Supplementary Information

Supramolecular Networks of Picrate with Tunable Hydrogen-bonding Densities for Selective Bacterial Killing

Sresha Sarkar,[a,#] Shabnam Sultana,[b,#] Jesús Jover,[c,d] Nilkanta Chowdhury,[e] Angshuman Bagchi,[f] Chandan Das,[g] Swapnadeep Goswami,[h] Dipankar Chattopadhyay,[a] Raj Kumar Roy,[i] Supriyo Saha,[i] Ennio Zangrando,*[j] Ria Sanyal*[b]

[a]*Department of Polymer Science and Technology, University of Calcutta, 92, A.P.C. Road, Kolkata 700009, West Bengal, India.*

[b]*Department of Chemistry, Diamond Harbour Women's University, Sarisha, West Bengal 743368, India.*

[c]*Secció de Química Inorgànica, Departament de Química Inorgànica i Orgànica, Universitat de Barcelona, Barcelona, Spain.*

[d]*Institut de Química Teòrica i Computacional (IQTC-UB), Universitat de Barcelona, Barcelona, Spain.*

[e]*Department of Biotechnology, Sidho-Kanho-Birsha University, Rachi-Purulia Road Campus, Purulia 723104, West Bengal, India.*

[f]*Department of Biochemistry and Biophysics, University of Kalyani, Kalyani, Nadia 741235, West Bengal, India.*

[g]*Department of Chemistry, IIT Bombay, Maharashtra 400076, India.*

[h]*Department of Physics, University of Calcutta, 92, A.P.C. Road, Kolkata 700009, West Bengal, India.*

[i]*Department of Chemistry, Visva-Bharati University, Santiniketan, West Bengal 731235, India.*

[j]*Department of Chemical and Pharmaceutical Sciences, University of Trieste, Via L. Giorgieri 1, 34127, Trieste, Italy.*

#Equal contribution

Table of Contents in ESI:

Table S1. Hydrogen bond parameters (Å /°) for compounds **1** - **5**.

D-H	d(D-H)	d(H..A)	d(D..A)	<DHA	A	Symmetry code
Compound 1						
N4-H1n	0.97(2)	1.76(2)	2.7032(15)	166.5(18)	O1	2-x,-y,1-z
N4-H1n	0.97(2)	2.34(2)	2.7710(18)	106.5(14)	O7	2-x,-y,1-z
N4-H2n	0.92(2)	2.02(2)	2.8818(17)	155.2(18)	O6	x,-1/2-y,1/2+z
N4-H3n	0.88(2)	2.33(2)	2.9149(17)	123.7(17)	O1	-
N4-H3n	0.88(2)	2.21(2)	3.0420(19)	156.5(19)	O2	-
C5-H5	0.93	2.48	3.1326(18)	127	O3	x,1/2-y,-1/2+z
C11-H11	0.93	2.58	3.3937(19)	147	O7	2-x,-1/2+y,1/2-z
Compound 2						
N4-H4a	0.91	1.92	2.8104(11)	167	O1	-
N4-H4b	0.91	2.04	2.9201(13)	162	O3	-x,1-y,2-z
N4-H4c	0.91	1.90	2.7935(12)	168	O1	-x,-y,2-z
N4-H4c	0.91	2.46	2.9446(12)	114	O7	-x,-y,2-z
O8-H8a	0.80(2)	2.02(2)	2.8194(14)	173(2)	O5	1-x,1-y,1-z
C11-H11	0.95	2.49	3.3642(18)	152	O2	1+x,y,z
Compound 3						
N4-H4a	0.91	2.09	2.805(4)	135	O1	x,1+y,z
N4-H4a	0.91	2.46	3.138(4)	132	O2	x,1+y,z
N4-H4b	0.91	2.22	3.103(4)	165	O6	1-x,2-y,1-z
N4-H4b	0.91	2.51	3.292(5)	145	O7	1-x,2-y,1-z
N4-H40c	0.91	1.88	2.728(4)	154	O1	-
C8-H8	0.95	2.46	3.266(5)	143	O6	1-x,2-y,1-z
C11-H11	0.95	2.60	3.378(5)	140	O3	3/2-x,1/2+y,1/2-z
C12-H12	0.95	2.41	3.221(5)	143	O2	x,1+y,z
C13-H13B	0.98	2.59	3.326(5)	132	O8	2-x,-y,1-z
Compound 4						
N1-H1n	0.95(3)	2.57(3)	3.308(3)	135(2)	O2	x,-1+y,z
N1-H1n	0.95(3)	2.39(3)	3.255(3)	151(2)	O8	1/2+x,1/2-y,z
N1-H2n	0.91(3)	2.36(3)	3.230(3)	162(3)	O12	-1/2+x,1/2-y,z
O3-H3a	0.85(3)	1.81(3)	2.571(3)	149(4)	O9	intra
O3-H3a	0.85(3)	2.41(3)	2.919(3)	119(3)	N5	intra
O10-H10a	0.86(3)	1.84(3)	2.553(3)	140(3)	O11	intra
O10-H10a	0.86(3)	2.52(4)	3.061(3)	122(3)	O14	x,-1+y,z
O10-H10a	0.86(3)	2.47(3)	2.898(3)	112(3)	N6	intra
C3-H3	0.95	2.48	3.267(3)	140	O7	1/2+x,3/2-y,z
C3-H3	0.95	2.52	3.394(10)	152	O3b	1/2+x,3/2-y,z
C5-H5	0.95	2.49	3.229(3)	135	O13	-1/2+x,3/2-y,z
C5-H5	0.95	2.48	3.330(9)	150	O10b	-1/2+x,3/2-y,z
C9-H9	0.95	2.24	3.191(3)	174	O16	1/2-x,1/2+y,-1/2+z
C17-H17	0.95	2.39	3.231(3)	147	O4	1/2-x,1/2+y,1/2+z
Compound 5						
N4-H4	0.88	2.00	2.864(4)	168	O5	1-x,-1/2+y,1/2-z
N5-H5a	0.91	2.19	2.632(4)	109	O8	intra
N5-H5a	0.91	2.03	2.830(4)	146	O8	-x,1-y,1-z
N5-H5b	0.91	1.94	2.788(4)	155	O1	-1+x,y,z
N5-H5c	0.91	1.80	2.672(4)	160	O1	-
N5-H5c	0.91	2.20	2.693(4)	113	O7	-
C9-H9	0.95	2.44	3.388(5)	173	O7	-x,1-y,1-z
C13-H13	0.95	2.59	3.305(5)	132	O5	1-x,-1/2+y,1/2-z

Table S2. Calculated conceptual DFT descriptors for the studied compounds, all values in eV.

Derivative	1	2	3	4	5
HOMO	-1.54	-5.13	-7.86	-6.58	-6.32
LUMO	-0.37	-3.95	-7.04	-4.84	-5.92
H-L gap	1.17	1.18	0.82	1.73	0.40
I	1.54	5.13	7.86	6.58	6.32
A	0.37	3.95	7.04	4.84	5.92
η	0.58	0.59	0.41	0.87	0.20
σ	0.86	0.85	1.22	0.58	2.51
μ	0.96	4.54	7.45	5.71	6.12
χ	-0.96	-4.54	-7.45	-5.71	-6.12
ω	0.78	17.44	67.53	18.84	94.18

Table S3. Percentual contributions of representative contact pairs within the Hirshfeld surface of the studied picrate derivatives.

Derivative	1	2	3	4	5
O···H	56.4	56.7	54.9	41.6	44.5
N···H	1.3	1.9	3.5	1.7	2.2
C···H	7.6	9.8	4.4	4.9	6.4
H···H	6.9	1.6	5.1	2.0	1.9
C···O	3.9	9.8	9.1	16.1	11.7
C···N	1.6	2.5	2.5	0.8	2.9
C···C	5.7	2.1	5.5	3.1	3.8
O···O	10.0	10.6	10.6	21.5	15.8
N···N	0.0	0.6	0.0	0.5	0.0
N···O	6.6	4.4	4.4	7.8	5.6
Cl···O	0.0	0.0	0.0	0.0	1.5
Cl···N	0.0	0.0	0.0	0.0	0.5
Cl···C	0.0	0.0	0.0	0.0	0.3
Cl···H	0.0	0.0	0.0	0.0	2.9

Table S4. MIC values (µg/mL) of controls towards *S. aureus* and *E. coli* along with their selectivity index.

Controls	***S. aureus (µg/mL)***	***E. coli (µg/mL)***	**Selectivity index (*E. coli : S. aureus*)**
Aniline	1000	200	0.2
OAP	10	500	50
OMe	100	1	0.01
NA	1000	500	0.5
CBH	10	100	10

Table S5. Data of Hemolytic assay on selected derivatives **3** and **5**.

Samples	**Mean optical density (577nm)**
Positive control	0.546
Negative control	0.202
3	0.186
5	0.190

Table S6. ADMET properties of the ligands **3** and **5**.

Molecule	**3**	**5**
Formula	C13H29N4O8	C13H27ClN5O8
MW	369.39	416.84
Heavy atoms	25	27
Aromatic heavy atoms	0	0
Fraction Csp3	0.92	0.85
Rotatable bonds	4	5
H-bond acceptors	11	11
H-bond donors	7	8
MR	80.51	87.22
TPSA	160.64	180.51
iLOGP	-5.18	-9.02
XLOGP3	-1.08	-0.93
WLOGP	0.51	0.38
MLOGP	-1.95	-1.32
Silicos-IT Log P	-5.86	-5.86
Consensus Log P	-2.71	-3.35
ESOL Log S	-1.19	-1.51

ESOL Solubility (mg/ml)	24.1	12.9
ESOL Solubility (mol/l)	0.0652	0.031
ESOL Class	Very soluble	Very soluble
Ali Log S	-1.8	-2.38
Ali Solubility (mg/ml)	5.8	1.75
Ali Solubility (mol/l)	0.0157	0.0042
Ali Class	Very soluble	Soluble
Silicos-IT LogSw	4.69	4.69
Silicos-IT Solubility (mg/ml)	18000000	20300000
Silicos-IT Solubility (mol/l)	48800	48800
Silicos-IT class	Soluble	Soluble
GI absorption	Low	Low
BBB permeant	No	No
Pgp substrate	Yes	Yes
CYP1A2 inhibitor	No	No
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	No	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
log Kp (cm/s)	-9.32	-9.5
Lipinski violations	2	2
Ghose violations	0	0
Veber violations	1	1
Egan violations	1	1
Muegge violations	3	3
Bioavailability Score	0.17	0.17
PAINS alerts	0	0
Brenk alerts	1	2
Leadlikeness violations	1	1
Synthetic Accessibility	4.37	4.72

Scheme S1. Light microscopic image of single-crystals for **1**–**5** showing variation is size, shape and color with slight modifications in the functional group of aniline/hydrazide.

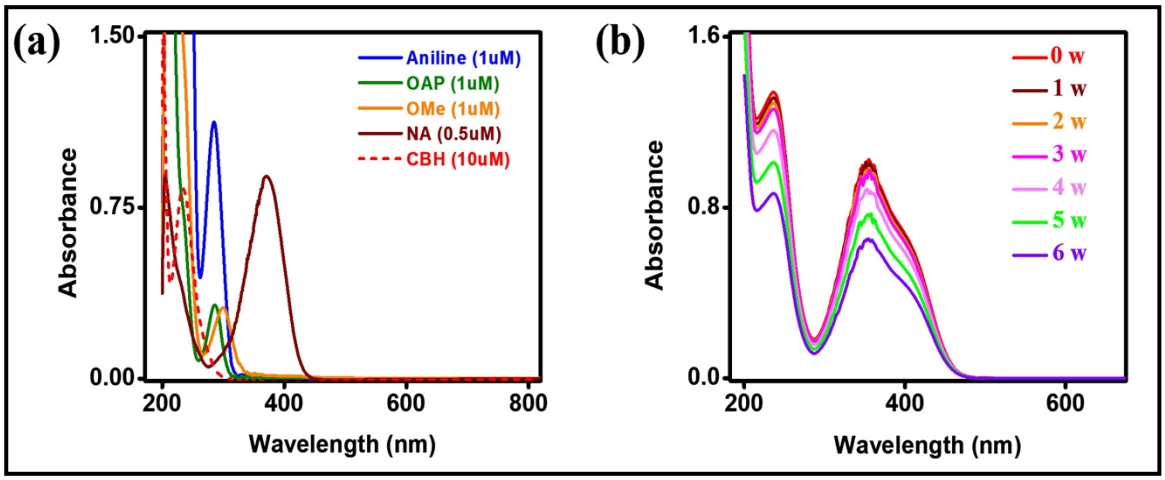

Figure S1. (a) UV-vis spectral overlay of negative controls for **1**–**5** in methanol: Aniline **(An)**, *ortho*-aminophenol (**OAP**), 4-Methoxyaniline (**OMe**), 4-Nitroaniline (**NA**), 4-Chloroenzhydrazide (**CBH**) respectively. λ_{max} = 285 nm (An), 286 nm (OAP), 300 nm (OMe), 371 nm (NA), 233 nm (CBH). (b) Representative stability assessment of derivative **5** by measurement of UV-vis spectra of 0.02 mM in H_2O over a period of 6 weeks (w). This data shows that our picrate are fairly stable upto 3 weeks in aqueous solution at room temperature.

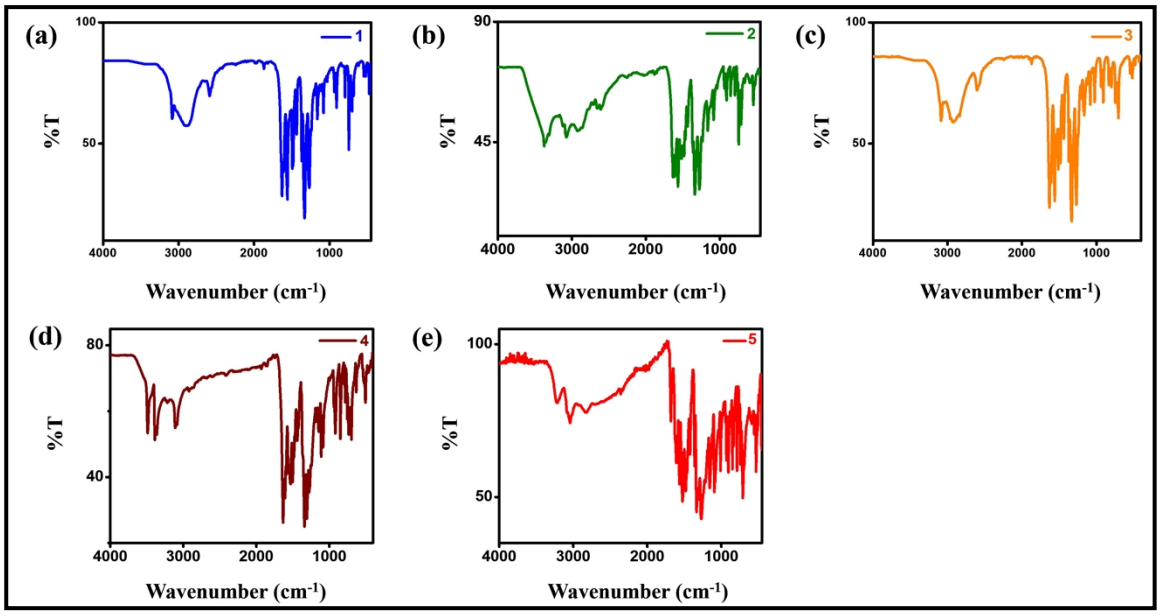

Figure S2. FT-IR spectra of derivatives **1-5** as KBr pellet**:** (a) **1** (b) **2** (c) **3** (d) **4** (e) **5.**

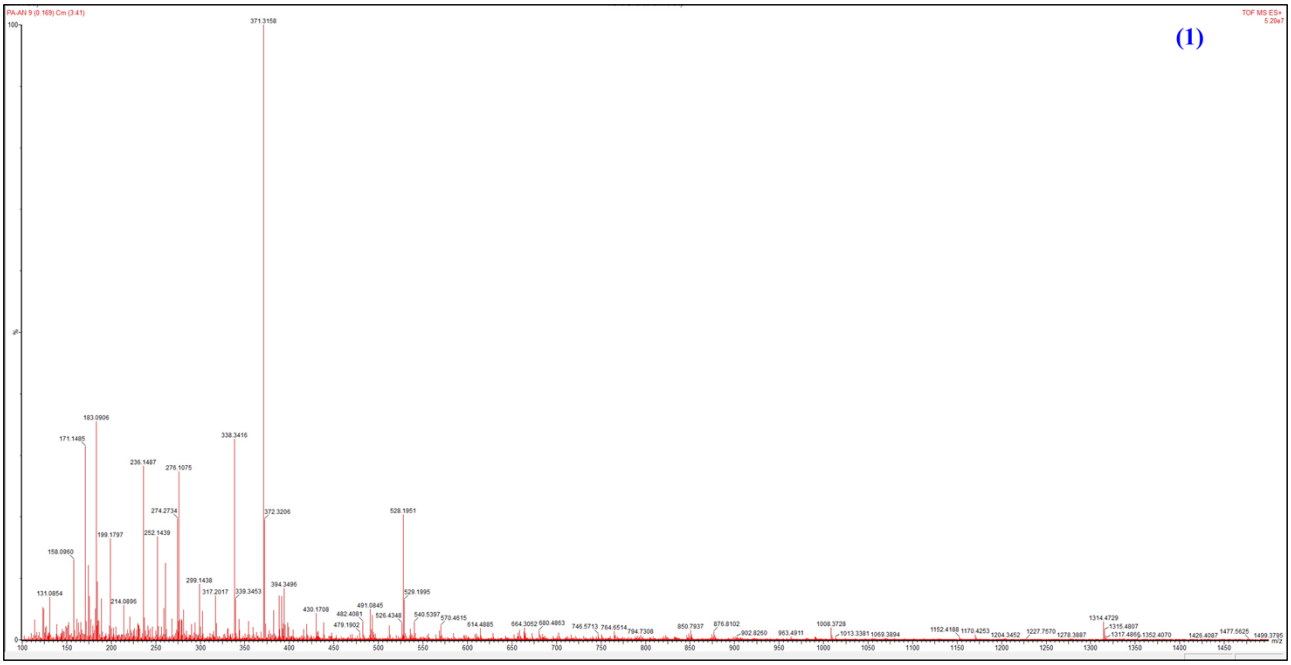

Figure S3. HRMS (ESI-TOF) spectrum of derivative **1**.

Figure S4. HRMS (ESI-TOF) spectrum of derivative **2**.

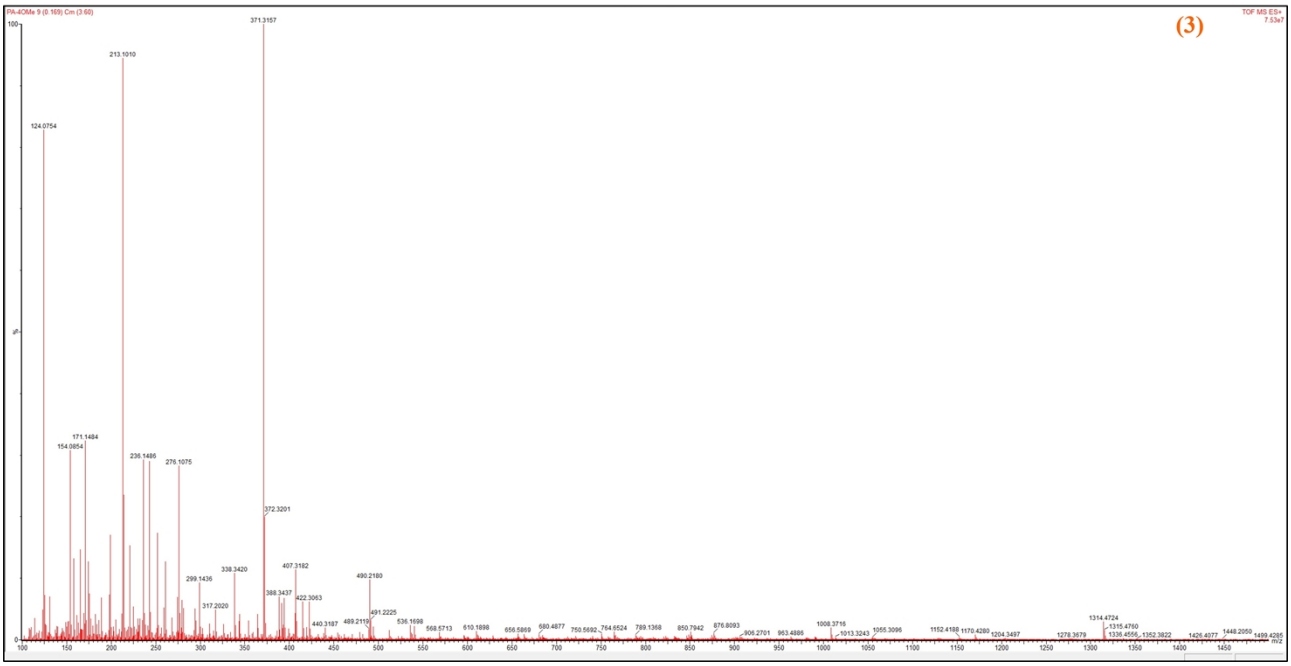

Figure S5. HRMS (ESI-TOF) spectrum of derivative **3**.

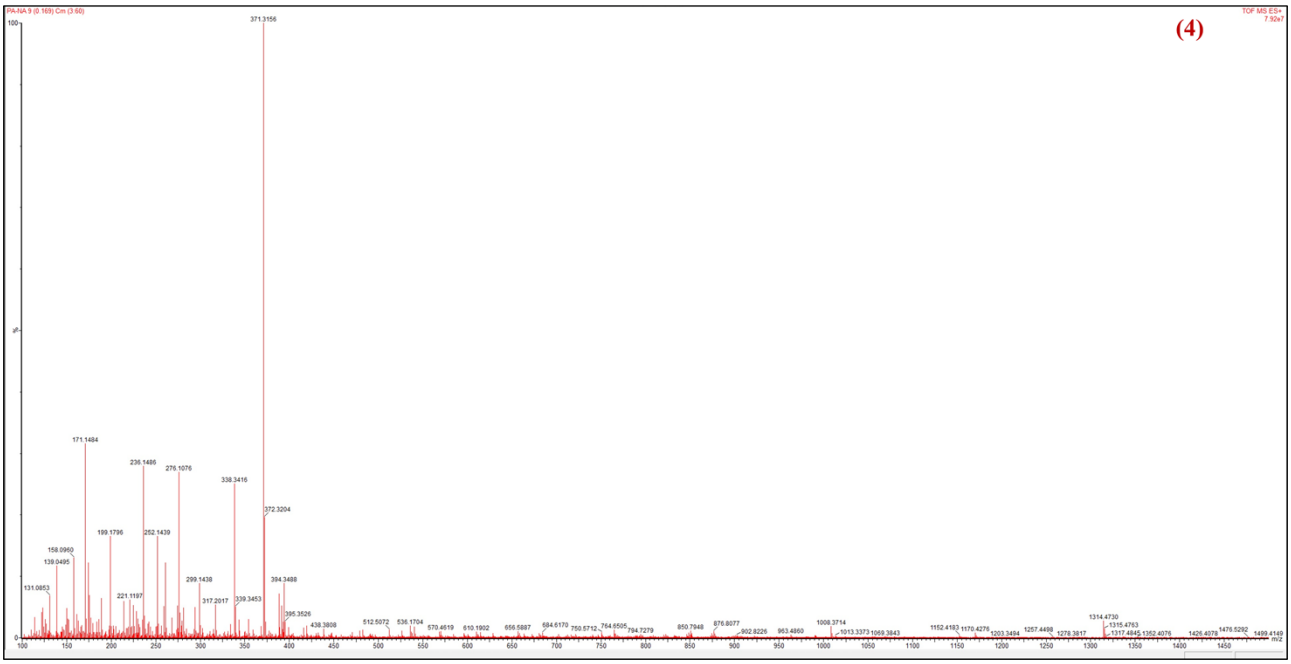

Figure S6. HRMS (ESI-TOF) spectrum of derivative **4**.

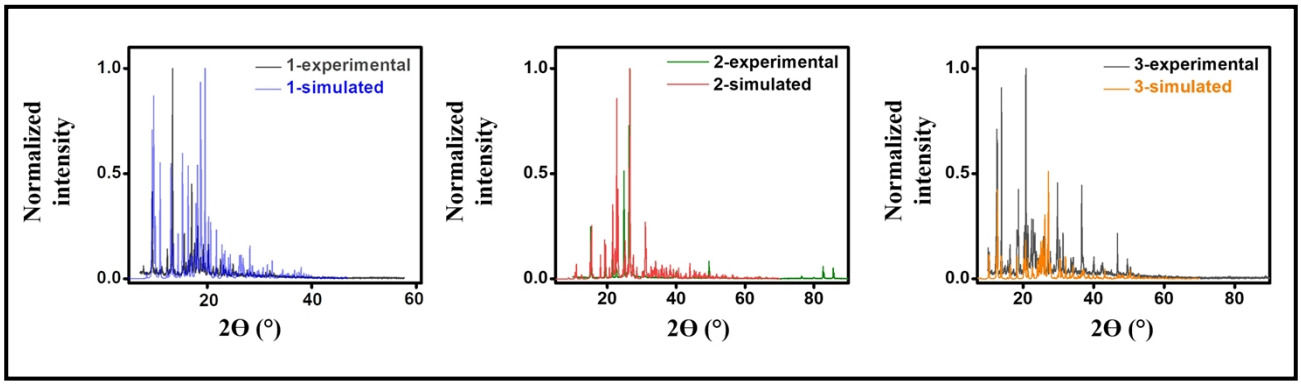

Figure S7. XRPD of **1-3** (left to right). Overlay of simulated and experimental powder pattern shows bulk phase purity of all compounds studied in this work.

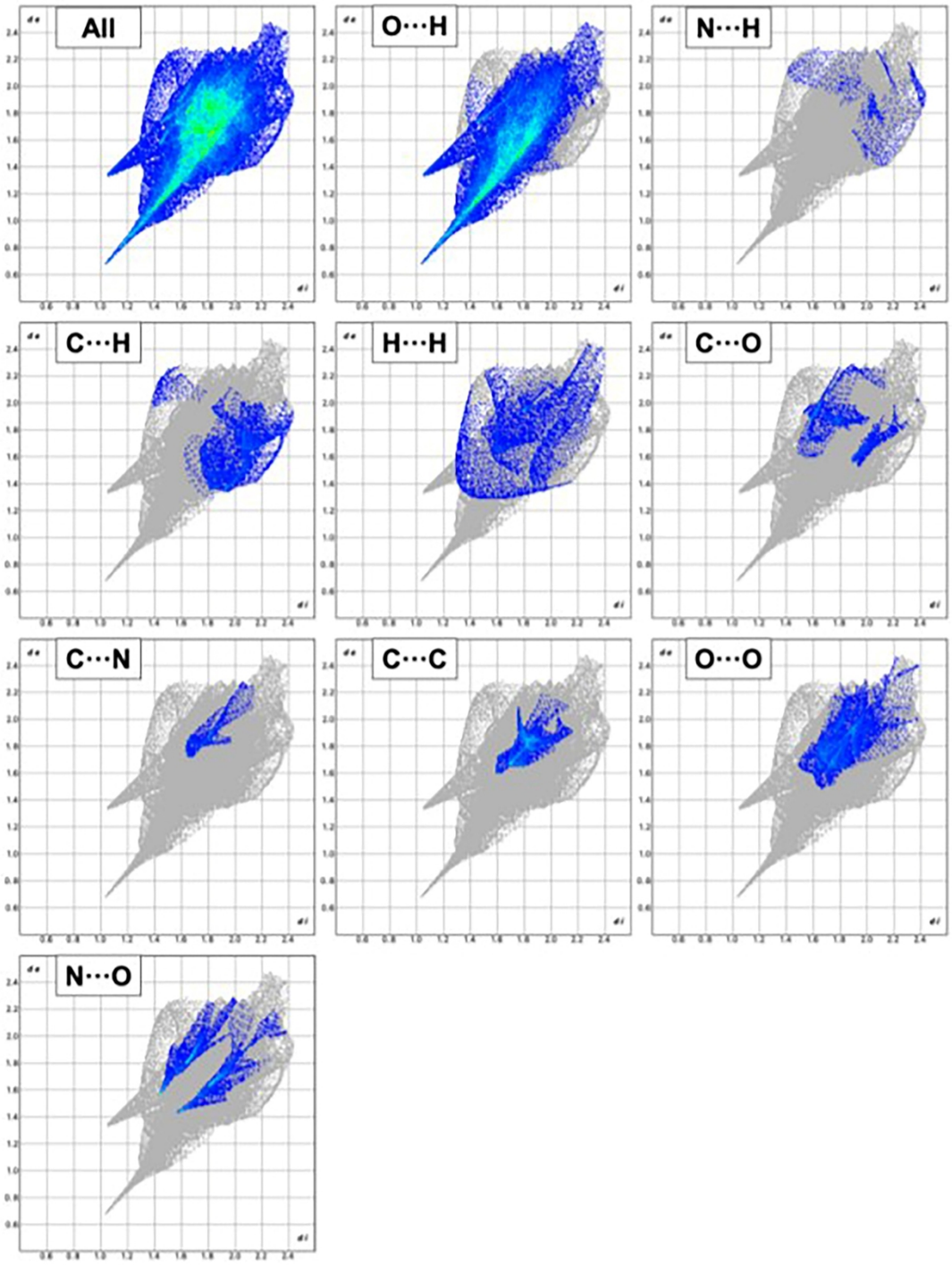

Figure S8. Fingerprint plots of derivative **1**.

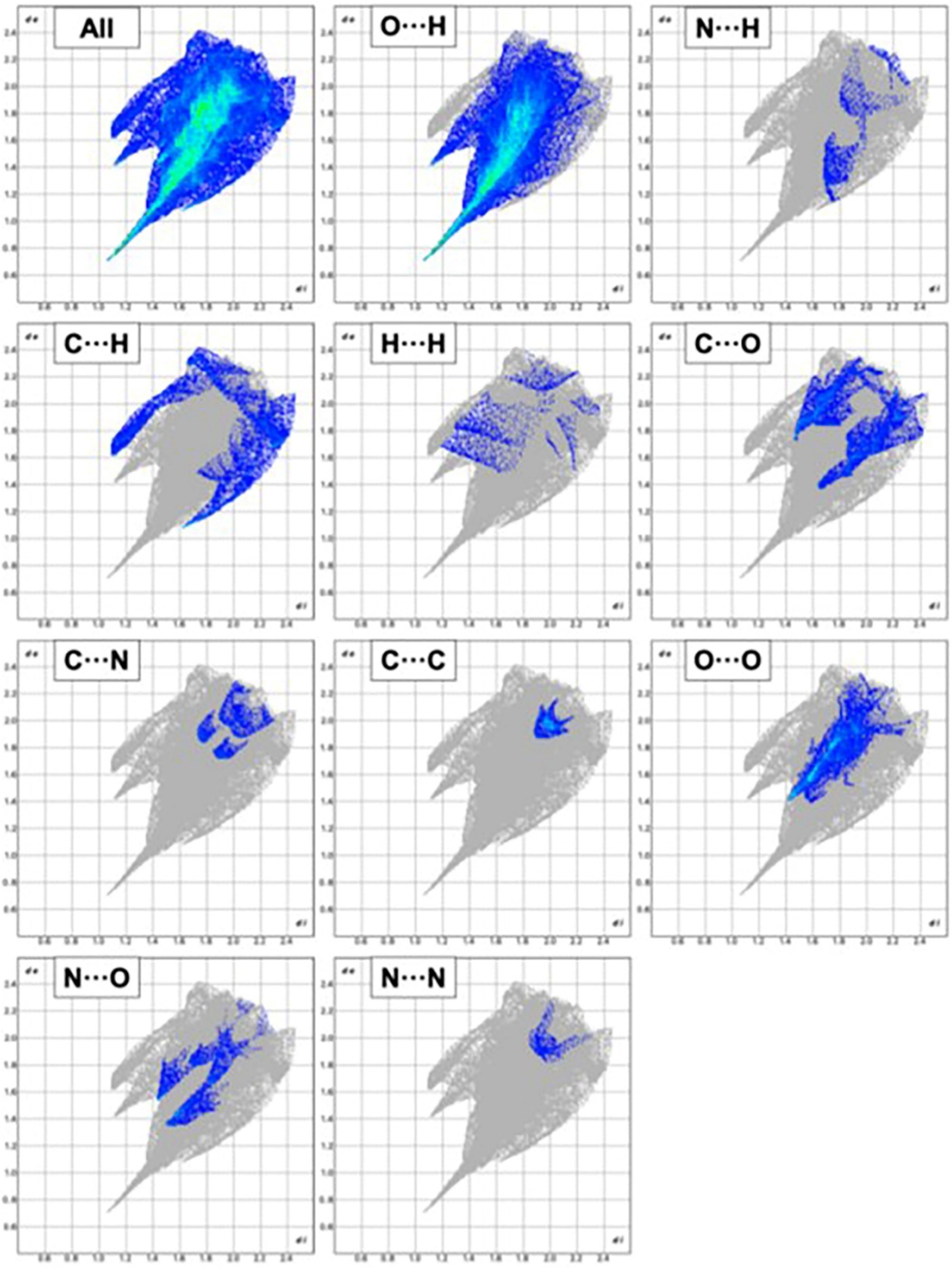

Figure S9. Fingerprint plots of derivative **2**.

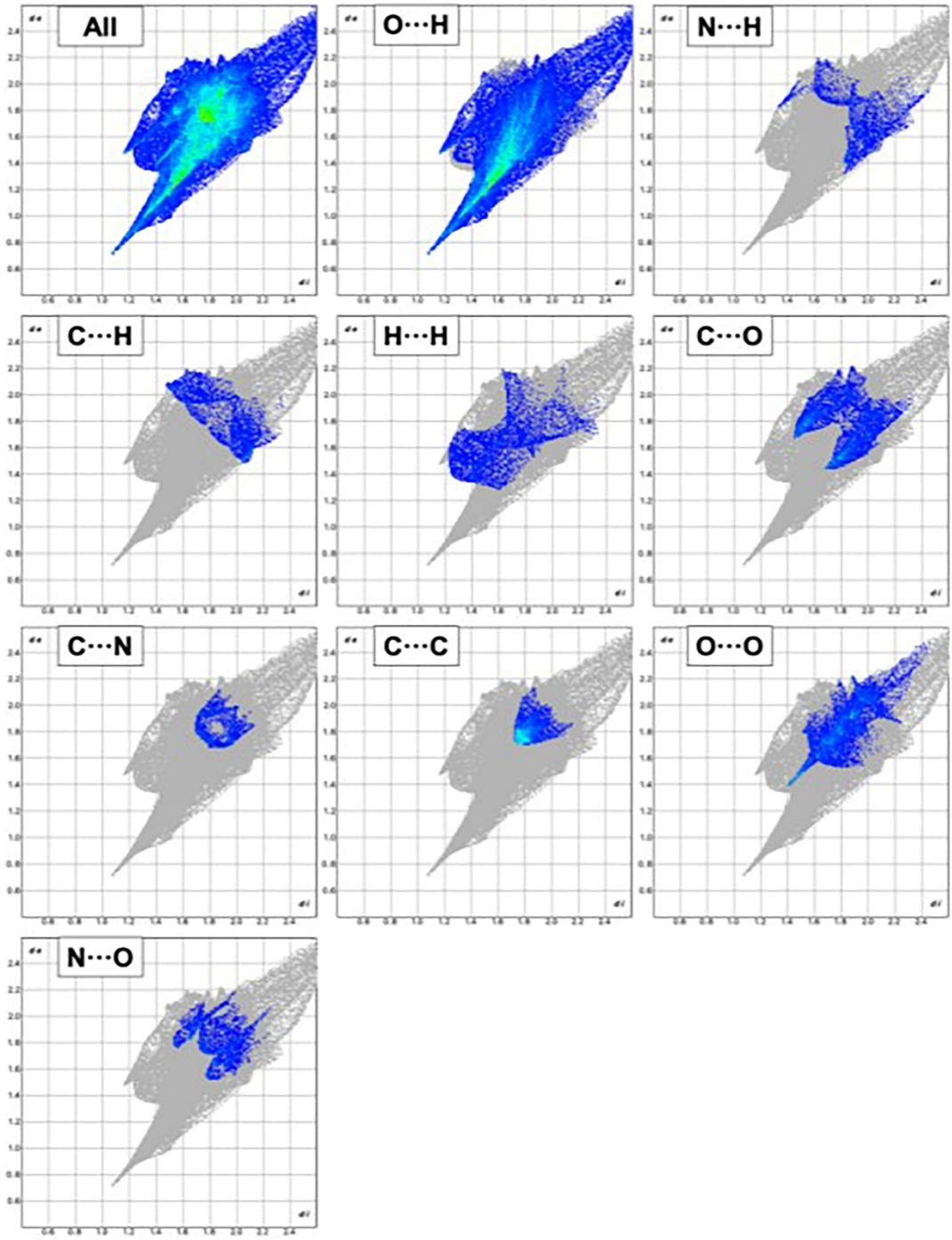

Figure S10. Fingerprint plots of derivative **3**.

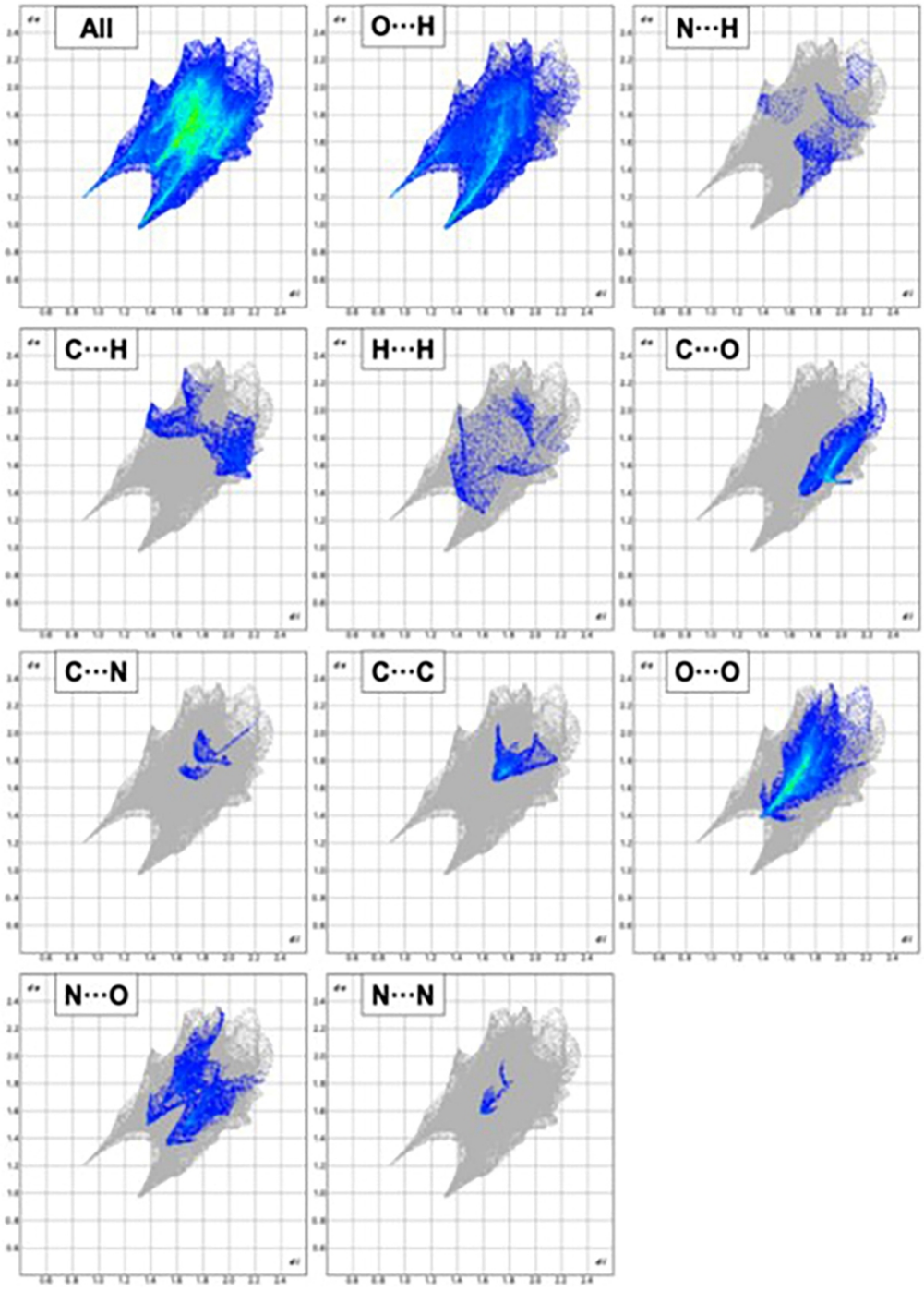

Figure S11. Fingerprint plots of derivative **4**.

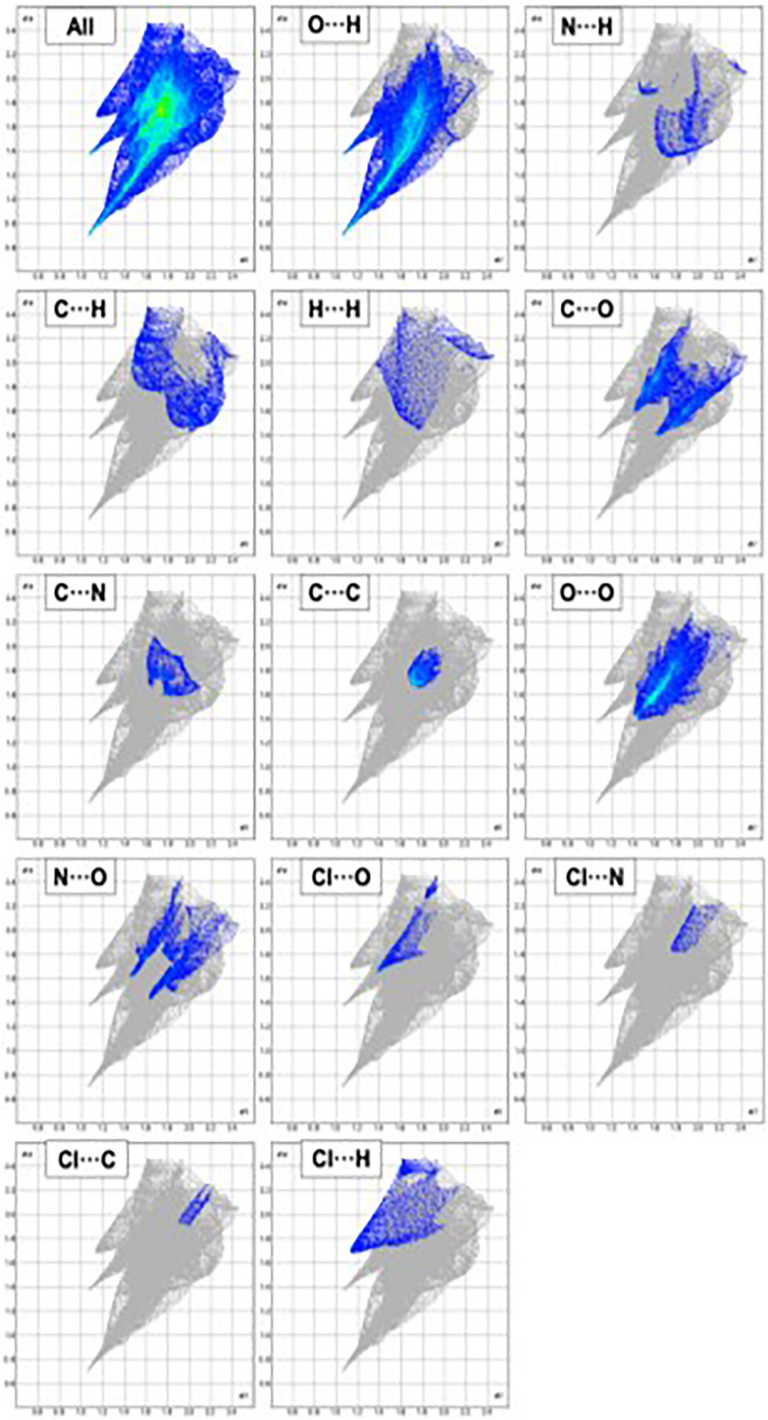

Figure S12. Fingerprint plots of derivative **5**.

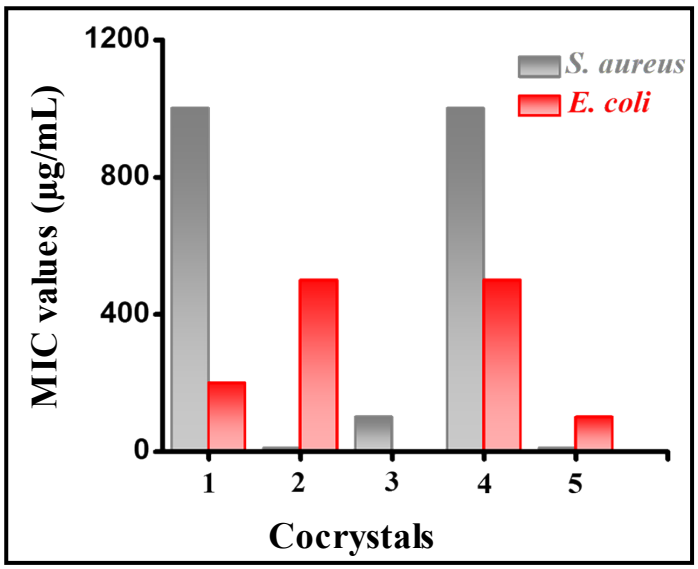

Figure S13. MIC (µg/mL) of controls of **1-5**: An, OAP, OMe, NA, CBH respectively. *S.aureus* data is in grey and *E. coli* in red color.

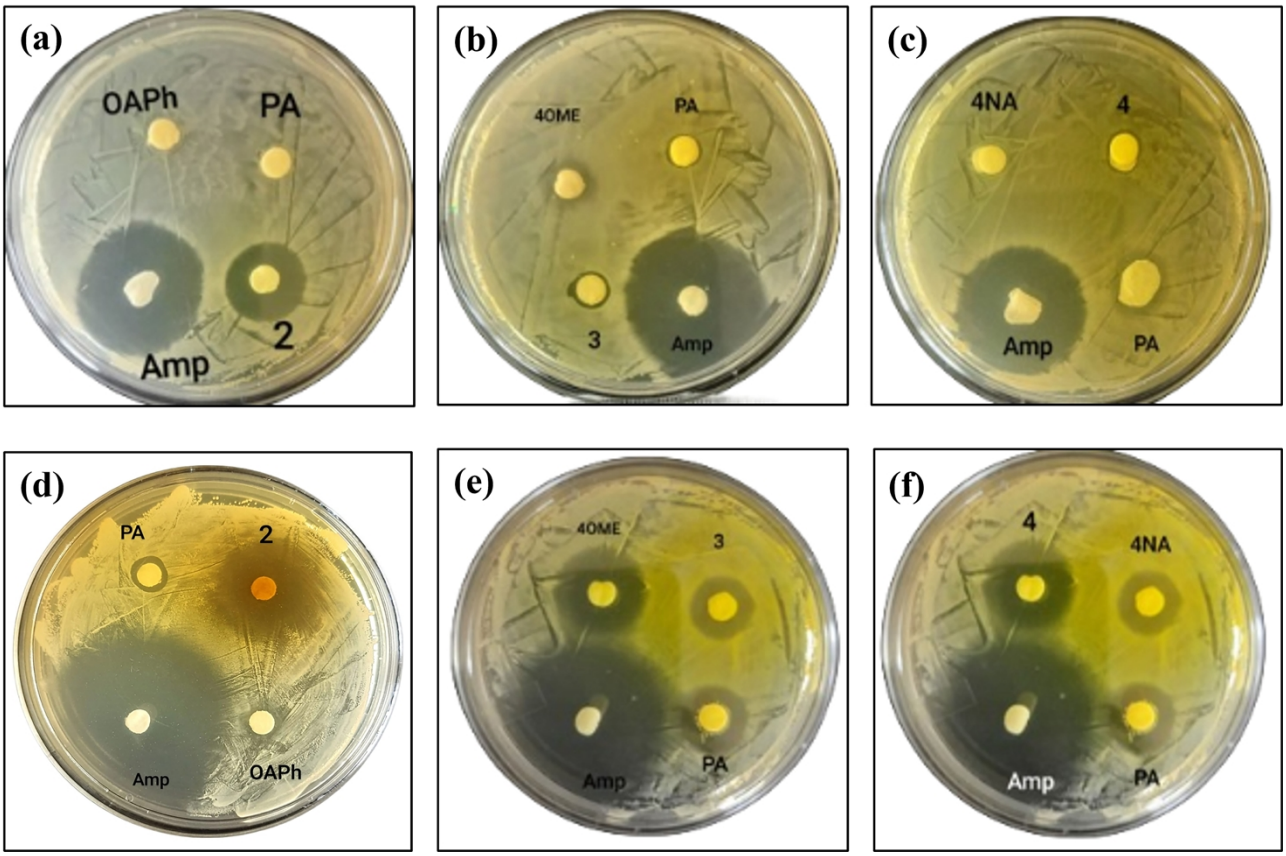

Figure S14. Images of zone of inhibition for picrate derivatives **2-4** on *E. coli* (top) and *S. aureus* (bottom) shown along with their positive and negative controls. (a, d): derivative **2**; (b, e): derivative **3**; (c, f): derivative **4**. Positive control: Ampicillin; Negative control: OAP (for **2**), OMe (for **3**) and NA (for **4**). MIC concentrations of **2-4** has been used and working concentration of Ampicillin.

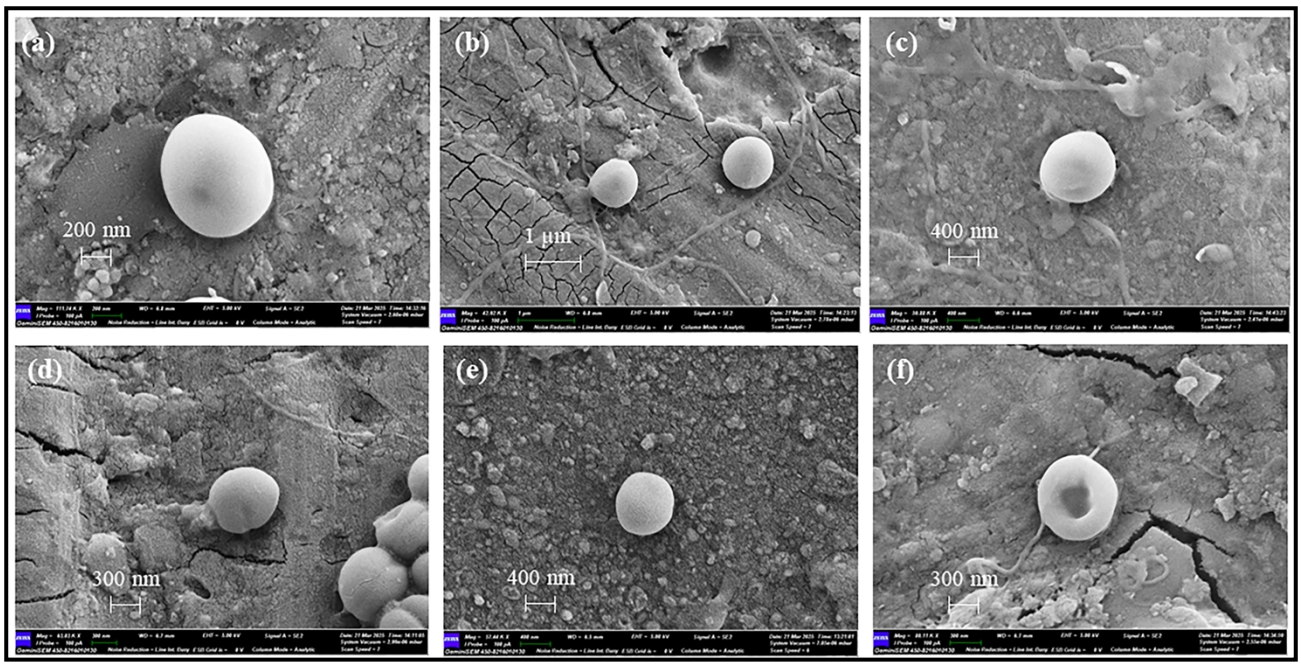

Figure S15. FE-SEM images for zoomed-in view of *S. aureus* cells (a) before and (b-f) after treatment with **1-5** for 24 h at MIC concentrations.

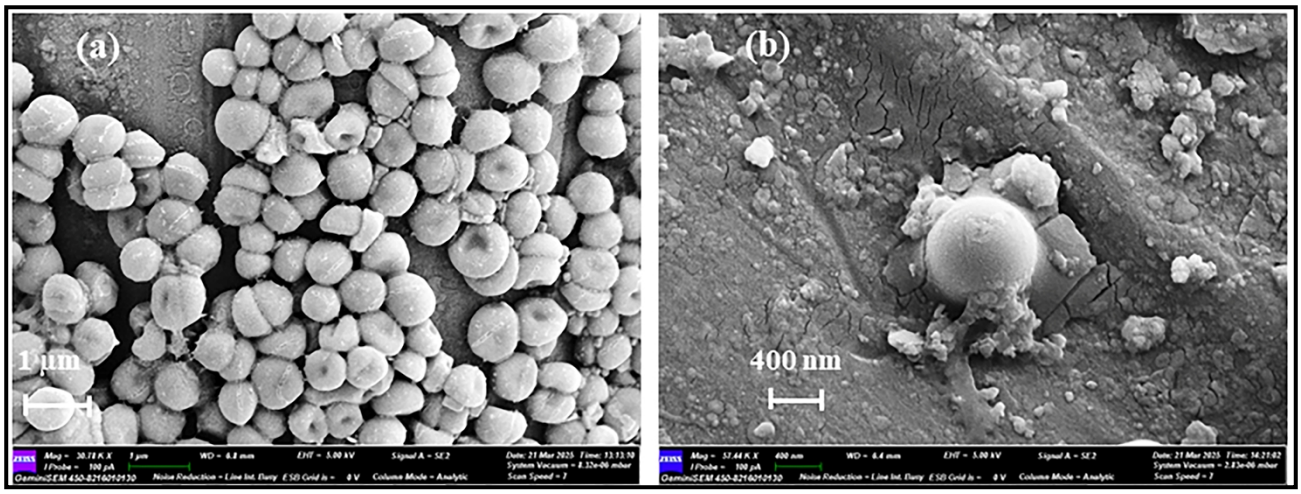

Figure S16. a, FE-SEM images for *S. aureus* cells after treatment with **Ampicillin** for 24 h at working concentrations. **b** shows a zoom-in view of a single SA96 cell.

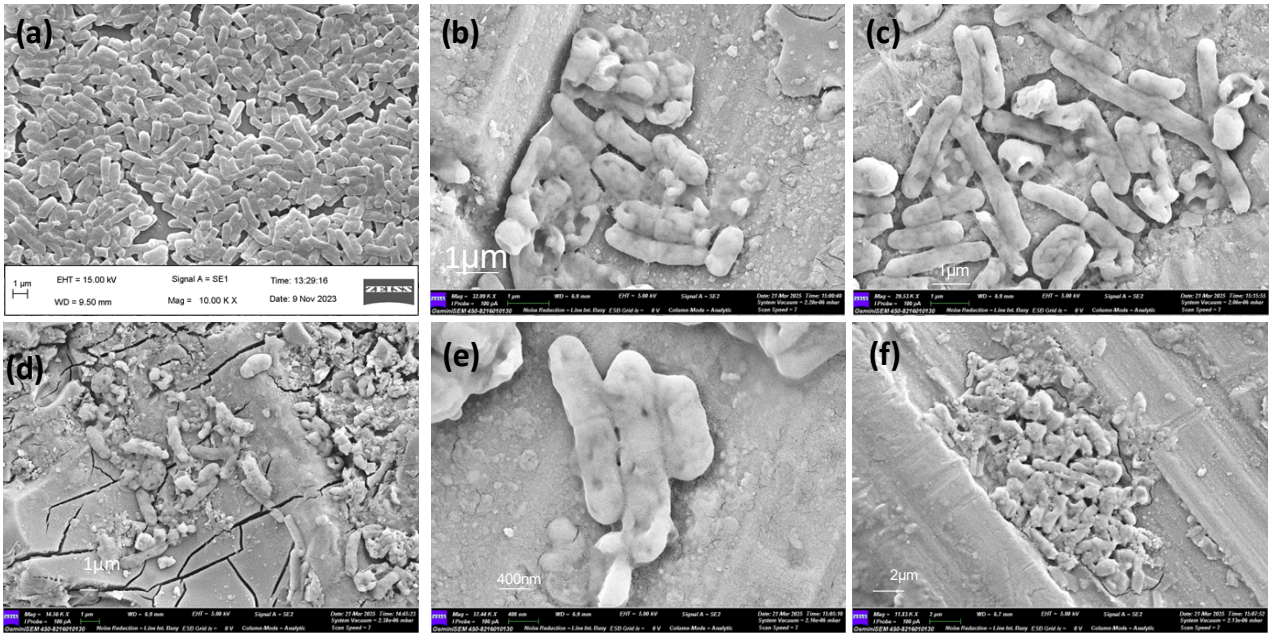

Figure S17. FE-SEM images of *E. coli* cells (a) before and (b-f) after treatment with **1-5** for 24 h at MIC concentrations. Scale bars are given on each s.

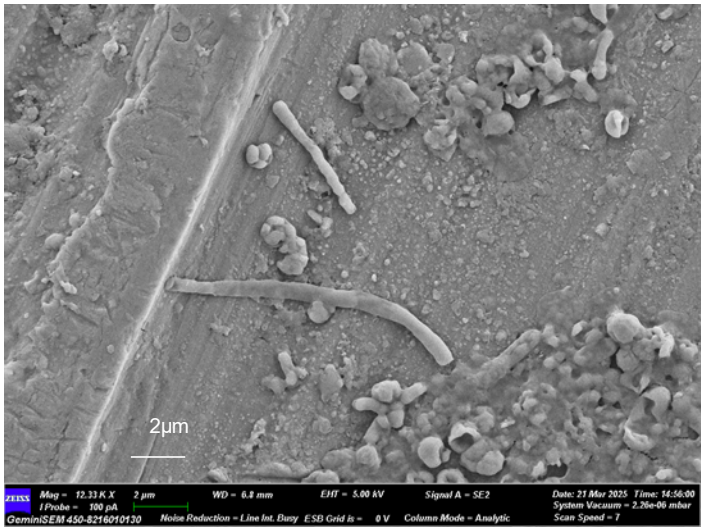

Figure S18. FE-SEM images for *E. coli* cells after treatment with **Ampicillin** for 24 h at working concentrations. Scale bar: 2µm.