Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

SUPPORTING INFORMATION

Discovery of Novel BET Inhibitors by Drug Repurposing of Nitroxoline and Its Analogues

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Contents

Table S1. Scores, ranking and bioactivity of compounds selected from virtual screening.

CAS	BRD4LGR Score	BRD4LGR Rank	BRD4LGR LE[a]	Glide Score	Glide Rank	Inhibition% @50μM	Inhibition% @5μM
112809-51-5	0.97	1	3.39	-6.49	66	16.66±1.41	3.14±1.04
50-28-2	0.95	3	3.49	-5.88	149	25.35±3.43	9.64±1.13
100-51-6[b]	0.94	5	8.66	-5.92	142	20.09±2.92	8.62±1.31
60719-84-8	0.86	14	4.59	-7.23	11	41.53±6.45	139.32±3.15
89-83-8	0.85	17	5.64	-6.56	58	18.58±3.12	7.12±2.75
130-16-5	0.84	18	4.69	-6.79	36	90.17±2.38	36.43±1.57
482-36-0	0.82	20	1.77	-6.84	33	31.03±5.40	5.71±1.70
124750-99-8	0.81	21	1.93	-5.91	144	24.42±0.93	1.54±2.43
2216-51-5	0.80	25	5.12	-6.55	60	12.76±0.62	0.93±1.68
67227-57-0	0.80	26	2.60	-6.66	46	25.66±5.85	9.19±4.21
97-53-0	0.78	29	4.76	-6.08	119	5.86±1.65	0.87±1.32
92-61-5	0.73	37	3.80	-6.83	34	37.60±6.53	19.03±1.72
5728-52-9	0.72	39	3.40	-5.83	159	21.49±2.76	7.04±3.66
5104-49-4	0.70	41	2.89	-6.48	68	12.09±1.68	8.60±0.99
25812-30-0	0.69	42	2.78	-5.28	243	17.52±1.59	9.27±4.97
1197-18-8	0.69	46	4.40	-6.35	82	8.42±3.63	6.79±3.05
100643-71-8	0.68	48	2.18	-6.15	113	28.20±0.40	10.33±1.13
42200-33-9	0.67	52	2.16	-5.53	203	19.97±1.48	14.12±2.50
50-91-9	0.63	62	2.57	-5.81	167	17.67±2.04	8.81±3.03
138982-67-9	0.58	75	1.41	-5.78	168	23.59±1.94	9.57±1.87
51-30-9	0.57	81	2.69	-5.97	135	18.45±1.11	12.43±0.46
73-22-3	0.57	82	2.79	-6.36	81	4.58±2.39	2.58±1.06
95-25-0	0.55	88	3.25	-6.61	52	13.60±1.37	3.68±0.01
532-03-6	0.53	97	2.21	-5.33	234	12.64±0.22	2.09±1.07
738-70-5	0.50	107	1.73	-6.07	124	30.71±0.60	10.00±2.82
637-07-0	0.49	112	2.02	-6.57	56	6.48±1.09	3.02±1.82
93106-60-6	0.46	133	1.27	-7.00	21	2.17±1.63	-3.51±2.15
121-33-5	0.44	144	2.89	-6.43	74	-3.99±1.04	-13.90±2.51
723-46-6	0.40	161	1.58	-5.21	252	17.73±1.73	5.35±1.34
75706-12-6	0.37	169	1.38	-6.33	84	-15.13±1.76	-20.16±1.60
22199-08-2[c]	0.37	171	1.48	-5.13	264	6.15±1.49	2.01±0.95

[a] Ligand efficiency was calculated as LE = BRD4LGR score/molecular weight*1000.

[b] Benzyl alcohol is used as a bacteriostatic preservative at low concentration in intravenous medications, which might be not safe at higher dose.

[c] Silver sulfadiazine is only for external use, which might be not safe for internal use.

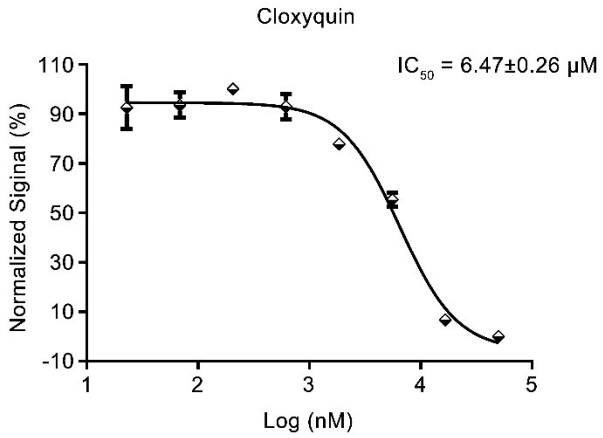

Figure S1. Dose-response behaviors of cloxyquin.

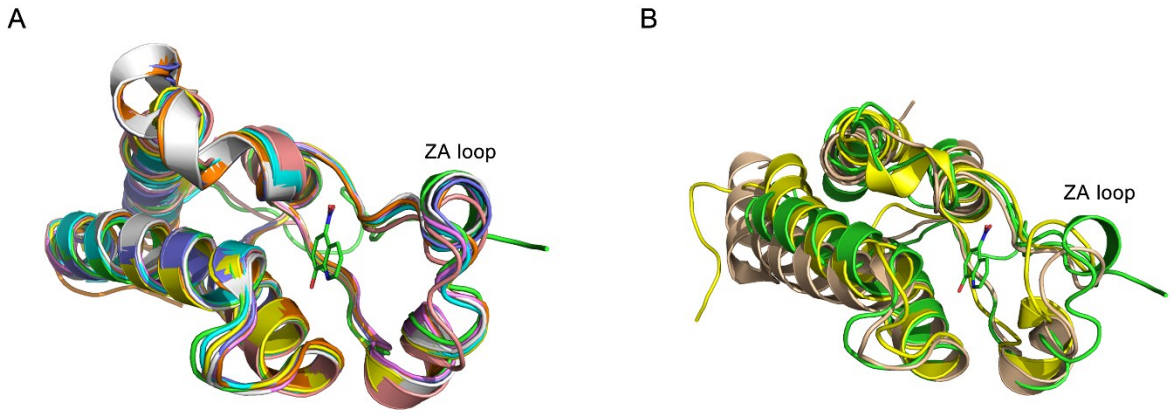

Figure S2. (A) Crystal structures of BET family (PDB IDs: 4ALG, salmon, 2DVV, slate, 3S91, yellow, 3S92, violent, 2WP1, organge, 2WP2, cyan, 2YEM, white) aligned to the complex of BRD4_BD1-nitroxoline(green). (B) Crystal structures of BRD7 (PDB ID: 2I7K, yellow) and BRD9 (PDB ID: 4Z6H, wheat) aligned to the complex of BRD4_BD1-nitroxoline(green).

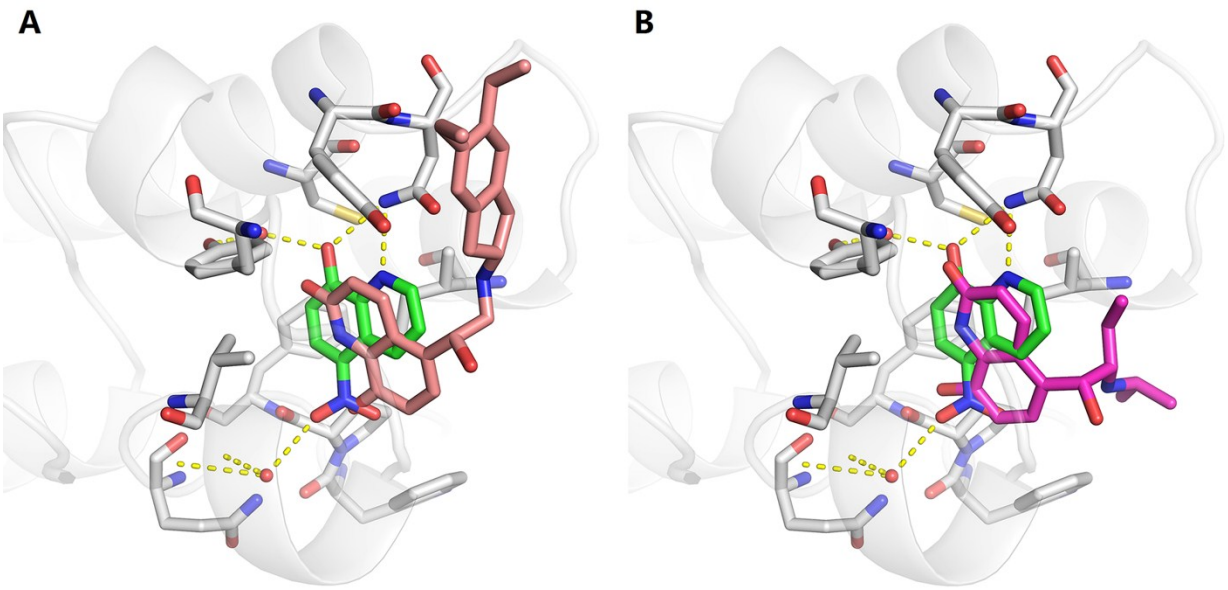

Figure S3. Predicted binding patterns of indacaterol (A) and procaterol (B), together with nitroxoine for comparison. nitroxoline was colored in green.

4. Table S2. Diffraction data statistics.

Dataset	Nitroxoline
Wavelength	0.9785
Resolution range	40.51 - 1.912 (1.98 - 1.912)
Space group	P 21 21 21
Unit cell	32.892 47.298 78.5 90 90 90
Total reflections	127742 (12905)
Unique reflections	9973 (983)
Multiplicity	12.8 (13.1)
Completeness (%)	1.00 (1.00)

Mean I/sigma(I)	36.87 (15.56)
Wilson B-factor	23.86
R-merge	0.04772 (0.1376)
R-meas	0.04981 (0.1433)
CC1/2	0.999 (0.998)
CC*	1 (0.999)
Reflections used in refinement	9966 (982)
Reflections used for R-free	997 (99)
R-work	0.1824 (0.2032)
R-free	0.2252 (0.2669)
CC(work)	0.963 (0.963)
CC(free)	0.959 (0.880)
Number of non-hydrogen atoms	1149
macromolecules	1037
ligands	14
Protein residues	125
RMS(bonds)	0.006
RMS(angles)	0.8
Ramachandran favored (%)	99
Ramachandran allowed (%)	0.82
Ramachandran outliers (%)	0
Rotamer outliers (%)	0
Clashscore	2.39
Average B-factor	29.07
macromolecules	28.44
ligands	36.11

solvent	34.77