

# New titanocene (IV) dicarboxylates with potential cytotoxicity: synthesis, structure, stability and electrochemistry

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## Supplementary information

### 1. Preparation of silver salts

**Silver benzoate (1h).** All procedures were performed in the dark. Benzoic acid (0.537 g, 4.40 mmol) was added to a solution of NaHCO<sub>3</sub> (0.370 g, 4.40 mmol) in 20 mL of water in a 100 ml beaker, and the mixture was stirred until gas evolution ceased. The solution was filtered through a paper filter and the filter was washed with 20 ml of water. A solution of AgNO<sub>3</sub> (0.679 g, 4.00 mmol) in 5 mL of water was added dropwise to the filtrate. The white precipitate was separated by filtration on a glass filter under reduced pressure, washed with water, ethanol, and dried in a stream of air. The resulting white powder was transferred to a flask and dried several times with benzene on a rotary evaporator to remove traces of water. **1h** was obtained as a white powder. Yield: 0.577 g (63%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz,  $\delta$  ppm): 7.93 - 8.00 (m, 2H, -CH $\alpha$ -Ar), 7.34 - 7.47 (m, 3H, -CH $\beta,\gamma$ -Ar ).

**Silver acetylsalicylate (1j).** All procedures were performed in the dark. Acetylsalicylic acid (0.757 g, 4.20 mmol) was added to a solution of NaHCO<sub>3</sub> (0.353 g, 4.20 mmol) in 20 mL of water in a 100 ml beaker, and the mixture was stirred until gas evolution ceased. The solution was filtered through a paper filter, the filter was washed with 20 ml of water. A solution of AgNO<sub>3</sub> (0.646 g, 3.80 mmol) in 5 mL of water was added dropwise to the filtrate. The white precipitate was separated by filtration on a glass filter under reduced pressure, washed with water, ethanol, and dried in a stream of air. The resulting white powder was transferred to a flask and dried several times with benzene on a rotary evaporator to remove traces of water. **1j** was obtained as a white powder. Yield: 0.594 g (42%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz,  $\delta$  ppm): 7.88 (dd, J=7.67, 1.70 Hz, 1H-CH $\alpha$ -Ar), 7.37 - 7.43 (m, 1H-CH $\beta$ -Ar), 7.23 (td, J=7.50, 1.12 Hz, 1H-CH $\beta'$ -Ar), 7.02 (dd, J=7.97, 1.01 Hz, 1H-CH $\gamma$ -Ar), 2.22 (s, 3H, -CH<sub>3</sub>).

## 2. IR Spectra of p-aminobenzoic and p-azidobenzoic acids

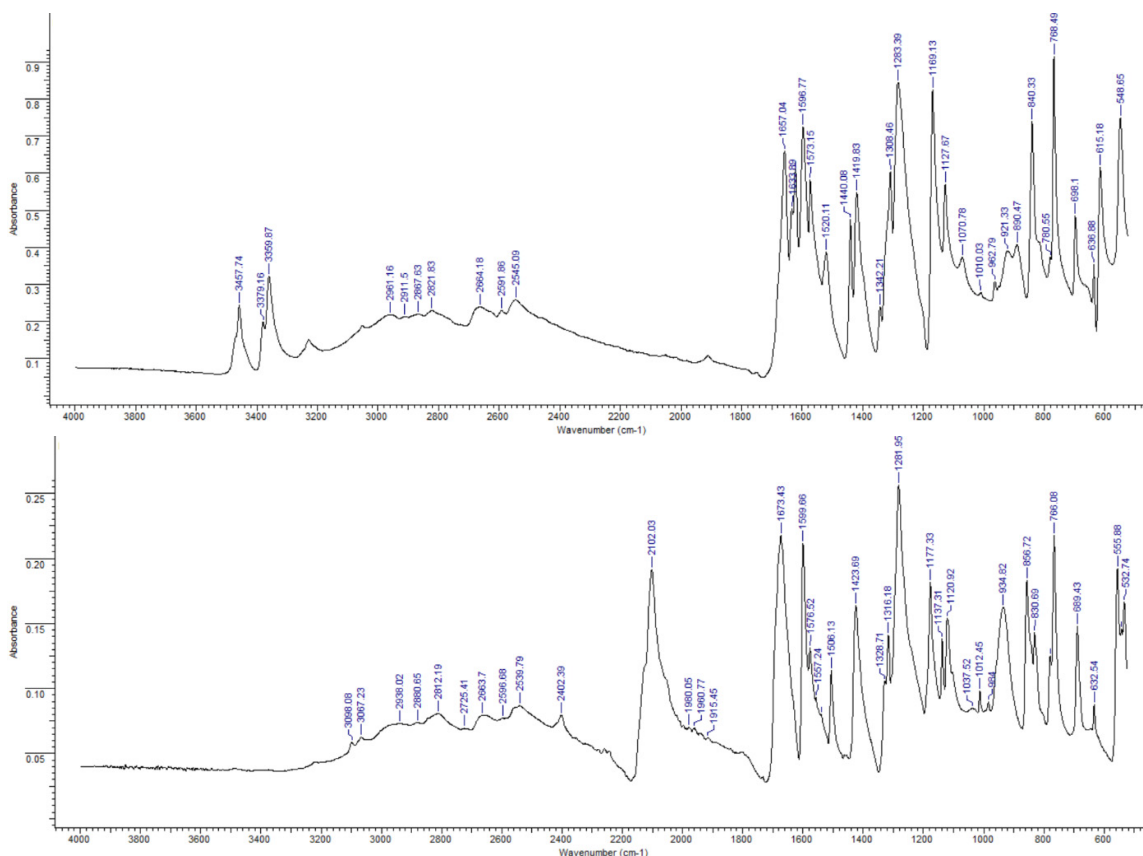


Figure S1. IR-Spectra of p-aminobenzoic acid (top) and p-azidobenzoic acid (bottom).

## 2. Selected NMR spectra of titanocene dicarboxylates.

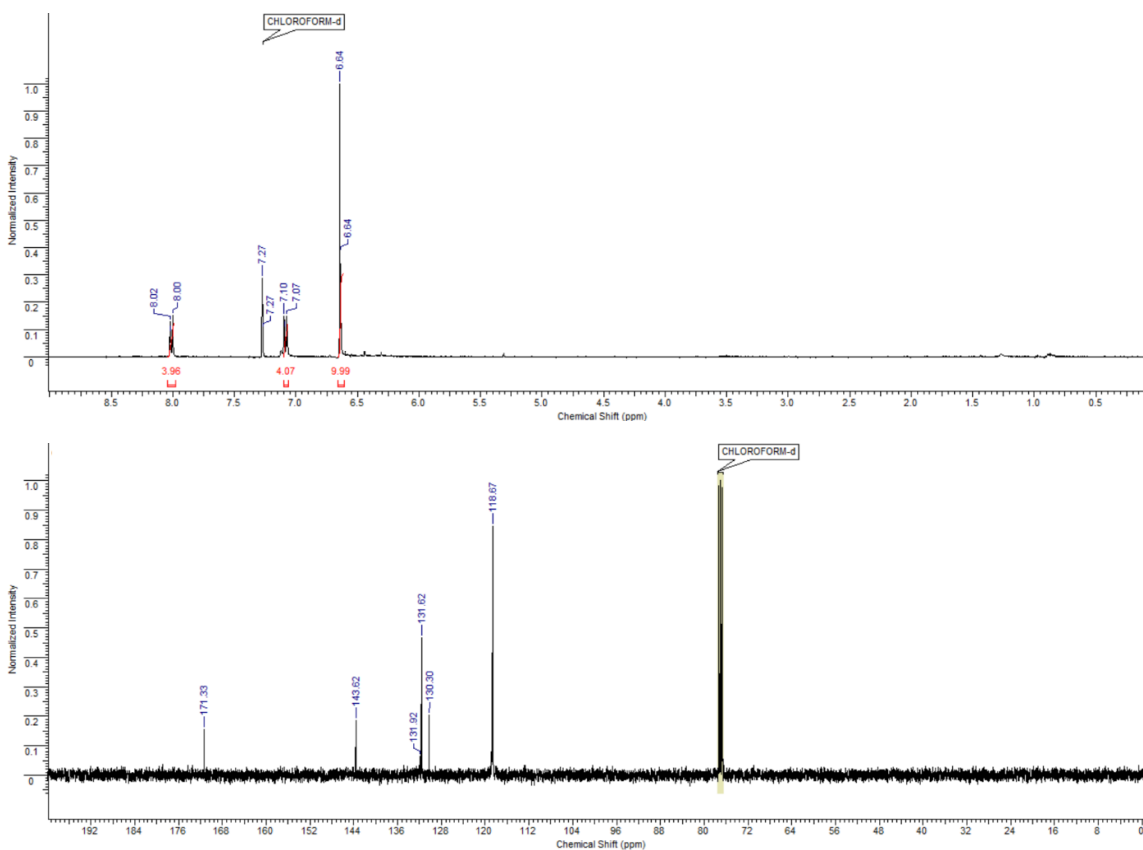
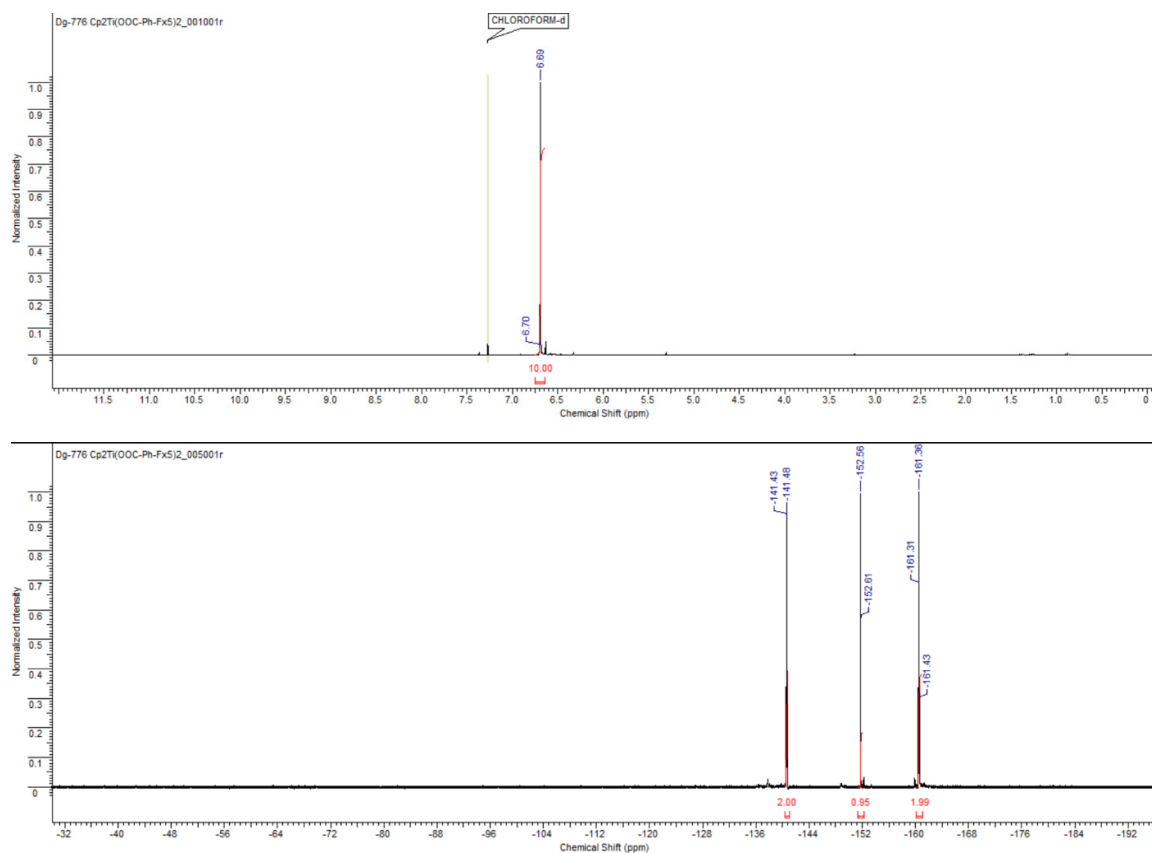
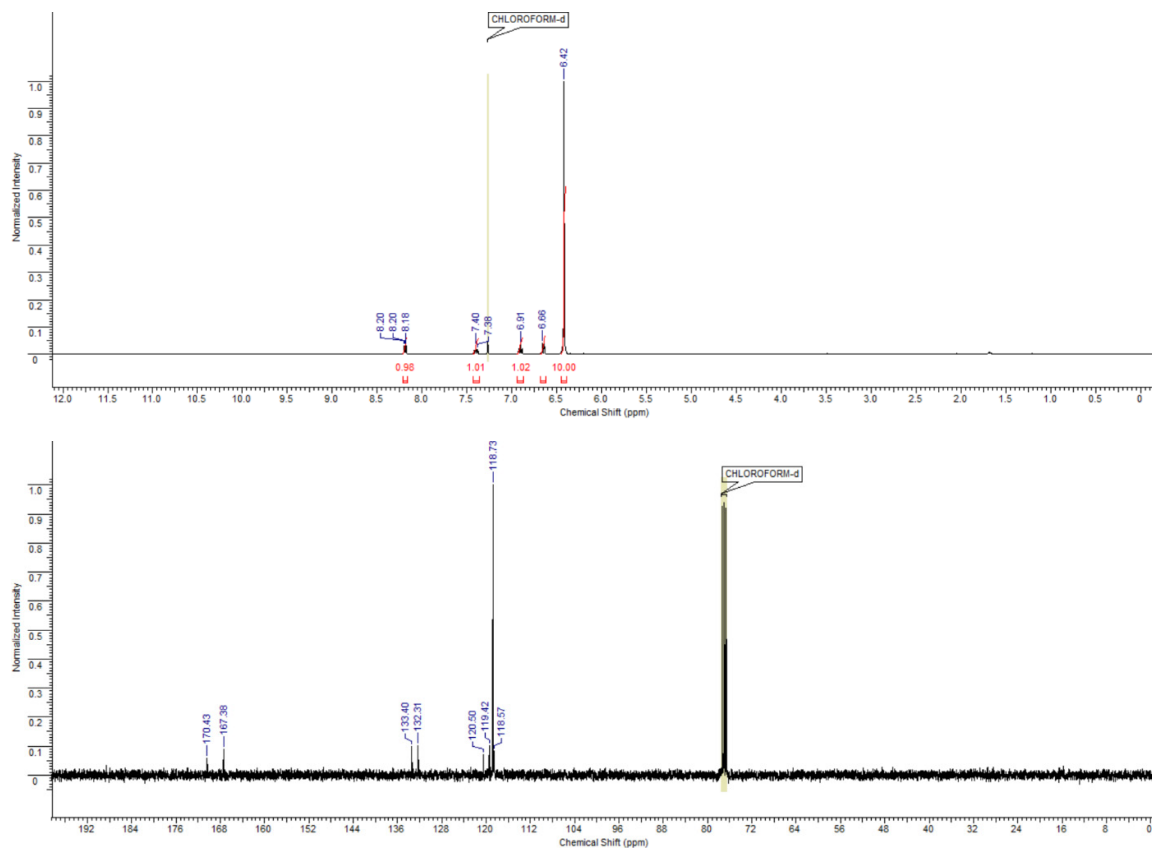


Figure S2. <sup>1</sup>H (top) and <sup>13</sup>C (bottom) NMR Spectra of compound 2c.



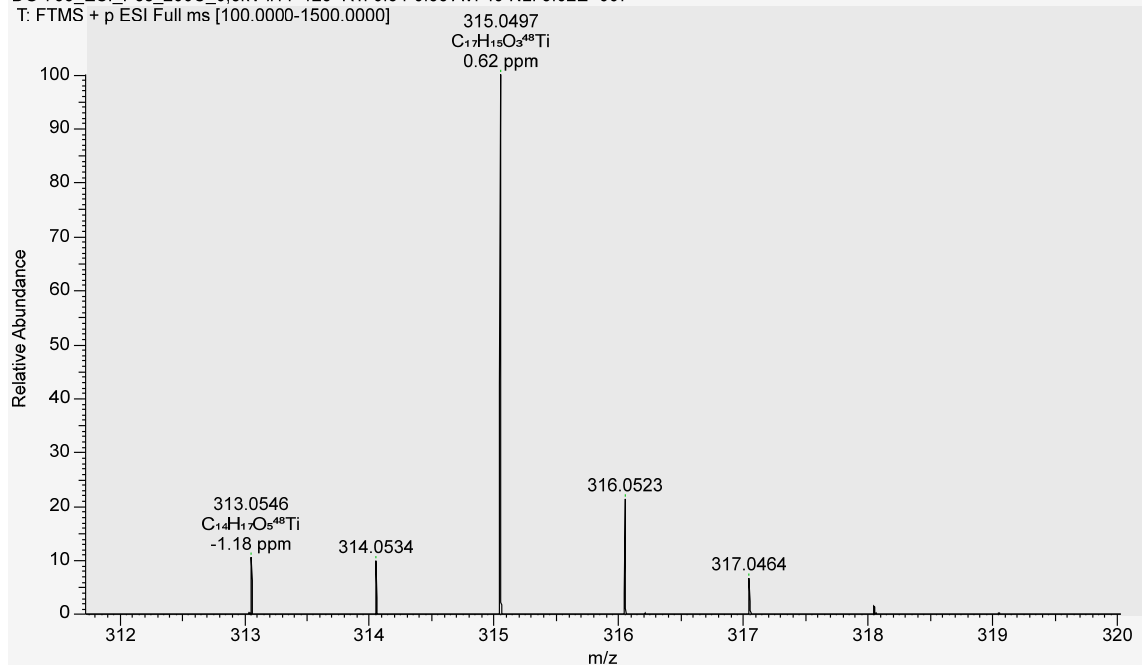
**Figure S3.**  $^1\text{H}$  (top) and  $^{19}\text{F}$  (bottom) NMR Spectra of compound **2e**.



**Figure S4.**  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR Spectra of compound **2g**.

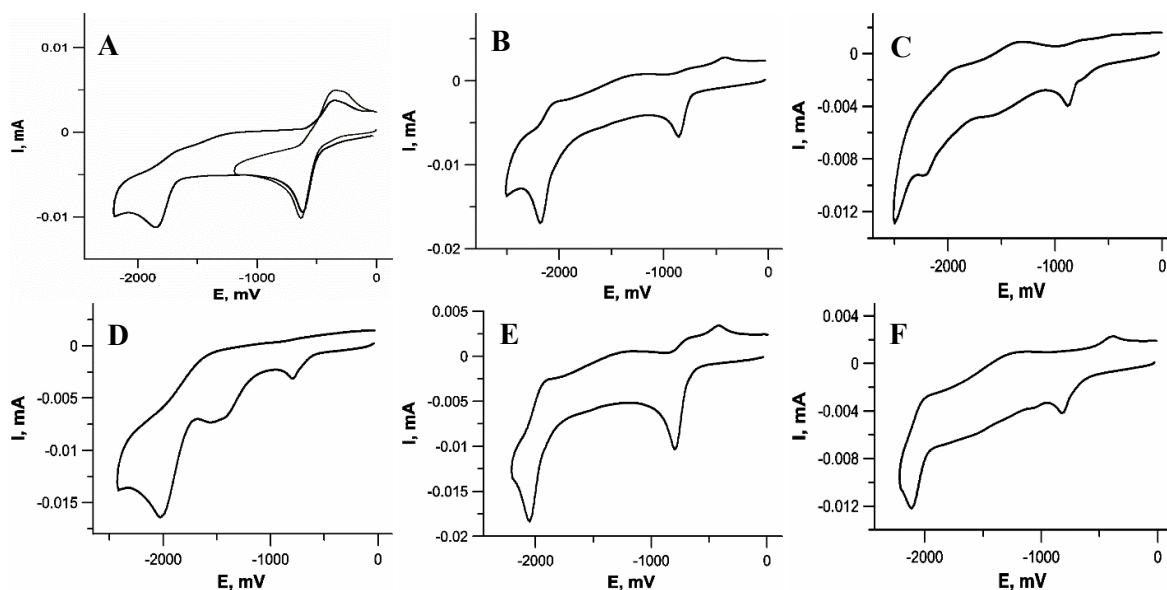
### 3. HRMS of compound 2g

DG-765\_ESI\_Pos\_200C\_0.8kV #77-125 RT: 0.34-0.55 AV: 49 NL: 5.02E+007  
T: FTMS + p ESI Full ms [100.0000-1500.0000]



**Figure S5.** HRMS spectrum of compound 2g.

### 4. CV-curves for titanocene dicarboxylates



**Figure S6.** CV-curves of titanocene dichloride (A), and compounds 2a (B), 2b (C), 2c (D), 2d (E), 2f (F).

### 5. Crystal data and structure refinement for compounds 2a, 2e, 2g

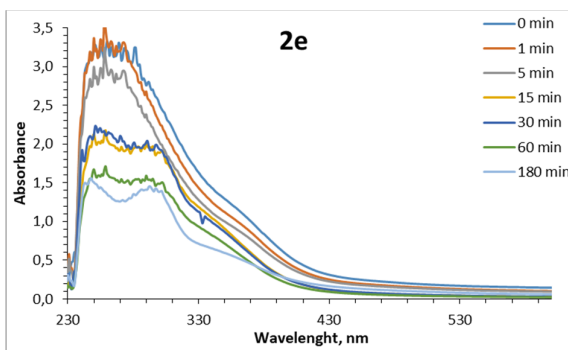
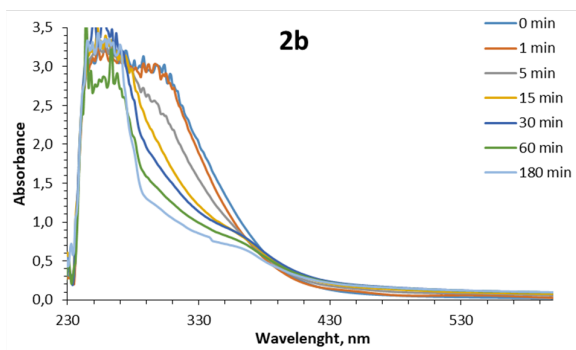
Absorption corrections based on measurements of equivalent reflections were carried out by *SADABS* (multi-scan methods) #. The structures were solved by direct methods with the *SHELXT* program and refined by full matrix least-squares on  $F^2$  with *SHELXL*. Positions of all non-H atoms were found from electron difference density maps and refined with individual anisotropic displacement parameters. Positions and individual isotropic displacement parameters for phenyl and cyclopentadienyl H-atoms were positioned geometrically and refined as riding atoms with relative isotropic displacement parameters. Crystal data, data collection and structure refinement details for 2a, 2e and 2g are summarized in Table S1. The structures have been deposited at the Cambridge Crystallographic Data Center with the reference CCDC numbers 2233054,

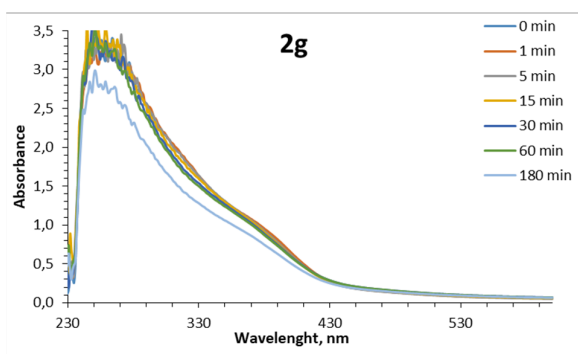
2233055, 2236508, and they also contain the supplementary crystallographic data. These data can be obtained free of charge from the CCDC *via* [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)

**Table S1.** Crystallographic data for synthesized titanocene derivatives.

Identification code	<b>2a</b>	<b>2e</b>	<b>2g</b>
Diffractometer	Bruker D8 Quest with Photon III detector	Stoe STADI VARI	Bruker D8 Quest with Photon III detector
Wavelength, Å	0.71072	1.54186	0.71072
Empirical formula	C <sub>24</sub> H <sub>20</sub> O <sub>4</sub> Ti	C <sub>24</sub> H <sub>10</sub> F <sub>10</sub> O <sub>4</sub> Ti	C <sub>17</sub> H <sub>14</sub> O <sub>3</sub> Ti
Formula weight	420.291	600.22	314.18
Temperature, K	110	295(2)	100(2)
Crystal system	Orthorhombic	Orthorhombic	Monoclinic
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	Pnna	P2 <sub>1</sub> /c
Unit cell dimensions			
<i>a</i> (Å)	7.500(4)	21.8684(5).	12.150(2)
<i>b</i> (Å)	12.510(5)	13.0894(4)	23.537(5)
<i>c</i> (Å)	21.126(10)	<i>c</i> 8.0409(2)	15.390(3)
$\beta$ (°)	90	90	108.02(3)
Volume	1982.0(16) Å <sup>3</sup>	2301.66(10) Å <sup>3</sup>	4185.3(16) Å <sup>3</sup>
Z(Z')	4(1)	4 (0.5)	12 (3)
Density (calculated)	1.408	1.732	1.496
Absorption coefficient	4.59	4.216	6.20
F(000)	872	1192	1944
$\theta$ range for data collection	1.89 to 29.	5.271 to 66.963.	1.76 to 29°.
Reflections collected	21893	15075	41278
Independent reflections	5261 [R(int) = 0.0932]	2046 [R(int) = 0.0672]	11105 [R <sub>int</sub> =0.0965]
Observed reflections	4391	1325	8029
Completeness to $\theta_{\max}$ , %	99.9	99.3	99.9
Data/parameters	5261/262	2046 / 198	11105/568
Goodness-of-fit on F <sup>2</sup>	1.051	0.977	1.051
Final R indices [I>2sigma(I)]	R1=0.0509, wR2=0.1034	R1 = 0.0421, wR2 = 0.1148	R1=0.0589, wR2=0.1462
R indices (all data)	R1 = 0.0656, wR2 = 0.1118	R1 = 0.0661, wR2 = 0.1279	R1=0.0840, wR2=0.1277
Largest diff. peak and hole	0.4557 and -0.6502 e.Å <sup>-3</sup>	0.217 and -0.343 e.Å <sup>-3</sup>	0.740 and -0.622 e.Å <sup>-3</sup>

## 6. Stability in aqueous media studies





**Figure S7.** Full absorption spectra of compounds **2b** (top left), **2e** (top right), **2g** (bottom), initial concentration = 0.4 mM obtained in water with addition of 10% per volume of DMSO, after different time intervals.