Supporting information

Synthesis section

General Chemical Reagents and Methods

All purchased reagents for synthesis were used without further purification. All solventswere available commercially, dried or freshly dried and distilledprior to use. Thin-layer chromatography (TLC) was performed on silica gel GF254 plates with detection using shortwaveUV light (λ=254 nm) and staining with 10% phosphomolybdic acid in EtOH, followed by heating on a hotplate. Flash chromatography was performed with silica gel (100-200 mesh) with EtOAc/ petroleum ether or CH_2Cl_2/ MeOH as eluent. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 400 spectrometer at 400 MHz (^1H NMR) and 100 MHz (^{13}C NMR), using $CDCl_3$ as solvents. Coupling constants are reported in Hertz.

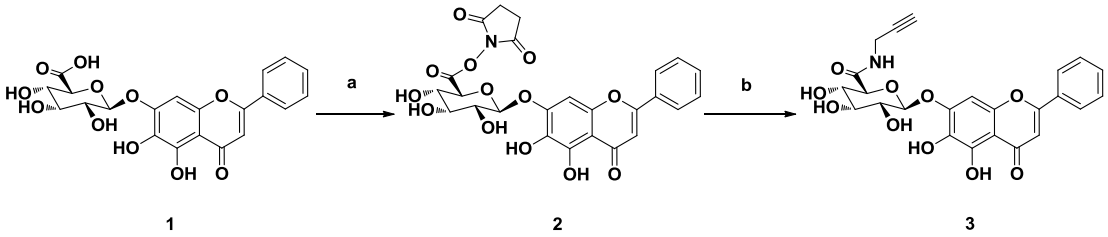
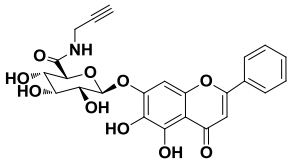


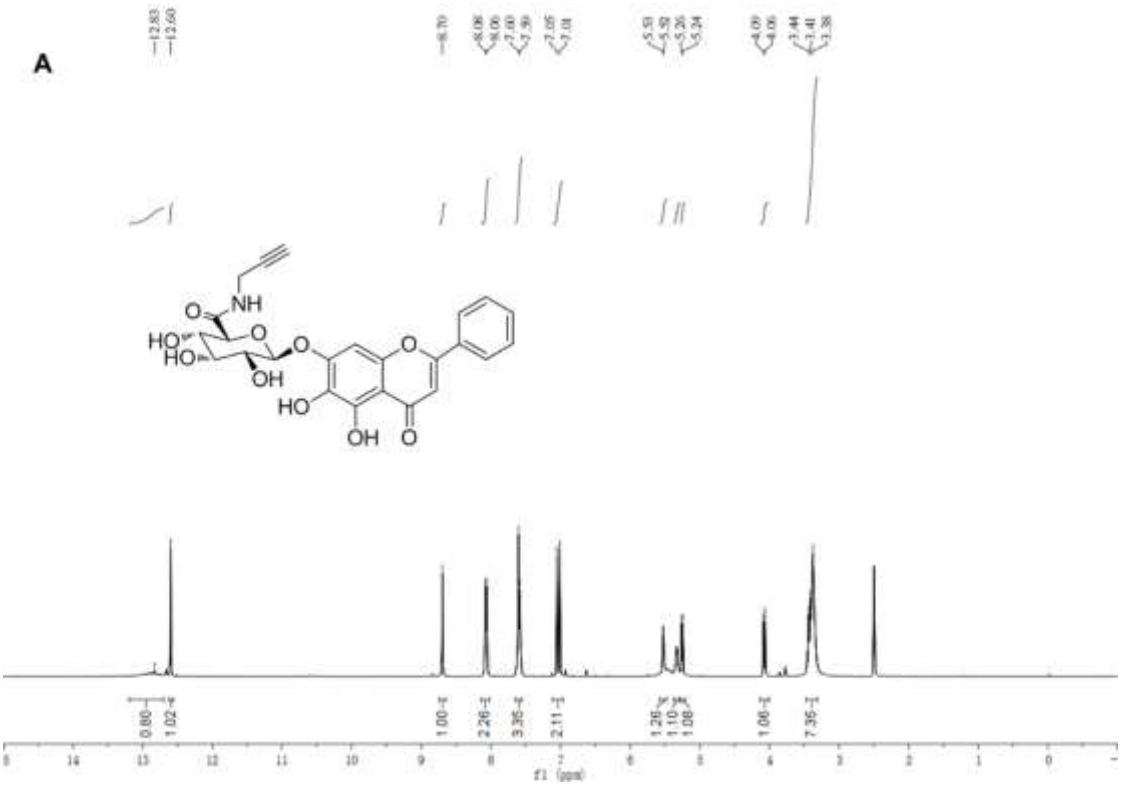
Figure S1. Synthetic route for compound 3 (alkynyl-modified baicalin probe). Reagents and conditions: (a) Di-succinimidyl carbonate , pyridine; (b) DIEA, propargylamine.

Compound 3 Synthesis (alkynyl-modified baicalin probe)



Di-succinimidyl carbonate (688mg，2.688mmol) was added to a solution of **compound 1** (400mg，0.896mmol) and pyridine (0.433ml，5.376mmol) in 20 ml of dichloromethane, and stirred at room temperature overnight. After completion of the reaction, 50 mL of dichloromethane was added for extraction, and the organic layer was washed with 20 mL of 1M HCl, 20 mL of saturated NaHCO3, and 20 mL of saturated brine in that order,

then the organic layer was collected as a yellow solida is the crude intermediate. **compound 2** and DIEA (178μL,1.075mmol) were dissolved in 20 mL of DMF, and propargylamine (59.2 μL，1.075 mmol) was added slowly under ice-cooling and slowly warmed to room temperature under argon protection for overnight. The mixture was concentrated in vacuo and purified by column chromatography on silica gel (dichloromethane: methanol=10:1) to obtain **compound 3** as a yellow solid. The yield of this reaction was 67% (290mg). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 12.83 (s, 1H), 12.60 (s, 1H), 8.70 (s, 1H), 8.07 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 7.1 Hz, 3H), 7.03 (d, *J* = 17.0 Hz, 2H), 5.53 (d, *J* = 3.4 Hz, 1H), 5.33 (s, 1H), 5.25 (d, *J* = 7.4 Hz, 1H), 4.08 (d, *J* = 9.5 Hz, 1H), 3.50 – 3.26 (m, 7H). ^{13}C NMR (100 MHz, DMSO-*d*6) δ 182.6, 170.1, 163.6, 151.3, 149.2, 146.8, 132.1, 130.9, 130.6, 129.2, 126.4, 106.2, 104.8, 99.9, 93.8, 75.5, 75.3, 72.8, 71.4. and the (-)-HR-ESI-MS spectrum of **compound 3** as shown in the Figure S3**.** m/z compound 3 calculated for $C_{24}H_{21}NO_{10}$: 483.1165 ; [M-H^{+}]=482.1093 ;found: [M-H^{+}] 482.1090.



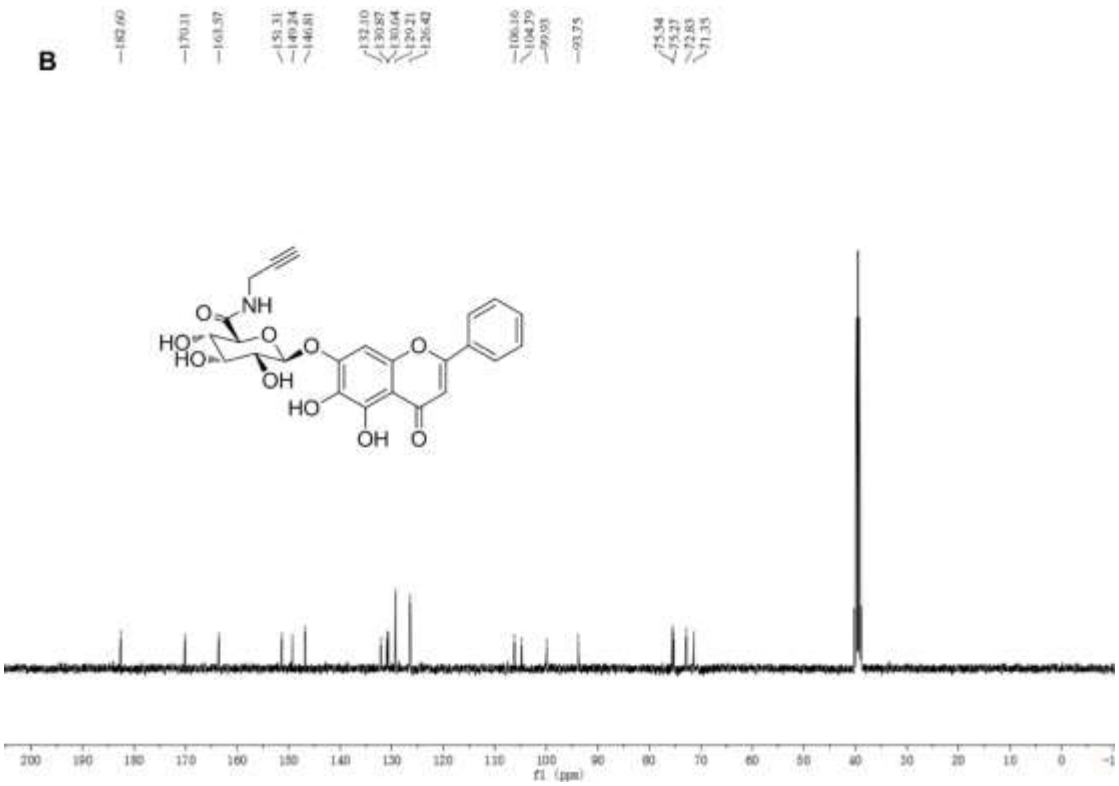


Figure S2. The NMR data of alkynyl-modified baicalin probe, (A) ^{1}H NMR spectrum of alkynyl-modified baicalin probe (400 MHz, DMSO-*d*6) and (B) ^{13}C NMR spectrum of alkynyl-modified baicalin probe (100 MHz, DMSO-*d*6).

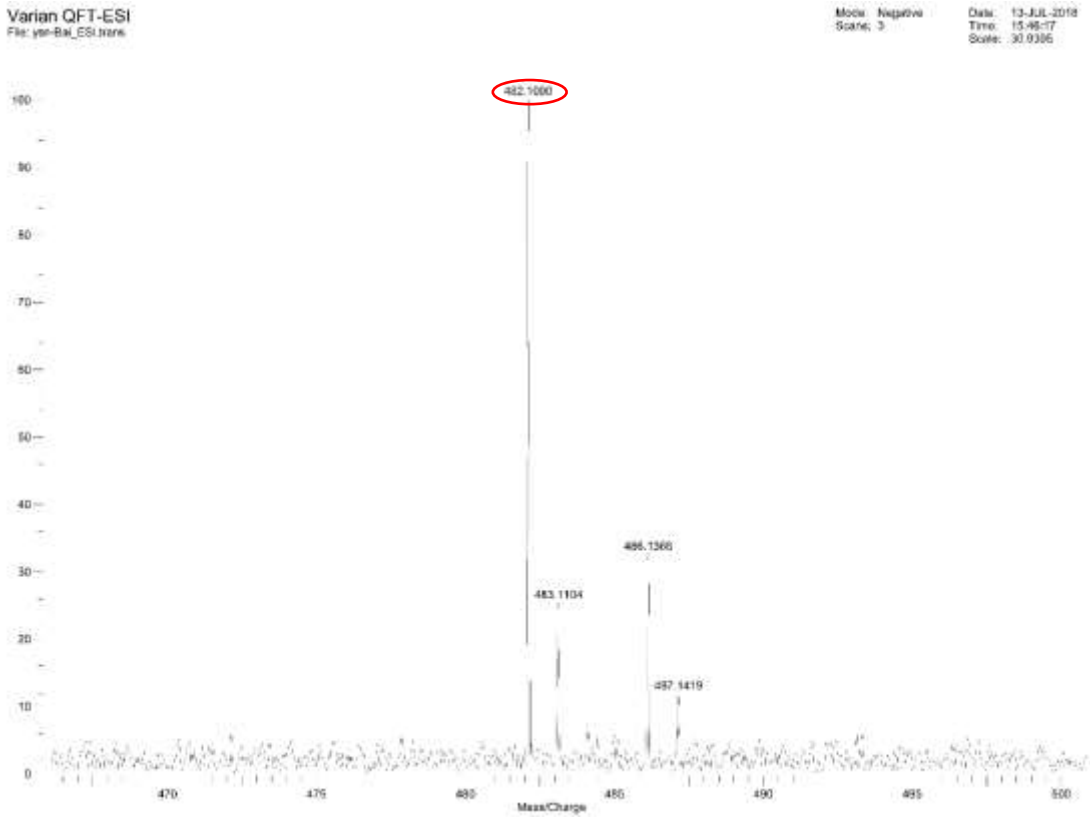


Figure S3 (-)-HR-ESI-MS spectrum of **compound 3** as shown in the Figure S3**.**

Preparation of baicalin-modified functionalized MMs

A total of 6 mL NH2-MMs (5 mg/mL) was suspended in 6 mL borate buffer and Sulfo-SADP (3 mg, 66 μM) was added. Then the mixture was reacted at four-dimensional rotator at room temperature for 12 h. Hereafter, the azide modified-MMs were enriched via magnetic separation and first washed 2 times with water followed by 2 times washes with methanol, respectively. The azide modified-MMs were collected and used for the subsequent steps. Alkynyl-modified baicalin probe (31.88 mg, 66 μM) and azide modified-MMs (30 mg, 5 mg/mL) was dissolved in degassed methanol (1 mL) and treated with 100 μL aqueous solution containing 200 μM Tris-triazoleamine, 100 μM CuSO4 and 200 μM sodium ascorbate. The reaction mixture was shaken at room temperature for 12 h. Then, the baicalin-modified functionalized MMs were separated with a magnet and washed with methanol and water for 2 times respectively. The enriched functionalized-MMs were reduced by dithiothreitol (DTT) and the released baicalin derivative was analyzed by UPLC/Q-TOF-MS/MS (Waters, USA). The details of baicalin-modified functionalized MMs were shown in the Figure S4 and Figure S5.

Baicalin-modified functionalized MMs characterization section

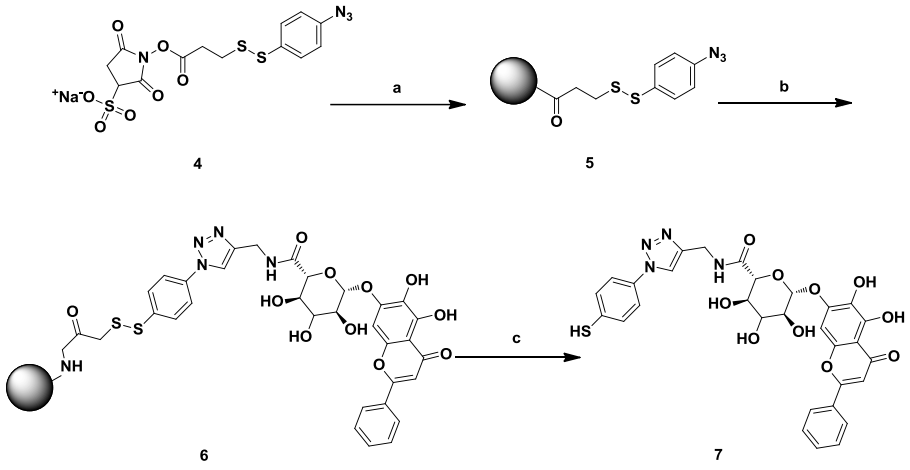
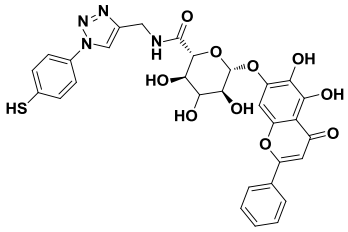


Figure S4. Synthetic route for baicalin-modified functionalized MMs (compound 6). Reagents and conditions: (a) NH_2-MMs, borate buffer, DMSO; (b) $CuSO_4$, VC, methanol ; (c) DTT, methanol.

compound 7



UPLC/Q-TOF-MS/MS: m/z **compound 7** calculated for $C_{30}H_{26}N_4O_{10}S$: 634.1370; found: $[M+H^+]$ 645.1486 (Figure S5). The results of UPLC/Q-TOF-MS/MS demonstrated that baicalin was successfully modified on the surfaces of MMs .

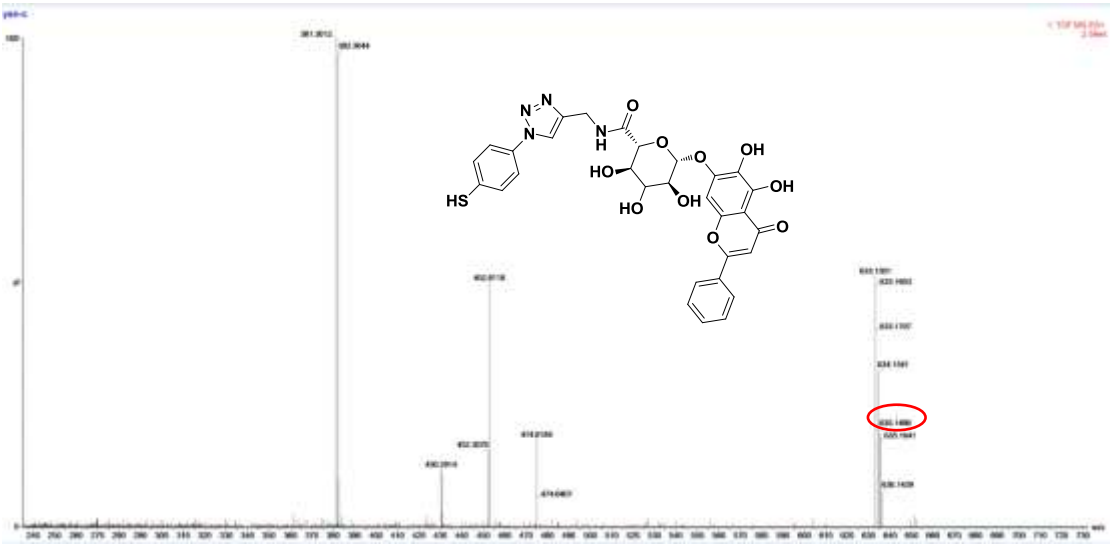


Figure S5. UPLC/Q-TOF-MS/MS analysis of the solution of baicain-modified functionalized MMs after DTT reduction.

MTT assay

HepG-2 cells were plated in 96-well plates with 200 µL of pre-warmed medium per well. After adherence, cells were switched to regular medium containing 0-100 µM of baicalin or the alkynyl-modified baicalin probe for 24 h. After the treatment, the cells were incubated with 200 µL of regular medium with 100 µg MTT (BBI Life Sciences) for 4 h. Finally, the purple precipitates were dissolved in150 µL of DMSO (Sigma-Aldrich) for measurement of absorbance at 490 nm by a microplate reader (Bio-Tek).

All the drugs are dissolved in DMSO before dilution. Each bar represents mean ± SD. ***P<0.001, **P<0.01 and *P<0.05 vs the untreated group, (n=3)

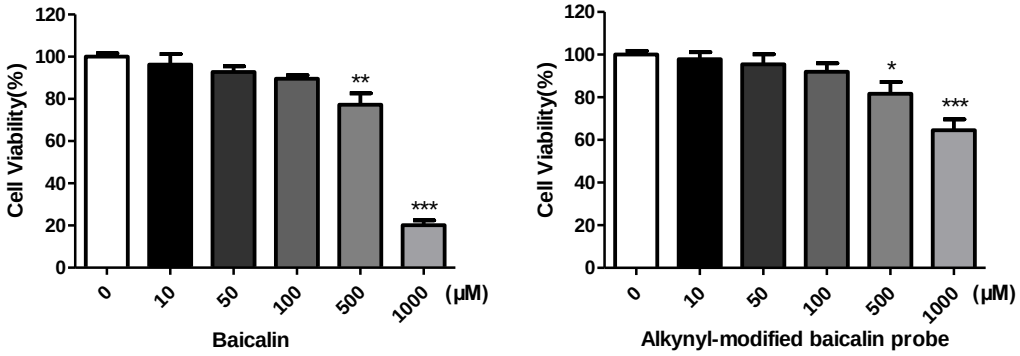


Figure S6. The effect of baicalin and alkynyl-modified baicalin probe on the cell viability of HepG 2 cells

Table S1 The top 30 target proteins (based on the fit value) predicted by Pharm-Mapper

Entry name	Protein names	Gene names	Length
G6PI_HUMAN	Glucose-6-phosphate isomerase	GPI	558
RASH_HUMAN	GTPase Hras	HRAS HRAS1	189
GSTT2_HUMAN	Glutathione S-transferase theta-2B	GSTT2B GSTT2	244
F261_RAT	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 1	Pfkfb1	471
PCKGC_HUMAN	Phosphoenolpyruvate carboxykinase, cytosolic	PCK1 PEPCK1	622
KTHY_HUMAN	Thymidylate kinase	DTYMK CDC8 TMPK TYMK	212
RAB9A_HUMAN	Ras-related protein Rab-9A	RAB9A RAB9	201
IF4E_HUMAN	Eukaryotic translation initiation factor 4E	EIF4E EIF4EL1 EIF4F	217
ELNE_HUMAN	Neutrophil elastase	ELANE ELA2	267
BTK_HUMAN	Tyrosine-protein kinase BTK	BTK AGMX1 ATK BPK	659
CBS_HUMAN	Cystathionine beta-synthase	CBS	551

FGF1_HUMAN	Fibroblast growth factor 1	FGF1 FGFA	155
MAP2_HUMAN	Methionine aminopeptidase 2	METAP2 MNPEP P67EIF2	478
AKT1_HUMAN	RAC-alpha serine/threonine-protein kinase	AKT1 PKB RAC	480
GSTP1_HUMAN	Glutathione S-transferase P	GSTP1 FAEES3 GST3	210
MK12_HUMAN	Mitogen-activated protein kinase 12	MAPK12 ERK6 SAPK3	367
CDK7_HUMAN	Cyclin-dependent kinase 7	CDK7 CAK CAK1 CDKN7 MO15 STK1	346
UCK2_HUMAN	Uridine-cytidine kinase 2	UCK2 UMPK	261
IMDH2_HUMAN	Inosine-5'-monophosphate dehydrogenase 2	IMPDH2 IMPD2	514
FA7_HUMAN	Coagulation factor VII	F7	466
SRC_HUMAN	Proto-oncogene tyrosine-protein kinase Src	SRC SRC1	536
CP2C9_HUMAN	Cytochrome P450 2C9	CYP2C9 CYP2C10	490
ACE_HUMAN	Angiotensin-converting enzyme	ACE DCP DCP1	1306
RAP2A_HUMAN	Ras-related protein Rap-2a	RAP2A	183
GSK3B_HUMAN	Glycogen synthase kinase-3 beta	GSK3B	420
CBR1_HUMAN	Carbonyl reductase	CBR1 CBR CRN SDR21C1	277
HS90A_HUMAN	Heat shock protein HSP 90-alpha	HSP90AA1 HSP90A HSPC1 HSPCA	732
PTN1_HUMAN	Tyrosine-protein phosphatase non-receptor type 1	PTPN1 PTP1B	435
INSR_HUMAN	Insulin receptor	INSR	1382
CDK2_HUMAN	Cyclin-dependent kinase 2	CDK2 CDKN2	298

Source: PharMmapper

Table S2 The top five pathways (based on the q value) were selected by String 10

pathway ID	pathway description	count in gene set	false discovery rate
4910	Insulin signaling pathway	7	2.05E-07
4151	PI3K-Akt signaling pathway	8	2.99E-06

4917	Prolactin signaling pathway	5	4.81E-06
5215	Prostate cancer	5	1.04E-05
4015	Rap1 signaling pathway	6	2.55E-05

Source: String 10