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Research Article

Zn(II) Based Potential Drug Containing Sertraline as a Strong Antidepressant Agent

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Abstract

A novel compound for depression treatment and other psychiatric disorders has been obtained being capable of displaying the combined benefits of sertraline and an essential element such as zinc in order to get better antidepressant and negative side effects. Our working group has synthesized a salt formulation $(SerH_2)_2^+[ZnCl_4]^{2-}$ ($C_{34}H_{36}N_2Cl_8Zn$, sertralonium tetrachlorozincate(II)). The crystal structure was determined by X-ray diffraction methods. It crystallizes in the monoclinic $P2_1$ space group with a=7.3869(2) Å, b=13.2888(4) Å, c=19.3541(6) Å, β=96.596(3)° Å, β=91.792(4)°, and Z=2 molecules per unit cell. Their antidepressant activity in the forced swimming test (FST) proved to be stronger than the one shown by the commercial drug sertraline hydrochloride *per se*. Furthermore, this compound suppressed the anorexigenic effect caused by the antidepressant and showed an improvement in the assimilation time during *in vitro* fluorescence studies with bovine serum albumin. The results of this work have led to a patent application which was filed (N° 20150103320) in Argentine country.

INTRODUCTION

Depression is a severe health problem in pharmacotherapy, characterized by several symptoms such as the existence of sad, empty, or irritable moods, together with somatic and cognitive changes that considerably affect the individual's capacity [1]. One of the most recent findings in this area of research is related to the involvement of Zn(II) in the pathophysiology of depression and anxiety [2,3] In fact, besides the well-recognized participation of this essential element in biological systems, this biometal has been studied in relation with its antidepressant activity. In depressed patients, lower-than-normal zinc serum content as compared with healthy individuals has been found. This tendency has also been determined in animals with increasing immobility time during forced swimming test (FST), tail suspension test (TST) and others models. Thus, zinc deficiency contributes to the development of depressive-like behavior, while it is observed that restoration of the zinc levels reverses depression symptoms in animal models and clinical studies. [2,4] Under hypozincemia condition, rats showed anorexia and anxiety behaviors and reduction of sucrose consumption, hence indicating an apparent anhedonia (one of the common symptoms seen in human depression) [5,6]. It has also been determined that the combined administration of zinc and antidepressant drugs [7-9] usually using ineffective doses of both compounds, produced a substantial reduction in the immobility time. Antidepressant drugs are the basis for the treatment of depression. In the last decade, serotonin selective reuptake inhibitors (SSRI) replaced the tricyclic antidepressants (TCAs, e.g. imipramine or desipramine) as the first-line of medications [10]. In general, the SSRIs have a mild side-effect profile and better tolerability than the TCAs. Even though they selectively block the reuptake of serotonin into presynaptic neuron, they have no much more effect on the reuptake of noradrenalin, dopamine or other transmitters. For that reason, the adverse events are not usually associated with the blockade of these receptors and the most common side-effects are nausea or gastrointestinal activation, headache, nervousness, anxiety, insomnia, drowsiness, fatigue and anorexia [11,12]. To reduce the possibility of adverse events, the likelihood of drug interactions should be taken into account [13]. One of the most commonly prescribed antidepressant agents is sertraline Figure (S1) due to its effectiveness in treating major depression, anxiety disorders and in a great number of patients with various psychiatric or medical comorbidities [14]. Also, it is quite likely that many patients will take more than one drug (e.g. antibiotic, nasal decongestant, antihistamines. analgesic) with their SSRI at some point during their treatment. As a consequence, it should be taken into account that adverse effects may occur due to the

well known interactions between drugs. Aspects of drug-drug interactions provide clinically relevant differences between the different antidepressants. Administration of sertraline with drugs metabolized by cytochrome P-450 enzymes (CYP2C9, CYP2D6, CYPIA2, and CYP3A4) must to be cautious because of their potency to inhibit them in contrast to other antidepressants such as escitalopram [12,13]. Sertraline overdose can be lethal and there exists a risk of increment of adverse effects with its increasing plasma levels [15] and it was proved that sertraline reduces food intake and body weight in lean rats and genetically obese mice [16] and also in clinical trials [17]. that is why new structures derived from sertraline and new formulations are required [18] although there are numerous patent documents [19-22] searching the generation of new (almost equally active) products with improved biochemical properties. In this context, our group is working on a new chemical strategy to develop novel compounds for the treatment of depression and other psychiatric disorders [23, 24], through the design of a compound sharing the combined benefits of sertraline and an essential element such as zinc in order to get a better antidepressant compound with less negative side-effects. We succeeded in synthesizing sertralonium tetrachlorozincate (II) salt (for short, $(SerH_2)_2[ZnCl_4]$), of chemical formula $C_{34}H_{36}N_2Cl_8Zn$, which has been characterized by structural X-ray diffraction methods, vibrational spectroscopy, and thermal analysis, among other techniques. A better antidepressant activity has been found and the results of this work had led to a patent application which was filed (Nº 20150103320) in Argentine country. It is concluded that there are not examples in the literature reporting a similar structure of an ionic compound containing a coordination anion complex of Zn(II) and a sertralonium cation. This novel compound reveals enhanced antidepressant activity in a FST model and suppresses the anorexigenic side-effect of the parent drug, a feature that possibly constitutes an additional second clinical advantage for its formulation as a commercial drug.

EXPERIMENTAL SECTION

Materials and methods

$ZnCl_2$ was obtained from Biopack (Bs As, Argentina) and sertraline hydrochloride ($C_{17}H_{17}Cl_2N$, $SerH_2^+Cl^-$) from Sigma Chemical Company (St. Louis, MO) and were used as supplied. All the solvents used were from analytical grade. Ammonium tetrachlorozincate (II) ($(NH_4)_2[ZnCl_4]$) was prepared according to the technique reported by Brauer [25] in order to be used as the starting material in method 2. Thermo-gravimetric and Differential Scanning Calorimetry studies were performed using a Shimadzu thermo-analytical system (models TG-50 and DTA-50, respectively), in a flowing N_2 atmosphere (50 ml min^{-1}). Experiments were carried out in platinum crucibles at a heating rate of 10 $^oC\ min^{-1}$. The sample mass ranged between 5 and 15 mg. The data were analyzed using TASYS program. FTIR spectra of powdered samples were measured with a Bruker IFS 66 FTIR-spectrophotometer from 4000 to 400 cm^{-1} as pressed KBr pellets. Spectra were recorded with a spectral resolution of 4 cm^{-1} and 64 scans were averaged for each spectrum. The data were analyzed using OPUS program (Bruker Optics, USA). Raman spectra were collected on a Raman Horiba Jobin Yvon T64000 (confocal microscopy Olympus BX41) spectrophotometer with a laser power of 400 mW and a spectral resolution of 4 cm^{-1}. Each spectrum was obtained as an average of 10 scans collected in the 4000-400 cm^{-1} range. Spectra plotting, processing, normalizations, manipulations, and evaluation were carried out with the OPUS software (Bruker Optics, Germany).

Preparation

Method 1: Under continuous stirring, 1 mmol of sertraline hydrochloride has been dissolved in a mixture of 50 mL of ethyl acetate and 25 mL of 96% ethanol and the solution was heated to boiling until it was entirely dissolved. A solution containing 0.5 mmol of $ZnCl_2$ was prepared in 2 mL of 37% HCl and it was slowly drop-wise added to the first solution of sertraline hydrochloride. After cooling to room temperature it was placed in the refrigerator for a week to favor the formation of single crystals suitable for structural X-ray diffraction work. The crystal crop was filtered out from the solution and washed with 96% ethanol.

Method 2: Sertraline hydrochloride (1mmol) was dissolved under continuous stirring in 50 mL of 90% ethanol. A solution prepared dissolving 0.5 mmol of $(NH_4)_2[ZnCl_4]$ in a minimum quantity of distilled water was slowly added to the sertraline solution and the resulting product was acidified to pH = 4 using 0.1M HCl. To ensure the total removal of NH_3 and to reduce the volume to one half of the original one, the solution was heated to its boiling point for 5 min. The remaining solution was left to cool down to room temperature and then it was placed in a refrigerator for at least three weeks. The obtained crystals were filtered out from the solution and washed with 96% ethanol. In both preparations, the yield of the new compound varied from 70 to 80%. The compound has a melting point of 235 ºC, presents solid state stability in air, and is soluble in dimethylsulfoxide and in a 1:1 ethanol:water solution (0.05g/500µL). Its molecular structure was determined by X-ray diffraction analysis as $(SerH_2)_2[ZnCl_4]$, chemical formula $C_{34}H_{36}N_2Cl_8Zn$. Along with others physicochemical characterizations, It is well-know the relevance in the study of potential pharmaceuticals of thermo-gravimetry (TGA) and differential scanning calorimetry (DSC) techniques, mainly to determine melting point, heat of transition, dessolvation, and decomposition process [26]. Concerning the thermal decomposition of $(SerH_2)_2[ZnCl_4]$ Figure (S2), TGA, two stages are observed: (i) the first occurs in the temperature range from 18 to 385 ºC (onset point: 244.8 ºC; endset point: 270.6 ºC) in which the greatest observed mass loss corresponds to 84.34% of the initial mass, (ii) the second stage occurs in the 385-600 ºC range (onset point: 423 ºC, endset point: 475 ºC), accounting for a mass loss of 13.84% and a residue of 0.119 mg. This residue could not be identified possibly because it is not the final residue, which would probably be expected at higher temperatures. The differential scanning calorimetry (Figure S1, DSC) shows a single endothermic peak associated with the melting point of $(SerH_2)_2[ZnCl_4]$ (235 ºC, ΔH_f = -44.80 J/g). (onset point: 244.8 ºC, endset point: 270.6 ºC). At higher temperatures, two endothermic peaks located at 280 ºC and 306 ºC have been observed due to different mass loss events. The final stage displays an endothermic peak located at 533 ºC (ΔH = -74.55 J/g).

Single crystal X-ray diffraction data: The measurements were performed on an Oxford Xcalibur Gemini, Eos CCD diffractometer with graphite-monochromated MoKα (λ=0.71073

Å) radiation. X-ray diffraction intensities were collected (ω scans with ϑ and κ-offsets), integrated and scaled with CrysAlisPro [27] suite of programs. The unit cell parameters were obtained by least-squares refinement (based on the angular settings for all collected reflections with intensities larger than seven times the standard deviation of measurement errors) using CrysAlisPro. Data were corrected empirically for absorption employing the multi-scan method implemented in CrysAlisPro. The structure was solved by direct methods with SHELXS of the SHELX suit of programs [28] and the corresponding molecular models developed by alternated cycles of Fourier methods and full-matrix least-squares refinement with SHELXL of the same package. At this stage, the dichlorophenyl group ($PhCl_2$) of one sertraline ($SerH_2^+$) molecule showed rotational disorder around the C-$PhCl_2$ bond which could be modeled in terms of two conformations rotated in 180º from each other around the bond and refined with anisotropic displacement parameters such as their occupancies added up to one. The hydrogen atoms were positioned stereo-chemically and refined with the riding model. The methyl H-positions were optimized by treating them as a rigid group which was allowed to rotate during the refinement around the corresponding N-C bonds such as to maximize the residual electron density at the calculated positions. Crystal data, data collection procedure, structure determination methods and refinement results are summarized in Table (1). Crystallographic structural data have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the reference number CCDC 1436826

Powder XRD: CuKα radiation (λ=1.5406 Å) was employed to obtain PXRD data of $(SerH_2)_2[ZnCl_4]$ at ambient conditions in a PANalytical X´Pert PRO diffractometer operated at 40 kV and 40 mA, provided with Bragg-Brentano θ-θ geometry, scintillation counter and an exit beam graphite monochromator. The XRD data were collected in the $2° \leq 2\theta \leq 60°$ range, with 0.02° step width and 1s counting time per step.

Antidepressant activity

Animals: Experiments were carried out on male Wistar rats weighing 200-310 g. The animals were maintained on a 12 hour light (08:00–20:00 h)-12 hour dark cycle, with free access to food and water, except during testing. Abundant evidence indicates their free access to food and water except during testing, to possible interference with experimental data. [29]**.** Rats were housed in groups of four, in individual polyethylene cages (55 x 38 x 30 cm). Their weights were recorded at the beginning and end of each experiment. Animals were used only in one experiment. All studies described were conducted in accordance with the Guide for Care and Use of Laboratory Animals provided by the National Institutes of Health, USA and AVMA Guidelines for the Euthanasia of Animals, 2013 Ed. The experiments were performed after approval of the protocol by the Ethics Committee for the care and use of Laboratory Animals of the Universidad Nacional de La Rioja, Argentina.

Drugs and treatment: $ZnCl_2$ was administered in a dose of 5.55 mg per Kg of the animal body-mass which corresponds to an non-effective dose of Zn (II) comparable to the non-effective Zn(II) dose present in a dose of 13.00 mg/Kg of the complex. It has previously been determined that higher doses of $ZnCl_2$ produced most robust effects in the force swimming test (FST) under similar experimental conditions. [30] For $(SerH_2)_2[ZnCl_4]$ the experimental dose of 13.00 mg/Kg has been selected because it resulted equivalent to the therapeutic dose of the antidepressant sertraline hydrochloride (10.00 mg/Kg) [31]. A dose of the complex of 26.00 mg/Kg has also been selected to evaluate its dose-response activity. All of the control rats received injections of saline solution (0.9% NaCl). Rats were treated with the saline solution (rats control) or $ZnCl_2$, sertraline hydrochloride and $(SerH_2)_2[ZnCl_4]$ once a day and all solutions were administered by oral route in a constant volume of 10 ml/Kg body weight. The rats were randomly distributed into five groups which were subjected to the following treatments: Group 1: saline (control group), Group 2: $ZnCl_2$ (5.55 mg/Kg), Group 3. Sertraline hydrochloride (10.0 mg/Kg), Group 4: $(SerH_2)_2[ZnCl_4]$ (13.00 mg/Kg) and Group 5: $(SerH_2)_2[ZnCl_4]$ (26.00 mg/Kg).

Forced swimming test (FST): The forced swimming test (FST) is a well-accepted procedure to test the antidepressant-like action of drugs [32], a behavioral test that predicts the efficacy of antidepressant treatments in humans [33]. Stress is a well-known risk factor in the development of depression. The FST employs forced swimming stimuli as stressor to generate a behavior characterized by increased immobility time. Swimming sessions were conducted by placing rats in individual Plexiglas cylinders 46 cm tall x 20 cm in diameter), filled with water (23-25 ºC) up to 30 cm from bottom. All swimming sessions were carried out between 12:00 and 18:00 h. In the protocol, two sessions were conducted: an initial 15 min pre-test on day 1 followed by a 5 min test on day 15. Drug treatments began on day 1 after the pre-test session and it was administered from day 1 to 14. This chronic treatment was selected because after 2–3 week is onset of clinical effectiveness, observed for all antidepressants, and that may reflect both pre- and post synaptic adaptative changes, such as a down-regulation of receptors in the NA and the 5-HT systems [34] At the end of both swimming sessions, rats were removed from the cylinders, dried with towels, placed in heated cages for 15 min, allowed to rest and recover, and then returned to their home cages. The cylinders were emptied and cleaned between rat tests. Each animal was assigned randomly to a treatment, and was only employed for one pre-test/test session. In our forced swimming test design, a pre-test is done first, chronic drug treatment is then administered, and the final test is presented [35-38]. Our protocol has at least two important advantages. First, administration of agents after the pre-test stressor allows the evaluation of drug action after the behavioral despair is induced in the animals [39]. Second, giving the study drug after the swimming pre-test session avoids taking as a performance improvement some anxiolytic effects described for antidepressants [40,41] This might be due to the fact that anxiolytics may ameliorate the stressor impact on the animal behavior [42-44]

Behavioral scoring: For behavioral sampling, rats were rated at 5 s intervals throughout the duration of the forced swimming session. At each 5 s interval, the predominant behavior was assigned to one of three categories: (1) immobility: floating in the water without struggling, and making only those movements necessary to keep the head above the water; (2) swimming:

making active swimming motions, more than necessary to merely keep the head above water (i.e., moving around in the cylinder); and (3) climbing: making active movements with forepaws in and out of the water, usually directed against the walls. Scores for each behavior were expressed as total behavioral counts per 5-min session. [34]

Open field test: Independent groups of animals were submitted to the open field test to investigate if the experimental treatments induced any significant motor effect, which could interfere in the FST results. Until day 14, these studies were conducted exactly as the forced swimming test studies: all rats underwent the first day of the forced swimming test but instead of re-testing in the forced swimming test on day 15, animals were subjected to an open field session. All animals were placed gently in the centre of the open field arena, afforded to explore freely, and its locomotion was measured by the number of squares entered with all four paws (counts), during a period of five minutes. The apparatus for the open field test consisted of a black, square open field (60 cm by 60 cm) with the floor divided in squares (15 × 15 cm) by means of white lines. Testing was performed between 1400 and 1700 h, illuminated with a 75 W electric bulb, hung 75 cm above it, in a quiet room. During all the experiments the laboratory room was dark. After each animal was removed, the open field was carefully cleaned with a damp cloth. The behavior was scored by an observer who was unaware of the experimental procedures previously performed on the animals and the results were expressed as mean ± S.E.M.

Albumin binding experiments: Bovine serum albumin (BSA) was dissolved in 0.1M Tris-HCl buffer (pH 7.4) to attain a final concentration of 6 μM. Sertraline hydrochloride and sertralonium tetrachlorozincate (II) solutions were added drop-wise to the 6 μM BSA solution to ensure the formation of a homogeneous solution and to obtain the desired concentration of 0-100 μM. Adequate solubility was reached under these experimental conditions then, the compounds did not show any fluorescence intensity that could interfere with the measurements. For each sample and concentration, three independent replicates were performed at 37 ºC. These solutions were used for the fluorescence measurements, that were carried out on a Perkin-Elmer LS-50B luminescence spectrometer (Beaconsfield, England) equipped with a pulsed xenon lamp (half peak height <10l s, 60 Hz), an R928 photomultiplier tube and a computer working with FL Winlab software. Both excitation and emission slits were 5 nm wide throughout this study. BSA 6μM was titrated by successive additions of Sertraline hydrochloride and sertralonium tetrachlorozincate (II) solutions from 0 to 500 μM and the fluorescence intensity was measured (excitation at 280 nm and emission at 348 nm) at 37 ºC. All the fluorescence quenching data were analyzed according to previous studies performed in the laboratory applying a traditional mathematical procedure [45] to obtain Stern-Volmer (K_{sv}) and molecular (K_q) quenching constants and the apparent binding constant (K_b) together with the binding site value (n). All the data corresponded to a curve fit involving at least three independent experiments. The correlation coefficient for the fitted curves (R^2) and the calculated standard deviation values (SD) for the Stern-Volmer constants (K_{sv}), the binding constants values (K_b) as well as the "n" binding sites are given for each determinations.

RESULTS AND DISCUSSION

One of the most important topics in active pharmaceutical ingredients is the understanding and control of its solid-state chemistry because they are usually delivered to the patient as a solid dosage form. So, the full characterization of the solid compound as a potential pharmaceutics is an important face of the drug development process including stability and solubility among others [46]. Other aspects comprise the exploration of their polymorphism, the crystallization of different hydrates and solvates forms, the synthesis of different salts to improve their solubility, co-crystals formations and all the possible combinations for a given compound. In this work, for the new salt $(SerH_2)[ZnCl_4]$, an effort was made to combine: solid stability, complete characterization, salt formation with the inclusion of Zn(II) ion as a new contributor to the antidepressant effect and the strategy that the hydrogen bonded structure of the salt preclude the presence of water or solvent molecules [46]. The characterization, discussed below, included all the fundamental techniques to fully characterize a potential pharmaceutical solid compound: single-crystal X-ray crystallography, FTIR and Raman spectroscopies, and the TGA and DTA measurements and solubility details (shown in the experimental section) [47]

Crystallographic structural results and discussion

The structure of the salt is displayed in Figure (1) in which an ORTEP [48] drawing of the solid state salt is presented while the corresponding intra-molecular bond distances and angles can be seen in Table (S1). The pair of pharmaceutical sertraline (Ser) molecules (#1 and #2), are found in the solid as the cationic moiety protonated at its amine group, namely (1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydro naphthalen-1-ammonium (for short, $SerH_2^+$). Because of extended molecular orbital π-delocalization the phenyl and dichlorophenyl groups of $SerH_2^+$ are planar [*rms* deviation of non-H atoms from the best least-square plane of 0.0047 and 0.0076 Å, respectively, for #1 and 0.0041 Å for the phenyl ring of #2]. The planes in turn subtend dihedral angles of 71.1(2)º for #1 and 85.8(1)º for #2. Intra-molecular bond distances and angles within the $SerH_2^+$ molecules in $(SerH_2)_2[ZnCl_4]$ solid agree with each other and with corresponding values reported for sertraline hydrochloride polymorphs [49, 50] and for other $SerH_2^+$ salts. [51,52]**.** The conformations of the two $SerH_2^+$ molecules differ significantly from each other and from the ones of the other related compounds. This can be traced to relatively unhinder rotational freedom of $SerH_2^+$ around the C-C σ-bond linking the dichlorophenyl and the naphthalen rings and also around the C (naph)-N σ-bond. As expected, the mayor differences in bond lengths of $SerH_2^+$ molecules as compared with neutral sertraline, [53] show up as a lengthening of C(naph)-N (of 0.046 Å for #1 and 0.042 Å for #2) and N-CH_3 (of 0.022 Å for #1 and 0.056 Å for #2) bond distances upon protonation at the amine groups. The crystalline salt is further stabilized by intermolecular H-bonds involving the $SerH_2^+$ amide $>NH_2^+$ as the donor group and as acceptors the chlorine atoms of neighboring $[ZnCl_4]^{2-}$ complex ions [N…Cl distances in the 3.179-3.488 Å range and N-H…Cl bond angles in the 130.2-160.5º interval]. The H-bonding structure is shown in Figure (1) and further detailed as supplementary information. Additional information was taken from the powder X-ray diffraction pattern

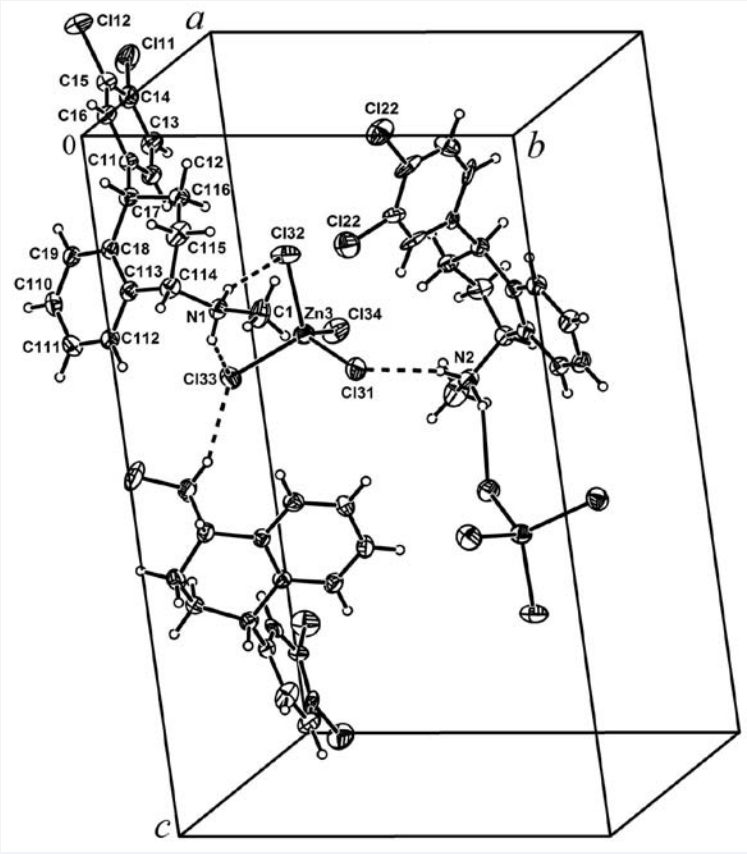

Figure 1 Drawing of $(SerH_2)_2[ZnCl_4]$ showing the labeling of the non-H atoms and their displacement ellipsoids at the 30% probability level. For clarity, only the ordered sertralineH and the tetrachlorozincate(II) ions have been fully labeled. The plot shows the conformation with the larger occupancy [52.2(4)%] of the other $SerH_2^+$ molecule having two-split disordered $PhCl_2$ group; a few representative atoms of this molecule have been labeled to indicate the numbering scheme. N-H...Cl bonds are indicated by dashed lines.

of $(SerH_2)_2[ZnCl_4]$ which was compared with the calculated [54] Figure (S3) derived from the solid state molecular structure determined by single crystal X-ray diffraction. It can be noticed that the material in its usual polycrystalline aggregation state has the same crystal structure as its single crystal counterpart without significant contribution of impurities, hence serving as a useful reference to quickly confirm the identity and purity of any powdered $(SerH_2)_2[ZnCl_4]$ pharmaceutical sample. It can be observed diagnostic powder diffraction peaks at unique 2Θ-values (in degrees) of 8.08, 11.36, 12.03, 13.29, 17.32, 17.96, 19.23, 20.52, 24.68, and 33.33, with an estimated error of ±0.03º. Since there are no structural differences between the crystal form and the polycrystalline state, one of the advantage of this compound is that it could eventually be used in the most convenient solid form.

Infrared and raman spectroscopies

Other typical and important characterization techniques are the vibrational spectroscopies, both FTIR and Raman (which are also complementary to each other) that gave structural additional information. Here, detailed bands assignments of the FTIR spectra of sertraline hydrochloride $(SerH_2^+Cl^-)$ and $(SerH_2)_2[ZnCl_4]$ were carried out (Table S2, Figure S4). It can be seen that the NH_2^+ groups displayed absorptions due to their symmetric and asymmetric N-H stretching vibrations. As expected, the NH_2^+ asymmetric stretching is observed at a higher frequency than the one of the symmetric counterpart. Usually, the reported frequency ranges for these modes are depicted in the 3420-3500 cm^{-1} range (asymmetric NH_2^+ stretching) and from 3340 to 3420 cm^{-1} (symmetric NH_2^+ stretching) [55]. It is also a well-known fact the presence of H-bonding, including intermolecular H-bonds involving as donors the H atoms of NH_2^+ group from the $SerH_2^+$ moiety and as acceptors the chlorine ions of neighboring $[ZnCl_4]^{2-}$, as shown by the X-ray diffraction structure (Figure 1 and Figure S3B). Hydrogen N^+H---X bonding affects the NH stretching vibration due to the withdrawal of the electron density from the N-H bond hence causing a red-shift in the stretching frequency. We have assigned these bands by comparison with those reported for the sertraline hydrochloride molecule [56]. Indeed four weak absorption bands have been observed in the corresponding spectral region. This band splitting could be related to the crystallographic different pairs of $SerH_2^+$ molecules (as described in the X-ray determinations) in the solid which give rise to four infrared active modes. [57]**.** The vibrational NH_2^+ scissoring deformation is observed at 1604 cm^{-1}. [55] and the NH_2^+ twisting (1327 cm^{-1}) and wagging (1450 cm^{-1}) vibration modes in conjunction with other modes of the $(SerH_2)_2[ZnCl_4]$ can be observed at lower frequencies. For the methyl group several vibration modes are expected. This group gives rise to two

Table 1: Crystal data and structure refinement results for $(SerH_2)_2[ZnCl_4]$.

Empirical formula	$C_{34}\ H_{35}\ Cl_8\ N_2\ Zn$
Formula weight	820.61
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 7.3869(2) Å
b = 13.2888(4) Å	
c = 19.3541(6) Å	
β = 96.596(3)°	
Volume	1887.3(1) Å3
Z, density (calculated)	2, 1.444 Mg/m3
Absorption coefficient	1.244 mm-1
F(000)	838
Crystal size	0.142 x 0.241 x 0.398 mm3
Crystal shape / color	Fragment / colorless
Θ-range for data collection	3.07 to 26.00°
Index ranges	-8 ≤ h ≤ 9, -16 ≤ k ≤ 15, -23 ≤ l ≤ 23
Reflections collected	10242
Independent reflections	6529 [R(int) = 0.0281]
Observed reflections	5677
Completeness to Θ = 26.00°	99.8 %
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	6529 / 3 / 445
Goodness-of-fit on $F2$	1.024
Final R indices [I>2σ(I)]	R1 = 0.0546, wR2 = 0.1386
R indices (all data)	R1 = 0.0644, wR2 = 0.1476
Absolute structure parameter	-0.003(16)
Largest diff. peak and hole	0.758 and -0.744 e.Å-3

[a] $R_1=\Sigma||F_o|-|F_c||/\Sigma|F_o|$, $wR_2=[\Sigma w(|F_o|^2-|F_c|^2)^2/\Sigma w(|F_o|^2)^2]^{1/2}$

different C-H modes, the symmetric and asymmetric stretches that typically fall in the 2800-3000 cm^{-1} range and again the asymmetric mode is expected to appear at a higher frequency than the symmetric one. It is then possible that the shoulders that appear at 3180 cm^{-1}, 3147 cm^{-1} and the band located at 3068 cm^{-1} are related to these C-H modes. The methyl symmetric deformation mode has been reported to appear at 1470 ± 5 cm^{-1} [58]. This correlates very well with the band observed at 1464 cm^{-1}, while the methyl asymmetric deformation mode shows up at 1491 cm^{-1}. The C–H in-plane bending frequencies and the C–H out-of-plane bending vibrations were located between 1306 cm^{-1} and 1051 cm^{-1} and in the 880-955 cm^{-1} range, respectively. The skeletal vibrations for the complex were observed around 1605 cm^{-1} and 1507 cm^{-1}. The assignment of the band observed at 499 cm^{-1} to the ν(C-Cl) stretching mode was made by comparison with the corresponding band for sertraline hydrochloride. The Raman dispersion spectrum (Table S2, Figure S5) has been compared with the FTIR counterpart. In particular, the Raman data allowed the assignment of the Zn-Cl vibration modes that appeared out of the FTIR measurement range [58,59].

Antidepressant activity

The mechanism of the therapeutic action of antidepressants is not fully understand and it is suggested that these drugs help correct the abnormality in neurotransmitter receptor function, such as glutamatergic, muscarinic, serotonergic and noradrenergic receptors, and also the antidepressants can induce neurogenesis in the adult brain [60]. In fact, the functional classification of antidepressants divides them in three classes: (1) monoamine oxidase inhibitors (MAOIs), (2) biogenic amine neurotransmitters (serotonin, norepinephrine, and dopamine) reuptake blockers, or (3) serotonin type 2A (5-HT2A) receptor blockers. According to this classification, sertraline hydrochloride belongs to the (2) group and behaves as a serotonin transporter blocker (serotonin selective reuptake inhibitors (SSRIs class)) [10]. On the other hand, the forced swimming test is a behavioral test used for evaluation of antidepressant drugs, antidepressant efficacy of new compounds [61]. In this work, and in accordance with a previous study [31], sertraline hydrochloride (10 mg/Kg) behaved as expected: a decrease of the immobility of the adult male rats and an increase in the animal swimming ability has been determined Figure (2A). It is well known that in the FST tests with subchronic treatment, the immobility displayed a dose-

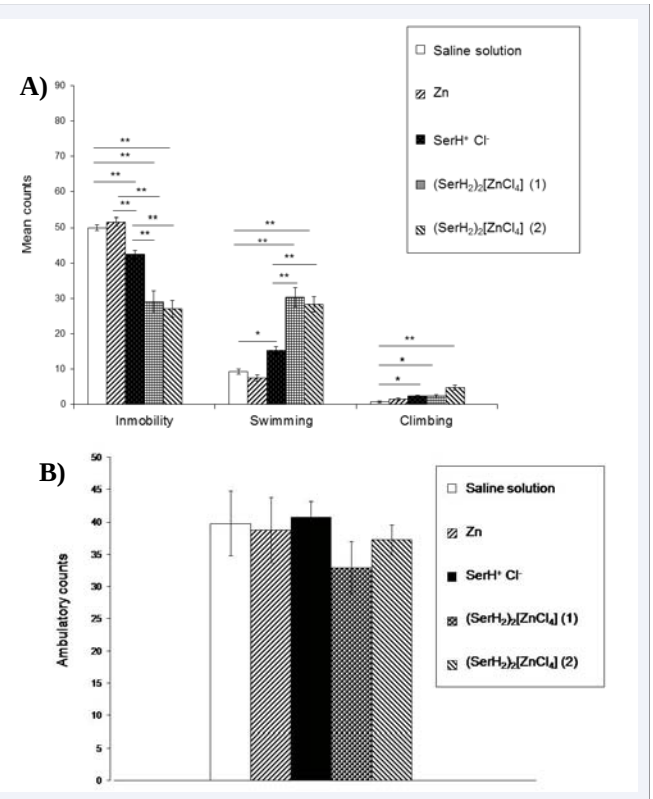

Figure 2 A. Effects of the standard antidepressant drug $SerH_2Cl$, Zn(II) and $(SerH_2)_2[ZnCl_4]$ treatments on the behaviors of the rats in the forced swimming test (FST).

B. Effects of the standard antidepressant drug $SerH_2Cl$, $ZnCl_2$ and $(SerH_2)_2[ZnCl_4]$ treatments on the behaviors in the Open Field test (OFT). Bars represent the mean number of counts over the 5-min period of the test (± S.E.M). *P < 0.05, ** P < 0.01, 5-10 rats per group. sal, saline; Zn ($ZnCl_2$, 5.55 mg/Kg), $SerH_2Cl$: 10.0mg/Kg; $(SerH_2)_2[ZnCl_4]$ (1): 13.0 mg/Kg); $(SerH_2)_2[ZnCl_4]$ (2): 26.0 mg/Kg. Data were analyzed with two-way ANOVA, followed by Tukey's test for multiple comparisons.

dependent behavior and it was statistically reduced in a dose range of 20-40 mg/Kg body-mass [62]. When a chronic treatment was administered [31], a dose of 10mg/Kg of sertraline decreased the immobility time in a 20% of magnitude comparable to the observed in this study (Table 2). As it was mentioned before, recent findings lend strong support to the antidepressant effect of Zn(II) [2] which action in the case of active dosis (e.g 30 mg/Kg) significantly shortened the immobility time in the FST test Table (2) [63,64]. Their mechanism of action is still being study. There are some experimental evidences suggesting attenuation of the glutamatergic system via inactivation of the glutamatergic NMDA (N-methyl-D-aspartate) receptor. [2] Taking into consideration that the new compound includes Zn (II) in the formulation, a dose of 5.55 mg/Kg of $ZnCl_2$ has also been tested to compare its effect with that observed for the Zn(II) complex in which the Zn(II) content always resulted lower than this value. As it was expected (Figure 2A) the treatment with this administered dose of the zinc cation had no significant effect (Table 2). Interestingly, when the treatment was carried out under administration of $(SerH_2)_2[ZnCl_4]$ in the doses of 13 and 26 mg/Kg, once a day for 14 days, the results showed Figure (2A) a considerably lower immobility time with a concomitant increase in swimming and climbing behavior observed from the FST results with respect to the control group and also in comparison with sertraline hydrochloride drug (Table 2). Additionally, the antidepressant action of the complex with an equivalent therapeutic dose of sertraline hydrochloride (10 mg/Kg) (13.00 mg/Kg of the $(SerH_2)_2[ZnCl_4]$ contained the equivalent quantity of the $SerH_2^+$ cation as in the antidepressant drug $SerH_2Cl$) Table (2) showed most robust effect in decreasing the immobility time in the FST test. The effect of the combined action of sertraline hydrochloride and the Zn (II) present in this new compound is a reduction of the immobility time to a half with respect to the effect shown by the antidepressant drug at a dose of 10.0 mg/Kg. Additionally, at a higher dose of 26.0 mg/Kg of the $(SerH_2)_2[ZnCl_4]$ complex, a reduction of a 46 % of the immobility time is produced (Table 2) showing a marked synergistic behavior. Considering that a non-effective Zn (II) dose is included in a 10.0 mg/Kg dose of this new compound the observed synergistic effect could be of relevance for new therapies. Therefore, it can be determined that the replacement of the chloride anion in sertraline hydrochloride drug by the tetrachlorozincate (II) anion, produces a better antidepressant effect. To perform a deeper analysis on the improvement of the antidepressant behavior of the new complex the effects on the Forced Swimming Test (FST) of other Zn (II) containing-salts are presented in Table (2). Even though different kind of animals were used in the experiments, it is possible to observe that the $(SerH_2)_2[ZnCl_4]$ complex produced one of the most important percentage of the decrease in the immobility time. This effect is higher in comparison with other Zn (II)-salts which also have ineffective Zn doses content (≤ 10mg Zn/Kg). Indeed, the complex contains the lowest proportions of Zn at both doses (13 and 26 mg/Kg). This effect could be compared with that produced by the $[Zn(S\text{-}Met)_2]$ complex and the $ZnSO_4$ salt. However, higher doses of the compounds were required to exert similar effects. The benefits of the potential use of the $(SerH_2)_2[ZnCl_4]$ complex are, therefore, the lower doses requirement, the lower Zn(II) content and the synergistic effect produced by the combined use of sertraline and Zn(II) cation. To ensure that the alterations in the duration of immobility in the FST are not the result of changes in motor activity, the effect of $(SerH_2)_2[ZnCl_4]$ on spontaneous locomotor activity was evaluated

Table 2: Effects of the $(SerH_2)_2$ [ZnCl4] complexes, $SerH_2Cl$ and $ZnCl_2$ in the Forced Swimming Test (FST) expressed in % of immobility time as a measure of the antidepressant effect.

Compounds	*Immobility time (s) (mean ± S.E.M)*	*% Decrease in relation with the control group*	*Zn Content (mg)*
Saline solution (control)	50.00 ± 0.89	0.0 %	
$ZnCl_2$ (5.55 mg/Kg)	51.63 ± 1.25	3.2 %	5.55 mg
$ZnCl_2$ ** [64] (30 mg/Kg)		~20%	14.38 mg
$SerH_2Cl$ (10.0 mg/Kg)	42.40 ± 1.21	15.2 %	
$SerH_2Cl$ [31] (10.0 mg/Kg)		~20%	
$(SerH_2)_2[ZnCl_4]$ (1) (13.0 mg/Kg)	29.00 ± 3.15	42.0 %	1.03 mg
$(SerH_2)_2[ZnCl_4]$ (2) (26.0 mg/Kg)	27.00 ± 2.39	46.0 %	2.07 mg
$[Zn(S\text{-}Met)_2]$ (51 mg/Kg) [23]		---------	10 mg
$[Zn(S\text{-}Met)_2]$ (153 mg/Kg) [23]		56.0%	30 mg
$Zn(hydroaspartate)_2$* (65 mg/Kg) [6]		~18%	12.98 mg
$Zn(hydroaspartate)_2$** (30 mg/Kg) [7]		~14%	5.95 mg
$ZnSO_4$** [63] (30 mg/Kg)		~50%	12.16 mg
*Wistar rats;**Swiss mice			

Figure (2B). Figure (2B) also shows the effects of Zn(II) (as the chloride salt) and $SerH_2Cl$ for the sake of comparisons. None of these treatments with antidepressant-like effects in the FST affected the activity levels when rats were tested in an open field chamber instead of the forced swimming cylinders during the re-test (means ± S.E.M.). In consequence these results confirm the specificity of the FST test supporting the fact that the immobility changes can be exclusively attributed to the effect produced by the new compound.

Body weight gain analysis during chronic treatments with$(SerH_2)_2[ZnCl_4]$: Multiple studies suggest that serotonergic neurons regulate food consumption in animals. [65,66] For that reason, sertraline hydrochloride and others SSIRs antidepressant drugs showed typical adverse effects (Gastrointestinal disturbances) including weight loss. This anorexigenic effect was also observed in clinical trials [66]. This adverse effect motivated us to control the body weight of the rats. As expected, body mass were significant lowered in animals treated with 10 mg/Kg of sertraline Figure (3) being these data consistent previous observations. On the contrary, the Zn(II) cation (in a subeffective antidepressant dose) increased body mass gain. Changes in body mass were evaluated with two doses of $(SerH_2)_2[ZnCl_4]$ (13.0 and 26.0 mg/Kg) (Figure 3). Different results were obtained. When the dose was 13.0 mg/Kg the treatment did not affect in extent mass gain compared with the control. At the higher tested dose of the complex, the body mass increased in relation to the control group, in contrast to the effect displayed by sertraline hydrochloride. Interestingly, at both doses the complex fully reversed the anorexic effect of sertraline hydrochloride which is a severe problem in depressed patients.

***In vitro* binding affinity to albumin by fluorescence and UV-vis spectroscopies:** It is well-known that serum albumin is able to bind to a diverse variety of metabolites, drugs, dyes and several others substances. A number of drugs and other bioactive small molecules bind reversibly to albumin and typical association constants (K_b) values from 10^4 to 10^6 M^{-1} indicate a carrier-like behavior [67]. Serum albumin often increases the apparent solubility of hydrophobic drugs in plasma and modulates their delivery to cell *in vivo* and *in vitro*. Thus, the investigation of compounds with respect to their binding to the albumin protein becomes a relevant topic to be studied from the pharmacological point of view. [68] Usually, the conformational changes in the albumin structure produced by its interaction with low molecular weight ligands can be analyzed by spectroscopic techniques. One of these methods is the quenching measurements that were employed in this work. The binding determinations of the metal complex were contrasted against sertraline hydrochloride, which pharmacokinetic behavior has been exhaustively studied. It is recognized that this antidepressant compound is able to bind at a 98% level to plasma protein and their maximum concentration is reached 6-8 hours after oral administration [69]. For this reason, the measurements were performed at 37 ºC, with an average time of 8 h following administration to ensure the formation of complexes with albumin and also after 2 hours for the comparative purposes. The fluorescence-quenching data were analyzed by the Stern-Volmer equation (1) [70].

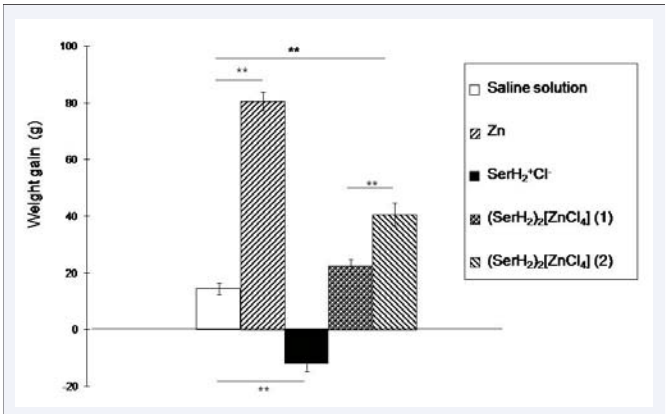

Figure 3 Effects of the standard antidepressant drug $SerH_2Cl$, Zn(II) and $(SerH_2)_2[ZnCl_4]$ treatments on weight gain of rats. Results are expressed as mean ± S.E.M, ** P < 0.01, 5-10 rats per group. sal, saline; Zn ($ZnCl_2$. 5.55 mg/Kg), $SerH_2Cl$: 10.0mg/Kg; $(SerH_2)_2[ZnCl_4]$ (1): 13.0 mg/Kg); $(SerH_2)_2[ZnCl_4]$ (2): 26.0 mg/Kg. Data were analyzed with two-way ANOVA, followed by Tukey's test for multiple comparisons.

$$F^o/F = 1 + K_{sv}[Q] \quad (1)$$

where F^o is the steady-state fluorescence intensity of the BSA alone while F is the steady-state fluorescence intensity upon increasing the quencher concentration, K_{sv} is the Stern-Volmer quenching constant and [Q] is the quencher concentration. Usually the curve of F^o/F vs [Q] is linear if the type of quenching involves a unique process: static or dynamic. Static quenching is due to complex formation between the fluorophore and the quencher and it becomes distinguishable from the collisional effect since the K_{sv} values are generally higher [70]. Based in the relationship $K_q = K_{sv}/\tau_0$ (where τ_0 is the average lifetime of the biomolecule without quencher), the dynamic quenching constant K_q has also been calculated. According to the literature, the maximum reference of the K_q value is 2×10^{-10} M^{-1} s^{-1}; if the estimated value of the constant is greater than this value, then a mechanism of interaction through the formation of the complex can be proposed, otherwise it would be a collisional quenching. When the quenching is static, it is assumed that there are specific binding sites for the de-activator which is similar but independent from each other. These binding sites, and their association constants, can be estimated using the following mathematical relationship

$$\log [(F^0-F)/F)] = \log K_b + n \log [Q]$$

Where K_b is the binding constant and "n" is the average number of biding site per protein molecule.

The results are given in Table (3) Figure (S6). In the present case, the calculated K_q values are greater than 2×10^{-10} M^{-1} s^{-1} hence suggesting that the compound probably would bind to BSA. Sertraline was previously studied by this technique and a comparison with previous data of others antidepressants such as fluoxetine, [71] citalopram, [72] and duloxetine, [73] shows that the K_{sv} value is of the same order of magnitude, except for clomipramine [68]. As it was shown, [74] a significant improvement in the sertraline apparent binding constant is found when the system is allowed to interact for 8 h, instead of 2 h interaction assuming the existence of at least one protein binding site. This result is in agreement with others [75] and it

Table 3: Stern-Volmer (K_{sv}) and molecular (K_q) quenching constants; apparent binding constant (K_b), and "n" binding sites for the systems $(SerH_2)_2[ZnCl_4]$-BSA and $SerH_2Cl$-BSA at 310 K and pH = 7.4.

Systems	K_{sv} (M^{-1}) ± DS	K_q ($M^{-1}s^{-1}$)	*R^2	K_b (M^{-1}) ± DS	n DS	*R^2
Incubation time: 2 h						
$SerH_2^+Cl$-BSA*	$2.37 \times 10^3 \pm 0.03$	$2.37 \times 10^{11} \pm 0.03$	0.998	40.74 1.10	0.45 ± 0.01	0.995
$(SerH_2)_2[ZnCl_4]$-BSA	$7.88 \times 10^3 \pm 0.10$	$7.88 \times 10^{11} \pm 0.10$	0.988	186.2 ± 1.23	0.57 ± 0.01	0.995
Incubation time: 8 h						
$SerH_2^+Cl$-BSA*	$2.03 \times 10^3 \pm 0.02$	$2.03 \times 10^{11} \pm 0.02$	0.980	$4.27 \times 10^3 \pm 0.07$	1.08 ± 0.03	0.992
$(SerH_2)_2[ZnCl_4]$-BSA	$3.46 \times 10^3 \pm 0.03$	$3.46 \times 10^{11} \pm 0.03$	0.979	81.28 ± 0.50	0.50 ± 0.05	0.996

R^2. is the correlation coefficient for the K_{sv} values.
DS: standard deviation
*Taken from Ref [74]

would reveal the *in vivo* tendency demonstrated for studies of oral sertraline administration versus assimilation time. [69,76] On the contrary, a longer interaction time causes a decrease in the parameters found for the $(SerH_2)_2[ZnCl_4]$-BSA association. But, at 2 h of incubation, an improvement in the uptake of the complex by the albumin compared with the time required for effective interaction of sertraline has been observed being the constant value four times larger. The interaction between the complex and BSA was also studied by UV-vis spectroscopy showing remarkably changes Figure (S7). The absorption band belonging to the α-helix BSA structure (c.a. 210 nm) strongly increased its intensity, suggesting changes in the protein conformation and exposition of the aromatic amino acid residues, possibly produced by an increased of the protein unfolding under the drug interaction. This behavior correlates with the changes in the 280 nm band characteristic of the tryptophan and tyrosine residues. This band in a first step raised its intensity, then decayed and finally (at a concentration of 100μM (Figure S7(e)) increased again, and splitted into three components accompanied by a blue shift. These changes suggested changes in the polarity around the tryptophan residue and a change in peptide strand of BSA molecules and hence a change in hydrophobicity leading to a more polar environment that would be consistent with the ionic nature of the compound [77].

CONCLUSIONS

A novel and improved antidepressant sertraline-based salt, consisting of a coordination complex anion containing Zinc(II) and sertralonium cation, $(SerH_2)_2[ZnCl_4]$, has been synthesized and characterized by structural X-ray diffraction, vibrational spectroscopy, and thermal analysis, among other physicochemical techniques. Though the literature reports several examples of other sertraline salts (without Zn (II)), however none of them suggests enhancement of sertraline antidepressant activity. The $(SerH_2)_2[ZnCl_4]$ complex demonstrates superior antidepressant activity than that showed by sertraline hydrochloride *per se* and, additionally, it suppress the anorexigenic effect caused by the antidepressant drug. Both effects constitute a potential clinical advantage for its possible formulation as a new drug. The results of this work led to an Argentinean patent application (Nº 20150103320). Interaction data with bovine serum albumin suggested an improvement in the assimilation of the complex after 2h of administration, as compared with sertraline hydrochloride.

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Appendix A. supplementary data

$(SerH)_2[ZnCl_4]$ (CCDC 1436826.): Tables: bond lengths and angles (Table S1), atomic coordinates and equivalent isotropic displacement parameters (Table S3), anisotropic displacement parameters (Table S4), hydrogen coordinates and isotropic displacement parameters (Table S5), hydrogen bond distances and angles (Table S6) and the vibrational wavenumbers of the infrared spectra (Table S2). Figures: Structural formula of sertraline (Figure S1), thermogravimetric curve (TGA) and differential scanning calorimetry curve (DSC) (Figure S2), experimental and calculated powder X-ray diffraction (PXRD) pattern Figure (S3), FTIR spectra (Figure S4), Raman spectra (Figure S5), Fluorescence spectra (Figure S6), Electronic spectra (Figure S7).

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