SUPPORTING INFORMATION

Glycosidase-targeting small molecules for biological and therapeutic applications

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Table S1. Summary of fluorescent probes (Abbreviation: S = Senescence).

Substance No	Target glycosidase	Cells	Absorption/emission wavelength (nm)	Ref.
1	β-Galactosidase	OVCAR-3 (Ovarian cancer)	450/550	34
2	β-Galactosidase	OVCAR-3 (Ovarian cancer)	490/640	35
3	β-Galactosidase	HEK293 (Kidney) SKOV-3 (Ovarian cancer)	465/676	40
4	β-Galactosidase	SKOV-3 (Ovarian cancer)	525/665	41
5	β-Galactosidase	SKOV-3 (Ovarian cancer) 4T1 (Breast cancer)	660/730	42
6	β-Galactosidase	OVCAR-3 (Ovarian cancer) SKOV-3 (Ovarian cancer)	570/764	43
7	β-Galactosidase	SKOV-3 (Ovarian cancer)	725/770	44
8	β-Galactosidase	OVCAR-3 (Ovarian cancer) HEK293T (Kidney)	410/500 (↓); 410/570 (↑) (FRET; Ratiometric)	46
9	β-Galactosidase	OVCAR-3 (Ovarian cancer) SKOV-3 (Ovarian cancer) HT-29 (Colon cancer)	510/620 (↓); 552/662 (↑) (FRET; Ratiometric)	47
10	β-Galactosidase	HepG2 (Liver cancer; S)	415/492	51
11	β-Galactosidase	SKOV-3 (Ovarian cancer) HepG2 (Liver cancer; S) Hep3B (Liver cancer; S)	425/662	52
12	β-Galactosidase	COS-7 (Kidney; S)	500/585	53
13a-b	β-Galactosidase	OVCAR-3 (Ovarian cancer) SKOV-3 (Ovarian cancer) A549 (Lung cancer; S) HL-7702 (Liver; S) MRC-5 (Lung; S)	460/560	54
14	β-Galactosidase	A549 (Lung cancer; S)	451/526	55
15	β-Galactosidase	SHIN3 (Ovarian cancer) A549 (Lung cancer; S)	380/445	56
16	β-Galactosidase	SKOV-3 (Ovarian cancer) A2780 (Ovarian cancer) IOSE80 (Ovary; S) HepG2 (Liver cancer; S) HeLa (Cervical cancer; S)	580/642	57
17	β-Galactosidase	OVCAR-3 (Ovarian cancer) HeLa (Cervical cancer; S)	415/570 (↓); 415/670 (↑) (FRET; Ratiometric)	58
18	β-Galactosidase	SKOV-3 (Ovarian cancer) Wi38 (Lung; S)	420/625	62
19	β-Galactosidase	MDA-MB-231 (Breast cancer; S) A549 (Lung cancer; S) C6 (Glioblastoma; S)	655/675	63
20	β-Glucosidase	-	600/636	69

Substance No	Target glycosidase	Cells	Absorption/emission wavelength (nm)	Ref.
21a-f	β-Glucosidase	-	350/535	71
22a,b,e	β-*N*-Acetylglucosaminidase	-	350/535	71
23a,b,e	β-Glucuronidase	-	350/535	71
24a	α-Galactosidase	SK-N-SH (Neuroblastoma)	545/590	74
24b	α-*N*-Acetylgalactosaminidase	SK-N-SH (Neuroblastoma)	545/590	74
25	β-Hexosaminidase	-	550/598	78
26	β-Hexosaminidase	-	470/545	79
27	β-Hexosaminidase	HCT116 (Colon cancer)	344/612	80
28	β-Hexosaminidase	-	690/716	81
29	β-Hexosaminidase	SW480 (Colon cancer)	438/475 (↓); 438/540 (↑) (Ratiometric)	82
30a-d	O-GlcNAcase	AGS (Stomach cancer) Capan-1 (Pancreatic cancer)	488/520	89
31	O-GlcNAcase	-	400/440 (Coumarin) 510/540 (Rhodol)	90
32a-c	α-Fucosidase	HeLa (Cervical cancer) SK-N-SH (Neuroblastoma)	385/502 (**32a**) 491/510 (**32b**) 571/585 (**32c**)	97
33	α-Fucosidase	SMMC-7721 (Liver cancer)	800/520-620 (Two-photon exication)	98
34	α-Fucosidase	HCT116 (Colon cancer)	543/586	99
35a-l	Various glycosidases	-	498/540	100
36a-e	Various glycosidases	-	680/710	108

Table S2. Summary of activity-based probes (Abbreviation: CA = Cyclitol aziridine; CE = Cyclitol epoxide; o-QM = ortho-Quinone methide; p-QM = para-Quinone methide; DF = 2-deoxy-2-fluoroglycoside).

No	Type	Target glycosidase	Reporter tag	Sample (Cells, lysates, secretome, etc.)	Ref.
37	CA	α-Mannosidase	Cy5 (**37a**) Biotin (**37b**) TAMRA (**37c**)	HEK293T (Kidney)	132
38	CA	β-Mannosidase	Cy5 (**38a**) Biotin (**38b**)	*C. mixtus* *B. thetaiotaomicron* HEK293T (Kidney)	133
39	Others	Endo-1,2-α-mannanase	Cy5	-	134
40	CA	α-galactosidase	Cy5 (**40a**) Biotin (**40b**)	*N. benthamiana*	137
41	CA	α-arabinofuranosidase	Cy5 (**41a**) Biotin (**41b**)	*A. niger* Basidiomycetes	141
42	CA	α-iduronidase	Cy5 (**42a**) Biotin (**42b**)	Normal human dermal fibroblasts Fibroblasts from MPS I patients	144
43	CA	β-xylosidase (**43a-b**) β-xylanase (**43c-d**)	Cy5 (**43a, 43c**) Biotin (**43b, 43d**)	Secretome from *A. niger*	146
44	CE (**44a-b**) CA (**44c-d**)	α-amylase	Cy5 (**44a, 44c-d**) Biotin (**44b**)	Human saliva Mouse pancreas tissue lysates Mouse salivary gland lysates *A. nidulans*	148
45	CE	β-gluocerebrosidase	BODIPY green (**45a**) BODIPY red (**45b**)	Normal human dermal fibroblasts	151
46	CE	β-1,4-glucanase	Cy5 (**46a**) Biotin (**46b**)	Secretomes from *A. niger* Complex fungal secretome	154
47	o-QM	α-fucosidase	Azide	*B. fragilis*	155
48	DF	α-fucosidase	Azide	-	156
49	p-QM	Sialidase	ROX	A549 (Lung cancer) HeLa (Cervical cancer) HepG2 (Liver cancer) MCF-7 (Breast cancer) U2OS (Bone cancer) Huh-7 (Liver cancer)	161
50	o-QM	O-GlcNAcase	Coumarin	HT-29 (Colon cancer)	163

Table S3. Summary of glycosidase inhibitors.

No	Target glycosidase	Biological Function	Activity	Ref.
51	α-Mannosidase	Anti-cancer	IC_{50} = 3.0 μM	177
52	α-Mannosidase	Anti-cancer	IC_{50} = 0.03 μM (hGMII) IC_{50} = 3.2 μM (hLMan)	178
53	α-Mannosidase	Anti-cancer	IC_{50} = 42 μM	179
54	α-Mannosidase	-	IC_{50} = 8 μM (hGMII) IC_{50} = 18 μM (hLMan)	180
55	α-Mannosidase	-	IC_{50} = 0.45 μM (hGMII) IC_{50} = 12 μM (hLMan)	181
56	α-Mannosidase	-	K_i = 0.23 μM (JBMan) K_i = 5 μM (α-glucosidase)	182
57	α-Mannosidase	-	K_d = 11.5 μM	184
58	β-Galactosidase	Pharmacological chaperone	IC_{50} = 10 nM EC_{50} = 500 nM	189
59	β-Galactosidase	Pharmacological chaperone	IC_{50} = 94 nM	190
60	β-Galactosidase	Pharmacological chaperone	IC_{50} = 1.5 mM K_i = 1.4 mM	191
61	α-Galactosidase	Pharmacological chaperone	K_i = 7.1 μM	194
62	α-Galactosidase	Pharmacological chaperone	K_i = 4.2 μM	195
63	β-Hexosaminidase	Pharmacological chaperone	K_i = 580 nM	200
64	β-Hexosaminidase	Insecticide	K_i = 3.7 μM	202
65	β-Hexosaminidase	Larvicide	IC_{50} = 47.5 μM	203
66	O-GlcNAcase	-	K_i = 0.6 μM	207
67	O-GlcNAcase	Drug for Alzheimer's disease	K_i = 8.7 nM	212
68	O-GlcNAcase	Drug for Alzheimer's disease	IC_{50} = 53 nM	213
69	O-GlcNAcase	-	K_i = 220 pM	214
70	O-GlcNAcase	Drug for tauopathies	IC_{50} = 46 nM	215
71	β-Glucocerebrosidase	Pharmacological chaperone	K_i = 13 nM (pH 7.0) K_i = 59 nM (pH 5.0)	217
72	β-Glucocerebrosidase	Pharmaceutical chaperone	K_i = 101 μM	221
73	β-Glucocerebrosidase	Pharmacological chaperone	K_i = 57.5 nM (pH 7.0) K_i = 476.9 nM (pH 5.5)	222
74	α-L-Fucosidase	Anti-cancer	IC_{50} = 2.5 μM	224
75	α-L-Fucosidase	-	K_i = 4.8 μM	225
76	α-L-Fucosidase	-	K_i = 0.15 nM	227
77	α-Glucosidase	-	IC_{50} = 0.11 μM	239
78	α-Glucosidase	Anti-diabetes	IC_{50} = 28 μM	240
79a	α-Amylase	-	K_i = 70 nM	244
79b	α-Amylase	-	K_i = 60 nM	244
80	Chitinase	-	IC_{50} = 29 nM	251

Table S4. Summary of glycosidase-activatable prodrugs.

No	Target glycosidase	Drug	Tumor cells	Animal model Xenograft	IC_{50}	Ref.
81 **81'**	β-Glucuronidase	MMAE	LS174T (Colon)	LS174T (Colon)	-	261
82	β-Glucuronidase	MMAE	MDA-MB-231 (Breast)	MDA-MB-231 (Breast)	3.3 nM	262
83	β-Glucuronidase	Curcumin	HCT116 (Colon)	HCT116 (Colon)	-	263
84	β-Glucuronidase	Synthetic anticancer agent	MDA-MB-231 (Breast) MCF-7 (Breast) HeLa (Cervix)	MDA-MB-231 (Breast)	9-16 nM	264
85	β-Galactosidase	Gemcitabine	HepG2 (Liver)	-	1.6 μM	265
86	β-Galactosidase	Linifanib	A549 (Lung) H1299 (Lung)	A549 (Lung)	-	268
87	β-Glucosidase	Losartan	-	Dog	-	269
88a-b	β-Galactosidase (**88a**) β-Glucuronidase (**88b**)	Amonafide	HeLa (Cervix) HCT116 (Breast) HepG2 (Liver)	-	-	273
89a	β-Galactosidase (**89a**) α-Mannosidase (**89b**) β-Glucuronidase (**89c**)	Resiquimod	B16 (Skin) TC2 (Prostate) 4T1 (Breast)	-	-	274