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Synthesis and inhibitory activities of novel C-3 substituted azafagomines: A new type of selective inhibitors of α-L-fucosidases

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ABSTRACT

The synthesis of a novel aminomethyl C-3 substituted L-*fuco*-azafagomine and of its C-6 epimer from D-lyxose is reported. The key step of the synthesis is the introduction of the biimino (–NH–NH–) moiety by reductive hydrazination of a 1-deoxy-ketohexose with *tert*-butyl carbazate. The 3-aminomethyl-azafagomine derivatives were used as lead compounds in the generation of libraries of novel types of derivatives by attaching different hydrophobic groups on the aminomethyl substituent through amide linkages. These polyhydroxylated hexahydropyridazines can be viewed as a new type of diaza-*C*-glycoside analogues having a biimino (–NH–NH–) moiety. The conformational analysis and the glycosidase inhibitory properties of all the new C-3 substituted azafagomines synthesized are also reported. Those having L-*fuco* configuration have shown a selective inhibition of α-L-fucosidases.

1. Introduction

α-L-Fucosidase is an exoglycosidase involved in the trimming of non-reducing terminal L-fucose units during the biosynthetic processing of fucose-containing glycoconjugates.[1] This enzyme, in common with other glycosidases, has glycosyl transfer activity and, therefore can be also used in the synthesis of fucosyl glycans.[2] Fucosidases are associated with many disorders including inflammation,[3] cancer,[4] cystic fibrosis,[5] and fucosidosis.[6] This enzyme is considered an early biomarker for detecting hepatocellular and colorectal carcinomas.[7] α-L-Fucosidases have been found in human seminal plasma and in the membranes of human sperm cells and facilitate sperm transport and sperm egg-interactions. Inhibitors of these enzymes can have anticonceptive properties.[8] Inhibitors of α-L-fucosidases have been also found to inhibit the cytophatic effect of HIV and reduce infection.[9]

Among the most powerful α-L-fucosidase inhibitors are L-*fuco* hydroxylated piperidines such as L-fuconojirimycin (FNJ) **1**[10] (Fig. 1), although the intrinsic instability caused by the lability of the *N*,*O*-acetal function prevents its biological use. The 1-hydroxymethyl-FNJ,[11] and 1-aminomethyl-FNJ[12] having a C–C bond at C-1 are stable *C*-glycosyl analogues[13] that have been used to generate potent inhibitors of α-L-fucosidases.[14] On the other hand, Bols and co-workers have described the preparation of (3*S*,4*R*,5*S*)-3-methylhexahydropyridazine-4,5-diol (**2**), the so-called '*fuco*-azafagomine' (Fig. 1) that showed interesting inhibitory properties towards α-L-fucosidases.[15] Although several hydroxylated hexahydropyridazines have been reported to inhibit galactosidases

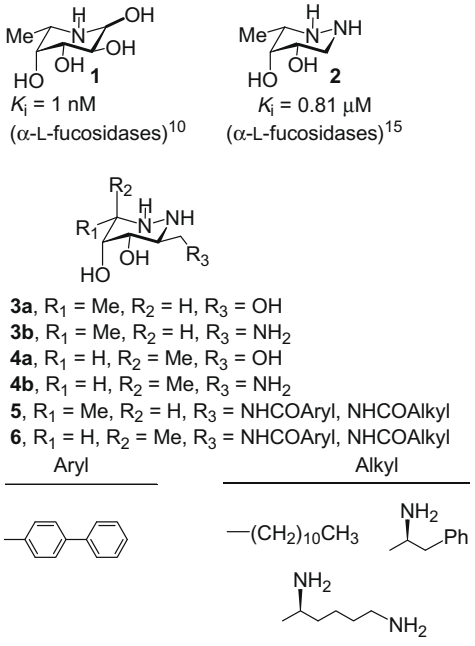

Figure 1.

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and glucosidases,[16] to the best of our knowledge, **2** is the only reported example of a L-*fuco* polyhydroxylated hexahydropyridazine.

In a preliminary communication,[17] we have reported the first synthesis and biological evaluation of L-*fuco*-3-hydroxymethyl (and aminomethyl) hexahydropyridazines **3a** and **3b**. Compound **3a** was a selective and competitive inhibitor of α-L-fucosidase from bovine kidney. The hydroxylated pyridazine moiety can be used as core structure to mimic the fucosyl cation generated in the enzymatic hydrolysis, and the hydroxymethyl or aminomethyl group at C-3 to be further functionalized giving a library of derivatives in a diversity-oriented synthesis. Although the interactions between some enzyme active sites and the corresponding inhibitors have been characterized by structural and mechanistic methods,[18] only limited information is available for the identification of important factors that contribute to high inhibition potency as well as to the dynamic motion of the glycosidase–inhibitor interaction changing from low to high binding affinity.

We describe herein the details of the synthesis of compounds **3a** and **3b** and their corresponding epimers at C-6, **4a** and **4b** (Fig. 1). These compounds can be viewed as a new type of diaza-*C*-glycoside analogues having a biimino (–NH–NH–) moiety. We also present the derivatization of **3b** and **4b** by linking different groups to the aminomethyl side chain with the generation of small libraries of enzymatic inhibitors, compounds **5** and **6**, having aryl/alkyl moieties. All the new compounds were tested for their inhibitory activity towards 12 commercially available glycosidases. Some of the compounds that present L-*fuco* configuration constitute new selective inhibitors of α-L-fucosidase in the micromolar range.

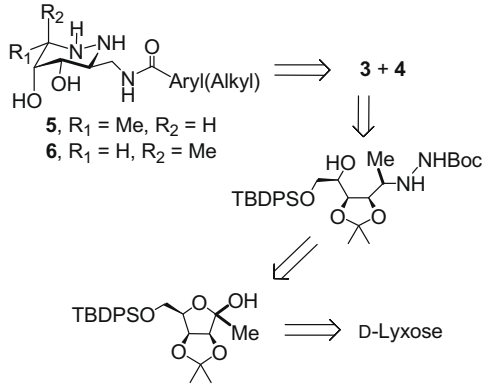
In this regard, these compounds could contribute to a better understanding of the inhibition mechanisms of fucosidases in terms of structural and conformational changes, charge dislocation and protonation as it has been made with azafagomine analogues in the case of glucosidases.[19]

2. Results and discussion

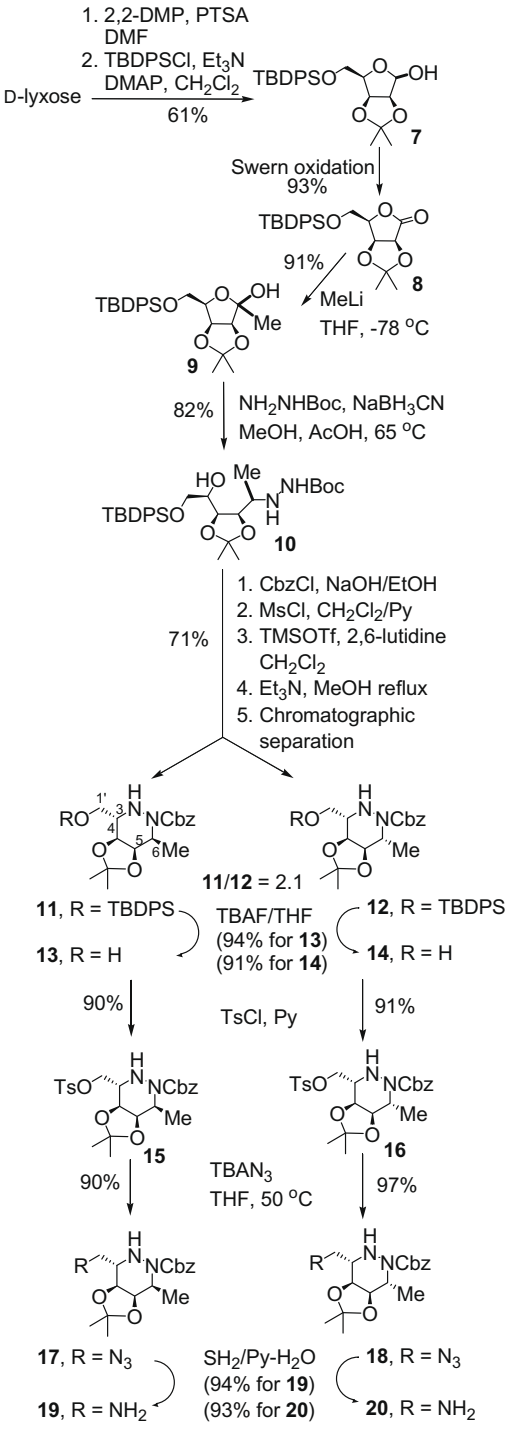
2.1. Synthesis of C-3 substituted azafagomines

The retrosynthetic analysis starting from D-lyxose is indicated in Scheme 1. The key steps of the synthesis imply cyclization of 2-methyl glycosylhydrazines, which were obtained by reductive hydrazination of a 1-deoxy-ketohexose easily prepared from D-lyxose.

Thus, starting from D-lyxose, tri-*O*-protected D-lyxonolactone **8** could be easily obtained following a similar procedure to that described in the literature[20] (Scheme 2). Addition of MeLi[21] to **8** afforded the protected 1-deoxy-ketohexose **9** as a 3:1 mixture of



Scheme 1. Retrosynthetic analysis for compounds **5** and **6**.



Scheme 2.

anomers. Reductive hydrazination of **9** using *tert*-butyl carbazate, $NaBH_3CN$ and acetic acid in MeOH at 65 °C afforded the mixture of hydrazines **10** in 82% yield. Reaction of **10** with benzyl chloroformate, followed by mesylation and selective Boc deprotection gave crude monohydrazides that were treated with Et_3N in MeOH at reflux to afford cyclic derivatives **11** and **12** as a 2.1:1 mixture of diasteroisomers. This sequence could be efficiently carried out without intermediate purification, affording the corresponding hexahydropyridazines in 71% overall yield after chromatographic separation. Deprotection of these compounds by treatment with TBAF in THF afforded the corresponding alcohols **13** and **14**.

Compounds **13** and **14** were fully characterized by their spectroscopic data but the configuration of C-6 was difficult to assign through NOE experiments. Fortunately, tosylation of **13** afforded crystalline tosyl derivative **15**, the structure of which was unambiguously confirmed by X-ray crystallography (Fig. 2).[17] Reaction of **15** with $TBAN_3$ (tetrabutylammonium azide) followed by reduction of the azido group with H_2S, afforded protected aminomethyl derivative **19**. The same reaction sequence but starting from alcohol **14** gave amine **20**.

Compounds **19** and **20** were used in the preparation of new azafagomine derivatives by linking different groups through the amine function (Scheme 3). Thus, coupling reaction of amines **19** and **20** with commercial aromatic and aliphatic carboxylic acids, including amino acid derivatives, were efficiently carried out by standard peptide synthesis using PyBOP/DIPEA as coupling reagent to give **21c–f** and **22c–e** in good yield. For the synthesis of compounds **21e**,**f** and **22e**, a further Fmoc deprotection step was performed after the coupling.

Deprotection of the acetonide group (and Boc group) in alcohol **13**, amine **19**, amides **21** and in their corresponding C-6 epimers (**14**, **20**, and **22**) under acidic conditions afforded *N*-Cbz protected hexahydropyridazines **23** and **24** in good yields. Final hydrogenolysis of these compounds under acidic conditions gave unprotected hexahydropyridazines **3**, **4**, **5**, and **6** in quantitative yields as the corresponding hydrochloride salts (Scheme 4).

The acidic conditions in the final deprotection step are critical to avoid undesired oxidations. In the absence of acidic conditions, hydrogenation of compound **11** afforded hydrazone **25** in good yield as major compound (Scheme 5). The formation of this product can be explained by oxidation of the hydrazine to the corresponding azo-compound, followed by isomerization of the double bond to the more stable hydrazone. Similar results have been previously reported in the hydrogenolysis of *N*-protected hexahydropyridazine derivatives.[19a,22]

2.2. Conformational analysis

A conformational analysis of alcohols **13** and **14** based on NMR data and molecular modeling using MacroModel[23] and the force field OPLS2001[24] has been carried out. The ^{1}H NMR spectrum of

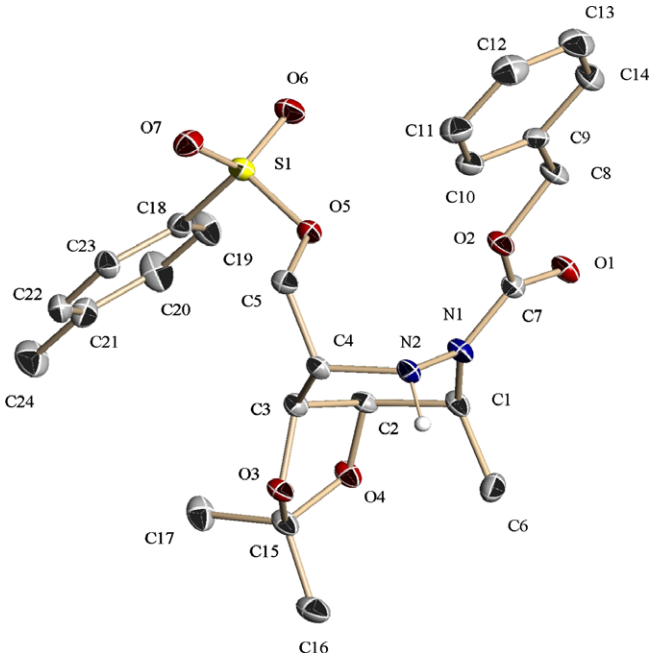
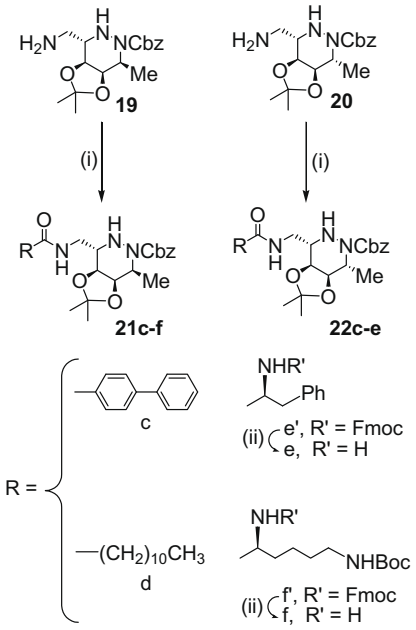


Figure 2. X-ray structure for compound **15**.

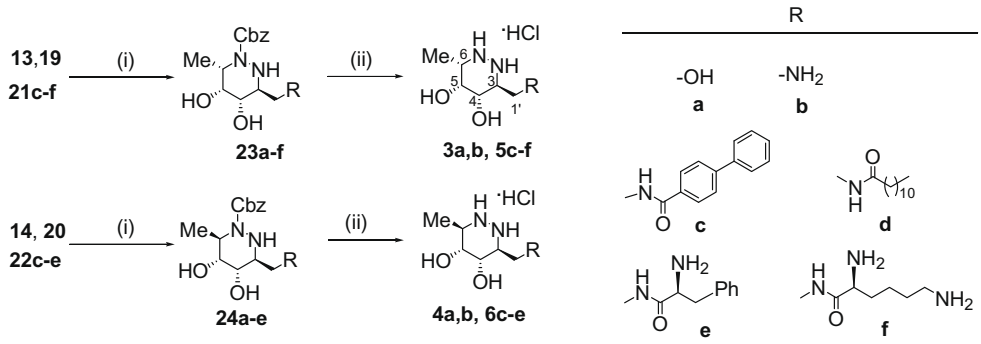


Scheme 3. Reagents and conditions: (i) RCOOH, PyBOP/DIPEA, DMF (90–100%); (ii) 20% piperidine in DMF (71–92%).

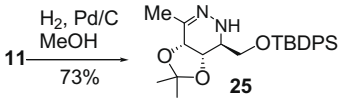
14 in DMSO-d_6 shows a large coupling constant (J = 9.1 Hz) between H-3 and H-4 whereas no coupling constant between H-5 and H-6 is observed. These results, together with a coupling constant of 5.0 Hz between H-4 and H-5, indicate that **14** adopts a chair conformation ($^2C_5$, Fig. 3a) with the C-3 substituent in equatorial and the Me-6 in axial positions. The results of the molecular dynamics are in agreement with the experimental observations.

In the case of the ^{1}H NMR spectrum of major alcohol **13** (C-6 epimer of **14**), the values for the coupling constants H-3/H-4, H-4/H-5, and H-5/H-6 are $J_{3,4}$ = 4.2 Hz, $J_{4,5}$ = 5.8 Hz, and $J_{5,6}$ = 5.1 Hz. In base of these data, the presence of only one chair conformation is discarded. Additionally, the observation of medium NOEs between Me-acetonide/H-3, H-1′/H-5, and H-1′/H-6 indicates that this compound adopts a mixture of conformations in solution of DMSO-d_6. When the minimized structure was obtained by molecular modeling using the experimental coupling constants, the result was a boat (^{2,5}B, Fig. 3c) which remains unchanged in a further minimization without any restraints. However, in this structure the observation of a NOE between Me-acetonide/H-3 is not expected. This fact indicates that the compound can also adopt a chair conformation ($^2C_5$, Fig. 3b). Thus, the experimental coupling constants are in agreement with the presence of $^2C_5$ and ^{2,5}B conformations in solution in a ratio 40:60, respectively. In the case of tosyl derivative **15**, although the X-ray structure (Fig. 2) indicated a chair conformation, its ^{1}H NMR spectrum showed coupling constant values of 4.5 Hz for $J_{3,4}$ and 5.5 Hz for $J_{4,5}$ and $J_{5,6}$. These values were previously observed for compound **13**, which indicates that the same conformational equilibrium takes place in solution in this case.

According to the ^{1}H NMR data (Table 1) of (3*S*,4*S*,5*R*,6*S*)-*N*,*O*-protected hexahydropyridazine derivatives **13**, **15**, **17**, **19**, **21c**,**d**, and **21e**′,**f**′, a correlation between coupling constant values is observed. Thus, the same conformational equilibrium described before for **13** can be predicted for these compounds. In the case of *N*-protected-*O*-unprotected derivatives **23a–c** and **23e**,**f**, the values for the coupling constants (Table 2) obtained in a CD_3OD solution indicate also the presence of a conformational equilibrium. However, in the case of completely unprotected derivatives **3a**,**b** and **5c**,**d**,**f** (Table 3), important changes were observed for $J_{3,4}$, $J_{4,5}$, and $J_{5,6}$ values, indicating a conformational change in CD_3OD



Scheme 4. Reagents and conditions: (i) HCl (1 M)/THF (1:1), 74–100%; (ii) H_2, Pd–C, MeOH–HCl (5 M), quant.



Scheme 5.

solution for these derivatives in relation to the *N*-protected-*O*-unprotected compounds. A large coupling constant between H-3 and H-4 (10.0–10.3 Hz) and a small $J_{5,6}$ value (1.2–1.3 Hz) indicated that completely unprotected derivatives adopt a major chair conformation in CD_3OD solution.

2.3. Enzymatic assays

Compounds **3a**,**b**, **4a**,**b**, **5c**–**f**, **6c**–**e**, **23**, and **24** have been analyzed for their inhibitory activities towards twelve commercially available glycosidases.[25] Compounds **23c** and **24d** could not be tested because of their low solubilities under the assay conditions. Table 4 shows the results for the inhibition analysis towards α-L-fucosidase from bovine kidney, β-galactosidase from *Escherichia coli*, amyloglucosidase from *Aspergillus niger*, maltase from yeast and β-glucosidase from almonds. These compounds did not inhibit any of the other enzymes assayed: α-galactosidase from coffe beans, β-galactosidase from *Aspergillus orizae*, α-glucosidase from rice, α-mannosidase from Jack beans, β-mannosidase from snail, β-xylosidase from *A. niger* and β-*N*-acetylglucosaminidase from Jack beans.

In general, (3*S*,4*S*,5*R*,6*S*)-hexahydropyridazine derivatives showed specific inhibitory activity towards α-L-fucosidase, presenting only some of them a very weak activity towards other enzymes. Compounds **3a**, **5c**–**f**, that share the same absolute configuration than C-(2,3,4,5) of α-L-fucopyranosides, showed a higher inhibitory activity towards α-L-fucosidase than their corresponding C-6 epimers, probably due to a lower similarity with the fucopyranosyl cation generated in the transition state of the enzymatic hydrolysis and so indicating the importance of the *S*-configuration at Me-6 to bind the enzyme. Hydroxymethyl derivative **3a** was a selective and competitive inhibitor of α-L-fucosidases from

Table 1
Coupling constants (*J*, Hz) in DMSO-d_6 for protons of the hexahydropyridazine ring in *N*,*O*-protected derivatives

Compound	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
13	4.2	5.8	5.1
15	4.5	5.5	5.5
17	4.2	5.9	5.2
19	2.0	6.0	6.0
21c	3.1	5.8	5.4
21d	3.0	5.9	5.5
21e′	2.5	5.9	5.9
21f′	3.0	6.0	5.5

Table 2
Coupling constants (*J*, Hz) in CD_3OD for protons of the hexahydropyridazine ring in *N*-protected-*O*-unprotected derivatives

Compound	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
23a	4.2	3.1	5.3
23b	3.8	3.0	5.6
23c	2.8	2.8	n.d.
23e	3.2	3.0	5.5
23f	n.d.	3.0	5.5

n.d.: not determined.

Table 3
Coupling constants (*J*, Hz) in CD_3OD for protons of the hexahydropyridazine ring in completely unprotected derivatives

Compound	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
3a	10.3	2.8	1.2
3b	10.2	2.6	n.d.
5c	10.2	2.6	—
5d	10.0	2.6	1.3
5f	10.1	2.4	—

n.d.: not determined.

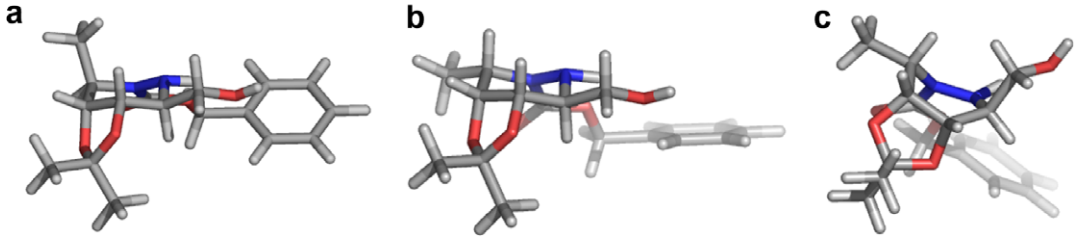


Figure 3. (a) Minimized chair conformation for compound **14**. (b) Minimized chair conformation for **13**. (c) Minimized twist boat conformation for **13**.

Table 4
Inhibitory activities of C-3 substituted azafagomines[a,b]

Compound	α-L-Fucosidase (bovine kidney)	β-Galactosidase (*Escherichia coli*)	Amyloglucosidase (*Aspergillus niger*)	Maltase (yeast)	β-Glucosidase (almonds)
3a	97% (IC_{50} = 30 μM) K_i = 4.2 μM	n.i.	n.i.	n.i.	n.i.
3b	44%	n.i.	n.i.	n.i.	n.i.
4a	17%	n.i.	n.i	n.i	23%
4b	53%	n.i.	n.i.	n.i.	n.i.
5c	85%[c] (IC_{50} = 8.6 μM) K_i = 1.0 μM	n.i.[c]	21%[c]	n.i.[c]	n.i.[c]
5d	70%	n.i.	n.i.	51%	n.i.
5e	82% (IC_{50} = 283 μM)	n.i.	n.i.	n.i.	n.i.
5f	77% (IC_{50} = 535 μM)	n.i.	n.i.	n.i.	n.i.
6c	53%	n.i.	n.i.	n.i.	33%
6d	40%	n.i.	24%	n.i.	n.i.
6e	n.i.	n.i.	n.i.	n.i.	n.i
23a	35%	n.i.	n.i.	n.i.	n.i.
23b	92% (IC_{50} = 117 μM)	32%	n.i.	n.i.	n.i.
23d	5%[c]	n.i.	n.i.	n.i.	n.i.
23e	65%	n.i.	n.i.	n.i.	n.i.
23f	77%	n.i.	n.i.	n.i.	n.i.
24a	27%	n.i.	n.i.	n.i.	n.i.
24b	54%	n.i.	n.i.	n.i.	n.i.
24c	n.i.[c]	n.i.[c]	n.i.[c]	n.i.[c]	n.i.[c]
24e	16%	n.i.	n.i.	n.i.	n.i.

Percentage of inhibition at 1 mM, IC_{50} and K_i in μM, when measured. Optimal pH, 37 °C.
n.i.: no inhibition at 1 mM.
[a] For measurement conditions see Ref. 25.
[b] Competitive mode of inhibition for given K_i.
[c] The percentage of inhibition was determined at 0.1 mM.

bovine kidney (97% at 1 mM concentration, K_i = 4.2 μM). The substitution of the hydroxyl group on **3a** for an amino group, compound **3b**, was detrimental for the inhibition towards α-L-fucosidase (only 44% at 1 mM concentration), suggesting that a compound with a hydroxymethyl group can establish more effective hydrogen bond interactions in the active site of the enzyme than an aminomethyl group. However the attachment of hydrophobic groups to compound **3b** via amide linkages, compounds **5c**–**f**, clearly improves their inhibitory activity towards α-L-fucosidase through unspecific contributions to the binding to the enzyme. Of special interest is the case of biphenyl derivative **5c** that showed competitive inhibition towards α-L-fucosidase with a K_i = 1.0 μM (85% at 0.1 mM concentration), being four times better inhibitor than alcohol **3a**. The efficiency in the inhibitory activity of biphenyl derivatives was precedent[26] having found that molecular motifs containing a biphenyl moiety are high affinity-ligands for proteins.[27] Thus, the incorporation of aromatic moieties to the L-*fuco*-hexahydropyridazine increases the inhibitory activity remarkably as it has been previously observed in piperidine- and pyrrolidine-based iminosugars.[28] The *N*-Cbz protected pyridazines **23b**,**e**,**f** showed moderate-to-high inhibition of α-L-fucosidase, 92%, 65%, and 77% at 1 mM concentration, respectively.

The inhibition potencies of the prepared compounds are rather low in comparison with other described inhibitors of α-L-fucosidase such as polyhydroxylated piperidines[12,14] which display inhibition constants in the low nanomolar range. This decrease in the inhibitory activity can be attributed to the supplementary nitrogen atom that diminishes the basicity of the N atoms and hence the ability of resembling the fucopyranosyl cation and/or to the presence of an extra carbon chain at C-3 instead of a hydroxyl group. However, it is worth noting that although the polyhydroxylated derivative **3a** (K_i = 4.2 μM) and L-*fuco*-azafagomine **2** (K_i = 0.81 μM) present values of inhibition in the same order of magnitude as biphenyl derivative **5c** (K_i = 1.0 μM), the latter has the advantage of bearing an aromatic group that could provide **5c** the appropriate characteristics for permeability through the membranes, due to the lipophilic nature of this group.

3. Conclusions

In summary, the synthesis of new C-3 substituted L-*fuco* configurated hydroxylated hexahydropyridazines and of their C-6 epimers from D-lyxose is reported. They can be considered the first examples of diaza-*C*-glycosides having a biimino (–NH–NH–) moiety and, in the case of *fuco* configurated compounds, constitute interesting lead compounds for the search of new α-L-fucosidase inhibitors. Protected C-3 aminomethyl L-*fuco*-azafagomine **19** and its C-6 epimer have been used to generate libraries of derivatives by attachment of hydrophobic groups through an amide linkage. All the new compounds have been evaluated as glycosidase inhibitors. The best result has been observed for L-*fuco*-azafagomine **5c**, which incorporates a biphenyl group on C-3, showing selective and competitive inhibition towards α-L-fucosidase from bovine kidney (K_i = 1.0 μM). This result shows that the incorporation of aromatic moieties on the C-3 substituent of these hexahydropyridazine derivatives increases the inhibitory activity towards α-L-fucosidases remarkably, what is in agreement with previous observations in more conventional piperidine- and pyrrolidine-based fucosidase inhibitors.

4. Experimental part

4.1. General methods

Optical rotations were measured in a 1.0 cm or 1.0 dm tube with a Perkin–Elmer 241MC spectropolarimeter. ^1H and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$, DMSO-d_6, and

CD_3OD; *J* values are given in Hz and δ in ppm. All the assignments were confirmed by two-dimensional NMR experiments. The FAB mass spectra were obtained using glycerol or 3-nitrobenzyl alcohol as the matrix. NMR and Mass spectra were registered in CITIUS (University of Seville). TLC was performed on silica gel HF_{254} (Merck), with detection by UV light charring with ninhydrine or with Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. Silica gel 60 (Merck, 230 mesh) was used for preparative chromatography. Glycosidases and the corresponding *p*-nitrophenyl-*O*-glycoside substrates for inhibition assays were purchased in Sigma–Aldrich. Molecular mechanics and molecular dynamics studies were carried out using the Macromodel[23] program (version 9.0) and the OPLS 2001[24] force field. The energies were minimized by using the PR conjugate gradient method. The starting coordinates for dynamics calculations where those obtained after energy minimizations. Simulations were carried out at 350 K.

4.1.1. 6-*O*-*tert*-Butyldiphenylsilyl-1-deoxy-3,4-*O*-isopropylidene-D-tagatofuranose (9)

To a stirred cooled (−78 °C) solution of **8** (1.24 g, 2.91 mmol) in dry THF (8 mL), MeLi (3.2 mL, 1 M in THF) was added under argon. After 2.5 h, H_2O (9 mL) was added and the mixture stirred at rt for 20 min. Then, the mixture was extracted with AcOEt and the organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography column on silica gel (AcOEt/petroleum ether 1:3) afforded **9** (1.17 g, 2.65 mmol, 91%) as a 1:3 mixture of distereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.74–7.67 (m, 8H, 4H-arom.-minor., 4H-arom.-major.), 7.44–7.34 (m, 12H, 6H-arom.-minor., 6H-arom.-major.), 4.79 (dd, 1H, $J_{3,2}$ = 5.8, $J_{3,4}$ = 3.9, H-4-major.), 4.76 (dd, 1H, *J* = 6.0, *J* = 3.6, H-4-minor.), 4.43 (d, 1H, H-3-major.), 4.28–4.22 (m, 2H, H-5-major., H-3-minor.), 4.02–3.93 (m, 2H, H-6a-major., H-6a-minor.), 3.89–3.83 (m, 2H, H-6b-major., H-6b-minor.), 3.74 (ddd, 1H, *J* = 7.4, *J* = 5.4, *J* = 3.5, H-5-minor.), 1.48, 1.45 (2s, 3H each, Me-mayor., Me-minor.), 1.37 (s, 3H, Me-minor.), 1.35 (br s, 6H, Me-major., Me-minor.), 1.29 (s, 3H, Me-minor.), 1.06 (s, 18H, $C(CH_3)_3$ de TBDPS-major., $C(CH_3)_3$ de TBDPS-minor.). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 135.9, 135.8, 133.9, 129.7, 127.8, 127.7, 127.6 (C-arom.), 112.7, 112.4 ($C(CH_3)_2$ major., $C(CH_3)_2$ minor.), 105.3 (C-2 major., C-2 minor.), 85.5 (C-3 major.), 82.3 (C-3 minor.), 80.8 (C-4 major.), 80.0 (C-4 minor.), 79.7 (C-5 major.), 76.7 (C-5 minor.), 61.9 (C-6 major.), 61.5 (C-6 minor.), 27.0 ($C(CH_3)_3$ of TBDPS-major., $C(CH_3)_3$ of TBDPS-minor.), 26.3, 26.1, 25.2, 25.0, 22.8, 22.2 (3 Me major, 3 Me minor.), 19.2 ($C(CH_3)_3$ major., $C(CH_3)_3$ minor). FABMS *m*/*z* 465 [40%, $(M+Na)^+$]. FABHRMS *m*/*z* found 465.2097, calcd for $C_{25}H_{34}O_5NaSi$ $(M+Na)^+$: 465.2073.

4.1.2. 6-*O*-*tert*-Butyldiphenylsilyl-2-(*tert*-butoxycarbonyl)-hydrazino-1,2-dideoxy-3,4-*O*-isopropylidene-D-talitol (10)

To a solution of **9** (1.36 g, 3.08 mmol) in dry MeOH (13 mL), *tert*-butylcarbazate (1.22 g, 9.24 mmol), $NaBH_3CN$ (0.813 g, 12.32 mmol) and glacial AcOH (315 μL) were added. After heating for 36 h at 65 °C, a satd aq soln of $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2. The organic phases were washed with brine, dried, filtered and concentrated. Purification by chromatography column on silica gel (AcOEt/petroleum ether 1:4) afforded **10** (1.41 g, 2.53 mmol, 82%) as an inseparable mixture of stereoisomers **10a** and **10b**. Data for **10a**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.70–7.64 (m, 4H, H-arom.), 7.45–7.34 (m, 6H, H-arom.), 6.45 (br s, 1H, N*H*Boc), 4.38 (dd, 1H, $J_{4,3}$ = 6.7, $J_{4,5}$ = 1.1, H-4), 4.11 (t, 1H, $J_{3,2}$ = 6.4, H-3), 4.04 (br t, 1H, H-5), 3.78 (d, 2H, $J_{6,5}$ = 6.6, H-6a, H-6b), 3.53 (m, 1H, H-2), 1.49, 1.35 (2s, 3H each, $C(CH_3)_2$), 1.46 (s, 9H, $C(CH_3)_3$ of Boc), 1.24 (d, 3H, $J_{Me\text{-}2,2}$ = 6.8, Me-2), 1.06 (s, 9H, $C(CH_3)_3$ of TBDPS). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 156.4 (C=O of Boc), 135.6, 133.5, 129.7, 127.7 (C arom.), 107.8 ($C(CH_3)_2$), 81.6 ($C(CH_3)_3$), 78.4 (C-3), 76.0 (C-4), 68.9 (C-5), 64.9 (C-6), 55.9 (C-2), 28.2 ($C(CH_3)_3$ of Boc), 26.9 ($C(CH_3)_3$ of TBDPS), 26.6, 24.8 ($C(CH_3)_2$), 19.4 ($C(CH_3)_3$), 14.3 (Me-2). FABMS *m*/*z* 581 [100%, $(M+Na)^+$] 559 [10%, $(M+H)^+$]. FABHRMS *m*/*z* found 581.3032, calcd for $C_{30}H_{46}N_2O_6NaSi$ $(M+Na)^+$: 581.3023. Data for **10b**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.72–7.64 (m, 4H, H-arom.), 7.45–7.34 (m, 6H, H-arom.), 6.40 (br s, 1H, N*H*Boc), 4.31 (d, 1H, $J_{4,3}$ = 7.2, H-4), 4.09 (dd, 1H, $J_{3,2}$ = 5.6, H-3), 3.80 (m, 1H, H-5), 3.76–3.72 (m, 2H, H-6a, H-6b), 3.34 (m, 1H, H-2), 1.51, 1.37 (2s, 3H each, $C(CH_3)_2$), 1.46 (s, 9H, $C(CH_3)_3$ of Boc), 1.20 (d, 3H, $J_{Me\text{-}2,2}$ = 6.4, Me-2), 1.06 (s, 9H, $C(CH_3)_3$ of TBDPS). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 156.6 (C=O of Boc), 135.7, 133.6, 129.8, 127.8 (C-arom.), 108.4 ($C(CH_3)_2$), 81.2 ($C(CH_3)_3$), 79.9 (C-3), 75.6 (C-4), 69.2 (C-5), 65.0 (C-6), 54.9 (C-2), 28.4 ($C(CH_3)_3$ of Boc), 27.0 ($C(CH_3)_3$ of TBDPS), 26.6, 24.7 ($C(CH_3)_2$), 19.4 ($C(CH_3)_3$), 16.3 (Me-2). FABMS *m*/*z* 581 [100%, $(M+Na)^+$], 559 [10%, $(M+H)^+$]. FABHRMS *m*/*z* found 581.3032, calcd for $C_{30}H_{46}N_2O_6NaSi$ $(M+Na)^+$: 581.3023.

4.1.3. (3*S*,4*S*,5*R*,6*S*) and (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-3-*O*-*tert*-butyldiphenylsilyl-4,5-*O*-isopropylidene-3-hydroxymethyl-6-methylhexahydropyridazine-4,5-diol (11 and 12)

To a solution of **10** (1.40 g, 2.51 mmol) in EtOH/H_2O (1.5:1, 40 mL), was added $NaHCO_3$ (0.37 g, 4.40 mmol) and CbzCl (421 μL, 2.94 mmol) and the mixture stirred at rt for 7 h. Then, a satd aq soln of $NaHCO_3$ was added, the mixture extracted with AcOEt (4 × 40 mL) and the organic phases dried, filtered and concentrated. The residue thus obtained was dissolved in dry CH_2Cl_2 and cooled to 0 °C. MsCl (0.58 mL, 7.5 mmol) in dry pyridine (4.6 mL) was slowly added and the mixture was stirred at rt overnight. Then, water was added at 0 °C and after stirring for 15 min. at rt, the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with H_2O and brine. The organic phases were then dried, filtered, and concentrated. The obtained residue was then dissolved in dry CH_2Cl_2 and 2,6-lutidine (2.5 mL) and TMSOTf (2.3 mL) were added under argon at 0 °C. After stirring at rt for 8 h, a 10% aq soln of Na_2CO_3 was added. After extraction with CH_2Cl_2, the organic phases were dried, filtered, and concentrated. The crude product was subsequently dissolved in MeOH, Et_3N was added and the mixture heated at reflux for 72 h. After evaporation, the residue was purified by chromatography column on silica gel (AcOEt/petroleum ether 1:8) affording **12** (0.327 g, 0.57 mmol, 23%) and **11** (0.702 g, 1.22 mmol, 49%), as oils. Data for **12**: $[\alpha]_D^{26}$ −64.5 (*c* 0.82, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.63–7.61 (m, 4H, H-arom.), 7.49–7.30 (m, 11H, H-arom.), 5.18 (br s, 2H, CH_2 of Cbz), 5.09 (br s, 1H, N*H*), 4.56 (q, 1H, $J_{6,Me\text{-}6}$ = 7.2, H-6), 3.99 (d, 1H, $J_{5,4}$ = 5.0, H-5), 3.80 (dd, 1H, $J_{4,3}$ = 9.4, H-4), 3.77 (dd, 1H, $^2J_{1'a,1'b}$ = 10.7, $J_{1'a,3}$ = 3.0, H-1′a), 3.59 (dd, 1H, $J_{1'b,3}$ = 9.0, H-1′b), 2.89 (m, 1H, H-3), 1.28 (d, 3H, Me-6), 1.20 (s, 6H, $C(CH_3)_2$), 0.98 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 155.2 (C=O of Cbz), 136.9, 135.0, 132.6, 129.9, 128.2, 127.9, 127.8, 127.7, 127.1 (C-arom.), 108.0 ($C(CH_3)_2$), 75.0 (C-5), 70.0 (C-4), 66.3 (CH_2 of Cbz), 63.3 (C-1′), 59.9 (C-3), 49.1 (C-6), 27.8, 26.3 ($C(CH_3)_2$), 26.5 ($C(CH_3)_3$), 18.7 ($C(CH_3)_3$), 16.1 (Me-6). FABMS *m*/*z* 597 [50%, $(M+Na)^+$], 575 [10%, $(M+H)^+$]. FABHRMS *m*/*z* found 597.2802, calcd for $C_{33}H_{42}N_2O_5NaSi$ $(M+Na)^+$: 597.2761. Data for **11**: $[\alpha]_D^{25}$ −18.2 (*c* 1.19, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.61–7.58 (m, 4H, H-arom.), 7.48–7.38 (m, 6H, H-arom.), 7.28–7.26 (m, 5H, H-arom.), 5.18 (br d, 1H, $J_{NH,3}$ = 3.2, N*H*), 5.05 (d, 1H, $^2J_{H,H}$ = 12.7, CH_2 of Cbz), 5.02 (d, 1H, CH_2 of Cbz), 4.08 (dd, 1H, $J_{5,4}$ = 5.5, $J_{5,6}$ = 4.8, H-5), 3.97 (qd, 1H, $J_{6,Me\text{-}6}$ = 7.2, H-6), 3.96 (t, 1H, $J_{4,3}$ = 5.5, H-4), 3.65 (d, 2H, $J_{1',3}$ = 6.7, H-1′), 3.05 (m, 1H, H-3), 1.34 (d, 3H, Me-6), 1.33, 1.24 (2s, 3H each, $C(CH_3)_2$), 0.99 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) 156.0 (C=O of Cbz), 136.7, 135.0, 132.7, 129.9, 128.2, 127.9, 127.8, 127.6, 127.3 (C-arom.), 108.0 ($C(CH_3)_2$), 72.6 (C-5), 70.8 (C-4), 66.2 (CH_2 of Cbz), 63.7 (C-1′),

58.7 (C-3), 50.9 (C-6), 26.8, 25.7 (C(CH_3)$_2$), 26.5 (C(CH_3)$_3$), 18.7 (*C*(CH_3)$_3$), 15.9 (Me-6). FABMS *m*/*z* 597 [40%, (M+Na)$^+$], 575 [8%, (M+H)$^+$] FABHRMS *m*/*z* found 597.2780, calcd for $C_{33}H_{42}N_2O_5NaSi$ (M+Na)$^+$: 597.2761.

4.1.4. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-4,5-*O*-isopropylidene-3-hydroxymethyl-6-methylhexahydropyridazine-4,5-diol (13)

To a solution of **11** (575.4 mg, 1.0 mmol) in THF (6 mL), TBAF (1 M in THF, 1.0 mL) was added. After stirring at rt for 1.5 h, the solvent was evaporated and the residue purified by chromatography column on silica gel (AcOEt/petroleum ether 2:1) to afford **13** (317 mg, 0.94 mmol, 94%) as an oil. $[\alpha]_D^{25}$ +29.0 (*c* 1.04, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.37–7.29 (m, 5H, H-arom.), 5.09 (d, 1H, $^2J_{H,H}$ = 12.6, CH_2 of Cbz), 5.07 (m, 1H, N*H*), 5.05 (d, 1H, CH_2 of Cbz), 4.56 (dd, 1H, $J_{OH,1'b}$ = 6.8, $J_{OH,1'a}$ = 4.6, O*H*), 4.19 (dd, 1H, $J_{5,4}$ = 5.8, $J_{5,6}$ = 5.1, H-5), 4.00 (qd, 1H, $J_{6,Me\text{-}6}$ = 7.1, H-6), 3.91 (dd, 1H, $J_{4,3}$ = 4.2, H-4), 3.41 (ddd, 1H, $^2J_{1'b,1'a}$ = 11.2, $J_{1'a,3}$ = 6.3, H-1′a), 3.33 (ddd, 1H, $J_{1'b,3}$ = 7.4, H-1′b), 2.90 (m, 1H, H-3), 1.38, 1.27 (2s, 3H each, C(CH_3)$_2$), 1.32 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, 353 K, δ ppm) δ 156.2 (C=O of Cbz), 136.8, 128.3, 127.6, 127.4 (C-arom.), 107.8 (*C*(CH_3)$_2$), 72.3 (C-5), 70.8 (C-4), 66.2 (CH_2 of Cbz), 60.5 (C-1′), 59.0 (C-3), 50.3 (C-6), 26.8, 25.6 (C(CH_3)$_2$), 15.9 (Me-6). CIMS *m*/*z* 337 [90%, (M+H)$^+$]. CIHRMS *m*/*z* found 337.1768, calcd for $C_{17}H_{25}N_2O_5$ (M+H)$^+$: 337.1763. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.66; H, 7.06; N, 8.30.

4.1.5. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-4,5-*O*-isopropylidene-3-hydroxymethyl-6-methylhexahydropyridazine-4,5-diol (14)

To a solution of **12** (825 mg, 1.44 mmol) in THF (9 mL), TBAF (1 M in THF, 1.46 mL) was added. After stirring at rt for 1.5 h, the solvent was evaporated and the residue purified by chromatography column on silica gel (AcOEt/petroleum ether 2:1) to afford **14** (440 mg, 1.31 mmol, 91%) as an oil. $[\alpha]_D^{25}$ −102.1 (*c* 1.3, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.36–7.28 (m, 5H, H-arom.), 5.17 (d, 1H, $^2J_{H,H}$ = 13.0, CH_2 of Cbz), 5.11 (d, 1H, CH_2 of Cbz), 4.93 (br s, 1H, N*H*), 4.81 (t, 1H, $J_{OH,H}$ = 5.5, O*H*), 4.53 (q, 1H, $J_{6,Me\text{-}6}$ = 7.2, H-6), 4.00 (d, 1H, $J_{5,4}$ = 4.9, H-5), 3.82 (dd, 1H, $J_{4,3}$ = 9.1, H-4), 3.60 (ddd, 1H, $^2J_{1'a,1'b}$ = 11.3, $J_{1'a,3}$ = 2.7, H-1′a), 3.27 (m, 1H, H-1′b), 2.71 (m, 1H, H-3), 1.32, 1.25 (2s, 3H each, C(CH_3)$_2$), 1.24 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, 353 K, δ ppm) δ 155.2 (C=O of Cbz), 137.0, 128.3, 127.6, 127.0 (C-arom.), 107.9 (*C*(CH_3)$_2$), 75.1 (C-5), 70.1 (C-4), 66.2 (CH_2 of Cbz), 60.5 (C-1′), 60.2 (C-3), 49.2 (C-6), 28.0, 26.4 (C(CH_3)$_2$), 16.2 (Me-6). CIMS *m*/*z* 337 [50%, (M+H)$^+$]. CIHRMS *m*/*z* found 337.1754, calcd for $C_{17}H_{25}N_2O_5$ (M+H)$^+$: 337.1763.

4.1.6. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-4,5-*O*-isopropylidene-3-*O*-tosyl-3-hydroxymethyl-6-methylhexahydropyridazine-4,5-diol (15)

To a 0 °C solution of **13** (957 mg, 2.84 mmol) in dry pyridine (8 mL) was slowly added TsCl (1.38 g, 7.21 mmol). After stirring at rt overnight, the mixture was cooled to 0 °C, water was added (0.5 mL), and the mixture was allowed to warm to rt. Solvent was then removed, and the residue was diluted with CH_2Cl_2, washed with water and brine, dried, filtered, and concentrated. Purification by chromatography column (AcOEt/petroleum ether 1:2) afforded **15** (1.25 g, 2.55 mmol, 90%) as a white solid. M.p. 130–132 °C (AcOEt/petroleum ether). $[\alpha]_D^{23}$ −6.4 (*c* 0.45, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.76 (d, 2H, $^3J_{H,H}$ = 8.0, H-Ts), 7.46 (d, 2H, H-Ts), 7.37–7.30 (m, 5H, H-arom.), 5.17 (br s, 1H, N*H*), 5.04 (d, 1H, $^2J_{H,H}$ = 12.7, CH_2 of Cbz), 5.01 (d, 1H, CH_2 of Cbz), 4.16 (t, 1H, $J_{5,4}$ = $J_{5,6}$ = 5.5, H-5), 4.04–3.97 (m, 3H, H-6, H-1′a, H-1′b), 3.83 (dd, 1H, $J_{4,3}$ = 4.5, H-4), 3.10 (m, 1H, H-3), 2.41 (s, 3H, CH_3 of Ts), 1.28 (d, 3H, $J_{6,Me\text{-}6}$ = 7.0, Me-6), 1.31, 1.23 (2s, 3H each, C(CH_3)$_2$). ^{13}C NMR (125.7 MHz, DMSO-d_6, 353 K, δ ppm) δ 156.1 (C=O of Cbz), 145.1, 136.7, 132.0, 130.2, 128.3, 127.8, 127.6, 127.5 (C-arom.), 108.1 (*C*(CH_3)$_2$), 72.2 (C-5), 70.0, 69.9 (C-4, C-1′), 66.3 (CH_2 of Cbz), 56.1 (C-3), 50.1 (C-6), 26.6, 25.6 (C(CH_3)$_2$), 21.1 (Me of Ts), 15.7 (Me-6). FABMS *m*/*z* 513 [100%, (M+Na)$^+$], 491 [10%, (M+H)$^+$]. FABHRMS *m*/*z* found 513.1678, calcd for $C_{24}H_{30}N_2O_7SNa$ (M+Na)$^+$: 513.1671. Anal. Calcd for $C_{24}H_{30}N_2O_7S$: C, 58.76; H, 6.16; N, 5.71; S, 6.54. Found: C, 58.75; H, 6.11; N, 5.82; S, 6.50.

4.1.7. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-4,5-*O*-isopropylidene-3-*O*-tosyl-3-hydroxymethyl-6-methylhexahydropyridazine-4,5-diol (16)

Following the same procedure as for the preparation of **15**, and starting from **14**, compound **16** (751 mg, 1.53 mmol, 91%) was obtained as an oil. $[\alpha]_D^{27}$ −66.1 (*c* 0.97, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.79 (d, 2H, $^3J_{H,H}$ = 8.0, H-Ts), 7.44 (d, 2H, H-Ts), 7.36–7.29 (m, 5H, H-arom.), 5.13 (br s, 2H, CH_2 of Cbz), 5.02 (br s, 1H, N*H*), 4.50 (q, 1H, $J_{6,Me\text{-}6}$ = 7.2, H-6), 4.06 (dd, 1H, $J_{4,3}$ = 10.8, $J_{4,5}$ = 2.6, H-4), 4.02–3.98 (m, 2H, H-5, H-1′a), 3.80 (m, 1H, H-1′b), 2.80 (m, 1H, H-3), 2.40 (s, 3H, CH_3 of Ts), 1.22 (d, 3H, Me-6), 1.21, 1.16 (2s, 3H each, C(CH_3)$_2$). ^{13}C NMR (125.7 MHz, DMSO-d_6, 353 K, δ ppm) δ 155.5 (C=O of Cbz), 145.0, 136.9, 132.1, 130.1, 128.3, 127.9, 127.6, 127.0, 125.4 (C-arom.), 108.2 (*C*(CH_3)$_2$), 74.8 (C-5), 68.9, 68.8 (C-4, C-1′), 66.2 (CH_2 of Cbz), 57.3 (C-3), 49.1 (C-6), 27.8, 26.2 (C(CH_3)$_2$), 21.0 (Me of Ts), 16.0 (Me-6). FABMS *m*/*z* 513 [40%, (M+Na)$^+$], 491 [15%, (M+H)$^+$]. FABHRMS *m*/*z* found 513.1691, calcd for $C_{24}H_{30}N_2O_7SNa$ (M+Na)$^+$: 513.1671.

4.1.8. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-azidomethyl-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (17)

To a solution of **15** (1.18 g, 2.40 mmol) in THF (25 mL), $TBAN_3$ (2.0 g, 7.07 mmol) was added. After heating at 50 °C for 3.5 h, the solvent was evaporated and the residue purified by chromatography column on silica gel (AcOEt/petroleum ether 1:3) to afford **17** (780 mg, 2.16 mmol, 90%) as an oil. $[\alpha]_D^{25}$ −13.8 (*c* 0.94, CH_2Cl_2). IR (γ cm^{-1}) 3422, 3054, 2303, 2105, 1263, 895, 737, 704. ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.39–7.28 (m, 5H, H-arom.), 5.15 (br s, 1H, N*H*), 5.10 (d, 1H, $^2J_{H,H}$ = 12.6, CH_2 of Cbz), 5.06 (d, 1H, CH_2 of Cbz), 4.23 (dd, 1H, $J_{5,4}$ = 5.9, $J_{5,6}$ = 5.2, H-5), 4.04 (qd, 1H, $J_{6,Me\text{-}6}$ = 7.1, H-6), 3.89 (dd, 1H, $J_{4,3}$ = 4.2, H-4), 3.35 (dd, 1H, $^2J_{1'a,1'b}$ = 12.8, $J_{1'a,3}$ = 5.0, H-1′a), 3.32 (dd, 1H, $J_{1'b,3}$ = 7.7, H-1′b), 3.02 (m, 1H, H-3), 1.37, 1.27 (2s, 3H each, C(CH_3)$_2$), 1.31 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, 353 K, δ ppm) δ 156.2 (C=O of Cbz), 136.8, 128.2, 127.7, 127.5 (C-arom.), 108.0 (*C*(CH_3)$_2$), 72.3 (C-5), 71.2 (C-4), 66.2 (CH_2 of Cbz), 56.9 (C-3), 50.8 (C-1′), 50.2 (C-6), 26.7, 25.6 (C(CH_3)$_2$), 15.7 (Me-6). CIMS *m*/*z* 362 [10%, (M+H)$^+$]. CIHRMS *m*/*z* found 362.1807, calcd for $C_{17}H_{24}N_5O_4$ (M+H)$^+$: 362.1828.

4.1.9. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-3-azidomethyl-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (18)

Following the same procedure as for the preparation of **17**, and starting from **16**, compound **18** (480 mg, 1.33 mmol, 97%) was obtained as an oil. $[\alpha]_D^{24}$ −99.5 (*c* 0.85, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.38–7.28 (m, 5H, H-arom.), 5.13 (s, 2H, CH_2 of Cbz), 5.04 (br d, 1H, $J_{NH,3}$ = 6.8, N*H*), 4.54 (br q, 1H, $J_{6,Me\text{-}6}$ = 7.3, H-6), 4.05 (d, 1H, $J_{5,4}$ = 4.9, $J_{5,6}$ = 0.9, H-5), 3.85 (dd, 1H, $J_{4,3}$ = 9.0, H-4), 3.46 (br d, 1H, H-1′a), 3.28 (dd, 1H, $^2J_{1'b,1'a}$ = 13.1, $J_{1'b,3}$ = 8.2, H-1′b), 2.81 (m, 1H, H-3), 1.31, 1.26 (2s, 3H each, C(CH_3)$_2$), 1.26 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, 353 K, δ ppm) δ 155.6 (C=O of Cbz), 137.0, 128.2, 127.6, 127.0 (C-arom.), 108.1 (*C*(CH_3)$_2$), 75.1 (C-5), 70.4 (C-4), 66.2 (CH_2 of Cbz), 58.0 (C-3), 50.0 (C-1′), 49.2 (C-6), 28.0, 26.3 (C(CH_3)$_2$), 16.0 (Me-6). CIMS *m*/*z* 362 [15%, (M+H)$^+$]. CIHRMS *m*/*z* found 362.1812, calcd for $C_{17}H_{24}N_5O_4$ (M+H)$^+$: 362.1828. Anal. Calcd for

$C_{17}H_{23}N_5O_4$: C, 56.50; H, 6.41; N, 19.38. Found: C, 56.55; H, 6.47; N, 19.07.

4.1.10. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-aminomethyl-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (19)

To a solution of **17** (750 mg, 2.076 mmol) in pyridine/H_2O 1:1 (40 mL), H_2S was bubbled for 1 h. Alter stirring at rt for 3 h, the solvent was evaporated and the residue purified by chromatography column on silica gel (CH_2Cl_2/MeOH, 6:1) to afford **19** (654 mg, 1.95 mmol, 94%) as an oil. $[\alpha]_D^{25}$ +26.2 (*c* 0.92, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.39–7.29 (m, 5H, H-arom.), 5.10 (d, 1H, $J_{NH,3}$ = 1.8, N*H*), 5.07 (s, 2H, C*H*$_2$ of Cbz), 4.22 (t, 1H, $J_{5,4} = J_{5,6}$ = 6.0, H-5), 4.05 (m, 1H, H-6), 3.84 (dd, 1H, $J_{4,3}$ = 2.0, H-4), 2.89 (m, 1H, H-3), 2.60 (dd, 1H, $^2J_{1'a,1'b}$ = 13.0, $J_{1'a,3}$ = 4.7, H-1′a), 2.47 (dd, 1H, $J_{1'b,3}$ = 10.4, H-1′b), 1.40, 1.27 (2s, 3H each, C(C*H*$_3$)$_2$), 1.26 (d, 3H, $J_{Me\text{-}6,6}$ = 7.3, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, 353 K, δ ppm) δ 156.3 (C=O of Cbz), 136.7, 130.4, 128.4, 127.7 (C-arom.), 107.6 (*C*(CH$_3$)$_2$), 71.3 (C-4, C-5), 66.5 (*C*H$_2$ of Cbz), 58.8 (C-3), 48.9 (C-6), 41.2 (C-1′), 26.4, 25.5 (C(*C*H$_3$)$_2$), 15.6 (Me-6). CIMS *m*/*z* 336 [80%, (M+H)$^+$], 305 [45%, (M-CH$_2$NH$_2$)$^+$]. CIHRMS *m*/*z* found 336.1914, calcd for $C_{17}H_{26}N_3O_4$ (M+H)$^+$: 336.1923.

4.1.11. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-3-aminomethyl-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (20)

Following the same procedure as for the preparation of **19**, and starting from **18**, compound **20** (389 mg, 1.16 mmol, 93%) was obtained as an oil. $[\alpha]_D^{25}$ −100.8 (*c* 0.72, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.37–7.28 (m, 5H, H-arom.), 5.15 (d, 1H, $^2J_{H,H}$ = 13.0, C*H*$_2$ of Cbz), 5.11 (d, 1H, C*H*$_2$ of Cbz), 5.08 (br s, 1H, N*H*), 4.52 (br q, 1H, $J_{6,Me\text{-}6}$ = 7.2, H-6), 3.98 (dd, 1H, $J_{5,4}$ = 5.0, $J_{5,6}$ = 0.6, H-5), 3.81 (dd, 1H, $J_{4,3}$ = 9.2, H-4), 2.82 (dd, 1H, $^2J_{1'a,1'b}$ = 13.0, $J_{1'a,3}$ = 3.0, H-1′a), 2.60 (m, 1H, H-3), 3.46 (dd, 1H, $J_{1'b,3}$ = 8.4, H-1′b), 1.31, 1.26 (2s, 3H each, C(C*H*$_3$)$_2$), 1.26 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 155.3 (C=O of Cbz), 137.0, 128.2, 127.6, 127.0 (C-arom.), 108.1 (*C*(CH$_3$)$_2$), 75.2 (C-5), 71.5 (C-4), 66.1 (*C*H$_2$ of Cbz), 60.0 (C-3), 49.3 (C-6), 41.5 (C-1′), 28.0, 26.4 (C(*C*H$_3$)$_2$), 16.2 (Me-6). CIMS *m*/*z* 336 [40%, (M+H)$^+$], 305 [30%, (M-CH$_2$NH$_2$)$^+$]. CIHRMS *m*/*z* found 336.1929, calcd for $C_{17}H_{26}N_3O_4$ (M+H)$^+$: 336.1923.

4.2. General procedure for the synthesis of amide derivatives

To a solution of the hexahydropyridazine **19** or **20** (0.1 mmol) in the minimum amount of DMF the corresponding carboxylic acid (0.1 mmol), DIPEA (0.2 mmol), and PyBOP (0.11 mmol) were added. The reaction mixture was stirred at rt for 3 h and then evaporated. The obtained residue was dissolved in CH_2Cl_2 and washed with water and brine. The organic phase was dried, filtered, concentrated, and purified by chromatography column on silica gel.

4.2.1. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-(*p*-phenylbenzoylaminomethyl)-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (21c)

The coupling reaction of **19** (82 mg, 0.245 mmol) with (1,1′-biphenyl)-4-carboxylic acid following the general procedure afforded after chromatographic purification (ether/petroleum ether 10:1) derivative **21c** (126 mg, 0.245 mmol, 100% yield) as a white solid. $[\alpha]_D^{26}$ −95.1 (*c* 1.08, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 8.60 (dd, 1H, $J_{NH,1'}$ = 7.3, $J_{NH,1'}$ = 4.5, CON*H*), 7.89 (m, 2H, H-arom., biphenyl), 7.76–7.72 (m, 4H, H-arom., biphenyl), 7.50 (m, 2H, H-arom., biphenyl), 7.41 (tt, 1H, *J* = 7.3, *J* = 1.1, H-arom., biphenyl), 7.30–7.23 (m, 5H, H-arom.), 5.20 (br s, 1H, N*H*), 5.09 (d, 1H, $^2J_{H,H}$ = 12.7, C*H*$_2$ of Cbz), 5.06 (d, 1H, C*H*$_2$ of Cbz), 4.28 (dd, 1H, $J_{5,4}$ = 5.8, $J_{5,6}$ = 5.4, H-5), 4.09 (qd, 1H, $J_{6,Me\text{-}6}$ = 7.0, H-6), 3.95 (dd, 1H, $J_{4,3}$ = 3.1, H-4), 3.54 (m, 1H, H-1′a), 3.16–3.11 (m, 2H, H-3, H-1′b), 1.41, 1.28 (2s, 3H each, C(C*H*$_3$)$_2$), 1.33 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 165.9 (*C*ONH), 156.4 (C=O of Cbz), 142.7, 139.1, 136.7, 133.1, 129.0, 128.3, 128.0, 127.7, 127.6, 127.5, 126.8, 126.5 (C-arom.), 107.8 (*C*(CH$_3$)$_2$), 72.1 (C-5), 71.4 (C-4), 66.4 (*C*H$_2$ of Cbz), 57.2 (C-3), 49.9 (C-6), 39.3 (C-1′), 26.6, 25.5 (C(*C*H$_3$)$_2$), 15.8 (Me-6). CIMS *m*/*z* 516 [80%, (M+H)$^+$]. CIHRMS *m*/*z* found 516.2481, calcd for $C_{30}H_{34}N_3O_5$ (M+H)$^+$: 516.2498.

4.2.2. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-3-(*p*-phenylbenzoylaminomethyl)-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (22c)

The coupling reaction of **20** (74.8 mg, 0.223 mmol) with (1,1′-biphenyl)-4-carboxylic acid following the general procedure afforded after chromatographic purification (ether/petroleum ether 10:1) derivative **22c** (103.4 mg, 0.20 mmol, 90% yield) as a white solid. $[\alpha]_D^{25}$ −31.0 (*c* 0.91, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 8.60 (br t, 1H, $J_{NH,1'a} = J_{NH,1'b}$ = 5.6, CON*H*), 7.92 (br d, 2H, *J* = 8.3, H-arom, biphenyl), 7.75 (br d, 2H, *J* = 8.2, H-arom, biphenyl), 7.73 (br d, 2H, *J* = 7.4, H-arom, biphenyl), 7.50 (m, 2H, H-arom, biphenyl), 7.41 (br t, 1H, *J* = 7.4, H-arom, biphenyl), 7.27–7.24 (m, 5H, H-arom.), 5.13–5.05 (m, 3H, N*H*, C*H*$_2$ of Cbz), 4.52 (q, 1H, $J_{6,Me\text{-}6}$ = 7.2, H-6), 4.02 (br d, 1H, $J_{5,4}$ = 4.8, H-5), 3.90 (dd, 1H, $J_{4,3}$ = 9.2, H-4), 3.55 (ddd, 1H, $^2J_{1'a,1'b}$ = 13.8, $J_{1'a,3}$ = 3.2, H-1′a), 3.24 (ddd, 1H, $J_{1'b,3}$ = 8.5, H-1′b), 2.89 (m, 1H, H-3), 1.36, 1.28 (2s, 3H each, C(C*H*$_3$)$_2$), 1.29 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 166.4 (*C*ONH), 155.3 (C=O of Cbz), 142.7, 139.2, 136.8, 133.3, 129.0, 128.2, 128.0, 127.8, 127.5, 126.9, 126.8, 126.4 (C-arom.), 107.9 (*C*(CH$_3$)$_2$), 75.3 (C-5), 71.8 (C-4), 66.2 (*C*H$_2$ of Cbz), 59.0 (C-3), 49.4 (C-6), 40.0–39.0 (C-1′), 28.0, 26.4 (C(*C*H$_3$)$_2$), 16.3 (Me-6). CIMS *m*/*z* 516 [100%, (M+H)$^+$]. CIHRMS *m*/*z* found 516.2484, calcd for $C_{30}H_{34}N_3O_5$ (M+H)$^+$: 516.2498.

4.2.3. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-dodecanoylaminomethyl-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (21d)

The coupling reaction of **19** (85.2 mg, 0.254 mmol) with dodecanoic acid following the general procedure afforded after chromatographic purification (CH_2Cl_2/MeOH 50:1) derivative **21d** (127 mg, 0.246 mmol, 97% yield) as a white solid. $[\alpha]_D^{24}$ −27.1 (*c* 0.54, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.57 (m, 1H, CON*H*), 7.38–7.29 (m, 5H, H-arom.), 5.08 (d, 1H, $J_{H,H}$ = 12.6, C*H*$_2$ of Cbz), 5.07 (br s, 1H, N*H*), 5.05 (d, 1H, C*H*$_2$ of Cbz), 4.21 (dd, 1H, $J_{5,4}$ = 5.9, $J_{5,6}$ = 5.5, H-5), 4.03 (qd, 1H, $J_{6,Me\text{-}6}$ = 7.1, H-6), 3.84 (dd, 1H, $J_{4,3}$ = 3.0, H-4), 3.25 (m, 1H, H-1′a), 2.92–2.85 (m, 2H, H-1′b, H-3), 1.95 (t, 2H, $J_{H,H}$ = 7.4, C*H*$_2$CONH), 1.43 (m, 2H, C*H*$_2$), 1.38 (s, 3H, C(C*H*$_3$)$_2$), 1.29 (d, 3H, Me-6), 1.26 (s, 3H, C(C*H*$_3$)$_2$), 1.23 (m, 16H, 8C*H*$_2$), 0.85 (t, 3H, $J_{H,H}$ = 6.9, C*H*$_3$). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 172.2 (*C*ONH), 156.2 (C=O of Cbz), 136.7, 128.3, 127.8, 127.6 (C-arom.), 107.7 (*C*(CH$_3$)$_2$), 71.9 (C-5), 71.2 (C-4), 66.3 (*C*H$_2$ of Cbz), 57.2 (C-3), 49.7 (C-6), 38.7 (C-1′), 35.5 (*C*H$_2$CONH), 31.3, 28.9, 28.8, 28.7, 28.6, 28.5, 26.6, 25.4, 25.1, 22.0 (9 *C*H$_2$, C(*C*H$_3$)$_2$), 15.4 (Me-6), 13.9 (*C*H$_3$). FABMS *m*/*z* 540 [55%, (M+Na)$^+$], 518 [25%, (M+H)$^+$]. FABHRMS *m*/*z* found 540.3393, calcd for $C_{29}H_{47}N_3O_5Na$ (M+Na)$^+$: 540.3413.

4.2.4. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-3-dodecanoylaminomethyl-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (22d)

The coupling reaction of **20** (77.1 mg, 0.230 mmol) with dodecanoic acid following the general procedure afforded after chromatographic purification (CH_2Cl_2/MeOH 50:1) derivative **22d** (112 mg, 0.217 mmol, 94% yield) as a white solid. $[\alpha]_D^{23}$ −35.3 (*c*

0.96, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, J Hz) δ 7.84 (m, 1H, CONH), 7.38–7.28 (m, 5H, H-arom.), 5.13 (d, 1H, $^2J_{H,H}$ = 13.2, CH_2 of Cbz), 5.10 (d, 1H, CH_2 of Cbz), 4.94 (br s, 1H, NH), 4.50 (br q, 1H, $J_{6,Me\text{-}6}$ = 7.2, H-6), 3.98 (dd, 1H, $J_{5,4}$ = 4.9, $J_{5,6}$ = 0.7, H-5), 3.79 (dd, 1H, $J_{4,3}$ = 9.3, H-4), 3.26 (ddd, 1H, $^2J_{1'a,1'b}$ = 13.9, J = 5.9, J = 3.2, H-1′a), 3.00 (ddd, 1H, J = 8.3, J = 6.2, H-1′b), 2.71 (m, 1H, H-3), 2.01 (t, 2H, $J_{H,H}$ = 7.5, CH_2CONH), 1.46 (m, 2H, CH_2), 1.31 (s, 3H, C(CH_3)$_2$), 1.26 (d, 3H, Me-6), 1.25 (s, 3H, C(CH_3)$_2$), 1.22 (m, 16H, 8CH_2), 0.85 (t, 3H, $J_{H,H}$ = 7.0, CH_3). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 172.7 (CONH), 155.3 (C=O of Cbz), 136.9, 128.2, 127.6, 127.0 (C-arom.), 107.8 (C(CH$_3$)$_2$), 75.2 (C-5), 71.6 (C-4), 66.2 (CH_2 of Cbz), 59.0 (C-3), 49.3 (C-6), 38.6 (C-1′), 35.4 (CH_2CONH), 31.2, 28.9, 28.8, 28.7, 28.6, 28.5, 28.0, 26.4, 25.2, 22.0 (9 CH_2, C(CH_3)$_2$), 16.2 (Me-6), 13.9 (CH_3). FABMS m/z 540 [55%, (M+Na)$^+$], 518 [30%, (M+H)$^+$]. FABHRMS m/z found 540.3381, calcd for $C_{29}H_{47}N_3O_5Na$ (M+Na)$^+$: 540.3413.

4.2.5. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-[((2*S*)-2-*N*-(9-fluorenylmethoxycarbonyl)amino-3-phenyl)propanoylaminomethyl]-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (21e′)

The coupling reaction of **19** (78.1 mg, 0.233 mmol) with Fmoc-Phe-OH following the general procedure afforded after chromatographic purification (CH_2Cl_2/MeOH 50:1) derivative **21e′** (147.8 mg, 0.21 mmol, 90% yield) as a white solid. $[\alpha]_D^{21}$ −15.9 (c 0.8, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, J Hz) δ 7.97 (dd, 1H, J = 7.2, J = 4.2, CONH), 7.87 (d, 2H, J = 7.5, H-arom.), 7.63–7.60 (m, 3H, H-arom.), 7.39 (td, 2H, J = 7.0, J = 3.2, H-arom.), 7.35–7.22 (m, 10H, H-arom.), 7.17 (br t, 1H, J = 6.7, H-arom.), 5.06 (s, 2H, CH_2 of Cbz), 4.21–4.16 (m, 2H, H-5, H-2″), 4.14–4.08 (m, 3H, CH_2 and CH of Fmoc), 4.02 (qd, 1H, $J_{Me\text{-}6,6}$ = 7.0, $J_{6,5}$ = 5.4, H-6), 3.84 (dd, 1H, J = 6.0, J = 3.0, H-4), 3.33 (m, 1H, H-1′a), 3.02 (dd, 1H, $^2J_{3''a,3''b}$ = 13.5, $J_{3''a,2''}$ = 4.5, H-3″a), 2.98–2.94 (m, 2H, H-1′b, H-3), 2.80 (dd, 1H, $J_{3''b,2''}$ = 10.2, H-5′b), 1.37, 1.26 (2s, 3H each, C(CH_3)$_2$), 1.29 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 171.5 (CONH), 156.3, 155.8 (C=O of Cbz and C=O of Fmoc), 143.8, 143.6, 140.6, 138.1, 136.8, 129.1, 128.2, 128.0, 127.7, 127.6, 127.4, 127.0, 126.2, 125.2, 120.0 (C-arom.), 107.7 (C(CH$_3$)$_2$), 72.0 (C-5), 71.2 (C-4), 66.2 (CH_2 of Cbz), 65.6 (CH_2 of Fmoc), 57.0 (C-3), 56.3 (C-2″), 49.8 (C-6), 46.5 (CH of Fmoc), 40.0–39.0 (C-1′), 37.4 (C-3″), 26.6, 25.5 (C(CH_3)$_2$), 15.8 (Me-6). FABMS m/z 727 [46%, (M+Na)$^+$], 705 [12%, (M+H)$^+$]. FABHRMS m/z found 727.3149, calcd for $C_{41}H_{44}N_4O_7Na$ (M+Na)$^+$: 727.3108.

4.2.6. (3*S*,4*S*,5*R*,6R)-1-*N*-Benzyloxycarbonyl-3-[((2*S*)-2-*N*-(9-fluorenylmethoxycarbonyl) amino-3-phenyl)propanoylaminomethyl]-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (22e′)

The coupling reaction of **20** (77 mg, 0.23 mmol) with Fmoc-Phe-OH following the general procedure afforded after chromatographic purification (CH_2Cl_2/MeOH 50:1) derivative **22e′** (161 mg, 0.228 mmol, 99% yield) as a white solid. $[\alpha]_D^{21}$ −37.2 (c 1, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, J Hz) δ 8.18 (br t, 1H, $J_{NH,1'a}$ = $J_{NH,1'b}$ = 5.7, CONH), 7.87 (d, 2H, J = 7.5, H-arom.), 7.64–7.58 (m, 2H, H-arom.), 7.42–7.38 (m, 2H, H-arom.), 7.32–7.22 (m, 11H, H-arom.), 7.17 (br t, 1H, J = 7.5, H-arom.), 5.13 (br d, 1H, $^2J_{H,H}$ = 13.0, CH_2 of Cbz), 5.04 (d, 1H, CH_2 of Cbz), 4.96 (br s, 1H, NH), 4.50 (q, 1H, $J_{6,Me\text{-}6}$ = 7.2, H-6), 4.19 (m, 1H, H-2″), 4.16–4.06 (m, 3H, CH_2 and CH of Fmoc), 3.98 (d, 1H, $J_{5,4}$ = 5.0, H-5), 3.83 (br dd, 1H, $J_{4,3}$ = 9.0, H-4), 3.42 (m, 1H, H-1′a), 3.06–2.99 (m, 2H, H-1′b, H-3″a), 2.80–2.75 (m, 2H, H-3, H-3″b), 1.32, 1.25 (2s, 3H each, C(CH_3)$_2$), 1.25 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 172.0 (CONH), 155.8, 155.4 (C=O of Cbz and C=O of Fmoc), 143.8, 143.7, 140.6, 138.4, 137.0, 129.2, 128.3, 128.0, 127.6, 127.0, 126.2, 125.4, 125.3, 120.1 (C-arom.), 108.0 (C(CH$_3$)$_2$), 75.2 (C-5), 71.5 (C-4), 66.2, 65.6 (CH_2 of Cbz and CH_2 of Fmoc), 58.3 (C-3), 56.3 (C-2″), 49.3 (C-6), 46.5 (CH of Fmoc), 38.8 (C-1′), 37.4 (C-3″), 28.0, 26.5 (C(CH_3)$_2$), 16.2 (Me-6). FABMS m/z 727 [50%, (M+Na)$^+$], 705 [12%, (M+H)$^+$]. FABHRMS m/z found 727.3148, calcd for $C_{41}H_{44}N_4O_7Na$ (M+Na)$^+$: 727.3108.

4.2.7. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-[(2*S*)-(6-*N*-(*tert*-butoxycarbonyl)amino-2-*N*-(9-fluorenylmethoxycarbonyl)-amino)hexanoylaminomethyl]-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (21f′)

The coupling reaction of **19** (91.4 mg, 0.273 mmol) with Fmoc-Lys(Boc)-OH following the general procedure afforded after chromatographic purification (CH_2Cl_2/MeOH 50:1) derivative **21f′** (206.2 mg, 0.263 mmol, 96% yield) as a white solid. $[\alpha]_D^{26}$ −16.8 (c 0.85, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, J Hz) δ 7.89 (d, 2H, J = 7.5, H-arom.), 7.83 (m, 1H, CONH), 7.72 (dd, 2H, J = 10.5, J = 7.5, H-arom.), 7.47 (d, 1H, $J_{NH,2''}$ = 8.0, NHFmoc), 7.41 (t, 2H, J = 7.5, H-arom.), 7.33–7.27 (m, 7H, H-arom.), 6.76 (br t, 1H, $J_{NH,6''}$ = 5.5, NHBoc), 5.06 (br s, 3H, CH_2 of Cbz, NH-2), 4.27–4.19 (m, 4H, H-5, CH_2 and CH of Fmoc), 4.04 (qd, 1H, $J_{6,Me\text{-}6}$ = 7.0, $J_{6,5}$ = 5.8, H-6), 3.86 (m, 1H, H-2″), 3.84 (dd, 1H, J = 6.0, J = 3.0, H-4), 3.31 (m, 1H, H-1′a), 2.92 (m, 1H, H-3), 2.89–2.84 (m, 3H, H-1′b, H-6″), 1.60 (m, 1H, H-3″a), 1.51 (m, 1H, H-3″b), 1.36 (s, 12H, C(CH_3)$_2$ and C(CH_3)$_3$), 1.34 (m, 2H, H-5″), 1.27 (d, 3H, Me-6), 1.25 (m, 2H, H-4″), 1.24 (s, 3H, C(CH_3)$_2$). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 172.2 (CONH), 156.3, 156.0, 155.6 (C=O of Cbz, C=O of Fmoc and C=O of Boc), 144.0, 143.7, 140.7, 136.9, 128.3, 127.8, 127.6, 127.5, 127.0, 125.3, 120.1 (C-arom.), 107.8 (C(CH$_3$)$_2$), 77.3 (C(CH$_3$)$_3$), 71.8 (C-5), 71.1 (C-4), 66.3 (CH_2 of Cbz), 65.6 (CH_2 of Fmoc), 56.9 (C-3), 54.9 (C-2″), 49.6 (C-6), 46.6 (CH of Fmoc), 40.0–38.8 (C-1′, C-6″), 31.5 (C-3″), 29.2 (C-4″), 28.3 (C(CH_3)$_3$), 26.5, 25.5 (C(CH_3)$_2$), 22.9 (C-5″), 15.7 (Me-6). FABMS m/z 808 [40%, (M+Na)$^+$]. FABHRMS m/z found 808.3842, calcd for $C_{43}H_{55}N_5O_9Na$ (M+Na)$^+$: 808.3897.

4.2.8. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-[((2*S*)-2-amino-3-phenyl)propanoyl-aminomethyl]-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (21e)

A solution of **21e′** (133 mg, 0.185 mmol) in piperidine/DMF (20%, 4 mL) was stirred at rt for 15 min. Then, the mixture was concentrated to dryness and the residue purified by chromatographic column (CH_2Cl_2/MeOH 20:1) to afford **21e** (74.5 mg, 0.155 mmol, 84%) as an oil. $[\alpha]_D^{21}$ −38.5 (c 1.1, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, J Hz) δ 7.97 (br dd, 1H, J = 7.2, J = 3.7, CONH), 7.35–7.25 (m, 7H, H-arom.), 7.21–7.17 (m, 3H, H-arom.), 5.08 (d, 1H, $^2J_{H,H}$ = 12.7, CH_2 of Cbz), 5.04 (d, 1H, CH_2 of Cbz), 5.03 (br s, 1H, NH), 4.22 (t, 1H, $J_{5,6}$ = $J_{5,4}$ = 5.9, H-5), 4.05 (qd, 1H, $J_{6,Me\text{-}6}$ = 7.0, H-6), 3.84 (dd, 1H, $J_{4,3}$ = 2.5, H-4), 3.37–3.30 (m, 2H, H-1′a, H-2″), 2.94 (dd, 1H, $^2J_{3''a,3''b}$ = 13.5, $J_{3''a,2''}$ = 4.8, H-3″a), 2.92–2.85 (m, 2H, H-3, H-1′b), 2.58 (dd, 1H, $J_{3''b,2''}$ = 8.4, H-3″b), 1.82 (br s, 2H, NH_2), 1.40, 1.27 (2s, 3H each, C(CH_3)$_2$), 1.28 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 174.2 (CONH), 156.2 (C=O of Cbz), 138.6, 136.8, 129.2, 128.3, 128.1, 127.7, 127.5, 126.1 (C-arom.), 107.6 (C(CH$_3$)$_2$), 71.7 (C-5), 71.1 (C-4), 66.2 (CH_2 of Cbz), 57.1 (C-3), 56.2 (C-2″), 49.2 (C-6), 40.8 (C-3″), 38.5 (C-1′), 26.5, 25.5 (C(CH_3)$_2$), 15.6 (Me-6). CIMS m/z 483 [100%, (M+H)$^+$]. CIHRMS m/z found 483.2607, calcd for $C_{26}H_{35}N_4O_5$ (M+H)$^+$: 483.2607.

4.2.9. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-3-[((2*S*)-2-amino-3-phenyl)propanoyl-aminomethyl]-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (22e)

Following the same procedure as for the preparation of **21e**, and starting from **22e′** (128 mg, 0.181 mmol), compound **22e** (80 mg, 0.165 mmol, 92%) was obtained as an oil. $[\alpha]_D^{27}$ −68.5 (c 0.91, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, J Hz) δ 8.60 (br t, 1H, J = 6.7, CONH), 7.33–7.17 (m, 10H, H-arom.), 5.14 (d, 1H, $^2J_{H,H}$ = 13.0, CH_2 of Cbz), 5.08 (d, 1H, CH_2 of Cbz), 5.01 (br s, 1H, NH), 4.50 (q, 1H,

$J_{6,Me-6}$ = 7.2, H-6), 3.97 (br d, 1H, $J_{5,4}$ = 5.5, H-5), 3.77 (dd, 1H, $J_{4,3}$ = 9.2, H-4), 3.37 (dd, 1H, $J_{2'',3''b}$ = 8.5, $J_{2'',3''a}$ = 4.5, H-2″), 3.30 (m, 1H, H-1′a), 3.08 (m, 1H, H-1′b), 2.95 (dd, 1H, $^2J_{3''a,3''b}$ = 13.5, H-3″a), 2.72 (m, 1H, H-3), 2.60 (dd, 1H, H-3″b), 1.69 (br s, 2H, NH_2), 1.31, 1.26 (2s, 3H each, C(CH_3)$_2$), 1.24 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 174.6 (*C*ONH), 155.4 (C=O of Cbz), 138.7, 136.9, 129.2, 128.2, 128.0, 127.6, 127.0, 126.0 (C-arom.), 107.8 (*C*(CH$_3$)$_2$), 75.2 (C-5), 71.4 (C-4), 66.1 (*C*H$_2$ of Cbz), 58.4 (C-3), 56.2 (C-2″), 49.3 (C-6), 40.8 (C-3″), 38.6 (C-1′), 28.0, 26.4 (C(*C*H$_3$)$_2$), 16.2 (Me-6). CIMS *m*/*z* 483 [50%, (M+H)$^+$]. CIHRMS *m*/*z* found 483.2615, calcd for $C_{26}H_{35}N_4O_5$ (M+H)$^+$: 483.2607.

4.2.10. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-[((2*S*)-6-*N*-(*tert*-butoxycarbonyl)amino-2-amino)hexanoylaminomethyl]-4,5-*O*-isopropylidene-6-methylhexahydropyridazine-4,5-diol (21f)

Following the same procedure as for the preparation of **21e**, and starting from **21f′** (189.7 mg, 0.242 mmol), compound **21f** (97.1 mg, 0.172 mmol, 71%) was obtained as an oil. $[\alpha]_D^{22}$ −22.1 (*c* 0.74, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 8.03 (br dd, 1H, *J* = 7.4, *J* = 4.4, N*H*CO), 7.36–7.30 (m, 5H, H-arom.), 6.71 (br t, 1H, $J_{NH,6''}$ = 5.5, N*H*Boc), 5.09 (s, 2H, C*H*$_2$ of Cbz), 5.06 (d, 1H, $J_{NH,3}$ = 3.0, N*H*), 4.23 (dd, 1H, $J_{5,4}$ = 6.0, $J_{5,6}$ = 5.5, H-5), 4.06 (qd, 1H, $J_{6,Me-6}$ = 7.0, H-6), 3.86 (dd, 1H, $J_{4,3}$ = 3.0, H-4), 3.34 (m, 1H, H-1′a), 3.17 (dd, 1H, *J* = 7.2, *J* = 5.2, H-2″), 2.94 (m, 1H, H-3), 2.90–2.86 (m, 2H, H-1′b, H-6″), 1.56 (m, 1H, H-3″a), 1.39 (s, 3H, C(C*H*$_3$)$_2$), 1.37 (s, 9H, C(C*H*$_3$)$_3$), 1.34 (m, 1H, H-3″b), 1.28 (d, 3H, Me-6), 1.26 (s, 3H, C(C*H*$_3$)$_2$), 1.29–1.19 (m, 4H, H-4″, H-5″). ^{13}C NMR (125.7 MHz, DMSO-d_6, δ ppm) δ 173.7 (*C*ONH), 156.3, 155.5 (C=O of Cbz and C=O of Boc), 136.8, 128.3, 127.8, 127.6 (C-arom.), 107.7 (*C*(CH$_3$)$_2$), 77.3 (*C*(CH$_3$)$_3$), 71.8 (C-5), 71.1 (C-4), 66.3 (*C*H$_2$ of Cbz), 57.0 (C-3), 54.1 (C-2″), 49.4 (C-6), 40.0–39.0 (C-6″), 38.6 (C-1′), 33.7 (C-3″), 29.3 (*C*H$_2$), 28.2 (C(*C*H$_3$)$_3$), 26.5, 25.5 (C(*C*H$_3$)$_2$), 22.3 (*C*H$_2$), 15.6 (Me-6). FABMS *m*/*z* 586 [40%, (M+Na)$^+$], 564 [30%, (M+H)$^+$]. FABHRMS *m*/*z* found 586.3195, calcd for $C_{28}H_{45}N_5O_7$Na (M+Na)$^+$: 586.3217.

4.2.11. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-hydroxymethyl-6-methylhexahydropyridazine-4,5-diol (23a)

Compound **13** (65 mg, 0.193 mmol) was stirred in HCl (1 M)/THF 1:1 (5 mL) at rt for 2 h. Solvent was then evaporated and the residue purified by chromatography column (CH_2Cl_2/MeOH 15:1) to afford **23a** (55 mg, 0.186 mmol, 96%) as a white solid. $[\alpha]_D^{26}$ +16.4 (*c* 0.65, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 7.39–7.29 (m, 5H, H-arom.), 5.16 (d, 1H, $^2J_{H,H}$ = 12.4, C*H*$_2$ of Cbz), 5.12 (d, 1H, C*H*$_2$ of Cbz), 4.15 (qd, 1H, $J_{6,Me-6}$ = 7.0, $J_{6,5}$ = 5.3, H-6), 3.72 (dd, 1H, $J_{5,4}$ = 3.1, H-5), 3.57 (dd, 1H, $J_{4,3}$ = 4.2, H-4), 3.52–3.50 (m, 2H, H-1′a, H-1′b), 3.00 (m, 1H, H-3), 1.34 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 158.6 (C=O of Cbz), 138.0, 129.5, 129.2, 129.0 (C-arom.), 69.1 (C-4), 68.8 (C-5), 68.6 (*C*H$_2$ of Cbz), 63.6 (C-3), 61.4 (C-1′), 54.7 (C-6), 13.5 (Me-6). CIMS *m*/*z* 297 [15%, (M+H)$^+$]. CIHRMS *m*/*z* found 297.1454, calcd for $C_{14}H_{21}N_2O_5$ (M+H)$^+$: 297.1450.

4.2.12. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-3-hydroxymethyl-6-methylhexahydropyridazine-4,5-diol (24a)

Deprotection of **14** (80 mg, 0.238 mmol) following the same procedure as for the preparation of **23a**, afforded **24a** (64 mg, 0.216 mmol, 91%) as a white solid. $[\alpha]_D^{26}$ −76.3 (*c* 0.72, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 7.40–7.28 (m, 5H, H-arom.), 5.17 (d, 1H, $^2J_{H,H}$ = 12.5, C*H*$_2$ of Cbz), 5.14 (d, 1H, C*H*$_2$ of Cbz), 4.47 (qd, 1H, $J_{6,Me}$ = 7.2, $J_{6,5}$ = 2.0, H-6), 3.84 (dd, 1H, $^2J_{1'a,1'b}$ = 11.3, $J_{1'a,3}$ = 2.6, H-1′a), 3.71 (m, 1H, H-5), 3.65 (dd, 1H, $J_{4,3}$ = 10.3, $J_{4,5}$ = 3.0, H-4), 3.62 (dd, 1H, $J_{1'b,3}$ = 6.4, H-1′b), 3.06 (ddd, 1H, H-3), 1.25 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 158.4 (C=O of Cbz), 138.1, 129.5, 129.0, 128.8 (C-arom.), 72.1 (C-5), 68.5 (*C*H$_2$ of Cbz), 66.4 (C-4), 61.6 (C-1′), 59.2 (C-3), 56.6 (C-6), 14.3 (Me-6). CIMS *m*/*z* 297 [30%, (M+H)$^+$]. CIHRMS *m*/*z* found 297.1452, calcd for $C_{14}H_{21}N_2O_5$ (M+H)$^+$: 297.1450.

4.2.13. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-aminomethyl-6-methylhexahydropyridazine-4,5-diol (23b)

Compound **19** (88.4 mg, 0.264 mmol) was stirred in HCl (1 M)/THF 1:1 (7 mL) at rt for 2 h. Solvent was then evaporated and the residue was purified using a Dowex 50WX8 column, eluting with MeOH (30 mL), H_2O (30 mL) and NH_4OH 10% (100 mL). Compound **23b** (73.5 mg, 0.249 mmol, 94%) was obtained as a foam. $[\alpha]_D^{24}$ +10.0 (*c* 0.81, MeOH). ^{1}H NMR (500 MHz, CD_3OD δ ppm, *J* Hz) δ 7.39–7.30 (m, 5H, H-arom.), 5.14 (d, 1H, $^2J_{H,H}$ = 12.4, C*H*$_2$ of Cbz), 5.12 (d, 1H, C*H*$_2$ of Cbz), 4.21 (m, 1H, H-6), 3.70 (dd, 1H, $J_{5,6}$ = 5.6, $J_{5,4}$ = 3.0, H-5), 3.48 (m, 1H, H-4), 2.89 (dt, 1H, $J_{3,1'b}$ = 10.8, $J_{3,1'a}$ = $J_{3,4}$ = 3.8, H-3), 2.63 (dd, 1H, $^2J_{1'a,1'b}$ = 13.0, H-1′a), 2.57 (dd, 1H, H-1′b), 1.32 (d, 3H, $J_{Me-6,6}$ = 7.0, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 158.5 (C=O of Cbz), 137.9, 129.6, 129.3, 129.1 (C-arom.), 70.4 (C-4), 68.7 (*C*H$_2$ of Cbz), 68.4 (C-5), 64.1 (C-3), 54.1 (C-6), 41.2 (C-1′), 13.2 (Me-6). CIMS *m*/*z* 296 [80%, (M+H)$^+$], 265 [40%, (M-CH$_2$NH$_2$)$^+$]. CIHRMS *m*/*z* found 296.1606, calcd for $C_{14}H_{22}N_3O_4$ (M+H)$^+$: 296.1610.

4.2.14. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-3-aminomethyl-6-methylhexahydropyridazine-4,5-diol (24b)

Deprotection of **20** (103 mg, 0.307 mmol) following the same procedure as for the preparation of **23b**, afforded **24b** (79.3 mg, 0.269 mmol, 88%) as a foam. $[\alpha]_D^{21}$ −66.0 (*c* 0.8, MeOH). ^{1}H NMR (500 MHz, CD_3OD δ ppm, *J* Hz) δ 7.38–7.28 (m, 5H, H-arom.), 5.17 (d, 1H, $^2J_{H,H}$ = 12.5, C*H*$_2$ of Cbz), 5.14 (d, 1H, C*H*$_2$ of Cbz), 4.48 (qd, 1H, $J_{6,Me-6}$ = 7.3, $J_{6,5}$ = 2.2, H-6), 3.70 (m, 1H, H-5), 3.50 (dd, 1H, $J_{4,3}$ = 10.1, $J_{4,5}$ = 3.0, H-4), 3.05–2.98 (m, 2H, H-3, H-1′a), 2.61 (dd, 1H, $^2J_{1'b,1'a}$ = 13.0, $J_{1'b,3}$ = 8.5, H-1′b), 1.24 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 158.6 (C=O of Cbz), 138.1, 129.5, 129.0, 128.8 (C-arom.), 72.1 (C-5), 68.5 (C-4), 68.3 (*C*H$_2$ of Cbz), 59.3 (C-3), 57.0 (C-6), 42.1 (C-1′), 14.3 (Me-6). CIMS *m*/*z* 296 [100%, (M+H)$^+$], 265 [45%, (M-CH$_2$NH$_2$)$^+$]. CIHRMS *m*/*z* found 296.1615, calcd for $C_{14}H_{22}N_3O_4$ (M+H)$^+$: 296.1610.

4.2.15. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-(*p*-phenylbenzoylaminomethyl)-6-methylhexahydropyridazine-4,5-diol (23c)

Compound **21c** (110 mg, 0.214 mmol) was stirred in HCl (1 M)/THF 1:1 (5 mL) at rt for 2 h. Solvent was then evaporated and the residue purified by chromatography column (CH_2Cl_2/MeOH 20:1) to afford **23c** (100.3 mg, 0.211 mmol, 98%) as a white solid. $[\alpha]_D^{26}$ −75.4 (*c* 0.42, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 7.84 (br d, 2H, H-arom, biphenyl), 7.73–7.65 (m, 4H, H-arom, biphenyl), 7.50–7.45 (m, 2H, H-arom, biphenyl), 7.37 (tt, 1H, *J* = 5.5, *J* = 1.2, H-arom, biphenyl), 7.33–7.22 (m, 5H, H-arom.), 5.16 (d, 1H, $^2J_{H,H}$ = 12.3, C*H*$_2$ of Cbz), 5.12 (d, 1H, C*H*$_2$ of Cbz), 4.27 (m, 1H, H-6), 3.86–3.80 (m, 2H, H-5, H-1′a), 3.63 (br t, 1H, $J_{4,3}$ = $J_{4,5}$ = 2.8, H-4), 3.15–3.09 (m, 2H, H-3, H-1′b), 1.36 (d, 3H, $J_{Me-6,6}$ = 7.0, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 169.4 (*C*ONH), 158.6 (C=O of Cbz), 145.7, 141.3, 137.8, 134.1, 130.0, 129.6, 129.2, 129.1, 129.0, 128.8, 128.1, 128.0 (C-arom.), 70.0 (C-4), 68.7 (*C*H$_2$ of Cbz), 68.2 (C-5), 62.0 (C-3), 54.4 (C-6), 39.9 (C-1′), 13.2 (Me-6). CIMS *m*/*z* 476 [25%, (M+H)$^+$]. CIHRMS *m*/*z* found 476.2193, calcd for $C_{27}H_{30}N_3O_5$ (M+H)$^+$: 476.2185.

4.2.16. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-3-(*p*-phenylbenzoyl-aminomethyl)-6-methylhexahydropyridazine-4,5-diol (24c)

Deprotection of **22c** (69.2 mg, 0.134 mmol) following the same procedure as for the preparation of **23c**, afforded **24c** (63.7 mg, 0.134 mmol, 100% yield) as a white solid. $[\alpha]_D^{25}$ −10.6 (*c* 0.84, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) 7.90 (m, 2H, H-arom, biphenyl), 7.69 (br d, 2H, *J* = 8.0, H-arom, biphenyl), 7.66 (m, 2H, H-arom,

biphenyl), 7.48–7.45 (m, 2H, H-arom, biphenyl), 7.41 (tt, 1H, J = 7.5, J = 1.5, H-arom, biphenyl), 7.34 (m, 2H, H-arom.), 7.25 (br s, 3H, H-arom.), 5.16 (d, 1H, $^2J_{H,H}$ = 12.5, CH_2 of Cbz), 5.12 (d, 1H, CH_2 of Cbz), 4.50 (qd, 1H, $J_{6,Me\text{-}6}$ = 7.2, $J_{6,5}$ = 2.2, H-6), 3.96 (br d, 1H, $^2J_{1'a,1'b}$ = 13.9, H-1′a), 3.75 (m, 1H, H-5), 3.55 (dd, 1H, $J_{4,3}$ = 10.0, $J_{4,5}$ = 3.1, H-4), 3.30 (m, 1H, H-1′b), 3.22 (td, 1H, $J_{3,1'b}$ = 9.5, $J_{3,1'a}$ = 2.5, H-3), 1.27 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 170.6 (*C*ONH), 158.6 (C=O of Cbz), 145.7, 141.3, 138.0, 134.3, 130.0, 129.5, 129.1, 129.0, 128.7, 128.1, 128.0 (C-arom.), 72.2 (C-5), 68.6 (*C*H$_2$ of Cbz), 68.2 (C-4), 58.3 (C-3), 56.9 (C-6), 41.1 (C-1′), 14.4 (Me-6). CIMS m/z 476 [30%, $(M+H)^+$]. CIHRMS m/z found 476.2184, calcd for $C_{27}H_{30}N_3O_5$ $(M+H)^+$: 476.2185.

4.2.17. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-dodecanoyl-aminomethyl-6-methylhexahydropyridazine-4,5-diol (23d)

Deprotection of **21d** (99 mg, 0.191 mmol) following the same procedure as for the preparation of **23c**, afforded **23d** (83.6 mg, 0.175 mmol, 92%) as an oil. $[\alpha]_D^{27}$ −22.3 (c 0.64, MeOH). ^{1}H NMR (300 MHz, CD_3OD, δ ppm, J Hz) δ 7.40–7.28 (m, 5H, H-arom.), 5.18 (d, 1H, $^2J_{H,H}$ = 12.3, CH_2 of Cbz), 5.11 (d, 1H, CH_2 of Cbz), 4.22 (m, 1H, H-6), 3.77 (dd, 1H, J = 5.6, J = 3.0, H-5), 3.58–3.53 (m, 2H, H-4, H-1′a), 2.97–2.85 (m, 2H, H-1′b, H-3), 2.04 (br t, 2H, $J_{H,H}$ = 7.5, CH_2CONH), 1.53 (m, 2H, CH_2), 1.33 (d, 3H, $J_{Me\text{-}6,6}$ = 7.0, Me-6), 1.29 (m, 16H, 8CH_2), 0.90 (t, 3H, $J_{H,H}$ = 6.9, CH_3). ^{13}C NMR (75.4 MHz, CD_3OD, δ ppm) δ 176.0 (*C*ONH), 158.5 (C=O of Cbz), 137.9, 129.6, 129.3, 129.1 (C-arom.), 69.9 (C-4), 68.7 (*C*H$_2$ of Cbz), 68.2 (C-5), 61.9 (C-3), 54.4 (C-6), 39.4 (C-1′), 37.2 (*C*H$_2$CONH), 33.1, 30.7, 30.6, 30.5, 30.4, 30.3, 26.9, 23.7 (9 *C*H$_2$), 14.4 (*C*H$_3$), 13.2 (Me-6). CIMS m/z 478 [100%, $(M+H)^+$]. CIHRMS m/z found 478.3293, calcd for $C_{26}H_{44}N_3O_5$ $(M+H)^+$: 478.3281. Anal. Calcd for $C_{26}H_{43}N_3O_5$: C, 65.38; H, 9.07; N, 8.80. Found: C, 64.82; H, 8.66; N, 8.86.

4.2.18. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-3-dodecanoyl-aminomethyl-6-methylhexahydropyridazine-4,5-diol (24d)

Deprotection of **22d** (86.2 mg, 0.167 mmol) following the same procedure as for the preparation of **23c**, afforded **24d** (77.4 mg, 0.162 mmol, 97%) as an oil. $[\alpha]_D^{22}$ −40.2 (c 0.79, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6, 363 K, δ ppm, J Hz) δ 7.42 (br s, 1H, CON*H*), 7.38–7.28 (m, 5H, H-arom.), 5.09 (s, 2H, CH_2 of Cbz), 4.75 (br d, 1H, $J_{NH,3}$ = 6.0, N*H*), 4.34–4.26 (m, 3H, H-6, OH-4, OH-5), 3.58 (m, 1H, H-5), 3.45–3.38 (m, 2H, H-4, H-1′a), 3.11 (m, 1H, H-1′b), 2.95 (m, 1H, H-3), 2.08 (t, 2H, $J_{H,H}$ = 7.3, CH_2CONH), 1.51 (m, 2H, CH_2), 1.27 (m, 16H, 8CH_2), 1.18 (d, 3H, $J_{Me\text{-}6,6}$ = 7.2, Me-6), 0.87 (t, 3H, $J_{H,H}$ = 6.6, CH_3). ^{13}C NMR (125.7 MHz, DMSO-d_6, 363 K, δ ppm) δ 172.4 (*C*ONH), 155.1 (C=O of Cbz), 136.7, 127.7, 127.0, 126.0 (C-arom.), 70.1 (C-5), 66.4 (C-4), 65.7 (*C*H$_2$ of Cbz), 56.8 (C-3), 54.2 (C-6), 38.4 (C-1′), 35.1 (*C*H$_2$CONH), 30.7, 28.4, 28.38, 28.3, 28.2, 28.1, 28.0, 24.7, 21.4 (9 *C*H$_2$), 13.7 (Me-6), 13.2 (*C*H$_3$). CIMS m/z 478 [80%, $(M+H)^+$]. CIHRMS m/z found 478.3261, calcd for $C_{26}H_{44}N_3O_5$ $(M+H)^+$: 478.3281.

4.2.19. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-[((*S*)-2-amino-3-phenyl)propanoyl-aminomethyl]-6-methylhexahydropyridazine-4,5-diol (23e)

Compound **21e** (78.5 mg, 0.163 mmol) was stirred in HCl (1 M)/THF 1:1 (8.5 mL) at rt for 5 h. Solvent was then evaporated and the residue was dissolved in water (1.5 mL) and treated with 25% NH_4OH (1.3 mL). After 1.5 h at rt, the solvent was evaporated and the residue purified by chromatography column (CH_2Cl_2/MeOH/NH_4OH 10:1:0.1) to afford **23e** (64 mg, 0.145 mmol, 89%) as an oil. $[\alpha]_D^{22}$ −8.5 (c 1.33, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, J Hz) δ 7.39–7.26 (m, 7H, H-arom.), 7.23–7.16 (m, 3H, H-arom.), 5.12 (d, 1H, $^2J_{H,H}$ = 12.3, CH_2 of Cbz), 5.09 (d, 1H, CH_2 of Cbz), 4.18 (m, 1H, H-6), 3.74 (dd, 1H, $J_{5,6}$ = 5.5, $J_{5,4}$ = 3.0, H-5), 3.53 (dd, 1H, $^2J_{1'a,1'b}$ = 13.5, $J_{1'a,3}$ = 4.7, H-1′a), 3.48 (br t, 1H, $J_{4,3}$ = 3.2, H-4), 3.37 (m, 1H, H-2″), 2.94 (dd, 1H, $^2J_{3''a,3''b}$ = 13.4, $J_{3''a,2''}$ = 6.4, H-3″a), 2.87 (dd, 1H, $J_{1'b,3}$ = 10.0, H-1′b), 2.79 (m, 1H, H-3), 2.74 (dd, $J_{3''b,2''}$ = 7.4, H-3″b), 1.31 (d, 3H, $J_{Me\text{-}6,6}$ = 7.0, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 176.5 (*C*ONH), 158.3 (C=O of Cbz), 138.9, 137.9, 130.4, 129.6, 129.58, 129.3, 129.1, 127.7 (C-arom.), 68.9 (C-4), 68.6 (*C*H$_2$ of Cbz), 68.3 (C-5), 61.6 (C-3), 57.8 (C-2″), 54.3 (C-6), 42.3 (C-3″), 39.3 (C-1′), 13.2 (Me-6). CIMS m/z 443 [65%, $(M+H)^+$]. CIHRMS m/z found 443.2289, calcd for $C_{23}H_{31}N_4O_5$ $(M+H)^+$: 443.2294.

4.2.20. (3*S*,4*S*,5*R*,6*R*)-1-*N*-Benzyloxycarbonyl-3-[((*S*)-2-amino-3-phenyl)propanoyl-aminomethyl]-6-methylhexahydropyridazine-4,5-diol (24e)

Compound **22e** (62.8 mg, 0.130 mmol) was stirred in HCl (1 M):THF 1:1 (3.4 mL) at rt for 5 h. Solvent was then evaporated and the residue was purified using a Dowex 50WX8 column, eluting with MeOH (30 mL), H_2O (30 mL), and NH_4OH 10% (150 mL). Compound **24e** (51.8 mg, 0.117 mmol, 90%) was obtained as an oil. $[\alpha]_D^{25}$ −26.9 (c 0.68, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, J Hz) δ 7.38–7.36 (m, 2H, H-arom.), 7.33 (t, 2H, J = 7.5, H-arom.), 7.29–7.26 (m, 3H, H-arom.), 7.22–7.18 (m, 3H, H-arom.), 5.17 (d, 1H, $^2J_{H,H}$ = 13.0, CH_2 of Cbz), 5.13 (d, 1H, CH_2 of Cbz), 4.46 (qd, 1H, $J_{6,Me\text{-}6}$ = 7.3, $J_{6,5}$ = 2.2, H-6), 3.70 (m, 1H, H-5), 3.62 (dd, 1H, $^2J_{1'a,1'b}$ = 14.0, $J_{1'a,3}$ = 2.7, H-1′a), 3.58 (m, 1H, H-2″), 3.44 (dd, 1H, $J_{4,3}$ = 10.5, $J_{4,5}$ = 3.1, H-4), 3.08 (dd, 1H, $J_{1'b,3}$ = 9.0, H-1′b), 3.02–2.97 (m, 2H, H-3″a, H-3), 2.81 (m, 1H, H-3″b), 1.22 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 176.8 (*C*ONH), 158.6 (C=O of Cbz), 138.7, 138.1, 130.4, 129.6, 129.5, 129.0, 128.8, 127.8 (C-arom.), 72.1 (C-5), 68.6 (*C*H$_2$ of Cbz), 68.0 (C-4), 57.8 (C-3), 57.6 (C-2″), 56.9 (C-6), 42.2 (C-3″), 40.3 (C-1′), 14.4 (Me-6). CIMS m/z 443 [95%, $(M+H)^+$]. CIHRMS m/z found 443.2296, calcd for $C_{23}H_{31}N_4O_5$ $(M+H)^+$: 443.2294.

4.2.21. (3*S*,4*S*,5*R*,6*S*)-1-*N*-Benzyloxycarbonyl-3-[((*S*)-2,6-diamino)-hexanoylaminomethyl]-6-methylhexahydropyridazine-4,5-diol (23f)

Deprotection of **21f** (74.1 mg, 0.131 mmol) following the same procedure as for the preparation of **24e**, afforded **23f** (41 mg, 0.097 mmol, 74%) as an oil. $[\alpha]_D^{22}$ −22.8 (c 0.55, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, J Hz) δ 7.36–7.31 (m, 5H, H-arom.), 5.18 (d, 1H, $^2J_{H,H}$ = 12.3, CH_2 of Cbz), 5.13 (d, 1H, CH_2 of Cbz), 4.06 (m, 1H, H-6), 3.78 (dd, 1H, $J_{5,6}$ = 5.5, $J_{5,4}$ = 3.0, H-5), 3.58–3.55 (m, 2H, H-4, H-1′a), 3.15 (m, 1H, H-2″), 3.01–2.94 (m, 2H, H-3, H-1′b), 2.71 (t, 2H, $J_{H,H}$ = 7.2, H-6″), 1.65 (m, 1H, H-3″a), 1.55–1.45 (m, 3H, H-5″, H-3″b), 1.36 (m, 2H, H-4″), 1.33 (d, 3H, $J_{6,Me\text{-}6}$ = 7.0, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 177.5 (*C*ONH), 158.5 (C=O of Cbz), 138.0, 129.3, 129.1, 129.0 (C-arom.), 70.0 (C-4), 68.7 (*C*H$_2$ of Cbz), 68.3 (C-5), 61.7 (C-3), 56.1 (C-2″), 54.5 (C-6), 41.8 (C-6″), 39.4 (C-1′), 35.9 (C-3″), 32.1 (C-5″), 23.9 (C-4″), 13.2 (Me-6). CIMS m/z 424 [5%, $(M+H)^+$]. CIHRMS m/z found 424.2560, calcd for $C_{20}H_{34}N_5O_5$ $(M+H)^+$: 424.2560.

4.3. Hydrogenation of Cbz. General procedure

To a solution of the *N*-protected hexahydropyridazine (0.1 mmol) in MeOH (4 mL), Pd/C (10%) and HCl (5 M, 0.4 mmol) were added. The mixture was hydrogenated at 1 atm for 2–4 h. The mixture was then diluted with MeOH, filtered through Celite, and evaporated, affording the corresponding unprotected derivatives in quantitative yields.

4.3.1. (3*S*,4*S*,5*R*,6*S*)-3-Hydroxymethyl-6-methylhexahydropyridazine-4,5-diol hydrochloride (3a)

Hydrogenation of **23a** (32.3 mg, 0.109 mmol) following the general procedure afforded **3a** (21.6 mg, 0.109 mmol) as an oil. $[\alpha]_D^{22}$ −44.6 (c 0.6, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, J Hz) 3.85–3.82 (m, 2H, H-5, H-1′a), 3.74 (dd, 1H, $^2J_{1'b,1'a}$ = 11.6, $J_{1'b,3}$ = 5.5, H-1′b), 3.63 (dd, 1H, $J_{4,3}$ = 10.3, $J_{4,5}$ = 2.8, H-4), 3.35 (qd,

1H, $J_{6,Me\text{-}6}$ = 6.8, $J_{6,5}$ = 1.2, H-6), 3.24 (ddd, 1H, $J_{3,1'a}$ = 2.9, H-3), 1.28 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 69.6 (C-5), 68.1 (C-4), 60.1 (C-1′), 58.0 (C-6), 57.5 (C-3), 14.0 (Me-6). CIMS *m*/*z* 163 [40%, $(M+H)^+$]. CIHRMS *m*/*z* found 163.1083, calcd for $C_6H_{15}N_2O_3$ $(M+H)^+$: 163.1083.

4.3.2. (3*S*,4*S*,5*R*,6*R*)-3-Hydroxymethyl-6-methylhexahydropyridazine-4,5-diol hydrochloride (4a)

Hydrogenation of **24a** (27.3 mg, 0.092 mmol) following the general procedure afforded **4a** (18.2 mg, 0.092 mmol) as an oil. $[\alpha]_D^{22}$ −12.3 (*c* 0.85, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) 3.85 (dd, 1H, $^2J_{1'a,1'b}$ = 11.5, $J_{1'a,3}$ = 3.7, H-1′a), 3.81 (dd, 1H, $J_{4,3}$ = 7.4, $J_{4,5}$ = 2.9, H-4), 3.77 (dd, 1H, $J_{1'b,3}$ = 6.9, H-1′b), 3.71 (m, 1H, H-5), 3.51 (qd, 1H, $J_{6,Me\text{-}6}$ = 6.9, $J_{6,5}$ = 5.4, H-6), 3.36 (td, 1H, H-3), 1.34 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 70.1 (C-5), 65.4 (C-4), 60.5 (C-3), 60.2 (C-1′), 56.6 (C-6), 13.2 (Me-6). CIMS *m*/*z* 163 [65%, $(M+H)^+$]. CIHRMS *m*/*z* found 163.1087, calcd for $C_6H_{15}N_2O_3$ $(M+H)^+$: 163.1083.

4.3.3. (3*S*,4*S*,5*R*,6*S*)-3-Aminomethyl-6-methylhexahydropyridazine-4,5-diol dihydrochloride (3b)

Hydrogenation of **23b** (43.2 mg, 0.146 mmol) following the general procedure afforded **3b** (34 mg, 0.146 mmol) as an oil. $[\alpha]_D^{22}$ −34.9 (*c* 0.74, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 3.92 (m, 1H, H-5), 3.57 (dd, 1H, $J_{4,3}$ = 10.2, $J_{4,5}$ = 2.6, H-4), 3.52 (m, 1H, H-6), 3.50 (m, 1H, H-3), 3.38 (dd, 1H, $^2J_{1'a,1'b}$ = 13.5, $J_{1'a,3}$ = 4.0, H-1′a), 2.98 (dd, 1H, $J_{1'b,3}$ = 8.9, H-1′b), 1.34 (d, 3H, $J_{6,Me\text{-}6}$ = 6.7, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 70.2 (C-4), 69.3 (C-5), 59.3 (C-6), 53.9 (C-3), 40.4 (C-1′), 13.6 (Me-6). CIMS *m*/*z* 162 [50%, $(M+H)^+$]. CIHRMS *m*/*z* found 162.1246, calcd for $C_6H_{16}N_3O_2$ $(M+H)^+$: 162.1243.

4.3.4. (3*S*,4*S*,5*R*,6*R*)-3-Aminomethyl-6-methylhexahydropyridazine-4,5-diol dihydrochloride (4b)

Hydrogenation of **24b** (41 mg, 0.138 mmol) following the general procedure afforded **4b** (32.6 mg, 0.138 mmol) as an oil. $[\alpha]_D^{22}$ −11.6 (*c* 0.33, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 3.86 (m, 1H, H-5), 3.72 (dd, 1H, $J_{4,3}$ = 8.9, $J_{4,5}$ = 2.7, H-4), 3.67 (qd, 1H, $J_{6,Me\text{-}6}$ = 7.2, $J_{6,5}$ = 3.7, H-6), 3.54 (td, 1H, $J_{3,1'b}$ = 8.8, $J_{3,1'a}$ = 4.5, H-3), 3.33 (m, 1H, H-1′a), 3.16 (dd, 1H, $^2J_{1'a,1'b}$ = 13.2, H-1′b), 1.45 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 69.6 (C-5), 66.1 (C-4), 58.3 (C-6), 55.3 (C-3), 40.0 (C-1′), 12.0 (Me-6). CIMS *m*/*z* 162 [40%, $(M+H)^+$]. CIHRMS *m*/*z* found 162.1247, calcd for $C_6H_{16}N_3O_2$ $(M+H)^+$: 162.1243.

4.3.5. (3*S*,4*S*,5*R*,6*S*)-3-(*p*-Phenylbenzoylaminomethyl)-6-methylhexahydropyridazine-4,5-diol hydrochloride (5c)

Hydrogenation of **23c** (50.5 mg, 0.106 mmol) following the general procedure afforded **5c** (40.5 mg, 0.106 mmol) as a solid. $[\alpha]_D^{22}$ −13.7 (*c* 0.88, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 7.95 (d, 2H, *J* = 8.5, H-arom.), 7.72 (d, 2H, *J* = 8.5, H-arom.), 7.66 (m, 2H, H-arom.), 7.46 (m, 2H, H-arom.), 7.38 (tt, 1H, *J* = 7.0, *J* = 1.5, H-arom.), 3.90 (m, 1H, H-5), 3.82 (dd, 1H, $^2J_{1'a,1'b}$ = 14.4, $J_{1'a,3}$ = 3.0, H-1′a), 3.59 (dd, 1H, $J_{1'b,3}$ = 7.3, H-1′b), 3.53 (dd, 1H, $J_{4,3}$ = 10.2, $J_{4,5}$ = 2.6, H-4), 3.47 (m, 1H, H-3), 3.43 (br q, 1H, $J_{6,Me\text{-}6}$ = 6.7, H-6), 1.31 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 170.8 (*C*ONH), 145.9, 141.2, 133.8, 129.1, 129.0, 128.1, 128.0 (C-arom.), 70.2 (C-4), 69.6 (C-5), 58.6 (C-6), 56.9 (C-3), 40.4 (C-1′), 13.7 (Me-6). CIMS *m*/*z* 342 [30%, $(M+H)^+$]. CIHRMS *m*/*z* found 342.1813, calcd for $C_{19}H_{24}N_3O_3$ $(M+H)^+$: 342.1818.

4.3.6. (3*S*,4*S*,5*R*,6*R*)-3-(*p*-Phenylbenzoylaminomethyl)-6-methylhexahydropyridazine-4,5-diol hydrochloride (6c)

Hydrogenation of **24c** (40.1 mg, 0.084 mmol) following the general procedure afforded **6c** (32 mg, 0.084 mmol) as a solid. $[\alpha]_D^{25}$ −5.5 (*c* 1.24, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 7.95 (br d, 2H, *J* = 7.5, H-arom.), 7.74 (br d, 2H, *J* = 8.5, H-arom.), 7.67–7.65 (m, 2H, H-arom.), 7.46 (br t, 2H, *J* = 7.5, H-arom.), 7.38 (tt, 1H, *J* = 7.5, *J* = 1.2, H-arom.), 3.82–3.76 (m, 3H, H-4, H-5, H-1′a), 3.67 (m, 1H, H-1′b), 3.60–3.52 (m, 2H, H-3, H-6), 1.40 (d, 3H, $J_{Me\text{-}6,6}$ = 6.8, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 170.8 (*C*ONH), 146.0, 141.1, 133.6, 130.0, 129.2, 129.0, 128.1 (C-arom.), 69.8, 66.4 (C-5, C-4), 59.3, 57.1 (C-3, C-6), 39.9 (C-1′), 12.9 (Me-6). CIMS *m*/*z* 342 [5%, $(M+H)^+$]. CIHRMS *m*/*z* found 342.1806, calcd for $C_{19}H_{24}N_3O_3$ $(M+H)^+$: 342.1818.

4.3.7. (3*S*,4*S*,5*R*,6*S*)-3-Dodecanoylaminomethyl-6-methylhexahydropyridazine-4,5-diol hydrochloride (5d)

Hydrogenation of **23d** (45.3 mg, 0.095 mmol) following the general procedure afforded **5d** (36 mg, 0.095 mmol) as a solid. $[\alpha]_D^{22}$ −20.4 (*c* 0.64, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 3.86 (dd, 1H, $J_{5,4}$ = 2.6, $J_{5,6}$ = 1.3, H-5), 3.59 (m, 1H, H-1′a), 3.41 (dd, 1H, $J_{4,3}$ = 10.0, H-4), 3.37 (qd, 1H, $J_{6,Me\text{-}6}$ = 6.7, H-6), 3.33–3.26 (m, 2H, H-1′b, H-3), 2.24 (t, 2H, $J_{H,H}$ = 7.5, CH_2CONH), 1.61 (m, 2H, CH_2), 1.32–1.29 (m, 19H, 8CH_2, Me-6), 0.90 (t, 3H, $J_{H,H}$ = 7.0, CH_3). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 177.4 (*C*ONH), 70.0 (C-4), 69.5 (C-5), 58.7 (C-6), 56.6 (C-3), 39.7 (C-1′), 37.0 (*C*H_2CONH), 33.1, 30.7, 30.6, 30.5, 30.4, 26.9, 23.7 (9 *C*H_2), 14.4 (*C*H_3), 13.7 (Me-6). CIMS *m*/*z* 344 [100%, $(M+H)^+$]. CIHRMS *m*/*z* found 344.2905, calcd for $C_{18}H_{38}N_3O_3$ $(M+H)^+$: 344.2913.

4.3.8. (3*S*,4*S*,5*R*,6R)-3-Dodecanoylaminomethyl-6-methylhexahydropyridazine-4,5-diol hydrochloride (6d)

Hydrogenation of **24d** (51.5 mg, 0.108 mmol) following the general procedure afforded **6d** (41 mg, 0.108 mmol) as a solid. $[\alpha]_D^{22}$ −4.5 (*c* 0.75, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 3.76 (m, 1H, H-5), 3.77 (br dd, 1H, $J_{4,3}$ = 7.3, $J_{4,5}$ = 2.5, H-4), 3.56–3.50 (m, 1H, H-6), 3.52 (dd, 1H, $^2J_{1'a,1'b}$ = 14.4, $J_{1'a,3}$ = 4.2, H-1′a), 3.43 (dd, 1H, $J_{1'b,3}$ = 7.2, H-1′b), 3.36 (m, 1H, H-3), 2.24 (t, 2H, $J_{H,H}$ = 7.5, CH_2CONH), 1.61 (m, 2H, CH_2), 1.37 (d, 3H, $J_{Me\text{-}6,6}$ = 7.0, Me-6), 1.32–1.29 (m, 16H, 8CH_2), 0.90 (t, 3H, $J_{H,H}$ = 7.0, CH_3). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 177.6 (*C*ONH), 69.8 (C-5), 66.2 (C-4), 59.2 (C-3), 56.9 (C-6), 39.2 (C-1′), 37.0 (*C*H_2CONH), 33.0, 30.73, 30.72, 30.6, 30.5, 30.4, 30.3, 26.9, 23.7 (9 *C*H_2), 14.4 (*C*H_3), 12.9 (Me-6). CIMS *m*/*z* 344 [100%, $(M+H)^+$]. CIHRMS *m*/*z* found 344.2903, calcd for $C_{18}H_{38}N_3O_3$ $(M+H)^+$: 344.2913.

4.3.9. (3*S*,4*S*,5*R*,6*S*)-3-[((2*S*)-2-Amino-6-phenyl)propanoylaminomethyl]-6-methylhexahydropyridazine-4,5-diol dihydrochloride (5e)

Hydrogenation of **23e** (25.3 mg, 0.057 mmol) following the general procedure afforded **5e** (22 mg, 0.057 mmol) as a solid. $[\alpha]_D^{22}$ +5.7 (*c* 0.67, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 7.38–7.35 (m, 2H, H-arom.), 7.32–7.29 (m, 3H, H-arom.), 4.16 (dd, 1H, $J_{2'',3''b}$ = 8.0, $J_{2'',3''a}$ = 7.0, H-2″), 3.85 (br s, 1H, H-5), 3.52 (dd, 1H, $^2J_{1'a,1'b}$ = 14.0, $J_{1'a,3}$ = 3.0, H-1′a), 3.47–3.44 (m, 2H, H-4, H-6), 3.41 (dd, 1H, $J_{1'b,3}$ = 7.0, H-1′b), 3.28 (m, 1H, H-3), 3.23 (dd, 1H, $^2J_{3''a,3''b}$ = 14.0, H-3″a), 3.04 (dd, 1H, H-3″b), 1.30 (d, 3H, $J_{Me\text{-}6,6}$ = 7.0, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 170.6 (*C*ONH), 135.7, 130.5, 130.1, 128.9 (C-arom.), 69.6 (C-4), 69.5 (C-5), 58.8 (C-6), 56.2 (C-3), 55.9 (C-2″), 39.8 (C-1′), 38.6 (C-3″), 13.6 (Me-6). CIMS *m*/*z* 309 [10%, $(M+H)^+$]. CIHRMS *m*/*z* found 309.1924, calcd for $C_{15}H_{25}N_4O_3$ $(M+H)^+$: 309.1927.

4.3.10. (3*S*,4*S*,5*R*,6*R*)-3-[((2*S*)-2-Amino-3-phenyl)propanoylaminomethyl]-6-methylhexahydropyridazine-4,5-diol dihydrochloride (6e)

Hydrogenation of **24e** (32 mg, 0.072 mmol) following the general procedure afforded **6e** (27.4 mg, 0.072 mmol) as a solid. $[\alpha]_D^{22}$ +21.4 (*c* 0.76, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 7.38–7.36 (m, 2H, H-arom.), 7.32–7.30 (m, 3H, H-arom.), 4.16 (dd, 1H, $J_{2'',3''b}$ = 8.2, $J_{2'',3''a}$ = 6.5, H-2″), 3.77 (br s, 1H, H-5), 3.66

(br d, 1H, $J_{4,3}$ = 6.0, H-4), 3.55–3.52 (m, 1H, H-6), 3.53 (dd, 1H, $^{2}J_{1'a,1'b}$ = 14.4, $J_{1'a,3}$ = 4.0, H-1′a), 3.45 (br dd, 1H, $J_{1'b,3}$ = 7.5, H-1′b), 3.34 (m, 1H, H-3), 3.24 (dd, 1H, $^{2}J_{3''a,3''b}$ = 14.0, H-3″a), 3.04 (dd, 1H, H-3″b), 1.38 (d, 3H, $J_{Me\text{-}6,6}$ = 6.9, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 170.6 (CONH), 135.6, 130.5, 130.2, 128.9, (C-arom.), 69.8 (C-5), 66.0 (C-4), 58.3 (C-3), 57.5 (C-6), 55.9 (C-2″), 39.6 (C-1′), 38.6 (C-3″), 12.6 (Me-6). CIMS *m*/*z* 309 [60%, $(M+H)^+$]. CIHRMS *m*/*z* found 309.1920, calcd for $C_{15}H_{25}N_4O_3$ $(M+H)^+$: 309.1927.

4.3.11. (3*S*,4*S*,5*R*,6*S*)-3-[((2*S*)-2,6-Diamino)hexanoylaminomethyl]-6-methylhexahydropyridazine-4,5-diol hydrochloride (5f)

Hydrogenation of **23f** (22 mg, 0.052 mmol) following the general procedure afforded **5f** (20 mg, 0.052 mmol) as a solid. $[\alpha]_D^{25}$ −1.6 (*c* 0.5, MeOH). ^{1}H NMR (500 MHz, CD_3OD, δ ppm, *J* Hz) δ 3.97 (br t, 1H, $J_{2'',3''a}$ = $J_{2'',3''b}$ = 6.5, H-2″), 3.89 (m, 1H, H-5), 3.66 (dd, 1H, $^{2}J_{1'a,1'b}$ = 14.2, $J_{1'a,3}$ = 2.7, H-1′a), 3.54 (dd, 1H, $J_{4,3}$ = 10.1, $J_{4,5}$ = 2.4, H-4), 3.50 (q, 1H, $J_{6,Me\text{-}6}$ = 6.6, H-6), 3.44 (dd, 1H, $J_{1'b,3}$ = 7.2, H-1′b), 3.37 (m, 1H, H-3), 2.98 (br t, 2H, $J_{6'',5''}$ = 7.5, H-6″), 1.95 (m, 1H, H-3″a), 1.89 (m, 1H, H-3″b), 1.75 (m, 2H, H-5″), 1.54 (m, 2H, H-4″), 1.32 (d, 3H, Me-6). ^{13}C NMR (125.7 MHz, CD_3OD, δ ppm) δ 170.8 (CONH), 69.7 (C-4), 69.5 (C-5), 58.8 (C-6), 56.1 (C-3), 54.3 (C-2″), 40.3 (C-6″), 39.9 (C-1′), 32.0 (C-3″), 28.0 (C-5″), 23.0 (C-4″), 13.7 (Me-6). CIMS *m*/*z* 290 [45%, $(M+H)^+$], 272 [100%, $(M\text{-}NH_3)^+$]. CIHRMS *m*/*z* found 290.2186, calcd for $C_{12}H_{28}N_5O_3$ $(M+H)^+$: 290.2192.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.05.026.

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