Supramolecular amphiphiles based on cyclodextrin and hydrophobic drugs

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Electronic Supporting Information

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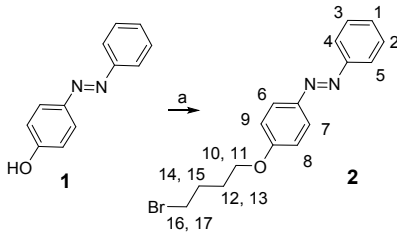
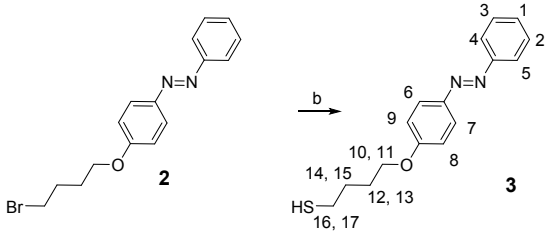
1. Synthesis



Compound **2**: Compounds **2** and **3** were synthesized in a similar way as reported.[1] *p*-Hydroxyazobenzene (1.98 g, 10 mmol, 1 eq), 1,4-dibromobutane (7.1 mL, 60 mmol, 6 eq) and KOH (1.12 g, 20 mmol, 2 eq) in EtOH (150 mL) was refluxed under an atmosphere of N_2 for 12 h. After cooling down to r.t., the solvent was removed by a rotavapor. The residue was suspended in dichloromethane (DCM, 100 mL) and the solid was filtered off. DCM was removed *in vacuo* and the crude product was purified by a flash column chromatography (SiO_2, ethyl acetate/petroleum ether (PE), from 1/10 to 1/5 v/v). **2** (1.50 g, 45%) was obtained as a brown powder.

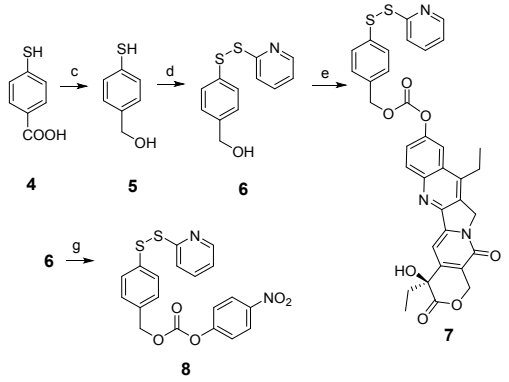
R*f* = 0.9 (ethyl acetate/PE, 1/8 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.92 (d, J = 8.8 Hz, 2H, H-4, 5), 7.88 (d, J = 7.6 Hz, 2H, H-6, 7), 7.51 (t, J = 7.6 Hz, 2H, H-2, 3), 7.45 (dd, J1= 6.0 Hz, J2= 7.6 Hz, 1H, H-1), 7.01 (d, J = 8.8 Hz, 2H, H-8, 9), 4.09 (t, J = 6.4 Hz, 2H, H-10, 11), 3.51 (t, J = 6.4 Hz, 2H, H-16, 17), 2.09 (m, 2H, H-14, 15), 2.00 (m, 2H, H-12, 13); ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 160.8, 152.1, 146.3, 129.8 (2C), 128.4 (2C), 124.2 (2C), 121.9 (2C), 66.6, 32.7, 28.8, 27.2; MS-ESI Calc. for $C_{16}H_{18}BrN_2O$ $[M+H]^+$ 333.1 (100%) and 335.1 (97%), Found, 333.0 (100%) and 335.0 (97%); IR (ν_{cm-1}): 2880.0 (m, $\nu_{CH2\text{-}O\text{-}Ar}$), 1605.2 (vs, $\nu_{N=N}$), 1258.2 (s, $w_{CH2\text{-}S}$), 776.4 (m, ν_{CH}), 689.7 (s, $\nu_{C\text{-}Br}$).



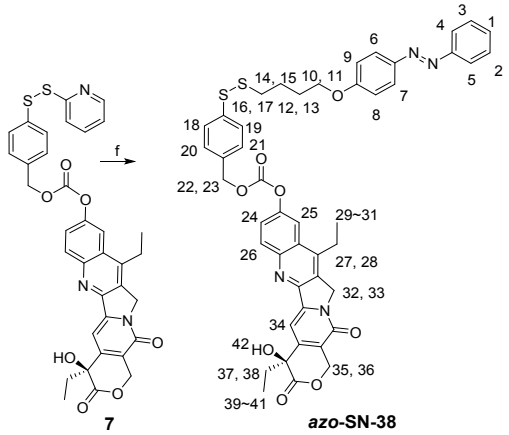
Compound **3**: A solution of **2** (0.19 g, 0.57 mmol, 1 eq) and thiourea (0.22 g, 2.89 mmol，5 eq) in EtOH (10 mL) was heated under reflux for 12 h. After cooling down to r.t., a solution of KOH (0.19 g, 3.47 mmol) in H_2O (10 mL) was then added into the above solution, refluxed for another 3 h under N_2 and cooled down to r.t.. The mixture was acidified by HCl (1N) to pH = 1 and extracted

by Et_2O (30 mL × 3). Organics were combined and washed with brine, dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by a flash column chromatography (SiO_2, ethyl acetate/PE, 1/5 v/v). **3** (0.12 g, 75%) was obtained as a brown oil.

R*f* = 0.8 (ethyl acetate/PE, 1/5 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.92 (d, J = 8.8 Hz, 2H, H-4,5), 7.88 (d, J = 7.6 Hz, 2H, H-6, 7), 7.51 (t, J = 7.6 Hz, 2H, H-2, 3), 7.45 (dd, J1= 6.0 Hz, J2= 7.6 Hz, 1H, H-1), 7.00 (d, J = 8.8 Hz, 2H, H-8, 9), 4.07 (t, J = 6.4 Hz, 2H, H-10, 11), 2.64 (dd, J1 = 6.8 Hz, J2 = 7.2 Hz, 2H, H-16, 17), 1.95 (m, 2H, H-14, 15), 1.85 (m, 2H, H-12, 13), 1.58 (m, 1H, H-18); ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 161.0, 151.8, 146.1, 129.8, 128.4 (2C), 124.4 (2C), 121.9 (2C), 114.1 (2C), 67.1, 29.9, 27.3, 23.8; MS-ESI Calc. for $C_{16}H_{19}N_2OS$ $[M+H]^+$ 287.1, Found, 287.0; IR (ν_{cm-1}): 2934.3 (vs, $\nu_{CH2\ linking\ SH}$), 2872.3 (m, $\nu_{CH2-O-Ar}$), 1600.5 (vs, $\nu_{N=N}$), 1253.5 (vs, w_{CH2-S}), 767.1 (m, ν_{CH}), 686.6 (m, ν_{C-SH}).



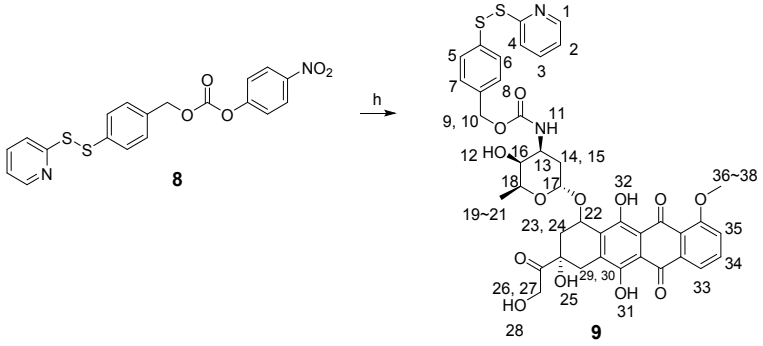
Compound **5**, **6**, **7 and 8** were synthesized based on our previous report.[2] All characterizing spectra of the compounds were in accordance with our previous results.



Compound **8**: To a stirred solution of **7** (180 mg, 0.27 mmol, 1.5 eq) in AcOH/EtOH (1/20 v/v, 5 mL, degassed by N_2 for 3 min) at r.t., **3** (51 mg, 0.18 mmol, 1 eq) in AcOH/EtOH (1/20 v/v, 2 mL, degassed with N_2 for 3 min) was injected dropwise over 20 min under an atmosphere of N_2. The

mixture was allowed to react at r.t. for 12 h. The solvents were then evaporated to dryness *in vacuo*. The resulting residue was subjected to a flash column chromatography (SiO_2, ethyl acetate/DCM, 1/2 v/v) to afford ***azo*-SN-38** (55 mg, 36%) as a pale yellowish powder.

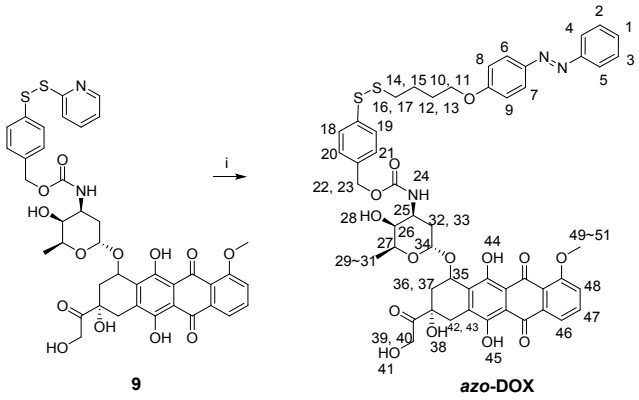
Rf = 0.7 (ethyl acetate/DCM, 1/1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.22 (d, J = 9.6 Hz, 1H, H-25), 7.88-7.81 (m, 5H, H-4, 5, 6, 7, 24), 7.65-7.59 (m, 4H, H-18, 19, 26, 34), 7.55-7.53 (m, 1H, H-1), 7.48-7.40 (m, 4H, H-2, 3, 20, 21), 6.95 (d, J = 8.8 Hz, 2H, H-8, 9), 6.74 (s, w, 1H, H-42), 5.74 (d, J = 16.4 Hz, 1H, H-22), 5.30 (d, J = 16.4 Hz, 1H, H-23), 5.30 (s, 2H, H-35, 36), 5.24 (s, 2H, H-32, 33), 4.02-3.99 (m, 2H, H-10, 11), 3.11 (q, J = 8.0 Hz, 2H, H-27, 28), 2.88-2.84 (m, 2H, H-16, 17), 1.98-1.84 (m, 6H, H-12~15, 37, 38), 1.37 (t, 3H, J = 8.0 Hz, H-29~31), 1.03 (t, 3H, J = 8.0 Hz, H-39~41); ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 174.3, 161.7, 158.0, 153.7, 153.0, 152.5, 150.5, 150.2, 147.9, 147.3, 147.2, 145.7, 139.2, 138.1, 133.3, 132.7, 130.7, 130.2, 130.0, 129.8 (2C), 129.4 (2C), 127.9 (2C), 127.7, 125.1 (2C), 122.9 (2C), 119.0, 115.0 (2C), 114.5, 98.4, 732.2, 70.6, 68.0, 66.7, 49.8, 39.0, 32.0, 29.7, 28.2, 27.6, 25.8, 23.5; MS-ESI Calc. for $C_{46}H_{43}N_4O_8S_2$ $[M+H]^+$ 843.3, Found, 843.0; IR (ν_{cm-1}): 2926.1 (vs, $\nu_{CH2\ linking\ SH}$), 2854.3 (m, $\nu_{CH2-O-Ar}$), 1747.0 (s, br, νC=O), 1695.7 (vs, $\nu_{N=N}$), 1216.8 (vs, w_{CH2-S}), 1137.4 (w, νC-OH), 758.6 (m, ν_{CH}).



Compound **10**: To a stirred solution of doxorubicin hydrochloride (**DOX·HCl**, 127 mg, 0.22 mmol, 1 eq) in dry DMF (4 mL, degassed by N_2 for 3 min) in the dark at r.t., Et_3N (34 mg, 46 μL, 0.33 mmol, 1.5 eq) was added dropwise. The mixture was allowed to react at r.t. for 0.5 h, followed by an injection with **8** (95 mg, 0.23 mmol, 1.05 eq) and trace DMAP in dry DMF (2 mL). The whole mixture was stirred in the dark at r.t. overnight and allowed to precipitate in water. The solid was collected by a filtration and the cake was washed by water and dried over *vacuum*. The crude was further purified by a flash column chromatography (SiO_2, MeOH/DCM, from 1/50 to 1/10 v/v) to obtain **9** (61 mg, 34%) as a deep-red solid.

Rf = 0.85 (MeOH/DCM, 1/10 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 13.97 (s, 1H, H-32), 13.25

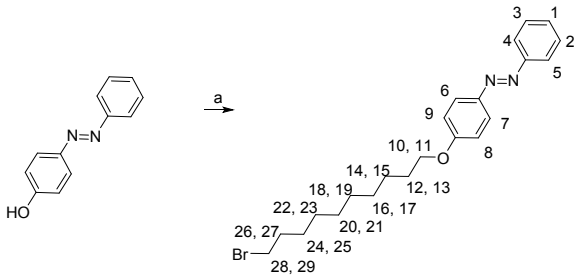
(s, 1H, H-30), 8.44 (d, 1H, J = 4.8 Hz, H-1), 8.05-8.01 (m, 2H, H-3, 4), 8.01 (s, w, 1H, H-11), 7.79 (t, 1H, J = 8.0 Hz, H-34), 7.60 (d, 2H, J = 3.2 Hz, H-5, 6), 7.46 (d, 1H, J = 8.0 Hz, H-33), 7.39 (d, 1H, J = 8.0 Hz, H-35), 7.24 (d, 2H, J = 3.2 Hz, H-7, 8), 7.10-7.08 (m, 1H, H-2), 5.50 (s, 1H, H-12), 5.28 (s, 1H, H-9), 5.18 (s, 1H, H-10), 4.97 (s, 2H, H-26, 27), 4.75 (s, 2H, H-17, 22), 4.17-4.10 (m, 1H, H-16), 4.08 (s, 3H, H-36~38), 4.06 (s, 1H, H-12), 3.85 (s, 1H, H-13), 3.65 (s, 1H, H-18), 3.27 (d, J = 18.4 Hz, 1H, H-28), 3.05-3.00 (m, 2H, H-29, 30), 2.34-2.14 (m, 2H, H-23, 24), 1.88-1.79 (m, 2H, H-14, 15), 1.268 (t, 3H, H-19~21); ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 213.2, 186.5, 186.1, 180.5, 158.8, 155.6, 155.1, 154.7, 148.7, 136.9, 135.3, 135.2, 134.9, 134.8, 132.9, 128.4, 128.3, 127.0, 126.9 (2C), 120.4, 120.3, 119.2 (2C), 117.9, 111.0, 110.8, 100.1, 69.1, 68.9, 66.6, 65.4, 64.9, 56.1, 46.4, 35.0, 33.4, 29.6, 29.1, 16.2; MS-ESI Calc. for $C_{40}H_{39}N_2O_{13}S_2$ $[M+H]^+$ 819.2, Found, 819.0; $C_{40}H_{38}N_2NaO_{13}S_2$ $[M+Na]^+$ 841.2, Found, 841.0.



Compound **8**: In the dark, **3** (32 mg, 0.11 mmol, 1.1 eq), **9** (82 mg, 0.1 mmol, 1 eq) and trace DMAP in dry DCM were stirred overnight at r.t. under Ar. The solvents were then evaporated to dryness *in vacuo*. The resulting residue was subjected to a prep-TLC plate (SiO_2 on glass, MeOH/DCM, 1/20 v/v) to afford ***azo*-DOX** (37 mg, 37%) as a deep red powder.

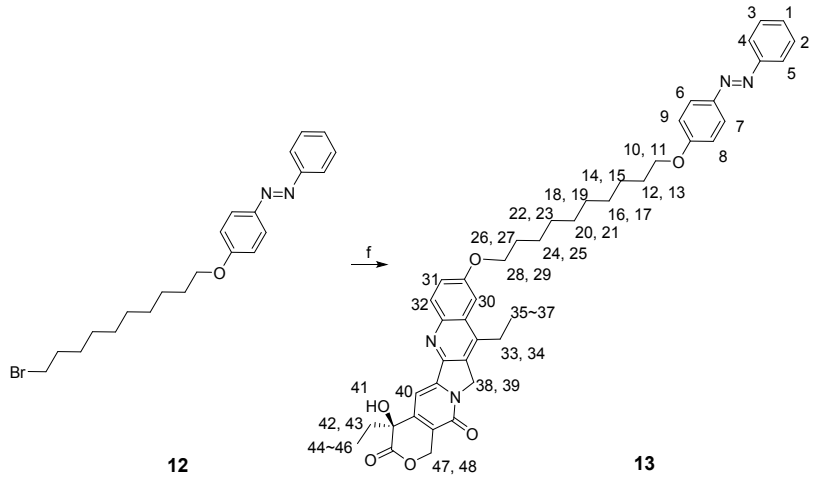
Rf = 0.2 (MeOH/DCM, 1/20 v/v); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 13.99 (s, 1H, H-44), 13.29 (s, 1H, H-45), 8.15 (d, 2H, J = 9.2 Hz, H-4, 5), 8.02 (s, w, 1H, H-24), 7.92-7.86 (m, 4H, H-6, 7, 46, 47), 7.58-7.53 (m, 4H, H-2, 3, 18, 19), 7.40-7.36 (m, 3H, H-20, 21), 7.01-6.96 (m, 1H, H-48), 6.91 (d, 2H, J = 9.2 Hz, H-8, 9), 6.75 (t, 1H, J = 6.4 Hz, H-1), 5.34 (t, 1H, J = 4.4 Hz, H-28), 5.00-4.99 (m, 1H, H-22), 4.77-4.75 (m, 1H, H-23), 4.13-4.04 (m, 4H, H-10, 11, 38, 41), 3.49 (s, 2H, H-39, 40), 2.96 (s, 3H, H-49~51), 2.91-2.90 (m, 3H, H-26, 42, 43), 2.81-2.78 (m, 2H, H-16, 17), 2.42-2.37 (m, 1H, H-25, 27), 2.25-2.20 (m, 2H, H-34, 35), 2.10 (s, 2H, H-32, 33), 1.95-1.93 (m, 2H, H-12, 13), 1.90-1.85 (m, 2H, H-36, 37), 1.18-1.15 (m, 3H, H-29~31), 0.88-0.86 (m, 2H, H-14, 15); MS-

ESI Calc. for $C_{51}H_{52}N_3O_{14}S_2$ $[M+H]^+$ 994.3, Found, 994.2; $C_{51}H_{51}N_3NaO_{14}S_2$ $[M+Na]^+$ 1016.3, Found, 1016.2; IR (ν_{cm-1}): 2921.6 (vs, $\nu_{CH2\ linking\ disulfide}$), 2845.2 (m, $\nu_{CH2-O-Ar}$), 1719.4 (w, br, νC=O), 1555.9 (vs, $\nu_{N=N}$), 1106.0 (vs, w_{CH2}), 799.8 (m, ν_{CH}).



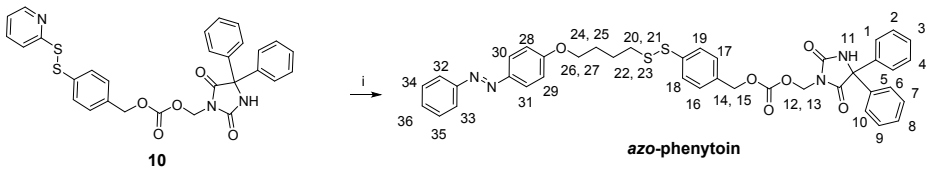
1 **12**

Compound **12**: *p*-Hydroxyazobenzene (0.99 g, 5 mmol, 1 eq), 1,4-dibromobutane (9 g, 30 mmol, 6 eq) and KOH (0.56 g, 10 mmol, 2 eq) in absolute EtOH (100 mL) was refluxed under an atmosphere of N_2 for 12 h. After cooling down to r.t., the solvent was removed by a rotavapor. The residue was suspended in dichloromethane (DCM, 100 mL) and the solid was filtered off. DCM was removed *in vacuo* and the crude product was purified by a flash column chromatography (SiO_2, ethyl acetate/PE, from 1/10 to 1/4 v/v). **12** (811 mg, 39%) was obtained as a brown powder. R*f* = 0.8 (ethyl acetate/PE, 1/8 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.92 (d, J = 8.8 Hz, 2H, H-4, 5), 7.89 (d, J = 7.6 Hz, 2H, H-6, 7), 7.50 (t, J = 7.6 Hz, 2H, H-2, 3), 7.44 (dd, J1= 6.0 Hz, J2= 7.6 Hz, 1H, H-1), 7.00 (d, J = 8.8 Hz, 2H, H-8, 9), 4.04 (t, J = 6.4 Hz, 2H, H-10, 11), 3.48 (t, J = 6.4 Hz, 2H, H-28, 29), 3.41-3.36 (m, 4H, H-12, 13, 26, 27), 1.86-1.83 (m, 4H, H-14, 15, 24, 25), 1.66-1.40 (m, 6H, H-16~19, H-22, 23), 1.23-1.13 (m, 2H, H-20, 21). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 161.9, 153.0, 147.0, 130.4, 129.2 (2C), 124.9 (2C), 122.7 (2C), 114.9 (2C), 70.9, 68.5, 66.2, 34.2, 33.0, 29.6, 29.3, 28.9, 28.3, 26.2; MS-ESI Calc. for $C_{22}H_{30}BrN_2O$ $[M+H]^+$ 417.2 (100%) and 419.2 (97%), Found, 417.2 (100%) and 419.0 (97%); IR (ν_{cm-1}): 2845.0 (vs, $\nu_{CH2-O-Ar}$), 1604.8 (m, $\nu_{N=N}$), 1258.1 (s, w_{CH2-S}), 884.1 (m, ν_{CH}), 688.3 (s, ν_{C-Br}).



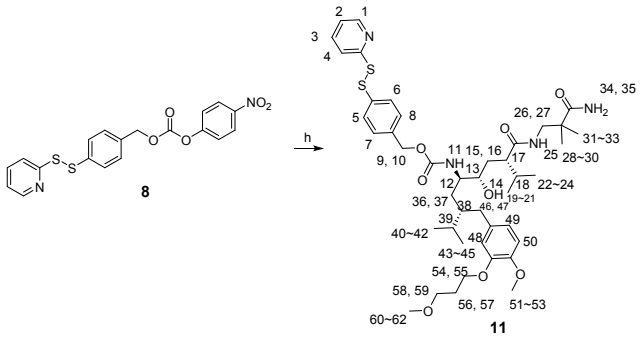
Compound **13**: SN-38 (392.2 mg, 1 mmol, 1 eq) and dry DMSO (1.5 mL) was stirred at r.t. until it was dissolved completely. Then **12** (2.5 g, 6 mmol, 6 eq) and K_2CO_3 (700 mg, 5 mmol, 5 eq) were added. The whole suspension was stirred at r.t. in the dark under N_2 for 6 h and monitored by TLC. The mixture was then poured into Et_2O. The precipitation was filtered, the cake was washed by Et_2O and air-dried. The crude product was further purified by a flash column chromatography (SiO_2, ethyl acetate/DCM, from 1/20 to 1/3 v/v) to obtain **13** (561 mg, 77%) as a brown solid.

Rf = 0.2 (ethyl acetate/DCM, 1/4 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.09 (d, J = 9.2 Hz, 2H, H-4, 5), 7.87-7.81 (m, 1H, H-32), 7.68-7.60 (m, 2H, H-2, 3), 7.45 (t, J = 6.4 Hz, 1H, H-1), 7.38-7.35 (m, 3H, H-6, 7, 30), 7.18-7.14 (m, 3H, H-8, 9, 31), 6.95 (d, J = 6.8 Hz, 1H, H-40), 5.68 (d, J = 16.0 Hz, 2H, H-28, 29), 5.24 (d, J = 16.0 Hz, 2H, H-10, 11), 5.16-5.10 (m, 4H, H-38, 39, 47, 48), 4.56-4.43 (s, 1H, H-41), 3.50 (q, J = 5.2 Hz, 2H, H-33, 34), 3.30 (q, J = 2.4 Hz, 2H, H-42, 43), 3.16-3.03 (m, 4H, H-12, 13, 26, 27), 1.56-1.52 (m, 7H, H-14, 15, 24, 25, 35~37), 0.99-0.95 (m, 11H, H-16~23, 44~46); ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 173.4, 161.0, 157.9, 157.1, 152.2, 149.6, 146.3, 131.2, 129.7, 128.4, 128.3, 127.7 (2C), 126.6, 126.2, 124.1, 123.2 (2C), 122.3, 121.9, 119.1 (2C), 117.2, 114.1 (2C), 113.5, 101.8, 97.0, 72.2, 67.9, 67.7, 65.8, 48.8, 31.0, 29.2, 28.7 (2C), 28.6, 25.6, 25.5, 23.4, 22.6, 13.0, 7.2; MS-ESI Calc. for $C_{44}H_{49}N_4O_6$ $[M+H]^+$ 729.4, Found, 729.4; IR (ν_{cm-1}): 2854.4 (m, $\nu_{CH2\text{-}O\text{-}Ar}$), 1742.3 (s, br, νC=O), 1600.2 (vs, $\nu_{N=N}$), 1248.9 (vs, $w_{CH2\text{-}S}$), 1146.6 (w, νC-OH), 834.9 (m, ν_{CH}).



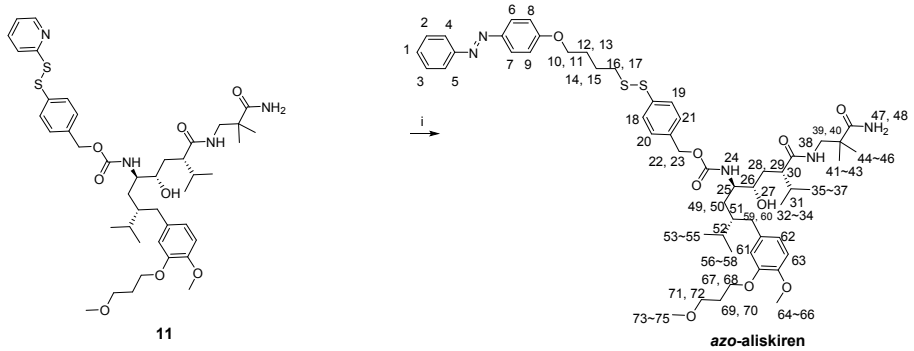
Compound ***azo*-phenytoin**: Compound **10** was synthesized based on our previous report.[2] All characterizing spectra of the compound were in accordance with our previous results. Then in the dark, **10** (18 mg, 0.032 mmol, 1.1 eq), **3** (10 mg, 0.032 mmol, 1 eq) and trace DMAP in dry DCM were stirred overnight at r.t. under N_2. The solvents were then evaporated to dryness *in vacuo*. The resulting residue was subjected to a flash column chromatography (SiO_2, DCM) to afford ***azo*-phenytoin** (37 mg, 37%) as a deep red powder.

Rf = 0.5 (DCM); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.92-7.87 (m, 4H, H-30~33), 7.84-7.48 (m, 4H, H-18, 19, 34, 35), 7.47-7.42 (q, 1H, J = 8.0 Hz, H-36), 7.37-7.32 (m, 12H, H-1~10, 16, 17), 7.00-6.94 (d, 2H, H-28, 29), 6.81 (s, w, 1H, H-11), 5.63 (s, 2H, H-12, 13), 5.14 (s, 2H, H-14, 15), 4.05-3.98 (m, 2H, H-26, 27), 2.84-2.79 (m, 2H, H-20, 21), 1.93-1.84 (m, 4H, H-22~25); ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 175.5, 172.2, 161.6, 154.5, 153.6, 152.9, 147.1, 138.5 (2C), 133.4, 130.5, 129.4 (2C), 129.2 (2C), 129.1 (4C), 129.0 (2C), 127.6 (2C), 126.9 (4C), 124.9 (2C), 122.7 (2C), 114.9 (2C), 70.5, 69.8, 67.8, 64.6, 38.5, 28.1, 25.5. MS-ESI Calc. for $C_{40}H_{37}N_4O_6S_2$ $[M+H]^+$ 733.2, Found, 733.2; $C_{40}H_{35}N_4NaO_6S_2$ $[M+Na]^+$ 755.2, Found, 755.2; IR (ν_{cm-1}): 2923.8 (vs, $\nu_{CH2\ linking\ disulfide}$), 2844.4 (m, $\nu_{CH2-O-Ar}$), 1733.0 (w, br, νC=O), 1508.4 (m, $\nu_{N=N}$), 1136.6 (vs, w_{CH2}), 770.7 (m, ν_{CH}).



Compound **10**: To a stirred solution of aliskiren hemifumarate (121 mg, 0.22 mmol, 1 eq) in dry DMF (4 mL, degassed by N_2 for 3 min) in the dark at r.t., Et_3N (34 mg, 46 μL, 0.33 mmol, 1.5 eq) was added dropwise. The mixture was allowed to react at r.t. for 0.5 h, followed by an injection with **8** (95 mg, 0.23 mmol, 1.05 eq) and trace DMAP in dry DMF (2 mL). The whole mixture was stirred in the dark at r.t. overnight and allowed to precipitate in water. The solid was collected by a filtration and the cake was washed by water and dried over *vacuum*. The crude was further purified by a flash column chromatography (SiO_2, MeOH/DCM, from 1/50 to 1/10 v/v) to obtain **11** (67 mg, 37%) as a white solid.

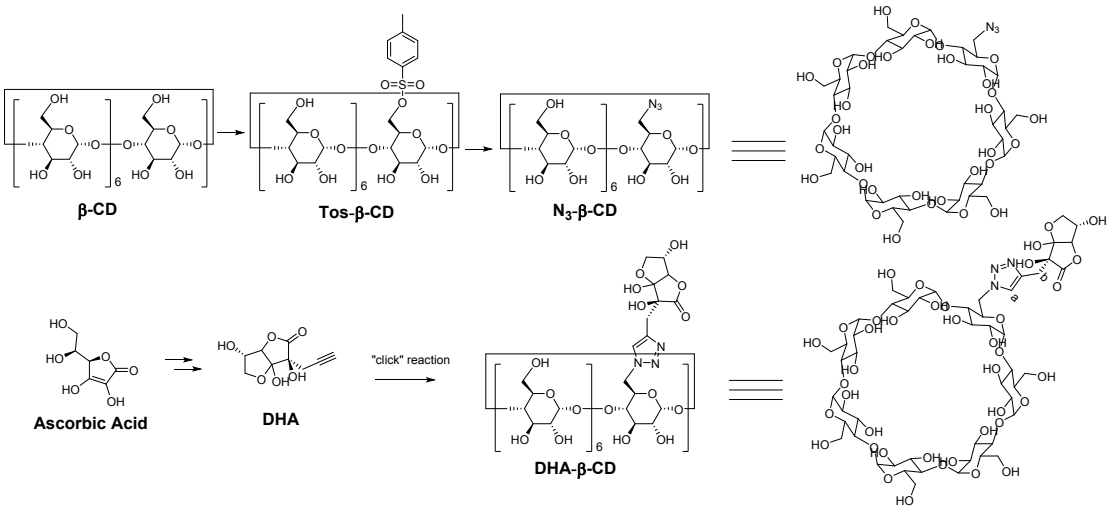
Rf = 0.80 (MeOH/DCM, 1/10 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.39 (d, 1H, J = 4.8 Hz, H-1), 7.72-7.64 (m, 2H, H-3, 4), 7.46 (d, 2H, J = 8.0 Hz, H-5, 6), 7.35 (d, 2H, J = 8.0 Hz, H-5, 6), 7.23-7.19 (m, 1H, H-2), 6.78-6.76 (m, 2H, H-49, 50), 6.59 (d, 1H, J = 9.2 Hz, H-48), 5.07 (dd, 2H, J1 = 9.2 Hz, J2 = 18.4 Hz, H-9, 10), 4.21 (dd, 1H, J1 = 5.2 Hz, J2 = 1.6 Hz, H-13), 4.01-3.96 (m, 2H, H-54, 55), 3.80 (s, 3H, H-51~53), 3.65-3.60 (m, 1H, H-25), 3.53 (t, 2H, J = 6.0 Hz, H-58, 59), 3.35-3.30 (m, 6H, H-12, 26, 27, 60~62), 2.48 (dd, 2H, J1 = 128.8 Hz, J2 = 13.6 Hz, H-46, 47), 2.26-2.21 (m, 1H, H-17), 1.96 (t, 1H, J = 6.0 Hz, H-18), 1.73-1.63 (m, 2H, H-56, 57), 1.58-1.44 (m, 3H, H-15, 16, 38), 1.37-1.28 (m, 3H, H-36, 37, 39), 1.18 (s, 3H, H-28~30), 1.17 (s, 3H, H-31~33), 0.92-0.88 (m, 6H, H-19~24), 0.78 (d, 3H, J = 6.8 Hz, H-40~42), 0.72 (d, 3H, J = 7.6 Hz, H-43~45); MS-ESI Calc. for $C_{43}H_{63}N_4O_8S_2$ $[M+H]^+$ 827.4, Found, 827.4; $C_{43}H_{62}N_4NaO_8S_2$ $[M+Na]^+$ 851.4, Found, 851.4.



Compound ***azo*-aliskiren**: In the dark, **11** (26 mg, 0.032 mmol, 1.1 eq), **3** (10 mg, 0.032 mmol, 1 eq) and trace DMAP in dry DCM were stirred overnight at r.t. under N_2. The solvents were then evaporated to dryness *in vacuo*. The resulting residue was subjected to a flash column chromatography (SiO_2, MeOH/DCM, from 1/50 to 1/10 v/v) to afford ***azo*-aliskiren** (11 mg, 34%) as a pink powder.

Rf = 0.60 (MeOH/DCM, 1/10 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.91-7.85 (m, 4H, H-5~7), 7.51-7.47 (m, 4H, H-2, H-3, H-18, H-19), 7.43 (q, 1H, J = 8.4 Hz, H-1), 7.30 (d, 2H, J = 8.4 Hz, H-20, 21), 6.96 (d, 2H, J = 8.4 Hz, H-8, 9), 6.77-6.73 (m, 2H, H-62, 63), 7.65-7.63 (m, 1H, H-61), 6.13 (w, s, 1H, H-38), 5.84 (w, s, 1H, H-24), 5.13-4.99 (m, 2H, H-22, 23), 5.07 (w, s, 2H, H-47, 48), 4.14-3.99 (m, 5H, H-10, 11, 26, 67, 68), 3.82 (s, 3H, H-64~66), 3.57-3.53 (m, 2H, H-71, 72), 3.47-3.42 (m, 1H, H-25), 3.31 (s, 3H, H-73~75), 3.30-3.24 (m, 2H, H-39, 40), 2.80-2.77 (m, 2H, H-16, 17), 2.44 (dd, 2H, J1 = 89 Hz, J2 = 9.6 Hz, H-59, 60), 2.09-2.00 (m, 5H, H-12~15, 31), 1.90-1.88 (m, 2H, H-69, 70), 1.68-1.52 (m, 3H, H-28, 29, 51), 1.27-1.23 (m, 3H, H-49, 50, 52), 1.19 (s,

3H, H-41~43), 1.18 (s, 3H, H-44~46), 0.90-0.86 (m, 6H, H-32~37), 0.82-0.76 (m, 6H, H53~58); MS-ESI Calc. for $C_{54}H_{76}N_5O_9S_2$ $[M+H]^+$ 1002.5, Found, 1002.4; $C_{54}H_{75}N_5NaO_9S_2$ $[M+Na]^+$ 1024.5, Found, 1024.4; IR (ν_{cm-1}): 2918.7 (vs, $\nu_{CH2\ linking\ disulfide}$), 2870.5 (m, $\nu_{CH2-O-Ar}$), 1650.6 (w, br, νC=O), 1510.5 (m, $\nu_{N=N}$), 1147.6 (vs, w_{CH2}), 804.2 (m, ν_{CH}).



Compound **DHA-β-CD**: **N_3-β-CD** was prepared followed by reported procedures.[3] DHA was synthesized from ascorbic acid as reported in our previous work.[4] DHA (538 mg, 2.5 mmol. 5 eq), **N_3-β-CD** (580 mg, 0.5 mmol, 1 eq), *L*-ascorbic acid sodium salt (200 mg, 1 mmol, 2 eq) and $CuSO_4 \cdot 5H_2O$ (6.25 mg, 0.025 mmol, 0.05 eq) were suspended in DMF (anhydrous, 2 mL) and allowed to react under N_2 at dark for 12 h. The mixture was then precipitated in acetone and the yielded yellowish solid was collected by filtration, dissolved in H_2O (5 mL), dialyzed against EDTA (10 mM in 20 mM PBS 7.4 solution, 3 × 200 mL) and then H_2O (3 × 2 L), freeze dried to obtain **DHA-β-CD** (653 mg, 95%) as a yellowish solid.

Rf = 0.50 (isopropanol/H_2O/$NH_3 \cdot H_2O$, 5/2/1 v/v, iodine treated); ^{1}H NMR (600 MHz, D_2O, δ, ppm): 8.16 (s, 1H, H-a), 5.62 (dd, J1 = 44 Hz, J2 = 12 Hz, 2H), 5.18-5.13 (m, 1H), 5.03-4.99 (m, 7H, H-1 of β-CD), 4.67-4.62 (m, 1H), 3.95-3.88 (m, 7H, H-3 of β-CD), 3.85-3.73 (m, 21H, H-5 and H-6 of β-CD), 3.68-3.49 (m, 14H, H-2 and H-4 of β-CD), 2.95 (dd, J1 = 180 Hz, J2 = 12 Hz, 2H), MS-ESI Calc. for $C_{51}H_{80}N_3O_{40}$ $[M+H]^+$ 1374.4, Found, 1374.4; $C_{51}H_{79}N_3NaO_{40}$ $[M+Na]^+$ 1396.4, Found, 1396.4; IR (ν_{cm-1}): 3378.8 (vs, ν_{-OH}), 2932.2 (m, $\nu_{CH2-O-CH2}$), 2347.2 (w, $\nu_{C=N}$), 1637.7 (m, br, $\nu_{C=O}$), 1248.9 (vs, w_{CH2-S}), 1146.6 (w, νC-OH), 834.9 (m, ν_{CH}).

2. Supporting results

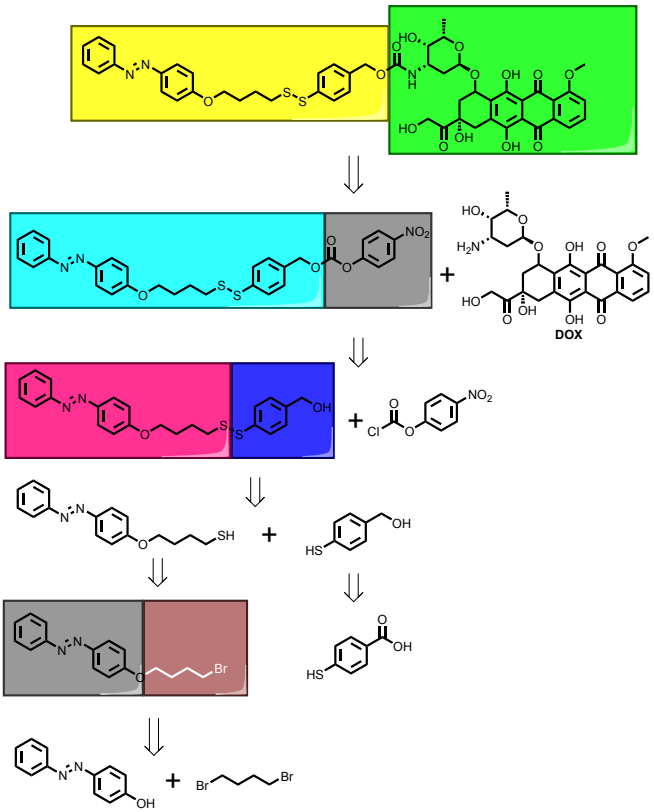


Figure S1. Retrosynthesis analysis of the guested prodrug molecule with compound ***azo*-DOX** as the example.

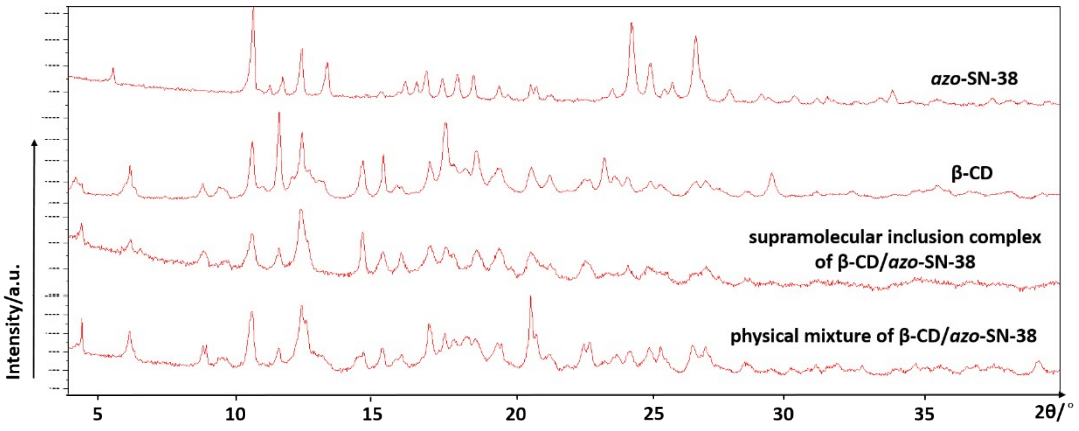


Figure S2. The comparison of the XRD spectra of β-CD, ***azo*-SN-38**, their physical mixture, and inclusion complex at 300 K.

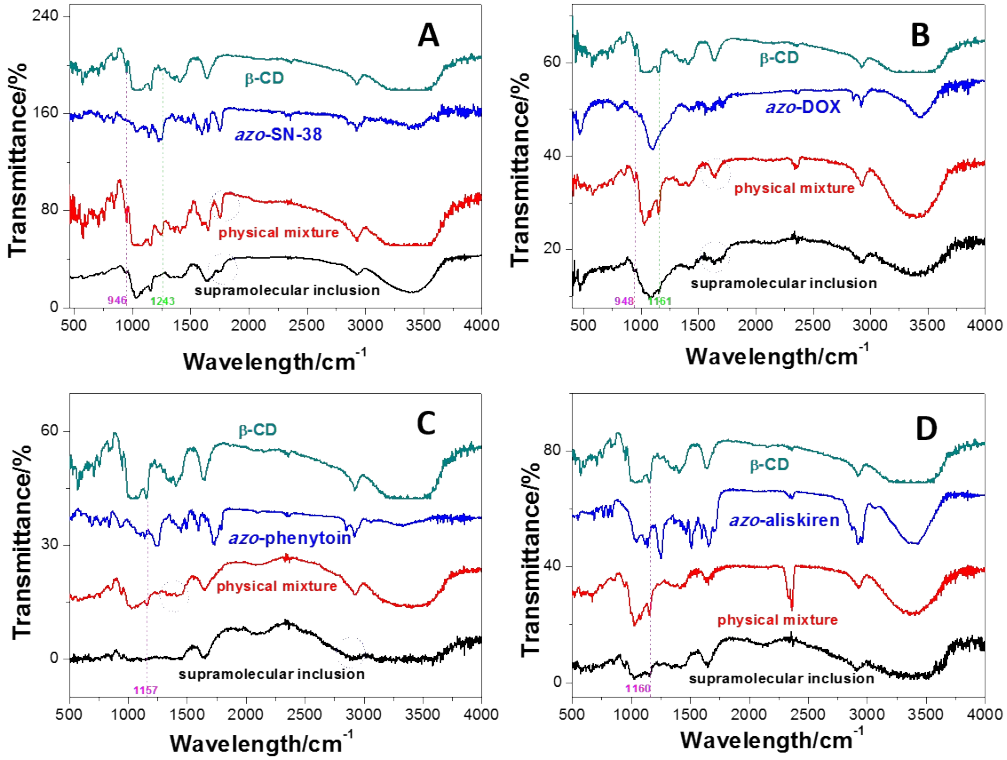


Figure S3. The comparison of the FTIR spectra in KBr capsules at 300 K. (A): β-CD, ***azo*-SN-38**, their physical mixture, and inclusion complex. Intensity change at peak 946 cm^{-1} (purple line)/1243 cm^{-1} (green line) and shape change in the blue circle; (B): β-CD, ***azo*-DOX**, their physical mixture, and inclusion complex. Intensity change at peak 948 cm^{-1} (purple line)/1161 cm^{-1} (green line) and shape change in the blue circle. (C): β-CD, ***azo*-phenytoin**, their physical mixture, and inclusion complex. Intensity change at peak 1157 cm^{-1} (purple line) and shape change in the blue circle; (D): β-CD, ***azo*-aliskiren**, their physical mixture, and inclusion complex. Intensity change at peak 1160 cm^{-1} (purple line). Wider peaks can be found around 3300 cm^{-1}, suggesting the formation of hydrogen bonds

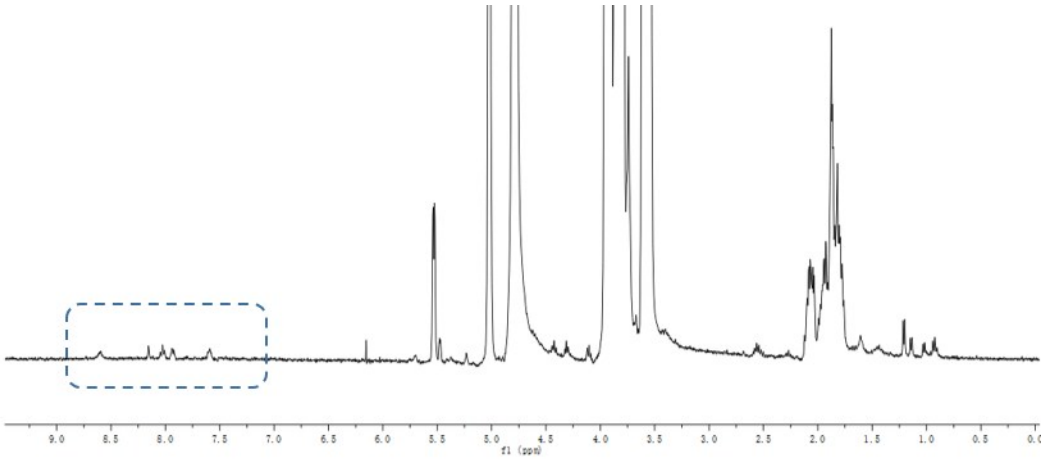


Figure S4. ^{1}H NMR spectrum of β-CD/***azo*-SN-38** in D_2O at ambient temperature. Clear peaks belonging to ***azo*-SN-38** can be detected as shown in the blue box.

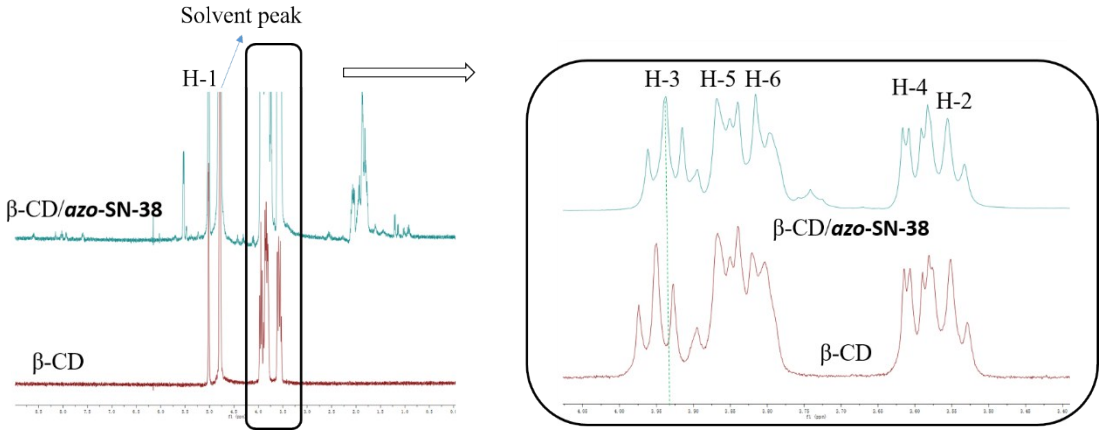


Figure S5. Comparison of ^{1}H NMR spectra of β-CD and β-CD/***azo*-SN-38** in D_2O at ambient temperature. Clear chemical shift of H-3 before and after the inclusion was detected.

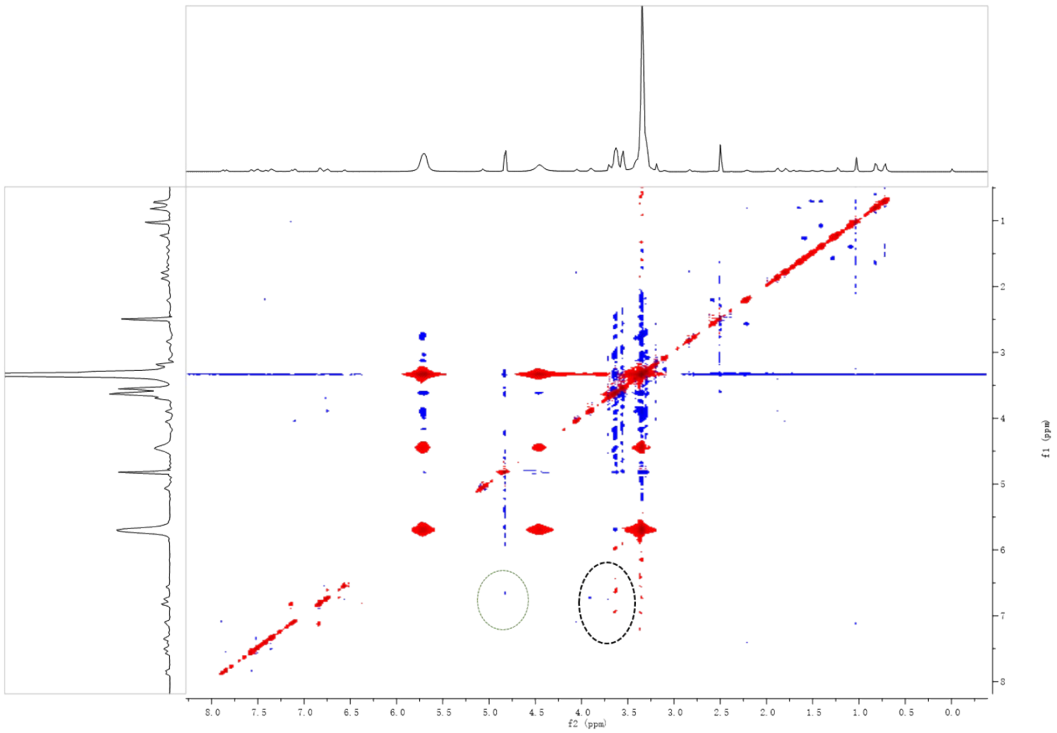


Figure S6. 2D NMR ROESY (600 MHz) spectrum of β-CD/***azo*-SN-38** in DMSO-δ6 at T = 300 K. The solubility of β-CD/***azo*-SN-38** in D_2O is too low to show the NMR peaks, and DMSO-δ6 was used instead. Green circle: interactions between ***azo*-SN-38** and H-1; black circle: interactions between ***azo*-SN-38** and H-3.

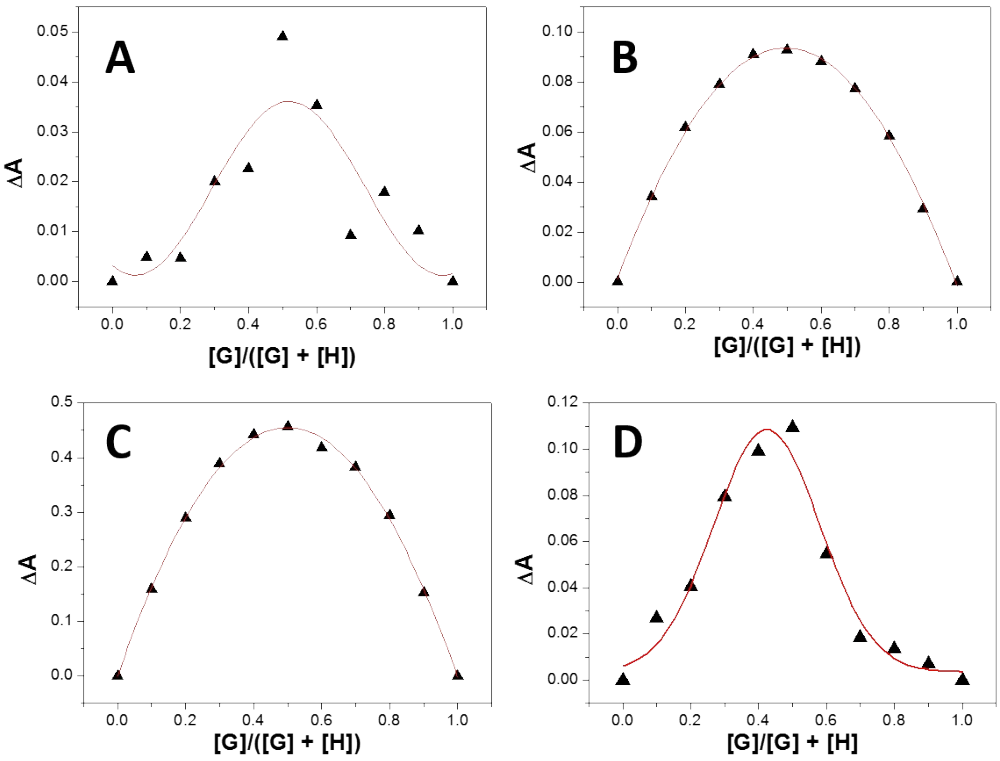


Figure S7. Job's plots by UV–vis for the binding stoichiometry of β-CD with compound ***azo*-SN-38** (A), ***azo*-DOX** (B), ***azo*-phenytoin** (C) and ***azo*-aliskiren** (D) in water at room temperature.

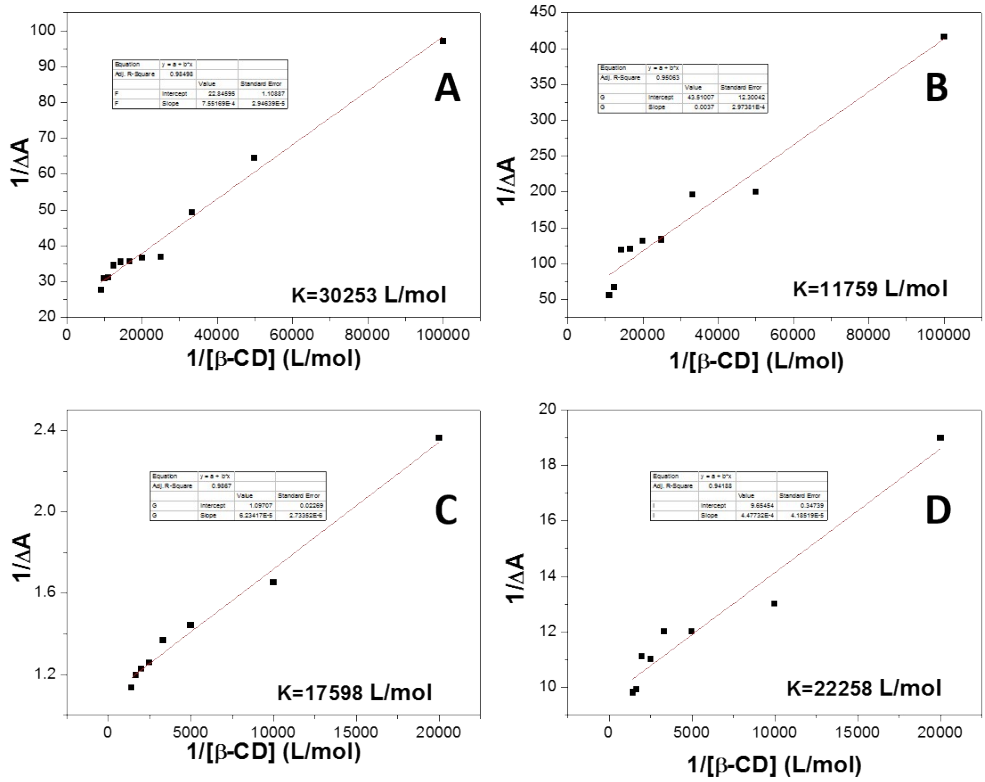


Figure S8. Double reciprocal plots of the supramolecular inclusion complexes in water: (A) the complex constant calculated of **β-CD/*azo*-SN-38** in 1:1 mode (G/H, r^2 = 0.98498, K=30253 L/mol); (B) the complex constant of **β-CD/*azo*-DOX** calculated in 1:1 mode (G/H, r^2 = 0.95063, K=11759 L/mol); (C) the complex constant of **β-CD/*azo*-phenytoin** calculated in 1:1 mode (G/H, r^2 = 0.9867, K=17598 L/mol); (D) the complex constant of **β-CD/*azo*-aliskiren** calculated in 1:1 mode (G/H, r^2 = 0.94188, K=22258 L/mol);. The Benesi-Hildebrand equation is expressed as $1/\Delta A = 1/\alpha + 1/\alpha Kap[\beta\text{-CD}]^n$, where ΔA is the change of UV absorbance of ***azo*-drugs** in presence of β-CD, α is a constant, [β-CD] is the initial concentration of β-CD. *Kap* is the constant for the formation of n:1 (H:G) inclusion complex, which could be calculated from a plot of 1/ΔA versus ***azo*-drug**/$[\beta\text{-CD}]^n$.

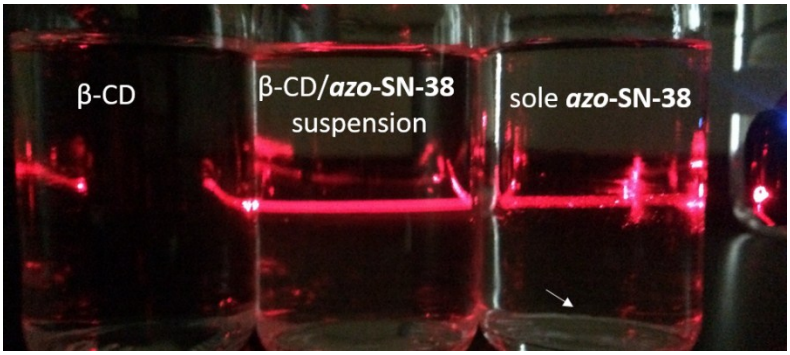


Figure S9. Different phenomenon of β-CD in aqueous solution (0.05 mM), β-CD/***azo*-SN-38** suspension (0.05 mM) and ***azo*-SN-38** aqueous dispersion in water (0.05 mM) illuminated by a laser pointer. Precipitated solid can be found if left to stand still for 2 h shown at the arrow.

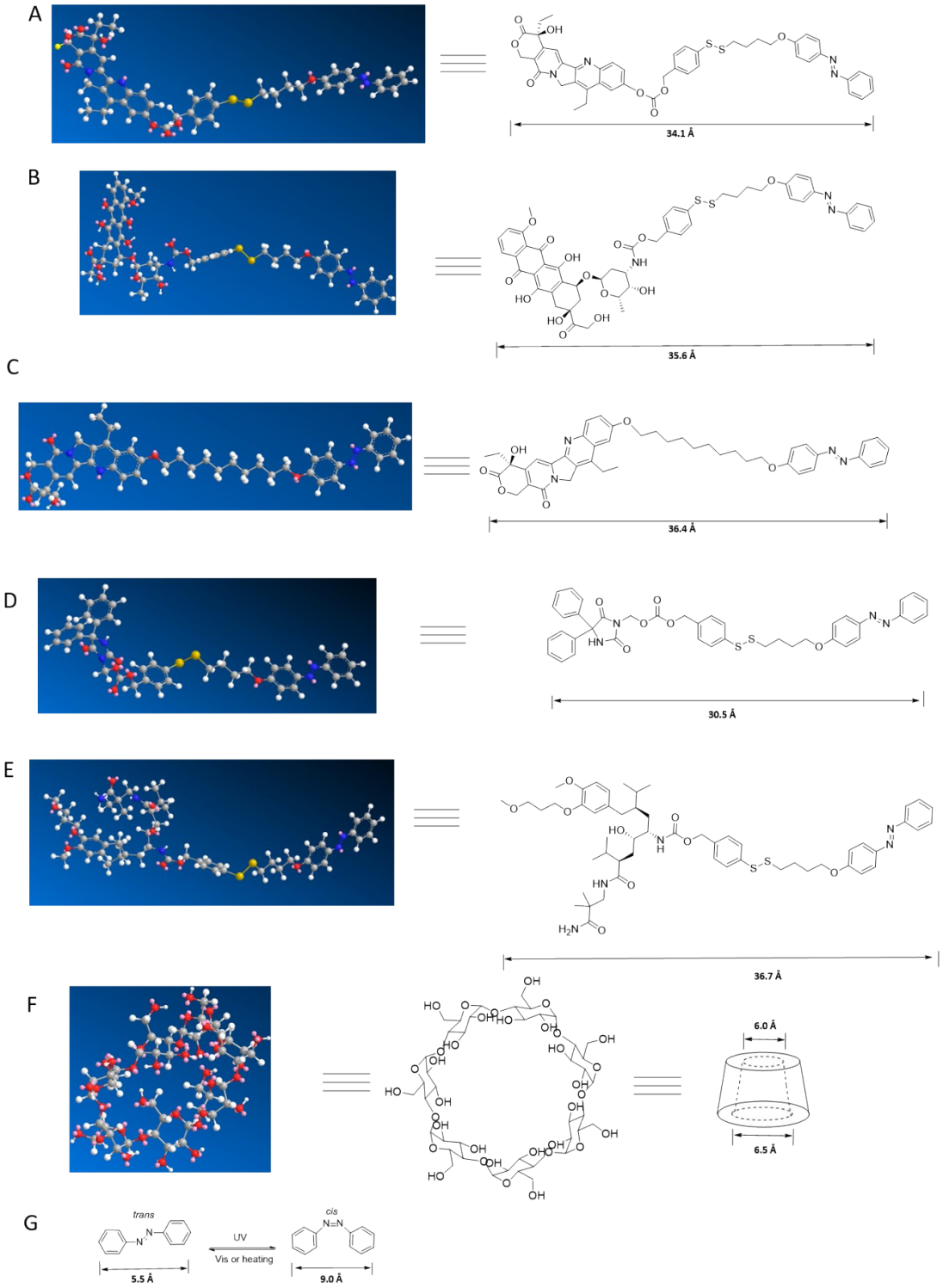


Figure S10. The molecular configuration after MM2 energy minimize calculation[7] and corresponding calculated molecular sizes: (A) ***azo*-SN-38**; (B) ***azo*-DOX**; (C) ***azo*-C_{10}-SN-38**; (D) ***azo*-phenytoin**; (E) ***azo*-aliskiren**; (F) β-CD; (G) *azo*benzene.

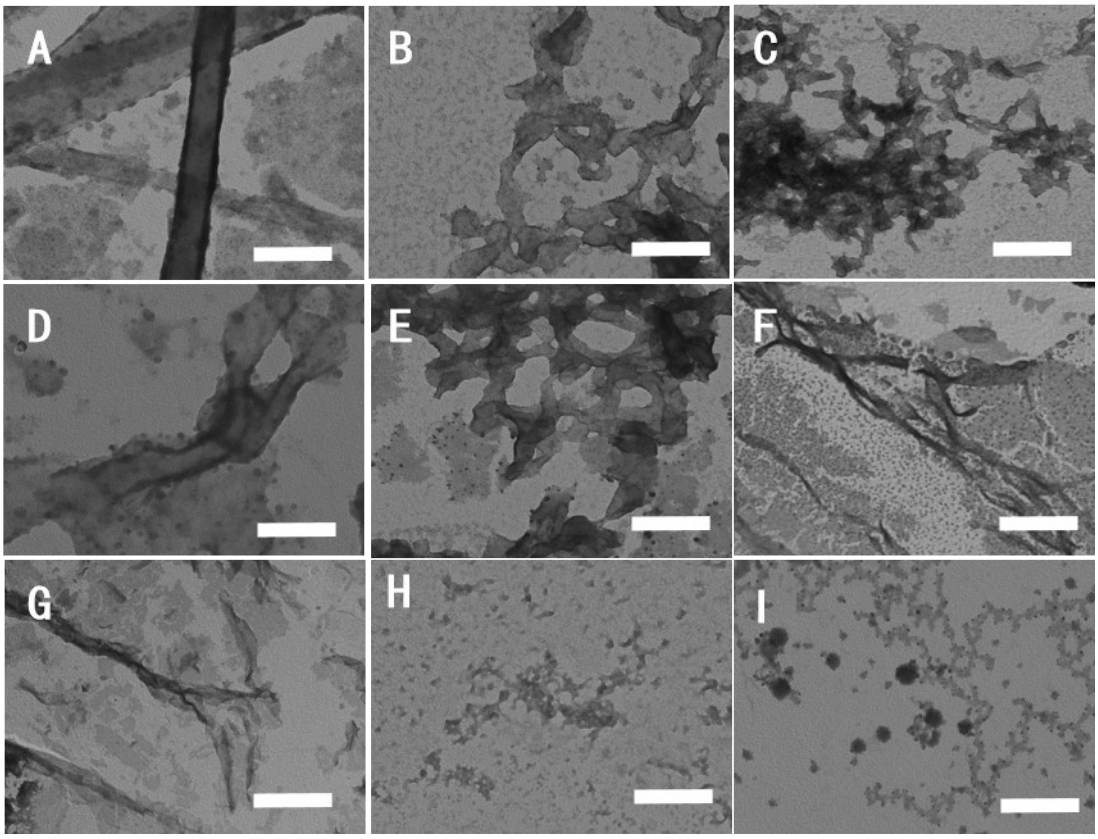


Figure S11. TEM micromorphology images of β-CD/***azo*-SN-38** samples treated by UV upon different time intervals (A: 0 min, B: 10 min, C: 20 min, D: 30 min, E: 40 min, F: 50 min, G: 60 min, H: 70 min, I: 80 min, scale bar = 1 μm) with phosphotungstic acid as the negative staining agent.

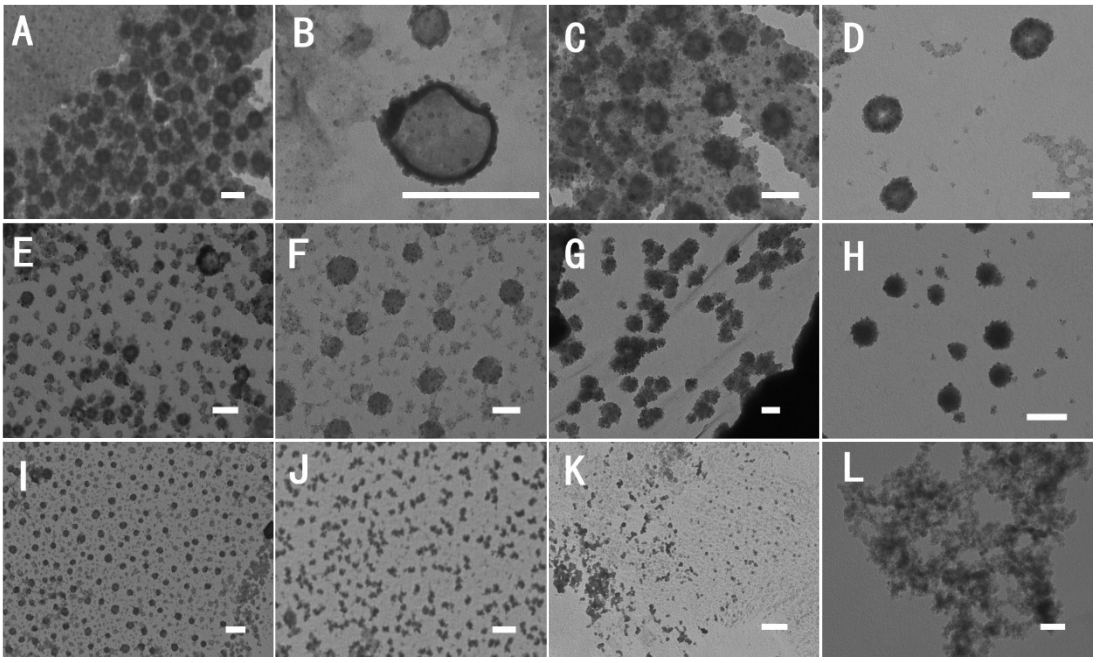


Figure S12. TEM micromorphology images of β-CD/***azo*-phenytoin** samples treated by UV upon different time intervals (A: 0 min, B: 10 min, C: 20 min, D: 30 min, E: 40 min, F: 50 min, G: 60 min, H: 70 min, I: 80 min, J: 90 min, K: 100 min, L: 110 min; scale bar = 500 nm) with phosphotungstic acid as the negative staining agent.

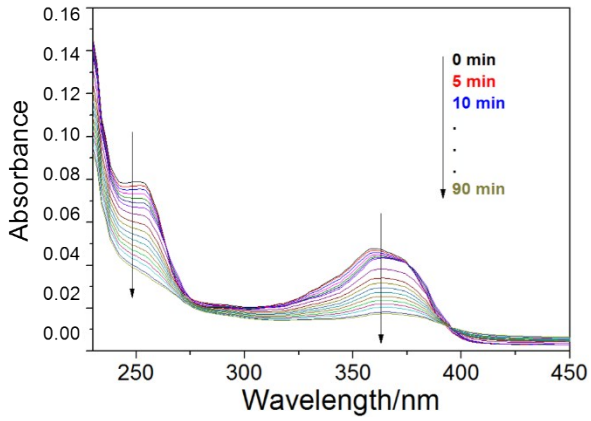


Figure S13. The UV-absorbance drop of the β-CD/***azo*-SN-38** sample in pure water treated by UV at different time intervals (from 0 to 90 min).

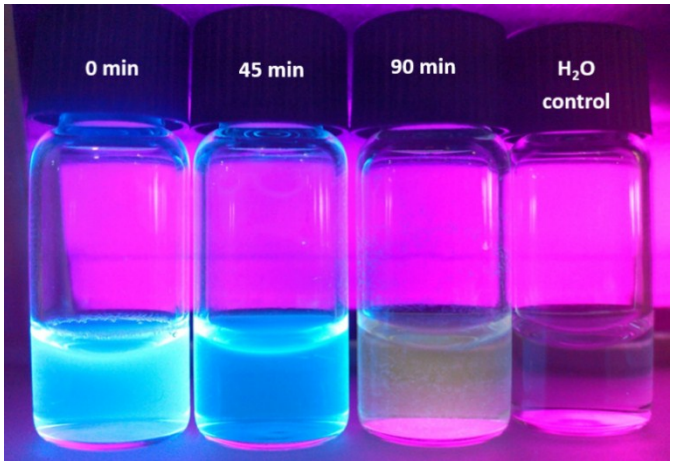


Figure S14. The fluorescence intensity variation of the β-CD/***azo*-SN-38** samples treated by UV irradiation at different time intervals (0 min, 45 min, 90 min and control).

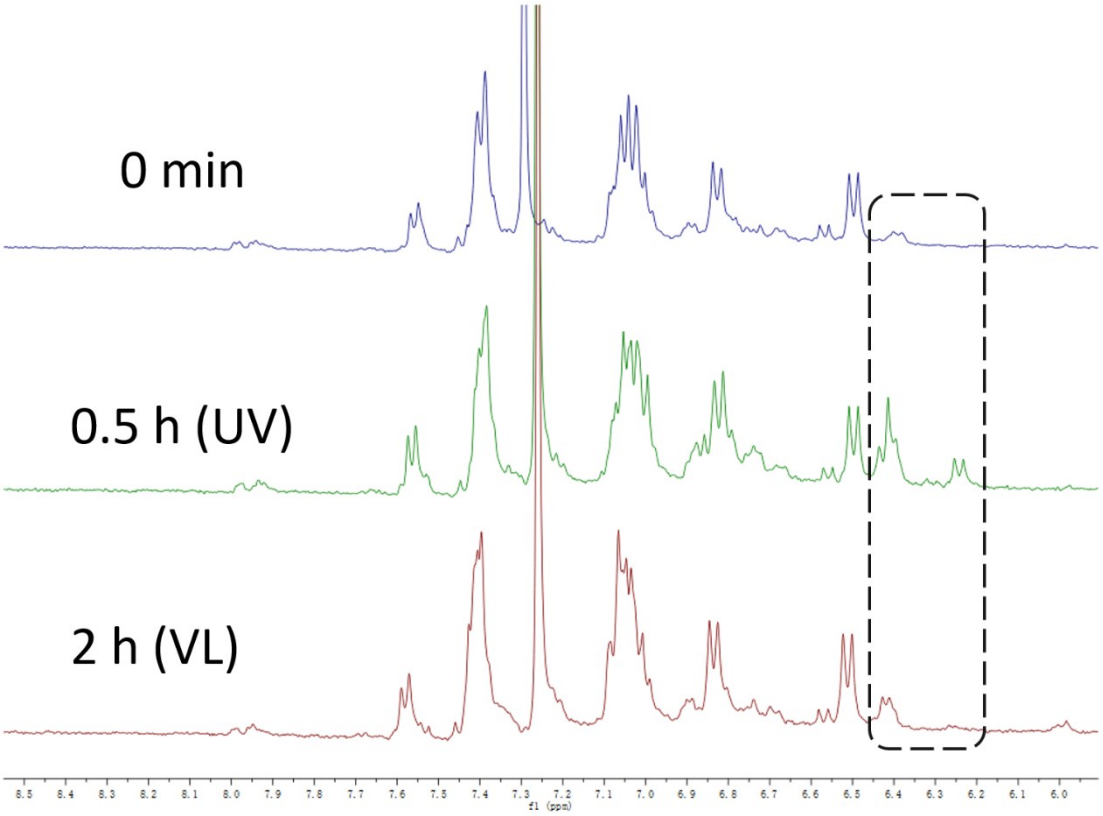


Figure S15. Enlarged ^{1}H NMR spectra (400 MHz in mixed $CD_3OD/CDCl_3$ (2/1 v/v) at 298 K) from the same tube of ***azo*-DOX** before (0 min), after the UV irradiation (365 nm, 60 mW·cm^{-2}, 0.5 h) and after visible light irradiation (λ = 434 nm, 20 mW·cm^{-2}, 2 h).

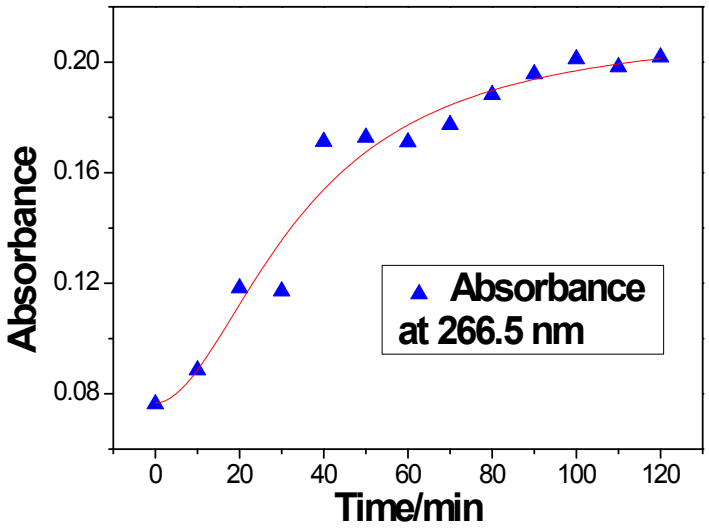


Figure S16. The UV-absorbance increase of the ***azo*-SN-38** sample in $MeOH/CHCl_3$ (2/1 v/v, 10^{-5} mol/L) treated by UV at different time intervals (from 0 to 120 min).

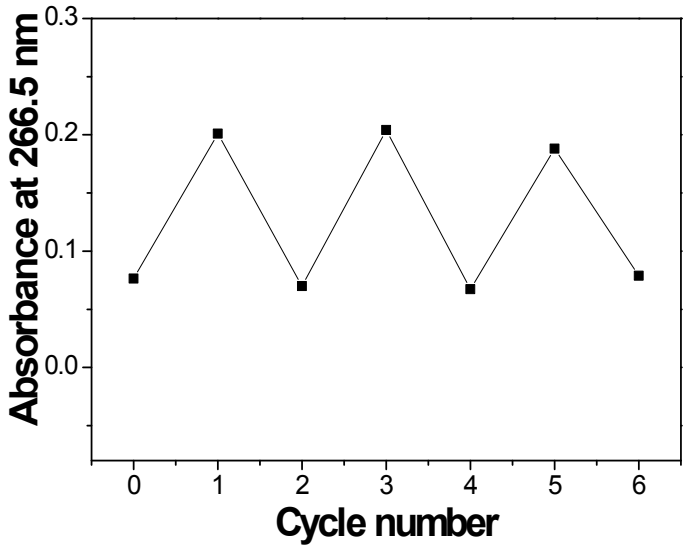


Figure S17. UV-absorbance variation at 266.5 nm of the ***azo*-SN-38** sample in MeOH/$CHCl_3$ (2/1 v/v, 10^{-5} mol/L) with commutative UV and visible light irradiation.

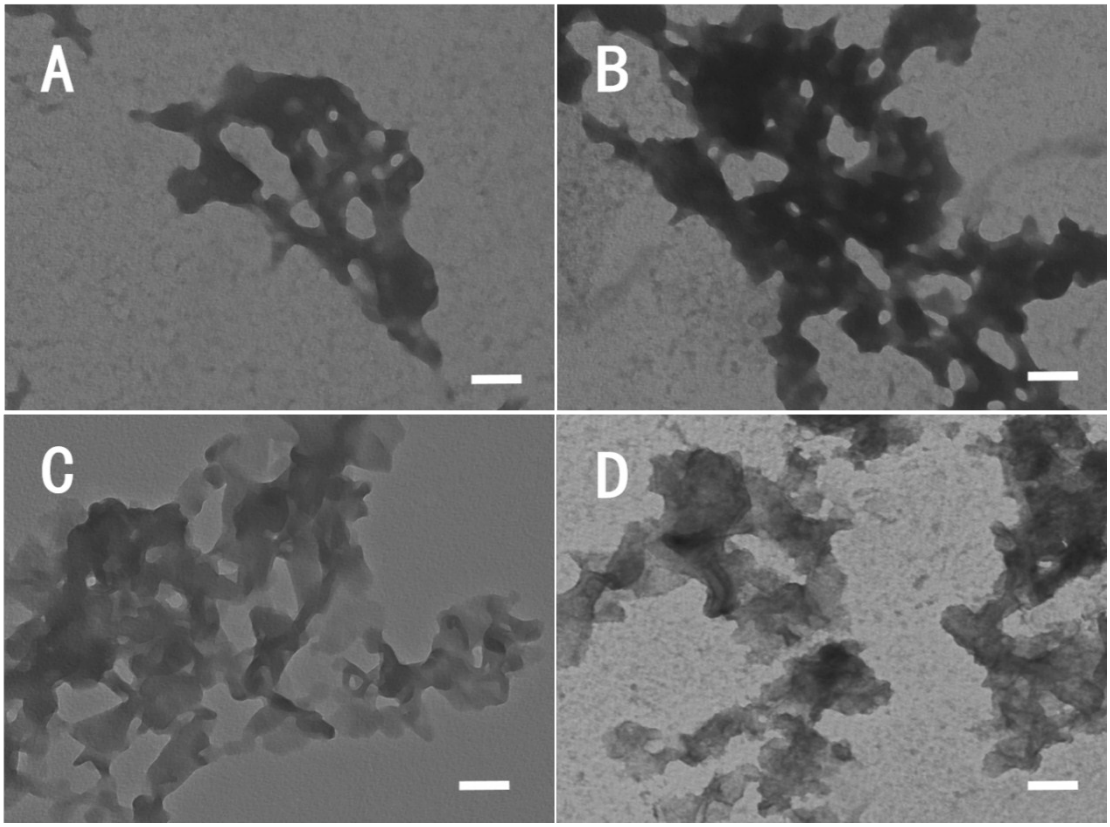


Figure S18. The micro morphologies after the treatment of excess reductant recorded by TEM (scale bar = 1 μm) with phosphotungstic acid as the negative staining agent: A: β-CD/***azo*-SN-38**+DTT; B: β-CD/***azo*-SN-38**+GSH; C: β-CD/***azo*-DOX**+DTT; D: β-CD/***azo*-DOX**+GSH.

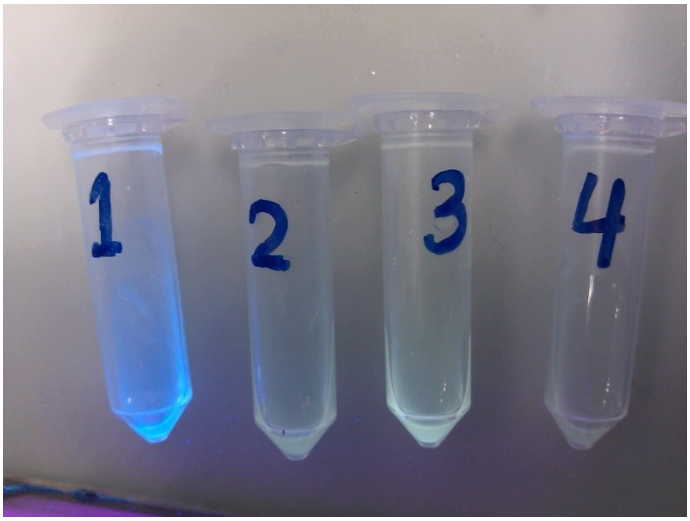


Figure S19. The fluorescence intensity change of the β-CD/***azo*-SN-38** samples treated by GSH at different time intervals (1: 0 min, 2: 30 min, 3: 60 min and 4: 90 min).

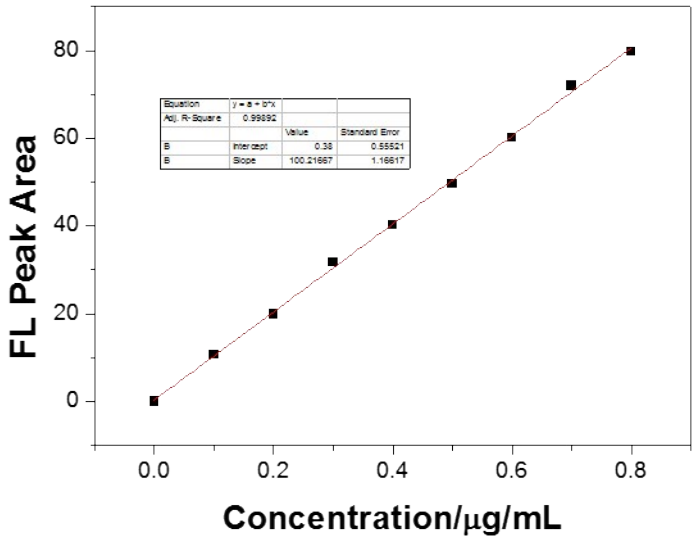


Figure S20. The standard curve of SN-38 concentration in aqueous solution determined by HPLC (n=3, r^2=0.99892).

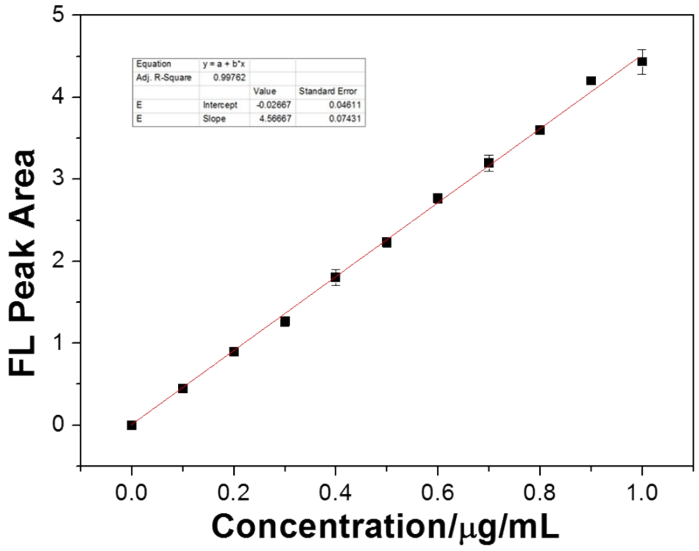


Figure S21. The standard curve of DOX concentration in aqueous solution determined by HPLC (n=3, r^2=0.99762).

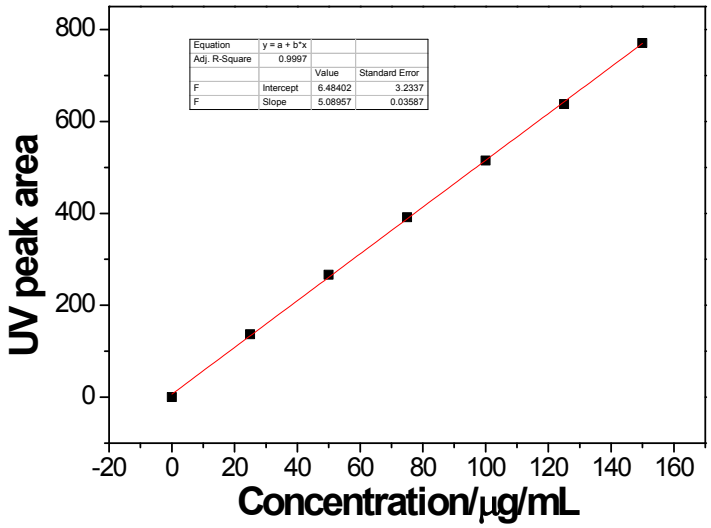


Figure S22. The standard curve of phenytoin concentration in aqueous solution determined by HPLC (n=3, r^2=0.9997).

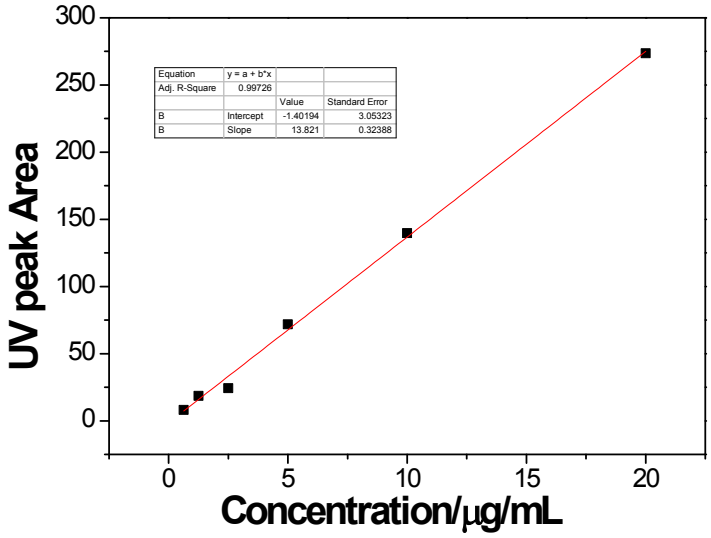


Figure S23. The standard curve of aliskiren concentration in aqueous solution determined by HPLC (r^2=0.99726).

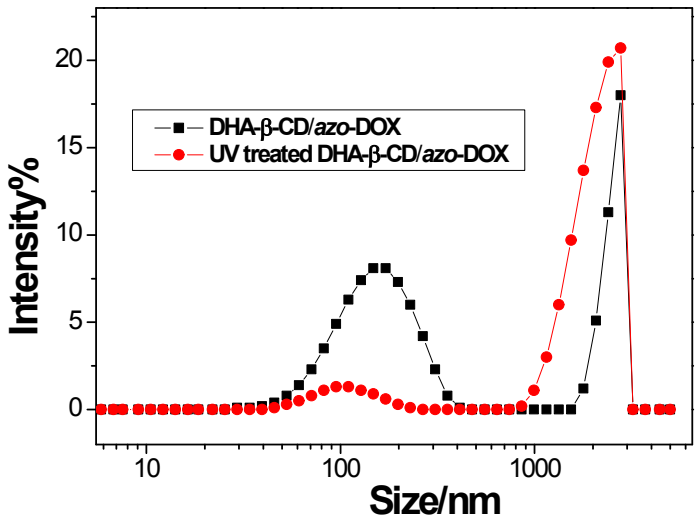


Figure S24. The size change of **DHA-β-CD/*azo*-DOX** sample in water (**10^{-4}** mol/L**)** before and after UV treatment (254 nm, 60 mW·cm^{-2}, 30 min) by DLS at room temperature.

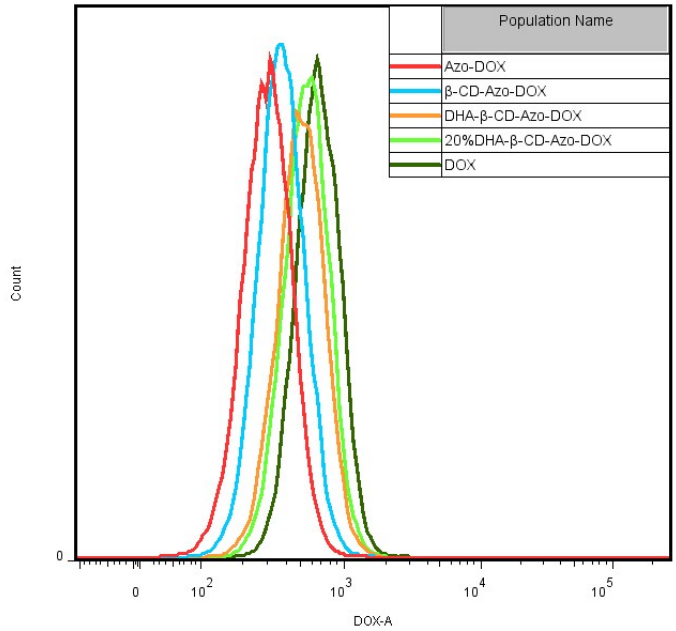


Figure S25. Flow cytometry quantitative analysis of different DOX formulations, including free DOX·HCl, ***azo*-DOX**, β-CD/***azo*-DOX**, **DHA-β-CD** (20% in β-CD)/***azo*-DOX** and **DHA-β-CD/*azo*-DOX**

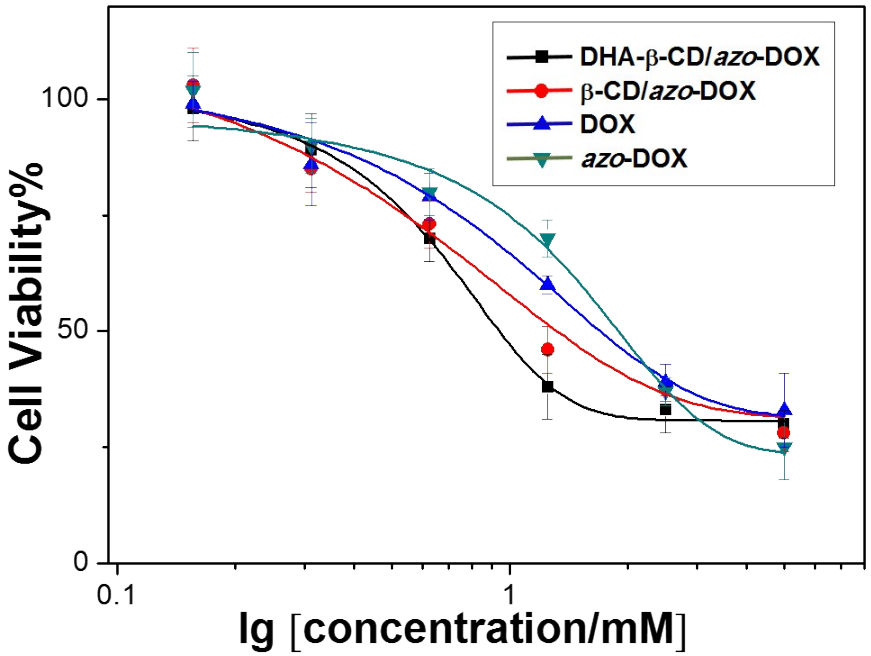


Figure S26. *In vitro* cytotoxicity of different DOX formulations at various concentrations against MDA-MB-231 tumor cells 48 h after incubation. Data are represented as mean ± SD (n = 3).

Characterizations of all compounds

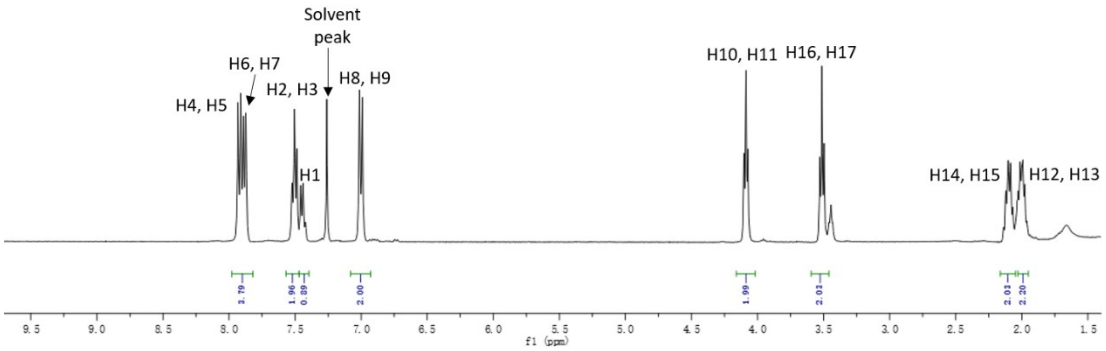


Figure S27. ^{1}H NMR spectrum of **2** in $CDCl_3$ at ambient temperature.

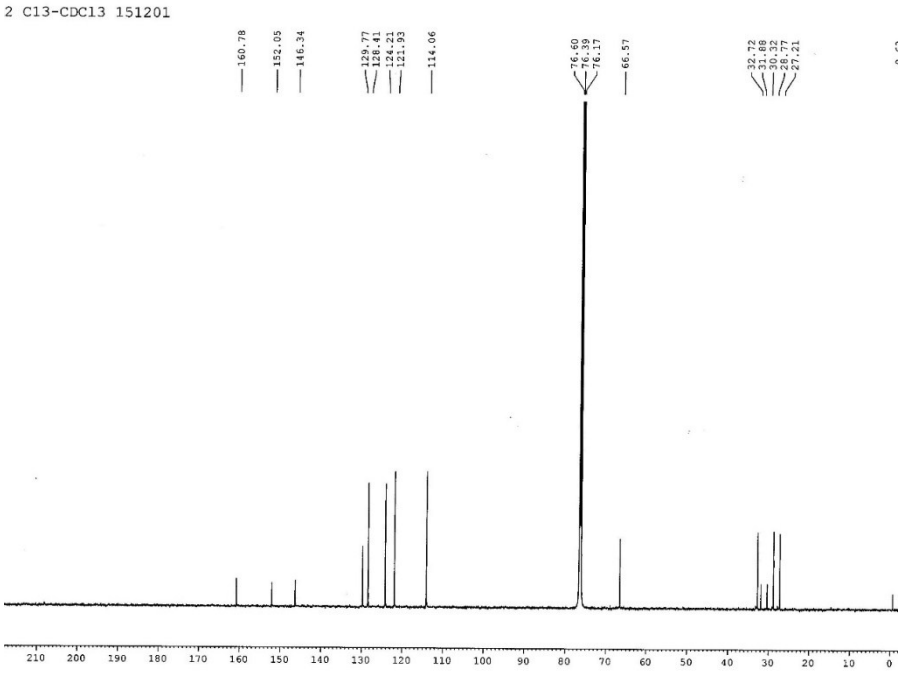


Figure S28. ^{13}C NMR spectrum of **2** in $CDCl_3$ at ambient temperature.

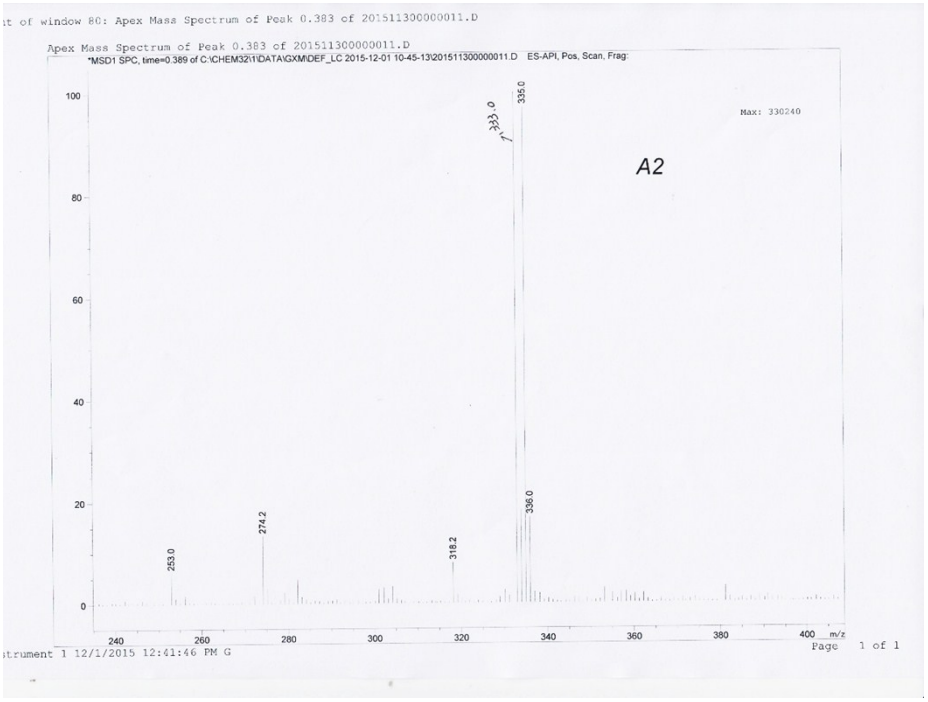


Figure S29. MS-ESI spectrum of **2** in $CDCl_3$ at ambient temperature.

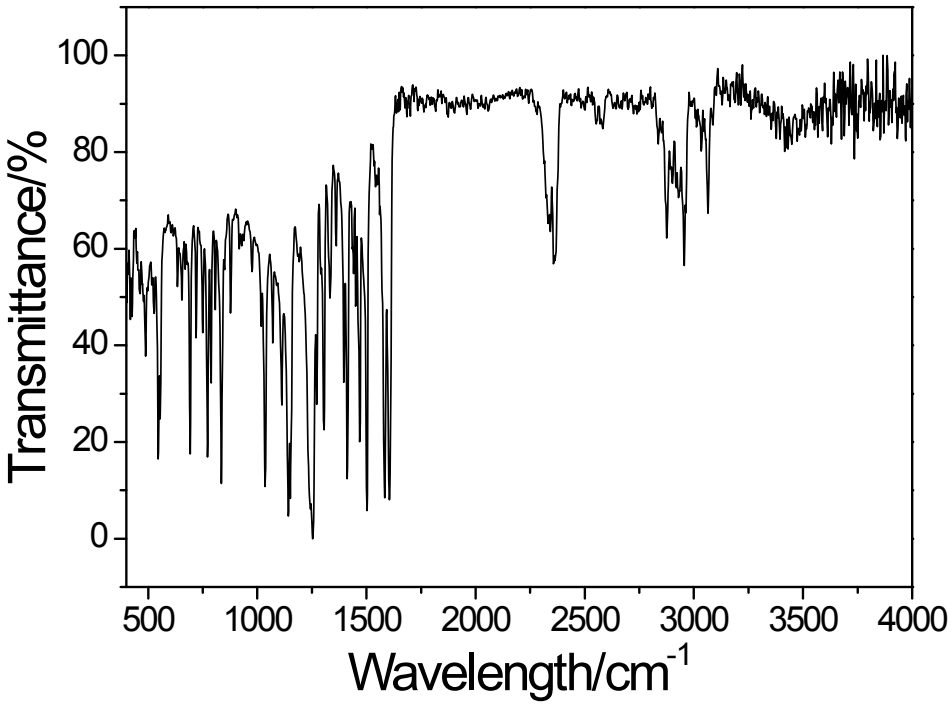


Figure S30. FT-IR spectrum of **3** in KBr tablet at ambient temperature.

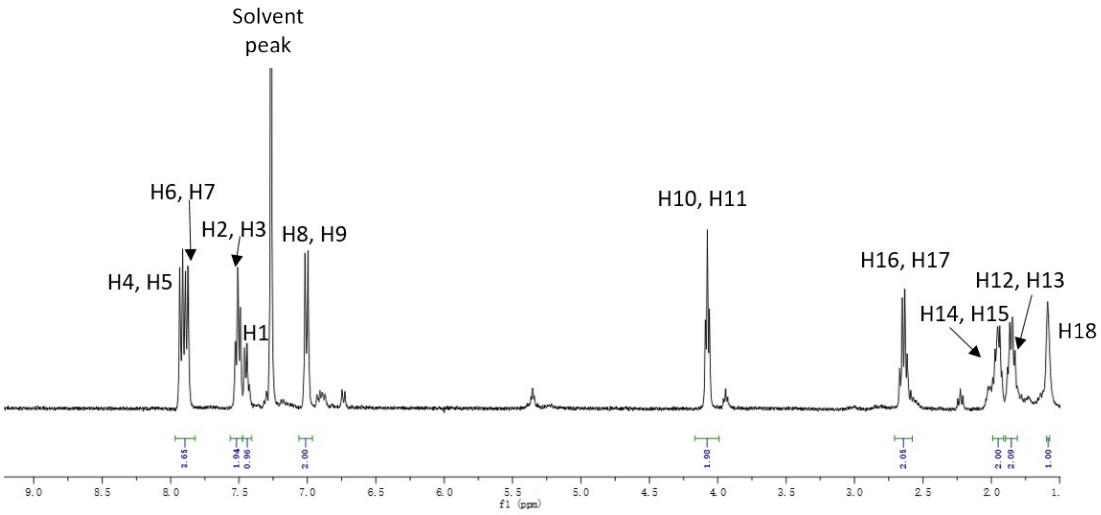


Figure S31. ^{1}H NMR spectrum of **3** in $CDCl_3$ at ambient temperature.

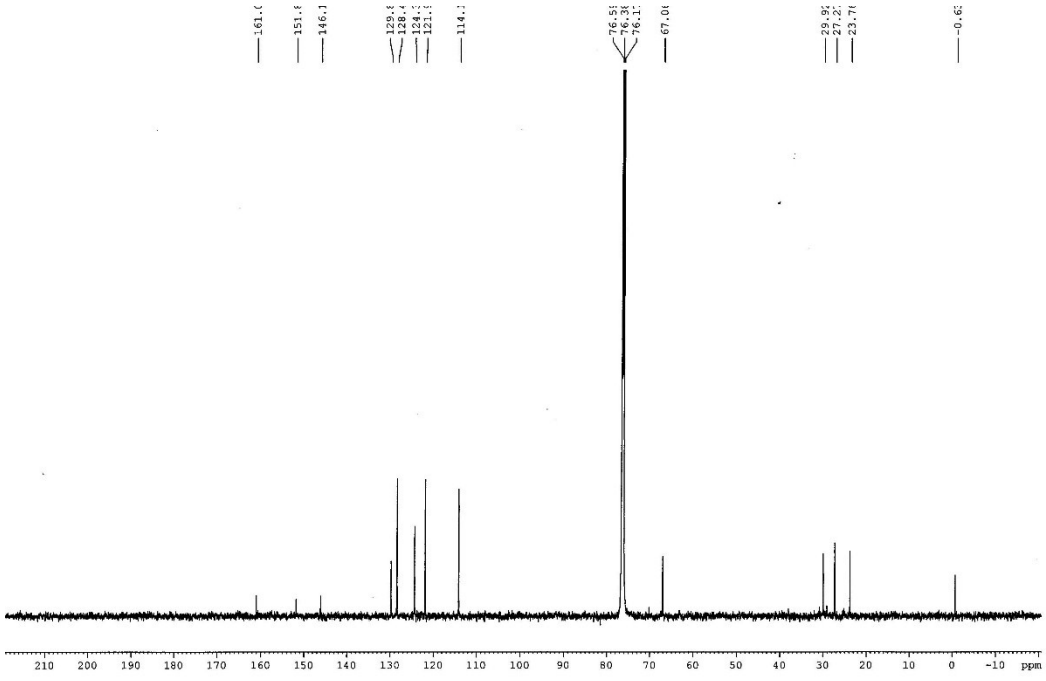


Figure S32. ^{13}C NMR spectrum of **3** in $CDCl_3$ at ambient temperature.

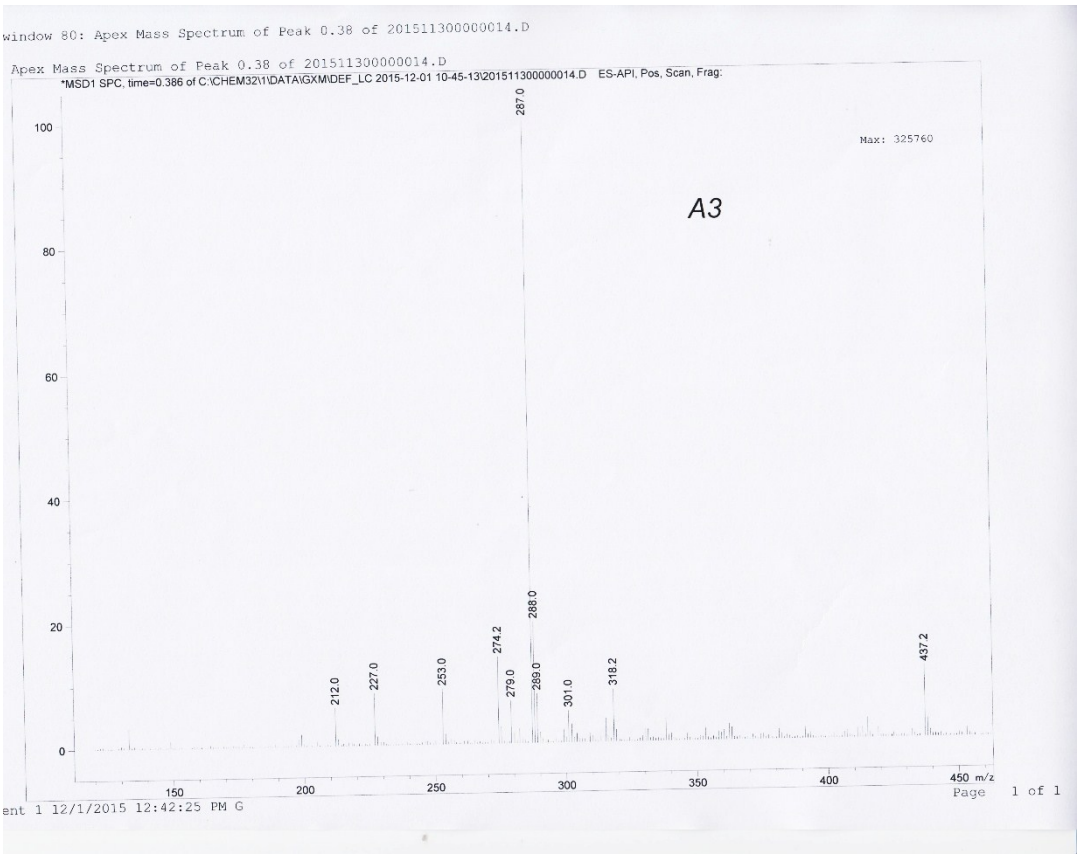


Figure S33. MS-ESI spectrum of **3** in $CDCl_3$ at ambient temperature.

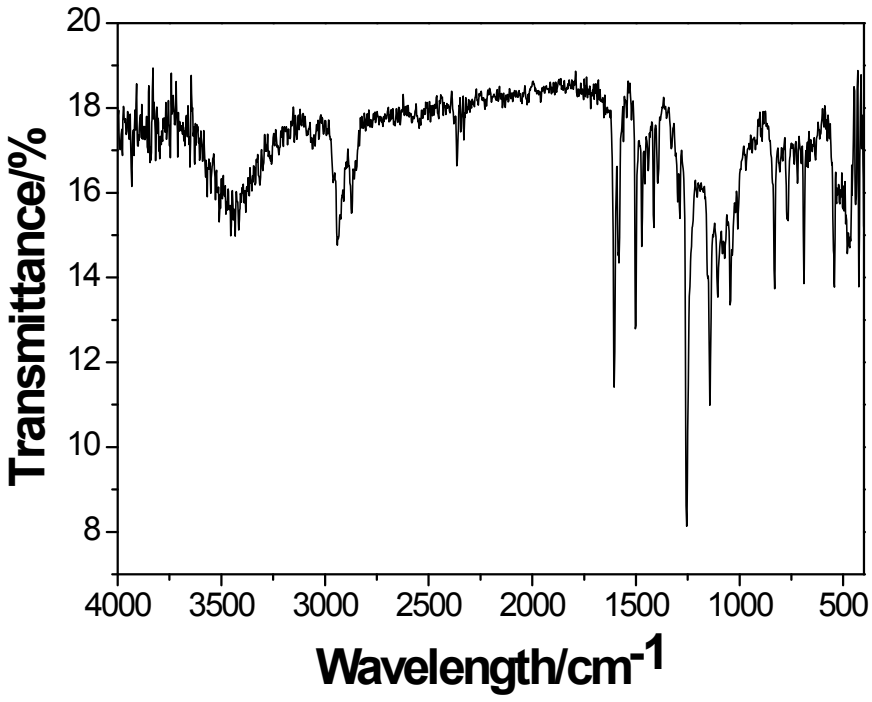


Figure S34. FT-IR spectrum of **3** in KBr tablet at ambient temperature.

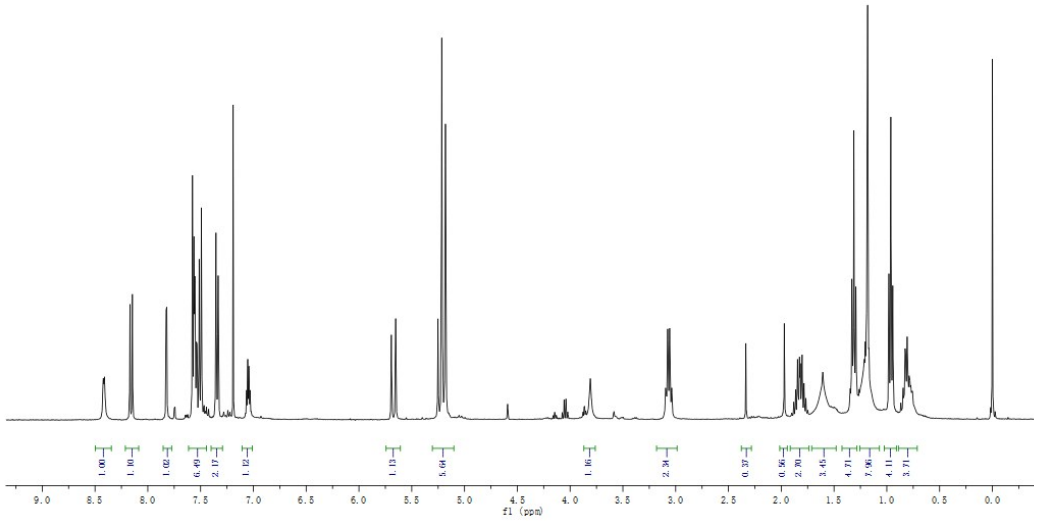


Figure S35. ^{1}H NMR spectrum of **7** in $CDCl_3$ at ambient temperature.

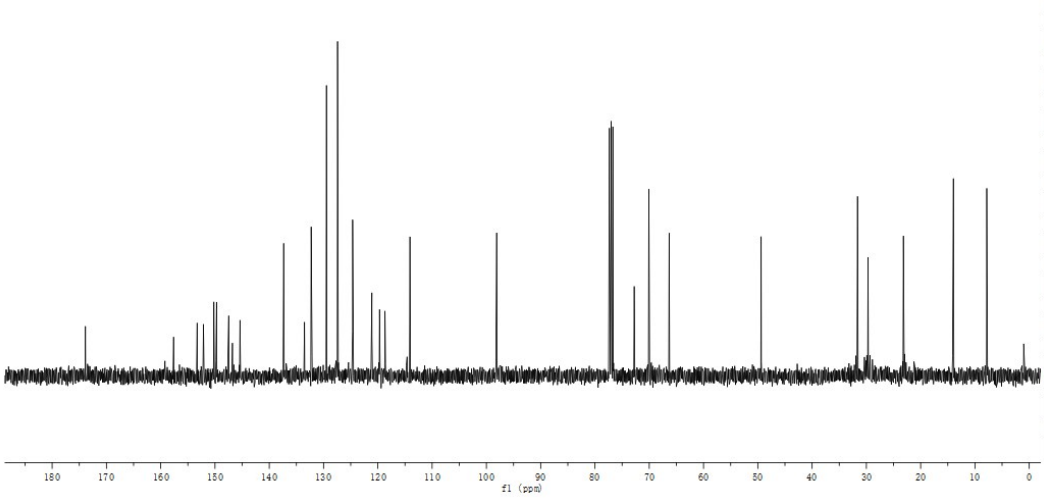


Figure S36. ^{13}C NMR spectrum of **7** in $CDCl_3$ at ambient temperature.

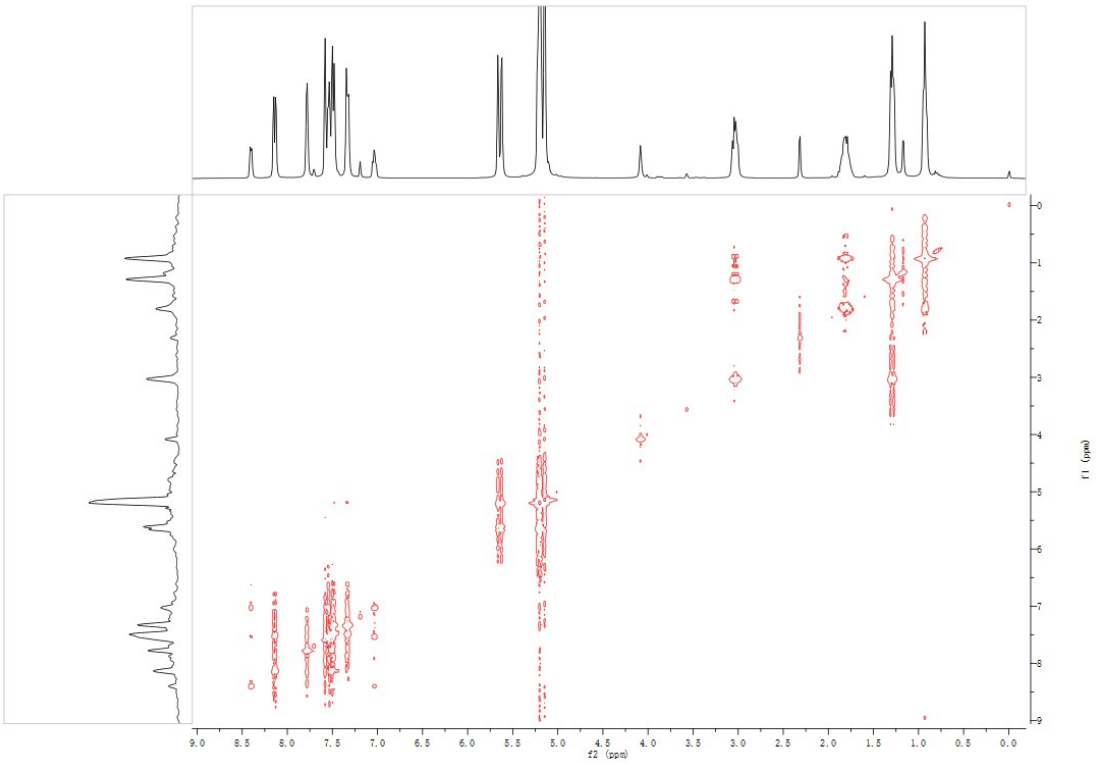


Figure S37. 2D NMR COSY spectrum of **7** in $CDCl_3$ at ambient temperature.

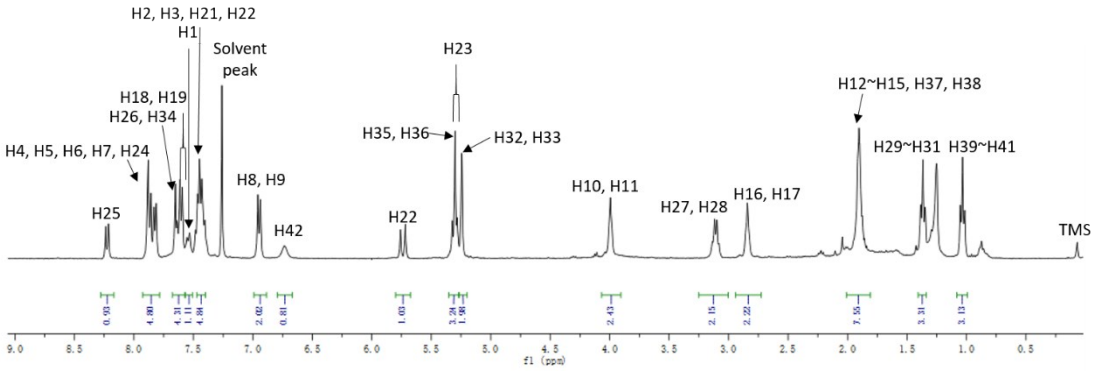


Figure S38. ^{1}H NMR spectrum of ***azo*-SN-38** in $CDCl_3$ at ambient temperature.

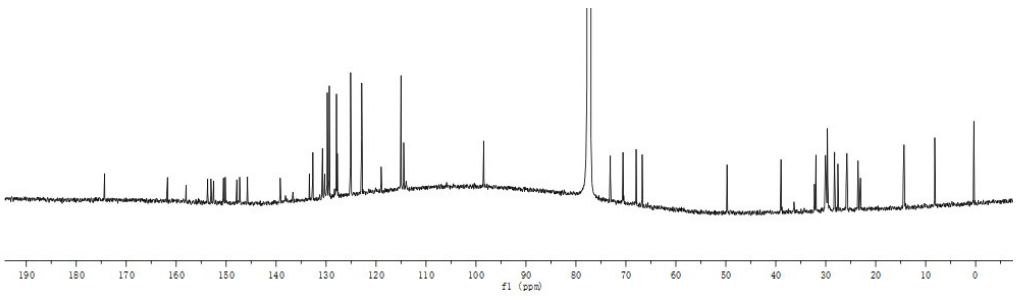


Figure S39. ^{13}C NMR spectrum of ***azo*-SN-38** in $CDCl_3$ at ambient temperature.

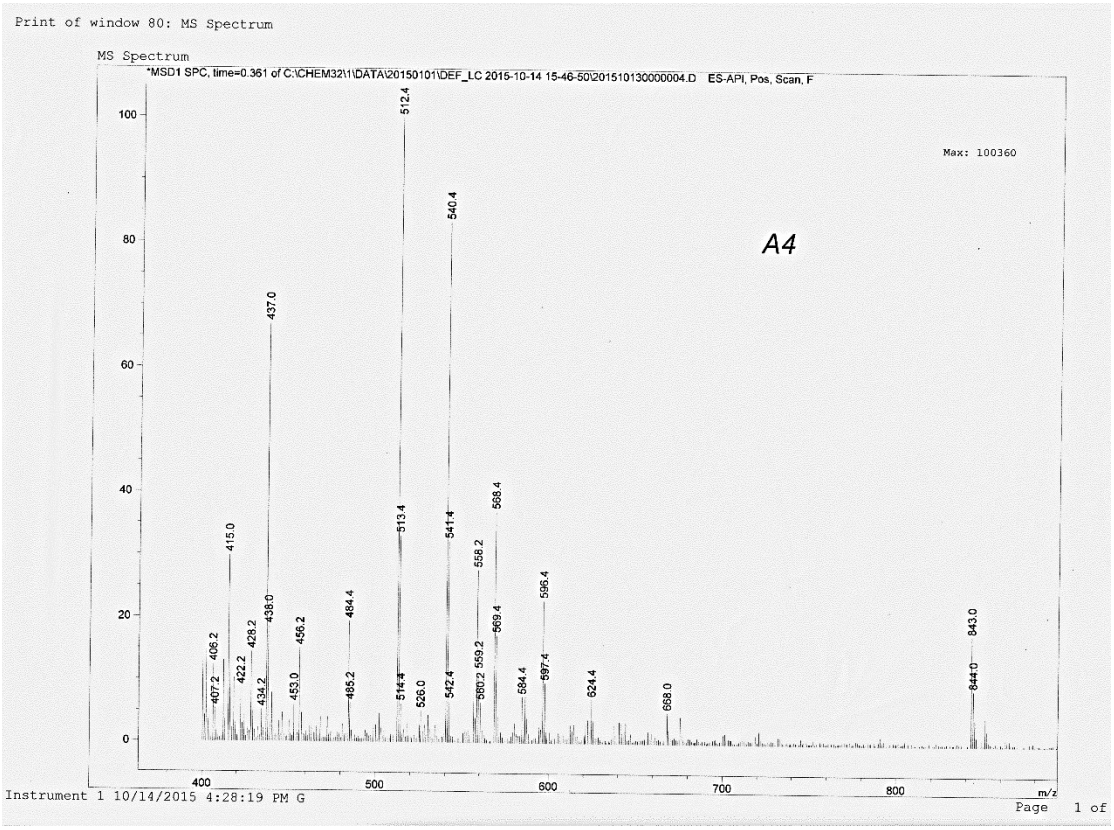


Figure S40. MS-ESI spectrum of ***azo*-SN-38** in $CDCl_3$ at ambient temperature.

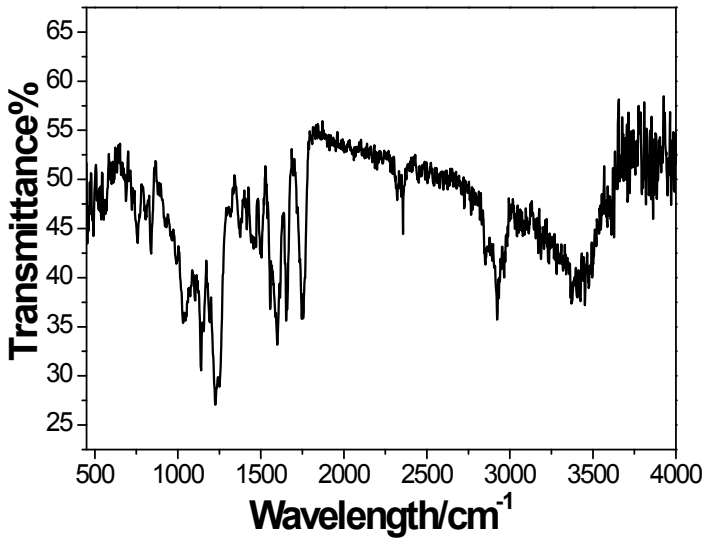


Figure S41. FT-IR spectrum of ***azo*-SN-38** in KBr tablet at ambient temperature.

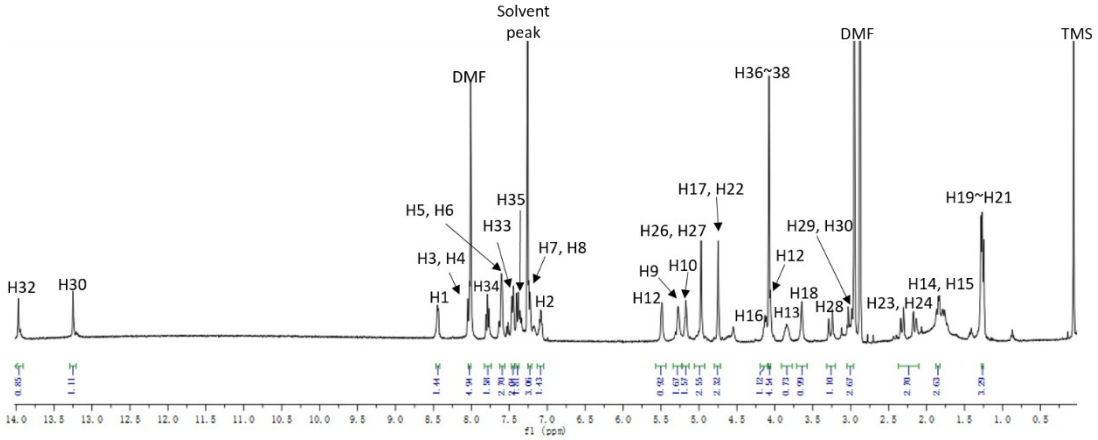


Figure S42. ^{1}H NMR spectrum of **9** in $CDCl_3$ at ambient temperature (with DMF residue).

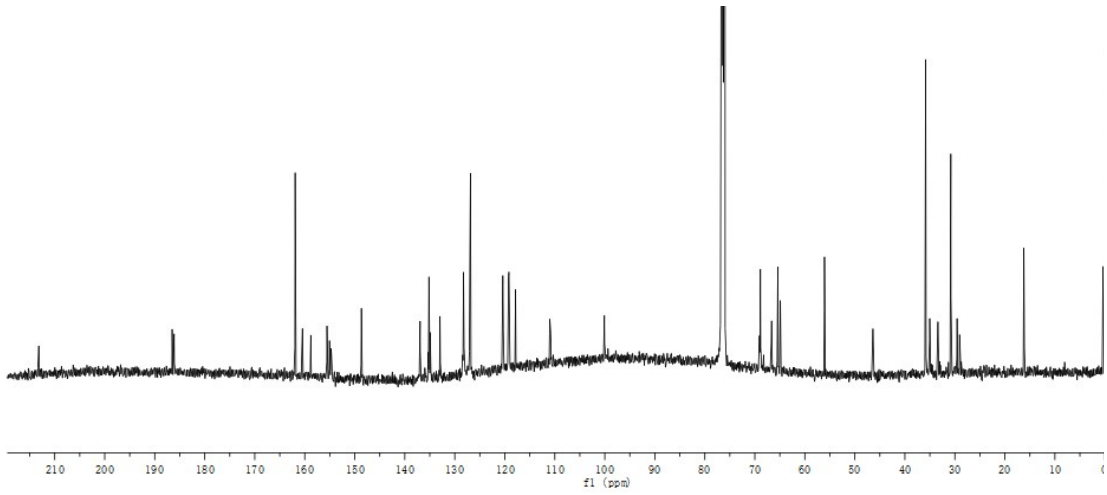


Figure S43. ^{13}C NMR spectrum of **9** in $CDCl_3$ at ambient temperature (with DMF residue).

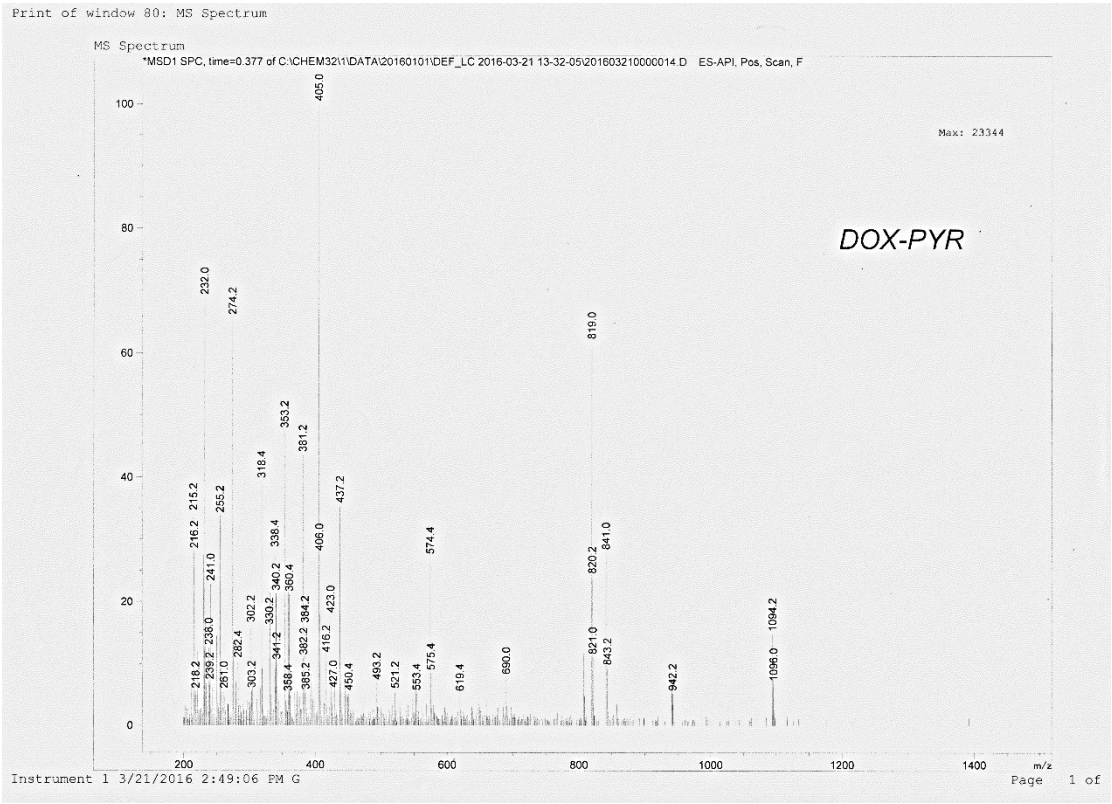


Figure S44. ESI-MS result of **9** at ambient temperature.

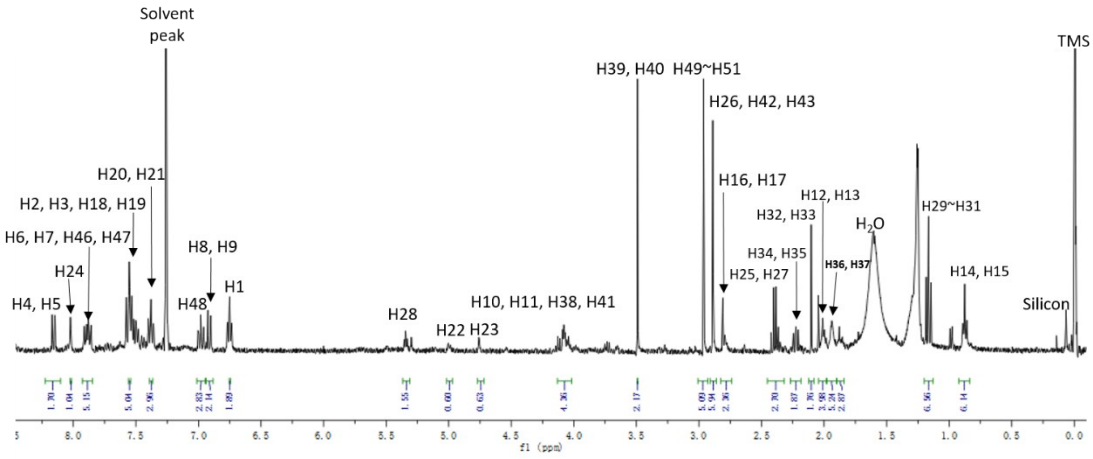


Figure S45. ^{1}H NMR spectrum of ***azo*-DOX** in $CDCl_3$ at ambient temperature.

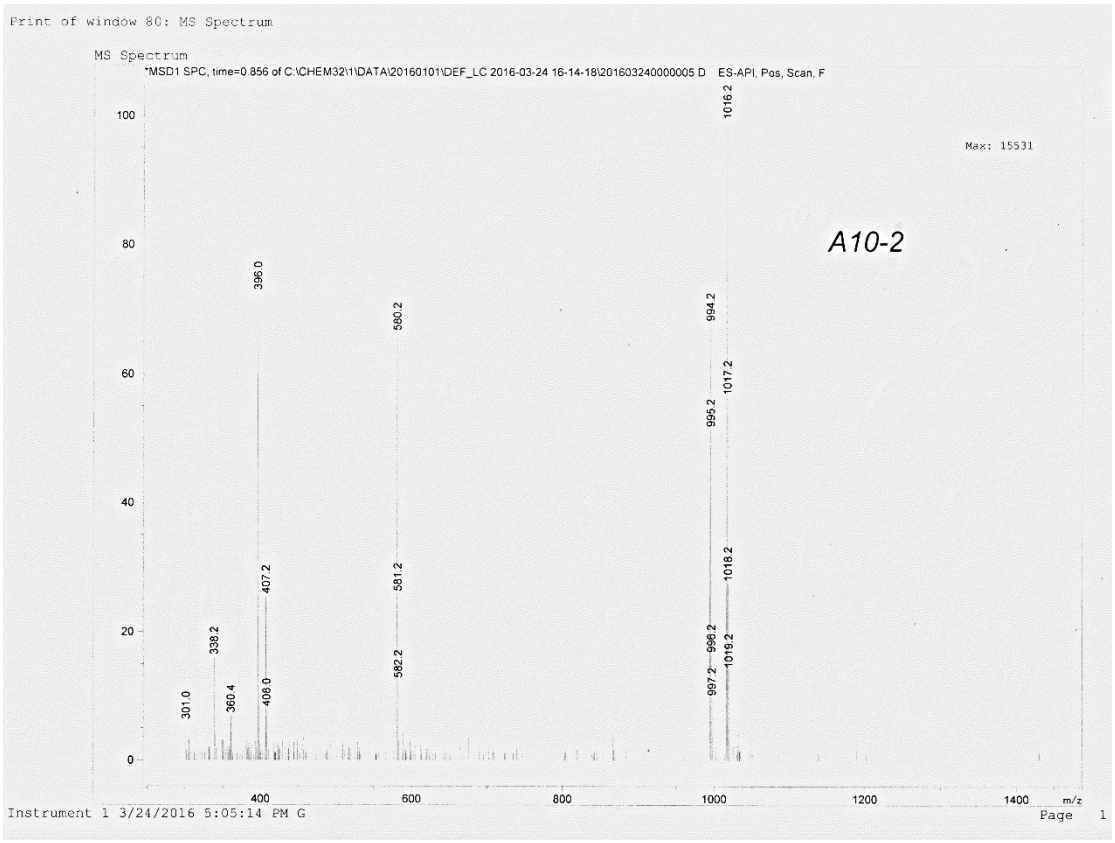


Figure S46. ESI-MS result of ***azo*-DOX** at ambient temperature.

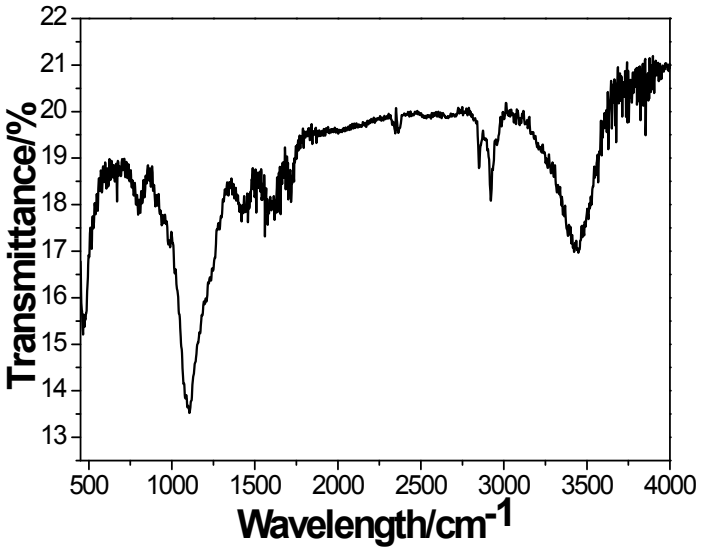


Figure S47. FT-IR spectrum of ***azo*-DOX** in KBr tablet at ambient temperature.

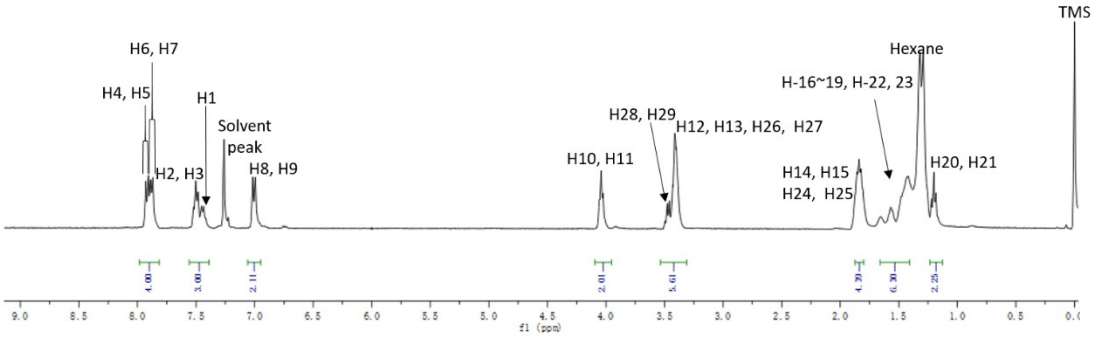


Figure S48. ^{1}H NMR spectrum of **12** in $CDCl_3$ at ambient temperature.

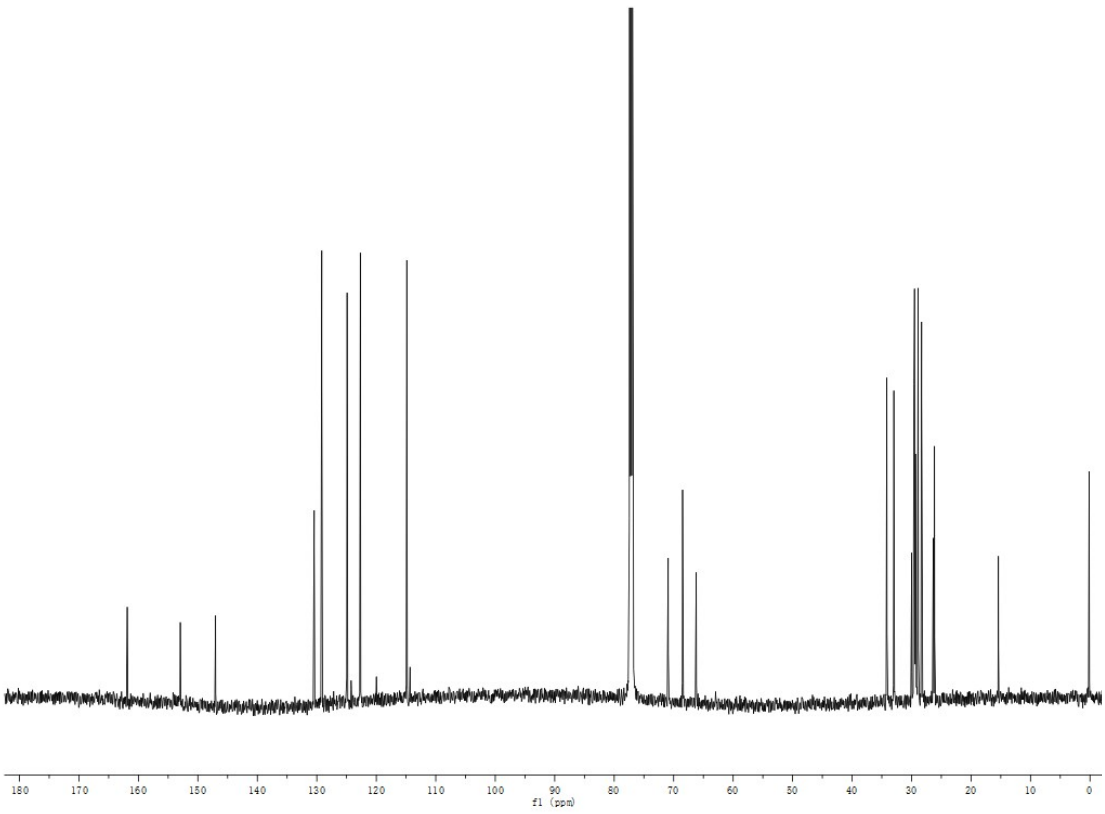


Figure S49. ^{13}C NMR spectrum of **12** in $CDCl_3$ at ambient temperature.

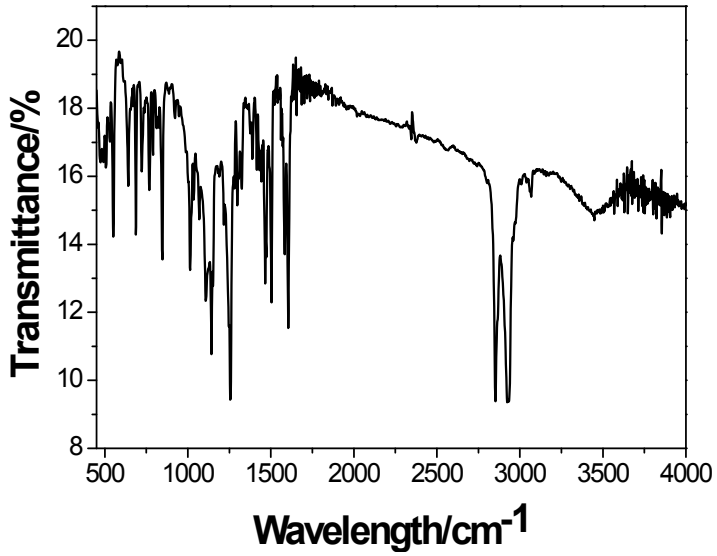


Figure S50. FT-IR spectrum of **12** in KBr tablet at ambient temperature.

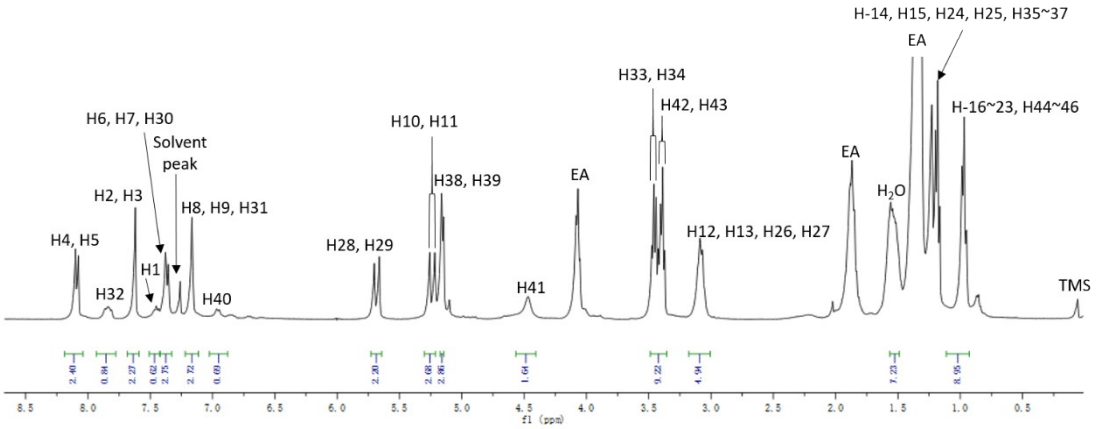


Figure S51. ^{1}H NMR spectrum of **13** in $CDCl_3$ at ambient temperature.

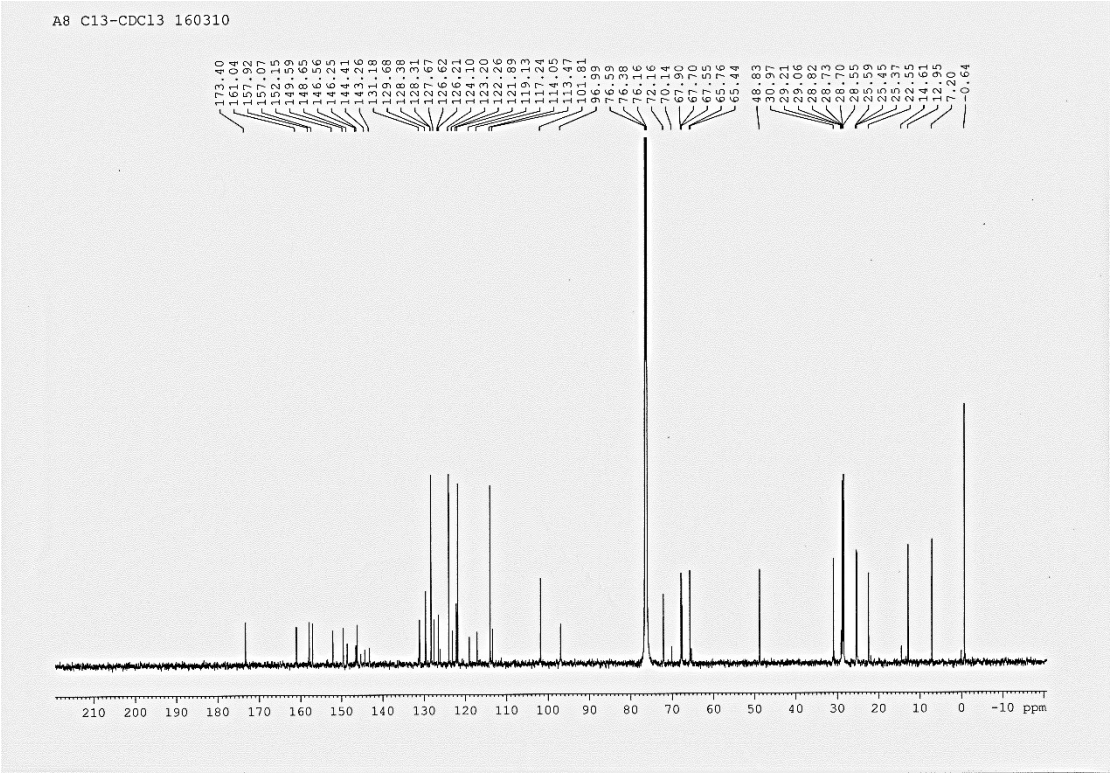


Figure S52. ^{13}C NMR spectrum of **13** in $CDCl_3$ at ambient temperature.

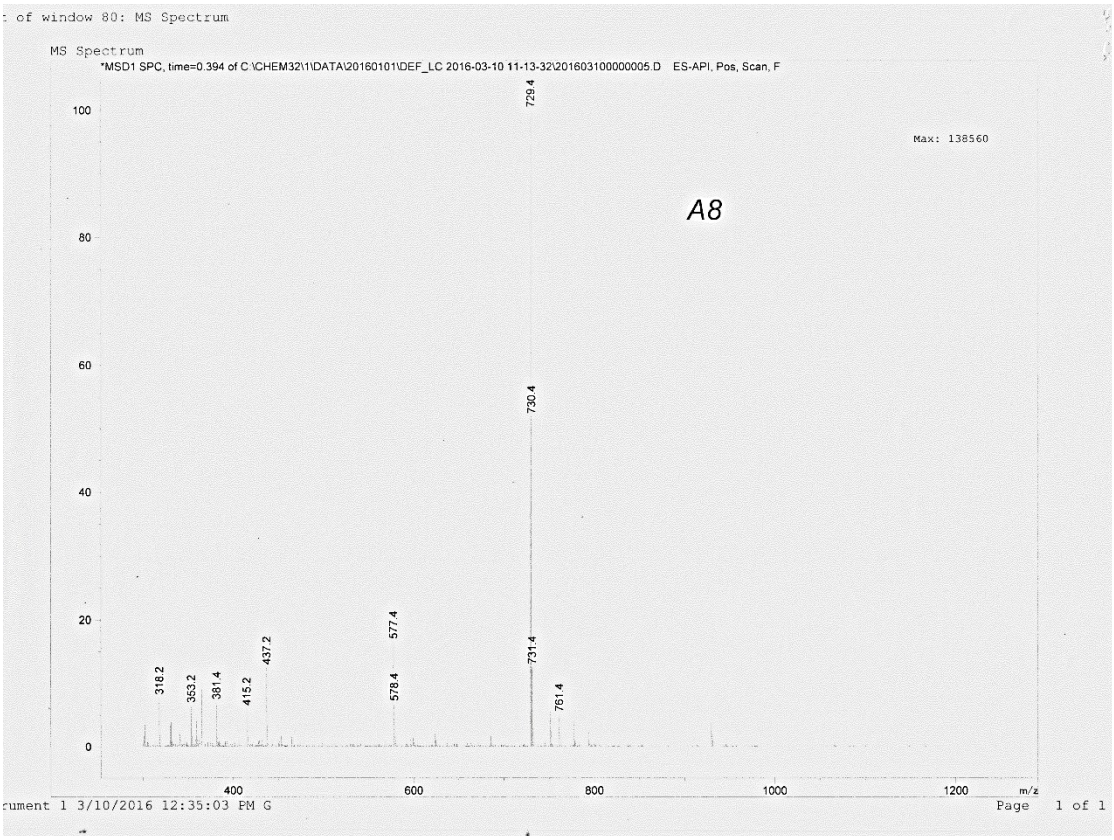


Figure S53. ESI-MS result of **13** at ambient temperature.

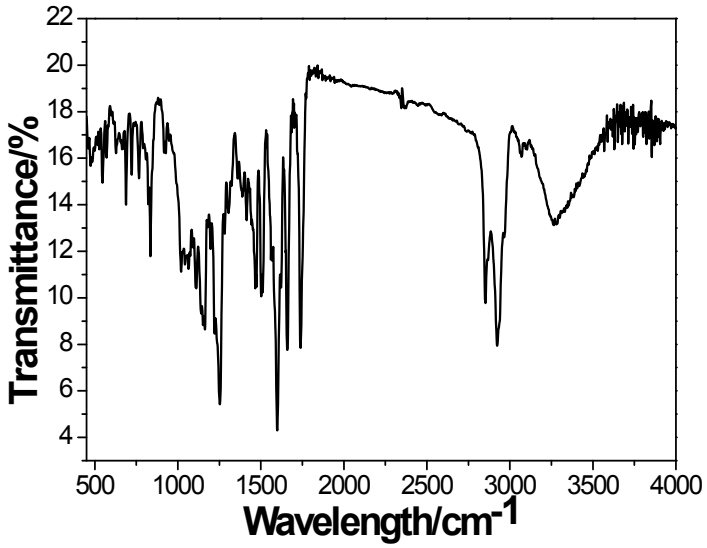


Figure S54. FT-IR spectrum of **13** in KBr tablet at ambient temperature.

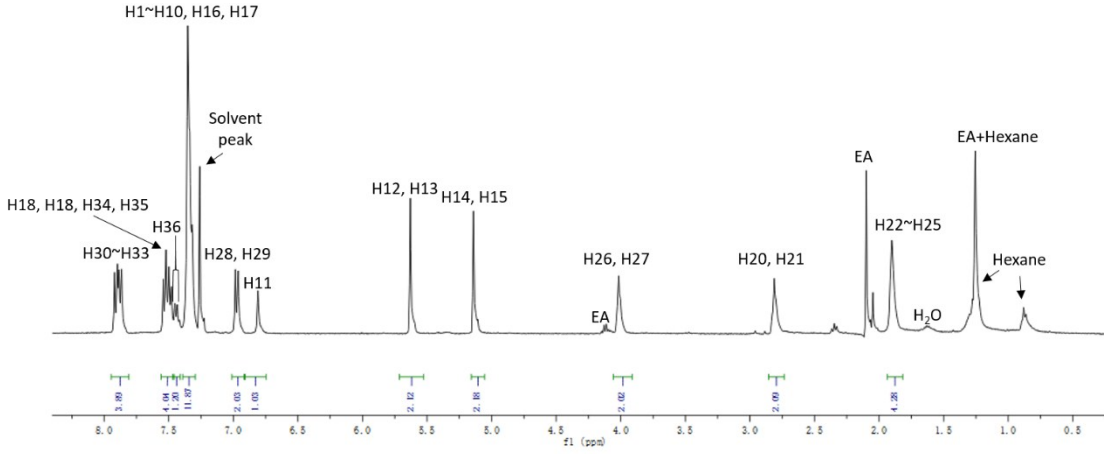


Figure S55. ^{1}H NMR spectrum of ***azo*-phenytoin** in $CDCl_3$ at ambient temperature.

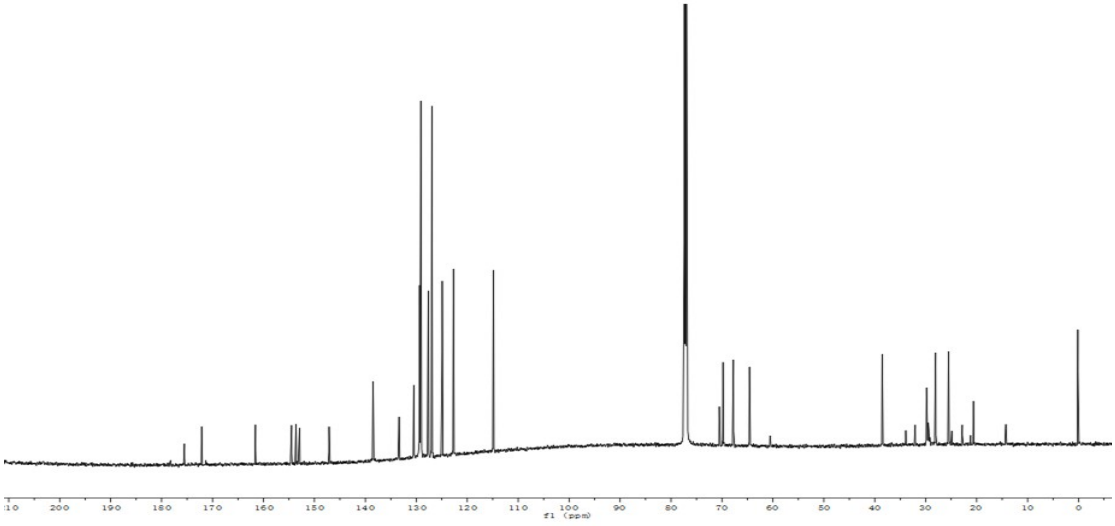


Figure S56. ^{13}C NMR spectrum of ***azo*-phenytoin** in $CDCl_3$ at ambient temperature (with residual ethyl acetate and hexane).

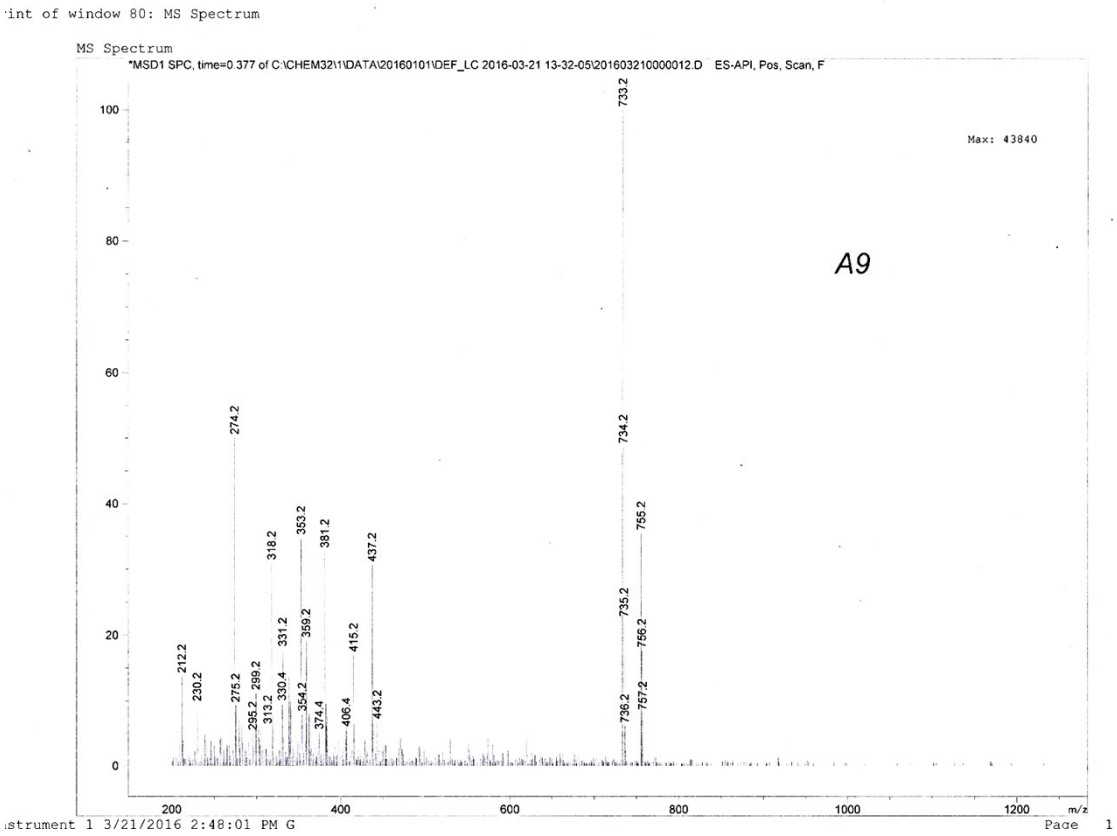


Figure S57. ESI-MS result of ***azo*-phenytoin** at ambient temperature.

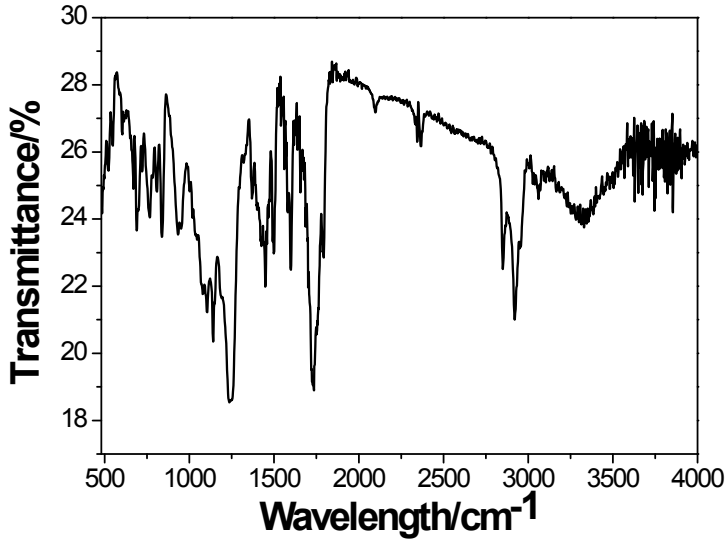


Figure S58. FT-IR spectrum of ***azo*-phenytoin** in KBr tablet at ambient temperature.

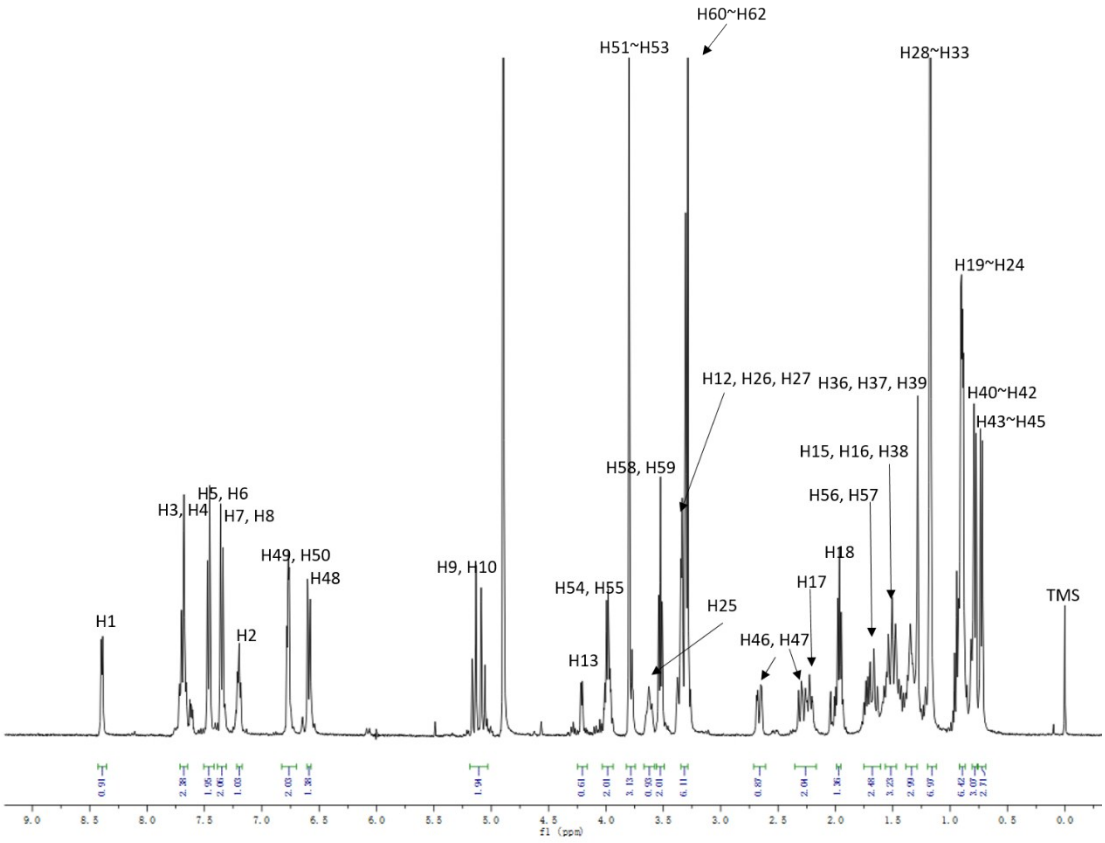


Figure S59. ^{1}H NMR spectrum of **11** in $CDCl_3$ at ambient temperature.

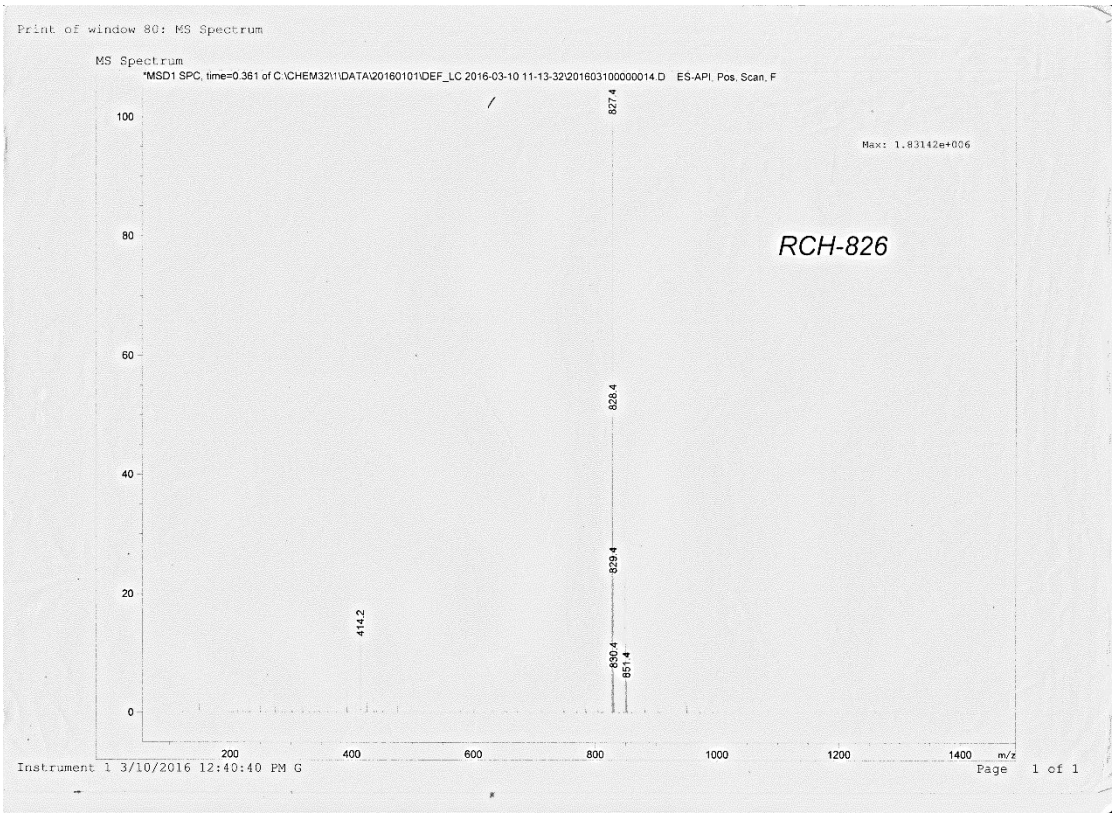


Figure S60. ESI-MS result of **11** at ambient temperature.

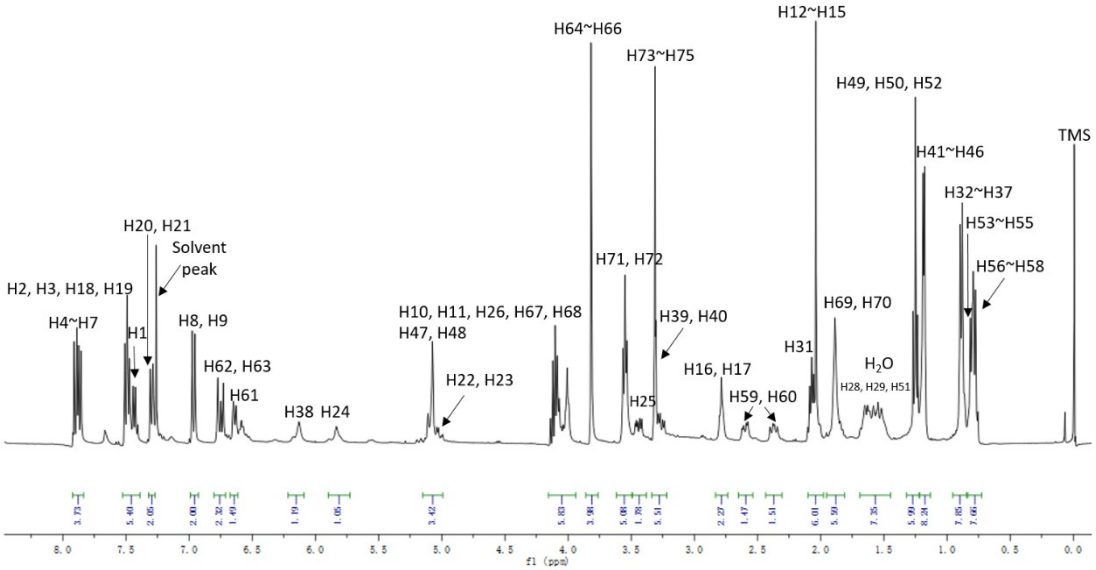


Figure S61. ^{1}H NMR spectrum of ***azo*-aliskiren** in $CDCl_3$ at ambient temperature.

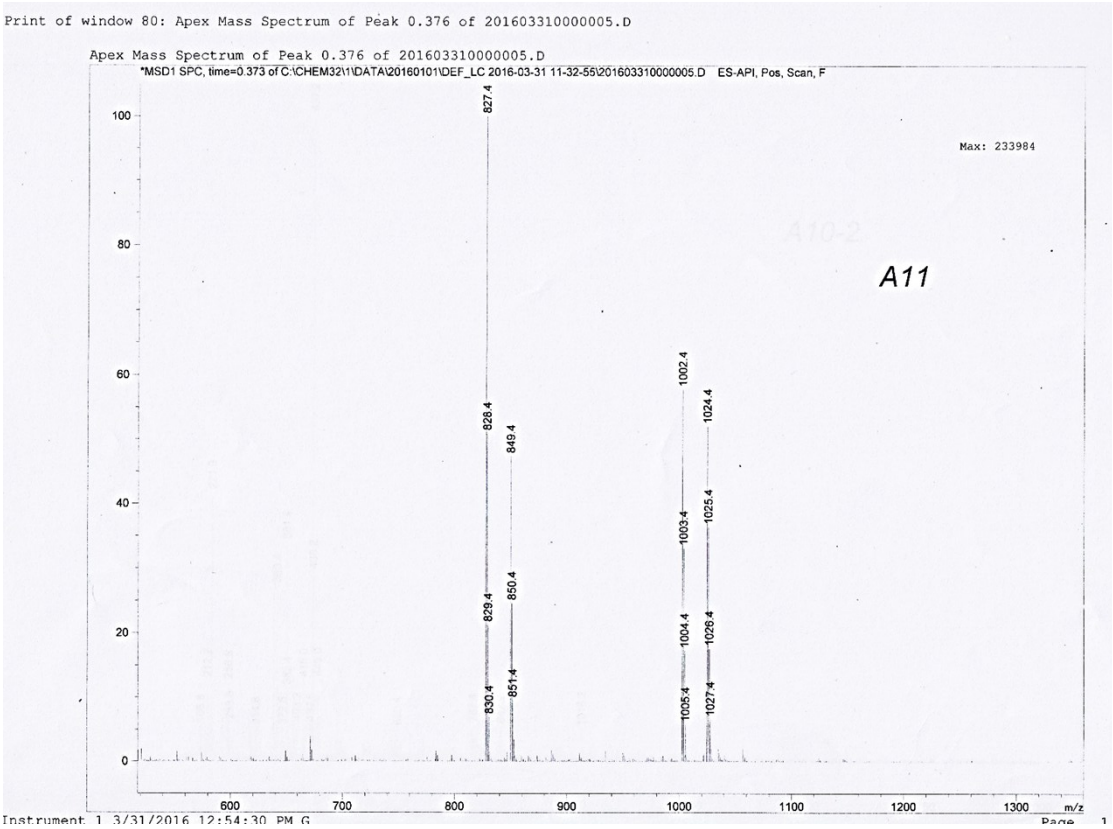


Figure S62. ESI-MS result of ***azo*-aliskiren** at ambient temperature.

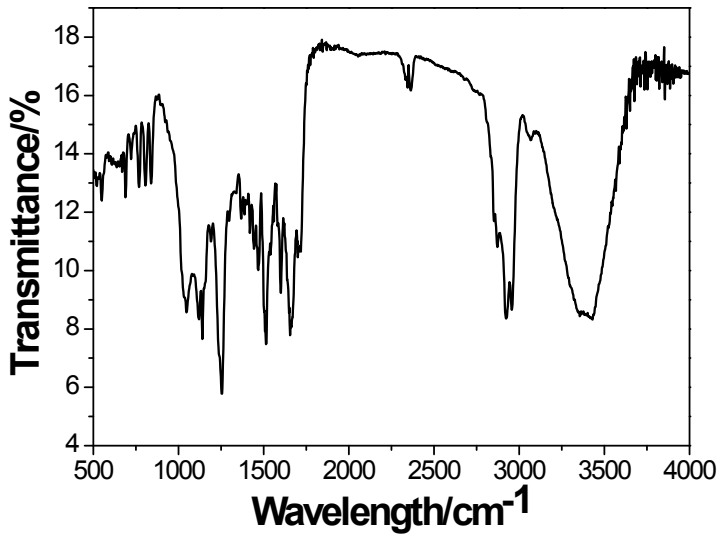


Figure S63. FT-IR spectrum of ***azo*-aliskiren** in KBr tablet at ambient temperature.

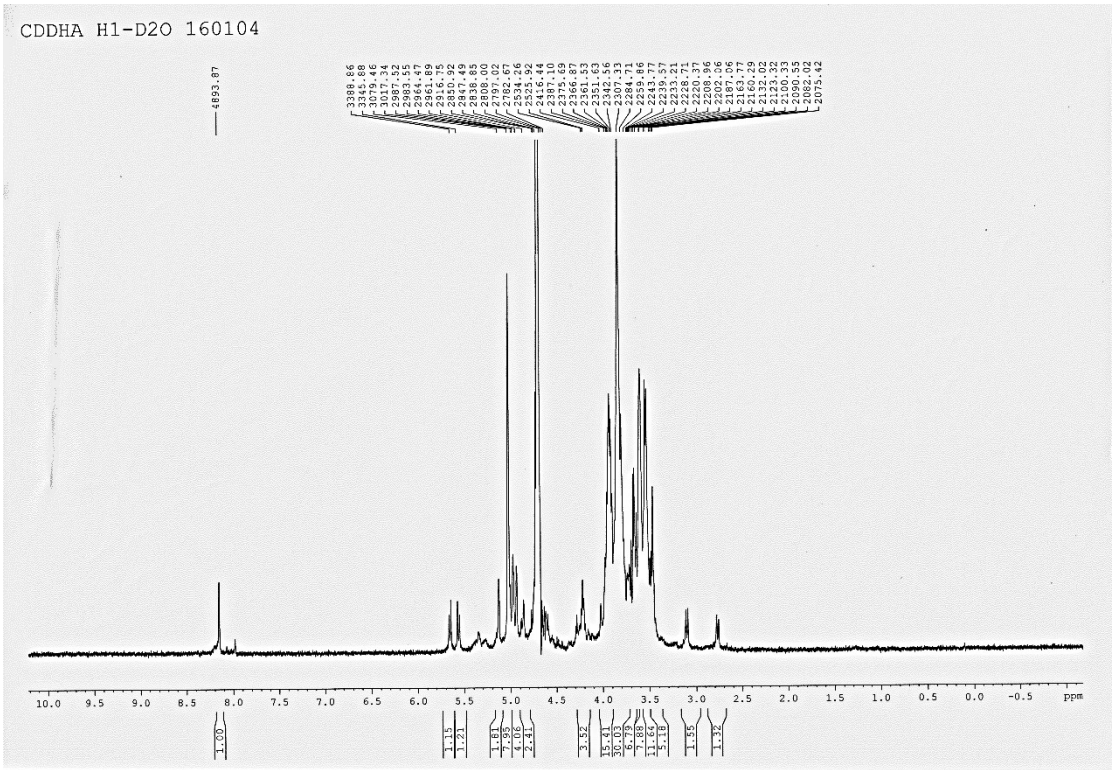


Figure S64. ^{1}H NMR spectrum (600 MHz) of **DHA-β-CD** in D_2O at ambient temperature.

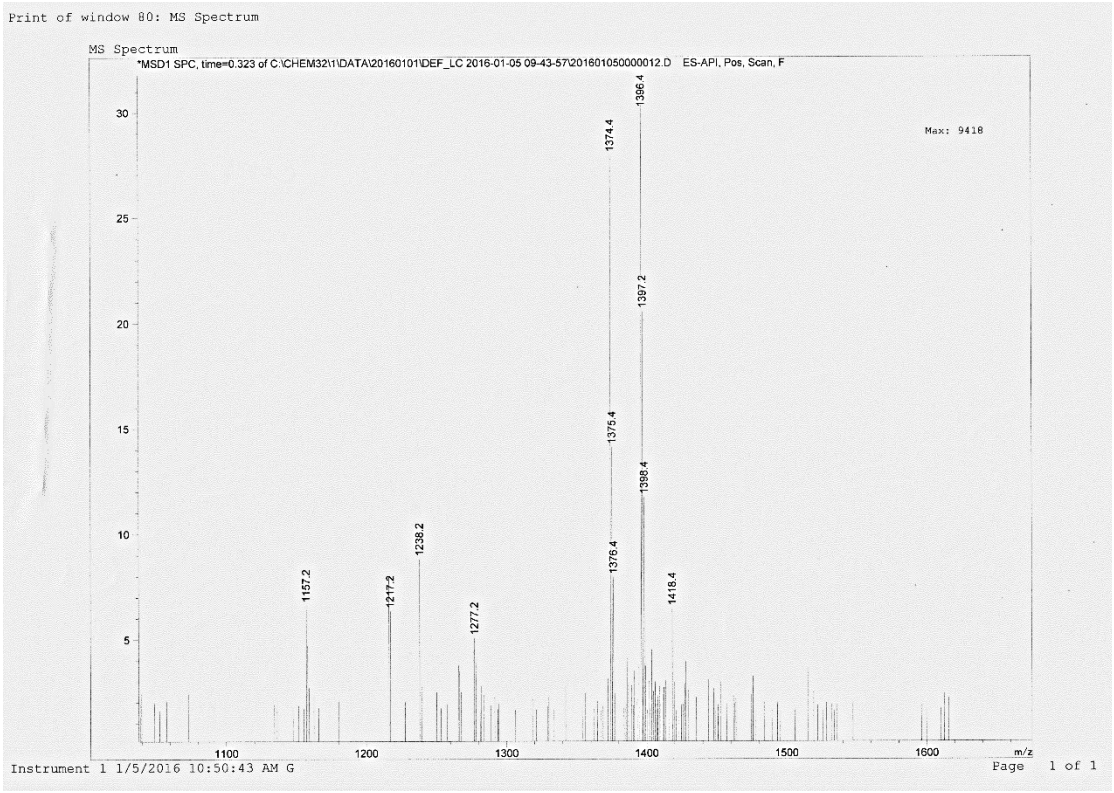


Figure S65. ESI-MS result of **DHA-β-CD** at ambient temperature.

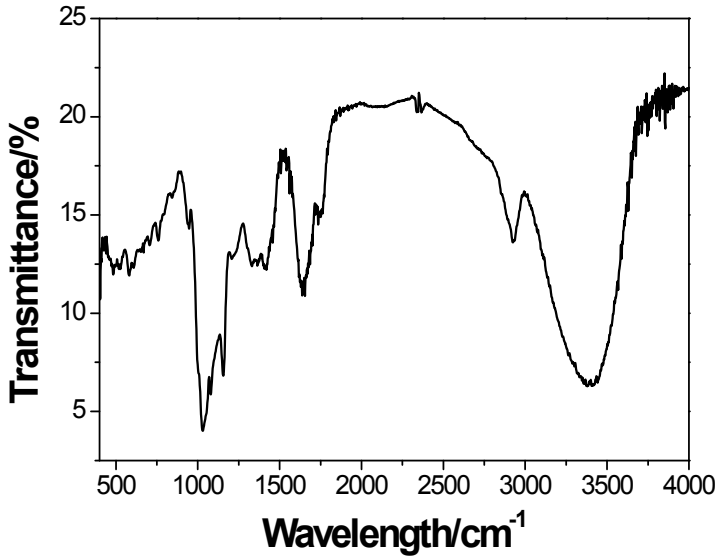


Figure S66. FT-IR spectrum of **DHA-β-CD** in KBr tablet at ambient temperature.

3. References of supporting information

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4. Guo, Y., Zhang, Y., Li, J., Zhang, Y., Lu, Y., Jiang, X., He, X., Ma, H., An, S., Jiang, C. *ACS Appl. Mater. Interfaces* 2015, **7**, 5444–5453.