Diversity-Oriented Synthesis of Diol-Based Peptidomimetics as Potential HIV Protease Inhibitors and Antitumor Agents

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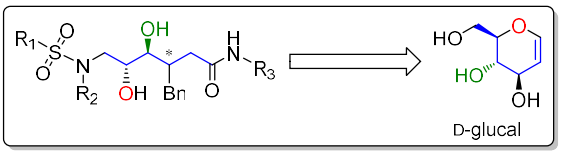
GRAPHICAL ABSTRACT



Sweet peptidomimetics: We prepare a new type of diol-based peptidomimetics starting from D-hexopyranose. Molecular docking simulations suggest that these compounds are potential inhibitors for the HIV protease. Antiproliferative activities exhihibited significant TGI and LC_{50} showing potent antitumor potencies.

Keywords: Diversity-oriented synthesis; Protease inhibitors; Carbohydrate approach; Conjugate addition; Peptidomimetics; Cancer therapeutics

ABSTRACT

Peptidomimetic HIV protease inhibitors are an important class of drugs used in the treatment of AIDS. The synthesis of a new type of diol-based peptidomimetics is described. Our route is flexible, utilises D-hexose as inexpensive starting material and makes minimal use of protection/deprotection cycles. Binding affinities from molecular docking simulations suggest that these compounds are potential inhibitors for the HIV protease. Moreover, the antiproliferative activities of compounds **33a**, **35a** and **35b** on HT-29, M21 and MCF7 cancer cell lines are in the low micromolar range. The results provide a platform that could facilitate the development of medically relevant nonsymmetrical diol-based peptidomimetics.

1. INTRODUCTION

It is well known that the human immunodeficiency virus (HIV) is the causative agent for acquired immunodeficiency syndrome (AIDS).[1] In the last few decades, advances in antiretroviral therapies have led to various approved protease inhibitors (PIs) for the treatment of HIV/AIDS. Several PIs have been used successfully in combination therapy with reverse transcriptase inhibitors and other antiviral drugs, and are among the top 200 drugs sold in the United States. As a consequence, HIV/AIDS can now be perceived as a manageable chronic infection. Despite major advances in antiretroviral therapies, current drugs have several drawbacks, such as i) high daily pill burden, ii) poor metabolic profiles, iii) decrease in efficacy through drug interactions, and iv) a high resistance barrier.[2] The emergence of drug resistance has become a serious problem leading to ineffective therapies.[3] Because of continuing resistance, there is a pressing need for new PIs with improved properties and activities.[4]

HIV protease cleaves viral proteins in order to generate mature infectious virions.[5] It is composed of two subunits where the catalytic active site of the enzyme is the dimer interface comprised of two aspartic acid residues (Asp25 and Asp25'). Also, the enzyme's active site possesses distinct subsites S1, S1', S2, S2', S3 and S3'. Different subsites can accommodate hydrophobic or polar side chains.[6] When the PI binds to the active site, it prevents cleavage of nascent viral proteins, thereby halting viral replication.[7]

First-generation PIs were approved by the Food and Drugs Administration (FDA) in the mid-90's. Also, this era marked the beginning of combination therapy for the treatment of HIV/AIDS. Careful inspection of the first generation inhibitors **1**-**5** reveals hydroxyethylene and hydroxyethylamine central cores (**Figure 1a**). The rapid emergence of resistance led to the development of second-generation PIs (**Figure 1b**). Inhibitors **6**-**8** were developed not only to overcome drug resistance but also to resolve other

challenging issues such as high metabolic clearance, low half-life and poor oral bioavailability. The pharmaceutical industry reduced substantially their investment in the development of PIs, because new therapies must demonstrate superiority over existing treatment. Nevertheless, recent progress in the development of new classes of inhibitors[8] has led to candidates showing clinical promise.[9] Some diol-based inhibitors have also emerged in recent years (**Figure 1c**). The diol moiety of inhibitors **9-11**[10] is believed to interact with the two aspartate residues of the binding site. Nonetheless, the development of new PIs is still ongoing[11] and finding novel PIs with broad-spectrum activities against multidrug-resistant variants is most certainly the biggest challenge to overcome.[12]

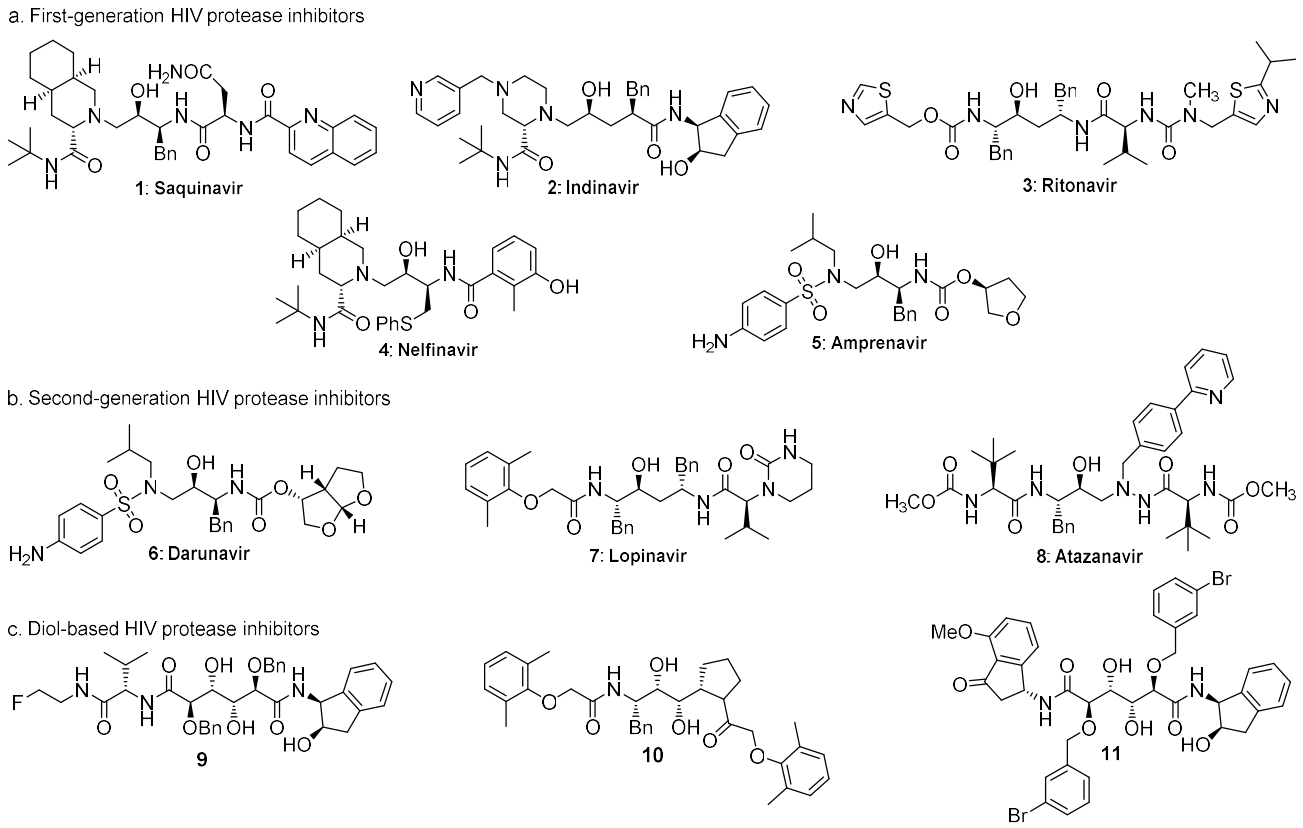
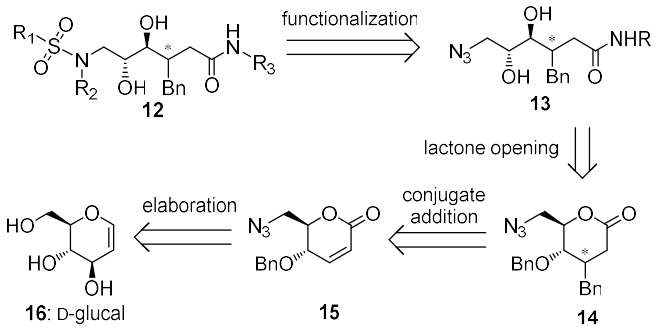


Fig. 1. HIV-1 protease inhibitors: a) First-generation FDA-approved inhibitors **1-5**; b) Second-generation FDA-approved inhibitors **6-8**; c) Diol-based inhibitors **9-11**

Typically, D-Mannitol[13] and L-mannonic-g-lactone[10c, 14] have been used as starting points for the preparation of PIs. However, this approach generally leads to C2-symmetrical compounds. Since nonsymmetrical inhibitors have superior activities,[15] new routes from simple chiral building blocks are clearly needed. To date, there is only one report describing the use of methyl b-D-mannopyranoside for the synthesis of PIs.[16] Similarly, peptidic diolbased PIs have been successfully designed for the purpose of probing favorable interactions with the HIV protease backbone.[10b, 17]

Besides HIV/AIDS, there has been growing interest in repurposing PIs for the treatment of cancer.[18] Although the mechanism of antitumor action of such drugs is under debate,[19] early clinical trials employing a PI alone or in combination with radiotherapy[20] have shown promise in treating patients with various types of cancer, including adenocarcinoma and non-small cell lung cancer (NSCLC).[21]

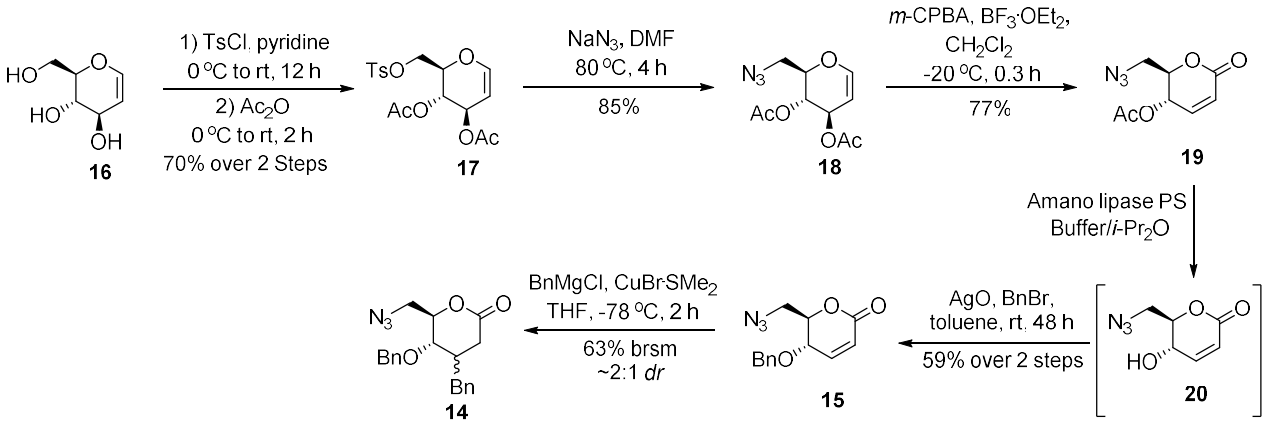
Herein, we describe the synthesis of novel nonsymmetrical diol-based peptidomimetics of general structure **12** (**Scheme 1**), which incorporate prominent structural features of the HIV protease inhibitors shown in **Figure 1**. From a retrosynthetic perspective, azides **13** were viewed as key intermediates, accessible through aminolysis of lactones **14** (**Scheme 1**). The desired benzyl substituent in **14** would be installed in stereodivergent fashion by conjugate addition onto α,β-unsaturated lactone **15**, derived from inexpensive D-glucal **16**. Our approach offers considerable flexibility as it enables parallel assemblage of small molecule libraries with distinct molecular architectures from chiral and achiral fragments.



Scheme 1. Retrosynthetic analysis of nonsymmetrical diol **12**

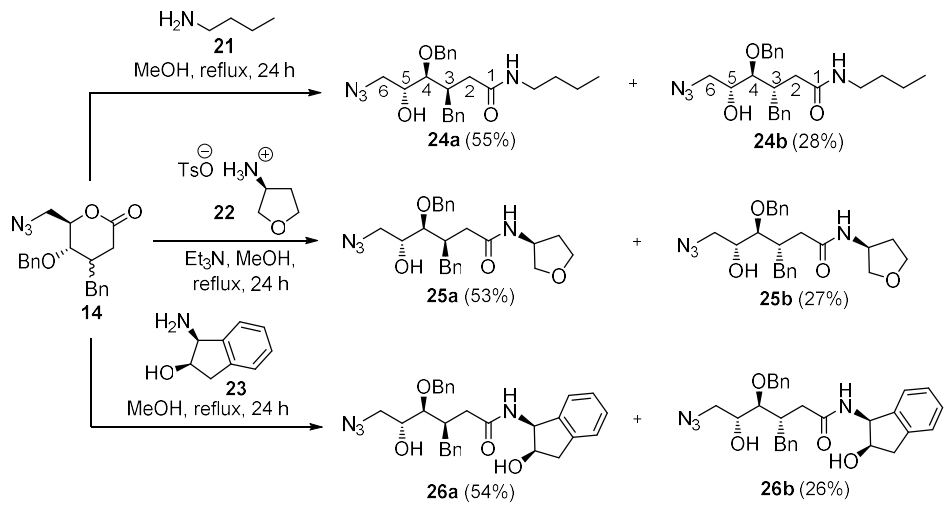
2. RESULTS AND DISCUSSION

The synthesis began from D-glucal **16** following a known 3-step sequence (**Scheme 2**).[22] Selective tosylation of the primary alcohol in **16**, followed by acetylation of the *sec*-hydroxyl groups provided intermediate **17** in 70% yield over 2 steps. Next, nucleophilic displacement of the tosylate with azide yielded glycal **18** in high yield. Treatment of **18** with boron trifluoride and 3-chloroperbenzoic acid (m-CPBA) at -20 °C for 0.5 h led directly to α,β-unsaturated g-lactone **19**.[23] Attempts to hydrolyze the acetyl ester group in **19** under standard basic conditions resulted in complete decomposition. Ultimately, the desired hydrolysis to alcohol **20** was successfully accomplished using Amano Lipase PS from Burkholderia cepacia.[24] Exposure of **20** to benzyl bromide and silver oxide afforded the rather unstable ether **15** in 59% yield over 2 steps.[25] Conjugate addition of in situ generated benzyl cuprate onto **15** proceeded with modest diastereoselectivity to afford lactone **14** as an inseparable ~2:1 mixture of isomers, whose respective identities were deduced after ring opening (vide infra).[26] The major isomer of **14** (not shown) arose by addition trans to the adjacent benyloxy substituent.



Scheme 2. Synthesis of intermediate **14**

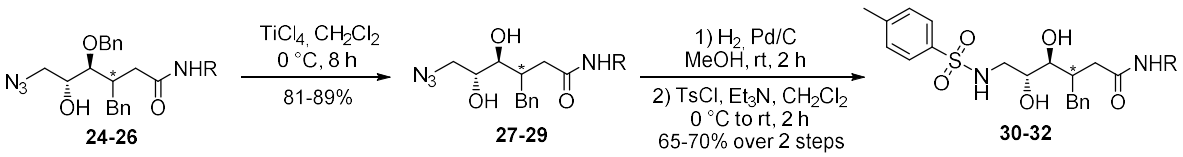
At this point the isomer mixture **14** was subjected to heating with amines **21**-**23** in MeOH to generate gluconamide derivatives **24**-**26** (**Scheme 3**).[27] The three amines used, namely, butylamine **21**, (S)-tetrahydrofuran-3-amine **22** and (1S,2R)-cis-1-amino-2-indanol **23**, were selected for the purpose of exploring interactions of amides **24**-**26** with the enzyme backbone, targeting hydrophobic S2/S2' pockets. Importantly, separation of the resulting diastereomeric mixtures of amides (**24**-**26**) could be readily achieved by flash column chromatography, allowing both the 3,4-*syn* (**24a**-**26a**, major) and 3,4-*anti* isomers (**24b**-**26b**, minor) to be obtained in pure form.

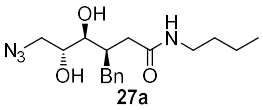
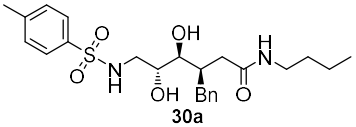
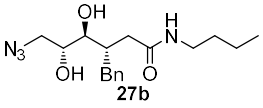
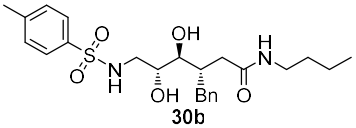
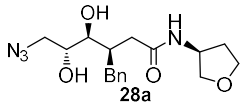
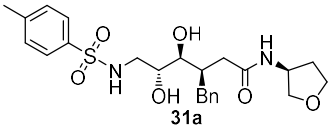
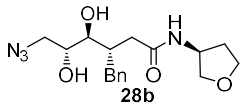
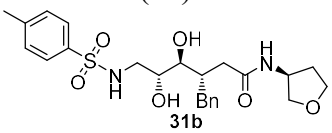
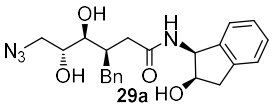
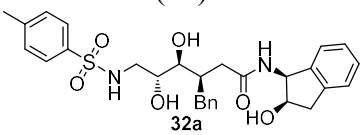
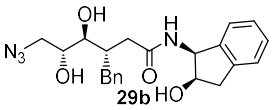
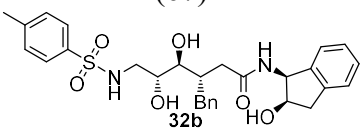


Scheme 3. Aminolysis of lactone **14**

With the individual diastereoisomers of **24**-**26** in hand, their transformation to sulfonamides was addressed (**Table 1**). First, $TiCl_4$ mediated cleavage of the *O*-benzyl group[28] provided the corresponding diols **27**-**29** in 81-89% yield. Compounds **27**-**29** were subjected to a hydrogen atmosphere with a catalytic amount of palladium allowing formation of the amine intermediates. The latter were transformed in situ to sulfonamides **30**-**32** upon treatment with *p*-toluenesulfonyl chloride and triethylamine.[29] It is important to note that a sulfonamide residue is encountered in several known PIs.[8]

Table 1. Synthesis of sulfonamides **30-32**



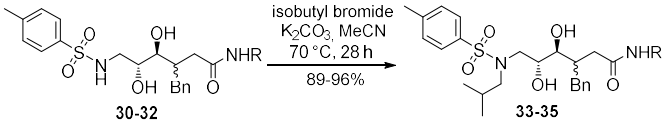
Entry	Starting materials	Benzyl ether deprotection products (Yield, %)[a]	Sulfonamide products (Yield over 2 steps, %)[a]
1	**24a**	 **27a** (89)	 **30a** (70)
2	**24b**	 **27b** (85)	 **30b** (66)
3	**25a**	 **28a** (84)	 **31a** (69)
4	**25b**	 **28b** (88)	 **31b** (68)
5	**26a**	 **29a** (81)	 **32a** (67)
6	**26b**	 **29b** (84)	 **32b** (65)

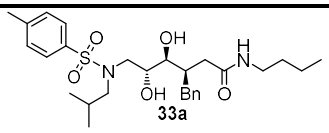
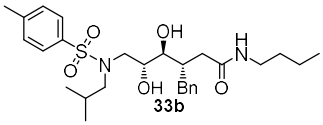
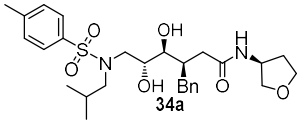
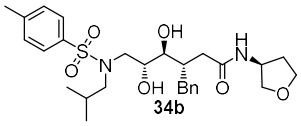
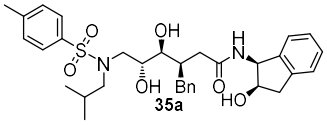
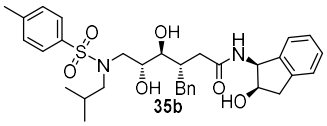
[a]Yields refer to isolated products after flash column chromatography

The final step of the synthesis of diol-based peptidomimetics is shown in **Table 2**. Alkylation of sulfonamides **30-32** was carried out using isobutyl bromide under basic conditions at 70 °C. Products **33-35** were isolated in yields ranging between 89−96%. Installation of a small alkyl group, such as

isobutyl, could improve interactions with the protease backbone. In fact, the structures of our target compounds specifically incorporate features found in darunavir **6** (**Figure 1**).

Table 2. Preparation of peptidomimetics **33-35**



Entry	Starting materials	Products	Yields (%)[a]
1	**30a**	 **33a**	96
2	**30b**	 **33b**	92
3	**31a**	 **34a**	89
4	**31b**	 **34b**	89
5	**32a**	 **35a**	90
6	**32b**	 **35b**	93

[a]Yields refer to isolated products after flash column chromatography

The stereochemistries of our peptidomimetics were determined by NMR, based on the crystal structure of diol **33b** (**Figure 2**).[30] This compound was prepared from minor isomer **24b**.

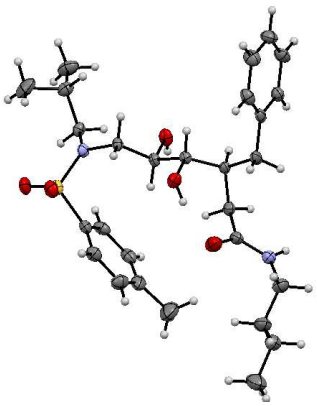


Figure 2. X-ray derived ORTEP of diol **33b**

3. MOLECULAR DOCKING SIMULATIONS

Compounds **33**-**35** were subjected to molecular docking simulations using Autodock Vina to evaluate their binding affinities for the HIV protease binding pocket. Such simulations give insight into the binding pattern of the compounds. The observed interactions between the compounds and the HIV protease and their predicted binding affinities are depicted in **Figure 3**. For the sake of comparison, we also examined the docking of Darunavir, found to have a predicted affinity of -9.5 kcal/mol, with an RMSD of 0.61 Å between the docked and the crystallographic structure. Overall, peptidomimetics **33**-**35** docked well into the protease binding pocket, displaying a mix of hydrophobic interactions with the non-polar residues and between 2 to 5 hydrogen bonds with polar residues. Although the number of hydrogen bonds between the compounds and the receptor are fewer than for Darunavir, the non-polar interactions are in general more present. Interestingly, all compounds have at least one hydroxyl group hydrogen-bonded to at least one of the two catalytic aspartic acids. Compounds **33a** and **33b** presented the lowest binding affinities, with predicted values of -9.0 kcal/mol for both compounds. These values are lower than that of darunavir, suggesting that compounds **33a**-**b** would be probably weaker inhibitors of HIV protease. Because **33a**-**b** are the most hydrophobic compounds of the set, their docking involved

the largest hydrophobic interactions with the receptor. In contrast, compounds **34a**-**b** and **35a**-**b** had predicted affinities equal or better than Darunavir (**Figure 3**), with the best affinity predicted for **35a**. These findings indicate that **34a**-**b** and **35a**-**b** have the potential for similar or better inhibitory activities than Darunavir. In agreement with their more hydrophilic character, compounds **34a** and **34b** presented the fewest non-polar interactions with the binding pocket residues. Nevertheless, the pair **35a** and **35b** presented a good balance between hydrophilic and hydrophobic interactions, leading to the best binding affinities. Interestingly, the sulfamoyl moiety of three compounds were involved in hydrogen bonding with one residue of the binding pocket: the side chain of Asp25A for compound **33b**, the backbone amide of Asp29A for compound **34b** and the side chain of Arg8B for compound **35a**. This crucial interaction is exemplified with the binding pose of compound **35a** as shown in **Figure 4**. Finally, while diastereoisomers **33a** and **33b** display similar binding affinities, the 3,4-*syn*-4,5-*anti* compounds **34a** and **35a** had slightly better predicted binding affinities than their respective 3,4-*anti*-4,5-*anti* stereoisomers **34b** and **35b**.

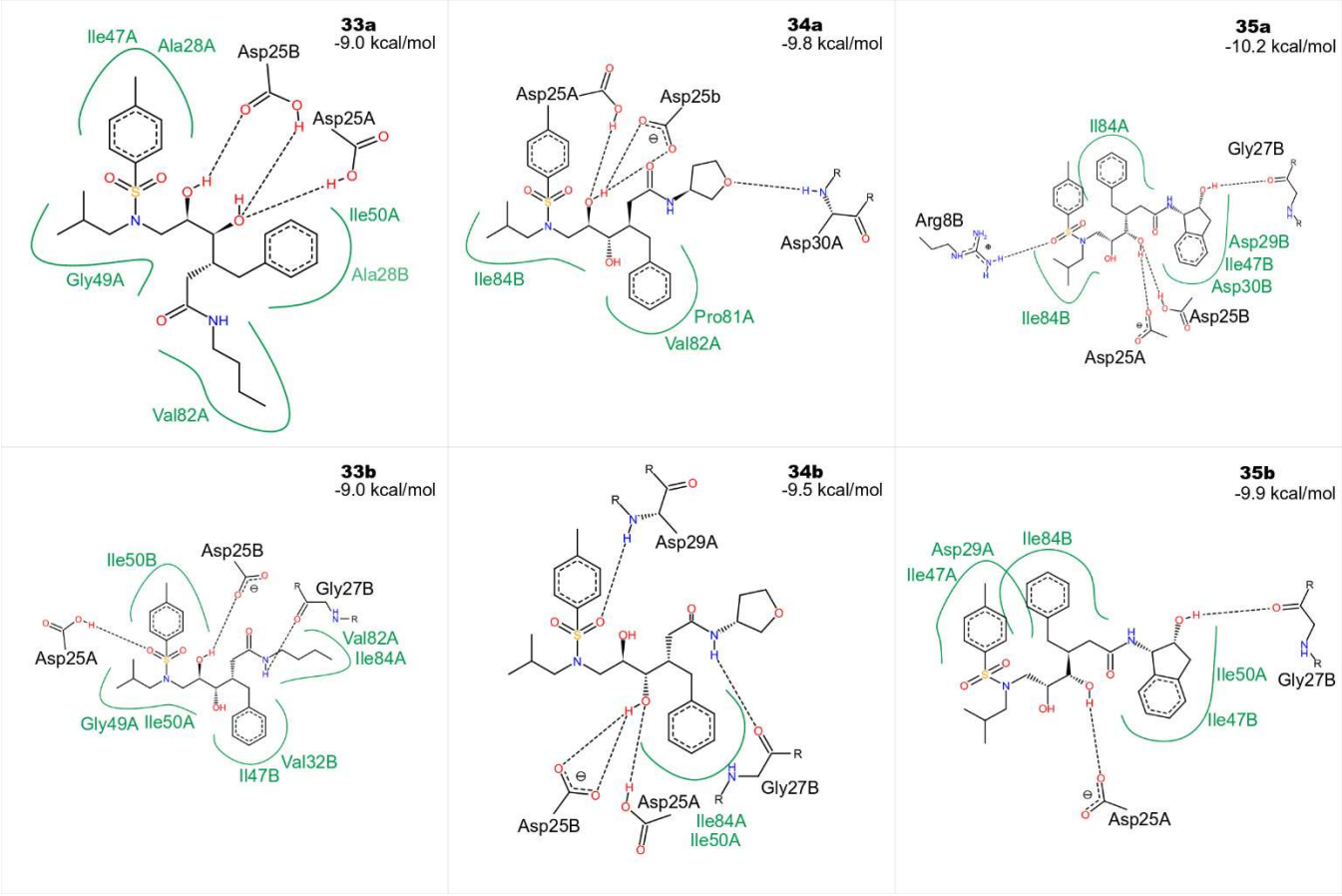


Figure 3. 2D diagram of the interactions between compounds **33-35** and the HIV protease binding pocket residues from the docking results, as generated by PoseView.[40, 41] Dashed lines are for hydrogen bonds and green lines are for hydrophobic interactions. The respective predicted binding affinities are also indicated.

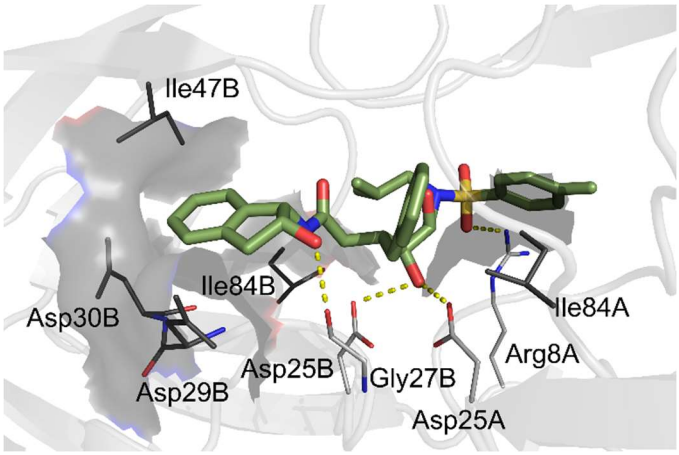


Fig. 5. Binding pose of compound **35a**. The HIV protease is represented in transparent light gray cartoon, compound **35a** in bold green sticks, the hydrogen-bonding residues in light gray small sticks and the hydrophobic residues in dark gray small sticks and semi-transparent surfaces. Hydrogen bonds are represented by yellow dashes.

4. ANTIPROLIFERATIVE ACTIVITY

Compounds **29a**, **33a**, **34ab**, and **35ab** were evaluated for their antiproliferative activity on human HT-29 colon adenocarcinoma, M21 skin melanoma, and MCF7 breast carcinoma cell lines according to the NCI/NIH Developmental Therapeutics Program.[31] These particular cell lines were chosen to reflect the types of cancer found in preclinical[32] and clinical trials[33] with existing HIV PIs. The results are summarized in **Table 3**; expressed as the concentration of drug inhibiting cell growth by 50% (IC_{50}), concentration of drug inhibiting totally cell proliferation (TGI), and concentration of drug killing 50% of the cell population (LC_{50}). It is seen from the results that the three cancer cell lines displayed similar sensitivity toward the new compounds assessed. Compound **34a** exhibited very weak IC_{50} ranging from 83 to > 100 μM and compounds **29a** and **34b** showed no antiproliferative activity. These results suggest that the tetrahydrofuranyl group is detrimental while the sulfonamide moiety is required for effective antiproliferative activity. Compounds **33a**, **35a** and **35b** exhibited IC_{50} ranging from 12 to 36 μM.

Moreover, compound **35b** bearing an amido indanol group was the most active, with IC_{50} values of 12 μM, 14 μM and 17 μM against HT-29, M21 and MCF7, respectively. Finally, **35b** exhibited TGI ranging from 23 to 29 μM and LC_{50} ranging from 32 to 41 μM showing that it is a potent cytotoxic agent.

Table 3. Antiproliferative activity (IC_{50}), total growth inhibition (TGI) and median lethal concentration (LC_{50}) of diol-based peptidomimetics **29a**, **33a**, **34ab**, and **35ab** on human HT-29 colon adenocarcinoma, M21 skin melanoma and MCF7 breast carcinoma cancer cells.

Compounds	IC_{50} (μM)[a]			TGI (μM)[b]			LC_{50} (μM)[c]		
	HT-29	M21	MCF7	HT-29	M21	MCF7	HT-29	M21	MCF7
29a	> 100	> 100	n.e[d]	> 100	> 100	n.e	> 100	> 100	n.e
33a	26	30	36	> 100	> 100	> 100	> 100	> 100	> 100
34a	85	83	> 100	> 100	> 100	> 100	> 100	> 100	> 100
34b	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
35a[e]	21	18	31	42	35	> 50	> 50	43	> 50
35b	12	14	17	23	26	29	36	32	41
Topotecan	0.34	2.0	2.2	> 10	> 10	> 10	> 10	> 10	> 10
Paclitaxel	0.0037	0.0046	0.0027	> 0.03	> 0.03	> 0.03	> 0.03	> 0.03	> 0.03

[a]IC_{50} is expressed as the concentration of drug inhibiting cell proliferation by 50% after 48 h of treatment. [b]TGI is expressed as the concentration of drug inhibiting totally cell proliferation after 48 h of treatment. [c]LC_{50} is expressed as the concentration of drug killing 50% of the cell population after 48 h of treatment. [d]n.e.: not evaluated. [e]The maximum concentration assessed was 50 μM for **35a**.

5. CONCLUSION

We have described the synthesis of a series of novel, non-symmetrical diol-based peptidomimetics using a carbohydrate approach. The synthetic route utilizes conjugate addition as a key step, enabling access to a wide range of analogues in few chemical steps from inexpensive D-glucal. Final products were subjected to molecular docking simulations to evaluate their binding affinities for the HIV protease binding pocket. Peptidomimetics **33-35** docked well into the protease binding pocket, displaying a mix of hydrophobic interactions with the non-polar residues and between two and five hydrogen bonds with

polar residues. It was also shown that the antiproliferative activities of compounds **33a**, **35a** and **35b** are in the low micromolar range. In addition, compound **35b** exhibited significant TGI and LC_{50} showing that is a potent antitumor agent. Collectively, the results provide a platform for further chemical and pharmacological exploration of this new class of diol peptidomimetics.

6. EXPERIMENTAL SECTION

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 and *N*,*N*′-dimethylformamide (DMF) from ninhydrin and kept over molecular sieves. Tetrahydrofuran (THF) was distilled from Na/benzophenone immediately before use. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and charring with a solution of 3 g of PhOH and 5 ml of H_2SO_4 in EtOH, followed by heating with a heatgun. SiliaFlash® P60 40-63 μm (230-400 mesh) was used for flash column chromatography. NMR spectra were recorded with an Agilent DD2 500 MHz spectrometer and calibrated using residual undeuterated solvent ($CDCl_3$: ^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm; $(CD_3)_2CO$: ^{1}H δ = 2.05 ppm, ^{13}C δ = 29.84 ppm; CD_3OD: ^{1}H δ = 3.31 ppm, ^{13}C δ = 49.00 ppm) as an internal reference. Coupling constants (*J*) are reported in Hertz (Hz), and the following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Infrared spectra were recorded using a Thermo Scientific Nicolet 380 FT-IR spectrometer. The absorptions are given in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were measured with an Agilent 6210 LC Time of Flight mass spectrometer in electrospray mode. Either protonated molecular ions $[M + nH]^{n+}$, sodium adducts $[M + Na]^+$ or ammonium adducts $[M + NH_4]^+$

were used for empirical formula confirmation. Optical rotations were measured with a JASCO DIP-360 digital polarimeter, and are reported in units of 10^{-1} (deg cm^2 g^{-1}).

6.1. General procedure I – lactone opening with various amines

To a solution of lactone **14** (1.0 equiv) in dry MeOH was added amine **21–23** (2.0 equiv). The mixture was stirred under refluxed for 16 h. After this time, the mixture was concentrated under reduced pressure and purified by flash column chromatography (hexanes / EtOAc) affording products **24–26**.

6.2. General procedure II – benzyl ether deprotection

To a solution of benzyl ether **24–26** (1.0 equiv) in CH_2Cl_2 at 0 °C was added $TiCl_4$ (1.0 M in CH_2Cl_2, 5.0 equiv) and the mixture was stirred at 0 °C for 3 h. The mixture was poured in cold water and extracted with ethyl acetate (3 × 10 mL). The combined organic phase were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (hexanes / EtOAc) afforded products **27–29**.

6.3. General procedure III – azide functionalization

To a solution of azide **27–29** (1.0 equiv) in MeOH was added Pd/C (10 mol%). The mixture was stirred under a balloon pressure of hydrogen for 8 h. After this time, the mixture was filtered through a pad of celite and concentrated under reduced pressure. The amine thus generated was used for the next step without further purification. To a solution of the resulting amine in CH_2Cl_2 at 0 °C was added Et_3N (1.5 equiv) and *p*-toluenesulfonyl chloride (1.2 equiv). The mixture was stirred at room temperature for 16 h, then concentrated under reduced pressure and purified by flash column chromatography (hexanes / EtOAc) affording products **30–32**.

6.4. General procedure IV – sulfonamide alkylation

To a solution of the sulfonamide **30–32** (1.0 equiv) in acetonitrile was added K_2CO_3 (2.0 equiv) and isobutyl bromide (2.0 equiv). The mixture was heated at 65 °C for 16 h. After this time, the mixture was filtered through celite and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes / EtOAc) yielding products **33–35**.

6.*5. 3,4-di-O-acetyl-6-O-(4-toluenesulfonyl)-D-glucal (**17**)*

To a solution of D-glucal **16** (1.6 g, 11.0 mmol) in anhydrous pyridine (30 mL) at 0 °C was added *p*-toluenesulfonyl chloride (2.3 g, 12.0 mmol, 1.1 equiv). The mixture was stirred vigorously at rt for 3 h, then acetic anhydride (4.1 mL, 43.8 mmol, 4.0 equiv) was added and the mixture was stirred at rt for 16 h. After this time, the mixture was concentrated under reduced pressure, then diluted with CH_2Cl_2 (100 mL). The organic solution was washed with sat aq $CuSO_4$ (3 × 30 mL), water (5 × 30 mL), and brine (1 × 30 mL). The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel (hexanes / EtOAc, 7 : 3) to give the title compound **17** (3.2 g, 70%) as colorless oil. The physical and spectroscopic properties for compound **17** match those reported in the literature[34] : IR (NaCl film) ν 2958, 2929, 1710, 1653, 1364, 1229, 1177, 1044, 816 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 6.35 (dd, J = 6.1, 1.4 Hz, 1H), 5.30 – 5.23 (m, 1H), 5.17 – 5.10 (m, 1H), 4.82 (dd, J = 6.2, 3.4 Hz, 1H), 4.31 – 4.16 (m, 3H), 2.46 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.6, 145.4, 145.3, 132.7, 130.0, 128.2, 99.1, 73.4, 67.1, 66.7, 66.5, 21.8, 21.1, 20.9; HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{17}H_{24}NO_8S$ 402.1217; Found 402.1224.

*6.6. 3,4-di-O-acetyl-6-deoxy-6-azido-D-glucal (**18**)*

To a solution of compound **17** (6.6 g, 17.2 mmol, 1.0 equiv) in dimethylformamide (70 mL) at rt was added sodium azide (4.5 g, 68.7 mmol, 4 equiv). The solution was stirred at 80 °C for 3 h, then cooled to rt and diluted with ethyl acetate (200 mL). The organic solution was washed with water (3 × 100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography on silica gel (hexanes / EtOAc, 8 : 2) afforded the title compound **18** (3.7 g, 85%) as a colorless oil. The physical and spectroscopic properties for compound **18** match those reported in the literature[35] : IR (NaCl film) ν 2963, 2944, 2105, 1750, 1652, 1558, 1373, 1225, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.41 (dd, *J* = 6.2, 1.4 Hz, 1H), 5.23 (dddd, *J* = 5.5, 3.4, 1.4, 0.8 Hz, 1H), 5.09 (ddd, *J* = 7.2, 5.4, 0.5 Hz, 1H), 4.80 (ddd, *J* = 6.1, 3.4, 0.5 Hz, 1H), 4.14 (tdd, *J* = 7.1, 3.8, 0.9 Hz, 1H), 3.49 (dd, *J* = 13.3, 7.0 Hz, 1H), 3.36 (dd, *J* = 13.3, 3.8 Hz, 1H), 2.01 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.4, 145.3, 99.0, 74.7, 67.9, 66.8, 50.0, 20.9, 20.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{13}N_3NaO_5$ 278.0747; Found 278.0735.

*6.7. (5S, 6R)-6-(azidomethyl)-5-(acetoxy)-5,6-dihydro-2H-pyran-2-one (**19**)*

To a solution of 80% anhydrous MCPBA (3.8 g, 17.5 mmol, 1.2 equiv) in dry CH_2Cl_2 (50 mL) at –20 °C was added a cooled solution (–20 °C) of compound **18** (3.7 g, 14.6 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL). Then, $BF_3{\cdot}OEt_2$ (0.9 mL, 7.29 mmol, 0.5 equiv) was added dropwise at –20 °C and the mixture was stirred for 15 min. After this time, the solution was poured into a sat aq $NaHCO_3$ solution (50 ml) containing 10-20 mg of $Na_2S_2O_3$ (prior warming to rt). The mixture was extracted with CH_2Cl_2 (3 × 50 ml) and the combined organic solutions were concentrated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (hexanes / EtOAc, 7 : 3) affording **19** (2.4 g, 77%) as a white amorphous solid: mp 89−90 °C; $[\alpha]_D$ = +102.3 (*c* 1.1, $CHCl_3$); IR (NaCl film) ν 2948, 2123, 1748, 1733, 1269, 1229, 1058, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 10.0, 2.8

Hz, 1H), 6.11 (dd, *J* = 10.0, 1.8 Hz, 1H), 5.57 (ddd, *J* = 8.3, 2.8, 1.8 Hz, 1H), 4.58 (ddd, *J* = 8.4, 4.7, 3.8 Hz, 1H), 3.62 (dd, *J* = 13.5, 3.8 Hz, 1H), 3.54 (dd, *J* = 13.5, 4.7 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 161.0, 143.8, 122.2, 78.3, 64.3, 51.2, 20.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_8H_{10}N_3O_4$ 212.0666; Found 212.0663.

*6.8. (5S, 6R)-6-(azidomethyl)-5-(benzyloxy)-5,6-dihydro-2H-pyran-2-one (**15**)*

To a solution of compound **19** (0.9 g, 4.26 mmol, 1.0 equiv) in a mixture of diisopropyl ether (40 mL) and phosphate buffer pH 7 (20 mL) was added amano lipase PS (from *Burkholderia cepacia*) (916 mg). The mixture was stirred at rt for 16 h. After this time, water (50 mL) was added and the mixture was extracted with ethyl acetate (2 × 80 ml). The combined organic solutions were washed with a sat aq $NaHCO_3$ solution (100 ml) and brine (100 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure affording the alcohol **20** (HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_6H_8N_3O_3$ 170.0560; Found 170.0558.) which was used for the next step without further purification. To a solution of the crude alcohol **20** in toluene (30 mL) at rt was added benzyl bromide (0.6 mL, 5.11 mmol, 1.2 equiv) followed by silver (I) oxide (1.5 g, 6.39 mmol, 1.5 equiv). The mixture was stirred for 48 h, then filtered through celite and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (hexanes / EtOAc, 75 : 25) to give the title compound **15** (654 mg, 59% over 2 steps) as a colorless oil: $[\alpha]_D$ = +55.5 (*c* 0.9, $CHCl_3$); IR (NaCl film) ν 3063, 3029, 2920, 2851, 2104, 1743, 1496, 1454, 1228, 1073, 749, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H), 6.89 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.99 (dd, *J* = 10.0, 1.9 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.47 – 4.36 (m, 2H), 3.69 (dd, *J* = 13.5, 2.6 Hz, 1H), 3.56 (dd, *J* = 13.5, 3.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 146.7, 136.6, 128.9, 128.7, 128.3, 120.4, 79.3, 72.6, 69.4, 50.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}N_3O_3$ 260.1030; Found 260.1032.

*6.9. Compound (**14**)*

To a solution of lactone **15** (100 mg, 0.39 mmol, 1.0 equiv) in dry THF (5 mL) at –78 °C was added CuBr.Me_2S (79.3 mg, 0.39 mmol, 1.0 equiv) and benzylmagnesium chloride (1.6 mL, 1.4 M in THF, 2.3 mmol, 6.0 equiv) over 10 min. The mixture was stirred at –78 °C for 0.5 h, then quenched by addition of sat aq NH_4Cl solution (10 mL). The mixture was extracted with ethyl acetate (3 × 15 ml) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated over reduced pressure. The product was purified by flash column chromatography on silica gel (hexanes / EtOAc, 8 : 2) to yield lactone **15** (30 mg) and compound **14** (60 mg, 63% based on recuperated starting material) as a mixture of diastereoisomers (HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}N_3O_3$ 352.1656; Found 352.1651).

*6.10. (3R, 4S, 5R)-6-azido-3-benzyl-4-(benzyloxy)-N-butyl-5-hydroxyhexanamide (**24a**) and (3S, 4S, 5R)-6-azido-3-benzyl-4-(benzyloxy)-N-butyl-5-hydroxyhexanamide (**24b**)*

Following general procedure I with lactone **14** (110 mg, 0.31 mmol, 1.0 equiv) and butyl amine (0.62 mL, 0.63 mmol, 2.0 equiv) in 4.0 mL of MeOH. Flash column chromatography on silica gel afforded amide **24a** (74 mg, 55%) and **24b** (37.2 mg, 28%) as colorless oils. (3*R*, 4*S*, 5*R*)-6-azido-3-benzyl-4-(benzyloxy)-*N*-butyl-5-hydroxyhexanamide (**24a**): $[\alpha]_D$ = +12.3 (*c* 1.0, $CHCl_3$); IR (NaCl film) ν 3306, 3028, 2930, 2099, 1650, 1495, 1455, 1286, 1094, 747, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.17 (m, 10H), 5.18 (dd, *J* = 5.9, 5.9 Hz, 1H), 4.56 (s, 2H), 3.93 – 3.83 (m, 1H), 3.61 – 3.45 (m, 3H), 3.41 (dd, *J* = 12.5, 6.0 Hz, 1H), 3.19 – 3.04 (m, 3H), 2.65 – 2.48 (m, 2H), 2.19 (ddt, *J* = 15.2, 6.2 Hz, 2H), 1.43 – 1.24 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 140.6, 138.2, 129.4, 128.6, 128.2, 128.1, 126.3, 80.4, 73.8, 72.0, 54.6, 39.4, 36.9, 36.0, 31.7, 20.2, 13.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{33}N_4O_3$ 425.2547; Found 425.2533. (3*S*, 4*S*, 5*R*)-6-azido-3-benzyl-4-

(benzyloxy)-*N*-butyl-5-hydroxyhexanamide (**24b**): $[\alpha]_D$ = +31.7 (*c* 1.0, $CHCl_3$); IR (NaCl film) ν 3312, 3028, 2930, 2872, 2100, 1644, 1496, 1455, 1293, 1097, 737, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 7H), 7.26 – 7.15 (m, 3H), 5.25 (t, *J* = 5.3 Hz, 1H), 4.99 (broad s, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 3.69 – 3.60 (m, 1H), 3.55 (dd, *J* = 9.1, 1.6 Hz, 1H), 3.51 (dd, *J* = 12.5, 2.7 Hz, 1H), 3.36 (dd, *J* = 12.5, 5.7 Hz, 1H), 3.16 – 3.07 (m, 2H), 2.92 (dd, *J* = 13.2, 5.1 Hz, 1H), 2.88 – 2.79 (m, 1H), 2.64 (dd, *J* = 13.1, 10.4 Hz, 1H), 2.56 (dd, *J* = 16.0, 8.1 Hz, 1H), 1.99 (dd, *J* = 16.0, 3.0 Hz, 1H), 1.38 – 1.30 (m, 2H), 1.28 – 1.18 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 139.9, 138.3, 129.3, 128.7, 128.7, 128.0, 127.7, 126.5, 82.0, 74.8, 71.3, 53.9, 39.6, 39.5, 37.4, 34.5, 31.5, 20.1, 13.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{33}N_4O_3$ 425.2547; Found 425.2541.

*6.11. (3R, 4S, 5R)-6-azido-3-benzyl-4-(benzyloxy)-5-hydroxy-N-((S)-tetrahydrofuran-3-yl)hexanamide (**25a**) and (3S, 4S, 5R)-6-azido-3-benzyl-4-(benzyloxy)-5-hydroxy-N-((S)-tetrahydrofuran-3-yl)hexanamide (**25b**)*

Following general procedure I with lactone **14** (60 mg, 0.17 mmol, 1.0 equiv), (*S*)-3-aminotetrahydrofuran tosylate (89 mg, 0.34 mmol, 2.0 equiv) and Et_3N (0.14 mL, 1.02 mmol, 6.0 equiv) in 2.0 mL of MeOH. Flash column chromatography on silica gel afforded amide **25a** (40 mg, 53%) and **25b** (20 mg, 27%) as colorless oils. (3*R*, 4*S*, 5*R*)-6-azido-3-benzyl-4-(benzyloxy)-5-hydroxy-*N*-((*S*)-tetrahydrofuran-3-yl)hexanamide (**25a**): $[\alpha]_D$ = +17.2 (*c* 1.0, $CHCl_3$); IR (NaCl film) ν 3306, 2925, 2866, 2100, 1642, 1546, 1453, 1285, 1073, 745, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 7H), 7.24 – 7.18 (m, 3H), 5.57 (d, *J* = 7.2 Hz, 1H), 4.55 (q, *J* = 11.5 Hz, 2H), 4.40 (dtt, *J* = 10.3, 5.6, 2.9 Hz, 1H), 3.88 – 3.81 (m, 2H), 3.73 (ddd, *J* = 17.0, 9.1, 5.5 Hz, 2H), 3.57 (dd, *J* = 12.5, 2.9 Hz, 1H), 3.54 – 3.49 (m, 2H), 3.41 (dd, *J* = 12.5, 6.0 Hz, 1H), 3.07 (dd, *J* = 13.4, 5.4 Hz, 1H), 2.65 – 2.58 (m,

1H), 2.54 (dd, *J* = 13.4, 9.7 Hz, 1H), 2.26 – 2.15 (m, 3H), 1.72 – 1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 140.5, 138.1, 129.4, 128.7, 128.7, 128.1, 128.1, 126.4, 80.4, 73.8, 73.4, 71.8, 66.9, 54.6, 50.4, 39.3, 37.1, 36.1, 33.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{31}N_4O_4$ 439.2340; Found 439.2677. (3*S*, 4*S*, 5*R*)-6-azido-3-benzyl-4-(benzyloxy)-5-hydroxy-*N*-((*S*)-tetrahydrofuran-3-yl)hexanamide (**25b**): $[\alpha]_D$ = +24.5 (*c* 0.8, $CHCl_3$); IR (NaCl film) *ν* 3307, 2925, 2856, 2101, 1641, 1495, 1453, 1293, 1075, 739, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 7H), 7.25 – 7.16 (m, 3H), 5.44 (d, *J* = 7.4 Hz, 1H), 4.75 (d, *J* = 3.5 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.59 (d, *J* = 11.3 Hz, 1H), 4.36 (dtt, *J* = 10.3, 5.4, 2.8 Hz, 1H), 3.82 – 3.74 (m, 1H), 3.70 (ddd, *J* = 8.7, 7.8, 5.5 Hz, 2H), 3.69 – 3.62 (m, 1H), 3.59 – 3.49 (m, 3H), 3.37 (dd, *J* = 12.6, 5.7 Hz, 1H), 2.92 (dd, *J* = 13.4, 4.9 Hz, 1H), 2.83 – 2.76 (m, 1H), 2.62 (dd, *J* = 13.3, 10.7 Hz, 1H), 2.56 (dd, *J* = 16.0, 7.8 Hz, 1H), 2.19 – 2.07 (m, 1H), 1.97 (dd, *J* = 16.0, 3.2 Hz, 1H), 1.57 – 1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 139.9, 138.2, 129.3, 128.8, 128.7, 128.1, 127.8, 126.6, 82.0, 74.7, 73.4, 71.3, 66.8, 53.9, 50.6, 39.6, 37.7, 34.5, 33.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{31}N_4O_4$ 439.2340; Found 439.2342.

*6.12. (3R, 4S, 5R)-6-azido-3-benzyl-4-(benzyloxy)-5-hydroxy-N-((1S, 2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)hexanamide (**26a**) and (3S, 4S, 5R)-6-azido-3-benzyl-4-(benzyloxy)-5-hydroxy-N-((1S, 2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)hexanamide (**26b**)*

Following general procedure I with lactone **14** (140 mg, 0.40 mmol, 1.0 equiv) and (1*S*, 2*R*)-(−)-cis-1-amino-2-indanol (119 mg, 0.80 mmol, 2.0 equiv) in 5.0 mL of MeOH. Flash column chromatography on silica gel afforded amide **26a** (108 mg, 54%) and **26b** (52 mg, 26%) as colorless oils. (3*R*, 4*S*, 5*R*)-6-azido-3-benzyl-4-(benzyloxy)-5-hydroxy-*N*-((1*S*, 2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)hexanamide (**26a**): $[\alpha]_D$ = +15.4 (*c* 1.0, $CHCl_3$); IR (NaCl film) *ν* 3395, 3026, 2924, 2101, 1646, 1454, 1300, 1090, 750, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.17 (m, 14H), 6.21 (d, *J* = 8.7

Hz, 1H), 5.32 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.49 (td, *J* = 5.2, 2.4 Hz, 1H), 3.81 (ddd, *J* = 8.6, 5.7, 2.8 Hz, 1H), 3.58 (dd, *J* = 8.5, 2.0 Hz, 1H), 3.53 (dd, *J* = 12.5, 2.7 Hz, 1H), 3.36 (dd, *J* = 12.5, 5.7 Hz, 1H), 3.06 (ddd, *J* = 18.1, 14.6, 4.8 Hz, 2H), 2.86 (dd, *J* = 16.6, 2.5 Hz, 1H), 2.67 – 2.53 (m, 2H), 2.46 – 2.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 140.5, 140.4, 140.2, 138.1, 129.5, 128.6, 128.6, 128.4, 128.0, 127.2, 126.3, 125.4, 124.6, 80.1, 74.2, 73.4, 71.4, 57.4, 54.6, 39.6, 39.5, 38.1, 35.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{33}N_4O_4$ 501.2496; Found 501.2496. (3*S*, 4*S*, 5*R*)-6-azido-3-benzyl-4-(benzyloxy)-5-hydroxy-*N*-((1*S*, 2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)hexanamide (**26b**): $[\alpha]_D$ = +12.9 (*c* 1.0, $CHCl_3$); IR (NaCl film) *ν* 3395, 3027, 2924, 2101, 1645, 1521, 1455, 1299, 1086, 1055, 750, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.16 (m, 14H), 6.96 (d, *J* = 7.1 Hz, 1H), 6.07 (d, *J* = 8.4 Hz, 1H), 5.22 (dd, *J* = 8.5, 4.9 Hz, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.53 (td, *J* = 5.0, 1.8 Hz, 1H), 3.81 (ddd, *J* = 8.6, 5.3, 3.7 Hz, 1H), 3.50 (dd, *J* = 7.9, 2.0 Hz, 1H), 3.45 – 3.38 (m, 2H), 2.98 (ddd, *J* = 21.2, 15.0, 5.3 Hz, 2H), 2.91 – 2.81 (m, 2H), 2.61 (dd, *J* = 13.3, 9.8 Hz, 1H), 2.49 (dd, *J* = 15.6, 8.9 Hz, 1H), 2.13 (dd, *J* = 15.5, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 140.3, 140.2, 139.9, 138.1, 129.2, 128.7, 128.7, 128.4, 128.1, 128.0, 127.2, 126.5, 125.4, 124.4, 80.6, 73.7, 73.5, 70.8, 57.9, 53.9, 39.3, 38.8, 37.6, 35.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{33}N_4O_4$ 501.2496; Found 501.2501.

*6.13. (3R, 4S, 5R)-6-azido-3-benzyl-N-butyl-4,5-dihydroxyhexanamide (**27a**)*

Following general procedure II with amide **24a** (60 mg, 0.14 mmol, 1.0 equiv) and $TiCl_4$ (0.71 ml, 0.71 mmol, 5.0 equiv) in CH_2Cl_2 (2.0 mL). Flash column chromatography on silica gel afforded alcohol **27a** (42 mg, 89%) as a colorless oil: $[\alpha]_D$ = –16.0 (*c* 1.0, $CHCl_3$); IR (NaCl film) *ν* 3335, 3026, 2930, 2872, 2101, 1624, 1557, 1454, 1291, 1068, 1030, 741, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.24 – 7.15 (m, 3H), 5.47 – 5.34 (m, 2H), 3.84 – 3.67 (m, 3H), 3.59 – 3.49 (m, 1H), 3.31 – 3.10

(m, 2H), 3.04 – 2.91 (m, 1H), 2.64 – 2.50 (m, 3H), 2.31 – 2.22 (m, 2H), 1.50 – 1.40 (m, 2H), 1.35 – 1.25 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 140.6, 129.1, 128.6, 126.4, 75.1, 71.4, 55.5, 39.7, 39.0, 38.8, 33.0, 31.6, 20.2, 13.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{27}N_4O_3$ 335.2078; Found 335.2086.

*6.14. (3S, 4S, 5R)-6-azido-3-benzyl-N-butyl-4,5-dihydroxyhexanamide (**27b**)*

Following general procedure II with amide **24b** (60 mg, 0.14 mmol, 1.0 equiv) and $TiCl_4$ (0.71 ml, 0.71 mmol, 5.0 equiv) in CH_2Cl_2 (2.0 mL). Flash column chromatography on silica gel afforded alcohol **27b** (40 mg, 85%) as a colorless oil: $[\alpha]_D$ = +17.4 (c 1.0, $CHCl_3$); IR (NaCl film) ν 3329, 3027, 2929, 2872, 2101, 1634, 1557, 1455, 1277, 1074, 745, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 2H), 7.26 – 7.16 (m, 3H), 5.46 (t, J = 5.0 Hz, 1H), 4.19 – 4.06 (m, 1H), 3.74 – 3.44 (m, 5H), 3.29 – 3.09 (m, 2H), 2.84 (dd, J = 13.3, 5.8 Hz, 1H), 2.73 – 2.56 (m, 2H), 2.31 (d, J = 4.7 Hz, 2H), 1.48 – 1.39 (m, 2H), 1.36 – 1.23 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 139.9, 129.2, 128.7, 126.5, 74.0, 71.9, 54.7, 39.8, 38.3, 37.7, 34.5, 31.5, 20.2, 13.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{27}N_4O_3$ 335.2078; Found 335.2088.

*6.15. (3R, 4S, 5R)-6-azido-3-benzyl-4,5-dihydroxy-N-((S)-tetrahydrofuran-3-yl)hexanamide (**28a**)*

Following general procedure II with amide **25a** (30 mg, 0.07 mmol, 1.0 equiv) and $TiCl_4$ (0.34 ml, 0.34 mmol, 5.0 equiv) in CH_2Cl_2 (1.5 mL). Flash column chromatography on silica gel afforded alcohol **28a** (20 mg, 84%) as a colorless oil: $[\alpha]_D$ = –15.3 (c 0.8, $CHCl_3$); IR (NaCl film) ν 3306, 3025, 2926, 2869, 2101, 1638, 1543, 1453, 1289, 1069, 751, 701, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.25 – 7.14 (m, 3H), 5.68 (d, J = 7.1 Hz, 1H), 5.15 (broad s, 1H), 4.47 (tdt, J = 7.6, 5.3, 2.8 Hz, 1H), 3.87 (dt, J = 8.6, 7.3 Hz, 1H), 3.80 – 3.68 (m, 5H), 3.59 – 3.51 (m, 2H), 3.04 – 2.92 (m, 1H), 2.63 – 2.50 (m, 3H), 2.30 – 2.21 (m, 3H), 1.81 – 1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 140.4,

129.2, 128.7, 126.5, 75.0, 73.3, 71.3, 66.8, 55.4, 50.7, 38.9, 38.6, 33.1, 33.0; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{25}N_4O_4$ 349.1870; Found 349.1882.

*6.16. (3S, 4S, 5R)-6-azido-3-benzyl-4,5-dihydroxy-N-((S)-tetrahydrofuran-3-yl)hexanamide (**28b**)*

Following general procedure II with amide **25b** (20 mg, 0.05 mmol, 1.0 equiv) and $TiCl_4$ (0.23 ml, 0.23 mmol, 5.0 equiv) in CH_2Cl_2 (1.5 mL). Flash column chromatography on silica gel afforded alcohol **28b** (14 mg, 88%) as a colorless oil: $[\alpha]_D$ = +5.2 (*c* 0.5, $CHCl_3$); IR (NaCl film) ν 3311, 2924, 2101, 1636, 1541, 1454, 1286, 1080, 749, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 5.64 (d, *J* = 7.2 Hz, 1H), 4.43 (dtt, *J* = 10.3, 5.4, 2.7 Hz, 1H), 3.88 – 3.47 (m, 10H), 2.85 (dd, *J* = 13.3, 5.6 Hz, 1H), 2.67 (dd, *J* = 13.2, 10.1 Hz, 1H), 2.64 – 2.57 (m, 1H), 2.36 – 2.15 (m, 3H), 1.69 – 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 139.8, 129.3, 128.8, 126.6, 74.1, 73.4, 71.9, 66.8, 54.7, 50.7, 38.3, 37.8, 34.4, 33.0; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{25}N_4O_4$ 349.1870; Found 349.1896.

*6.17. (3R, 4S, 5R)-6-azido-3-benzyl-4,5-dihydroxy-N-((1S, 2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)hexanamide (**29a**)*

Following general procedure II with amide **26a** (90 mg, 0.18 mmol, 1.0 equiv) and $TiCl_4$ (0.17 ml, 0.90 mmol, 5.0 equiv) in CH_2Cl_2 (2.5 mL). Flash column chromatography on silica gel afforded alcohol **29a** (60 mg, 81%) as a colorless oil: $[\alpha]_D$ = +6.7 (*c* 0.2, acetone); IR (NaCl film) ν 3333, 3040, 2920, 2105, 1610, 1560, 1455, 1320, 1067, 1055, 741, 702 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.27 – 7.11 (m, 9H), 5.28 (d, *J* = 5.1 Hz, 1H), 4.49 (td, *J* = 5.1, 1.9 Hz, 1H), 3.82 (ddd, *J* = 9.0, 6.3, 2.6 Hz, 1H), 3.73 (dd, *J* = 9.0, 1.9 Hz, 1H), 3.56 (dd, *J* = 12.6, 2.6 Hz, 1H), 3.40 (dd, *J* = 12.6, 6.4 Hz, 1H), 3.25 (s, 1H), 3.08 (dd, *J* = 16.3, 5.2 Hz, 1H), 2.97 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.85 (dd, *J* = 16.4, 1.9 Hz, 1H), 2.73 – 2.66 (m, 1H), 2.55 – 2.46 (m, 2H), 2.30 (dd, *J* = 14.9, 3.9 Hz, 1H); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ

174.7, 142.5, 142.1, 141.7, 130.3, 129.1, 128.5, 127.4, 126.7, 125.8, 125.3, 74.0, 73.4, 72.3, 58.3, 56.0, 40.4, 39.9, 38.2, 34.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{27}N_4O_4$ 411.2027; Found 411.2021.

*6.18. (3S, 4S, 5R)-6-azido-3-benzyl-4,5-dihydroxy-N-((1S, 2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)hexanamide (**29b**)*

Following general procedure II with amide **26b** (45 mg, 0.09 mmol, 1.0 equiv) and $TiCl_4$ (0.09 ml, 0.45 mmol, 5.0 equiv) in CH_2Cl_2 (2.0 mL). Flash column chromatography on silica gel afforded alcohol **29b** (31 mg, 84%) as a colorless oil: $[\alpha]_D$ = +25.7 (*c* 1.0, MeOH); IR (NaCl film) ν 3331, 3050, 2922, 2100, 1635, 1524, 1455, 1300, 1053, 748, 701 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.31 – 7.14 (m, 9H), 5.32 (d, *J* = 5.1 Hz, 1H), 4.57 (td, *J* = 5.2, 2.3 Hz, 1H), 3.67 (ddd, *J* = 9.3, 7.0, 2.5 Hz, 1H), 3.46 (dd, *J* = 12.7, 2.5 Hz, 1H), 3.42 (dd, *J* = 9.2, 1.9 Hz, 1H), 3.28 (dd, *J* = 12.8, 7.1 Hz, 1H), 3.13 (dd, *J* = 16.5, 5.2 Hz, 1H), 2.93 (dd, *J* = 16.4, 2.2 Hz, 1H), 2.79 (dd, *J* = 7.4, 1.7 Hz, 2H), 2.69 – 2.57 (m, 2H), 2.35 (dd, *J* = 14.8, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.5, 142.1, 141.8, 141.6, 130.4, 129.4, 129.0, 127.8, 127.1, 126.1, 125.3, 74.0, 72.9, 72.8, 58.9, 55.6, 40.5, 39.8, 38.6, 35.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{27}N_4O_4$ 411.2027; Found 411.2020.

*6.19. (3R, 4S, 5R)-3-benzyl-N-butyl-4,5-dihydroxy-6-(4-methylphenylsulfonamido)hexanamide (**30a**)*

Following general procedure III with azide **27a** (30 mg, 0.09 mmol, 1.0 equiv) and Pd/C (10 mg, 10 mol%) in 2.0 mL of MeOH. Then, Et_3N (18 μL, 0.13 mmol, 1.5 equiv) and TsCl (21 mg, 0.11 mmol, 1.2 equiv) in CH_2Cl_2 (2.0 mL) was used to give the desired sulfonamide. Flash column chromatography on silica gel afforded sulfonamide **30a** (29 mg, 70%) as a colorless oil: $[\alpha]_D$ = –8.4 (*c* 0.8, $CHCl_3$); IR (NaCl film) ν 3321, 3027, 2929, 2872, 1634, 1557, 1454, 1324, 1158, 1092, 753, 701, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.21 (m, 4H), 7.22 – 7.13 (m, 3H), 5.69 (t, *J*

= 6.6 Hz, 1H), 5.54 (t, *J* = 5.7 Hz, 1H), 5.03 (d, *J* = 2.5 Hz, 1H), 3.71 (s, 2H), 3.56 (s, 1H), 3.31 – 3.07 (m, 4H), 2.95 (d, *J* = 10.4 Hz, 1H), 2.58 – 2.45 (m, 2H), 2.40 (s, 3H), 2.27 – 2.22 (m, 2H), 1.47 – 1.38 (m, 2H), 1.34 – 1.23 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 143.6, 140.6, 136.8, 129.9, 129.3, 128.6, 127.2, 126.2, 74.7, 70.8, 46.9, 39.7, 38.7, 38.6, 33.4, 31.5, 21.7, 20.2, 13.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{35}N_2O_5S$ 463.2261; Found 463.2236.

*6.20. (3S, 4S, 5R)-3-benzyl-N-butyl-4,5-dihydroxy-6-(4-methylphenylsulfonamido)hexanamide (**30b**)*

Following general procedure III with azide **27b** (30 mg, 0.09 mmol, 1.0 equiv) and Pd/C (10 mg, 10 mol%) in 2.0 mL of MeOH. Then, Et_3N (18 μL, 0.13 mmol, 1.5 equiv) and TsCl (21 mg, 0.11 mmol, 1.2 equiv) in CH_2Cl_2 (2.0 mL) was used to give the desired sulfonamide. Flash column chromatography on silica gel afforded sulfonamide **30b** (28 mg, 66%) as a colorless oil: $[\alpha]_D$ = +4.5 (*c* 1.0, $CHCl_3$); IR (NaCl film) ν 3368, 3027, 2928, 2872, 1726, 1636, 1455, 1288, 1159, 1092, 745, 704, 661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.25 (m, 4H), 7.24 – 7.14 (m, 3H), 5.52 (t, *J* = 5.7 Hz, 1H), 5.21 (t, *J* = 6.1 Hz, 1H), 4.45 (broad s, 1H), 3.88 (broad s, 1H), 3.57 (d, *J* = 9.2 Hz, 1H), 3.49 – 3.43 (m, 1H), 3.30 – 3.22 (m, 1H), 3.18 – 3.04 (m, 3H), 2.81 (dd, *J* = 12.5, 5.0 Hz, 1H), 2.70 – 2.57 (m, 2H), 2.41 (s, 3H), 2.36 (dd, *J* = 16.2, 6.9 Hz, 1H), 2.17 (dd, *J* = 16.2, 2.1 Hz, 1H), 1.44 – 1.35 (m, 2H), 1.33 – 1.23 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 143.6, 140.0, 136.8, 129.9, 129.3, 128.7, 127.2, 126.5, 73.6, 71.0, 46.1, 39.7, 38.6, 37.2, 34.1, 31.5, 21.7, 20.1, 13.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{35}N_2O_5S$ 463.2261; Found 463.2243.

*6.21. (3R, 4S, 5R)-3-benzyl-4,5-dihydroxy-6-(4-methylphenylsulfonamido)-N-((S)-tetrahydrofuran-3-yl)hexanamide (**31a**)*

Following general procedure III with azide **28a** (20 mg, 0.06 mmol, 1.0 equiv) and Pd/C (7 mg, 10 mol%) in 2.0 mL of MeOH. Then, Et_3N (12 μL, 0.09 mmol, 1.5 equiv) and TsCl (13 mg, 0.07 mmol, 1.2

equiv) in CH_2Cl_2 (1.5 mL) was used to give the desired sulfonamide. Flash column chromatography on silica gel afforded sulfonamide **31a** (19 mg, 69%) as a colorless oil: $[\alpha]_D$ = –3.3 (*c* 0.8, acetone); IR (NaCl film) ν 3355, 2980, 2919, 1715, 1610, 1455, 1362, 1222, 1158 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 7.80 – 7.74 (m, 2H), 7.43 – 7.37 (m, 2H), 7.28 – 7.21 (m, 2H), 7.19 – 7.13 (m, 3H), 6.27 (t, *J* = 6.2 Hz, 1H), 5.34 (d, *J* = 3.4 Hz, 1H), 4.36 (tdt, *J* = 7.3, 5.7, 3.7 Hz, 1H), 4.27 – 4.15 (m, 2H), 3.82 – 3.65 (m, 3H), 3.65 (broad s, 1H), 3.52 (d, *J* = 8.8 Hz, 1H), 3.46 (dd, *J* = 9.1, 3.6 Hz, 1H), 3.31 (ddd, *J* = 12.8, 6.5, 3.9 Hz, 1H), 2.95 (ddd, *J* = 13.0, 7.0, 6.1 Hz, 1H), 2.89 – 2.83 (m, 1H), 2.57 – 2.48 (m, 1H), 2.46 (dd, *J* = 13.2, 11.0 Hz, 1H), 2.40 (s, 3H), 2.34 (dd, *J* = 15.5, 7.5 Hz, 1H), 2.22 – 2.11 (m, 2H), 1.85 – 1.75 (m, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 206.1, 173.6, 143.8, 142.1, 139.0, 130.4, 130.0, 129.1, 127.9, 126.6, 76.4, 73.4, 71.3, 67.2, 51.2, 48.6, 39.6, 38.4, 33.7, 33.3, 21.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{33}N_2O_6S$ 477.2054; Found 477.2129.

*6.22. (3S, 4S, 5R)-3-benzyl-4,5-dihydroxy-6-(4-methylphenylsulfonamido)-N-((S)-tetrahydrofuran-3-yl)hexanamide (**31b**)*

Following general procedure III with azide **28b** (14 mg, 0.04 mmol, 1.0 equiv) and Pd/C (5 mg, 10 mol%) in 2.0 mL of MeOH. Then, Et_3N (8 μL, 0.06 mmol, 1.5 equiv) and TsCl (9 mg, 0.05 mmol, 1.2 equiv) in CH_2Cl_2 (1.5 mL) was used to give the desired sulfonamide. Flash column chromatography on silica gel afforded sulfonamide **31b** (13 mg, 68%) as a colorless oil: $[\alpha]_D$ = +18.9 (*c* 0.4, $CHCl_3$); IR (NaCl film) ν 3360, 3004, 2917, 2849, 1714, 1420, 1362, 1222, 1161, 1092, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.24 (m, 4H), 7.25 – 7.15 (m, 3H), 5.74 (d, *J* = 7.6 Hz, 1H), 5.15 (t, *J* = 6.4 Hz, 1H), 4.39 (tdd, *J* = 7.1, 6.3, 5.3, 2.6 Hz, 1H), 3.93 – 3.76 (m, 1H), 3.74 (dd, *J* = 9.2, 5.4 Hz, 2H), 3.60 (d, *J* = 9.6 Hz, 2H), 3.51 – 3.41 (m, 1H), 3.30 – 3.20 (m, 1H), 3.17 – 3.04 (m, 1H), 2.82 (dd, *J* = 12.4, 4.7 Hz, 1H), 2.71 – 2.56 (m, 1H), 2.42 (s, 3H), 2.39 – 2.01 (m, 5H), 1.68 – 1.56

(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 143.7, 139.9, 136.8, 129.9, 129.3, 128.7, 127.2, 126.6, 73.6, 73.3, 71.0, 66.8, 50.7, 47.7, 46.1, 38.7, 37.3, 33.9, 33.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{33}N_2O_6S$ 477.2054; Found 477.2107.

*6.23. (3R, 4S, 5R)-3-benzyl-4,5-dihydroxy-N-((1S, 2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-6-(4-methylphenylsulfonamido)hexanamide (**32a**)*

Following general procedure III with azide **29a** (60 mg, 0.15 mmol, 1.0 equiv) and Pd/C (16 mg, 10 mol%) in 2.0 mL of MeOH. Then, Et_3N (30 μL, 0.22 mmol, 1.5 equiv) and TsCl (33 mg, 0.18 mmol, 1.2 equiv) in CH_2Cl_2 (2.0 mL) was used to give the desired sulfonamide. Flash column chromatography on silica gel afforded sulfonamide **32a** (53 mg, 67%) as a colorless oil: $[\alpha]_D$ = +7.5 (*c* 1.0, MeOH); IR (NaCl film) ν 3359, 3050, 2924, 1636, 1522, 1455, 1323, 1158, 1092, 1054, 749, 702, 666 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.12 (m, 9H), 5.25 (d, *J* = 5.0 Hz, 1H), 4.48 (td, *J* = 5.2, 2.0 Hz, 1H), 3.70 – 3.56 (m, 2H), 3.37 – 3.23 (m, 2H), 3.09 (dd, *J* = 16.5, 5.0 Hz, 1H), 2.96 – 2.83 (m, 3H), 2.71 – 2.58 (m, 1H), 2.50 – 2.35 (m, 5H), 2.25 (dd, *J* = 14.7, 4.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.7, 144.7, 142.2, 142.1, 141.7, 138.7, 130.8, 130.5, 129.3, 128.9, 128.2, 127.9, 127.0, 126.1, 125.5, 74.7, 73.9, 71.7, 58.8, 48.4, 40.5, 40.2, 38.1, 34.5, 21.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{35}N_2O_6S$ 539.2210; Found 539.2228.

*6.24. (3S, 4S, 5R)-3-benzyl-4,5-dihydroxy-N-((1S, 2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-6-(4-methylphenylsulfonamido)hexanamide (**32b**)*

Following general procedure III with azide **29b** (30 mg, 0.07 mmol, 1.0 equiv) and Pd/C (8 mg, 10 mol%) in 2.0 mL of MeOH. Then, Et_3N (15 μL, 0.11 mmol, 1.5 equiv) and TsCl (17 mg, 0.09 mmol, 1.2 equiv) in CH_2Cl_2 (1.5 mL) was used to give the desired sulfonamide. Flash column chromatography on silica gel afforded sulfonamide **32b** (26 mg, 65%) as a colorless oil: $[\alpha]_D$ = +11.2 (*c* 0.5, MeOH); IR

(NaCl film) ν 3350, 3020, 2923, 1635, 1522, 1455, 1321, 1156, 1091, 1052, 749, 701, 663 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.12 (m, 9H), 5.30 (d, *J* = 5.1 Hz, 1H), 4.56 (td, *J* = 5.2, 2.3 Hz, 1H), 3.52 (td, *J* = 8.5, 2.9 Hz, 1H), 3.29 – 3.22 (m, 2H), 3.13 (dd, *J* = 16.4, 5.3 Hz, 1H), 2.92 (dd, *J* = 16.4, 2.3 Hz, 1H), 2.78 – 2.66 (m, 3H), 2.63 – 2.48 (m, 2H), 2.41 (s, 3H), 2.30 (dd, *J* = 14.7, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.5, 144.6, 142.1, 141.8, 141.6, 138.7, 130.7, 130.4, 129.4, 129.0, 128.2, 127.8, 127.1, 126.1, 125.3, 74.0, 73.6, 72.0, 58.9, 47.9, 40.6, 39.9, 38.6, 35.7, 21.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{35}N_2O_6S$ 539.2210; Found 539.2219.

*6.25. (3R, 4S, 5R)-3-benzyl-N-butyl-4,5-dihydroxy-6-(N-isobutyl-4-methylphenylsulfonamido) hexanamide (**33a**)*

Following general procedure IV with amine **30a** (25 mg, 0.05 mmol, 1.0 equiv), K_2CO_3 (15 mg, 0.11 mmol, 2.0 equiv) and isobutyl bromide (15 mg, 0.11 mmol, 2.0 equiv) in MeCN (1.5 mL). Flash column chromatography on silica gel afforded product **33a** (27 mg, 96%) as a colorless oil: $[\alpha]_D$ = –22.2 (*c* 0.5, $CHCl_3$); IR (NaCl film) ν 3379, 2959, 2871, 1635, 1557, 1455, 1331, 1155, 1089, 757, 701, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.24 (m, 4H), 7.25 – 7.15 (m, 3H), 5.51 (d, *J* = 2.8 Hz, 1H), 5.39 (t, *J* = 5.4 Hz, 1H), 3.77 (t, *J* = 8.9 Hz, 1H), 3.65 (d, *J* = 2.3 Hz, 1H), 3.55 (d, *J* = 8.5 Hz, 1H), 3.38 (dd, *J* = 15.2, 2.1 Hz, 1H), 3.31 – 3.09 (m, 4H), 3.01 (dd, *J* = 13.4, 3.7 Hz, 1H), 2.79 (dd, *J* = 13.2, 5.9 Hz, 1H), 2.70 – 2.62 (m, 1H), 2.61 – 2.52 (m, 1H), 2.43 (s, 3H), 2.30 – 2.24 (m, 2H), 2.03 – 1.91 (m, 1H), 1.49 – 1.40 (m, 2H), 1.36 – 1.27 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 143.7, 140.9, 135.5, 129.9, 129.3, 128.5, 127.5, 126.2, 76.2, 71.1, 59.3, 55.1, 39.7, 39.1, 38.8, 33.3, 31.6, 27.2, 21.7, 20.4, 20.2, 20.0, 13.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{43}N_2O_5S$ 519.2887; Found 519.2891.

*6.26. (3S, 4S, 5R)-3-benzyl-N-butyl-4,5-dihydroxy-6-(N-isobutyl-4-methylphenylsulfonamido) hexanamide (**33b**)*

Following general procedure IV with amine **30b** (25 mg, 0.05 mmol, 1.0 equiv), K_2CO_3 (15 mg, 0.11 mmol, 2.0 equiv) and isobutyl bromide (15 mg, 0.11 mmol, 2.0 equiv) in MeCN (1.5 mL). Flash column chromatography on silica gel afforded product **33b** (26 mg, 92%) as white needle after crystallisation: mp (CH_2Cl_2/MeOH) 140−142 °C; $[\alpha]_D$ = –2.4 (*c* 0.5, $CHCl_3$); IR (NaCl film) ν 3375, 2959, 2929, 1636, 1455, 1330, 1155, 1090, 755, 701, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.24 (m, 4H), 7.24 – 7.16 (m, 3H), 5.50 (t, *J* = 5.6 Hz, 1H), 5.13 (d, *J* = 8.3 Hz, 1H), 4.05 (d, *J* = 2.6 Hz, 1H), 3.64 (t, *J* = 8.2 Hz, 1H), 3.44 – 3.33 (m, 2H), 3.30 – 3.12 (m, 3H), 3.08 (dd, *J* = 13.3, 8.8 Hz, 1H), 2.85 (ddd, *J* = 22.3, 13.4, 6.5 Hz, 2H), 2.72 (dd, *J* = 13.6, 9.6 Hz, 1H), 2.65 – 2.56 (m, 1H), 2.53 (dd, *J* = 15.9, 2.8 Hz, 1H), 2.42 (s, 3H), 2.25 (dd, *J* = 16.0, 6.2 Hz, 1H), 2.07 – 1.95 (m, 1H), 1.52 – 1.38 (m, 2H), 1.39 – 1.25 (m, 2H), 0.95 – 0.90 (m, 6H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 143.7, 140.3, 135.6, 129.9, 129.3, 128.6, 127.5, 126.3, 74.1, 72.7, 59.1, 54.5, 39.8, 37.8, 37.6, 35.1, 31.6, 27.0, 21.7, 20.3, 20.2, 20.0, 13.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{43}N_2O_5S$ 519.2887; Found 519.2884.

*6.27. (3R, 4S, 5R)-3-benzyl-4,5-dihydroxy-6-(N-isobutyl-4-methylphenylsulfonamido)-N-((S)-tetrahydrofuran-3-yl)hexanamide (**34a**)*

Following general procedure IV with amine **31a** (12 mg, 0.03 mmol, 1.0 equiv), K_2CO_3 (7 mg, 0.05 mmol, 2.0 equiv) and isobutyl bromide (7 mg, 0.05 mmol, 2.0 equiv) in MeCN (1.5 mL). Flash column chromatography on silica gel afforded product **34a** (12.0 mg, 89%) as a colorless oil: $[\alpha]_D$ = –2.4 (*c* 0.8, $CHCl_3$); IR (NaCl film) ν 3365, 2959, 2926, 2871, 1642, 1541, 1454, 1330, 1155, 1089, 735, 702, 656 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.24 (m, 4H), 7.24 – 7.17 (m, 3H),

5.64 (d, *J* = 7.5 Hz, 1H), 5.29 (s, 1H), 4.45 (tdt, *J* = 7.6, 5.5, 2.9 Hz, 1H), 3.92 – 3.83 (m, 1H), 3.82 – 3.72 (m, 3H), 3.64 (broad s, 1H), 3.60 – 3.52 (m, 2H), 3.37 (dd, *J* = 15.3, 2.1 Hz, 1H), 3.25 (dd, *J* = 15.3, 8.7 Hz, 1H), 3.13 (dd, *J* = 13.2, 9.1 Hz, 1H), 3.02 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.79 (dd, *J* = 13.2, 6.0 Hz, 1H), 2.67 (broad s, 1H), 2.57 (dd, *J* = 13.7, 11.4 Hz, 1H), 2.44 (s, 3H), 2.34 – 2.20 (m, 3H), 2.03 – 1.91 (m, 1H), 1.82 – 1.72 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 143.8, 140.7, 135.4, 129.9, 129.3, 128.6, 127.5, 126.3, 76.1, 73.3, 71.2, 66.9, 59.4, 55.0, 50.7, 39.0, 38.6, 33.2, 33.1, 27.2, 21.7, 20.4, 20.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{41}N_2O_6S$ 533.2680; Found 533.2763.

*6.28. (3S, 4S, 5R)-3-benzyl-4,5-dihydroxy-6-(N-isobutyl-4-methylphenylsulfonamido)-N-((S)-tetrahydrofuran-3-yl)hexanamide (**34b**)*

Following general procedure IV with amine **31b** (7 mg, 0.01 mmol, 1.0 equiv), K_2CO_3 (4 mg, 0.03 mmol, 2.0 equiv) and isobutyl bromide (4 mg, 0.03 mmol, 2.0 equiv) in MeCN (1.5 mL). Flash column chromatography on silica gel afforded product **34b** (7 mg, 89%) as a colorless oil: $[\alpha]_D$ = –35.6 (*c* 0.5, $CHCl_3$); IR (NaCl film) ν 3360, 2958, 2924, 2870, 1776, 1641, 1547, 1453, 1331, 1156, 1089, 736, 702, 656 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.26 (m, 4H), 7.24 – 7.18 (m, 3H), 5.65 (d, *J* = 7.4 Hz, 1H), 4.83 (s, 1H), 4.45 (tdt, *J* = 7.7, 5.5, 2.9 Hz, 1H), 4.06 (broad s, 1H), 3.92 – 3.84 (m, 1H), 3.84 – 3.73 (m, 2H), 3.68 – 3.61 (m, 2H), 3.45 – 3.33 (m, 2H), 3.25 (dd, *J* = 15.3, 7.5 Hz, 1H), 3.08 (dd, *J* = 13.3, 8.7 Hz, 1H), 2.86 (ddd, *J* = 24.7, 13.4, 6.4 Hz, 2H), 2.72 (dd, *J* = 13.7, 9.9 Hz, 1H), 2.65 – 2.58 (m, 1H), 2.48 (dd, *J* = 16.0, 2.9 Hz, 1H), 2.43 (s, 3H), 2.31 – 2.18 (m, 2H), 2.05 – 1.98 (m, 1H), 1.75 – 1.66 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 143.7, 140.2, 135.6, 129.9, 129.3, 128.7, 127.5, 126.4, 74.0, 73.4, 72.8, 66.9, 59.2, 54.4, 50.8, 37.9, 37.7, 34.9, 33.0, 27.0, 21.7, 20.3, 20.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{41}N_2O_6S$ 533.2680; Found 533.2664.

*6.29. (3R, 4S, 5R)-3-benzyl-4,5-dihydroxy-N-((1S, 2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-6-(N-isobutyl-4-methylphenylsulfonamido)hexanamide (**35a**)*

Following general procedure IV with amine **32a** (30 mg, 0.06 mmol, 1.0 equiv), K_2CO_3 (15 mg, 0.11 mmol, 2.0 equiv) and isobutyl bromide (15 mg, 0.11 mmol, 2.0 equiv) in MeCN (1.5 mL). Flash column chromatography on silica gel afforded product **35a** (30 mg, 90%) as a white amorphous solid: mp 133−135 °C; $[\alpha]_D$ = –16.7 (*c* 0. 5, $CHCl_3$); IR (NaCl film) ν 3300, 2958, 2927, 2857, 1728, 1458, 1287, 1273, 1122, 1072, 1040, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.16 (m, 9H), 6.18 (d, *J* = 8.2 Hz, 1H), 5.33 (dd, *J* = 8.1, 5.1 Hz, 1H), 5.13 (d, *J* = 3.4 Hz, 1H), 4.59 (broad s, 1H), 3.81 (ddd, *J* = 8.8, 6.5, 2.3 Hz, 1H), 3.66 (d, *J* = 2.8 Hz, 1H), 3.62 (dd, *J* = 8.9, 2.1 Hz, 1H), 3.38 (dd, *J* = 15.3, 2.1 Hz, 1H), 3.27 (dd, *J* = 15.3, 8.7 Hz, 1H), 3.19 – 3.10 (m, 2H), 3.05 (dd, *J* = 13.0, 3.3 Hz, 1H), 2.91 (dd, *J* = 16.5, 2.4 Hz, 1H), 2.81 (dd, *J* = 13.3, 6.1 Hz, 1H), 2.74 – 2.61 (m, 3H), 2.48 – 2.34 (m, 5H), 2.02 – 1.92 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 143.8, 140.7, 140.2, 140.0, 135.4, 129.9, 129.4, 128.6, 127.6, 127.5, 126.3, 125.6, 124.8, 75.9, 73.5, 71.1, 59.3, 57.8, 54.9, 39.8, 39.1, 38.9, 33.5, 27.2, 21.7, 20.4, 20.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{33}H_{43}N_2O_6S$ 595.2836; Found 595.2838.

*6.30. (3S, 4S, 5R)-3-benzyl-4,5-dihydroxy-N-((1S, 2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-6-(N-isobutyl-4-methylphenylsulfonamido)hexanamide (**35b**)*

Following general procedure IV with amine **32b** (25 mg, 0.05 mmol, 1.0 equiv), K_2CO_3 (13 mg, 0.09 mmol, 2.0 equiv) and isobutyl bromide (13 mg, 0.09 mmol, 2.0 equiv) in MeCN (1.5 mL). Flash column chromatography on silica gel afforded product **35b** (26 mg, 93%) as a white amorphous solid: mp 119−122 °C; $[\alpha]_D$ = +11.7 (*c* 0.3, $CHCl_3$); IR (NaCl film) ν 3320, 3026, 2959, 2924, 2853, 1738, 1636, 1522, 1456, 1260, 1155, 1090, 1048, 750, 702, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3

Hz, 2H), 7.34 – 7.25 (m, 5H), 7.27 – 7.12 (m, 6H), 6.27 (d, *J* = 8.4 Hz, 1H), 5.36 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.70 – 4.63 (m, 1H), 4.33 (d, *J* = 7.9 Hz, 1H), 4.09 (d, *J* = 3.8 Hz, 1H), 3.82 – 3.69 (m, 1H), 3.50 – 3.37 (m, 2H), 3.22 – 3.08 (m, 2H), 3.07 – 2.85 (m, 4H), 2.81 – 2.70 (m, 2H), 2.54 (dd, *J* = 16.0, 2.3 Hz, 2H), 2.46 – 2.35 (m, 4H), 2.06 – 1.96 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 143.7, 140.2, 140.1, 135.6, 129.9, 129.4, 128.7, 128.5, 127.5, 127.4, 126.4, 125.5, 124.6, 74.4, 73.5, 73.0, 59.0, 57.8, 53.9, 39.9, 38.1, 37.7, 35.1, 27.0, 21.7, 20.3, 20.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{33}H_{43}N_2O_6S$ 595.2836; Found 595.2818.

6.31. Molecular docking

Compounds **33**-**35** were built in PyMOL Molecular Graphics System (Version 1.8.5.0 Schrödinger, LLC) based on the Darunavir structure, and energy minimized using ConfBuster.[36] Docking simulations were performed using Autodock VINA 1.1.2.[37] The crystal structure coordinates of the wild-type HIV protease in complex with Darunavir were taken from PDB 4LL3.[38] Hydrogen atoms were added using PyMOL for Darunavir and the reduce software version 3.23 for the protease.[39] One crystallographic water molecule, located in the binding pocket and hydrogen-bonded to the amine of ILE50 of both subunits, was kept for the dockings. Docking simulations were carried out using a rigid receptor for the protein with flexibility for the ASP30 and ILE84 side chains, a search space centered on Darunavir from the crystallographic structure of size of 22.5 Å along the X and Y axis and 26.5 Å along the Z axis, and an exhaustiveness of 48. Validation of the docking protocol was carried out using self-docking of Darunavir, leading to an RMSD of 0.61 Å between the docked and crystallographic structures. Because compounds **33**-**35** have a scaffold similar to Darunavir, no further optimization of the docking protocol was considered. In presence of multiple poses with a similar score, the pose with the highest similarity with the Darunavir crystallographic structure was considered as the best pose. The

interactions between the compounds and the HIV protease has been analyzed using the Poseview tool from the ProteinsPlus server.[40, 41]

6.32. Cell lines culture

Human HT-29 colon adenocarcinoma and MCF7 breast carcinoma cancer cells were purchased from the American Type Culture Collection (Manassas, VA) while M21 human skin melanoma cells were kindly provided by Dr. David Cheresh (University of California, San Diego School of Medicine). All cell lines were maintained in high-glucose Dulbecco's minimal essential medium (DMEM, Gibco, Thermo Fisher Scientific) supplemented with 5 % (v/v) fetal bovine serum (FBS, Gibco, Thermo Fisher Scientific) and they were grown at 37 °C in a moisturesaturated atmosphere containing 5% CO_2.

6.33. Antiproliferative activity assay

The growth inhibition potency of all compounds was assessed using the procedure recommended by the National Cancer Institute (NCI) Developmental Therapeutics Program for its drug screening program with slight modifications.[31] Briefly, 96-well Costar microtiter clear plates were seeded with 75 µL of a suspension of either HT-29 (5×10^3), M21 (3×10^3), or MCF7 (3.5×10^3) cells per well in medium. Plates were incubated for 24 h. Freshly solubilised drugs in DMSO (40 mM) were diluted in fresh medium and 75 µL aliquots containing serially diluted concentrations of the drug were added. Final drug concentrations ranged from 100 µM to 78 nM. DMSO concentration was kept constant at < 0.5% (v/v) to prevent any related toxicity. Plates were incubated for 48 h, after which growth was stopped by the addition of cold trichloroacetic acid to the wells (10% w/v, final concentration). Afterward, plates were incubated at 4 °C for 1 h. Then, plates were washed 5-times with distilled water and a sulforhodamine B solution (0.1% w/v) in 1% acetic acid was added to each well. After 15 min at room temperature, the exceeding dye was removed and was washed 5-times with a solution of 1% acetic acid. Bound dye was

solubilized in 20 mM Tris base and the absorbance was read using an optimal wavelength (530-580 nm) with a SpectraMax® i3x (Molecular Devices). Data obtained from treated cells were compared to the control cell plates fixed on the treatment day and the percentage of cell growth was thus calculated for each drug. The experiments were done at least twice in triplicate. The assays were considered valid when the coefficient of variation was < 10% for a given set of conditions within the same experiment.

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