## Supporting Information

Name <sup>1</sup>	Chemical Formula	Molecular Weight	Exact Mass [M]	Found [M]
Aptscl56-a	$C_{423}H_{540}N_{153}O_{263}P_{41}S$	13277.8	13271.3	13268.3
Aptscl56-b	$C_{425}H_{544}N_{153}O_{263}P_{41}S$	13305.8	13299.3	13296.1
Aptscl56-c	$C_{427}H_{548}N_{153}O_{263}P_{41}S$	13333.9	13327.3	13324.3
Aptscl56-d	C427H549N154O263P41S	13348.9	13342.3	13339.5
Aptscl56-e	$C_{427}H_{549}N_{154}O_{263}P_{41}S$	13348.9	13342.3	13343.3
Aptscl56-f	$C_{424}H_{543}N_{154}O_{263}P_{41}S$	13306.8	13300.3	13299.7
Aptscl56-g	$C_{424}H_{543}N_{154}O_{263}P_{41}S$	13306.8	13300.3	13300.3
Aptscl56-h	$C_{425}H_{545}N_{154}O_{263}P_{41}S$	13320.8	13314.3	13314.2
Aptscl56-i	$C_{425}H_{545}N_{154}O_{263}P_{41}S$	13320.8	13314.3	13314.0
Aptscl56-j	C426H547N154O263P41S	13334.9	13328.3	13328.1
Aptscl56-k	C430H547N154O263P41S	13382.9	13376.3	13377.3
Aptscl56-I	$C_{430}H_{547}N_{154}O_{263}P_{41}S$	13382.9	13376.3	13376.3
Aptscl56-m	C426H545N154O263P41S	13332.9	13326.3	13326.4

Table S1. ESI MS-identification of modified aptamers

<sup>1</sup> Biotin labeled



**Figure S1**. ESI-MS spectra of representative modified aptamers. (a-m) Aptscl56-a, Aptscl56-b, Aptscl56-c, Aptscl56-d, Aptscl56-e, Aptscl56-f, Aptscl56-g, Aptscl56-h, Aptscl56-i, Aptscl56-j, Aptscl56-k, Aptscl56-l, Aptscl56-m. *Notes*: Biotin labeled

## Name

## Aptscl56 CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT Aptscl56-5alkyne CGGGGalkyneTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT CGGGGTGalkyneTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT Aptscl56-7alkyne CGGGGTGTGalkyneGGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT Aptscl56-9alkyne Aptscl56-10alkyne CGGGGTGTGGalkyneGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT CGGGGTGTGGGalkyneTTCGTCGTTAGCTTGATTTGGCAGCTGCCT Aptscl56-11alkyne CGGGGTGTGGGTTCGalkyneTCGTTAGCTTGATTTGGCAGCTGCCT Aptscl56-15alkyne CGGGGTGTGGGTTCGTCGalkyneTTAGCTTGATTTGGCAGCTGCCT Aptscl56-18alkyne Aptscl56-22alkyne CGGGGTGTGGGTTCGTCGTTAGalkyneCTTGATTTGGCAGCTGCCT Aptscl56-26alkyne CGGGGTGTGGGTTCGTCGTTAGCTTGalkyneATTTGGCAGCTGCCT Aptscl56-31alkyne CGGGGTGTGGGTTCGTCGTTAGCTTGATTT**G**alkyneGCAGCTGCCT Aptscl56-32alkyne CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGalkyneCAGCTGCCT Aptscl56-35alkyne CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGalkyneCTGCCT

Sequence (5'-3')



Figure S2. Design and synthesis of chemically modified aptamers through Copper (I)-Catalyzed Alkyne– Azide Cycloaddition (CuAAC). (a) The sequences of alkyne modified aptamer. The functional propargyl group was modified at the 2'-hydroxyl of guanosines ( $G_{alkyne}$ ) in the sclerostin aptamer Aptscl56, including site 5, 7, 9, 10, 11, 15, 18, 22, 26, 31, 32, and 35. (b) The scheme of synthetic route of aptamer modification. The functional azide group was conjugated to the small modification molecules. The reaction was catalyzed by reduction product of Cu<sup>2+</sup> by tris(2-carboxyethyl)phosphine (TCEP) in a mixed solvent of CH<sub>3</sub>CN/H<sub>2</sub>O (6%, v/v).

b

Name	Sequence (5'-3')
Aptscl56-x1	xGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-x2	${\tt Cx} {\tt GGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC}$
Aptscl56-x3	$CG\mathbf{x}GGTGTGGGGTTCGTCGTTGGCTTGCCGCTGCCC$
Aptscl56-x4	$CGG{\mathbf{x}}GTGTGGGGTTCGTCGTTGGCTGCCGCTGCCCCCCCCCC$
Aptscl56-x5	$CGGG\mathbf{x}TGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC$
Aptscl56-x6	$CGGGG\mathbf{x}GTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC$
Aptscl56-x8	$CGGGGTG \mathbf{x} GGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC$
Aptscl56-x11	CGGGGTGTGG <b>x</b> TTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-x13	CGGGGTGTGGGTxCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-x18	CGGGGTGTGGGTTCxTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-x29	CGGGGTGTGGGTTCGTCGTTAGCTTGATxTGGCAGCTGCC
Aptscl56-x30	CGGGGTGTGGGTTCGTCGTTAGCTTGATTxGGCAGCTGCC
Aptscl56-x32	CGGGGTGTGGGTTCGTCGTTAGCTTGATTT <b>x</b> GCAGCTGCC
Aptscl56-x32	2CGGGGTGTGGGTTCGTCGTTAGCTTGATTTG <b>x</b> CAGCTGCC
Aptscl56-x33	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGG <b>x</b> AGCTGCC
Aptscl56-x34	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGC <b>x</b> GCTGCC
Aptscl56-x38	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCA <b>x</b> CTGCC
Aptscl56-x36	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAG <b>x</b> TGCC
Aptscl56-x37	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGC <b>x</b> GCC
Aptscl56-x38	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCT <b>x</b> CC
Aptscl56-x39	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTG <b>x</b> C
Aptscl56-x40	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGC <b>x</b>



а



**Figure S3**. **Design of chemically modified aptamers through solid-phase phosphoramidite method.** (a) The sequences of chemically modified aptamer. The incorporated sites included 1, 2, 3, 4, 5, 6, 8, 11, 13, 15, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, and 40. (b) Substituting the key sites with chemical modifications.

Model	MAE	MSE	RMSE	R2	RMSLE	MAPE
CatBoost	0.3631	0.3118	0.5106	0.4711	0.1809	0.2697
Random Forest	0.3574	0.3039	0.506	0.4539	0.175	0.2572
Light Gradient Boosting Machine	0.4322	0.4447	0.6219	0.3528	0.1949	0.2774
Gradient Boosting	0.39661	0.3576	0.5501	0.3413	0.1954	0.2891
Extreme Gradient Boosting	0.40341	0.36821	0.5599	0.32991	0.2002	0.3244
K Neighbors	0.4272	0.45761	0.63301	0.29881	0.1982	0.2725
Huber	0.42961	0.44971	0.61955	0.2987	0.2032	0.27611
Bayesian Ridge	0.4533	0.4378	0.62071	0.2797	0.2055	0.3169
AdaBoost	0.49351	0.46751	0.6443	0.22735	0.2157	0.3671
Decision Tree	0.4284	0.5079	0.60401	0.1964	0.2107	0.3128
Ridge	0.4673	0.4423	0.6301	0.1932	0.2125	0.3262
Extra Trees	0.4351	0.5217	0.61741	0.1706	0.2162	0.3205
Orthogonal Matching Pursuit	0.48721	0.4513	0.6446	0.1282	0.2213	0.3486
Linear	0.48391	0.4595	0.64431	0.1162	0.2203	0.3382
Lasso	0.6525	0.8368	0.8562	-0.2095	0.301	0.5087
Elastic Net	0.6525	0.8368	0.8562	-0.2095	0.301	0.5087
Lasso Least Angle	0.6525	0.8368	0.8562	-0.2095	0.301	0.5087
Dummy	0.6525	0.8368	0.8562	-0.2095	0.301	0.5087
Passive Aggressive	0.6028	0.6333	0.7446	-0.2124	0.2824	0.4822
Least Angle	6.742×10 <sup>10</sup>	5.569×10 <sup>22</sup>	7.470×10 <sup>10</sup>	4.264×10 <sup>22</sup>	11.5441	5.854×
						10 <sup>10</sup>

Table S2. Model comparison of twenty regressors on modified aptamers' affinity estimation

Name	Sequence (5'-3')
Aptscl56	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-5 <b>sg</b>	CGGG <b>sg</b> TGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-7 <b>sg</b>	CGGGGT <b>sg</b> TGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-9 <b>sg</b>	CGGGGTGT <b>sg</b> GGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-10 <b>sg</b>	CGGGGTGTG <b>sg</b> GTTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-11 <b>sg</b>	CGGGGTGTGG <b>sg</b> TTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-15 <b>sg</b>	CGGGGTGTGGGTTC <b>sg</b> TCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-18 <b>sg</b>	CGGGGTGTGGGTTCGTC <b>sg</b> TTAGCTTGATTTGGCAGCTGCCT
Aptscl56-22 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTA <b>sg</b> CTTGATTTGGCAGCTGCCT
Aptscl56-26 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTT <b>sg</b> ATTTGGCAGCTGCCT
Aptscl56-31 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTT <b>sg</b> GCAGCTGCCT
Aptscl56-32 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTG <b>sg</b> CAGCTGCCT
Aptscl56-35 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCA <b>sg</b> CTGCCT



**Figure S4. The first round of the modified aptamer-affinity dataset for AI model construction.** 5 types of ring modifications at 12 sites, respectively. (a) The modified sequences of sclerostin aptamer Aptscl56. Note: substitutional group (**sg**) = **k**, **I**, **m**, **n**, **o**. (b) The measured binding affinity data of the modified aptamer to sclerostin by Biolayer interferometry.

Name	Sequence (5′-3′)
Aptscl56	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-5 <b>sg</b>	CGGG <b>sg</b> TGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-7 <b>sg</b>	CGGGGT <b>sg</b> TGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-9 <b>sg</b>	CGGGGTGT <b>sg</b> GGTTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-10 <b>sg</b>	CGGGGTGTG <b>sg</b> GTTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-11 <b>sg</b>	CGGGGTGTGG <b>sg</b> TTCGTCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-15 <b>sg</b>	CGGGGTGTGGGTTC <b>sg</b> TCGTTAGCTTGATTTGGCAGCTGCCT
Aptscl56-18 <b>sg</b>	CGGGGTGTGGGTTCGTC <b>sg</b> TTAGCTTGATTTGGCAGCTGCCT
Aptscl56-22 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTA <b>sg</b> CTTGATTTGGCAGCTGCCT
Aptscl56-26 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTT <b>sg</b> ATTTGGCAGCTGCCT
Aptscl56-31 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTT <b>sg</b> GCAGCTGCCT
Aptscl56-32 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTG <b>sg</b> CAGCTGCCT
Aptscl56-35 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCA <b>sg</b> CTGCCT



Figure S5. The second round of the modified aptamer-affinity dataset. 10 types of ring modifications at 12 sites, respectively. (a) The modified sequences of sclerostin aptamer Aptscl56. Note: substitutional group (sg) = a, b, c, d, e, f, g, h, i, j. (b) The measured binding affinity data of the modified aptamer to sclerostin by Biolayer interferometry.

Name	Sequence (5'-3')
Aptscl56-1 <b>sg</b>	<b>sg</b> GGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-2 <b>sg</b>	CsgGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-3 <b>sg</b>	CG <b>sg</b> GGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-4 <b>sg</b>	CGGsgGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-5 <b>sg</b>	CGGG <b>sg</b> TGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-6 <b>sg</b>	CGGGGsgGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-8 <b>sg</b>	CGGGGTG <b>sg</b> GGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-11 <b>sg</b>	CGGGGTGTGG <b>sg</b> TTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-13 <b>sg</b>	CGGGGTGTGGGT <b>sg</b> CGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-15 <b>sg</b>	CGGGGTGTGGGTTC <b>sg</b> TCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-29 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGAT <b>sg</b> TGGCAGCTGCC
Aptscl56-30 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATT <b>sg</b> GGCAGCTGCC
Aptscl56-31 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTT <b>sg</b> GCAGCTGCC
Aptscl56-32 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTG <b>sg</b> CAGCTGCC
Aptscl56-33 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGG <b>sg</b> AGCTGCC
Aptscl56-34 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGC <b>sg</b> GCTGCC
Aptscl56-35 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCA <b>sg</b> CTGCC
Aptscl56-36 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAG <b>sg</b> TGCC
Aptscl56-37 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGC <b>sg</b> GCC
Aptscl56-38 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCT <b>sg</b> CC
Aptscl56-39 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTG <b>sg</b> C
Aptscl56-40 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCsg

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,d 1	<u> </u>	x - 8	3.5	10.3	10.2	8.0	5.3	10.2	8.9	6.5	6.8	3.3	4.9	8.2	2.0	1.1	3.1	2.3	4.1	3.5	4.9	1.6	1.6	4.8		12.0 <b>Buipt</b>
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,,0 ,,0		z - 1	1.0	1.0	0.8	0.4	0.5	0.6	0.6	0.7	0.8	0.7	0.8	1.1	1.0	0.2	0.3	0.4	0.3	0.4	0.2	0.4	0.6	0.1		Relati
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**Figure S6. The third round of the modified aptamer-affinity dataset**. 4 types of modifications at 22 sites, respectively. (a) The modified sequences of sclerostin aptamer Aptscl56. Note: substitutional group (**sg**) = **w**, **x**, **y**, **z**. (b) The measured binding ability data of the modified aptamer to sclerostin by Enzyme-Linked Oligonucleotide Assay (ELONA).

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Name	Sequence (5'-3')
Aptscl56-1 <b>sg</b>	<b>sg</b> GGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-2 <b>sg</b>	CsgGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-3 <b>sg</b>	CG <b>sg</b> GGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-4 <b>sg</b>	CGG <b>sg</b> GTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-5 <b>sg</b>	CGGG <b>sg</b> TGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-6 <b>sg</b>	CGGGG <b>sg</b> GTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-8 <b>sg</b>	CGGGGTG <b>sg</b> GGGTTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-11 <b>sg</b>	CGGGGTGTGG <b>sg</b> TTCGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-13 <b>sg</b>	CGGGGTGTGGGT <b>sg</b> CGTCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-15 <b>sg</b>	CGGGGTGTGGGTTC <b>sg</b> TCGTTAGCTTGATTTGGCAGCTGCC
Aptscl56-29 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGAT <b>sg</b> TGGCAGCTGCC
Aptscl56-30 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATT <b>sg</b> GGCAGCTGCC
Aptscl56-31 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTT <b>sg</b> GCAGCTGCC
Aptscl56-32 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTG <b>sg</b> CAGCTGCC
Aptscl56-33 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGG <b>sg</b> AGCTGCC
Aptscl56-34 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGC <b>sg</b> GCTGCC
Aptscl56-35 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCA <b>sg</b> CTGCC
Aptscl56-36 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAG <b>sg</b> TGCC
Aptscl56-37 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGC <b>sg</b> GCC
Aptscl56-38 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCT <b>sg</b> CC
Aptscl56-39 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTG <b>sg</b> C
Aptscl56-40 <b>sg</b>	CGGGGTGTGGGTTCGTCGTTAGCTTGATTTGGCAGCTGC <b>sg</b>

b																									
	Site	1	2 3	3 4	5 6	7 8	<b>9</b> 1	10 11	12 13	14 1	5 16	17 18	19 20	21	22 23	24 25	26 2	7 28	29 30	31 32	2 33	34 35	36 37	38	39 40
P=0 ON N H CO	Aptscl	56 🧲	GG	GG	G T	G <mark>1</mark>	G	G <mark>G</mark>	T T		<mark>G</mark> T	CG	ТΤ		GC	ΤT	GA	<b>\ T</b>	T T	GC	<b>GC</b>	A G	CT	G	$\mathbf{C}$
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le l	۹۰ م	5.7	9.0	8.3	9.7	1.4	1.4	7.2	7.5	3.3	5.7	3.1	4.7	4.7	6.4	6.3	4.2	0.9	3.7	3.1	3.0	2.1	3.9		1
"ii l	<b>r</b>	9.9	9.4	11.3	7.9	11.1	9.8	11.7	13.8	8.9	8.7	10.0	11.0	6.9	10.2	11.1	5.8	7.7	9.6	8.0	7.0	7.0	7.1		<b>-</b> 14.0
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	s ·	9.6	13.2	10.5	13.1	12.6	15.8	15.2	16.0	14.9	8.8	13.2	13.0	13.6	15.5	13.9	15.1	10.8	12.0	13.9	6.0	6.2	6.0		10.0
				• •														• •							8.0
	— t·	4.0	6.1	3.9	12.0	11.2	0.9	6.9	2.8	5.1	2.7	4.2	3.9	3.8	9.7	3.1	6.9	2.6	4.7	5.0	1.0	1.6	8.8		
	- u ·	7.8	6.9	7.7	8.0	6.9	5.2	5.9	5.3	5.8	7.8	6.2	7.0	4.3	4.4	3.8	3.1	4.0	3.6	3.7	3.7	4.4	5.8		- 6.0
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" Les	/ v ·	4.0	1.1	5.6	4.8	6.2	4.5	9.2	10.5	5.5	11.6	4.5	4.3	7.3	7.0	6.5	10.5	5.9	11.4	10.3	4.0	3.5	8.8		2.0
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Figure S7. The third round of the modified aptamer-affinity dataset. 7 types of modifications at 22 sites, respectively. (a) The modified sequences of sclerostin aptamer Aptscl56. Note: substitutional group (sg) = p, q, r, s, t, u, v. (b) The measured binding ability data of the modified aptamer to sclerostin by Enzyme-Linked Oligonucleotide Assay (ELONA).



Figure S8. The training data represented model. (a) fingerprint for each candidate small molecule. (b) 40-bit one-hot vectors for modification sites.



**Figure S9. Model interpretability analysis.** (**a**) Distances between classes in clustering results. (**b**) Distortion Score Elbow for K-Means. (**c**) Silhouette score Elbow for K-Means. (**d**) The importance of the modified sites for the results was assessed by the shap value on model output.



Figure S10. The association and dissociation curves of the naturally unmodified Aptscl56 and the selected aptamers with chemical modification.

	Residue Number	Residue	Nucleoside Number	Nucleoside	Distance	Interaction
index	in Protein	Туре	in Aptamer	Туре	Distance	Туре
1	110		25	11	1 66	Hydrogen
I	112	PRO	25	U	1.00	Bonds
2	11/	APC	17	C	2 62	Hydrogen
2	114	ANG	17	C	2.02	Bonds
3	11/	APC	22	C	3 7 2	Hydrogen
5	114	ANG	22	9	5.72	Bonds
4	11/		16		1 1	Hydrogen
4	114	ARG	10	U	1.1	Bonds
Б	11/		22	C	2 16	Hydrogen
5	114	ANG	23	C	2.10	Bonds
6	11/	APC	23	C	3 51	Hydrogen
0	114	ANG	23	C	5.51	Bonds
7	11/	APC	24		2 37	Hydrogen
1	114	ANG	24	0	2.51	Bonds
8	115	TVP	23	C	2.08	Hydrogen
0	115	TTIX	23	C	2.90	Bonds
0	110	APC	20		3.26	Hydrogen
9	119	ANG	20	0	5.20	Bonds
10	116	ARG	19	U	3.25	Salt Bridges
11	134	LYS	22	G	4.54	Salt Bridges
12	136	ARG	23	С	4.44	Salt Bridges

 $\textbf{Table S3.} \ \textbf{The predicted interactions between } \textbf{Aptscl56 and sclerostin protein}$ 

Index	Residue Number	Residue	Nucleoside Number	Nucleoside	Distanco	Interaction
IIIUEX	in Protein	Туре	in Aptamer	Туре	Distance	Туре
1	110	ARG	3	G	3 27	Hydrophobic
	115	ANO	0	0	5.21	Interactions
2	121	GLN	Λ	G	3 01	Hydrophobic
2	121	OLIN	-	0	0.01	Interactions
3	100		31	G	3.84	Hydrophobic
5	122	LLO	51	0	5.04	Interactions
4	135	\/Δ1	33	C	3 51	Hydrophobic
4	155	VAL		5.51	Interactions	
5	137		3/	Δ	2 95	Hydrophobic
0	107	LLO	04	~	2.35	Interactions
6	116	ARG	38	G	2 07	Hydrogen
0	110	////0	00	0	2.07	Bonds
7	117	ΔΙΔ	2	G	3.13	Hydrogen
I	117	/ L/ (	L		0.10	Bonds
8	118	GLN	36	C	2 51	Hydrogen
0	110	OLIN	00	0	2.01	Bonds
q	118	GLN	34	Δ	3 15	Hydrogen
0	110	OLIN	04		0.10	Bonds
10	121	GLN	5	G	2 21	Hydrogen
10	121	OLIN	0	0	2.21	Bonds
11	116	ARG	2	G	5.37	Salt Bridges
12	119	ARG	3	G	5.43	Salt Bridges
13	133	ARG	32	G	5.43	Salt Bridges
14	133	ARG	33	С	3.87	Salt Bridges
15	134	LYS	3	G	5.13	Salt Bridges

Table S4. The predicted interactions between Aptscl56-9b and sclerostin protein

Index	Residue Number	Residue	Nucleoside Number Nucleoside		Distanco	Interaction
muex	in Protein	Туре	in Aptamer	Туре	Distance	Туре
1	121	GLN	37	11	3.09	Hydrophobic
•	121	OLIN	01	0	0.00	Interactions
2	122	I FU	1	C	3 34	Hydrophobic
2	122	LLO	ľ	Ũ	0.04	Interactions
3	123	I FU	37		3 75	Hydrophobic
0	120	LLO	01	0	0.10	Interactions
4	135	\\Δ۱	2	G	3.96	Hydrophobic
-	100	V/	L	0	0.00	Interactions
5	116	ARG	31	G	3 17	Hydrogen
U	110	7470	UT UT	0	0.11	Bonds
6	116	ARG	31	G	3 03	Hydrogen
0	110	/11/0	01	0	0.00	Bonds
7	117	ΔΙΔ	33	C	2 71	Hydrogen
,	,	, (L) (	00	Ũ	2.11	Bonds
8	118	GI N	4	G	19	Hydrogen
U	110	OLIN	·	U U	1.0	Bonds
9	119	ARG	36	C	2 24	Hydrogen
0	110	7470	00	U	<b>L</b> . <b>L</b> .T	Bonds
10	121	GI N	37	U	1 94	Hydrogen
10	121	OLIN	01	0	1.01	Bonds
11	121	GLN	36	C	2 46	Hydrogen
	121	OLIN	00	U	2.40	Bonds
12	116	ARG	32	G	5.22	Salt Bridges
13	119	ARG	35	G	4.86	Salt Bridges
14	133	ARG	2	G	4.28	Salt Bridges
15	134	LYS	34	А	5.09	Salt Bridges

 Table S5. The predicted interactions between Aptscl56-11s and sclerostin protein



Figure S11. The association and dissociation curves of Aptscl56-9b11s to HSA protein.

Index	Residue Number	Residue Type	Nucleoside Number Nucleoside Number Nucleoside Number Nucleoside	Nucleoside	e Distance	Interaction
	in Protein			Туре		Туре
1	121	GLN	37	U	3.14	Hydrophobic
						Interactions
2	122	LEU	1	С	3.08	Hydrophobic
						Interactions
3	123	LEU	37	U	3.84	Hydrophobic
						Interactions
4	114	ARG	11	G	3.08	Hydrogen
						Bonds
5	116	ARG	33	С	2.89	Hydrogen
						Bonds
6	116	ARG	34	A	2.92	Hydrogen
						Bonds
7	118	GLN	4	G	2.11	Hydrogen
						Bonds
8	118	GLN	34	A	2.2	Hydrogen
						Bonds
9	119	ARG	36	С	2.33	Hydrogen
						Bonds
10	119	ARG	34	А	2.83	Hydrogen
						Bonds
11	121	GLN	37	U	1.99	Hydrogen
						Bonds
12	121	GLN	36	С	2.25	Hydrogen
						Bonds
13	114	ARG	32	G	4.28	Salt Bridges
14	119	ARG	35	G	3.99	Salt Bridges
15	133	ARG	2	G	4.29	Salt Bridges

 Table S6. The predicted interactions between Aptscl56-9b11s and sclerostin protein