

Supplemental section 1: Fragment library used for co-crystallization

1	Gelatin	25	Sudan III
2	DHA supp	26	Ibuprofen
3	Glutamine (supp)	27	Famotidine
4	Biotin supp	28	P amino benzoic Acid H2O
5	Co-Q-10 (supp) Coenzyme	29	Aleuritic Acid
6	5-HTP supp (5-Hydroxy-L-tryptophan)	30	Acetaminophin "A"
7	Vitamin B6 (supp)	31	Fexofenadine hydrochlorite
8	L-Isoleucine	32	Cimetidine
9	Niacine (supp)	33	Cetirizine Hydrochloride
10	4-Aminosalicylic Acid 99%	34	Bromobenzene
11	3-Aminophenol 98%	35	4-Aminodiphenylamine HCl
12	Sunset Yellow FCF	36	Cyanocobalamin (B12)
13	Tartrazine	37	2-Picolinic acid
14	Allura Red AC	38	trans-4-hydroxy-L-proline
15	Indigo	39	hexammincobalt (III) chloride
16	Eythrosine B	40	Trypan Blue
17	L Lysine Monodrochloride	41	Quinine Sulfate, Dihydrate
18	L-Methionine	42	TetMet/PhenDi
19	L-Threonine	43	N-Formyl-L-proline
20	L-Leucine	44	Crystal Violet TS
21	L-Proline	45	Ciproflaxin
22	4-Fluoroaniline	46	Methylene Blue 1% H2O
23	N-Bromosuccinimide	47	Guaifenesin
24	Eosin 1% aqueous	48	Aspirin

Supplemental section 2:

The hypergeometric distribution computes the probability of observing k successes (here $k=0$, because none of the observed electron density perturbations occurred among crystals that grew using conventional co-crystallization) from n random draws (here $n=3$, because three electron density perturbations were observed) taken from N objects ($N=48$, because electron densities were obtained from diffraction experiments using 48 distinct chemical co-crystals), of which K are success states ($K=26$, because there were 26 successful conventional co-crystallizations) and $(N-K)$ are non-success states ($N-K=22$, because 22 co-crystals grew only using gel exclusion). Hence, there were 0 successes from 3 random draws taken from 48 objects, of which 26 are success states and 22 are failure states. The probability for this observation is:

$$P = \frac{\binom{K}{k} \binom{N-K}{n-k}}{\binom{N}{n}} = \frac{\binom{26}{0} \binom{22}{3}}{\binom{48}{3}} = \frac{(1)(1540)}{(17296)} = 9\%$$

where $\binom{x}{y}$ is the binomial distribution:

$$\binom{x}{y} = \frac{x!}{y! (x-y)!}$$