

Supplementary Material

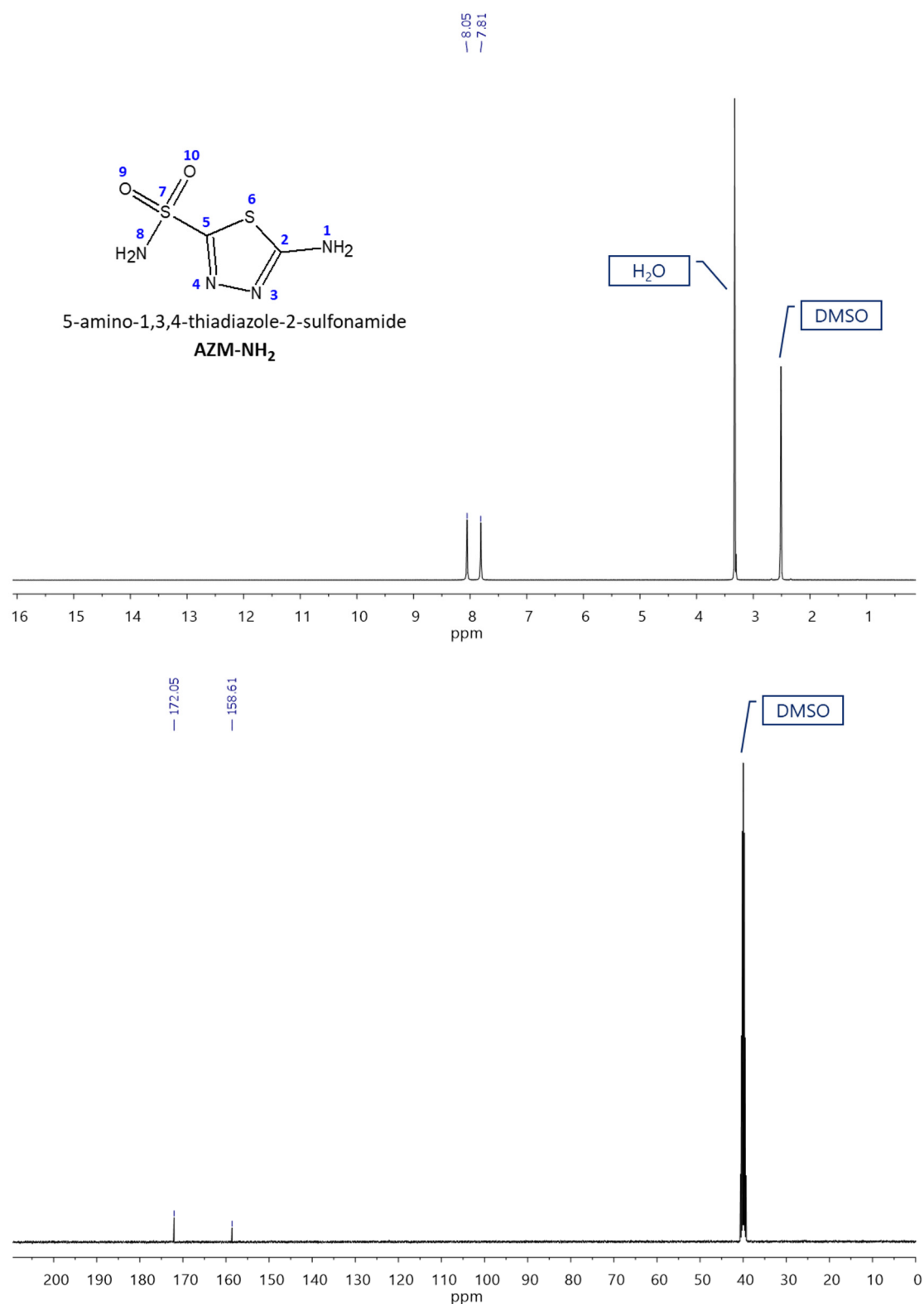


Figure S1. (*top*) ¹H NMR spectrum of AZM-NH₂: (DMSO-d₆, 400 MHz) δ (ppm): 7.81 (s, 2H, H₈-NH₂), 8.05 (s, 2H, H₁-NH₂); spectral contaminants: 3.33 (s, 2H, H₂O) and 2.51 (t, 6H, DMSO). (*bottom*) ¹³C NMR of spectrum AZM-NH₂: (DMSO-d₆, 400 MHz) δ (ppm): 158.61 (C₂), 172.05 (C₅); spectral contaminants: 39.35-40.61 (m, DMSO).

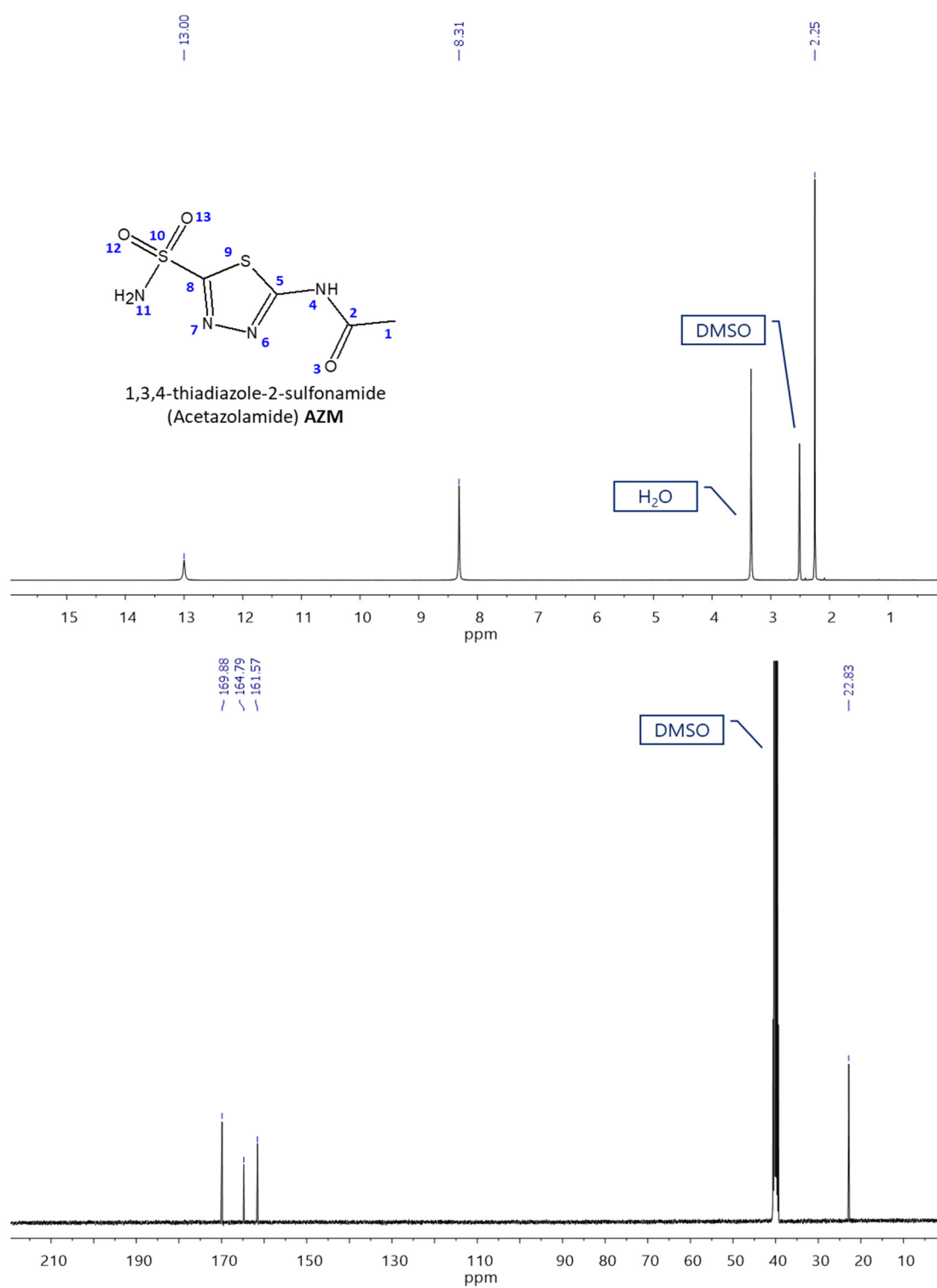


Figure S2. (top) ¹H NMR spectrum of AZM: (DMSO-d₆, 400 MHz) δ (ppm): 2.25 (s, 3H, H1 -CH₃), 8.31 (s, 2H, H11 -NH₂) and 13.00 (s, 1H, H4 -NH); spectral contaminants: 3.34 (s, 2H, H₂O) and 2.51 (t, 6H, DMSO).

(bottom) ^{13}C NMR of spectrum AZM: (DMSO- d_6 , 400 MHz) δ (ppm): 22.83 (C1), 161.57 (C2), 164.79 (C5) and 169.88 (C8); spectral contaminants: 39.37-40.62 (m, DMSO).

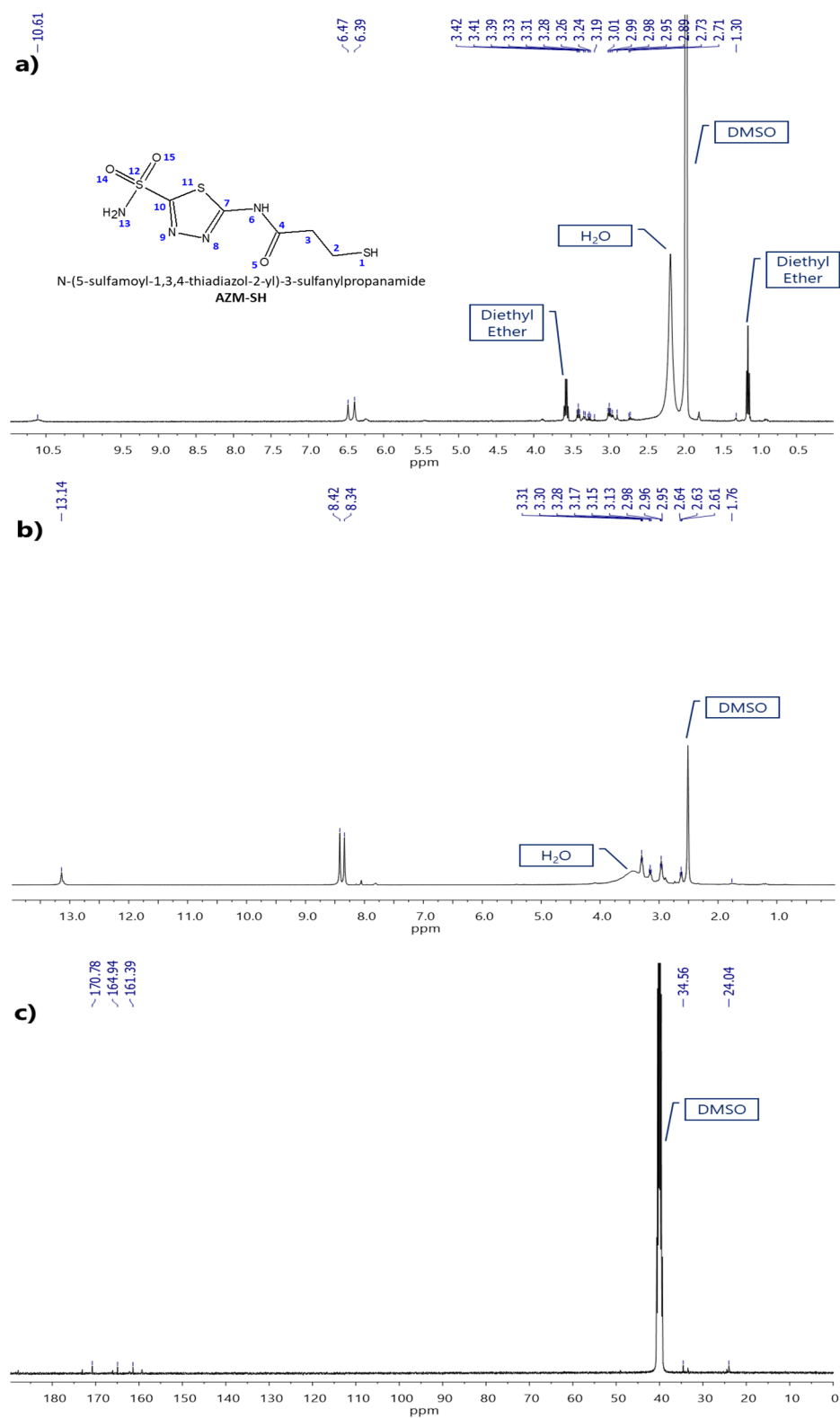


Figure S3. (a) ^1H NMR spectrum of AZM-SH (CD_3CN , 400 MHz), spectral contaminants: 3.55 (q, 2H, $-\text{CH}_2$, diethyl ether) 2.22 (s, 2H, H_2O), 1.97 (s, 3H, CH_3CN), 1.15 (t, 3H, $-\text{CH}_3$, diethyl ether). (b) ^1H NMR spectrum of AZM-SH ($\text{DMSO}-d_6$, 400 MHz), spectral contaminants: 3.33 (s, 2H, H_2O) and 2.51 (t, 6H, DMSO). (c) ^{13}C NMR of spectrum AZM-SH ($\text{DMSO}-d_6$, 400 MHz), spectral contaminants: 39.35-40.61 (m, DMSO).

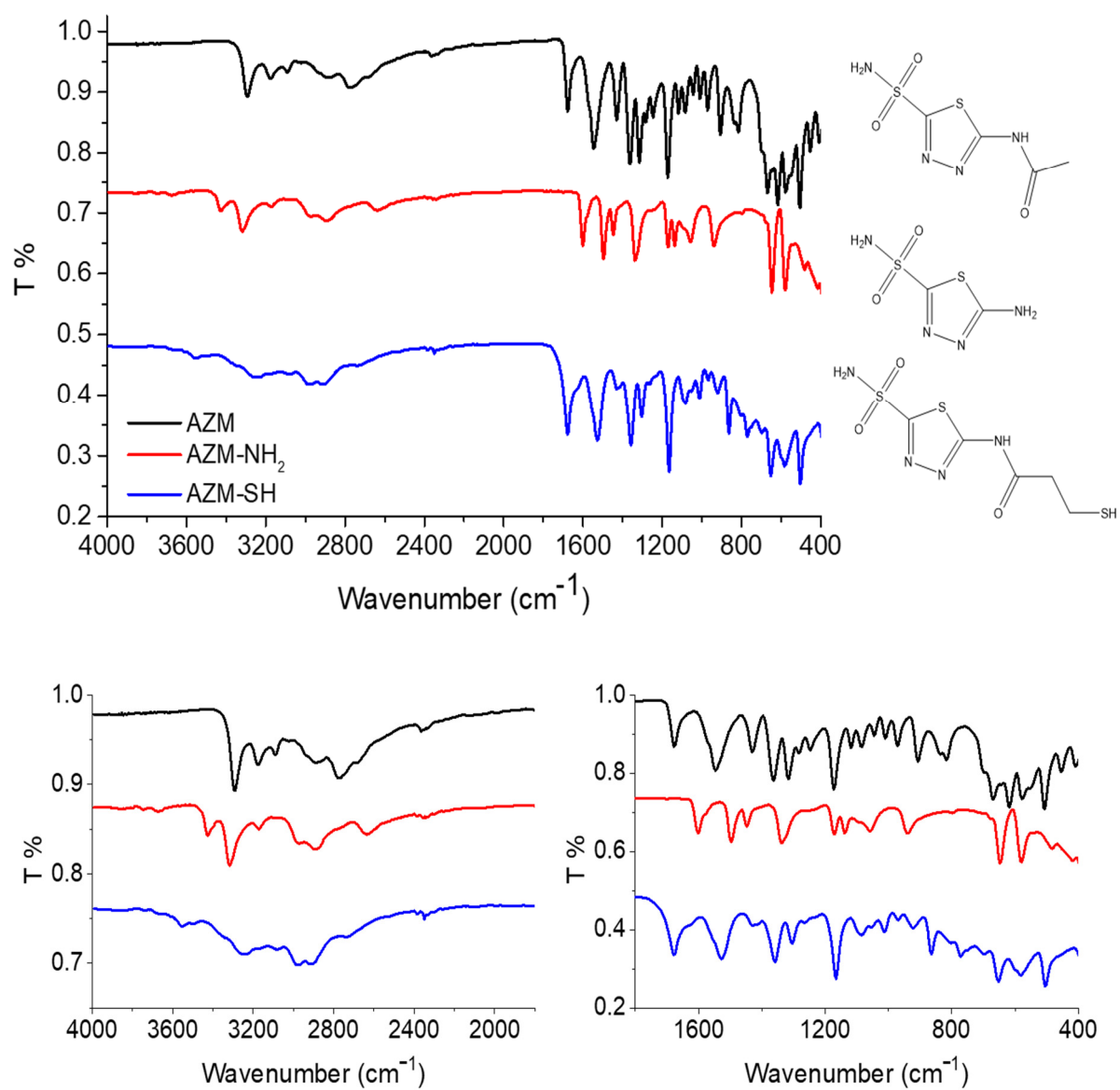


Figure S4. (*top*) Complete ATR-FTIR spectra for AZM, AZ-NH₂ and AZM-SH. (*bottom*) Close-up to the same spectra for the selected wavenumbers ranges.

Table S1. Assignment of all collected FT-IR peaks, for AZM, AZM-NH₂ and AZM-SH.

AZM	AZM-NH ₂	AZM-SH	
FT-IR wavenumber (cm ⁻¹)			Assignment
-	3676	3676	ν_1
-	-	3549	ν_2
-	-	3491	ν_{as} N-H
-	3425 <i>str</i>	-	R-NH ₂ <i>stretch</i>
-	-	3375 <i>brd sh</i>	ν_{as} RSO ₂ N-H/-NH ₂
-	3317 <i>str</i>	-	R-NH ₂ <i>stretch</i>
3294 <i>str</i>	-	3248 <i>str</i>	ν_{as} RSO ₂ N-H/-NH ₂
3175 <i>med</i>	3170 <i>wk</i>	3170 <i>brd</i>	ν_s RSO ₂ N-H/-NH ₂
3090	-	3086 <i>brd</i>	ν N-H (RCONH)
-	2974	2974	ν_6
2889	2889	2889	ν_7
2773	-	2723	ν ring-NH ₂
2685	2638	-	ν_9
-	-	2515 <i>wk</i>	ν SH
2361	2341	2345	ν_{10}
1678 <i>str</i>	-	1678 <i>str</i>	C=O <i>stretch</i> ν CO-NH-R
	1601 <i>str</i>		ν ring-NH ₂
1543	-	1528	ν CO-NH-R ν_{as} ring C=N
-	1497	-	ν azole ring
1431	-	1427	ν_s ring C=N ν n-propyl/ethyl
-	1447	-	ν R-SO ₂ -NH ₂
1362	-	1362	ν_{as} SO ₂
-	1335	-	ν ring-NH ₂
1311	-	1304	ν_{as} C-N-C
1284	-	1265	ν C-N ring
1246	1246	-	ν_{12}
1173	1173	1162	ν_s SO ₂
1119	1138	-	ν_{13}
1084	-	1084 <i>med</i>	ν n-propyl/ethyl
1045	1057	1057	ν_{14}
1011	-	1011	ν_{15}
972	-	972 <i>wk</i>	ν n-propyl/ethyl ν N-N
906	-	923	ν S-N ν n-propyl/ethyl
-	-	864	ν n-propyl
837	-	-	ν ethyl
818	-	-	ν ethyl
-	-	802 <i>wk</i>	ν SH
-	-	771 <i>med</i>	ν_1 n-propyl
702	-	702	ν_{as} C-S ring
671	-	-	ν_{20}
-	648	652	ν_{21}
617	-	-	ν_{22}
579	579	582	δ R-SO ₂ -NH ₂
555	-	-	ν_{23}
505	-	505	ν_{24}
455	482	-	ν_{25}
409	420	-	ν_{26}

wk, weak; *med*, medium; *str*, strong; *sh*, shoulder
s, symmetric; *as*, asymmetric

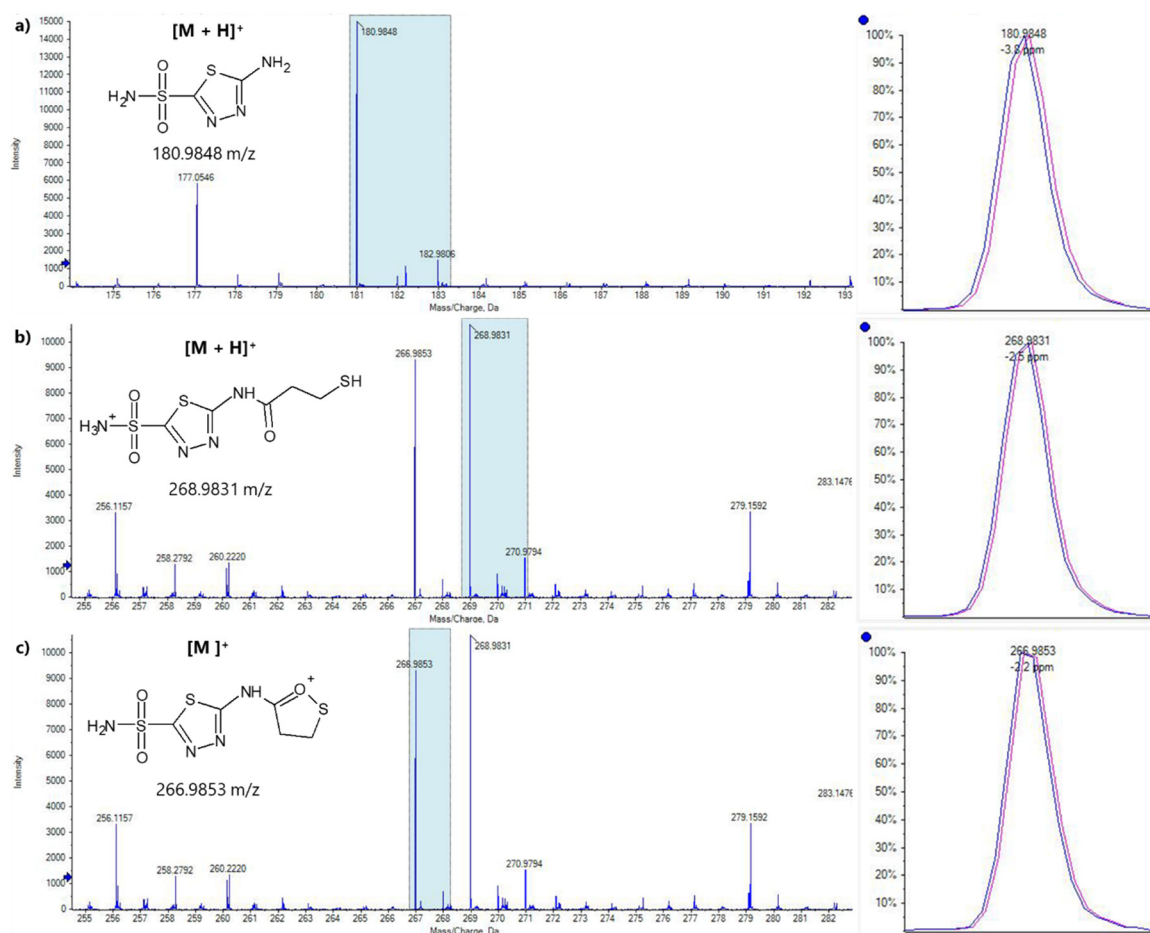


Figure S5. ESI+QTOF MS spectra of (a) AZM-NH₂, (b) AZM-SH [M+H]⁺ ion and (c) AZM-SH [M]⁺ ion.

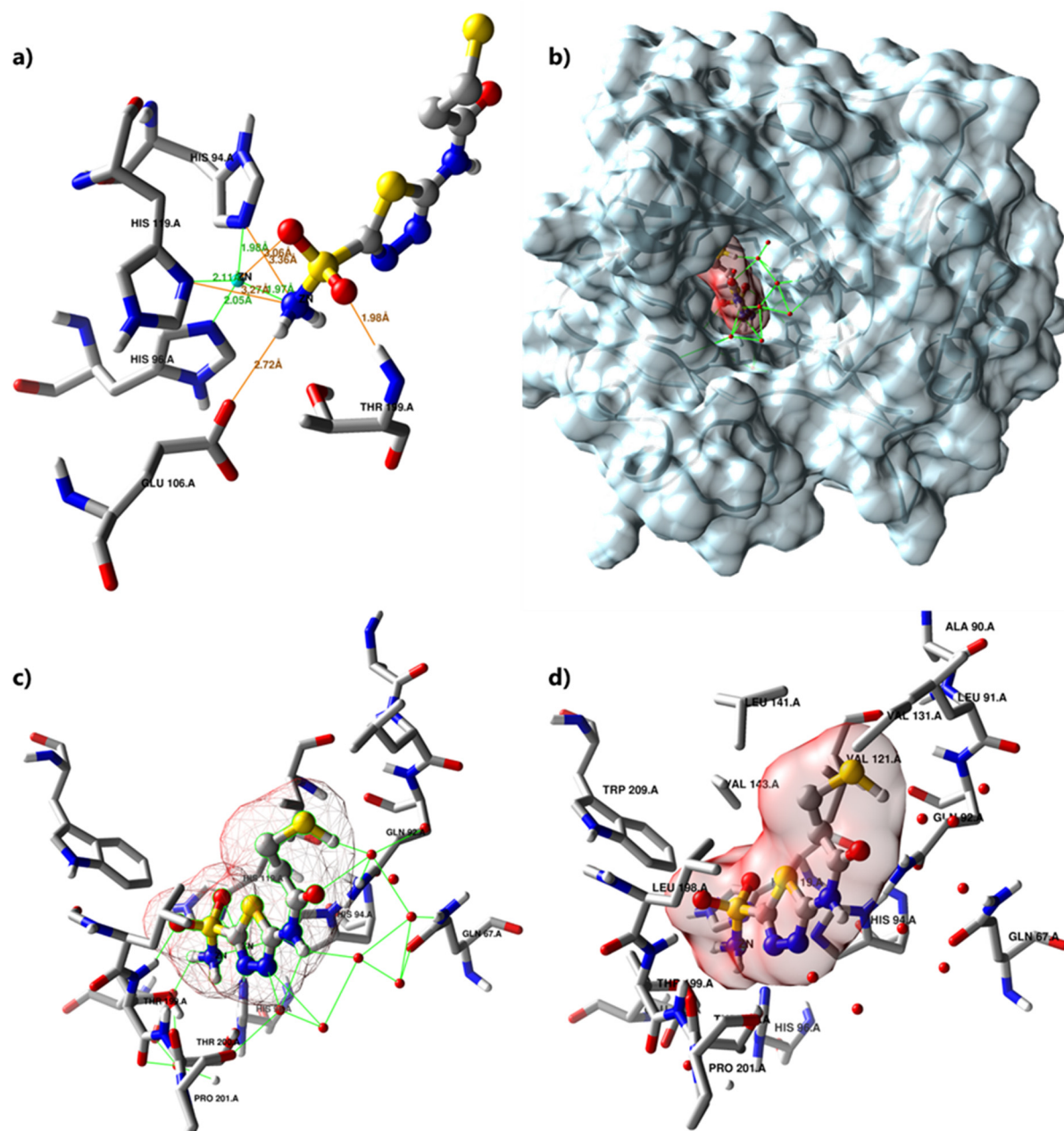


Figure S6. (a) Predicted zinc coordination interactions and hydrogen bonds for the AZM-SH sulfonamide moiety, with Zn^{2+} ion and GLU106 and THR199 CA IX residues, respectively. (b) Spatial surface representation of AZM-SH binding to CA IX active site. (c) Hydrogen bonds network between AZM-SH thiadiazole N(8)-atom, sulfanylpropanamide N(6), O(5) and S(1)H moieties, and water molecules. (d) Hydrophobic alignment of the aliphatic AZM-SH sulfanylpropanamide carbons and the hydrophobic residues of CA IX.

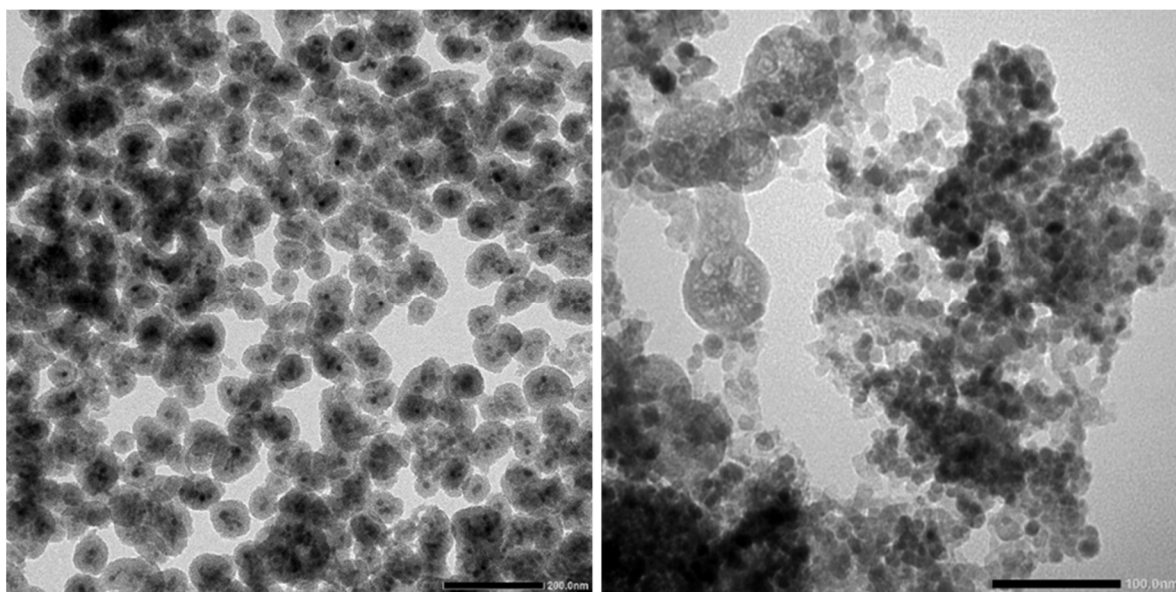


Figure S7. TEM micrographs at 0 (*left*) and 1-month (*right*) NANO3-SH systems from degradation studies in physiological simulated conditions; scale bars at 200 μm and 100 μm , respectively.

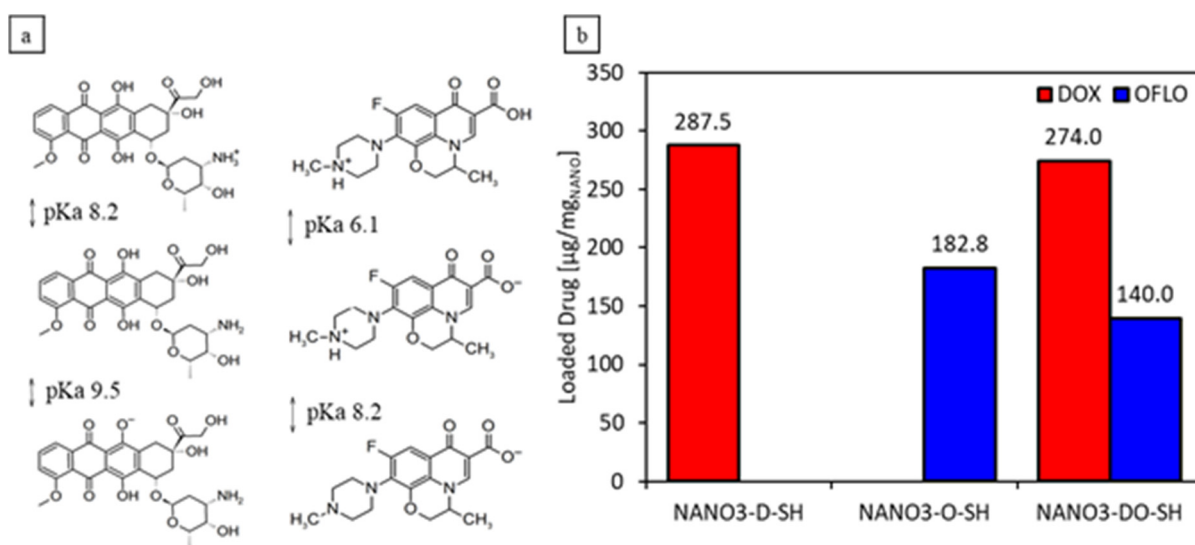


Figure S8. (a) DOX and OFLO pKa in aqueous solutions; (b) NANO3-SH systems loading capacities of DOX and OFLO ($n=3$), in single and dual combinatory formulations

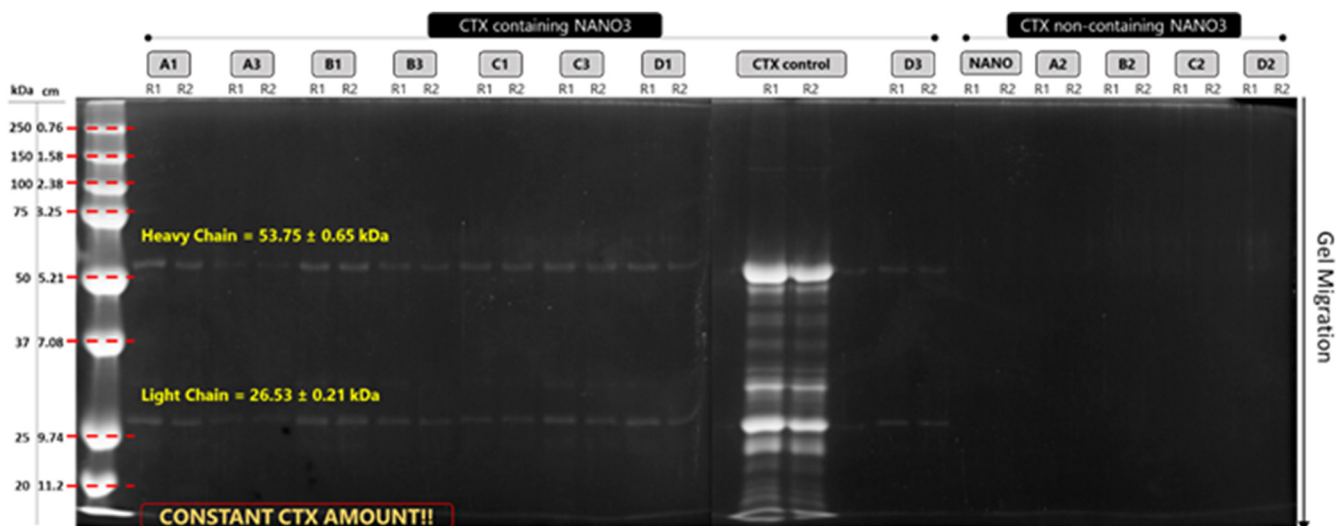


Figure S9. Gel electrophoresis of reduced biofunctionalized NANO3-SH systems loaded with DOX and OFLO (n=2), in single and dual combinatory formulations. Samples: A1= NANO3-CTX, A2 = NANO3-AZM, A3= NANO3-CTX+AZM, B1= NANO3@D-CTX, B2 = NANO3@D-AZM, B3= NANO3@D-CTX+AZM, C1= NANO3@DO-CTX, C2 = NANO3@DO-AZM, C3= NANO3@DO-CTX+AZM, D1= NANO3@O-CTX, D2 = NANO3@O-AZM, D3= NANO3@O-CTX+AZM.