Electronic Supplementary Material (ESI) for CrystEngComm.

Supporting materials

Artemisinin-Acetylenedicarboxylic acid Cocrystal: Screening, Structure determination, and Physicochemical Property Characterisation

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Table S1. Results of Single Crystal Structure Determination

Empirical formula	$C_{17}H_{23}O_7$
Formula weight	339.35
Temperature/K	149.99
Crystal system	orthorhombic
Space group	$P2_12_12$
a/Å	10.5089(4)
b/Å	24.0830(11)
c/Å	6.4952(3)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1643.84(12)
Z	4
ρ_{calc} g/cm^3	1.371
μ/mm^{-1}	0.106
F(000)	724.0
Crystal size/mm^3	0.7 × 0.49 × 0.2
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.228 to 72.506
Index ranges	-14 ≤ h ≤ 9, -37 ≤ k ≤ 37, -10 ≤ l ≤ 10
Reflections collected	17651
Independent reflections	5737 [R_{int} = 0.0240, R_{sigma} = 0.0254]
Data/restraints/parameters	5737/0/309
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0353, wR_2 = 0.0884
Final R indexes [all data]	R_1 = 0.0416, wR_2 = 0.0922
Largest diff. peak/hole / e Å^{-3}	0.33/-0.17
Flack parameter	0.2(2)

Table S2. Conquest structure search results using the name and structure of Artemisinin

CCDC database identifier	Compound Name	Space Group	Cell: a, b, c (Å)	Cell: α, β, γ (°)
ADAHAP	9,10-Dehydrodexyartemisinin	P 2_1 2_1 2_1	*a* 6.2460 *b* 9.0416 *c* 25.132	*α* 90 *β* 90 *γ* 90
ANIWEA	(9S, 10S)-9-eqideoxydihydroartemisinin	P 2_1 (4)	*a* 13.73020 *b* 9.12650 *c* 17.1569	*α* 90 *β* 90 *γ* 90
EBIWIV	10β-(p-methoxyphenoxy)-dihydroartemisinin	P 2_1 2_1 2_1	*a* 10.238 *b* 10.720 *c* 18.818	*α* 90° *β* 90° *γ* 90°
EBIWIV01	10β-(p-methoxyphenoxy)-dihydroartemisinin	P 2_1 2_1 2_1	*a* 10.238 *b* 10.720 *c* 18.818	*α* 90 *β* 90 *γ* 90
FAWBEK	1S,3R,5aS,6R,8aS,9R,12R-Desoxyartemisinin	P 2_1 2_1 2_1	*a* 12.706 *b* 17.998 *c* 6.226	*α* 90 *β* 90 *γ* 90
FIZMOS	10-Aminoartemisinin	P 2_1 2_1 2_1	*a* 5.6539 *b* 14.2347 *c* 18.9058	*α* 90 *β* 90 *γ* 90
GISRIK	7β-Hydroxyartemisinin	P 2_1 2_1 2_1	*a* 6.3047 *b* 9.1266 *c* 24.5309	*α* 90 *β* 90 *γ* 90
IDOYUV	9,9',16,16'-Tetrahydro-9,16'-biartemisitene	$P2_1$	a 9.214 b 11.282 c 14.181	*α* 90 *β* 90 *γ* 90
ISIMEF	11-azaartemisinin 5-bromosalicylic acid	P 2_1	*a* 9.9325 *b* 9.0196 *c* 12.3942	α 90 β 93.844 γ 90
ISIMOP	11-azaartemisinin 4-bromosalicylic acid	P 2_1	*a* 11.0814 *b* 9.28293 *c* 11.1404	*α* 90 *β* 98.638 *γ* 90
JAQTED	Artemisinin	P 2_1 2_1 2_1	*a* 6.32081 *b* 9.31057 *c* 23.9696	*α* 90 *β* 90 *γ* 90
JABDUO	5-azido-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.04,13.08,13] hexadecan-10-one	$P2_1$	a 6.359 b 22.998 c 32.023	*α* 90 *β* 90 *γ* 90

JEXGUO	(+)-4,5-Secoartemisinin	P $2_1/n$	*a* 9.957 *b* 9.212 *c* 15.965	*α* 90 *β* 93.15 *γ* 90
JUXGOY	Artemisinin epoxide	P 2_1 2_1 2_1	*a* 9.092 *b* 25.250 *c* 6.273	*α* 90 *β* 90 *γ* 90
MEZQIU	11-aza-artemisinin trans-cinnamic acid	P 1 (1)	*a* 9.5552 *b* 10.3175 *c* 11.9645	*α* 91.085 *β* 110.515 *γ* 93.998
MEZQOA	11-aza-artemisinin maleic acid	P 2_1 2_1 2_1	*a* 9.62162 *b* 10.4023 *c* 19.6935	*α* 90 *β* 90 *γ* 90
MEZQUG	bis(11-aza-artemisinin) maleic acid	P 2_1 2_1 2_1	*a* 9.78850 *b* 9.99650 *c* 33.7661	*α* 90 *β* 90 *γ* 90
MEZRAN	bis(11-aza-artemisinin) fumaric acid	P 2_1	*a* 9.57929 *b* 10.05214 *c* 17.7765	*α* 90 *β* 96.4731 *γ* 90
OZIDAD	10-Aminoartemisinin	P 2_1 2_1 2_1	*a* 9.2901 *b* 9.3435 *c* 17.2037	*α* 90 *β* 90 *γ* 90
PICTON	6-(4-bromobenzoyl)-9-desmethyl-6-aza-artemisinin	P 2_1	*a* 8.7395 *b* 8.7830 *c* 11.9719	*α* 90 *β* 95.873 *γ* 90
QEYCEC	(R)-2-(4-Bromophenyl)-2-(dihydroartemisininyloxy) acetonitrile	P 2_1	*a* 11.634 *b* 8.354 *c* 11.828	*α* 90 *β* 96.54 *γ* 90
QNGHSU	Artemisinin	P 2_1 2_1 2_1	*a* 24.077 *b* 9.443 *c* 6.356	*α* 90 *β* 90 *γ* 90
QNGHSU01	Artemisinin	P 1	*a* 9.891 *b* 15.343 *c* 9.881	*α* 90.92 *β* 102.99 *γ* 93.28
QNGHSU02	Artemisinin	P 2_1 2_1 2_1	*a* 9.450 *b* 24.090 *c* 6.364	*α* 90 *β* 90 *γ* 90
QNGHSU03	Artemisinin	P 2_1 2_1 2_1	*a* 6.3543 *b* 9.439 *c* 24.066	*α* 90 *β* 90 *γ* 90
QNGHSU10	Artemisinin	P 2_1 2_1 2_1	*a* 6.373 *b* 9.452 *c* 24.106	*α* 90 *β* 90 *γ* 90
QNGHSU11	(+)-Artemisinin	P 2_1 2_1 2_1	*a* 6.3618 *b* 9.4621 *c* 24.087	*α* 90 *β* 90 *γ* 90

RIQKOS	N-(Methanesulfonyl)-11-aza-artemisinin	P 2_1	*a* 8.5196 *b* 10.7659 *c* 9.8361	*α* 90 *β* 113.450 *γ* 90
ROMMOW	12-(3-hydroxy,5-hydroxymethyl)phenoxy dihydroartemisinin	P 2_1	*a* 10.3088 *b* 10.2844 *c* 10.3218	*α* 90 *β* 113.140 *γ* 90
SIKLAZ	12-(3-hydroxy,5-hydroxymethyl)phenoxy dihydroartemisinin	P 2_1 2_1 2_1	*a* 10.133 *b* 10.633 *c* 18.461	*α* 90 *β* 90 *γ* 90
TAFWUT	10β-(4'-Fluorophenyl)-10-deoxo-10-dihydroartemisinin	P 2_1 2_1 2_1	*a* 6.0150 *b* 14.2590 *c* 22.075	*α* 90 *β* 90 *γ* 90
TAFXAA	10β-(9'-Phenanthryl)-10-deoxo-10-dihydroartemisinin	P 4_3	*a* 9.3690 *b* 9.3690 *c* 26.782	*α* 90 *β* 90 *γ* 90
TAFXEE	10β-(4'-(1''-Morpholino)phenyl)-10-deoxo-10-dihydroartemisinin	P 2_1	*a* 8.427 *b* 6.202 *c* 22.557	*α* 90 *β* 99.23 *γ* 90
TAFX11	10β-(4'-N,N-Dimethylaminophenyl)-10-deoxo-10-dihydroartemisinin	P 2_1 2_1 2_1	*a* 6.3560 *b* 17.932 *c* 18.651	*α* 90 *β* 90 *γ* 90
TAFXOO	10α-(2'-Methoxynaphthyl)-10-deoxo-10-dihydroartemisinin	P 2_1 2_1 2_1	*a* 10.2137 *b* 10.6084 *c* 40.654	*α* 90 *β* 90 *γ* 90
TALCOA	Artemisinin hemikis (resorcinol)	P 2_1	*a* 9.5298 *b* 17.3699 *c* 10.4197	*α* 90 *β* 94.0170 *γ* 90
TALCUG	Artemisinin orcinol	P 2_1 2_1 2_1	*a* 9.0658 *b* 14.1061 *c* 16.5554	*α* 90 *β* 90 *γ* 90
TAZNIR	(1aS,3S,5aS,6R,8aS,9R,12S)-10-Deoxo-13-carba-artemisinin	P 2_1 2_1 2_1	*a* 9.304 *b* 14.130 *c* 21.876	*α* 90 *β* 90 *γ* 90
TAZNOX	(+)-10-Deoxo-13-carba-artemisininn	P 2_1 2_1 2_1	*a* 5.833 *b* 9.485 *c* 27.164	*α* 90 *β* 90 *γ* 90
VESWOI	11-azaartemisinin	P 3_2	*a* 11.71759 *b* 11.71759 *c* 9.48728	*α* 90 *β* 90 *γ* 120
VESYAW	bis(11-Azaartemisinin) pimelic acid	P 2_1 2_1 2	*a* 17.5836 *b* 10.3594 *c* 9.9524	*α* 90 *β* 90 *γ* 90
WEHZUF	α-Dihydroartemisinin β-dihydroartemisinin ether	P 2_1	*a* 10.338 *b* 12.012 *c* 12.065	*α* 90 *β* 93.39 *γ* 90

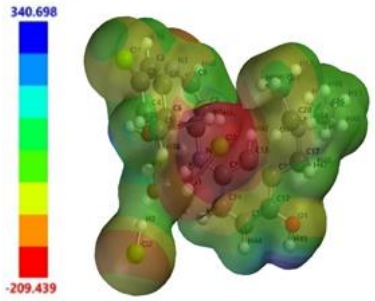
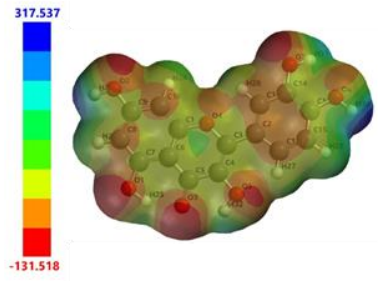
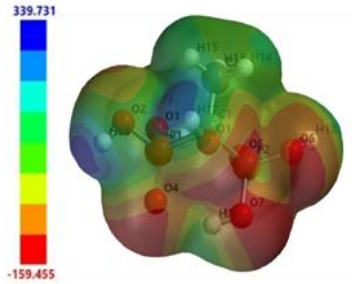
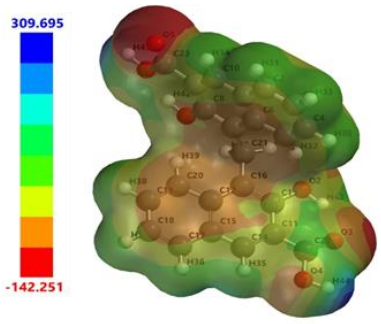
WIMMEK	Epiartemisinin	P 2_1 2_1 2	*a* 6.4443 *b* 9.445 *c* 23.182	*α* 90 *β* 90 *γ* 90
XAZPEW	catena-(tetrakis(μ-2,4,6-tris(pyridin-4-yl)-1,3,5-triazine)-dodecakis(iodo)-hexa-zinc (+)-artemisinin t-butyl methyl ether solvate)	C 2	*a* 35.252 *b* 14.8612 *c* 35.233	*α* 90 *β* 108.1167 *γ* 90
XIMLIP	Dihydroartemisinin	P 2_1 2_1 2_1	*a* 5.5910 *b* 14.1309 *c* 18.8062	*α* 90 *β* 90 *γ* 90
XIMLIPO1	1,5,9-Trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.04,13.08,13]hexadecan-10-ol, dihydroartemisinin	P 2_1 2_1 2_1	*a* 5.5881 *b* 14.131 *c* 18.801	*α* 90 *β* 90 *γ* 90
ZILMUC	3(R)-(p-Nitrophenyl)-3-(10β-dihydroartemisininoxy)propionic acid	C 2	*a* 26.555 *b* 8.737 *c* 11.494	*α* 90 *β* 114.32 *γ* 90
ZILNAJ	Ethyl 3(S)-(p-nitrophenyl)-3-(10β-dihydroartemisininoxy)propionate	P 2_1	*a* 12.392 *b* 10.639 *c* 20.081	*α* 90 *β* 91.51 *γ* 90

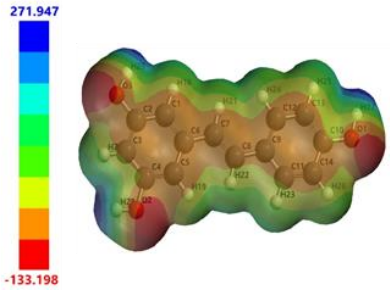
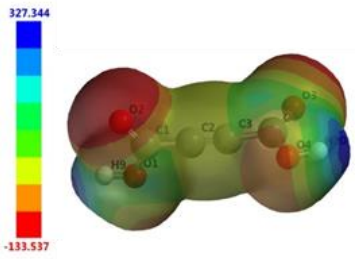
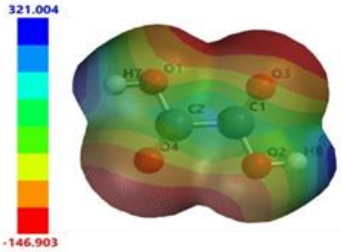
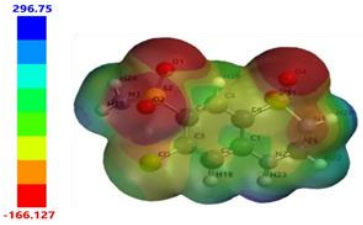
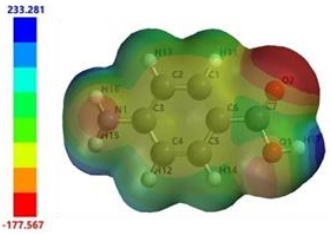
Table S3: Interaction site pairing energy difference (ΔE), the probability of cocrystal formation in a 1:1 stoichiometric ratio with ART and complementarity screening

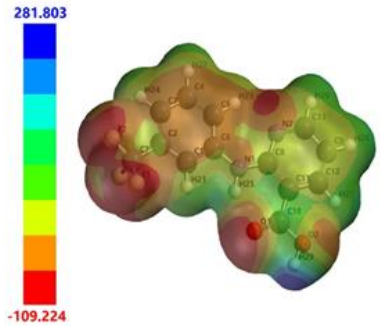
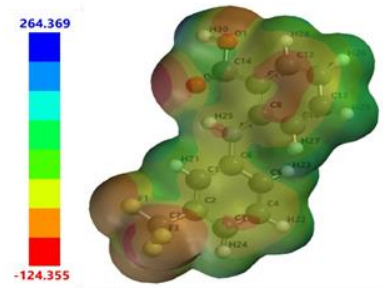
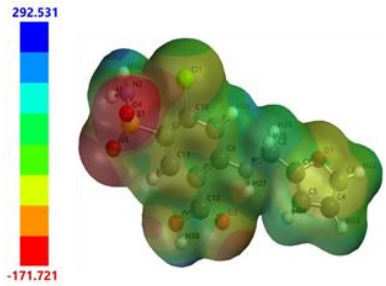
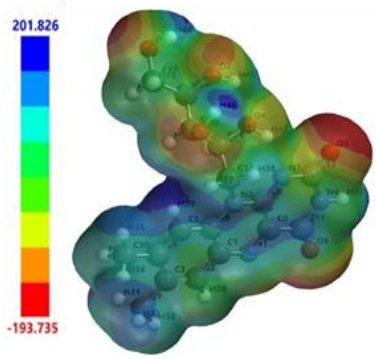
Rank	Coformers	ΔE (KJ mol $^{-1}$)	Probability (%)	Complementarity Screening tools
1	Amodiaquine dihydrochloride dihydrate (AQD)	-35.71	100.00	fail
2	Quercetin (QUC)	-21.32	98.47	pass
3	Etidronic acid (HEDP)	-20.78	98.10	fail
4	Pamoic acid (PMA)	-18.70	95.72	pass
5	Resveratrol (Trans) (RSV)	-18.66	95.65	fail
6	Acetylenedicarboxylic acid (ACA)	-18.52	95.40	fail
7	Oxalic acid (OXA)	-17.23	92.51	fail
8	Furosemide (FUR)	-15.77	87.26	fail
9	4-aminobenzoic acid (ABA)	-15.32	85.10	pass
10	Niflumic acid (NFA)	-15.29	84.92	pass
11	Flufenamic acid (FFA)	-15.00	83.39	pass
12	Hydrochlorothiazide (HCT)	-14.07	77.50	fail
13	Riboflavin (RFN)	-13.56	73.72	fail
14	2-amino-5-methylbenzoic acid (AMBA)	-13.10	70.02	fail
15	Hesperetin (HES)	-12.79	67.31	pass
16	Phthalamide (PTA)	-12.30	62.85	pass
17	Biotin (BIO)	-12.28	62.67	pass
18	Acedoben (ADB)	-11.19	51.96	fail
19	4-hydroxybenzoic acid (HBA)	-11.12	51.17	fail
20	4-hydroxybenzohydrazide (HBD)	-11.08	50.85	fail
21	Tryptophan	-9.12	31.92	pass
22	Cyclamic acid	-8.95	30.44	fail
23	Tolfenamic acid	-8.81	29.28	pass
24	L-Glutamic acid	-8.70	28.37	pass
25	EDTA	-8.53	27.00	pass
26	Maltitol	-8.42	26.12	pass
27	L-Methionine	-8.41	26.05	pass
28	Xylitol	-8.41	26.04	pass
29	Piroxicam	-8.39	25.84	pass
30	L-Leucine	-7.90	22.30	pass
31	T-Butylhydroxyanisole	-7.64	20.50	fail
32	T-Butylamine	-7.64	20.50	fail
33	Cholic acid	-7.44	19.23	fail
34	Atenolol	-7.34	18.58	fail
35	Glutaric acid	-7.32	18.48	fail
36	Alitame	-7.11	17.22	fail
37	Carbamazepine	-6.82	15.61	pass
38	Aspartame	-6.79	15.49	pass
39	Folic acid	-6.67	14.87	pass
40	Mefenamic acid	-6.62	14.61	fail
41	Acetophenone Oxime	-6.61	14.56	fail
42	Indomethacin	-6.60	14.49	pass
43	Meglumine	-6.34	13.26	fail
44	Camphoric acid	-5.95	11.53	pass
45	Itraconazole	-5.79	10.88	fail
46	Z-L-Glutamic acid	-5.77	10.81	fail

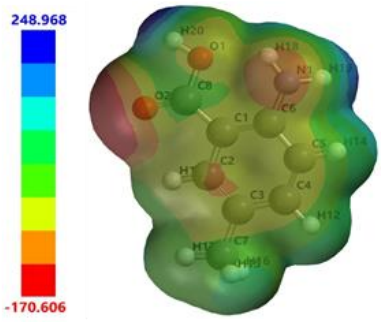
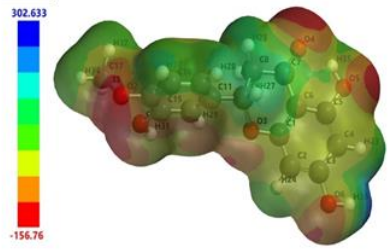
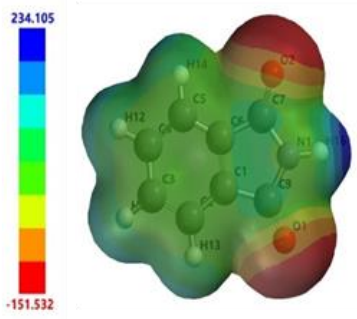
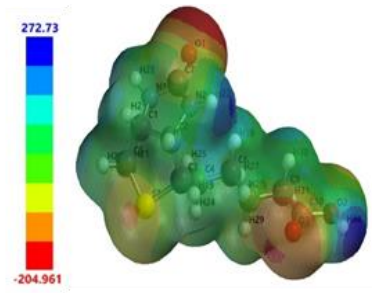
47	Pimelic acid	-5.75	10.75	pass
48	Cinnamic acid (Trans)	-5.61	10.21	pass
49	Z-L-Aspartic acid	-5.57	10.07	fail
50	Isonicotinamide	-5.40	9.44	pass
51	Azelaic acid	-5.15	8.64	fail
52	4,4-bipyridine	-4.84	7.70	fail
53	Imidazole	-4.74	7.40	fail
54	Methylparaben	-4.45	6.64	fail
55	Capsaicin	-4.28	6.23	fail
56	D-Phenylalanine	-4.19	6.01	fail
57	Adipic acid	-4.15	5.93	fail
58	Monobutyrin	-3.89	5.37	pass
59	Acesulfame K	-3.72	5.04	pass
60	Hydroxycinnamic acid	-3.64	4.89	fail
61	Isonicotinic acid	-3.20	4.12	pass
62	Aspirin	-3.17	4.07	pass
63	Propranolol	-3.13	4.02	pass
64	Propylparaben	-3.01	3.83	pass
65	Ketoprofen	-2.96	3.76	pass
66	Nicotinic acid	-2.82	3.55	fail
67	Triphenylacetic acid	-2.77	3.49	fail
68	Sorbic acid	-2.75	3.46	fail
69	Nadolol	-2.30	2.91	fail
70	Ethylparaben	-2.23	2.82	fail
71	Pyrazine	-2.22	2.82	fail
72	2-aminopyrazine	-2.18	2.77	fail
73	L-Proline	-2.16	2.75	pass
74	D-Pantothenol (Panthenol)	-2.09	2.67	pass
75	Caprolactam (Epsilon)	-1.68	2.28	pass
76	Valerolactam (Delta)	-1.62	2.22	pass
77	Piracetam	-1.60	2.21	fail
78	Praziquantel	-1.53	2.14	pass
79	D-Proline	-0.83	1.62	pass
80	3-Methylpyridine	-0.70	1.54	fail

Table S4: MEPSs of top 20 coformers

Ranking	coformer	MEPS
1	Amodiaquine dihydrochloride dihydrate (AQD)	
2	Quercetin (QUC)	
3	Etidronic acid (HEDP)	
4	Pamoic acid (PMA)	

5	Resveratrol (Trans) (RSV)	
6	Acetylenedicarboxylic acid (ACA)	
7	Oxalic acid (OXA)	
8	Furosemide (FUR)	
9	4-aminobenzoic acid (ABA)	

10	Niflumic acid (NFA)	
11	Flufenamic acid (FFA)	
12	Hydrochlorothiazide (HCT)	
13	Riboflavin (RFN)	

14	2-amino-5-methylbenzoic acid (AMBA)	
15	Hesperetin (HES)	
16	Phthalamide (PTA)	
17	Biotin (BIO)	

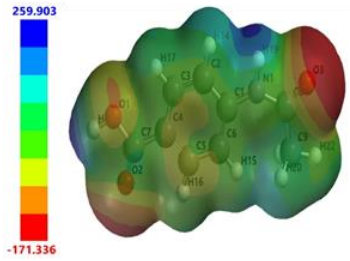
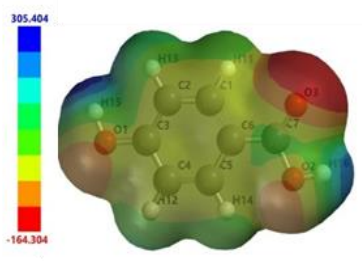
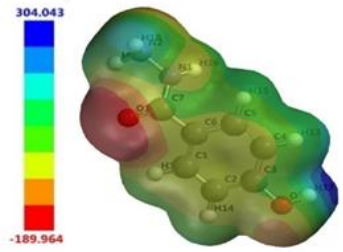
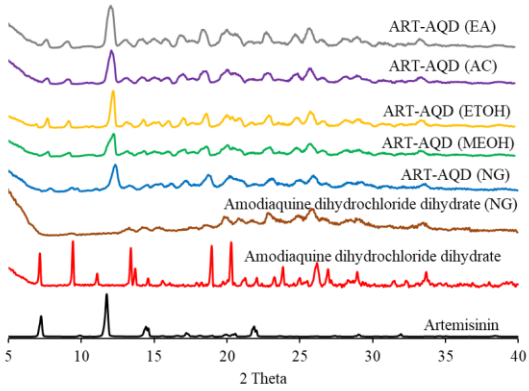
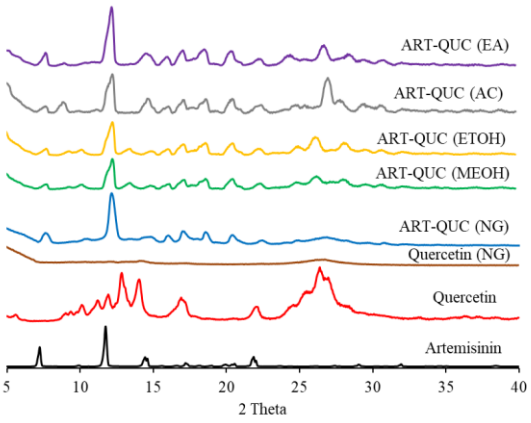
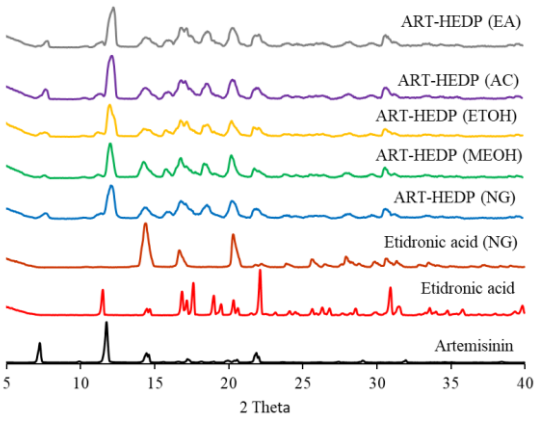
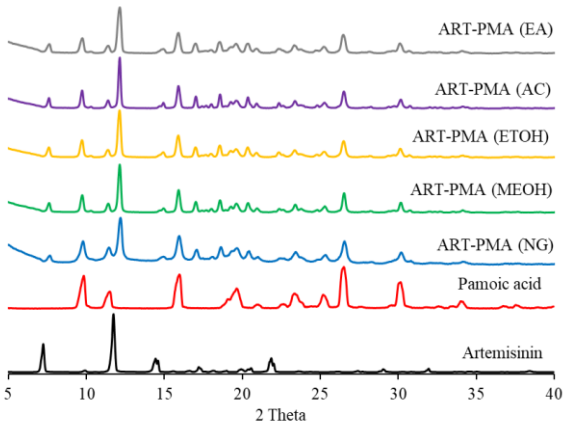
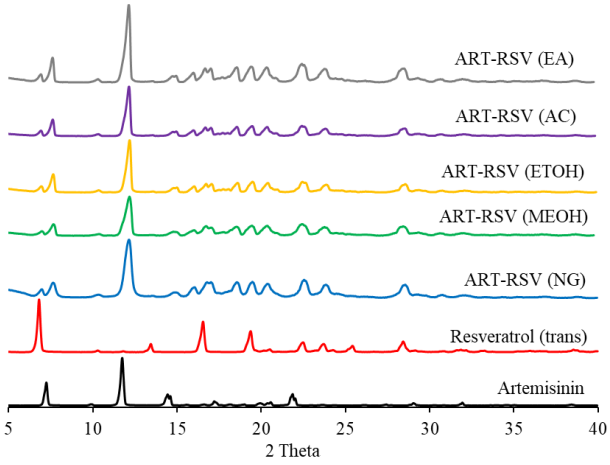
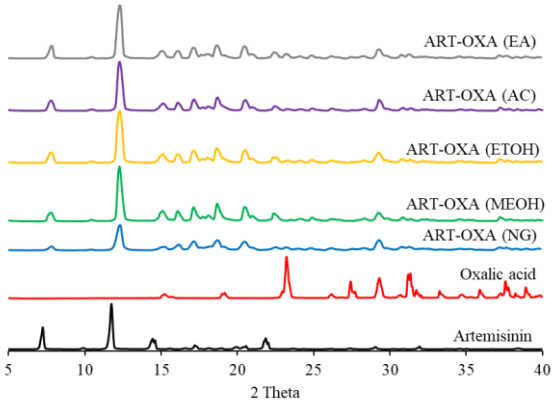
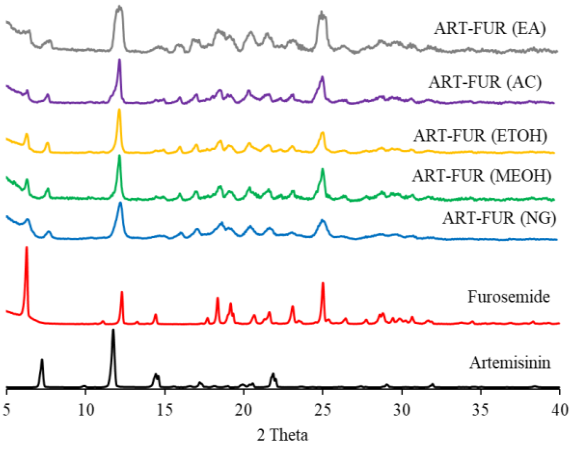
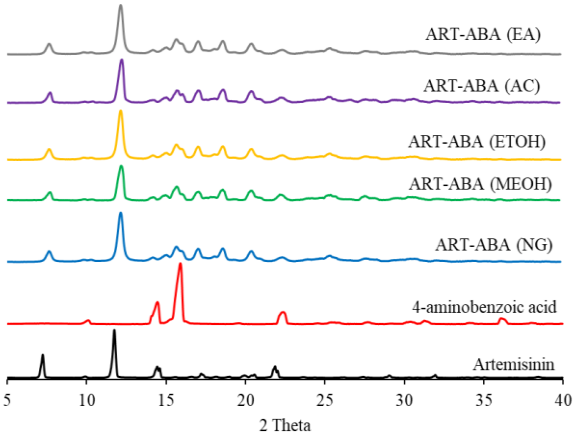
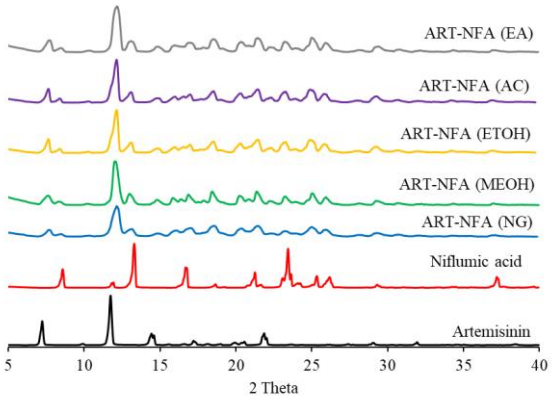
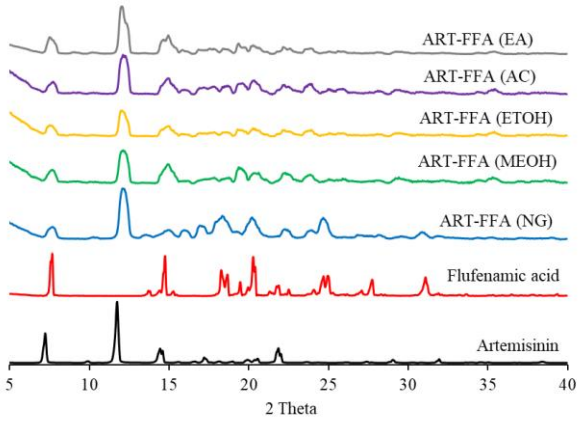
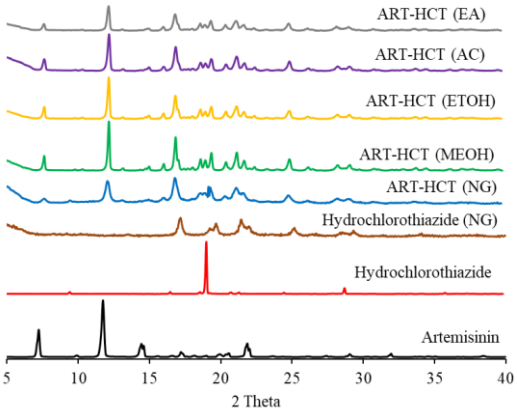
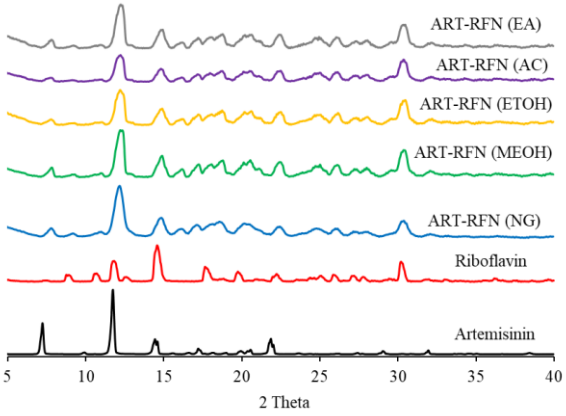
18	Acedoben (ADB)	
19	4-hydroxybenzoic acid (HBA)	
20	4-hydroxybenzohydrazide (HBD)	

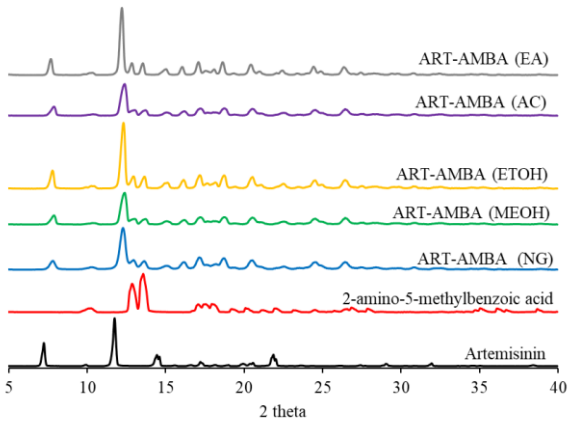
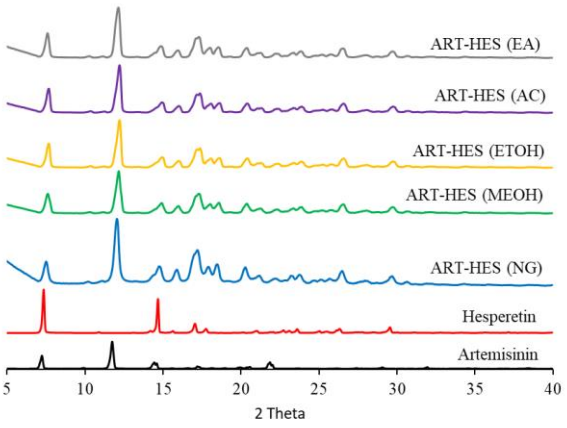
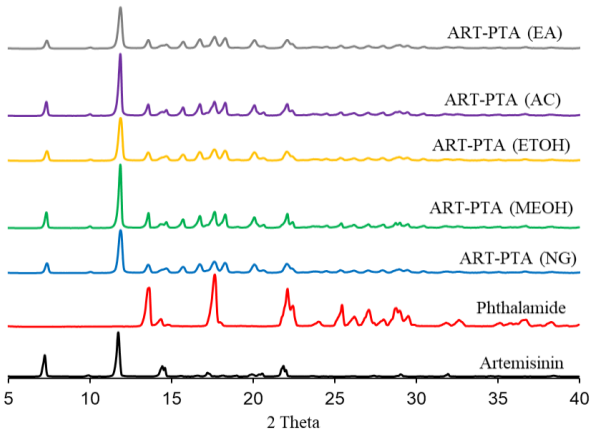
Table S5: PXRD patterns of experimental screening

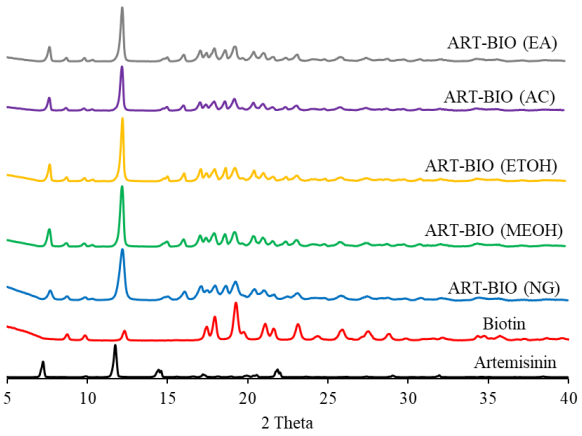
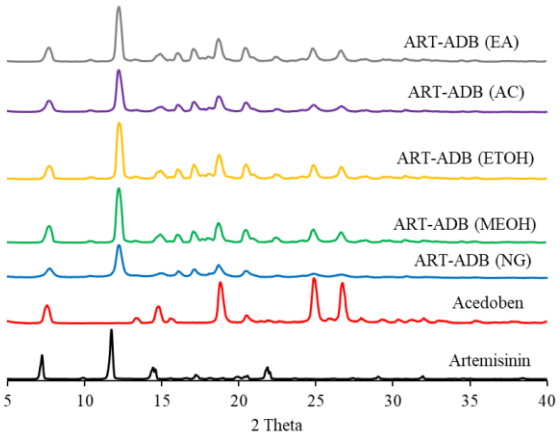
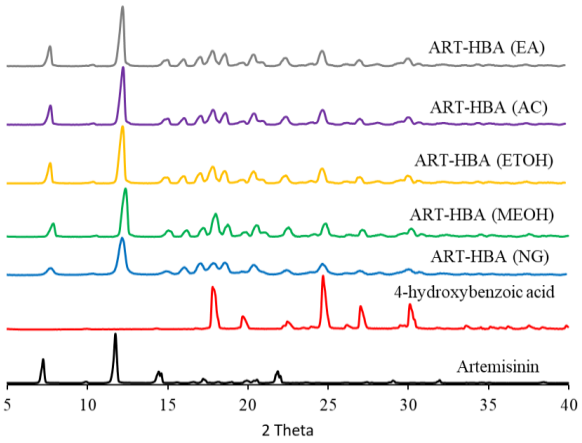
Ranking	coformer	PXRD pattern
(1)	AQD	
(2)	QUC	
(3)	HEDP	

(4)	PMA	
(5)	RSV	
(7)	OXA	

(8)	FUR	
(9)	ABA	
(10)	NFA	

(11)	FFA	
(12)	HCT	
(13)	RFN	

(14)	AMBA	
(15)	HES	
(16)	PTA	

(17)	BIO	
(18)	ADB	
(19)	HBA	

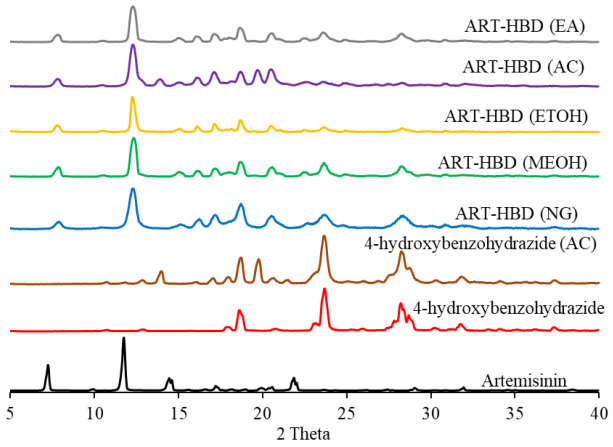
(20)	HBD	 ART-HBD (EA) ART-HBD (AC) ART-HBD (ETOH) ART-HBD (MEOH) ART-HBD (NG) 4-hydroxybenzohydrazide (AC) 4-hydroxybenzohydrazide Artemisinin 5 10 15 20 25 30 35 40 2 Theta

Table S6: Calibration models of ART on HPLC and ACA on UV. The concentration units are in µg/mL; Cr: real concentration of validation sample (theoretical) and Cm: measured concentration of validation sample

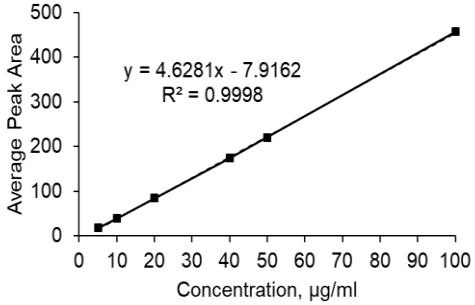
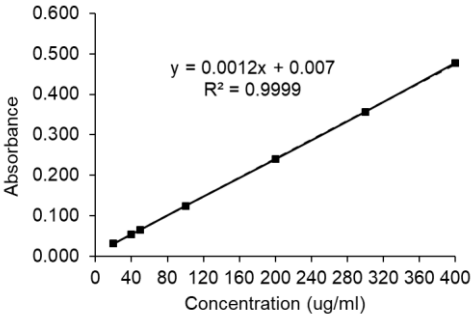
Calibration Curve range (µg/mL)	Concentration points (µg/mL)	Calibration graph	Validation samples		
			C_r (µg/mL)	C_m (µg/mL)	$\frac{C_m - C_r}{C_r}\ x100$
ART					
5-100	5, 10, 20, 40, 50 and 100		15	14.96	0.30
			30	30.06	0.20
			60	61.50	2.50
ACA					
20-400	20, 40, 50, 100, 200, 300, 400		30	30.58	1.94
			60	61.83	3.06
			150	148.50	1.00

Table S7: calibration models of ART on HPLC and ACA on UV by a mixture of ART and ACA. The concentration units are in µg/mL; Cr: real concentration of validation sample (theoretical) and Cm: measured concentration of validation sample

Validation samples		
ART		
C_r (µg/mL)	C_m (µg/mL)	$\frac{C_m - C_r}{C_r} x100$
25	24.53	1.87
50	48.82	2.37
ACA		
C_r (µg/mL)	C_m (µg/mL)	$\frac{C_m - C_r}{C_r} x100$
25	23.85	4.62
50	52.31	4.62

Fig. S1: Comparison of DSC thermographs of ART, ACA, ART^2-ACA

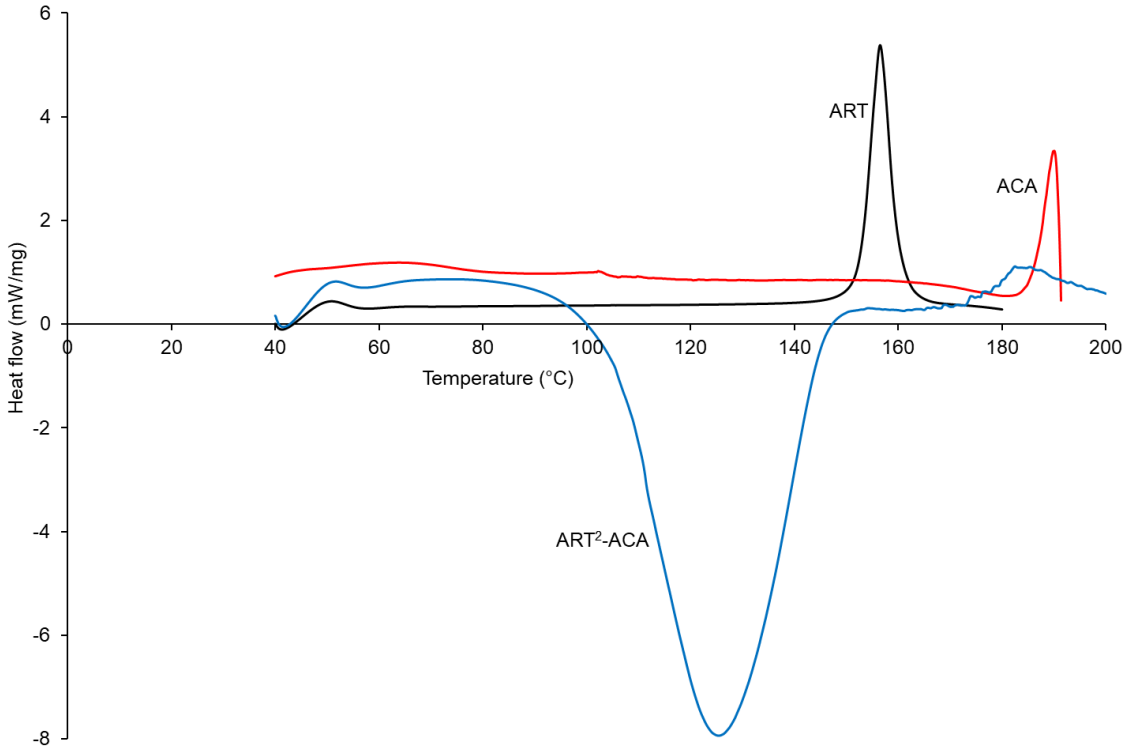


Fig. S2: UV Spectra of ART and ACA

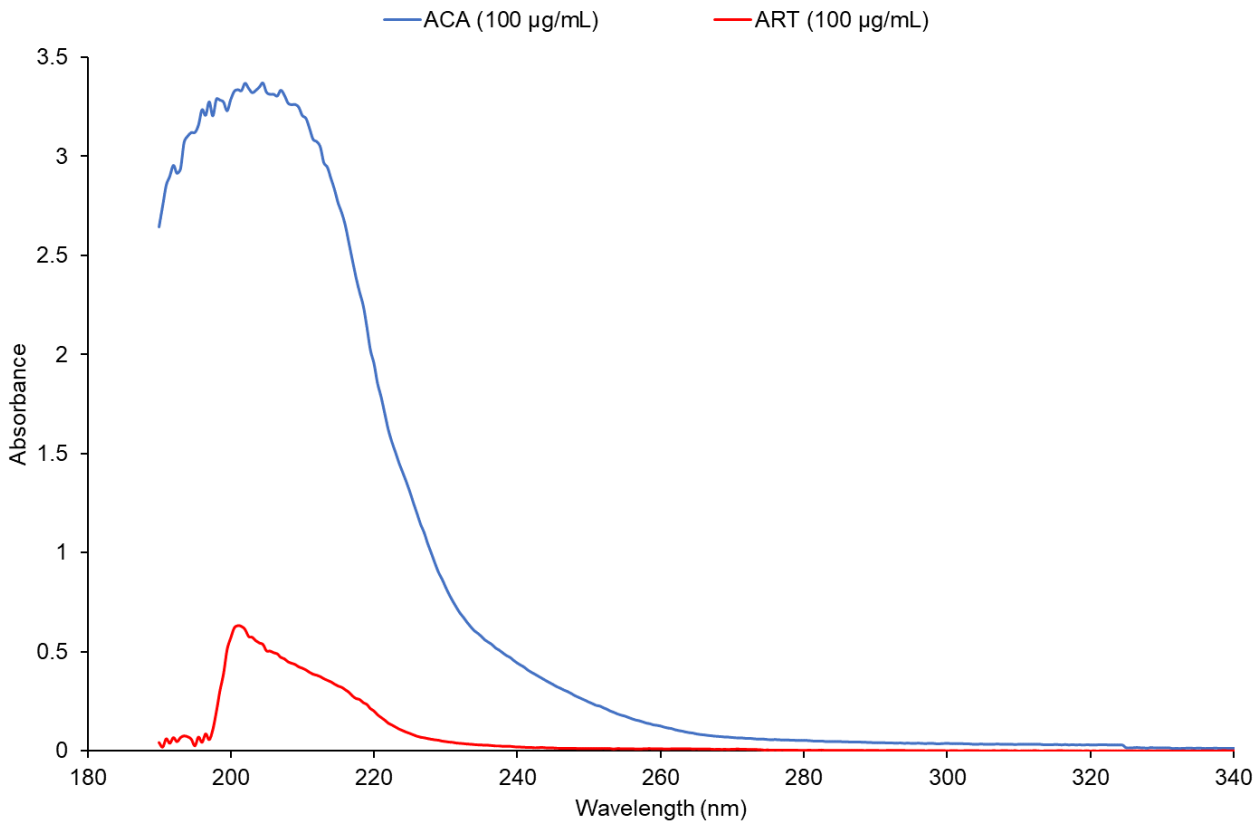


Fig. S3: PXRD patterns of solid residues after ART^{2}-ACA dissolution tests