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Rational Design and Structure−Activity Relationship of Coumarin Derivatives effective on HIV-1 Protease and partially on HIV-1 Reverse Transcriptase

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ABSTRACT: Since dual inhibitors may yield lower toxicity and reduce the likelihood of drug resistance, as well as inhibitors of HIV-1 PR and RT constitute the core of chemotherapy for AIDS treatment, we herein designed and synthesized new coumarin derivatives characterized by various linkers that exhibited excellent potency against PR and a weak inhibition of RT. Among which, compounds **6f** and **7c** inhibited PR with IC_{50} values of 15.5 and 62.1 nM, respectively, and weakly affected also RT with IC_{50} values of 241.8 and 188.7 μM, respectively, showing the possibility in the future of developing dual HIV-1 PR/RT inhibitors. Creative stimulation for further research of more potent dual HIV-1 inhibitors was got according to the molecular docking studies.

Keywords: coumarin; HIV-1 PR inhibitors; HIV-1 RT inhibitors; pharmacophore fusion types

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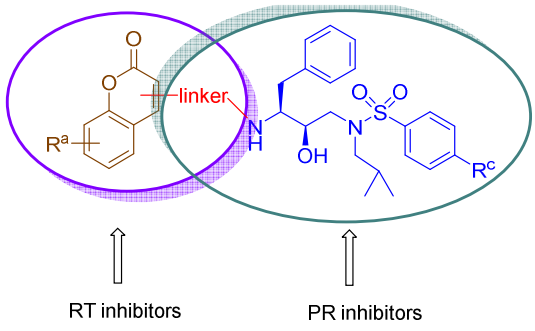
[1]These authors made equal contributions to this work.



Inhibitors against PR and RT

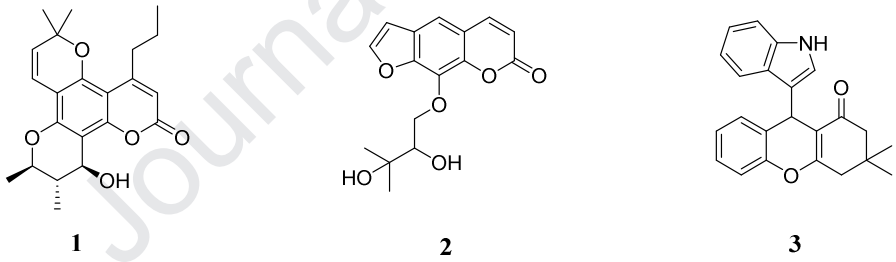
1. Introduction

Highly active antiretroviral therapy (HAART) plays an important role in the treatment of AIDS patients. Nevertheless, the adverse effects, the risk of drug interactions, and the emergence of cross-resistant HIV strains brought by HAART have promoted to discovering new strategy against HIV-1 [1,2]. Dual inhibitors are single compounds that are able to inhibit two enzyme activities, which could yield lower toxicity, simplify dosing, and reduce the likelihood of drug resistance. Dual inhibitors have been reported in different disease arena, such as Alzheimer [3], Parkinson [4], inflammation [5], cancer [6−8], as well as virologic [9]. Particularly, an increasing number of dual inhibitors research has been focused on inhibiting HIV-1 replication, such as dual inhibitors targeting HIV-1 integrase (IN) and reverse transcriptase (RT) or reverse transcriptase ribonuclease H (RNase H) [10−21], dual-action against HIV-1 CCR5 and integrase [22], or targeting HIV-1 reverse transcriptase-associated RNase H and RNA-dependent DNA polymerase (RDDP) functions [23], and so forth. However, research on dual HIV-1 protease (PR) and reverse transcriptase inhibitors is inappreciable [24,25], and dual inhibitor is still not available for clinical use to treat AIDS.

As inhibitors of HIV-1 PR and RT constitute the core of chemotherapy for AIDS treatment, and dual therapy with a PR inhibitor and RT inhibitors has been confirmed to be safe and effective [26], our attention has been given to the design and synthesis of dual inhibitors of HIV-1 PR and RT. HIV-1 PR is responsible for the production of all viral enzymes and structural proteins necessary to produce mature, virulent virions [27]. PR is a homodimer of two 99 amino acid subunits, and two flexible

glycine-dense β-sheets form a flap region over the top of the active site [28,29]. RT is a 117 kDa heterodimer consisting of p66 and p51 subunits [30], and is responsible for the conversion of single-stranded viral RNA into double-stranded proviral DNA.

Given that hydrogen bonding interactions are indispensable for both PR and RT to combining with inhibitors [30−32], it is possible that two scaffolds of RT and PR inhibitors are merged into one scaffold with dual activities, according to the Designed Multifunctional Ligands (DMLs) [33] or "portmanteau inhibitors" [21]. In previous studies, both naturally occurring and synthetic coumarin derivatives show potent RT inhibition activity, such as Calanolide A (**1**) [34], fesumtuorin A (**2**) [35], and 4r (**3**) in **Figure 1** [36]. Inspired by the above, we introduced the coumarin moieties into the HIV-1 protease inhibitors, and designed new inhibitors of pharmacophore fusion types, which contained a coumarin moiety as novel P2 ligands coupled with the nonpeptide PIs structural scaffolds containing hydroxyethylsulfonamide isosteres (**Figure 2**), aiming at obtaining RT inhibition and keeping excellent potency against PR at the same time.



1 **2** **3**

Figure 1. Structures of coumarin derivatives active against RT.

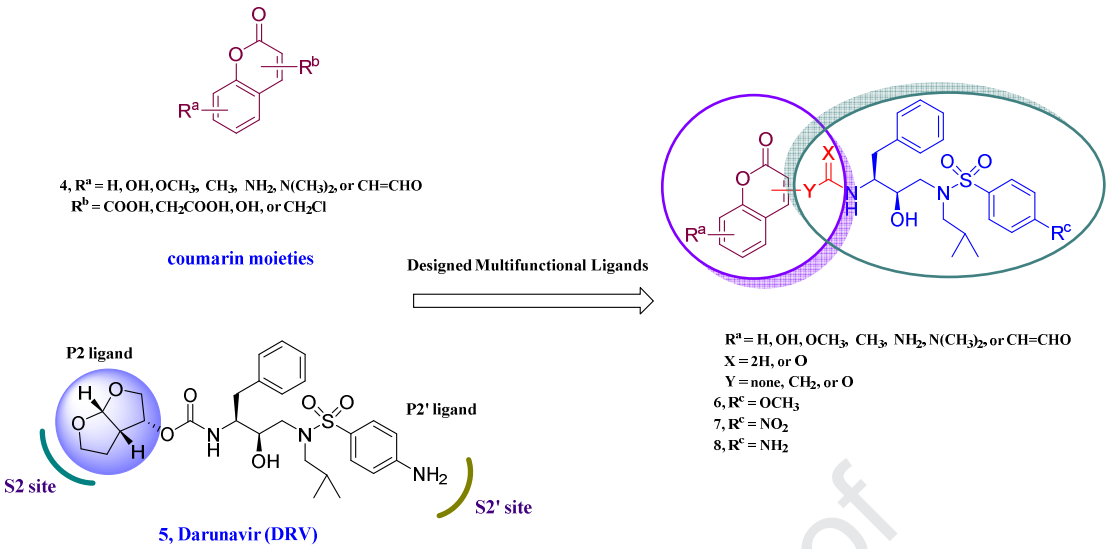
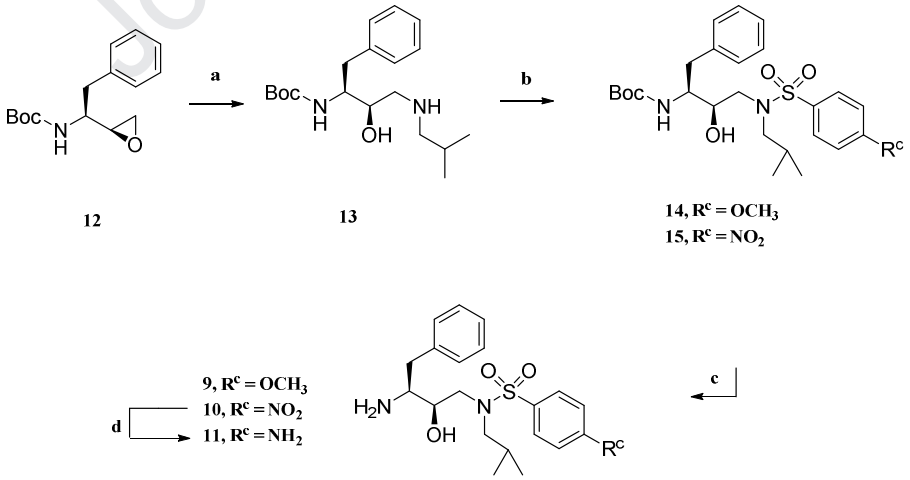


Figure 2. Design of portmanteau inhibitors against RT and PR, combining coumarin moieties **4** with PR inhibitor **5**.

2. Results and discussion

2.1.2.1. Chemistry

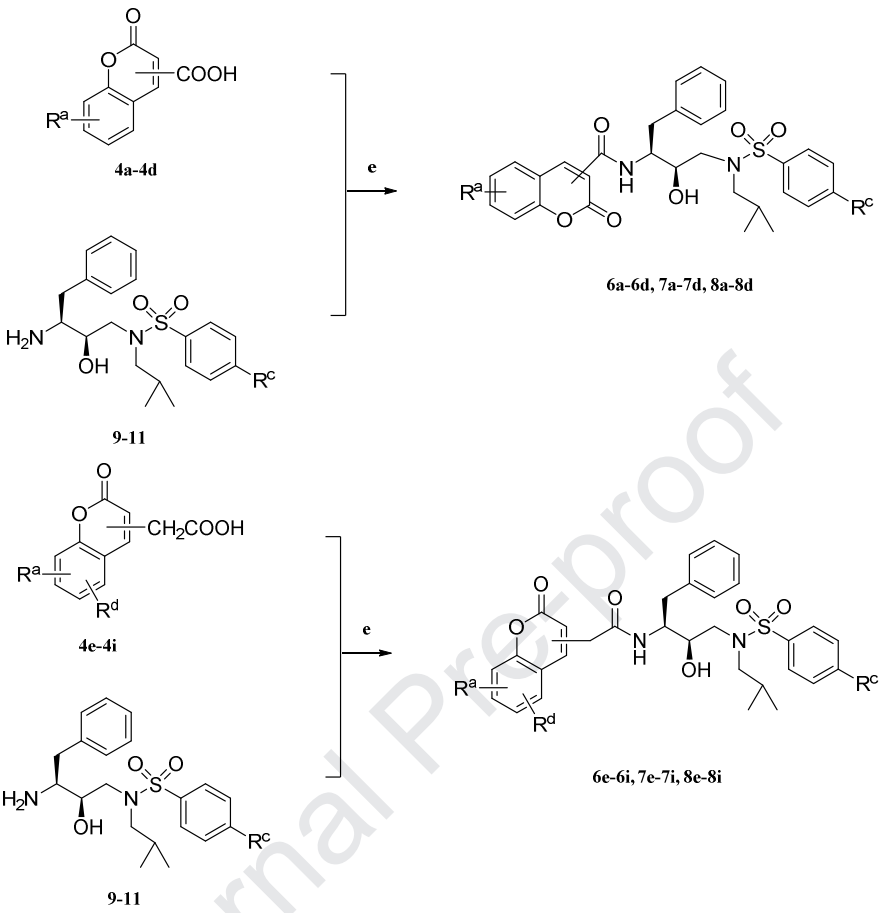
Synthesis of amine derivatives. Compounds **9-11** were prepared from the commercially available material (2*S*, 3*S*)-1,2-epoxy-3-(boc-amino)-4-phenylbutane (**12**), as reported in the literature and shown in **Scheme 1** [37,38].



Scheme 1. Syntheses of Amines **9-11**. Reagents and conditions: (a) *i*-BuNH$_2$, CH$_3$CN, 80 °C, 6 h; (b) Aryl sulfonyl chloride, DIEA, DMAP(Cat.), THF, 0 °C ~ r.t, 3-5 h; (c) CH$_2$Cl$_2$-CF$_3$COOH (1:1), 0 °C~r.t, 3 h; (d) H$_2$ (gas), 50 psi, 10% Pd/C, CH$_3$OH, r.t, 2 h.

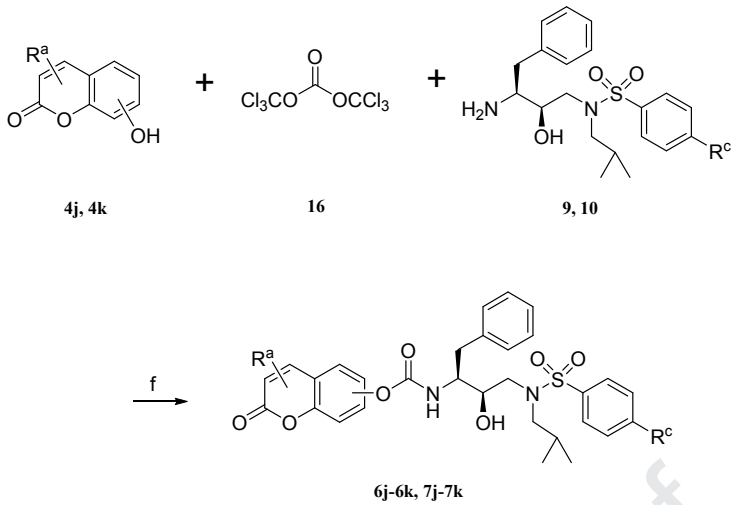
Synthesis of target compounds-amide isosteres. The syntheses of inhibitors **6a-8i**

shown in **Scheme 2** were carried out by coupling coumarin acids **4a-d** with amines **9-11** under an EDCI/HOBt/DMAP-mediated coupling method [38].



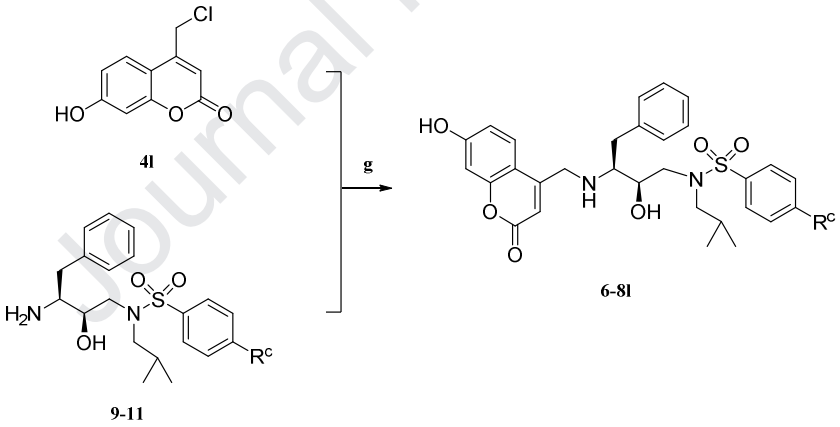
Scheme 2. Syntheses of Inhibitors **6a-8i**. Reagents and conditions: (e) EDCI, HOBt, DMAP, anhydrous DMF, Argon, 0 ℃~r.t, 3 h.

Synthesis of target compounds-carbamate isosteres. The syntheses of inhibitors **6j-7k** shown in **Scheme 3** were synthesized by hydroxycoumarins **4j**, **4k** and amines **9**, **10** under the condensing of bis(trichloromethyl) caebonate (BTC) undergoing an one-pot reaction [39].



Scheme 3. Syntheses of inhibitors **6j-7k**. Reagents and conditions: (f) DIEA, anhydrous DCM, anhydrous THF, 0 °C ~ r.t, 1.5 h.

Synthesis of target compounds-amine isosteres. The syntheses of inhibitors **6-8l** shown in **Scheme 4** were synthesized by chlorocoumarins **4l** and amines **9-11** by catalyzed of DIEA under the condition of refluxing [40].



Scheme 4. Syntheses of inhibitors **6-8l**. Reagents and conditions: (g) DIEA, anhydrous EtOH, reflux, 7 h.

2.2. Anti-PR activity assay

All newly synthesized compounds were tested *in vitro* PR activity assays against HIV-1 wild-type protease using a fluorescence resonance energy transfer (FRET) method [41,42], and the results are summarized in **Tables 1**, **2**, and **3**. Among these compounds, amide derivatives were very potent PR inhibitors, showing IC_{50} values in

the nanomolar range (298.4−0.40 nM), with the exception of **7h** and **7i**, which exhibited higher IC_{50} values of 557 nM and 563 nM. In particularly, compound **8a** with 2-oxo-2H-chromene-6-carboxamide as the P2 ligand and a 4-aminophenylsulfonamide as the P2' ligand exhibited four-fold activity with IC_{50} value of 0.40 nM compared to the reference compound Darunavir (DRV). This might account for the exposure of both carbonyl and oxygen atom, which could form strengthen hydrogen bonding interactions with the backbone atoms and residues in the protease S2 subsite [43]. Meanwhile, compound **6e** demonstrated comparable potency as DRV with IC_{50} value of 1.62 nM. Carboxamide substitution in the 3-position led to a decrease in the activity (**6b**−**8d**, IC_{50} value of 298.4−27.7 nM), compared with substitution in the 6-position (**6a**−**8a**, IC_{50} value of 2.60−0.40 nM). The rigid and bulkier hindrance might impose restrictions on the ability of hydrogen to bond with the protease S2 subsite. But the introducing of hydroxy in the 7-positon showed better inhibitory activity (**6c**−**8c**) than the substitution of hydrogen atoms (**6b**−**8b**). It caused slightly decreasing activity when hydroxy was replaced by methoxyl group (**6d**−**8d**).

Acetamide substitution in the 4-position showed activity against PR with IC_{50} values in the low nanomolar range (55.8−1.62 nM), with the exception of massive substitution in position 7 (**6g**−**8g**, IC_{50} value of 211.3−75.1 nM), but the shift of acetamide substitution from position 4 to 3 gave an decreased activity (**6h**−**8i**, with the IC_{50} value range of 563−95.4 nM). Just as reported previously, phenylsulfonamide derivatives with 4-methoxy (**6a**−**i**) and 4-amino (**7a**−**i**) groups displayed generally higher potency than the corresponding substituted compounds with 4-nitro (**8a**−**i**) groups [43−45].

However, carbamate isosteres decreased in the activity, with IC_{50} values in the range of 1.53−0.12 μM, as well as phenylsulfonamide derivatives with 4-methoxy (**6j**−**k**) groups displayed generally higher potency than the corresponding substituted compounds with 4-nitro (**7j**−**k**) groups by an order of magnitude. While amine derivatives showed increasing activity (**6l**−**8l**, IC_{50} value of 143.5−53.0 nM).

In brief, amide derivatives exhibited higher potency than those of carbamate and amine isosteres, which might be due to the conformational restrictions.

On the basis of these results above, selected inhibitors were further evaluated in cell-based assays. In the assay, virus-producing cells were treated with the compounds at 10 μM, and the infectivity of the resultant virus was determined, which reflects the effect of the compounds on the late stage of HIV-1 life cycle including viral maturation [46]. In particularly, the most active compounds **6a**−**8a** were equipotent as DRV. Notably, compound **6e** showed a slightly decreased antiviral activity (82.94% inhibition) compared with DRV, although equipotent in biochemical assays *in vitro*. While, the amine compounds **6l** and **7l** exhibited satisfactory active in cell-based assays with inhibition of 88.80% and 73.17%, respectively. The results might suggest a correlation between the activity *in vitro* and *in vivo*, as well as excellent cell membrance penetration, as shown in **Tables 1** and **3**.

To further confirm anti-HIV activity of these compounds, we next investigated their effect on the growth of wild type HIV-1 in SupT1 cells. Notably, inhibitor **6e** exhibited a promising inhibition ratio of 45.54% against wild-type HIV-1 at a concentration of 100 nM, compared with the reference compound Nevirapine (NVP) with 77% inhibition, which was worthy for in-depth study [47].

2.3. Anti-RT activity assay

The amide derivatives were tested for RT inhibition using *in vitro* RT-activity assay [48], and the results were listed in **Table 1**. Unfortunately, all the compounds showed limited potency compared with the reference compound Efavirenz (EFV). Next, we analyzed antiviral activity of all the compounds in HIV-1 infected cells using a one round infectivity assay, which was calculated as a percentage of inhibition at a concentration of 10 μM [18]. Likewise, most of the compounds showed poor inhibitory effect on the early step of viral replication including reverse transcription of viral genome by RT.

Surprisingly, compound **8b** was confirmed as a weak inhibitor, with IC_{50} value of 75.25 μM in *in vitro* RT activity assay. And **6f** and **7c** exhibited IC_{50} value of 241.8 and 188.7 μM, respectively.

Taken together, these results suggest that carboxamide substitution in the 3-position with 7-hydoxy or 7-methoxy groups led to a decrease in the activity of RT, compared with unsubstituted compounds in the 7-position, such as 8b *vs* 8c, and 8d. The rigid and bulkier hindrance might impose restrictions on the ability of this kind of derivatives to bind with the reverse transcriptase. In addition, acetamide substitution in the 4-position with biggish substitution in position 7 showed better activity against RT than those with minor substitution in the 7-position (6f, 6g *vs* 6e). The shift of acetamide substitution from position 4 to 3 led to a decrease in the activity, but compounds with 7-hydoxy groups displayed higher potency than those with 7-amino groups (8h *vs* 8i).

2.4. Evaluation of biological activity

To better rationalize structure−activity relationships (SARs) of all the amide isosteres, the IC_{50} values in the inhibition of both PR and RT enzyme were plotted against each other in correlation plots (**Figure 3**). The compounds are distributed around two perpendicular axes crossing the PR IC_{50} axis (X axis) at 150 nM and the RT IC_{50} axis (Y axis) at 250 μM (bolded crosshair in the center of each graph). These two axes spliced the graph into four quarters corresponding to PR/RT dual inhibitors (lower left quarter), RT selective inhibitors (lower right quarter), PR selective inhibitors (upper left quarter), and inhibitors of lower potency (upper right quarter). However, these graphs do not show any particular correlation between RT and PR inhibition. As can be seen in **Figure 3**, most of the compounds are distributed in the left half of the graph, suggesting of critical for PR inhibition but not critical for RT inhibition, which confirms that the amide compounds are selective PR inhibitors. Taking a comprehensive view of the activity above, amide isosteres **6f** and **7c** emerged possibility of developing dual HIV-1 PR/RT inhibitors, which should be optimized further.

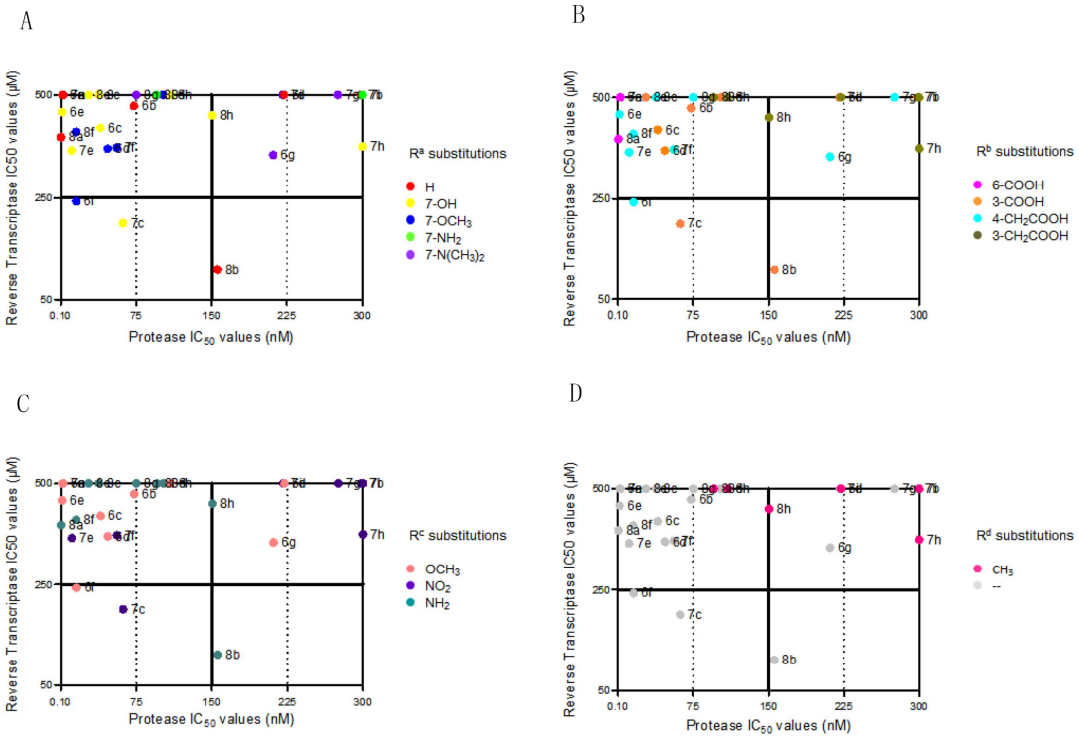
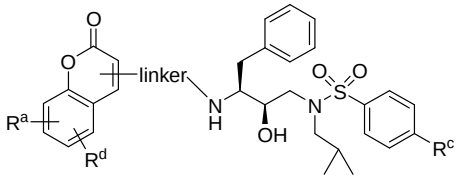


Figure 3. Scatter plot for the inhibition of RT and PR enzymes. (A) Compounds are categorized according to the nature of their R^a substitution. (B) Compounds are categorized according to the nature of their R^b substitution. (C) Compounds are categorized according to the nature of their R^c substitution. (D) Compounds are categorized according to the nature of their R^d substitution. Compounds with IC_{50} values against PR above 300 nM and IC_{50} values against RT above 500 μM have been arbitrary positioned at the 300 nM and 500 μM value, respectively.

Table 1. Antiviral and Enzymatic Activity of Amide Compounds 6a−8i



compd.	R^a	linker	R^c	R^d	PR		RT	
					Inhibition (%)[A,E]	IC_{50} (nM)[B]	Inhibition (%)[A,F]	IC_{50} (μM)[B]
6a	H	6-CO	OCH_3	H	99.53	1.84± 0.53	1.26	597.4± 5.1
7a	H	6-CO	NO_2	H	98.54	2.60± 0.40	-	nd[D]
8a	H	6-CO	NH_2	H	98.72	0.40± 0.11	5.61	398± 2.6
6b	H	3-CO	OCH_3	H	-[C]	72.84±7.63	44.78	473.8± 2.5
7b	H	3-CO	NO_2	H	-	298.4±41.5	27.06	nd
8b	H	3-CO	NH_2	H	-	155.9±18.7	1.34	75.3±2.5
6c	7-OH	3-CO	OCH_3	H	-	39.5±16.9	12.32	420.7± 0

7c	7-OH	3-CO	NO_2	H	73.99	62.1±36.2	91.04	188.7± 0
8c	7-OH	3-CO	NH_2	H	-	27.7±16.9	27.04	554.4± 2.5
6d	7-OCH_3	3-CO	OCH_3	H	-	46.7±16.0	8.28	370.4± 0
7d	7-OCH_3	3-CO	NO_2	H	-	220.9±145.8	0.45	nd
8d	7-OCH_3	3-CO	NH_2	H		102.1±53.9	23.24	705.7±2.4
6e	7-OH	4-CH_2CO	OCH_3	H	82.94	1.62±0.55	-	458.6±2.6
7e	7-OH	4-CH_2CO	NO_2	H	73.36	11.1±4.97	3.91	367.0±2.1
8e	7-OH	4-CH_2CO	NH_2	H	17.94	37.9±15.3	-	nd
6f	7-OCH_3	4-CH_2CO	OCH_3	H	-	15.5±2.75	17.72	241.8± 2.5
7f	7-OCH_3	4-CH_2CO	NO_2	H	-	55.8±14.9	43.72	372.8± 7.6
8f	7-OCH_3	4-CH_2CO	NH_2	H	-	15.4±6.89	7.72	410.6± 0
6g	7-$N(CH_3)_2$	4-CH_2CO	OCH_3	H	-	211.3±84.7	43.75	355.1± 0
7g	7-$N(CH_3)_2$	4-CH_2CO	NO_2	H	-	275.6±219.6	14.65	nd
8g	7-$N(CH_3)_2$	4-CH_2CO	NH_2	H	-	75.1±39.1	18.37	572.2± 0
6h	7-OH	3-CH_2CO	OCH_3	4-CH_3	-	109.2±57.0	31.91	nd
7h	7-OH	3-CH_2CO	NO_2	4-CH_3	-	557±194.1	34.41	375.4± 5.00
8h	7-OH	3-CH_2CO	NH_2	4-CH_3	-	150.6±36.1	23.51	450.8± 0
6i	7-NH_2	3-CH_2CO	OCH_3	4-CH_3	-	222.3±63.5	19.90	nd
7i	7-NH_2	3-CH_2CO	NO_2	4-CH_3	-	563±193.1	24.80	nd
8i	7-NH_2	3-CH_2CO	NH_2	4-CH_3	30.77	95.4±56.6	11.26	nd
DRV					99.97	1.72± 0.73		
EFV								0.091± 0.008

[A] All assays were conducted in quadruplicate or triplicate.

[B] IC_{50}, half maximal inhibitory concentration. All assays were conducted in triplicate, and the data shown represent mean values (±1 standard deviation) derived from the results of three independent experiments.

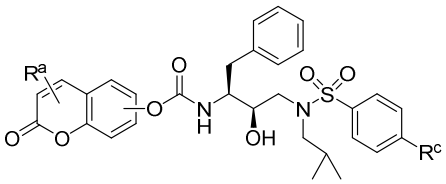
[C] -: not determined, the inhibition was 0.

[D] nd: not determined, the value of IC_{50} exceeding 1000 μM.

[E] the inhibitory effect on virus-producing cell at 10 μM

[F] the inhibitory effect on virus-infected cells at 10 μM

Table 2. Enzymatic Activity of Carbamate Compounds 6j−7k

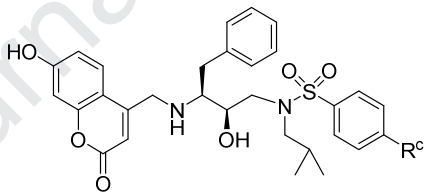


compd.	R^a	R^c	PR IC_{50} (μM)[A]	RT IC_{50} (μM)[A]
6j	4-CH_3	OCH_3	0.16±0.02	nd[B]
7j	4-CH_3	NO_2	1.02±0.56	nd
6k	6,7-CH=CHO	OCH_3	0.12±0.02	nd
7k	6,7-CH=CHO	NO_2	1.53±0.59	nd
DRV			0.00057±0.00017	
EFV				0.091± 0.008

[A] IC_{50}, half maximal inhibitory concentration. All assays were conducted in triplicate, and the data shown represent mean values (±1 standard deviation) derived from the results of three independent experiments.

[B] nd: not determined, the value of IC_{50} exceeding 1000 μM.

Table 3. Antiviral and Enzymatic Activity of Amine Compounds 6l−8l



compd.	R^c	PR		RT
		Inhibition (%)[A]	IC_{50} (μM)[B]	IC_{50} (μM)[B]
6l	OCH_3	88.80	0.053± 0.02	nd[C]
7l	NO_2	73.17	0.14± 0.06	nd
8l	NH_2	-	0.11± 0.05	nd
DRV		99.97	0.0017±0.0007	
EFV				0.091± 0.008

[A] All assays were conducted in quadruplicate. The inhibitory effect on virus-producing cell at 10 μM.

[B] IC_{50}, half maximal inhibitory concentration. All assays were conducted in triplicate, and the data shown represent mean values (±1 standard deviation) derived from the results of three independent experiments.

[C] nd: not determined, the value of IC_{50} exceeding 1000 μM.

2.5. Molecular modeling studies

To explore the antiviral action of the inhibitors, molecular docking studies were performed on inhibitor **7e** as a representative example, with highly potent activity against PR as well as less active RT inhibition. The common mode of inhibitory binding was explored through molecular docking using a HIV PR crystal structure (PDB-ID: 4mc9) [49], and RT crystal structure (PDB-ID: 2yng) [50]. Significantly, the inhibitor **7e** fits perfectly into the PR binding site through hydrogen bonds and van der Waals interactions. As can be seen, several hydrogen-bonding interactions are possible between the residues Arg8 and Gly48, as well as van der Waals interactions with the outer enzyme atoms, both of which might account for the promising HIV-1 PR inhibitory activity (**Figure 4**). While, compound **7e** with moiety of 2-oxo-2H-chromen could not be situated right in the narrow pocket of RT by as much as approximately thirty thousand-fold in contrast with PR potency. Albeit unsatisfactory, hydrogen-bonding interaction between the residues Lys223 may provide the weak activity against RT. Overall, in order to better rationalize the activity of this kind of dual inhibitors, the coumarin moieties for sterically hindering fitting of the RT active site, could exert their RT inhibitory activity by eliminating the bulkier furanone ring and replacing by the miniature linker, such as a flexible chain, which would not affect the activity against PR meanwhile, according to the molecular docking studies.

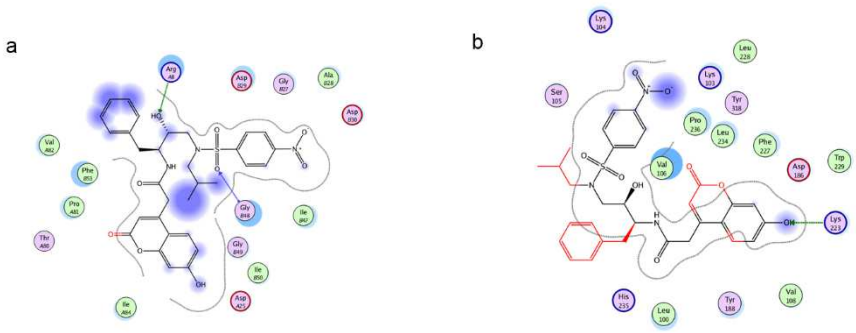


Figure 4. (a) Binding mode of compound **7e** within the HIV-1 PR model. (b) Binding mode of compound **7e** within the HIV-1 RT model. Ligand exposures are represented as purple spheres. Amino acid side chains important for the ligand binding are depicted as blue arrows.

2.6. Correlation for amide isosteres as HIV PR

Further validation was achieved by correlation of the SAR of docked inhibitors **6a**, **7a**, **7b**, **8b**, **8c**, **7e**, **6g**, **8g** and **8h**, as shown in **Figure 5**. The correlation observed between these two sets of IC_{50} data (expt *vs* calcd, correlation coefficiency = 0.86) supports our docking model with a common mode of binding as a valid platform for PR inhibitor design. However, inhibitors should be optimized further for activity against RT.

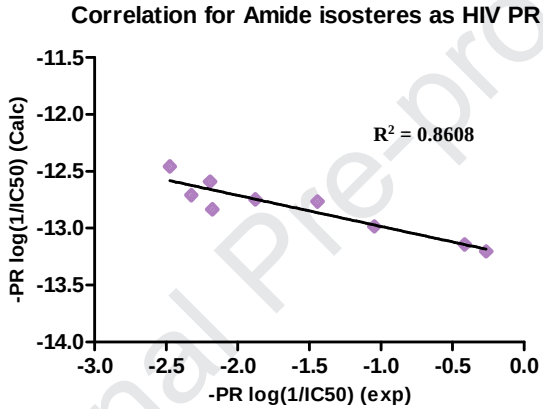


Figure 5. Strong correlation of docked amide isosteres analogues supports a common mode of binding for HIV PR

3. Conclusion

Since inhibitors of HIV-1 PR and RT constitute the core of chemotherapy for AIDS treatment, and dual inhibitors might yield lower toxicity and reduce drug resistance, our attention has been given to the design, synthesis and biological assays of dual inhibitors of HIV-1 PR and RT. In this paper, we describe a series of new coumarin derivatives that are characterized by various linkers. All the compounds were tested in HIV-1 PR and RT activity assay. Amide derivatives were very active PR inhibitors, showing IC_{50} values in the nanomolar range (298.4−0.40 nM), with the exception of **7h** and **7i** (557 nM and 563 nM, respectively), conferring better activity against carbamate and amine isosteres. In particularly, compound **8a** with 2-oxo-2H-chromene-6-carboxamide as the P2 ligand and a

4-aminophenylsulfonamide as the P2' ligand exhibited four-fold activity with IC_{50} value 0.40 nM compared to clinically available PR inhibitor DRV, and the most active compounds **6a**−**8a** were equipotent as DRV in cell-based assays with 99.53−98.72% inhibition. Notably, inhibitor **6e** demonstrated comparable potency as DRV with IC_{50} value of 1.62 nM, and exhibited a promising inhibition ratio of 54.46% against wild-type HIV-1 at a concentration of 100 nM.

However, these compounds showed poor inhibition activity against RT if compared to their anti-PR potency. Among which, compound **8b** was confirmed as a weak RT inhibitor, with IC_{50} value of 75.25 μM. Compounds **6f** and **7c** inhibited PR with IC_{50} values of 15.5 and 62.1 nM, respectively, and also weakly affected RT with IC_{50} values of 241.8 and 188.7 μM, respectively, showing the possibility in the future of developing dual HIV-1 PR/RT inhibitors. According to the molecular docking studies, the 2-oxo-2H-chromen of coumarin moieties might be steric hindrance for fitting into the narrow pocket of RT active site. Eliminating the bulkier furanone ring and replacing by a flexible, miniature linker may exert their RT inhibitory activity and not affect the activity against PR meanwhile.

In conclusion, the design of new coumarin derivatives confirm the possibility of developing dual HIV-1 PR/RT inhibitors and give information for further development of effective dual HIV-1 inhibitors.

4. Experimental section

4.1. Chemistry

All experiments requiring anhydrous conditions were conducted in flame-dried glassware fitted with rubber septa under a positive pressure of dry argon, unless otherwise noted. THF was distilled under argon from sodium-benzophenone ketyl and CH_2Cl_2 was distilled under argon from calcium hydride. All reactions were monitored by thin-layer chromatography on silica gel plates (GF-254) and visualized with the UV light. Flash column chromatography was performed on a CombiFlash®Rf 200

system employing silica gel (50-75 μm, Qingdao Haiyang Chemical Co.,Ltd). Melting points were taken on MP70 Melting Point System with revised. High resolution mass spectra were obtained on an Autospee Ultima-TOF spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD, $(CD_3)_2CO$ or DMSO-d_6 on a Bruker AVANCE III 400 MHz, 500 MHz or 600 MHz spectrometer (Bruker Inc) with tetramethylsilane (TMS) as an internal reference. The chemical shifts are given in δ (ppm) referenced to the respective solvent peak ($CDCl_3$: ^{1}H, δ = 7.26 ppm, ^{13}C, δ = 77.16 ppm; CD_3OD: ^{1}H, δ = 3.31 ppm, ^{13}C, δ = 49.00 ppm; $(CD_3)_2CO$: ^{1}H, δ = 2.05 ppm, ^{13}C, δ = 30, 205 ppm; DMSO-d_6: ^{1}H, δ = 2.49 ppm, ^{13}C, δ = 39.5 ppm), and coupling constants are reported in Hz. All the target compounds were characterized by ^{1}H and ^{13}C NMRs and HRMS spectra.

4.1.1.

*N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)-2-oxo-2H-chromene-6-carboxamide (**6a**)*

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI, 0.029 g, 0.15 mmol) and 1-hydroxybenzotriazole (HOBt, 0.015 g, 0.11 mmol) were sequentially added in batches to a stirring solution of 2-oxo-2H-chromene-6-carboxylic acid (**4a**, 0.019 g, 0.10 mmol) and *N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-methoxybenzenesulfonamide (**9**, 0.043 g, 0.105 mmol) in dry DMF (1 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 10 min at 0 °C and then additional 1 hour at room temperature. 4-Dimethylaminopyridine (DMAP, 0.0024 g, 0.020 mmol) was added and the reaction mixture was stirred for another 2 hours at room temperature. The solvent was removed under reduced pressure. Water (4 mL) was added to the residue and extracted with ethyl acetate (3 × 4 mL). The combined organic phases were dried over Na_2SO_4, and evaporated, i*n vacuo*. The residue was purified by chromatography on a silica gel column (30 × 6 cm). Elution with 1:1 to 2:3 hexanes-ethyl acetate gave **6a** as pale yellow crystalline powder: yield 0.050 g (87%); mp 118-120 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (s, 1H), 7.92 (d,

J = 9.6 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.47 (d, *J* = 9.6 Hz, 1H), 4.25 (dd, *J* = 9.4, 4.3 Hz, 1H), 4.00 – 3.96 (m, 1H), 3.80 (s, 3H), 3.46 (d, *J* = 15.0 Hz, 1H), 3.10 (dd, *J* = 13.3, 8.5 Hz, 1H), 3.00 (d, *J* = 13.4 Hz, 1H), 2.95 – 2.91 (m, 1H), 2.83 – 2.77 (m, 2H), 2.08 – 1.99 (m, 1H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) *δ* 168.4, 164.9, 164.5, 161.9, 157.1, 145.1, 140.2, 132.3, 131.8, 130.6, 130.3, 129.3, 128.8, 127.3, 120.0, 118.1, 117.7, 115.3, 74.7, 59.1, 56.2, 56.1, 54.4, 36.6, 28.0, 20.5, 20.4; HRMS (ESI) m/z calcd. for $C_{31}H_{34}N_2O_7S$ ([M - H]$^-$): 577.2015, found 577.2024.

4.1.2.

*N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl) -2-oxo-2H-chromene-6-carboxamide (**7a**)*

The title compound was obtained by **4a** which was coupled with **10** through EDCI/HOBt/DMAP coupling procedure in 78% yield (white powder) as described for **6a**: mp 178-180 °C; ^{1}H NMR (400 MHz, CD_3OD) *δ* 8.27 (d, *J* = 8.0 Hz, 2H), 7.99 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 9.6 Hz, 1H), 7.87 (s, 1H), 7.83 (d, *J* = 9.6 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.27 – 7.19 (m, 4H), 7.12 (t, *J* = 7.2 Hz, 1H), 6.48 (d, *J* = 9.6 Hz, 1H), 4.21 – 4.19 (m, 1H), 3.92 (t, *J* = 7.6 Hz, 1H), 3.49 (d, *J* = 15.0 Hz, 1H), 3.24 (dd, *J* = 13.4, 10.2 Hz, 2H), 3.15 (dd, *J* = 15.0, 8.9 Hz, 1H), 2.98 – 2.95 (m, 1H), 2.82 – 2.75 (m, 1H), 2.10 – 2.00 (m, 1H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) *δ* 168.5, 161.9, 157.1, 151.4, 146.7, 145.0, 140.1, 132.2, 131.7, 130.3, 129.8, 129.4, 128.9, 127.3, 125.3, 120.1, 118.2, 117.8, 73.8, 58.1, 56.3, 53.5, 36.6, 27.8, 20.4, 20.3; HRMS (ESI) m/z calcd. for $C_{30}H_{31}N_3O_8S$ ([M - H]$^-$): 592.1766, found 592.1772.

4.1.3.

*N-((2S,3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-y l)-2-oxo-2H-chromene-6-carboxamide (**8a**)*

The title compound was obtained by **4a** which was coupled with **11** through

EDCI/HOBt/DMAP coupling procedure in 84% yield (pale yellow powder) as described for **6a**: mp 155-157 °C; ^{1}H NMR (400 MHz, CD3OD) δ 7.97 (brs, 2H), 7.91 (d, *J* = 9.6 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 2H), 6.46 (d, *J* = 9.6 Hz, 1H), 4.26 (t, *J* = 9.2 Hz, 1H), 3.99 (t, *J* = 7.6 Hz, 1H), 3.43 (d, *J* = 15.0 Hz, 1H), 3.04 (dd, *J* = 13.3, 8.6 Hz, 2H), 2.91 – 2.83 (m, 1H), 2.80 – 2.73 (m, 2H), 2.07 – 1.97 (m, 1H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 168.5, 164.9, 157.0, 154.3, 145.1, 140.3, 132.4, 131.8, 130.4, 130.3, 129.3, 128.8, 127.2, 125.6, 120., 118.1, 117.7, 114.3, 74.9, 59.5, 56.2, 54.7, 36.9, 28.1, 20.6, 20.5; HRMS (ESI) m/z calcd. for $C_{30}H_{33}N_3O_6S$ ([M - H]$^-$): 562.2018, found 562.2043.

4.1.4.

*N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)-2-oxo-2H-chromene-3-carboxamide (**6b**)*

The title compound was obtained by **4b** which was coupled with **9** through EDCI/HOBt/DMAP coupling procedure in 98% yield (yellow oil) as described for **6a**: mp 152-155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (d, *J* = 8.3 Hz, 1H), 8.79 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.67 (dd, *J* = 15.4, 7.9 Hz, 2H), 7.39 (dd, *J* = 15.8, 8.1 Hz, 2H), 7.29 – 7.26 (m, 4H), 7.20 (d, *J* = 5.7 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 2H), 4.37 – 4.35 (m, 1H), 3.98- 3.97 (m, 1H), 3.86 (s, 3H), 3.25 – 3.17 (m, 2H), 3.11 (d, *J* = 15.0 Hz, 1H), 3.02- 2.97 (m, 2H), 2.85 (dd, *J* = 13.3, 6.7 Hz, 1H), 1.86 (dt, *J* = 13.5, 6.6 Hz, 1H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 161.8, 161.1, 154.4, 148.6, 137.5, 134.3, 130.1, 129.8, 129.5, 129.46, 128.5, 126.5, 125.3, 118.5, 117.8, 116.7, 114.3, 72.5, 58.5, 55.6, 54.8, 53.4, 35.9, 27.1, 20.1, 19.9; HRMS (ESI) m/z calcd. for $C_{31}H_{34}N_2O_7S$ ([M - H]$^-$): 577.2003, found 577.1974.

4.1.5.

*N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl)-2-oxo-2H-chromene-3-carboxamide (**7b**)*

The title compound was obtained by **4b** which was coupled with **10** through

EDCI/HOBt/DMAP coupling procedure in 96% yield (pale yellow powder) as described for **6a**: mp 201-204 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.71 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 2H), 8.04 (d, *J* = 8.6 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.26 (d, *J* = 7.2 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 2H), 7.14 (t, *J* = 7.0 Hz, 1H), 4.29 (dt, *J* = 9.5, 5.0 Hz, 1H), 3.81 – 3.78 (m, 1H), 3.54 (dd, *J* = 15.0, 3.0 Hz, 1H), 3.26 – 3.23 (m, 1H), 3.20 – 3.17 (m, 1H), 3.13 (dd, *J* = 13.9, 4.0 Hz, 1H), 3.03 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.82 (dd, *J* = 13.9, 9.8 Hz, 1H), 2.07 – 2.01 (m, 1H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 163.3, 162.5, 155.9, 149.5, 147.0, 144.2, 139.2, 135.7, 131.3, 130.6, 129.8, 129.4, 127.5, 126.6, 125.4, 119.8, 119.3, 117.5, 72.5, 57.8, 55.6, 52.8, 36.2, 27.7, 20.3; HRMS (ESI) m/z calcd. for $C_{30}H_{31}N_3O_8S$ ([M - H]$^-$): 592.1748, found 592.1739.

4.1.6.

*N-((2S,3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-oxo-2H-chromene-3-carboxamide (**8b**)*

The title compound was obtained by **4b** which was coupled with **11** through EDCI/HOBt/DMAP coupling procedure in 22% yield (yellow granular solid) as described for **6a**: mp 177-179 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.69 (s, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 4.36 (dt, *J* = 9.5, 5.0 Hz, 1H), 3.94 – 3.91 (m, 1H), 3.45 (dd, *J* = 15.0, 3.5 Hz, 1H), 3.21 (dd, *J* = 13.9, 3.5 Hz, 1H), 3.06 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.95 (dd, *J* = 15.0, 8.0 Hz, 1H), 2.84 – 2.77 (m, 2H), 2.01 – 1.96 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 163.2, 162.5, 157.1, 155.8, 149.5, 139.6, 135.6, 131.3, 130.6, 129.8, 129.7, 129.3, 127.4, 126.5, 119.9, 119.2, 117.5, 113.2, 73.5, 59.1, 55.6 54.0, 36.3, 28.1, 20.6, 20.5; HRMS (ESI) m/z calcd. for $C_{30}H_{33}N_3O_6S$ ([M - H]$^-$): 562.2018, found 562.2040.

4.1.7.

7-Hydroxy-N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-ph

*enylbutan-2-yl)-2-oxo-2H-chromene-3-carboxamide (**6c**)*

The title compound was obtained by **4c** which was coupled with **9** through EDCI/HOBt/DMAP coupling procedure in 98% yield (pale yellow oil) as described for **6a**: mp 188-190 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.26 – 7.18 (m, 4H), 7.12 (t, J = 7.2 Hz, 1H), 6.96 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.6 Hz, 1H), 6.75 (s, 1H), 4.32 – 4.29 (m, 1H), 3.89 – 3.85 (m, 1H), 3.41 (dd, J = 15.0, 3.2 Hz, 1H), 3.17 (dd, J = 13.8, 3.2 Hz, 1H), 3.09 (dd, J = 13.5, 8.0 Hz, 1H), 2.98 – 2.93 (m, 1H), 2.87 – 2.74 (m, 2H), 2.03 – 1.96 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 165.8, 164.8, 164.5, 164.0, 158.2, 149.8, 139.5, 1323.0, 131.9, 130.6, 130.5, 129.3, 127.4, 115.8, 115.3, 114.1, 114.0, 112.7, 103.1, 73.4, 58.8, 56.1, 55.5, 53.8, 36.9, 28.0, 20.5, 20.4; HRMS (ESI) m/z calcd. for $C_{31}H_{34}N_2O_8S$ ([M - H]$^-$): 593.1964, found 593.1955.

4.1.8.

*7-Hydroxy-N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenyl butan-2-yl)-2-oxo-2H-chromene-3-carboxamide (**7c**)*

The title compound was obtained by **4c** which was coupled with **10** through EDCI/HOBt/DMAP coupling procedure in 94% yield (yellow crystalline powder) as described for **6a**: mp 252-254 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.30 (d, J = 8.2 Hz, 2H), 8.00 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.6 Hz, 1H), 7.23 – 7.17 (m, 4H), 7.11 (t, J = 6.8 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 6.74 (s, 1H), 4.30 – 4.19 (m, 1H), 3.76 – 3.74 (m, 1H), 3.51 (d, J = 15.0 Hz, 1H), 3.25 – 3.14 (m, 2H), 3.09 (dd, J = 13.9, 4.0 Hz, 1H), 3.04 – 3.00 (m, 1H), 2.82 – 2.76 (m, 1H), 2.07 – 1.97 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 165.9, 164.9, 164.0, 158.3, 151.4, 149.9, 146.9, 139.2, 133.0, 130.6, 129.8, 129.3, 127.5, 125.4, 115.8, 114.0, 112.7, 103.1, 72.6, 57.7, 55.4, 52.8, 36.9, 27.7, 20.3; HRMS (ESI) m/z calcd. for $C_{30}H_{31}N_3O_9S$ ([M - H]$^-$): 608.1709, found 608.1700.

4.1.9.

*N-((2S,3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-7-hydroxy-2-oxo-2H-chromene-3-carboxamide (**8c**)*

The title compound was obtained by **4c** which was coupled with **11** through EDCI/HOBt/DMAP coupling procedure in 88% yield (pale yellow oil) as described for **6a**: mp 267-270 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.59 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.26 – 7.17 (m, 4H), 7.11 (t, J = 7.0 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.74 (s, 1H), 6.61 (d, J = 8.0 Hz, 2H), 4.35 – 4.31 (m, 1H), 3.87 (t, J = 8.6 Hz, 1H), 3.39 (dd, J = 14.9, 3.6 Hz, 1H), 3.17 (dd, J = 13.9, 3.8 Hz, 1H), 3.03 – 2.99 (m, 1H), 2.90 (dd, J = 15.0, 8.0 Hz, 1H), 2.80 – 2.72 (m, 2H), 1.99 - 1.93 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 165.8, 164.9, 158.2, 154.3, 149.8, 139.6, 133.0, 127.3, 125.89, 115.7, 114.4, 114.2, 114.1, 112.7, 103.1, 73.6, 59.1, 55.5, 54.1, 37.0, 28.2, 20.6, 20.5; HRMS (ESI) m/z calcd. for $C_{30}H_{33}N_3O_7S$ ([M - H]$^-$): 578.1967, found 578.1991.

4.1.10.

*N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)-7-methoxy-2-oxo-2H-chromene-3-carboxamide (**6d**)*

The title compound was obtained by **4d** which was coupled with **9** through EDCI/HOBt/DMAP coupling procedure in 68% yield (colorless oil) as described for **6a**: mp 177-179 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.61 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.66 (d, J = 8.6 Hz, 1H), 7.26 (d, J = 7.4 Hz, 2H), 7.21 (t, J = 7.6 Hz, 2H), 7.13 (t, J = 7.3 Hz, 1H), 6.99 – 6.97 (m, 4H), 4.32 (ddd, J = 10.0, 5.9, 4.2 Hz, 1H), 3.92 (s, 3H), 3.89- 3.86 (m, 1H), 3.79 (s, 3H), 3.43 (dd, J = 15.0, 3.7 Hz, 1H), 3.18 (dd, J = 14.0, 4.0 Hz, 1H), 3.10 (dd, J = 13.6, 8.1 Hz, 1H), 2.98 – 2.95 (m, 1H), 2.87 – 2.84 (m, 1H), 2.78 (dd, J = 14.0, 10.0 Hz, 1H), 2.04 – 1.97 (m, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 166.9, 164.5, 163.7, 162.9, 158.1, 149.6, 139.5, 132.5, 132.0, 130.6, 130.5, 129.3, 127.4, 115.3, 115.2, 115.1, 113.5, 101.3, 73.4, 58.8, 56.8, 56.1, 55.5, 53.8, 36.4, 28.1, 20.5, 20.4; HRMS (ESI) m/z calcd. for $C_{32}H_{36}N_2O_8S$ ([M - H]$^-$): 607.2120, found 607.2100.

4.1.11.

*N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl) -7-methoxy-2-oxo-2H-chromene-3-carboxamide (**7d**)*

The title compound was obtained by **4d** which was coupled with **10** through EDCI/HOBt/DMAP coupling procedure in 50% yield (yellow crystalline powder) as described for **6a**: mp 263-265 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.65 (s, 1H), 8.32 (d, *J* = 8.9 Hz, 2H), 8.02 (d, *J* = 8.9 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.01 (dt, *J* = 7.1, 2.3 Hz, 2H), 4.26 (ddd, *J* = 10.0, 6.0, 4.3 Hz, 1H), 3.76 (ddd, *J* = 9.0, 6.2, 3.2 Hz, 1H), 3.52 (dd, *J* = 15.2, 3.2 Hz, 1H), 3.24 (dd, *J* = 13.6, 8.1 Hz, 1H), 3.18 (dd, *J* = 15.2, 8.7 Hz, 1H), 3.11 (dd, *J* = 14.0, 4.2 Hz, 1H), 3.04 – 2.99 (m, 1H), 2.81 (dd, *J* = 14.0, 9.6 Hz, 1H), 2.07 – 2.02 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 167.0, 163.8, 163.0, 158.2, 151.4, 149.7, 147.0, 139.2, 132.6, 130.6, 129.8, 129.4, 127.5, 125.4, 115.3, 115.1, 113.6, 101.3, 72.6, 57.8, 56.8 55.5, 52.8, 36.3, 27.7, 20.3; HRMS (ESI) m/z calcd. for $C_{31}H_{33}N_3O_9S$ ($[M - H]^-$): 622.1866, found 622.1842.

4.1.12.

*N-((2S,3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-y l)-7-methoxy-2-oxo-2H-chromene-3-carboxamide (**8d**)*

The title compound was obtained by **4d** which was coupled with **11** through EDCI/HOBt/DMAP coupling procedure in 83% yield (yellow crystalline powder) as described for **6a**: ^{1}H NMR (600 MHz, CD_3OD) δ 8.60 (s, 1H), 7.97 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 6.97 – 6.94 (m, 2H), 6.63 (d, *J* = 8.6 Hz, 2H), 4.35 (ddd, *J* = 10.0, 5.6, 4.2 Hz, 1H), 3.92 – 3.89 (m, 4H), 3.42 (dd, *J* = 15.0, 4.0 Hz, 1H), 3.19 (dd, *J* = 13.9, 4.0 Hz, 1H), 3.02 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.93 (dd, *J* = 14.9, 8.0 Hz, 1H), 2.82 – 2.75 (m, 2H), 2.02 – 1.95 (m, 1H), 0.91 (t, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 166.9, 164.8, 163.7, 162.9, 158.1, 154.3, 149.6, 139.6, 132.5, 130.6, 130.5, 129.3, 127.3, 125.9, 115.2, 114.4, 113.5, 101.3,

73.6, 59.2, 56.77 (s), 55.5, 54.1, 36.9, 28.2, 20.6, 20.5; HRMS (ESI) m/z calcd. for $C_{31}H_{35}N_3O_7S$ ([M - H]$^-$): 592.2124, found 592.2092.

4.1.13.

*2-(7-Hydroxy-2-oxo-2H-chromen-4-yl)-N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)acetamide (**6e**)*

The title compound was obtained by **4e** which was coupled with **9** through EDCI/HOBt/DMAP coupling procedure in 92% yield (colorless oil) as described for **6a**: mp 132-135 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 9.2 Hz, 1H), 7.09 – 7.08 (m, 4H), 7.06 – 7.04 (m, 1H), 6.95 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 9.2 Hz, 2H), 5.89 (s, 1H), 4.01 – 3.95 (m, 1H), 3.77 (s, 3H), 3.74 – 3.69 (m, 1H), 3.31 (dd, J = 14.8, 3.2 Hz, 1H), 3.08 (dd, J = 13.8, 3.2 Hz, 1H), 2.95 – 2.92 (m, 1H), 2.84 – 2.78 (m, 1H), 2.74 – 2.70 (m, 1H), 2.52 (dd, J = 13.8, 11.6 Hz, 1H), 1.88 (dq, J = 20.4, 6.8 Hz, 1H), 0.79 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 168.8, 163.1, 161.9, 161.4, 155.3, 150.8, 138.4, 130.6, 129.2, 128.8, 127.8, 126.2, 125.9, 113.9, 113.0, 111.6, 111.5, 102.1, 72.8, 57.5, 54.8, 54.1, 52.6, 38.7, 35.0, 26.6, 19.1, 19.0; HRMS (ESI) m/z calcd. for $C_{32}H_{36}N_2O_8S$ ([M - H]$^-$): 607.2109, found 607.2132.

4.1.14.

*2-(7-Hydroxy-2-oxo-2H-chromen-4-yl)-N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl)acetamide (**7e**)*

The title compound was obtained by **4e** which was coupled with **10** through EDCI/HOBt/DMAP coupling procedure in 72% yield (white powder) as described for **6a**: mp 223-225 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 9.2 Hz, 1H), 7.24 – 7.13 (m, 5H), 6.67 – 6.66 (m, 2H), 6.00 (s, 1H), 4.05 – 4.02 (m, 1H), 3.79 – 3.75 (m, 1H), 3.50 – 3.45 (m, 1H), 3.18 – 3.09 (m, 3H), 2.99 – 2.95 (m, 1H), 2.62 (t, J = 12.6 Hz, 1H), 2.00 (dq, J = 13.6, 6.8 Hz, 1H), 0.89 (d, J = 6.4 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 170.4, 163.4, 162.9, 156.7, 152.2, 151.4, 147.0, 139.7, 130.2, 129.8, 129.3,

127.6, 127.4, 125.4, 114.4, 113.1, 113.0, 103.6, 73.4, 57.9, 55.7, 53.2, 40.2, 36.4, 27.8, 20.3; HRMS (ESI) m/z calcd. for $C_{31}H_{33}N_3O_9S$ ([M - H]$^-$): 622.1854, found 622.1888.

4.1.15.

*N-((2S,3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-(7-hydroxy-2-oxo-2H-chromen-4-yl)acetamide (**8e**)*

The title compound was obtained by **4e** which was coupled with **11** through EDCI/HOBt/DMAP coupling procedure in 51% yield (yellow powder) as described for **6a**: mp 179-181 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.76 (brs, 2H), 7.41 (d, J = 12.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.24 – 7.15 (m, 7H), 6.67 (brs, 2H), 4.11 (m, 2H), 3.85 (m, 1H), 3.64 (m, 3H), 3.37 (m, 2H), 2.90 (m, 2H), 2.69 (d, J = 10.0 Hz, 1H), 1.97 (m, 1H), 0.86 (d, J = 10.0 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ 166.2, 162.6, 156.4, 152.2, 143.5, 139.6, 134.8, 130.5, 130.3, 130.1, 129.1, 127.5, 127.2, 120.6, 114.3, 112.9, 112.8, 103.3, 73.5, 58.4, 55.54 (s), 53.5, 31.6, 27.8, 20.3, 20.2; HRMS (ESI) m/z calcd. for $C_{31}H_{35}N_3O_7S$ ([M - H]$^-$): 592.2112, found 592.2136.

4.1.16.

*N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)-2-(7-methoxy-2-oxo-2H-chromen-4-yl)acetamide (**6f**)*

The title compound was obtained by **4f** which was coupled with **9** through EDCI/HOBt/DMAP coupling procedure in 48% yield (pale yellow crystalline powder) as described for **6a**: mp 115-117 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.69 (brs, 2H), 7.34 (d, J = 5.0 Hz, 1H), 7.16 (m, 5H), 7.02 (brs, 2H), 6.84 (m, 4H), 6.75 – 6.74 (m, 1H), 6.02 (brs, 1H), 4.07 (brs, 1H), 3.84 (s, 6H), 3.59 – 3.54 (m, 2H), 3.42 – 3.38 (m, 1H), 3.17 - 3.14 (m, 1H), 2.97 -2.83 (m, 4H), 2.62 – 2.57 (m, 1H), 1.98 (brs, 1H), 0.83 (d, J = 22.0 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ 170.2, 164.6, 164.5, 163.1, 156.7, 152.0, 139.9, 132.1, 130.6, 130.3, 129.3, 127.4, 127.3, 115.4, 114.0, 113.7, 101.8, 74.2, 59.0, 56.4, 56.2, 55.6, 54.1, 40.1, 36.4, 28.1, 20.5, 20.4; HRMS (ESI) m/z calcd. for $C_{33}H_{38}N_2O_8S$ ([M - H]$^-$): 621.2277, found 621.2276.

4.1.17.

*N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl) -2-(7-methoxy-2-oxo-2H-chromen-4-yl)acetamide (**7f**)*

The title compound was obtained by **4f** which was coupled with **10** through EDCI/HOBt/DMAP coupling procedure in 39% yield (white powder) as described for **6a**: mp 266-268 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.36 (d, J = 8.6 Hz, 2H), 8.02 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.8 Hz, 1H), 7.19 – 7.14 (m, 5H), 6.86 (s, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.05 (s, 1H), 4.05 – 4.03 (m, 1H), 3.87 (s, 3H), 3.78 – 3.76 (t, J = 5.6 Hz, 1H), 3.57 (dd, J = 32.6, 14.9 Hz, 2H), 3.47 (d, J = 13.2 Hz, 1H), 3.17 – 3.09 (m, 3H), 2.98 (dd, J = 12.8, 5.6 Hz, 1H), 2.64 – 2.60 (m, 1H), 2.01 – 1.98 (m, 1H), 0.89 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 170.3, 164.5, 163.1, 156.7, 152.0, 151.4, 147.0, 139.7, 130.2, 129.8, 129.3, 127.4, 125.4, 113.9, 113.8, 113.7, 101.8, 73.5, 57.9, 56.4, 55.7, 53.2, 40.2, 36.4, 27.8, 20.3; HRMS (ESI) m/z calcd. for $C_{32}H_{35}N_3O_9S$ ($[M - H]^-$): 636.2022, found 636.2060.

4.1.18.

*N-((2S,3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-y l)-2-(7-methoxy-2-oxo-2H-chromen-4-yl)acetamide (**8f**)*

The title compound was obtained by **4f** which was coupled with **11** through EDCI/HOBt/DMAP coupling procedure in 30% yield (yellow powder) as described for **6a**: mp 215-217 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.46 (d, J = 8.6 Hz, 2H), 7.34 (dt, J = 8.8, 3.2 Hz, 1H), 7.18 – 7.16 (m, 4H), 7.14 – 7.11 (m, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 8.8, 2.4 Hz, 1H), 6.68 (d, J = 8.6 Hz, 2H), 6.03 (d, J = 2.4 Hz, 1H), 4.11 – 4.08 (m, 1H), 3.86 (s, 3H), 3.84 – 3.81 (m, 1H), 3.57 – 3.54 (m, 1H), 3.38 (dd, J = 14.8, 3.6 Hz, 1H), 3.19 (dd, J = 14.0, 3.6 Hz, 1H), 2.97 – 2.95 (m, 1H), 2.87 (d, J = 4.8 Hz, 1H), 2.84 (m, 1H), 2.77 (dd, J = 13.8, 6.6 Hz, 1H), 2.61 (dd, J = 14.0, 11.4 Hz, 1H), 1.96 (dt, J = 13.9, 6.6 Hz, 1H), 0.89 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 170.2, 164.9, 164.4, 163.1, 156.6, 154.3, 152.0, 139.9, 130.5, 130.3, 129.3, 127.4, 127.3, 114.4, 114.0, 113.9, 113.7, 101.8, 74.4, 59.3, 56.4, 55.5, 54.3, 40.2, 36.9, 28.2, 20.6, 20.5; HRMS (ESI) m/z calcd. for

$C_{32}H_{37}N_3O_7S$ ([M - H]$^-$): 606.2280, found 606.2298.

4.1.19.

*2-(7-(Dimethylamino)-2-oxo-2H-chromen-4-yl)-N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)acetamide (**6g**)*

The title compound was obtained by **4g** which was coupled with **9** through EDCI/HOBt/DMAP coupling procedure in 63% yield (pale yellow crystalline powder) as described for **6a**: mp 133-135 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 9.0 Hz, 1H), 7.19 – 7.18 (m, 4H), 7.15 – 7.13 (m, 1H), 7.03 (d, J = 8.0 Hz, 2H), 6.56 (d, J = 9.0 Hz, 1H), 6.48 (s, 1H), 5.85 (s, 1H), 4.09 – 4.04 (m, 1H), 3.85 (s, 3H), 3.81 (t, J = 7.2 Hz, 1H), 3.51 (d, J = 9.0 Hz, 2H), 3.42 (dd, J = 14.9, 2.8 Hz, 1H), 3.17 (dd, J = 13.9, 2.4 Hz, 1H), 3.03 (s, 6H), 2.92 (dd, J = 14.9, 8.5 Hz, 2H), 2.83 – 2.79 (m, 1H), 2.66 – 2.60 (m, 1H), 2.04 – 1.92 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 170.5, 164.9, 164.5, 157.1, 154.6, 152.5, 139.9, 132.1, 130.6, 130.3, 129.3, 127.3, 127.0, 115.4, 110.7, 110.5, 109.8, 98.7, 74.2, 58.9, 56.2, 55.6, 54.1, 40.2, 40.1, 36.9, 28.1, 20.5, 20.4; HRMS (ESI) m/z calcd. for $C_{34}H_{41}N_3O_7S$ ([M - H]$^-$): 634.2593, found 634.2593.

4.1.20.

*2-(7-(Dimethylamino)-2-oxo-2H-chromen-4-yl)-N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl)acetamide (**7g**)*

The title compound was obtained by **4g** which was coupled with **10** through EDCI/HOBt/DMAP coupling procedure in 35% yield (yellow powder) as described for **6a**: mp 233-235 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.33 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 9.0 Hz, 1H), 7.20 – 7.15 (m, 5H), 6.61 (d, J = 9.0 Hz, 1H), 6.51 (s, 1H), 5.88 (s, 1H), 4.03 – 4.00 (m, 1H), 3.78 – 3.75 (m, 1H), 3.53 – 3.45 (m, 4H), 3.20 (dd, J = 12.8, 5.2 Hz, 1H), 3.10 (d, J = 4.5 Hz, 1H), 3.05 (s, 6H), 2.98 – 2.95 (m, 1H), 2.65 – 2.60 (m, 1H), 1.99 – 1.94 (m, 1H), 0.88 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.3, 160.6, 155.3, 152.6, 149.5, 145.2, 139.0, 129.1, 128.5, 128.1, 127.9,126.0, 125.8, 124.4, 109.4, 108.8,

108.1, 97.4, 55.6, 53.5, 51.3, 40.3, 34.8, 25.8, 19.8, 19.7; HRMS (ESI) m/z calcd. for $C_{33}H_{38}N_4O_8S$ ([M - H]$^-$): 649.2338, found 649.2306.

4.1.21.

*N-((2S,3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-2-(7-(dimethylamino)-2-oxo-2H-chromen-4-yl)acetamide (**8g**)*

The title compound was obtained by **4g** which was coupled with **11** through EDCI/HOBt/DMAP coupling procedure in 32% yield (yellow oil) as described for **6a**: mp 197-200 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.45 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 9.0 Hz, 1H), 7.19 – 7.18 (m, 4H), 7.16 – 7.12 (m, 1H), 6.67 (d, J = 8.8 Hz, 2H), 6.56 (dd, J = 9.0, 2.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 5.85 (s, 1H), 4.08 (ddd, J = 10.8, 6.6, 3.6 Hz, 1H), 3.82 (ddd, J = 8.4, 6.9, 3.6 Hz, 1H), 3.55 – 3.47 (m, 2H), 3.37 (dd, J = 14.9, 3.6 Hz, 1H), 3.18 (dd, J = 13.9, 3.6 Hz, 1H), 2.99 (s, 3H), 2.94 (dd, J = 13.8, 8.4 Hz, 1H), 2.88 – 2.85 (m, 1H), 2.86 (s, 3H), 2.77 (dd, J = 13.6, 6.9 Hz, 1H), 2.62 (dd, J = 14.0, 11.4 Hz, 1H), 1.97 – 1.92 (m, 1H), 0.88 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 170.5, 164.3, 157.1, 154.7, 154.3, 152.5, 139.9, 130.5, 130.3, 129.3, 127.3, 126.9, 125.9, 114.4, 110.7, 110.6, 109.8, 98.7, 74.4, 59.3, 55.6, 54.4, 40.2, 36.9, 36.5, 28.2, 20.6, 20.5; HRMS (ESI) m/z calcd. for $C_{33}H_{40}N_4O_6S$ ([M - H]$^-$): 619.2597, found 619.2621.

4.1.22.

*N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)-2-(7-hydroxy-4-methyl-2-oxo-2H-chromen-3-yl)acetamide (**6h**)*

The title compound was obtained by **4h** which was coupled with **9** through EDCI/HOBt/DMAP coupling procedure in 87% yield (pale yellow powder) as described for **6a**: mp 196-198 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 8.8 Hz, 1H), 7.16 (q, J = 7.4 Hz, 4H), 7.08 – 7.04 (t, J = 8.5 Hz, 3H), 6.80 (d, J = 8.8 Hz, 1H), 6.68 (s, 1H), 4.06 (t, J = 5.8 Hz, 1H), 3.86 (s, 3H), 3.80 (dd, J = 10.3, 4.8 Hz, 1H), 3.45 – 3.38 (m, 3H), 3.18 (d, J = 13.6 Hz, 1H), 3.06 – 3.01 (m, 1H), 2.92 (dd, J = 15.0, 8.6 Hz, 1H), 2.85 – 2.81 (m, 1H), 2.61 (t, J = 12.5 Hz, 1H),

2.08 (s, 3H), 2.04 – 1.98 (m, 1H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) *δ* 172.2, 164.5, 164.3, 162.4, 155.3, 152.2, 140.0, 132.0, 130.6, 130.3, 129.2, 127.6, 127.2, 116.7, 115.4, 114.3, 114.2, 103.2, 74.2, 59.1 56.2, 55.4, 54.2, 36.7, 35.1, 28.0, 20.5, 20.4, 15.4; HRMS (ESI) m/z calcd. for $C_{33}H_{38}N_2O_8S$ ([M - H]$^-$): 621.2277, found 621.2300.

4.1.23.

*N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl) -2-(7-hydroxy-4-methyl-2-oxo-2H-chromen-3-yl)acetamide (**7h**)*

The title compound was obtained by **4h** which was coupled with **10** through EDCI/HOBt/DMAP coupling procedure in 63% yield (white powder) as described for **6a**: mp 293-295 °C; ^{1}H NMR (400 MHz, CD_3OD) *δ* 8.40 (d, *J* = 8.0 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.17 – 7.15 (m, 4H), 7.09 – 7.07 (m, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.69 (s, 1H), 3.99 (t, *J* = 6.8 Hz, 1H), 3.76 (t, *J* = 8.0 Hz, 1H), 3.50 – 3.47 (m, 1H), 3.42 (d, *J* = 13.6 Hz, 2H), 3.20 – 3.06 (m, 3H), 2.98 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.60 (t, *J* = 12.4 Hz, 1H), 2.13 (s, 3H), 2.03 (dt, *J* = 13.2, 6.8 Hz, 1H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) *δ* 172.3, 164.3, 162.5, 155.4, 152.2, 151.4, 146.8, 139.9, 130.3, 129.9, 129.3, 127.7, 127.2, 125.4, 116.7, 114.3, 114.2, 103.3, 73.6, 58.2, 55.6, 53.5, 36.9, 35.1, 27.8, 20.4, 20.3, 15.4; HRMS (ESI) m/z calcd. for $C_{32}H_{35}N_3O_9S$ ([M - H]$^-$): 636.2022, found 636.2047.

4.1.24.

*N-((2S,3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-y l)-2-(7-hydroxy-4-methyl-2-oxo-2H-chromen-3-yl)acetamide (**8h**)*

The title compound was obtained by **4h** which was coupled with **11** through EDCI/HOBt/DMAP coupling procedure in 58% yield (yellow oil) as described for **6a**: mp 232-234 °C; ^{1}H NMR (400 MHz, CD_3OD) *δ* 7.54 – 7.49 (m, 3H), 7.18 – 7.11 (m, 4H), 7.03 (t, *J* = 7.0 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 2H), 6.67 (s, 1H), 4.10 – 4.05 (m, 1H), 3.79 (t, *J* = 7.2 Hz, 1H), 3.43 (brs, 2H), 3.36 (d, *J* = 13.6

Hz, 1H), 3.17 (d, *J* = 13.6 Hz, 1H), 2.96 – 2.94 (m, 1H), 2.91 – 2.89 (m, 1H), 2.78 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.60 (t, *J* = 12.4 Hz, 1H), 2.07 (s, 3H), 1.99 – 1.94 (m, 1H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) *δ* 172.2, 164.9, 162.4, 155.3, 153.7, 152.3, 140.0, 130.5, 130.4, 129.2, 127.7, 127.1, 126.4, 116.7, 114.9, 114.3, 114.2, 103.2, 74.3, 59.3, 55.3, 54.4, 36.9, 35.1, 28.1, 20.6, 20.5, 15.4; HRMS (ESI) m/z calcd. for $C_{32}H_{37}N_3O_7S$ ([M - H]$^-$): 606.2280, found 606.2289.

4.1.25.

*2-(7-Amino-4-methyl-2-oxo-2H-chromen-3-yl)-N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)acetamide (**6i**)*

The title compound was obtained by **4i** which was coupled with **9** through EDCI/HOBt/DMAP coupling procedure in 87% yield (yellow oil) as described for **6a**: mp 253-255 °C; ^{1}H NMR (500 MHz, CD_3OD) *δ* 7.74 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.19 – 7.11 (m, 4H), 7.05 – 7.02 (m, 3H), 6.63 (d, *J* = 8.5 Hz, 1H), 6.49 (brs, 1H), 4.04 – 4.02 (m, 1H), 3.85 (s, 3H), 3.78 (t, *J* = 6.0 Hz, 1H), 3.42 – 3.35 (m, 3H), 3.15 (dd, *J* = 13.5, 2.5 Hz, 1H), 3.02 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.92 (dd, *J* = 15.0, 8.5 Hz, 1H), 2.84 – 2.81 (m, 1H), 2.62 – 2.57 (m, 1H), 2.04 (s, 3H), 2.01 – 1.97 (m, 1H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) *δ* 172.6, 165.0, 164.5, 155.9, 154.0, 152.9, 139.9, 132.0, 130.6, 130.3, 129.2, 127.4, 127.2, 115.4, 114.1, 113.2, 111.8, 100.4, 74.1, 59.0, 56.2, 55.3, 54.1, 36.7, 35.1, 28.0, 20.5, 15.3; HRMS (ESI) m/z calcd. for $C_{33}H_{39}N_3O_7S$ ([M - H]$^-$): 620.2437, found 620.2452.

4.1.26.

*2-(7-Amino-4-methyl-2-oxo-2H-chromen-3-yl)-N-((2S,3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl)acetamide (**7i**)*

The title compound was obtained by **4i** which was coupled with **10** through EDCI/HOBt/DMAP coupling procedure in 97% yield (pale yellow powder) as described for **6a**: mp 253-255 °C; ^{1}H NMR (500 MHz, DMSO-d_6) *δ* 8.39 (d, *J* = 8.5

Hz, 2H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.20 – 7.13 (m, 5H), 6.56 (d, *J* = 8.5 Hz, 1H), 3.81 – 3.74 (m, 1H), 3.57 (brs, 1H), 3.42 (brs, 1H), 3.34 – 3.31 (m, 1H), 3.22 (d, *J* = 16.0 Hz, 1H), 3.13 (dd, *J* = 13.5, 9.0 Hz, 1H), 3.02 – 2.96 (m, 2H), 2.89 – 2.87 (s, 1H), 2.55 (brs, 1H), 1.99 – 1.95 (m, 1H), 1.95 (s, 3H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.79 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 172.8, 164.9, 156.0, 151.4, 146.8, 139.9, 130.3, 129.9, 129.3, 127.4, 127.2, 125.4, 119.4, 116.9, 114.0, 113.1, 108.0, 100.4, 73.5, 58.0, 55.5, 53.3, 37.0, 31.7, 27.7, 20.4, 15.3; HRMS (ESI) m/z calcd. for $C_{32}H_{36}N_4O_8S$ ([M - H]$^-$): 635.2182, found 635.2153.

4.1.27.

2-(7-Amino-4-methyl-2-oxo-2H-chromen-3-yl)-N-((2S,3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)acetamide ***(8i)***

The title compound was obtained by **4i** which was coupled with **11** through EDCI/HOBt/DMAP coupling procedure in 26% yield (yellow powder) as described for **6a**: mp 253-255 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.50 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.18 – 7.17 (m, 2H), 7.14 – 7.11 (m, 2H), 7.04 (t, *J* = 7.0 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.51 (s, 1H), 4.08 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.81 (d, *J* = 5.5 Hz, 1H), 3.41 – 3.38 (m, 2H), 3.35 (d, *J* = 2.5 Hz, 1H), 3.17 (dd, *J* = 13.7, 2.6 Hz, 1H), 2.98 – 2.95 (m, 1H), 2.93 – 2.90 (m, 1H), 2.80 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.64 – 2.59 (m, 1H), 2.06 (s, 3H), 1.99 (dt, *J* = 13.5, 7.0 Hz, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 172.2, 164.8, 155.6, 154.0, 153.7, 152.6, 139.6, 130.2, 130.0, 128.9, 127.1, 126.8, 125.7, 114.2, 113.8, 112.9, 111.5, 100.2, 73.9, 59.0, 55.0, 54.0, 39.5, 36.3, 27.9, 20.3, 20.2, 15.0; HRMS (ESI) m/z calcd. for $C_{32}H_{38}N_4O_6S$ ([M - H]$^-$): 605.2440, found 605.2422.

4.1.28. 4-Methyl-2-oxo-2H-chromen-7-yl ((2S,3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate ***(6j)***

To an oven-dried, argon-flushed round-bottom flask was added bis(trichloromethyl)

caebonate (**BTC**, **16**, 0.059g, 0.20 mmol) and anhydrous CH_2Cl_2 (2 mL) at 0 °C, and the mixture of 7-hydroxy-4-methyl-2H-chromen-2-one (**4k**, 0.035 g, 0.20 mmol) and diisopropylethylamine (**DIEA**, 0.036 mL, 0.22 mmol) in anhydrous THF (2 mL) was added dropwise to form pale yellow solution, which was stirred for 5 minutes at 0 °C and additional 30 min of continuous stirring at 25 °C. To another an oven-dried, argon-flushed round-bottom flask was added *N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4- methoxybenzene sulfonamide (**9**, 0.089 g, 0.22 mmol) and diisopropylethylamine (**DIEA**, 0.036 mL, 0.22 mmol) in dry CH_2Cl_2 (2 mL) for 30 min of continuous stirring at 25 °C, and the mixture was added dropwise to pale yellow solution above at 0 °C. Then the reaction was stirred for additional 1 hour at 25 °C. The solvent was removed under reduced pressure. CH_2Cl_2 (5 mL) was added to the sludge and washed with saturated ammonium chloride (3 × 5 mL). The organic layer was dried over Na_2SO_4, and evaporated, i*n vacuo*. A crude product as the yellow oil was purified by chromatography on a silica gel column (30 × 6 cm). Elution with 2:1 to 1:1 hexanes-ethyl acetate gave **6j** as white powder: yield 0.092 g (76%); mp 145-147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.5 Hz, 1H), 7.41 – 7.36 (m, 3H), 7.32 - 7.31 (m, 3H), 7.02 – 6.99 (m, 3H), 6.26 (s, 1H), 4.01 – 3.97 (m, 2H), 3.90 (s, 3H), 3.23 – 3.20 (m, 1H), 3.11 (d, J = 10.6 Hz, 1H), 3.05 – 3.00 (m, 3H), 2.84 (dd, J = 13.0, 6.2 Hz, 1H), 2.43 (s, 3H), 1.94 – 1.82 (m, 1H), 0.97 (d, J = 6.2 Hz, 3H), 0.92 (d, J = 6.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1, 160.6, 153.5, 153.3, 151.9, 137.3, 129.6, 129.5, 129.4, 128.65 (s), 126.8, 125.7, 117.8, 117.1, 115.0, 114.4, 114.2, 110.1, 72.4, 58.9, 55.6, 55.3, 53.7, 35.3, 27.3, 20.2, 19.9, 18.7; HRMS (ESI) m/z calcd. for $C_{32}H_{36}N_2O_8S$ ([M - H]$^-$): 607.2109, found 607.2108.

*4.1.29. 4-Methyl-2-oxo-2H-chromen-7-yl ((2S,3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**7j**)*

The title compound was obtained by **4j** and **10** under the condensing of BTC undergoing an one-pot reaction in 49% yield (white powder) as described for **6j**: mp222-224 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.37 (d, J = 8.5 Hz, 2H), 7.94 (d, J =

8.5 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.35 (m, 2H), 7.30 – 7.23 (m, 5H), 6.34 (s, 1H), 4.34 (q, *J* = 7.7 Hz, 1H), 3.75 (brs, 1H), 3.58 – 3.51 (m, 2H), 3.16 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.94 (dd, *J* = 14.5, 6.0 Hz, 2H), 2.82 (dd, *J* = 14.0, 8.5 Hz, 1H), 2.50 (s, 3H), 1.98 – 1.92 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) *δ* 162.5, 160.6, 155.3, 155.1, 155.0, 154.8, 151.5, 146.2, 138.4, 130.1, 130.0, 129.9, 128.00 (s), 127.3, 125.5, 118.8, 115.0, 110.7, 79.4, 57.7, 56.6, 56.3, 36.5, 27.6, 20.2, 20.1, 18.7; HRMS (ESI) m/z calcd. for $C_{31}H_{33}N_3O_9S$ ([M - H]$^-$): 622.1854, found 622.1819.

*4.1.30. 7-Oxo-7H-furo[3,2-g]chromen-9-yl ((2S,3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**6k**)*

The title compound was obtained by **4k** and **9** under the condensing of BTC undergoing an one-pot reaction in 78% yield (pale yellow powder) as described for **6j**: mp 301-303 °C; ^{1}H NMR (400 MHz, CD_3OD) *δ* 7.98 (d, *J* = 9.2 Hz, 1H), 7.82 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 2H), 7.36 – 7.32 (m, 3H), 7.26 – 7.23 (m, 3H), 7.02 (d, *J* = 7.8 Hz, 2H), 6.89 (s, 1H), 6.33 (d, *J* = 9.2 Hz, 1H), 4.30 (dd, *J* = 14.6, 7.2 Hz, 1H), 3.86 (s, 3H), 3.54 (d, *J* = 15.4 Hz, 1H), 3.33 – 3.30 (m, 1H), 3.25 (d, *J* = 14.2 Hz, 1H), 3.04 – 2.98 (m, 1H), 2.94 – 2.85 (m, 1H), 2.80 – 2.75 (dd, *J* = 13.9, 7.4 Hz, 2H), 1.94 (dt, *J* = 13.6, 6.4 Hz, 1H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) *δ* 164.6, 163.0, 160.8, 148.3, 147.0, 138.4, 131.6, 130.6, 130.0, 129.9, 127.9, 127.3, 117.8, 115.4, 114.6, 111.3, 107.9, 80.4, 58.5, 56.7, 56.2, 49.8, 36.6, 27.8, 20.3; HRMS (ESI) m/z calcd. for $C_{33}H_{34}N_2O_9S$ ([M - H]$^-$): 633.1901, found 633.1893.

*4.1.31. 7-Oxo-7H-furo[3,2-g]chromen-9-yl ((2S,3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**7k**)*

The title compound was obtained by **4k** and **10** under the condensing of BTC undergoing an one-pot reaction in 66% yield (pale yellow acicular crystal) as described for **6j**: mp342-345 °C; ^{1}H NMR (400 MHz, CD_3OD) *δ* 8.35 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 9.6 Hz, 1H), 7.93 (d, *J* = 9.2 Hz, 3H), 7.82 (s, 1H), 7.35 (t, *J* = 7.2

Hz, 2H), 7.29 – 7.25 (m, 3H), 7.02 (s, 1H), 6.41 (d, *J* = 9.6 Hz, 1H), 4.32 (dd, *J* = 14.8, 7.6 Hz, 1H), 4.24 (brs, 1H), 3.57 – 3.48 (m, 2H), 3.14 (dd, *J* = 13.6, 9.0 Hz, 1H), 2.92 (dd, *J* = 13.6, 6.2 Hz, 2H), 2.80 (dd, *J* = 14.0, 8.4 Hz, 1H), 1.99 – 1.89 (m, 1H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 161.6, 160.6, 154.3, 151.5, 149.3, 148.3, 147.1, 146.2, 138.4, 128.0, 127.7, 119.1, 117.8, 115.4, 111.2, 108.2, 79.4, 57.7, 57.0, 56.6, 36.5, 27.6, 20.2, 20.1; HRMS (ESI) m/z calcd. for $C_{32}H_{31}N_3O_{10}S$ ([M - H]$^-$): 648.1646, found 648.1640.

4.1.32.

*N-((2R,3S)-2-hydroxy-3-(((7-hydroxy-2-oxo-2H-chromen-4-yl)methyl)amino)-4-phenylbutyl)-N-isobutyl-4-methoxybenzenesulfonamide (**6l**)*

To an anhydrous EtOH (3 mL) solution of 4-(chloromethyl)-7-hydroxy-2H-chromen-2-one (**4l**, 0.021 g, 0.10 mmol) and *N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-methoxybenzenesulfonamide (**9**, 0.041 g, 0.10 mmol) were added dropwise DIEA (0.032 g, 0.25 mmol). After refluxing for 7 h, the solvent was removed under reduced pressure. Water (4 mL) was added to the residue and extracted with ethyl acetate (3 × 4 mL). The combined organic phases were dried over Na_2SO_4, and evaporated, i*n vacuo*. The residue was purified by chromatography on a silica gel column (30 × 6 cm). Elution with 1:10 hexanes-ethyl acetate gave **6l** as yellow powder: yield 0.033 g (57%); mp 106-108 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.36 – 7.20 (m, 7H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 1H), 3.86 (s, 3H), 3.81 – 3.77 (m, 1H), 3.40 (dd, *J* = 14.9, 3.6 Hz, 1H), 3.14 (dt, *J* = 8.8, 4.4 Hz, 1H), 3.09 – 3.06 (m, 1H), 3.04 – 2.94 (m, 3H), 2.87 (dd, *J* = 13.6, 7.2 Hz, 2H), 2.57 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.03 – 1.87 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 164.56, 157.1, 157.0, 140.0, 132.0, 130.7, 130.6, 130.5, 130.4, 129.7, 129.5, 127.6, 126.8, 115.4, 109.3, 103.9, 73.5, 63.5, 59.0, 57.0, 56.2, 53.1, 38.6, 28.1, 20.5, 20.4; HRMS (ESI) m/z calcd. for $C_{31}H_{36}N_2O_7S$ ([M - H]$^-$): 579.2171, found 579.2154.

4.1.33.

*N-((2R,3S)-2-hydroxy-3-(((7-hydroxy-2-oxo-2H-chromen-4-yl)methyl)amino)-4-phenylbutyl)-N-isobutyl-4-nitrobenzenesulfonamide (**7l**)*

The title compound was synthesized by **4l** and **10** by catalyzed of DIEA under the condition of refluxing in 57% yield (yellow oil) as described for **6l**: mp 143-145 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (d, J = 8.8 Hz, 2H), 8.34 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 8.8 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.26 – 7.17 (m, 5H), 3.77 (d, J = 14.8 Hz, 1H), 3.71 – 3.67 (m, 1H), 3.49 (dd, J = 14.8, 2.8 Hz, 1H), 3.28 – 3.21 (m, 1H), 3.18 – 3.12 (m, 1H), 3.10 – 2.87 (m, 4H), 2.57 (dd, J = 13.6, 8.8 Hz, 1H), 2.03 – 1.92 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 164.2, 157.1, 157.0, 151.4, 147.0, 140.0, 130.5, 130.4, 129.9, 129.8, 129.7, 129.6, 127.6, 125.3, 115.0, 109.4, 103.9, 72.8, 63.6, 57.8, 57.3, 51.9, 39.2, 27.8, 203., 20.2; ； HRMS (ESI) m/z calcd. for $C_{30}H_{33}N_3O_8S$ ([M - H]$^-$): 594.1916, found 594.1942.

4.1.34.

*4-Amino-N-((2R,3S)-2-hydroxy-3-(((7-hydroxy-2-oxo-2H-chromen-4-yl)methyl)amino)-4-phenylbutyl)-N-isobutylbenzenesulfonamide (**8l**)*

The title compound was synthesized by **4l** and **11** by catalyzed of DIEA under the condition of refluxing in 27% yield (pale yellow powder) as described for **6l**: mp 117-119 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.48 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 1H), 7.34 – 7.30 (m, 4H), 7.26 – 7.22 (m, 3H), 6.70 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 1H), 3.38 – 3.33 (m, 2H), 3.08 (dd, J = 13.8, 4.8 Hz, 1H), 2.98 – 2.89 (m, 4H), 2.85 – 2.77 (m, 2H), 2.68 – 2.64 (m, 1H), 1.93 (dt, J = 13.8, 6.6 Hz, 1H), 0.89 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H);^{13}C NMR (151 MHz, CD_3OD) δ 164.1, 157.0, 156.8, 154.4, 139.3, 130.5, 130.4, 129.8, 129.5, 127.8, 125.6, 114.6, 114.5, 114.4, 109.9, 103.6, 72.7, 61.5, 59.5, 56.9, 53.4, 36.9, 28.3, 20.6, 20.5; HRMS (ESI) m/z calcd. for $C_{30}H_{35}N_3O_6S$ ([M - H]$^-$): 564.2175, found 564.2154.

4.2. In vitro HIV-1 PR activity assay

The inhibitory effect of all new designed inhibitors were measured using fluorescence resonance energy transfer (FRET) method as described previously [38,41,42].

4.3. In vitro HIV-1 RT activity assay

To quantify the activity of HIV-1 reverse transcriptase (RT) in vitro, we exploited a novel one-step RT-PCR assay [48]. HIV-1 RT has been derived from clone HIV_{NL4-3} and belongs to Group B of HIV-1, which was a gift from Ying Guo (Institute of Materia Medica, PUMC). RT were used in the first step of Real-time PCR reaction for converting RNA to DNA. Real-time PCR reaction was performed using one step RT-PCR Kit (Takara, RR066A) according to the manual from the manufacturer. Each reaction mixture had a total volume of 20μL, comprising 2X reaction buffer 10μL, random mRNA 20 ng (template), GAPDH primers 10μM (primer), compounds 1μL at different concentrations, Ex Taq HS (polymerase) and 100 mU HIV-1 RT. Primer sequence was as followed: GAPDH-forward: GAAGGTGAAGGTCGGAGT; GAPDH-reverse: GAAGATGGTGATGGGATTTC. The results were normalized using the DMSO group levels and calculated by the $2^{-\triangle\triangle Ct}$ comparative method.

4.4. One round HIV-1 infectivity assay

The inhibitory effect of compounds on HIV-1 infectivity was determined using a single-round HIV-1 infectivity assay [46]. For analyzing effect on the late stage of HIV-1 life cycle, the compounds were added into culture medium of virus-producing cells at 5 hours of post-transfection. After incubating for 48 hours, pseudotyped viruses in supernatant were used to infect SupT1 cells for 48 hours, followed by measuring luciferase activity of newly infected cells using Centro LB960 (Berthold). For analyzing effect on the early stage of HIV-1 life cycle, SupT1 cells were firstly infected with pseudotyped viruses, and then treated with the compound for 48 hours,

followed by measurement of luciferase activity.

4.5. Wild type HIV-1 infectivity assay

1×10^6 SupT1 cells were infected with HIV-1 NL4-3 in the presence of 100 nM chemicals and 10 μg/mL polybrene using a spin infection method [47]. At 48 hpi, viruses were harvested and used to infect TZM-bl cells, followed by measuring luciferase activity in the infected cells.

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Supplementary data

Experimental details for the syntheses and spectroscopic characterization of the compounds in this paper and details related to enzyme and cellular studies.

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We reported a series of new coumarin derivatives characterized by various linkers that exhibited good potency against PR and weak inhibition of RT in this manuscript.

Compound **6f** and **7c** inhibited PR with IC_{50} values of 15.5 and 62.1 nM, respectively, and weakly affected also RT with IC_{50} values of 241.8 and 188.7μM, respectively, showing the possibility in the future of developing dual HIV-1 PR/RT inhibitors.

New inspiration for further research of effective dual HIV-1 inhibitors was obtained according to the molecular docking studies.

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: