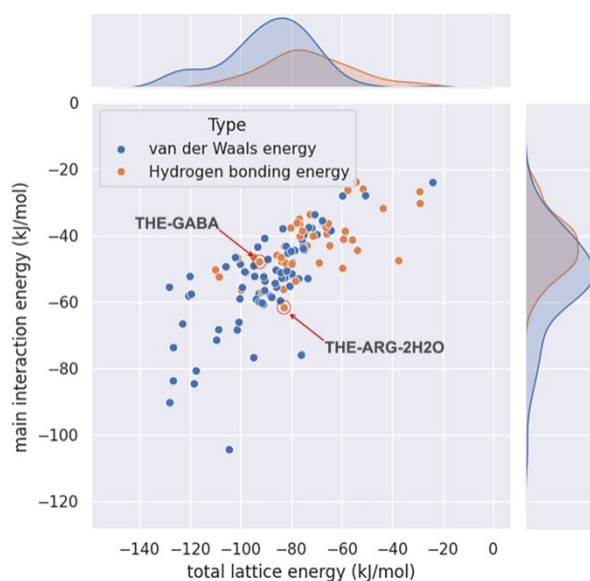
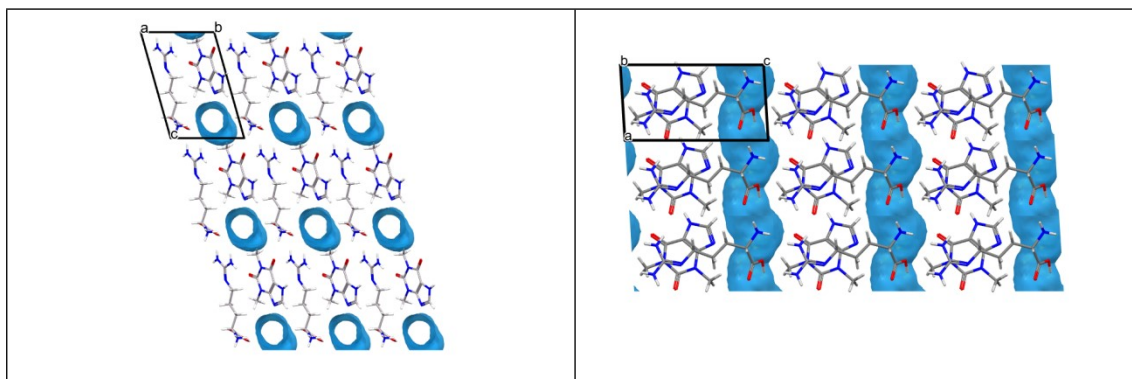


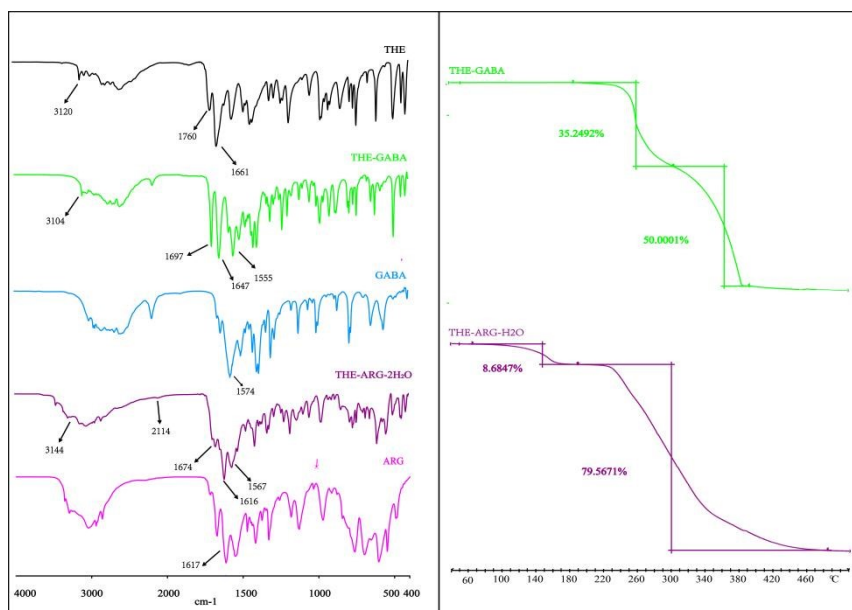
## Supporting Information



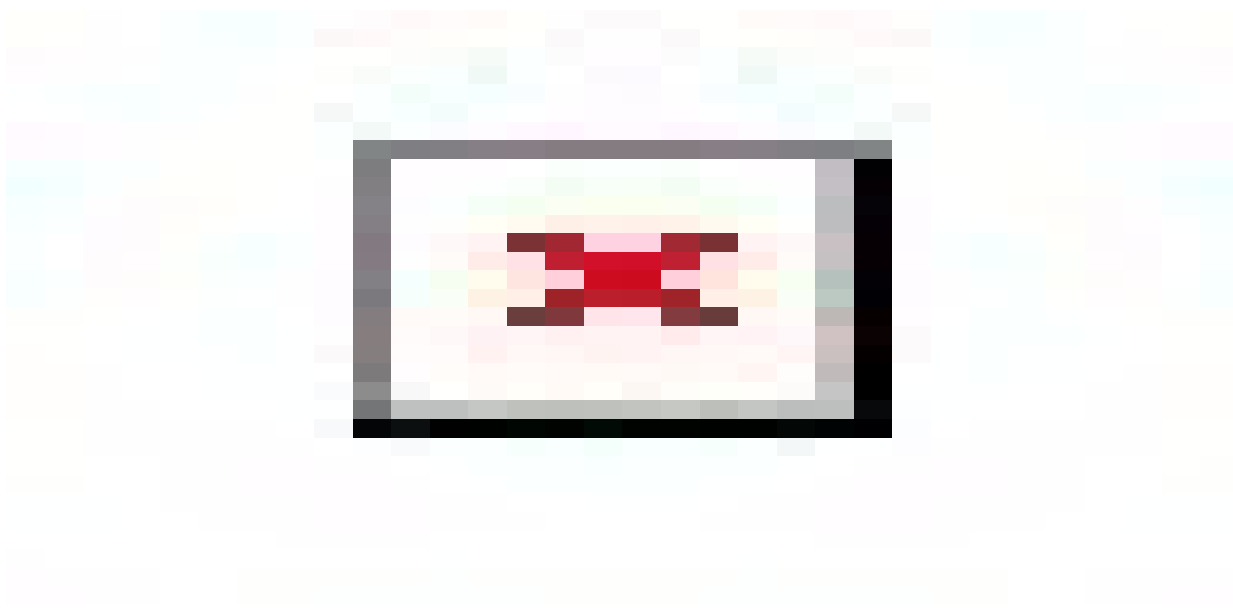
**Figure S1.** Energy distribution of theophylline cocrystals in CSD database and two new cocrystals of theophylline with amino acids



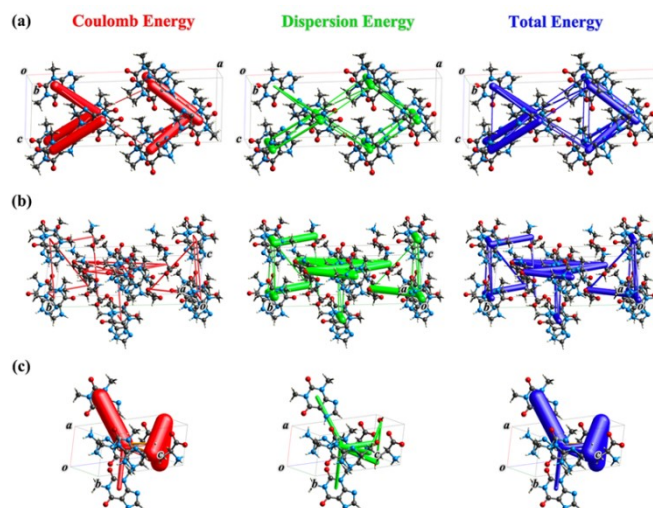
**Figure S2.** Water space in  $3 \times 3$  packing structure of THE-ARG-2H<sub>2</sub>O from a-axis(left) and b-axis(right).



**Figure S3.** IR (left) and TGA (right) profiles of API, CCFs, and the corresponding cocrystals.



**Figure S4.** DVS of THE, GABA, ARG, THE-GABA, and THE-ARG-2H<sub>2</sub>O.



**Figure S5.** Energy frameworks of THE (a), THE-GABA (b), and THE-ARG-2H<sub>2</sub>O (c).

**Table S1.** Parameters (Å, Degree) of the Main Hydrogen Bonds for the Cocrystals.

Cocrystal	D-H...A	D...A(Å)	D-H...A(°)	D-H...A	D...A(Å)	D-H...A(°)
THE-GABA	N <sub>4</sub> -H <sub>4</sub> ...O <sub>15</sub>	2.68	163.78	N <sub>15</sub> -H <sub>15B</sub> ...O <sub>25</sub>	2.76	165.41
	N <sub>15</sub> -H <sub>15A</sub> ...O <sub>25</sub>	2.84	168.29	N <sub>15</sub> -H <sub>15C</sub> ...N <sub>3</sub>	3.09	169.67
THE-ARG-	O <sub>1W</sub> <sup>-</sup>	2.80	173.00	N <sub>45</sub> -H <sub>45B</sub> ...O <sub>15</sub>	2.81	161.71
2H <sub>2</sub> O	H <sub>1WA</sub> ...O <sub>15</sub>					
	N <sub>15</sub> -H <sub>15A</sub> ...O <sub>25</sub>	2.78	177.17	O <sub>1W</sub> <sup>-</sup>	2.80	167.15
				H <sub>1WB</sub> ...N <sub>3</sub>		
	N <sub>15</sub> -H <sub>15B</sub> ...O <sub>2W</sub>	2.86	167.42	N <sub>15</sub> -H <sub>15C</sub> ...O <sub>2</sub>	2.87	169.48
	N <sub>35</sub> -H <sub>35A</sub> ...O <sub>1</sub>	2.86	161.77			

**Table S2.** The cocrystals of THE involved in Figure S1.

NO.	Cocrystals	Code	NO.	Cocrystals	Code
1	Theophylline-Isonicotinamide	EVEYAH	55	Theophylline-rac-dihydromyricetin acetonitrile solvate	NEXSIW
2	Theophylline-tegafur monohydrate	DOXFIH	56	Theophylline- 9-(2-methoxyphenyl)-9H-xanthen-9-ol	NIJJIB
3	Theophylline-urea	DUXZAX	57	Theophylline- L-tartaric acid	NUJCAJ
4	Theophylline-methyl gallate	GAFTUE	58	Theophylline-DL-tartaric acid	NUJCEC
5	Theophylline-nicosamide	HEBFEB	59	Theophylline-diclofenac	OPOFUW
6	Theophylline-nicosamide acetonitrile solvate	HEBFIF	60	Theophylline-difunisal	OPOGAD
7	Theophylline-Glibenclamide	GEKMUH	61	Theophylline-2,3,5-trifluorobenzoic acid	OPUKIV
8	Theophylline-Lamotrigine	FISNIH	62	Theophylline-2,3,6-trifluorobenzoic acid	OPUKOB
9	Theophylline-gentisic acid	DUCROJ	63	Theophylline-2,4,5-trifluorobenzoic acid	OPUKUH
10	Theophylline-aspirin	DIPJAJ	64	Theophylline-2,4,5-trifluorobenzoic acid	OPUKUH01

11	Theophylline-pyridine-2,6-diamine	DEDMEH	65	Theophylline-2,4,6-trifluorobenzoic acid	OPULES
12	Theophylline-N,N'-ethane-1,2-diylidiformamide	DUWXAW	66	Theophylline-2,4,6-trifluorobenzoic acid	OPULES01
13	Theophylline-Sulfacetamide	HOCCUZ	67	Theophylline-pentafluorobenzoic acid	OPUMAP
14	Theophylline-4-aminobenzoic acid	HUMNEK01	68	Theophylline-pentafluorobenzoic acid	OPUMAP01
15	Theophylline-pterostilbene dichloromethane solvate	HURPOC	69	Theophylline-2,3,4-trifluorobenzoic acid	OPUMIX
16	Theophylline-3-hydroxybenzoic acid	DOPMUS	70	Theophylline-3-fluorobenzoic acid	OPUMOD
17	Theophylline- DL-malic acid	DOPMUS	71	Theophylline-3,5-difluorobenzoic acid	OPUMUJ
18	Theophylline- D-malic acid	CIZTAH	72	Theophylline-2-fluorobenzoic acid	OPUNAQ
19	Theophylline-5-Chlorosalicylic acid	CODCOO	73	Theophylline-2-fluorobenzoic acid nitromethane solvate	OPUNOE
20	Theophylline-2,4-dihydroxybenzoic acid monohydrate	CSATEO	74	Theophylline-2,3,4,6-tetrafluorobenzoic acid	OPUPIA
21	Theophylline-2,3-dihydroxybenzoic acid	DOPNAZ	75	Theophylline-3,4-difluorobenzoic acid	OPUPOG
22	Theophylline-2,4-dihydroxybenzoic acid	DOPNED	76	Theophylline-2,3,4,6-tetrafluorobenzoic acid	OPUPUM
23	Theophylline-p-coumaric aci	IJIBEJ	77	Theophylline-dihydromyricetin acetonitrile solvate	OQFIUR
24	Theophylline-p-coumaric aci	IJIBEJ01	78	Theophylline-pyrrolidin-2-one	PICMIA
25	Theophylline-benzamide	RABXIE01	79	Theophylline-pyrrolidin-2-one	PICMOG
26	Theophylline-rucaparib monohydrate	JIBMAM	80	Theophylline-benzamide	RABXIE
27	Theophylline-baicalein trihydrate	KAMQIB	81	Theophylline-benzamide	RABXIE02
28	Theophylline-Pyrimethamine	KICWIE	82	Theophylline-pyrazinamide	RACFIN
29	Theophylline-citric acid	KIGKAN	83	Theophylline-pyrazinamide	RACFIN01
30	Theophylline-salicylic acid	KIGLES	84	Theophylline-3-hydroxysalicylaldoxime dihydrate	RUYXUG
31	Theophylline-4-hydroxybenzoic acid	KIGLOC	85	Theophylline-belinostat	SIBZAI
32	Theophylline-paracetamol	KIGLUI	86	Theophylline-phenobarbital	THOPBA
33	Theophylline-3-(Dihydroxyboryl)benzoic acid	LEDVOH	87	Theophylline-p-nitrophenol	TOPPNP
35	Theophylline-phthalic acid	LUKXUL	88	Theophylline-3,5-dinitrobenzoic acid	UKEXOA
36	Theophylline-Caffeine	NEHJER	89	Theophylline-(4-chlorophenyl)boronic acid	ULUQUP
37	Theophylline-(pyridine-2,6-dicarboxylic acid) dihydrate	UNITIV	90	Theophylline-(4-iodophenyl)boronic acid	ULURAW
38	Theophylline-benzoic acid	VAXSAQ	91	Theophylline-(4-hydroxyphenyl)boronic acid	ULUREA
39	Theophylline-1,10-phenanthroline dihydrate	WAKJIF	92	Theophylline-1,4-phenylenediboronic acid hemihydrate	ULURIE
40	Theophylline-orcinol dihydrate	WOCHAZ	93	Theophylline-pyrazole-3,5-dicarboxylic acid monohydrate	UNITER

41	Theophylline- 3,4-dihydroxybenzoic acid	WOCHON	94	Theophylline-resorcinol monohydrate	WOCGOM
42	Theophylline-anthranilic acid	WUTHEA	95	Theophylline-phluroglucinol monohydrate	WOCGUS
43	Theophylline-2-aminobenzoic acid tetrahydrate	WUTHOK	96	Theophylline-3,5-dihydroxybenzoic acid	WOCHIH
44	Theophylline-2-aminobenzoic acid tetrahydrate	WUTHUQ	97	Theophylline-cinnamic acid	WOCHUT
45	Theophylline-oxalic acid	XEJWUF	98	Theophylline-2-aminobenzoic acid isobutanol solvate	WUTHIE
46	Theophylline-malonic acid	XEJXAM	99	Theophylline-3-aminobenzoic acid	WUTJAY
47	Theophylline-malonic acid	XEJXAM01	100	Theophylline-maleic acid	XEJXEQ
48	Theophylline-entacapone	XIPNOC	101	Theophylline-glutaric acid	XEJXIU
49	Theophylline-4-hydroxybenzamide	YEVMIY	102	Theophylline-saccharin	XOBCUN
50	Theophylline-3,4-dichlorobenzoic acid	YEVNAR	103	Theophylline-acetazolamide	YEVMIK
51	Theophylline-4-chloro-3-nitrobenzoic acid	YEVNIZ	104	Theophylline-picolinamide	YEVNEV
52	Theophylline-5-fluorouracil monohydrate	ZAYLOA	105	Theophylline-4-aminosalicylic acid	YUJLOG
53	Theophylline-p-nitroaniline	ZEXTIF	106	Theophylline-4-fluoro-3-nitrobenzoic acid	ZEKPIR01
54	Theophylline-Vanillic acid	ZOYBIA	107	Theophylline-2-((3-(trifluoromethyl)phenyl)amino)benzoic acid	ZIQDUA

**Table S3.** Main Vibrational Data ( $\text{cm}^{-1}$ ) with Tentative Assignments for cocrystals

Vibrational data					Vibrational assignment
THE	THE-GABA	THE-ARG-2H <sub>2</sub> O	GABA	ARG	
----	----	2114	----	----	H <sub>2</sub> O
3120	3104	3144	----	----	Secondary amine
1706	1697	1674	----	----	Carbonyl group (amide group)
1659	1647	1567	----	----	Imine group
----	1555	1616	1574	1614	Carbonyl (carboxyl)