ORIGINAL ARTICLE

NEW ACYL-OXIMINE DERIVATIVES SYNTHESIS AND THEIR PRELIMINARY PHARMACOTOXICOLOGICAL INVESTIGATION

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Abstract

The present study represents a continuation of previous research with the aim to obtain and to physicochemical characterize some new compounds having tricyclic structure. We performed also a preliminary pharmacotoxicological investigation in order to evaluate the compounds systemic toxicity. The structure of these substances, which are O-acyl-oximine derivatives with 5H-dibenzo[a,d]cycloheptatrienic structure, was confirmed by elemental analysis, IR and nuclear magnetic resonance (NMR) NMR-spectrometry.

Rezumat

Studiul reprezintă o continuare a cercetărilor anterioare, în scopul obţinerii şi caracterizării fizico-chimice a unor noi compuşi cu structură triciclică. De asemenea, au fost efectuate şi cercetări farmacotoxicologice în scopul investigării preliminare a toxicităţii lor sistemice. Structura acestor compuşi, derivaţi O-acil-oximinici cu structură 5H-dibenz[a,d]cicloheptatrienică, a fost confirmată prin analiză elementală şi spectrometrie în IR şi RMN.

Keywords: oximes, oximines, acylation, dibenzocycloheptatriene, 5H-dibenzo[a,d]cycloheptatriene

Introduction

It is known that tricyclic systems, like dibenzocycloheptadienic and dibenzocycloheptatrienic derivatives, such as amitryptiline [1, 11], nortryptiline [10], doxepin [8], noxiptyline [6], are important substances with antidepressant effect.

All these antidepressants block the reuptake of norepinephrine and serotonin [4]. Recent studies have shown pro-inflammatory cytokine mediated process taking place during clinical depression, maniac and bipolar disorders and it is possible that symptoms of these conditions could be attenuated by the pharmacological effect of antidepressants on the immune system [5]. In addition antidepressants have important analgesic properties [9].

These tricyclic derivatives can also ease migraines, headaches, anxiety and some schizophrenia symptoms; also they reduce aggression and violent behaviour [14]. These compounds represent a new therapeutic strategy for functional dyspepsia [13] and some of them can reduce pain in peripheral neuropathy caused by cancer chemotherapy [15]; this effect is similar to the one produced by gabapentin associated with tramadol in the prophylaxis of paclitaxel-induced neuropathy [16].

Despite these important therapeutic effects, many of these tricyclic derivatives have side effects, such as: muscle stiffness, changes in appetite, nausea, tremor, constipation, dizziness, urinary retention, blurred vision, or other rare side effects, like hypotension, tinnitus, seizures, arrhythmias, lips and mouth ulcers, extra-pyramidal symptoms, suicidal thoughts [7].

In this paper we present a continuation of previous researches [2, 3, 12] of our department, in order to obtain new derivatives with potential antidepressant, analgesic or antianxiety effects.

Materials and Methods

Melting points were measured in open capillary tubes on an Electrothermal 9100 apparatus and they are uncorrected. Infrared spectra were recorded on a Fourier transform infrared spectroscopy attenuated total reflectance (FT/IR-solid in ATR) spectrometer and the signal intensities (height) were denoted by

the following abbreviations: w = weak, m = medium, s = strong, v = variable). The NMR spectra were recorded on a Gemini 300BB instrument at room temperature, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. The chemical shifts were recorded in δ units (ppm), relative to residual peak of the deuterated solvent ($CDCl_3$ and DMSO-d6). Tetrametylsilane was used as internal standard. The coupling constants values are reported in hertz and the splitting patterns are abbreviated as following: s-singlet; d-doublet; t-triplet; m-multiplet; b-broad. The elemental analyses were performed on a Perkin Elmer CHNS/O Analyser Series II 2400 apparatus and the results were in agreement with the calculated values. Those assigned structures could be confirmed by other experiments (GHMBC – Gradient Heteronuclear Multiple Bond Coherence and GHSQC – Gradient Heteronuclear Single Quantum Coherence spectra).

Synthesis of the new compounds

The new O-acyl-oximes (II–X) were obtained by acylation of oxime (I) with substituted aromatic acid chlorides in anhydrous benzene (C_6H_6 anh.), using anhydrous pyridine (Py anh.) as hydracid acceptor agent [3].

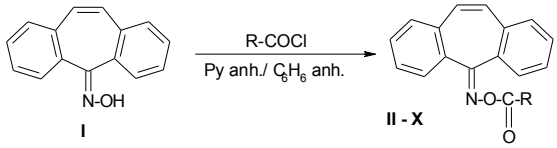


Figure 1.
Synthesis of the new O-acyl-oximines (II–X)

The main compound, oxime I was obtained by condensation of dibenzosuberenone (5H-dibenzo-[a,d]cyclohepten-5-one) with hydroxylamine hydrochloride using a method described in our previous work [3].

Oxime I (0.0052 mol) was dissolved in 25 mL anhydrous benzene; the corresponding acid chloride (0.0052 mol) in 25 mL anhydrous benzene and anhydrous pyridine (0.0052 mol) were added gradually. A white precipitate immediately appeared. After refluxing for 3 hours, the reaction mixture was filtered. After the evaporation to dryness, the final crude product was obtained. The purified substances were obtained by crystallization from isopropanol.

The obtained acyl-oximines were solid, crystalline, white, or light yellow substances with well-defined melting points, soluble in heated alcohols, chloroform, benzene, toluene, and insoluble in water.

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

Acute oral toxicity was evaluated on mice, using the "up & down" method, in accordance with European Guidelines regarding the ethic of experimental research on animals [17]. These guidelines stipulate that chemicals that are likely to have low toxicity can be tested using a limit test, with a test dose of 2000 mg/kg, exceptionally 5000 mg/kg. According to the compounds density and to the maximum volume of suspension that can be administered once to mice, we decided to perform the limit test at the dose of 1500 mg/kg.

Mice weighing 25 ± 2 g were provided by the rodent farm of "Carol Davila" University of Medicine and Pharmacy. The animals were housed in plexiglass cages with sawdust litter, water and food being supplied *ad libitum*. The temperature and relative humidity were continuously monitored using an electronic hygro-thermometer. The temperature was between 21 - 23ºC and the relative humidity was generally maintained at 40 - 60%. The lighting schedule was 12 h light/dark cycle. Prior to administration, animals were fasted for 12 hours. Nine groups of two mice each received the compounds in a dose of 1500 mg/kg bw *per os*.

The following parameters were observed for 14 days: lethality, body weight, motor behaviour, external stimulus reactions, and palpebral ptosis.

Research was carried out in accordance with the Directive 2010/63/UE, regarding the protection of animals used for experimental and other scientific purposes. All experimental procedures were approved by the Ethical Committee of the Faculty of Pharmacy Bucharest, Romania.

Results and Discussion

Using the above general method of synthesis, we obtained nine new acyl-oximines, and their structures were confirmed by elemental analysis, IR and NMR spectra (^{1}H-NMR and ^{13}C-NMR).

The elemental analysis results were in good agreement with those calculated using the suggested formula, and the accuracy of experimental values in respect to the theoretical values was ± 0.4%.

The chemical structures of all compounds were characterized by spectroscopic methods, and the spectral data were in full agreement with the proposed structures.

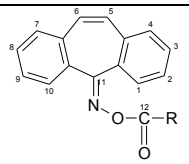
The ^{1}H-NMR data are reported in the following order: chemical shifts, multiplicity, the coupling constants, number of protons and signal/atom attribution.

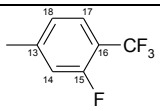
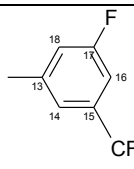
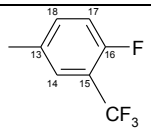
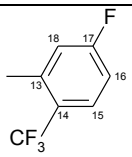
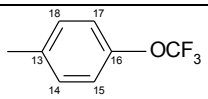
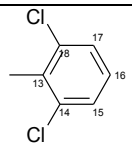
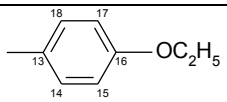
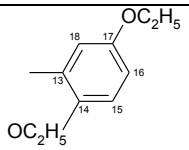
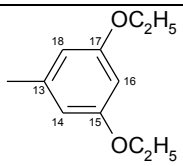
For the ^{13}C-NMR data the following order was: chemical shifts and signal/atom attribution (Cq - quaternary carbon).

The chemical structures, molecular formula and molecular mass of the new compounds are presented in Table I. We mentioned that the numbering of atoms was made arbitrarily, in accordance with our previously published work, to relieve the NMR spectra interpretation.

Table I

Characterization of the new acyl-oximine derivatives



Compound	R	Molecular formula	Molecular mass
II		$C_{23}H_{13}F_4NO_2$	411.35
III		$C_{23}H_{13}F_4NO_2$	411.35
IV		$C_{23}H_{14}F_3NO_2$	411.35
V		$C_{23}H_{13}F_4NO_2$	411.35
VI		$C_{23}H_{14}F_3NO_3$	409.36
VII		$C_{22}H_{13}Cl_2NO_2$	394.24
VIII		$C_{24}H_{19}NO_3$	369.41
IX		$C_{26}H_{23}NO_4$	413.37
X		$C_{26}H_{23}NO_4$	413.37

Following, there are presented the melting points (m.p.), reaction yield and spectral data for the synthetized compounds II-X.

Compound II: **O-(3-Fluoro-4-trifluoromethyl-benzoyl)-5-oximino-5H-dibenzo- [a,d]-cycloheptene:** m.p. 167 - 168ºC; yield 82.5%

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T = 298 K): 7.83 (m, 1H, H-1); 7.73 (bd, 1H, H-18, 8.0); 7.68÷7.62 (m, 3H, H-10, H-14, H-17); 7.56÷7.43 (m, 6H, H-arom); 7.02 (d, 1H, H-5 or H-6, syst. AB, 12.1); 6.98 (d, 1H, H-5 or H-6, syst. AB, 12.1).

^{13}C-NMR ($CDCl_3$, δ ppm, T = 298 K): 165.32 (C-11); 161.41 (d, C-12, *J* (F^{15}-C^{12}) = 2.6 Hz); 159.49 (dq, C-15, *J* (F^{15}-C^{15}) = 258.7 Hz, ^3J (3F-C^{15}) =2.1 Hz); 134.48 (d, C-13, ^3J (F^{15}-C^{13}) = 8.0 Hz); 134.34 (Cq); 133.49 (Cq); 133.03 (Cq); 130.92 (C-5 or C-6); 130.07 (C-5 or C-6); 129.94 (CH); 129.80 (CH); 129.63 (Cq); 129.54 (CH); 129.13 (CH); 129.09 (CH); 128.18 (C-1); 128.17 (C-10); 127.68 (CH); 127.57 (qd, C-17, *J* (3F-C^{17}) = 4.6 Hz, *J* (F^{15}-C^{17}) = 1.6 Hz); 125.24 (d, C-18, *J* (C^{18}-F^{15}) = 4.1 Hz); 122.57 (qd, C-16, *J* (3F-C^{16}) = 33.2 Hz, *J* (F^{15}-C^{16}) =

12.6 Hz); 121.98 (qd, CF_3, *J* (3F-C) = 273.2 Hz, *J* (F^{15}-CF_3) = 1.5 Hz); 118.07 (d, C-14, *J* (C^{14}-F^{15}) = 22.6 Hz).

FT-IR (solid in ATR, ν cm^{-1}): 3069w; 1754vs (υC=O); 1630m (υC=N-); 1588m; 1425s; 1327s; 1273s; 1251s (υC-O); 1198m; 1177s; 1141m; 1122vs; 1082s (υC-F); 1045m; 986w (υN-O); 925m; 895m; 868m; 846m; 802m; 774m; 756m; 730m; 721m; 693w; 670w.

Compound III: **O-(5-Fluoro-3-trifluoromethyl-benzoyl)-5-oximino-5H-dibenzo[a,d]-cycloheptene:** m.p. 126 - 127ºC; yield 75%

^{1}H-NMR ($CDCl_3$, δ ppm, J Hz, T = 298 K): 7.90 (bs, 1H, H-18); 7.83 (m, 1H, H-1); 7.77 (bd, 1H, H-14, J (F15-H14) = 8.8 Hz); 7.68 (m, 1H, H-10); 7.57÷7.43 (m, 6H, H-arom); 7.02 (d, 1H, H-5 or H-6, syst. AB, 12.1); 6.98 (d, 1H, H-5 or H-6, syst. AB, 12.1).

^{13}C-NMR ($CDCl_3$, δ ppm, T = 298 K): 165.32 (C-11); 162.29 (d, C-15, J (F15-C15) = 251.3 Hz); 161.18 (d, C-12, J (F15-C12) = 2.9 Hz); 134.35 (Cq); 133.43 (Cq); 132.99 (Cq); 132.94 (qd, C-17, J (3F-C17) = 34.1 Hz, J (F15-C17) = 7.7 Hz); 132.02 (d, C-13, J (F15-C13) = 7.5 Hz); 130.89 (C-5 or C-6); 130.10 (C-5 or C-6); 129.96 (CH); 129.81 (CH); 129.58 (CH); 129.53 (Cq); 129.14 (CH); 129.07 (CH); 128.26 (C-1); 128.20 (C-10); 127.64 (CH); 122.71 (qd, CF3, J (3F-C) = 274.1 Hz, J (F15-CF3) = 3.0 Hz); 122.41 (qv, C-18, J (F15-C18) = J (3F-C18) = 3.3 Hz); 120.17 (d, C-14, J (F15-C14) = 23.4 Hz); 117.50 (dq, C-16, J (F15-C16) = 24.3 Hz, J (3F-C16) = 3.6 Hz).

FT-IR (solid in ATR, ν cm^{-1}): 3067w; 2966w; 1755vs (υC=O); 1630m (υC=N);1602w; 1584w; 1452m; 1352vs; 1252s; 1183s; 1123vs; 1085m (υC-F); 936s (υN-O); 900w; 886m; 871m; 849w; 811m; 781w; 768w; 749m; 724w; 685m.

Compound IV: O**-(4-Fluoro-3-trifluoromethyl-benzoyl)-5-oximino-5H-dibenzo[a,d]-cycloheptene:** m.p. 116 - 117ºC; yield 82%

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T = 298 K): 8.15÷8.07 (m, 2H, H-18, H-14); 7.82 (m, 1H, H-1); 7.67 (m, 1H, H-10); 7.56÷7.43 (m, 6H, H-arom); 7.24 (bt, 1H, H-17, *J* (F^{16}-H^{17}) = *J* (H^{18}-H^{17}) = 9.1 Hz); 7.02 (d, 1H, H-5 or H-6, syst. AB, 12.3); 6.97 (d, 1H, H-5 or H-6, syst. AB, 12.3).

^{13}C-NMR ($CDCl_3$, δ ppm, T = 298 K): 165.00 (C-11); 162.67 (dq, C-16, *J* (F^{16}-C^{16}) = 264.5 Hz, *J* (3F-C^{16}) = 1.9 Hz); 161.43 (C-12); 135.81 (dq, C-18, *J* (F^{16}-C^{18}) = 9.8 Hz, *J* (3F-C^{18}) = 0.9 Hz); 134.35 (Cq); 133.46 (Cq); 133.13 (Cq); 130.92 (C-5 or C-6); 130.09 (C-5 or C-6); 129.90 (CH); 129.71 (CH); 129.68 (Cq); 129.55 (CH); 129.27 (qd, C-14, *J* (3F-C^{14}) = 4.8 Hz, *J* (F^{16}-C^{14}) = 2.6 Hz); 129.12 (CH); 129.06 (CH); 128.25 (C-1); 128.22 (C-10); 127.62 (CH); 125.26 (d, C-13, *J* (F^{16}-C^{13}) = 3.6 Hz); 121.94 (qd, CF_3, *J* (3F-C) = 273.1 Hz, ^3J (F^{16}-CF_3) = 1.0 Hz); 118.89 (qd, C-15, *J* (3F-C^{15}) = 33.8 Hz, *J* (F^{16}-C^{15}) = 13.6 Hz); 117.49 (d, C-17, *J* (F^{16}-C^{17}) = 21.4 Hz).

FT-IR (solid in ATR, ν cm^{-1}): 3084w; 3027w; 1750vs (υC=O); 1621w (υC=N-); 1602m; 1499m; 1425m; 1324s; 1272m; 1247m (υC-O); 1228s; 1163m; 1127vs; 1075s (υC-F); 1054s; 979m (υN-O); 959w; 921w; 893m; 872m; 847w; 797m; 769m; 751m; 729w; 717w; 699m.

Compound V: **O-(5-Fluoro-2-trifluoromethyl-benzoyl)-5-oximino-5H-dibenzo[a,d]-cycloheptene:** m.p. 127 - 128ºC; yield 80.5%

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T = 298 K): 7.83 (m, 1H, H-1); 7.72 (dd, 1H, H-15, *J* (F^{17}-H^{15}) = 5.2 Hz, *J* (H^{16}-H^{15}) = 8.8 Hz); 7.56÷7.36 (m, 7H, H-arom); 7.32÷7.22 (m, 2H, H-16, H-18); 7.01 (d, 1H, H-5 or H-6, syst. AB, 12.4); 6.97 (d, 1H, H-5 or H-6, syst. AB, 12.4).

^{13}C-NMR ($CDCl_3$, δ ppm, T = 298 K): 165.65 (C-11); 163.74 (d, C-15, *J* (F^{15}-C^{15}) = 255.2 Hz); 162.68 (d, C-12, *J* (F^{17}-C^{12}) = 2.3 Hz); 134.32 (Cq); 133.24 (Cq); 133.02 (Cq); 132.06 (dq, C-13, *J* (F^{15}-C^{13}) = 8.3 Hz, *J* (3F- C^{13})=2.1 Hz); 130.70 (C-5 or C-6); 130.14 (C-5 or C-6); 129.85 (CH); 129.60 (Cq); 129.53 (CH); 129.40 (dq, C-17, *J* (F^{15}-C^{17}) =8.9 Hz, *J* (3F-C^{17}) =5.4 Hz); 129.20 (CH); 129.03 (CH); 129.00 (CH); 128.12 (C-1); 128.11 (C-10); 127.81 (CH); 125.20 (qd, C-14, *J* (3F-C^{18}) = 33.2 Hz, *J* (F^{15}-C^{18}) = 3.7 Hz); 122.76 (q, CF_3, *J* (3F-C) = 273.1 Hz); 118.36 (d, C-16, *J* (F^{15}-C^{16}) = 21.7 Hz); 117.78 (d, C-18, *J* (F^{15}-C^{14}) = 24.6 Hz).

FT-IR (solid in ATR, ν cm^{-1}): 3073w; 1767vs (υC=O); 1628 m (υC=N-); 1591m; 1332w; 1303s; 1279m; 1254s (υC-O); 1187m; 1149vs; 1122m; 1072m; 1030s (υC-F); 985m (υN-O); 930m; 897w; 884w; 870w; 837m; 806m; 774s; 727m; 691w.

Compound VI: **O-(4-Trifluoromethoxy-benzoyl)-5-oximino-5H-dibenzo[a,d]-cycloheptene:** m.p. 110 - 111ºC; yield 83%

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T = 298 K): 7.91 (d, 2H, H-14, H-18, 8.8); 7.83 (m, 1H, H-1); 7.66 (m, 1H, H-10); 7.57÷7.41 (m, 6H, H-arom); 7.22 (bd, 2H, H-15, H-17, 8.8); 7.01 (d, 1H, H-5 or H-6, syst. AB, 12.1); 6.97 (d, 1H, H-5 or H-6, syst. AB, 12.1).

^{13}C-NMR ($CDCl_3$, δ ppm, T = 298 K): 164.55 (C-11); 162.51 (C-12); 152.79 (q, C-16, ^4J (3F-C^{16}) = 1.7 Hz); 134.34 (Cq); 133.49 (Cq); 133.35 (Cq); 129.96 (Cq); 127.04 (Cq); 120.24 (q, CF_3, *J* (3F-C) = 258.4 Hz); 131.72 (C-14, C-18); 130.91 (C-5 or C--6); 130.10 (C-5 or C--6); 129.79 (CH); 129.59 (CH); 129.43(CH); 129.04 (CH); 129.03 (CH); 128.36 (C-1); 128.28 (C-10); 127.62 (CH); 120.34 (q, C-15, C-17, ^4J (3F-$C^{15,17}$) = 1.2 Hz).

FT-IR (solid in ATR, ν cm^{-1}): 3055w; 3022w; 1752vs (υC=O); 1610m (υC=N-); 1591m; 1506w; 1333w; 1306w; 1222vs (υC-O); 1188vs; 1160vs; 1079s (υC-F); 1016w; 980m (υN-O); 926w; 902w;

887w; 873w; 849m; 797m; 783m; 770m; 754m; 703w; 688w; 662w.

Compound VII: **O-(2,6-Dichloro-benzoyl)-5-oximino-5H-dibenzo[a,d]-cycloheptene:** m.p. 153 - 154ºC; yield 80.5%

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T = 298 K): 7.82 (m, 1H, H-1); 7.63 (m, 1H, H-10); 7.51÷7.36(m, 6H, H-arom); 7.28 (m, 2H, H-15, H-17, syst. A_2B); 7.23 (m, 1H, H-16, syst. A_2B); 6.99 (d, 1H, H-5 or H-6, syst. AB, 12.1); 6.94 (d, 1H, H-5 or H-6, syst. AB, 12.1).

^{13}C-NMR ($CDCl_3$, δ ppm, T = 298 K): 165.49 (C-11); 162.72 (C-12); 134.37 (Cq); 133.26 (Cq); 133.08 (Cq); 132.36(C-13); 132.11 (C-14, C-18); 129.58 (Cq); 131.21 (C-16); 130.58 (C-5 or C-6); 130.26 (C-5 or C-6); 129.79 (CH); 129.49 (CH); 129.12 (CH); 129.00 (CH); 128.95 (CH); 128.72 (CH); 128.24 (C-10); 127.88 (C-1); 127.84 (C-15, C-17).

FT-IR (solid in ATR, ν cm^{-1}): 3075w; 3027w; 1757vs (υC=O); 1612w (υC=N-); 1580m; 1562m; 1433s; 1329w; 1328vs; 1198m; 1222s (υC-O); 1077m; 1041m; 970s (υN-O); 897w; 877w; 839m; 799s; 774s; 737m; 722m; 687w.

Compound VIII: **O-(4-Ethoxy-benzoyl)-5-oximino-5H-dibenzo[a,d]-cycloheptene:** m.p. 156 - 157ºC; yield 78.5%

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T = 298 K): 7.82 (m, 1H, H-1); 7.81 (d, 2H, H-14, H-18, 8.1); 7.68 (m, 1H, H-10); 7.54÷7.39 (m, 6H, H-arom); 6.99 (d, 1H, H-5 or H-6, syst. AB, 12.3); 6.95 (d, 1H, H-5 or H-6, syst. AB, 12.3); 6.84 (d, 2H, H-15, H-17, 8.1); 4.06 (q, 2H, CH_2, 7.0); 1.41 (t, 3H, CH_3, 7.0).

^{13}C-NMR ($CDCl_3$, δ ppm, T = 298 K): 163.62 (C-11); 163.47 (C-12); 163.02 (C-16); 134.36 (Cq); 133.72 (Cq); 133.46 (Cq); 131.80 (C-14, C-18); 130.50 (C-5 or C-6); 130.17 (C-5 or C-6); 129.59 (CH); 129.35 (CH); 129.31 (CH); 128.96 (CH); 128.93 (CH); 128.61 (C-10); 128.39 (C-1); 127.54 (CH); 114.18 (C-15, C-17); 63.70 (CH_2); 14.65(CH_3).

FT-IR (solid in ATR, ν cm^{-1}): 3071w; 3052w; 3021w; 2987w; 2939w; 2887w; 1745vs (υC=O); 1618s (υC=N-); 1506m; 1474w; 1390w; 1331w; 1311w; 1247vs (υC-O); 1162s; 1117m; 1065s; 1034s; 976s (υN-O); 922w; 903w; 866m; 847m; 835m; 798m; 757s; 714w; 686m; 642w.

Compound IX: **O-(2,5-Diethoxy-benzoyl)-5-oximino-5H-dibenzo[a,d]-cycloheptene:** m.p. 118 - 119ºC; yield 75%

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T = 298 K): 7.83 (m, 1H, H-1); 7.66 (m, 1H, H-10); 7.51÷7.38 (m, 6H, H-arom); 7.06 (d, 1H, H-18, 3.0); 6.98 (d, 1H, H-5 or H-6, syst. AB, 12.1); 6.96 (dd, 1H, H-16, 3.0, 9.1); 6.94 (d, 1H, H-5 or H-6, syst. AB, 12.1); 6.86 (d, 1H, H-15, 9.1); 4.05÷3.81 (m, 4H, CH_2); 1.35 (t, 3H, CH_3, 7.0); 1.29 (t, 3H, CH_3, 7.0).

^{13}C-NMR ($CDCl_3$, δ ppm, T = 298 K): 163.74 (C-11); 163.29 (C-12); 153.12 (C-14); 152.33 (C-17); 134.38 (Cq); 133.81 (Cq); 133.46 (Cq); 130.54 (Cq); 119.71 (C-13); 130.86 (C-5 or C-6); 130.17 (C-5 or C-6); 129.55 (CH); 129.15 (CH); 129.10 (CH); 128.94 (CH); 128.90 (C-10); 128.42 (C-1); 127.57 (CH); 120.97 (C-16); 115.92 (C-15); 115.85 (C-18); 65.75 (CH_2); 64.09 (CH_2); 14.81 (CH_3); 14.78 (CH_3).

FT-IR (solid in ATR, ν cm^{-1}): 3053w; 2979w; 2937w; 2897w; 1760vs (υC=O); 1602w (υC=N-); 1585w; 1500m; 1472m; 1395m; 1334w; 1314w; 1284w; 1258w; 1233m (υC-O); 1191s; 1107m; 1045m; 1029s; 988m (υN-O); 947m; 922m; 892m; 806m; 772m; 714w.

Compound X: **O-(3,5-Diethoxy-benzoyl)-5-oximino-5H-dibenzo[a,d]-cycloheptene:** m.p. 150 - 151ºC; yield 79.5%

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T = 298 K): 7.83 (m, 1H, H-1); 7.69 (m, 1H, H-10); 7.53÷7.40 (m, 6H, H-arom); 7.00 (d, 1H, H-5 or H-6, syst. AB, 12.1); 6.98 (d, 2H, H-14, H-18, 2.3); 6.95 (d, 1H, H-5 or H-6, syst. AB, 12.1); 6.61 (t, 1H, H-16, 2.3); 3.94 (m, 4H, CH_2); 1.38 (t, 3H, CH_3, 7.0).

^{13}C-NMR ($CDCl_3$, δ ppm, T = 298 K): 164.12 (C-11); 163.36 (C-12); 159.91 (C-15, C-17); 134.37 (Cq); 133.56 (Cq); 133.54 (Cq); 130.94 (C-5 or C-6); 130.31 (Cq); 130.29 (Cq); 130.12 (C-6 or C-5); 129.69 (CH); 129.38 (CH); 129.21 (CH); 129.01 (CH); 128.99 (CH); 128.58 (C-10); 128.31 (C-1); 127.48 (CH); 105.57 (C-14, C-18); 105.54 (C-16); 63.76 (CH_2); 14.71 (CH_3).

FT-IR (solid in ATR, ν cm^{-1}): 3054w; 2979w; 2938w; 2898w; 1759vs (υC=O); 1603w (υC=N-); 1584w; 1500m; 1472m; 1395m; 1335w; 1315w; 1284w; 1258w; 1233m (υC-O); 1191s; 1107m; 1047m; 1029s; 988m (υN-O); 948m; 892w; 874m; 806m; 772m; 689w.

The acute toxicity research showed no lethal effect of the nine compounds at the dose of 1500 mg/kg bw. We concluded that *per os* lethal dose is probably much higher and for bioethical reasons, we did not conduct our research at higher doses.

The body weight was registered every two days for fourteen days. The treated mice had the same evolution of their body weight as the control group. The initial and final median values are presented in Table II and the body weight variation during the experiment is showed in Figure 2.

Table II

Mice body weight (g) at the beginning and at 14 days after the compounds acute administration

Group / Body weight (g)	Control	II	III	IV	V	VI	VII	VIII	IX	X
Initial (i)	25.7	25.4	26.0	25.4	25.7	25.6	26.1	25.8	25.5	25.7
Final (f)	27.8	27.5	28.3	27.7	28.0	28.0	27.9	27.8	27.5	27.6
Δ (f-i)	+2.1	+2.1	+2.3	+2.3	+2.3	+2.4	+1.8	+2.0	+2.0	+1.9

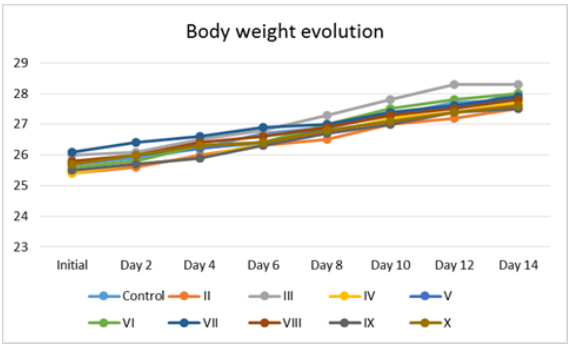


Figure 2.
Evolution of body weight after the compounds acute administration

We observed no difference between treated mice and control group regarding all the other monitored parameters. Regarding the motor behaviour, the treated mice were a little sedated just after the administration, but it was probably an effect due to the volume of liquid ingested and to the administration technique. All mice responded to the external auditory and tactile stimuli, the differences between treated and control mice being insignificant. No animal developed palpebral ptosis.

Conclusions

We have synthesized a series of nine new acyl-oximines with dibenzocycloheptatrienic structure. These compounds were obtained by an acylation reaction between 5-oximino-5H-dibenzo[a,d]cyclo-heptatriene and different carboxylic acid chlorides.
The structures of these compounds have been confirmed by elemental analysis and spectrometric methods (IR, ^{1}H-NMR and ^{13}C-NMR).
The preliminary pharmacotoxicological tests showed that new acyl-oximines have a very low acute toxicity, the lethal *per os* doses being higher than 1500 mg/kg bw. Further pharmacological tests will be performed.

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