New bedaquiline salt with improved bioavailability and reduced food effect

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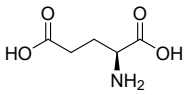
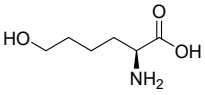
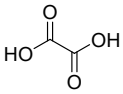
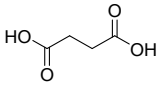
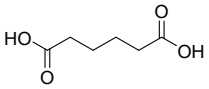
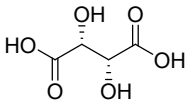
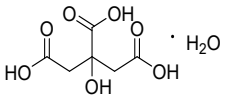
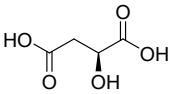
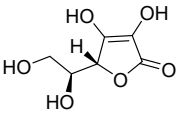
Table S1 Screening results of CCF (√ means the formation of a co-crystal; × means that no cocrystal is formed)

No.	CCF	Chemical structure	Molar ratio	Evaporation	Slurry	Cooling	Grinding
1	L-Glutamic acid		1:1	×	×	×	×
2	L-Lysine		1:1	×	×	×	×
3	Oxalic acid		1:1	×	×	×	×
4	Succinic acid		1:1	×	×	×	×
5	Adipic acid		1:1	×	×	×	×
6	L-Tartaric acid		1:1	×	×	×	×
7	Citric acid monohydrate		1:1	×	×	×	×
8	L-Malic acid		1:1	×	×	×	×
9	Ascorbic acid		1:1	×	×	×	×

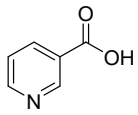
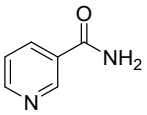
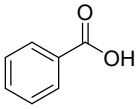
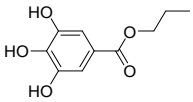
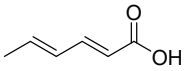
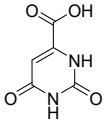
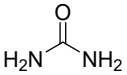
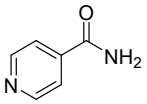
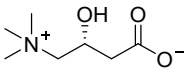
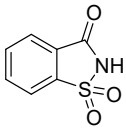
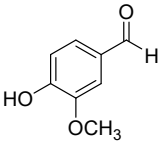
10	Nicotinic acid		1:1	×	×	×	×
11	Niacinamide		1:1	×	×	×	×
12	Benzoic acid		1:1	×	×	×	×
13	Propyl gallate		1:1	×	×	×	×
14	Sorbic acid		1:1	×	×	×	×
15	Lactic acid		1:1	×	×	×	×
16	Urea		1:1	×	×	×	×
17	Nicotinamide		1:1	×	×	×	×
18	L-Carnitine		1:1	×	×	×	×
19	Saccharin		1:1	√	√	√	√
20	Vanillin		1:1	×	×	×	×

Table S2 Dosing regimen for Beagle dogs (*：The dose, concentration, and volume of administration are all based on BDQ free base.; IG: Intragastric gavage.)

Group	1	2	3	4
Food Requirements	Fasting for 12 hours prior to administration		Administering concomitantly with a standard meal	
Compound	BDQ-FA	BDQ-SA	BDQ-FA	BDQ-SA
Quantity	4	4	4	4
Route of Administration	IG	IG	IG	IG
Dose* (mg/kg)	10	10	10	10
Concentration* (mg/mL)	4	4	4	4
Volume* (mL/kg)	2.5	2.5	2.5	2.5
Solvent Medium	A mixed aqueous solution containing 10% (w/v) HPMC-E15 and 0.1% (v/v) Tween 80			
Sampling Time Points	0.25, 0.5, 1, 2, 4, 8, 12, 24, 28, 32, 48, 72, 96, 144, 192, 216, 188, 360, 432 and 624 h			

Table S3 Crystallographic data for BDQ-SA solvate

Compounds	BDQ-SA
formula	$C_{41}H_{41}BrN_4O_6S$
Stoichiometry	1:1
Formula weight	797.75
Temperature/K	100
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.0487(4)
b/Å	16.0617(10)
c/Å	26.2120(16)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	3809.6(4)
Z	4
ρ_{calc} /g cm^{-3}	1.391
μ/mm^{-1}	1.187
F(000)	1656.0
Crystal size/mm^3	0.12 × 0.08 × 0.05
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	4.012 to 52.826
Index ranges	-11 ≤ h ≤ 11, -16 ≤ k ≤ 20, -21 ≤ l ≤ 32
Reflections collected	20424
Independent reflections	7785 [Rint = 0.0855, Rsigma = 0.1257]
Data/restraints/parameters	7785/0/486
Goodness-of-fit on F2	0.997
Final R indexes [I ≥ 2σ (I)]	R_1 = 0.0514, wR_2 = 0.0820
Final R indexes [all data]	R_1 = 0.0950, wR_2 = 0.0997
Largest diff. peak/hole / e Å^{-3}	0.36/-0.51
Flack parameter	0.005(8)

Table S4 Hydrogen bonding distance and angles for BDQ-SA solvate

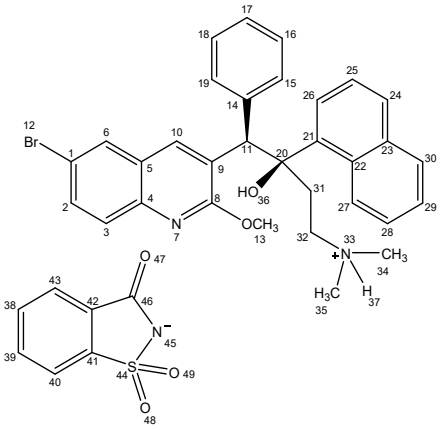
D-H...A	Symmetry	D-H(Å)	H...A(Å)	D...A(Å)	∠D-H...A(°)
O5-H4...O6	x, y, z	0.84	2.31	2.824(4)	120.4
O6-H3...O2	-1+x, y, z	0.87	2.03	2.899(4)	173.1
O6-H2...O1	x, y, z	0.87	1.95	2.768(4)	156.3
N2-H1...O1	x, y, z	0.93	1.80	2.712(5)	166.8

Table S5 The IR spectral characteristic peaks of BDQ, SA and BDQ-SA

Compound	Wave number	Vibration type	Group attribution
BDQ	3052cm^{-1}	δ_{C-H}	-phenyl
	1455 cm^{-1}	δ_{C-C}	
	1017 cm^{-1}, 919 cm^{-1}, 710 cm^{-1}, 697 cm^{-1}	ν_{C-H}	
	2945 cm^{-1}, 2826 cm^{-1}, 2781 cm^{-1}	δ_{C-H}	-N(CH_3)$_2$
	1596 cm^{-1}	δ_{C-C}	-quinolyl
	1394 cm^{-1}	δ_{C-H}	-naphthyl
	1246 cm^{-1}	δ_{C-C}	
	1340 cm^{-1}	ν_{C-H}	-methylene
SA	3091 cm^{-1}, 2946 cm^{-1}, 2691 cm^{-1}	δ_{C-H}	-phenyl
	1592 cm^{-1}, 701 cm^{-1}	δ_{C-C}	
	1457 cm^{-1}, 1174 cm^{-1}, 1118 cm^{-1}, 898 cm^{-1}, 757 cm^{-1}	ν_{C-H}	
	1715 cm^{-1}	$\delta_{C=O}$	-carbonyl
	1332 cm^{-1}, 588 cm^{-1}	$\nu_{S=O}$	-sulfonyl
	1295 cm^{-1}	ν_{N-H}	imino-
BDQ-SA	3440 cm^{-1}	ν_{O-H}	-OH
	3048 cm^{-1}, 2952 cm^{-1}	δ_{C-H}	-NH(CH_3)$_2^+$
	2817 cm^{-1}	ν_{C-H}	
	1680 cm^{-1}	$\delta_{C=O}$	-carbonyl
	1590 cm^{-1}	δ_{C-C}	-quinolyl

	1340 cm^{-1}, 1240 cm^{-1}	ν_{C-H}	-naphthyl
	1460 cm^{-1}	δ_{C-C}	
	1390 cm^{-1}, 1150 cm^{-1}, 1120 cm^{-1}, 1090 cm^{-1}, 1020 cm^{-1}, 959 cm^{-1}, 869 cm^{-1}, 818 cm^{-1}, 788 cm^{-1}, 771 cm^{-1}	ν_{C-H}	-phenyl
	604 cm^{-1}	$\nu_{S=O}$	-sulfonyl

Table S6 ^{1}H-NMR results of BDQ-SA



position	δ H(ppm)	position	δ H(ppm)	position	δ H(ppm)
2	8.04-7.59 (m, 13H)	19	7.27-7.28 (m, 2H)	32	3.67-3.59 (m, 2H)
3	8.04-7.59 (m, 13H)	24	8.38 (d, *J* = 7.4 Hz, 1H)	34	2.90 (s, 6H)
6	8.95 (d, *J* = 8.8 Hz, 1H)	25	8.04-7.59 (m, 13H)	35	2.90 (s, 6H)
10	8.04-7.59 (m, 13H)	26	8.04-7.59 (m, 13H)	36	6.27 (s, 1H)
11	5.91(s, 1H)	27	8.22 (dd, *J* = 8.8, 5.0 Hz, 2H),	37	7.24 (s, 1H)
13	4.60 (s, 3H)	28	8.22 (dd, *J* = 8.8, 5.0 Hz, 2H),	38	8.04-7.59 (m, 12H)
15	7.27-7.28 (m, 2H)	29	8.04-7.59 (m, 13H)	39	8.04-7.59 (m, 13H)
16	8.04-7.59 (m, 13H)	30	8.04-7.59 (m, 13H)	40	8.04-7.59 (m, 13H)

17	8.04-7.59 (m, 13H)	31	2.44-2.36 (m, 2H)	43	8.82 (s, 1H)
18	8.04-7.59 (m, 13H)	--	--	--	--

Table S7 The results of hygroscopicity and chemical stability

Investigation Items	Content (%)		
	60 °C	25 °C/RH 60%	45 °C/RH 75%
0 d	99.74	99.74	99.74
5 d	99.74	99.70	99.74
10 d	99.72	99.71	99.73
30 d	99.67	99.70	9973

Table S8 Comparison of solubility of BDQ in different dissolution mediums

The dissolution media	LOD (μg/mL)	BDQ (μg/mL)
pH 1.0	0.2	81.5
pH 2.0	0.2	104.2
pH 4.5	0.2	8.2
pH 4.5 (added 0.1% Tween 80)	0.2	35.9
pH 6.8	0.2	5.0
pH 6.8(added 0.1% Tween 80)	0.2	26,3
Water	0.2	4.4
Water (added 0.1% Tween 80)	0.2	21.8

Table S9 Comparison of buffer pH before and after dissolution experiments

The dissolution media	BDQ-SA		BDQ-FA	
	before	after	before	after
pH1.0	1.02	1.06	1.02	1.07
pH2.0	2.03	2.10	2.03	2.09
pH4.5	4.55	4.59	4.55	4.61
pH6.8	6.87	6.92	6.87	6.90
Water	6.69	6.77	6.69	6.75

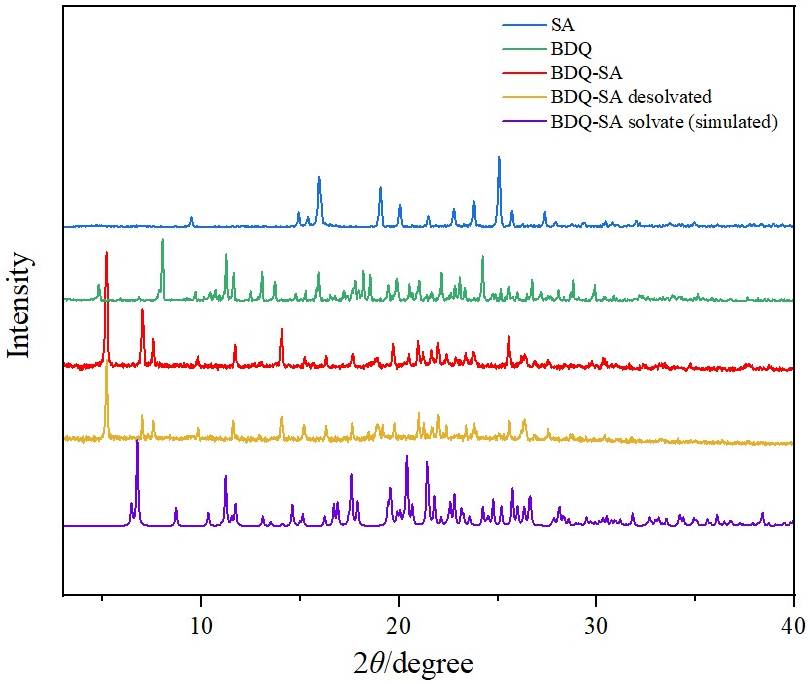


Figure S1 PXRD patterns of BDQ, SA, BDQ-SA, BDQ-SA desolvated and BDQ-SA solvate (simulated)

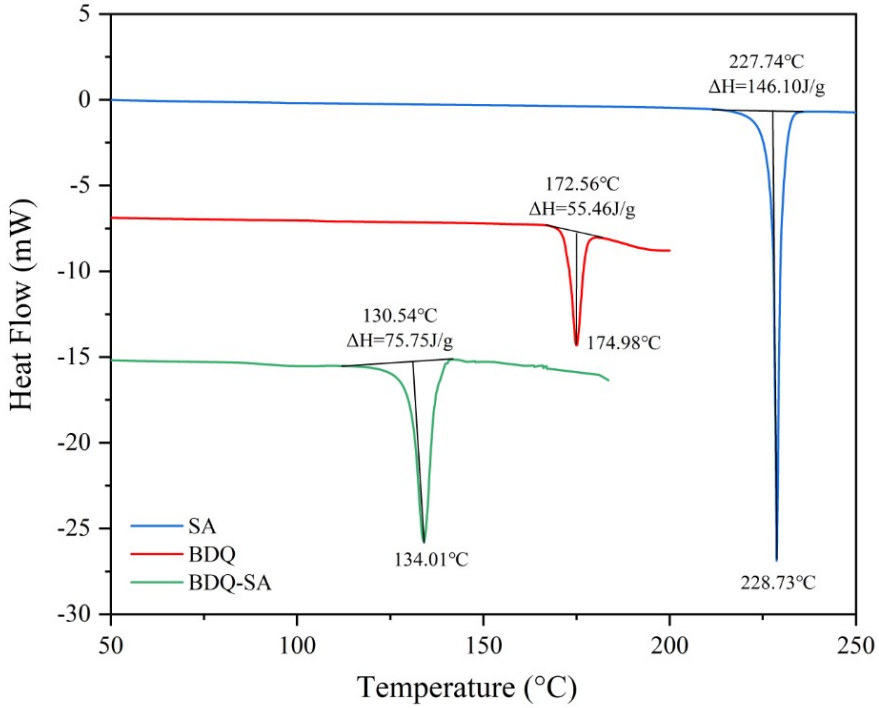


Figure S2 DSC maps of BDQ, SA and BDQ-SA

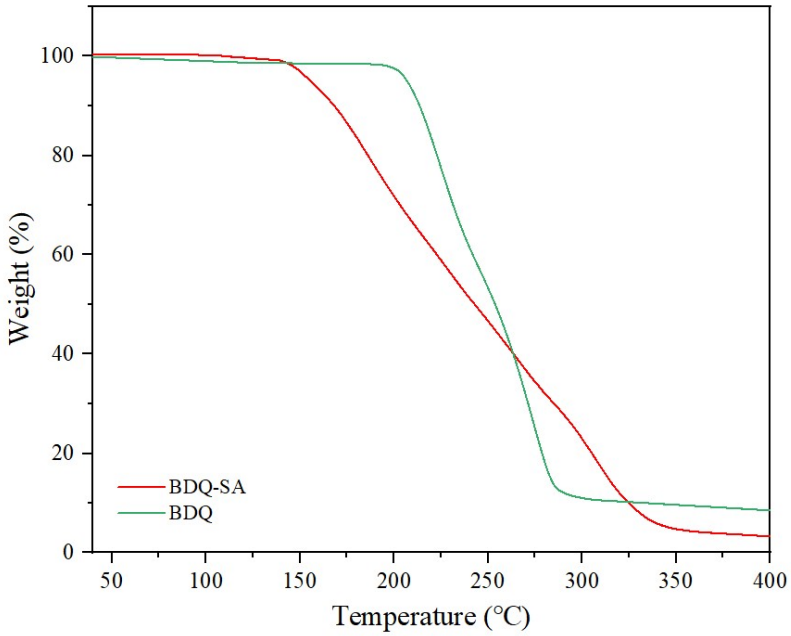


Figure S3 TGA maps of BDQ and BDQ-SA

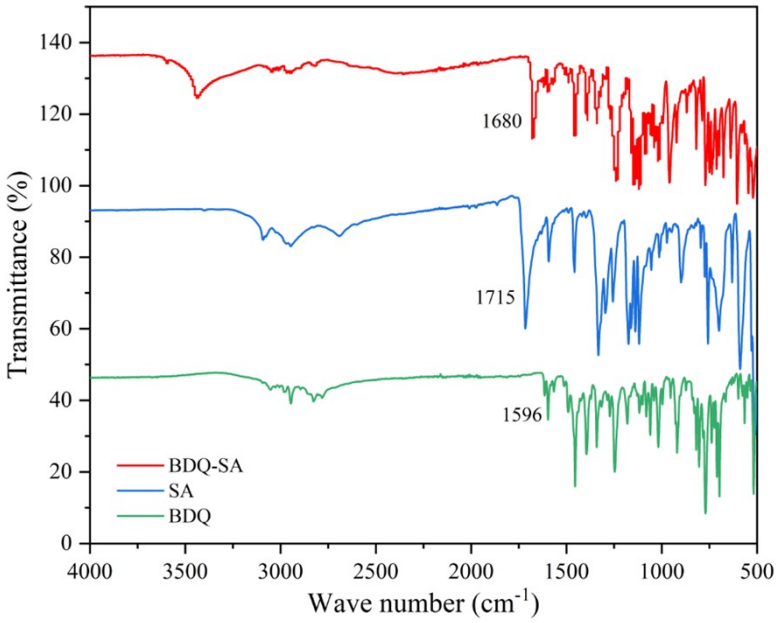


Figure S4 FT-IR maps of BDQ, SA and BDQ-SA

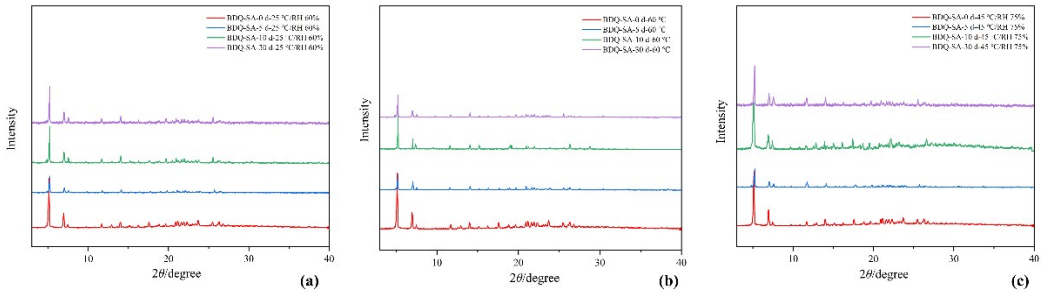


Figure S5 PXRD results of stability experiment

(a) 25 ℃/ RH 60%, (b)60 ℃, (c)45 ℃/ RH 75%

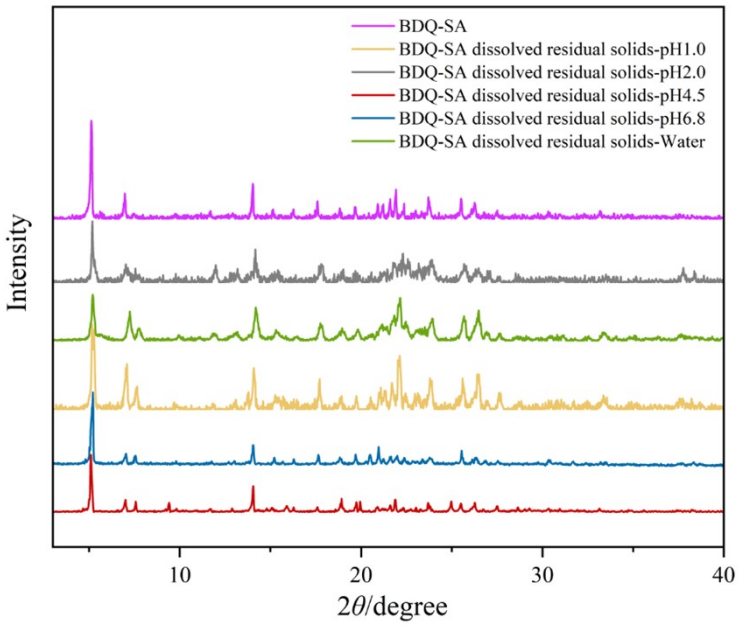


Figure S6 PXRD results of dissolved residual solids