Supporting Information

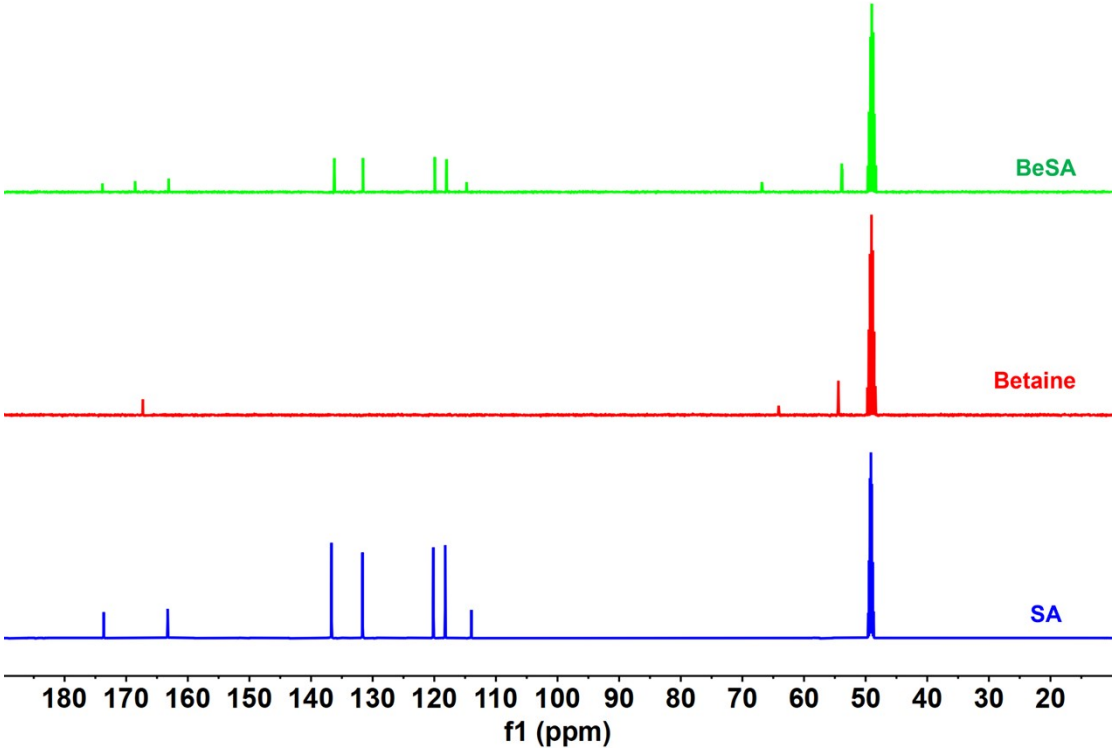

Figure S1. ^{13}C-NMR spectra of BeSA and its precursors.

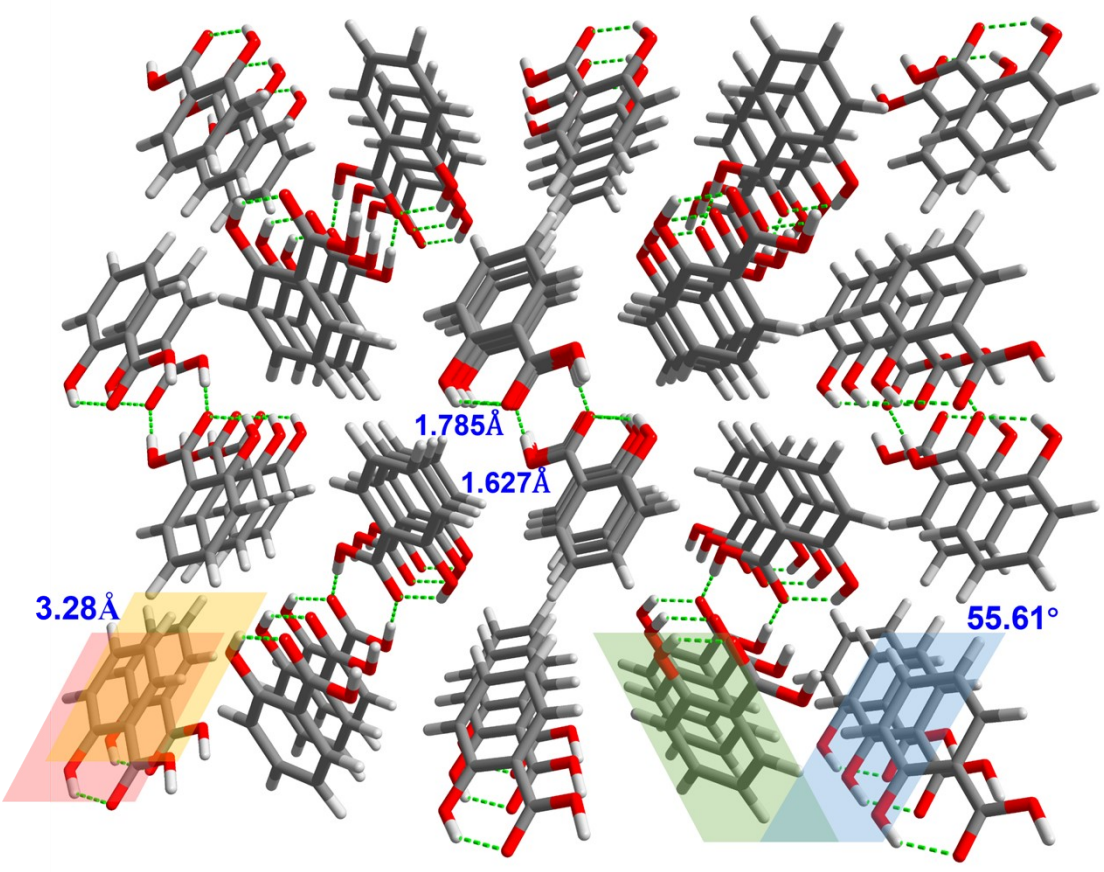

Figure S2. Single-crystal analysis of SA.

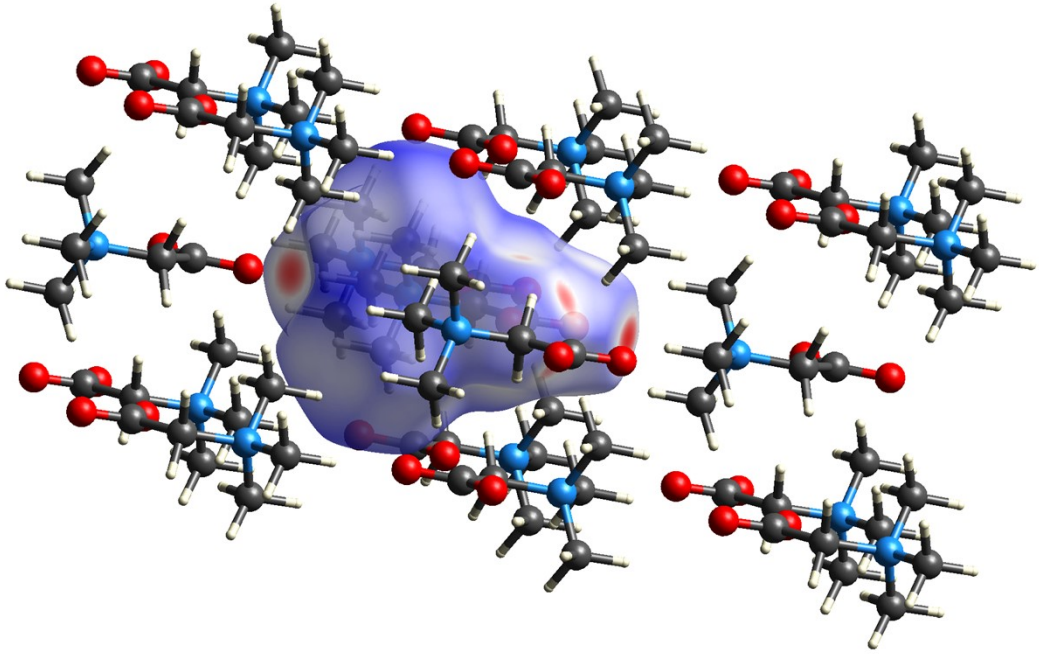

Figure S3. 3D Hirshfeld d_{norm} surface of SA.

Table S1. Crystal data and structure refinement

Compound	BeSA
CCDC	2101906
Empirical formula	$C_{12}H_{17}NO_5$
Formula weight	255.26
Temperature/K	100.00(10)
Crystal system	orthorhombic
Space group	Pbca
a/Å	10.2107(8)
b/Å	10.7746(8)
c/Å	22.5314(17)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2478.8(3)
Z	8
ρ_{calc}g/cm^3	1.368
μ/mm^{-1}	0.107
F(000)	1088.0
Crystal size/mm^3	0.12 × 0.11 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.384 to 59.18
Index ranges	$-14 \leq h \leq 13$, $-14 \leq k \leq 14$, $-29 \leq l \leq 30$
Reflections collected	12746
Independent reflections	3120 [R_{int} = 0.0466, R_{sigma} = 0.0464]
Data/restraints/parameters	3120/1/171
Goodness-of-fit on F^2	1.089
Final R indexes [I>=2σ (I)]	R_1 = 0.0465, wR_2 = 0.0997
Final R indexes [all data]	R_1 = 0.0658, wR_2 = 0.1117
Largest diff. peak/hole / e Å^{-3}	0.28/-0.26

Table S2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for BeSA. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O2	3556.3(10)	7227.7(10)	4111.5(5)	19.6(3)
O4	2075.4(10)	4768.2(9)	4572.9(5)	20.7(3)
O3	3821.2(10)	5241.8(10)	3858.6(5)	21.3(3)
O5	3254.6(10)	3664.7(10)	5232.8(5)	21.8(3)
O1	4799.9(11)	8944.1(9)	3571.7(5)	23.2(3)
N1	838.4(12)	2829.3(11)	5791.5(5)	15.0(3)
C1	4978.3(13)	6768.5(13)	3312.9(6)	15.3(3)
C8	2222.1(14)	4049.8(13)	5025.4(6)	17.3(3)
C2	5301.4(14)	8026.4(14)	3230.8(6)	17.3(3)
C7	4056.2(14)	6406.6(14)	3796.7(6)	16.3(3)
C6	5537.3(14)	5888.2(14)	2936.2(6)	18.3(3)
C9	884.2(14)	3736.4(14)	5287.2(6)	17.0(3)
C10	-574.6(14)	2699.8(14)	5964.3(7)	19.6(3)
C3	6180.5(14)	8363.0(15)	2783.4(6)	19.9(3)
C5	6392.4(15)	6222.5(15)	2489.0(7)	21.3(3)
C4	6718.2(15)	7468.2(16)	2419.2(7)	22.2(3)
C11	1573.3(16)	3301.4(16)	6316.4(7)	23.1(4)
C12	1337.5(16)	1586.3(14)	5599.9(7)	24.6(4)

Table S3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for BeSA. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O2	19.2(5)	17.4(6)	22.2(6)	-0.8(5)	5.9(4)	-0.8(4)
O4	22.3(6)	17.1(5)	22.7(5)	3.6(5)	2.9(5)	-1.5(4)
O3	22.8(6)	16.1(6)	25.1(6)	1.8(5)	6.3(5)	-1.3(4)
O5	15.5(5)	25.8(6)	24.0(6)	0.2(5)	0.0(4)	-0.4(4)
O1	26.0(6)	17.0(6)	26.7(6)	0.8(5)	10.0(5)	-1.0(5)
N1	15.7(6)	14.4(6)	14.9(6)	0.4(5)	0.0(5)	1.1(5)
C1	13.1(7)	18.3(7)	14.6(7)	0.9(6)	-3.1(6)	-0.8(6)
C8	19.3(7)	14.4(7)	18.3(7)	-3.4(6)	1.1(6)	-1.7(6)
C2	15.3(7)	18.7(7)	17.9(7)	1.3(6)	-2.2(6)	1.8(6)
C7	13.8(7)	17.5(7)	17.6(7)	0.8(6)	-2.6(6)	0.9(6)
C6	17.9(7)	20.1(8)	16.9(7)	-0.5(6)	-4.5(6)	0.6(6)
C9	16.5(7)	17.5(7)	16.9(7)	2.4(6)	-1.5(6)	0.4(6)
C10	16.4(7)	22.0(8)	20.4(7)	1.1(6)	3.3(6)	-2.6(6)
C3	18.0(7)	21.7(8)	20.0(8)	6.9(7)	-2.8(6)	-1.5(6)
C5	18.7(7)	28.7(9)	16.5(7)	-2.2(7)	-2.7(6)	5.0(6)
C4	15.9(7)	35.5(9)	15.1(7)	5.3(7)	0.9(6)	1.8(7)
C11	21.4(8)	30.3(9)	17.7(7)	-1.9(7)	-5.2(6)	1.3(7)
C12	30.3(9)	15.1(8)	28.3(8)	0.4(7)	9.6(7)	3.6(6)

Table S4. Bond Lengths for BeSA.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O2	C7	1.2436(17)	C1	C2	1.407(2)
O4	C8	1.2888(18)	C1	C7	1.492(2)
O3	C7	1.2853(18)	C1	C6	1.395(2)
O5	C8	1.2255(17)	C8	C9	1.526(2)
O1	C2	1.3528(18)	C2	C3	1.398(2)
N1	C9	1.4996(18)	C6	C5	1.381(2)
N1	C10	1.5009(19)	C3	C4	1.380(2)
N1	C11	1.4902(19)	C5	C4	1.392(2)
N1	C12	1.4966(18)			

Table S5. Bond Angles for BeSA.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C9	N1	C10	106.69(11)	O1	C2	C1	122.73(13)
C11	N1	C9	111.30(12)	O1	C2	C3	117.58(13)
C11	N1	C10	108.05(11)	C3	C2	C1	119.69(14)
C11	N1	C12	111.29(12)	O2	C7	O3	123.79(13)
C12	N1	C9	110.73(11)	O2	C7	C1	119.32(13)
C12	N1	C10	108.60(11)	O3	C7	C1	116.88(13)
C2	C1	C7	119.71(13)	C5	C6	C1	121.69(14)
C6	C1	C2	118.63(13)	N1	C9	C8	117.72(12)
C6	C1	C7	121.67(13)	C4	C3	C2	120.20(15)
O4	C8	C9	109.55(12)	C6	C5	C4	119.02(15)
O5	C8	O4	127.22(14)	C3	C4	C5	120.77(14)
O5	C8	C9	123.23(13)				

Table S6. Hydrogen Bonds for BeSA.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O3	H4	O4	0.94	1.53	2.455(3)	170.9
O1	H1	O4	0.82	2.52	3.089(3)	128.0
O1	H1	O2	0.82	1.83	2.552(3)	146.2

Table S7. Torsion Angles for BeSA.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O1	C2	C3	C4	-179.63(13)	C6	C1	C7	O2	-178.17(13)
C1	C2	C3	C4	0.7(2)	C6	C1	C7	O3	1.4(2)
C2	C1	C6	C5	0.0(2)	C7	C1	C2	O1	-0.6(2)
C2	C1	C7	O2	2.0(2)	C7	C1	C2	C3	179.04(13)
C2	C1	C7	O3	-178.46(13)	C7	C1	C6	C5	-179.90(13)
C2	C3	C4	C5	0.3(2)	O4	C8	C9	N1	175.48(12)
C3	C4	C5	C6	-1.2(2)	O5	C8	C9	N1	-5.2(2)
C4	C5	C6	C1	1.0(2)	C10	N1	C9	C8	179.57(12)
C6	C1	C2	O1	179.52(13)	C11	N1	C9	C8	61.94(16)
C6	C1	C2	C3	-0.8(2)	C12	N1	C9	C8	-62.44(16)

Table S8. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for BeSA.

Atom	*x*	*y*	*z*	U(eq)
H1	4306.18	8644.7	3820.54	35
H6	5328.97	5054.86	2987.58	22
H9A	485.92	4504.21	5421.12	20
H9B	340.43	3413.4	4969.75	20
H10A	-900.12	3486.17	6099.91	29
H10B	-653.28	2098.55	6276.72	29
H10C	-1074.29	2431.99	5626.9	29
H3	6403.77	9192.65	2730.95	24
H5	6745.11	5624.09	2238.15	26
H4A	7305.18	7700.18	2123.74	27
H11A	2487.3	3359.93	6220.53	35
H11B	1458.03	2741.49	6643.69	35
H11C	1248.06	4107.03	6423.18	35
H12A	833.01	1296.08	5268.18	37
H12B	1259.15	1008.7	5922.34	37
H12C	2240.54	1656.7	5486.12	37
H4	3220(20)	5050(30)	4159(10)	86(9)

Table S9. Hydrogen bonds between SA and TIR

Donor	Donor	Acceptor
Gln636 NE2	Gln636 1HE2	SYS O0A
Lys677 NZ	Lys677 HZ1	SYS O07
Lys677 NZ	Lys677 HZ1	SYS O08
Lys689 NZ	Lys689 HZ1	SYS O07
Lys689 NZ	Lys689 HZ1	SYS O08
Lys689 NZ	Lys689 HZ1	SYS O0A

Table S10. Hydrogen bonds between BeSA and TIR

Donor	Donor	Acceptor
Gln636 NE2	Gln636 1HE2	SYS O0A
Asn672 ND2	Asn672 1HD1	SYS O07
Asn672 ND2	Asn672 1HD1	SYS O08
Lys677 NZ	Lys677 HZ1	TCJ O06
Lys677 NZ	Lys677 HZ1	TCJ O07
Thr685 OG1	Thr685 HG1	TCJ O06
Thr685 OG1	Thr685 HG1	TCJ O07

Table S11. Enclosed skin patch tests on 31 volunteers

Group	Time (h)	Number of volunteers with different irritation scores				
		0	1	2	3	4
SA	0.5	31	0	0	0	0
	24	31	0	0	0	0
	48	31	0	0	0	0
BeSA	0.5	31	0	0	0	0
	24	31	0	0	0	0
	48	31	0	0	0	0