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Research paper

Development of coumarine derivatives as potent anti-filovirus entry inhibitors targeting viral glycoprotein

Yinyi Gao [a, 1], Han Cheng [b, 1], Sameer Khan [b], Gaokeng Xiao [c], Lijun Rong [b, **], Chuan Bai [a, *]

[a] Institute of Human Virology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong, 510080, China
[b] Department of Microbiology and Immunology, College of Medicine, University of Illinois at Chicago, Chicago, IL, USA
[c] Guangzhou Molcalx Information & Technology Ltd, Guangzhou, Guangdong, 510630, China

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ABSTRACT

Filoviruses, including Ebolavirus (EBOV), Marburgvirus (MARV) and Cuevavirus, cause hemorrhagic fevers in humans with up to 90% mortality rates. In the 2014–2016 West Africa Ebola epidemic, there are 15,261 laboratory confirmed cases and 11,325 total deaths. The lack of effective vaccines and medicines for the prevention and treatment of filovirus infection in humans stresses the urgency to develop antiviral therapeutics against filovirus-associated diseases. Our previous study identified a histamine receptor antagonist compound **CP19** as an entry inhibitor against both EBOV and MARV. The preliminary structure-activity relationship (SAR) studies of **CP19** showed that its piperidine, coumarin and linker were related with its antiviral activities. In this study, we performed detailed SAR studies on these groups with synthesized **CP19** derivatives. We discovered that 1) the piperidine group could be optimized with heterocycles, 2) the substitution groups of C3 and C4 of coumarin should be relatively large hydrophobic groups and 3) the linker part should be least substituted. Based on the SAR analysis, we synthesized compound **32** as a potent entry inhibitor of EBOV and MARV (IC_{50} = 0.5 μM for EBOV and 1.5 μM for MARV). The mutation studies of Ebola glycoprotein and molecular docking studies showed that the coumarin and its substituted groups of compound **32** bind to the pocket of Ebola glycoprotein in a similar way to the published entry inhibitor compound **118a**. However, the carboxamide group of compound **32** does not have strong interaction with N61 as compound **118a** does. The coumarin skeleton structure and the binding model of compound **32** elucidated by this study could be utilized to guide further design and optimization of entry inhibitors targeting the filovirus glycoproteins.

1. Introduction

Filoviruses, consisting of Marburgvirus (MARV), Ebolavirus (EBOV), and Ceuvavirus, are negative-sense RNA enveloped viruses with filamentous morphology. The Marburgvirus was the first discovered filovirus as the infectious agent responsible for a few small outbreaks in Marburg, Germany in 1967, which led to 7 deaths among the 31 reported cases. The Ebolavirus was discovered later in 1976 in the Democratic Republic of Congo (formerly Zaire). Since then small Ebolavirus outbreaks occurred sporadically in Africa, during which EBOV typically infected less than 500 people with high mortality rate (up to 90%). The world witnessed the biggest Ebolavirus outbreak in 2014–2016 West Africa Ebola epidemics which results in 15,261 laboratory-confirmed infections and 11,325 reported deaths (74% mortality rate). The 2018 Kivu Ebola outbreak started 1st August 2018 again in the Democratic Republic of Congo. Although a few experimental treatment options like rVSV-ZEBOV Ebola vaccine, Zmapp, GS-5734, REGN monoclonal antibody combination, and mAb114 have been approved for use in the current outbreak [1–6], they haven't shown dramatically effect against ebolavirus disease spread. The case figures are still rising and a total of 3444 cases (confirmed and probable) and 2264 deaths (66% mortality rate) have been reported as of 8th March 2020 [7]. Novel treatment options, especially small molecule based new drugs which are more affordable and easier to store and deliver in these economically disadvantaged countries, are in urgent need to prevent and control future outbreaks and potential bioterrorism attacks.

Viral entry has been proved to be a suitable target for antiviral

* Corresponding author.
** Corresponding author.
E-mail addresses: lijun@uic.edu (L. Rong), baichuan@mail.sysu.edu.cn (C. Bai).
[1] These authors contributed equally to this work.

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0223-5234/

development since the approval of anti-HIV drug maraviroc and T-20 by FDA, which target HIV-1 entry receptor CCR5 and HIV-1 fusion with the target cell respectively [8]. Filovirus entry is mediated by a single viral glycoprotein (GP), which is composed of two subunits, GP1 and GP2 [9, 10]. GP1 mediates the initial attachment of virion to the host cell surface which triggers the viral internalization via macropinocytosis and trafficking of the virion to late endosomes/lysosomes where the mucin-like domain and the glycan cap of GP1 are removed by cathepsin B/L to expose the receptor binding domain (RBD) [11–15]. Then the interaction of RBD and Niemann-Pick C1 (NPC1) protein anchors the virion and induces conformational change of GP2, leading to viral-endosomal membrane fusion [16–19]. The critical role of viral GP in the indispensable entry process makes it a promising target protein for developing small molecule entry inhibitors.

We previously identified compound **CP19** as a potent entry inhibitor against EBOV and MARV from a focused GPCR antagonist library [20]. In this study, we performed SAR studies with 58 derivatives of **CP19** on both EBOV and MARV. From these SAR studies, compound **32** was identified as a potent inhibitor of EBOV and MARV (IC_{50} = 0.5 μM for EBOV and 1.2 μM for MARV). The molecular docking analysis revealed that compound **32** binds in the same pocket on EBOV glycoprotein as a few previous reported EBOV entry inhibitors (e.g. toremifene and compound **118a**) do [21, 22]. However, the mutation studies showed that compound **32** did not form vital interactions with N61 or D522, which have been proved to be important for the binding of compound **118a**. The coumarin and its hydrophobic substituted groups may bind to the pocket close to Y517 which is occupied by the hydroxyphenol ring of compound **118a**. Our studies showed that the carboxamide group should interact with R164 on the surface of Ebola glycoprotein and the coumarin skeleton of compound **32** could be further optimized for more potent anti-filovirus lead compounds with better drug-like properties.

2. Results

The previous preliminary SAR studies of compound **CP19** mainly focused on the substitutions of its piperidine ring (Fig. 1.Cyan oval). The carboxamide group on the piperidine ring was important for **CP19**'s activity and replacement with alkyl substitution groups resulted in dramatic antiviral activity loss. These results indicated that the piperidine and carboxamide group may interact with amino acid residues possibly via H-bond. Thus, groups with hetero atoms that can form H-bond interactions would probably show better activity. Moreover, the benzyl substitution at the C-3 of coumarin (Fig. 1.Magentas oval) was also a key group for the activity because the unsubstituted counterpart was totally inactive. Based on these results, herein we performed SAR studies on the carboxamide, C-3 and C-4 (Fig. 1.Green oval) positions of coumarin. We also studied the SAR on the secondary hydroxyl group (Fig. 1.Yellow circle) in the linker, which has not been reported before.

We conducted the SAR studies with the general synthesis method (Scheme 1).

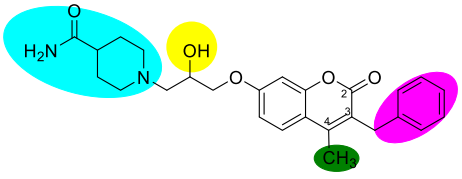
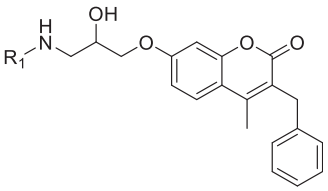


Fig. 1. The strategy of SAR studies in this work.

2.1. The SAR study on the carboxamide group (Table 1)

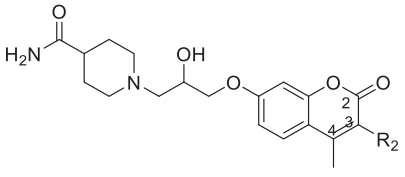
We first tested if the hydrophobic alkyne (**2**), cyclopropane (**3**), phenyl (**4**–**6**) and benzyl (**7**) groups could increase the antiviral activity compared with **CP19** (**1**). Only benzyl (**7**) group displayed comparable anti-filovirus activity and SI value than **CP19**. This result provided partial support for our postulation that the nitrogen atom of carboxamide could form H-bond with residues in the active site. We then tested if the oxygen atom in the alcohol (**8, 9**) and cyclic ether substitution groups (**10**) could form the desired interactions as carboxamide dose. However, these modifications did not significantly improve the activity. Then compounds with hetero cycles (**11**–**18**) were synthesized and most of them exhibited slightly better antiviral activities but more cytotoxicity in A549 cell line when compared with **CP19**. The compounds with ethyl-*o*-pyridine (**13**) showed the best inhibitory activity on EBOV entry and best SI in this series of compounds. However, other larger hetero cycles (**17**–**18**) did not increase the activity, which indicated that the binding pocket for this part is relatively small or has strict requirement for ligands.

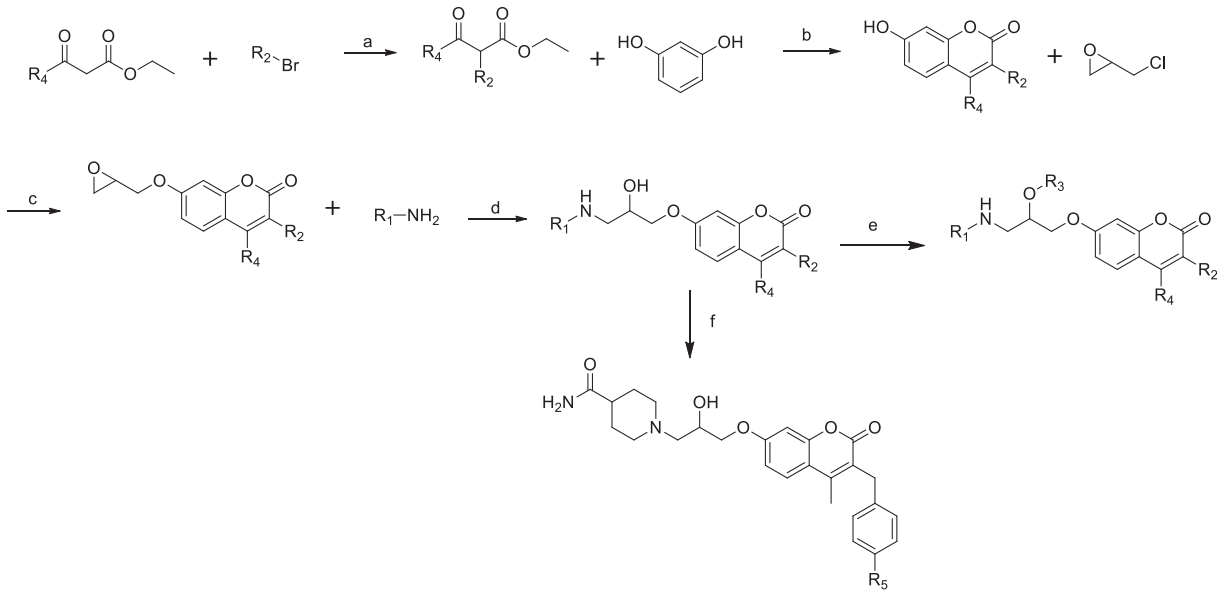


2.2. The SAR study on the C-3 of coumarin (Table 2)

Previous reported data suggested that the benzyl groups on the C-3 of coumarin was vital for the activity. Consistent with this result, the coumarin without any substitutions (**19**) lost most of the activity. Thereof, the effects of large aromatic groups with different substitutions on this site were evaluated. First, we synthesized compounds with substituted benzyl rings (**20**–**33**). Basically, most the halogen substitutions (**21**–**27**) afforded better antiviral activities than **CP19** and compound **21** and **23** showed good SI. Moreover, most other larger phenyl groups with strong electro-withdrawing substitutions (**28**–**32**) also displayed improved activity. Compound **32** showed the strongest antiviral activity against EBOV. This indicated that the binding pocket for this part could be relatively large and thus large aromatic substitution groups would benefit the binding. However, these modifications did not improve the cytotoxicity significantly, indicating that the metabolism properties of halogen and strong electro-withdrawing groups on the aromatic ring should be optimized.

To further exploit the possibly large binding pocket for this part, we synthesized compounds with larger aromatic groups such as naphthalene (**34**) and phenyl-heterocycle group (**35**). The naphthalene group displayed similar IC_{50} and SI value as **CP19**. We then increased the size of substitution by installing bi-phenyl groups (**36**–**43**). Compound **36** showed better antiviral activities for EBOV and MARV with better SI values than **CP19**. These results showed that the binding pocket could accommodate ligands with groups as large as bi-phenyl.

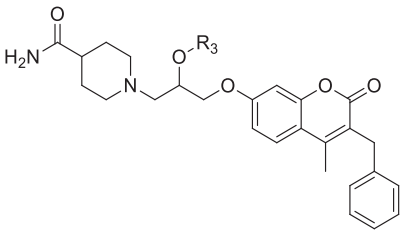




Scheme 1. The synthesis route of the target compounds.Reagents and conditions:(a)Ethyl acetoacetate, Benzyl bromide, CH_3ONa, Methonal, RT→68 °C, 0.5 h; (b)Resorcino, PPA, 65 °C, 4 h, 67%; (c)Epichlorohydrin, K_2CO_3, TBAB, 80 °C, 2.3 h, 81%; (d)Organic amine, $AcNMe_2$, 50 °C, 24 h, 85%; (e)PPh_3, DIAD, THF/DMF, 0 °C, 66%; (f)$Pd(PPh_3)_4$, diox-$NaHCO_3$ solution, under Ar protection, 95 °C, overnight, 65%.

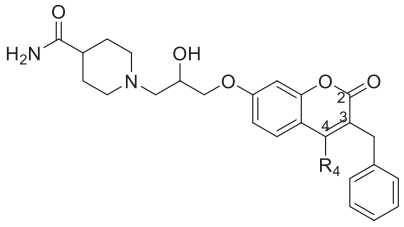
2.3. The SAR study on the linker (Table 3)

The SAR of the linker in **CP19** had not been studied. Herein, we focused on the substitutions of the secondary hydroxyl group of the linker. We first studied whether the stereochemistry of the secondary carbon could affect the activity. The two isomers of compound **32** (**44, 45**) showed little difference in activity and cytotoxicity, which indicated that this secondary hydroxyl group had not stereospecific interactions in the binding site. So we did not consider stereochemistry in further SAR studies on the linker. The phenyl ring with EWG and EDG (**46**–**49**) caused obvious loss of activity compared with **CP19,** which indicated that the aromatic substitution groups in this site may not be favored. To test whether the hydroxyl group itself may have important H-bond at the active site, we installed a group with multiple heteroatoms (**50**), but compound **50** did not afford better activity. Then we proposed that the binding pocket for the linker was small and thus had no vital interaction with the linker part. Compound **51** with smallest methyl group afforded less anti-viral activity than compound **13**. Then we removed the hydroxyl group on the linker (**52**) and it showed lower antiviral activity and SI compared with compound **15**. These results indicated that the binding site of the linker should be tunnel-like and so the linker should not have large substitution groups.



2.4. The SAR study on the C-4 of coumarin (Table 4)

The previous study showed that the substitutions on the C-4 of coumarin could reduce the cytotoxicity but had little effect on the antiviral activity of **CP19**. In this study, the cyclopropane (**53**) and phenyl (**54**) groups on this site were evaluated but they did not display better activity and cytotoxicity. Considering the steric hindrance between the substitution groups on the sterically adjacent C-3 and C-4, we removed the benzyl group on C-3 (**55**) but this compound lost most of the antiviral activity. These results confirmed that R3 group had vital roles for the activity its functions on the binding pocket and could not be replaced by the adjacent R4 group.



2.5. The synergy of R_1, R_2 and R_3 groups (Table 5)

To test whether the synergic effects could be acquired from the groups of R_1, R_2 and R_3, we accordingly synthesized compounds with the substitution groups that had afforded best activity or had reduced toxicity in our SAR studies (**56**–**59**). Among them, compound (**56**) afforded strong activity and low cytotoxicity. The synergic effect was not as high as expected ($SI_{EBOV} = 66$ for compound **56** and $SI_{EBOV} = 29$ for **CP19**). Considering that the linker group took minor roles for the activity, we proposed that the C_3 on coumarin and the terminal carboxamide groups influenced each other and cross talk between these groups should be considered.

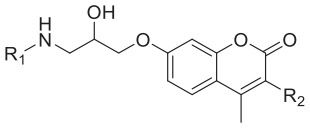
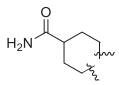
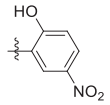
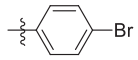
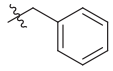
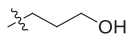
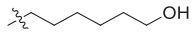
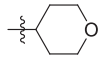
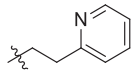
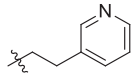
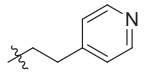
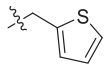
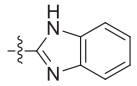
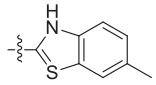


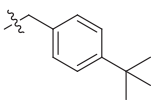
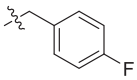
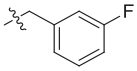
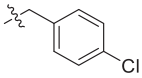
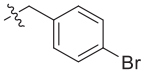
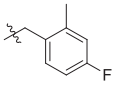
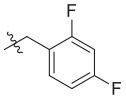
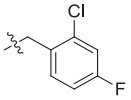
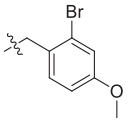
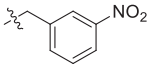
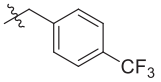
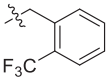
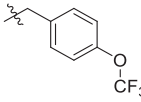
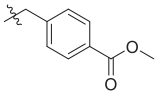
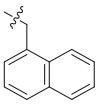
Table 1
The SAR study on the carboxamide group (R_1).

Compd. NO.	R_1	IC_{50}(μM) EBOV	IC_{50}(μM) MARV	CC_{50}(μM)	SI EBOV	SI MARV
1 (CP19)		3.4 ± 0.6	29.5 ± 11.7	> 100	29.4	3.4
2		5.9 ± 2.1	5.6 ± 1.5	95.5 ± 4.5	16.1	17.2
3		3.0 ± 1.1	3.2 ± 0.9	> 100	33.3	31.6
4		> 100	> 100	> 100	1	1
5		81.3 ± 18.8	> 100	> 100	1.2	1
6		> 100	> 100	> 100	1	1
7		1.3 ± 0.3	2.2 ± 0.5	> 100	75.0	45.5
8		8.9 ± 1.9	8.4 ± 1.6	53.4 ± 3.7	6.0	6.3
9		Q1	2.4 ± 0.2	40.3 ± 2.6	14.6	16.6
10		2.2 ± 0.8	2.2 ± 0.7	38.2 ± 3.8	17.4	17.1
11		3.6 ± 1.0	5.9 ± 0.8	54.9 ± 8.3	15.6	9.3
12		1.3 ± 0.3	1.7 ± 0.3	27.4 ± 6.5	20.5	16.4
13		0.9 ± 0.1	2.7 ± 0.4	> 100	111.1	36.6
14		3.5 ± 0.3	3.5 ± 0.6	87.3 ± 12.7	24.9	24.9
15		2.1 ± 0.0	2.8 ± 0.7	93.0 ± 7.0	44.3	33.2
16		> 100	> 100	> 100	1	1
17		> 100	> 100	> 100	1	1
18		10.2 ± 2.0	8.8 ± 0.4	> 100	9.8	11.3

2.6. The binding model of compound 32 in GP protein

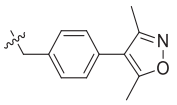
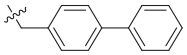
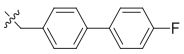
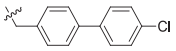
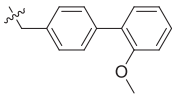
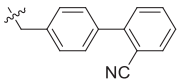
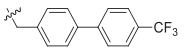
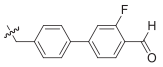
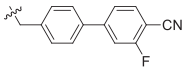
Compound **CP19** has been shown to target a late step of Ebola virus entry, very likely via binding to the GP to prevent GP-mediated fusion event. Its analog compound **32** has a similar structure to compound **118a**, which has been reported to be able to bind EBOV GP and inhibit virus entry. Thus, based on the crystal structure of EBOV GP complexed with compound **118a**, we located a few key amino acid residues which might be involved in the GP-compound **32** interaction. Then we evaluated the inhibitory activities of compound **32** against a few EBOV pseudovirions carrying mutated glycoprotein. Compound **32** did not show obvious loss of activity against EBOV pseudovirions carrying glycoprotein mutant N61A, N61V, N61D (Fig. 2A) or D522A (Fig. 2B). These data suggest

Table 2
The SAR studies on the C-3 of coumarin (R_2).

Compd. NO.	R_2	IC_{50}(μM) EBOV	IC_{50}(μM) MARV	CC_{50}(μM)	SI EBOV	SI MARV
19		9.3 ± 0.9	8.4 ± 0.7	> 100	10.8	12.0
20		11.7 ± 2.0	5.8 ± 1.7	14.7 ± 1.3	1.3	2.5
21		1.1 ± 0.1	1.1 ± 0.1	89.3 ± 5.0	78.8	83.7
22		1.6 ± 0.4	2.4 ± 0.2	53.3 ± 9.2	34.0	22.5
23		2.5 ± 0.5	2.9 ± 0.3	40 ± 0.2	16.3	13.8
24		0.9 ± 0.1	1.2 ± 0.2	> 100	111.1	85.7
25		1.2 ± 0.3	3.0 ± 0.7	> 100	81.1	33.3
26		1.2 ± 0.1	4.2 ± 0.4	> 100	81.1	23.6
27		3.1 ± 1.0	11.9 ± 5.4	90.8 ± 2.5	29.0	7.7
28		2.5 ± 0.1	5.2 ± 1.0	44.4 ± 2.9	18.0	8.6
29		3.7 ± 1.4	2.7 ± 0.9	90.5 ± 9.5	24.2	33.5
30		1.1 ± 0.0	1.1 ± 0.1	89.3 ± 5.0	78.8	83.7
31		1.6 ± 0.1	3.0 ± 0.3	> 100	63.8	33.0
32		0.5 ± 0.0	1.2 ± 0.1	68.2 ± 14.3	136.4	56.8
33		7.5 ± 1.9	9.1 ± 2.2	> 100	13.3	11.0
34		1.5 ± 0.4	1.2 ± 0.1	42.4 ± 8.2	28.5	36.6

(*continued on next page*)

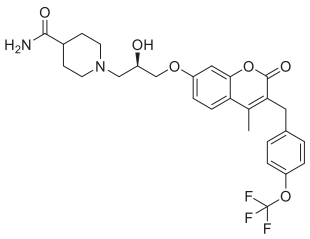
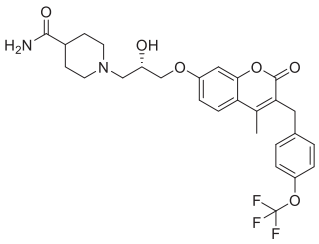
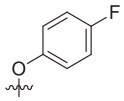
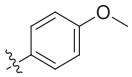
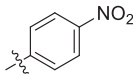
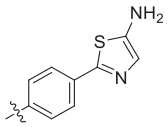
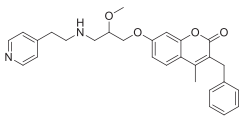
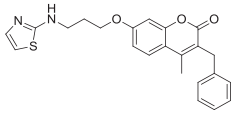
Table 2 (*continued*)

Compd. NO.	R_2	IC_{50}(μM) EBOV	IC_{50}(μM) MARV	CC_{50}(μM)	SI EBOV	SI MARV
35		5.2 ± 2.5	3.2 ± 0.8	36.9 ± 1.4	7.1	11.4
36		0.7 ± 0.1	0.9 ± 0.0	> 100	142.9	111.1
37		1.5 ± 0.2	1.1 ± 0.1	19.3 ± 2.7	13.1	18.1
38		1.4 ± 0.4	1.0 ± 0.4	32.9 ± 10.3	22.9	31.8
39		1.5 ± 0.4	2.1 ± 0.1	91.6 ± 7.3	16.6	30.0
40		1.8 ± 0.7	1.8 ± 0.2	33.2 ± 4.2	17.5	18.2
41		1.2 ± 0.0	1.3 ± 0.3	> 100	85.7	76.9
42		10.9 ± 0.3	5.2 ± 1.5	62.4 ± 10.8	5.7	11.9
43		3.5 ± 0.1	2.3 ± 0.6	29.1 ± 9.4	8.2	12.8

that the carboxamide piperidine group of compound **32** does not have key interaction with N61 or D522 of Ebola GP, which is substantially different to the interaction profile of compound **118a**, even though these two compounds have the same carboxamide group. Moreover, compound **32** showed ~3 fold lower activity against the infection of pseudovirion carrying Y517S mutant compared with the WT pseudovirions (Fig. 2C). It has been shown that methylpyrazole group of compound **118a** interacts with Y517 via ring stacking and chlorophenyl ring of compound **118a** binds to a hydrophobic pocket formed by V106, A101, L515 and Y517. These data indicates that the trifluomethoxybenzyl group of compound **32** binds to the hydrophobic pocket close to Y517 via hydrophobic interaction or/and ring stacking interaction like compound **118a**.

To further elucidate the binding mechanism of compound **32**, we performed molecular docking simulations with the crystal structure of Ebola glycoprotein complexed with compound **118a**. The co-crystal structure (PDB: 6HRO) was prepared by removing all ligands and unrelated water molecules and the whole protein was used as binding pocket for compound **32**. The docking results showed that the model of compound **32** with the highest binding affinity score bound to the same pocket as the reported molecule I of compound **118a**[22] (Fig. 3A). Thus this pocket was chosen for further docking studies. As shown in Fig. 3B, except the carboxamide part, compound **32** has a similar binding pose to that of compound **118a** [1]: The linker moiety of compound **32** takes almost the same pose as the ethyl moiety of **118a**. Although the linker of compound **32** is one carbon-carbon bond longer than that of **118a** and possesses a hydroxyl group that **118a** does not have, neither the linker chain nor the hydroxyl group produces key interactions with EBOV GP. Moreover, the docking results of compound **32** showed that the hydroxyl groups is in the "neck" of the tunnel-like binding pocket, which is consistent with the SAR results that the substitutions on the hydroxyl group reduced activity (Fig. S1) [2]. The coumarin moiety of compound **32** occupies similar space as the phenol group of **118a**. Due to the lack of ring structure between coumarin and benzyl group on C-3, compound **32** does not form ring stacking with Y517 as the methylpyrazole group of compound **118a** does. The oxygen atoms of the lactone structure of compound **32** does not form hydrogen bond with GP protein, which is comparable with the fact that the phenol group of **118a** is not involved in key interactions with GP protein [3]. The trifluomethoxybenzyl group of compound **32** also has a very similar pose as the *o*-chlorobenzene of **118a**. However, because lack of the σ-hole in the fluorine atom, compound **32** (Fig. 3C) cannot form the critical halogen bond with G67 which was an important contributor for the high efficacy of **118a** (Fig. 3D). In the SAR studies of this part, we synthesized compounds (**23, 24 27** and **28**) which had halogen substitutions on the benzene, but none of them increased antiviral activities. We also performed docking studies of compound **23** and **24** with 4-chlorobenzyl and 4-bromobenzyl groups respectively, but these two compounds did not form halogen bond with G67 in the docking results. These results are consistent with the halogen-bond requirement that the carbonyl group of amino acid residues must strictly point to the σ-hole in the halogen atom of the ligand to form the electrostatic interactions. Moreover, the docking results show that the carboxamide group of compound **32** forms H-bond with R164 but does not interact with N61 or R587 as compound **118a** does, probably due to that glycerol linker of compound **32** is longer than the ethyl linker of compound **118a**, which may afford more freedom for carboxamide and cause more entropy loss in binding process. Finally, we compared the binding mechanism of compound **32** in glycoprotein of Ebola virus (PDB: 6HRO) and Marburg Virus (PDB: 6BP2) with docking studies. Compound **32** is shown to bind in the same binding pocket in glycoprotein of Marburg virus as it does in Ebola GP, but in an obviously different pose. The oxygen atom of coumarine ring may form hydrogen bond with Gly547 and the nitrogen atom of piperidine ring may form hydrogen bind with Glu45 of Marburg GP (Fig. S2).

Table 3
The SAR study on the linker (R_3).

Compd. NO.	R_3	IC_{50}(μM) EBOV	IC_{50}(μM) MARV	CC_{50}(μM) MARV	SI EBOV	SI MARV
44 (R)		0.9 ± 0.1	1.4 ± 0.2	52.0 ± 14.3	55.7	36.3
45 (S)		0.7 ± 0.1	1.4 ± 0.3	64.9 ± 11.6	92.6	46.3
46		22.5 ± 6.4	20.3 ± 5.6	79.6 ± 9.0	3.5	3.9
47		10.4 ± 0.8	12.1 ± 2.3	66.4 ± 7.8	6.4	5.5
48		10.5 ± 2.0	8.0 ± 1.2	94.9 ± 5.1	9.1	11.9
49		16.0 ± 5.6	8.2 ± 1.7	94.8 ± 3.2	5.9	11.5
50		14.2 ± 7.1	13.4 ± 4.3	> 100	7.0	7.4
51		2.8 ± 0.4	1.7 ± 0.3	16.6 ± 7.5	5.9	9.6
52		18.0 ± 1.7	16.0 ± 0.7	50.1 ± 1.4	2.8	3.1

3. Materials and methods

3.1. Cell culture

Human embryonic kidney cells (239T, ATCC# CRL-1573), human lung epithelial cells (A549, ATCC#CCL185) were cultured in DMEM (Cellgro, Manassas, VA, USA) supplemented with 10% fetal bovine serum (FBS, Sigma, St. Louis, MO, USA), 100 μg/mL of streptomycin and 100 units of penicillin (Invitrogen, Carlsbad, CA, USA).

3.2. Generation of Zaire Ebolavirus glycoprotein mutants

Plasmid containing the Zaire Ebolavirus glycoprotein gene was mutated using the Agilent Technologies QuickChange Lightning Site-Directed Mutagenesis Kit (Agilent, Santa Clara, CA, USA). Primer pairs were designed using QuickChange Primer Design program and purchased through Sigma (Sigma, St. Louis, MO, USA). Plasmids containing GP mutations were made following manufacturer's instructions and were sequenced to ensure the correct mutation.

3.3. Pseudovirion infection assay and cell viability assay

The HIV/MARV and HIV/EBOV pseudovirions were generated by transient co-transfection of replication-defective HIV vector (pNL4-3.Luc.R-E-) and plasmid encoding MARV GP or EBOV GP into 293T

Table 4
The SAR studies on the C-4 of coumarin (R_4).

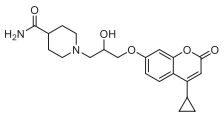
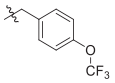
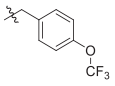
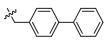
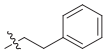
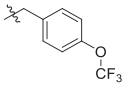
Compd. NO	R_4	IC_{50}(μM) EBOV	IC_{50}(μM) MARV	CC_{50}(μM) MARV	SI EBOV	SI MARV
53		9.4 ± 1.6	6.5 ± 2.7	> 100	10.6	15.3
54		2.9 ± 1.0	2.2 ± 0.7	25.2 ± 2.4	8.6	11.6
55		17.7 ± 4.2	33.5 ± 0.5	> 100	5.7	3.0

Table 5
The synergy of all R_1, R_2 and R_3 groups.

Compd. NO.	R_1	R_2	IC_{50}(μM) EBOV	IC_{50}(μM) MARV	CC_{50}(μM) MARV	SI EBOV	SI MARV
56			1.5 ± 0.1	1.2 ± 0.2	99.0 ± 0.9	66	82.5
57			2.2 ± 0.5	1.3 ± 0.1	14.3 ± 0.9	6.6	10.7
58			2.7 ± 0.4	1.3 ± 0.4	38.1 ± 2.4	14.1	29.3
59			3.4 ± 0.9	1.3 ± 0.2	42.2 ± 0.8	12.4	32.5

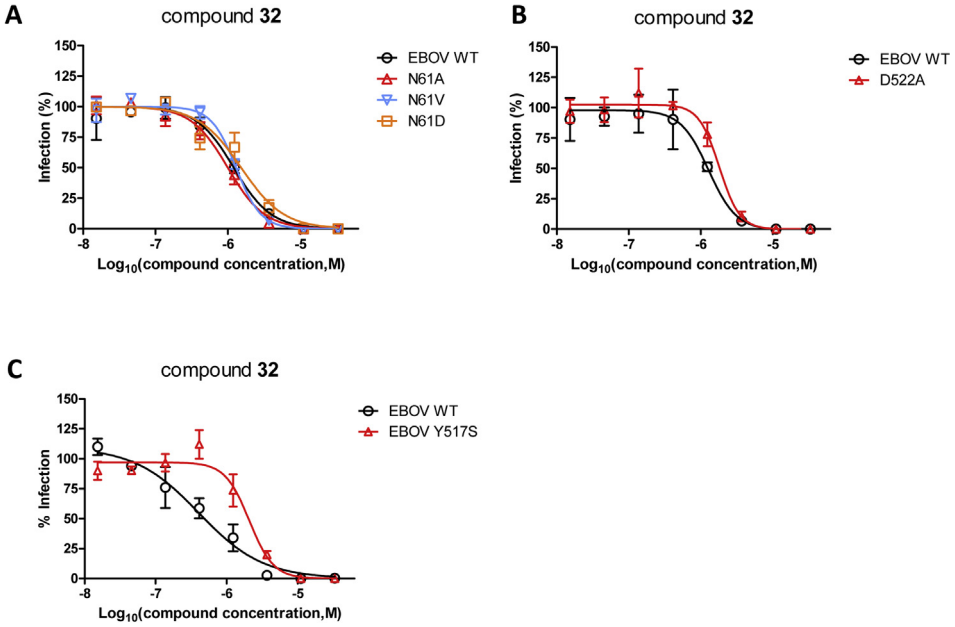


Fig. 2. The *in vitro* dose-response curves of compound **32** are shown in **(A)** against the infections of pseudotyped EBOV carrying wild-type GP (black) or GP with N61A (red), N61V(blue) or N61D (orange), **(B)** GP with D522A (red), and **(C)** GP with Y517S (red) in A549 cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

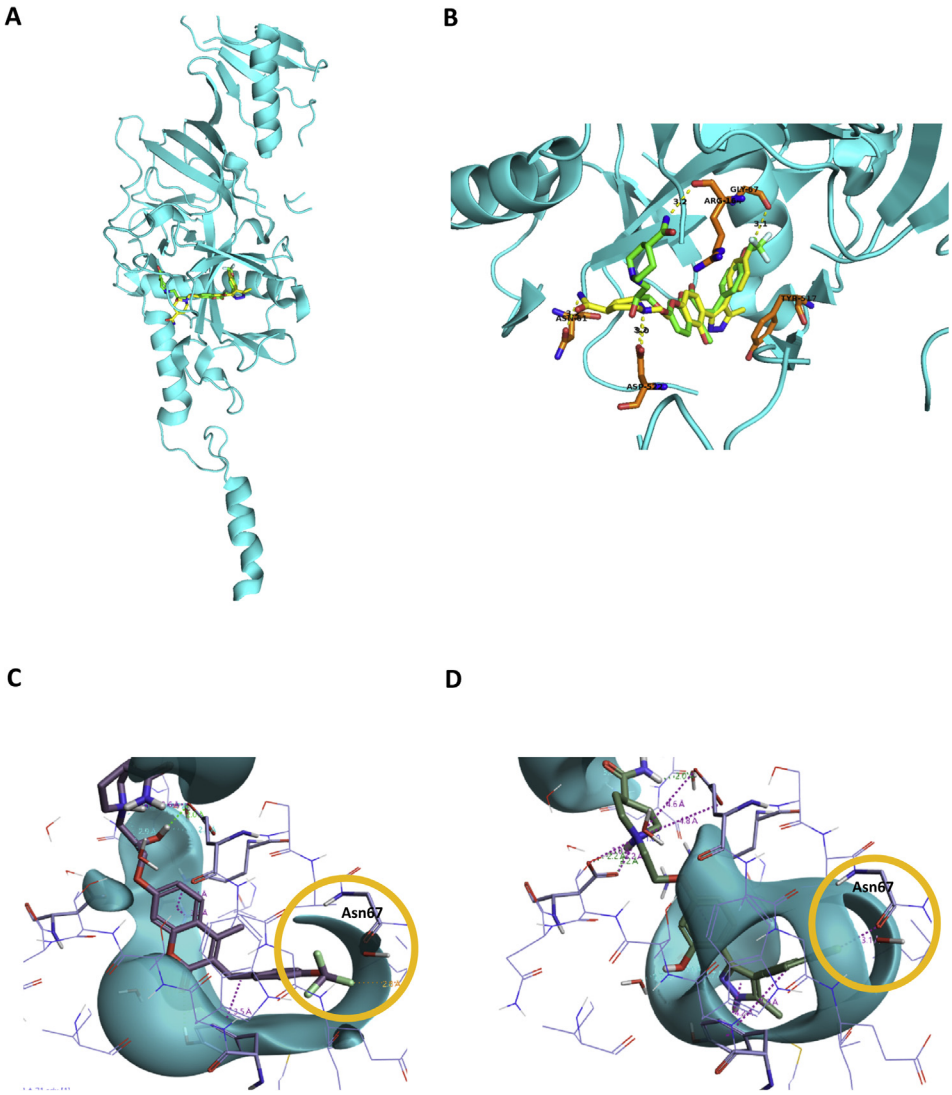


Fig. 3. The molecular docking studies of compound **32**. (A) Compound **32** (Green) bound in the GP protein, sharing the binding site of compound **118a** (Yellow). (B) The details of the interactions of compound **32** with GP protein, comparing with **118a**. The carboxamide formed a hydrogen bond with R164 with distance 3.2 Å between the nitrogen atom of carboxamide and the oxygen atom carbonyl group of R164. The carboxamide of comound 118a formed H-bond with N61. The trifluoromethoxy group on the benzene of compound **32** could not form hydrogen bond as the o-chloride group of **118a** did. (C) The fluorine atom in trifluoromethoxyl group of compound **32** could not form halogen bond with Asn67 (yellow circle) because the fluorine atom does not have σ-hole (yellow circle). The electrostatic density is shown in blue. (D) The Chlorine atom in *o*-chlorobezene group of compound **118a** formed halogen bond with N67 via the σ-hole on chlorine (yellow circle). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

cells, using a polyethylenimine (PEI)-based transfection protocol. Six hours after transfection, cells were washed with phosphate-buffered saline (PBS) and 20 mL of fresh media was added to each plate (150 mm). Twenty-four hours post-transfection, the supernatants were collected and filtered through 0.45 μm pore size filter (Nalgene, Rochester, NY, USA). The pseudovirion stocks were stored at 4 °C prior to use.

Low-passage A549 cells were seeded at the density of 5000/well in 96-well plates 24 h before infection. The synthesized compounds were prepared as 3-fold serial dilutions and mixed with HIV/MARV or HIV/EBOV pseudotyped virus or fresh media for IC_{50} and CC_{50} evaluation. The A549 cells were incubated with 100 μL/well of above-mentioned mixtures for 48 h. The luciferase activity of infected A549 cells was quantified using the neolite Reporter Gene Assay System (PerkinElmer, Waltham, MA, USA). The cell viability was measured with the CellTiter-Glo kit (Promega, Madison, WI, USA). Cells incubated with virus or medium alone was used as the negative controls and the signals from these cells were used for data normalization. IC_{50} and CC_{50} values were determined by fitting the dose-response curves with logistic regression in GraphPad.

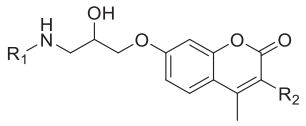
General Methods for Chemistry. All starting materials were commercially available and used without further purification. All reactions were carried out with the use of standard techniques under an inert atmosphere (Ar or N2). NMR spectra were generated on a Bruker 500 or 400 MHz instrument and obtained as CDCl3 or DMSO-d_6 solutions (reported in ppm), using CDCl3 as the reference standard (7.26 ppm) or DMSO-d_6 (2.50 ppm). Mass spectral data (ESI) were gathered on Thermofisher LCQ or QE Mass spectrometry. HPLC (Agilent Prostar 218 or 1200) was employed for purity determination, using the following method: Eclipse XDB C18 column, 5 μm, 4.6 mm × 150 mm, column temperature 40 °C; solvent A: H_2O or 0.1 formic acid in H_2O; solvent B: methanol or ACN; gradient of 40–70% B (0–10 min), 70–90% B (10–15 min), 90–40% B (15–20 min), with minor adjustoin according to the retention

time of the target compounds; flow rate of 1.5 mL/min. Compound purity was determined by high pressure liquid chromatography (HPLC) with a confirming purity of ≥95% for all of the final biologically tested compounds.

3.4. Synthesis of derivatives of CP19

The syntheses of derivatives of CP19 in this study were performed according to the methods in Scheme 2 with minor modifications as described in each compounds.

Reagents and conditions:(a) Ethyl acetoacetate, Benzyl bromide, CH_3ONa, Methonal, RT→68 °C, 0.5 h; (b) Resorcino, PPA, 65 °C, 4 h, 67%; (c) Epichlorohydrin, K_2CO_3, TBAB, 80 °C, 2.3 h, 81%; (d)Organic amine, $AcNMe_2$, 50 °C, 24 h, 85%.



Reagents and conditions:(a) Ethyl acetoacetate, 4-(Trifluoro methoxy)benzyl bromide, CH_3ONa, Methonal, RT→68 °C, 0.5 h; (b) Resorcino, PPA, 65 °C, 4 h, 67%; (c) (R)-(-)-Epichlorohydrin or (S)-(+)-Epichlorohydrin, K_2CO_3, TBAB, 80 °C, reflux 2.3 h, 53%; (d) Hexahydroisonicotinamide, $AcNMe_2$, 50 °C, 24 h, 89%.

3.4.1. 1-(3-((3-benzyl-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide [1]

A mixture of ethyl acetoacetate (5 mmol) and CH_3ONa (1 eq) in MeOH (4 mL) was stirred at room temperature for 10 min. Then, benzyl bromide derivatives (1.1 eq) in 5 mL MeOH was added dropwise when the reaction solution was slightly boiling. The reaction mixture was continued to heat under reflux until it was almost neutral. After cooling, the reaction solution was filtered off and concentrated by vacuum to give ethyl acetoacetate derivatives.

To a stirred solution of the above mentioned products in PPA 3 g, resorcino (1 eq) was added. The reaction mixture was stirred at 65 °C for 4 h. The mixture solution had to rest overnight, then diluted with 100 mL water. The precipitated solid was filtered off, washed with water to give the crude product. The crude product was purified by silica gel chromatography using cyclohexane-ethyl acetate as eluate to give 7-hydroxy-chromen-2-one derivatives (67%).

A mixture of the above products, epichlorohydrin (1–3 mL), potassium carbonate (2 eq) and TBAB (1 eq) was stirred at 80 °C for 2.3 h. Then the mixture was extracted with ethyl acetate, washed with water. The organic phase was collected and the solvent was removed under vacuum. The product was purified by silica gel chromatography using cyclohexane-ethyl acetate as eluate to give 4-methyl-7-(oxiran-2-ylmethoxy)-chromen-2-one derivatives(81%).

The above mentioned products was added to a stirred solution of organic amine (2.5 eq) in 1–2 mL dimentylacetamide then the reaction mixture was stirred at 50 °C for 24 h. The reaction solution was allowed to cool to room temperature and concentrated by vacuum. The residue was dissolved in acetone, absorbed onto silica and purified by flash column chromatography using dichloro methane-methanol as eluate to give compound NO.**1** (85%).

^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, J = 9.5 Hz, 1H), 7.25 (t, J = 7.4 Hz, 3H), 7.17 (dd, J = 17.2, 8.6 Hz, 4H), 6.99–6.90 (m, 2H), 4.11–4.01 (m, 1H), 3.97–3.94 (m, 2H), 3.93 (s, 2H), 2.90 (d, J = 11.2 Hz, 1H), 2.84 (d, J = 11.2 Hz, 1H), 2.40 (d, J = 6.6 Hz, 3H), 2.33 (dd, J = 12.6, 5.8 Hz, 1H), 2.08–1.86 (m, 4H), 1.61 (d, J = 2.4 Hz, 2H), 1.57–1.46 (m, 2H). ESI-MS m/z: 451.07 $[M+H]^+$.

^{13}C NMR (101 MHz, DMSO) δ 178.42 (s), 163.11 (s), 155.18 (s), 150.19 (s), 141.16 (s), 130.25 (s), 129.86 (s), 128.42 (s), 127.89 (s), 122.82 (s), 115.34 (s), 114.31 (s), 111.37 (s), 102.89 (s), 73.61 (s), 68.27 (s), 62.97 (s), 55.50 (d, J = 9.7 Hz), 43.47 (s), 33.97 (s), 30.45 (s), 17.02 (s).

3.4.2. 3-Benzyl-7-(2-hydroxy-3-(prop-2-yn-1-ylamino)propoxy)-4-methyl-2H-chromen-2-one [2]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, J = 9.6 Hz, 1H), 7.27–7.22 (m, 2H), 7.20 (d, J = 7.0 Hz, 2H), 7.16 (d, J = 7.1 Hz, 1H), 6.98–6.92 (m, 2H), 4.07 (dd, J = 10.0, 4.1 Hz, 1H), 3.98–3.93 (m, 2H), 3.93 (s, 2H), 3.75 (dd, J = 5.7, 2.4 Hz, 1H), 3.08 (s, 1H), 3.04 (t, J = 2.4 Hz, 1H), 2.93 (s, 1H), 2.77 (s, 1H), 2.67–2.64 (m, 2H), 2.62 (s, 1H), 2.41 (s, 3H), 1.97 (s, 1H), 1.94 (s, 1H). ESI-MS m/z: 377.16 $[M+H]^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.02 (s), 155.17 (s), 150.22 (s), 141.15 (s), 130.26 (s), 129.85 (s), 128.43 (s), 127.90 (s), 122.84 (s), 115.36 (s), 114.36 (s), 102.86 (s), 84.66 (s), 75.63 (s), 74.85 (s), 73.20 (s), 70.17 (s), 69.75 (s), 67.05 (s), 52.74 (s), 48.37 (s), 39.46 (s), 33.96 (s), 31.62 (s), 17.02 (s).

3.4.3. 3-Benzyl-7-(3-((cyclopropylmethyl)amino)-2-hydroxypropoxy)-4-methyl-2H-chromen-2-one [3]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (400 MHz, DMSO) δ 7.28–7.14 (m, 6H), 6.95 (dd, J = 6.0, 2.4 Hz, 2H), 4.07 (dd, J = 10.0, 4.3 Hz, 1H), 3.97 (dd, J = 10.0, 6.1 Hz, 1H), 3.93 (s, 2H), 3.90 (d, J = 4.6 Hz, 1H), 2.70 (d, J = 4.9 Hz, 1H), 2.65 (d, J = 6.9 Hz, 1H), 2.44 (s, 1H), 2.41 (s, 3H), 2.33 (d, J = 12.6 Hz, 1H), 0.39 (ddd, J = 8.0, 5.6, 4.0 Hz, 2H), 0.09 (dt, J = 15.4, 7.6 Hz, 2H). ESI-MS m/z: 394.23 $[M+H]^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.02 (s), 155.18 (s), 150.19 (s), 141.16 (s), 130.25 (s), 129.86 (s), 128.43 (s), 127.89 (s), 122.85 (s), 115.36 (s), 114.35 (s), 102.86 (s), 73.22 (s), 69.60 (s), 55.88 (s), 53.65 (s), 33.97 (s), 17.02 (s), 12.64 (s), 5.08 (s).

3.4.4. 3-Benzyl-7-(2-hydroxy-3-(phenylamino)propoxy)-4-methyl-2H-chromen-2-one [4]

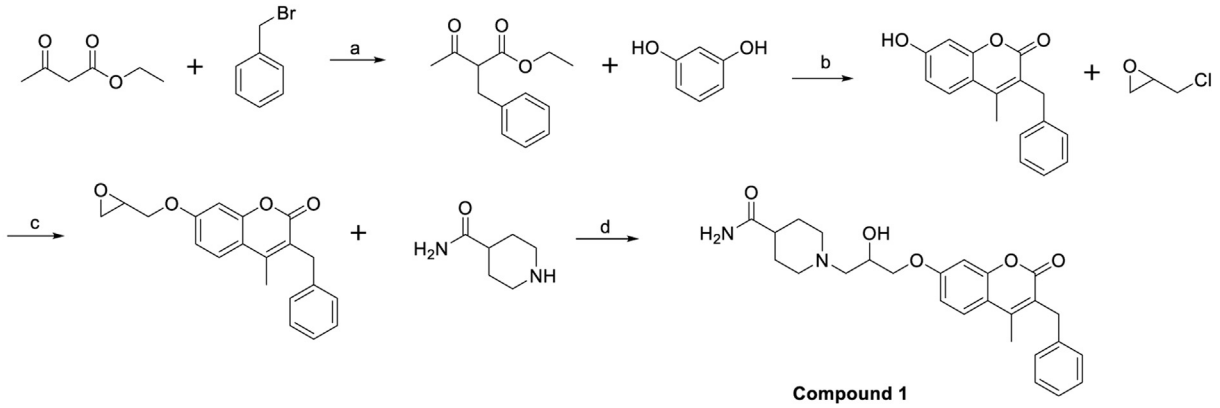
The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (400 MHz, DMSO) δ 7.74–7.68 (m, 1H), 7.26–7.14 (m, 5H), 7.04 (dd, J = 8.4, 7.4 Hz, 2H), 6.97 (dd, J = 6.9, 2.4 Hz, 2H), 6.60 (d, J = 7.7 Hz, 2H), 6.50 (t, J = 7.2 Hz, 1H), 4.12 (dd, J = 9.8, 3.8 Hz, 1H), 4.06–3.97 (m, 2H), 3.93 (s, 2H), 3.24–3.18 (m, 1H), 3.13–3.04 (m, 1H), 2.41 (s, 3H), 1.40–1.18 (m, 2H). ESI-MS m/z: 415.97 $[M+H]^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.04 (d, J = 8.2 Hz), 155.17 (s), 150.60 (s), 150.19 (s), 141.15 (s), 130.72 (s), 130.26 (s), 129.86 (s), 128.44 (s), 127.90 (s), 122.87 (s), 117.57 (s), 115.39 (s), 114.36 (s), 113.96 (s), 102.87 (s), 72.88 (s), 69.22 (s), 47.91 (s), 33.97 (s), 17.03 (s).

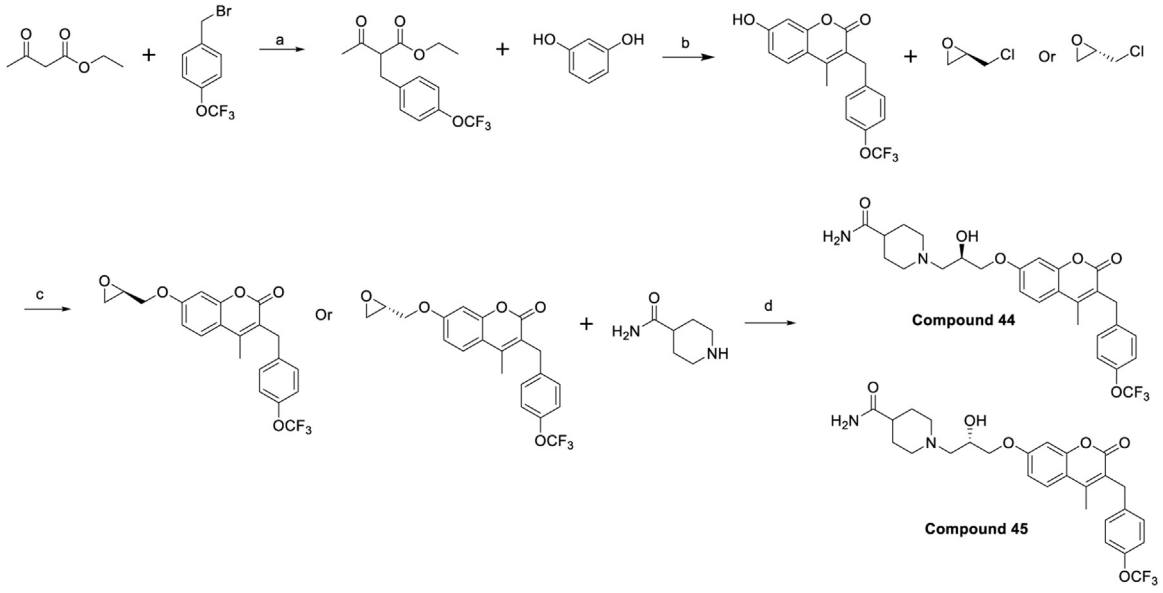
3.4.5. 3-Benzyl-7-(2-hydroxy-3-((2-hydroxy-5-nitrophenyl)amino)propoxy)-4-methyl-2H-chromen-2-one [5]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, J = 9.3 Hz, 1H), 7.44 (dd, J = 8.6, 2.7 Hz, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.27–7.22 (m, 2H), 7.20 (d, J = 7.1 Hz, 2H), 7.16 (t, J = 7.1 Hz, 1H), 7.01–6.96 (m, 2H), 6.78 (d, J = 8.6 Hz, 1H), 4.14–4.10 (m, 1H), 4.09–4.05 (m, 2H), 3.93 (s, 2H), 3.15 (d, J = 5.0 Hz, 3H), 2.93 (s, 1H), 2.77 (s, 1H), 2.41 (s, 3H). ESI-MS m/z: 475.64 $[M+H]^-$.

^{13}C NMR (101 MHz, DMSO) δ 163.35–163.11 (m), 162.96 (d, J = 20.6 Hz), 155.16 (s), 152.85 (s), 150.17 (s), 142.34 (s), 141.14 (s), 139.70 (s), 130.25 (s), 129.85 (s), 128.43 (s), 127.89 (s), 122.90 (s), 115.26 (d, J = 38.6 Hz), 114.16 (d, J = 31.8 Hz), 113.99–113.71 (m), 105.03 (s), 102.88 (s), 72.82 (s), 68.96 (s), 47.64 (s), 33.97 (s), 17.01 (s).



Reagents and conditions:(a) Ethyl acetoacetate, Benzyl bromide, CH_3ONa, Methonal, RT→68°C, 0.5h; (b) Resorcino, PPA, 65°C, 4h, 67%; (c) Epichlorohydrin, K_2CO_3, TBAB, 80°C, 2.3h, 81%;(d)Organic amine, $AcNMe_2$, 50°C, 24h, 85%.



Reagents and conditions:(a) Ethyl acetoacetate, 4-(Trifluoromethoxy)benzyl bromide, CH_3ONa, Methonal, RT→68℃, 0.5 h; (b) Resorcino, PPA, 65°C, 4 h, 67%; (c) (R)-(-)-Epichlorohydrin or (S)-(+)-Epichlorohydrin, K_2CO_3, TBAB, 80℃, reflux 2.3 h, 53%;(d) Hexahydroisonicotinamide, $AcNMe_2$, 50℃, 24 h, 89%.

Scheme 2. The synthesis route of the target compounds.

3.4.6. 3-Benzyl-7-(3-((4-bromophenyl)amino)-2-hydroxypropoxy)-4-methyl-2H-chromen-2-one [6]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.73−7.69 (m, 1H), 7.25 (t, J = 7.4 Hz, 2H), 7.20 (d, J = 7.1 Hz, 2H), 7.18−7.15 (m, 3H), 6.97 (dd, J = 5.7, 2.4 Hz, 2H), 6.57 (d, J = 8.9 Hz, 2H), 4.09 (dd, J = 10.0, 4.1 Hz, 1H), 4.03 (dd, J = 10.0, 5.9 Hz, 1H), 3.97 (dd, J = 10.3, 5.2 Hz, 1H), 3.93 (s, 2H), 3.20 (dd, J = 12.8, 6.4 Hz, 1H), 3.07 (dd, J = 12.5, 6.4 Hz, 1H), 2.41 (s, 3H). ESI-MS m/z: 494.20 $[M+H]^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.01 (d, J = 12.6 Hz), 155.17 (s), 150.19 (s), 149.93 (s), 141.15 (s), 133.18 (s), 130.26 (s), 129.86 (s), 128.44 (s), 127.90 (s), 122.89 (s), 115.86 (s), 115.42 (s), 114.35 (s), 108.03 (s), 102.89 (s), 72.74 (s), 69.12 (s), 47.83 (s), 33.97 (s), 17.03 (s).

3.4.7. 3-Benzyl-7-(3-(benzylamino)-2-hydroxypropoxy)-4-methyl-2H-chromen-2-one [7]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (400 MHz, DMSO) δ 7.70 (d, J = 9.6 Hz, 1H), 7.34–7.17 (m, 10H), 6.94 (dd, J = 7.2, 2.4 Hz, 2H), 4.09 (dd, J = 9.9, 4.1 Hz, 1H), 3.97 (dd, J = 9.9, 6.2 Hz, 2H), 3.93 (s, 2H), 3.71 (s, 2H), 2.61 (ddd, J = 18.3, 11.9, 5.8 Hz, 2H), 2.41 (s, 3H), 2.32 (d, J = 14.1 Hz, 1H). ESI-MS m/z: 430.24 [M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.06 (s), 155.18 (s), 150.20 (s), 142.62 (s), 141.17 (s), 130.25 (s), 130.08–129.47 (m), 127.89 (s), 122.83 (s), 115.33 (s), 114.37 (s), 102.84 (s), 73.24 (s), 69.89 (s), 54.89 (s), 53.40 (s), 33.97 (s), 17.02 (s).

3.4.8. 3-Benzyl-7-(2-hydroxy-3-((3-hydroxypropyl)amino) propoxy)-4-methyl-2H-chromen-2-one [8]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.71 (s, 1H), 7.24 (d, J = 7.2 Hz, 3H), 7.21 (s, 3H), 7.17 (d, J = 7.1 Hz, 2H), 6.95 (d, J = 2.5 Hz, 1H), 4.07 (dd, J = 9.6, 3.8 Hz, 2H), 4.00–3.96 (m, 2H), 3.93 (s, 3H), 3.45 (t, J = 6.2 Hz, 4H), 2.93 (s, 1H), 2.81–2.77 (m, 1H), 2.77 (s, 1H), 2.69 (dd, J = 9.2, 4.7 Hz, 4H), 2.40 (s, 3H), 1.94 (s, 1H), 1.60 (d, J = 6.7 Hz, 2H), 1.22 (s, 2H). ESI-MS m/z: 397.90 [M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 162.99 (d, J = 16.5 Hz), 155.16 (s), 150.19 (s), 141.15 (s), 130.26 (s), 129.86 (s), 128.44 (s), 127.90 (s), 122.89 (s), 115.41 (s), 114.34 (s), 102.88 (s), 72.99 (s), 68.88 (s), 60.91 (s), 53.38 (s), 48.27 (s), 33.97 (s), 33.30 (s), 17.03 (s).

3.4.9. 3-Benzyl-7-(2-hydroxy-3-((6-hydroxyhexyl)amino) propoxy)-4-methyl-2H-chromen-2-one [9]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, J = 9.6 Hz, 1H), 7.24 (d, J = 7.3 Hz, 2H), 7.20 (d, J = 7.0 Hz, 2H), 7.17 (d, J = 7.1 Hz, 1H), 6.95 (dd, J = 6.1, 2.5 Hz, 2H), 4.06 (dd, J = 10.0, 4.2 Hz, 1H), 3.95 (dd, J = 10.1, 6.3 Hz, 1H), 3.93 (s, 2H), 3.88–3.82 (m, 1H), 3.37 (d, J = 6.5 Hz, 2H), 2.64 (d, J = 5.2 Hz, 1H), 2.62 (d, J = 5.0 Hz, 1H), 2.57 (s, 1H), 2.56 (s, 1H), 2.40 (d, J = 9.0 Hz, 3H), 2.22 (s, 1H), 1.39–1.36 (m, 5H), 1.26–1.24 (m, 4H). ESI-MS m/z: 439.98 [M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.07 (s), 155.18 (s), 150.20 (s), 141.16 (s), 130.25 (s), 129.85 (s), 128.41 (s), 127.89 (s), 122.82 (s), 115.32 (s), 114.34 (s), 102.84 (s), 73.28 (s), 69.80 (s), 62.49 (d, J = 6.9 Hz), 54.12 (s), 51.30 (s), 34.68–33.89 (m), 31.47 (s), 28.58 (s), 27.34 (s), 27.10 (s), 17.02 (s).

3.4.10. 3-Benzyl-7-(2-hydroxy-3-((tetrahydro-2H-pyran-4-yl) amino)propoxy)-4-methyl-2H-chromen-2-one [10]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, J = 9.2 Hz, 1H), 7.31–7.11 (m, 5H), 6.96 (d, J = 7.9 Hz, 2H), 4.07 (dd, J = 10.0, 4.2 Hz, 1H), 3.97 (dd, J = 10.1, 6.1 Hz, 2H), 3.93 (s, 2H), 3.85 (d, J = 4.9 Hz, 1H), 3.81–3.74 (m, 2H), 3.27–3.17 (m, 2H), 2.70 (dd, J = 11.8, 5.1 Hz, 1H), 2.64–2.54 (m, 2H), 2.40 (d, J = 7.9 Hz, 3H), 1.73 (dd, J = 8.5, 4.5 Hz, 2H), 1.38 (s, 1H), 1.21 (dd, J = 18.3, 11.5 Hz, 2H). ESI-MS m/z: 424.21 [M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.05 (s), 155.18 (s), 150.18 (s), 141.16 (s), 130.25 (s), 129.85 (s), 128.41 (s), 127.89 (s), 122.83 (s), 115.33 (s), 114.36 (s), 102.84 (s), 73.24 (s), 70.08 (s), 67.64 (s), 55.23 (s), 50.58 (s), 35.06 (s), 33.97 (s), 17.02 (s).

3.4.11. 3-Benzyl-7-(2-hydroxy-3-((2-(pyridin-2-yl)ethyl)amino) propoxy)-4-methyl-2H-chromen-2-one [11]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 8.47 (d, J = 4.8 Hz, 1H), 7.71 (t, J = 7.1 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.27 (s, 1H), 7.24 (d, J = 7.3 Hz, 2H), 7.20 (d, J = 7.0 Hz, 3H), 7.17 (d, J = 7.2 Hz, 1H), 6.95 (d, J = 7.9 Hz, 2H), 4.09 (dd, J = 10.0, 4.2 Hz, 1H), 3.98 (dd, J = 9.9, 6.2 Hz, 1H), 3.93 (s, 3H), 3.81 (d, J = 2.2 Hz, 2H), 2.68 (dd, J = 11.8, 5.1 Hz, 1H), 2.61 (dd, J = 11.9, 6.5 Hz, 1H), 2.41 (s, 3H), 1.38 (s, 1H). ESI-MS m/z: 430.92 [M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.07 (d, J = 5.4 Hz), 162.02 (s), 155.18 (s), 150.60 (s), 150.20 (s), 141.16 (s), 138.28 (s), 130.26 (s), 129.86 (s), 128.42 (s), 127.89 (s), 123.67 (d, J = 7.3 Hz), 122.83 (s), 115.34 (s), 114.37 (s), 102.85 (s), 73.17 (s), 69.93 (s), 56.52 (s), 53.64 (s), 33.97 (s), 17.02 (s).

3.4.12. 3-Benzyl-7-(2-hydroxy-3-((2-(pyridin-3-yl)ethyl)amino) propoxy)-4-methyl-2H-chromen-2-one [12]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 8.43 (d, J = 1.8 Hz, 1H), 8.37 (dd, J = 4.7, 1.5 Hz, 1H), 7.73–7.68 (m, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.28–7.26 (m, 1H), 7.24 (d, J = 7.3 Hz, 2H), 7.21 (d, J = 7.0 Hz, 2H), 7.16 (t, J = 7.1 Hz, 1H), 6.94 (dd, J = 5.8, 2.4 Hz, 2H), 4.04 (dd, J = 10.0, 4.3 Hz, 1H), 3.95 (d, J = 6.2 Hz, 1H), 3.93 (s, 2H), 3.86 (d, J = 5.2 Hz, 1H), 2.76 (d, J = 6.2 Hz, 1H), 2.70 (dd, J = 12.0, 5.7 Hz, 3H), 2.66 (s, 1H), 2.63–2.57 (m, 1H), 2.41 (s, 3H). ESI-MS m/z: 444.83 [M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.06 (d, J = 5.7 Hz), 155.18 (s), 151.70 (s), 150.19 (s), 148.96 (s), 141.17 (s), 137.86 (d, J = 16.7 Hz), 130.26 (s), 129.86 (s), 128.41 (s), 127.89 (s), 125.13 (s), 122.84 (s), 115.34 (s), 114.33 (s), 102.84 (s), 73.22 (s), 69.86 (s), 53.86 (s), 52.49 (s), 34.76 (s), 33.97 (s), 17.02 (s).

3.4.13. 3-Benzyl-7-(2-hydroxy-3-((2-(pyridin-4-yl)ethyl)amino) propoxy)-4-methyl-2H-chromen-2-one [13]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 8.45 (d, J = 5.9 Hz, 1H), 8.40 (d, J = 5.9 Hz, 2H), 7.70 (d, J = 9.6 Hz, 1H), 7.27 (s, 1H), 7.25 (s, 1H), 7.23 (s, 2H), 7.22 (d, J = 4.9 Hz, 3H), 7.20 (s, 1H), 7.16 (t, J = 7.1 Hz, 1H), 6.95 (s, 2H), 6.93 (d, J = 2.5 Hz, 1H), 5.01 (d, J = 4.9 Hz, 1H), 4.05 (d, J = 4.3 Hz, 1H), 4.03 (d, J = 4.3 Hz, 1H), 3.95 (d, J = 6.1 Hz, 1H), 3.93 (d, J = 4.6 Hz, 2H), 3.86 (d, J = 5.3 Hz, 1H), 3.15 (d, J = 5.2 Hz, 1H), 2.78 (d, J = 6.6 Hz, 2H), 2.72 (d, J = 6.9 Hz, 2H), 2.69 (s, 1H), 2.66 (s, 1H), 2.60 (dd, J = 11.9, 6.6 Hz, 1H), 2.41 (s, 3H). ESI-MS m/z: 444.99[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 161.68 (d, J = 7.9 Hz), 153.80 (s), 150.50–150.07 (m), 149.87 (d, J = 21.1 Hz), 148.83 (s), 139.79 (s), 128.88 (s), 128.48 (s), 127.05 (s), 126.52 (s), 124.70 (s), 121.47 (s), 113.97 (s), 112.97 (s), 101.47 (s), 71.82 (s), 68.47 (s), 52.44 (s), 50.33 (s), 35.54 (s), 32.60 (s), 15.66 (s).

3.4.14. 3-Benzyl-7-(2-hydroxy-3-((thiophen-2-ylmethyl)amino) propoxy)-4-methyl-2H-chromen-2-one [14]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (400 MHz, DMSO) δ 7.72 (d, J = 8.7 Hz, 1H), 7.35 (dd, J = 4.7, 1.5 Hz, 1H), 7.29 (s, 1H), 7.27 (s, 1H), 7.25 (s, 1H), 7.22 (s, 1H), 7.20 (s, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 6.96 (d, J = 3.4 Hz, 2H), 6.94 (s, 2H), 4.09 (dd, J = 9.8, 3.9 Hz, 1H), 3.98 (t, J = 4.9 Hz, 2H), 3.94 (s, 2H), 3.92 (s, 2H), 2.73–2.62 (m, 2H), 2.42 (s, 3H). ESI-MS m/z: 435.94 [M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.06 (s), 162.86 (s), 155.16 (s), 152.86 (s), 150.17 (s), 142.34 (s), 141.14 (s), 139.70 (s), 130.25 (s), 129.85 (s), 128.43 (s), 127.89 (s), 122.90 (s), 115.45 (s), 115.06 (s), 114.32 (s), 114.00 (s), 105.03 (s), 102.88 (s), 72.82 (s), 68.96 (s), 50.43 (s), 47.64 (s), 33.97 (s), 17.01 (s).

3.4.15. 3-Benzyl-7-(2-hydroxy-3-(thiazol-2-ylamino)propoxy)-4-methyl-2H-chromen-2-one [15]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.72 (d, J = 9.5 Hz, 1H), 7.20 (qd, J = 14.6, 7.4 Hz, 6H), 6.98–6.92 (m, 2H), 6.73 (d, J = 4.9 Hz, 1H), 4.18–4.11 (m, 1H), 3.99 (dt, J = 14.3, 5.1 Hz,

2H), 3.93 (s, 2H), 3.89 (d, J = 4.2 Hz, 1H), 3.86 (s, 1H), 3.74 (dd, J = 14.0, 7.1 Hz, 1H), 2.93 (s, 1H), 2.77 (s, 1H), 2.41 (s, 3H). ESI-MS m/z: 423.13732[M+H] $^+$, delta (ppm) < 0.04.

^{13}C NMR (126 MHz, DMSO) δ 161.67 (s), 161.35 (s), 153.76 (s), 148.81 (s), 139.76 (s), 130.34 (s), 128.88 (s), 128.48 (s), 127.12 (s), 126.53 (s), 121.62 (s), 114.18 (s), 112.95 (s), 101.52 (s), 71.00 (s), 67.23 (s), 49.85 (s), 32.61 (s), 15.68 (s).

3.4.16. 7-(3-((1H-1,2,3-triazol-1-yl)amino)-2-hydroxypropoxy)-3-benzyl-4-methyl-2H-chromen-2-one [16]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.89 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.27 (s, 1H), 7.24 (d, J = 7.3 Hz, 2H), 7.20 (d, J = 7.0 Hz, 2H), 7.17 (d, J = 7.1 Hz, 1H), 6.99 (t, J = 2.8 Hz, 2H), 6.97 (s, 1H), 5.92 (s, 2H), 5.65 (d, J = 4.4 Hz, 1H), 4.08 (s, 1H), 4.05 (d, J = 4.2 Hz, 1H), 4.02 (d, J = 4.1 Hz, 1H), 3.98 (dd, J = 6.3, 3.6 Hz, 1H), 3.96–3.95 (m, 1H), 3.93 (s, 2H), 3.85 (dd, J = 14.5, 7.9 Hz, 1H), 2.90 (dd, J = 14.5, 7.2 Hz, 1H), 2.42 (s, 3H). ESI-MS m/z: 407.12 [M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.05 (s), 162.66 (s), 155.14 (s), 150.18 (s), 142.56 (s), 141.12 (s), 130.26 (s), 129.85 (s), 128.49 (s), 127.90 (s), 123.02 (s), 115.60 (s), 114.35 (s), 102.92 (s), 72.11 (s), 68.88 (s), 50.42 (s), 47.46 (s), 33.97 (s), 17.02 (s).

3.4.17. 7-(3-((1H-benzo[d]imidazole-2-yl)amino)-2-hydroxypropoxy)-3-benzyl-4-methyl-2H-chromen-2-one [17]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.73 (d, J = 9.5 Hz, 1H), 7.28–7.23 (m, 2H), 7.21 (d, J = 7.1 Hz, 2H), 7.16 (dd, J = 7.3, 3.6 Hz, 2H), 7.11 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.97 (s, 1H), 6.90 (t, J = 7.1 Hz, 1H), 6.82 (t, J = 7.2 Hz, 1H), 6.23 (s, 2H), 5.60 (d, J = 5.3 Hz, 1H), 4.17 (d, J = 8.2 Hz, 1H), 4.12 (d, J = 4.2 Hz, 1H), 4.08 (dd, J = 10.0, 3.9 Hz, 1H), 4.06–4.00 (m, 2H), 3.93 (s, 2H), 2.42 (s, 3H). ESI-MS m/z: 455.93 [M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.06 (s), 162.73 (s), 157.14 (s), 155.14 (s), 150.19 (s), 144.48 (s), 141.14 (s), 136.71 (s), 130.26 (s), 129.87 (s), 128.50 (s), 127.90 (s), 122.98 (s), 122.11 (s), 119.90 (s), 116.59 (s), 115.53 (s), 114.33 (s), 109.72 (s), 102.89 (s), 72.11 (s), 69.54 (s), 46.74 (s), 33.98 (s), 17.04 (s).

3.4.18. 3-Benzyl-7-(2-hydroxy-3-((6-methylbenzo[d]thiazol-2-yl)amino)propoxy)-4-methyl-2H-chromen-2-one [18]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.70 (d, J = 8.9 Hz, 1H), 7.25 (t, J = 7.5 Hz, 2H), 7.21–7.13 (m, 4H), 7.01 (d, J = 8.2 Hz, 1H), 6.97–6.91 (m, 2H), 6.90 (d, J = 2.3 Hz, 1H), 4.26–4.21 (m, 1H), 4.07 (dd, J = 10.5, 3.9 Hz, 2H), 4.02–3.99 (m, 1H), 3.92 (s, 2H), 2.40 (s, 3H), 2.21 (s, 3H). ESI-MS m/z: 487.15 [M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 163.05 (s), 162.79 (s), 161.76 (s), 155.11 (s), 150.19 (s), 141.14 (s), 140.52 (s), 132.16 (s), 130.25 (s), 129.85 (s), 128.40 (d, J = 8.3 Hz), 127.90 (s), 123.97 (s), 123.62 (s), 122.92 (s), 115.45 (s), 114.29 (s), 111.69 (s), 111.36 (s), 102.81 (s), 72.59 (s), 68.49 (s), 47.82 (s), 33.97 (s), 22.21 (s), 17.03 (s).

3.4.19. 1-(2-Hydroxy-3-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)propyl)piperidine-4-carboxamide [19]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.68 (d, J = 9.2 Hz, 1H), 7.19 (s, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.97 (s, 1H), 6.69 (s, 1H), 6.20 (d, J = 1.1 Hz, 1H), 4.08 (t, J = 6.4 Hz, 1H), 4.02–3.93 (m, 2H), 2.92 (d, J = 11.1 Hz, 1H), 2.86 (d, J = 11.1 Hz, 1H), 2.45–2.41 (m, 1H), 2.40 (d, J = 0.9 Hz, 3H), 2.35 (dd, J = 12.7, 5.9 Hz, 1H), 2.06–1.88 (m, 3H), 1.68–1.59 (m, 2H), 1.54 (qd, J = 11.8, 3.0 Hz, 2H). ESI-MS m/z: 361.24 [M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.05 (s), 162.38 (s), 160.63 (s), 155.18 (s), 153.88 (s), 126.90 (s), 113.52 (s), 112.88 (s), 111.55 (s), 101.76 (s), 72.26 (s), 66.88 (s), 61.58 (s), 54.12 (d, J = 14.4 Hz), 42.09 (s), 29.07 (s), 18.59 (s).

3.4.20. 1-(3-((3-(4-(tert-butyl)benzyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide [20]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.68 (s, 1H), 7.28 (d, J = 8.3 Hz, 3H), 7.23 (t, J = 7.3 Hz, 3H), 7.19 (t, J = 6.9 Hz, 4H), 7.14 (t, J = 7.3 Hz, 3H), 7.00 (s, 1H), 6.69 (s, 1H), 4.82 (s, 2H), 4.08 (s, 1H), 4.02 (t, J = 3.7 Hz, 1H), 4.00 (d, J = 4.1 Hz, 1H), 3.98 (s, 1H), 3.96 (d, J = 4.9 Hz, 3H), 3.89 (s, 3H), 2.85 (d, J = 11.3 Hz, 1H), 2.74 (d, J = 11.0 Hz, 1H), 2.44 (s, 1H), 2.42 (s, 3H), 2.39–2.34 (m, 1H), 2.28 (dd, J = 12.6, 6.3 Hz, 1H), 2.12 (s, 1H), 2.05–1.96 (m, 2H), 1.91 (dt, J = 11.5, 8.7 Hz, 3H), 1.60 (t, J = 11.9 Hz, 3H), 1.51 (dq, J = 11.8, 8.1 Hz, 3H), 1.24 (s, 12H), 1.23 (s, 8H), 1.21 (s, 2H), 1.15 (s, 1H). ESI-MS m/z: 653.43 [M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.10 (s), 161.80 (s), 159.40 (s), 152.61 (s), 149.30–148.43 (m), 148.43–148.17 (m), 138.08 (s), 136.70 (s), 128.59 (s), 128.15 (d, J = 7.2 Hz), 126.97 (d, J = 9.0 Hz), 125.60 (s), 125.30 (s), 121.55 (s), 113.36 (s), 99.81 (s), 71.81 (s), 66.89 (s), 61.45 (s), 54.07 (d, J = 13.5 Hz), 42.13 (s), 35.17 (s), 34.48 (d, J = 4.2 Hz), 32.08 (s), 31.61 (s), 29.05 (s), 15.66 (s).

3.4.21. 1-(3-((3-(4-fluorobenzyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide [21]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, J = 9.5 Hz, 1H), 7.24 (dd, J = 8.5, 5.7 Hz, 2H), 7.17 (s, 1H), 7.07 (t, J = 8.9 Hz, 2H), 6.98–6.91 (m, 2H), 6.67 (s, 1H), 4.87 (s, 1H), 4.06 (t, J = 6.3 Hz, 1H), 3.97–3.92 (m, 2H), 3.90 (s, 2H), 2.90 (d, J = 11.2 Hz, 1H), 2.84 (d, J = 11.1 Hz, 1H), 2.41 (s, 3H), 2.39 (d, J = 5.5 Hz, 1H), 2.34 (d, J = 5.7 Hz, 1H), 2.31 (d, J = 5.3 Hz, 1H), 2.05–1.91 (m, 3H), 1.61 (d, J = 2.3 Hz, 2H), 1.52 (dd, J = 23.2, 11.5 Hz, 2H). ESI-MS m/z: 469.15 [M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.05 (s), 161.72 (d, J = 11.7 Hz), 153.81 (s), 148.90 (s), 135.90 (s), 130.28 (d, J = 7.9 Hz), 127.09 (s), 121.37 (s), 115.62 (s), 115.45 (s), 113.93 (s), 112.96 (s), 101.50 (s), 72.23 (s), 66.88 (s), 61.57 (s), 54.11 (d, J = 12.2 Hz), 42.07 (s), 31.81 (s), 29.05 (s), 15.62 (s).

3.4.22. 1-(3-((3-(3-fluorobenzyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide [22]

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.75–7.67 (m, 1H), 7.30 (dd, J = 14.3, 7.9 Hz, 1H), 7.17 (s, 1H), 7.07–6.93 (m, 5H), 6.68 (s, 1H), 4.08 (q, J = 6.2 Hz, 1H), 4.01 (q, J = 7.1 Hz, 1H), 3.98–3.93 (m, 4H), 2.88 (dd, J = 29.9, 11.2 Hz, 2H), 2.44–2.38 (m, 4H), 2.36–2.31 (m, 1H), 2.04–1.93 (m, 4H), 1.89 (s, 1H), 1.67–1.58 (m, 2H), 1.53 (dd, J = 23.3, 11.6 Hz, 2H), 1.38 (s, 1H), 1.16 (t, J = 7.1 Hz, 1H). ESI-MS m/z: 469.06 [M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.06 (s), 163.66 (s), 162.19–161.59 (m), 153.86 (s), 149.27 (s), 142.76 (d, J = 7.2 Hz), 130.72 (d, J = 8.3 Hz), 127.14 (s), 124.56 (s), 120.80 (s), 115.15 (s), 113.92 (s), 113.35 (d, J = 20.9 Hz), 113.26–113.25 (m), 112.96 (s), 101.51 (s), 72.24 (s), 66.88 (s), 61.57 (s), 54.11 (d, J = 12.0 Hz), 42.08 (s), 32.36 (s), 29.06 (s), 26.80 (s), 15.65 (s).

3.4.23. 1-(3-((3-(4-chlorobenzyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (23)

^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, J = 9.6 Hz, 1H), 7.65 (s, 1H), 7.31 (s, 1H), 7.29 (s, 1H), 7.27–7.25 (m, 1H), 7.24 (s, 1H), 7.22 (s, 1H), 7.20 (s, 1H), 6.99 (s, 1H), 6.97 (s, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.70 (s, 1H), 6.18 (s, 1H), 4.07 (d, J = 6.6 Hz, 1H), 3.96 (d, J = 7.4 Hz, 2H), 3.91 (s, 2H), 3.15 (s, 1H), 2.91 (dd, J = 22.3, 6.0 Hz, 2H), 2.40 (s, 3H), 2.37

(s, 1H), 2.05 (d, J = 15.4 Hz, 3H), 1.62 (s, 2H), 1.59–1.48 (m, 2H), 1.21 (s, 1H), 0.89–0.79 (m, 1H). ESI-MS m/z: 485.40 [M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 176.96 (s), 161.73 (d, J = 14.0 Hz), 153.84 (s), 149.13 (s), 138.86 (s), 131.13 (s), 130.39 (s), 128.79 (s), 127.14 (s), 121.05 (s), 113.94 (s), 112.99 (s), 101.53 (s), 72.17 (s), 66.70 (s), 61.40 (s), 53.99 (s), 49.06 (s), 41.86 (s), 31.99 (s), 28.85 (s), 15.66 (s).

3.4.24. 1-(3-((3-(4-bromobenzyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (24)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, J = 9.5 Hz, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.7 Hz, 3H), 6.96 (d, J = 6.4 Hz, 2H), 6.68 (s, 1H), 4.07 (d, J = 6.3 Hz, 1H), 3.95 (d, J = 6.3 Hz, 2H), 3.89 (s, 2H), 2.91 (d, J = 8.8 Hz, 1H), 2.85 (d, J = 8.1 Hz, 1H), 2.40 (s, 3H), 2.35 (s, 1H), 2.00 (d, J = 11.4 Hz, 2H), 1.61 (s, 2H), 1.53 (d, J = 11.8 Hz, 2H), 1.21 (s, 1H). ESI-MS m/z: 530.94 [M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 176.77 (s), 161.67 (d, J = 8.0 Hz), 153.82 (s), 149.13 (s), 139.27 (s), 131.70 (s), 130.77 (s), 127.13 (s), 121.00 (s), 119.55 (s), 113.96 (s), 112.99 (s), 101.53 (s), 72.05 (s), 66.40 (s), 61.08 (s), 53.80 (s), 41.52 (s), 32.05 (s), 29.48 (s), 28.49 (s), 15.65 (s).

3.4.25. 1-(3-((3-(4-fluoro-2-methylbenzyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (25)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.75 (d, J = 9.6 Hz, 1H), 7.22 (s, 1H), 7.16 (dd, J = 15.1, 6.9 Hz, 1H), 7.06 (dd, J = 10.0, 2.6 Hz, 1H), 6.99 (dd, J = 6.9, 2.4 Hz, 2H), 6.84 (td, J = 8.5, 2.6 Hz, 1H), 6.81–6.77 (m, 1H), 6.73 (s, 1H), 6.54–6.49 (m, 1H), 4.93 (s, 1H), 4.10 (d, J = 6.5 Hz, 1H), 3.97 (dd, J = 12.2, 5.5 Hz, 2H), 3.81 (s, 2H), 2.94 (d, J = 10.7 Hz, 1H), 2.87 (d, J = 10.7 Hz, 1H), 2.45 (d, J = 5.7 Hz, 1H), 2.42 (d, J = 4.6 Hz, 1H), 2.38 (s, 3H), 2.34 (s, 3H), 2.31 (d, J = 4.8 Hz, 1H), 2.08–1.93 (m, 3H), 1.63 (s, 2H), 1.55 (dd, J = 23.3, 11.6 Hz, 2H), 1.23 (s, 1H). ESI-MS m/z: 483.63[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 176.94 (s), 163.83 (s), 161.37 (s), 153.89 (s), 146.67 (s), 131.30 (d, J = 6.1 Hz), 127.17 (s), 122.48 (d, J = 12.5 Hz), 118.64 (s), 113.89 (s), 113.00 (s), 111.85 (s), 111.75 (d, J = 21.0 Hz), 104.10 (s), 101.53 (s), 72.20 (s), 66.76 (s), 61.45 (s), 54.02 (s), 41.95 (s), 29.47 (s), 28.93 (s), 25.64 (s), 15.53 (s).

3.4.26. 1-(3-((3-(2,4-difluorobenzyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (26)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.73 (d, J = 9.5 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.18 (s, 1H), 7.17 (d, J = 1.6 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.96 (s, 2H), 6.94 (d, J = 2.2 Hz, 1H), 6.92 (d, J = 2.1 Hz, 1H), 6.68 (s, 1H), 4.07 (d, J = 6.5 Hz, 1H), 3.96 (d, J = 6.2 Hz, 2H), 3.89 (s, 2H), 2.89 (d, J = 23.7 Hz, 2H), 2.40 (s, 3H), 2.35 (s, 1H), 2.01 (d, J = 9.4 Hz, 2H), 1.62 (s, 2H), 1.53 (d, J = 11.0 Hz, 2H), 1.22 (s, 2H). ESI-MS m/z: 487.02[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 176.97 (s), 161.83 (s), 161.37 (s), 153.89 (s), 149.60 (s), 131.30 (d, J = 6.1 Hz), 127.17 (s), 122.48 (d, J = 12.5 Hz), 119.65 (s), 113.89 (s), 113.00 (s), 111.85 (s), 111.75 (d, J = 21.0 Hz), 104.10 (s), 101.53 (s), 72.20 (s), 66.76 (s), 61.45 (s), 54.02 (s), 41.95 (s), 29.47 (s), 28.93 (s), 25.54 (s), 15.51 (s).

3.4.27. 1-(3-((3-(2-chloro-4-fluorobenzyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (27)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.76–7.71 (m, 1H), 7.44 (dd, J = 8.7, 2.1 Hz, 1H), 7.20 (s, 1H), 7.07–7.03 (m, 2H), 7.00–6.96 (m, 2H), 6.70 (s, 1H), 4.08 (d, J = 6.8 Hz, 1H), 3.96 (d, J = 7.7 Hz, 2H), 3.93 (s, 2H), 3.15 (s, 2H), 2.87 (dd, J = 31.6, 11.1 Hz, 2H), 2.43–2.37 (m, 1H), 2.33 (s, 3H), 2.06–1.89 (m, 4H), 1.61 (s, 2H), 1.52 (dt, J = 11.9, 8.9 Hz, 2H). ESI-MS m/z: 503.55[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.09 (s), 161.71 (d, J = 62.2 Hz), 159.94 (s), 154.04 (s), 150.36 (s), 133.98 (d, J = 10.4 Hz), 133.00 (s), 130.46 (s), 127.20 (s), 119.37 (s), 116.84 (s), 114.90 (s), 113.87 (s), 113.04 (s), 101.56 (s), 72.27 (s), 66.88 (s), 61.59 (s), 54.14 (d, J = 17.1 Hz), 49.06 (s), 42.09 (s), 29.91 (s), 29.08 (s), 15.66 (s).

3.4.28. 1-(3-((3-(2-bromo-4-methoxybenzyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (28)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.73 (d, J = 9.5 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.19 (s, 1H), 6.99 (s, 1H), 6.98–6.94 (m, 1H), 6.80–6.73 (m, 1H), 6.70 (s, 1H), 6.51–6.47 (m, 1H), 6.43 (d, J = 2.9 Hz, 1H), 4.91 (s, 1H), 4.08 (d, J = 6.6 Hz, 1H), 3.96 (d, J = 6.8 Hz, 2H), 3.89 (s, 2H), 3.68 (s, 1H), 3.61 (s, 3H), 3.15 (d, J = 4.8 Hz, 1H), 2.91 (d, J = 10.8 Hz, 1H), 2.85 (d, J = 10.9 Hz, 1H), 2.41 (d, J = 10.1 Hz, 2H), 2.34 (d, J = 2.2 Hz, 1H), 2.31 (s, 3H), 2.06–1.91 (m, 4H), 1.61 (s, 2H), 1.53 (t, J = 12.0 Hz, 2H), 1.23 (dd, J = 15.0, 10.3 Hz, 1H), 0.89–0.77 (m, 1H). ESI-MS m/z: 561.38[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.08 (s), 161.95 (s), 161.54 (s), 159.30 (s), 154.05 (s), 150.40 (s), 139.35 (s), 133.67 (s), 127.20 (s), 119.48 (s), 115.44 (s), 114.72 (s), 113.84 (s), 113.37 (s), 113.02 (s), 101.59 (s), 72.26 (s), 66.87 (s), 61.59 (s), 55.72 (s), 54.13 (d, J = 14.1 Hz), 42.09 (s), 33.36 (s), 29.06 (s), 15.72 (s).

3.4.29. 1-(2-Hydroxy-3-((4-methyl-3-(3-nitrobenzyl)-2-oxo-2H-chromen-7-yl)oxy)propyl)piperidine-4-carboxamide (29)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 8.06 (dd, J = 18.6, 9.0 Hz, 2H), 7.74 (t, J = 9.9 Hz, 1H), 7.69 (dd, J = 17.5, 8.4 Hz, 1H), 7.60–7.51 (m, 1H), 7.20 (s, 1H), 7.02–6.93 (m, 2H), 6.71 (s, 1H), 4.14–4.02 (m, 3H), 3.97 (s, 2H), 2.91 (d, J = 27.7 Hz, 2H), 2.47 (s, 3H), 2.39 (d, J = 9.4 Hz, 1H), 2.02 (s, 3H), 1.63 (s, 2H), 1.55 (s, 2H), 1.20 (d, J = 9.6 Hz, 1H). ESI-MS m/z: 596.20[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 176.96 (s), 161.90 (s), 161.68 (s), 153.90 (s), 149.68 (s), 148.30 (s), 142.19 (s), 135.35 (s), 130.37 (s), 127.25 (s), 123.13 (s), 121.69 (s), 120.40 (s), 113.86 (s), 113.05 (s), 101.55 (s), 72.20 (s), 66.74 (s), 61.43 (s), 54.01 (s), 41.92 (s), 32.29 (s), 28.91 (s), 15.72 (s).

3.4.30. 1-(2-Hydroxy-3-((4-methyl-2-oxo-3-(4-(trifluoromethyl) benzyl)-2H-chromen-7-yl)oxy)propyl)piperidine-4-carboxamide (30)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.78–7.69 (m, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.18 (s, 1H), 6.98 (s, 1H), 6.97 (d, J = 2.4 Hz, 1H), 4.07 (d, J = 6.6 Hz, 1H), 4.03 (s, 2H), 3.99–3.92 (m, 2H), 2.91 (d, J = 11.0 Hz, 1H), 2.85 (d, J = 10.9 Hz, 1H), 2.42 (s, 3H), 2.40–2.37 (m, 1H), 2.37–2.29 (m, 1H), 2.06–1.92 (m, 3H), 1.61 (d, J = 2.4 Hz, 2H), 1.52 (dd, J = 23.6, 11.7 Hz, 2H). ESI-MS m/z: 519.10[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.03 (s), 161.90 (s), 161.76 (d, J = 29.5 Hz), 153.89 (s), 149.47 (s), 144.81 (s), 129.30 (s), 127.44 (s), 127.18 (s), 125.71 (d, J = 3.2 Hz), 123.75 (s), 120.58 (s), 113.87 (s), 113.01 (s), 101.53 (s), 72.26 (s), 66.89 (s), 61.58 (s), 54.13 (d, J = 13.8 Hz), 42.09 (s), 32.54 (s), 29.07 (s), 15.70 (s).

3.4.31. 1-(2-Hydroxy-3-((4-methyl-2-oxo-3-(2-(trifluoromethyl) benzyl)-2H-chromen-7-yl)oxy)propyl)piperidine-4-carboxamide (31)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.76 (t, J = 7.4 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.21 (s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.02 (dd, J = 4.7, 2.4 Hz, 1H), 7.00 (d, J = 2.5 Hz, 1H), 6.73 (s, 1H), 4.93 (s, 1H), 4.12 (s, 1H), 4.10 (s, 2H), 4.02−3.94 (m, 2H), 3.35 (s, 2H), 2.93 (d, J = 11.0 Hz, 1H), 2.87 (d, J = 11.1 Hz, 1H), 2.44 (d, J = 6.1 Hz, 1H), 2.42 (d, J = 5.5 Hz, 1H), 2.37 (d, J = 5.8 Hz, 1H), 2.32 (s, 3H), 2.04 (ddd, J = 15.5, 7.6, 3.8 Hz, 1H), 2.01−1.94 (m, 2H), 1.63 (d, J = 2.3 Hz, 2H), 1.60−1.49 (m, 2H). ESI-MS m/z: 519.43[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.05 (s), 161.72 (d, J = 11.7 Hz), 153.81 (s), 148.90 (s), 135.90 (s), 130.28 (d, J = 7.9 Hz), 127.09 (s), 121.37 (s), 115.62 (s), 115.45 (s), 113.93 (s), 112.96 (s), 101.50 (s), 72.23 (s), 66.88 (s), 61.57 (s), 54.11 (d, J = 12.2 Hz), 42.07 (s), 31.81 (s), 29.05 (s), 15.62 (s).

3.4.32. 1-(2-Hydroxy-3-((4-methyl-2-oxo-3-(4-(trifluoromethoxy) benzyl)-2H-chromen-7-yl)oxy)propyl)piperidine-4-carboxamide (32)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.72 (d, J = 9.4 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.17 (s, 1H), 6.97 (d, J = 2.5 Hz, 1H), 6.95 (s, 1H), 6.67 (s, 1H), 4.06 (t, J = 6.4 Hz, 1H), 3.97 (s, 1H), 3.95 (s, 2H), 3.94 (s, 1H), 2.90 (d, J = 11.3 Hz, 1H), 2.84 (d, J = 11.1 Hz, 1H), 2.42 (s, 3H), 2.39 (d, J = 5.3 Hz, 1H), 2.34 (d, J = 5.8 Hz, 1H), 2.31 (d, J = 5.5 Hz, 1H), 2.06−1.87 (m, 3H), 1.66−1.58 (m, 2H), 1.53 (t, J = 11.7 Hz, 2H). ESI-MS m/z: 535.2052 [M+H] $^+$, Delta <0.5 ppm.

^{13}C NMR (126 MHz, DMSO) δ 177.05 (s), 162.11−161.90 (m), 161.73 (d, J = 22.5 Hz), 153.85 (s), 149.19 (s), 147.13 (s), 139.33 (s), 130.28 (s), 127.15 (s), 121.48 (s), 120.97 (s), 113.90 (s), 112.98 (s), 101.51 (s), 72.24 (s), 66.89 (s), 61.58 (s), 54.12 (d, J = 13.3 Hz), 42.09 (s), 40.48 (t, J = 10.5 Hz), 31.99 (s), 29.07 (s), 15.66 (s).

3.4.33. Methyl-4-((7-(3-(4-carbamoylpiperidin-1-yl)-2-hydroxypropoxy)-4-methyl-2-oxo-2H-chromen-3-yl)methyl) benzoate (33)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (400 MHz, DMSO) δ 7.87 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 9.6 Hz, 1H), 7.68 (d, J = 9.2 Hz, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.17 (s, 1H), 7.01−6.96 (m, 2H), 4.10 (d, J = 6.7 Hz, 1H), 4.03 (s, 2H), 4.00−3.93 (m, 2H), 3.83 (s, 3H), 2.89 (dd, J = 22.7, 11.2 Hz, 2H), 2.43 (s, 3H), 2.40 (s, 1H), 2.37 (d, J = 5.8 Hz, 1H), 2.33 (s, 1H), 2.07−1.95 (m, 3H), 1.64 (d, J = 12.9 Hz, 2H), 1.59−1.48 (m, 2H). ESI-MS m/z: 509.30[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.06 (s), 162.38 (s), 160.62 (s), 155.18 (s), 153.87 (s), 126.90 (s), 113.52 (s), 112.88 (s), 111.55 (s), 101.76 (s), 72.26 (s), 66.89 (s), 61.58 (s), 54.12 (d, J = 14.5 Hz), 42.10 (s), 29.07 (s), 18.59 (s).

3.4.34. 1-(2-Hydroxy-3-((4-methyl-3-(naphthalen-1-ylmethyl)-2-oxo-2H-chromen-7-yl)oxy)propyl)piperidine-4-carboxamide (34)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 8.27 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 4.9 Hz, 1H), 8.21 (s, 1H), 7.95 (t, J = 7.3 Hz, 1H), 7.93−7.92 (m, 1H), 7.82−7.77 (m, 2H), 7.76 (s, 1H), 7.70−7.67 (m, 1H), 7.65−7.61 (m, 1H), 7.61−7.59 (m, 1H), 7.59 (t, J = 2.2 Hz, 1H), 7.58−7.56 (m, 1H), 7.55−7.53 (m, 1H), 7.52 (s, 1H), 7.44−7.39 (m, 1H), 7.38−7.34 (m, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.21 (s, 2H), 7.16 (d, J = 8.2 Hz, 1H), 7.03 (dd, J = 5.9, 2.4 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.99 (d, J = 3.7 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 6.96 (s, 1H), 6.71 (s, 1H), 6.55−6.49 (m, 1H), 5.54 (dd, J = 10.9, 5.0 Hz, 1H), 4.93 (s, 1H), 4.83 (s, 1H), 4.39 (s, 2H), 4.12 (t, J = 6.7 Hz, 1H), 4.02 (dd, J = 11.7, 5.7 Hz, 3H), 2.92 (dd, J = 29.2, 10.2 Hz, 3H), 2.35 (s, 3H), 2.18 (s, 1H), 2.04 (dd, J = 11.5, 4.0 Hz, 4H), 1.65 (s, 2H), 1.59−1.53 (m, 3H). ESI-MS m/z: 501.30[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.03 (s), 162.24−161.99 (m), 161.79 (d, J = 20.7 Hz), 154.05 (s), 150.25 (s), 134.88 (s), 133.87 (s), 132.05 (s), 129.04 (s), 127.07 (s), 126.67 (s), 126.19 (d, J = 23.1 Hz), 123.87 (d, J = 8.9 Hz), 120.26 (s), 114.04 (s), 113.01 (s), 101.71 (d, J = 19.2 Hz), 72.27 (s), 66.88 (s), 61.55 (s), 54.08 (s), 42.05 (s), 29.54 (s), 29.03 (s), 15.66 (s).

3.4.35. 1-(3-((3-(4-(3,5-dimethylisoxazol-4-yl)benzyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (35)

A solution of compound NO.**24** (0.227 mmol), phenylboronic acid or benzene boric acid ester derivatives (2 eq) in diox(4 mL) and saturated sodium bicarbonate solution (0.7 mL) was replaced the air with argon for 10 min then $Pd(PPh_3)_4$ (0.05 eq) was added and the reaction mixture was stirred at 95 °C overnight. Then, the mixture was extracted with ethyl acetate, washed with saline. The organic phase was collected and the solvent was removed under vacuum. The product was purified by silica gel chromatography using DCM-methaonl as eluate to give compound NO. **35**. Yield: 72%. ^{1}H NMR (500 MHz, DMSO) δ 7.76−7.67 (m, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.29 (dd, J = 20.6, 8.2 Hz, 3H), 7.17 (d, J = 8.2 Hz, 4H), 6.98−6.94 (m, 3H), 4.07 (d, J = 6.4 Hz, 2H), 3.99−3.93 (m, 5H), 3.89 (s, 2H), 2.90 (d, J = 11.1 Hz, 2H), 2.84 (d, J = 11.2 Hz, 2H), 2.40 (s, 4H), 2.35 (s, 3H), 2.31 (d, J = 5.6 Hz, 1H), 2.18 (s, 2H), 1.99 (ddd, J = 28.7, 15.9, 8.2 Hz, 5H), 1.61 (s, 3H), 1.53 (t, J = 11.7 Hz, 3H). ESI-MS m/z: 546.10[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.05 (s), 165.35 (s), 161.81 (s), 158.57 (s), 153.82 (s), 149.66−149.19 (m), 149.04 (d, J = 20.9 Hz), 139.56−139.33 (m), 139.17 (d, J = 27.9 Hz), 131.69 (s), 130.77 (s), 129.35 (s), 128.97 (s), 128.09 (s), 127.10 (s), 121.26 (s), 121.09 (d, J = 34.8 Hz), 119.55 (s), 116.12 (s), 113.92 (d, J = 5.8 Hz), 112.97 (s), 101.51 (s), 72.24 (s), 66.90 (s), 61.60 (s), 54.13 (d, J = 13.3 Hz), 42.10 (s), 32.21 (d, J = 39.3 Hz), 32.01−31.59 (m), 29.08 (s), 15.64 (s), 11.77 (s), 10.95 (s).

3.4.36. 1-(3-((3-([1,1′-biphenyl]-4-ylmethyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (36)

The title compound was synthesized according to the procedure of preparing Compound NO.**35**.^{1}H NMR (500 MHz, DMSO) δ 7.74−7.70 (m, 1H), 7.59 (d, J = 7.3 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.42 (t, J = 7.7 Hz, 2H), 7.31 (dd, J = 12.0, 7.8 Hz, 3H), 7.17 (s, 1H), 6.97 (dd, J = 4.6, 2.3 Hz, 2H), 4.07 (t, J = 6.2 Hz, 1H), 3.97 (s, 2H), 3.96 (d, J = 6.9 Hz, 2H), 2.88 (dd, J = 29.8, 10.3 Hz, 2H), 2.45 (s, 3H), 2.41 (s, 1H), 2.35 (s, 1H), 2.06−1.92 (m, 3H), 1.61 (s, 2H), 1.54 (t, J = 12.0 Hz, 2H). ESI-MS m/z: 527.37[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.02 (s), 161.74 (s), 153.82 (s), 148.89 (s), 140.43 (s), 139.08 (s), 138.51 (s), 129.37 (s), 129.21 (d, J = 33.1 Hz), 127.68 (s), 127.42−126.77 (m), 121.38 (s), 113.98 (s), 112.96 (s), 101.52 (s), 72.22 (s), 66.84 (s), 61.53 (s), 54.08 (d, J = 8.7 Hz), 42.03 (s), 32.27 (s), 29.01 (s), 15.70 (s).

3.4.37. 1-(3-((3-((4′-fluoro-[1,1′-biphenyl]-4-yl)methyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (37)

The title compound was synthesized according to the procedure of preparing Compound NO.**35**.^{1}H NMR (500 MHz, DMSO) δ 7.74−7.70 (m, 1H), 7.66−7.61 (m, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.24 (t, J = 8.9 Hz, 2H), 7.17 (s, 1H), 6.97 (td, J = 4.8, 2.5 Hz, 2H), 4.07 (q, J = 6.0 Hz, 1H), 3.96 (d, J = 7.9 Hz, 4H), 2.88 (dd, J = 29.8, 10.1 Hz, 2H), 2.44 (s, 3H), 2.39 (d, J = 14.0 Hz, 1H), 2.35 (s,

1H), 2.01 (dd, J = 13.5, 9.9 Hz, 3H), 1.61 (s, 2H), 1.53 (dd, J = 24.0, 12.0 Hz, 2H). ESI-MS m/z: 545.10[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.02 (s), 163.16 (s), 161.74 (s), 161.22 (s), 153.82 (s), 148.90 (s), 139.07 (s), 137.47 (s), 136.91 (s), 129.10 (s), 128.90 (d, J = 8.0 Hz), 127.17 (s), 121.35 (s), 116.23 (s), 116.11 (d, J = 21.3 Hz), 113.97 (s), 112.96 (s), 101.52 (s), 72.21 (s), 66.83 (s), 61.53 (s), 54.08 (d, J = 9.0 Hz), 42.02 (s), 32.25 (s), 29.00 (s), 15.69 (s).

3.4.38. 1-(3-((3-((4′-chloro-[1,1′-biphenyl]-4-yl)methyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (38)

The title compound was synthesized according to the procedure of preparing Compound NO.**35**.^{1}H NMR (500 MHz, DMSO) δ 7.76–7.70 (m, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.20 (s, 1H), 6.98 (dd, J = 5.8, 2.4 Hz, 2H), 6.70 (s, 1H), 4.09 (d, J = 6.4 Hz, 1H), 3.98 (s, 3H), 3.97 (s, 1H), 2.93 (d, J = 11.2 Hz, 1H), 2.87 (d, J = 11.1 Hz, 1H), 2.46 (s, 3H), 2.43 (d, J = 5.0 Hz, 1H), 2.37 (d, J = 5.6 Hz, 1H), 2.35 (d, J = 5.6 Hz, 1H), 2.09–1.94 (m, 3H), 1.64 (d, J = 12.8 Hz, 2H), 1.55 (td, J = 12.0, 2.9 Hz, 2H), 1.23 (s, 1H). ESI-MS m/z: 561.10[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.02 (s), 161.74 (d, J = 4.6 Hz), 153.82 (s), 148.94 (s), 139.53 (s), 139.22 (s), 137.13 (s), 132.55 (s), 129.23 (d, J = 15.4 Hz), 128.70 (s), 127.13 (d, J = 9.5 Hz), 121.29 (s), 113.96 (s), 112.96 (s), 101.52 (s), 72.22 (s), 66.84 (s), 61.54 (s), 54.09 (d, J = 9.9 Hz), 42.04 (s), 32.28 (s), 29.02 (s), 15.70 (s).

3.4.39. 1-(2-Hydroxy-3-((3-((2′-methoxy-[1,1′-biphenyl]-4-yl)methyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)propyl)piperidine-4-carboxamide (39)

The title compound was synthesized according to the procedure of preparing Compound NO.**35**.^{1}H NMR (500 MHz, DMSO) δ 7.76–7.69 (m, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 1.7 Hz, 1H), 7.29 (s, 1H), 7.28 (d, J = 1.7 Hz, 1H), 7.25–7.20 (m, 3H), 7.17 (s, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.97 (d, J = 2.3 Hz, 2H), 4.07 (t, J = 6.3 Hz, 1H), 3.96 (t, J = 6.3 Hz, 4H), 3.72 (s, 3H), 2.91 (d, J = 11.2 Hz, 1H), 2.85 (d, J = 10.9 Hz, 1H), 2.46 (s, 3H), 2.40 (s, 1H), 2.34 (s, 1H), 1.99 (ddd, J = 22.5, 15.5, 8.5 Hz, 3H), 1.61 (s, 2H), 1.53 (dd, J = 23.7, 11.8 Hz, 2H). ESI-MS m/z: 557.10[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.04 (s), 161.73 (s), 156.53 (s), 153.81 (s), 148.82 (s), 138.30 (s), 136.43 (s), 130.71 (s), 129.76 (s), 129.15 (s), 128.12 (s), 127.10 (s), 121.18 (s), 112.11 (s), 101.52 (s), 72.23 (s), 66.87 (s), 61.57 (s), 55.85 (s), 54.11 (d, J = 10.3 Hz), 42.07 (s), 32.35 (s), 29.05 (s), 15.73 (s).

3.4.40. 1-(3-((3-((2′-cyano-[1,1′-biphenyl]-4-yl)methyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (40)

The title compound was synthesized according to the procedure of preparing Compound NO.**35**.^{1}H NMR (500 MHz, DMSO) δ 7.91 (d, J = 7.7 Hz, 1H), 7.77 (d, J = 1.2 Hz, 1H), 7.76–7.72 (m, 2H), 7.59–7.52 (m, 3H), 7.48 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.17 (s, 1H), 6.98 (dd, J = 5.7, 2.4 Hz, 2H), 6.68 (s, 1H), 4.87 (s, 1H), 4.08 (d, J = 6.6 Hz, 1H), 4.02 (s, 2H), 3.96 (d, J = 7.0 Hz, 2H), 2.91 (d, J = 11.0 Hz, 1H), 2.85 (d, J = 10.4 Hz, 1H), 2.47 (s, 3H), 2.39 (d, J = 6.2 Hz, 1H), 2.34 (d, J = 1.7 Hz, 1H), 2.03–1.93 (m, 4H), 1.61 (s, 2H), 1.53 (d, J = 11.9 Hz, 2H). ESI-MS m/z: 552.26[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.04 (s), 161.75 (d, J = 10.3 Hz), 153.86 (s), 149.12 (s), 144.78 (s), 140.53 (s), 136.10 (s), 134.31 (s), 133.98 (s), 130.51 (s), 129.24 (s), 128.86 (s), 128.51 (s), 127.15 (s), 121.09 (s), 119.09 (s), 113.96 (s), 112.98 (s), 110.48 (s), 101.53 (s), 72.25 (s), 66.87 (s), 61.58 (s), 54.11 (d, J = 11.0 Hz), 42.08 (s), 32.41 (s), 29.05 (s), 15.76 (s).

3.4.41. 1-(2-Hydroxy-3-((4-methyl-2-oxo-3-((4′-(trifluoromethyl)-[1,1′-biphenyl]-4-yl)methyl)-2H-chromen-7-yl)oxy)propyl) piperidine-4-carboxamide (41)

The title compound was synthesized according to the procedure of preparing Compound NO.**35**.^{1}H NMR (500 MHz, DMSO) δ 7.83 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.74–7.70 (m, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.18 (s, 1H), 6.97 (dd, J = 4.6, 2.3 Hz, 2H), 4.07 (d, J = 6.3 Hz, 1H), 3.99 (s, 2H), 3.96 (d, J = 6.4 Hz, 2H), 2.89 (d, J = 20.6 Hz, 2H), 2.45 (s, 3H), 2.35 (d, J = 1.8 Hz, 1H), 2.09–1.85 (m, 3H), 1.62 (s, 2H), 1.53 (d, J = 12.0 Hz, 2H). ESI-MS m/z: 557.10[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 176.99 (s), 161.75 (s), 153.83 (s), 149.03 (s), 144.41 (s), 140.29 (s), 136.89 (s), 129.27 (s), 127.65 (d, J = 16.7 Hz), 127.12 (s), 126.21 (s), 121.22 (s), 113.97 (s), 112.98 (s), 101.53 (s), 72.18 (s), 66.76 (s), 61.44 (s), 54.02 (s), 32.32 (s), 28.91 (s), 15.72 (s).

3.4.42. 1-(3-((3-((3′-fluoro-4′-formyl-[1,1′-biphenyl]-4-yl)methyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl) piperidine-4-carboxamide (42)

The title compound was synthesized according to the procedure of preparing Compound NO.**35**.^{1}H NMR (500 MHz, DMSO) δ 10.23 (s, 1H), 7.89 (t, J = 7.9 Hz, 1H), 7.75 (s, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 6.7 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.21 (s, 1H), 7.01–6.95 (m, 2H), 6.71 (s, 1H), 4.12–4.06 (m, 1H), 4.01 (s, 2H), 3.98 (d, J = 6.3 Hz, 2H), 2.96 (d, J = 10.7 Hz, 1H), 2.90 (d, J = 10.7 Hz, 1H), 2.46 (s, 3H), 2.42 (d, J = 8.2 Hz, 1H), 2.11–2.00 (m, 3H), 1.91 (s, 1H), 1.64 (s, 2H), 1.61–1.51 (m, 2H), 1.34 (s, 1H), 1.23 (s, 1H), 0.85 (t, J = 6.7 Hz, 1H), 0.07 (s, 1H), 0.03 to −0.14 (m, 1H). ESI-MS m/z: 573.10[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 187.89 (s), 176.95 (s), 165.25 (s), 163.21 (s), 161.72 (s), 153.83 (s), 149.10 (s), 141.24 (s), 135.77 (s), 130.41 (s), 129.33 (s), 127.75 (s), 127.13 (s), 123.37 (s), 122.75 (s), 121.12 (s), 114.68 (d, J = 21.4 Hz), 114.59–114.40 (m), 113.96 (s), 112.99 (s), 101.53 (s), 72.17 (s), 66.71 (s), 61.39 (s), 53.99 (s), 41.86 (s), 32.37 (s), 28.85 (s), 15.72 (s).

3.4.43. 1-(3-((3-((4′-cyano-3′-fluoro-[1,1′-biphenyl]-4-yl)methyl)-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl) piperidine-4-carboxamide (43)

The title compound was synthesized according to the procedure of preparing Compound NO.**35**.^{1}H NMR (500 MHz, DMSO) δ 8.00–7.94 (m, 1H), 7.84 (dd, J = 11.1, 1.3 Hz, 1H), 7.75 (s, 1H), 7.73 (s, 1H), 7.72–7.69 (m, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.21 (s, 1H), 7.01–6.95 (m, 2H), 6.72 (s, 1H), 4.09 (d, J = 6.6 Hz, 1H), 4.01 (s, 2H), 4.00–3.92 (m, 2H), 2.96 (s, 1H), 2.90 (s, 1H), 2.46 (s, 3H), 2.42 (d, J = 3.1 Hz, 1H), 2.39 (d, J = 19.7 Hz, 1H), 2.06 (s, 3H), 1.91 (s, 1H), 1.65 (s, 2H), 1.57 (d, J = 11.5 Hz, 2H), 1.22 (s, 1H). ESI-MS m/z: 570.10 [M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 176.93 (s), 164.40 (s), 162.37 (s), 161.73 (d, J = 6.4 Hz), 153.83 (s), 149.11 (s), 148.03 (s), 141.45 (s), 135.33 (s), 134.70 (s), 129.35 (s), 127.81 (s), 127.13 (s), 123.82 (s), 121.08 (s), 114.64 (s), 113.96 (s), 112.99 (s), 101.53 (s), 98.82 (d, J = 15.3 Hz), 72.15 (s), 66.66 (s), 61.38 (s), 53.97 (s), 41.82 (s), 32.37 (s), 28.81 (s), 15.72 (s).

3.4.44. (R)-1-(2-hydroxy-3-((4-methyl-2-oxo-3-(4-(trifluoromethoxy)benzyl)-2H-chromen-7-yl)oxy)propyl) piperidine-4-carboxamide (44)

Step 1: A mixture of ethyl acetoacetate (1.3 mL, 10 mmol) and CH_3ONa (540 mg, 10 mmol, 1 eq) in MeOH (6 mL) was stirred at room temperature for 10 min. Then, 4-(Trifluoromethoxy) benzyl bromide (2805 mg, 11 mmol, 1.1 eq) in 5 mL MeOH was added dropwise when the reaction solution was slightly boiling. The reaction mixture was continued to heat under reflux condition until it was almost neutral. After cooling, the reaction solution was filtered

off and concentrated by vacuum to give ethyl acetoacetate derivatives which was used in subsequent steps without further purification.

Step 2: To a stirred solution of the above mentioned products in PPA 5 g, resorcino (1102 mg, 10 mmol, 1 eq) was added. The reaction mixture was stirred at 65 °C for 4 h. The mixture solution had to rest overnight, then diluted with 300 mL water. The precipitated solid was filtered off, washed with water to give the crude product. The crude product was purified by silica gel chromatography using 16% ethyl acetate-cyclohexane as eluate to give the intermediate as a white solid 7-hydroxy-4-methyl-3-(4-(trifluoromethoxy)benzyl)-2H-chromen-2-one (1.4 g, 45%).

Step 3: A mixture of the above products (700 mg, 2 mmol), (R)-(-)-Epichlorohydrin (2 mL), potassium carbonate (553 mg, 4 mmol, 2 eq) and TBAB (645 mg, 2 mmol, 1 eq) was stirred at 80 °C for 2.3 h. Then the mixture was extracted with ethyl acetate, washed with water. The organic phase was collected and the solvent was removed under vacuum. The product was purified by silica gel chromatography using 14% ethyl acetate-cyclohexane as eluate to give the intermediate as a white solid (R)-3-benzyl-4-methyl-7-(oxiran-2-ylmethoxy)-2H-chromen-2-one (410 mg, 51%).

Step 4: The above mentioned products(390 mg, 0.96 mmol) was added to a stirred solution of Hexahydroisonicotinamide (246 mg, 2 mmol, 2 eq) in 2 mL dimentylacetamide then the reaction mixture was stirred at 50 °C for 24 h. The reaction solution was allowed to cool to room temperature and concentrated by vacuum. The residue was dissolved in acetone, absorbed onto silica and purified by flash column chromatography using 4% methanol-dichloromethane as eluate to give white compound NO.**44** (467 mg, 85%).^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, J = 9.5 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 7.25 (s, 1H), 7.17 (s, 1H), 6.99–6.92 (m, 2H), 6.68 (s, 1H), 4.87 (s, 1H), 4.07 (d, J = 6.6 Hz, 1H), 3.96 (d, J = 8.3 Hz, 4H), 2.90 (d, J = 11.1 Hz, 1H), 2.84 (d, J = 11.2 Hz, 1H), 2.42 (s, 3H), 2.39 (d, J = 5.4 Hz, 1H), 2.34 (d, J = 5.8 Hz, 1H), 2.32 (d, J = 5.6 Hz, 1H), 2.23 (t, J = 6.7 Hz, 1H), 2.05–1.92 (m, 3H), 1.77–1.71 (m, 1H), 1.62 (dd, J = 6.9, 3.8 Hz, 2H), 1.52 (dd, J = 23.3, 11.6 Hz, 2H). ESI-MS m/z: 535.20[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.04 (s), 161.84 (s), 161.65 (s), 153.87 (s), 149.19 (s), 147.14 (s), 139.35 (s), 130.29 (s), 127.16 (s), 121.49 (s), 120.98 (s), 113.91 (s), 112.99 (s), 101.52 (s), 72.26 (s), 66.90 (s), 61.59 (s), 54.13 (d, J = 13.4 Hz), 42.10 (s), 41.79 (s), 32.00 (s), 29.08 (s), 26.91 (s), 15.67 (s).

3.4.45. (S)-1-(2-hydroxy-3-((4-methyl-2-oxo-3-(4-(trifluoromethoxy)benzyl)-2H-chromen-7-yl)oxy)propyl) piperidine-4-carboxamide (45)

The title compound was synthesized according to the procedure of preparing Compound NO.**44** except using the (S)-(+)-Epichlorohydrin to replace the (R)-(-)-Epichlorohydrin.^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, J = 9.5 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 7.17 (s, 1H), 7.02–6.91 (m, 2H), 6.68 (s, 1H), 4.87 (s, 1H), 4.06 (t, J = 6.4 Hz, 1H), 3.95 (s, 4H), 2.90 (d, J = 11.1 Hz, 1H), 2.84 (d, J = 11.1 Hz, 1H), 2.42 (s, 3H), 2.39 (d, J = 5.3 Hz, 1H), 2.34 (d, J = 5.7 Hz, 1H), 2.32 (d, J = 5.6 Hz, 1H), 2.23 (t, J = 6.7 Hz, 1H), 2.05–1.92 (m, 3H), 1.74 (dt, J = 12.6, 6.2 Hz, 1H), 1.66–1.58 (m, 2H), 1.52 (dd, J = 23.3, 11.6 Hz, 2H). ESI-MS m/z: 535.20[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.04 (s), 161.84 (s), 161.65 (s), 153.87 (s), 149.19 (s), 147.14 (s), 139.35 (s), 130.30 (s), 127.16 (s), 121.49 (s), 120.98 (s), 113.92 (s), 112.99 (s), 101.53 (s), 72.26 (s), 66.89 (s), 61.59 (s), 54.13 (d, J = 13.3 Hz), 42.10 (s), 41.79 (s), 32.00 (s), 29.08 (s), 15.67 (s).

3.4.46. 1-(3-((3-benzyl-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-(2-fluorophenoxy)propyl)piperidine-4-carboxamide (46)

A solution of compound NO.**1** (0.267 mmol), phenol derivative (2 eq), and PPh_3(1.2 eq) was stirred in dry THF (4 mL) and DMF(0.5 mL) at 0 °C under a nitrogen atmosphere. To this mixture was added dropwise DIAD (1.2 eq) over a period of 5 min, and the reaction was monitored by TLC. After 4.5 h, the solvent was evaporated under reduced pressure and the resulting oil purified by flash column chromatography, eluting with 0–12% methanol in dichloromethane to give compound NO.**46**.Yield: 68%.^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, J = 8.9 Hz, 1H), 7.62 (d, J = 1.2 Hz, 2H), 7.61 (d, J = 1.2 Hz, 4H), 7.60 (s, 3H), 7.58 (s, 2H), 7.55 (d, J = 3.1 Hz, 3H), 7.54 (d, J = 2.9 Hz, 3H), 7.52 (s, 1H), 4.25 (ddd, J = 18.5, 12.2, 5.6 Hz, 3H), 3.93 (s, 2H), 2.87 (s, 3H), 2.71 (s, 3H), 2.41 (s, 3H), 1.16 (d, J = 6.2 Hz, 11H). ESI-MS m/z: 545.00[M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 178.40 (s), 164.14 (s), 163.06 (s), 158.00 (s), 150.17 (s), 141.14 (s), 135.08 (s), 133.97 (d, J = 18.1 Hz), 133.32 (d, J = 9.7 Hz), 130.59 (d, J = 11.8 Hz), 130.25 (s), 129.85 (s), 128.47 (s), 127.90 (s), 126.63 (s), 122.95 (s), 117.15 (s), 114.42 (s), 103.00 (s), 69.66 (s), 63.53 (s), 37.61 (s), 33.98 (s), 32.61 (s), 31.08 (s), 23.75 (s), 17.03 (s).

3.4.47. 1-(3-((3-benzyl-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-(4-fluorophenoxy)propyl)piperidine-4-carboxamide (47)

The title compound was synthesized according to the procedure of preparing Compound NO.**46**.^{1}H NMR (500 MHz, DMSO) δ 7.70 (d, J = 8.9 Hz, 1H), 7.25 (t, J = 7.5 Hz, 2H), 7.20 (d, J = 7.1 Hz, 2H), 7.16 (t, J = 7.1 Hz, 2H), 7.08 (t, J = 8.8 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.99–6.93 (m, 2H), 6.66 (s, 1H), 4.26 (dd, J = 18.9, 5.9 Hz, 1H), 4.13 (dd, J = 19.2, 5.7 Hz, 1H), 4.01 (dd, J = 14.2, 7.1 Hz, 1H), 3.93 (s, 2H), 2.40 (s, 3H), 1.97 (s, 1H), 1.38 (s, 4H), 1.18–1.12 (m, 5H). ESI-MS m/z: 545.33[M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 178.39 (s), 163.05 (s), 162.69 (s), 156.57 (s), 155.18 (s), 150.16 (s), 141.14 (s), 130.25 (s), 129.85 (s), 128.17 (d, J = 55.6 Hz), 127.85–127.17 (m), 122.94 (s), 117.75 (s), 117.52 (s), 114.99 (d, J = 105.3 Hz), 102.98 (s), 68.30 (s), 63.58 (s), 61.59 (s), 51.48 (s), 43.82 (s), 33.97 (s), 31.07 (s), 28.18 (s), 23.63 (s), 17.03 (s).

3.4.48. 1-(3-((3-benzyl-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-(4-methoxyphenoxy)propyl)piperidine-4-carboxamide (48)

The title compound was synthesized according to the procedure of preparing Compound NO.**46**.^{1}H NMR (500 MHz, MeOD) δ 8.52 (d, J = 8.8 Hz, 1H), 8.05 (d, J = 7.3 Hz, 2H), 8.01 (d, J = 7.2 Hz, 3H), 7.97 (d, J = 7.3 Hz, 2H), 7.82 (d, J = 2.3 Hz, 1H), 7.80–7.73 (m, 2H), 7.69 (d, J = 9.1 Hz, 2H), 7.64 (s, 2H), 5.10 (d, J = 10.0 Hz, 1H), 4.92 (d, J = 5.5 Hz, 1H), 4.82 (dd, J = 14.3, 7.2 Hz, 2H), 4.74 (s, 2H), 4.48 (s, 3H), 3.22 (s, 4H), 2.78 (s, 2H), 2.70 (s, 1H), 2.45 (d, J = 11.8 Hz, 2H), 2.29 (d, J = 10.9 Hz, 2H), 1.97 (t, J = 7.1 Hz, 5H). ESI-MS m/z: 557.17 [M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 178.40 (s), 163.06 (s), 155.18 (s), 154.23 (s), 150.18 (s), 141.15 (s), 130.25 (s), 129.85 (s), 128.45 (s), 127.90 (s), 122.92 (s), 117.40 (s), 116.42 (s), 114.98 (d, J = 104.0 Hz), 114.38–114.16 (m), 102.98 (s), 63.65 (s), 57.18 (s), 51.38 (s), 43.83 (s), 33.97 (s), 31.07 (s), 23.67 (s), 17.03 (s).

3.4.49. 1-(3-((3-benzyl-4-methyl-2-oxo-2H-chromen-7-yl)oxy)-2-(4-nitrophenoxy)propyl)piperidine-4-carboxamide (49)

The title compound was synthesized according to the procedure of preparing Compound NO.**46**.^{1}H NMR (500 MHz, DMSO) δ 8.18 (dd, J = 9.2, 4.8 Hz, 2H), 7.70 (d, J = 8.9 Hz, 1H), 7.24 (d, J = 7.3 Hz, 3H), 7.20 (s, 1H), 7.18 (s, 2H), 7.16 (d, J = 4.7 Hz, 2H), 7.02 (s, 1H), 6.97 (dd, J = 8.9, 2.5 Hz, 1H), 6.67 (s, 1H), 4.31 (ddd, J = 23.7, 14.3, 4.9 Hz, 4H), 4.01 (dd, J = 14.2, 7.1 Hz, 1H), 3.92 (s, 2H), 2.97 (d, J = 11.0 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 1H), 2.02 (d, J = 11.9 Hz, 1H), 1.97 (s, 1H), 1.89 (s, 1H), 1.64 (d, J = 11.0 Hz, 3H), 1.48 (d, J = 11.6 Hz, 2H), 1.38 (s, 1H), 1.16 (t, J = 7.1 Hz, 1H). ESI-MS m/z: 572.27[M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 178.36 (s), 165.55 (s), 163.04 (s),

162.61 (s), 155.16 (s), 150.15 (s), 142.73 (s), 141.13 (s), 130.25 (s), 129.85 (s), 128.44 (s), 127.79 (d, J = 20.8 Hz), 122.96 (s), 117.90 (s), 117.02 (s), 115.54 (s), 114.47 (s), 111.36 (s), 103.01 (s), 68.67 (s), 68.28 (s), 63.37 (s), 51.38 (d, J = 20.8 Hz), 51.11–50.90 (m), 43.78 (s), 33.97 (s), 31.35–31.15 (m), 30.74 (d, J = 63.4 Hz), 28.17 (s), 19.96 (s), 17.03 (s).

3.4.50. 1-(2-(4-(2-aminothiazol-4-yl)phenoxy)-3-((3-benzyl-4-methyl-2-oxo-2H-chromen-7-yl)oxy)propyl)piperidine-4-carboxamide (50)

The title compound was synthesized according to the procedure of preparing Compound NO.**46**.^{1}H NMR (500 MHz, DMSO) δ 7.72 (dd, J = 8.8, 4.8 Hz, 3H), 7.28–7.25 (m, 2H), 7.21 (d, J = 7.1 Hz, 3H), 7.18 (d, J = 7.2 Hz, 1H), 7.05 (d, J = 2.2 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.99 (d, J = 2.5 Hz, 1H), 6.98 (s, 2H), 6.96 (s, 1H), 4.47 (s, 3H), 4.35 (d, J = 16.5 Hz, 2H), 4.25 (d, J = 16.1 Hz, 2H), 4.03 (q, J = 7.1 Hz, 2H), 3.94 (s, 2H), 2.42 (s, 3H), 1.98 (s, 2H), 1.91 (s, 1H), 1.17 (t, J = 7.1 Hz, 2H). ESI-MS m/z: 625.30[M+H] $^+$.

^{13}C NMR (101 MHz, DMSO) δ 169.91 (s), 163.04 (s), 155.16 (s), 151.40 (s), 150.17 (s), 141.13 (s), 130.26 (s), 129.85 (s), 128.58 (d, J = 16.9 Hz), 127.91 (s), 123.04 (s), 116.41 (s), 114.48 (s), 103.09 (s), 101.35 (s), 64.63 (s), 63.78 (s), 51.60 (s), 33.98 (s), 30.59 (s), 17.04 (s).

3.4.51. 3-Benzyl-7-(2-methoxy-3-((2-(pyridin-4-yl)ethyl)amino) propoxy)-4-methyl-2H-chromen-2-one (51)

To a solution of compound NO.**13** (0.112 mmol) in 5 mLTHF was added MeI(1.1 eq) slowly and the mixture was stirred vigorously for 15 min at room temperature. To the resulting solution, Ag_2O (1.6 eq) was added slowly. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. When complete, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine two times and dried over anhydrous Na_2SO_4. After filtration, organic layer is concentrated under reduced pressure. The reaction mixture was concentrated under reduced pressure. Then, the crude product was purified by column chromatography to give compound NO.**51**. Reaction time: 24 h. Yield: 40.4%.^{1}H NMR (500 MHz, DMSO) δ 8.39 (dd, J = 4.4, 1.5 Hz, 2H), 7.75–7.71 (m, 1H), 7.68 (dd, J = 5.9, 3.2 Hz, 1H), 7.30–7.26 (m, 2H), 7.25–7.21 (m, 4H), 7.18 (t, J = 7.1 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 4.89 (s, 1H), 4.45 (s, 1H), 4.14 (t, J = 5.3 Hz, 1H), 3.99 (t, J = 6.4 Hz, 1H), 3.95 (d, J = 10.0 Hz, 2H), 3.93–3.85 (m, 2H), 3.45–3.38 (m, 2H), 2.72 (t, J = 8.3 Hz, 2H), 2.70–2.62 (m, 2H), 2.57 (dd, J = 12.7, 6.3 Hz, 1H), 2.44 (s, 3H), 2.29 (s, 2H), 1.63 (dd, J = 12.0, 6.0 Hz, 1H), 1.40–1.33 (m, 1H), 1.30 (d, J = 8.5 Hz, 3H), 0.93–0.82 (m, 3H). ESI-MS m/z: 459.10 [M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 161.71 (s), 153.80 (s), 150.02 (s), 149.70 (s), 148.84 (s), 139.79 (s), 132.06 (s), 129.12 (s), 128.89 (s), 128.48 (s), 127.04 (s), 126.52 (s), 124.70 (s), 121.45 (s), 113.95 (s), 112.92 (s), 101.42 (s), 71.94 (s), 67.88 (s), 67.31 (s), 63.26 (s), 60.16 (s), 58.60 (s), 43.11 (s), 38.55 (s), 32.53 (d, J = 18.4 Hz), 30.27 (s), 28.83 (s), 23.72 (s), 22.86 (s), 15.67 (s), 14.36 (s), 11.27 (s).

3.4.52. 3-Benzyl-4-methyl-7-(3-(thiazol-2-ylamino)propoxy)-2H-chromen-2-one (52)

To a solution of thiazol-2-amine (10 mmol) in 2 mL DMF, K_2CO_3 (1.6 eq) was added slowly and the mixture was stirred vigorously for 15 min at room temperature. To the resulting solution, 1, 3-dibromopropane (3 equiv, 6057 mg, 30 mmol) in 2 mL of DMF was added dropwise. The reaction mixture was heated at 60 °C, and the progress of the reaction was monitored by TLC. The reaction mixture was quenched by addition of water and extracted with ethyl acetate. The organic layer was washed with brine two times and dried over anhydrous Na_2SO_4. After filtration, organic layer is concentrated under reduced pressure. Then, the crude product was purified by column chromatography using ethyl acetate-hexane. Reaction time: 24 h, Yield: 11.5%.

To a solution of 3-benzyl-7-hydroxy-4-methyl-2H-chromen-2-one (0.338 mmol) in DMF (2 mL) was added TBAI (2.2 eq) and $CsCO_3$ (2 eq). To the resulting solution, the above-mentioned products (2 eq) was added dropwise. The mixture was stirred for 31 h at 100 °C, followed by addition of 2 mL water. The mixture was extracted with 2 × 10 mL ethyl acetate, and the organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane-EtOAc) to give **compound NO.52**. Yield: 21%.

^{1}H NMR (600 MHz, DMSO) δ 7.73 (d, J = 8.5 Hz, 1H), 7.61 (s, 1H), 7.27 (d, J = 7.5, Hz, 2H), 7.23 (d, J = 7.4 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H),7.01 (d, J = 3.6 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.61 (d, J = 3.6 Hz, 1H), 4.16 (t, J = 6.2 Hz, 2H), 3.99 (t, J = 6.4 Hz, 1H), 3.95 (d, J = 10.0 Hz, 2H), 3.93–3.85 (m, 2H), 3.45–3.38 (m, 2H), 2.72 (t, J = 8.3 Hz, 2H), 2.70–2.62 (m, 2H), 2.57 (dd, J = 12.7, 6.3 Hz, 1H), 2.44 (s, 3H), 2.29 (s, 2H), 1.63 (dd, J = 12.0, 6.0 Hz, 1H), 1.40–1.33 (m, 1H), 1.30 (d, J = 8.5 Hz, 3H), 0.93–0.82 (m, 3H). ESI-MS m/z: 407.00 [M+H] $^+$.

^{13}C NMR (151 MHz, DMSO) δ 169.65 (s), 161.71 (s), 161.49 (s), 153.84 (s), 148.84 (s), 139.79 (s), 139.23 (s), 128.89 (s), 128.49 (s), 127.08 (s), 126.53 (s), 121.49 (s), 114.01 (s), 112.97 (s), 106.45 (s), 101.43 (s), 66.42 (s), 41.69 (s), 32.60 (s), 28.67 (s), 15.66 (s).

3.4.53. 1-(3-((3-benzyl-4-cyclopropyl-2-oxo-2H-chromen-7-yl) oxy)-2-hydroxypropyl)piperidine-4-carboxamide (53)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (400 MHz, DMSO) δ 7.95 (s, 1H), 7.90 (s, 1H), 7.29–7.19 (m, 4H), 7.14 (s, 2H), 6.99 (s, 1H), 6.76 (s, 1H), 6.64 (s, 1H), 5.88 (d, J = 6.4 Hz, 1H), 5.84 (s, 1H), 4.15–3.88 (m, 5H), 3.65 (d, J = 13.0 Hz, 1H), 3.04–2.96 (m, 1H), 2.83 (s, 1H), 2.76 (s, 1H), 2.67–2.57 (m, 1H), 2.32 (dd, J = 7.4, 2.9 Hz, 1H), 2.29–2.23 (m, 1H), 2.14 (d, J = 7.3 Hz, 1H), 1.96 (s, 1H), 1.91 (s, 1H), 1.87 (s, 1H), 1.72 (t, J = 15.3 Hz, 1H), 1.60 (s, 2H), 1.55–1.46 (m, 2H), 1.41 (d, J = 4.5 Hz, 1H), 1.38 (d, J = 4.7 Hz, 1H), 1.34 (s, 1H), 1.31 (d, J = 5.8 Hz, 1H), 1.28 (d, J = 3.5 Hz, 1H), 1.22 (s, 2H), 1.07 (dd, J = 8.1, 2.3 Hz, 1H), 0.90–0.80 (m, 2H). ESI-MS m/z: 477.10[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.06 (s), 176.19 (s), 161.16 (s), 160.04 (s), 141.03 (s), 129.00 (s), 128.83 (s), 128.65 (s), 126.30 (s), 105.63 (s), 66.87 (s), 61.54 (s), 54.11 (s), 44.92 (s), 42.09 (s), 38.86 (s), 29.28 (d, J = 56.3 Hz), 28.24 (s), 14.42 (s), 11.84 (s), 9.56 (s), 9.07 (s).

3.4.54. 1-(3-((3-benzyl-4-cyclopropyl-2-oxo-2H-chromen-7-yl) oxy)-2-hydroxypropyl)piperidine-4-carboxamide(54)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.56 (d, J = 6.4 Hz, 1H), 7.53 (d, J = 2.3 Hz, 1H), 7.52 (s, 1H), 7.50 (d, J = 6.7 Hz, 1H), 7.33–7.29 (m, 1H), 7.26 (dd, J = 7.6, 1.7 Hz, 1H), 7.21–7.16 (m, 4H), 7.15–7.09 (m, 2H), 7.06 (d, J = 2.5 Hz, 1H), 7.04 (s, 1H), 7.00 (t, J = 7.2 Hz, 2H), 6.89 (d, J = 2.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 6.83 (s, 1H), 6.82 (s, 1H), 6.69 (d, J = 7.8 Hz, 1H), 4.89 (d, J = 27.9 Hz, 1H), 4.14 (d, J = 5.2 Hz, 1H), 4.08 (d, J = 6.4 Hz, 1H), 4.04–4.00 (m, 1H), 3.96 (d, J = 6.5 Hz, 1H), 3.83 (d, J = 5.4 Hz, 1H), 3.61 (d, J = 4.8 Hz, 2H), 3.17 (d, J = 4.9 Hz, 1H), 2.91 (d, J = 11.0 Hz, 1H), 2.84 (t, J = 11.1 Hz, 1H), 2.74 (d, J = 11.1 Hz, 1H), 2.42 (dd, J = 12.7, 5.4 Hz, 1H), 2.38–2.31 (m, 1H), 2.31–2.24 (m, 1H), 2.07–1.97 (m, 2H), 1.91 (dd, J = 21.2, 10.3 Hz, 1H), 1.61 (s, 2H), 1.58–1.46 (m, 2H). ESI-MS m/z: 513.10[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.11 (s), 161.92 (s), 161.51 (s), 159.64 (s), 154.32 (s), 153.24 (s), 152.30 (s), 140.52 (s), 139.54 (d, J = 8.9 Hz), 134.70 (d, J = 9.2 Hz), 129.25 (d, J = 11.2 Hz), 128.93–128.85 (m), 128.69 (t, J = 13.4 Hz), 128.37 (s), 126.85 (s), 126.35 (d, J = 22.3 Hz), 121.41 (s), 114.06 (s), 113.38 (s), 113.22 (s), 101.66 (s), 100.07 (s), 72.27 (s), 72.08 (s), 66.85 (s), 61.51 (s), 54.09

(d, J = 11.9 Hz), 49.07 (s), 42.06 (s), 35.42 (s), 33.75 (s), 29.02 (s).

3.4.55. 1-(3-((4-cyclopropyl-2-oxo-2H-chromen-7-yl)oxy)-2-hydroxypropyl)piperidine-4-carboxamide (55)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (400 MHz, DMSO) δ 7.29−7.19 (m, 1H), 7.15 (t, J = 8.0 Hz, 2H), 7.03−6.92 (m, 1H), 6.66 (s, 1H), 6.51 (dd, J = 8.2, 2.6 Hz, 2H), 4.05−3.86 (m, 5H), 3.85−3.78 (m, 1H), 3.73 (dd, J = 11.1, 4.6 Hz, 1H), 3.67−3.61 (m, 1H), 2.86 (s, 1H), 2.07 (s, 2H), 1.97 (s, 2H), 1.68−1.47 (m, 3H), 1.22 (s, 1H), 1.16 (t, J = 7.1 Hz, 2H), 1.08 (d, J = 7.9 Hz, 1H), 0.89−0.81 (m, 1H). ESI-MS m/z: 387.00[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 177.05 (s), 160.43 (s), 160.04 (s), 130.44 (s), 129.80−129.04 (m), 128.83 (d, J = 42.9 Hz), 107.61 (s), 107.14 (s), 101.76 (s), 71.57 (s), 69.42 (s), 69.06 (s), 66.92 (s), 61.70 (s), 60.22 (s), 54.05 (s), 47.18 (s), 42.04 (s), 31.16 (s), 29.00 (s), 21.23 (s), 14.55 (s), 11.84 (s), 9.56 (s), 9.22 (s).

3.4.56. 7-(2-Hydroxy-3-(thiazol-2-ylamino)propoxy)-4-methyl-3-(4-(trifluoromethoxy)benzyl)-2H-chromen-2-one (56)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.73 (d, J = 9.6 Hz, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.01−6.94 (m, 2H), 6.84 (d, J = 4.5 Hz, 1H), 6.15 (s, 1H), 4.16 (d, J = 6.9 Hz, 1H), 4.01 (ddd, J = 16.1, 10.4, 5.2 Hz, 3H), 3.96 (s, 2H), 3.92 (d, J = 3.9 Hz, 1H), 3.81 (dd, J = 13.9, 7.3 Hz, 1H), 2.43 (s, 3H), 1.21 (d, J = 4.8 Hz, 4H), 0.84 (t, J = 6.8 Hz, 1H). ESI-MS m/z: 507.11981[M+H] $^+$, delta <0.5 ppm.

^{13}C NMR (126 MHz, DMSO) δ 161.61 (s), 161.44 (s), 153.80 (s), 149.18 (s), 147.14 (s), 139.31 (s), 130.29 (s), 127.22 (s), 121.49 (s), 121.13 (s), 114.11 (s), 113.00 (s), 101.52 (s), 71.02 (s), 67.25 (s), 49.75 (s), 32.00 (s), 29.47 (s), 15.69 (s).

3.4.57. 7-(2-Hydroxy-3-((2-(pyridin-4-yl)ethyl)amino)propoxy)-4-methyl-3-(4-(trifluoromethoxy)benzyl)-2H-chromen-2-one (57)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 8.44 (dd, J = 15.6, 4.5 Hz, 6H), 7.73 (d, J = 9.4 Hz, 2H), 7.35 (d, J = 8.3 Hz, 3H), 7.29 (d, J = 6.6 Hz, 2H), 7.28−7.20 (m, 8H), 6.96 (s, 2H), 5.75 (s, 1H), 5.43 (s, 1H), 5.02 (d, J = 34.1 Hz, 1H), 4.06 (dd, J = 9.8, 4.0 Hz, 1H), 3.97 (s, 2H), 3.95−3.92 (m, 2H), 3.89 (d, J = 6.9 Hz, 1H), 3.83 (s, 1H), 3.61 (dd, J = 10.9, 4.4 Hz, 2H), 3.53 (dd, J = 11.0, 5.3 Hz, 2H), 3.25 (d, J = 6.3 Hz, 2H), 2.81 (s, 2H), 2.76−2.71 (m, 5H), 2.69 (d, J = 4.7 Hz, 1H), 2.64 (d, J = 6.2 Hz, 1H), 2.44 (s, 3H), 2.07 (d, J = 10.3 Hz, 1H), 1.98 (d, J = 10.5 Hz, 1H), 1.76 (d, J = 16.2 Hz, 1H), 1.19 (dd, J = 21.0, 13.9 Hz, 1H), 1.07 (d, J = 30.0 Hz, 1H). ESI-MS m/z: 529.40 [M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 161.69 (d, J = 9.6 Hz), 156.43 (s), 153.84 (s), 149.82 (d, J = 11.4 Hz), 148.69 (s), 147.14 (s), 139.33 (s), 130.28 (s), 127.15 (s), 124.70 (s), 121.48 (s), 120.99 (s), 113.91 (s), 113.01 (s), 101.47 (s), 71.82 (s), 68.84 (s), 68.43 (s), 65.29 (s), 52.40 (s), 50.29 (s), 47.08 (s), 41.08 (s), 35.48 (s), 34.91 (s), 31.99 (s), 15.67 (s).

3.4.58. 3-([1,1′-biphenyl]-4-ylmethyl)-7-(2-hydroxy-3-(thiazol-2-ylamino)propoxy)-4-methyl-2H-chromen-2-one (58)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.74 (d, J = 9.3 Hz, 1H), 7.61−7.55 (m, 7H), 7.54 (s, 1H), 7.51 (dd, J = 8.1, 3.2 Hz, 4H), 7.44−7.38 (m, 6H), 7.34−7.27 (m, 7H), 7.25 (d, J = 8.2 Hz, 2H), 7.10−7.06 (m, 1H), 7.03−6.90 (m, 4H), 4.12 (s, 4H), 4.03−3.96 (m, 10H), 3.93 (dd, J = 5.6, 4.1 Hz, 4H), 3.88 (dd, J = 15.0, 5.7 Hz, 9H), 3.76−3.71 (m, 3H), 3.64 (ddd, J = 11.2, 7.0, 4.9 Hz, 3H), 2.45 (s, 2H), 1.97 (s, 3H), 1.89 (s, 2H), 1.21 (d, J = 3.7 Hz, 5H), 1.15 (t, J = 7.1 Hz, 3H), 1.12 (s, 1H). ESI-MS m/z: 499.29[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 172.51 (s), 161.69 (s), 160.05 (s), 140.58 (s), 140.42 (s), 131.16 (s), 130.67 (d, J = 39.0 Hz), 130.27−129.98 (m), 129.98−129.27 (m), 129.09 (s), 127.58 (s), 127.21 (s), 126.93 (s), 121.57 (s), 112.98 (s), 107.54 (s), 102.71−101.92 (m), 101.68 (d, J = 34.5 Hz), 100.22 (s), 70.90 (s), 70.29 (s), 69.44 (s), 69.05 (s), 67.27 (s), 67.09 (s), 60.22 (s), 50.47 (s), 49.06 (s), 47.16 (s), 34.96 (s), 32.28 (s), 29.47 (s), 21.56 (s), 21.23 (s), 14.55 (s).

3.4.59. 7-(2-Hydroxy-3-(phenethylamino)propoxy)-4-methyl-3-(4-(trifluoromethoxy)benzyl)-2H-chromen-2-one (59)

The title compound was synthesized according to the procedure of preparing Compound NO.**1**.^{1}H NMR (500 MHz, DMSO) δ 7.75 (d, J = 8.6 Hz, 1H), 7.34 (t, J = 7.0 Hz, 3H), 7.30 (d, J = 7.4 Hz, 1H), 7.25 (d, J = 4.4 Hz, 2H), 7.24−7.19 (m, 3H), 6.99 (s, 1H), 6.97 (d, J = 2.5 Hz, 1H), 4.15−4.09 (m, 1H), 4.09−4.02 (m, 2H), 3.96 (s, 2H), 3.11−3.01 (m, 3H), 2.98−2.85 (m, 3H), 2.44 (s, 3H), 2.24 (t, J = 6.7 Hz, 1H), 1.90 (s, 1H), 1.77−1.70 (m, 1H), 1.67−1.59 (m, 1H), 0.88−0.81 (m, 1H). ESI-MS m/z: 528.00[M+H] $^+$.

^{13}C NMR (126 MHz, DMSO) δ 161.62 (s), 161.37 (s), 153.84 (s), 149.18 (s), 147.17 (s), 139.32 (s), 138.59 (s), 130.31 (s), 129.05 (d, J = 11.5 Hz), 127.12 (d, J = 34.2 Hz), 121.51 (s), 121.20 (s), 114.16 (s), 113.05 (s), 101.58 (s), 71.14 (s), 66.11 (s), 50.53 (s), 49.47 (s), 41.80 (s), 33.15 (s), 32.01 (s), 26.91 (s), 15.70 (s).

3.5. Molecular docking

The docking studies were prepared with Ligandscout (4.1) with MMFF 94 energy minimization. The HBV capsid protein (PDB: 6HRO) were prepared with ligandscout (4.1) by removing the ligand and unnecessary water molecules. Then the whole protein was selected for docking and the prepared molecules were inserted. The docking was carried out by AutoDock Vina 1.1(Exhaustiveness = 20, Max. Energy difference = 3). The halogen bond analysis was performed with Flare.

4. Discussion

We previously identified compound **CP19** as an entry inhibitor against Ebola virus infection. The preliminary SAR analysis of ten CP19 derivatives indicated that the hydrophobic or aromatic substitutions on the C3 or C4 of coumarin were vital for its antiviral activity and the carboxamide moiety was important for its activity. However, the detailed SAR of these sites and the roles of the linker between the coumarin and the piperidine were still elusive. In this research, we performed a detailed SAR studies based on **CP19** and elucidate the different weights of these parts on their antivirus efficacy. Our analysis discovered that the substitutions of large aromatic groups on the C3 and C4 of coumarin could afford potent antiviral activities and the most important part of **CP19** derivatives was the substitution groups on C3 of coumarin. In addition, the piperidine group could be optimized with heterocycles, but not with small hydrophilic groups, which indicates that this moiety should have hydrogen bond interactions with the GP protein. However, the substitutions on the linker would decrease its activity, and the stereo structure had little influence on the activity, which suggests that the linker structure did not take important role in the interactions with the binding pocket.

Compound **32** is similar to compound **118a** in its carboxamide and piperidine groups, but compound **118a** has more potent activity to inhibit Ebolavirus entry. The crystal structure of Ebola GP complexed with compound **118a** and our studies strongly indicate that [1] the coumarin of compound **32** occupies almost the same pocket as the phenol ring of compound **118a**. However, the lactone of coumarin does not form H-bond or strong electrostatic interactions with Ebola glycoprotein, and thus this structure could be replaced by groups with smaller volume or better chemical

accessibility. [2] The trifluomethoxybenzyl group of compound **32** occupied more hydrophobic space in the binding pocket than the *o*-chlorobenzene group of compound **118a**, but the docking studies show that the halogen bond between the chlorine atom of compound **118a** and G67 of GP protein contributes significantly to afford high binding score. Thereof, new derivatives of compound **32** that has halogen bond with G67 probably could afford higher activity.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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