Table S1 Data collection and refinement statistics for apo-form, **ALD1**(meta-aldehyde benzimidamide) and **ALD2**(para-aldehyde benzimidamide) complexes.

Compound #	**Apo-form**	**ALD1**	**ALD2**
Data collection			
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions			
a, *b*, *c* (Å)	54.5, 58.5, 66.6	54.6, 58.4, 66.6	54.4, 58.5, 66.5
Resolution (Å)	50-1.75 (1.81-1.75)	50-1.75 (1.81-1.75)	50-1.75 (1.81-1.75)
R_{merge}	0.050 (0.092)	0.033 (0.073)	0.082 (0.207)
$I / \sigma I$	33.4 (18.3)	37.2 (14.1)	19.4 (6.3)
Completeness (%)	97.7 (95.2)	99.2 (94.9)	99.4 (93.6)
Redundancy	7.1 (7.2)	5.5 (4.0)	6.7 (4.7)
Refinement			
Resolution (Å)	20.0-1.75	20.0-1.75	20.0-1.75
No. reflections	20,435	20,734	20,670
R_{work} / R_{free}	0.142 / 0.170	0.145 / 0.176	0.148 / 0.178
No. atoms			
Protein	1629	1629	1629
Ligand/ion	29	23	23
Water	412	406	389
B-factors			
Protein	9.0	9.1	11.6
Ligand/ion	32.9	20.8	23.9
Water	27.1	26.0	27.8
R.m.s. deviations			
Bond lengths (Å)	0.006	0.010	0.010
Bond angles (°)	1.1	1.2	1.2

Table S2 Data collection and refinement statistics for crystallographic screening of tuning molecules.

Compound #	**ALD2-OXA4**	**ALD2-OXA9**	**ALD2-OXA13**	**ALD2-OXA14**	**ALD2-OXA16**
Data collection					
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions					
a, *b*, *c* (Å)	54.4, 58.5, 66. 6	53.7, 56.9, 66.1	54.4, 58.5, 66.5	54.3, 58.5, 66.6	54.1, 56.8, 66.1
Resolution (Å)	50-1.75 (1.81-1.75)	50-1.75 (1.81-1.75	50-1.81 (1.87-1.81)	50-1.80 (1.86-1.80)	50-1.75 (1.81-1.75)
R_{merge}	0.059 (0.148)	0.034(0.092)	0.026 (0.057)	0.034 (0.071)	0.081 (0.289)
$I / \sigma I$	25.6 (8.1)	39.8 (11.7)	41.6 (18.9)	43.5 (21.4)	15.4 (3.6)
Completeness (%)	99.9 (99.3)	99.9 (98.9)	95.1 (91.7)	97.2 (94.2)	98.7 (91.5)
Redundancy	6.8 (4.9)	5.6 (4.0)	4.9 (4.8)	7.2 (7.0)	5.5 (3.8)
Refinement					
Resolution (Å)	20.0-1.75	20.0-1.75	20.0-1.81	20.0-1.80	20.0-1.75
No. reflections	20,739	19,853	17,996	18,658	19,644
R_{work} / R_{free}	0.142 / 0.168	0.156 / 0.183	0.140 / 0.172	0.150 / 0.185	0.164 / 0.193
No. atoms					
Protein	1629	1629	1629	1629	1629
Ligand/ion	30	35	26	26	19
Water	406	241	414	303	270
B-factors					
Protein	7.9	13.1	10.0	8.8	16.0
Ligand/ion	24.2	28.1	21.6	23.0	23.8
Water	25.7	28.1	28.2	22.4	31.7
R.m.s. deviations					
Bond lengths (Å)	0.010	0.010	0.011	0.011	0.012
Bond angles (°)	1.2	1.3	1.2	1.2	1.3

Table S2 continued.

Compound #	**ALD2-HYD6**
Data collection	
Space group	$P2_12_12_1$
Cell dimensions	
a, *b*, *c* (Å)	54.6, 58.4, 66.6
Resolution (Å)	50-1.80 (1.86-1.80)
R_{merge}	0.043 (0.070)
$I / \sigma I$	37.9 (21.0)
Completeness (%)	97.4 (92.0)
Redundancy	7.1 (6.5)
Refinement	
Resolution (Å)	20.0-1.80
No. reflections	19,445
R_{work} / R_{free}	0.144 / 0.183
No. atoms	
Protein	1629
Ligand/ion	37
Water	379
B-factors	
Protein	14.9
Ligand/ion	30.3
Water	29.8
R.m.s. deviations	
Bond lengths (Å)	0.011
Bond angles (°)	1.2

Table S3 Data collection and refinement statistics for pre-synthesized product complexes.

Compound #	**Pre-synthesized ALD2-OXA9**	**Pre-synthesized ALD2-HYD6**
Data collection		
Space group	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions		
a, *b*, *c* (Å)	54.2, 58.3, 66.8	54.5, 58.4, 66.6
Resolution (Å)	50-1.75 (1.81-1.75)	50-1.78 (1.84-1.78)
R_{merge}	0.071 (0.162)	0.045 (0.065)
$I / \sigma I$	20.9 (6.4)	34.3 (23.3)
Completeness (%)	99.9 (98.8)	97.8 (92.4)
Redundancy	5.4 (3.7)	7.1 (6.5)
Refinement		
Resolution (Å)	20-1.75 (1.81-1.75)	20-1.78 (1.84-1.78)
No. reflections	20,620	19,450
R_{work} / R_{free}	15.2 / 17.9	14.4 / 18.4
No. atoms		
Protein	1629	1629
Ligand/ion	33	27
Water	247	390
B-factors		
Protein	11.9	7.1
Ligand/ion	26.0	32.4
Water	26.4	24.2
R.m.s. deviations		
Bond lengths (Å)	0.010	0.010
Bond angles (°)	1.2	1.2

Table S4 Data collection and refinement statistics for time-resolved crystallographic study of **ALD2-OXA9**.

Reaction Time #	**5 seconds**	**15 seconds**	**30 seconds**	**45 seconds**
Data collection				
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions				
a, *b*, *c* (Å)	54.4, 58.2, 66.4	54.0, 56.9, 66.1	53.8, 56.8, 66.1	53.7, 56.9, 66.1
Resolution (Å)	50-1.75 (1.81-1.75)	50-1.75 (1.81-1.75)	50-1.75 (1.81-1.75)	50-1.75 (1.81-1.75
R_{merge}	0.073 (0.225)	0.034 (0.094)	0.036 (0.118)	0.034 (0.092)
$I / \sigma I$	19.6 (4.4)	40.8 (11.8)	36.2 (8.6)	39.8 (11.7)
Completeness (%)	99.4 (93.9)	99.5 (94.9)	99.1 (94.3)	99.9 (98.9)
Redundancy	5.4 (3.7)	5.7 (4.2)	5.7 (4.2)	5.6 (4.0)
Refinement				
Resolution (Å)	20.0-1.75	20.0-1.75	20.0-1.75	20.0-1.75
No. reflections	20,532	19,866	19,671	19,853
R_{work} / R_{free}	15.3 / 18.8	15.6 / 18.3	15.3 / 18.5	0.156 / 0.183
No. atoms				
Protein	1629	1629	1629	1629
Ligand/ion	23	29	41	35
Water	323	309	258	241
B-factors				
Protein	13.5	12.6	13.0	13.1
Ligand/ion	25.1	23.1	31.9	28.1
Water	29.1	29.2	30.0	28.1
R.m.s. deviations				
Bond lengths (Å)	0.011	0.011	0.011	0.010
Bond angles (°)	1.2	1.3	1.3	1.3

Table S5 Data collection and refinement statistics for time-resolved crystallographic study of **ALD2-HYD6**.

Reaction Time #	**5 minutes**	**30 minutes**	**4 hours**	**8 hours**
Data collection				
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions				
a, *b*, *c* (Å)	54.5, 58.3, 66.6	54.5, 58.3, 66. 6	54.4, 58.3, 66.5	54.6, 58.4, 66.6
Resolution (Å)	50-1.75 (1.81-1.75)	50-1.75 (1.81-1.75)	50-1.80 (1.86-1.80)	50-1.80 (1.86-1.80)
R_{merge}	0.030 (0.072)	0.045 (0.131)	0.041 (0.086)	0.043 (0.070)
$I / \sigma I$	31.5 (8.9)	29.3 (8.6)	29.5 (11.9)	37.9 (21.0)
Completeness (%)	99.7 (97.6)	98.9 (90.8)	99.8 (98.5)	97.4 (92.0)
Redundancy	4.1 (2.9)	5.5 (4.2)	5.6 (5.4)	7.1 (6.5)
Refinement				
Resolution (Å)	20-1.75	20-1.75	20.0-1.80	20.0-1.80
No. reflections	20,825	20,574	19,217	19,445
R_{work} / R_{free}	15.5 / 19.3	15.6 / 18.8	14.3 / 19.3	0.144 / 0.183
No. atoms				
Protein	1629	1629	1629	1629
Ligand/ion	32	43	37	37
Water	358	327	424	379
B-factors				
Protein	10.1	10.7	7.9	14.9
Ligand/ion	34.3	30.2	25.2	30.3
Water	26.6	25.2	25.8	29.8
R.m.s. deviations				
Bond lengths (Å)	0.011	0.011	0.011	0.011
Bond angles (°)	1.2	1.2	1.2	1.2

Table S6 Data collection and refinement statistics for **ALD2-aniline**

Compound #	**ALD2-aniline**
Data collection	
Space group	$P2_12_12_1$
Cell dimensions	
a, *b*, *c* (Å)	54.3, 58.4, 66.3
Resolution (Å)	50-1.4 (1.45-1.40)
R_{merge}	0.039 (0.069)
$I / \sigma I$	35.9 (23.2)
Completeness (%)	97.0 (98.6)
Redundancy	6.9 (6.8)
Refinement	
Resolution (Å)	20-1.4
No. reflections	37,897
R_{work} / R_{free}	16.5 / 18.7
No. atoms	
Protein	1629
Ligand/ion	29
Water	426
B-factors	
Protein	6.6
Ligand/ion	17.1
Water	25.9
R.m.s. deviations	
Bond lengths (Å)	0.007
Bond angles (°)	1.1

Table S7 Data collection and refinement statistics for **ALD2-OXA9** complex selected from cocktail solution containing two tuning molcules (**OXA9** and **OXA16**)

Compound #	**ALD2-OXA9**
Data collection	
Space group	$P2_12_12_1$
Cell dimensions	
a, *b*, *c* (Å)	53.9, 56.9, 66.2
Resolution (Å)	50-1.85 (1.92-1.85)
R_{merge}	0.044 (0.112)
$I / \sigma I$	32.6 (12.3)
Completeness (%)	95.6 (92.5)
Redundancy	6.1 (6.2)
Refinement	
Resolution (Å)	20-1.85 (1.92-1.85)
No. reflections	16,161
R_{work} / R_{free}	15.2 / 19.0
No. atoms	
Protein	1,629
Ligand/ion	17
Water	202
B-factors	
Protein	13.6
Ligand/ion	24.4
Water	27.1
R.m.s. deviations	
Bond lengths (Å)	0.011
Bond angles (°)	1.3