq); 133.14(CH); 132.96(Cq); 131.81(Cq); 130.68(CH); 130.46(CH); 129.99(CH); 128.71(CH); 128.48(CH); 128.08(CH): 127.93(CH); 126.52(CH); 125.87(CH); 33.59(C-5 or C-6); 32.04(C-6 or C-5).

FT-IR (solid in ATR, ν cm^{-1}): 3106w; 3091w; 3057w; 3011w; 2923w; 2863w; 1719vs; 1605w; 1564w; 1518w; 1483w; 1415s; 1356w; 1320m; 1259s; 1162w; 1084w; 1064m; 1021s; 971s; 941w; 865m; 783w; 767m; 750w; 737m; 714m; 659w.

O-(2-Trifluoromethyl-benzoyl)-5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene



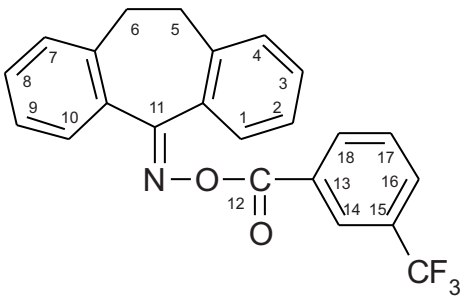
$C_{23}H_{16}F_3NO_2$: ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T=298K): 7.79(dd, 1H, H-1, 1.2, 7.6); 7.69(dd, 1H, H-arom, 1.8, 8.6); 7.62÷7.50(m, 3H, H-arom); 7.34(td, 1H, H-arom, 7.4, 1.6); 7.32÷7.23(m, 4H, H-arom); 7.19(dd, 1H, H-arom, 1.8, 7.6); 7.16(td, 1H, H-arom, 7.8, 1.8); 3.20(bs, 4H, H-5, H-6).

^{13}C-NMR ($CDCl_3$, δ ppm, T=298K): 168.64(C-12); 164.28(C-11); 139.22(Cq); 137.76(Cq); 133.99(Cq); 132.66(Cq); 129.62(q, C-13, J(3F-C^{13})=2.5Hz); 128.95(q, C-14, J(3F-C^{14})=32.2 Hz); 122.14(q, CF_3, J(3F-C)=274.0 Hz); 131.70(CH); 131.33(CH); 130.68(CH); 130.41(CH); 130.16(CH); 129.86(CH); 129.43(CH); 128.18(CH); 127.31(CH); 126.74(q, C-15, ^3J(3F-C^{15})=5.2 Hz); 126.39(CH); 125.84(CH); 33.45(C-5 or C-6); 31.45(C-6 or C-5).

^{19}F-NMR ($CDCl_3$, δ ppm, T=298K): -59.87(F_3C).

FT-IR (solid in ATR, ν cm^{-1}): 3074w; 2969w; 2924w; 2863w; 1766vs; 1604w; 1587w; 1486w; 1449w; 1332m; 1310s; 1277m; 1259vs; 1164s; 1121s; 1085s; 1045s; 1032s; 980m; 867m; 782m; 768m; 753m; 693m; 643m.

O-(3-Trifluoromethyl-benzoyl)-5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene



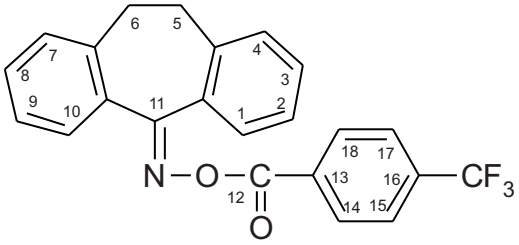
$C_{23}H_{16}F_3NO_2$: ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T=298K): 8.08÷8.05(2H, H-14, H-16); 7.80(dd, 1H, H-1, 1.4, 7.8); 7.78(dd, 1H, H-18, 1.1, 7.6); 7.45(dd, 1H, H-arom, 1.6, 7.8); 7.42÷7.31(m, 4H, H-arom); 7.28(td, 1H, H-arom, 7.8, 1.4); 7.18(dd, 1H, H-arom, 1.2,7.8); 3.22(bs, 4H, H-5, H-6).

^{13}C-NMR ($CDCl_3$, δ ppm, T=298K): 168.15(C-12); 162.39(C-11); 139.35(Cq); 138.01(Cq); 133.85(Cq); 132.55(Cq); 131.13(q, C-15, J(3F-C^{15})=32.9Hz); 129.72(Cq); 123.53(q, CF_3, J(3F-C)=270.9 Hz); 132.92(CH); 130.68(CH); 130.50(CH); 130.08(CH); 129.68(q, C-14, J(3F-C^{14})=3.7 Hz); 129.53(CH); 129.20(CH); 128.53(CH); 127.56(CH); 126.64(q, C-16, ^3J(3F-C^{16})=3.9 Hz); 126.45(CH); 125.77(CH); 33.50(C-5 or C-6); 31.88(C-6 or C-5).

^{19}F-NMR($CDCl_3$, δ ppm, T=298K): -63.38(F_3C).

FT-IR (solid in ATR, ν cm^{-1}): 3073w; 2932w; 2913w; 2880w; 2826w; 1747vs; 1615w; 1592w; 1484w; 1444w; 1424w; 1330s; 1220vs; 1173s; 1159s; 1112vs; 1090s; 985w; 917w; 888m; 870m; 816w; 744s; 693w; 680m; 646w.

O-(4-Trifluoromethyl-benzoyl)-5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene



$C_{23}H_{16}F_3NO_2$: ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T=298K): 8.00(d, 2H, H-15, H-17, 8.2); 7.80(dd, 1H, H-1, 1.2, 7.6); 7.65(d, 2H, H-14, H-18, 8.2); 7.44÷7.30(m, 5H, H-arom); 7.27(td, 1H, H-arom, 1.4, 7.4); 7.18(dd, 1H, H-arom, 1.1, 7.8); 3.22(bs, 4H, H-5, H-6).

^{13}C-NMR ($CDCl_3$, δ ppm, T=298K): 168.09(C-12); 162.60(C-11); 139.26(Cq); 138.01(Cq); 134.62(q, C-16, J(3F-C^{16})=32.7 Hz); 133.87(Cq); 132.51(Cq); 132.07(Cq); 123.54(q, CF_3, J(3F-C)=274.2 Hz); 130.68(CH); 130.50(CH); 130.08(C-14, C-18); 130.07(CH); 129.51(CH); 128.50(CH); 127.44(CH); 126.44(CH); 125.77(CH); 125.52(q, C-15, C-17, ^3J(3F-C$^{15-17}$)=3.9 Hz); 33.43(C-5 or C-6); 31.81 (C-6 or C-5).

^{19}F-NMR ($CDCl_3$, δ ppm, T=298K): -63.63(F_3C).

FT-IR (solid in ATR, ν cm^{-1}): 3067w, 2950w; 2916w; 2864w; 2834w; 1745vs; 1611w; 1594w; 1511w; 1487w; 1427w; 1410m; 1321vs; 1254s; 1237s; 1162m; 1120s; 1080vs; 1063vs; 1014s; 980m; 913w; 856s; 782m; 759m; 693m; 645w.

CONCLUSIONS

We have synthesized new compounds with potential therapeutical effects. The new acyl-oximines are 5-oximino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene derivatives and their structures have been confirmed by elemental analysis and spectrometric methods (IR, ^{1}H-NMR and ^{13}C-NMR). In the near future we intend to test their therapeutical activity.

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