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Enhancing aqueous solubility of a psoralen derivative via cyclodextrin inclusion complexation: In silico and *in vitro* study

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Abstract

N-(4-Bromobenzoyl)-8-methoxypsoralen-4-amine (BNB) is a psoralen derivative with potent cytotoxic activity against breast cancer cells but with limited pharmaceutical application and therapeutic potential due to its extremely low aqueous solubility. To overcome this limitation, β-cyclodextrin (βCD) and its derivatives dimethyl-βCD (DMβCD), hydroxypropyl-βCD (HPβCD), and sulfobutylether-βCD (SBEβCD) were investigated as carriers to enhance BNB's aqueous solubility via cyclodextrin inclusion complexation. A combined computational–experimental strategy was employed, integrating molecular docking, 500-ns all-atom molecular dynamics simulations in quintuplicate runs (2.5 μs in total), and experimental validation by phase solubility analysis, scanning electron microscopy (SEM), and differential scanning calorimetry (DSC). Docking and simulations revealed stable host–guest interactions, with SBEβCD showing the most favorable binding free energies, the highest number of atomic contacts, and the lowest solvent-accessible surface area, indicative of deep and stable encapsulation. Phase solubility studies corroborated these findings, with BNB/SBEβCD exhibiting the highest apparent stability constant. The formation of the inclusion complex was further supported by SEM and DSC, which revealed pronounced morphological changes and thermal evidence consistent with encapsulation, including suppression of the BNB melting endotherm. ^{1}H NMR spectroscopic analysis further confirmed complex formation through observed peak broadening and chemical shift perturbations upon complexation. Collectively, these results identify SBEβCD as a highly effective carrier for BNB, offering a rational approach to improve solubility through stable complex formation, and supporting its potential as a promising chemotherapeutic candidate for breast cancer treatment.

Table S1. MM/GBSA and MM/PBSA binding free energy components of BNB/βCDs complexes for B- and C-forms over last 100 ns (MD 1-4, mean ± SD). "ND" indicates that the stable corresponding form was not detected, while "NA" indicates that the form was not applicable to the given system.

	$T\Delta S$	ΔE_{vdw}	ΔE_{ele}	MM/GBSA			MM/PBSA		
				$\Delta G_{sol,polar}$	$\Delta G_{sol,non\text{-}polar}$	$\Delta G_{bind}^{MM/GBSA}$	$\Delta G_{sol,polar}$	$\Delta G_{sol,non\text{-}polar}$	$\Delta G_{bind}^{MM/PBSA}$
MD1									
BNB/βCD									
B-form	NA	NA	NA	NA	NA	NA	NA	NA	NA
C-form	–17.63 ± 1.55	–26.48 ± 6.28	–11.16 ± 4.55	22.42 ± 4.52	–3.00 ± 0.59	–0.59 ± 3.64	27.85 ± 5.59	–3.57 ± 0.65	4.26 ± 2.93
BNB/DMβCD									
B-form	–17.90 ± 1.40	–26.05 ± 5.77	–5.19 ± 3.91	11.28 ± 5.29	–3.01 ± 0.59	–5.08 ± 3.93	16.14 ± 6.71	–3.77 ± 0.68	–0.96 ± 3.36
C-form	ND	ND	ND	ND	ND	ND	ND	ND	ND
BNB/HPβCD									
B-form	–16.91 ± 2.01	–28.37 ± 6.85	–5.07 ± 4.12	13.51 ± 3.78	–2.98 ± 0.52	–6.0 ± 3.89	19.29 ± 4.84	–3.52 ± 0.63	-0.78 ± 3.11
C-form	–19.79 ± 2.12	–3.49 ± 4.09	–7.82 ± 4.91	15.15 ± 3.95	–3.65 ± 0.38	–11.02 ± 3.31	21.26 ± 4.95	-4.44 ± 0.36	–5.69 ± 3.37
BNB/SBEβCD									
B-form	–22.13 ± 2.78	–42.42 ± 4.79	–9.90 ± 6.79	20.48 ± 6.22	–4.07 ± 0.35	–13.78 ± 4.10	24.51 ± 6.70	–5.18 ± 0.30	–10.86 ± 3.81
C-form	–19.69 ± 1.58	–42.68 ± 3.24	–12.91 ± 5.55	21.61 ± 4.90	–4.11 ± 0.27	–18.41 ± 3.12	29.45 ± 4.91	–5.04 ± 0.22	–11.50 ± 3.38
MD2									
BNB/βCD									
C-form	–18.48 ± 1.81	–30.42 ± 6.04	–11.63 ± 3.70	23.94 ± 3.80	–3.14 ± 0.35	–2.76 ± 4.30	31.61 ± 4.85	–3.80 ± 0.51	4.25 ± 3.94
C-form	NA	NA	NA	NA	NA	NA	NA	NA	NA
BNB/DMβCD									
B-form	–18.09 ± 1.07	–26.84 ± 2.98	–7.14 ± 1.98	13.99 ± 2.13	–3.24 ± 0.23	–5.13 ± 2.80	19.21 ± 2.86	–4.01 ± 0.22	–0.68 ± 2.62
C-form	ND	ND	ND	ND	ND	ND	ND	ND	ND
BNB/HPβCD									
B-form	–20.71 ± 1.71	–41.81 ± 2.26	–12.42 ± 3.27	21.58 ± 3.0	–3.49 ± 0.25	–15.43 ± 2.59	28.80 ± 3.1	–4.85 ± 0.13	–9.57 ± 3.34
C-form	–18.29 ± 1.65	–32.90 ± 4.27	–6.13 ± 4.29	13.10 ± 3.65	–3.46 ± 0.37	–11.09 ± 3.76	18.43 ± 4.59	–4.31 ± 0.37	–6.62 ± 3.38
BNB/SBEβCD									
B-form	–20.0 ± 2.10	–37.51 ± 4.05	–8.34 ± 7.53	19.63 ± 7.0	–4.01 ± 0.35	–10.23 ± 3.46	23.76 ± 7.59	4.99 ± 0.34	–7.07 ± 3.62
C-form	–19.42 ± 1.97	–37.38 ± 6.49	–6.90 ± 7.01	17.67 ± 6.04	–3.94 ± 0.63	–11.12 ± 4.81	22.51 ± 6.08	–4.79 ± 0.57	–7.13 ±4.63
MD3									
BNB/βCD									
C-form	–19.81 ± 1.7	–30.51 ± 3.82	–13.70 ± 6.47	24.60 ± 5.36	–3.13 ± 0.28	–2.93 ± 2.88	30.09 ± 5.65	–4.02 ± 0.39	1.67 ± 3.45
B-form	NA	NA	NA	NA	NA	NA	NA	NA	NA
BNB/DMβCD									
B-form	NA	NA	NA	NA	NA	NA	NA	NA	NA
C-form	ND	ND	ND	ND	ND	ND	ND	ND	ND
BNB/HPβCD									
B-form	–18.51 ± 1.78	–33.88 ± 6.51	–6.87 ± 3.60	15.86 ± 3.84	–3.27 ± 0.50	–9.66 ± 5.37	23.26 ± 5.56	–3.99 ± 0.58	–2.99 ± 4.56
C-form	–18.59 ± 1.51	–30.70 ± 2.94	–4.98 ± 3.30	11.64 ± 2.71	–3.33 ± 0.30	–8.77 ± 2.91	16.61 ± 3.64	–4.17 ± 0.30	–4.65 ± 2.79
BNB/SBEβCD									
B-form	–19.93 ± 1.75	–36.36 ± 3.69	–10.52 ± 5.4	21.49 ± 5.68	–4.02 ± 0.35	–9.49 ± 3.74	24.92 ± 6.46	–4.99 ± 0.39	–7.02 ± 3.72
C-form	–19.13 ± 1.86	–34.02 ± 4.07	–7.23 ± 7.39	15.55 ± 6.40	–3.58 ± 0.43	–10.14 ± 3.74	19.77 ± 6.65	–4.42 ± 0.41	–6.76 ± 3.47
MD4									
BNB/βCD									
C-form	–18.95 ± 1.97	–30.78 ± 5.80	–10.21 ± 6.08	22.29 ± 4.87	–3.18 ± 0.36	–2.93 ± 4.47	27.51 ± 5.28	–4.06 ± 0.52	1.41 ± 4.42
B-form	–18.98 ± 1.58	–31.47 ± 4.02	–4.27 ± 3.0	14.92 ± 3.46	–3.21 ± 0.36	–5.05 ± 2.72	20.64 ± 4.08	–3.99 ± 0.42	–0.12 ± 2.57
BNB/DMβCD									
B-form	NA	NA	NA	NA	NA	NA	NA	NA	NA
C-form	ND	ND	ND	ND	ND	ND	ND	ND	ND
BNB/HPβCD									
B-form	–17.58 ± 2.14	–29.72 ± 5.83	–5.74 ± 4.49	14.46 ± 4.77	–2.99 ± 0.53	–6.41 ± 4.16	21.32 ± 6.66	–3.57 ± 0.60	–0.13 ± 3.97
C-form	–19.94 ± 1.59	–34.24 ± 3.65	–8.78 ± 3.0	15.76 ± 2.83	–3.74 ± 0.34	–11.06 ± 2.97	22.28 ± 4.47	–4.54 ± 0.35	–5.34 ± 3.87
BNB/SBEβCD									
B-form	–20.06 ± 1.99	–36.30 ± 4.53	–11.71 ± 6.22	22.49 ± 6.06	–3.88 ± 0.41	–9.33 ± 4.21	26.22 ± 6.50	–4.82 ± 0.41	–6.55 ± 4.28
C-form	–18.97 ± 2.12	–37.96 ± 5.12	–5.50 ± 5.94	16.30 ± 5.18	–4.03 ± 0.49	–12.23 ± 3.63	21.05 ± 5.22	–4.78 ± 0.43	–8.24 ± 3.40

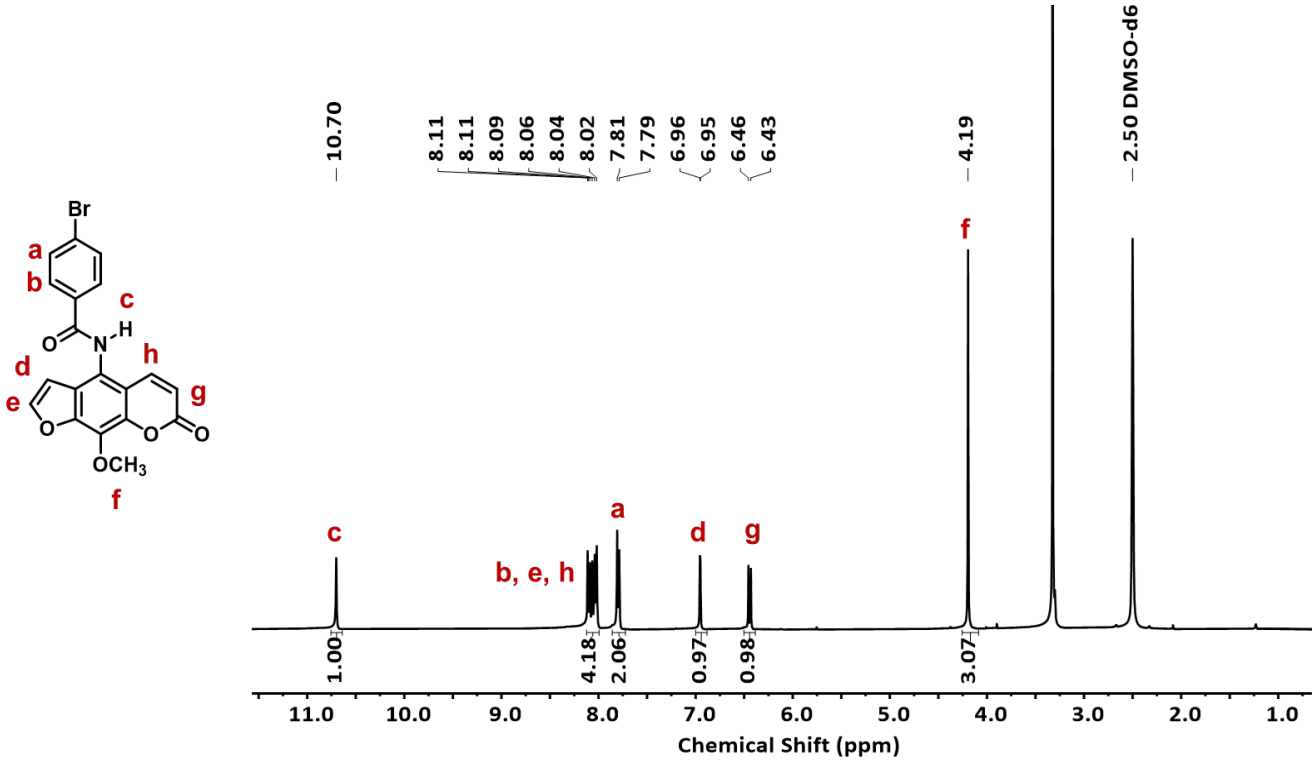

Figure S1. ^{1}H NMR spectrum of BNB in DMSO-d_6 (400 MHz).

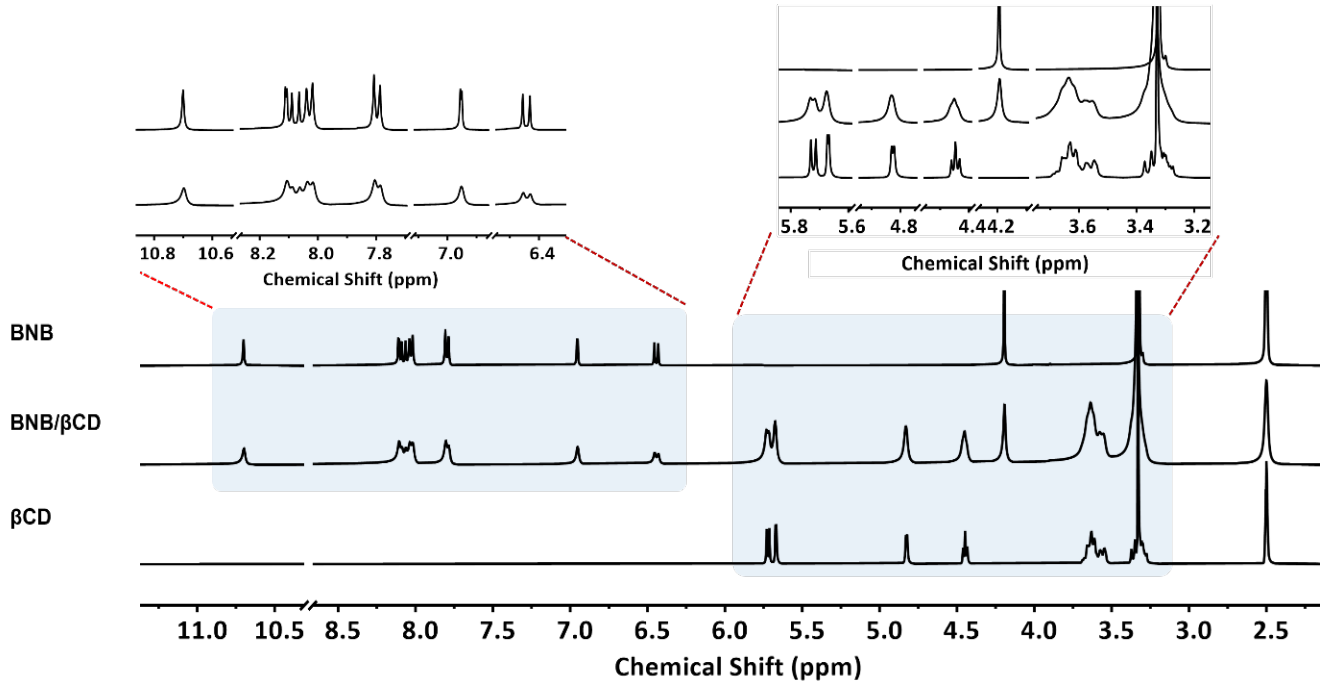

Figure S2. Comparison of the ^{1}H NMR spectra of free BNB, BNB/βCD, and βCD in DMSO-d_6 (400 MHz).

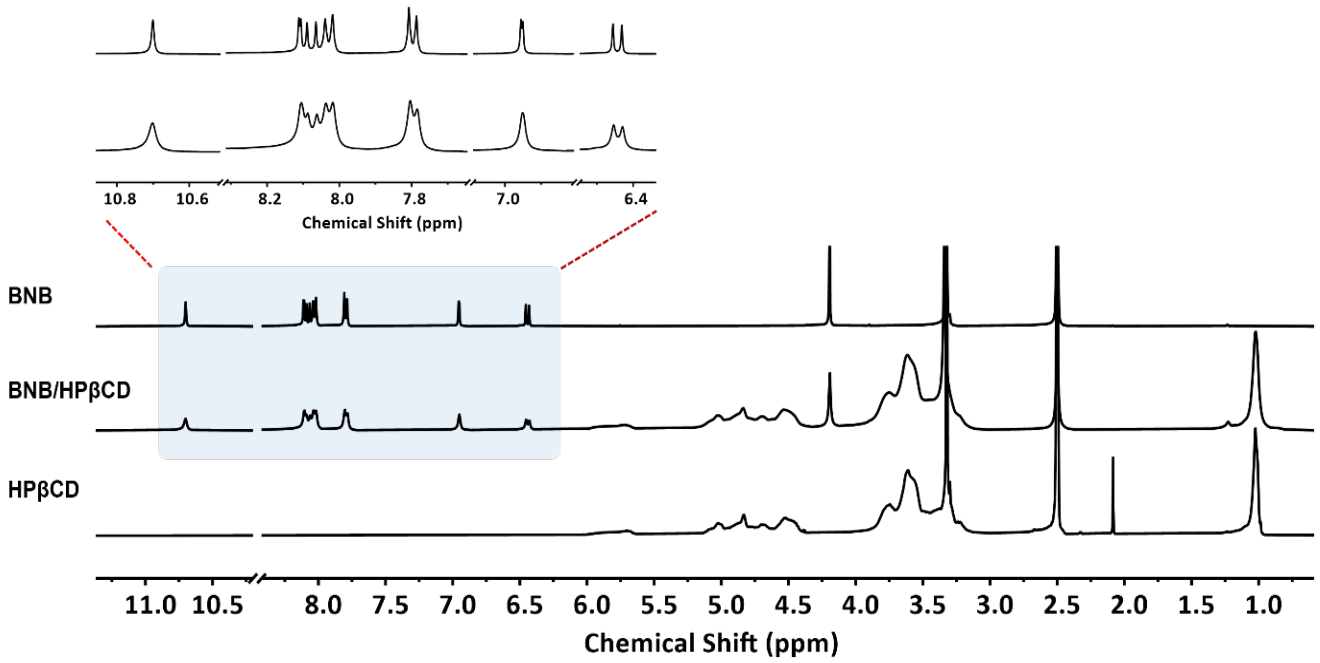

Figure S3. Comparison of the ^{1}H NMR spectra of free BNB, BNB/HPβCD, and HPβCD in DMSO-d_6 (400 MHz).

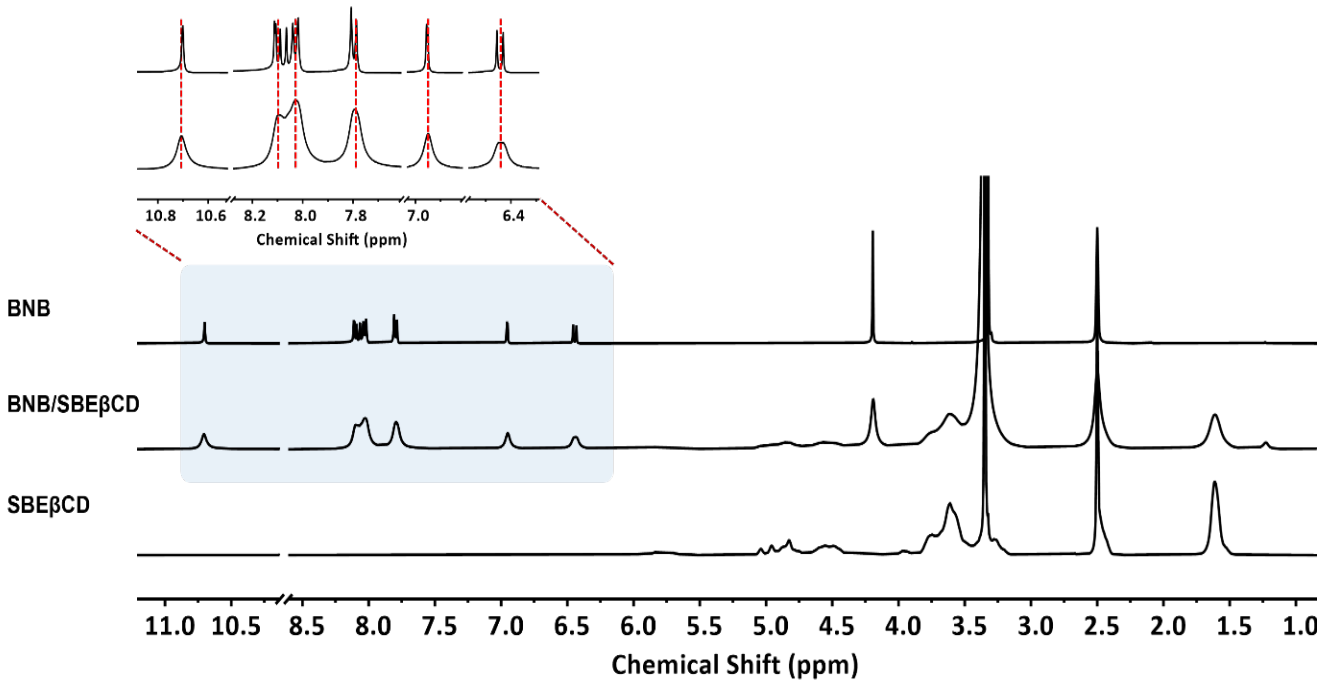

Figure S4. Comparison of the 1H NMR spectra of free BNB, BNB/SBEβCD, and SBEβCD in DMSO-d_6 (400 MHz).