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Bicyclic carbohydrate-derived scaffolds for combinatorial libraries

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Abstract—A bicyclic scaffold derived from the natural monosaccharide D-glucose, and possessing several diversity sites, was linked to various resins through the primary (C-6) hydroxyl and decorated on the solid phase: the hydroxyl group at C-4 was functionalized as ester, ether, and carbamate, the amino group in the second cycle (C-3′ position) was functionalized as amide, sulfonamide, and ureido- and thioureido-derivatives. The compounds synthesized on the solid phase were tested for their antiproliferative activity on tumor cell lines.

1. Introduction

In the current era of genomics, proteomics, and other -omics, the exponential increase in potential therapeutic targets is placing an ever-growing demand on access to novel and diverse chemical libraries. Even though physicochemical and particularly biological properties are hard to correlate with molecular properties, many models exist which employ a set of 1D (physicochemical), 2D (topological) or 3D (geometrical) descriptors to assess molecular diversity or similarity.[1–3] One way to interpret molecular diversity is to divide it into a functional and a structural part, and then reduce the structural part to just the rigid portion of the scaffold. A monosaccharide is an ideal chiral scaffold containing five functionalized positions. In principle, various substituents can be appended at each position and the stereochemistry at each center can be altered. Sugar scaffolds provide an unparalleled opportunity to generate libraries of high functional and structural diversity.[4] Indeed, the last decade has witnessed new roles of carbohydrate chemistry in the drug discovery process. In fact, the sugar template has been used as a tool to generate new drugs by first mimicking non-carbohydrate structures such as peptides.[5] More recently, it has been used as a structural scaffold bearing pharmacophoric functionalities in combinatorial chemistry approaches.[6] Hence, recent efforts have focused on developing efficient methods of selective protection, deprotection, and functionalization, both in solution and on solid supports, to build up libraries of compounds based on carbohydrate scaffolds. It has also been reported that, according to Lipinski's 'rule of five',[7] the high number of hydrogen bond acceptors and donors in carbohydrate scaffolds can decrease their cellular and tissue absorption.[8] This problem is often bypassed in the case of monosaccharide-derived drugs by the presence of specific biological transporters that improve cellular uptake.[8]

In order to increase the conformational rigidity of carbohydrate derivatives as scaffolds for the production of libraries, and to generate original molecules, the formation of a second cycle in the sugar skeleton is desirable. Examples of this strategy have been already proposed by some of us[9] and by others.[10] According to this strategy, we envisaged that fused perhydrofuropyrans[11,12] could be appropriate scaffolds to develop a library and to generate diversity through their functionalities. The conformational rigidity of very similar sugar-derived bicyclic scaffolds has been proved by molecular modeling studies and NMR analysis in solution.[9b]

In this paper, we describe the synthesis of derivatives of the sugar-based *cis*-fused perhydrofuropyrans **1** and **2** (Fig. 1), and their decoration with different functional groups both in solution and in the solid phase. A library

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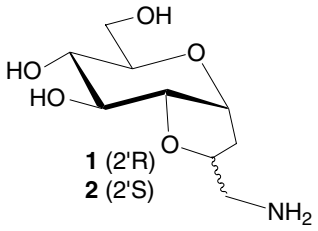


Figure 1.

of 37 different compounds was prepared and tested on tumor cell lines, namely colon carcinoma cells (HT29) and prostatic carcinoma cells (DU145), for their antiproliferative activity.

2. Results and discussion

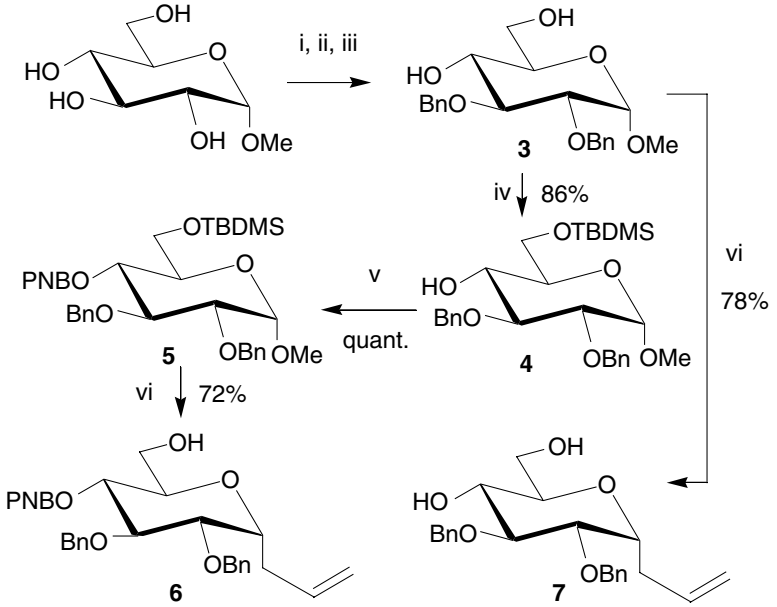
2.1. Synthesis in solution of the bicyclic core

Orthogonally protected derivatives of the bicyclic scaffolds **1** and **2** were first synthesized in solution. Commercially available methyl α-D-glucopyranoside was reacted with benzaldehyde dimethylacetal in the presence of camphorsulfonic acid (CSA) in acetonitrile (MeCN) to give methyl 4,6-di-*O*-benzylidene-α-D-glucopyranoside, which was benzylated (BnBr, NaH in DMF) (Scheme 1).

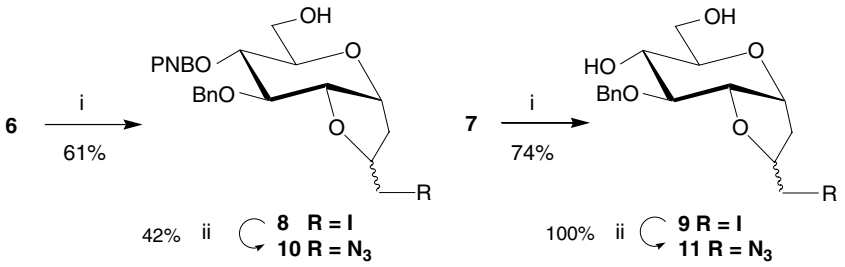
The benzylidene ring was then hydrolyzed under acidic conditions (90% TFA in dichloromethane) to afford compound **3**, which was regioselectively silylated at the primary hydroxyl on C-6[13] with *tert*-butyl-dimethylsilyl chloride (TBDMSCl) in the presence of imidazole to give compound **4** (86% yield). The free hydroxyl group of **4** was protected as *p*-nitrobenzoyl (PNB) ester to yield compound **5** (quant. yield), which was allylated at the anomeric carbon with allyltrimethylsilane in the presence of trimethylsilyltriflate, with concomitant O-desilylation at C-6, to afford the α-C-glucoside **6** (72% yield). When performing the work-up of the C-allylation reaction (leading to compound **6**) on a large scale, migration of the PNB ester from C-4 to C-6 was observed. We avoided this undesired side reaction by quenching the crude reaction mixture with an aqueous sodium acetate solution, thus maintaining the aqueous phase buffered at pH $\geqslant$ 5. The same allylation reaction was conducted directly on compound **3**, and afforded the α-C-glucoside **7** (78% yield) with two free hydroxyl groups (at C-4 and C-6), which was used to investigate the possibility of a regioselective attachment of the scaffold to the solid support. Treatment of compounds **6** and **7** with iodine in dichloromethane resulted in the debenzylation–cyclization reaction leading to the bicyclic iododerivatives **8** (61% yield) and **9** (74% yield), respectively, as mixtures of diastereoisomers at C-2′ (diastereomeric ratio 3:1 in favor of the *R*-isomer determined by ^{1}H NMR spectroscopy) (Scheme 2). Finally, nucleophilic displacement of the iodide with tetrabutylammonium azide (n-Bu_4NN_3) allowed the synthesis of azides **10** (42% yield) and **11** (quantitative yield), both as mixtures of diastereomers which can be separated by column chromatography (Scheme 2). The azido-derivatives (**10** or **11**), as 3:1 diastereomeric mixtures, seemed to be the ideal candidates for the generation of the library, possessing three hydroxyl groups and a masked amine (azide) which can be orthogonally functionalized.

2.2. Preliminary solid phase studies

We envisaged a number of possible intermediates which could be linked to the solid phase. Desilylated **5**, namely methyl 2,3-di-*O*-benzyl-4-*O*-(4-nitrobenzoyl)-α-D-glucopyranoside, could be linked to the resin through its C-6 position and reacted on the solid phase to obtain resin-bound **6**, **8**, and **10**. We tried to link this



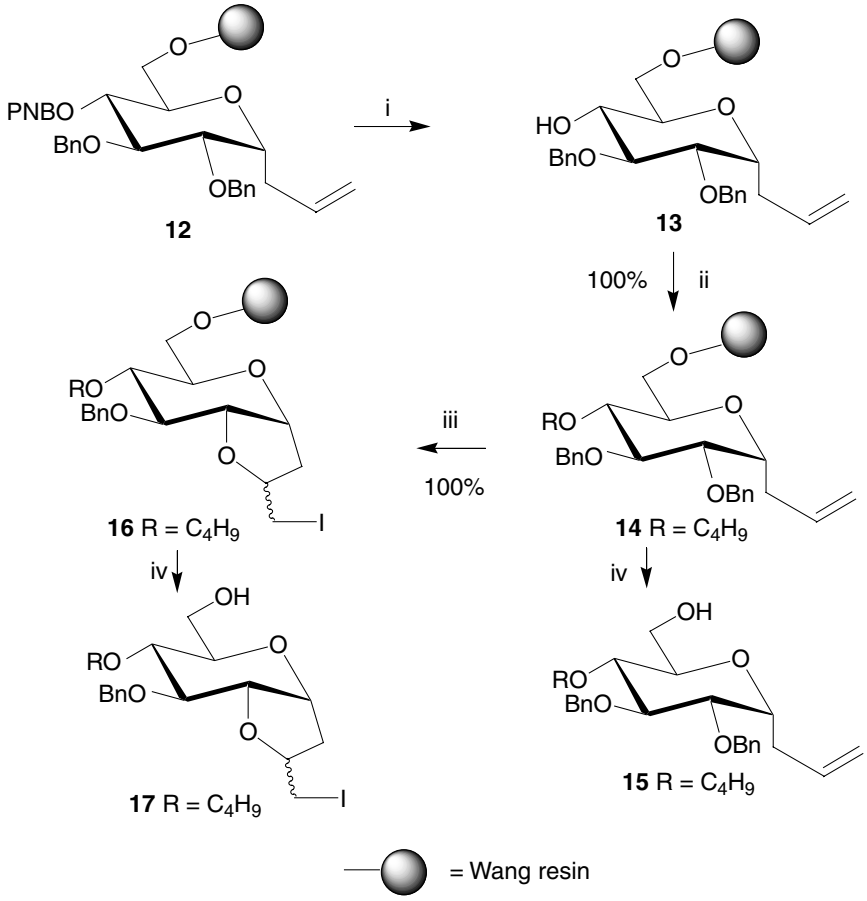
Scheme 1. Reagents and condition: (i) $PhCH(OMe)_2$, CSA, MeCN; (ii) BnBr, NaH, DMF; (iii) 90% TFA, CH_2Cl_2; (iv) TBDMSCl, imidazole, DMF, −40 °C; (v) PNBCl, CH_2Cl_2, Py; (vi) allyltrimethylsilane, TMSOTf, MeCN.



Scheme 2. Reagents and condition: (i) I_2, CH_2Cl_2; (ii) *n*-Bu_4NN_3, toluene, 60 °C.

monosaccharide to different types of resins through its primary hydroxyl group. Diisopropylsilyl chloride polystyrene resin did not show any appreciable loading, while trityl chloride resin gave an apparent loading of about 46% (based on product recovery after cleavage). Trichloroacetimidate-activated (TCA) Wang resin[14] gave the best loading results (70%), again calculated by attachment to the resin, cleavage, and product recovery. We then explored the possibility to perform on the solid phase the synthetic pathways described in Schemes 1 and 2. However, the allylation on the solid phase, using different Lewis acids (TMSOTf, BF_3-Et_2O, and $SnCl_4$) and in different solvents (THF, acetonitrile, and CH_2Cl_2), gave negative results (no reaction or cleavage of the starting monosaccharide from the resin). Therefore, we decided to load on the resin the allyl C-glucoside **6**, which is downstream in the synthetic pathway. The allyl C-glucoside **6** was anchored to a Wang resin affording **12** with high loading. Resin **12** was used to investigate the feasibility of the iodocyclization reaction and decoration at C-4 on the solid phase, as shown in Scheme 3.

Hydrolysis of the *p*-nitrobenzoyl ester and subsequent etherification at C-4 (for example with a *n*-butyl group) gave **14**, which was then cyclized to the bicyclic iododerivative **16** (Scheme 3). This process was successful on the solid phase and the high yield was witnessed by the substantial recovery of compound **17** after cleavage from the resin. However, the subsequent conversion of iodide **16** into the corresponding azide was problematic, suggesting to consider the direct loading of azide **10** onto the resin as a valuable alternative.



Scheme 3. Reagents: (i) KOtBu, DMF or NaOMe, MeOH, THF; (ii) *n*-BuBr, KOtBu, DMF; (iii) I_2, CH_2Cl_2; (iv) 10% TFA, CH_2Cl_2.

2.3. Solid phase library synthesis

Bicyclic scaffold **10** bears three hydroxyl groups and a protected amine (azide) which can be orthogonally functionalized and thus was selected as a good candidate for developing a library of compounds on solid phase. Our strategy aimed at the different decoration of at least two of the four diversity sites of the scaffold. A further point of diversity is inherent in the structure of **10**, which is a mixture of diastereoisomers at C-2′ (diastereomeric ratio = 3:1). We decided to synthesize the library as a mixture of epimers at C-2′, taking into account that once a 'hit' is hopefully identified during the screening, the two epimers can be separated and tested singularly. We decided to use the primary hydroxyl group as anchor for the attachment to the solid support, with the additional advantage to have a free hydroxyl group in the final compound after the cleavage from the resin, which might be used to modulate the product solubility. Compound **10** was thus reacted with trichloroacetimidate Wang resin in the presence of the promoter TMSOTf to give **18** (Scheme 4).

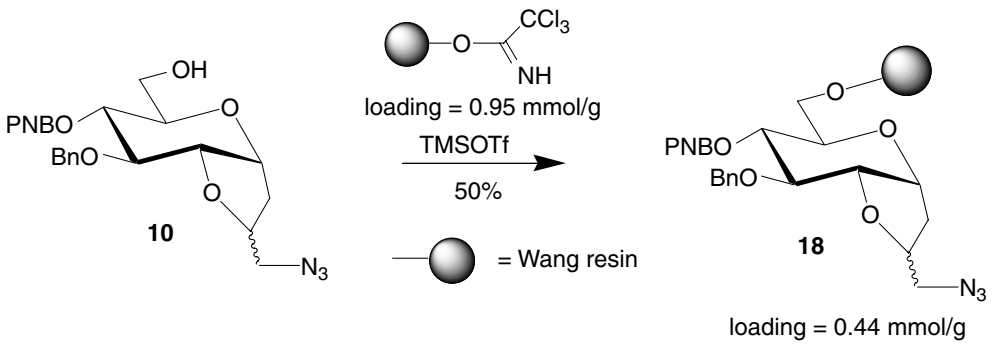
To optimize this loading, we found that it was possible to perform a second coupling cycle (after Wang linker re-activation by trichloroacetimidate formation) without release or decomposition of resin-bound compound. After the second cycle, the loading of the scaffold increased and reached a value of about 0.60 mmol/g. Interestingly, the unloaded scaffold was quantitatively recovered from the effluents (filtrates and washings) and re-used after purification by filtration through a silica gel plug. This indicates that it is possible to perform further coupling cycles on the loaded resin in order to obtain even higher loadings, if necessary. We set up a standard procedure comprising two loading cycles. The Wang resin-grafted scaffold **18** was exploited to produce a library by taking advantage of the orthogonally protected hydroxyl group at C-4 of the pyranose ring and the azido group at C-3′ of the furanose ring, which can be converted into an amino group. Cleavage of the *p*-nitrobenzoyl ester was effected with sodium methoxide in methanol–THF (1:8), affording **19** with the free hydroxyl group at C-4, which was subsequently decorated by acylation or carbamoylation (Scheme 5).

Esterification was performed with a variety of carboxylic acids by using diisopropyl carbodiimide (DIC) as condensing agent, to afford esters **20**. Formation of carbamate **22** was accomplished by reaction with *p*-nitrophenyloxycarbonyl chloride and subsequent treatment with a primary amine. After derivatization of the hydroxyl group at C-4, the azido group was converted to the corresponding amine by reduction with $SnCl_2$, thiophenol, and triethylamine or by reaction with triphenylphosphine in the presence of water (this methods turned out to be more efficient). The primary amines **21** and **23** were then derivatized in different ways to decorate the second diversity site, as shown in Table 1.

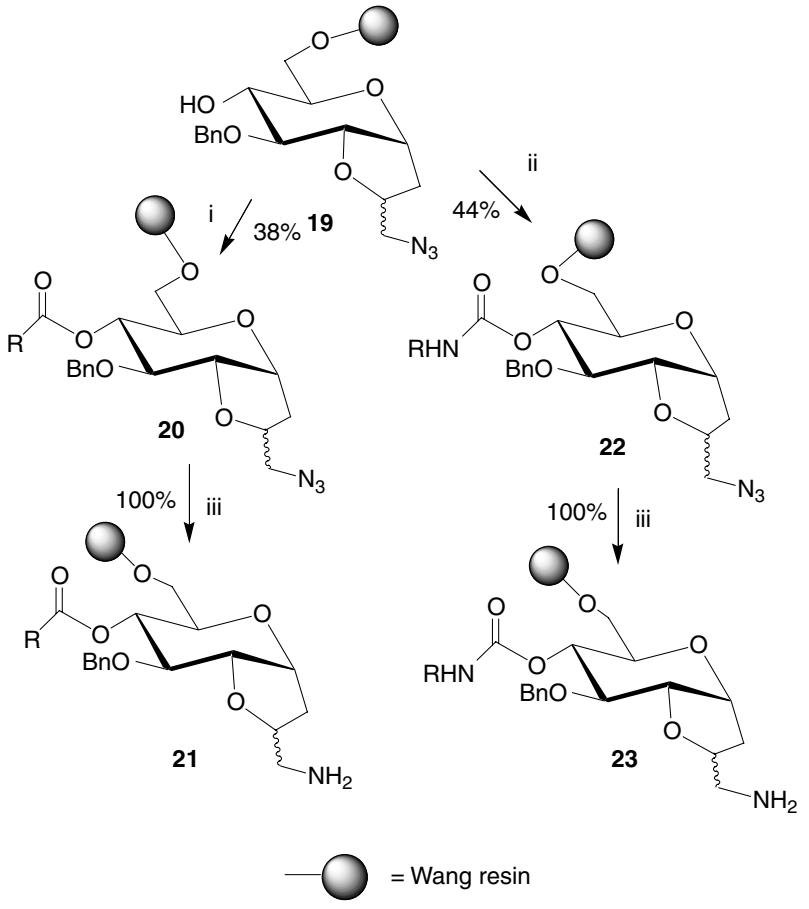
The amino group of **21** was reacted with different carboxylic acids (Table 1) by using three alternative coupling procedures (HBTU, method A; DIC, HOBt, method B; HATU, method C), with DIPEA as base and DMF as solvent. Method C resulted to be the more efficient and reproducible, and it was employed for the preparation of all amides **24** (Scheme 6). The sulfonamides **25** were prepared by treatment with a sulfonyl chloride, while the ureido-derivatives **26** and the thioureido-derivatives **27** by condensation of the amine with an isocyanate or an isothiocyanate, respectively. Finally, reductive amination of the primary amino group of compounds **21** and **23** with different aldehydes in the presence of $NaBH_3CN$ afforded the secondary amines **28**, which were further derivatized by condensation with a carboxylic acid (HATU, DIPEA) or with an isocyanate to give compounds **29.**

Compounds **30**–**31**, **45**–**48**, and **63**–**66** (Fig. 2) were prepared starting from the Wang resin-bound *p*-nitrobenzoate **18** following the synthetic pathways reported in Schemes 5 and 6.

In order to reduce the number of protection–deprotection steps in the overall synthetic process, we linked azide **11**, bearing two unprotected hydroxyls, to a silyl chloride resin (Scheme 7). 1,3-Dichloro-5,5-dimethylhydantoin generated the resin-bound silyl chloride in situ. This reaction was monitored by IR and the complete absence of the Si–H stretch (2094 cm^{-1}) was detected within 2 h. The different reactivity between the primary and secondary hydroxyl groups of scaffold **11** ensured the regioselective attachment to the diethylsilyl resin through the C-6 primary OH to give the diethylsilyl resin-bound azide **19a** with a high loading (Scheme 7). After a subsequent acylation step, NMR and HPLC analysis of the cleaved product demonstrated the high regioselectivity of the loading reaction: the



Scheme 4.



Scheme 5. Reagents: (i) RCOOH, DIC, DMAP, CH_2Cl_2; (ii) *p*-NO_2PhOCOCl, NMM, THF, then RNH_2; (iii) $SnCl_2$, PhSH, TEA or PPh_3, H_2O, THF.

Table 1. Methods for C-3′ amino group acylation in resin-bound compound **21**

Method	C-4 substituent	Acylating agent	Coupling reagent	Coupling cycles	Yield (%)[a]
A	*p*-Nitrobenzoyl	Benzoic acid	HBTU	2	[b]
B	*p*-Nitrobenzoyl	Benzoic acid	DIC, HOBt	1	15
C	*p*-Nitrobenzoyl	Benzoic acid	HATU	4	34
B	*p*-Nitrobenzoyl	Caprylic acid	DIC, HOBt	1	15
C	*p*-Nitrobenzoyl	Caprylic acid	HATU	5	27
C	Naphth-1-ylacetyl	3,5-$(OMe)_2$PhCOOH	HATU	2	22
C	Naphth-1-ylacetyl	Phenylpropionic acid	HATU	2	34

[a] Yield of the purified product over three reaction steps (azide reduction, acylation, and cleavage).
[b] Yield not reproducible.

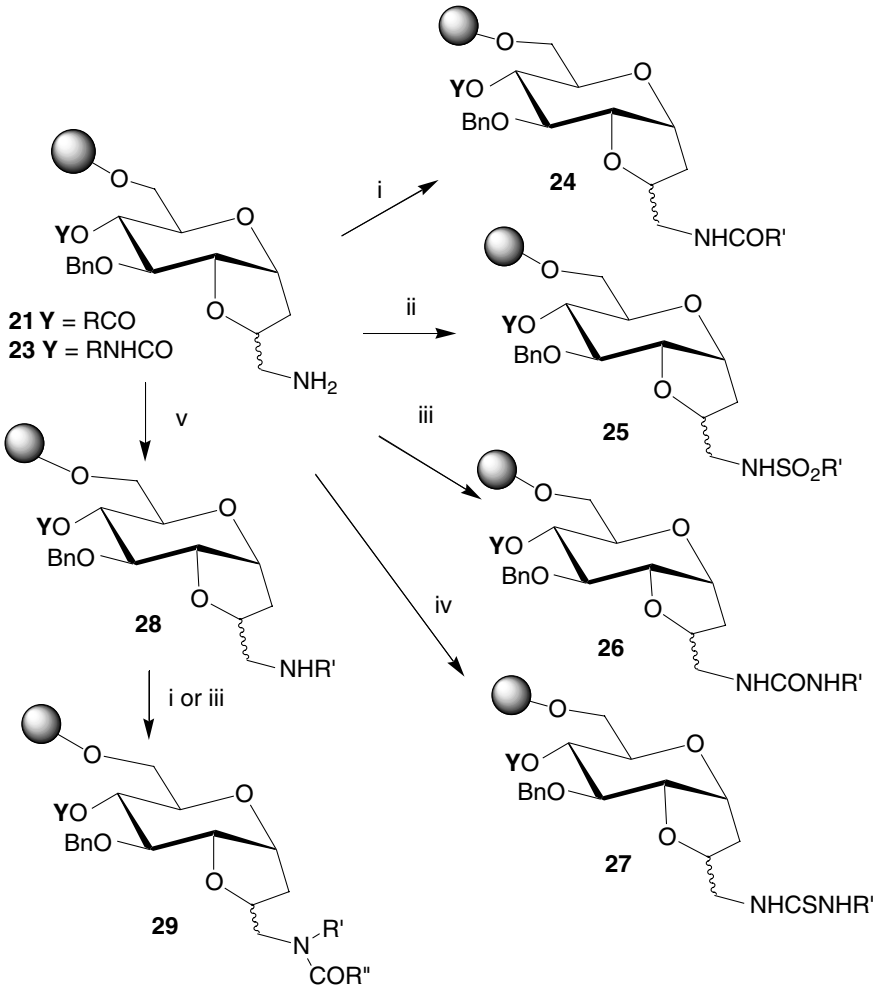
scaffold selectively acylated at C-4 was recovered. The rest of the library (compounds **32**–**44**, **49**–**62**, Fig. 2) was synthesized using this modified strategy, which avoids the steps of PNB ester protection–deprotection at C-4 required for the Wang-resin supported scaffolds **18** and **19**. This simpler and straightforward procedure also uses milder conditions for the activation of the linker and the loading of the scaffold and resulted to be the method of choice for the synthesis of the library.

2.4. Biological tests

All the synthesized compounds (**30**–**66**, Fig. 2) were tested against different tumor cell lines. We report here the antiproliferative activity on a colon carcinoma cell line (HT29) and a prostatic carcinoma cell line (DU145). A first screening was performed measuring the cell proliferation as percent of a control: selected data are reported in Table 2. In particular, compound **59** (3:1 mixture of diastereomers at C-2′) shows promising activity on both cell lines. Either one or both diastereomers could be responsible for the activity detected. Now that a 'hit' has been identified, work is in progress to elucidate in detail the structure–activity relationships in this class of compounds.

3. Conclusions

In conclusion, we have developed an original scaffold derived from the natural sugar D-glucose for combinatorial synthesis presenting interesting properties such as



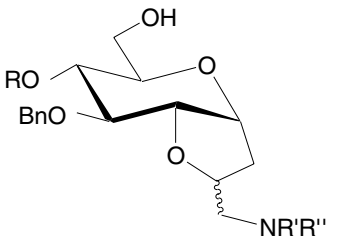
Scheme 6. Reagents: (i) RCOOH, DMF/CH_2Cl_2, HATU, DIPEA; (ii) RSO_2Cl, DMAP, CH_2Cl_2; (iii) RNCO CH_2Cl_2, TEA; (iv) RNCS, CH_2Cl_2, TEA; (v) RCHO, AcOH, $NaCNBH_3$.

conformational rigidity, multiple and orthogonal functionalization sites, and presence of two similarly reacting epimers which increase the diversity of the final library. We explored different alternatives for the synthetic methodology on the solid phase, setting up a convenient approach for this scaffold. We have exploited the scaffold in order to generate a library of 37 compounds on the solid phase, one of which presented promising antiproliferative activity on tumor cell lines.

4. Experimental

4.1. General methods

All solvents were dried over molecular sieves (Fluka), for at least 24 h prior to use. When dry conditions were required, the reactions were performed under Ar atmosphere. Thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} plates (Merck) with detection with UV light when possible, or charring with a solution containing concd H_2SO_4/EtOH/H_2O in a ratio of 5/45/45 followed by heating at 180 °C. Flash chromatography was performed on silica gel 230–400 mesh (Merck). The boiling range of petroleum ether used as eluent in column chromatography is 40–60 °C. Wang resin (1% polystyrene-divinylbenzene, 100–200 mesh, 0.95 mmol/g substitution) and butyldiethylsilane polymer-bound (PS-DES-SiH) (1% polystyrene-divinylbenzene, 100–200 mesh, 1.37 mmol/g substitution) were purchased from Aldrich. HPLC/MS was performed on a Waters X Terra RP 18 (4.6 × 50 mm, 3.5 μm) column using a Waters 2790 HPLC system equipped with a 996 Waters PDA detector and a Micromass mod. ZQ single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source. Mobile phase A was ammonium acetate 5 mM buffer (pH 5.5 with $AcONH_4$/MeCN 95:5) and Mobile phase B was H_2O/acetonitrile (5:95). Gradient from 10% to 90% B in 8 min, hold 90% B 2 min. UV detection at 220 and 254 nm. Flow rate 1 mL/min. Injection volume 10 μL. Full scan, mass range from 100 to 800 amu. Capillary voltage was 2.5 kV; Source temp. was 120 °C; Cone was 10 V. Retention Times (HPLC rt) are given in minutes at 220 or 254 nm. Mass is given as *m*/*z* ratio. ^1H NMR spectroscopy was performed on a Mercury VX 400 operating at 400.45 MHz equipped with a 5 mm double resonance probe (^1H {^{15}N–^{31}P} ID_PFG

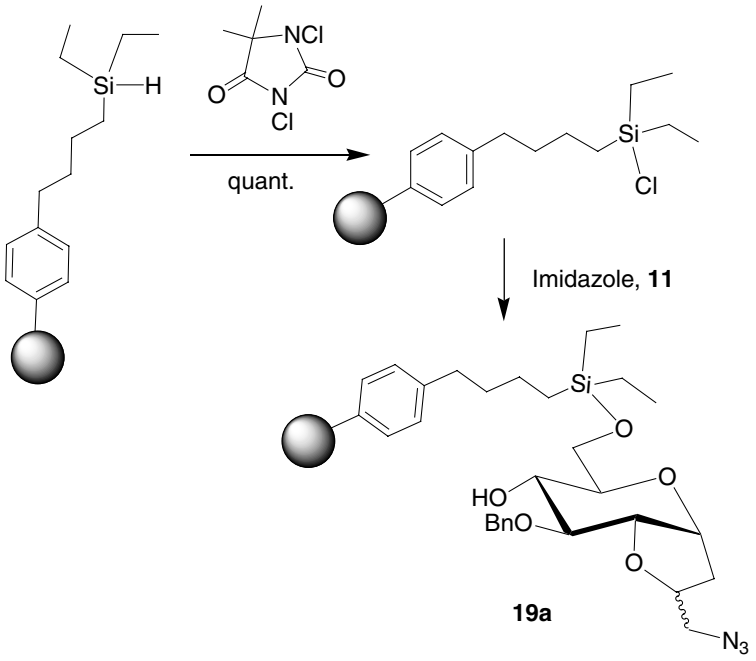


30 R= *p*-NO_2PhCO, R' = PhCO, R'' =H
31 R= *p*-NO_2PhCO, R'= nC_7H_{15}CO, R'' =H
32 R= 1-naphthylacetyl , R'= $PhCH_2CH_2CO$, R'' =H
33 R= 1-naphthylacetyl , R'= 3,5-$(MeO)_2$PhCO, R'' =H
34 R= cyclopropylCO, R' = *i*PrCO, R'' =H
35 R= cyclopropylCO, R' = $MeOCH_2CO$, R'' =H
36 R= C_2H_5CO, R' = *i*PrCO, R'' =H
37 R= 3-pyridylCO, R' = *i*PrCO, R'' =H
38 R= 3-pyridylCO, R' = $MeOCH_2CO$, R'' =H
39 R= 3-pyridylCO, R' = Me_2NCH_2CO, R'' =H
40 R= *p*-F-PhCO, R' = *i*PrCO,R''=H
41 R= *p*-F-PhCO, R' =Me_2NCH_2CO, R'' =H
42 R= 2-thienylCO, R' = *i*PrCO, R''=H
43 R= 2-thienylCO, R' = $MeOCH_2CO$, R'' =H
44 R= 2-thienylCO, R' = Me_2NCH_2CO, R'' =H
45 R= butylNHCO, R' = $PhCH_2CH_2CO$, R'' =H
46 R= $PhCH_2CH_2CO$, R' = *p*-$MeOPhSO_2$, R'' =H
47 R= $PhCH_2CH_2CO$, R' = PhNHCO, R'' =H
48 R= $nC_7H_{15}CO$, R' = PhNHCO, R'' =H
49 R= *p*-NO_2PhCO, R' = PhNHCO, R'' =H
50 R= cyclopropylCO, R' = *i*PrNHCO, R'' =H
51 R= cyclopropylCO, R' = *m*-FPhNHCO, R'' =H
52 R= cyclopropylCO, R' = *m*-MeOPhNHCO, R'' =H
53 R= C_2H_5CO, R' = *m*-FPhNHCO, R'' =H
54 R= C_2H_5CO, R' = *i*PrNHCO, R'' =H
55 R= 3-pyridylCO, R' = *m*-FPhNHCO, R'' =H
56 R= 3-pyridylCO, R'= *i*PrNHCO, R'' =H
57 R= *p*-F-PhCO, R' = *i*PrNHCO, R'' =H
58 R= *p*-F-PhCO, R' = *m*-MeOPhNHCO, R'' =H
59 R= *p*-F-PhCO, R' = *m*-FPhNHCO, R''=H
60 R= 2-thienylCO, R' = *i*PrNHCO, R''=H
61 R= 2-thienylCO, R' = *m*-FPhNHCO, R'' =H
62 R= 2-thienylCO, R' = *m*-MeOPhNHCO, R'' =H
63 R= $PhCH_2CH_2CO$, R' = PhNHCS, R'' =H
64 R= $PhCH_2CH_2CO$, R' = PhNHCO, R'' =Bn
65 R= $PhCH_2CH_2CO$, R' = $nC_7H_{15}CO$, R'' =Bn
66 R= $PhCH_2CH_2CO$, R' = 1-naphthylacetyl, R'' = *p*-CH_3O-Bn

Figure 2. Library of compounds obtained by solid phase decoration of D-glucose-derived bicyclic scaffold.

Varian). Or alternatively, ^{1}H NMR spectroscopy was performed on a Varian Mercury VX 300 operating at 300.069 MHz or on a Bruker 200 MHz spectrometer. ^{13}C NMR spectra were recorded on 400 (100 MHz), 300 (75 MHz) or 200 (50 MHz) spectrometers with complete proton decoupling.

4.1.1. Methyl 2,3-di-*O*-benzyl-6-*O*-terbutyldimethylsilyl-α-D-glucopyranoside (4). To a solution of **3**[12] (4.4 g, 11.8 mmol) in 40 mL of dry DMF, imidazole (4.02 g, 59 mmol, 5 equiv) and TBDMSCl (3.03 g, 20.1 mmol, 1.7 equiv) were added under argon atmosphere and the solution was vigorously stirred at −40 °C overnight. The crude was then diluted with 200 mL of CH_2Cl_2, washed with water, organic layer dried on sodium sulfate, filtered, and concentrated. The product was purified by flash chromatography on silica gel (petroleum ether/EtOAc 9:1) and pure **4** was recovered as a colorless oil (5.5 g, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 0.10 (s, 6H), 0.90 (s, 9H), 3.37 (s, 3H), 3.48



Scheme 7. Regioselective loading of the azide **11** onto a polymeric support.

Table 2. Antiproliferative activity of selected compounds on tumor cell lines

Compound	HT29		DU145	
	% proliferation at 50 μM	IC_{50} (μM)	% proliferation at 50 μM	IC_{50} (μM)
32	44.3	>50	16.7	35.2
33	63.5	>50	54.7	49.5
45	75.3	50.0	63.1	45.8
48	75.3	>50	89.3	>50
58	17.9	>50	13.3	>50
59	9.0	32.4	1.5	26.3
61	32.3	51.7	32.0	49.5

(dd, 1H, J = 9.7, 3.4 Hz), 3.52–3.62 (m, 2H), 3.80 (t, 1H, J = 9.7 Hz), 3.80 (d, 2H, J = 5.1 Hz), 4.61 (d, 1H, J = 3.4 Hz), 4.64 (d, 1H, J = 12.0 Hz), 4.75 (d, 1H, J = 12.0 Hz), 4.76 (d, 1H, J = 11.5 Hz), 4.97 (d, 1H, J = 11.5 Hz), 7.20–.60 (m, 10H). MS-EI m/z = 488.5 (M^+). $[\alpha]_D$ +17.4°. Anal. Calcd for $C_{27}H_{40}O_6Si$ (488.7): C, 66.36; H, 8.25. Found: C, 66.10; H, 8.16.

4.1.2. Methyl 2,3-di-*O*-benzyl-4-*O*-(4-nitrobenzoyl)-6-*O*-terbutyldimethylsilyl-α-D-glucopyranoside (5). To a solution of **4** (4.8 g, 9.8 mmol, 1 equiv) in 80 mL of dry CH_2Cl_2, pyridine (7.9 mL, 98.0 mmol, 10 equiv) and 4-nitrobenzoyl chloride (3.6 g, 19.6 mmol, 2 equiv) were added under argon atmosphere and the solution was stirred at room temperature overnight. The solution was then diluted with 100 mL of CH_2Cl_2, washed with water, the organic layer was dried on sodium sulfate, filtered, and concentrated. The product was purified by flash chromatography on silica gel (petroleum ether/EtOAc 9:1) and pure **5** was recovered as a white solid (6.2 g, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): −0.11 (s, 6H), 0.83 (s, 9H), 3.43 (s, 3H), 3.60–4.70 (m, 3H), 3.84 (m, 1H), 4.05 (t, 1H, J = 9.6 Hz), 4.56 (d, 1H, J = 11.7 Hz), 4.66 (d, 1H, J = 4.0 Hz), 4.68 (d, 1H, J = 11.9 Hz), 4.79 (d, 1H, J = 11.9 Hz), 4.84 (d, 1H, J = 3.4 Hz), 5.17 (t, 1H, J = 9.9 Hz), 7.00–7.60 (m, 10H), 8.00–8.30 (AA′XX′q, 4 H). MS-EI: m/z = 637.4 (M^+). $[\alpha]_D$ −23.1°. Mp = 78.5 °C. Anal. Calcd for $C_{34}H_{43}NO_9Si$ (637.80): C, 64.03; H, 6.79; N, 2.20. Found: C, 63.98; H, 6.43; N, 2.52.

4.1.3. 3-C-[2′,3′-Di-*O*-benzyl-4′-*O*-(4-nitrobenzoyl)-α-D-glucopyranosyl]-1-propene (6). To a solution of **5** (1.46 g, 2.3 mmol, 1 equiv) in 6 mL of dry MeCN, allyltrimethylsilane (1.75 mL, 11 mmol, 5 equiv) and TMSOTf (1.99 mL, 11 mmol, 5 equiv) were added under argon atmosphere and the mixture was stirred at room temperature for 72 h. The mixture was then diluted with AcOEt and carefully kept at 0 °C; then 22 mL of 1 M aqueous NaOAc, previously stored in ice at 0 °C, was added. In this way, 22 mmol of base, exactly twice as much the equiv of TMSOTf, was added, obtaining a buffer solution (pH 5). Mixing of the two phases, extraction with AcOEt, washing to neutrality, and evaporation afforded a crude mixture which by chromatography on silica gel (petroleum ether/EtOAc 6:4) gave pure **6** as a white solid (880 mg, 72% yield). ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 2.51 (m, 2H), 3.61 (m, 2H), 3.70–3.80 (m, 1H), 3.80 (dd, 1H, J = 8.4, 5.1 Hz), 3.94 (t, 1H, J = 8.4 Hz), 4.15 (dt, 1H), 4.66 (ABq, 2H), 4.74 (ABq, 2H), 5.12 (m, 1H), 5.16 (t, 1H, J = 8.4 Hz), 5.21 (m, 1H), 5.81 (m, 1H), 7.20–7.40 (m, 10H), 8.30 (AA′XX′q, 4 H). HRMS (CI^+, CH_4) Calcd for $C_{30}H_{31}NO_8$ [M+H$^+$]: 534.2128. Found: 534.2129.

4.1.4. 3-C-[2′,3′-Di-*O*-benzyl-α-D-glucopyranosyl]-1-propene (7). Compound **3** (9.35 g, 23.95 mmol, 1 equiv) was dissolved in 51.1 mL of dry MeCN under argon atmosphere. Allyltrimethylsilane (19.27 mL, 119 mmol, 5 equiv) and TMSOTf (21.63 mL, 97.3 mmol, 4 equiv)

were added and the mixture was stirred for 3 h. The mixture was carefully kept at 0 °C and diluted with AcOEt (150 mL) and water (150 mL), then Na_2CO_3 was added until neutrality. Mixing of the two phases, extraction with AcOEt, and evaporation afforded a crude mixture which, by chromatography on silica gel (petroleum ether/EtOAc 1:1), gave the title compound **7** (7.16 g; 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.12 (m, 1H), 2.53 (m, 2H), 3.51 (m, 2H), 3.60–3.80 (m, 4H), 4.02 (m, 1H), 4.65 (ABq, 2H), 4.81 (ABq, 2H), 5.05 (m, 2H), 5.83 (m, 1H), 7.20–7.40 (m, 10H). HRMS (CI^+, CH_4) Calcd for $C_{23}H_{29}O_5$ [M+H$^+$]: 385.2015. Found: 385.2016.

4.1.5. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) 4-Nitro-benzoic acid 7-benzyloxy-5-hydroxymethyl-2-iodomethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (8). To a solution of the C-glycoside **6** (400 mg, 0.75 mmol, 1 equiv) in dry THF (3 mL) cooled at 0 °C in an ice bath, I_2 (570 mg, 2.25 mmol, 3 equiv) was added and the solution was stirred at 0 °C for 1 h. The crude was then diluted with AcOEt (100 mL), 200 mL of water was added and the mixture was vigorously stirred at room temperature adding $Na_2S_2O_3$ portionwise until the two phases discolored. The organic layer was washed with water, and the crude purified by flash chromatography (petroleum ether/EtOAc 6:4) affording pure compound **8** as a yellow solid (260 mg, 61% yield). ^{1}H NMR (400 MHz, DMSO-d_6); we report the signals of the major diastereomer δ (ppm): 2.21 (m, 1H), 2.32 (m, 1H), 3.50 (m, 2H), 3.70–4.20 (m, 5H), 4.34 (m, 1H), 4.98 (m, 1H), 4.75 (ABq, 2H), 5.21 (br t, J = 6.6 Hz, 1H), 7.20 (m, 5H), 8.20 (A_2X_2, 4H). HRMS (CI^+, CH_4) Calcd for $C_{30}H_{31}NO_8$ [M+H$^+$]: 534.2128. Found: 534.2129.

4.1.6. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a (*R*),5(*R*),6(*S*),7(*S*),7a(*R*) 2-Iodomethyl-7-benzyloxy-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-ol (9). To a solution of compound **7** (1.0 g, 2.6 mmol, 1 equiv) in dry CH_2Cl_2 (10.4 mL) cooled at 0 °C in an ice bath, I_2 (1.32 g, 5.2 mmol, 2 equiv) was added and the solution was stirred at 0 °C for 3 h. The crude was then diluted with AcOEt (100 mL), 200 mL of water was added and the mixture was vigorously stirred at room temperature adding $Na_2S_2O_3$ portionwise until the two phases discolored. The organic layer was washed with water, and the crude purified by flash chromatography (petroleum ether/EtOAc 4:6) affording the title compound **9** as a yellow oil (800 mg, 74% yield mixture of epimers). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.02 (m, 1H), 2.24 (m, 1H), 3.40–3.80 (m, 6H), 4.05 (m, 1H), 4.54–4.95 (m, 4H), 5.05 (m, 2H), 5.82 (m, 1H), 7.40–7.20 (m, 5H). HRMS (CI^+, CH_4) Calcd for $C_{16}H_{22}IO_5$ [M+H$^+$]: 421.0512. Found: 421.0515.

4.1.7. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) 4-Nitro-benzoic acid 7-benzyloxy-5-hydroxymethyl-2azidomethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (10). The *n*-Bu_4NN_3 (caution: explosive if heated in the absence of solvent) was prepared from the commercial NaN_3 using the following procedure: 40% aqueous *n*-$Bu_4N^+OH^-$ (23 mL) was diluted with water (23 mL), a solution of NaN_3 (1140 mg, 35 mmol) in water (10 mL) was added, and the mixture was stirred for 30 min at room temperature. The aqueous solution was extracted three times with $CHCl_3$ and the *n*-$Bu_4NN_3$was recovered as a colorless oil that became a white solid after removal of moisture by stripping several times with toluene. The iododerivative **8** (250 mg, 0.44 mmol, 1 equiv) was dissolved in dry toluene (5 mL) under argon atmosphere, *n*-Bu_4NN_3 (375 mg, 1.32 mmol, 3 equiv) was added, and the solution was stirred at 60 °C for 12 h. The reaction crude was concentrated in vacuo and purified by flash chromatography (petroleum ether/EtOAc 1:1) affording the title compound **10** as a colorless solid (90 mg, 42% yield). Compound **10** is a mixture of diastereomers that are visible by TLC analysis (petroleum ether/EtOAc 6:4). ^{1}H NMR (400 MHz, DMSO-d_6); we report the signals of the major diastereomer δ (ppm): 1.90 (m, 1H), 2.30 (m, 1H), 3.50 (m, 2H), 3.70–4.20 (m, 5H), 4.2 (m, 1H), 4.67 (m, 1H), 4.75 (ABq, 2H), 5.21 (br t, J = 6.6 Hz, 1H), 7.20 (m, 5H), 8.20 (A_2X_2, 4H). HRMS (CI^+, CH_4) Calcd for $C_{23}H_{25}N_4O_8$ [M+H$^+$]: 485.1672. Found: 485.1670.

4.1.8. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) 2-Azidomethyl-7-benzyloxy-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-ol (11). Compound **9** (670 mg, 1 equiv, 1.60 mmol) was dissolved in DMF (5 mL) under argon atmosphere, *n*-Bu_4NN_3 (900 mg, 3.19 mmol, 2 equiv) was added, and the solution was stirred at 60 °C for 12 h. The reaction crude was concentrated in vacuo and purified by flash chromatography (petroleum ether/EtOAc 4:6), giving the title compound **11** as a colorless oil (593 mg, 100% yield). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.67 (m, 1H), 2.12 (m, 1H), 3.25–3.50 (m, 7H), 3.76 (m, 1H), 4.50 (m, 1H), 4.62 (br s, 1H), 4.69 (d, 1H, J = 12 Hz), 4.42 (d, 1H, J = 12 Hz), 5.12 (m, 1H), 7.2–7.4 (m, 5H). HRMS (CI^+, CH_4) Calcd for $C_{16}H_{22}N_3O_5$ [M+H$^+$]: 336.1559. Found: 336.1562.

4.2. Resin-linked intermediate 12

Wang trichloroacetimidate resin was prepared starting from commercially available Wang resin, according to known procedure.[15] The HMP-trichloroacetimidate resin (1 g, maximum loading 0.8 mmol) was allowed to swell for 30 min in dry CH_2Cl_2 under argon atmosphere. Then the resin was washed with dry THF to remove the moisture and suspended in 5 mL of anhydrous cyclohexane. A threefold excess of C-glucoside **6** (1280 mg, 2.4 mmol, 3 equiv) dissolved in 2 mL of anhydrous CH_2Cl_2 and a catalytic amount of BF_3-OEt_2 (25 μL) were added to the suspension that was shaken for 10 min at room temperature under argon atmosphere. The resin was then washed with anhydrous CH_2Cl_2 and THF, and the loading and washing cycle was repeated by recycling the C-glucoside **6**. The resin loaded with the C-allyl derivative **12** was finally dried overnight in vacuo. The loading was determined by cleaving a part of resin (100 mg) in TFA 10% in CH_2Cl_2 (2× 30 min, room temperature) and resulted to be of 0.58 mmol/g (average value from three independent experiments of loading).

4.3. Resin-linked intermediate 13

4.3.1. Method A. The resin **12** (500 mg, about 0.4 mmol of bound sugar, 1 equiv) was washed with anhydrous

CH_2Cl_2 (2× 10 mL) and THF (2× 10 mL) under argon atmosphere in order to remove moisture and then was suspended in 10 mL of anhydrous DMF and a fivefold excess of *t*BuOK (220 mg, 2 mmol, 5 equiv) was added. The solution turned to a dark blue color and the resin was stirred at room temperature for 2 h under argon atmosphere. Three other cycles of hydrolysis of 2 h each were performed to ensure a complete deprotection of the position C-4. The solvent was finally removed and the resin was washed with dry DMF, acetone, THF, and DMF, affording the resin linked intermediate **13**.

4.3.2. Method B. Resin **12** (100 mg, 0.45 mmol/g, 45×10^{-3} mmol) was washed four times with dry THF to remove moisture, suspended in dry THF (5 mL) under inert atmosphere, and MeONa (625 μL of a 0.5 M in MeOH, 0.312 mmol, 7 equiv) was added. The suspension was shaken for 16 h at room temperature and drained. The resin was washed with 2× CH_2Cl_2, 2× DMF, 2× MeOH, 2× DMF, and 3× CH_2Cl_2, and dried in vacuo overnight (absence of PNB ester was evaluated by TLC analysis after cleavage of 10 mg of resin) to give **13**.

4.4. Resin-linked intermediate 14

4.4.1. Method A. To a suspension of the resin (670 mg, 0.6 mmol/g, 0.4 mmol) in 10 mL of anhydrous DMF, a fivefold excess of KOtBu (220 mg, 2 mmol, 5 equiv) and of *n*-butyl bromide (215 μL, 2 mmol, 5 equiv) and a catalytic amount of *n*-Bu_4NI (5 mg) were added and the mixture was shaken at room temperature overnight. The resin was then washed with anhydrous DMF, THF, CH_2Cl_2, and DMF under argon atmosphere. The O-alkylation and washing cycle was repeated two more times. After the last cycle of reaction, the resin was washed with DMF, water, acetone, and THF, and dried in vacuo overnight affording the resin-linked intermediate **14**. One hundred milligrams of dried resin was cleaved (10% TFA in CH_2Cl_2, 2× 30 min, room temperature) and the C-glucoside recovered in the effluents resulted to be almost pure according to TLC analysis. After purification by flash chromatography on silica gel (petroleum ether/EtOAc 7:3), 26 mg of pure 3′-C-[2,3-di-*O*-benzyl-4-*O*-(*n*-butyl)-α-D-glucopyranosyl]-1′-propene **15** was recovered, corresponding to a loading of 0.6 mmol/g. ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 0.90 (t, 3H, J = 7.5 Hz), 1.30 (m, 2H), 1.50 (br m, 2H), 2.47 (m, 2H), 3.26 (t, 1H), 3.40–3.80 (m, 7H), 4.02 (dt, 1H), 4.64 (ABq, 2H), 4.82 (ABq, 2H), 5.10 (m, 2H), 5.80 (m, 1H), 7.2–7.4 (m, 10 H). HRMS (CI^+, CH_4) Calcd for $C_{27}H_{36}O_5$ [M+H$^+$]: 441.2641. Found: 441.2651.

4.4.2. Method B. Forty milligrams of resin **13** (0.48 mmol/g, 20×10^{-3} mmol) was washed four times with dry THF to remove moisture, suspended in dry DMF (2 mL) under inert atmosphere, and KHMDS (152 μL of 15% solution in toluene, 0.10 mmol, 5 equiv) was added. The suspension was shaken for 15 min and the excess base was removed by filtration under inert atmosphere. Butyl bromide (22 μL, 0.20 mmol, 10 equiv) and tetrabutyl ammonium iodide (1.5 mg, 4×10^{-3} mmol, 0.2 equiv) were added and the resulting mixture was shaken for 2 h and drained. The conversion was followed by TLC after cleavage of a small aliquot of resin (10 mg). Other two cycles of reaction were performed. After the last cycle of reaction, the resin **14** was washed with 2× DMF, 2× MeOH, and 3× CH_2Cl_2. This method also showed almost complete conversion.

4.5. Iodo-cyclization on solid phase

4.5.1. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) 2-Iodomethyl-7-benzyloxy-6-butoxy-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran (17). Resin **14** (400 mg, 0.24 mmol of bound C-glucoside) was allowed to swell in dry CH_2Cl_2 for 30 min at room temperature under argon atmosphere then suspended in a solution of iodine (300 mg, 1.2 mmol, 5 equiv) in 10 mL of anhydrous CH_2Cl_2 and shaken at room temperature for 24 h under argon atmosphere. The resin was then washed with anhydrous THF and CH_2Cl_2, and another cycle of reaction was performed. At the end of the reaction, the resin was carefully washed with THF, acetone, and CH_2Cl_2 until the effluents were colorless and was dried in vacuo overnight to give the resin **16**. A sample of 100 mg of dried resin 16 was cleaved (10% TFA in CH_2Cl_2, 2× 30 min) and compound **17** was recovered almost pure as judged from a preliminary TLC analysis. Iododerivative **17** revealed to be resistant to the acidic conditions of the cleavage and was purified by flash chromatography on silica gel (petroleum ether/EtOAc 6:4). Twenty-three milligrams of pure compound **17** was recovered corresponding to a loading of 0.5 mmol/g of the resin and to an almost quantitative yield of the iodocyclization step. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 0.90 (t, 3H, J = 7.5 Hz), 1.35 (m, 2H), 1.55 (m, 2H), 1.94 (dt, 1H, J = 13.0, 6.0 Hz), 2.26 (dt, 1H, J = 13.0, 6.8 Hz), 3.24 (m, 1H), 3.26 (m, 1H), 3.32 (m, 1H), 3.30 (m, 1H), 3.65 (m, 1H), 3.7–3.8 (m, 4H), 4.00 (t, 1H, J = 5.7 Hz), 4.10 (br t, 1H), 4.56 (dt, 1H, J = 5.7, 6.0 Hz), 4.78 (ABq, 2H), 7.2–7.4 (m, 5 H). HRMS (CI^+, CH_4) Calcd for $C_{20}H_{30}IO_5$ [M+H$^+$]: 477.1138. Found: 477.1131.

4.6. Loading of bicyclic azide 10 onto Wang resin

Bicyclic azide **10** (mixture of diastereoisomers) was loaded onto Wang resin activated as trichloroacetimidate by performing two reaction cycles. Wang trichloroacetimidate resin (203 mg, 0.95 mmol/g, 0.193 mmol) was washed several times with dry THF to remove moisture, then a solution of **10** (470 mg, 0.965 mmol, 5 equiv) in dry CH_2Cl_2 (3 mL) was added under inert atmosphere and the suspension was shaken for 5 min at rt. $BF_3 \cdot Et_2O$ (12 μL, 0.095 mmol, 0.5 equiv) was added and the suspension was shaken for 15 min at rt. The resin was then washed with CH_2Cl_2 (2× 3 mL), THF (2× 3 mL), MeOH (2× 3 mL), and CH_2Cl_2 (4× 3 mL), and dried in vacuo overnight. The effluents were collected to recover the unloaded scaffold **10**, which was purified by filtration through a silica gel plug (petroleum ether/EtOAc 4:6); weight of recovered **10**: 410 mg. To determine the loading, 49 mg of resin was cleaved with 20% TFA in CH_2Cl_2 (2× 5 mL, 20 min) and pure azide **10** was recovered after purification on a silica gel plug (10.5 mg indicating a loading of 0.44 mmol/g, corre-

sponding to a 50% conversion) and fully characterized by ^{1}H NMR and HRMS. The partially loaded resin (197 mg; 0.44 mmol/g of loaded scaffold; 0.44 mmol/g of free OH corresponding to 0.087 mmol of free OH) was washed, under inert atmosphere, several times with dry THF to remove moisture, then was suspended in dry CH_2Cl_2 (2.9 mL) and trichloroacetonitrile (175 μL, 1.74 mmol, 20.0 equiv) was added. A 1:9 DBU–CH_2Cl_2 solution (110 μL, corresponding to 11 μL, 0.074 mmol of pure DBU, 0.85 equiv) was added dropwise in 5 min to the suspension, then the resulting suspension was shaken for 40 min at room temperature, drained, and washed with dry CH_2Cl_2 twice. A second trichloroacetimidate formation cycle was performed with the same procedure, then the solution was drained and the resin was washed with DMF (2× 3 mL), CH_2Cl_2 (2 × 3 mL), DMF (2× 3 mL), and CH_2Cl_2 (4× 3 mL), and dried in vacuo overnight. The Wang trichloroacetimidate resin so obtained was washed several times with dry THF under inert atmosphere to remove moisture, then a solution of **10** (423 mg, 0.870 mmol, 5 equiv) in dry CH_2Cl_2 (3 mL) was added and the suspension was shaken 5 min at room temperature. $BF_3 \cdot Et_2O$ (11 μL, 0.5 equiv, 0.087 mmol) was added and the suspension was shaken for 15 min at room temperature. The resin was then washed with CH_2Cl_2 (2× 3 mL), THF (2× 3 mL), MeOH (2× 3 mL), and CH_2Cl_2 (4× 3 mL), and dried in vacuo overnight to give a batch of the resin-linked derivative **12a**. The effluents were collected to recover the unloaded compound **10**, which was purified by filtration through a silica gel plug (eluant: petroleum ether/EtOAc 4:6; weight of recovered **10**: 350 mg). To determine the loading, 68 mg of the resin was cleaved with 20% TFA in CH_2Cl_2 (2× 5 mL, 20 min) and pure azide **10** was recovered after purification on a silica gel plug (20 mg indicating a loading of 0.60 mmol/g, corresponding to a 78% conversion) and fully characterized by ^{1}H NMR and HRMS.

4.7. Resin-linked intermediate 19

Resin **18** (100 mg, 0.45 mmol/g, 45×10^{-3} mmol) was washed four times with dry THF to remove moisture, suspended in dry THF (5 mL) under inert atmosphere, and MeONa (625 μL of 0.5 M in MeOH, 0.312 mmol, 7 equiv) was added. The suspension was shaken for 16 h at room temperature and drained. The resin was washed with 2× CH_2Cl_2, 2× DMF, 2× MeOH, 2× DMF, and 3× CH_2Cl_2, and dried in vacuo overnight to give **19** (absence of PNB ester was confirmed by TLC analysis after cleavage of 10 mg of resin). In order to verify the yield of loading and conversion, the resin was cleaved with 20% TFA in CH_2Cl_2 (2× 1.0 mL, 20 min), and monosaccharide **11** was recovered after evaporation (18 mg). The crude compound was analyzed by TLC and ^{1}H NMR, and then purified by flash chromatography. Ten milligrams was obtained (66% yield).

4.8. Resin-linked intermediate 19a

Activation of the resin (PS-DES-SiCl). Resin PS-DES-SiH (100 mg, 1.37 mmol/g, 0.138 mmol) was washed four times with dry THF to remove moisture, suspended in dry CH_2Cl_2 (1.37 mL) under inert atmosphere, and 1,3-dichloro-5,5-dimethylhydantoin (162 mg, 0.822 mmol, 6 equiv) was added. The suspension was shaken for 1.5 h at room temperature and drained. The resin was washed with 2× CH_2Cl_2, 2× DMF, 2× MeOH, 2× DMF, and 3× CH_2Cl_2, and dried by nitrogen flux to get the resin PS-DES-SiCl. Absence of Si–H (stretching at 2094 cm^{-1}) was confirmed by IR analysis.

Loading of the substrate: A solution of compound **11** (275.7 mg, 0.822 mmol, 3 equiv) and imidazole (65.2 mg, 0.959 mmol, 3.5 equiv) in dry CH_2Cl_2 (4 mL) was added to the resin PS-DES-Si-Cl (theoretical 0.274 mmol) and shaken overnight under inert atmosphere. The solution was filtered and the unloaded scaffold recovered. The resin was washed with 2× CH_2Cl_2, 2× DMF, 2× MeOH, 2× DMF, and 3× CH_2Cl_2 obtaining **19a**, directly employed in the further reactions.

4.9. Functionalization of C-4 hydroxyl group, representative procedures

4.9.1. Acylation. Resin **19** (50 mg, 0.43 mmol/g, 21.5×10^{-3} mmol) was suspended in dry CH_2Cl_2 (2 mL) under inert atmosphere and 3-phenylpropionic acid (32 mg, 0.215 mmol, 10 equiv), DMAP (26 mg, 0.215 mmol, 10 equiv), and DIC (33 μL, 0.215 mmol, 10 equiv) were added. The suspension was shaken for 16 h at room temperature and drained. The completeness of the reaction was followed by cleavage of minute quantities of the resin (<10 mg) and TLC comparison with a prototype sample prepared in solution. Typically, the reaction was complete after one overnight cycle with the quantities described above. The resin was washed with 2× CH_2Cl_2, 2× DMF, 2× MeOH, 2× DMF, and 3× CH_2Cl_2, and dried in vacuo overnight (absence of starting material was evaluated by TLC analysis after cleavage of 10 mg of resin) to give resin type **20**. The resin was cleaved with 20% TFA in CH_2Cl_2 (2× 0.5 mL, 20 min), and the crude was purified by flash chromatography (4 mg, 38% yield). ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.90 (m, 1H), 2.23 (m, 1H), 2.65 (m, 2H), 2.95 (m, 2H), 3.3–3.85 (m, 6H), 3.90 (dd, 1H, J = 7.0, 4.0 Hz), 4.15 (m, 1H), 4.6 (m, 1H), 4.75 (ABq, 2H, J = 12.8 Hz), 4.97 (dd, 1H, J = 6.8, 4.0 Hz), 7.10–7.40 (m, 10H).

4.9.2. Carbamoylation. Resin **19** (100 mg 0.42 mmol/g, 4.2×10^{-2} mmol) was washed with dry THF (4× 2 mL) under inert atmosphere. The resin was then suspended in 1.25 mL of THF, and 4-nitrophenyl chloroformate (85 mg, 0.420 mmol, 10 equiv) and *N*-methyl morpholine (93 μL, 0.840 mmol, 20 equiv) were added. The suspension was shaken for 3 h at room temperature and drained. A second cycle with the same quantities was performed for 3 h, then the solution was drained and the resin was washed with THF (2× 2 mL), CH_2Cl_2 (2× 2 mL) and THF (2× 2 mL) obtaining the resin–*p*-nitrophenyloxycarbonyl derivative. The resin–*p*-nitrophenyloxycarbonyl derivative was suspended in dry

THF and *n*-butyl amine (125 μL, 1.26 mmol, 30 equiv) was added. The suspension was shaken overnight at room temperature, then the solution was drained and the resin was washed with CH_2Cl_2 (2× 2 mL), DMF (2× 2 mL), CH_2Cl_2 (2× 2 mL), DMF (2× 2 mL), and CH_2Cl_2 (4× 2 mL), and dried in vacuo overnight (absence of starting material was evaluated by TLC analysis after cleavage of 10 mg of resin) to obtain a resin type **22**. The resin **22** was cleaved with 20% TFA in CH_2Cl_2 (2× 2 mL, 20 min), and the bicyclic azide with a carbamate in C-4 was recovered after evaporation (22 mg). The crude compound was analyzed by TLC and ^1H NMR, and then purified by flash chromatography (8 mg, 44% yield). ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 0.92 (t, 3H, $J = 7$ Hz), 1.25–1.55 (m, 4H), 1.92 (ddd, 1H, $J_1 = 3.7$, 6.5, 11.5 Hz), 2.25 (m, 1H), 3.18 (m, 2H), 3.42 (m, 2H), 3.65–3.9 (m, 4H), 3.97 (m, 1H), 4.18 (m, 1H), 4.63 (m, 1H), 4.7–4.9 (m, 4H), 7.34 (m, 5H).

4.10. Reduction of azido group on solid phase. Preparation of the resin-loaded aminoderivative 21

4.10.1. Method A. A clear solution of PPh_3 (210 mg, 0.8 mmol, 10 equiv), H_2O (144 μL, 8.0 mmol, 100 equiv) in THF (2.9 mL) was added to 200 mg of resin **20** (0.4 mmol/g, 0.08 mmol) pre-swelled in CH_2Cl_2 for 30 min. The resulting mixture was shaken overnight, the solution was removed, and the resin was washed with 2× THF, 2× CH_2Cl_2, 2× THF, and 2× CH_2Cl_2. The TBNS test (visualizing the presence/absence of free amino groups was carried out as described)[16] gave a favorable result: absence of starting material was evaluated by TLC analysis after cleavage of 10 mg of resin. After the above-mentioned washing cycles, the resin **21** was kept under inert atmosphere and used immediately for the next reaction.

4.10.2. Method B. Resin **20** (250 mg, 0.4 mmol/g, 0.1 mmol) was suspended in THF (4 mL) and $SnCl_2$ (152 mg, 0.80 mmol, 8 equiv), thiophenol (327 μL, 3.2 mmol, 32 equiv), and TEA (558 μL, 4 mmol, 40 equiv) were added to provide a solution that was 0.2, 0.8, and 1.0 M in the reagents, respectively. The mixture was shaken for 3 h. The resin was washed with 2× DMF, 2× MeOH, 2× DMF, 2× MeOH, 2× DMF, and 4× CH_2Cl_2. Both the color tests (TBNS[16] and dyed-*p*-nitrophenylglycolate[17] tests) gave positive results (absence of starting material was evaluated by TLC analysis after cleavage of 10 mg of resin). After the above-mentioned washing cycles, the resin **21** was kept under inert atmosphere and used immediately for the next reaction.

4.11. Functionalization of the free amino group

4.11.1. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) 4-Nitro-benzoic acid 2-(benzoylamino-methyl)-7-benzyloxy-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (30).

4.11.1.1. Method A. Resin **21** (R = *p*-nitrophenyl) (50 mg, loading: 0.56 mmol/g, 0.028 mmol) was suspended in 2 mL of dry DMF, benzoic acid (7 mg, 0.056 mmol, 2 equiv), HBTU (21 mg, 0.056 mmol, 2 equiv), and DIPEA (20 μL, 0.11 mmol, 4 equiv) were added and the mixture was shaken at room temperature for 40 min. This coupling step was repeated twice. The resin was then washed with DMF (2× 10 min) and CH_2Cl_2 (2× 10 min) and dried in vacuum overnight obtaining resin **24** (R = *p*-nitrophenyl; R′ = phenyl). The IR spectrum of the resin beads showed the appearance of the C=O stretching absorption band at 1680 cm^{-1}, typical of secondary amides in dilute solutions. The amide was then cleaved treating the resin with 50% TFA in CH_2Cl_2 (2× 30 min at room temperature) and a few milligrams of compound **30** were recovered after chromatography (yield not reproducible).

4.11.1.2. Method B. A solution of benzoic acid (34 mg, 0.2 mmol, 4 equiv), DIC (43 μL, 0.2 mmol, 4 equiv), and HOBt (38 mg, 0.2 mmol, 4 equiv) in 2 mL of dry DMF was stirred at room temperature for 20 min. Resin **21** (R = *p*-nitrophenyl) (95 mg, loading 0.49 mmol/g, 0.046 mmol) was suspended in 1 mL of dry DMF with DIPEA (96 μL, 0.4 mmol, 8 equiv), and then the solution of the pre-activated carboxylic acid was added in the reactor. The suspension was shaken at room temperature for 45 min and then the reaction mixture was filtered, washed with 2× DMF, 2× CH_2Cl_2, Et_2O, and dried in vacuum for 1 h, obtaining resin **24** (R = *p*-nitrophenyl; R′ = phenyl). The resin was cleaved with TFA 20% in CH_2Cl_2 (2× 20 min) and washed with 2× THF and 2× CH_2Cl_2. After evaporation of the solvent, 18 mg of crude benzamide was obtained. The mixture was then purified by chromatography on silica gel (AcOEt/hexane 9:1) recovering mg 4 (15% yield) of pure benzamide **30**.

4.11.1.3. Method C. A more powerful acylation method, by using HATU [*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluroniumhexafluorophos phate, was also essayed. Resin **21** (R = *p*-nitrophenyl) (150 mg, loading 0.38 mmol/g, 0.057 mmol) was suspended in 4 mL of dry DMF–CH_2Cl_2 1:1 and HATU (87 mg, 0.228 mmol, 4 equiv), DIPEA (78 μL, 0.456 mmol, 8 equiv) and benzoic acid (28 mg, 0.228 mmol, 4 equiv) were added. The reaction was shaken for 45 min, then filtered and washed with 2× DMF, 2× CH_2Cl_2, THF. The coupling reaction was repeated four times and after every coupling cycle the presence of unreacted free amino groups was revealed with dyed-*p*-nitrophenylglycolate test. According to this method, the amine was revealed by a colorimetric assay directly on few beads suspended in 100 μL of a 0.002 M solution of the reagent (NF31) in MeCN.[17] After heating at 70 °C for 10 min in a sand bath, the beads were rapidly washed with DMF, MeOH, and CH_2Cl_2 (three times for each solvent), obtaining resin **24** (R = *p*-nitrophenyl; R′ = phenyl). The resin was then cleaved with TFA 20% in CH_2Cl_2 (2× 20 min) and washed with THF and CH_2Cl_2. We recovered 25 mg of crude and, after chromatography, 11 mg (34% yield) of pure **30**. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.06 (m, 1H), 2.42 (m, 1H), 3.61 (m, 1H), 3.71 (m, 1H), 3.68–4.18 (m, 4H), 4.40 (bd, 1H), 4.61 (br s, 1H), 4.73 (br s,

2H), 5.15 (br s, 1H), 7.08 (br s, 1H), 7.32 (m, 8H), 7.61 (m, 2H), 8.02 (m, 4H). HRMS (CI^+, CH_4) Calcd for $C_{30}H_{31}N_2O_9$ [M+H$^+$]: 563.2030. Found: 563.2035.

4.11.2. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) 4-Nitro-benzoic acid 7-benzyloxy-2-heptylaminomethyl-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (31).

4.11.2.1. Method A. A solution of caprylic acid (44 μL, 0.2 mmol, 4 equiv), DIC (43 μL, 0.2 mmol, 4 equiv), and HOBt (38 mg, 0.2 mmol, 4 equiv) in dry DMF was stirred for 20 min and added to the suspension of resin **21** (R = *p*-nitrophenyl) (100 mg, loading 0.49 mmol/g, 0.049 mmol), DIPEA (96 μL, 0.4 mmol, 8 equiv) in 1 mL of dry DMF. The suspension was shaken for 45 min, then filtered and washed with 2× DMF, 2× CH_2Cl_2, and Et_2O, and dried in vacuo for 1 h to get resin **24** (R = *p*-nitrophenyl; R′ = *n*-heptyl), stored overnight at −18 °C. The resin was then cleaved with TFA 20% in CH_2Cl_2 (2× 20 min) and washed with 2× THF and 2× CH_2Cl_2. The cleavage afforded 34 mg of crude product that, after silica gel chromatography (AcOEt-hexane 9:1), gave pure amide **31** (4 mg, 15% yield).

4.11.2.2. Method B. Resin **21** (R = *p*-nitro) (150 mg, loading 0.38 mmol/g, 0.057 mmol) was suspended in 4 mL of a mixture of DMF–CH_2Cl_2 dry 1:2, and HATU (87 mg, 0.228 mmol, 4 equiv), DIPEA (78 μL, 0.456 mmol, 8 equiv), and caprylic acid (36 μL, 0.228 mmol, 4 equiv) were added. The reaction was shaken for 45 min, and then filtered and washed exactly as in method C of the previous experimental procedure for acylation. In the same way and by using dyed-*p*-nitrophenylglycolate test, we still found the presence of unreacted amino groups after the fourth coupling cycle, and we thus proceeded with the fifth one until the test was negative, to obtain resin **24** (R = *p*-nitrophenyl; R′ = *n*-heptyl). The resin was cleaved with TFA 20% in CH_2Cl_2 (2× 20 min) and washed with THF and CH_2Cl_2. We recovered after purification amide **31** (9 mg, 27% yield). ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 0.89 (m, 3H), 1.40–1.95 (m, 10H), 2.05 (m, 2H), 2.14 (m, 1H), 2.33 (m, 1H), 3.53 (m, 2H), 3.68–4.39 (m, 5H), 4.61 (m, 1H), 4.75 (br s, 2H), 5.25 (q, 1H), 5.19 (br s, 1H), 6.08 (br s, 1H), 7.49–7.68 (m, 5H), 8.22 (A_2X_2q, 4 H). HRMS (CI^+, CH_4) Calcd for $C_{30}H_{39}N_2O_9$ [M+H$^+$]: 571.2656. Found: 571.2660.

4.12. Representative procedure for the acylation of the free NH_2 with other carboxylic acids

4.12.1. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Naphthalene-1-carboxylic acid 7-benzyloxy-5-hydroxymethyl-2-[(3-phenyl-propionylamino)-methyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (32); 2(*R*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) Naphthalene-1-carboxylic acid 7-benzyloxy-2-[(3,5-dimethoxy-benzoylamino)-methyl]-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (33). This procedure is essentially similar to the one described in method C for the preparation of compound **30**, but using fewer cycles with longer reaction times. A 4 mL DMF–CH_2Cl_2 (1:1 ratio) solution of acid R′COOH (e.g., R′ = 3,5-$(OMe)_2C_6H_3$–, or R′ = $PhCH_2CH_2$–) (0.50 mmol, 5 equiv), HATU (190 mg, 0.50 mmol, 5 equiv), and DIPEA (171 μL, 1.00 mmol, 10 equiv) was added to resin **21** (e.g., with *R* = 1-naphthyl-CH_2–) (250 mg, 0.4 mmol/g, 0.1 mmol, 1 equiv). Subsequently, the resulting slurry was shaken for 3 days, the solution was drained, and the resin was washed with 2× CH_2Cl_2, 2× DMF and 3× CH_2Cl_2. The dyed-*p*-nitrophenylglycolate test gave a pale red staining (about 2–5% free amines). A second cycle with the same quantities was performed for 48 h, then the solution was drained and the resin was washed with 2× CH_2Cl_2, 2× DMF, 2× CH_2Cl_2, 2× DMF, and 3× CH_2Cl_2, and dried in vacuo overnight (TNBS test and the dyed-*p*-nitrophenylglycolate test were negative after the second cycle) to obtain a resin type **24**. The resin was cleaved with 20% TFA in CH_2Cl_2 (2× 2.5 mL, 20 min), and crude compounds **32** (52 mg) and **33** (44 mg) were recovered after evaporation. They were analyzed by TLC and ^{1}H NMR, and then purified by flash chromatography, thus yielding 21 mg (34% yield) of **32** and 14 mg (22% yield) of **33**.

Compound ***32***. ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.67 (m, 1H), 2.16 (m, 1H), 2.36 (m, 2H), 2.92 (m, 2H), 3.35 (m, 2H), 3.55–3.8 (m, 5H), 4.05 (m, 3H), 4.45 (m, 1H), 4.56 (m, 2H), 4.96 (m, 1H), 5.95 (dt, 1H), 7.1–7.5 and 7.7–7.95 (m, 17H). HRMS Calcd for $C_{37}H_{40}NO_7$ [M+H$^+$]: 610.2805. Found: 610.2810.

Compound ***33***. ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 2.03 (m, 1H); 2.35 (m, 1H); 3.37 (m, 2H); 3.58–3.88 (m, 11H); 4.05 (m, 2H); 4.28 (m, 1H); 4.55 (m, 1H); 4.61 (d, 2H, J = 2.7 Hz); 5.0 (m, 1H); 5.9 (m, 1H); 7.1–7.5 and 7.7–7.95 (m, 17H). HRMS Calcd for $C_{37}H_{40}NO_9$ [M+H$^+$]: 642.2703. Found: 642.2709.

The following compounds have been prepared by using the same experimental procedure:

4.12.2. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Cyclopropanecarboxylic acid 7-benzyloxy-5-hydroxymethyl-2-(isobutyrylamino-methyl)-hexahydro-furo[3,2-*b*]pyran-6-yl ester (34). Crude HPLC assay: 56% (area at 220 nm), isolated yield 19.0 mg (17% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 0.82 (m, 4H), 0.97 (m, 6H), 1.59 (m, 1H), 1.65 (m, 1H), 2.11 (m, 1H), 2.36 (m, 1H), 3.05–4.00 (br m, 8H), 4.50 (m, 1H), 4.60 (d, 1H, J = 12.0 Hz), 4.69 (d, 1H, J = 12.0 Hz), 4.85 (br s, 1H), 4.86 (m, 1H), 7.2–7.35 (m, 5H), 7.67 (br t, 1H). HRMS Calcd for $C_{24}H_{34}NO_7$ [M+H$^+$]: 448.2330. Found: 448.2325.

4.12.3. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Cyclopropanecarboxylic acid 7-benzyloxy-5-hydroxymethyl-2-[(2-methoxy-acetylamino)-methyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (35). Crude HPLC assay: 60% (area at 220 nm), isolated yield 19.9 mg (18% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 0.87 (m, 4H), 1.59 (m, 1H), 2.17 (m, 1H), 2.36 (m, 1H), 3.05–3.8 (br m, 9H), 4.01 (m, 1H), 4.46 (m, 1H), 4.60 (d, 1H), 4.69 (d, 1H), 4.76 (br s, 1H), 4.86 (m, 1H), 7.2–7.4 (m, 5H), 7.66 (br t, 1H). HRMS Calcd for $C_{23}H_{32}NO_8$: [M+H$^+$] 450.2122. Found: 450.2128.

4.12.4. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Propionic acid 7-benzyloxy-5-hydroxymethyl-2-(isobutyrylamino-methyl)-hexahydro-furo[3,2-*b*]pyran-6-yl ester (36). Crude HPLC assay: 38% (area at 220 nm), isolated yield 22.4 mg (21% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.00 (m, 9H), 1.59 (m, 1H), 2.11 (m, 1H), 2.44 (m, 3H), 3.05-4.00 (br m, 8H), 4.50 (m, 1H), 4.60 (d, 1H, J = 12.1 Hz), 4.69 (d, 1H, J = 12.1 Hz), 4.86 (m, 1H), 5.3 (br s, 1H), 7.2–7.4 (m, 5H), 7.67 (br t, 1H). HRMS Calcd for $C_{23}H_{34}NO_7$ [M+H$^+$]: 436.2330. Found: 436.2334.

4.12.5. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Nicotinic acid 7-benzyloxy-5-hydroxymethyl-2-(isobutyrylamino-methyl)-hexahydro-furo[3,2-*b*]pyran-6-yl ester (37). Crude HPLC assay: 70% (area at 220 nm), isolated yield 19.4 mg (16% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 0.96 (m, 6H), 1.72 (m, 1H), 2.17 (m, 1H), 2.34 (m, 1H), 3.2–4.0 (m, 8H), 4.57 (m, 1H), 4.61 (d, 1H, J = 12.2 Hz), 4.69 (d, 1H, J = 12.2 Hz), 4.81 (br m, 1H), 5.15 (m, 1H), 7.16 (m, 5H), 7.56 (m, 1H), 7.69 (br m, 1H), 8.24 (m, 1H), 8.80 (m, 1H), 9.06 (s, 1H). HRMS Calcd for $C_{26}H_{33}N_2O_7$ [M+H$^+$]: 485.2282. Found: 485.2273.

4.12.6. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Nicotinic acid 7-benzyloxy-5-hydroxymethyl-2-[(2-methoxy-acetylamino)-methyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (38). Crude HPLC assay: 65% (area at 220 nm), isolated yield 21.9 mg (18% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.72 (m, 1H), 2.23 (m, 1H), 3.21 (s, 3H), 3.4–4.0 (m, 10H), 4.51 (m, 1H), 4.64 (d, 1H, J = 12.1 Hz), 4.67 (d, 1H, J = 12.1 Hz), 5.14 (m, 1H), 7.20 (m, 5H), 7.55 (m, 1H), 7.68 (br m, 1H), 8.23 (m, 1H), 8.81 (m, 1H), 9.06 (s, 1H). HRMS Calcd for $C_{25}H_{31}N_2O_8$ [M+H$^+$]: 487.2075. Found: 487.2068.

4.12.7. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Nicotinic acid 7-benzyloxy-2-[(2-dimethylamino-acetylamino)-methyl]-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (39). Crude HPLC assay: 65% (area at 220 nm), isolated yield 6.5 mg (5% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.72 (m, 1H), 2.23 (m, 1H), 2.48 (m, 6H), 3.3–4.0 (m, 10H), 4.57 (m, 1H), 4.61 (d, 1H, J = 12.1 Hz), 4.69 (d, 1H, J = 12.1 Hz), 4.81 (br m, 1H), 5.17 (m, 1H), 7.18 (m, 5H), 7.57 (m, 1H), 8.24 (m, 1H), 8.81 (m, 1H), 9.07 (s, 1H). HRMS Calcd for $C_{26}H_{34}N_3O_7$ [M+H$^+$]: 500.2391. Found: 500.2394.

4.12.8. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) 4-Fluoro-benzoic acid 7-benzyloxy-5-hydroxymethyl-2-(isobutyrylamino-methyl)-hexahydro-furo[3,2-*b*]pyran-6-yl ester (40). Crude HPLC assay: 80% (area at 220 nm), isolated yield 18.6 mg (15% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 0.96 (m, 6H), 1.73 (m, 1H), 2.17 (m, 1H), 2.33 (m, 1H), 3.0–4.0 (br m, 8H), 4.55 (m, 1H), 4.60 (d, 1H, J = 12.2 Hz), 4.70 (d, 1H, J = 12.1 Hz), 4.80 (br s, 1H), 5.11 (m, 1H), 7.1–7.2 (m, 5H), 7.34 (t, 2H, J = 8.9 Hz), 7.67 (br t, 1H, J = 5.4 Hz), 8.0 (m, 2H). HRMS Calcd for $C_{27}H_{33}FNO_7$ [M+H$^+$]: 502.2236. Found: 502.2234.

4.12.9. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) 4-Fluoro-benzoic acid 7-benzyloxy-2-[(2-dimethylamino-acetylamino)-methyl]-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (41). Crude HPLC assay: 72% (area at 220 nm), isolated yield 2.1 mg (2% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.72 (m, 1H), 2.13 (m, 6H), 2.23 (m, 1H), 3.3–4.0 (m, 10H), 4.52 (m, 1H), 4.61 (d, 1H, J = 12.1 Hz), 4.69 (d, 1H, J = 12.1 Hz), 4.80 (br m, 1H), 5.11 (m, 1H), 7.21 (m, 5H), 7.34 (m, 2H), 7.74 (br m, 1H), 8.01 (m, 2H). MS-ESI m/z = 517.4 (M+H)$^+$. HRMS Calcd for $C_{27}H_{33}FN_2O_7$ [M+H$^+$]: 517.2350. Found: 517.2332.

4.12.10. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Thiophene-2-carboxylic acid 7-benzyloxy-5-hydroxymethyl-2-(isobutyrylamino-methyl)-hexahydro-furo[3,2-*b*]pyran-6-yl ester (42). Crude HPLC assay: 66% (area at 220 nm), isolated yield 14.2 mg (12% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 0.97 (t, 6H, J = 6.8), 1.72 (m, 1H), 2.15 (m, 1H), 2.34 (m, 1H), 3.15–4.00 (m, 8H), 4.56 (m, 1H), 4.60 (d, 1H, J = 12.1 Hz), 4.69 (d, 1H, J = 12.1 Hz), 4.81 (br m, 1H), 5.06 (t, 1H, J = 7.8 Hz), 7.2 (m, 6H), 7.66 (br t, 1H), 7.79 (m, 1H), 7.96 (m, 1H). HRMS Calcd for $C_{25}H_{32}NO_7S$ [M+H$^+$]: 490.1894. Found: 490.1877.

4.12.11. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Thiophene-2-carboxylic acid 7-benzyloxy-5-hydroxymethyl-2-[(2-methoxy-acetylamino)-methyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (43). Crude HPLC assay: 65% (area at 220 nm), isolated yield 16.7 mg (14% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.72 (m, 1H), 2.20 (m, 1H), 3.15–4.00 (m, 11H), 4.51 (m, 1H), 4.63 (d, 1H, J = 12.1 Hz), 4.67 (d, 1H, J = 12.2 Hz), 4.81 (br m, 1H), 5.06 (t, 1H, J = 6.7 Hz), 7.22 (m, 6H), 7.67 (br t, 1H, J = 5.5 Hz), 7.78 (m, 1H), 7.95 (m, 1H). HRMS Calcd for $C_{24}H_{30}NO_8S$ [M+H$^+$]: 492.1687. Found: 492.1685.

4.12.12. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Thiophene-2-carboxylic acid 7-benzyloxy-2-[(2-dimethylamino-acetylamino)-methyl]-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (44). Crude HPLC assay: 67% (area at 220 nm), isolated yield 6.6 mg (5% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.71 (m, 1H), 2.20 (m, 1H), 2.52 (s, 6H), 3.15–4.00 (m, 8H), 4.56 (m, 1H), 4.60 (d, 1H, J = 12.1 Hz), 4.68 (d, 1H, J = 12.1 Hz), 4.82 (br t, 1H), 5.08 (t, 1H, J = 7.7), 7.2 (m, 6H), 7.79 (m, 1H), 7.95 (m, 1H). HRMS Calcd for $C_{25}H_{33}N_2O_7S$ [M+H$^+$]: 505.2003. Found: 505.1993.

4.13. Azide reduction of the carbamoyl derivative and acylation of the amino group on solid phase

4.13.1. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Butyl-carbamic acid 7-benzyloxy-5-hydroxymethyl-2-[(3-phenyl-propionylamino)-methyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (45). Following method B of azido group reduction, described for the preparation of the resin-loaded aminoderivative **21**, the carbamoyl derivative resin-linked type **22** (e.g., with R = *n*-butyl) was functionalized also in the 3 position through ($SnCl_2$/

PhSH/TEA) reduction of the azide to amine. The resulting free amino group was acylated (e.g., with phenylpropionic acid) by working according to the previous experimental procedure, to give the resin type **24** (with Y = *n*-butylNHCO, R′ = 2-phenylethyl). The resin was cleaved with 20% TFA in CH_2Cl_2 (2× 2 mL, 20 min), and compound **45** was recovered after evaporation (50 mg). The crude compound **45** was analyzed by TLC and ^1H NMR, and purified by flash chromatography. Twenty-five milligrams of pure **45** was obtained; yield for the five steps: 55%. ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 0.92 (t, 3H, J = 7.4 Hz), 1.25–1.55 (m, 4H), 1.75 (ddd, 1H, J = 2.5, 5.7, 8.3 Hz), 2.25 (m, 1H), 2.5 (m, 2H), 2.95 (m, 2H), 3.18 (m, 2H), 3.44 (m, 2H), 3.65–3.86 (m, 4H), 3.97 (m, 1H), 4.13 (m, 1H), 4.51 (m, 1H), 4.72 (s, 2H), 4.84 (dd, 1H, J = 5.0, 5.5 Hz), 4.92 (br t, 1H, J = 5.6 Hz), 6.14 (m, 1H), 7.15–7.4 (m, 10H). HRMS Calcd for $C_{30}H_{41}N_2O_7$ [M+H$^+$]: 541.2908. Found: 541.2887.

4.14. Sulfonylation of the free NH_2

4.14.1. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) 3-Phenyl-propionic acid 7-benzyloxy-5-hydroxymethyl-2-[(4-methoxy-benzenesulfonylamino)-methyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (46). Resin **21** (R = 2-phenylethyl) (200 mg, 0.4 mmol/g, 0.080 mmol) was suspended under inert atmosphere in dry CH_2Cl_2 (2 mL) and DMAP (196 mg, 1.60 mmol, 20 equiv), tosyl chloride (153 mg, 0.80 mmol, 10 equiv) were added. After the resulting mixture was shaken for 5 h, the solution was removed and the resin was washed with 2× CH_2Cl_2, 2× DMF, and 3× CH_2Cl_2. After the first cycle, the TNBS test gave a pale red staining. A second cycle was performed overnight, then the resin was washed with 2× CH_2Cl_2, 2× DMF, 2× CH_2Cl_2, 2× DMF, and 3× CH_2Cl_2, and dried in vacuo overnight (TNBS test was negative after the second cycle) giving a resin type 25. The resin was cleaved with 20% TFA in CH_2Cl_2 (2× 2.0 mL, 20 min), and compound **46** was recovered after evaporation (40 mg). The crude compound was analyzed by TLC and ^1H NMR, and then purified by flash chromatography. Six milligrams of pure **46** was thus obtained (yield for the five steps: 12%). ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.73 (m, 1H), 2.17 (m, 1H), 2.43 (s, 3H), 2.68 (m, 2H), 2.95 (m, 2H), 3.25 (m, 2H), 3.55–3.7 (m, 5H), 4.05 (m, 1H), 4.52 (m, 1H), 4.68 (m, 2H), 4.95 (dd, 1H, H4 J = 5.5, 5.4 Hz), 5.07 (m, 1H), 7.15–7.38 (m, 12H), 7.70 (d, 2H, J = 9.2 Hz). HRMS Calcd for $C_{32}H_{38}NO_9S$ [M+H$^+$]: 612.2267. Found: 612.2255.

4.15. Representative procedure for the formation of ureido derivatives

4.15.1. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) 3-Phenyl-propionic acid 7-benzyloxy-5-hydroxymethyl-2-[(3-phenyl-ureido)-methyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (47); 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) Octanoic acid 7-benzyloxy-5-hydroxymethyl-2-[(3-phenyl-ureido)-methyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (48). Resin **21** (R = 2-phenylethyl or R = *n*-heptyl) (200 mg, 0.40 mmol/g, 0.080 mmol) was suspended under inert atmosphere in dry CH_2Cl_2 (2 mL), and TEA (11 μL, 0.080 mmol, 1 equiv) and phenyl isocyanate (87 μL, 0.80 mmol, 10 equiv) were added. After the resulting mixture was shaken for 5 h, the solution was removed by suction and the resin was washed with 2× CH_2Cl_2, 2× DMF and 3× CH_2Cl_2. After the first cycle the TNBS test was negative, while the dyed-*p*-nitrophenylglycolate test, mentioned in the text, gave a pale red staining. A second cycle with the same quantities was performed overnight and the resin was washed with 2× CH_2Cl_2, 2× DMF 2× CH_2Cl_2, 2× DMF and 3× CH_2Cl_2 and dried in vacuo overnight to get a resin type **26**. The resin was cleaved with 20% TFA in CH_2Cl_2 (2× 2.0 mL, 20 min), and compounds **47** (40 mg) and **48** (32 mg) were recovered after evaporation. The crude compounds were analyzed by TLC and ^1H NMR, and then purified by flash chromatography obtaining 10 mg of **47** (22% yield over 5 steps) and 16 mg of **48** (36% yield over 5 steps).

*Compound **47***. ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.85 (m, 1H), 2.24 (m, 1H), 2.60 (m, 2H), 2.91 (m, 2H), 3.37–3.65 (m, 5H), 3.72 (m, 1H, H3), 3.85 (t, 1H, J = 4.3 Hz), 4.12 (m, 1H), 4.54 (m, 1H), 4.68 (m, 2H), 4.91 (dd, 1H, J = 6.0, 5.9 Hz), 5.35 (br t, 1H), 6.68 (s, 1H), 7.1–7.4 (m, 15H). MS (FAB$^+$): m/z = 561 (M$^+$+1). HRMS Calcd for $C_{32}H_{37}N_2O_7$ [M+H$^+$]: 561.2595. Found: 561.2584.

*Compound **48***. ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 0.85 (t, 3H, J = 6.7, 6.0 Hz), 1.27 (m, 8H), 1.6 (m, 2H), 1.90 (m,1H), 2.2–2.4 (m, 3H), 3.48 (m, 2H), 3.6–3.81 (m, 4H), 3.86 (m, 1H), 4.16 (m, 1H), 4.54 (m, 1H), 4.7 (s, 2H), 4.92 (t, 1H, J = 5.9 Hz), 5.38 (br t, 1H), 6.69 (s, 1H), 7.25–7.4 (m, 10H). HRMS Calcd for $C_{31}H_{43}N_2O_7$ [M+H$^+$]: 555.3065. Found: 555.3058.

4.15.2. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) 4-Nitro-benzoic acid 7-benzyloxy-5-hydroxymethyl-2-[(3-phenyl-ureido)-methyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (49). By working in an analogous way and by starting from 100 mg of resin **21** (R = *p*-nitrobenzoyl), the recovered crude product (25 mg) was chromatographed on silica gel (AcOEt/hexane 9:1) affording the pure ureido-derivative **49** (4 mg, 15% overall yield). ^1H NMR (200 MHz, $CDCl_3$) mixture of diastereoisomers, δ (ppm): 2.30 (m, 2H), 3.21–4.30 (m, 8H), 4.61 (m, 1H), 4.71 (br s, 2H), 5.19 (m, 1H), 6.35 (br s, 1H), 6.75 (br s, 1H), 7.3 (m, 10H), 8.2 (m, 4H). HRMS Calcd for $C_{30}H_{32}N_3O_9$ [MH$^+$]: 578.2133. Found: 578.2112.

The following compounds have been prepared by using the same experimental procedure:

4.15.3. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) Cyclopropanecarboxylic acid 7-benzyloxy-5-hydroxymethyl-2-(3-isopropyl-ureidomethyl)-hexahydro-furo[3,2-*b*]pyran-6-yl ester (50). Crude HPLC assay: 30% (area at 220 nm), isolated yield 34.9 mg (31% over six steps). ^1H NMR (400 MHz, DMSO-d_6), δ (ppm): 0.82 (m, 4H), 1.0 (m, 6H), 1.59 (m, 2H), 2.10 (m, 1H), 3.1–3.8 (m, 9H), 4.52 (m, 1H), 4.60 (d, 1H), 4.69 (d, 1H), 4.75 (br s,

1H), 4.85 (m, 1H), 5.70 (br t, 1H), 5.57 (br m, 1H), 7.28 (m, 5H). HRMS Calcd for $C_{24}H_{35}N_2O_7$ [M+H$^+$]: 463.2439. Found: 463.2449.

4.15.4. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Cyclopropanecarboxylic acid 7-benzyloxy-2-[3-(3-fluoro-phenyl)-ureidomethyl]-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (51). Crude HPLC assay: 15% (area at 220 nm), isolated yield 5.8 mg (5% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 0.82 (m, 4H), 1.59 (m, 1H), 1.71 (m, 1H), 2.17 (m, 1H), 3.2–4.0 (br m, 8H), 4.52 (m, 1H), 4.60 (d, 1H, J = 12.1 Hz), 4.70 (d, 1H, J = 12.1 Hz), 4.76 (br s, 1H), 4.86 (m, 1H), 6.34 (br t, 1H), 6.66 (t, 1H, J = 6.6 Hz), 7.2–7.4 (m, 7H), 7.42 (m, 1H), 7.66 (br t, 1H). HRMS Calcd for $C_{27}H_{32}FN_2O_7$ [M+H$^+$]: 515.2188. Found: 515.2177.

4.15.5. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Cyclopropanecarboxylic acid 7-benzyloxy-5-hydroxymethyl-2-[3-(3-methoxy-phenyl)-ureidomethyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (52). Crude HPLC assay: 15% (area at 220 nm), isolated yield 9.6 mg (7% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 0.82 (m, 4H), 1.59 (m, 1H), 1.71 (m, 1H), 2.16 (m, 1H), 3.2–4.0 (br m, 10H), 4.52 (m, 1H), 4.60 (d, 1H, J = 12.1 Hz), 4.70 (d, 1H, J = 12.1 Hz), 4.76 (br s, 1H), 4.86 (m, 1H), 6.18 (br t, 1H), 6.45 (m, 1H), 6.82 (m, 1H), 7.05–7.3 (m, 7H), 8.54 (br t, 1H). HRMS Calcd for $C_{28}H_{35}N_2O_8$ [M+H$^+$]: 527.2388. Found: 527.2374.

4.15.6. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Propionic acid 7-benzyloxy-2-[3-(3-fluoro-phenyl)-ureidomethyl]-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (53). Crude HPLC assay: 30% (area at 220 nm), isolated yield 6.0 mg (5% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 0.97 (t, 3H, J = 5.5 Hz), 1.70 (m, 1H), 2.26 (m, 3H), 3.15–4.00 (m, 8H), 4.56 (m, 1H), 4.60 (d, 1H), 4.69 (d, 1H), 4.79 (br m, 1H), 4.86 (t, 1H, J = 7.0 Hz), 6.30 (br t, 1H), 6.67 (m, 1H), 7.0–7.4 (m, 7H), 7.42 (m, 1H), 8.82 (br s, 1H). HRMS Calcd for $C_{26}H_{32}FN_2O_7$ [MH$^+$]: 503.2188. Found: 503.2191.

4.15.7. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Propionic acid 7-benzyloxy-5-hydroxymethyl-2-(3-isopropyl-ureidomethyl)-hexahydro-furo[3,2-*b*]pyran-6-yl ester (54). Crude HPLC assay: 45% (area at 220 nm), isolated yield 37.7 mg (34% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.0 (m, 9H), 1.59 (m, 1H), 2.10 (m, 1H), 2.35 (m, 2H), 3.1–3.8 (m, 8H), 4.52 (m, 1H), 4.60 (d, 1H, J = 12.1 Hz), 4.69 (d, 1H, J = 12.1 Hz), 4.75 (br s, 1H), 4.85 (m, 1H), 5.40 (br t, 1H), 5.75 (br m, 2H), 7.28 (m, 5H). HRMS Calcd for $C_{23}H_{35}N_2O_7$ [M+H$^+$]: 541.2439. Found: 541.2438.

4.15.8. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Nicotinic acid 7-benzyloxy-2-[3-(4-fluoro-phenyl)-ureidomethyl]-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (55). Crude HPLC assay: 50% (area at 220 nm), isolated yield 17.1 mg (14% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.74 (m, 1H), 2.23 (m, 1H), 3.3–4.0 (m, 8H), 4.61 (m, 1H), 4.62 (d, 1H, J = 12.1 Hz), 4.71 (d, 1H, J = 12.1 Hz), 4,81 (br m, 1H), 5.16 (m, 1H), 6.27 (m, 1H), 6.67 (m, 1H), 6.98 (m, 1H), 7.17 (m, 6H), 7.4–7.55 (m, 2H), 8.22 (m, 1H), 8.76 (m, 2H), 9.06 (s, 1H). HRMS Calcd for $C_{29}H_{31}FN_3O_7$ [M+H$^+$]: 552.2141. Found: 552.2138.

4.15.9. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Nicotinic acid 7-benzyloxy-5-hydroxymethyl-2-(3-isopropyl-ureidomethyl)-hexahydro-furo[3,2-*b*]pyran-6-yl ester (56). Crude HPLC assay: 48% (area at 220 nm), isolated yield 38.7 mg (31% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 0.98 (m, 6H), 1.59 (m, 1H), 2.15 (m, 1H), 3.29 (m, 2H), 3.62 (m, 3H), 3.85 (m, 4H), 4.58 (m, 3H), 4.80 (br s, 1H), 5.14 (m, 1H), 5.76 (br m, 2H), 7.16 (m, 5H), 7.55(m, 1H), 8.24 (m, 1H), 8.80 (m, 1H), 9.06 (m, 1H). HRMS Calcd for $C_{26}H_{34}N_3O_7$ [M+H$^+$]: 500.2391. Found: 500.2381.

4.15.10. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) 4-Fluoro-benzoic acid 7-benzyloxy-5-hydroxymethyl-2-(3-isopropyl-ureidomethyl)-hexahydro-furo[3,2-*b*]pyran-6-yl ester (57). Crude HPLC assay: 53% (area at 220 nm), isolated yield 45.8 mg (36% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.00 (d, 6H, J = 8.3), 1.73 (m, 1H), 2.16 (m, 1H), 3.29 (m, 2H), 3.62 (m, 3H), 3.82 (m, 4H), 4.54 (m, 1H), 4.60 (d, 1H, J = 12.1 Hz), 4.69 (d, 1H, J = 12.1 Hz), 4.79 (br m, 1H), 5.10 (m, 1H), 5.76 (m, 2H), 7.18 (m, 5H), 7.34 (m, 2H), 7.99 (m, 2H). HRMS Calcd for $C_{27}H_{34}FN_2O_7$ [M+H$^+$]: 517.2345. Found: 517.2333.

4.15.11. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) 4-Fluoro-benzoic acid 7-benzyloxy-5-hydroxymethyl-2-[3-(3-methoxy-phenyl)-ureidomethyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (58). Crude HPLC assay: 30% (area at 220 nm), isolated yield 15.1 mg (11% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.73 (m, 1H), 2.20 (m, 1H), 3.10–4.10 (br m, 11H), 4.56 (m, 1H), 4.60 (d, 1H, J = 12.1 Hz), 4.69 (d, 1H, J = 12.1 Hz), 4.80 (br m, 1H), 5.11 (m, 1H), 6.20 (br t, 1H), 6.46 (m, 1H), 6.6–7.35 (m, 10H), 7.99 (m, 2H), 8.53 (s, 1H). HRMS Calcd for $C_{31}H_{34}FN_2O_8$ [M+H$^+$]: 581.2294. Found: 581.2294.

4.15.12. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) 4-Fluoro-benzoic acid 7-benzyloxy-2-[3-(3-fluoro-phenyl)-ureidomethyl]-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (59). Crude HPLC assay: 40% (area at 220 nm), isolated yield 22.6 mg (16% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.73 (m, 1H), 2.22 (m, 1H), 3.29–4.0 (br m, 6H), 4.70 (m, 3H), 4.80 (br s, 1H), 5.11 (m, 1H), 6.26 (br t, 1H), 6.67 (t, 1H, J = 7.2 Hz), 6.99 (m, 1H), 7.2–7.4 (m, 9H), 7.99 (m, 2H), 8.75 (br s, 1H). HRMS Calcd for $C_{30}H_{31}F_2N_2O_7$ [M+H$^+$]: 569.2094. Found: 569.2090.

4.15.13. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Thiophene-2-carboxylic acid 7-benzyloxy-5-hydroxymethyl-2-(3-isopropyl-ureidomethyl)-hexahydro-furo[3,2-*b*]pyran-6-yl ester (60). Crude HPLC assay: 60% (area at 220 nm), isolated yield 32.5 mg (26% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.00 (d, 6 H, J = 6.5), 1.68 (m, 1H), 2.14 (m, 1H), 3.29 (m, 2H), 3.6

(m, 3H), 3.84 (m, 4H), 4.58 (m, 1H), 4.62 (d, 1H, $J = 12.1$ Hz), 4.70 (d, 1H, $J = 12.1$ Hz), 4.80 (br m, 1H), 5.05 (t, 1H, $J = 7.2$), 5.75 (m, 2H), 7.19 (m, 6H), 7.79 (m, 1H), 7.95 (m, 1H). HRMS Calcd for $C_{25}H_{33}N_2O_7S$ [M+H$^+$]: 505.2003. Found: 505.1994.

4.15.14. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Thiophene-2-carboxylic acid 7-benzyloxy-2-[3-(3-fluoro-phenyl)-ureidomethyl]-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (61). Crude HPLC assay: 45% (area at 220 nm), isolated yield 16.5 mg (12% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.73 (m, 1H), 2.20 (m, 1H), 3.2–4.0 (m, 8H), 4.57 (m, 1H), 4.62 (d, 1H, $J = 12.1$ Hz), 4.70 (d, 1H, $J = 12.1$ Hz), 4.81 (br m, 1H), 5.06 (t, 1H, $J = 7.2$ Hz), 6.26 (br t, 1H), 6.67 (m, 1H), 7.0 (d, 1H), 7.17 (m, 7H), 7.44 (m, 1H), 7.79 (m, 1H), 7.92 (m, 1H), 8.77 (br s, 1H). HRMS Calcd for $C_{28}H_{30}FN_2O_7S$ [M+H$^+$]: 557.1752. Found: 557.1732.

4.15.15. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) Thiophene-2-carboxylic acid 7-benzyloxy-5-hydroxymethyl-2-[3-(3-methoxy-phenyl)-ureidomethyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (62). Crude HPLC assay: 10% (area at 220 nm), isolated yield 6.7 mg (5% over six steps). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.73 (m, 1H), 2.19 (m, 1H), 3.29 (m, 4H), 3.67 (s, 3H), 3.80–4.10 (m, 4H), 4.57 (m, 1H), 4.62 (d, 1H, $J = 12.1$ Hz), 4.70 (d, 1H, $J = 12.1$ Hz), 4.81 (br m, 1H), 5.06 (t, 1H, $J = 7.1$ Hz), 6.19 (m, 1H), 6.46 (br t, 1H), 6.84 (m, 1H), 7.08 (m, 1H), 7.12 (m, 7H), 7.78 (m, 1H), 7.93 (m, 1H), 8.55 (br s, 1H). HRMS Calcd for $C_{29}H_{33}N_2O_8S$ [M+H$^+$]: 569.1952. Found: 569.1945.

4.16. Representative procedure for thioureido derivative formation

4.16.1. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) 3-Phenyl-propionic acid 7-benzyloxy-5-hydroxymethyl-2-[3-(3-methoxy-phenyl)-thioureidomethyl]-hexahydro-furo[3,2-*b*]pyran-6-yl ester (63). Resin **21** (R = 2-phenylethyl) (120 mg, 0.28 mmol/g, 0.034 mmol) was suspended under inert atmosphere in dry CH_2Cl_2 (2 mL), TEA (5 μL, 0.034 mmol, 1 equiv) and phenyl isothiocyanate (41 μL, 0.340 mmol, 10 equiv) were added. The resulting mixture was then shaken overnight; the solution removed by suction and the resin washed with CH_2Cl_2 (2× 2 mL), DMF (2× 2 mL), CH_2Cl_2 (2× 2 mL), DMF (2× 2 mL), and CH_2Cl_2 (4× 2 mL). After the first cycle, the TNBS test was negative, while the dyed-*p*-nitrophenylglycolate test gave a pale red staining. A second cycle with the same quantities was performed overnight and the resin was washed with CH_2Cl_2 (2× 2 mL), DMF (2× 2 mL), CH_2Cl_2 (2× 2 mL), DMF (2× 2 mL), and CH_2Cl_2 (4× 2 mL) obtaining a resin type **27**. The resin was cleaved with 20% TFA in CH_2Cl_2 (2× 2.0 mL, 20 min), and compound **63** was recovered after evaporation (13 mg). The crude compound was analyzed by TLC and ^{1}H NMR, and then purified by flash chromatography. Pure compound **63** was obtained (5 mg, 21% yield for the four steps). ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.84 (m, 1H), 2.3 (m, 1H), 2.55 (m, 2H), 2.92 (m, 2H), 3.4–3.9 (m, 6H), 3.96 (m, 1H), 4.25 (m, 1H), 4.47 (m, 1H), 4.54 (d, 1H, $J = 11.9$ Hz), 4.64 (d, 1H, $J = 11.9$ Hz), 4.82 (dd, 1H, $J = 6.3$, 6.2 Hz), 6.8 (br t, 1H), 7.12–7.38 (m, 15H), 7.6 (s, 1H). HRMS Calcd for $C_{32}H_{36}N_2O_6S$ [M+H$^+$]: 577.2372. Found: 577.2332.

4.17. Representative procedure for the reductive alkylation of the free amino group

Resin **21** (R = 2-phenylethyl) (200 mg, 0.42 mmol/g, 0.084 mmol) was suspended under inert atmosphere in trimethyl orthoformate (TMOF) (2.5 mL) and the aldehyde (benzaldehyde or *p*-methoxybenzaldehyde) (1.68 mmol, 20 equiv) was added. After the resulting mixture was shaken overnight at room temperature, the solution was removed by suction and the resin was washed with TMOF (2× 4 mL). After the first cycle, the TNBS test was positive. Therefore, a second cycle with the same quantities was performed for 3 h and the resin was washed with TMOF (2× 4 mL). The resin was suspended in TMOF (2.5 mL), and AcOH (25 μL, 1% in TMOF) and $NaCNBH_3$ (106 mg, 1.68 mmol, 20 equiv) were added. The suspension was shaken for 3 h at room temperature, then the solution was drained and the resin was washed with DMF (2× 3 mL), MeOH (2× 3 mL), 10%TEA/CH_2Cl_2 (1× 4 mL), MeOH (2× 3 mL), CH_2Cl_2 (2× 3 mL), MeOH (2× 3 mL), and CH_2Cl_2 (2× 3 mL). After the above-mentioned washing cycles, the resin type **28** (Y = 2-phenylpropanoyl, R′ = benzyl or *p*-methoxybenzyl) was kept under inert atmosphere and used immediately for the functionalization of the secondary amine.

4.18. Procedure for the formation of ureido derivatives at the secondary amino group

4.18.1. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*), 5(*R*),6(*S*),7(*S*),7a(*R*) 3-Phenyl-propionic acid 2-[(benzyl-octanoyl-amino)-methyl]-7-benzyloxy-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (64). Resin **28** (Y = 2-phenylpropanoyl, R′ = benzyl) (120 mg, 0.28 mmol/g, 0.034 mmol) was suspended under inert atmosphere in dry CH_2Cl_2 (2 mL), and TEA (5 μL, 0.034 mmol, 1 equiv) and phenyl isocyanate (37 μL, 0.34 mmol, 10 equiv) were added. After the resulting mixture was shaken overnight, the solution was removed by suction and the resin was washed with 2× CH_2Cl_2, 2× DMF and 3× CH_2Cl_2. After the first cycle, the dyed-*p*-nitrophenylglycolate test gave a pale red staining. A second cycle with the same quantities was performed overnight and the resin was washed with CH_2Cl_2 (2× 2 mL), DMF (2× 2 mL), CH_2Cl_2 (2× 2 mL), DMF (2× 2 mL), and CH_2Cl_2 (3× 2 mL), and dried in vacuo overnight, to obtain a resin type **29**. The resin was cleaved with 20% TFA in CH_2Cl_2 (2× 2.0 mL, 20 min), filtering and solvent evaporation affording 30 mg of crude product. The crude compound was analyzed by TLC and ^{1}H NMR, and then purified by flash chromatography. Pure compound **64** were obtained (7 mg, 38% yield for the

six steps). ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.85 (m, 1H), 2.27 (m, 1H), 2.45 (m, 2H), 2.82 (m, 2H), 3.48–3.74 (m, 5H), 3.87 (m, 1H), 3.92 (m, 1H), 4.06 (m, 1H), 4.57–4.75 (m, 5H), 5.0 (dd, 1H, J = 6.0, 5.9 Hz), 6.95–7.4 (m, 20H), 7.7 (s, 1H). HRMS Calcd for $C_{39}H_{42}N_2O_7$ [M+H$^+$]: 651.3070. Found: 651.3067.

4.19. Procedure for the acylation of the secondary amino group

4.19.1. 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) 3-Phenyl-propionic acid 7-benzyloxy-2-(1-benzyl-3-phenyl-ureidomethyl)-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (65); 2(*R*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) and 2(*S*),3a(*R*),5(*R*),6(*S*),7(*S*),7a(*R*) 3-phenyl-propionic acid 2-{[*p*-methoxybenzyl-(naphthalene-1-carbonyl)-amino]-methyl}-7-benzyloxy-5-hydroxymethyl-hexahydro-furo[3,2-*b*]pyran-6-yl ester (66). A 3 mL DMF/CH_2Cl_2 (1:1 ratio) solution of carboxylic acid (e.g., caprylic acid or napht-1-yl acetic acid) (0.270 mmol, 5 equiv), HATU (103 mg, 0.270 mmol, 5 equiv), and DIPEA (93 μL, 0.540 mmol, 10 equiv) was added to resin **28** (Y = 2-phenylpropanoyl, R′ = benzyl or *p*-methoxybenzyl) (194 mg, 0.28 mmol/g, 0.054 mmol, 1 equiv). Subsequently, the resulting slurry was shaken for 1 day, the solution was drained, and the resin was washed with 2× CH_2Cl_2, 2× DMF, and 3× CH_2Cl_2. The dyed-*p*-nitrophenylglycolate test gave a pale red staining. (ca. 2–5% free amines). A second cycle with the same quantities was performed overnight, then the solution was drained and the resin was washed with CH_2Cl_2 (2× 3 mL), DMF (2× 3 mL), CH_2Cl_2 (2× 3 mL), DMF (2× 3 mL), and CH_2Cl_2 (3 × 3 mL), and dried in vacuo overnight (the dyed-*p*-nitrophenylglycolate test was negative after the second cycle), to get a resin type **29**. The resin was cleaved with 20% TFA in CH_2Cl_2 (2× 2.5 mL, 20 min), and crude compounds **65** (32 mg) and **66** (63 mg) were recovered after evaporation. The crude compounds were analyzed by TLC and ^{1}H NMR, and then purified by flash chromatography affording pure compounds **65** (8 mg, 23% yield for the six steps) and **66** (12 mg, 20% yield for the six steps).

Compound ***65***. ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 0.88 (m, 3H), 1.2–1.45 (m, 10H), 1.6–1.8 (m, 3H), 2.3 (m, 1H), 2.62 (m, 2H), 2.92 (m, 2H), 3.5–3.94 (m, 7H), 4.18 (m, 1H), 4.58 (m, 1H), 4.64–4.82 (m, 4H), 4.96 (dd, 1H, J = 7.5, 7.3 Hz), 7.08–7.4 (m, 15H). HRMS Calcd for $C_{40}H_{52}NO_7$ [M+H$^+$]: 658.3738. Found: 658.3745.

Compound ***66.*** ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.8 (m, 1H), 2.28 (m, 1H), 2.6 (m, 2H), 2.94 (m, 2H), 3.5 (m, 2H), 3.7–4.0 (m, 9H), 4.12 (m, 1H), 4.26 (m, 1H), 4.52–4.78 (m, 4H), 4.97 (m, 1H), 6.8–7.02 (m, 4H), 7.12–7.5 (m, 8H), 7.8 (m,3H). MS (FAB$^+$): m/z = 730 ([M+H$^+$]).

4.20. Antiproliferative assay

Human colon carcinoma cells (HT29) and human prostatic carcinoma cells (DU145) were seeded in 96-well plates in complete medium and treated with the compounds 24 h after seeding. After 72 h of treatment, the plates were processed for the ATPLite-M assay (Packard) following the manufacturer's instruction. Results are expressed as percentage of untreated control cells.[18,19]

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