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Synthesis, structure and cytotoxicity of a zinc(II) bromide complex with caffeine

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Experimental

All chemicals were obtained from commercial sources and used as purchased. Preliminary prepared $ZnBr_2 \cdot nH_2O$ (ca. 1-2 g) was dissolved in a minimum volume of distilled water and mixed with an aqueous solution of the calculated caffeine amount (Scheme 1). ^{1}H NMR spectra were obtained using a Bruker Avance III NanoBay spectrometer, CD_3CN, ppm, 300.28 MHz. IR spectra were recorded on IR–Fourier spectrometer EQUINOX 55, «BRUKER», Germany; 4000 – 400 cm^{-1}. ESI-MS spectra were obtained using a electrospray mass spectrometer AmaZon Bruker Daltonik GmbH, UltraScan positive and negative ionization mode; m/z range: 70–2200; acetonitrile solution; 240 μL h^{-1}; needle source voltage 3.5 kV, carrier gas flow rate 6 L min^{-1}; capillary temperature 100° C, signal accumulation 300000 ions in the ion trap, signal averaging of 13 scans.

Procedure for the synthesis of [Zn(caf)(H₂O)Br₂]

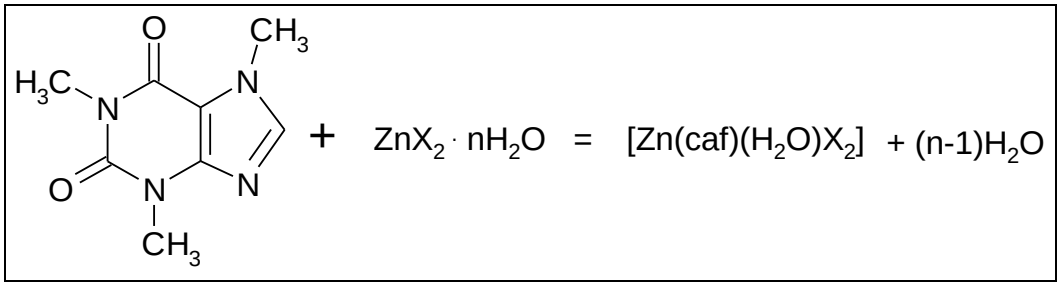
A solution of **$ZnBr_2 \cdot 2H_2O$** (1.05 g; 4.02 mmol) in water (15 mL) was added to a stirred solution of caffeine (0.26 g, 1.34 mmol) in water (25 mL). The combined solution was heated at ca. 60-70° C for solvent evaporation (about 50% of the total volume). X-ray quality colorless crystals of [**Zn(caf)(H_2O)Br_2**] were obtained by slow evaporation at room temperature. Yield: 0.36 g (61%).

Found (wt. %): Zn, 14.98; Br, 36.59; C, 21.86; H, 2.88; N, 12.79. Calc. (wt. %) for **$C_8H_{12}Br_2N_4O_3Zn$** (437.392): Zn, 14.95; Br, 36.53; C, 21.97; H, 2.77; N, 12.81. Caffeine was additionally determined gravimetrically (extraction by chloroform). The results are in good agreement with the elemental analysis data.

IR-spectra (cm^{-1}): (KBr pellets) and 680 – 30 cm^{-1} (Nujol mulls): 80-200 ν(Zn-O)+ν(Zn-N)+δ(OZnN)+ν(Zn-Br)+δ(BrZnBr); 215 ν_s(Zn-Br); 255 ν_{as}(Zn-Br); 297 ν(Zn-Br)+ρ_r(H_2O); 437, 463 ν(Zn-N)+δ_{ring}+$\gamma_{ring;}$ 500 τ(caffeine)+**ν(Zn-O)**+ν(**Zn-N**); 551 ν(Zn-O)+δ_{ring}+ρ_w(H_2O); 613 δ_{ring}+γ_{ring}+δ(ZnNC); 1185 δ(CH)+ρ_r(CH_3)+**ν(Zn-N)**; 1563 ν(C=C)+δ(NCN)+ν(Zn-N); 1636 ν_{as}(C=O)+ν(C=N)+δ_{ring}+δ(H_2O); 1692 ν_s(C=O)+δ_{ring}; 3200-3500 ν(O-H).

^{1}H NMR (CD_3CN): δ 7.74 (s, CH A), 3.87 (s, CH_3 B), 3.45 (s, CH_3 C), 3.23 (s, CH_3 D) **(Figure S1**).

ESI-MS spectra for **[Zn(C$_8$H$_{10}$N$_4$O$_2$)(H$_2$O)Br$_2$]** the peaks in the positive mode at 195.08, 289.01, 361.03, 411.06 and in the negative mode at 304.89 and 530.32 are assigned to cafH$^+$ (195.087), Zn$_2$Br$_2^+$ (289.690), [Zn(C$_8$H$_{10}$N$_4$O$_2$)BrNa]$^+$ (361.933), (caf)$_2$Na$^+$ (411.151) and ZnBr$_3^-$ (304.680) and Zn$_2$Br$_5^-$ (530.441), respectively (**Scheme S2**).



Scheme S1. Preparation of [Zn(caf)(H$_2$O)X$_2$] complexes.

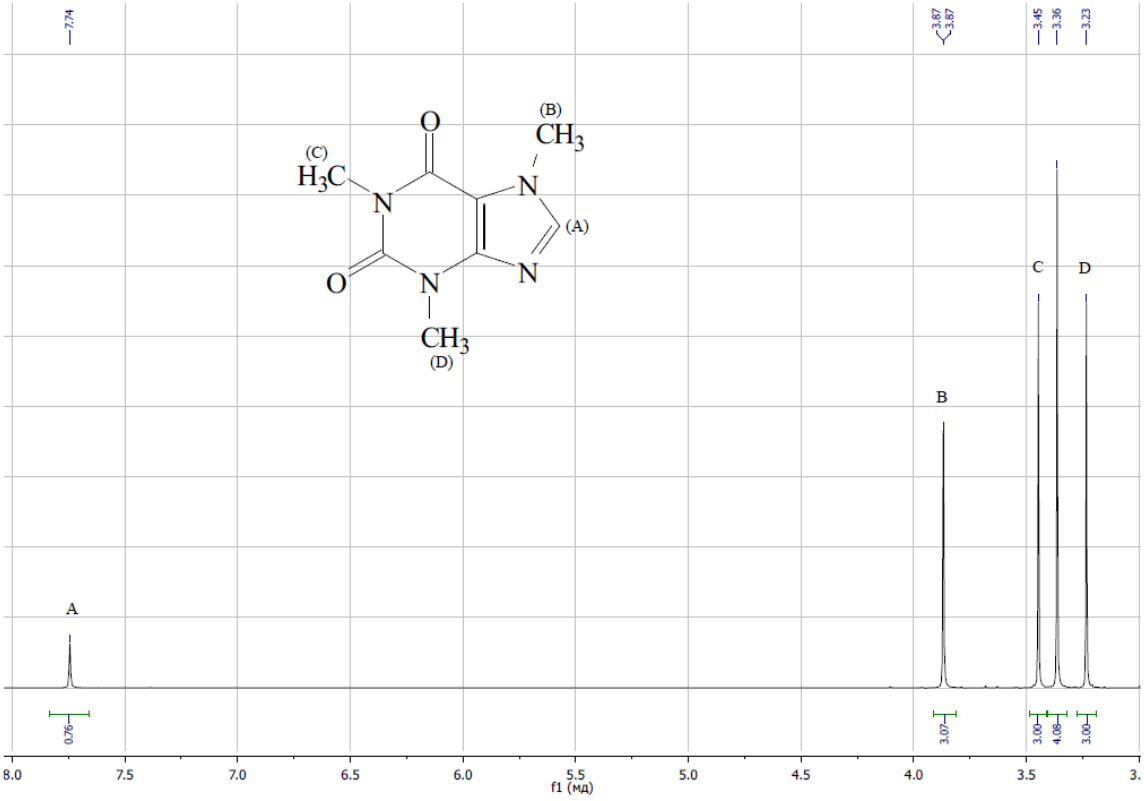
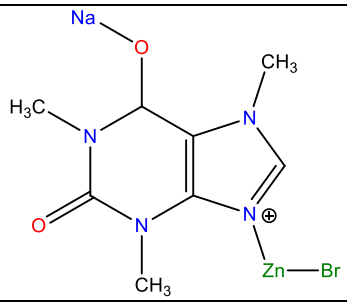
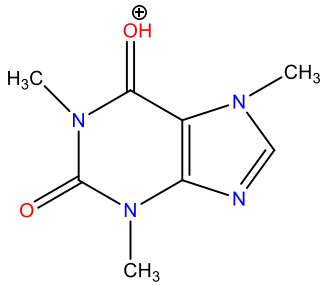
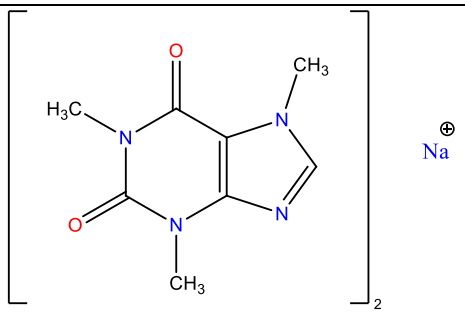


Figure S1. ^{1}H NMR spectrum of **[Zn(caf)(H$_2$O)Br$_2$]** (CD$_3$CN solution).

Scheme S2. Fragments data

Fragments	m/z
$[ZnBr]_2^+$	289.690 (100.0%), 287.693 (87.2%), 289.691 (76.9%), 291.688 (68.5%), 291.689 (67.2%), 287.692 (51.4%), 293.686 (45.2%), 285.695 (44.8%)
	361.933 (100.0%), 363.931 (97.3%), 363.930 (57.4%), 365.928 (55.9%), 365.929 (38.6%), 367.927 (37.5%)
	195.087 (100.0%), 196.091 (8.7%), 196.084 (1.5%)
	411.151 (100.0%), 412.154 (17.3%), 412.148 (3.0%), 413.157 (1.4%)
$[ZnBr_3]^-$	304.680 (100.0%), 302.682 (90.5%), 306.678 (63.4%), 304.679 (51.9%), 306.677 (50.5%), 308.676 (33.9%), 300.684 (31.0%), 302.681 (17.8%)
$[Zn_2Br_5]^-$	528.444 (100.0%), 530.441 (99.3%), 530.442 (90.9%), 528.443 (87.2%), 526.446 (79.0%), 532.440 (61.5%)

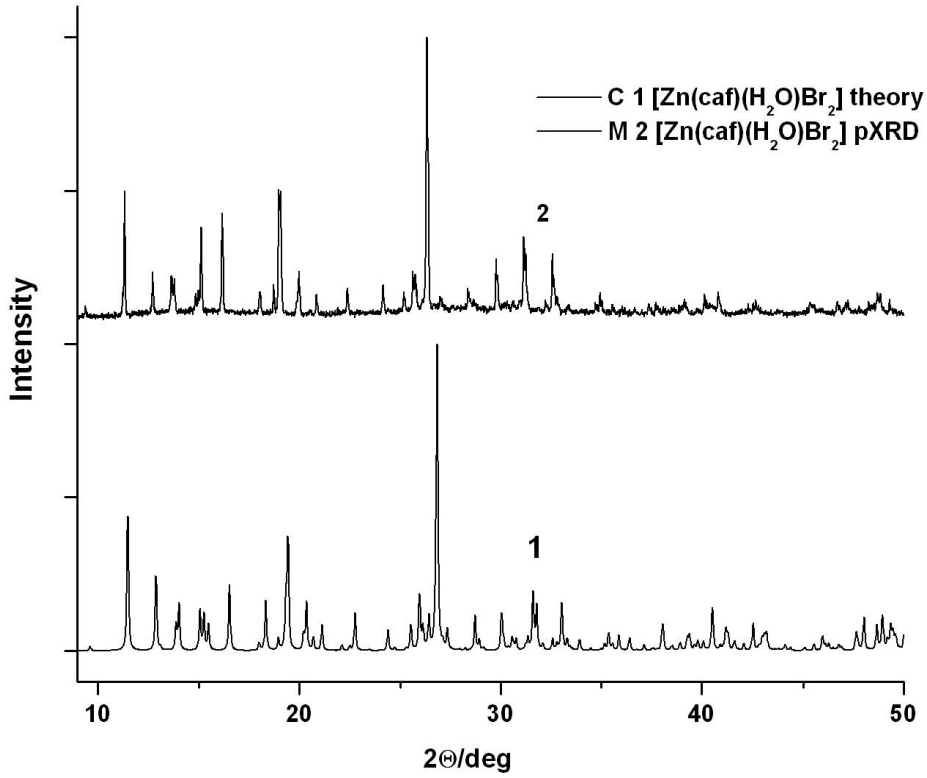


Figure S2. Theoretical (1) and experimental (2) pXRD patterns.

Table S1. Crystal data and structure refinement for compound **1**	
Compound	$[Zn(C_8H_{10}N_4O_2)(H_2O)Br_2]$ (**1**)
Empirical Formula	$C_8H_{12}Br_2N_4O_3Zn$
Formula weight	437.41
Radiation, T, K	Mo Kα (λ = 0.71073), 150 K
Crystal system, Sp. gr., Z	Monoclinic, $P2_1/n$, 4
a, b, c, Å	7.5774(15), 11.442(2), 15.383(3)
α, β, γ, °; V, $Å^3$	90.00, 91.259(3), 90.00; 1333.4(5)
Crystal size, mm^3	0.38 x 0.08 x 0.07 Colorless needle
2Θ range for data collection, °	4.44 – 56.68
Index ranges	$-10 \leq h \leq 10$; $-15 \leq k \leq 15$; $-20 \leq l \leq 20$
Reflections collected /Independent reflections	13670/3327
Data/restraints/parameters	3327/0/164
μ, mm^{-1}; ρ, $g \cdot cm^{-3}$	7.840; 2.179
GOOF	1.026
R1/wR2 [I≥2σ(I)]; R1/wR2	0.0223/0.0564; 0.0259/0.0580
Largest diff. peak/hole/ e $Å^{-3}$	0.46/-0.47
Flack parameter	-

Table S2. Selected bond distances (Å) and angles (°) for **1**.

Bond lengths					
Zn(1)–Br(1)	2.3697(6)	N(1)–C(2)	1.347(3)	N(3)–C(7)	1.472(2)
Zn(1)–Br(2)	2.3444(5)	N(2)–C(2)	1.330(3)	N(4)–C(1)	1.366(2)
Zn(1)–O(3)	2.0253(14)	N(2)–C(3)	1.381(2)	N(4)–C(5)	1.373(2)
Zn(1)–N(1)	2.0736(17)	N(2)–C(6)	1.463(2)	N(4)–C(8)	1.464(2)
O(1)–C(4)	1.234(2)	N(3)–C(4)	1.394(3)	C(1)–C(3)	1.372(3)
O(2)–C(5)	1.227(2)	N(3)–C(5)	1.396(2)	C(3)–C(4)	1.422(3)
N(1)–C(1)	1.369(2)				

Bond angles			
Br(2)–Zn(1)–Br(1)	115.191(15)	C(1)–N(4)–C(8)	121.07(16)
O(3)–Zn(1)–Br(1)	107.46(4)	C(5)–N(4)–C(8)	119.06(16)
O(3)–Zn(1)–Br(2)	105.47(4)	N(1)–C(1)–C(3)	110.51(17)
O(3)–Zn(1)–N(1)	99.29(6)	N(4)–C(1)–N(1)	127.80(17)
N(1)–Zn(1)–Br(1)	103.69(5)	N(4)–C(1)–C(3)	121.67(17)
N(1)–Zn(1)–Br(2)	123.75(5)	N(2)–C(2)–N(1)	113.13(18)
C(1)–N(1)–Zn(1)	141.51(13)	N(2)–C(3)–C(4)	130.87(17)
C(2)–N(1)–Zn(1)	114.07(13)	C(1)–C(3)–N(2)	106.06(16)
C(2)–N(1)–C(1)	103.84(16)	C(1)–C(3)–C(4)	122.93(18)
C(2)–N(2)–C(3)	106.45(16)	O(1)–C(4)–N(3)	120.92(18)
C(2)–N(2)–C(6)	125.94(17)	O(1)–C(4)–C(3)	127.02(19)
C(3)–N(2)–C(6)	127.54(16)	N(3)–C(4)–C(3)	112.06(16)
C(4)–N(3)–C(5)	126.05(16)	O(2)–C(5)–N(3)	120.44(17)
C(4)–N(3)–C(7)	118.46(16)	O(2)–C(5)–N(4)	121.56(17)
C(5)–N(3)–C(7)	115.38(16)	N(4)–C(5)–N(3)	117.98(16)
C(1)–N(4)–C(5)	119.21(16)		

Table S3. Effect of different compounds on survivability of: DPSC line (24 h)						
Compound/Concentration, mol/L	$1\cdot10^{-7}$	$1\cdot10^{-6}$	$1\cdot10^{-5}$	$5\cdot10^{-5}$	$1\cdot10^{-4}$	$1\cdot10^{-3}$
$[Zn(H_2O)(caf)I_2]$[20]	109,14±15,19	113,97±13,11	88,96±12,62	37,98±5,06	27,03±8,16	12,40±2.44
$[Zn(caf)(H_2O)Cl_2]$[20]	84,7±12,27	62,43±18,67	79,62±13,83	53,05±16,5	35,64±8,52	18,98±5.47
$[Zn(caf)(H_2O)Br_2]$	95,7±15,57	90,64±14,10	85,97±8,31	74,35±12,04	59,23±7,06	23,46±5,23
$ZnCl_2$[20]	89,78±11.43	87,14±9,35	66,68±9,32	33,99±4.81	23,29±7.96	9,65±4.36
ZnI_2[20]	79.85±9.28	74,19±9,48	69,27±34,63	35,13±11.54	35,01±6.33	10,46±3.39
$ZnBr_2$	106,16±6,81	89,27±4,95	78,51±16,73	71,77±7,98	62,37±5,82	11,43±6,01
doxorubicin	92,37±12,05	101,59±6,84	79,09±5,63	64,87±12,68	58,79±10,92	49,53±7,28
caffeine[20]	88.01±10,80	91,08±11.34	96,19±10.59	88,15±17.49	91,81±13.24	110,50±8,37

Table S4. Effect of different compounds on survivability of: MCF-7 cells (24 h)						
Compound/Concentration, mol/L	$1\cdot10^{-7}$	$1\cdot10^{-6}$	$1\cdot10^{-5}$	$5\cdot10^{-5}$	$1\cdot10^{-4}$	$1\cdot10^{-3}$
$[Zn(H_2O)(caf)I_2]$[20]	114,11±22.15	108,41±12.73	112,48±7.46	54,76±10.64	29,09±4.09	24,36±3.50
$[Zn(caf)(H_2O)Cl_2]$[20]	81,14±6.60	59,77±12.63	58,46±10.75	61,91±15.98	24,68±1,57	19,70±4,65
$[Zn(caf)(H_2O)Br_2]$	93,46±10,32	84,80±12,25	82,16±15,35	15,70±5,58	16,78±6,08	9,61±4,72
$ZnCl_2$[20]	99,23±13.40	98,87±9.63	92,28±11.29	47,11±6.41	28,45±6,33	21,43±6,6
ZnI_2[20]	93,06±10,46	85,80±12,63	85,59±14,88	67,85±12,47	58,83±12,13	17,9±6,9
$ZnBr_2$	78,64±7,92	62,65±2,80	59,21±2,60	28,44±2,49	17,87±5,17	16,70±6,70
doxorubicin	92,78±11,27	90,86±6,75	81,73±9,23	68,97±7,55	39,76±5,09	27,63±6,11
caffeine[20]	100,80±19,75	82,52±16,89	108,49±11.18	82,58±15,91	74,10±14,43	85,67±12,14

Table S5. Results of DNA cometa assay (tail DNA, **%,** τ = 24 h) for **[Zn(caf)(H_2O)Br_2]** (**1**) (C = 1.10^{-4} mol/L) **with respect to DPSC and MCF-7 cell lines**

Compound	DPSC	MCF-7
1	8.37±1.47	31.83±2.54
Control	4.12±0.53	6.41±0.77