A new Metal-Organic Polymeric system capable of Stimuli-responsive controlled release of the drug ibuprofen.

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Supplementary material

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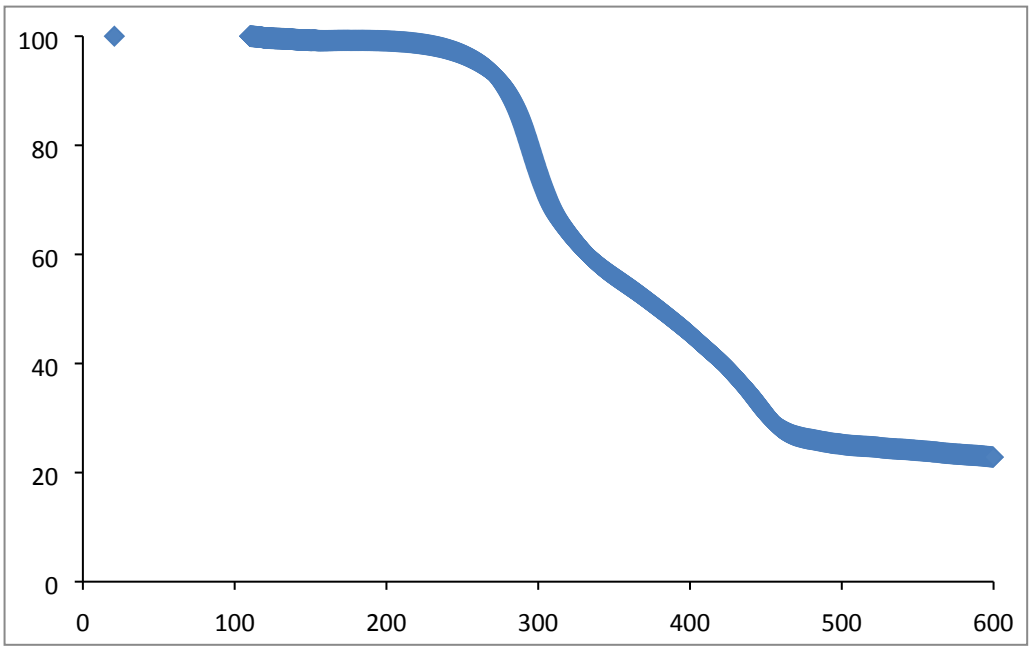
1. Characterization



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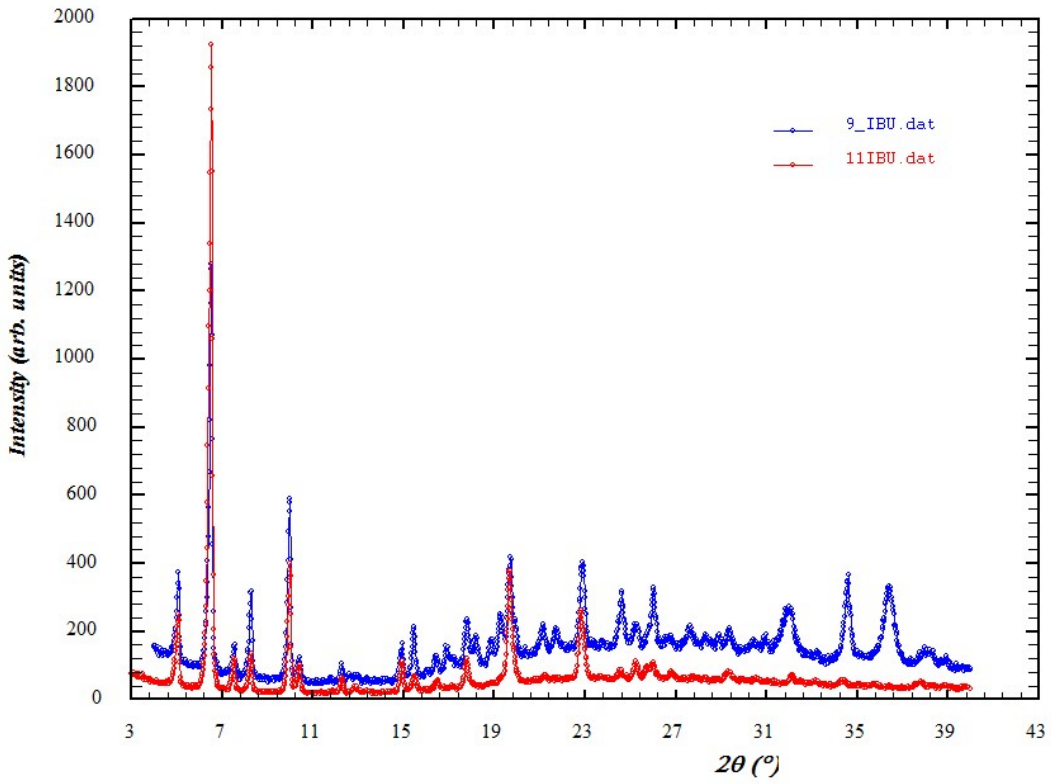

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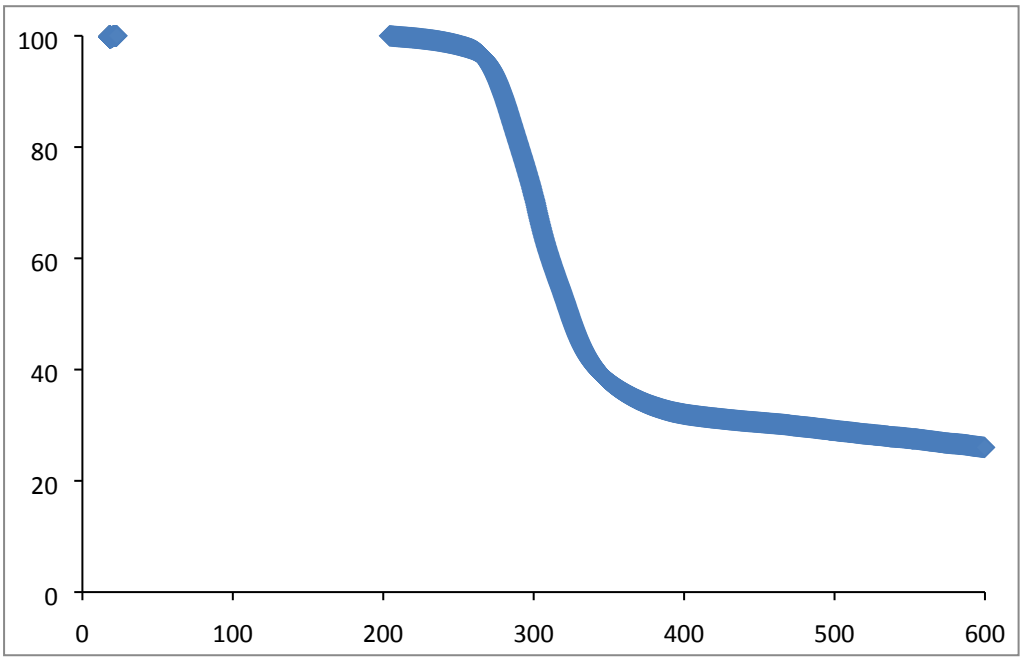
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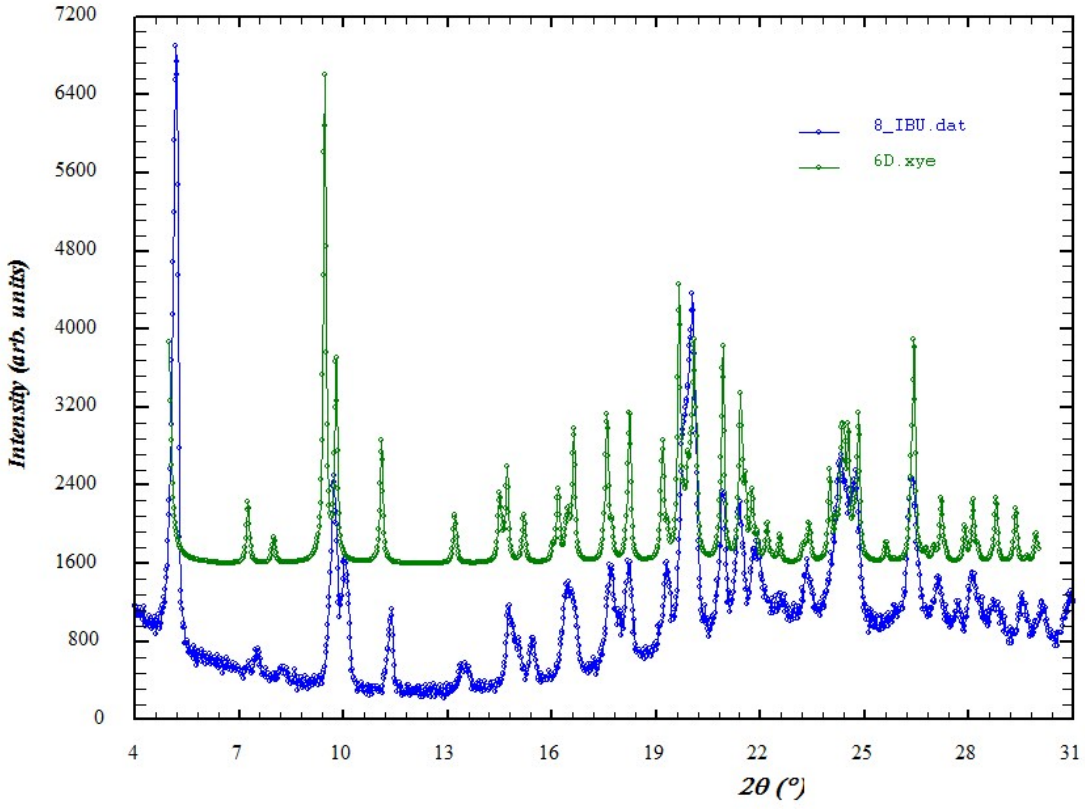
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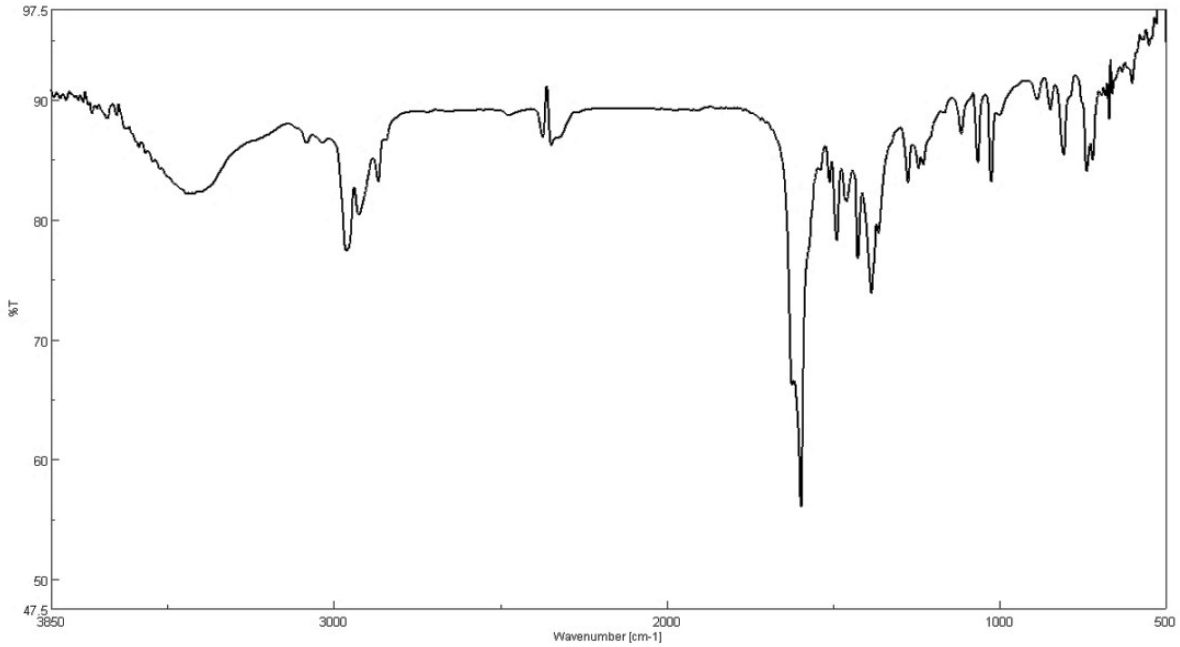
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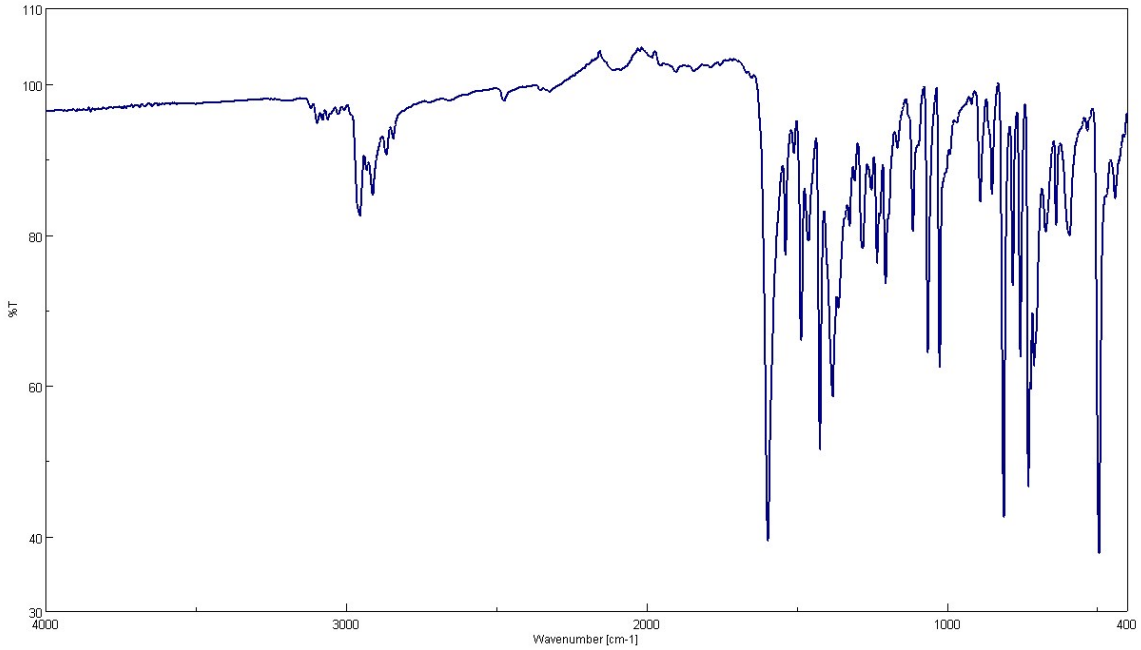
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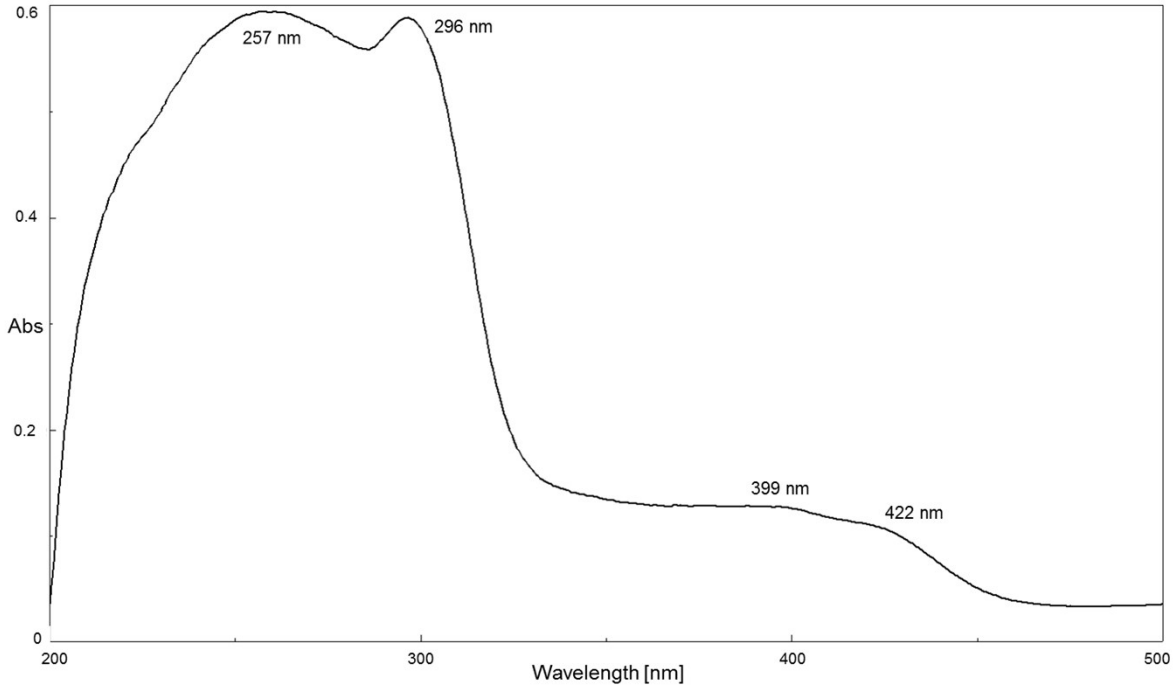

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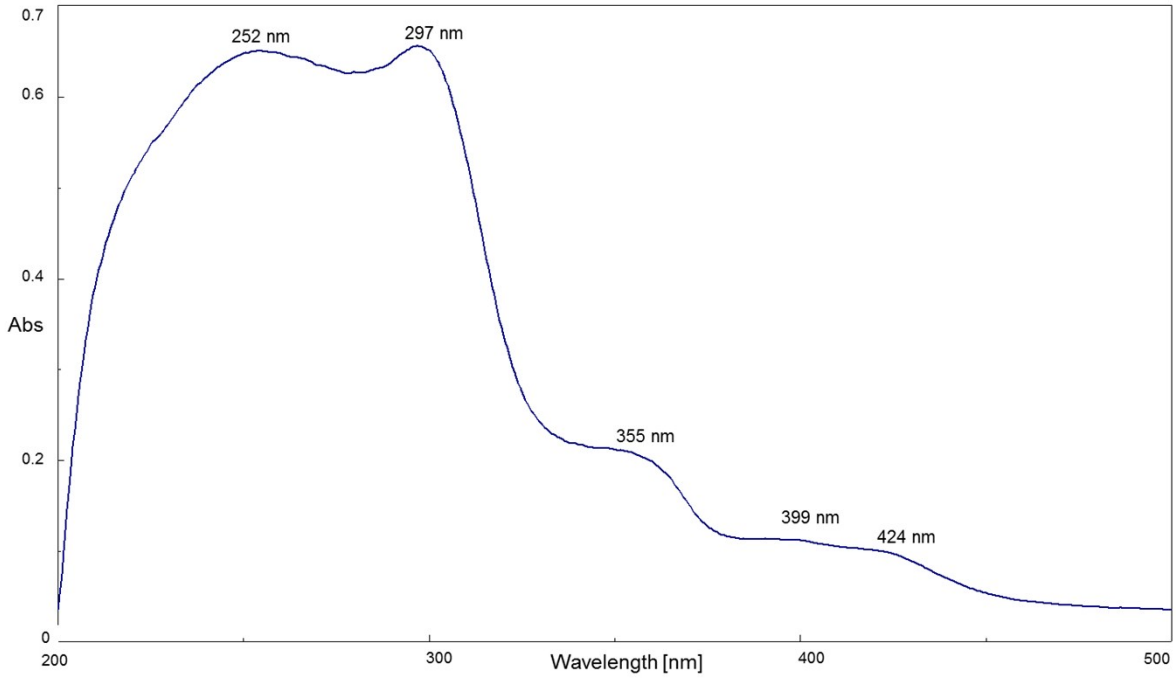
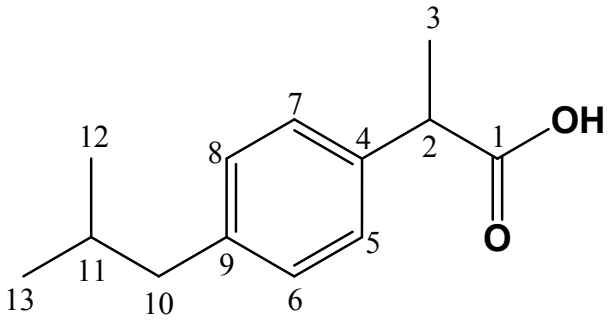
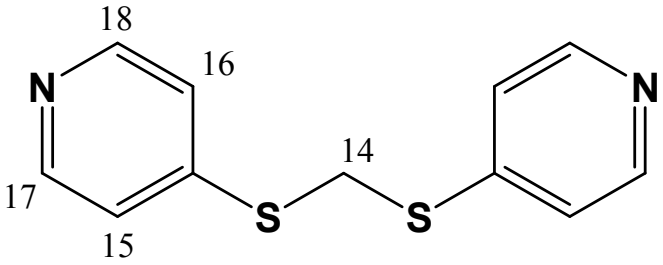


H)

Figure S1A. A) Thermogravimetric analysis (TGA) of **1** carried out between 25 and 600 ºC B) Powder X-ray diffractograms of **1** obtained by different synthesis methods C) TGA of **2** carried out between 25 and 600 ºC. D) Powder X-ray diffractograms of **2** calculated from single crystal and as-synthesized product. E) IR spectra of **1**. F) IR spectra of **2**. G) UV-Vis spectra data (solid state) of **1**. H) UV-Vis spectra data (solid state) of **2**.



Hibu



SCS

Figure S1B. Labelling scheme for Hibu and SCS

2. Crystallography

Crystallographic data for **2**, **3**, **4**, **5** and [H_2-SCS][$ZnCl_4$] (**Zn-HSCSH**) were collected on a microfocal Bruker Smart 6000 CCD diffractometer at 293 K using graphite monochromated Cu-K_α radiation (λ = 1.54178 Å) and were corrected for Lorentz and polarization effects. The frames were integrated with the Bruker SAINT [S1] software package and the data were corrected for absorption using the program SADABS. [S2]

The structures were solved by direct methods using the program SHELXS97. [S3] All non-hydrogen atoms were refined with anisotropic thermal parameters by full-matrix least-squares calculations on F^2 using the program SHELXL97. [S4]

Hydrogen atoms were inserted at calculated positions and were constrained with isotropic thermal parameters.

Drawings were produced with MERCURY [S5] and special computations for the crystal structure discussions were carried out with PLATON. [S6]

Powder X-ray diffraction data were obtained using Cu-K_α radiation and were collected on a Siemens D-5000 diffractometer over the range 5.0–45.0° in steps of 0.20° (2θ) with a count time per step of 5.0 s.

The structural data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) with the reference numbers included in Table S1. Selected bond lengths are listed in Tables S2.

Table S1. Crystal and structure refinement data

Compound	**2**	**3**	**4**	**5**	**Zn-HSCSH**
Empirical formula	$C_{24}H_{26}N_2O_2S_2ClZn$	$C_{26}H_{34}O_6Zn$	$C_{11}H_{10}Cl_2N_2S_2Zn$	$C_{22}H_{20}N_4S_4Cl_2Zn$	$C_{22}H_{24}N_4OS_4Cl_8Zn$
Formula weight	539.91	507.90	370.60	604.93	903.03
Crystal system	Triclinic	Monoclinic	Triclinic	Monoclinic	Triclinic
Space group	*P-1*	*C2*	*P-1*	P 2_1	*P-1*
CCDC ref	1422661	1422662	1422663	1422664	1422665
Unit cell dimensions *a* (Å) *b* (Å) *c* (Å) α (°) β (°) γ (°)	 5.5566(4) 12.6547(10) 18.5385(14) 78.2167(18) 81.8265(19) 77.7451(18)	 9.7324(9) 5.9746(5) 22.871(2) 93.764(3) 	 5.9374(8) 10.3678(13) 12.6958(15) 72.367(4) 77.524(5) 89.593(5)	 8.1234(4) 10.1959(5) 15.7514(8) 102.3633(14) 	 7.61430(10) 7.78860(10) 29.5202(4) 92.63 93.7690(10) 90.3270(10)
V (Å^3)	1240.35(16)	1327.0(2)	725.79(16)	1274.36(11)	1744.99(4)
Z	2	2	2	4	2
T/K	100	100	296	296	293
ρ_{calc} (g cm^{-3})	1.446	1.7271	1.696	1.576	1.719
Absorption coeff. (mm^{-1})	4.128	1.579	8.281	6.487	9.785
F(000)	559	536	372	616	904
Crystal size (mm)	0.245 × 0.205 × 0.044	0.167 × 0.153 × 0.046	0.142 × 0.098 × 0.081	0.22 × 0.12 × 0.05	0.207 × 0.182 × 0.098
θ Range (º)	2.448-68.453	1.936-67.769	4.878 -68.105	2.872-68.339	1.501-68.253
Reflections collected	19922	7131	6763	20644	28365
Indep. reflections (R_{int})	4411 (0.0328)	2240 (0.0364)	2355 (0.0404)	4588 (0.0485)	6156 (0.0324)
Max/min transmission	0.7531/0.4905	0.7530/0.5242	0.7530/0.4584	0.7531/0.4079	0.7531/0.4481
Data/restraints/parameters	4411/0/303	2240/1/154	2355 / 0 / 163	4588/1/299	6156/0/466
Final *R*indices [$I>2\sigma(I)$]	R_1 = 0.0383 wR_2 = 0.1026	R_1 = 0.0791 wR_2 = 0.2021	R1 = 0.0644 wR2 = 0.1548	R_1 = 0.0439 wR_2 = 0.1185	R1 = 0.0329 wR2 = 0.0881

Table S2. Selected interatomic bond lengths (Å) and angles (º).

		3		
Bond lengths	Zn-O(3)	1.943(5)	Zn-O(1)	1.973(6)
	Zn-O(3)#1	1.943(5)	Zn-O(1)#1	1.973(6)
Angles	O(3)-Zn-O(3)#1	125.3(4)	O(3)#1-Zn-O(1)	102.0(2)
	O(3)-Zn-O(1)	111.0(3)	O(1)-Zn-O(1)#1	103.9(4)
		#1=-x,y,-z+1		
		5		
Bond lengths	Zn-N(2)	2.041(4))	Zn-Cl1	2.2315(14)
	Zn-N(3)	2.049(4)	Zn-Cl2	2.2343(13)
Angles	N(2)-Zn-N(3)	110.70(17)	N(2)-Zn-Cl(2)	104.74(12)
	N(2)-Zn-Cl(1)	107.73(12)	N(3)-Zn-Cl(2)	113.02(13)
	N(3)-Zn-Cl(1)	104.89(13)	Cl(1)-Zn-Cl(2)	115.72(6)
		4		
Bond lengths	Zn-N(2)	2.039(5)	Zn-Cl(2)	2.2065(16)
	Zn-N(1)	2.048(4)	Zn-Cl(1)	2.2531(16)
Angles	N(2)-Zn-N(1)	106.84(18)	N(2)-Zn-Cl(1)	104.96(14)
	N(2)-Zn-Cl(2)	106.42(14)	N(1)-Zn-Cl(1)	102.86(13)
	N(1)-Zn-Cl(2)	112.63(14)	Cl(2)-Zn-Cl(1)	122.09(7)
		2		
Bond lengths	Zn-O(3)	1.9567(19)	Zn-N(2)#1	2.056(2)
	Zn-N(1)	2.0388(19)	Zn-Cl	2.2862(7)
	Zn-O(2)	2.561		
Angles	O(3)-Zn-N(1)	134.90(8)	O(3)-Zn-Cl	104.51(7)
	O(3)-Zn-N(2)#1	100.17(8)	N(1)-Zn-Cl	101.38(6)
	N(1)-Zn-N(2)#1	109.62(8)	N(2)#1-Zn-Cl	102.22(6)
		#1= x-1,y+1,z		
		Zn-HSCSH		
Bond lengths	Zn(1)-Cl(4)	2.2510(7)	Zn(4)-Cl(8)	2.2499(6)
	Zn(1)-Cl(2)	2.2510(7)	Zn(4)-Cl(6)	2.2619(7)
	Zn(1)-Cl(3)	2.2636(7)	Zn(4)-Cl(5)	2.2649(7)
	Zn(1)-Cl(1)	2.2799(7)	Zn(4)-Cl(7)	2.2911(7)
Angles	Cl(4)-Zn(1)-Cl(2)	109.46(3)	Cl(8)-Zn(4)-Cl(6)	110.54(3)
	Cl(4)-Zn(1)-Cl(3)	109.21(3)	Cl(8)-Zn(4)-Cl(5)	111.08(3)
	Cl(2)-Zn(1)-Cl(3)	111.58(3)	Cl(6)-Zn(4)-Cl(5)	106.84(3)
	Cl(4)-Zn(1)-Cl(1)	113.44(3)	Cl(8)-Zn(4)-Cl(7)	106.37(3)
	Cl(2)-Zn(1)-Cl(1)	107.67(3)	Cl(6)-Zn(4)-Cl(7)	109.71(3)
	Cl(3)-Zn(1)-Cl(1)	105.47(3)	Cl(5)-Zn(4)-Cl(7)	112.34(3)

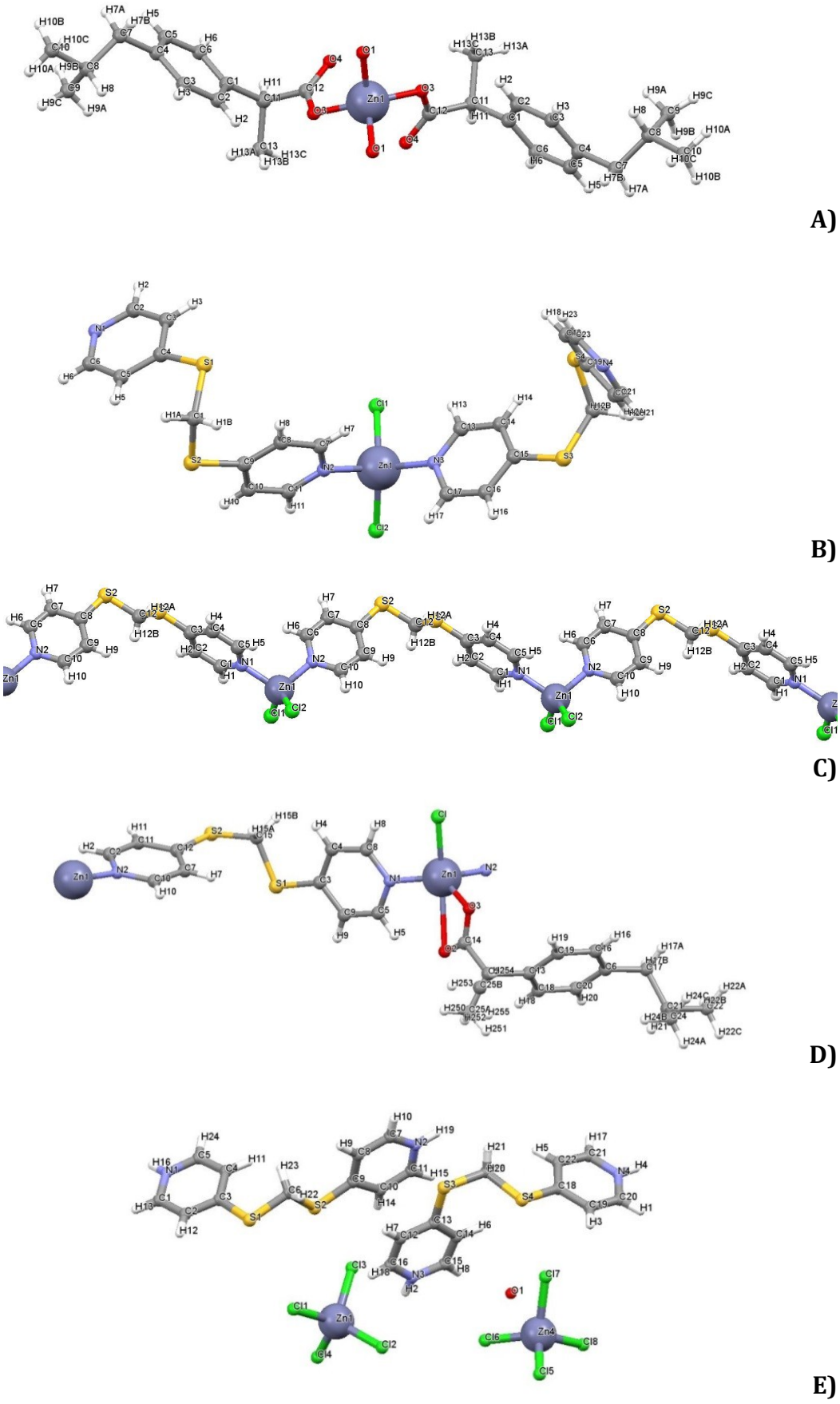


Figure S2A. View of the structures of **3** (A); **5** (B); **4** (C); **2** (D) and **Zn-HSCSH** (E) showing details of the zinc atom environment with the corresponding labeling scheme.

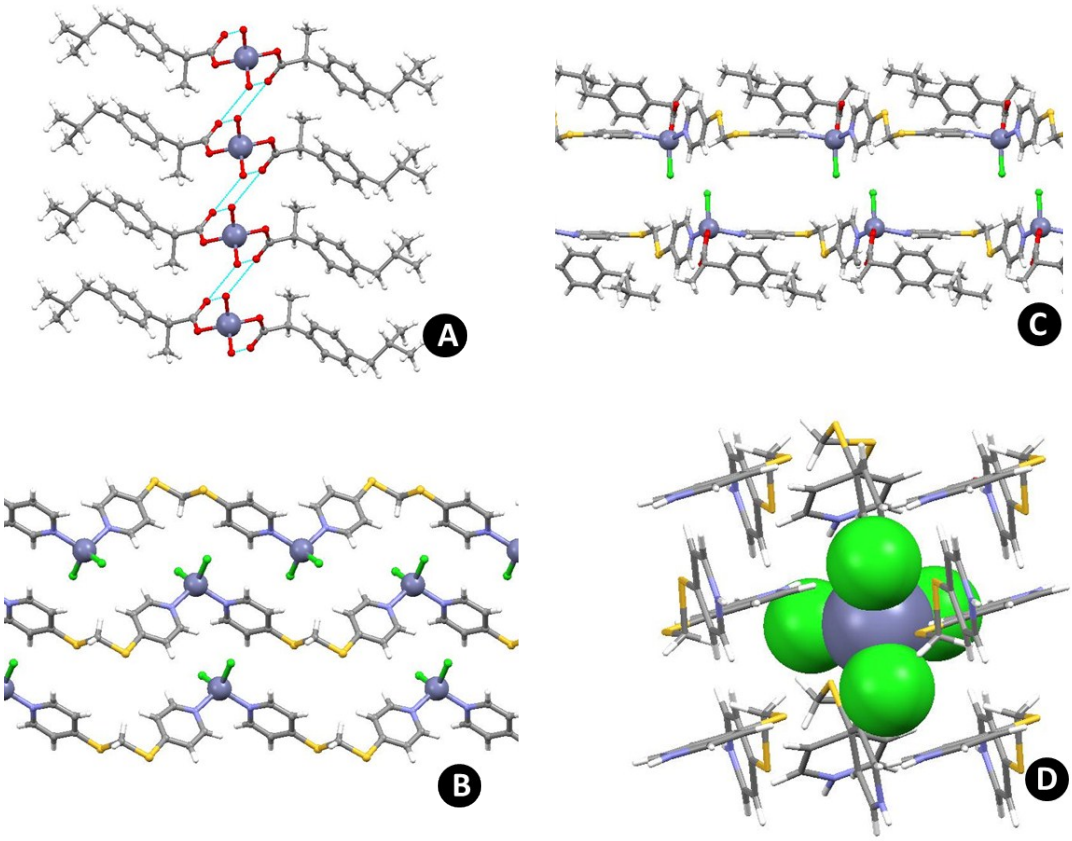


Figure S2B. Supramolecular packing in **3** (A); **4** (B); **2** (C) and **Zn-HSCSH** (D)

Chloride ligands present in some of the structures play a crucial role in the supramolecular organizations by acting as acceptors in different interactions. The associations are established by means of CH···Cl and NH···Cl hydrogen bonds, which also involve the –CH pyridine rings or –NH protonated pyridine groups of SCS ligands as donor. Oxygen atoms are responsible for the supramolecular association through different OH···O hydrogen bonds established between water molecules as donors and the uncoordinated oxygen atoms of the ibuprofen molecules as acceptors, in **3** (SI).

3. Stability and degradation in water:

15 mg of polymeric ibuprofen materials (**1** and **2**) were soaked in liquid water for 3 months at different temperatures; 40 ºC (2 months), 60 ºC (3 weeks) and 80 ºC (1week), in order to study the aqueous stability of the compounds. After this treatment the post-exposure powder X-ray diffraction patterns were compared to those of the pristine samples. Extension of the water soaking time to 3 months led to the disappearance and broadening of PXRD peaks in **2**, which is indicative of some degree of decomposition. In comparison, **1** retained its crystallinity after immersion in water, as evidenced by the absence of significant changes in the PXRD patterns. The IR spectra of the resulting solids show the presence of ibuprofen molecules due to the observation of bands due to the C–H alkyl moiety of ibuprofen vibrations around 2890 cm^{-1}. UV-Vis studies of the resulting solutions were performed in order to assess the degree of solubility.

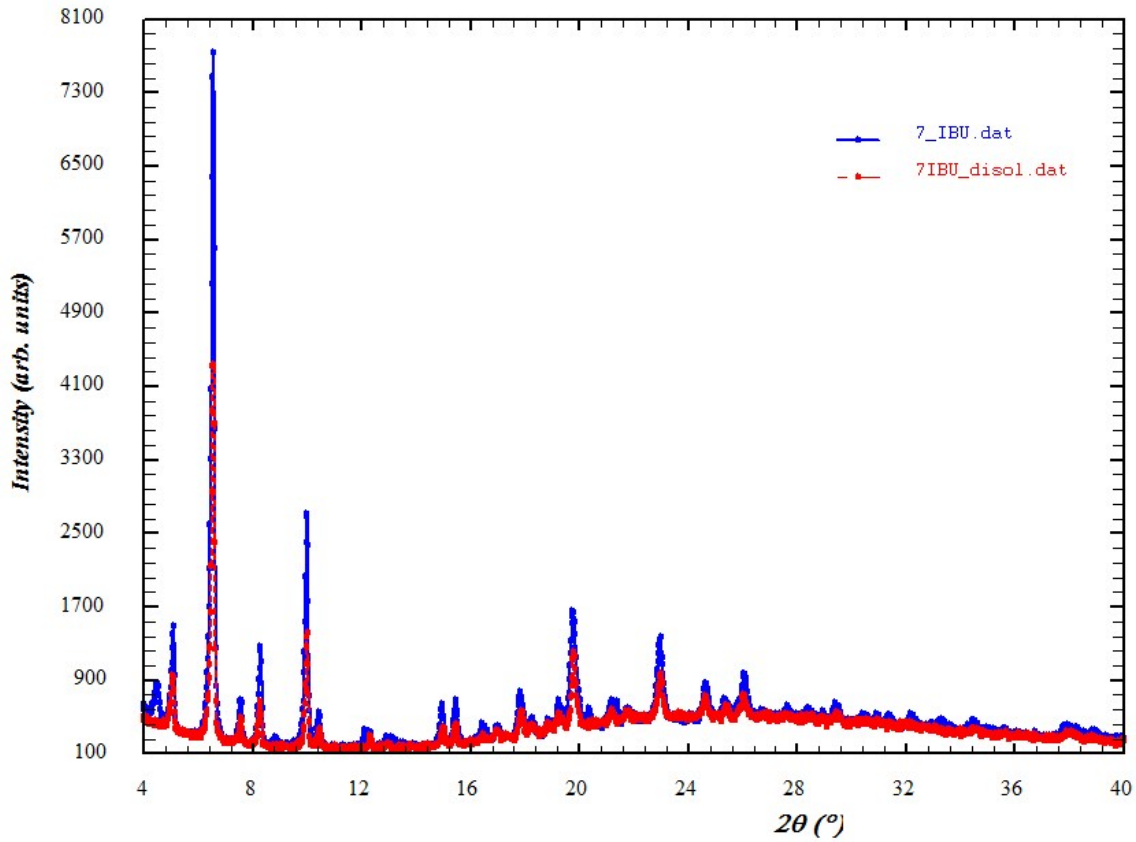


Figure S3. Powder X-ray diffractograms of **1** *before* (blue) and *after* (red) treatment with water.

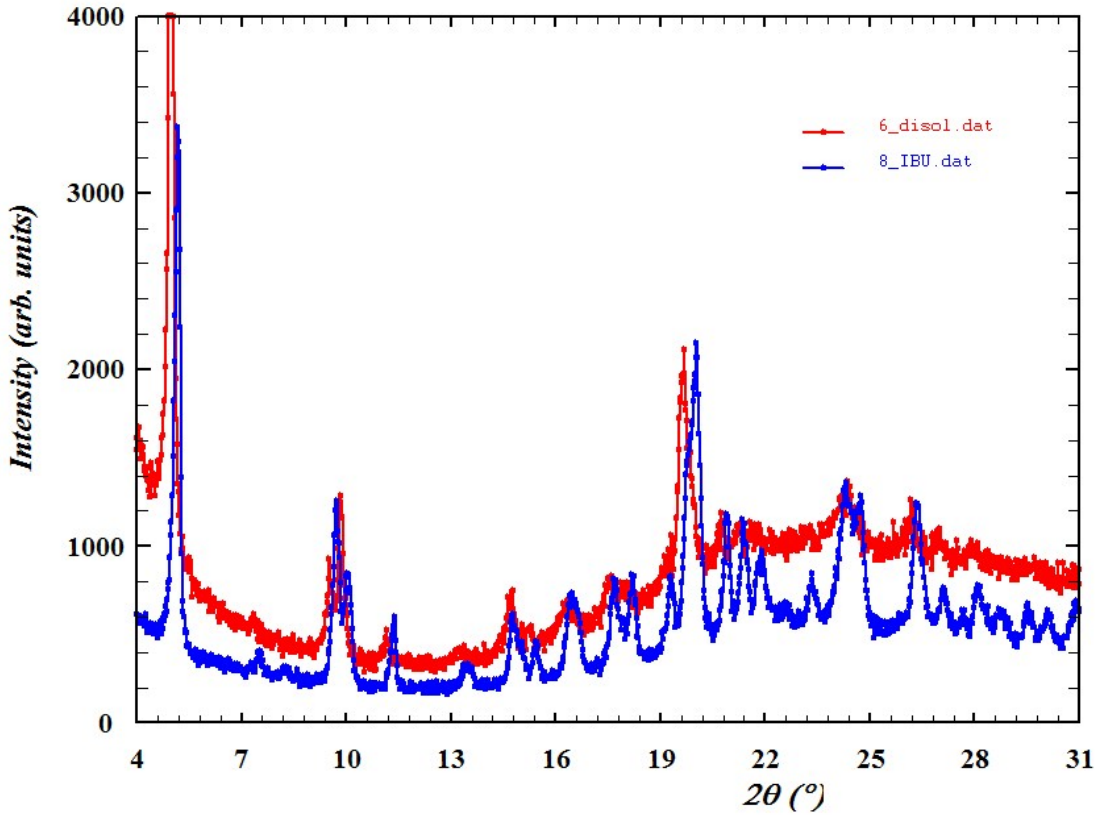


Figure S4. Powder X-ray diffractograms of **2** *before* (blue) and *after* (red) the treatment with water.

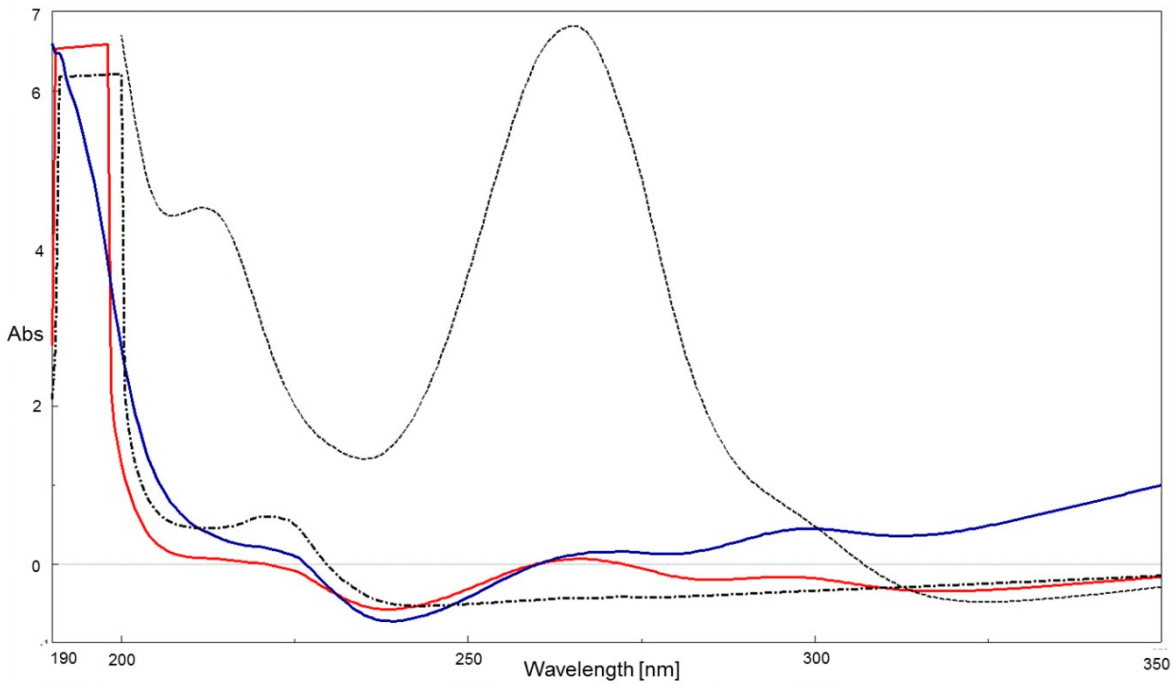
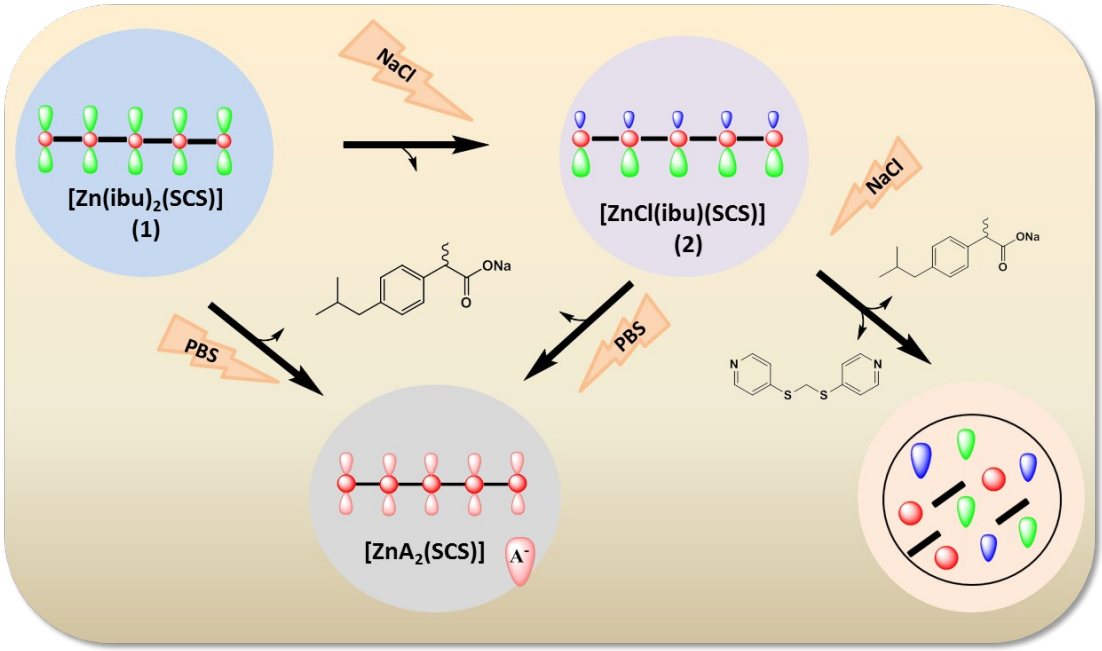


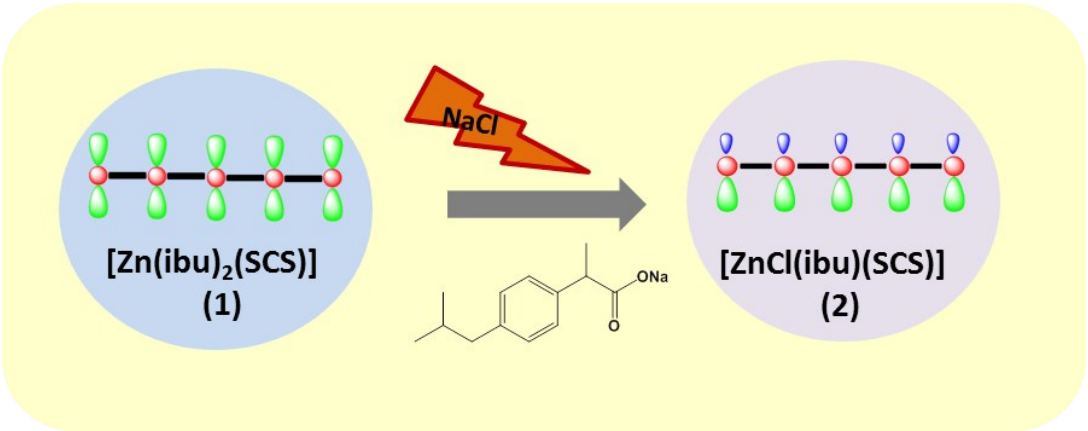
Figure S5. UV-Vis spectra (a.u) of the supernatant solutions in $[Zn(ibu)_2(SCS)]$ (red) and in [ZnCl(ibu)(SCS)] (blue) after treatment. UV-Vis of SCS and Hibu solutions in dashed black lines.

4. Release of ibuprofen anion by ion-exchange



Scheme S1

4.1. Study of the behavior of [Zn(ibu)$_2$(SCS)] (1) in sodium chloride solution: Transformation to [ZnCl(ibu)(SCS)] (2)

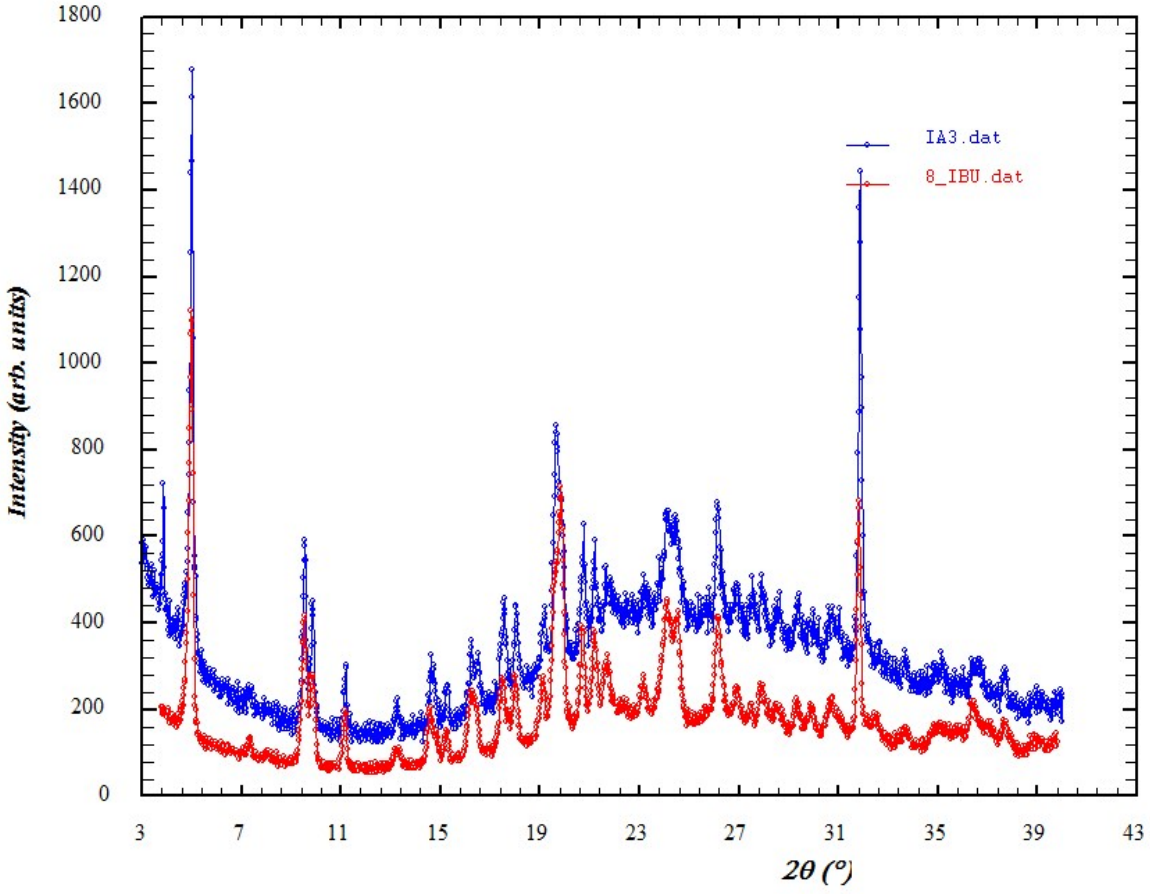


Scheme S2

30 mg (0.044 mmol) of [Zn(ibu)$_2$(SCS)] (**1**) was soaked in 5 mL of NaCl solution (2 M) during 6 days and the mixture was then filtered. The ibuprofen anion exchange was characterized in the filtered-off solid powder (after washing with distilled water and vacuum drying on $CaCl_2$) by elemental analysis, NMR, IR and X-ray powder diffraction (XRPD). The UV-Vis spectrum of the resulting solution showed the bands of the ibuprofen molecule. The powder X-ray diffraction pattern of the bulk sample showed a good correlation with that calculated from the single crystals of [ZnCl(ibu)(SCS)] (**2**) (Figure S6)

whereas the elemental analysis and ^{1}H-NMR spectrum of the solid powder in DMSO-*d*6 confirmed the 1:1 ratio of ligands.

White solid powder: Anal. found: C, 52.62; H, 4.57; N, 4.69; S, 10.93 $C_{24}H_{26}N_2S_2O_2ClZn$ ([ZnCl(ibu)(SCS)]) requires: C, 53.44; H, 4.86; N, 5.19; S, 11.89. ^{1}H-NMR (400 MHz, [D_6]-DMSO, 25 ºC): δ 0.84-0.86 (d, 6H, C12-H3, C11-H3, ibu); 1.24-1.26 (d, 3H, C3-H3, ibu); 1.73-1.84 (m, 1H, C11-H, ibu), 2.36-2.38 (d, 2H, C10-H2); 3.39-3.41 (dd, 1H, C2-H, ibu); 5.0 (s, 2H, C14-H2, SCS); 6.98-7.00 (d, 2H, C5arom, C7arom, ibu), 7.17-7.19 (d, 2H, C6arom, C8arom, ibu), 7.40-7.46 (d, 4H, C15arom, C16arom, SCS), 8.42-8.44 (d, 4H, C17arom, C18arom, SCS). IR (KBr):*ν(cm^{-1})* = 2960m, 2912m (CH stretching), 1597s (ν_{asym}(OCO), ν (CC) + ν (CN)), 1383m (ν_{sym}(OCO)), 1233w (ω (CH,CH_2)), 1064m (ν (CH) + δ (C-H)), 730m (ν (CS)).



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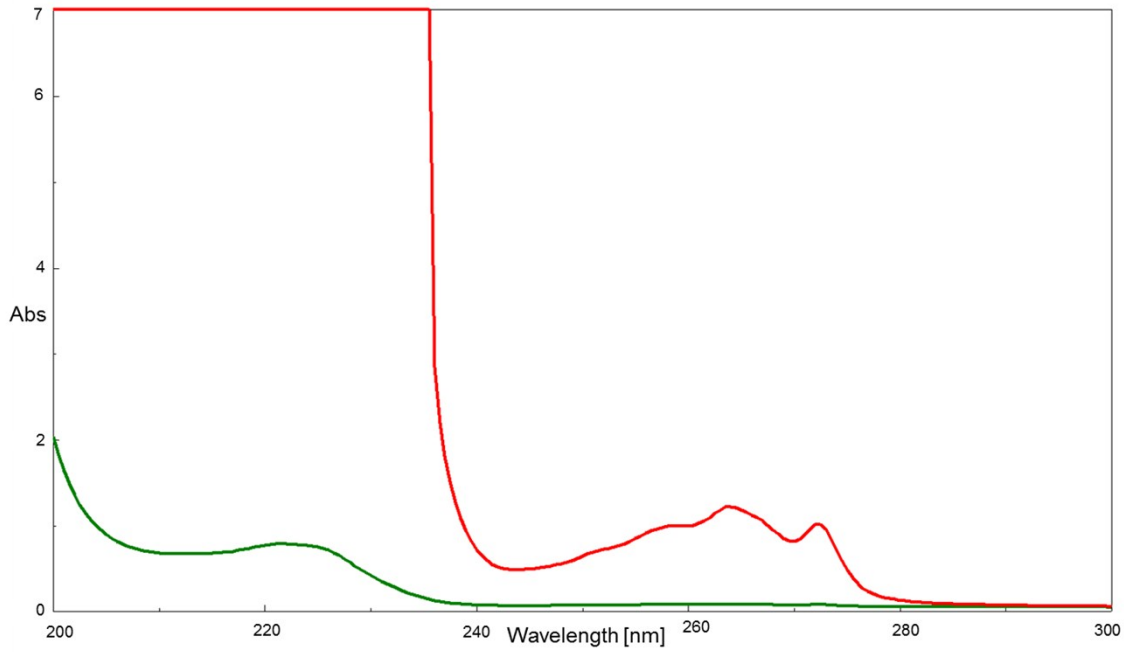
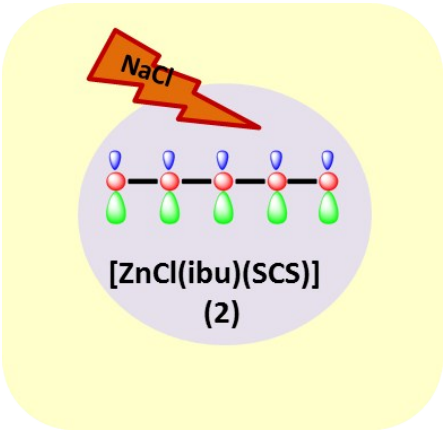


B

)

Figure S6. A) Powder X-ray matching diffratograms of [ZnCl(ibu)(SCS)] (**2**) (red) and [Zn(ibu)$_2$(SCS)] (**1**) *after* the treatment in sodium chloride solution (blue). B) UV-Vis (a.u) spectra of the resulting solution, fresh solution in red and diluted solution in green.

4.2. Study of the behavior of [ZnCl(ibu)(SCS)] (2) in sodium chloride solution



Scheme S3

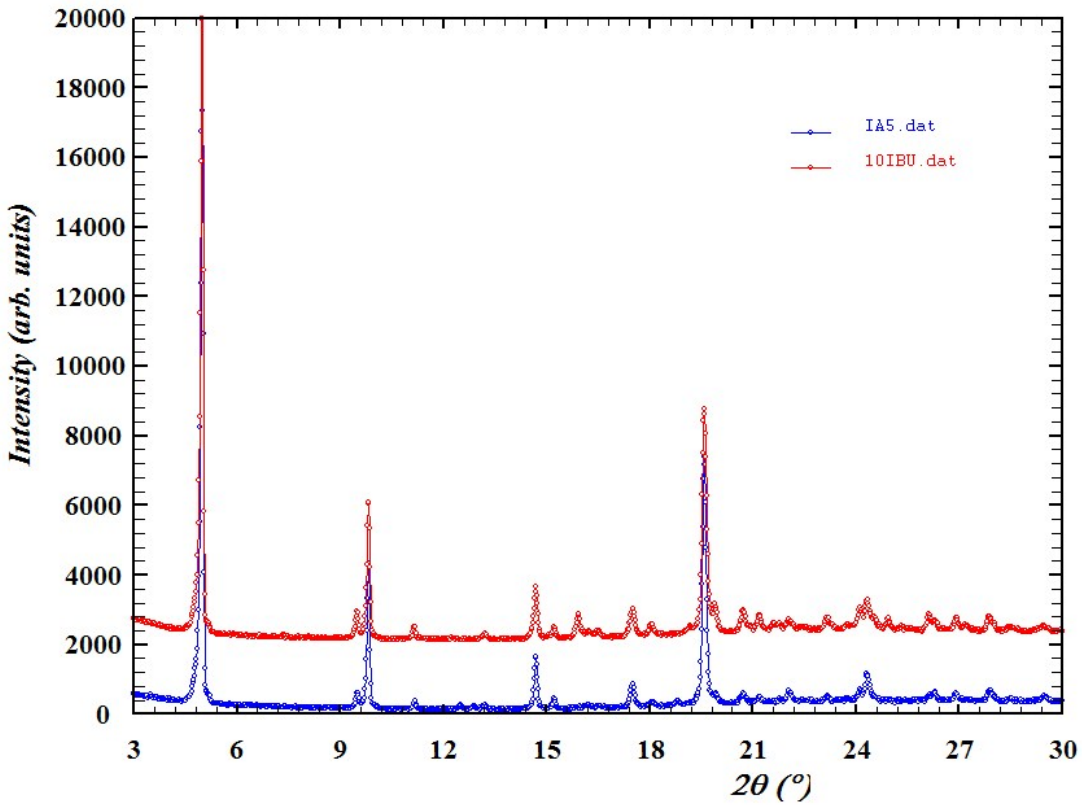
Method A: 30 mg (0.056 mmol) of [ZnCl(ibu)(SCS)] (**2**) was soaked in 5 mL of NaCl solution (2 M) for 21 days. The white solid was filtered off, washed with distilled water, vacuum dried on $CaCl_2$ and characterized by elemental analysis, NMR, IR and X-ray powder diffraction (XRPD). The powder X-ray diffraction pattern of the bulk sample showed a correlation with that calculated from the crystal structure of NaCl whereas elemental analysis showed the decrease in the organic composition in the bulk sample

indicating the presence of inorganic salts in the sample. ^{1}H-NMR spectrum of the solid powder in DMSO-d^{6} showed a 1:1 ratio of ligands. UV-Vis spectra of the resulting solutions were recorded after centrifugation of the supernatant solutions after 7 and 21 days.

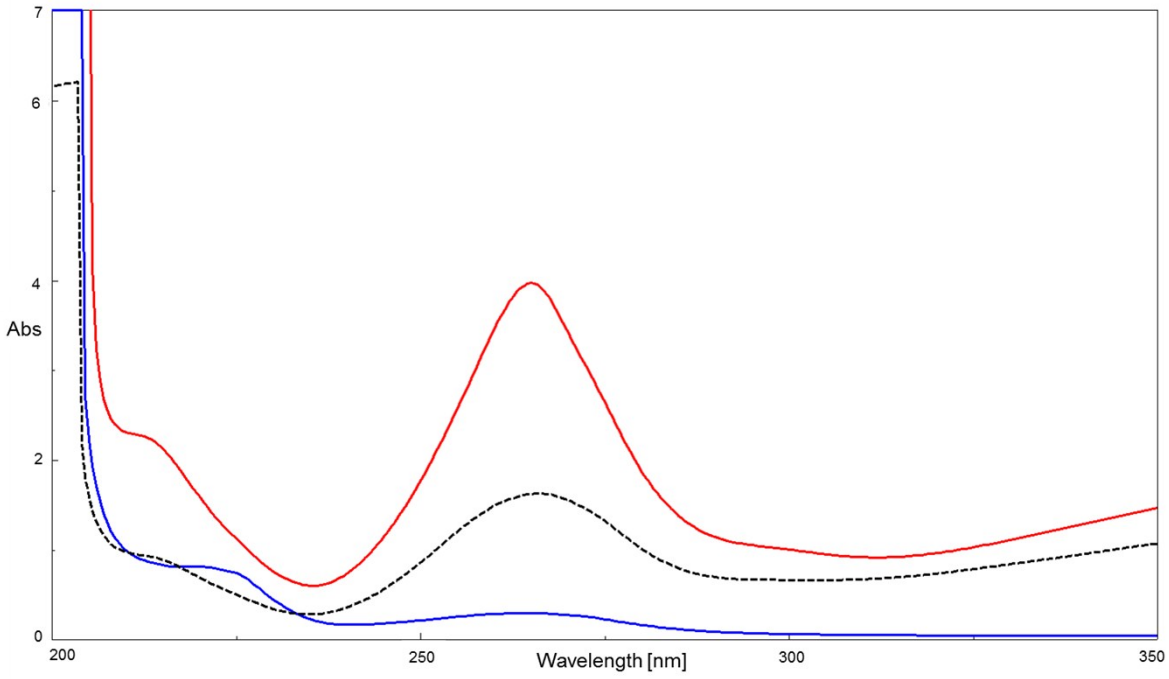
Method B: 25 mg (0.046 mmol) of [ZnCl(ibu)(SCS)] (**2**) was heated under reflux in 5 mL of NaCl solution (2M) for 12 hours. The white solid was filtered off and characterized by elemental analysis, NMR, IR and X-ray powder diffraction (XRPD). The powder X-ray diffraction pattern of the bulk sample showed a correlation with the original compound whereas the elemental analysis and ^{1}H-NMR spectrum of the solid powder in DMSO-*d*6 confirmed the 1:1 ratio of ligands. A weight loss of 50% was observed with this method. UV-Vis spectra of the solution separated from the solid by filtration were recorded.

Table S3: Elemental analysis of the compounds:

Sample(% exp)	**%C**	**%H**	**%N**	**%S**	**%total (C,H,N,S)**
Original (2)	51.24	4.74	5.36	11.96	73.3
Method A	6.96	0.55	0.75	1.44	9.7
Method B	48.48	4.84	4.99	11.23	69.54



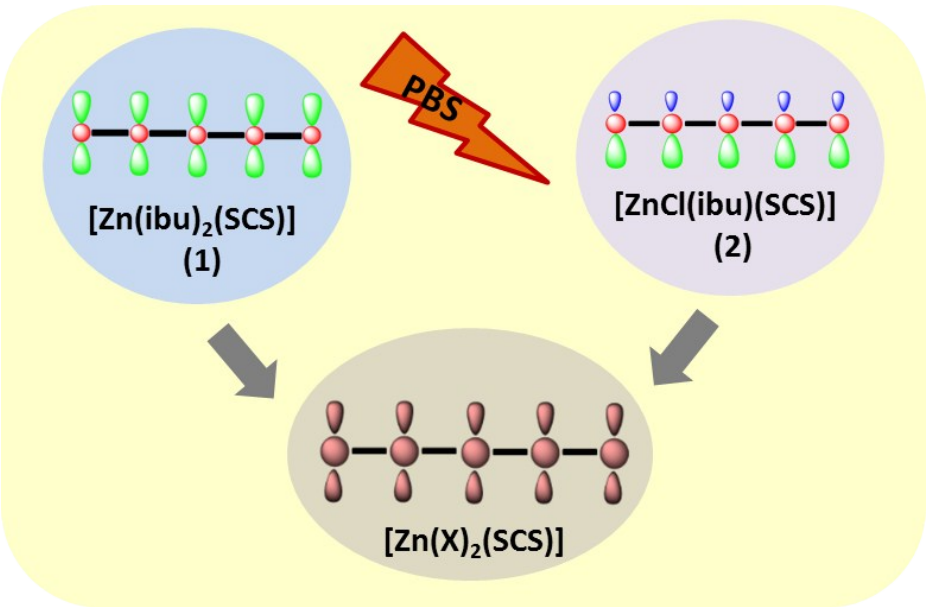
A)



B)

Figure S7. A) Podwer X-ray diffractograms of the resulting compounds after the treatment *Method B*; **B**) UV-Vis (a.u) spectra of supernatant solutions obtained from *method B* (dashed black) and from *method A* at 7 days (blue) and after 21 days (red).

4.3. Study of the behavior of $[Zn(ibu)_2(SCS)]$ (1) and $[ZnCl(ibu)(SCS)]$ (2) in PBS buffer solution



Scheme S4

Method A: 34 mg (0.050 mmol) of [Zn(ibu)$_2$(SCS)] (**2**) were soaked in 10 mL of PBS buffer (0.1M, pH 7.4) solution. 200 µL of the solution from the vial was removed each day and 200 µL of the fresh PBS solution was added to the vial over 4 days. The same procedure, but with 800 µL, was carried out from the 4th to the 8th day. UV-Vis spectra of the solution separated from the solid by centrifugation were recorded. The same treatment was performed with 27 mg (0.050 mmol) of [ZnCl(ibu)(SCS)] (**2**).

Method B: After the previous treatment, the solutions were separated from the solids by filtration every 2-5 days and the batch was completely replaced with fresh PBS solution. UV-Vis spectra of each solution separated from the solid by filtration were recorded.

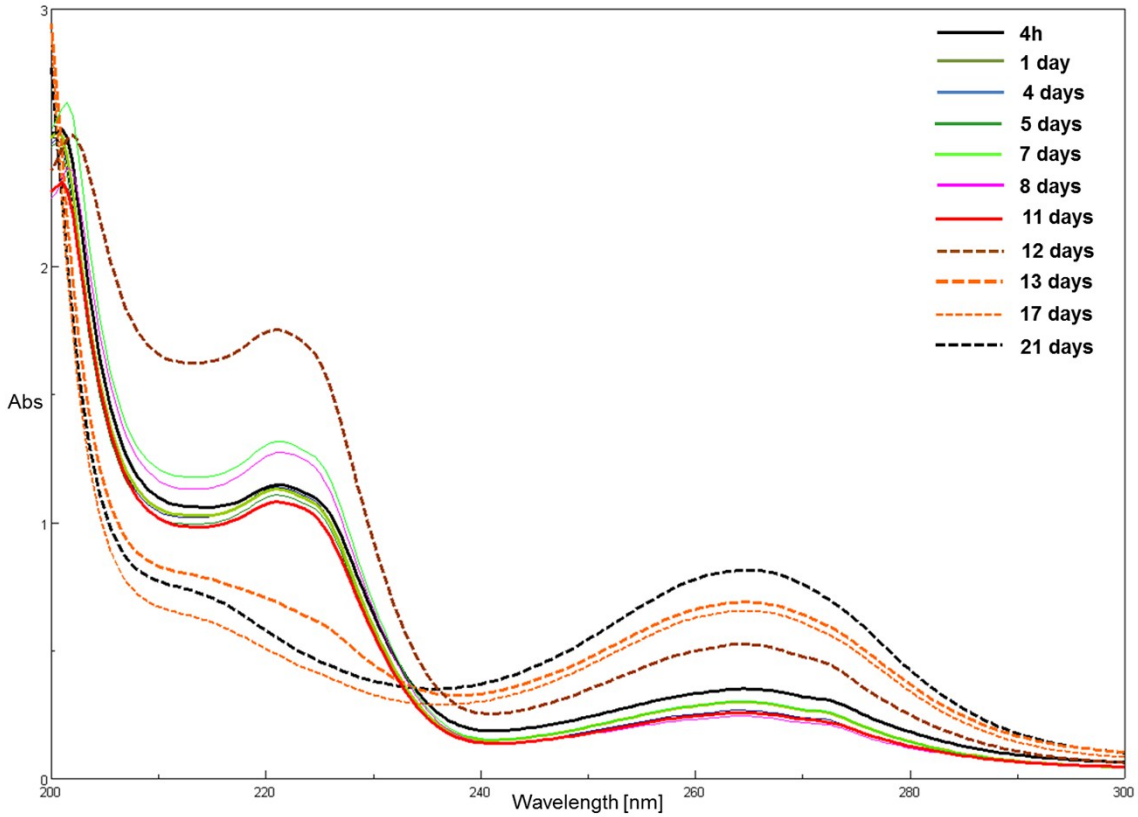


Figure S8. UV-vis. (a.u.) spectrum of compound (**1**) after treatment with PBS: Method A; continuous line. Experiment after 4 h (black continuous line); Method B; dashed line. change to Method B (dashed brown line); final measurement (dashed black line)

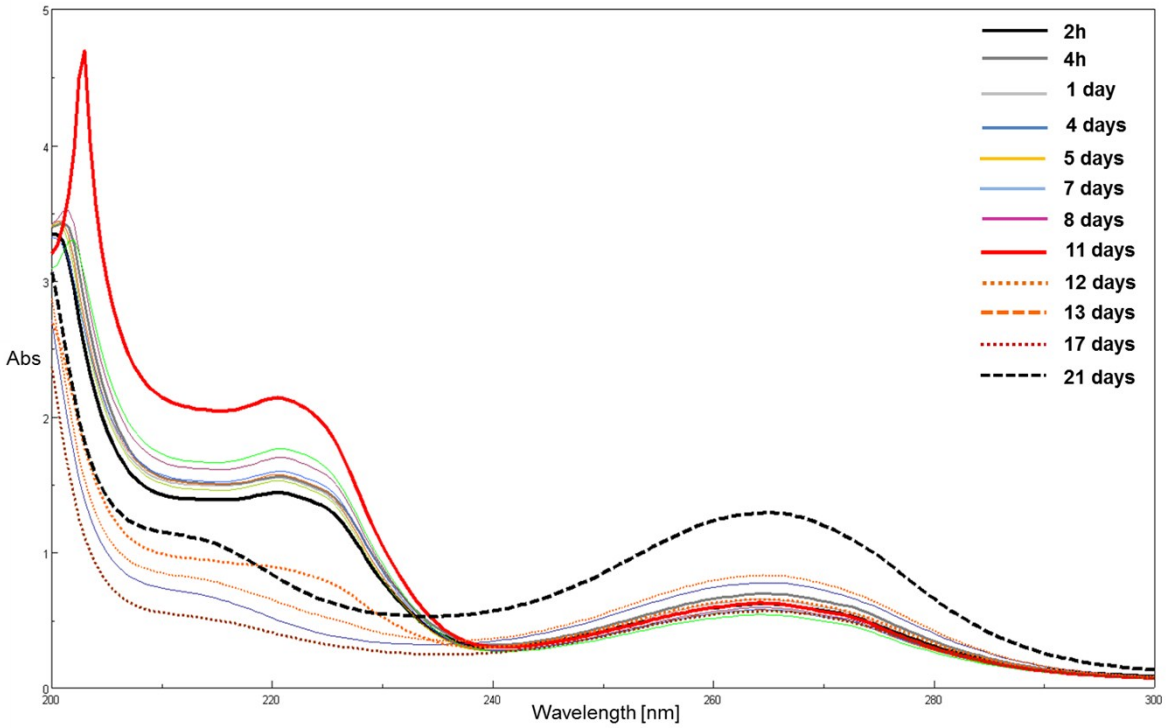


Figure S9. UV-vis. (a.u.) spectrum of compound (**2**) after treatment with PBS: Experiment after 2h (black continuous line); change to *Method B* (red continuous line); last measurement (dashed black line)

The remaining white solids in **1** and **2** were filtered off, washed with distilled water, vacuum dried on $CaCl_2$ and characterized by elemental analysis, NMR, IR and X-ray powder diffraction (XRPD). The powder X-ray diffraction patterns showed that both products present the same unidentified final structure and elemental analysis showed that they also have similar compositions. The IR spectra show the characteristic strong bands of the phosphate anion at 1000 cm^{-1}. ^{1}H-NMR spectra of the white powders in DMSO-d^6 showed indicated the almost complete absence of ibuprofen molecules in the product obtained from [Zn(ibu)$_2$(SCS)](**1**) whereas the ^{1}H-NMR spectrum of product resulting from [ZnCl(ibu)(SCS)] (**2**) showed a 1:4 molar ratio of ligands (ibu:SCS) .

Table S4: Elemental analysis of the compounds:

Original Sample	**%C**	**%H**	**%N**	**%S**	**%total (C,H,N,S)**
[Zn(ibu)$_2$(SCS)]*	23.13	1.22	3.01	7.31	34.67
[ZnCl(ibu)(SCS)]*	25.75	1.81	4.96	10.81	43.33

* after treatment in PBS

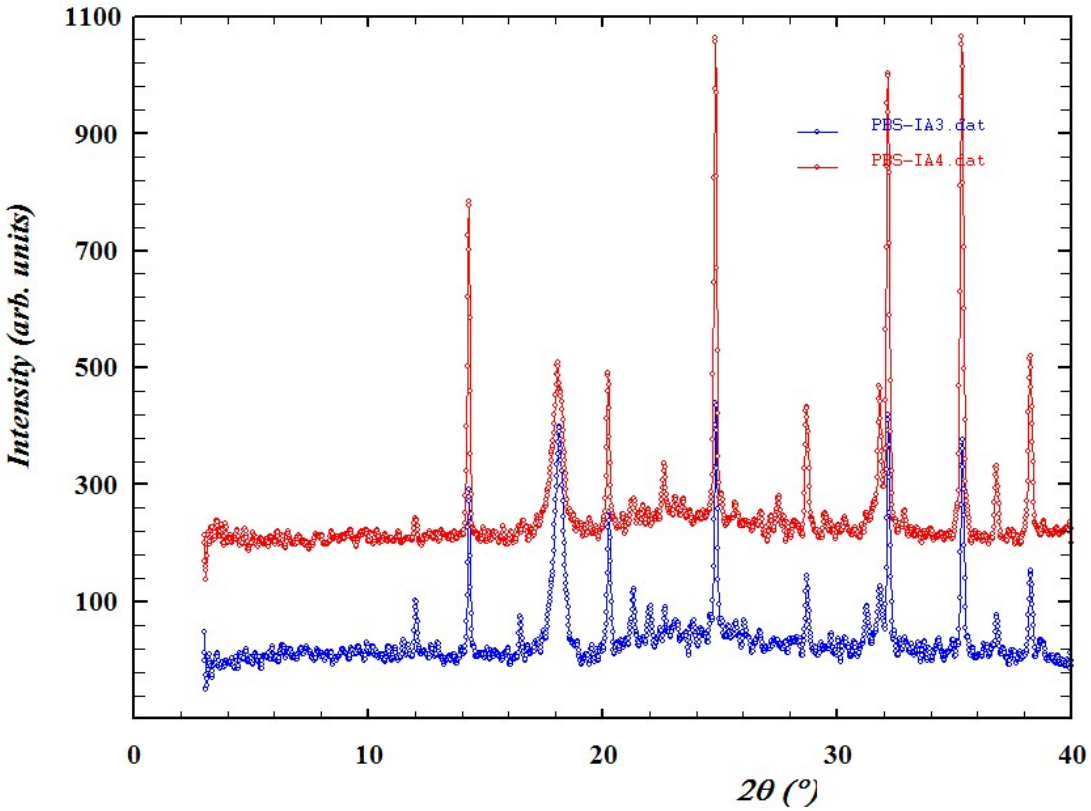


Figure S10. Podwer X-ray diffractograms of the resulting compounds after the treatment in PBS buffer in **1** (blue) and **2** (red)

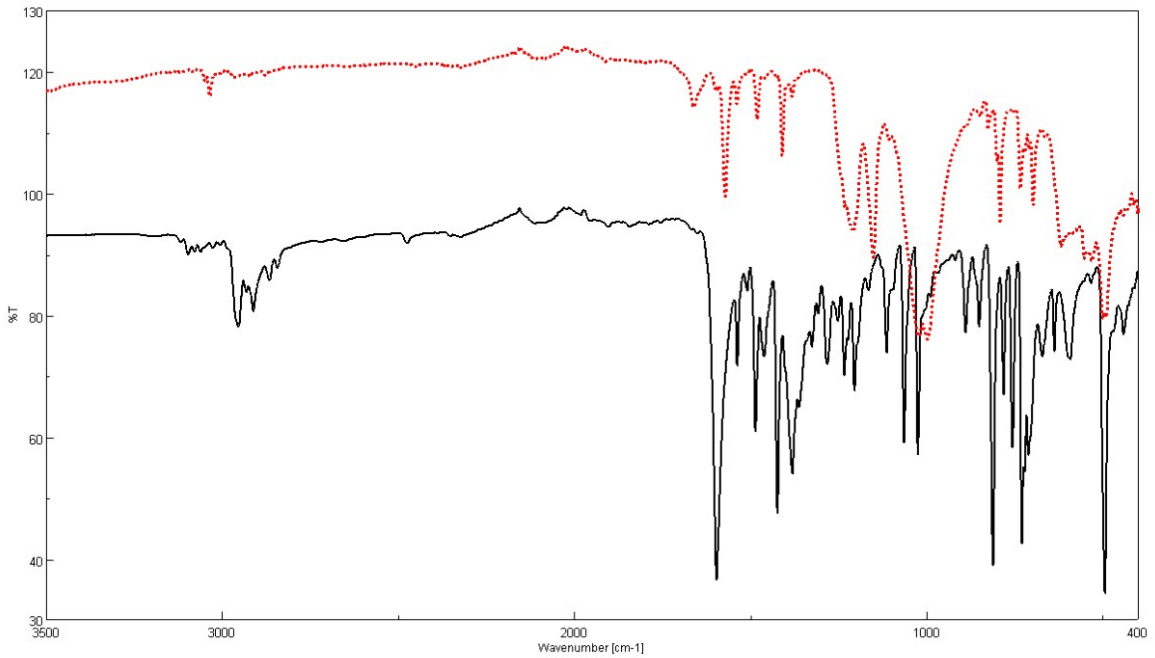
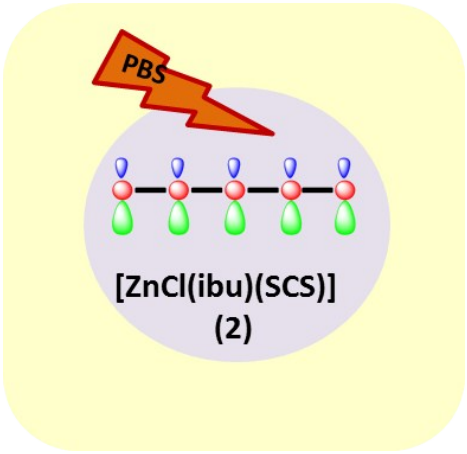


Figure S11. IR spectra of compound **2** before (continuous black line) and after the treatment (dotted red line) with PBS buffer

4.4. Ibuprofen release mechanism in [ZnCl(ibu)(SCS)] (2)



Scheme S5

*A) Experimental procedure for measuring anion **ibuprofen:SCS molar ratio** released in [ZnCl(ibu)(SCS)] (**2**) over time*

27 mg (0.045 mmol) of [ZnCl(ibu)(SCS)] (**2**) were soaked in 5 mL of PBS buffer (0.1M, pH 7.4) solution prepared in D_2O solvent. At different times, 0.5 mL of the resulting solution was analyzed by ^{1}H-NMR (400 MHz, D_2O, 25 ºC). The solution was separated from the solid by centrifugation. The ibu:SCS molar ratios of the supernatant were determined by the signal intensity ratios of the two ligands in the ^{1}H-NMR spectra.

^{1}H-NMR (400 MHz, D_2O, 25ºC) *(batch after4 days)*: δ 0.85-0.87 (d, 6H, C12-H3, C11-H3, ibu); 1.36-1.38 (d, 3H, C3-H3, ibu); 1.80-1.84 (m, 1H, C11-H, ibu), 2.45-2.47 (d, 2H, C10-H2); 3.57-3.66 (m, 1H, C2-H, ibu); 7.19-7.21 (d, 2H, C5arom, C7arom, ibu), 7.24-7.26 (d, 2H, C6arom, C8arom, ibu), 7.42-7.43 (d, 0.40H, C15arom, C16arom, SCS), 8.34-8.36 (d, 0.40H, C17arom, C18arom, SCS).

Table S5. Ibuprofen anion:SCS molar ratio released over time

Time	*Molar ratio ibu:SCS*
2 h	5:1
4 h	10:1
4 days	10:1
7 days	8:1
14 days	8:1
1 month	8:1

B) *Experimental procedure for measuring anion **ibuprofen concentration** released in [ZnCl(ibu)(SCS)] (**2**) over time.*

The previously described procedure was followed but an equimolar amount of DMSO (0.045 mmol, 3.23 µL) was added to the solution. At different times, the solution was separated from the solid by centrifugation and 0.5 mL was analyzed by ^{1}H-NMR spectroscopy (400 MHz, D_2O, 25 ºC). The concentration of the DMSO sample and the intensity of the methyl singlet at 2.71 ppm were used at the inputs for quantification of the ibuprofen concentration. The reference substance (DMSO) and the sample did not react with each other or with the solvent. The signal intensity ratio of ibu:DMSO was used to calculate the ibuprofen concentration in solution. The results indicate that the concentration in solution is stable and does not vary with time.

Table S6. Concentration released over time

Time	*Molar ratio ibu: SCS: DMSO*	*[DMSO]*	*[ibu]*	*[SCS]*
2 h	14:1:46	9.10^{-3}	$2.8.10^{-3}$	$0.196.10^{-3}$
3 days	8:1:27	9.10^{-3}	$2.6.10^{-3}$	$0.325.10^{-3}$
12 days	8:1:28	9.10^{-3}	$2.5.10^{-3}$	$0.312.10^{-3}$
1 month	8:1:26	9.10^{-3}	$2.7.10^{-3}$	$0.337.10^{-3}$

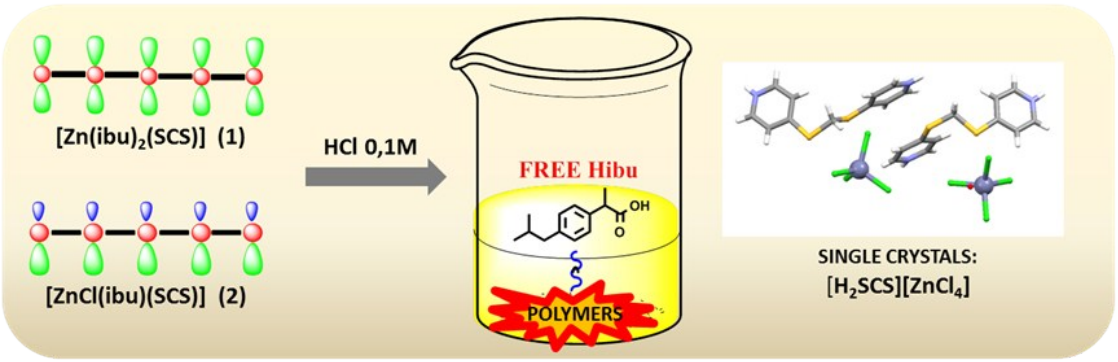
C) *Experimental procedure for Ibuprofen anion release quantification in [ZnCl(ibu)(SCS)](**2**)*

The procedure described previously was followed in this treatment but at different times the solution was separated from the solid by filtration and the solvent was completely replaced with 5 mL of fresh D_2O solvent. The supernatant was analyzed by ^{1}H-NMR spectroscopy (400 MHz, D_2O, 25ºC). Ibuprofen concentrations were calculated by qNMR using DMSO as the qNMR reference (Table S7).

Table S7. Ibuprofen anion release quantification

Batch	*Added DMSO(mol)*	*Molar ratio ibu:SCS:DMSO*	*[ibu]*	*Removed ibuprofen moles*	*Removed SCS moles*
1st batch	$4.50.10^{-5}$	8:1:32	$2.25.10^{-3}$	$1.12.10^{-5}$	$1.40.10^{-6}$
2nd batch	$4.50.10^{-5}$	8:1:32	$2.25.10^{-3}$	$1.12.10^{-5}$	$1.40.10^{-6}$
3rd batch	$4.50.10^{-5}$	8:1:32	$2.25.10^{-3}$	$1.12.10^{-5}$	$1.40.10^{-6}$
4th batch	$4.50.10^{-5}$	5:1:12.5	$3.60.10^{-3}$	$1.80.10^{-5}$	$3.60.10^{-6}$
5th batch	$4.50.10^{-5}$	1:5:57.5	$1.56.10^{-4}$	$7.82.10^{-7}$	$3.91.10^{-6}$

5. Release of ibuprofen in acid media:



Scheme S6

General procedure:

21 mg (0.031 mmol) of [Zn(ibu)$_2$(SCS)] (**1**) was soaked in 6 mL of distilled water in three different glass vials with an initial pH around 7. 100, 300 and 1000 µL of 0.1 M HCl solution were added to the vials and the suspensions were stirred for 30 min and 24 h, and then the pH was measured (Table S8). The same procedure was performed with 22 mg (0.040 mmol) of [ZnCl(ibu)(SCS)] (**2**) with an initial pH around 6.5. The same process was carried out on (**1**) but using D_2O solvent instead of water in order to follow the experiment by NMR (*vide infra*).

Table S8. pH variation over time after the addition of different amounts of HCl

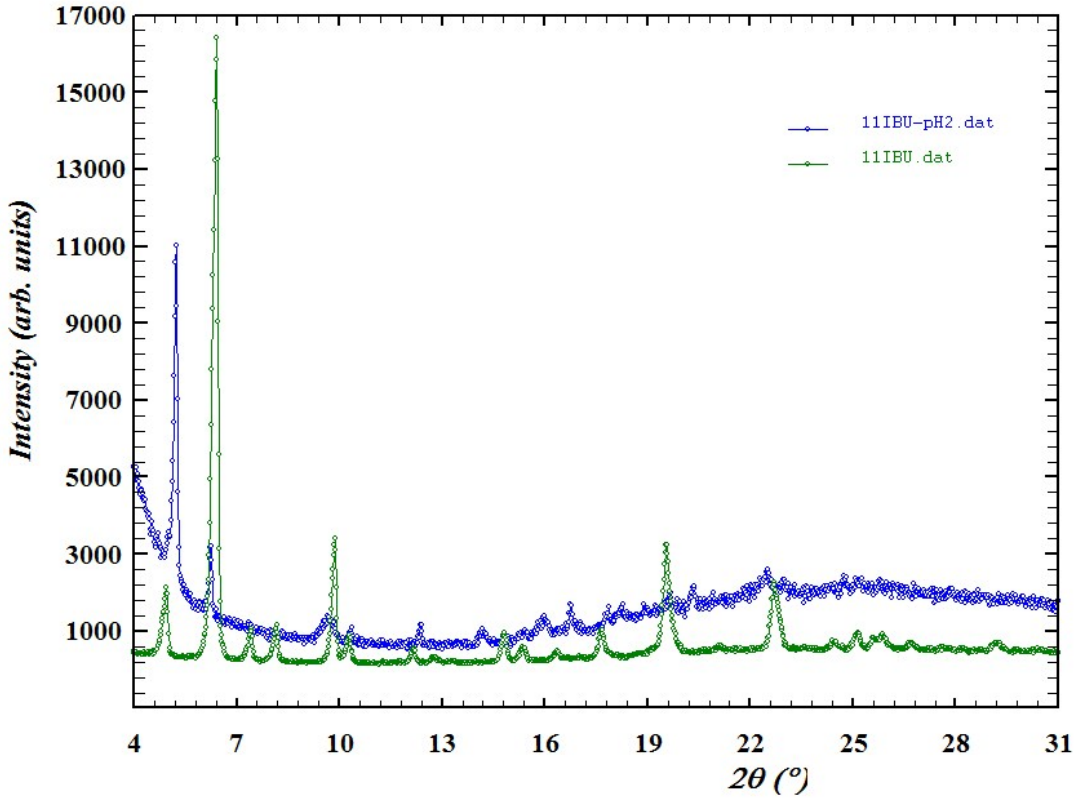
	100 µL	**300 µL**	**1000 µL**
	[Zn(ibu)$_2$(SCS)];≈ 30µmol		
initial	7.1	7.2	7.1
30 min	4.7	4.5	2.5
24 h	4.6	4.5	2.2
	[ZnCl(ibu)(SCS)];≈ 40µmol;		
initial	6.3	6.5	6.7
30 min	4.8	4.1	2.7
24h	4.9	4.1	2.6

Study of the remaining solid powders:

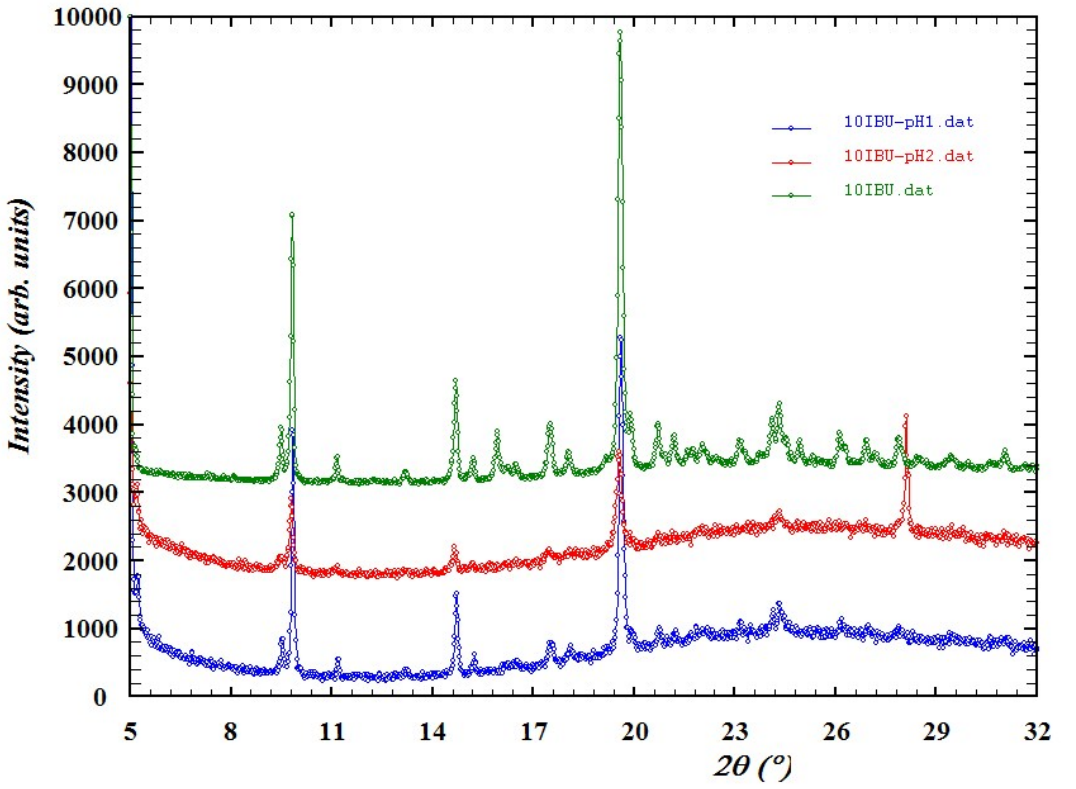
The white solids present after the acidic treatment were filtered off and characterized by elemental analysis, NMR, IR and X-ray powder diffraction (XRPD). The powder X-ray diffraction pattern of the bulk samples showed a good correlation with the patterns of the initial compounds whereas the ^{1}H-NMR spectrum of bulk powders digested in DMSO-d_6 confirmed the expected SCS:ibu ratio of ligands in each compound with a slight increase in the amount of ibuprofen. Elemental analysis showed a slight decrease of the organic compositions in the bulk samples.

Table S9. Elemental analysis after acid treatment

Sample (% exp)	**%C**	**%H**	**%N**	**%S**	**%total (C, H,N, S)**
[Zn(ibu)$_2$(SCS)]	*61.83*	*6.24*	*3.96*	*8.71*	*80.7*
+ 100 µL HCl	55.20	4.69	3.19	6.63	69.7
+ 300 µL HCl	51.35	4.22	2.43	4.80	52.8
[ZnCl(ibu)(SCS)]	*51.24*	*4.74*	*5.36*	*11.96*	*73.3*
+ 100 µL HCl	53.05	3.39	4.86	9.95	71.3
+ 300 µL HCl	52.83	1.66	5.64	9.26	69.4



A)



B)

Figure S12. A) [Zn(ibu)$_2$(SCS)] (**1**) after adding 100 µL of 0.1 M HCl. **B**) [ZnCl(ibu)(SCS)] (**2**) in acid media at different pH values (green, initial; blue, after 100 µL of HCl; red, after 300 µL).

Excess of acid

Upon addition of 1000 µL of 0.1 M HCl solution, pristine compounds were totally dissolved and free ibuprofen adhered to the walls and were floating in the liquid phase. The ^{1}H-NMR spectrum of the solid powder in DMSO-d^{6} confirmed that the ibuprofen was pure. Glass vials were sealed and single crystals of **[H_2SCS][$ZnCl_4$]** were obtained from both initial compounds (**1** and **2**) in one week.

Study of the resulting solutions

The supernatants were centrifuged in order to remove any precipitate and 25 µL of the supernatant liquids were diluted in 3 mL of water for analysis by UV-Vis. Protonation of the SCS ligand induced a bathochromic shift in the band at 265 nm to 296 nm (Figure S13).

The addition of acid led to a progressive increase in the intensity of the band at 296 nm and this change was accompanied by a decrease in the absorption bands at 212 and 265 nm. The band at 212 nm was shifted with the protonation continuously until 222 nm. This behavior is observed in both compounds (Figures S13 and S14).

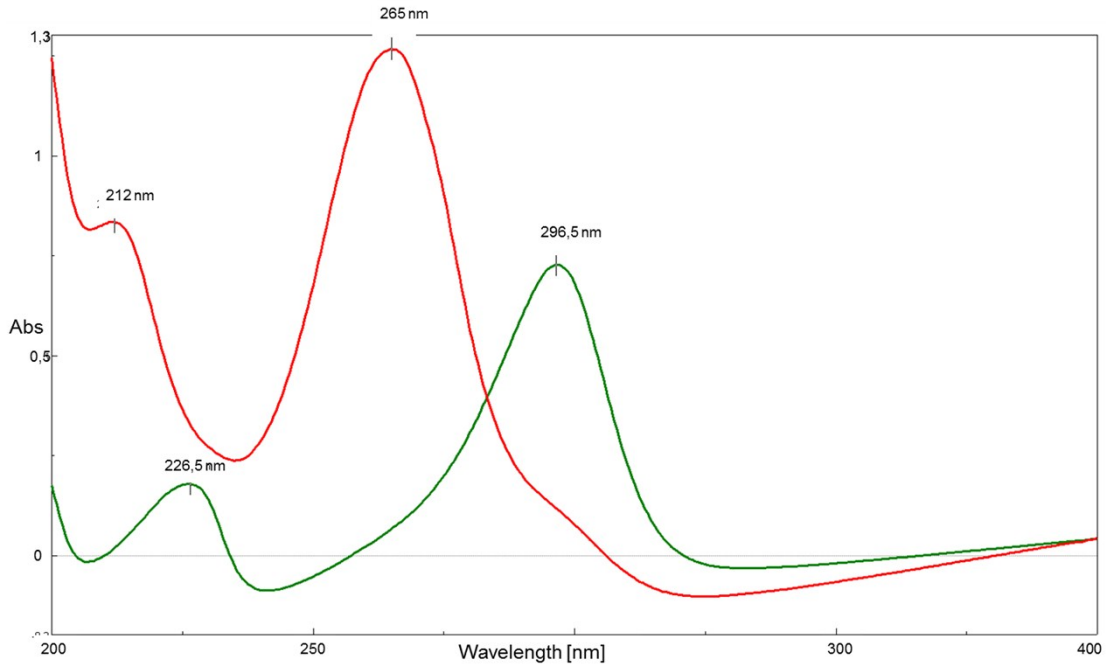


Figure S13. UV-Vis spectra of SCS (red) and protonated SCS (green)

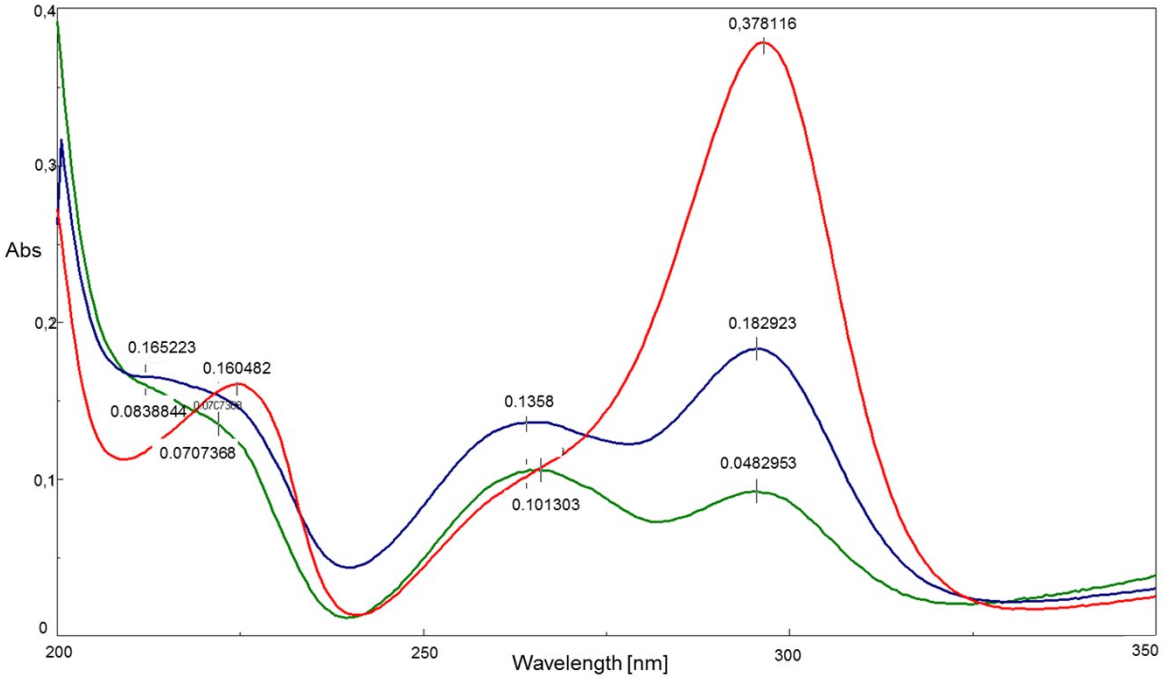


Figure S14. UV-Vis spectra of solutions of [Zn(ibu)$_2$(SCS)] (**1**) at different pH; green, (addition of 100 µL 0.1 M HCl); blue; (300 µL added); Red, (1000 µL added)

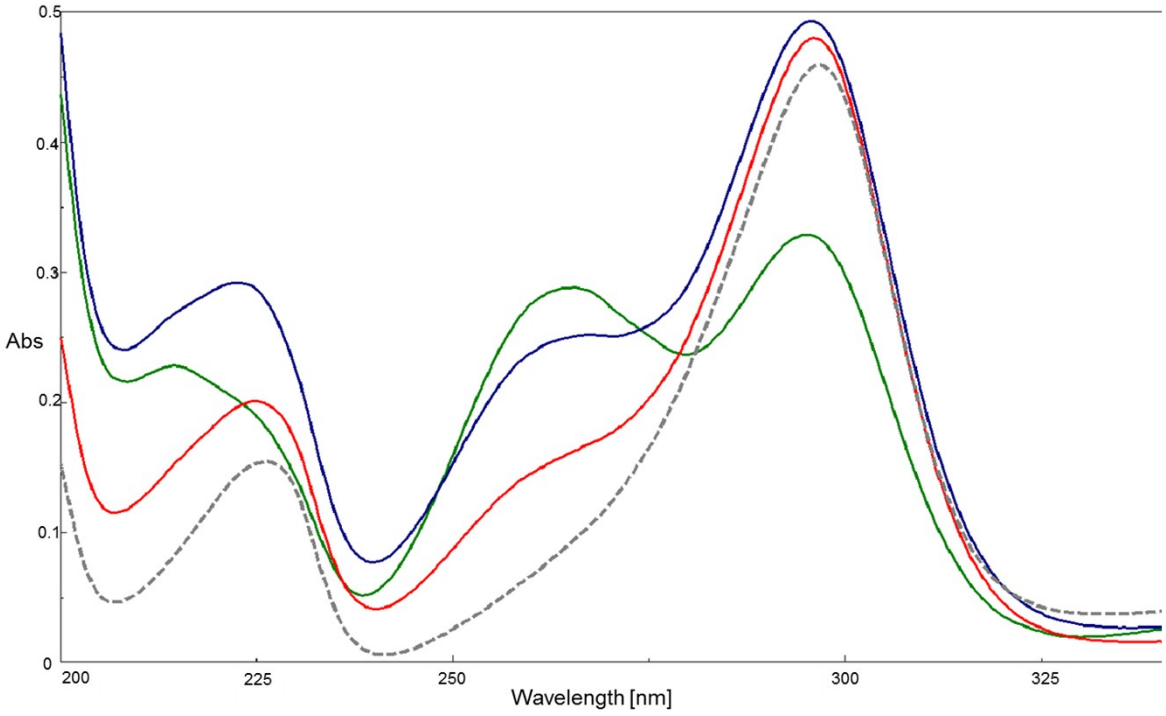
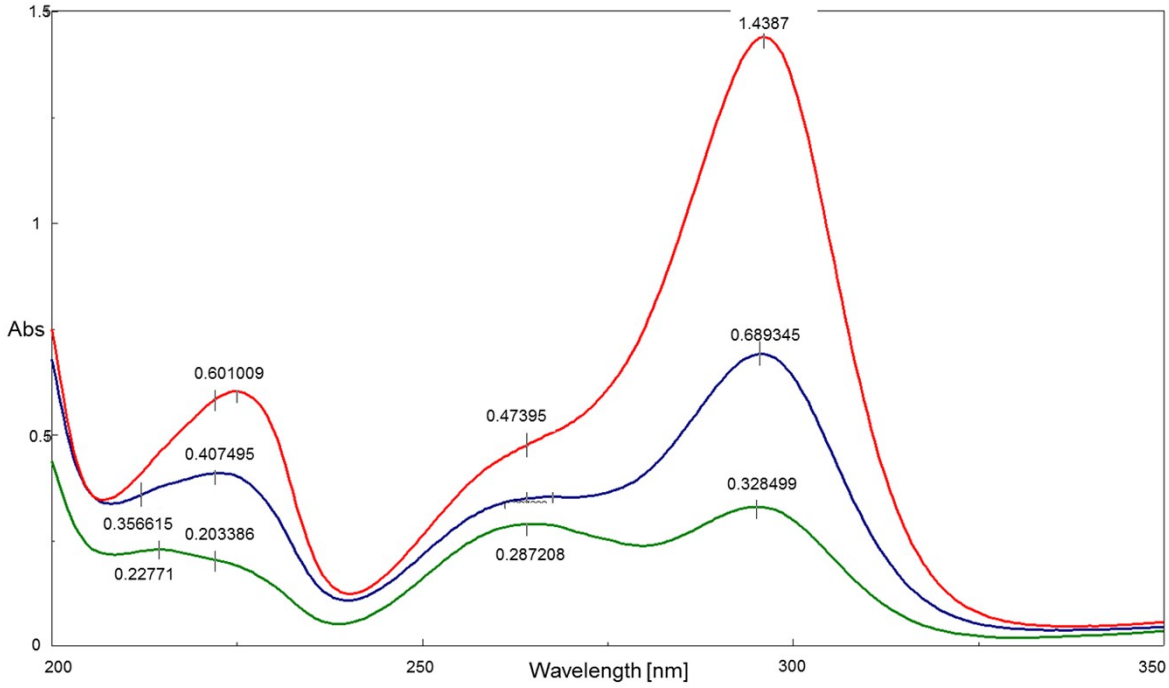


Figure S15. UV-Vis spectra of solutions of [ZnCl(ibu)(SCS)] (**2**) at different pH; green (addition of 100 µL 0.1 M HCl) ; blue; (300 µL added); red (1000 µL added) compared to the protonated SCS-H (dashed gray) (down, normalized)



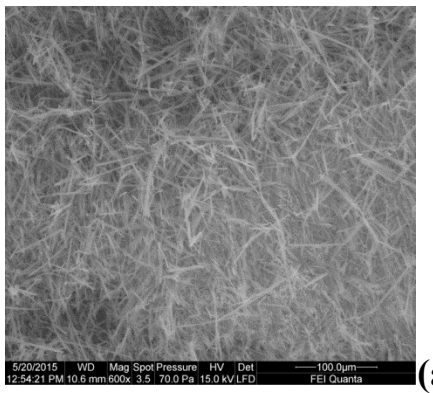
*Study of the resulting solutions from (**1**) using D_2O as solvent:*

20 mg (0.030 mmol) of $[Zn(ibu)_2(SCS)]$ (**1**) was soaked in 5 mL of D_2O solvent. At different times, 100, 200 and 700 µL of 0.1 M HCl solution prepared in D_2O were added to the batch. Suspensions were left to stir for 1 h, after which the remaining solutions were centrifuged and analyzed by ^{1}H-NMR spectroscopy (400 MHz, D_2O, 25 ºC). The ibu:SCS signal ratio was used to calculate molar ratios. The samples were returned to the solution after measurements. Upon protonation of the SCS ligand the pyridine ring signals were shifted to lower field (Table S10). The molar ratio $[SCS\text{-}H_2]^{+2}$:ibu$^-$ increased with acidification of the medium; at a pH around 5 (100 µL of HCl) the $[SCS\text{-}H_2]^{+2}$:Hibu molar ratio was 2:1; at pH around 4 (300 µL of HCl) it was 13:1; and at pH around 2 (1000 µL of HCl) ibuprofen was not detected in solution.

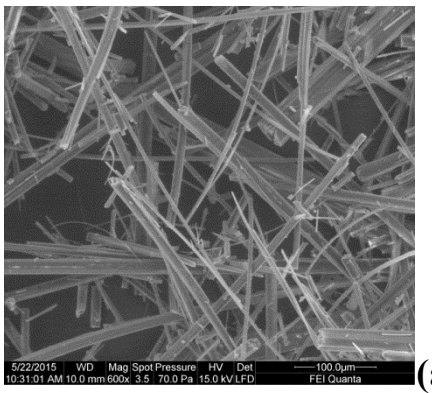
Table S10. ^{1}H-NMR signals variation of SCS in acidic media:

	C14-H2(s, 2H)	C15,16-Harom, (dd, 4H)	C17,18-Harom, (dd, 4H)	$[SCS\text{-}H_2]^{+2}$:ibu Ratio
$[Zn(ibu)_2(SCS)]$	-	7.38-7.40	8.33-8.35	-
100 µL	4.97	7.68-7.70	8.42-8.43	2:1
300 µL	5.02	7.76-7.77	8.45-8.46	13:1
1000 µL	5.12	7.90-7.93	8.49-8.51	1:0

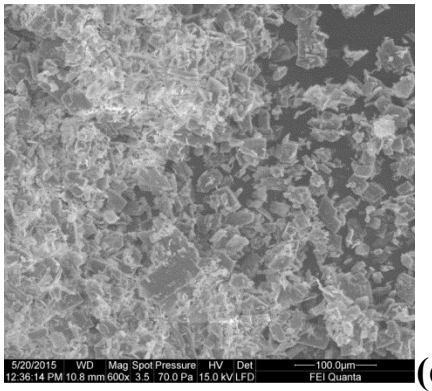
6. SEM images:



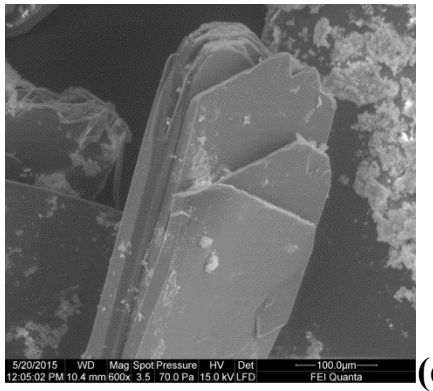
(a)



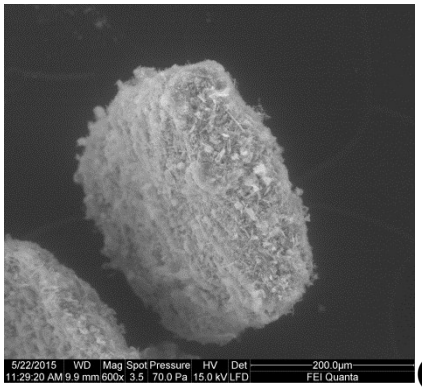
(a´)



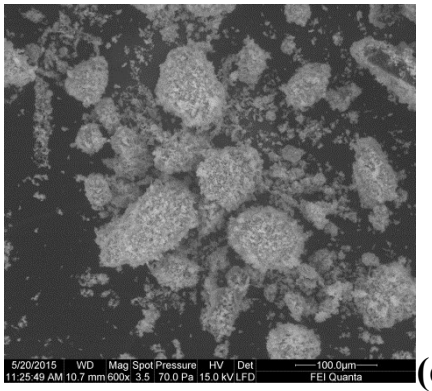
(d)



(d´)



(b)



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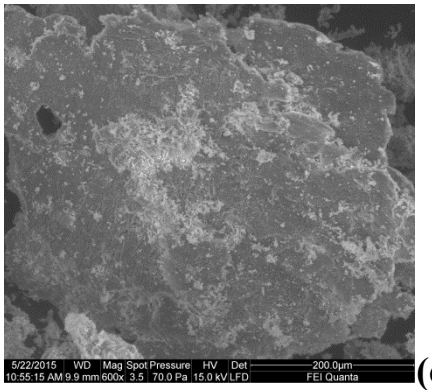
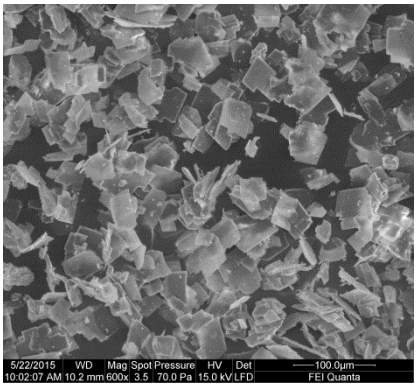


(c)



(f)

Figure S16. SEM images of (a) [$Zn(ibu)_2(SCS)$] (1) and (d) [ZnCl(ibu)(SCS)] (2) with their respective singles crystals (a' and d'); post-treatment materials; (b) (1) at pH = 5; (e) (2) at pH = 5; (c) product after anionic exchange in PBS solution, (f) (2) in an aqueous environment.

7. References

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