DOI: 10.1002/ejoc.200700178

Design, Synthesis and Biological Activity of Azasugar-Based CD163 Ectodomain Shedding Inhibitors

Mohamed I. Attia,[a] Meike Timmermann,[b] Petra Högger,[b] and Claus Herdeis*[a]

Keywords: Hydroxamic acid / Azasugar / Wittig reaction / Metalloproteinase

A series of metalloproteinase CD163 ectodomain shedding inhibitors based on azasugar hydroxamic acid scaffold has been synthesized. Among the synthesized compounds, the benzyl derivative **4a** and the methyl derivative **4f** exhibits 66 and 51 % inhibition, respectively, at 1 μM concentration on CD163 shedding from human monocytes.

Introduction

CD163 is a membrane glycoprotein of the cysteine-rich scavenger receptor (SRCR) superfamily. It is expressed exclusively on human monocytes and macrophages.[1] CD163 has a function in host defence and homeostasis and serves as a scavenger receptor for haemoglobin-haptoglobin complexes. CD163 is subjected to proteinase-mediated ectodomain shedding upon an inflammatory stimulus in vitro and it also exists as a soluble protein. Shedding of CD163 is mediated by a TIMP-3-sensitive metalloproteinase.[2,3] This shedding-inducing proteinase is attributed to the ADAM family (a desintegrin and metalloproteinase) with TACE (TNFα converting enzyme) as prominent member. Thus, CD163 might serve as a model molecule for a membrane protein undergoing metalloproteinase-mediated ectodomain shedding and it could be an attractive target for medicinal chemists.

Azasugar scaffold containing hydroxamic acid moiety is a well-known class of compounds possessing metalloproteinase inhibitor activity (**1**–**3**, Figure 1).[4] All of them possess the structural features of pipecolic acid derivatives.

In the present report, we describe the design and synthesis of certain azasugar-containing hydroxamic acid functionalities based on homopipecolic acid derivatives to be evaluated as CD163-shedding inhibitors. The stereochemistry of the azasugar moiety, derived from D-ribose in a modified manner, of the target compounds **4a**–**g** was assigned to be 3′a*S*,4′*R*,7′*R*,7′a*R*, namely *all-cis* configuration, which is in accordance with our previously published results.[5]

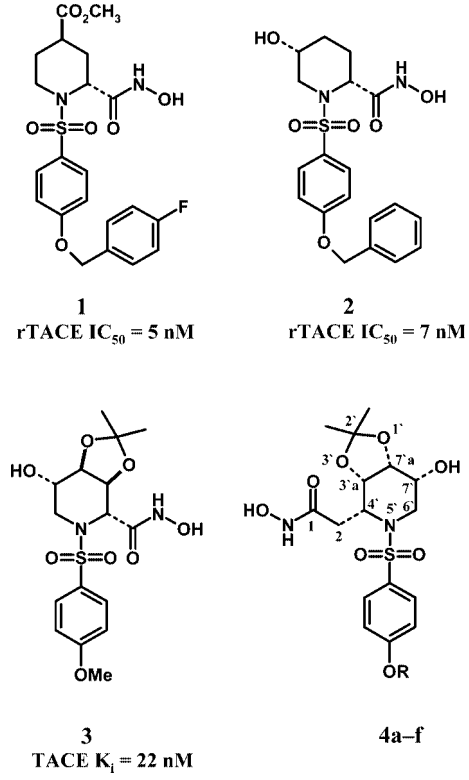


Figure 1. Hydroxamic acid derivatives possessing metalloproteinase inhibitory activities.

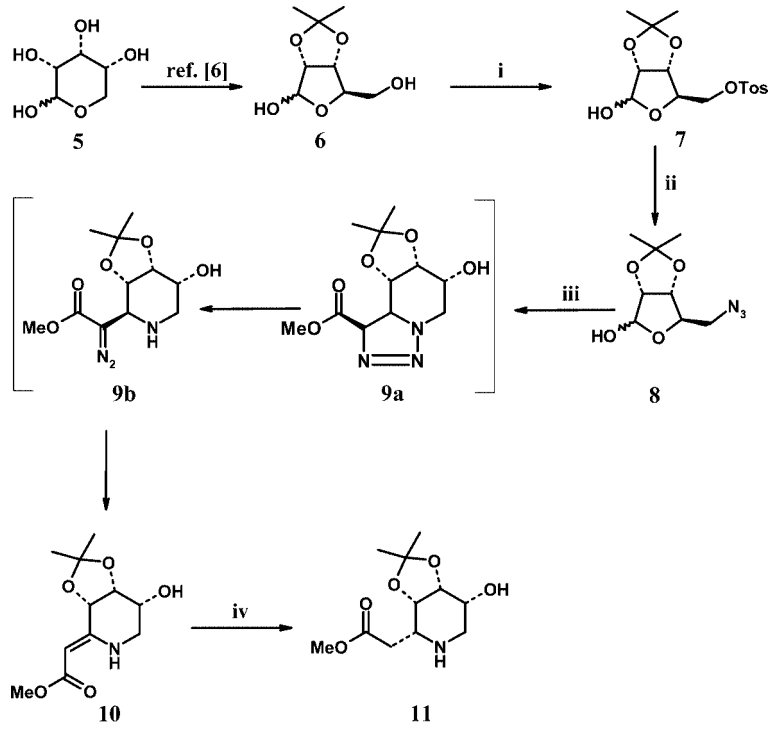
Results and Discussion

Chemistry

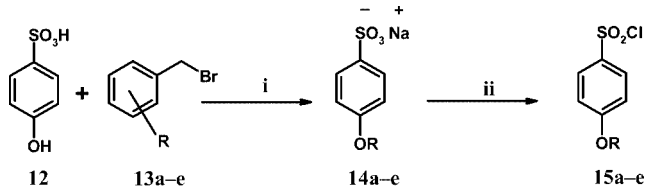
Synthetic approaches for the preparation of the target compounds **4a**–**g** and their intermediates are described in Schemes 1, 2, 3, and 4.

D-Ribose contains the required configuration in the 3′a and 7′a positions of the target compounds **4a**–**g**. Thus, D-ribose was transformed to the known isopropylidene deriv-

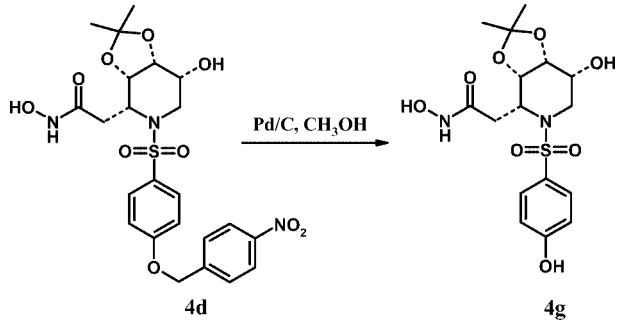
[a] Pharmazeutische Chemie Division, Würzburg Universität, Institut für Pharmazie und Lebensmittelchemie,
Am Hubland, 97074 Würzburg, Germany
Fax: +49-931-8885494
E-mail: herdeis@pharmazie.uni-wuerzburg.de
[b] Klinische Pharmazie Division, Würzburg Universität,
Am Hubland, 97074 Würzburg, Germany



Scheme 1. (i) TosCl, pyridine; (ii) NaN_3, DMSO; (iii) $Ph_3P{=}CHCO_2CH_3$, $Rh_2(OAc)_4$, Et_3N, CH_2CL_2; (iv) H_2, Pd/C, CH_3OH.

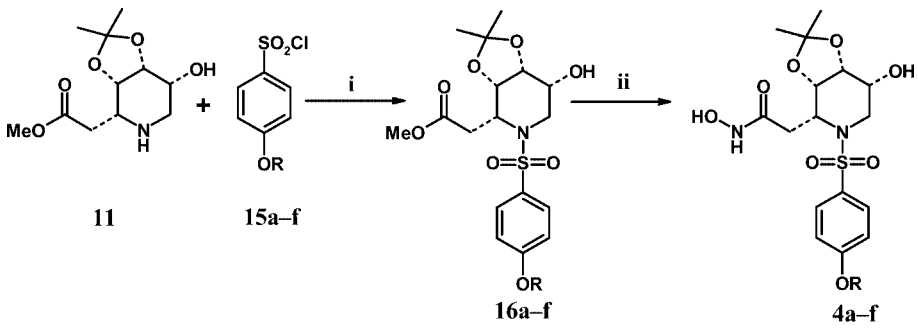


Scheme 2. (i) NaOH, C_2H_5OH; (ii) SO_2Cl_2, DMF.



Scheme 4.

ative **6** according to the published procedure.[6] Selective tosylation of **6** has previously been reported.[7] We employed the reaction under slightly different conditions obtaining monotosylate **7** in 75% yield. Subsequently, the tosylate derivative **7** was subjected to nucleophilic substitution using sodium azide in DMSO to furnish azidolactol **8** in 85% yield. When **8** was treated with (methoxycarbonylmethylene)triphenylphosphorane at ambient temperature a smooth Wittig reaction took place. This reaction is followed by an intramolecular [2+3] cycloaddition reaction of the azide functionality to the double bond to produce the triazoline **9a** which was not isolated but isomerised to give diazoamine **9b** as a single diastereomer. Compound **9b** was subjected to nitrogen extrusion using rhodium acetate catalyst with concomitant 1,2-H shift to provide vinylogous urethane **10**. This four-step reaction sequence was then upscaled as a one-pot reaction in 52% yield based on **8**.



Scheme 3. (i) K_2CO_3, CH_3CN; (ii) NH_2OK, CH_3OH.

Thus, an optimized procedure for the preparation of the vinylogous urethane **10** on a multi-gram scale using cheap and commercially available starting material has been successfully achieved. Vinylogous urethane **10** was synthesized previously[8] by adopting tandem retro-Michael [3+2]-cycloaddition on ε-sugar amino acids obtained from D-ribose in four steps. The double bond of **10** was hydrogenated over 10% Pd/C under 55 bar of hydrogen in methanol to afford the homopipecolic acid derivative **11** (Scheme 1). Compound **11** possesses exclusively *R*-configuration at C-4 position which is a prerequisite for the metalloproteinase inhibitors.[4c]

Gribble et al. reported the synthesis of 4-(benzyloxy)benzenesulfonyl chloride derivatives in a patent literature.[9] Thus, bis(4-hydroxyphenyl) disulfide was treated with benzyl bromide derivatives in DMF to afford bis[4-(benzyloxyphenyl)] disulfide derivatives which were subsequently oxidised to give the corresponding 4-(benzyloxy)benzenesulfonyl chloride derivatives using *N*-chlorosuccinimide in acetic acid.

We developed a simple alternative route to achieve 4-(benzyloxy)benzenesulfonyl chloride derivatives **15a**–**e**. Therefore, disodium salt formation of the commercially available 4-hydroxyphenylsulfonic acid **12** followed by in-situ monobenzylation with benzyl bromide derivatives **13a**–**e** furnished the respective ether derivatives **14a**–**e** in 62–96% yield. Compounds **14a**–**e** were elaborated to the corresponding sulfonyl chloride derivatives **15a**–**e** through reaction with thionyl chloride in DMF (Scheme 2).

Sulfonylation of the amino ester **11** with **15a**–**f** in acetonitrile using K_2CO_3 afforded sulfonamides **16a**–**f** in 76–90% yield. Compounds **16a**–**f** were transformed into the corresponding hydroxamic acid derivatives **4a**–**f** (Table 1) in moderate yields as depicted in Scheme 3.

Furthermore, hydrogenolysis of the benzyl ether of **4d** gave compound **4g** in 67% yield (Scheme 4).

Biological Evaluation

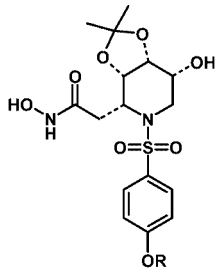
Isolation and Culture of Blood Monocytes

Human monocytes were isolated from blood cell suspensions pooled from different donors by Biocoll and subsequent Ficoll density gradient centrifugation.[1]

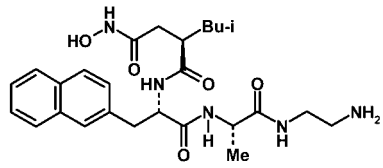
Shedding Experiments and Flow Cytometric Analysis (FACS)

2×10^6 cells were pre-stimulated for 30 min in the presence or absence of the inhibitors in a concentration of 1 μM. 1 mM H_2O_2 was added to each well, followed by an incubation period of 30 min. Cells were incubated with the CD163-specific antibody RM3/1 followed by an incubation with FITC-labeled secondary antibody goat *anti*-mouse IgG1. The fluorescence intensity of 10.000 living cells was measured by FACS analysis.[3] Table 1 shows the inhibition activity of compounds **4a**–**g** on CD163 shedding where compounds **4a** and **4f** are the most active congeners as compared to the commercially available hydroxamate-based metalloproteinase inhibitor TAPI-1.[10]

Table 1. CD163 shedding inhibitory activities of **4a**–**g**.



4a–g



TAPI-1

Compound	R	% inhibition (CD163) ± SD[a]
4a	benzyl	66 ± 1.96
4b	2-methylbenzyl	40 ± 8.05
4c	4-bromobenzyl	34 ± 1.61
4d	4-nitrobenzyl	17 ± 9.83
4e	3-chlorobenzyl	35 ± 2.62
4f	methyl	51 ± 4.84
4g	H	28 ± 3.64
TAPI-1[b]		95 ± 0.64

[a] Standard deviation; the values are the means ± SD (n = 6). [b] From Merck Biosciences GmbH, Bad Soden, Germany.

Conclusions

A convenient four-step reaction sequence was developed to achieve vinylogous urethane **10** on multi-gram scale and as one-pot reaction. Compound **10** was further elaborated to the novel hydroxamic acid derivatives **4a**–**g**. A straightforward route to 4-(benzyloxy)benzenesulfonyl chloride derivatives **15a**–**e** is also reported. The new azasugar-based hydroxamic acid derivatives **4a**–**g** revealed significant activity towards a shedding-inducing metalloproteinase with **4a** and **4f** being the most potent compounds. Thus, inhibition of CD163-shedding is a valuable tool for screening and optimization of new metalloproteinase inhibitors and might lead to further insights into biological regulation and significance of membrane protein-shedding reactions.

Experimental Section

General: Melting points were determined on Büchi capillary melting point apparatus and are uncorrected. IR spectra, recorded as ATR, were obtained by using a Biorad PharmalyzIR FT-IR spectrometer. 400-MHz ^{1}H and 100-MHz ^{13}C-NMR spectra were determined on a Bruker AV-400 spectrometer. The chemical shifts are reported in ppm on δ scales. Mass spectra were acquired in the positive ion mode under electrospray ionization (ESI) on a LC/MSD Ion Trap system. Column chromatography was carried out on silica gel 60 (0.063–0.200 mm) obtained from Merck. Combustion analyses were performed by the microanalytical section of the Institute of Inorganic Chemistry, University of Würzburg.

(3a*R*,4*R*,6a*R*)-2,2-Dimethyl-6-(tosyloxymethyl)-tetrahydro-2*H*-furo-[3,4-*d*]-1,3-dioxol-4-ol (7): A solution of TsCl (5.7 g, 30.0 mmol) in pyridine (10 mL) was added dropwise to a mixture of **6** (5.2 g, 27.3 mmol) in pyridine (10 mL) at –30 °C. The resulting mixture was stirred at 0 °C for one hour and then at 25 °C for 4 h. Ethyl acetate (100 mL) was added and the resulting solution was extracted with 10% H_2SO_4 (4 × 20 mL). The organic layer was separated, washed with $NaHCO_3$ (3 × 15 mL), dried (Na_2SO_4) and the solvents evaporated under vacuum. The residue was recrystallized from CH_2Cl_2/*n*-pentane to give 7.06 g (75%) of **7** as a white solid m.p. 95–96 °C. The spectroscopic data of **7** were identical to those previously reported.[7]

(3a*R*,6*R*,6a*R*)-6-(Azidomethyl)-2,2-dimethyl-tetrahydro-2*H*-furo-[3,4-*d*]-1,3-dioxol-4-ol (8): To a stirred solution of **7** (19.0 g, 55.18 mmol) in DMSO (300 mL) was added sodium azide (7.2 g, 110.52 mmol) at room temperature. The reaction mixture was heated at 75 °C for 18 h. The reaction mixture was cooled, poured into water (600 mL) and extracted with diethyl ether (3 × 200 mL). The organic extracts were combined, dried (Na_2SO_4) and evaporated under reduced pressure to afford 10.09 g (85%) of **8** as a pale yellow viscous oil which was pure enough to be used in the next step without further purification. The spectroscopic data of **8** were identical to those previously reported.[5]

Methyl (3a*S*,4*Z*,7*R*,7a*R*)-2-[Tetrahydro-7-hydroxy-2,2-dimethyl-1,3-dioxolo[4,5-*c*]pyridin-4(5*H*)-ylidene]acetate (10): To a stirred solution of **8** (11.19 g, 52.0 mmol) in dry CH_2Cl_2 (150 mL) was added (methoxycarbonylmethylene)triphenylphosphorane (17.39 g, 52.0 mmol). The reaction mixture was stirred at room temperature for 72 h (TLC-controlled). Triethylamine (14.62 mL, 104.0 mmol) and rhodium acetate (80 mg) were added and the reaction mixture was stirred for further 24 h at room temperature. The solvent was evaporated under vacuum and the residue was recrystallized from methanol to yield 6.63 g (52%) of **10** as a white solid m.p. 162–163 °C. $[\alpha]_D^{25}$ = +71.8 (*c* = 1.0, $CHCl_3$). FT-IR (ATR): $\tilde{\nu}$ = 3292, 2981, 1656, 1607, 1246, 787, 678 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 1.32 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 3.09–3.19 (m, 2 H, 6-H), 3.51 (s, 3 H, OCH_3), 3.62–3.74 (m, 1 H, 7-H), 4.39 (dd, *J* = 6.8, 3.0 Hz, 1 H, 7a-H), 4.53 (s, 1 H, 2′-H), 4.59 (d, *J* = 6.8 Hz, 1 H, 3a-H), 5.09 (d, *J* = 5.6 Hz, 1 H, OH), 8.33 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 24.5 (CH_3), 26.1 (CH_3), 40.8 (C-6), 49.6 (OCH_3), 65.9 (C-7), 73.9 (C-7a), 74.4 (C-3a), 82.2 (C-2′), 108.9 (C-2), 157.9 (C-4), 169.5 (O=C) ppm.

Methyl (3a*S*,4*R*,7*R*,7a*R*)-2-[Hexahydro-7-hydroxy-2,2-dimethyl-1,3-dioxolo[4,5-*c*]pyridin-4-yl]acetate (11): A solution of **10** (4.5 g, 18.5 mmol) in methanol (160 mL) was hydrogenated over 10% Pd/C (0.87 g) under 50 bar of H_2 for 72 h at 50 °C. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/methanol, 9:1) to give 4.00 g (88%) of **11** as a white solid m.p. 56–58 °C. $[\alpha]_D^{25}$ = –15.6 (*c* = 1.0, $CHCl_3$). FT-IR (ATR): $\tilde{\nu}$ = 3482, 3303, 2986, 1726, 1213, 793, 635 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.29 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 2.23 (d, *J* = 2.8 Hz, 1 H, OH), 2.55 (d, *J* = 7.1 Hz, 2 H, 2′-H), 2.59 (dd, *J* = 13.6, 2.0 Hz, 1 H, H^a-6), 3.07 (dd, *J* = 13.6, 4.0 Hz, 1 H, H^b-6), 3.23 (ddd, *J* = 7.1, 6.8, 2.8 Hz, 1 H, 7-H), 3.62–3.63 (m, 1 H, 4-H), 3.64 (s, 3 H, OCH_3), 4.05–4.09 (m, 2 H, 3a-H, 7a-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.2 (CH_3), 25.9 (CH_3), 36.8 (C-2′), 48.0 (C-6), 51.7 (C-7), 52.5 (OCH_3), 63.4 (C-4), 72.9, 74.1 (C-3a, C-7a), 108.9 (C-2), 172.4 (O=C) ppm. $C_{11}H_{19}NO_5$ (245.27): calcd. C 53.87, H 7.81, N 5.71; found C 53.63, H 7.52, N 5.54.

General Procedure for the Synthesis of Arylsulfonic Acid Derivatives 14a–e: The appropriate benzyl bromide derivative **13a**–**e** (10.0 mmol) in ethanol (25 mL) was added to a stirred solution of 65% 4-hydroxybenzenesulfonic acid **12** (2 mL, 10.0 mmol) and sodium hydroxide (0.8 g, 20.0 mmol) in water (25 mL). The reaction mixture was heated at 100 °C for 18 h, cooled and filtered. The collected solid was washed with cold ethanol (2 × 10 mL) and dried to give **14a**–**e** which were pure enough to be used in the next step without further purification.

Sodium 4-(Benzyloxy)benzenesulfonate (14a):[11] Following the general procedure 1.78 g (62%) of **14a** was obtained as a white solid m.p. 296–298 °C. FT-IR (ATR): $\tilde{\nu}$ = 3061, 1595, 1497, 1180, 857, 621 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 5.12 (s, 2 H, -C*H*$_2$-C$_6$H$_5$), 6.95 (d, *J* = 8.8 Hz, 2 H, ArH), 7.31–7.46 (m, 5 H, ArH), 7.55 (d, *J* = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 69.2 (-*C*H$_2$ -C$_6$H$_5$), 113.7, 116.3, 127.1, 127.6, 127.8, 128.4 (ArCH), 136.9, 140.9, 153.3 (ArC) ppm.

Sodium 4-(2-Methylbenzyloxy)benzenesulfonate (14b): Following the general procedure 1.92 g (64%) of **14b** was obtained as a white solid m.p. 272–273 °C. FT-IR (ATR): $\tilde{\nu}$ = 3529, 3474, 1598, 1499, 1176, 833, 698 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 2.32 (s, 3 H, CH_3), 5.09 (s, 2 H, -C*H*$_2$-C$_6$H$_4$), 6.98 (d, *J* = 8.6 Hz, 2 H, ArH), 7.18–7.25 (m, 3 H, ArH), 7.39–7.41 (m, 1 H, ArH), 7.57 (d, *J* = 8.6 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 18.4 (CH_3), 67.9 (-*C*H$_2$-C$_6$H$_4$), 113.6, 114.0, 125.7, 127.1, 128.0, 128.4, 130.1 (ArCH), 134.8, 136.5, 140.9, 157.6, 158.5 (ArC) ppm.

Sodium 4-(4-Bromobenzyloxy)benzenesulfonate (14c): Following the general procedure 2.81 g (77%) of **14c** was obtained as a white solid m.p. > 300 °C. FT-IR (ATR): $\tilde{\nu}$ = 3528, 3471, 1593, 1497, 1181, 807, 697 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 5.11 (s, 2 H, -C*H*$_2$-C$_6$H$_4$), 6.94 (d, *J* = 8.8 Hz, 2 H, ArH), 7.39–7.45 (m, 2 H, ArH), 7.53–7.60 (m, 4 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 68.4 (-*C*H$_2$-C$_6$H$_4$), 113.7, 113.9, 127.1, 129.7, 131.3 (ArCH), 136.5, 139.1, 141.1, 157.5, 158.1 (ArC) ppm.

Sodium 4-(4-Nitrobenzyloxy)benzenesulfonate (14d): Following the general procedure 2.65 g (80%) of **14d** was obtained as a pale yellow solid m.p. 279–280 °C. FT-IR (ATR): $\tilde{\nu}$ = 3660, 3457, 1601, 1166, 831, 690 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 5.30 (s, 2 H, -C*H*$_2$-C$_6$H$_4$), 6.98 (d, *J* = 8.8 Hz, 2 H, ArH), 7.57 (d, *J* = 8.8 Hz, 2 H, ArH), 7.72 (d, *J* = 8.8 Hz, 2 H, ArH), 8.25 (d, *J* = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 68.0 (-*C*H$_2$-C$_6$H$_4$), 113.8, 114.0, 123.6, 127.1, 128.2 (ArCH), 141.1, 144.9, 146.9, 157.7, 157.9 (ArC) ppm.

Sodium 4-(3-Chlorobenzyloxy)benzenesulfonate (14e): Following the general procedure 3.08 g (96%) of **14e** was obtained as a white solid m.p. > 300 °C. FT-IR (ATR): $\tilde{\nu}$ = 3531, 3472, 1597, 1177, 836, 689 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 5.14 (s, 2 H, -C*H*$_2$-C$_6$H$_4$), 6.96 (d, *J* = 8.8 Hz, 2 H, ArH), 7.43–7.45 (m, 3 H, ArH), 7.51–7.52 (m, 1 H, ArH), 7.56 (d, *J* = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 68.3 (-*C*H$_2$-C$_6$H$_4$), 113.7, 114.0, 126.1, 127.1, 127.2, 127.7, 130.4 (ArCH), 133.1, 139.6, 140.9, 157.6, 158.1 (ArC) ppm.

General Procedure for the Synthesis of Arylsulfonyl Chloride Derivatives (15a–e): Thionyl chloride (0.67 mL, 9.16 mmol) was added dropwise to a stirred suspension of the appropriate sodium arylsulfonate derivative **14a**–**e** (7.0 mmol) in dry DMF (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 5 min, poured onto ice, stirred further for 5 min and the precipitated solid was filtered. The collected solid was dissolved in CH_2Cl_2 (20 mL) and washed with water (2 × 10 mL). The organic layer was separated, dried (Na_2SO_4) and the solvents evaporated under vacuum to afford **15a**–**e** which were used directly without further purification.

4-Benzyloxybenzenesulfonyl chloride (15a):[11] Following the general procedure 1.25 g (63%) of **15a** was obtained as a white solid m.p. 103–105 °C. FT-IR (ATR): $\tilde{\nu}$ = 3534, 1572, 1491, 1159, 698 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 5.10 (s, 2 H, -CH_2-C$_6$H$_5$), 6.96 (d, J = 8.8 Hz, 2 H, ArH), 7.28–7.45 (m, 5 H, ArH), 7.55 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 69.2 (-CH_2-C$_6$H$_5$), 113.8, 127.1, 127.6, 127.8, 128.4 (ArCH), 136.9, 140.1, 153.6 (ArC) ppm.

4-(2-Methylbenzyloxy)benzenesulfonyl Chloride (15b):[9] Following the general procedure 1.39 g (67%) of **15b** was obtained as a white solid m.p. 114–115 °C. FT-IR (ATR): $\tilde{\nu}$ = 3655, 1583, 1491, 1161, 683 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 2.31 (s, 3 H, CH$_3$), 5.09 (s, 2 H, -CH_2-C$_6$H$_4$), 6.99 (d, J = 8.8 Hz, 2 H, ArH), 7.16–7.26 (m, 3 H, ArH), 7.38–7.39 (m, 1 H, ArH), 7.57 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 18.4 (CH$_3$), 67.9 (-CH_2-C$_6$H$_4$), 113.8, 125.7, 127.1, 128.0, 128.4, 130.1 (ArCH), 134.7, 136.5, 139.9, 158.8 (ArC) ppm.

4-(4-Bromobenzyloxy)benzenesulfonyl Chloride (15c):[9] Following the general procedure 1.92 g (76%) of **15c** was obtained as a white solid m.p. 100–102 °C. FT-IR (ATR): $\tilde{\nu}$ = 3578, 1657, 1588, 1493, 1155, 623 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 5.10 (s, 2 H, -CH_2-C$_6$H$_4$), 6.95 (d, J = 8.8 Hz, 2 H, ArH), 7.39–7.41 (m, 2 H, ArH), 7.53–7.59 (m, 4 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 68.4 (-CH_2-C$_6$H$_4$), 113.9, 127.1, 129.7, 131.3 (ArCH), 120.9, 136.4, 140.2, 158.4 (ArC) ppm.

4-(4-Nitrobenzyloxy)benzenesulfonyl Chloride (15d): Following the general procedure 1.26 g (55%) of **15d** was obtained as a pale yellow solid m.p. 152–153 °C. FT-IR (ATR): $\tilde{\nu}$ = 3444, 1578, 1516, 1340, 1157, 698 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 5.29 (s, 2 H, -CH_2-C$_6$H$_4$), 6.98 (d, J = 8.8 Hz, 2 H, ArH), 7.56 (d, J = 8.8 Hz, 2 H, ArH), 7.70 (d, J = 8.8 Hz, 2 H, ArH), 8.23 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 68.0 (-CH_2-C$_6$H$_4$), 113.9, 123.6, 127.2, 128.2 (ArCH), 140.4, 144.9, 146.9, 158.1 (ArC) ppm.

4-(3-Chlorobenzyloxy)benzenesulfonyl Chloride (15e):[9] Following the general procedure 1.62 g (73%) of **15e** was obtained as a white solid m.p. 62–63 °C. FT-IR (ATR): $\tilde{\nu}$ = 3659, 1659, 1584, 1494, 1157, 679 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 5.14 (s, 2 H, -CH_2-C$_6$H$_4$), 6.96 (d, J = 8.8 Hz, 2 H, ArH), 7.36–7.41 (m, 3 H, ArH), 7.50–7.51 (m, 1 H, ArH), 7.56 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 68.3 (-CH_2-C$_6$H$_4$), 113.9, 126.1, 127.1, 127.2, 127.7, 130.3 (ArCH), 133.1, 139.5, 140.4, 158.3 (ArC) ppm.

4-Methoxybenzenesulfonyl Chloride (15f):[12] Following the literature procedure[12] 0.72 g (50%) of **15f** was obtained as a white solid m.p. 39–40 °C. FT-IR (ATR): $\tilde{\nu}$ = 3451, 1584, 1491, 1152, 626 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 3.74 (s, 3 H, OCH$_3$), 6.88 (d, J = 8.8 Hz, 2 H, ArH), 7.56 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 55.2 (OCH$_3$), 113.0, 127.1 (ArCH), 139.3, 159.7 (ArC) ppm.

General Procedure for the Synthesis of Methyl (3a*S*,4*R*,7*R*,7a*R*)-2-[5-(4-Arylsulfonyl)-hexahydro-7-hydroxy-2,2-dimethyl-1,3-dioxolo-[4,5-*c*]pyridin-4-yl]acetate Derivatives 16a–f: A solution of the appropriate arylsulfonyl chloride derivative **15a**–**f** (1.1 mmol) in dry acetonitrile (5 mL) was added at room temperature to a stirred suspension of **11** (0.25 g, 1 mmol) and anhydrous K_2CO_3 (0.22 g, 1.6 mmol) in dry acetonitrile (5 mL). The reaction mixture was vigorously stirred at room temperature for 18 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (diethyl ether/*n*-pentane, 8:2) to afford **16a**–**f**.

Methyl (3a*S*,4*R*,7*R*,7a*R*)-2-[5-(4-Benzyloxyphenylsulfonyl)-hexahydro-7-hydroxy-2,2-dimethyl-1,3-dioxolo[4,5-*c*]pyridin-4-yl]acetate (16a): Following the general procedure 0.38 g (78%) of **16a** was obtained as a white solid m.p. 94–96 °C. $[\alpha]_D^{25}$ = –19.2 (c = 0.5, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3487, 1726, 1591, 1146, 706, 610 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH$_3$), 1.39 (s, 3 H, CH$_3$), 2.50–2.53 (m, 1 H, H^a-2′), 2.83 (dd, J = 16.0, 7.9 Hz, 1 H, H^b-2′), 2.99 (dd, J = 13.2, 10.6 Hz, 1 H, H^a-6), 3.32–3.38 (m, 7-H, 2 H, H^b-6), 3.53 (s, 3 H, OCH$_3$), 4.24–4.27 (m, 1 H, 4-H), 4.29–4.33 (m, 2 H, 3a-H, 7a-H), 5.18 (d, J = 5.0 Hz, 1 H, OH), 5.21 (s, 2 H, -CH_2-C$_6$H$_5$), 7.23 (d, J = 8.8 Hz, 2 H, ArH), 7.34 (m, 5 H, ArH), 7.75 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 24.6 (CH$_3$), 25.4 (CH$_3$), 36.1 (C-2′), 42.3 (C-6), 50.1 (C-4), 51.3 (OCH$_3$), 63.8 (C-7), 69.7 (-CH_2-C$_6$H$_5$), 72.6, 73.2 (C-3a, C-7a), 108.4 (C-2) 115.5, 127.9, 128.1, 128.5, 129.1 (ArCH), 130.9, 136.2, 161.8 (ArC), 170.9 (O=C) ppm. $C_{24}H_{29}NO_8S$ (491.55): calcd. C 58.64, H 5.95, N 2.85; found C 58.34, H 5.66, N 2.76.

Methyl (3a*S*,4*R*,7*R*,7a*R*)-2-[Hexahydro-7-hydroxy-2,2-dimethyl-5-[4-(2-methylbenzyloxy)phenylsulfonyl]-1,3-dioxolo[4,5-*c*]pyridin-4-yl-]acetate (16b): Following the general procedure 0.46 g (90%) of **16b** was obtained as a white solid m.p. 156–158 °C. $[\alpha]_D^{25}$ = +9.5 (c = 0.2, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3433, 1713, 1589, 1148, 756, 678 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH$_3$), 1.39 (s, 3 H, CH$_3$), 2.33 (s, 3 H, H_3C-C$_6$H$_4$), 2.53–2.55 (m, 1 H, H^a-2′), 2.85–2.89 (m, 1 H, H^b-2′), 2.90–2.94 (m, 1 H, H^a-6), 3.37–3.42 (m, 2 H, H^b-6, 7-H), 3.45 (s, 3 H, OCH$_3$), 4.09–4.10 (m, 1 H, 4-H), 4.29–4.33 (m, 2 H, 3a-H, 7a-H), 5.19 (s, 2 H, -CH_2-C$_6$H$_4$), 7.22 (d, J = 8.8 Hz, 2 H, ArH), 7.23–7.26 (m, 3 H, ArH), 7.24–7.43 (m, 1 H, ArH), 7.69 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 18.4 (H_3C-C$_6$H$_4$), 24.6 (CH$_3$), 25.4 (CH$_3$), 36.1 (C-2′), 42.2 (C-6), 50.1 (C-4), 51.3 (OCH$_3$), 63.9 (C-7), 68.7 (-CH_2-C$_6$H$_4$), 72.7, 73.2 (C-3a, C-7a), 108.4 (C-2) 115.2, 125.8, 128.3, 128.7, 129.2, 130.1 (ArCH), 132.5, 134.2, 136.7, 161.6 (ArC), 172.2 (O=C) ppm. $C_{25}H_{31}NO_8S$ (505.58): calcd. C 59.39, H 6.18, N 2.77; found C 59.14, H 6.09, N 2.63.

Methyl (3a*S*,4*R*,7*R*,7a*R*)-2-[5-[4-(4-Bromobenzyloxy)phenylsulfonyl]-hexahydro-7-hydroxy-2,2-dimethyl-1,3-dioxolo[4,5-*c*]-pyridin-4-yl]acetate (16c): Following the general procedure 0.47 g (82%) of **16c** was obtained as a white solid m.p. 144–146 °C. $[\alpha]_D^{25}$ = –1.7 (c = 0.12, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3437, 1716, 1591, 1148, 758, 685 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH$_3$), 1.39 (s, 3 H, CH$_3$), 2.52–2.55 (m, 1 H, H^a-2′), 2.85–2.88 (m, 1 H, H^b-2′), 2.89–2.91 (m, 1 H, H^a-6), 3.32–3.44 (m, 2 H, H^b-6, 7-H), 3.52 (s, 3 H, OCH$_3$), 4.25–4.26 (m, 1 H, 4-H), 4.28–4.33 (m, 2 H, 3a-H, 7a-H), 5.19 (s, 2 H, -CH_2-C$_6$H$_4$), 7.18 (d, J = 8.8 Hz, 2 H, ArH), 7.44 (d, J = 8.3 Hz, 2 H, ArH), 7.61 (d, J = 8.3 Hz, 2 H, ArH), 7.68 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 24.6 (CH$_3$), 25.8 (CH$_3$), 36.1 (C-2′), 42.4 (C-6), 50.1 (C-4), 51.3 (OCH$_3$), 63.8 (C-7), 68.7 (-CH_2-C$_6$H$_4$), 72.6, 73.3 (C-3a, C-7a), 108.4 (C-2) 115.5, 128.7, 129.9, 131.4 (ArCH), 121.3, 130.0, 135.7, 161.7 (ArC), 174.4 (O=C) ppm. $C_{24}H_{28}BrNO_8S$ (570.45): calcd. C 50.53, H 4.95, N 2.46; found C 50.29, H 4.83, N 2.08.

Methyl (3a*S*,4*R*,7*R*,7a*R*)-2-[Hexahydro-7-hydroxy-2,2-dimethyl-5-[4-(4-nitrobenzyloxy)phenylsulfonyl]-1,3-dioxolo[4,5-*c*]pyridin-4-yl]-acetate (16d): Following the general procedure 0.44 g (82%) of **16d** was obtained as a pale yellow solid m.p. 62–64 °C. $[\alpha]_D^{25}$ = –13.5 (c = 0.4, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3600–3400, 1732, 1591, 1151, 837, 648 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH$_3$), 1.39 (s, 3 H, CH$_3$), 2.46–2.50 (m, 1 H, H^a-2′), 2.83 (dd, J = 16.0, 7.9 Hz, 1 H, H^b-2′), 2.99 (dd, J = 13.2, 10.6 Hz, 1 H, H^a-6), 3.34–3.36 (m, 1 H, H^b-6), 3.39–3.43 (m, 1 H, 7-H), 3.53 (s, 3 H, OCH$_3$), 4.24–4.27 (m, 1 H, 4-H), 4.28–4.33 (m, 2 H, 3a-H, 7a-H), 5.39 (s, 2 H, -CH_2 -C$_6$H$_4$), 7.25 (d, J = 8.8 Hz, 2 H, ArH), 7.74–7.78 (m, 4 H,

ArH), 8.27 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 24.6 (CH_3), 25.8 (CH_3), 36.1 (C-2′), 42.4 (C-6), 50.1 (C-4), 51.3 (OCH_3), 63.8 (C-7), 68.7 (-CH_2-C_6H_4), 72.6, 73.3 (C-3a, C-7a), 108.4 (C-2) 115.5, 128.7, 129.9, 131.4 (ArCH), 121.3, 130.0, 135.7, 161.7 (ArC), 174.4 (O=C) ppm. $C_{24}H_{28}N_2O_{10}S$ (536.55): calcd. C 53.72, H 5.26, N 5.22; found C 53.38, H 4.89, N 5.12.

Methyl (3a*S*,4*R*,7*R*,7a*R*)-5-[4-(3-Chlorobenzyloxy)phenylsulfonyl]-hexahydro-7-hydroxy-2,2-dimethyl-1,3-dioxolo[4,5-*c*]piperid-4-yl]-acetate (16e): Following the general procedure 0.39 g (76%) of **16e** was obtained as white solid m.p. 65–67 °C. $[\alpha]_D^{25}$ = –16.0 (c = 0.5, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3400–3200, 1732, 1591, 1151, 682, 609 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 2.50–2.52 (m, 1 H, H^a-2′), 2.84 (dd, J = 16.2, 7.8 Hz, 1 H, H^b-2′), 2.99 (dd, J = 13.2, 10.5 Hz, 1 H, H^a-6), 3.37–3.39 (m, 1 H, H^b-6), 3.43–3.48 (m, 1 H, 7-H), 3.53 (s, 3 H, OCH_3), 4.25–4.27 (m, 1 H, 4-H), 4.28–4.33 (m, 2 H, 3a-H, 7a-H), 5.23 (s, 2 H, -CH_2-C_6H_4), 7.23 (d, J = 8.8 Hz, 2 H, ArH), 7.41–7.47 (m, 3 H, ArH), 7.45–7.56 (m, 1 H, ArH), 7.76 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 24.6 (CH_3), 25.4 (CH_3), 36.0 (C-2′), 42.3 (C-6), 50.1 (C-4), 51.3 (OCH_3), 63.9 (C-7), 68.8 (-CH_2-C_6H_4), 72.7, 73.3 (C-3a, C-7a), 108.4 (C-2), 115.5, 126.4, 127.5, 128.0, 129.1, 130.4 (ArCH), 131.1, 133.2, 138.8, 161.5 (ArC), 170.9 (O=C) ppm. $C_{24}H_{28}ClNO_8S$ (525.99): calcd. C 54.80, H 5.37, N 2.66; found C 54.73, H 5.26, N 2.54.

Methyl (3a*S*,4*R*,7*R*,7a*R*)-2-[Hexahydro-7-hydroxy-5-(4-methoxyphenylsulfonyl)-2,2-dimethyl-1,3-dioxolo[4,5-*c*]pyridin-4-yl]acetate (16f): Following the general procedure 0.33 g (80%) of **16f** was obtained as colorless viscous oil. $[\alpha]_D^{25}$ = –20.6 (c = 0.5, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3499, 1733, 1596, 1150, 805, 672 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 2.51–2.53 (m, 1 H, H^a-2′), 2.83 (dd, J = 16.3, 8.2 Hz, 1 H, H^b-2′), 2.99 (dd, J = 13.1, 10.4 Hz, 1 H, H^a-6), 3.33–3.45 (m, 2 H, H^b-6, 7-H), 3.55 (s, 3 H, CO_2CH_3), 3.86 (s, 3 H, OCH_3), 4.24–4.26 (m, 1 H, 4-H), 4.28–4.32 (m, 2 H, 3a-H, 7a-H), 5.14 (d, J = 5.3 Hz, 1 H, OH), 7.14 (d, J = 8.8 Hz, 2 H, ArH), 7.75 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 24.5 (CH_3), 25.4 (CH_3), 36.1 (C-2′), 42.4 (C-6), 50.1 (C-4), 51.3 (CO_2CH_3), 55.7 (OCH_3), 63.8 (C-7), 72.7, 73.2 (C-3a, C-7a), 108.4 (C-2), 114.7, 129.1, (ArCH), 130.6, 162.7 (ArC), 170.9 (O=C) ppm. $C_{18}H_{25}NO_8S$ (415.46): calcd. C 52.04, H 6.07, N 3.37; found C 51.75, H 5.99, N 3.18.

General Procedure for the Synthesis of [(3′a*S*,4′*R*,7′*R*,7′a*R*)-5′-(4-Arylsulfonyl)-7′-hydroxy-2′,2′-dimethyl-1′,3′-dioxolo[4,5-*c*]pyridine-4′-yl]acetohydroxamic Acid Derivatives 4a–f: A solution of 1.25 M NH_2OK (2 mL; prepared from NH_2OH·HCl and KOH as described in the literature[13]) was added dropwise to a stirred solution of the appropriate methyl ester **16a**–**f** (0.86 mmol) in methanol (4 mL). The resulting reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure and the residue was recrystallized from chloroform to give **4a**–**f**.

2-[(3′a*S*,4′*R*,7′*R*,7′a*R*)-5′-(4-Benzyloxyphenylsulfonyl)-hexahydro-7′-hydroxy-2′,2′-dimethyl-1′,3′-dioxolo[4,5-*c*]pyridin-4′-yl]acetohydroxamic Acid (4a): Following the general procedure 0.3 g (71%) of **4a** was obtained as a white solid m.p. 173–175 °C. $[\alpha]_D^{25}$ = –20.25 (c = 0.4, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3515, 3443, 1667, 1589, 1152, 704, 611 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 2.51–2.53 (m, 2 H, 2-H), 3.01 (dd, J = 14.3, 12.2 Hz, 1 H, H^a-6′), 3.28–3.35 (m, 2 H, H^b-6′, 7′-H), 4.17–4.19 (m, 1 H, 4′-H), 4.22–4.32 (m, 2 H, 3′a-H, 7′a-H), 5.02 (d, J = 5.6 Hz, 1 H, OH), 5.20 (s, 2 H, -CH_2-C_6H_5), 7.21 (d, J = 8.8 Hz, 2 H, ArH), 7.35–7.49 (m, 5 H, ArH), 7.76 (d, J = 8.8 Hz, 2 H, ArH), 8.72, 10.38 (2 s, 2 H, NH and OH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 24.6 (CH_3), 25.8 (CH_3), 34.2 (C-2), 42.6 (C-6′), 49.9 (C-4′), 63.9 (C-7′), 69.8 (-CH_2-C_6H_5), 72.9, 73.3 (C-3′a, C-7′a), 108.0 (C-2′) 115.3, 127.9, 128.1, 128.5, 129.3 (ArCH), 130.7, 136.2, 161.7 (ArC), 166.5 (O=C) ppm. ESI MS: m/z = 493.4 [M + 1]$^+$. $C_{23}H_{28}N_2O_8S$ (492.54): calcd. C 56.09, H 5.73, N 5.69; found C 55.84, H 5.33, N 5.36.

2-[(3′a*S*,4′*R*,7′*R*,7′a*R*)-Hexahydro-7′-hydroxy-2′,2′-dimethyl-5′-[4-(2-methylbenzyloxy)phenylsulfonyl]-1′,3′-dioxolo[4,5-*c*]pyridin-4′-yl-]acetohydroxamic Acid (4b): Following the general procedure 0.38 g (86%) of **4b** was obtained as a pale yellow solid m.p. 172–173 °C. $[\alpha]_D^{25}$ = –19.25 (c = 0.4, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3418, 3258, 1665, 1591, 1150, 745, 617 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 2.34 (s, 3 H, H_3C-C_6H_4), 2.51–2.53 (m, 2 H, 2-H), 3.01 (dd, J = 14.3, 12.3 Hz, 1 H, H^a-6′), 3.29–3.35 (m, 2 H, H^b-6′, 7′-H), 4.17–4.22 (m, 1 H, 4′-H), 4.23–4.33 (m, 2 H, 3′a-H, 7′a-H), 5.03 (d, J = 5.6 Hz, 1 H, OH), 5.19 (s, 2 H, -CH_2-C_6H_5), 7.23 (d, J = 8.8 Hz, 2 H, ArH), 7.26–7.27 (m, 3 H, ArH), 7.43–7.44 (m, 1 H, ArH), 7.77 (d, J = 8.8 Hz, 2 H, ArH), 8.72, 10.37 (2 s, 2 H, NH and OH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 18.4 (H_3C-C_6H_4), 24.6 (CH_3), 25.8 (CH_3), 34.2 (C-2), 42.6 (C-6′), 49.9 (C-4′), 63.9 (C-7′), 68.4 (-CH_2-C_6H_5), 72.9, 73.3 (C-3′a, C-7′a), 108.0 (C-2′), 115.3, 128.7, 129.3, 130.2 (ArCH), 130.7, 134.1, 136.7, 161.8 (ArC), 166.5 (O=C) ppm. ESI MS: m/z = 507.4 [M + 1]$^+$. $C_{24}H_{30}N_2O_8S$ (506.57): calcd. C 56.90, H 5.97, N 5.53; found C 56.83, H 5.76, N 5.28.

2-[(3′a*S*,4′*R*,7′*R*,7′a*R*)-5′-[4-(4-Bromobenzyloxy)phenylsulfonyl]-hexahydro-7′-hydroxy-2′,2′-dimethyl-1′,3′-dioxolo[4,5-*c*]pyridin-4′-yl]acetohydroxamic Acid (4c): Following the general procedure 0.35 g (71%) of **4c** was obtained as a white solid m.p. 193–194 °C. $[\alpha]_D^{25}$ = –20.75 (c = 0.4, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3509, 3247, 1645, 1589, 1153, 723, 634 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 2.50–2.53 (m, 2 H, 2-H), 3.01 (dd, J = 14.4, 12.38 Hz, 1 H, H^a-6′), 3.28–3.39 (m, 2 H, H^b-6′, 7′-H), 4.16–4.21 (m, 1 H, 4′-H), 4.22–4.36 (m, 2 H, 3′a-H, 7′a-H), 5.02 (d, J = 5.3 Hz, 1 H, OH), 5.19 (s, 2 H, -CH_2-C_6H_5), 7.20 (d, J = 8.8 Hz, 2 H, ArH), 7.45 (d, J = 8.5 Hz, 2 H, ArH), 7.62 (d, J = 8.5 Hz, 2 H, ArH), 7.76 (d, J = 8.8 Hz, 2 H, ArH), 8.71, 10.36 (2 s, 2 H, NH and OH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 24.6 (CH_3), 25.8 (CH_3), 34.2 (C-2), 42.6 (C-6′), 49.9 (C-4′), 63.9 (C-7′), 69.9 (-CH_2-C_6H_5), 72.9, 73.3 (C-3′a, C-7′a), 108.0 (C-2′), 115.3, 129.3, 130.0, 131.4 (ArCH), 121.3, 130.1, 135.7, 161.5 (ArC), 166.5 (O=C) ppm. ESI MS: m/z = 572.2 [M + 1]$^+$. $C_{23}H_{27}BrN_2O_8S$ (571.44): calcd. C 48.34, H 4.76, N 4.90; found C 47.98, H 4.69, N 4.76.

2-[(3′a*S*,4′*R*,7′*R*,7′a*R*)-Hexahydro-7′-hydroxy-2′,2′-dimethyl-5′-[4-(4-nitrobenzyloxy)phenylsulfonyl]-1′,3′-dioxolo[4,5-*c*]pyridin-4′-yl]-acetohydroxamic Acid (4d): Following the general procedure 0.36 g (77%) of **4d** was obtained as a yellow solid m.p. 138–140 °C. $[\alpha]_D^{25}$ = –23.75 (c = 0.4, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3442, 1663, 1594, 1153, 702, 647 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 2.50–2.54 (m, 2 H, 2-H), 2.97–3.03 (m, 1 H, H^a-6′), 3.27–3.33 (m, 2 H, H^b-6′, 7′-H), 4.17–4.20 (m, 1 H, 4′-H), 4.22–4.32 (m, 2 H, 3′a-H, 7′a-H), 5.03 (d, J = 5.3 Hz, 1 H, OH), 5.39 (s, 2 H, -CH_2-C_6H_5), 7.23 (d, J = 8.8 Hz, 2 H, ArH), 7.75–7.79 (m, 4 H, ArH), 8.28 (d, J = 8.8 Hz, 2 H, ArH), 8.71, 10.36 (2 s, 2 H, NH and OH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 24.6 (CH_3), 25.8 (CH_3), 34.1 (C-2), 42.5 (C-6′), 49.9 (C-4′), 63.9 (C-7′), 68.5 (-CH_2-C_6H_5), 73.0, 73.3 (C-3′a, C-7′a), 108.1 (C-2′) 115.4, 123.7, 128.4, 129.4 (ArCH), 131.1, 144.1, 147.2, 161.3 (ArC), 166.4 (O=C) ppm. ESI MS: m/z = 538.3 [M + 1]$^+$. $C_{23}H_{27}N_3O_{10}S$ (537.54): calcd. C 51.39, H 5.06, N 7.82; found C 51.01, H 4.87, N 7.56.

2-[(3′a*S*,4′*R*,7′*R*,7′a*R*)-5′-[4-(3-Chlorobenzyloxy)phenylsulfonyl]-7′-hydroxy-2′,2′-dimethyl-1′,3′-dioxolo[4,5-*c*]pyridin-4′-yl]acetohydroxamic Acid (4e): Following the general procedure 0.39 g (85%) of **4e** was obtained as a white solid m.p. 174–175 °C. $[\alpha]_D^{25}$ = –23.25 (*c* = 0.4, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3445, 3280, 1661, 1593, 1151, 681, 614 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 2.50–2.52 (m, 2 H, 2-H), 3.01 (dd, *J* = 14.3, 12.3 Hz, 1 H, H^a-6′), 3.28–3.32 (m, 2 H, H^b-6′, 7′-H), 4.17–4.19 (m, 1 H, 4′-H), 4.21–4.32 (m, 2 H, 3′a-H, 7′a-H), 5.02 (d, *J* = 5.0 Hz, 1 H, OH), 5.22 (s, 2 H, -CH_2-C$_6$H$_5$), 7.22 (d, *J* = 8.8 Hz, 2 H, ArH), 7.41–7.46 (m, 3 H, ArH), 7.55–7.59 (m, 1 H, ArH), 7.77 (d, *J* = 8.8 Hz, 2 H, ArH), 8.71, 10.36 (2 s, 2 H, NH and OH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 24.6 (CH_3), 25.8 (CH_3), 34.2 (C-2), 42.6 (C-6′), 49.9 (C-4′), 63.9 (C-7′), 68.8 (-CH_2-C$_6$H$_5$), 72.9, 73.3 (C-3′a, C-7′a), 108.0 (C-2′), 115.3, 126.4, 127.6, 128.0, 129.4, 130.4 (ArCH), 130.9, 133.1, 138.8, 161.5 (ArC), 166.5 (O=C) ppm. ESI MS: *m*/*z* = 527.3 [M + 1]$^+$. $C_{23}H_{27}ClN_2O_8S$ (526.99): calcd. C 52.42, H 5.16, N 5.32; found C 52.08, H 5.09, N 5.29.

2-[(3′a*S*,4′*R*,7′*R*,7′a*R*)-Hexahydro-7′-hydroxy-5′-(4-methoxyphenylsulfonyl)-2′,2′-dimethyl-1′,3′-dioxolo[4,5-*c*]pyridin-4′-yl]acetohydroxamic Acid (4f): Following the general procedure 0.22 g (61%) of **4f** was obtained as colorless solid m.p. 149–151 °C. $[\alpha]_D^{25}$ = –27.0 (*c* = 0.4, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3441, 3240, 1672, 1596, 1153, 673 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 1.25 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 2.50–2.52 (m, 2 H, 2-H), 2.99 (dd, *J* = 14.2, 12.1 Hz, 1 H, H^a-6′), 3.27–3.31 (m, 2 H, H^b-6′, 7′-H), 3.86 (s, 3 H, OCH_3), 4.15–4.21 (m, 1 H, 4′-H), 4.22–4.32 (m, 2 H, 3′a-H, 7′a-H), 5.02 (br. s, 1 H, OH), 7.13 (d, *J* = 8.8 Hz, 2 H, ArH), 7.75 (d, *J* = 8.8 Hz, 2 H, ArH), 8.73, 10.35 (2 s, 2 H, NH and OH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 24.6 (CH_3), 25.8 (CH_3), 34.2 (C-2), 42.6 (C-6′), 49.9 (C-4′), 55.7 (OCH_3), 63.9 (C-7′), 72.9, 73.3 (C-3′a, C-7′a), 108.0 (C-2′), 114.6, 129.3, (ArCH), 130.5, 162.6 (ArC), 166.5 (O=C) ppm. ESI MS: *m*/*z* = 417.4 [M + 1]$^+$. $C_{17}H_{24}N_2O_8S$ (416.45): calcd. C 49.03, H 5.81, N 6.73; found C 48.78, H 5.54, N 6.54.

2-[(3′a*S*,4′*R*,7′*R*,7′a*R*)-Hexahydro-7′-hydroxy-5′-(4-hydroxyphenylsulfonyl)-2′,2′-dimethyl-1′,3′-dioxolo[4,5-*c*]pyridin-4′-yl]acetohydroxamic Acid (4g): To a stirred solution of **4d** (0.22 g, 0.41 mmol) in methanol (10 mL) was added 10% Pd/C (0.13 g). The reaction mixture was hydrogenated under normal pressure of H_2 at room temperature for 2 h. The catalyst was removed by filtration and the solvent was evaporated under vacuum. The residue was recrystallized from chloroform to afford 0.11 g (67%) of **4g** as a white solid m.p. 131–132 °C. $[\alpha]_D^{25}$ = –20.0 (*c* = 0.4, MeOH). FT-IR (ATR): $\tilde{\nu}$ = 3400–3350, 1652, 1584, 1151, 679 cm^{-1}. ^1H NMR ([D$_6$]-DMSO): δ = 1.16 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 2.51–2.54 (m, 2 H, 2-H), 2.88 (dd, *J* = 11.5, 9.7 Hz, 1 H, H^a-6′), 3.14–3.21 (m, 2 H, H^b-6′, 7′-H), 4.01–4.05 (m, 1 H, 4′-H), 4.13–4.23 (m, 2 H, 3′a-H, 7′a-H), 6.74 (d, *J* = 8.8 Hz, 2 H, ArH), 7.47 (d, *J* = 8.8 Hz, 2 H, ArH), 8.23, 9.85 (2 s, 2 H, NH and OH) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 24.5 (CH_3), 25.8 (CH_3), 34.3 (C-2), 42.7 (C-6′), 49.6 (C-4′), 63.8 (C-7′), 72.9, 73.4 (C-3′a, C-7′a), 107.8 (C-2′), 116.3, 129.4, (ArCH), 125.7, 164.5 (ArC), 166.6 (O=C) ppm. ESI MS: *m*/*z* = 403.3 [M + 1]$^+$. $C_{16}H_{22}N_2O_8S$ (402.42): calcd. C 47.75, H 5.51, N 6.96; found C 47.46, H 5.37, N 6.60.

Acknowledgments

We thank Dipl.-Chem. S. Ries for help in the preparation of starting materials. We also thank Dr. M. Unger and A. Frank for MS (ESI) analyses and TauroPharm GmbH for financial support. We express our gratitude to Mrs. A. Betz for technical assistance.

[1] S. K. Moestrup, H. J. Moller, *Ann. Med.* **2004**, *36*, 347–354.
[2] N. Matsushita, M. Kashiwagi, R. Wait, R. Nagayoshi, M. Nakamura, T. Matsuda, P. Högger, P. M. Guyre, H. Nagase, T. Matsuyama, *Clin. Exp. Immunol.* **2002**, *130*, 156–161.
[3] M. Timmermann, P. Högger, *Free Radical Biol. Med.* **2005**, *39*, 98–107.
[4] a) M. A. Letavic, M. Z. Axt, J. T. Barberia, T. J. Carty, D. E. Danley, K. F. Geoghegan, N. S. Halim, L. R. Hoth, A. V. Kamath, E. R. Laird, L. L. Lopresti-Morrow, K. F. McClure, P. G. Mitchell, V. Natarajan, M. C. Noe, J. Pandit, L. Reeves, G. K. Schulte, S. L. Snow, F. J. Sweeney, D. H. Tan, C. H. Yu, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1387–1390; b) H. Moriyama, T. Tuskida, Y. Inoue, H. Kondo, K. Yoshino, S.-I. Nishimura, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2741–2744; c) H. Moriyama, T. Tsukida, Y. Inoue, H. Kondo, K. Yoshino, S.-I. Nishimura, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2737–2740.
[5] C. Herdeis, T. Schiffer, *Tetrahedron* **1996**, *52*, 14745–14756.
[6] N. A. Hughes, P. R. H. Speakman, *Carbohydr. Res.* **1965**, *1*, 171–175.
[7] D. H. R. Barton, J. Camara, X. Cheng, S. D. Géro, J. C. Jaszberenyi, B. Quiclet-Sire, *Tetrahedron* **1992**, *48*, 9261–9276.
[8] E. V. Carstensen, H. I. Duynstee, G. A. van der Marel, J. H. van Boom, J. Nielsen, H. S. Overkleeft, M. Overhand, *J. Carbohydr. Chem.* **2003**, *22*, 241–252.
[9] A. D. Gribble, I. T. Forbes, A. Lightfoot, A. H. Payne and D. G. Cooper, WO Patent 095428, 2003, *Chem. Abstr.* **2003**, *139*, 395835.
[10] S. Fabre-Lafay, S. Garrido-Urbani, N. Reymond, A. Goncalves, P. Dubreuil, M. Lopez, *J. Biol. Chem.* **2005**, *280*, 19543–19550.
[11] E. Toja, C. Gorini, C. Zirotti, F. Barzaghi, G. Galliani, *Eur. J. Med. Chem.* **1991**, *26*, 403–413.
[12] M. S. Morgan, L. H. Cretcher, *J. Am. Chem. Soc.* **1948**, *70*, 375–378.
[13] C. R. Hauser, W. B. Renfrow, Jr., *Org. Synth., Coll. Vol.* **1943**, *2*, 67–68.

Received: February 27, 2007
Published Online: June 8, 2007

