European Journal of Medicinal Chemistry 220 (2021) 113498

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Design and biological evaluation of cinnamic and phenylpropionic amide derivatives as novel dual inhibitors of HIV-1 protease and reverse transcriptase

Mei Zhu [a, 1], Qi Shan [a, 1], Ling Ma [a], Jiajia Wen [a], Biao Dong [a], Guoning Zhang [a], Minghua Wang [a], Juxian Wang [a], Jinming Zhou [b, **], Shan Cen [a, ***], Yucheng Wang [a, *]

[a] Institute of Medicinal Biotechnology, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, 100050, China
[b] Key Laboratory of the Ministry of Education for Advanced Catalysis Materials, Department of Chemistry, Zhejiang Normal University, Jinhua, 321004, China

ARTICLE INFO

Article history:
Received 21 November 2020
Received in revised form
15 April 2021
Accepted 17 April 2021
Available online 24 April 2021

Keywords:
HIV-1 PR/RT dual inhibitors
Cinnamic acids
Phenylpropionic acids
Disparate ratio
Molecular modeling

ABSTRACT

Upon the basis of both possible ligand-binding site interactions and the uniformity of key residues in active sites, a novel class of HIV-1 PR/RT dual inhibitors was designed and evaluated. Cinnamic acids or phenylpropionic acids with more flexible chain and smaller steric hindrance were introduced into the inhibitors, giving rise to significant improvement in HIV-1 RT inhibitory activity by one or two orders of magnitude, with comparable or even improved potency against PR at the same time, compared with coumarin anologues in our previous studies. Among these inhibitors, **38d** displayed a 19-fold improvement in *anti*-PR activity with IC_{50} value of 0.081 nM compared to the control DRV. In addition, inhibitor **38c** exhibited an excellent *anti*-RT IC_{50} value of 0.43 μM, only a 4.7-fold less potent activity than the control EFV. More significantly, the disparate ratio between HIV-1 PR and RT inhibition became more reasonable with ratio of 1: 10.4, just as **37b**. Furthermore, the assays on HIV-1 late stage and early stage supported the rationality of designing dual inhibitors. The SAR data as well as molecular modeling studies provided new insight for further optimization of more potent HIV-1 PR/RT dual inhibitors.

1. Introduction

The application of highly active antiretroviral therapy (HAART) since the mid-1990s has ushered a new era for HIV/AIDS and reduced the mortality and morbidity rates among HIV infection patients dramatically [1–3]. However, the complicated side effects, increased virulence and continuous emergence of multidrug resistant HIV-1 variants call for novel and potent HIV-1 inhibitors imminently [4–6]. In consideration of the high resistance barrier and low toxicity, multi-target drugs have gradually came into focus on *anti*-HIV-1 drug development, and an increasing number of research on HIV-1 dual inhibitors has been emerged, with the rapid development of systematic biology and pharmacology in recent years [7–17]. In fact, our attention is continuously focused on the design of dual inhibitors of HIV-1 protease (PR) and reverse transcriptase (RT), which constitute the core of HIV/AIDS chemotherapy [18].

As is known, both HIV-1 PR and RT play key roles in virus replication [19,20]. Among which, HIV-1 RT converts RNA as a template into proviral DNA, while PR catalyzes the proteolytic cleavage of polypeptide precursors into mature enzyme [21]. Furthermore, the aspartic acid (Asp) residues in the catalytically active homodimer of HIV-1 PR form hydrogen bond interactions with the central hydroxy group of inhibitors [22]. Intriguingly, Asp residues of the catalytically active β-sheet in p66 of RT will be repositioned and deactivated, when non-nucleoside reverse transcriptase inhibitors (NNRTIs) are bounded to the allosteric pocket of heterodimer RT [23,24]. Thus, the uniformity of key residues in active sites of the two viral enzymes makes it reasonable to search for common inhibitors. In addition, hydrogen bonds are indispensable for enhancing backbone binding of PR and RT with

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: zhoujinming@zjnu.edu.cn (J. Zhou), shancen@imb.pumc.edu.cn (S. Cen), wangyucheng@imb.pumc.edu.cn (Y. Wang).
[1] These authors made equal contributions to this work.

https://doi.org/10.1016/j.ejmech.2021.113498
0223-5234/

inhibitors [25–27]. In brief, it makes sense that dual inhibitors of HIV-1 PR and RT are worth investing in, according to the designed multifunctional ligands (DMLs).

In previous studies, we designed a series of coumarin derivatives that were effective on HIV-1 PR and partially on RT [18]. Taken compounds **A** and **B** for example, they exhibited $IC_{50,\ PR}$ values of 11.1 and 155.9 nM, respectively, and $IC_{50,\ RT}$ values of 367.0 and 75.3 μM, respectively. Molecular modeling suggested that the steric hindrance might be the causation for suboptimal RT inhibitory activity. In an effort to develop potent dual inhibitors of HIV-1 PR and RT, modifications have been done as follows: (1) Introduction of cinnamic acids or phenylpropionic acids with long linear linker instead of coumarins to better fit into the spindly binding pocket of RT; (2) Maintenance of aromatic rings in P2 ligand to keep π-π interactions with both PR and RT [28]; (3) Introduction of hydroxy group or methoxy group to aromatic rings to strengthen interactions with the active sites; (4) Maintenance of nonpeptide HIV-1 protease inhibitor (PI) structural scaffold to keep excellent PR inhibitory activity; (5) Introduction of aliphatic chains or rings in P1′ ligand to better adapt into both active cavities. Notably, the results showed that the *anti*-RT activity of the new designed inhibitors enhanced significantly by one or two orders of magnitude, with comparable or even improved potency against PR at the same time. As exemplified by compound **38c**, it exhibited dual inhibitory activity with $IC_{50,\ PR}$ value of 2.02 nM and $IC_{50,\ RT}$ value of 0.43 μM, respectively, which was close to the two positive controls (DRV with $IC_{50,\ PR}$ value of 1.52 nM and EFV $IC_{50,\ RT}$ value of 0.091 μM). Furthermore, the disparate ratio between PR and RT inhibition decreased sharply from 1: 15548 of compound **A** to 1: 10.4 of **37b** and seemed more reasonable as shown in Fig. 1.

2. Results and discussion

2.1. Chemistry

Strategies outlined in Scheme 1 are the synthesis of amine compounds **21**–**28** prepared from the commercially available material (2*S*, 3*S*)-1, 2-epoxy-3-(boc-amino)-4-phenylbutane (**1**), similarly as reported in the literature [29]. The epoxide **1** was reacted with isobutylamine (**2**), n-propylamine (**3**), cyclopropylamine (**4**) or isoprppylamine (**5**) in acetonitrile at reflux for 6 h to provide the corresponding amino alcohols (**6**–**9**) in yields of 83–90%. Treatment of the corresponding amino alcohols with *p*-substitutedbenzenesulfonyl chlorides (**10**–**12**) or 6-methoxypyridine-3-sulfonyl chloride (**13**) in the presence of DIEA and DMAP furnished sulfonamide derivatives (**14**–**20**), in excellent yields (82%–91%), which were then exposed to trifluoroacetic acid at 0–25 °C for 3 h to remove the BOC-group and afforded the corresponding amines in yields of 75–88% [30]. Catalytic hydrogenation of **22** over 10% Pd/C in methanol effected reduction of the nitro group to the corresponding diamine **23** in 94% yield [31].

Reaction of the amines with substituted cinnamic acids **29**–**31** or substituted phenylpropionic acids **32**–**34** (which were reduced via cinnamic acids under the condition of hydrogen and 10% Pd/C), in anhydrous DMF in the presence of EDCI/HOBt/DMAP at 0–25 °C for 2–3 h provided the corresponding target inhibitors **35a**- **40g** in yields of 75–87%, as shown in Scheme 2 [31,32].

2.2. Anti-PR activity assay

We first evaluated the activity of inhibitors against HIV-1 wild-type protease using the FRET-based protease activity assay *in vitro* [33]. The results are shown in Tables 1 and 2, and darunavir (DRV) is chosen as the control. Most of these inhibitors exhibited very potent inhibitory effect with IC_{50} values in low nanomolar range. Particularly, inhibitor **38d** with a 3, 4-dihydroxyphenylpropiony group as the P2 ligand and 6-methoxypyridine-4-sulfonamide as the P2′ ligand displayed a 19-fold improvement in antiviral activity with IC_{50} value of 0.081 nM compared to DRV. Furthermore, inhibitors **35a**, **35b**, **38a**, **38b** and **38e** containing a 3, 4-dihydroxyphenylacryloy group or 3, 4-dihydroxyphenylpropiony group in P2 ligand showed appreciable antiviral IC_{50} values under 1 nM.

In general, as shown in Table 1 and **2** and Fig. 2, inhibitors with phenylpropiony groups as the P2 ligands exhibited an improvement in activity than those with phenylacryloy groups as the P2 ligands, presumably due to some degree of flexibility that adapted to intra-protease better. And going forward, inhibitors with 3, 4-dihydroxy substitution in P2 ligands showed better activity than those with 3-methoxy-4-hydroxy substitution or tri-substitution in P2 ligands. Namely, introduction of methoxy group resulted in a significant loss of activity, which might be attributed to both steric bulk and reduced van der Waals contacts, such as **37a**, **36a** *vs* **35a** or **40a**, **39a** *vs* **38a**. Indeed, it could also be verified via the molecular modeling for inhibitors **38a**, **38c** and **38d** in Fig. 6, which showed important ligand-binding site interactions between hydroxy group in P2 ligand and the S2 subsite of PR.

In order to investigate the effect of functionalized hydrophobic P1′ ligand on HIV-1 protease activity, n-propyl, cyclopropyl and isopropyl were taken into consideration at the same time. However, these new introduced structures resulted in obvious loss of inhibitory activity compared to an isobutyl P1′ ligand, which might be due to the steric hindrance or flexibility to some extent, or the impaired hydrophobic interaction with the active site of PR.

Besides, for the aim of promoting van der Waals interactions in the S2′ subsite of HIV-1 PR, several electron-donating groups were introduced into the P2′ ligand. As a whole, inhibitors with a 4-methoxy substituent exhibited superior activity than the corresponding 4-amino and 4-methylthio substituents, except for **35d**, **37d**, **39a** and **40a**. The oxygen atom in 4-methoxy group might form powerful hydrogen bond (O···H—N) with Asp30′ or Asp29′ in the protease S2′ subsite and other van der Waals interactions [34]. The 4-amino group could make weak hydrogen bonds involved directly interactions (N—H···N) with the main chain amides or water-mediated interactions (NH···H_2O···HOOC) with the side chain oxygen of Asp30′ or Asp29′ in S2′ active subsite [35]. However, the weaker electron-donating ability of sulfur atom might form feeble hydrogen bond (S···H—N) with Asp30′ or Asp29′ in the protease S2′ subsite.

In addition, the types of aromatic rings in P2′ ligand showed remarkable effects on antiviral activity of inhibitors. In general, inhibitors containing a pyridine ring showed more robust activity than those with a benzene ring, such as **36d** *vs* **36a**, **38d** *vs* **38a**, **39d** *vs* **39a** and **40d** *vs* **40a**, except for **35d** and **37d**. Taken **38d** for example, it displayed an almost 5-fold improved antiviral IC_{50} value of 0.081 nM compared to **38a** with IC_{50} value of 0.39 nM. The results above indicated that the methoxypyridine P2′ ligand exerted more favorable interactions with the S2′ subsite of protease than a 4-methoxybenzene P2′ ligand as shown in Fig. 6 [36].

2.3. Anti-RT activity assay

All the inhibitors were evaluated in an *in vitro* HIV-1 RT activity assay as shown in Tables 1 and 2 [37]. Just as expected, inhibitors with a linear linker in P2 ligand exhibited a significant enhancement of RT activity compared with coumarin derivatives in our previous studies [18]. Further confirmation could be acquired through the molecular modeling of **38a**, **38c** and **38d** in Fig. 7, in which phenylacryloy groups or phenylpropiony groups with linear linkers in P2 ligands fitted into the spindly binding pocket of RT

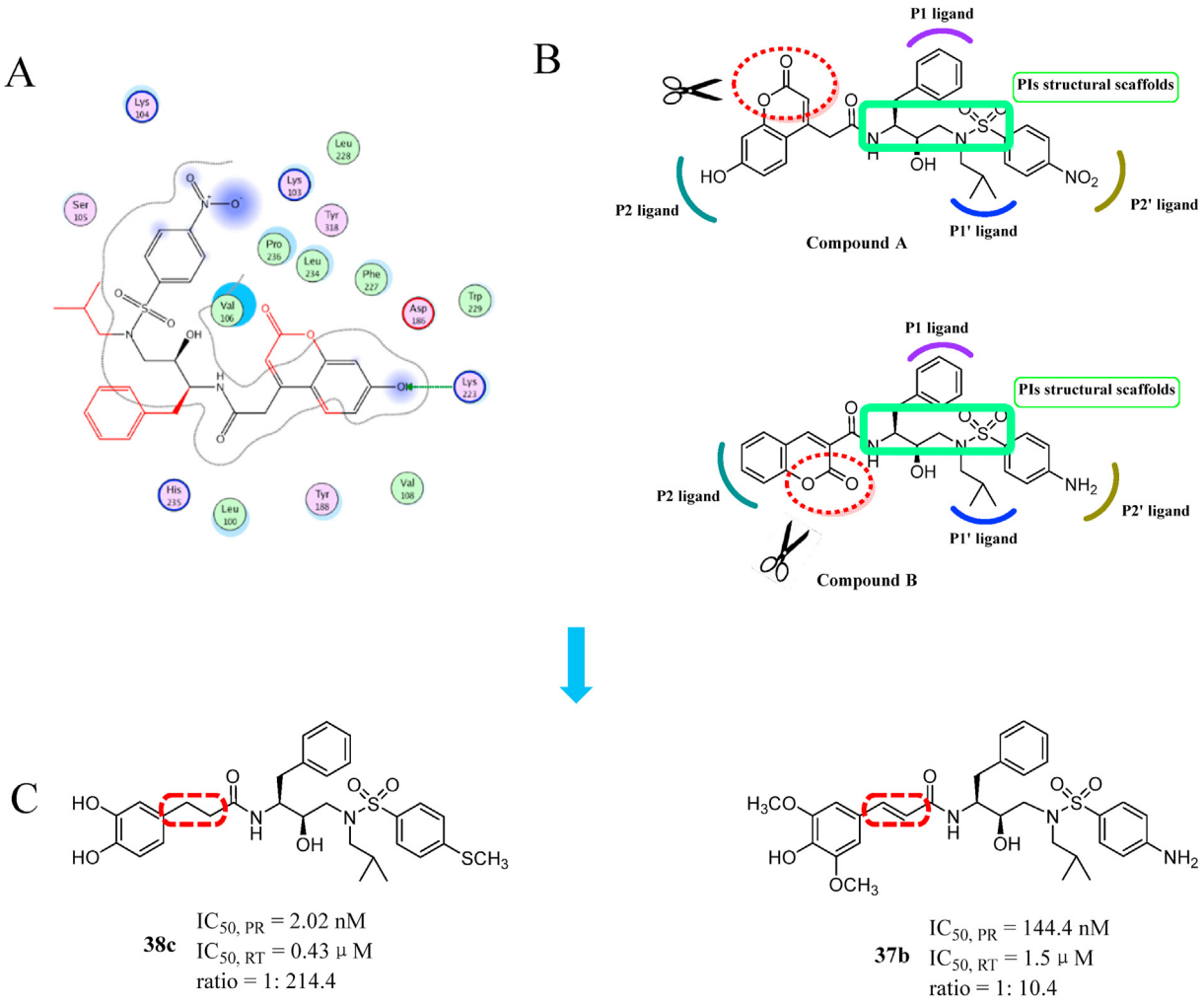


Fig. 1. Design and modification of novel dual inhibitors of HIV-1 PR and RT. (A) Molecular modeling of compound **A** with HIV-1 RT. (B) Compound **A** and **B**. (C) Novel dual inhibitors of HIV-1 PR and RT with rational ratio.

well.

Many inhibitors showed potency with RT IC_{50} values in low micromolar range in the biochemical assays. In particularly, inhibitor **38c** with a 3, 4-dihydroxyphenylpropiony group as the P2 ligand and 4-(methylthio) phenylsulfonamide as the P2′ ligand exhibited an excellent antiviral IC_{50} value of 0.43 μM, only a 4.7-fold less potent than the control Efavirenz (EFV).

In generally, just as appeared in HIV-1 PR inhibitory activity, compounds with phenylpropiony groups as the P2 ligands showed superior *anti*-RT activity than those with phenylacryloy groups as the P2 ligands to a greater or lesser extent in Fig. 3. Among the phenylpropionic amide analogues, inhibitors with the 4-(methylthio) phenylsulfonamide or 6-methoxypyridine-4-sulfonamide P2′ ligand exhibited optimal activity, such as **38c**, **38d**, **39c** and **40d**. While, among cinnamic amide analogues, inhibitors with the 4-aminophenylsulfonamide P2′ ligand showed slight enhancement of antiviral activity, such as **35b**, **36b** and **37b**. However, there was no discernible regularity in potency for inhibitors with different aliphatic chains in P1′ ligands.

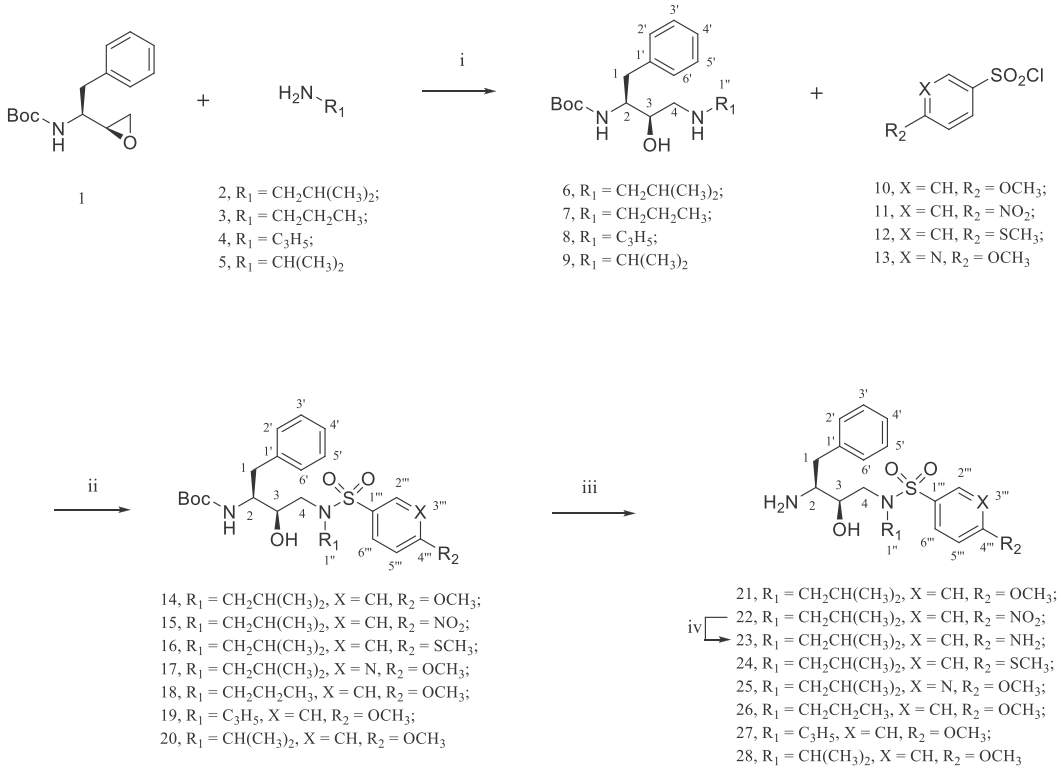
2.4. Evaluation of biological activity

Both HIV-1 PR and RT antiviral IC_{50} values of inhibitors were plotted against each other in the correlation plots as shown in Fig. 4, for the aim of rationalizing structure-activity relationships (SARs) precisely. Inhibitors were distributed around two perpendicular axes crossing the PR IC_{50} axis (X axis) at 30 nM and the RT IC_{50} axis (Y axis) at 50 μM (bolded crosshair in the center of each graph). The 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).

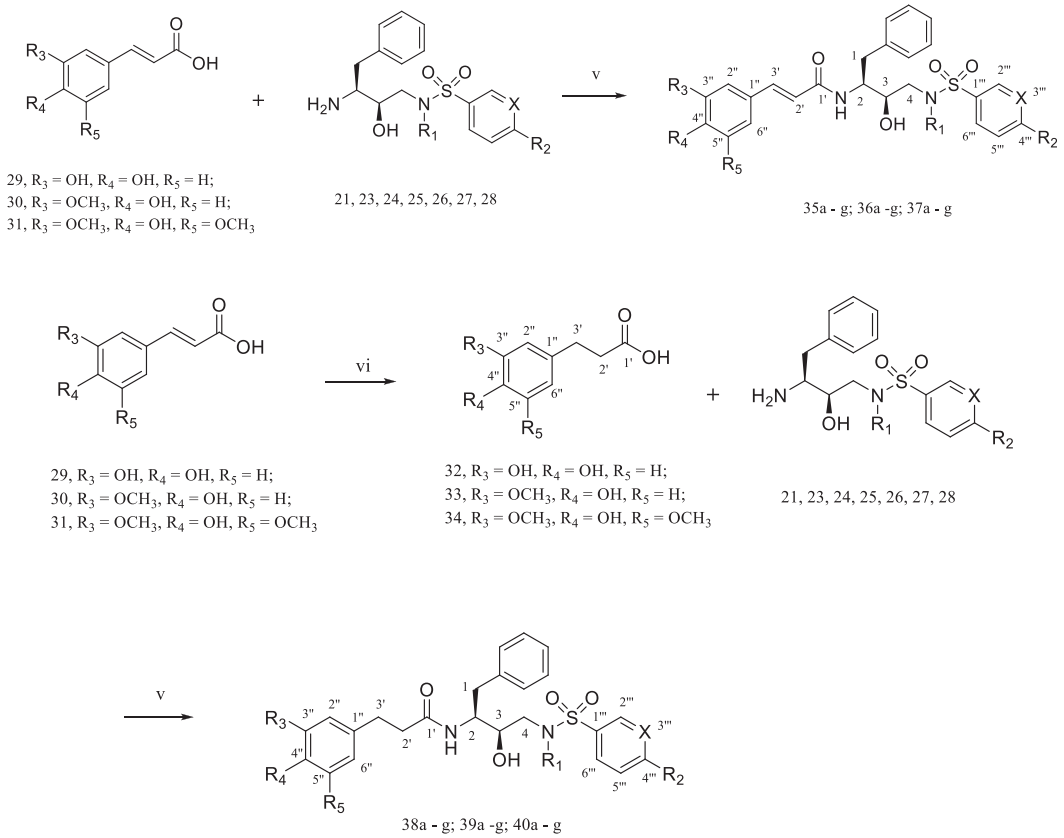
As can be seen in Fig. 4, many of these inhibitors were distributed in the lower left quarter, suggesting of potency for both HIV-1 PR inhibitory activity and RT inhibitory activity, such as **35a**, **35b**, **35c**, **35d**, **35f**, **36b**, **38a**, **38b**, **38c**, **38d**, **38e**, **38f**, **38g**, **39b**, **39c**, **39g**. The preliminary results of the new kind of HIV-1 PR/RT dual inhibitors were encouraging for further optimization to improve antiviral activity.

2.5. HIV-1 infectivity assay on HIV-1 late stage and early stage

By extension, in order to further verify the targets of the dual inhibitors, compounds **37b** and **38c** were carried out assays on the late stage and early stage of HIV-1 life cycle, with DRV and EFV as the controls [38]. As shown in Table 3 and Fig. 5, inhibitor **38c** exhibited antiviral EC_{50} value of 2.31 μM and inhibition of 97% on HIV-1 late stage at the concentration of 10 μM, as well as EC_{50} value

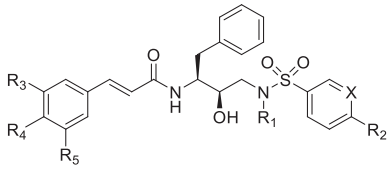


Scheme 1. Syntheses of compounds **21**–**28**. Reagents and conditions: (i) R_1NH_2, CH_3CN, 80 °C, 6 h; (ii) Aryl sulfonyl chloride, DIEA, DMAP, THF, 0 °C ~ r.t, 3–5 h; (iii) CF_3COOH, DCM, 0 °C ~ r.t, 3 h; (iv) H_2 (gas), 50 psi, 10% Pd/C, CH_3OH, r. t, 2 h.



Scheme 2. Syntheses of compounds **35a-40g**. Reagents and conditions: (v) EDCI, HOBt, DMAP, anhydrous DMF, Argon, 0 °C ~ r.t, 3 h; (vi) H_2 (gas), 50 psi, 10% Pd/C, CH_3OH, r. t, 2–3 h.

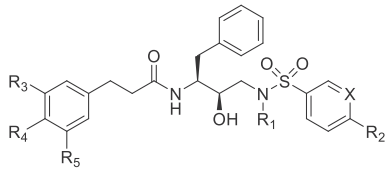
Table 1
Inhibitory activity of inhibitors 35a–37 g.



Comp.	R_1	R_2	R_3	R_4	R_5	X	PR IC_{50} (nM) [a]	RT IC_{50} (μM) [a]
35a	$CH_2CH(CH_3)_2$	OCH_3	OH	OH	H	CH	0.16 ± 0.01	40.8 ± 0.7
35b	$CH_2CH(CH_3)_2$	NH_2	OH	OH	H	CH	0.20 ± 0.06	7.5 ± 1.0
35c	$CH_2CH(CH_3)_2$	SCH 3	OH	OH	H	CH	16.15 ± 6.37	21.5 ± 2.0
35d	$CH_2CH(CH_3)_2$	OCH_3	OH	OH	H	N	2.86 ± 0.45	35.5 ± 1.0
35e	$CH_2CH_2CH_3$	OCH_3	OH	OH	H	CH	2.55 ± 0.92	53.5 ± 4.0
35f	C_3H_5	OCH_3	OH	OH	H	CH	19.48 ± 4.02	31.5 ± 5.0
35g	$CH(CH_3)_2$	OCH_3	OH	OH	H	CH	53.96 ± 8.16	53.5 ± 2.0
36a	$CH_2CH(CH_3)_2$	OCH_3	OCH_3	OH	H	CH	2.93 ± 0.38	146 ± 8.0
36b	$CH_2CH(CH_3)_2$	NH_2	OCH_3	OH	H	CH	3.09 ± 1.14	43.5 ± 2.0
36c	$CH_2CH(CH_3)_2$	SCH 3	OCH_3	OH	H	CH	15.83 ± 3.31	99.5 ± 3.5
36d	$CH_2CH(CH_3)_2$	OCH_3	OCH_3	OH	H	N	2.42 ± 1.15	124.0 ± 1.0
36e	$CH_2CH_2CH_3$	OCH_3	OCH_3	OH	H	CH	24.11 ± 1.47	106.0 ± 3.0
36f	C_3H_5	OCH_3	OCH_3	OH	H	CH	97.63 ± 23.28	43.5 ± 2.0
36g	$CH(CH_3)_2$	OCH_3	OCH_3	OH	H	CH	98.81 ± 15.41	87.5 ± 5.0
37a	$CH_2CH(CH_3)_2$	OCH_3	OCH_3	OH	OCH_3	CH	13.1 ± 3.31	125.0 ± 1.0
37b	$CH_2CH(CH_3)_2$	NH_2	OCH_3	OH	OCH_3	CH	144.4 ± 48.2	1.5 ± 1.0
37c	$CH_2CH(CH_3)_2$	SCH 3	OCH_3	OH	OCH_3	CH	65.05 ± 18.17	51.5 ± 3.0
37d	$CH_2CH(CH_3)_2$	OCH_3	OCH_3	OH	OCH_3	N	69.51 ± 9.53	11.5 ± 2.0
37e	$CH_2CH_2CH_3$	OCH_3	OCH_3	OH	OCH_3	CH	36.66 ± 11.80	90.5 ± 7.0
37f	C_3H_5	OCH_3	OCH_3	OH	OCH_3	CH	294.10 ± 67.50	33.5 ± 6.0
37g	$CH(CH_3)_2$	OCH_3	OCH_3	OH	OCH_3	CH	527.20 ± 86.27	199.0 ± 7.0
DRV	–	–	–	–	–	–	1.52 ± 0.38	–
EFV	–	–	–	–	–	–	–	0.091 ± 0.008

[a] All assays were conducted in triplicate, and the data shown represent mean values (±1 standard deviation) derived from the results of three independent experiments.

Table 2
Inhibitory activity of inhibitors 38a–40 g.



Comp.	R_1	R_2	R_3	R_4	R_5	X	PR IC_{50} (nM) [a]	RT IC_{50} (μM) [a]
38a	$CH_2CH(CH_3)_2$	OCH_3	OH	OH	H	CH	0.39 ± 0.14	3.5 ± 2.0
38b	$CH_2CH(CH_3)_2$	NH_2	OH	OH	H	CH	0.56 ± 0.03	9.5 ± 2.0
38c	$CH_2CH(CH_3)_2$	SCH 3	OH	OH	H	CH	2.02 ± 0.50	0.43 ± 0.100
38d	$CH_2CH(CH_3)_2$	OCH_3	OH	OH	H	N	0.081 ± 0.017	2.5 ± 0.5
38e	$CH_2CH_2CH_3$	OCH_3	OH	OH	H	CH	0.54 ± 0.08	7.5 ± 1.0
38f	C_3H_5	OCH_3	OH	OH	H	CH	4.04 ± 1.22	45.5 ± 2.0
38g	$CH(CH_3)_2$	OCH_3	OH	OH	H	CH	1.47 ± 0.66	20.5 ± 2.0
39a	$CH_2CH(CH_3)_2$	OCH_3	OCH_3	OH	H	CH	1.10 ± 0.53	206.0 ± 9.0
39b	$CH_2CH(CH_3)_2$	NH_2	OCH_3	OH	H	CH	0.58 ± 0.23	31.5 ± 5.0
39c	$CH_2CH(CH_3)_2$	SCH 3	OCH_3	OH	H	CH	7.73 ± 2.99	3.5 ± 0.0
39d	$CH_2CH(CH_3)_2$	OCH_3	OCH_3	OH	H	N	0.16 ± 0.05	241.0 ± 8.0
39e	$CH_2CH_2CH_3$	OCH_3	OCH_3	OH	H	CH	1.70 ± 0.90	234.0 ± 5.0
39f	C_3H_5	OCH_3	OCH_3	OH	H	CH	32.47 ± 14.17	285.0 ± 4.0
39g	$CH(CH_3)_2$	OCH_3	OCH_3	OH	H	CH	9.56 ± 6.81	40.5 ± 1.0
40a	$CH_2CH(CH_3)_2$	OCH_3	OCH_3	OH	OCH_3	CH	104.1 ± 20.3	73.0 ± 4.0
40b	$CH_2CH(CH_3)_2$	NH_2	OCH_3	OH	OCH_3	CH	68.91 ± 17.09	113.0 ± 12.0
40c	$CH_2CH(CH_3)_2$	SCH 3	OCH_3	OH	OCH_3	CH	89.81 ± 28.4	60.7 ± 4.0
40d	$CH_2CH(CH_3)_2$	OCH_3	OCH_3	OH	OCH_3	N	42.20 ± 3.604	2.97 ± 0.14
40e	$CH_2CH_2CH_3$	OCH_3	OCH_3	OH	OCH_3	CH	86.44 ± 32.42	6.5 ± 1.0
40f	C_3H_5	OCH_3	OCH_3	OH	OCH_3	CH	160.8 ± 74.87	9.0 ± 2.0
40g	$CH(CH_3)_2$	OCH_3	OCH_3	OH	OCH_3	CH	70.11 ± 49.95	299.0 ± 10.0
DRV	–	–	–	–	–	–	1.52 ± 0.38	–
EFV	–	–	–	–	–	–	–	0.091 ± 0.008

[a] All assays were conducted in triplicate, and the data shown represent mean values (±1 standard deviation) derived from the results of three independent experiments.

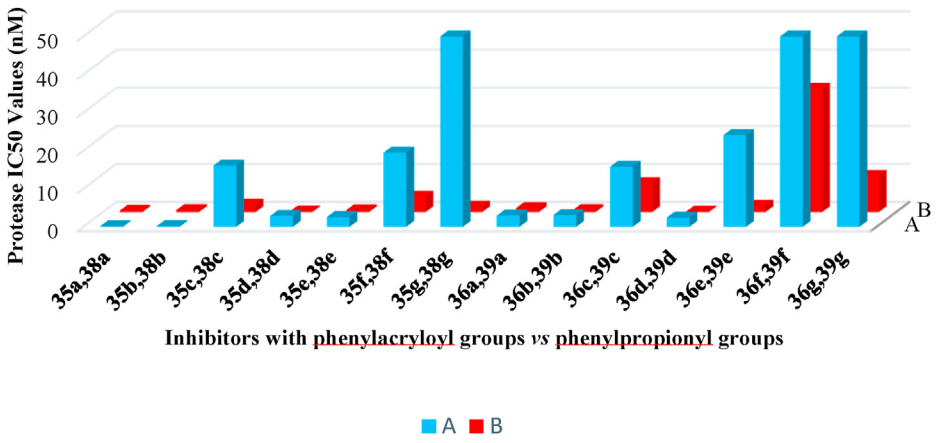


Fig. 2. *Anti*-HIV-1 PR activity of inhibitors with phenylacryloy groups *vesus* phenylpropiony groups. (A) Inhibitors with phenylacryloy groups. (B) Inhibitors with phenylpropiony groups.

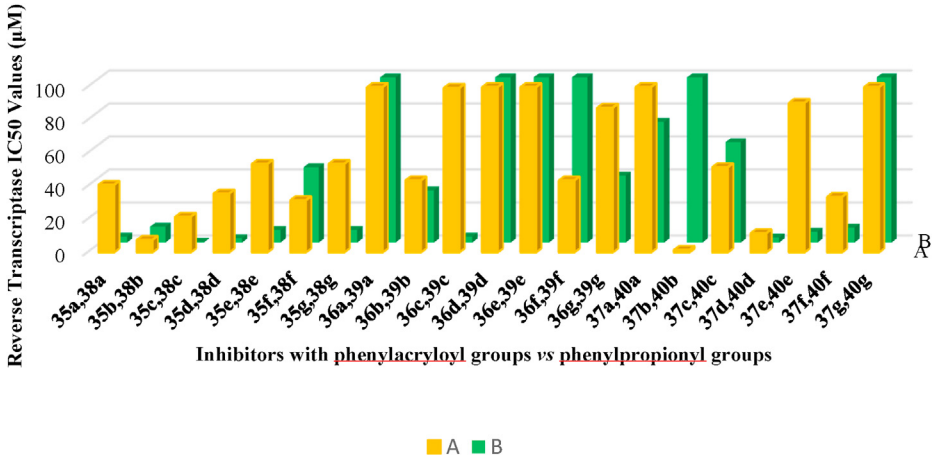


Fig. 3. *Anti*-HIV-1 RT activity of inhibitors with phenylacryloy groups *vesus* phenylpropiony groups. (A) Inhibitors with phenylacryloy groups s. (B) Inhibitors with phenylpropiony groups.

of 8.32 μM and inhibition of 68% on HIV-1 early stage, respectively. And **37b** showed antiviral EC_{50} value of 37.35 μM and inhibition of 30% on HIV-1 late stage, and EC_{50} value of 68.02 μM and inhibition of 14% on HIV-1 early stage. Both of the two inhibitors exhibited small difference of inhibition on HIV-1 late stage and early stage. However, the controls DRV (HIV-1 PR inhibitor) and EFV (HIV-1 RT inhibitor) showed sharp disparity on the late stage and early stage of HIV-1 life cycle. For instance, DRV exhibited inhibition of 99% on HIV-1 late stage and 2% on early stage. EFV exhibited inhibition of 15% on HIV-1 late stage and 85% on early stage, respectively. The results above supported the rationality of designing dual inhibitors.

2.6. Molecular modeling studies

For the aim of investigating possible hydrogen bonding interactions and hydrophobic contacts, molecular modeling work for inhibitors **38a**, **38c** and **38d** were performed using the molecular modeling software MOE (Molecular Operating Environment) (version 2009.06). Both HIV-1 PR crystal structure (PDB-ID: 4mc9) and RT crystal structure (PDB-ID: 2yng) were obtained from the protein data bank [39].

As shown in Fig. 6, inhibitor **38a** adapted into HIV-1 PR binding site nicely with a binding score of −13.54 kcal/mol. Furthermore, there formed hydrogen bonding as well as other van der Waals interactions between the P2 ligand and the S2 subsite of PR, which verified the importance of hydroxy group that formed additional ligand-binding site interactions. In addition, hydrogen bonding interaction was also observed between the hydroxy group in the scaffold and residue Asp25'. And one of the sulfonamide oxygens formed hydrogen bonding interaction with amide NHs of Ile50′ located in the flaps. Moreover, favorable van der Waals interactions between P2′ ligand and the S2′ subsite made great contributions to the potent antiviral activity. Moreover, inhibitor **38c** also fitted into the protease cave well, but with a slightly lower negative binding score of −12.18 kcal/mol compared to **38a**, which implied weaker binding with the enzyme and was in accordance with its PR inhibitory activity [40]. As shown in Fig. 6 (C), inhibitor **38d** fitted into the active cavity of the protease and formed several strong hydrogen-bonding contacts with PR. What's particularly important was that the nitrogen atom of pyridine in P2′ moiety formed direct hydrogen bond interaction with the backbone NH of Asp30′, which was in line with its high *anti*-PR potency.

In Fig. 7 (A), inhibitor **38a** with a flexible chain in P2 ligand could fit into the narrow pocket (non-nucleoside inhibitor binding pocket, NNIBP) of HIV-1 reverse transcriptase with a binding score of −8.10 kcal/mol. One of the sulfonamide oxygens formed a strong hydrogen bond with residue Lys103, which formed π-π interaction with the aromatic ring in P1 ligand at the same time. The benzene

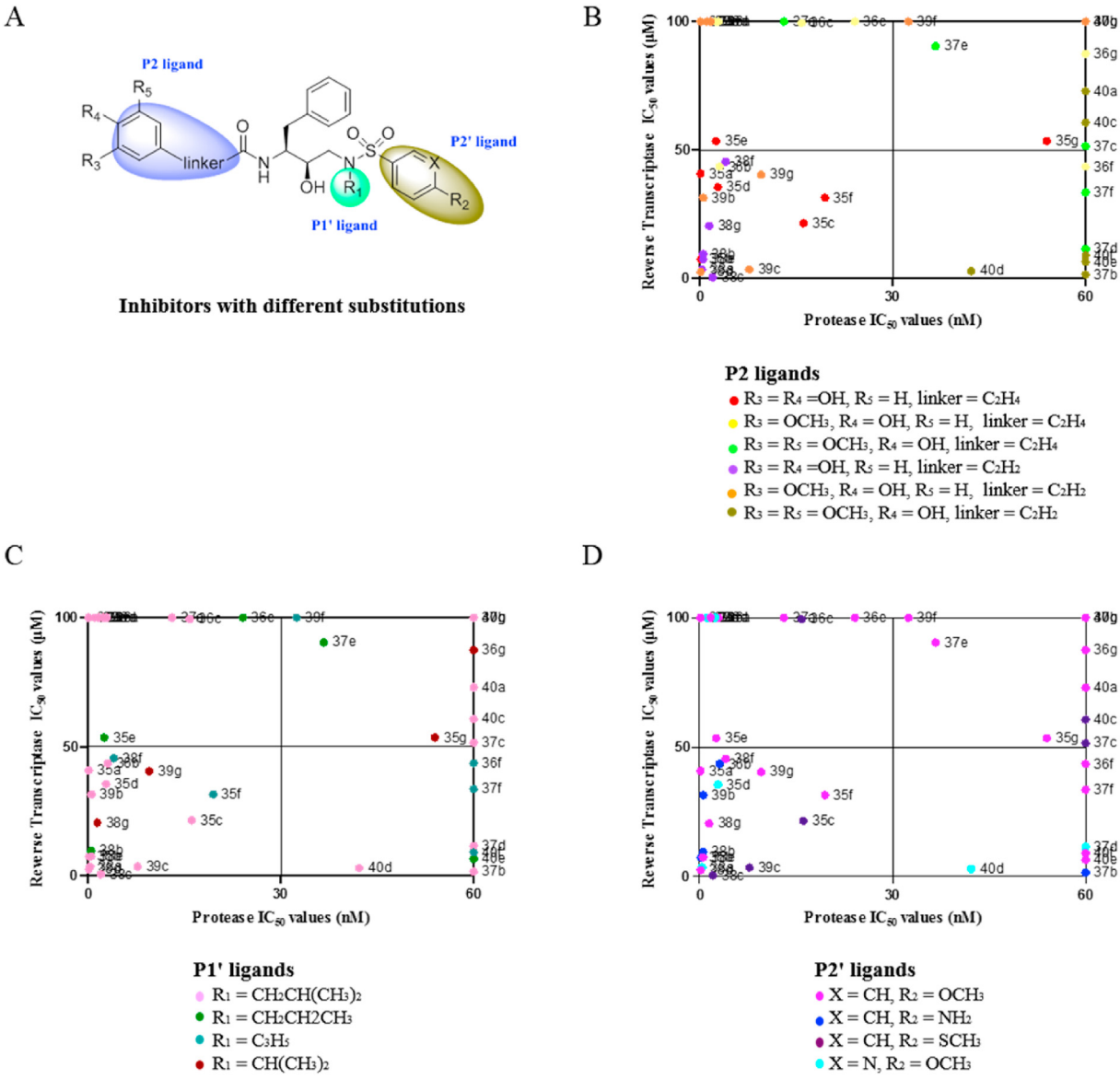


Fig. 4. Scatter plot for the inhibition of PR and RT enzymes. (A) HIV-1 PR/RT dual inhibitors with different substitutions. (B) Inhibitors were categorized according to their P2 ligands. (C) Inhibitors were categorized according to their P1′ ligands. (D) Inhibitors were categorized according to their P2′ ligands. Inhibitors with IC_{50} values against PR above 60 nM or IC_{50} values against RT above 100 μM had been arbitrary positioned at the 60 nM or 100 μM value, respectively.

Table 3
Antiviral Activity of 37b and 38c on HIV-1 late stage and early stage.

Compd.	Activity on HIV-1 late stage [a]		Activity on HIV-1 early stage [a]		Ratio [b]
	EC_{50} (μM)	Inhibition (%) (10 μM)	EC_{50} (μM)	Inhibition (%) (10 μM)	
37b	37.35 ± 0.42	30	68.02 ± 0.21	14	2.14
38c	2.31 ± 0.03	97	8.32 ± 0.28	68	1.43
DRV	–	99	–	2	49.50
EFV	–	15	–	85	5.67

[a] All assays were conducted in quintuplicate.
[b] Ratio is defined by inhibition on HIV-1 late stage/inhibition on HIV-1 early stage, or inhibition on HIV-1 early stage/inhibition on HIV-1 late stage.

ring in P2 ligand kept π-π interaction with Tyr188 of RT [28]. As shown in Fig. 7 (B), inhibitor **38c** fitted into the RT active cavity well, with a binding score of −9.56 kcal/mol. The aromatic ring of P2′ ligand formed π-π interactions with both residues Val106 and Pro236. Similarly, π-π interaction was also observed between the aromatic ring in P2 ligand and Lys223 residue of RT. Moreover, the sulfur atom in P2′ ligand interacted with the backbone of Val106 by a hydrogen bond, which played an important role in enhancing *anti*-RT activity [41]. Likewise, π-π interaction, hydrogen bonding or hydrophobic contacts were also observed in the structural analysis of **38d** modeled into the active subsite of HIV-1 reverse transcriptase in Fig. 7 (C).

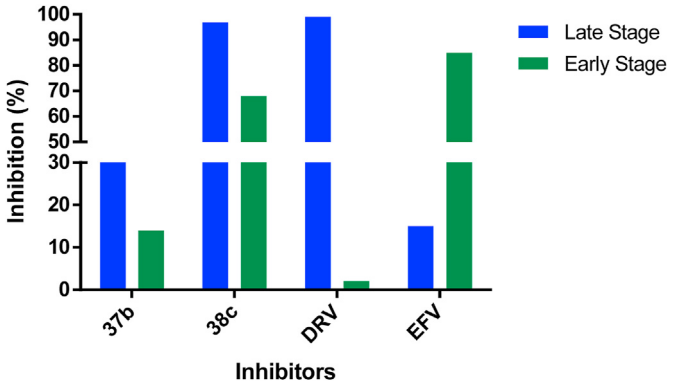


Fig. 5. Inhibition of compounds **37b**, **38c**, **DRV** and **EFV** on HIV-1 late stage and early stage.

2.7. Molecular dynamic simulation studies

In order to confirm the druggability nature of the ligands and their binding mechanism, we run 10 ns MD simulations (molecular dynamic simulations) for the complex **38c/PR**, **38c/RT**, **38 d/PR**, and **38d/RT** as shown in Fig. 8. The RMSD analysis (<2.5 Å) showed that the binding mode for all four complexes during the simulation changed little. Thus, it indicated that the docked initial binding modes could represent the interactions between the inhibitors and the active sites of HIV-1 PR or RT, and validated the rationality of designing dual inhibitors.

Also, on the basis of the MD simulation trajectory, the binding energies for the **38c/PR**, **38c/RT**, **38 d/PR**, and **38d/RT** complexes were evaluated using the MMPBSA method, and the results are listed in Table 4. As results, both **38c** and **38d** showed good binding affinity with the protease with the calculated ΔG (−11.59 and −13.88 kcal/mol). While the predicted binding free energy between **38c**、**38d** and **RT** was −8.37 and −8.75 kcal/mol, respectively. Thus, the molecular dynamic results indicated that **38c** and **38d** would bind to the dual targets (PR and RT).

3. Conclusion

In conclusion, we have designed a novel class of HIV-1 PR/RT dual inhibitors on the basis of both possible ligand-binding site interactions and the uniformity of the key residues in active sites. Compared with coumarin derivatives in our previous studies, introduction of phenylpropiony groups or phenylacryloy groups as P2 ligands made notable enhancement in HIV-1 RT inhibitory activity with one or two orders of magnitude, with comparable or even improved potency against PR at the same time. More importantly, the disparate ratio between PR and RT inhibition decreased sharply and seemed more reasonable with ratio of 1: 10.4, as example of **37b**, which gave encouragement for further optimization to improve both PR and RT inhibitory potency. Besides, the inconspicuous disparity in the assays of inhibitors **37b** and **38c** on the late stage and early stage of HIV-1 life cycle supported the rationality of designing dual inhibitors as shown in Fig. 5.

In addition, the PR antiviral activity of inhibitors with a methoxypyridine P2′ ligand showed improved antiviral IC_{50} values than those with a 4-methoxybenzene as the P2′ ligand. For instance, inhibitor **38d** with a 3, 4-dihydroxyphenylpropiony group as the P2 ligand and a 6-methoxypyridine-4-sulfonamide as the P2′ ligand displayed an almost 5-fold improved PR antiviral IC_{50} value of 0.081 nM compared to **38a** with a benzene in the P2′ ligand.

Moreover, to a certain extent, inhibitors with phenylpropiony P2 ligands exhibited superior *anti*-RT activity than those with phenylacryloy groups as the P2 ligands. Taken **38c** with a 3, 4-dihydroxyphenylpropiony group as the P2 ligand for example, it exhibited an excellent antiviral IC_{50} value of 0.43 μM. In comparison, inhibitor **35c** with a 3, 4-dihydroxyphenylacrylol P2 ligand displayed a nearly 50-fold decrement in RT activity with IC_{50} value of 21.5 μM.

According to the molecular modeling studies, both hydroxy

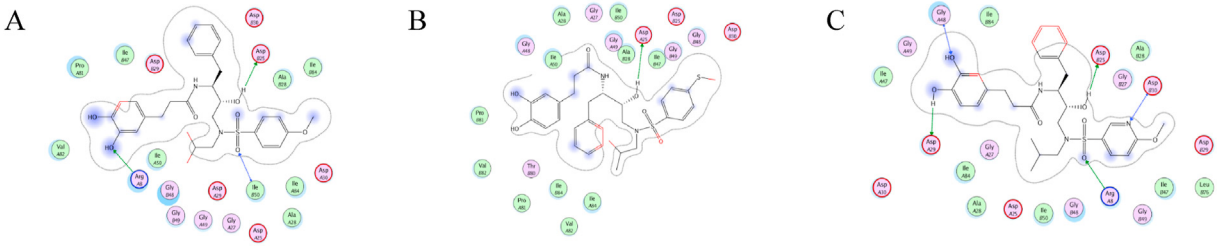


Fig. 6. Molecular modeling for inhibitors **38a**, **38c** and **38d** within HIV-1 PR model. (A) Ligplot interaction of **38a**. (B) Ligplot interaction of **38c**. (C) Ligplot interaction of **38d**. Ligand exposures were represented as purple spheres and hydrogen bonding was depicted as blue or green arrows.

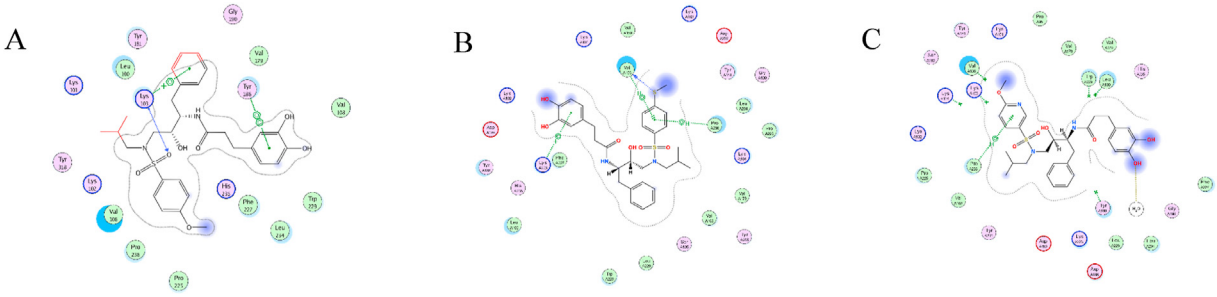


Fig. 7. Molecular modeling for inhibitors **38a**, **38c** and **38d** within HIV-1 RT model. (A) Ligplot interaction of **38a**. (B) Ligplot interaction of **38c**. (C) Ligplot interaction of **38d**. Ligand exposures were represented as purple spheres, hydrogen bonding was depicted as blue or green arrows, and π-π interactions were depicted as green line.

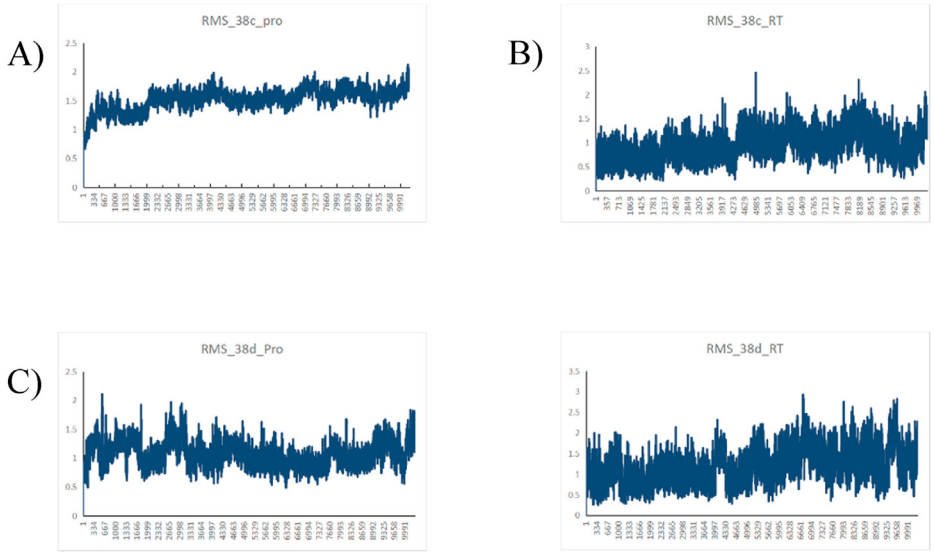


Fig. 8. Molecular dynamic simulations for the complex **38c/PR**, **38c/RT**, **38 d/PR**, and **38d/RT**. (A) Molecular dynamic simulations for the complex **38c/PR**. (B) Molecular dynamic simulations for the complex **38c/RT**. (A) Molecular dynamic simulations for the complex **38 d/PR**. (B) Molecular dynamic simulations for the complex **38d/RT**.

Table 4
The predicted binding free energy between 38c、38d and HIV-1 PR and RT using MMPBSA (kcal/mol).

Complexes	ΔG_{polar}	$\Delta G_{nopolar}$	$\Delta G_{mm/pbsa}$	-TS	ΔG_{Bind}
38c/PR	59.95	−100.20	−40.25	28.66	−11.59
38 d/PR	58.32	−100.62	−42.3	28.42	−13.88
38c/RT	62.61	−96.06	−33.45	25.08	−8.37
38d/RT	63.74	−97.21	−34.47	25.72	−8.75

group and aromatic ring in P2 ligands were indispensable for additional hydrogen bondings and other van der Waals interactions in both PR and RT inhibitory potency, which was consistent with our anticipation. Moreover, the flexible chain in P2 ligand resulted in a significant enhancement of dual antiviral activity. In addition, substitutions in P2′ ligand played an important role in antiviral potency. We would put focus on improving *anti*-RT activity in our next study, and the benzene ring in P1 ligand might be an appropriate modification site inspired by molecular modeling studies in Fig. 7 (A).

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. The solvent dichloromethane was distilled under an argon atmosphere from calcium hydride. All reactions were monitored by the thin-layer chromatography (TLC) 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). 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 or DMSO-d_6 on a Bruker AVANCE III 400 MHz, 500 MHz or 600 MHz spectrometer (Bruker Inc) with tetramethylsilane (TMS) as the internal reference. The chemical shifts were 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; DMSO-d_6: ^{1}H, δ = 2.49 ppm, ^{13}C, δ = 39.5 ppm), and coupling constants were reported in Hz. All the target compounds were characterized by ^{1}H and ^{13}C NMRs and HRMS spectra.

4.1.1. Tert-butyl ((2S, 3R)-3-hydroxy-4-(isobutylamino)-1-phenylbutan-2-yl)carbamate (**6**)

To a stirred solution of (2*S*, 3*S*)-1, 2-epoxy-3-(boc-amino)-4-phenylbutane (**1**, 20.0 g, 75.94 mmol) in acetonitrile (82 mL) at 25 °C was added isobutylamine (**2**, 19.0 mL, 189.46 mmol). The resulting mixture was heated at reflux for 6 h. After this period, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (10% CH_3OH in CH_2Cl_2 as the eluent) to provide the corresponding amine (21.2 g, 83%) as white amorphous solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.29−7.16 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 3.71−3.59 (m, 2H, H-2, H-3), 3.16−3.08 (m, 1H, H-1a), 2.83−2.74 (m, 1H, H-4a), 2.68−2.56 (m, 2H, H-1b, H-4b), 2.54−2.48 (m, 1H, H-1″a), 2.46−2.39 (m, 1H, H-1″b), 1.88−1.77 (m, 1H, H-2″), 1.32 (s, 9H, Boc-CH_3), 0.96 (d, J = 6.4 Hz, 6H, 3″a-CH_3, 3″b-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 137.9, 129.5, 128.4, 126.3, 79.3, 70.6, 58.0, 54.2, 51.4, 36.7, 28.4, 28.3, 20.5; LC-MS (ESI) $[M+H]^+$ *m/z* 337.2.

4.1.2. Tert-butyl ((2S, 3R)-3-hydroxy-1-phenyl-4-(propylamino) butan-2-yl)carbamate (**7**)

The compound was obtained from n-propylamine (**3**) in 90% yield as white powder as described for **6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.27 (m, 2H, H-3′, H-5′), 7.23−7.22 (m, 3H, H-2′, H-4′, H-6′), 4.65 (s, 1H, 2-NH), 3.80 (s, 1H, H-3), 3.46 (s, 1H, H-2), 2.98 (d, J = 13.5 Hz, 1H, H-1a), 2.86 (s, 1H, H-4a), 2.69 (s, 2H, H-1b, H-4b), 2.57 (s, 2H, H-1″a, H-1″b), 1.50−1.48 (m, 2H, H-2″a, H-2″b), 1.36 (s, 9H, Boc-CH_3), 0.93 (t, J = 6.0 Hz, 3H, 3″-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 137.9, 129.5, 128.34, 126.3, 79.4, 70.8, 54.2, 51.7, 51.3, 36.6, 28.3, 23.2, 11.7; LC-MS (ESI, M + H^+) *m/z* 323.3.

4.1.3. Tert-butyl ((2S, 3R)-4-(cyclopropylamino)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**8**)

The compound was obtained from cyclopropylamine (**4**) in 86% yield as white powder as described for **6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22−7.16 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 3.71 (s, 1H, H-3), 3.41 (s, 1H, H-2), 2.91 (d, J = 13.5 Hz, 1H, H-1a), 2.78−2.72 (m, 3H,

H-1b, H-4a, H-4b), 2.07 (s, 1H, H-1″), 1.29 (s, 9H, Boc-CH_3), 0.39 (s, 2H, H-2″a, H-3″a), 0.28 (s, 2H, H-2″b, H-3″b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 137.9, 129.6, 128.4, 126.4, 79.5, 70.7, 54.0, 51.4, 36.6, 30.6, 28.3, 6.81, 6.26; LC-MS (ESI, M + H^+) *m*/*z* 321.3.

4.1.4. Tert-butyl ((2S, 3R)-3-hydroxy-4-(isopropylamino)-1-phenylbutan-2-yl)carbamate (**9**)

The compound was obtained from n-propylamine (**3**) in 85% yield as white powder as described for **6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.27 (m, 2H, H-3′, H-5′), 7.24–7.22 (m, 3H, H-2′, H-4′, H-6′), 4.59 (s, 1H, 3-OH), 3.79 (s, 1H, H-3), 3.41 (s, 1H, H-2), 3.00 (d, *J* = 13.5 Hz, 1H, H-1a), 2.86 (s, 1H, H-4a), 2.76 (s, 1H, H-1″), 2.69–2.67 (m, 2H, H-1b, H-4b), 1.36 (s, 9H, Boc-CH_3), 1.06 (s, 3H, 2″a-CH_3), 1.05 (s, 3H, 2″b −CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 137.9, 129.6, 128.4, 126.3, 79.4, 71.0, 54.0, 49.0, 48.7, 36.6, 28.3, 23.3, 22.9; LC-MS (ESI, M + H^+) *m*/*z* 323.3.

4.1.5. Tert-butyl ((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**14**)

To a stirred solution of **6** (5.0 g, 14.86 mmol) in tetrahydrofuran (40 mL) at 0 °C was added DIEA (3.68 mL, 16.34 mmol) and DMAP (0.18 g, 1.49 mmol) in batches, followed by a mixture of 4-methoxybenzenesulfonyl chloride (**10**, 3.37 g, 16.34 mmol) and tetrahydrofuran (15 mL). The resulting mixture was stirred at 0 °C for 0.5 h and at 25 °C for another 3–5 h. The mixture was then concentrated under reduced pressure and extracted with ethyl acetate and dried over anhydrous Na_2SO_4. Removal of solvent, followed by column chromatography over silica gel (20% EtOAc in n-hexane as the eluent), yielded compound **14** (6.14 g, 82%) as white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 6.9 Hz, 2H, H-2‴, H-6‴), 7.33–7.17 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.98 (d, *J* = 6.9 Hz, 2H, H-3‴, H-5‴), 3.87 (s, 3H, 4‴-OCH_3), 3.84–3.74 (m, 2H, H-2, H-3), 3.13–2.80 (m, 6H, H-1a, H-1b, H-4a, H-4b, H-1″a, H-1″b), 1.92–1.80 (m, 1H, H-2″), 1.35 (s, 9H, Boc-CH_3), 0.89 (dd, *J* = 14.4, 5.2 Hz, 6H, 3″a-CH_3, 3″b-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 156.0, 137.9, 130.0, 129.6, 129.5, 128.5, 126.4, 114.3, 79.7, 72.8, 58.6, 55.6, 54.7, 53.7, 35.5, 28.3, 27.2, 20.1, 19.9; LC-MS (ESI, M + H^+) *m*/*z* 507.0.

4.1.6. Tert-butyl ((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-nitrophenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**15**)

The compound was obtained by **6** coupling with 4-nitrobenzenesulfonyl chloride (**11**) in the presence of DIEA and DMAP procedure in 91% yield (white amorphous solid) as described for **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.8 Hz, 2H, H-3‴, H-5‴), 7.98 (d, *J* = 8.8 Hz, 2H, H-2‴, H-6‴), 7.35–7.31 (m, 2H, H-3′, H-5′), 7.29–7.22 (m, 3H, H-2′, H-4′, H-6′), 3.85–3.76 (m, 2H, H-2, H-3), 3.25–3.20 (m, 2H, H-4a, H-4b), 3.03–2.96 (m, 3H, H-1a, H-1″a, H-1″b), 2.94–2.87 (m, 1H, H-1b), 1.95–1.86 (m, 1H, H-2″), 1.38 (s, 9H, Boc-CH_3), 0.90 (dd, *J* = 6.4, 4.8 Hz, 6H, 3″a-CH_3, 3″b-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 150.0, 145.0, 137.5, 129.4, 128.6, 128.5, 126.7, 124.3, 80.2, 72.2, 57.5, 55.2, 52.5, 35.6, 28.2, 26.9, 20.0, 19.8; LC-MS (ESI, M + H^+) *m*/*z* 521.9.

4.1.7. Tert-butyl ((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-(methylthio)phenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**16**)

The compound was obtained by **6** coupling with 4-(methylthio) benzenesulfonyl chloride (**12**) in the presence of DIEA and DMAP procedure in 85% yield (white amorphous solid) as described for **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.0 Hz, 2H, H-2‴, H-6‴), 7.30–7.24 (m, 7H, H-2′, H-3′, H-4′, H-5′, H-6′, H-3‴, H-5‴), 3.81–3.75 (m, 2H, H-2, H-3), 3.13–2.92 (m, 5H, H-1a, H-4a, H-4b, H-1″a, H-1″b), 2.83 (s, 1H, H-1b), 2.52 (s, 3H, 4‴-SCH_3), 1.85 (s, 1H, H-2″), 1.34 (s, 9H, Boc-CH_3), 0.90 (d, *J* = 4.5 Hz, 3H, 3″a-CH_3), 0.87 (d, *J* = 4.5 Hz, 3H, 3″b-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 145.9, 137.8, 134.1, 129.6, 128.5, 127.7, 126.4, 125.4, 79.7, 72.7, 58.6, 54.7, 53.7, 35.5, 29.7, 28.3, 27.2, 20.1, 19.9, 14.8; LC-MS (ESI, M + H^+) *m*/*z* 523.3.

4.1.8. Tert-butyl ((2S, 3R)-3-hydroxy-4-((N-isobutyl-6-methoxypyridine)-3-sulfonamido)-1-phenylbutan-2-yl)carbamate (**17**)

The compound was obtained by **6** coupling with 6-methoxypyridine-3-sulfonyl chloride (**13**) in the presence of DIEA and DMAP procedure in 80% yield (white amorphous solid) as described for **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H, H-6‴), 7.87 (d, *J* = 8.0 Hz, 1H, H-2‴), 7.30–7.24 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.81 (d, *J* = 8.0 Hz, 1H, H-5‴), 4.65 (s, 1H, H-3), 4.00 (s, 3H, 4‴-OCH_3), 3.85–3.76 (m, 3H, H-2, H-4a, H-4b), 3.01–2.90 (m, 4H, H-1a, H-1b, H-1″a, H-1″b), 1.87 (s, 1H, H-2″), 1.35 (s, 9H, Boc-CH_3), 0.89 (s, 6H, 3″a-CH_3, 3″b-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 156.2, 147.4, 137.7, 137.3, 129.5, 128.5, 128.0, 126.5, 111.5, 79.9, 72.7, 58.3, 54.9, 54.3, 53.4, 35.5, 28.2, 27.1, 20.1, 19.9; LC-MS (ESI, M + H^+) *m*/*z* 509.3.

4.1.9. Tert-butyl ((2S, 3R)-3-hydroxy-4-((4-methoxy-N-propylphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**18**)

The compound was obtained by **7** coupling with 4-methoxybenzenesulfonyl chloride (**10**) in the presence of DIEA and DMAP procedure in 80% yield (white amorphous solid) as described for **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.5 Hz, 2H, H-2‴, H-6‴), 7.30–7.22 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.97 (d, *J* = 7.5 Hz, 2H, H-3‴, H-5‴), 3.87 (s, 3H, 4‴-OCH_3), 3.80 (s, 2H, H-2, H-3), 3.12–3.10 (m, 3H, H-4a, H-4b, H-1a), 3.04–2.99 (m, 2H, H-1b, H-1″a), 2.94 (s, 1H, H-1″b), 1.55–1.51 (m, 2H, H-2″a, H-2″b), 1.35 (s, 9H, Boc-CH_3), 0.85 (d, *J* = 6.0 Hz, 3H, 3″-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 156.2, 137.9, 130.4, 129.6, 129.4, 128.5, 126.5, 114.4, 79.8, 72.7, 55.7, 54.7, 52.6, 52.3, 35.4, 29.7, 28.3, 22.0, 11.2; LC-MS (ESI, M + H^+) *m*/*z* 493.3.

4.1.10. Tert-butyl ((2S, 3R)-4-((N-cyclopropyl-4-methoxyphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**19**)

The compound was obtained by **8** coupling with 4-methoxybenzenesulfonyl chloride (**10**) in the presence of DIEA and DMAP procedure in 80% yield (white amorphous solid) as described for **14**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.80 (d, *J* = 8.5 Hz, 2H, H-2‴, H-6‴), 7.25–7.23 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.17–7.12 (m, 1H, H-4′), 7.09 (d, *J* = 8.5 Hz, 2H, H-3‴, H-5‴), 3.92–3.89 (m, 1H, H-3), 3.87 (s, 3H, 4‴-OCH_3), 3.68–3.64 (m, 1H, H-2), 3.40 (dd, *J* = 14.5, 3.0 Hz, 1H, H-1a), 3.14 (dd, *J* = 13.5, 3.0 Hz, 1H, H-1b), 3.03 (dd, *J* = 14.0, 9.0 Hz, 1H, H-4a), 2.57 (dd, *J* = 13.5, 11.0 Hz, 1H, H-4b), 2.04–1.97 (m, 1H, H-1″), 1.29 (s, 9H, Boc-CH_3), 1.02–0.89 (m, 2H, H-2″a, H-3″a), 0.77–0.70 (m, 1H, H-2″b), 0.68–0.61 (m, 1H, H-3″b); ^{13}C NMR (101 MHz, CD_3OD) δ 164.8, 157.9, 140.4, 131.1, 130.5, 130.4, 129.1, 127.0, 115.3, 79.9, 73.5, 56.6, 56.3, 56.2, 37.1, 33.3, 28.7, 8.84, 7.56; LC-MS (ESI, M + H^+) *m*/*z* 491.4.

4.1.11. Tert-butyl ((2S, 3R)-3-hydroxy-4-((N-isopropyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**20**)

The compound was obtained by **9** coupling with 4-methoxybenzenesulfonyl chloride (**10**) in the presence of DIEA and DMAP procedure in 85% yield (white amorphous solid) as described for **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 2H, H-2‴, H-6‴), 7.30–7.22 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.96 (d, *J* = 7.5 Hz, 2H, H-3‴, H-5‴), 4.10–4.05 (m, 1H, H-3), 3.87 (s, 3H, 4‴-OCH_3), 3.78 (s, 2H, H-2, H-4a), 3.20 (d, *J* = 15.5 Hz, 1H, H-4b), 3.07 (dd, *J* = 15.0, 9.5 Hz, 2H, H-1a, H-1b), 2.94 (s, 1H, H-1″), 1.35 (s, 9H, Boc-CH_3), 1.03 (d, *J* = 5.0 Hz, 3H, 2″a-CH_3), 0.90 (s, 3H, 2″b −CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 155.9, 137.8, 131.4, 129.6, 129.3, 128.4, 126.4, 114.3, 79.5, 74.3, 55.6, 54.4, 50.2, 46.7, 35.7, 29.7, 28.3,

21.7, 19.8; LC-MS (ESI, M + H^+) *m/z* 493.3.

*4.1.12. N-((2R, 3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-4-methoxybenzenesulfonamide (**21**)*

A solution of **14** (5.0 g, 9.87 mmol) in a mixture of 10 mL trifluoroacetic acid and 10 mL CH_2Cl_2 was stirred for 3 h at 25 °C. After this period, the reaction mixture was concentrated under reduced pressure and the residue was redissolved in 10 mL CH_2Cl_2. Saturated aqueous sodium bicarbonate were added dropwise to neutralize the superfluous acid. The mixture was then extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure, followed by column chromatography over silica gel (10% CH_3OH in CH_2Cl_2 as the eluent), yielded compound **21** (3.13 g, 78%) as white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.8 Hz, 2H, H-2‴, H-6‴), 7.29–7.20 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.95 (d, J = 8.8 Hz, 2H, H-3‴, H-5‴), 4.22–4.15 (m, 1H, H-3), 3.85 (s, 3H, 4‴-OCH_3), 3.81–3.78 (m, 1H, H-2), 3.23–3.18 (m, 1H, H-4a), 3.13–3.00 (m, 3H, H-4b, H-1″a, H-1″b), 2.81–2.70 (m, 2H, H-1a, H-1b), 1.69–1.59 (m, 1H, H-2″), 0.75 (d, J = 2.8 Hz, 3H, 3″a-CH_3), 0.73 (d, J = 2.8 Hz, 3H, 3″b-CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 164.5, 140.2, 132.0, 130.6, 130.4, 129.6, 127.5, 115.3, 73.7, 58.9, 57.0, 56.2, 53.1, 39.1, 28.1, 20.5, 20.4; LC-MS (ESI, M + H^+) *m/z* 407.3.

*4.1.13. N-((2R, 3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-4-nitrobenzenesulfonamide (**22**)*

The compound was obtained by **15** which was exposed to trifluoroacetic acid to remove the BOC-group in 83% yield (white amorphous solid) as described for **21**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J = 8.0 Hz, 2H, H-3‴, H-5‴), 8.06 (d, J = 8.0 Hz, 2H, H-2‴, H-6‴), 7.38–7.27 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 5.64 (s, 1H, 3-OH), 3.91 (s, 1H, H-3), 3.49–3.37 (m, 2H, H-2, H-4a), 3.07 (dd, J = 13.6, 8.4 Hz, 2H, H-4b, H-1″a), 2.99 (dd, J = 14.0, 6.4 Hz, 1H, H-1″b), 2.87 (dd, J = 14.0, 6.4 Hz, 1H, H-1a), 2.83–2.72 (m, 1H, H-1b), 1.93–1.84 (m, 1H, H-2″), 0.82 (d, J = 6.4 Hz, 3H, 3″a-CH_3), 0.76 (d, J = 6.4 Hz, 3H, 3″b-CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 151.4, 147.0, 140.0, 130.4, 129.9, 129.7, 127.5, 125.3, 72.8, 57.8, 57.2, 51.9, 39.3, 27.8, 20.3; LC-MS (ESI, M + H^+) *m/z* 422.3.

*4.1.14. 4-Amino-N-((2R, 3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutylbenzenesulfonamide (**23**)*

To a solution of compound **22** (1.26 g, 3.0 mmol) in 10 mL CH_3OH was added 10% Pd/C (0.13 g). The mixture was stirred at 25 °C under a 50 psi hydrogen pressure for 2 h. The reaction mixture was filtered over Celite and washed with CH_3OH. Removal of solvent under reduced pressure, followed by column chromatography on silica gel (10% CH_3OH in CH_2Cl_2 as the eluent) afforded the corresponding aromatic amine (1.10 g, 94%) as white amorphous solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.52 (d, J = 8.6 Hz, 2H, H-2‴, H-6‴), 7.35–7.29 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.26–7.23 (m, 1H, H-4′), 6.73 (d, J = 8.6 Hz, 2H, H-3‴, H-5‴), 3.83–3.80 (m, 1H, H-3), 3.37 (dd, J = 14.9, 3.8 Hz, 1H, H-2), 3.15 (dt, J = 8.8, 4.3 Hz, 1H, H-4a), 3.08–3.00 (m, 2H, H-4b, H-1″a), 2.95 (dd, J = 13.6, 7.8 Hz, 1H, H-1″b), 2.86 (dd, J = 13.6, 7.2 Hz, 1H, H-1a), 2.58 (dd, J = 13.5, 9.4 Hz, 1H, H-1b), 2.00–1.95 (m 1H, H-2″), 0.91 (d, J = 6.6 Hz, 3H, 3″a-CH_3), 0.88 (d, J = 6.6 Hz, 3H, 3″b-CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.5, 138.7, 130.9, 129.5, 129.3, 128.6, 126.5, 114.1, 73.0, 58.7, 55.7, 52.6, 39.0, 27.2, 20.2, 19.9; LC-MS (ESI) [M + H]$^+$ *m/z* 392.5.

*4.1.15. N-((2R, 3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-4-(methylthio)benzenesulfonamide (**24**)*

The compound was obtained by **16**, which was exposed to trifluoroacetic acid to remove the BOC-group in 81% yield (white amorphous solid) as described for **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 7.5 Hz, 2H, H-2‴, H-6‴), 7.30–7.21 (m, 7H, H-2′, H-3′, H-4′, H-5′, H-6′, H-3‴, H-5‴), 3.75 (s, 1H, H-3), 3.30–3.21 (m, 2H, H-2, H-4a), 3.14 (d, J = 4.0 Hz, 1H, H-4b), 3.03–2.99 (m, 1H, H-1″a), 2.96 (d, J = 13.5 Hz, 1H, H-1″b), 2.90–2.86 (m, 1H, H-1a), 2.52–2.48 (m, 4H, H-1b, 4‴-SCH_3), 1.93–1.86 (m, 1H, H-2″), 0.92 (d, J = 5.0 Hz, 3H, 3″a-CH_3), 0.89 (d, J = 5.0 Hz, 3H, 3″b-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8, 138.7, 134.4, 129.3, 128.7, 127.7, 126.5, 125.5, 73.0, 58.5, 55.7, 52.6, 39.0, 27.2, 20.2, 19.9, 14.8; LC-MS (ESI) [M + H]$^+$ *m/z* 423.2.

*4.1.16. N-((2R, 3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl-6-methoxypyridine-3-sulfonamide (**25**)*

The compound was obtained by **17**, which was exposed to trifluoroacetic acid to remove the BOC-group in 77% yield (white amorphous solid) as described for **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H, H-6‴), 7.93 (d, J = 8.5 Hz, 1H, H-2‴), 7.31–7.30 (m, 2H, H-3′, H-5′), 7.26–7.21 (m, 3H, H-2′, H-4′, H-6′), 6.83 (d, J = 8.5 Hz, 1H, H-5‴), 4.01 (s, 3H, 4‴-OCH_3), 3.76 (s, 1H, H-3), 3.32–3.28 (m, 2H, H-2, H-4a), 3.13 (d, J = 4.0 Hz, 1H, H-4b), 3.03–2.91 (m, 3H, H-1a, H-1″a, H-1″b), 2.50 (t, J = 11.5 Hz, 1H, H-1b), 1.92 (t, J = 5.5 Hz, 1H, H-2″), 0.92 (d, J = 6.5 Hz, 3H, 3″a-CH_3), 0.90 (d, J = 6.5 Hz, 3H, 3″b-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 147.1, 138.3, 137.1, 128.9, 128.3, 128.0, 126.2 111.1, 72.5, 57.8, 55.3, 53.9, 52.0, 38.7, 26.7, 19.8, 19.6; LC-MS (ESI) [M + H]$^+$ *m/z* 408.3.

*4.1.17. N-((2R, 3S)-3-amino-2-hydroxy-4-phenylbutyl)-4-methoxy-N-propylbenzenesulfonamide (**26**)*

Compound **18** was exposed to trifluoroacetic acid at 0–25 °C for 3 h to remove the BOC-group and afforded the corresponding amine **26** in yield of 88% as white amorphous solid as described for **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 7.5 Hz, 2H, H-2‴, H-6‴), 7.30–7.22 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.98 (d, J = 7.5 Hz, 2H, H-3‴, H-5‴), 3.87 (s, 3H, 4‴-OCH_3), 3.81 (s, 1H, H-3), 3.27–3.20 (m, 3H, H-2, H-4a, H-4b), 3.15–3.05 (m, 2H, H-1a, H-1b), 2.99 (d, J = 13.5 Hz, 1H, H-1″a), 2.60–2.51 (m, 1H, H-1″b), 1.55 (d, J = 6.0 Hz, 2H, H-2″a, H-2″b), 0.85 (t, J = 6.5 Hz, 3H, 3″-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 138.4, 130.6, 129.4, 129.3, 128.7, 126.6, 114.3, 72.4, 55.6, 55.5, 52.1, 51.4, 38.2, 21.9, 11.2; LC-MS (ESI) [M + H]$^+$ *m/z* 393.3.

*4.1.18. N-((2R, 3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-cyclopropyl-4-methoxybenzenesulfonamide (**27**)*

Compound **19** was exposed to trifluoroacetic acid at 25 °C for 3 h to remove the BOC-group and afforded the corresponding amine **27** in yield of 75% as white amorphous solid as described for **21**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.80 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.32–7.20 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 7.10 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 3.96–3.93 (m, 1H, H-3), 3.88 (s, 3H, 4‴-OCH_3), 3.43 (dd, J = 14.0, 4.0 Hz, 1H, H-2), 3.16–3.09 (m, 2H, H-1a, H-1b), 3.02 (dd, J = 13.5, 4.5 Hz, 1H, H-4a), 2.56 (dd, J = 13.5, 9.5 Hz, 1H, H-4b), 2.04–1.93 (m, 1H, H-1″), 0.97–0.84 (m, 2H, H-2″a, H-3″a), 0.74–0.67 (m, 1H, H-2″b), 0.67–0.58 (m, 1H, H-3″b); ^{13}C NMR (101 MHz, CD_3OD) δ 164.8, 140.2, 131.1, 130.6, 130.5, 129.7, 127.5, 115.3, 72.9, 57.0, 56.2, 55.2, 38.7, 33.1, 8.58, 7.53; LC-MS (ESI) [M + H]$^+$ *m/z* 391.3.

*4.1.19. N-((2R, 3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isopropyl-4-methoxybenzenesulfonamide (**28**)*

Compound **20** was exposed to trifluoroacetic acid at 25 °C for 3 h to remove the BOC-group and afforded the corresponding amine **28** in yield of 85% as white amorphous solid as described for **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 7.0 Hz, 2H, H-2‴, H-6‴), 7.30–7.21 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.97 (d, J = 7.0 Hz, 2H, H-3‴, H-5‴), 4.08 (t, J = 5.5 Hz, 1H, H-3), 3.88 (s, 1H, H-2), 3.86 (s, 3H, 4‴-OCH_3), 3.36 (d, J = 15.0 Hz, 1H, H-4a), 3.24–3.16 (m, 2H, H-1a, H-4b), 3.05 (d, J = 13.5 Hz, 1H, H-1b), 2.60 (t, J = 11.5 Hz, 1H, H-

1″), 1.04 (d, J = 4.5 Hz, 3H, 2″a-CH_3), 1.01 (d, J = 4.5 Hz, 3H, 2″b-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 138.6, 131.5, 129.4, 128.7, 126.7, 114.4, 73.9, 56.0, 55.6, 50.3, 45.7, 38.4, 21.4, 20.5; LC-MS (ESI) $[M + H]^+$ m/z 393.5.

*4.1.20. 3-(3, 4-Dihydroxyphenyl)propanoic acid (**32**)*

To a solution of (*E*)-3-(3, 4-dihydroxyphenyl)acrylic acid (**29**, 0.50 g, 2.78 mmol) in CH_3OH (4 mL) was added 10% Pd/C (0.05 g). The mixture was stirred at 25 °C under a 50 psi hydrogen pressure for 3 h. The reaction mixture was filtered over Celite and washed with CH_3OH. Removal of solvent under reduced pressure, followed by column chromatography on silica gel (12% CH_3OH in CH_2Cl_2 as the eluent) afforded the corresponding aromatic amine (0.48 g, 95%) as pale yellow amorphous solid: ^{1}H NMR (500 MHz, CD_3OD) δ 6.67–6.64 (m, 2H, H-2′, H-5′), 6.52 (d, J = 7.0 Hz, 1H, H-6′), 2.75 (t, J = 7.5 Hz, 2H, H-3a, H-3b), 2.52 (t, J = 7.5 Hz, 2H, H-2a, H-2b); ^{13}C NMR (101 MHz, CD_3OD) δ 177.0, 146.2, 144.6, 133.8, 120.5, 116.4, 116.3, 37.2, 31.5; LC-MS (ESI) $[M - H]^-$ m/z 181.4.

*4.1.21. 3-(4-Hydroxy-3-methoxyphenyl)propanoic acid (**33**)*

The compound was obtained by (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylic acid (**30**) via reduction reaction under the condition of hydrogen and 10% Pd/C in 92% yield (white amorphous solid) as described for **32**: ^{1}H NMR (500 MHz, CD_3OD) δ 6.78 (s, 1H, H-2′), 6.70 (d, J = 8.0 Hz, 1H, H-5′), 6.64 (d, J = 8.0 Hz, 1H, H-6′), 3.81 (s, 3H, 3′-OCH_3), 2.82 (t, J = 7.5 Hz, 2H, H-3a, H-3b), 2.55 (t, J = 7.5 Hz, 2H, H-2a, H-2b); ^{13}C NMR (101 MHz, CD_3OD) δ 177.0, 148.8, 145.8, 133.7, 121.6, 116.1, 113.0, 56.3, 37.1, 31.7; LC-MS (ESI) $[M - H]^-$ m/z 195.4.

*4.1.22. 3-(4-Hydroxy-3, 5-dimethoxyphenyl)propanoic acid (**34**)*

The compound was obtained by (*E*)-3-(4-hydroxy-3, 5-dimethoxyphenyl)acrylic acid (**31**) via reduction reaction under the condition of hydrogen and 10% Pd/C in 94% yield (pale yellow amorphous solid) as described for **32**: ^{1}H NMR (500 MHz, CD_3OD) δ 6.49 (s, 2H, H-2′, H-6′), 3.81 (s, 6H, 3′-OCH_3, 5′-OCH_3), 2.82 (t, J = 7.5 Hz, 2H, H-3a, H-3b), 2.57 (t, J = 7.5 Hz, 2H, H-2a, H-2b); ^{13}C NMR (101 MHz, CD_3OD) δ 176.9, 149.2, 134.8, 133.0, 106.5, 56.7, 37.1, 32.1; LC-MS (ESI) $[M - H]^-$ m/z 225.4.

*4.1.23. (E)-3-(3, 4-dihydroxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl) acrylamide (**35a**)*

N-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI, 0.29 g, 1.5 mmol) and 1-hydroxybenzotriazole (HOBt, 0.15 g, 1.1 mmol) were sequentially added in batches to a stirred solution of (*E*)-3-(3, 4-dihydroxyphenyl)acrylic acid (**29**, 0.18 g, 1.0 mmol) and *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4- methoxybenzenesulfonamide (**21**, 0.43 g, 1.05 mmol) in 3 mL dry DMF at 0 °C under an argon atmosphere. The reaction mixture was stirred for 10 min at 0 °C and additional 1 h at 25 °C. 4-Dimethylaminopyridine (DMAP, 0.024 g, 0.20 mmol) was added and the reaction mixture was stirred for another 2 h at 25 °C. The solvent was removed under reduced pressure. Water (6 mL) was added to the residue and extracted with CH_2Cl_2 (3 × 6 mL). The combined organic layers were dried over Na_2SO_4. Removal of solvent under reduced pressure, followed by column chromatography over silica gel column. Elution with 5% CH_3OH in CH_2Cl_2 gave compound **35a** (0.40 g, 78%) as white amorphous solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.69 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.28–7.21 (m, 5H, H-3′, four of 1-phenyl-H), 7.14 (t, J = 7.0 Hz, 1H, one of 1-phenyl-H), 7.01 (s, 1H, H-2″), 6.94–6.90 (m, 3H, H-5″, H-3‴, H-5‴), 6.77 (d, J = 8.0 Hz, 1H, H-6″), 6.34 (d, J = 15.0 Hz, 1H, H-2′), 4.10 (dd, J = 12.5, 5.0 Hz, 1H, H-3), 3.91 (t, J = 7.0 Hz, 1H, H-2), 3.70 (s, 3H, 4‴-OCH_3), 3.33 (d, J = 14.0 Hz, 1H, H-4a), 3.26 (dd, J = 14.0, 2.6 Hz, 1H, H-4b), 3.10 (dd, J = 13.5, 9.0 Hz, 1H, isobutyl-C$\underline{H}_2$a), 2.85 (dd, J = 13.5, 6.0 Hz, 1H, isobutyl-C$\underline{H}_2$b), 2.76 (dd, J = 13.5, 6.0 Hz, 1H, H-1a), 2.68 (dd, J = 13.5, 11.5 Hz, 1H, H-1b), 2.05–1.99 (m, 1H, isobutyl-C$\underline{H}$), 0.94 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H}_3$), 0.86 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H}_3$); ^{13}C NMR (126 MHz, CD_3OD) δ 168.4, 164.3, 148.4, 146.3, 142.0, 139.6, 130.9, 130.2, 129.8, 128.8, 127.7, 126.7, 121.6, 117.7, 116.0, 114.8, 114.6, 74.4, 59.0, 55.5, 55.0, 54.0, 36.4, 27.5, 20.0; HRMS (ESI) m/z calcd. for $C_{30}H_{35}N_2O_7S$ ($[M - H]^-$): 567.2159, found 567.2175.

*4.1.24. (E)-N-((2S, 3R)-4-((4-amino-N-isobutylphenyl) sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(3,4-dihydroxyphenyl)acrylamide (**35b**)*

The compound was obtained by **29** which was coupled with 4-amino-*N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutylbenzenesulfonamide (**23**) through EDCI/HOBt/DMAP coupling procedure in 75% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.45 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.29–7.21 (m, 5H, H-3′, four of 1-phenyl-H), 7.13 (t, J = 7.0 Hz, 1H, one of 1-phenyl-H), 6.99 (s, 1H, H-2″), 6.88 (d, J = 8.0 Hz, 1H, H-5″), 6.76 (d, J = 8.0 Hz, 1H, H-6″), 6.62 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 6.32 (d, J = 16.0 Hz, 1H, H-2′), 4.14 (t, J = 6.5 Hz, 1H, H-3), 3.90 (t, J = 6.5 Hz, 1H, H-2), 3.32 (d, J = 8.5 Hz, 1H, H-4a), 3.24 (brd, J = 12.0 Hz, 1H, H-4b), 3.01 (dd, J = 13.5, 8.5 Hz, 1H, isobutyl-C$\underline{H}_2$a), 2.88 (dd, J = 15.0, 8.5 Hz, 1H, isobutyl-C$\underline{H}_2$b), 2.77–2.67 (m, 2H, H-1a, H-1b), 2.02–1.95 (m, 1H, isobutyl-C$\underline{H}$), 0.92 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H}_3$), 0.86 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H}_3$); ^{13}C NMR (126 MHz, CD_3OD) δ 169.0, 154.1, 148.9, 146.8, 142.5, 140.1, 130.5, 130.3, 129.2, 128.2, 127.2, 125.7, 122.2, 118.2, 116.5, 115.1, 114.5, 74.7, 59.4, 55.5, 54.5, 36.8, 28.1, 20.6, 20.5; HRMS (ESI) m/z calcd. for $C_{29}H_{34}N_3O_6S$ ($[M - H]^-$): 552.2163, found 552.2191.

*4.1.25. (E)-3-(3, 4-dihydroxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-(methylthio)phenyl)sulfonamido)-1-phenylbutan-2-yl) acrylamide (**35c**)*

The title compound was obtained by **29** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-(methylthio)benzenesulfonamide (**24**) through EDCI/HOBt/DMAP coupling procedure in 76% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.64 (d, J = 7.0 Hz, 2H, H-2‴, H-6‴), 7.28–7.24 (m, 7H, four of 1-phenyl-H, H-3′, H-3‴, H-5‴), 7.14 (s, 1H, one of 1-phenyl-H), 7.01 (s, 1H, H-2″), 6.91 (d, J = 7.5 Hz, 1H, H-5″), 6.77 (d, J = 7.0 Hz, 1H, H-6″), 6.34 (d, J = 15.5 Hz, 1H, H-2′), 4.08 (s, 1H, H-3), 3.90 (s, 1H, H-2), 3.35 (s, 1H, H-4a), 3.25 (d, J = 14.0 Hz, 1H, H-4b), 3.14–3.10 (m, 1H, isobutyl-C$\underline{H}_2$a), 2.85 (dd, J = 13.0, 10.0 Hz, 1H, isobutyl-C$\underline{H}_2$b), 2.77 (d, J = 13.5 Hz, 1H, H-1a), 2.67 (t, J = 12.0 Hz, 1H, H-1b), 2.34 (s, 3H, 4‴-SCH_3), 2.03 (s, 1H, isobutyl-C$\underline{H}$), 0.95 (d, J = 4.5 Hz, 3H, one of isobutyl-C$\underline{H}_3$), 0.86 (d, J = 4.5 Hz, 3H, one of isobutyl-C$\underline{H}_3$); ^{13}C NMR (101 MHz, CD_3OD) δ 168.9, 148.9, 147.4, 146.8, 142.6, 140.1, 135.3, 130.3, 129.3, 129.0, 128.2, 127.2, 126.3, 122.2, 118.1, 116.6, 115.1, 74.9, 59.4, 55.5, 54.4, 37.1, 28.0, 20.5, 14.4; HRMS (ESI) m/z calcd. for $C_{30}H_{35}N_2O_6S_2$ ($[M - H]^-$): 583.1937, found 583.1914.

*4.1.26. (E)-3-(3, 4-dihydroxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-6-methoxypyridine)-3-sulfonamido)-1-phenylbutan-2-yl) acrylamide (**35d**)*

The title compound was obtained by **29** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-6-methoxypyridine-3-sulfonamide (**25**) through EDCI/HOBt/DMAP coupling procedure in 82% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.55 (s, 1H, H-6‴), 7.97 (d, J = 8.5 Hz, 1H, H-2‴), 7.28–7.24 (m, 5H, H-3′, four of 1-phenyl-H), 7.14 (s, 1H, one of 1-phenyl-H), 6.98 (s, 1H, H-2″), 6.88 (d, J = 8.0 Hz, 1H, H-5″), 6.82 (d, J = 8.5 Hz, 1H, H-5‴), 6.75 (d,

J = 7.5 Hz, 1H H-6″), 6.30 (d, J = 15.5 Hz, 1H, H-2′), 4.10 (s, 1H, H-3), 3.89 (s, 3H, 4‴-OCH_3), 3.86 (s, 1H, H-2), 3.37 (d, J = 15.5 Hz, 1H, H-4a), 3.21 (d, J = 14.0 Hz, 1H, H-4b), 3.15−3.11 (m, 1H, isobutyl-CH_2a), 3.04−3.00 (m, 1H, isobutyl-CH_2b), 2.86 (dd, J = 13.0, 3.5 Hz, 1H, H-1a), 2.68 (t, J = 12.0 Hz, 1H, H-1b), 2.02 (s, 1H, isobutyl-CH), 0.93 (d, J = 5.0 Hz, 3H, one of isobutyl-CH_3), 0.87 (d, J = 5.0 Hz, 3H, one of isobutyl-CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 169.1, 167.8, 148.9, 148.5, 146.7, 142.6, 140.0, 139.0, 130.3, 130.1, 129.3, 128.2, 127.2, 122.2, 118.0, 116.4, 115.1, 112.3, 74.2, 58.5, 55.6, 54.7, 53.8, 36.9, 27.9, 205, 20.4; HRMS (ESI) m/z calcd. for $C_{29}H_{34}N_3O_7S$ ([M − H]$^-$): 568.2117, found 568.2094.

4.1.27. (E)-3-(3, 4-dihydroxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((4-methoxy-N-propylphenyl)sulfonamido)-1-phenylbutan-2-yl) acrylamide (**35e**)

The title compound was obtained by **29** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-4-methoxy-*N*-propylbenzenesulfonamide (**26**) through EDCI/HOBt/DMAP coupling procedure in 80% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.70 (d, J = 7.5 Hz, 2H, H-2‴, H-6‴), 7.28−7.23 (m, 5H, H-3′, four of 1-phenyl-H), 7.14 (s, 1H, one of 1-phenyl-H), 7.00 (s, 1H, H-2″), 6.95 (d, J = 7.5 Hz, 2H, H-3‴, H-5‴), 6.89 (d, J = 7.5 Hz, 1H, H-5″), 6.76 (d, J = 7.0 Hz, 1H, H-6″), 6.33 (d, J = 15.5 Hz, 1H, H-2′), 4.14 (s, 1H, H-3), 3.87 (d, J = 8.0 Hz, 1H, H-2), 3.72 (s, 3H, 4‴-OCH_3), 3.36 (d, J = 14.5 Hz, 2H, H-4a, H-4b), 3.24 (d, J = 15.0 Hz, 1H, propyl-1-CH_2a), 3.00 (d, J = 5.5 Hz, 1H, propyl-1-CH_2b), 2.90 (dd, J = 13.5, 9.0 Hz, 1H, H-1a), 2.69 (t, J = 12.0 Hz, 1H, H-1b), 1.61−1.54 (m, 2H, propyl-2-CH_2a, propyl-2-CH_2b), 0.86 (t, J = 6.0 Hz, 3H, propyl-CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 169.0, 164.5, 149.0, 146.8, 142.6, 140.2, 131.8, 130.6, 130.3, 129.3, 128.2, 127.3, 122.2, 118.2, 116.6, 115.4, 115.1, 74.7, 56.1, 55.4, 53.5, 53.2, 36.8, 22.7, 11.5; HRMS (ESI) m/z calcd. for $C_{29}H_{33}N_2O_7S$ ([M − H]$^-$): 553.2008, found 553.2002.

4.1.28. (E)-N-((2S, 3R)-4-((N-cyclopropyl-4-methoxyphenyl) sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(3, 4-dihydroxyphenyl)acrylamide (**35f**)

The title compound was obtained by **29** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-cyclopropyl-4-methoxybenzenesulfonamide (**27**) through EDCI/HOBt/DMAP coupling procedure in 75% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.74 (d, J = 7.5 Hz, 2H, H-2‴, H-6‴), 7.29−7.23 (m, 5H, H-3′, four of 1-phenyl-H), 7.14 (s, 1H, one of 1-phenyl-H), 7.00 (s, 1H, H-2″), 6.97 (d, J = 7.5 Hz, 2H, H-3‴, H-5‴), 6.91 (d, J = 7.5 Hz, 1H, H-5″), 6.77 (d, J = 7.0 Hz, 1H, H-6″), 6.35 (d, J = 15.5 Hz, 1H, H-2′), 4.14 (s, 1H, H-3), 3.99 (s, 1H, H-2), 3.73 (s, 3H, 4‴-OCH_3), 3.37 (d, J = 20.0 Hz, 2H, H-4a, H-4b), 3.26 (s, 1H, cyclopropyl-CH), 2.97−2.92 (m, 1H, H-1a), 2.69 (t, J = 12.0 Hz, 1H, H-1b), 1.03 (s, 1H, cyclopropyl-CH_2a), 0.96 (s, 1H, cyclopropyl-CH_2a'), 0.77 (s, 1H, cyclopropyl-CH_2b), 0.62 (s, 1H, cyclopropyl-CH_2b'); ^{13}C NMR (101 MHz, CD_3OD) δ 168.9, 164.7, 148.9, 146.8, 142.5, 140.2, 131.2, 130.3, 129.7, 129.3, 128.2, 127.2, 122.1, 118.2, 116.5, 115.3 115.1, 74.0, 56.7, 56.1, 55.2, 36.7, 33.8, 9.38, 7.37; HRMS (ESI) m/z calcd. for $C_{29}H_{31}N_2O_7S$ ([M − H]$^-$): 551.1852, found 551.1852.

4.1.29. (E)-3-(3, 4-dihydroxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isopropyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl) acrylamide (**35g**)

The title compound was obtained by **29** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isopropyl-4-methoxybenzenesulfonamide (**28**) through EDCI/HOBt/DMAP coupling procedure in 79% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (s, 1H, 3′-OH), 9.13 (s, 1H, 4′-OH), 8.04 (d, J = 8.0 Hz, 1H, 2-NH), 7.70 (d, J = 7.6 Hz, 2H, H-2‴, H-6‴), 7.26−7.23 (m, 4H, four of 1-phenyl-H), 7.17−7.13 (m, 2H, one of 1-phenyl-H, H-3′), 6.96 (brs, 3H, H-3‴, H-5‴, H-2″), 6.84 (d, J = 7.0 Hz, 1H, H-5″), 6.74 (d, J = 7.0 Hz, 1H, H-6″), 6.38 (d, J = 15.5 Hz, 1H, H-2′), 5.16 (s, 1H, 3-OH), 4.06−3.97 (m, 2H, H-3, H-2), 3.78 (s, 1H, isopropyl-CH), 3.71 (s, 3H, 4‴-OCH_3), 3.24−3.16 (m, 2H, H-4a, H-4b), 2.77 (dd, J = 14.5, 7.5 Hz, 1H, H-1a), 2.61 (t, J = 12.5 Hz, 1H, H-1b), 1.13 (d, J = 4.0 Hz, 3H, one of isopropyl -CH_3), 0.80 (d, J = 4.0 Hz, 3H, one of isopropyl -CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.6, 162.7, 147.8, 146.0, 140.1, 139.6, 131.8, 129.6, 128.4, 126.8, 126.2, 120.9, 118.9, 116.3, 114.7, 114.2, 74.1, 55.9, 53.8, 50.1, 47.2, 35.6, 22.7, 19.6; HRMS (ESI) m/z calcd. for $C_{29}H_{33}N_2O_7S$ ([M − H]$^-$): 553.2008, found 553.2015.

4.1.30. (E)-3-(4-hydroxy-3-methoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)acrylamide (**36a**)

The title compound was obtained by (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylic acid (**30**) which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-methoxybenzenesulfonamide (**21**) through EDCI/HOBt/DMAP coupling procedure in 87% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.69 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.32 (d, J = 16.0 Hz, 1H, H-3′), 7.24−7.21 (m, 4H, four of 1-phenyl-H), 7.15−7.11 (m, 2H, one of 1-phenyl-H, H-2″), 7.03 (d, J = 8.0 Hz, 1H, H-5″), 6.94 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 6.80 (d, J = 8.0 Hz, 1H, H-6″), 6.39 (d, J = 16.0 Hz, 1H, H-2′), 4.11 (dd, J = 12.0, 5.5 Hz, 1H, H-3), 3.90 (d, J = 7.5 Hz, 1H, H-2), 3.87 (s, 3H, 3″-OCH_3), 3.72 (s, 3H, 4‴-OCH_3), 3.34 (d, J = 16.0 Hz, 1H, H-4a), 3.26−3.23 (m, 1H, H-4b), 3.09 (dd, J = 13.5, 9.0 Hz, 1H, isobutyl-CH_2a), 2.86 (dd, J = 15.0, 8.5 Hz, 1H, isobutyl-CH_2b), 2.77 (dd, J = 13.5, 6.0 Hz, 1H, H-1a), 2.68 (dd, J = 13.5, 11.5 Hz, 1H, H-1b), 2.03−2.00 (m, 1H, isobutyl-CH), 0.94 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3), 0.86 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3b); ^{13}C NMR (126 MHz, CD_3OD) δ 168.8, 164.5, 150.0, 149.4, 142.4, 140.1, 131.5, 130.7, 130.3, 129.3, 128.2, 127.2, 123.2, 118.5, 116.6, 115.3, 111.6, 74.8, 59.3, 56.4, 56.1, 55.5, 54.4, 37.0, 28.0, 20.5; HRMS (ESI) m/z calcd. for $C_{31}H_{37}N_2O_7S$ ([M − H]$^-$): 581.2316, found 581.2337.

4.1.31. (E)-N-((2S, 3R)-4-((4-amino-N-isobutylphenyl) sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide (**36b**)

The title compound was obtained by **30** which was coupled with 4-amino-*N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutylbenzenesulfonamide (**23**) through EDCI/HOBt/DMAP coupling procedure in 80% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.46 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.34 (d, J = 16.0 Hz, 1H, H-3′), 7.27−7.20 (m, 4H, four of 1-phenyl-H), 7.13 (t, J = 6.5 Hz, 1H, one of 1-phenyl-H), 7.07 (s, 1H, H-2″), 7.00 (d, J = 8.0 Hz, 1H, H-5″), 6.79 (d, J = 8.0 Hz, 1H, H-6″), 6.63 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 6.39 (d, J = 16.0 Hz, 1H, H-2′), 4.20−4.13 (m, 1H, H-3), 3.92−3.89 (m, 1H, H-2), 3.84 (s, 3H, 3″-OCH_3), 3.38 (d, J = 13.5 Hz, 1H, H-4a), 3.24 (d, J = 13.5 Hz, 1H, H-4b), 3.01 (dd, J = 13.5, 8.5 Hz, 1H, isobutyl-CH_2a), 2.90 (dd, J = 15.0, 8.5 Hz, 1H, isobutyl-CH_2b), 2.78−2.68 (m, 2H, H-1a, H-1b), 2.03−1.97 (m, 1H, isobutyl-CH), 0.92 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3), 0.86 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3); ^{13}C NMR (126 MHz, CD_3OD) δ 168.4, 153.7, 149.4, 148.8, 141.9, 139.7, 130.1, 129.9, 128.8, 127.8, 126.8, 125.3, 122.8, 118.2, 116.1, 114.0, 111.1, 74.3, 59.0, 56.0, 55.1, 54.1, 36.4, 27.7, 20.2, 20.1; HRMS (ESI) m/z calcd. for $C_{30}H_{36}N_3O_6S$ ([M − H]$^-$): 566.2319, found 566.2300.

4.1.32. (E)-3-(4-hydroxy-3-methoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-(methylthio)phenyl)sulfonamido)-1-phenylbutan-2-yl)acrylamide (**36c**)

The title compound was obtained by **30** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-

(methylthio)benzenesulfonamide (**24**) through EDCI/HOBt/DMAP coupling procedure in 85% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, J = 9.0 Hz, 1H, 4″-OH), 7.67 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.33 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 7.27–7.24 (m, 5H, H-3′, four of 1-phenyl-H), 7.17 (dd, J = 8.5, 4.0 Hz, 1H, one of 1-phenyl-H), 7.14 (s, 1H, H-2″), 7.02 (d, J = 8.0 Hz, 1H, H-5″), 6.83 (d, J = 8.0 Hz, 1H, H-6″), 6.48 (d, J = 16.0 Hz, 1H, H-2′), 5.19 (d, J = 6.0 Hz, 1H, 3-OH), 4.03–3.98 (m, 1H, H-3), 3.84 (s, 3H, 3″-OCH_3), 3.73 (d, J = 4.0 Hz, 1H, H-2), 3.33 (s, 1H, H-4a), 3.13 (d, J = 12.0 Hz, 1H, H-4b), 3.08 (dd, J = 13.5, 9.0 Hz, 1H, isobutyl-C$\underline{H}_2$a), 2.79 (dd, J = 15.0, 8.5 Hz, 1H, isobutyl-C$\underline{H}_2$b), 2.73 (dd, J = 13.5, 6.0 Hz, 1H, H-1a), 2.62 (dd, J = 13.5, 11.5 Hz, 1H, H-1b), 2.44 (s, 3H, 4‴-SCH_3), 2.04–1.99 (m, 1H, isobutyl-C$\underline{H}$), 0.90 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H}_3$), 0.82 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H}_3$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.6, 148.8, 148.3, 145.2, 140.0, 139.6, 134.8, 129.5, 128.5, 128.1, 126.8, 126.3, 125.6, 122.0, 119.3, 116.2, 111.2, 73.1, 57.5, 56.0, 53.9, 53.1, 35.6, 26.6, 20.4, 14.2; HRMS (ESI) m/z calcd. for $C_{31}H_{37}N_2O_6S_2$ ([M − H]$^-$): 597.2093, found 597.2091.

4.1.33. (E)-3-(4-hydroxy-3-methoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-6-methoxypyridine)-3-sulfonamido)-1-phenylbutan-2-yl)acrylamide (**36d**)

The title compound was obtained by **30** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-6-methoxypyridine-3-sulfonamide (**25**) through EDCI/HOBt/DMAP coupling procedure in 85% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.60 (d, J = 2.0 Hz, 1H, H-6‴), 8.02 (dd, J = 9.0, 2.0 Hz, 1H, H-2‴), 7.37 (d, J = 15.5 Hz, 1H, H-3′), 7.32–7.26 (m, 4H, four of 1-phenyl-H), 7.19 (t, J = 6.5 Hz, 1H, one of 1-phenyl-H), 7.14 (s, 1H, H-2″), 7.06 (d, J = 8.0 Hz, 1H, H-5″), 6.87 (d, J = 8.5 Hz, 1H, H-5‴), 6.83 (d, J = 8.0 Hz, 1H, H-6″), 6.41 (d, J = 15.5 Hz, 1H, H-2′), 4.17–4.13 (m, 1H, H-3), 3.94 (s, 3H, 3″-OCH_3), 3.92 (s, 3H, 4‴-OCH_3), 3.90 (d, J = 8.0 Hz, 1H, H-2), 3.42 (dd, J = 15.0, 2.0 Hz, 1H, H-4a), 3.26 (dd, J = 14.0, 3.5 Hz, 1H, H-4b), 3.18 (dd, J = 13.5, 8.5 Hz, 1H, isobutyl-C$\underline{H}_2$a), 3.07 (dd, J = 15.0, 9.0 Hz, 1H, isobutyl-C$\underline{H}_2$b), 2.92 (dd, J = 13.5, 6.5 Hz, 1H, H-1a), 2.73 (dd, J = 14.0, 11.0 Hz, 1H, H-1b), 2.13–2.05 (m, 1H, isobutyl-C$\underline{H}$), 0.98 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H}_3$), 0.91 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H}_3$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.5, 165.1, 148.2, 147.7, 146.7, 139.3, 139.0, 138.0, 128.9, 127.9, 126.3, 125.7, 121.5, 118.7, 115.6, 111.0, 110.6, 71.8, 56.0, 55.4, 53.9, 53.4, 51.9, 35.0, 25.9, 19.8; HRMS (ESI) m/z calcd. for $C_{30}H_{36}N_3O_7S$ ([M − H]$^-$): 582.2274, found 582.2262.

4.1.34. (E)-3-(4-hydroxy-3-methoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((4-methoxy-N-propylphenyl)sulfonamido)-1-phenylbutan-2-yl)acrylamide (**36e**)

The title compound was obtained by **30** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-4-methoxy-*N*-propylbenzenesulfonamide (**26**) through EDCI/HOBt/DMAP coupling procedure in 82% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.76 (d, J = 9.0 Hz, 2H, H-2‴, H-6‴), 7.37 (d, J = 16.0 Hz, 1H, H-3′), 7.32–7.26 (m, 4H, four of 1-phenyl-H), 7.19 (t, J = 7.0 Hz, 1H, one of 1-phenyl-H), 7.15 (s, 1H, H-2″), 7.07 (d, J = 8.0 Hz, 1H, H-5″), 7.01 (d, J = 9.0 Hz, 2H, H-3‴, H-5‴), 6.84 (d, J = 8.0 Hz, 1H, H-6″), 6.44 (d, J = 16.0 Hz, 1H, H-2′), 4.22–4.18 (m, 1H, H-3), 3.94–3.89 (m, 4H, H-2, 3″-OCH_3), 3.79 (s, 3H, 4‴-OCH_3), 3.43 (dd, J = 15.0, 3.0 Hz, 1H, H-4a), 3.32–3.27 (m, 2H, H-4b, propyl-1-C$\underline{H}_2$a), 3.08–3.03 (m, 1H, propyl-1-C$\underline{H}_2$b), 2.97 (dd, J = 15.0, 8.5 Hz, 1H, H-1a), 2.75 (dd, J = 14.0, 11.0 Hz, 1H, H-1b), 1.70–1.58 (m, 2H, propyl-2-C$\underline{H}_2$a, propyl-2-C$\underline{H}_2$b), 0.90 (t, J = 7.5 Hz, 3H, propyl-C$\underline{H}_3$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.1, 162.3, 148.3, 147.8, 139.5, 139.0, 130.6, 129.2, 129.1, 128.0, 126.3, 125.8, 121.6, 118.9, 115.7, 114.3, 110.7, 72.4, 55.5, 53.3, 51.6, 50.9, 34.8, 21.0, 11.1; HRMS (ESI) m/z calcd. for $C_{30}H_{35}N_2O_7S$ ([M − H]$^-$): 567.2165, found 567.2161.

4.1.35. (E)-N-((2S, 3R)-4-((N-cyclopropyl-4-methoxyphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide (**36f**)

The title compound was obtained by **30** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-cyclopropyl-4-methoxybenzenesulfonamide (**27**) through EDCI/HOBt/DMAP coupling procedure in 79% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.79 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.37 (d, J = 16.0 Hz, 1H, H-3′), 7.32 (d, J = 7.5 Hz, 2H, two of 1-phenyl-H), 7.27 (t, J = 7.5 Hz, 2H, two of 1-phenyl-H), 7.18 (t, J = 7.5 Hz, 1H, one of 1-phenyl-H), 7.15 (s, 1H, H-2″), 7.07 (d, J = 8.0 Hz, 1H, H-5″), 7.02 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 6.84 (d, J = 8.0 Hz, 1H, H-6″), 6.46 (d, J = 16.0 Hz, 1H, H-2′), 4.23–4.19 (m, 1H, H-3), 4.06–4.03 (m, 1H, H-2), 3.92 (s, 3H, 3″-OCH_3), 3.79 (s, 3H, 4‴-OCH_3), 3.44 (dd, J = 14.5, 3.5 Hz, 1H, H-4a), 3.32 (dd, J = 14.5, 3.0 Hz, 1H, H-4b), 3.02 (s, 1H, cyclopropyl-C$\underline{H}$), 3.01 (dd, J = 14.5, 8.5 Hz, 1H, H-1a), 2.74 (dd, J = 14.0, 11.0 Hz, 1H, H-1b), 1.08–1.05 (m, 1H, cyclopropyl-C$\underline{H}_2$a), 1.01–0.94 (m, 1H, cyclopropyl-C$\underline{H}_2$a'), 0.83–0.78 (m, 1H, cyclopropyl-C$\underline{H}_2$b), 0.69–0.64 (m, 1H, cyclopropyl-C$\underline{H}_2$b'); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.0, 162.4, 148.2, 147.7, 139.5, 138.9, 129.6, 128.9, 128.4, 127.8, 126.3, 125.6, 121.4, 118.8, 115.6, 114.2, 110.6, 71.3, 55.4, 54.8, 52.9, 34.4, 32.0, 8.0, 6.1; HRMS (ESI) m/z calcd. for $C_{30}H_{33}N_2O_7S$ ([M − H]$^-$): 565.2008, found 565.1999.

4.1.36. (E)-3-(4-hydroxy-3-methoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isopropyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)acrylamide (**36g**)

The title compound was obtained by **30** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isopropyl-4-methoxybenzenesulfonamide (**28**) through EDCI/HOBt/DMAP coupling procedure in 79% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.39 (d, J = 16.0 Hz, 1H, H-3′), 7.33 (d, J = 7.5 Hz, 2H, two of 1-phenyl-H), 7.28 (t, J = 7.5 Hz, 2H, two of 1-phenyl-H), 7.19 (d, J = 7.0 Hz, 1H, one of 1-phenyl-H), 7.16 (s, 1H, H-2″), 7.08 (d, J = 8.0 Hz, 1H, H-5″), 6.97 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 6.84 (d, J = 8.0 Hz, 1H, H-6″), 6.48 (d, J = 16.0 Hz, 1H, H-2′), 4.24–4.20 (m, 1H, H-3), 4.15–4.09 (m, 1H, H-2), 4.01 (t, J = 7.0 Hz, 1H, isopropyl-C$\underline{H}$), 3.91 (s, 3H, 3″-OCH_3), 3.76 (s, 3H, 4‴-OCH_3), 3.39 (d, J = 3.0 Hz, 1H, H-4a), 3.31 (d, J = 2.0 Hz, 1H, H-4b), 3.02–2.96 (m, 1H, H-1a), 2.75 (dd, J = 14.0, 11.0 Hz, 1H, H-1b), 1.20 (d, J = 6.5 Hz, 3H, one of isopropyl -C$\underline{H}_3$), 0.94 (d, J = 6.5 Hz, 3H, one of isopropyl -C$\underline{H}_3$); ^{13}C NMR (151 MHz, CD_3OD) δ 168.9, 164.5, 150.1, 149.4, 142.5, 140.3, 132.7, 130.6, 130.4, 129.3, 128.2, 127.2, 123.3, 118.6, 116.6, 115.4, 111.7, 75.7, 56.5, 56.1, 55.5, 51.7, 48.3, 37.2, 22.5, 20.1; HRMS (ESI) m/z calcd. for $C_{30}H_{35}N_2O_7S$ ([M − H]$^-$): 567.2165, found 567.2160.

4.1.37. (E)-3-(4-hydroxy-3, 5-dimethoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)acrylamide (**37a**)

The title compound was obtained by (*E*)-3-(4-hydroxy-3,5-dimethoxyphenyl)acrylic acid (**31**) which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-methoxybenzenesulfonamide (**21**) through EDCI/HOBt/DMAP coupling procedure in 83% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.80 (s, 1H, 4″-OH), 7.93 (d, J = 8.5 Hz, 1H, 2-NH), 7.69 (d, J = 7.5 Hz, 2H, H-2‴, H-6‴), 7.32–7.24 (m, 5H, H-3′, four of 1-phenyl-H), 7.14 (s, 1H, one of 1-phenyl-H), 7.00 (d, J = 7.5 Hz, 2H, H-3‴, H-5‴), 6.85 (s, 2H, H-2″, H-6″), 6.49 (d, J = 15.5 Hz, 1H, H-2′), 5.15 (d, J = 5.0 Hz, 1H, 3-OH), 4.01 (d, J = 4.5 Hz, 1H, H-3), 3.80 (s, 6H, 3″-OCH_3, 5″-OCH_3), 3.73 (s,

4H, H-2, 4‴-OCH_3), 3.32 (d, J = 12.5 Hz, 1H, H-4a), 3.11 (d, J = 13.5 Hz, 1H, H-4b), 3.06–3.01 (m, 1H, isobutyl-CH_2a), 2.77–2.73 (m, 1H, isobutyl-CH_2b), 2.70–2.64 (m, 1H, H-1a), 2.60 (t, J = 12.0 Hz, 1H, H-1b), 1.99 (s, 1H, isobutyl-CH), 0.87 (d, J = 4.5 Hz, 3H, one of isobutyl-CH_3), 0.80 (d, J = 4.5 Hz, 3H, one of isobutyl-CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.5, 162.7, 148.6, 140.0, 139.8, 137.8, 130.7, 129.8, 129.5, 128.5, 126.2, 125.7, 119.7, 114.7, 105.6, 73.1, 57.6, 56.4, 55.9, 53.8, 53.2, 36.2, 35.5, 26.7, 20.5; HRMS (ESI) m/z calcd. for $C_{32}H_{39}N2O_8S$ ([M − H]$^-$): 611.2422, found 611.2398.

4.1.38. (E)-N-((2S, 3R)-4-((4-amino-N-isobutylphenyl) sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(4-hydroxy-3,5-dimethoxyphenyl)acrylamide (**37b**)

The title compound was obtained by **31** which was coupled with 4-amino-*N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutylbenzenesulfonamide (**23**) through EDCI/HOBt/DMAP coupling procedure in 75% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.46 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.32 (d, J = 15.5 Hz, 1H, H-3′), 7.26–7.19 (m, 4H, four of 1-phenyl-H), 7.11 (t, J = 7.0 Hz, 1H, one of 1-phenyl-H), 6.78 (s, 2H, H-2″, H-6″), 6.62 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 6.41 (d, J = 15.5 Hz, 1H, H-2′), 4.19 (m, 1H, H-3), 3.92 (m, 1H, H-2), 3.81 (s, 6H, 3″-OCH_3, 5″-OCH_3), 3.38 (d, J = 12.0 Hz, 1H, H-4a), 3.24 (d, J = 12.0 Hz, 1H, H-4b), 3.00 (dd, J = 13.5, 8.5 Hz, 1H, isobutyl-CH_2a), 2.90 (dd, J = 15.0, 8.5 Hz, 1H, isobutyl-CH_2b), 2.78–2.68 (m, 2H, H-1a, H-1b), 2.03–1.97 (m, 1H, isobutyl-CH), 0.91 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3), 0.85 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3); ^{13}C NMR (151 MHz, CD_3OD) δ 168.2, 153.6, 148.9, 142.0, 139.6, 138.4, 130.0, 129.8, 128.8, 126.7, 126.6, 125.2, 118.4, 114.0, 105.9, 74.2, 58.8, 56.3, 54.9, 53.9, 36.3, 27.6, 20.1, 20.0; HRMS (ESI) m/z calcd. for $C_{31}H_{38}N_3O_7S$ ([M − H]$^-$): 596.2425, found 596.2426.

4.1.39. (E)-3-(4-hydroxy-3, 5-dimethoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-(methylthio)phenyl)sulfonamido)-1-phenylbutan-2-yl)acrylamide (**37c**)

The title compound was obtained by **31** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-(methylthio)benzenesulfonamide (**24**) through EDCI/HOBt/DMAP coupling procedure in 85% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (d, J = 9.0 Hz, 1H, 4″-OH), 7.67 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.33 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 7.28–7.25 (m, 5H, H-3′, four of 1-phenyl-H), 7.18–7.16 (m, 1H, one of 1-phenyl-H), 6.87 (s, 2H, H-2″, H-6″), 6.51 (d, J = 16.0 Hz, 1H, H-2′), 5.20 (d, J = 4.5 Hz, 1H, 3-OH), 4.03–4.01 (m, 1H, H-3), 3.82 (s, 6H, 3″-OCH_3, 5″-OCH_3), 3.73 (brs, 1H, H-2), 3.13 (d, J = 12.0 Hz, 1H, H-4a), 3.10–3.05 (m, 2H, H-4b, isobutyl-CH_2a), 2.79 (dd, J = 15.0, 8.5 Hz, 1H, isobutyl-CH_2b), 2.73 (dd, J = 14.0, 5.5 Hz, 1H, H-1a), 2.62 (dd, J = 13.5, 11.5 Hz, 1H, H-1b), 2.44 (s, 3H, 4‴-SCH_3), 2.05–1.99 (m, 1H, isobutyl-CH), 0.90 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3), 0.82 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.5, 148.6, 145.2, 140.0, 139.9, 137.9, 134.8, 129.5, 128.5, 128.1, 126.3, 125.7, 125.6, 119.7, 105.7, 73.1, 57.5, 56.4, 53.9, 53.1, 35.6, 26.6, 20.4, 14.2; HRMS (ESI) m/z calcd. for $C_{32}H_{39}N_2O_7S_2$ ([M − H]$^-$): 627.2199, found 627.2200.

4.1.40. (E)-3-(4-hydroxy-3, 5-dimethoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-6-methoxypyridine)-3-sulfonamido)-1-phenylbutan-2-yl)acrylamide (**37d**)

The title compound was obtained by **31** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-6-methoxypyridine-3-sulfonamide (**25**) through EDCI/HOBt/DMAP coupling procedure in 82% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (s, 1H, 4″-OH), 8.60 (s, 1H, H-6‴), 8.06 (d, J = 8.5 Hz, 1H, 2-NH), 7.94 (d, J = 9.0 Hz, 1H, H-2‴), 7.27–7.24 (m, 5H, H-3′, four of 1-phenyl-H), 7.17 (d, J = 4.0 Hz, 1H, one of 1-phenyl-H), 6.96 (d, J = 8.5 Hz, 1H, H-5‴), 6.85 (s, 2H, H-2″, H-6″), 6.47 (d, J = 16.0 Hz, 1H, H-2′), 5.17 (d, J = 6.5 Hz, 1H, 3-OH), 4.04–4.02 (m, 1H, H-3), 3.92 (s, 3H, 4‴-OCH_3), 3.82 (s, 6H, 3″-OCH_3, 5″-OCH_3), 3.69 (d, J = 7.0 Hz, 1H, H-2), 3.39 (s, 1H, H-4a), 3.14–3.06 (m, 2H, H-4b, isobutyl-CH_2a), 2.97 (dd, J = 15.0, 8.5 Hz, 1H, isobutyl-CH_2b), 2.83 (dd, J = 13.5, 6.0 Hz, 1H, H-1a), 2.65–2.60 (m, 1H, H-1b), 2.03–1.99 (m, 1H, isobutyl-CH), 0.89 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3), 0.83 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3); ^{3}C NMR (151 MHz, DMSO-d_6) δ 166.1, 165.6, 148.5, 147.3, 139.9, 138.5, 137.8, 129.5, 128.5, 126.3, 125.7, 119.7, 111.5, 105.7, 72.4, 56.5, 56.4, 54.5, 53.9, 52.4, 35.5, 26.5, 20.4, 20.3; HRMS (ESI) m/z calcd. for $C_{31}H_{38}N_3O_8S$ ([M − H]$^-$): 612.2380, found 612.2379.

4.1.41. (E)-3-(4-hydroxy-3, 5-dimethoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((4-methoxy-N-propylphenyl)sulfonamido)-1-phenylbutan-2-yl)acrylamide (**37e**)

The title compound was obtained by **31** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-4-methoxy-*N*-propylbenzenesulfonamide (**26**) through EDCI/HOBt/DMAP coupling procedure in 84% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (d, J = 9.0 Hz, 1H, 4″-OH), 7.73 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.28–7.25 (m, 5H, H-3′, four of 1-phenyl-H), 7.21–7.15 (m, 1H, one of 1-phenyl-H), 7.06 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 6.87 (s, 2H, H-2″, H-6″), 6.51 (d, J = 16.0 Hz, 1H, H-2′), 5.23 (d, J = 6.5 Hz, 1H, 3-OH), 4.07 (d, J = 8.0 Hz, 1H, H-3), 3.82 (s, 6H, 3″-OCH_3, 5″-OCH_3), 3.79 (s, 3H, 4‴-OCH_3), 3.73 (brs, 1H, H-2), 3.38 (brs, 1H, H-4a), 3.27–3.21 (m, 1H, H-4b), 3.12 (d, J = 12.0 Hz, 1H, propyl-1-CH_2a), 2.95 (dt, J = 14.0, 7.0 Hz, 1H, propyl-1-CH_2b), 2.83 (dd, J = 14.5, 8.0 Hz, 1H, H-1a), 2.64 (dd, J = 13.5, 11.5 Hz, 1H, H-1b), 1.56–1.52 (m, 2H, propyl-2-CH_2a, propyl-2-CH_2b), 0.81 (t, J = 7.5 Hz, 3H, propyl-CH_3); ^{3}C NMR (151 MHz, DMSO-d_6) δ 165.0, 162.2, 148.1, 139.5, 139.3, 137.3, 130.6, 129.2, 129.0, 128.0, 125.8, 125.2, 119.3, 114.3, 105.2, 72.4, 55.9, 55.5, 53.2, 51.6, 50.9, 34.7, 21.0, 11.1; HRMS (ESI) m/z calcd. for $C_{30}H_{35}N_2O_7S$ ([M − H]$^-$): 567.2165, found 567.2175.

4.1.42. (E)-N-((2S, 3R)-4-((N-cyclopropyl-4-methoxyphenyl) sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(4-hydroxy-3, 5-dimethoxyphenyl)acrylamide (**37f**)

The title compound was obtained by **31** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-cyclopropyl-4-methoxybenzenesulfonamide (**27**) through EDCI/HOBt/DMAP coupling procedure in 78% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, J = 9.0 Hz, 1H, 4″-OH), 7.75 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.30–7.26 (m, 5H, H-3′, four of 1-phenyl-H), 7.18–7.14 (m, 1H, one of 1-phenyl-H), 7.08 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 6.87 (s, 2H, H-2″, H-6″), 6.53 (d, J = 16.0 Hz, 1H, H-2′), 5.24 (s, 1H, 3-OH), 4.06 (brs, 1H, H-3), 3.87 (brs, 1H, H-2), 3.82 (s, 6H, 3″-OCH_3, 5″-OCH_3), 3.79 (s, 3H, 4‴-OCH_3), 3.40 (d, J = 4.0 Hz, 1H, H-4a), 3.14 (d, J = 12.5 Hz, 1H, H-4b), 2.83 (dd, J = 14.0, 8.0 Hz, 1H, H-1a), 2.67–2.62 (m, 1H, H-1b), 1.97 (brs, 1H, cyclopropyl-CH), 1.03–0.97 (m, 2H, cyclopropyl-CH_2a, cyclopropyl-CH_2a'), 0.76 (d, J = 7.0 Hz, 1H, cyclopropyl-CH_2b), 0.59 (d, J = 7.0 Hz, 1H, cyclopropyl-CH_2b'); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.0, 162.5, 148.1, 139.6, 139.3, 137.3, 129.7, 129.0, 128.6, 127.9, 125.7, 125.2, 119.3, 114.3, 105.2, 71.4, 55.9, 55.5, 54.8, 53.0, 34.5, 32.0, 8.07, 6.15; HRMS (ESI) m/z calcd. for $C_{31}H_{35}N_2O_8S$ ([M − H]$^-$): 595.2114, found 595.2103.

4.1.43. (E)-3-(4-hydroxy-3, 5-dimethoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isopropyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)acrylamide (**37g**)

The title compound was obtained by **31** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isopropyl-4-

methoxybenzenesulfonamide (**28**) through EDCI/HOBt/DMAP coupling procedure in 79% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01 (d, J = 9.0 Hz, 1H, 4″-OH), 7.74 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.29–7.25 (m, 5H, H-3′, four of 1-phenyl-H), 7.17 (t, J = 7.0 Hz, 1H, one of 1-phenyl-H), 7.01 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 6.88 (s, 2H, H-2″, H-6″), 6.55 (d, J = 16.0 Hz, 1H, H-2′), 5.19 (d, J = 6.0 Hz, 1H, 3-OH), 4.10 (d, J = 8.5 Hz, 1H, H-3), 3.98 (dt, J = 13.0, 6.5 Hz, 1H, H-2), 3.82 (s, 7H, isopropyl-C$\underline{H}$, 3″-OC$\underline{H_3}$, 5″-OC$\underline{H_3}$), 3.75 (s, 3H, 4‴-OC$\underline{H_3}$), 3.28 (dd, J = 15.0, 2.5 Hz, 1H, H-4a), 3.20 (d, J = 12.5 Hz, 1H, H-4b), 2.83 (dd, J = 15.0, 8.0 Hz, 1H, H-1a), 2.66 (dd, J = 13.5, 11.5 Hz, 1H, H-1b), 1.15 (d, J = 6.5 Hz, 3H, one of isopropyl-C$\underline{H_3}$), 0.84 (d, J = 6.5 Hz, 3H, one of isopropyl-C$\underline{H_3}$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.0, 162.2, 148.1, 139.6, 139.3, 137.3, 131.5, 129.1, 129.0, 127.9, 125.7, 125.2, 119.3, 114.2, 105.2, 73.4, 55.9, 55.4, 53.2, 49.6, 46.7, 35.0, 22.1, 19.1; HRMS (ESI) m/z calcd. for $C_{31}H_{37}N_2O_8S$ ([M − H]$^-$): 597.2271, found 597.2298.

4.1.44. 3-(3, 4-Dihydroxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl) propanamide (**38a**)

The title compound was obtained by 3-(3, 4-dihydroxyphenyl) propanoic acid (**32**) which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-methoxybenzenesulfonamide (**21**) through EDCI/HOBt/DMAP coupling procedure in 77% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.28 (t, J = 7.5 Hz, 2H, two of 1-phenyl-H), 7.24–7.19 (m, 3H, three of 1-phenyl-H), 7.10 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 6.63 (d, J = 8.0 Hz, 1H, H-5″), 6.61 (s, 1H, H-2″), 6.44 (d, J = 8.0 Hz, 1H, H-6″), 4.07–4.03 (m, 1H, H-3), 3.89 (s, 3H, 4‴-OC$\underline{H_3}$), 3.79 (t, J = 6.0 Hz, 1H, H-2), 3.31 (d, J = 2.5 Hz, 1H, H-4a), 3.17 (dd, J = 14.0, 3.5 Hz, 1H, H-4b), 3.04 (dd, J = 13.5, 8.0 Hz, 1H, isobutyl-C$\underline{H_2}$a), 2.97 (dd, J = 15.0, 8.5 Hz, 1H, isobutyl-C$\underline{H_2}$b), 2.90 (dd, J = 13.5, 7.0 Hz, 1H, H-1a), 2.65 (dd, J = 13.5, 11.0 Hz, 1H, H-1b), 2.60–2.50 (m, 2H, H-3′), 2.36–2.25 (m, 2H, H-2′), 2.05–1.97 (m, 1H, isobutyl-C$\underline{H}$), 0.94 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H_3}$), 0.90 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H_3}$); ^{13}C NMR (151 MHz, CD_3OD) δ 175.4, 164.7, 146.4, 144.8, 140.2, 133.9, 132.2, 130.8, 130.6, 129.4, 127.4, 120.6, 116.6, 116.5, 115.6, 74.2, 59.2, 56.4, 55.5, 54.3, 39.5, 36.8, 32.5, 28.3, 20.7, 20.6; HRMS (ESI) m/z calcd. for $C_{30}H_{37}N_2O_7S$ ([M − H]$^-$): 569.2321, found 569.2316.

4.1.45. N-((2S, 3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(3, 4-dihydroxyphenyl) propanamide (**38b**)

The title compound was obtained by **32** which was coupled with 4-amino-*N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutylbenzenesulfonamide (**23**) through EDCI/HOBt/DMAP coupling procedure in 75% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.49 (d, J = 7.0 Hz, 2H, H-2‴, H-6‴), 7.25–7.18 (m, 5H, 1-phenyl-H), 6.71 (d, J = 7.0 Hz, 2H, H-3‴, H-5‴), 6.62 (d, J = 7.5 Hz, 1H, H-5″), 6.59 (s, 1H, H-2″), 6.43 (d, J = 7.0 Hz, 1H, H-6″), 4.04 (s, 1H, H-3), 3.78 (s, 1H, H-2), 3.29–3.24 (m, 1H, H-4a), 3.16 (d, J = 13.0 Hz, 1H, H-4b), 2.94 (dd, J = 18.5, 9.5 Hz, 1H, isobutyl-C$\underline{H_2}$a), 2.89–2.85 (m, 1H, isobutyl-C$\underline{H_2}$b), 2.84–2.80 (m, 1H, H-1a), 2.65–2.60 (m, 1H, H-1b), 2.54 (dd, J = 18.5, 8.0 Hz, 2H, H-3′), 2.29 (d, J = 6.0 Hz, 2H, H-2′), 1.97 (s, 1H, isobutyl-C$\underline{H}$), 0.92 (d, J = 4.5 Hz, 3H, one of isobutyl-C$\underline{H_3}$), 0.88 (d, J = 4.5 Hz, 3H, one of isobutyl-C$\underline{H_3}$); ^{13}C NMR (101 MHz, CD_3OD) δ 175.2, 154.3, 146.2, 144.6, 140.0, 133.8, 130.5, 130.4, 129.2, 127.2, 125.8, 120.4, 116.4, 116.3, 114.4, 74.2, 59.4, 55.3, 54.4, 39.4, 36.7, 32.3, 28.2, 20.6, 20.5; HRMS (ESI) m/z calcd. for $C_{29}H_{36}N_3O_6S$ ([M − H]$^-$): 554.2325, found 554.2317.

4.1.46. 3-(3, 4-Dihydroxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-(methylthio)phenyl)sulfonamido)-1-phenylbutan-2-yl) propanamide (**38c**)

The title compound was obtained by **32** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-(methylthio)benzenesulfonamide (**24**) through EDCI/HOBt/DMAP coupling procedure in 78% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.73 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.41 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 7.27 (t, J = 7.5 Hz, 2H, two of 1-phenyl-H), 7.23–7.18 (m, 3H, three of 1-phenyl-H), 6.63 (d, J = 8.0 Hz, 1H, H-5″), 6.61 (s, 1H, H-2″), 6.44 (d, J = 7.0 Hz, 1H, H-6″), 4.06–4.02 (m, 1H, H-3), 3.80–3.77 (m, 1H, H-2), 3.32 (d, J = 2.5 Hz, 1H, H-4a), 3.16 (dd, J = 14.0, 3.5 Hz, 1H, H-4b), 3.05 (dd, J = 13.5, 8.0 Hz, 1H, isobutyl-C$\underline{H_2}$a), 2.99 (dd, J = 15.0, 8.5 Hz, 1H, isobutyl-C$\underline{H_2}$b), 2.92 (dd, J = 13.5, 7.0 Hz, 1H, H-1a), 2.67–2.62 (m, 1H, H-1b), 2.58 (dd, J = 13.5, 6.5 Hz, 1H, H-3′a), 2.54 (s, 3H, 4‴-SC$\underline{H_3}$), 2.51 (d, J = 8.5 Hz, 1H, H-3′b), 2.34–2.28 (m, 2H, H-2′), 2.04–1.99 (m, 1H, isobutyl-C$\underline{H}$), 0.94 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H_3}$), 0.90 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H_3}$); ^{13}C NMR (151 MHz, CD_3OD) δ 175.3, 147.4, 146.2, 144.6, 140.0, 136.2, 133.8, 130.4 129.3, 128.9, 127.3, 126.5, 120.5, 116.4, 74.0, 58.9, 55.4, 54.1, 39.4, 36.7, 32.4, 28.1, 20.6, 20.5, 14.7; HRMS (ESI) m/z calcd. for $C_{30}H_{37}N_2O_6S_2$ ([M − H]$^-$): 585.2093, found 585.2079.

4.1.47. 3-(3, 4-Dihydroxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-6-methoxypyridine)-3-sulfonamido)-1-phenylbutan-2-yl) propanamide (**38d**)

The title compound was obtained by **32** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-6-methoxypyridine-3-sulfonamide (**25**) through EDCI/HOBt/DMAP coupling procedure in 80% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.57 (d, J = 2.0 Hz, 1H, H-6‴), 7.99 (dd, J = 9.0, 2.0 Hz, 1H, H-2‴), 7.23 (t, J = 7.5 Hz, 2H, two of 1-phenyl-H), 7.18–7.14 (m, 3H, three of 1-phenyl-H), 6.90 (d, J = 9.0 Hz, 1H, H-5‴), 6.59 (d, J = 8.0 Hz, 1H, H-5″), 6.57 (s, 1H, H-2″), 6.40 (d, J = 8.0 Hz, 1H, H-6″), 3.99 (d, J = 11.0 Hz, 1H, H-3), 3.96 (s, 3H, 4‴-OC$\underline{H_3}$), 3.75–3.72 (m, 1H, H-2), 3.27 (d, J = 2.0 Hz, 1H, H-4a), 3.12 (dd, J = 14.0, 3.5 Hz, 1H, H-4b), 3.07–3.00 (m, 2H, isobutyl-C$\underline{H_2}$a, isobutyl-C$\underline{H_2}$b), 2.89 (dd, J = 13.5, 6.5 Hz, 1H, H-1a), 2.64–2.53 (m, 2H, H-3′), 2.49 (dt, J = 14.1, 7.8 Hz, 1H, H-1b), 2.52–2.46 (m, 1H, H-3′b), 2.33–2.21 (m, 2H, H-2′), 2.02–1.95 (m, 1H, isobutyl-C$\underline{H}$), 0.91 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H_3}$), 0.86 (d, J = 6.5 Hz, 3H, one of isobutyl-C$\underline{H_3}$); ^{13}C NMR (151 MHz, CD_3OD) δ 175.3, 167.9, 148.5, 146.2, 144.6, 140.0, 139.1, 133.8, 130.5, 130.4, 129.3, 127.3, 120.5, 116.5, 116.4, 112.5, 73.6, 58.4, 55.4, 54.8, 53.6, 39.4, 36.9, 32.3, 28.0, 20.5; HRMS (ESI) m/z calcd. for $C_{29}H_{36}N_3O_7S$ ([M − H]$^-$): 570.2274, found 570.2288.

4.1.48. 3-(3, 4-Dihydroxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((4-methoxy-N-propylphenyl)sulfonamido)-1-phenylbutan-2-yl) propanamide (**38e**)

The title compound was obtained by **32** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-4-methoxy-*N*-propylbenzenesulfonamide (**26**) through EDCI/HOBt/DMAP coupling procedure in 80% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.97 (s, 1H, 4″-OH), 7.73 (d, J = 7.5 Hz, 2H, H-2‴, H-6‴), 7.23–7.16 (m, 5H, 1-phenyl-H), 7.05 (d, J = 7.5 Hz, 2H, H-3‴, H-5‴), 6.60–6.57 (m, 2H, H-5″, H-2″), 6.40 (d, J = 7.5 Hz, 1H, H-6″), 4.03 (brs, 1H, H-3), 3.84 (s, 3H, 4‴-OC$\underline{H_3}$), 3.73 (brs, 1H, H-2), 3.22–3.11 (m, 3H, H-4a, H-4b, propyl-1-C$\underline{H_2}$a), 3.06–3.00 (m, 1H, propyl-1-C$\underline{H_2}$b), 2.94 (d, J = 10.0 Hz, 1H, H-1a), 2.64–2.59 (m, 1H, H-1b), 2.53 (dd, J = 16.5, 7.5 Hz, 2H, H-3′), 2.32–2.26 (m, 2H, H-2′), 1.56–1.50 (m, 2H, propyl-2-C$\underline{H_2}$a, propyl-2-C$\underline{H_2}$b), 0.84 (s, 3H, propyl-C$\underline{H_3}$); ^{13}C NMR (101 MHz, CD_3OD) δ 175.2, 164.5, 146.2, 144.6, 140.0, 133.7, 132.2, 130.5, 130.4, 129.2,

127.2, 120.4, 116.4, 116.3, 115.4, 73.9, 56.2, 55.2, 53.2, 52.8, 39.3, 36.5, 32.3, 22.7, 11.5; HRMS (ESI) *m/z* calcd. for $C_{29}H_{35}N_2O_7S$ ([M − H]$^-$): 555.2165, found 555.2185.

4.1.49. N-((2S, 3R)-4-((N-cyclopropyl-4-methoxyphenyl) sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(3, 4-dihydroxyphenyl)propanamide (**38f**)

The title compound was obtained by **32** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-cyclopropyl-4-methoxybenzenesulfonamide (**27**) through EDCI/HOBt/DMAP coupling procedure in 75% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.97 (s, 2H, 3″-OH, 4″-OH), 7.77 (d, J = 7.5 Hz, 2H, H-2‴, H-6‴), 7.23−7.15 (m, 5H, 1-phenyl-H), 7.08 (d, J = 7.5 Hz, 2H, H-3‴, H-5‴), 6.58 (d, J = 9.0 Hz, 2H, H-5″, H-2″), 6.40 (d, J = 7.0 Hz, 1H, H-6″), 4.05 (s, 1H, H-3), 3.88 (s, 1H, H-2), 3.85 (s, 3H, 4‴-OCH_3), 3.34−3.31 (m, 1H, H-4a), 3.16 (d, J = 13.5 Hz, 1H, H-4b), 3.01 (d, J = 11.5 Hz, 1H, H-1a), 2.65−2.50 (m, 3H, H-1b, H-3′), 2.28 (d, J = 8.5 Hz, 2H, H-2′), 1.98 (d, J = 4.5 Hz, 1H, cyclopropyl-C<u>H</u>), 0.93 (s, 2H, cyclopropyl-C<u>H</u>$_2$a, cyclopropyl-C<u>H</u>$_2$a'), 0.69 (s, 1H, cyclopropyl-C<u>H</u>$_2$b), 0.62 (s, 1H, cyclopropyl-C<u>H</u>$_2$b'); ^{13}C NMR (101 MHz, CD_3OD) δ 173.7, 163.4, 163.3, 144.8, 143.1, 138.7, 132.3, 129.7, 129.0, 127.8, 125.8, 119.0, 115.0, 114.9, 113.9, 71.7, 54.8, 53.7, 37.9, 35.5, 35.0, 31.7, 30.9, 30.2, 7.24, 6.14; HRMS (ESI) *m/z* calcd. for $C_{29}H_{33}N_2O_7S$ ([M − H]$^-$): 553.2008, found 553.2025.

4.1.50. 3-(3, 4-Dihydroxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isopropyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl) propanamide (**38g**)

The title compound was obtained by **32** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isopropyl-4-methoxybenzenesulfonamide (**28**) through EDCI/HOBt/DMAP coupling procedure in 83% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.97 (s, 1H, 4″-OH), 7.76 (d, J = 7.5 Hz, 2H, H-2‴, H-6‴), 7.22−7.16 (m, 5H, 1-phenyl-H), 7.04 (d, J = 7.5 Hz, 2H, H-3‴, H-5‴), 6.62 (d, J = 7.0 Hz, 1H, H-5″), 6.58 (s, 1H, H-2″), 6.42 (d, J = 7.5 Hz, 1H, H-6″), 4.08 (s, 1H, H-3), 4.03−3.95 (m, 1H, H-2), 3.84 (s, 4H, isopropyl-C<u>H</u>, 4‴-OCH_3), 3.21−3.17 (m, 2H, H-4a, H-4b), 2.97−2.94 (m, 1H, H-1a), 2.64 (t, J = 12.0 Hz, 1H, H-1b), 2.56−2.50 (m, 2H, H-3′), 2.35−2.23 (m, 2H, H-2′), 1.09 (d, J = 4.5 Hz, 3H, one of isopropyl-C<u>H</u>$_3$), 0.93 (d, J = 4.5 Hz, 3H, one of isopropyl-C<u>H</u>$_3$); ^{13}C NMR (101 MHz, CD_3OD) δ 175.3, 164.6, 146.3, 144.7, 140.2, 133.8, 133.1, 130.6, 130.5, 129.3, 127.3, 120.5, 116.5, 116.4, 115.5, 75.1, 56.3, 55.4, 51.5, 48.0, 39.5, 36.8, 32.5, 22.2, 20.4; HRMS (ESI) *m/z* calcd. for $C_{29}H_{35}N_2O_7S$ ([M − H]$^-$): 555.2165, found 555.2172.

4.1.51. 3-(4-Hydroxy-3-methoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl) propanamide (**39a**)

The title compound was obtained by 3-(4-hydroxy-3-methoxyphenyl)propanoic acid (**33**) which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-methoxybenzenesulfonamide (**21**) through EDCI/HOBt/DMAP coupling procedure in 77% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (d, J = 9.0 Hz, 2H, H-2‴, H-6‴), 7.26 (t, J = 7.5 Hz, 2H, two of 1-phenyl-H), 7.23−7.18 (m, 3H, three of 1-phenyl-H), 7.10 (d, J = 9.0 Hz, 2H, H-3‴, H-5‴), 6.73 (s, 1H, H-5″), 6.65 (d, J = 8.0 Hz, 1H, H-6″), 6.55 (d, J = 8.0 Hz, 1H, H-2″), 4.07−4.03 (m, 1H, H-3), 3.89 (s, 3H, 4‴-OCH_3), 3.83 (s, 3H, 3″-OCH_3), 3.80−3.77 (m, 1H, H-2), 3.32 (dd, J = 15.0, 3.0 Hz, 1H, H-4a), 3.17 (dd, J = 14.0, 3.5 Hz, 1H, H-4b), 3.02 (dd, J = 13.5, 8.0 Hz, 1H, isobutyl-C<u>H</u>$_2$a), 2.97 (dd, J = 15.0, 9.0 Hz, 1H, isobutyl-C<u>H</u>$_2$b), 2.89 (dd, J = 13.5, 7.0 Hz, 1H, H-1a), 2.70−2.58 (m, 3H, H-1b, H-3′), 2.39−2.29 (m, 2H, H-2′), 2.04−1.96 (m, 1H, isobutyl-C<u>H</u>), 0.93 (d, J = 6.5 Hz, 3H, one of isobutyl-C<u>H</u>$_3$), 0.89 (d, J = 6.5 Hz, 3H, one of isobutyl-C<u>H</u>$_3$); ^{13}C NMR (151 MHz, CD_3OD) δ 175.3, 164.7, 149.0, 146.0, 140.1, 133.8, 132.2, 130.8, 130.5, 129.4, 127.4, 121.8, 116.3, 115.5, 113.1, 74.2, 59.1, 56.5, 56.3, 55.5, 54.2, 39.4, 36.8, 32.6, 28.3, 20.7, 20.6; HRMS (ESI) *m/z* calcd. for $C_{31}H_{39}N_2O_7S$ ([M − H]$^-$): 583.2478, found 583.2488.

4.1.52. N-((2S, 3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(4-hydroxy-3-methoxyphenyl) propanamide (**39b**)

The title compound was obtained by **33** which was coupled with 4-amino-*N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutylbenzenesulfonamide (**23**) through EDCI/HOBt/DMAP coupling procedure in 75% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.47 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.23−7.13 (m, 5H, 1-phenyl-H), 6.69 (d, J = 7.0 Hz, 3H, H-3‴, H-5‴, H-5″), 6.62 (d, J = 8.0 Hz, 1H, H-6″), 6.51 (d, J = 8.0 Hz, 1H, H-2″), 4.02−4.01 (m, 1H, H-3), 3.77 (s, 3H, 3″-OCH_3), 3.75−3.73 (m, 1H, H-2), 3.25−3.22 (m, 1H, H-4a), 3.15−3.12 (m, 1H, H-4b), 2.93−2.86 (m, 2H, isobutyl-C<u>H</u>$_2$a, isobutyl-C<u>H</u>$_2$b), 2.79 (dd, J = 13.5, 7.0 Hz, 1H, H-1a), 2.66−2.54 (m, 3H, H-1b, H-3′), 2.35−2.25 (m, 2H, H-2′), 1.96−1.90 (m, 1H, isobutyl-C<u>H</u>), 0.89 (d, J = 6.5 Hz, 3H, one of isobutyl-C<u>H</u>$_3$), 0.85 (d, J = 6.5 Hz, 3H, one of isobutyl-C<u>H</u>$_3$); ^{13}C NMR (126 MHz, CD_3OD) δ 174.1, 153.3, 147.8, 144.8, 139.0, 132.7, 129.5, 129.4, 128.2 126.2, 124.8, 120.6, 115.1, 113.5, 112.0, 73.2, 58.3, 55.3, 54.3, 53.4, 38.3, 35.7, 31.4, 27.2, 19.6, 19.5; HRMS (ESI) *m/z* calcd. for $C_{30}H_{38}N_3O_6S$ ([M − H]$^-$): 568.2476, found 568.2470.

4.1.53. 3-(4-Hydroxy-3-methoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-(methylthio)phenyl)sulfonamido)-1-phenylbutan-2-yl)propanamide (**39c**)

The title compound was obtained by **33** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-(methylthio)benzenesulfonamide (**24**) through EDCI/HOBt/DMAP coupling procedure in 78% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.73 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.41 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 7.26 (t, J = 7.5 Hz, 2H, two of 1-phenyl-H), 7.22−7.18 (m, 3H, three of 1-phenyl-H), 6.73 (s, 1H, H-5″), 6.65 (d, J = 8.0 Hz, 1H, H-6″), 6.55 (d, J = 8.0 Hz, 1H, H-2″), 4.06−4.02 (m, 1H, H-3), 3.82 (s, 3H, 3″-OCH_3), 3.80−3.77 (m, 1H, H-2), 3.31 (d, J = 2.5 Hz, 1H, H-4a), 3.16 (dd, J = 14.0, 3.5 Hz, 1H, H-4b), 3.06−2.96 (m, 2H, isobutyl-C<u>H</u>$_2$a, isobutyl-C<u>H</u>$_2$b), 2.91 (dd, J = 13.5, 7.0 Hz, 1H, H-1a), 2.68−2.60 (m, 3H, H-1b, H-3′), 2.54 (s, 3H, 4‴-SCH_3), 2.37−2.30 (m, 2H, H-2′), 2.04−1.98 (m, 1H, isobutyl-C<u>H</u>), 0.94 (d, J = 6.5 Hz, 3H, one of isobutyl-C<u>H</u>$_3$), 0.90 (d, J = 6.5 Hz, 3H, one of isobutyl-C<u>H</u>$_3$); ^{13}C NMR (151 MHz, CD_3OD) δ 175.2, 148.9, 147.4, 145.9, 140.0, 136.2, 133.7, 130.4, 129.3, 128.9, 127.3, 126.5, 121.7, 116.2, 113.0, 74.0, 58.9, 56.4, 55.4, 54.1, 39.3, 36.7, 32.5, 28.1, 20.5, 14.7; HRMS (ESI) *m/z* calcd. for $C_{31}H_{39}N_2O_6S_2$ ([M − H]$^-$): 599.2250, found 599.2280.

4.1.54. 3-(4-Hydroxy-3-methoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-6-methoxypyridine)-3-sulfonamido)-1-phenylbutan-2-yl)propanamide (**39d**)

The title compound was obtained by **33** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-6-methoxypyridine-3-sulfonamide (**25**) through EDCI/HOBt/DMAP coupling procedure in 80% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.57 (s, 1H, H-6‴), 8.00 (d, J = 8.5 Hz, 1H, H-2‴), 7.26−7.12 (m, 5H, 1-phenyl-H), 6.91 (d, J = 8.5 Hz, 1H, H-5‴), 6.69 (s, 1H, H-5″), 6.61 (d, J = 7.0 Hz, 1H, H-6″), 6.52 (d, J = 7.0 Hz, 1H, H-2″), 3.97 (s, 4H, H-3, 4‴-OCH_3), 3.78 (s, 3H, 3″-OCH_3), 3.73 (s, 1H, H-2), 3.26 (s, 1H, H-4a), 3.12 (d, J = 13.5 Hz, 1H, H-4b), 3.06−2.99 (m, 2H, isobutyl-C<u>H</u>$_2$a, isobutyl-C<u>H</u>$_2$b), 2.89 (dd, J = 12.5, 6.0 Hz, 1H, H-1a), 2.63−2.57 (m, 3H, H-1b,

H-3′), 2.36–2.28 (m, 2H, H-2′), 2.03–1.91 (m, 1H, isobutyl-CH), 0.90 (d, J = 5.0 Hz, 3H, one of isobutyl-CH_3), 0.86 (d, J = 5.0 Hz, 3H, one of isobutyl-CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 175.2, 167.8, 148.8, 148.4, 145.8, 139.9, 139.0, 133.7, 130.4, 130.3, 129.3, 127.3, 121.6, 116.1, 112.9, 112.4, 73.6, 58.3, 56.3, 55.4, 54.8, 53.6, 39.3, 36.8, 32.4, 27.9, 20.4; HRMS (ESI) m/z calcd. for $C_{30}H_{38}N_3O_7S$ ([M − H]$^-$): 584.2430, found 584.2443.

*4.1.55. 3-(4-Hydroxy-3-methoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((4-methoxy-N-propylphenyl)sulfonamido)-1-phenylbutan-2-yl) propanamide (**39e**)*

The title compound was obtained by **33** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-4-methoxy-*N*-propylbenzenesulfonamide (**26**) through EDCI/HOBt/DMAP coupling procedure in 80% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.73 (d, J = 7.0 Hz, 2H, H-2‴, H-6‴), 7.22–7.15 (m, 5H, 1-phenyl-H), 7.05 (d, J = 7.0 Hz, 2H, H-3‴, H-5‴), 6.69 (s, 1H, H-5″), 6.61 (d, J = 7.0 Hz, 1H, H-6″), 6.51 (d, J = 7.0 Hz, 1H, H-2″), 4.04 (s, 1H, H-3), 3.84 (s, 3H, 4‴-OCH_3), 3.78 (s, 3H, 3″-OCH_3), 3.73 (s, 1H, H-2), 3.28 (s, 1H, H-4a), 3.14–3.11 (m, 2H, H-4b, propyl-1-CH_2a), 3.05 (d, J = 6.0 Hz, 1H, propyl-1-CH_2b), 2.95 (dd, J = 13.5, 9.5 Hz, 1H, H-1a), 2.69–2.53 (m, 3H, H-1b, H-3′), 2.31 (d, J = 8.0 Hz, 2H, H-2′), 1.57–1.51 (m, 2H, propyl-2-CH_2a, propyl-2-CH_2b), 0.83 (s, 3H, propyl-CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 175.1, 164.5, 148.8, 145.8, 140.0, 133.7, 132.3, 130.5, 130.4, 129.2, 127.2, 121.6, 116.1, 115.4, 112.9, 73.9, 56.3, 56.2, 55.2, 53.2, 52.7, 39.3, 36.5, 32.5, 22.7, 11.5; HRMS (ESI) m/z calcd. for $C_{30}H_{37}N_2O_7S$ ([M − H]$^-$): 569.2321, found 569.2333.

*4.1.56. N-((2S, 3R)-4-((N-cyclopropyl-4-methoxyphenyl) sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(4-hydroxy-3-methoxyphenyl)propanamide (**39f**)*

The title compound was obtained by **33** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-cyclopropyl-4-methoxybenzenesulfonamide (**27**) through EDCI/HOBt/DMAP coupling procedure in 75% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.78 (d, J = 7.0 Hz, 2H, H-2‴, H-6‴), 7.20–7.15 (m, 5H, 1-phenyl-H), 7.08 (d, J = 7.5 Hz, 2H, H-3‴, H-5‴), 6.69 (s, 1H, H-5″), 6.60 (d, J = 7.0 Hz, 1H, H-6″), 6.51 (d, J = 7.5 Hz, 1H, H-2″), 4.05 (s, 1H, H-3), 3.88–3.82 (m, 5H, H-2, H-4a, 4‴-OCH_3), 3.78 (s, 3H, 3″-OCH_3), 3.16 (d, J = 13.5 Hz, 1H, H-4b), 3.00 (dd, J = 12.0, 9.5 Hz, 1H, H-1a), 2.61–2.59 (m, 3H, H-1b, H-3′), 2.39–2.24 (m, 2H, H-2′), 1.98 (s, 1H, cyclopropyl-CH), 0.91 (s, 2H, cyclopropyl-CH_2a, cyclopropyl-CH_2a'), 0.68 (s, 1H, cyclopropyl-CH_2b), 0.61 (s, 1H, cyclopropyl-CH_2b'); ^{13}C NMR (101 MHz, CD_3OD) δ 175.0, 164.7, 148.8, 145.8, 140.1, 133.6, 131.1, 130.5, 130.4, 129.2, 127.2, 121.6, 116.1, 115.3, 112.9, 73.1, 56.3, 56.2, 55.1, 39.2, 36.4, 33.1, 32.5, 8.64, 7.55; HRMS (ESI) m/z calcd. for $C_{30}H_{35}N_2O_7S$ ([M − H]$^-$): 567.2165, found 567.2164.

*4.1.57. 3-(4-Hydroxy-3-methoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isopropyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl) propanamide (**39g**)*

The title compound was obtained by **33** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isopropyl-4-methoxybenzenesulfonamide (**28**) through EDCI/HOBt/DMAP coupling procedure in 83% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.76 (d, J = 7.5 Hz, 2H, H-2‴, H-6‴), 7.21–7.16 (m, 5H, 1-phenyl-H), 7.04 (d, J = 7.5 Hz, 2H, H-3‴, H-5‴), 6.70 (s, 1H, H-5″), 6.65 (d, J = 7.5 Hz, 1H, H-6″), 6.53 (d, J = 7.5 Hz, 1H, H-2″), 4.09 (s, 1H, H-3), 4.02–3.94 (m, 1H, H-2), 3.84 (s, 4H, isopropyl-CH, 4‴-OCH_3), 3.78 (s, 3H, 3″-OCH_3), 3.20 (d, J = 13.5 Hz, 1H, H-4a), 2.97–2.94 (m, 2H, H-4b, H-1a), 2.70–2.55 (m, 3H, H-1b, H-3′), 2.38–2.33 (m, 2H, H-2′), 1.08 (d, J = 5.0 Hz, 3H, one of isopropyl-CH_3), 0.93 (d, J = 5.0 Hz, 3H, one of isopropyl-CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 175.1, 164.5, 148.8, 145.8, 140.1, 133.7, 133.0, 130.5, 130.4, 129.2, 127.2, 121.6, 116.1, 115.4, 112.9, 75.1, 56.3, 56.2, 55.3, 51.4, 47.9, 39.3, 36.7, 32.5, 22.1, 20.3; HRMS (ESI) m/z calcd. for $C_{30}H_{37}N_2O_7S$ ([M − H]$^-$): 569.2321, found 569.2348.

*4.1.58. 3-(4-Hydroxy-3, 5-dimethoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)propanamide (**40a**)*

The title compound was obtained by 3-(4-hydroxy-3,5-dimethoxyphenyl)propanoic acid (**34**) which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-methoxybenzenesulfonamide (**21**) through EDCI/HOBt/DMAP coupling procedure in 80% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.27–7.24 (m, 2H, two of 1-phenyl-H), 7.21–7.18 (m, 3H, three of 1-phenyl-H), 7.09 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 6.44 (s, 2H, H-2″, H-6″), 4.08–4.03 (m, 1H, H-3), 3.88 (s, 3H, 4‴-OCH_3), 3.82 (s, 7H, 3″-OCH_3, 5″-OCH_3, H-2), 3.38 (d, J = 2.5 Hz, 1H, H-4a), 3.15 (dd, J = 14.0, 3.5 Hz, 1H, H-4b), 3.05 (dd, J = 13.5, 8.0 Hz, 1H, isobutyl-CH_2a), 2.96 (dd, J = 15.0, 8.5 Hz, 1H, isobutyl-CH_2b), 2.89 (dd, J = 13.5, 7.0 Hz, 1H, H-1a), 2.71–2.59 (m, 3H, H-1b, H-3′), 2.42–2.31 (m, 2H, H-2′), 2.04–1.96 (m, 1H, isobutyl-CH), 0.93 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3), 0.88 (d, J = 6.5 Hz, 3H, one of isobutyl-CH_3); ^{13}C NMR (151 MHz, CD_3OD) δ 175.1, 164.5, 149.1, 139.9, 134.9, 133.0, 132.0, 130.6, 130.3, 129.2, 127.2, 115.3, 106.5, 74.1, 58.9, 56.7, 56.2, 55.3, 54.0, 39.3, 36.6, 32.9, 28.1, 20.5, 20.4; HRMS (ESI) m/z calcd. for $C_{32}H_{41}N_2O_8S$ ([M − H]$^-$): 613.2584, found 613.2585.

*4.1.59. N-((2S, 3R)-4-((4-amino-N-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(4-hydroxy-3, 5-dimethoxyphenyl) propanamide (**40b**)*

The title compound was obtained by **34** which was coupled with 4-amino-*N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutylbenzenesulfonamide (**23**) through EDCI/HOBt/DMAP coupling procedure in 81% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.46 (d, J = 7.5 Hz, 2H, H-2‴, H-6‴), 7.20–7.16 (m, 5H, 1-phenyl-H), 6.68 (d, J = 7.5 Hz, 2H, H-3‴, H-5‴), 6.40 (s, 2H, H-2″, H-6″), 4.02 (s, 1H, H-3), 3.77 (s, 7H, 3″-OCH_3, 5″-OCH_3, H-2), 3.27 (s, 1H, H-4a), 3.12 (d, J = 14.0 Hz, 1H, H-4b), 2.95–2.85 (m, 2H, isobutyl-CH_2a, isobutyl-CH_2b), 2.79 (dd, J = 12.0, 7.0 Hz, 1H, H-1a), 2.63–2.53 (m, 3H, H-1b, H-3′), 2.32 (d, J = 6.0 Hz, 2H, H-2′), 1.98–1.82 (m, 1H, isobutyl-CH), 0.88 (d, J = 4.5 Hz, 3H, one of isobutyl-CH_3), 0.85 (d, J = 4.5 Hz, 3H, one of isobutyl-CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 175.1, 154.4, 149.2, 140.1, 134.9, 133.1, 130.5, 130.4, 129.3, 127.3, 125.9, 114.5, 106.5, 74.4, 59.4, 56.7, 55.4, 54.4, 39.4, 36.7, 33.0, 28.3, 20.7, 20.6; HRMS (ESI) m/z calcd. for $C_{31}H_{40}N_3O_7S$ ([M − H]$^-$): 598.2587, found 598.2590.

*4.1.60. 3-(4-Hydroxy-3, 5-dimethoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-4-(methylthio)phenyl)sulfonamido)-1-phenylbutan-2-yl)propanamide (**40c**)*

The title compound was obtained by **34** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-(methylthio)benzenesulfonamide (**24**) through EDCI/HOBt/DMAP coupling procedure in 78% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.73 (d, J = 8.5 Hz, 2H, H-2‴, H-6‴), 7.41 (d, J = 8.5 Hz, 2H, H-3‴, H-5‴), 7.27–7.24 (m, 2H, two of 1-phenyl-H), 7.21–7.18 (m, 3H, three of 1-phenyl-H), 6.45 (s, 2H, H-2″, H-6″), 4.07–4.03 (m, 1H, H-3), 3.82 (s, 6H, 3″-OCH_3, 5″-OCH_3), 3.79 (d, J = 6.5 Hz, 1H, H-2), 3.39 (d, J = 2.5 Hz, 1H, H-4a), 3.15 (dd, J = 14.0, 3.5 Hz, 1H, H-4b), 3.07 (dd, J = 13.5, 8.0 Hz, 1H, isobutyl-CH_2a), 2.99 (dd, J = 15.0, 8.5 Hz, 1H, isobutyl-CH_2b), 2.92 (dd, J = 13.5, 7.0 Hz, 1H, H-1a), 2.70–2.61 (m, 3H, H-1b, H-3′), 2.54 (s, 3H, 4‴-SCH_3), 2.42–2.31 (m, 2H, H-2′), 2.05–1.97 (m, 1H,

isobutyl-CH), 0.93 (d, $J = 6.5$ Hz, 3H, one of isobutyl-CH_3), 0.89 (d, $J = 6.5$ Hz, 3H, one of isobutyl-CH_3); ^{13}C NMR (151 MHz, CD_3OD) δ 175.2, 149.3, 147.5, 140.0, 136.3, 135.0, 133.0, 130.4, 129.3, 128.9, 127.3, 126.6, 106.6, 74.1, 58.9, 56.8, 55.5, 54.0, 39.4, 36.7, 33.0, 28.1, 20.6, 20.5, 14.7; HRMS (ESI) m/z calcd. for $C_{32}H_{41}N_2O_7S_2$ ([M − H]$^-$): 629.2355, found 629.2358.

4.1.61. 3-(4-Hydroxy-3, 5-dimethoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isobutyl-6-methoxypyridine)-3-sulfonamido)-1-phenylbutan-2-yl)propanamide (**40d**)

The title compound was obtained by **34** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-6-methoxypyridine-3-sulfonamide (**25**) through EDCI/HOBt/DMAP coupling procedure in 80% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H, H-6‴), 8.05 (d, $J = 8.0$ Hz, 1H, H-2‴), 7.77 (d, $J = 8.0$ Hz, 1H, 4″-OH), 7.22−7.15 (m, 5H, 1-phenyl-H), 6.98 (d, $J = 8.0$ Hz, 1H, H-5‴), 6.39 (s, 2H, H-2″, H-6″), 3.92 (s, 3H, 4‴-OCH_3), 3.84 (d, $J = 5.5$ Hz, 1H, H-3), 3.70 (s, 6H, 3″-OCH_3, 5″-OCH_3), 3.59 (s, 1H, H-2), 3.31 (d, $J = 14.5$ Hz, 1H, H-4a), 3.09−3.04 (m, 1H, H-4b), 3.00 (d, $J = 13.5$ Hz, 1H, isobutyl-CH_2a), 2.93 (dd, $J = 12.5$, 10.0 Hz, 1H, isobutyl-CH_2b), 2.80 (d, $J = 13.0$ Hz, 1H, H-1a), 2.54−2.50 (m, 3H, H-1b, H-3′), 2.23−2.20 (m, 2H, H-2′), 1.95 (s, 1H, isobutyl-CH), 0.85 (d, $J = 3.5$ Hz, 3H, one of isobutyl-CH_3), 0.80 (d, $J = 3.5$ Hz, 3H, one of isobutyl-CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.1, 165.5, 147.7, 146.7, 139.2, 137.9, 133.5, 131.2, 129.1, 129.0, 127.8, 125.6, 111.0, 105.3, 71.5, 55.8, 53.9, 53.3, 51.7, 37.6, 35.0, 31.3, 25.9, 19.8, 19.7; HRMS (ESI) m/z calcd. for $C_{31}H_{40}N_3O_8S$ ([M − H]$^-$): 614.2536, found 614.2533.

4.1.62. 3-(4-Hydroxy-3, 5-dimethoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((4-methoxy-N-propylphenyl)sulfonamido)-1-phenylbutan-2-yl)propanamide (**40e**)

The title compound was obtained by **34** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-4-methoxy-*N*-propylbenzenesulfonamide (**26**) through EDCI/HOBt/DMAP coupling procedure in 80% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.73 (d, $J = 7.0$ Hz, 2H, H-2‴, H-6‴), 7.21−7.17 (m, 5H, 1-phenyl-H), 7.06 (d, $J = 7.0$ Hz, 2H, H-3‴, H-5‴), 6.41 (s, 2H, H-2″, H-6″), 4.03 (s, 1H, H-3), 3.85 (s, 3H, 4‴-OCH_3), 3.77 (s, 6H, 3″-OCH_3, 5″-OCH_3), 3.74 (s, 1H, H-2), 3.35 (s, 1H, H-4a), 3.17 (d, $J = 6.0$ Hz, 1H, H-4b), 3.11 (d, $J = 14.0$ Hz, 1H, propyl-1-CH_2a), 3.05 (d, $J = 6.0$ Hz, 1H, propyl-1-CH_2b), 2.94 (dd, $J = 13.0$, 9.5 Hz, 1H, H-1a), 2.69−2.60 (m, 3H, H-1b, H-3′), 2.33 (d, $J = 8.0$ Hz, 2H, H-2′), 1.53 (s, 2H, propyl-2-CH_2a, propyl-2-CH_2b), 0.83 (s, 3H, propyl-CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 175.1, 164.6, 149.2, 140.0, 133.0, 132.3, 130.5, 130.4, 129.2, 127.2, 115.4, 106.5, 74.0, 56.7, 56.2, 55.2, 53.1, 52.7, 39.3, 36.5, 32.9, 22.7, 11.5; HRMS (ESI) m/z calcd. for $C_{31}H_{39}N_2O_8S$ ([M − H]$^-$): 599.2427, found 599.2442.

4.1.63. N-((2S, 3R)-4-((N-cyclopropyl-4-methoxyphenyl) sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-3-(4-hydroxy-3, 5-dimethoxyphenyl)propanamide (**40f**)

The title compound was obtained by **34** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-cyclopropyl-4-methoxybenzenesulfonamide (**27**) through EDCI/HOBt/DMAP coupling procedure in 75% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, $J = 7.5$ Hz, 2H, H-2‴, H-6‴), 7.21−7.15 (m, 5H, 1-phenyl-H), 7.08 (d, $J = 7.5$ Hz, 2H, H-3‴, H-5‴), 6.41 (s, 2H, H-2″, H-6″), 4.04 (s, 1H, H-3), 3.86 (s, 4H, H-2, 4‴-OCH_3), 3.77 (s, 6H, 3″-OCH_3, 5″-OCH_3), 3.35−3.31 (m, 1H, H-4a), 3.14 (d, $J = 14.0$ Hz, 1H, H-4b), 2.99 (dd, $J = 13.0$, 9.0 Hz, 1H, H-1a), 2.70−2.54 (m, 3H, H-1b, H-3′), 2.38−2.32 (m, 2H, H-2′), 1.99 (s, 1H, cyclopropyl-CH), 0.90 (d, $J = 3.0$ Hz, 2H, cyclopropyl-CH_2a, cyclopropyl-CH_2a'), 0.68 (s, 1H, cyclopropyl-CH_2b), 0.61 (s, 1H, cyclopropyl-CH_2b'); ^{13}C NMR (101 MHz, CD_3OD) δ 175.0, 164.8, 149.1, 140.1, 134.9, 132.9, 131.1, 130.6, 130.4, 129.2, 127.2, 115.3, 106.5, 73.2, 56.7, 56.2, 56.1, 55.1, 39.2, 36.4, 33.1, 33.0, 8.67, 7.57; HRMS (ESI) m/z calcd. for $C_{31}H_{37}N_2O_8S$ ([M − H]$^-$): 597.2271, found 597.2267.

4.1.64. 3-(4-Hydroxy-3, 5-dimethoxyphenyl)-N-((2S, 3R)-3-hydroxy-4-((N-isopropyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)propanamide (**40g**)

The title compound was obtained by **34** which was coupled with *N*-((2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isopropyl-4-methoxybenzenesulfonamide (**28**) through EDCI/HOBt/DMAP coupling procedure in 83% yield (white amorphous solid) as described for **35a**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.75 (d, $J = 7.5$ Hz, 2H, H-2‴, H-6‴), 7.20−7.15 (m, 5H, 1-phenyl-H), 7.04 (d, $J = 7.5$ Hz, 2H, H-3‴, H-5‴), 6.41 (s, 2H, H-2″, H-6″), 4.08 (s, 1H, H-3), 4.03−3.93 (m, 1H, H-2), 3.84 (s, 4H, isopropyl-CH, 4‴-OCH_3), 3.78 (s, 6H, 3″-OCH_3, 5″-OCH_3), 3.33 (s, 1H, H-4a), 3.18 (d, $J = 13.5$ Hz, 1H, H-4b), 2.96 (dd, $J = 14.5$, 8.0 Hz, 1H, H-1a), 2.67−2.57 (m, 3H, H-1b, H-3′), 2.41−2.33 (m, 2H, H-2′), 1.08 (d, $J = 5.5$ Hz, 3H, one of isopropyl-CH_3), 0.92 (d, $J = 5.5$ Hz, 3H, one of isopropyl-CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 175.1, 164.5, 149.1, 140.1, 134.9, 133.1, 132.9, 130.5, 130.4, 129.2, 127.2, 115.4, 106.5, 75.1, 56.7, 56.2, 55.4, 51.4, 48.0, 39.3, 36.7, 32.9, 22.1, 20.3; HRMS (ESI) m/z calcd. for $C_{31}H_{39}N_2O_8S$ ([M − H]$^-$): 599.2427, found 599.2434.

4.2. Anti-HIV-1 PR activity assay

The inhibitory effect of all newly designed inhibitors were tested using the method of fluorescence resonance energy transfer (FRET). Peptide (Arg-Glu (EDANS)-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-Lys(-DABCYL)-Arg) purchased from AnaSpec was chosen as the substrate. The energy transfer donor (EDANS) and acceptor (DABCYL) dyes were labeled at two ends of the peptide to perform FRET. Excitation and emission wavelengths were set at 340 nm and 490 nm. Inhibitors were dissolved in DMSO and diluted to appropriate concentrations. HIV-1 PR was cloned and heterologously expressed in *Escherichia coli* and purified. The FRET assay reaction buffer contained 0.1 M sodium acetate, 1 M sodium chloride, 1 mM ethylenediaminetetraacetic acid (EDTA), 1 mM dithiothreitol (DTT), 2% DMSO and 1 mg/mL bovine serum albumin (BSA) with an adjusted pH 4.7. The experiment was carried out in 96-well plates. HIV-1 PR and the inhibitor were mixed and incubated for 20−30 min at room temperature and then the substrate was added. Each reaction was recorded for about 10 min.

4.3. Anti-HIV-1 RT activity assay

The activity of HIV-1 reverse transcriptase (RT) assay *in vitro* was exploited on a novel one-step RT-PCR assay [37]. HIV-1 RT was derived from clone HIV_{NL4-3} and belonged to Group B of HIV-1, which was a gift from Ying Guo (Institute of Materia Medica, PUMC). HIV-1 RT were used in the first step of Real-time PCR reaction for converting RNA to DNA. Real-time PCR reaction was performed using a one-step RT-PCR Kit (Takara, RR066A) according to the manual from the manufacturer. Each reaction mixture had a total volume of 20 μL, comprising 2X reaction buffer 10 μL, random mRNA 20 ng (template), GAPDH primers 10 μM (primer), compounds 1 μL at different concentrations, Ex Taq HS (polymerase) and HIV-1 RT. The amount of RT per reaction was approximately 5 ng, which was equivalent to 100 mU. All the components were added under an ice-cold condition. Primer sequence was as followed: GAPDH-forward: GAAGGTGAAGGTCGGAGT; GAPDH-reverse: GAAGATGGTGATGGGATTTC. We used a conventional real-time PCR machine (Agilent Mx3000P) to measure the fluorescence. QRT-PCR cycles consisting of 42 °C for 5 min, 95 °C for 10 s

and 60 °C for 60 s for 40 rounds were used. The results were normalized using the DMSO group levels and calculated by the $2^{-\triangle\triangle Ct}$ comparative method.

4.4. Infectivity assay on HIV-1 late stage

The inhibitory effect of compounds on HIV-1 infectivity were determined using a single-round HIV-1 infectivity assay [38]. 293T cells were co-transfected with either plasmid pNL4-3-E$^-$R$^-$ (pHIV-1_{NL4-3}) or DRV-resistant pNL4-3-E$^-$R$^-$ variants (pHIV-1^R_{DRVS}) and pHCMV-G (VSV-G) to produce VSV-G pseudotyped HIV-1. Inhibitors dissolved in dimethylsulfoxide and diluted to appropriate concentrations. Then they were added into culture medium for 5 h of post-transfection. After incubating for 48 h at 37 °C, pseudotyped viruses in 10 μL of supernatant were used to infect SupT1 cells for 48 h, followed by measuring luciferase activity of newly infected cells using Centro LB960 (Berthold).

4.5. Infectivity assay on HIV-1 early stage

To assess the effect of the compounds on HIV-1 infectivity, experiments were carried out using VSVG-pseudotyped HIV-1. SupT1 cells (1×10^5/mL) were infected with VSVG-pseudotyped HIV-1(NL4-3) in 96-well plates, and then the compounds were added at the concentration of 10 μM. Equal volumes of DMSO were added into the culture medium, in order to keep constant final DMSO concentration as 1% (v/v). After 48 h, SupT1 cells were lysed and firefly luciferase activities were determined using a firefly Luciferase Assay System (Promega).

4.6. Molecular modeling

The molecular modeling work for inhibitors **38a**, **38c** and **38d** were performed in the molecular modeling software Molecular Operating Environment (MOE) [42]. The HIV-1 protease crystal structure (PDB-ID: 4mc9) and reverse transcriptase crystal structure (PDB-ID: 2yng) were both obtained from protein data bank website (www.pdb.org). In general, the docking was performed through "DOCK" module in MOE using the alpha triangle placement method. Refinement of the docked poses was carried out using the Forcefield refinement scheme and scored using both the affinity dG and london dG scoring system.

Before docking, preparation procedures were needed for both receptors and inhibitors. The proteins were examined for missing atoms, bonds and contacts, meanwhile ionization states and hydrogen positions were assigned with the "Protonate-3D" tool in the MOE suite. The water molecules farther than 4.5 Å from the ligand or protein were also deleted. Then the structures were subjected to energy minimization with Amber99 force field until the root mean square (RMS) gradient fell below 0.1 cal mol^{-1} Å^{-1}, to minimize contacts among hydrogen atoms. After the protein preparation step, the coordinates of the binding site were determined by MOE Site Finder module based on the co-crystallized ligand and saved as dummy atoms. The ligand structures with stereochemistry were generated by Chemdraw 18.0. Then the hydrogen atoms were added and protonation state (pH 7.0) was assigned. All ligand structures were energy minimized with MMFF94x force field. After optimization, the ligands were positioned into binding site (dummy atoms) of receptors using Dock module in MOE software. The triangle matcher and induced fit were applied as the placement and refinement method, with London dG as initial scoring function and GBVI/WSA dG as the final scoring function. Before the molecular docking for our compounds, we used the ligand that complexed with the proteins (both HIV-1 PR and RT) to verify the docking protocol. As results, for PR (PDB-ID: 4mc9), the highest score is −11.75 kcal/mol, the value of RMSD between the pose with highest score and the structure in crystal complex is 1.92 Å. As for RT (PDB-ID: 2yng), the value of RMSD between the pose with highest score (−12.25 kcal/mol) and the structure in crystal complex is 2.00 Å. Thus, the docking results for both PR and RT are consistent to the crystal structures, and the docking protocol is suitable for the systems.

Notes

The authors declare no competing financial interest.

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.

Acknowledgments

This work was supported by National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program", China (2019ZX09201001-003-007 and 2019ZX09721001-004-006), Natural Science Foundation of Zhejiang Province (LY21B020006), CAMS Innovation Fund for Medical Sciences (CIFMS 2016-I2M-1−011 and 2018-I2M-3−004) and The National Mega-Project for Infectious Disease (2018ZX10301408).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2021.113498.

References

[1] J.S.G. Montaner, V.D. Lima, R. Barrios, B. Yip, E. Wood, T. Kerr, K. Shannon, P.R. Harrigan, R.S. Hogg, P. Daly, P. Kendall, Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study, Lancet 376 (2010) 532−539.
[2] P. Braitstein, M.W.G. Brinkhof, F. Dabis, M. Schechter, A. Boulle, P. Miotti, R. Wood, C. Laurent, E. Sprinz, C. Seyler, D.R. Bangsberg, E. Balestre, J.A.C. Sterne, M. May, M. Egger, Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries, Lancet 367 (2006) 817−824.
[3] J.A. Este, T. Cihlar, Current status and challenges of antiretroviral research and therapy, Antivir. Res. 85 (2010) 25−33.
[4] E. De Clercq, Antiretroviral drugs, Curr. Opin. Pharmacol. 10 (2010) 507−515.
[5] E. De Clercq, Chapter nine - the nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors in the treatment of HIV infections (AIDS), in: E. De Clercq (Ed.), Advances in Pharmacology, Academic Press, 2013, pp. 317−358.
[6] E. De Clercq, Dancing with chemical formulae of antivirals: a personal account, Biochem. Pharmacol. 86 (2013) 711−725.
[7] M.H. Manyeruke, T.O. Olomola, S. Majumder, S. Abrahams, M. Isaacs, N. Mautsa, S. Mosebi, D. Mnkandhla, R. Hewer, H.C. Hoppe, R. Klein, P.T. Kaye, Synthesis and evaluation of 3-hydroxy-3-phenylpropanoate ester-AZT conjugates as potential dual-action HIV-1 Integrase and Reverse Transcriptase inhibitors, Bioorg. Med. Chem. 23 (2015) 7521−7528.
[8] G. Cuzzucoli Crucitti, M. Metifiot, L. Pescatori, A. Messore, V.N. Madia, G. Pupo, F. Saccoliti, L. Scipione, S. Tortorella, F. Esposito, A. Corona, M. Cadeddu, C. Marchand, Y. Pommier, E. Tramontano, R. Costi, R. Di Santo, Structure-activity relationship of pyrrolyl diketo acid derivatives as dual inhibitors of HIV-1 integrase and reverse transcriptase ribonuclease H domain, J. Med. Chem. 58 (2015) 1915−1928.
[9] L. Pescatori, M. Metifiot, S. Chung, T. Masoaka, G. Cuzzucoli Crucitti, A. Messore, G. Pupo, V.N. Madia, F. Saccoliti, L. Scipione, S. Tortorella, F.S. Di Leva, S. Cosconati, L. Marinelli, E. Novellino, S.F. Le Grice, Y. Pommier, C. Marchand, R. Costi, R. Di Santo, N-Substituted quinolinonyl diketo acid derivatives as HIV integrase strand transfer inhibitors and their activity against RNase H function of reverse transcriptase, J. Med. Chem. 58 (2015) 4610−4623.
[10] L. Sun, P. Gao, G. Dong, X. Zhang, X. Cheng, X. Ding, X. Wang, D. Daelemans, E. De Clercq, C. Pannecouque, L. Menendez-Arias, P. Zhan, X. Liu, 5-

Hydroxypyrido[2,3-b]pyrazin-6(5H)-one derivatives as novel dual inhibitors of HIV-1 reverse transcriptase-associated ribonuclease H and integrase, Eur. J. Med. Chem. 155 (2018) 714–724.
[11] Y. Sun, W. Xu, N. Fan, X. Sun, X. Ning, L. Ma, J. Liu, X. Wang, Design, synthesis and biological evaluation of (E)-3,4-dihydroxystyryl 4-acylaminophenethyl sulfone, sulfoxide derivatives as dual inhibitors of HIV-1 CCR5 and integrase, Bioorg. Med. Chem. 25 (2017) 1076–1084.
[12] A. Corona, V. Onnis, A. Deplano, G. Bianco, M. Demurtas, S. Distinto, Y.C. Cheng, S. Alcaro, F. Esposito, E. Tramontano, Design, synthesis and antiviral evaluation of novel heteroarylcarbothioamide derivatives as dual inhibitors of HIV-1 reverse transcriptase-associated RNase H and RDDP functions, Pathog. Dis. 75 (2017) ftx078.
[13] T.O. Olomola, R. Klein, K.A. Lobb, Y. Sayed, P.T. Kaye, Towards the synthesis of coumarin derivatives as potential dual-action HIV-1 protease and reverse transcriptase inhibitors, Tetrahedron Lett. 51 (2010) 6325–6328.
[14] T.O. Olomola, R. Klein, N. Mautsa, Y. Sayed, P.T. Kaye, Synthesis and evaluation of coumarin derivatives as potential dual-action HIV-1 protease and reverse transcriptase inhibitors, Bioorg. Med. Chem. 21 (2013) 1964–1971.
[15] S.X. Gu, P. Xue, X.L. Ju, Y.Y. Zhu, Advances in rationally designed dual inhibitors of HIV-1 reverse transcriptase and integrase, Bioorg. Med. Chem. 24 (2016) 5007–5016.
[16] M.S.A. Gill, S.S. Hassan, N. Ahemad, Evolution of HIV-1 reverse transcriptase and integrase dual inhibitors: recent advances and developments, Eur. J. Med. Chem. 179 (2019) 423–448.
[17] F. Esposito, F.A. Ambrosio, R. Maleddu, G. Costa, R. Rocca, E. Maccioni, R. Catalano, I. Romeo, P. Eleftheriou, D.C. Karia, P. Tsirides, N. Godvani, H. Pandya, A. Corona, S. Alcaro, A. Artese, A. Geronikaki, E. Tramontano, Chromenone derivatives as a versatile scaffold with dual mode of inhibition of HIV-1 reverse transcriptase-associated Ribonuclease H function and integrase activity, Eur. J. Med. Chem. 182 (2019) 111617.
[18] M. Zhu, L. Ma, J. Wen, B. Dong, Y. Wang, Z. Wang, J. Zhou, G. Zhang, J. Wang, Y. Guo, C. Liang, S. Cen, Y. Wang, Rational design and Structure-Activity relationship of coumarin derivatives effective on HIV-1 protease and partially on HIV-1 reverse transcriptase, Eur. J. Med. Chem. 186 (2020) 111900.
[19] M.C. Graves, J.J. Lim, E.P. Heimer, R.A. Kramer, An 11-kDa form of human immunodeficiency virus protease expressed in Escherichia coli is sufficient for enzymatic activity, Proc. Natl. Acad. Sci. U. S. A. 85 (1988) 2449–2453.
[20] D.D. Farmerie Wg Fau - Loeb, N.C. Loeb Dd Fau - Casavant, C.A. Casavant Nc Fau - Hutchison 3rd, M.H. Hutchison Ca 3rd Fau - Edgell, R. Edgell Mh Fau - Swanstrom, R. Swanstrom, Expression and processing of the AIDS virus reverse transcriptase in Escherichia coli, Science 236 (1987) 305–308.
[21] A. Brik, C.H. Wong, HIV-1 protease: mechanism and drug discovery, Org. Biomol. Chem. 1 (2003) 5–14.
[22] A.K. Ghosh, H.L. Osswald, G. Prato, Recent progress in the development of HIV-1 protease inhibitors for the treatment of HIV/AIDS, J. Med. Chem. 59 (2016) 5172–5208.
[23] K. Das, S.E. Martinez, J.J. DeStefano, E. Arnold, Structure of HIV-1 RT/dsRNA initiation complex prior to nucleotide incorporation, Proc. Natl. Acad. Sci. U. S. A. 116 (2019) 7308–7313.
[24] J.D. Bauman, D. Patel, C. Dharia, M.W. Fromer, S. Ahmed, Y. Frenkel, R.S.K. Vijayan, J.T. Eck, W.C. Ho, K. Das, A.J. Shatkin, E. Arnold, Detecting allosteric sites of HIV-1 reverse transcriptase by X-ray crystallographic fragment screening, J. Med. Chem. 56 (2013) 2738–2746.
[25] A.K. Ghosh, D.D. Anderson, I.T. Weber, H. Mitsuya, Enhancing protein backbone binding–a fruitful concept for combating drug-resistant HIV, Angew. Chem. Int. Ed. 51 (2012) 1778–1802.
[26] Y. Koh, H. Nakata, K. Maeda, H. Ogata, G. Bilcer, T. Devasamudram, J.F. Kincaid, P. Boross, Y.F. Wang, Y. Tie, P. Volarath, L. Gaddis, R.W. Harrison, I.T. Weber, A.K. Ghosh, H. Mitsuya, Novel bis-tetrahydrofuranylurethane-containing nonpeptidic protease inhibitor (PI) UIC-94017 (TMC114) with potent activity against multi-PI-resistant human immunodeficiency virus in vitro, Antimicrob. Agents Chemother. 47 (2003) 3123–3129.
[27] R. Morphy, Z. Rankovic, Designed multiple ligands. An emerging drug discovery paradigm, J. Med. Chem. 48 (2005) 6523–6543.
[28] C. Tintori, A. Corona, F. Esposito, A. Brai, N. Grandi, E.R. Ceresola, M. Clementi, F. Canducci, E. Tramontano, M. Botta, Inhibition of HIV-1 reverse transcriptase dimerization by small molecules, Chembiochem 17 (2016) 683–688.
[29] A.K. Ghosh, S. Leshchenko, M. Noetzel, Stereoselective photochemical 1,3-dioxolane addition to 5-alkoxymethyl-2(5H)-furanone: synthesis of bis-tetrahydrofuranyl ligand for HIV protease inhibitor UIC-94017 (TMC-114), J. Org. Chem. 69 (2004) 7822–7829.
[30] M. Zhu, L. Ma, H. Zhou, B. Dong, Y. Wang, Z. Wang, J. Zhou, G. Zhang, J. Wang, C. Liang, S. Cen, Y. Wang, Preliminary SAR and biological evaluation of potent HIV-1 protease inhibitors with pyrimidine bases as novel P2 ligands to enhance activity against DRV-resistant HIV-1 variants, Eur. J. Med. Chem. 185 (2020) 111866.
[31] M. Nakano, Y. Sato, Rearrangement of (substituted benzyl)trimethylammonium ylides in a nonbasic medium: the improved Sommelet-Hauser rearrangement, J. Org. Chem. 52 (1987) 1844–1847.
[32] M. Zhu, B. Dong, G.N. Zhang, J.X. Wang, S. Cen, Y.C. Wang, Synthesis and biological evaluation of new HIV-1 protease inhibitors with purine bases as P2-ligands, Bioorg. Med. Chem. Lett 29 (2019) 1541–1545.
[33] E. Matayoshi, G. Wang, G. Krafft, J. Erickson, Novel fluorogenic substrates for assaying retroviral proteases by resonance energy transfer, Science 247 (1990) 954–958.
[34] C. Meier, H.J. Jessen, T. Schulz, L. Weinschenk, F. Pertenbreiter, J. Balzarini, Rational development of nucleoside diphosphate prodrugs: DiPPro-compounds, Curr. Med. Chem. 22 (2015) 3933–3950.
[35] M.A. Perez, P.A. Fernandes, M.J. Ramos, Drug design: new inhibitors for HIV-1 protease based on Nelfinavir as lead, J. Mol. Graph. Model. 26 (2007) 634–642.
[36] A.K. Ghosh, K.V. Rao, P.R. Nyalapatla, H.L. Osswald, C.D. Martyr, M. Aoki, H. Hayashi, J. Agniswamy, Y.F. Wang, H. Bulut, D. Das, I.T. Weber, H. Mitsuya, Design and development of highly potent HIV-1 protease inhibitors with a crown-like oxotricyclic core as the P2-ligand to combat multidrug-resistant HIV variants, J. Med. Chem. 60 (2017) 4267–4278.
[37] K.K. Sharma, F. Przybilla, T. Restle, J. Godet, Y. Mely, FRET-based assay to screen inhibitors of HIV-1 reverse transcriptase and nucleocapsid protein, Nucleic Acids Res. 44 (2016) e74.
[38] J.M. Garcia, A. Gao, P.L. He, J. Choi, W. Tang, R. Bruzzone, O. Schwartz, H. Naya, F.J. Nan, J. Li, R. Altmeyer, J.P. Zuo, High-throughput screening using pseudotyped lentiviral particles: a strategy for the identification of HIV-1 inhibitors in a cell-based assay, Antivir. Res. 81 (2009) 239–247.
[39] A.K. Ganguly, S.S. Alluri, C.-H. Wang, A. Antropow, A. White, D. Caroccia, D. Biswas, E. Kang, L.-K. Zhang, S.S. Carroll, C. Burlein, J. Fay, P. Orth, C. Strickland, Structural optimization of cyclic sulfonamide based novel HIV-1 protease inhibitors to picomolar affinities guided by X-ray crystallographic analysis, Tetrahedron 70 (2014) 2894–2904.
[40] M. Zhu, L. Ma, B. Dong, G. Zhang, J. Wang, J. Zhou, S. Cen, Y. Wang, Synthesis and evaluation of potent human immunodeficiency virus 1 protease inhibitors with epimeric isopropanol as novel P1′ ligands, Future Med. Chem. 12 (2020) 775–794.
[41] D. Kang, Z. Wang, H. Zhang, G. Wu, T. Zhao, Z. Zhou, Z. Huo, B. Huang, D. Feng, X. Ding, J. Zhang, X. Zuo, L. Jing, W. Luo, S. Guma, D. Daelemans, E. Clercq, C. Pannecouque, P. Zhan, X. Liu, Further exploring solvent-exposed tolerant regions of allosteric binding pocket for novel HIV-1 NNRTIs discovery, ACS Med. Chem. Lett. 9 (2018) 370–375.
[42] A.F. Mohammed, S.G. Abdel-Moty, M.A. Hussein, A.A. Abdel-Alim, Design, synthesis and molecular docking of some new 1,2,4-triazolobenzimidazol-3-yl acetohydrazide derivatives with anti-inflammatory-analgesic activities, Arch Pharm. Res. 36 (2013) 1465–1479.