The Synthesis and Human FP Receptor Binding Affinity of 13,14-Dihydro Prostaglandin $F_{1\alpha}$ Sulfonamides: Potential Treatments for Osteoporosis

Yili WANG, David L. SOPER, Michelle J. DIRR, Mitchell A. DELONG, Biswanath DE, and John A. WOS*

Procter and Gamble Pharmaceuticals, 8700 Mason-Montgomery Rd, Mason, OH 45040–8006.
Received May 18, 2000; accepted June 15, 2000

A novel class of saturated prostaglandin $F_{2\alpha}$ sulfonamide analogs have been synthesized and evaluated in the human FP receptor binding assay for potential use in the treatment of osteoporosis. These compounds have been modified at the C_1 carboxylic acid moiety and at the C_{16}—C_{20} region of the prostaglandin. Based on the structure–activity relationships, it was found that at C_1, the aryl sulfonamide analogs possessed greater affinity for the hFP receptor when compared to alkyl sulfonamides. When the sulfonamide was introduced into the C_{16}—C_{20} region (omega chain) of the prostaglandin, a significant reduction in binding was observed. These results are discussed within the framework of a proposed model for the human FP receptor.

Key words osteoporosis; 13,14 dihydro $PGF_{1\alpha}$; sulfonamide; Sulprostone

Prostaglandins of the E-family and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) are potent, naturally occurring hormones produced locally upon demand by various stimuli and have been implicated in a myriad of physiological processes, including the growth of new bone in animal models.[1] By design, they are short-lived, and are inactivated rapidly by a variety of chemical and metabolic pathways.[2] As therapeutic agents, their success has been limited primarily due to metabolic instability and a side-effect profile resulting from the indiscriminant binding of individual ligands to multiple receptors. However, with the recent cloning and expression of the individual prostaglandin receptors,[3] the tools are now available to design and synthesize potent prostaglandin agonists and antagonists which may potentially possess enhanced therapeutic benefits based on a greater receptor and/or tissue specificity.

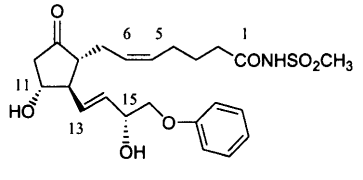
During the course of our work on identifying novel bone anabolic agents for the treatment of osteoporosis, we have recently discovered a family of saturated prostaglandin F ligands, the 13,14-dihydro prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$) class, which have proven to be potent and selective agonists for the human FP receptor,[4] and bone anabolic agents *in vivo* in the ovariectomized rat model.[5] In an effort to further our understanding of how prostaglandin structure relates to hFP receptor binding affinity and potential anabolic effect in this series, we explored the use of the sulfonamide moiety in the 13,14 dihydro $PGF_{1\alpha}$ skeleton. This concept is based on previous work in the prostaglandin-E family describing the therapeutic benefits of sulfonamide incorporation; the end result being the fertility control agent Sulprostone (**1**) (Fig. 1).[6] As there is currently no data available on the binding affinity of sulfonamide analogs to any of the individual human prostaglandin receptors,[7] (the earlier Sulprostone work involved animal tissue preparations) we subsequently synthesized a series of 13,14-dihydro $PGF_{1\alpha}$ sulfonamides and screened them at the human FP receptor in a preliminary attempt to better our understanding of the relationship between sulfonamide structure and receptor binding affinity.

Chemistry We focused our efforts for sulfonamide incorporation in two areas of the molecules, the C_1 carboxylic acid of the alpha chain, and the C_{16}—C_{20} region of the omega "tail" of the prostaglandin. For sulfonamide replacement at C_1 we chose the more potent 17-thiophenyl and 17-aminophenyl omega "tails", based on previous work done on the parent carboxylic acid series.[8] Accordingly, the 17-thiophenyl and 17-aminophenyl groups were incorporated into the 13,14-dihydro $PGF_{1\alpha}$ skeleton from the epoxide (**2**) and then converted to the appropriate sulfonamides as outlined in Chart 1.

The epoxide (**2**)[8] was ring-opened with the appropriate thiol or aniline under either basic or Lewis acid conditions[9] to provide, after silylation, the tris-*tert*-butyldimethylsilyl ether (**3**) as a 1 : 1 mixture of diastereomers at C_{15}. The ester was cleaved with base under mild conditions to provide the free acid, which was activated for nucleophilic displacement as the mixed anhydride[10] and then condensed with the appropriate sulfonamide[11] to provide the intermediate (**4**). The final desilylation step was performed with hydrogen fluoride/pyridine to provide the desired sulfonamide (**5**). Careful monitoring of the reaction by TLC was critical in this step, as slow decomposition of the sulfonamide was noted with prolonged reaction times under these conditions. Attempts to separate the C_{15} diastereomers using conventional flash chromatography were unsuccessful and the compounds were tested as the mixture.

For analogs in which the sulfonamide was incorporated in to the C_{16}—C_{20} region (tail), we concentrated on the aryl sulfonamide series, based on the earlier precedent of increased binding affinity for the human FP receptor with the 13,14 dihydro-16-aryl $PGF_{1\alpha}$ skeleton *versus* the aliphatic counterpart.[12] The synthesis of these compounds is outlined in Chart 2.

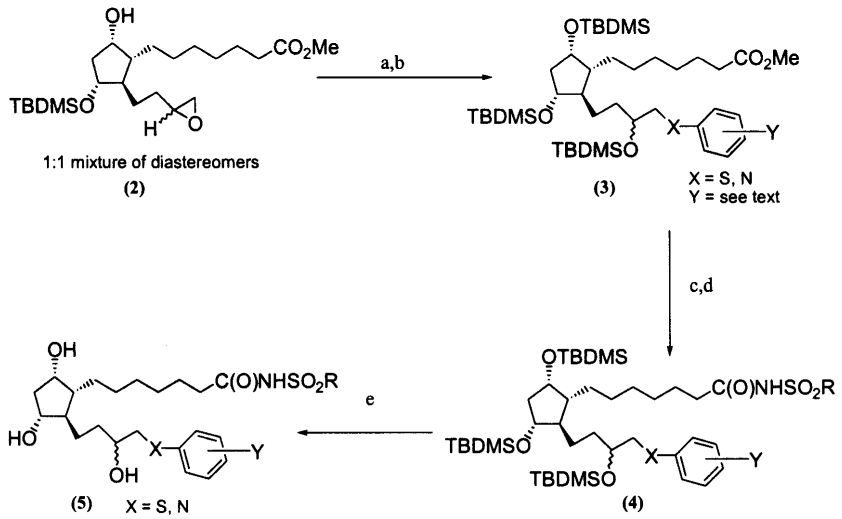
The epoxide intermediate (**6**) was opened regioselectively with sodium azide and then protected with *tert*-butyldimethylsilyltrifluoromethanesulfonate[13] to give (**7**). The



(1) Sulprostone

Fig. 1

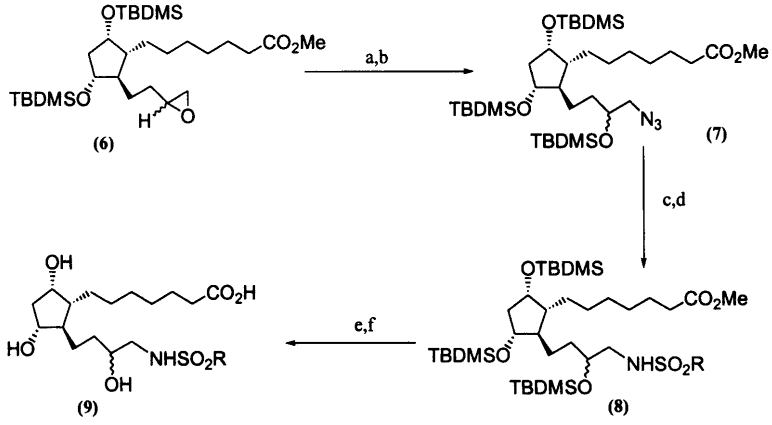
* To whom correspondence should be addressed. e-mail: wos.ja@pg.com



Key:

a) Et_3N, thiophenol or $Mg(ClO_4)_2$, aniline b)TBDMSOTf, 2,6-Lutidine, 75% c) LiOH, THF/H_2O, 74 % d) CDI, THF, DBU, RSO_2NH_2, 35-70% e) HF/pyridine, 30-90 %

Chart 1



Key:

a)NaN_3, $Mg(ClO_4)_2$, CH_3CN, 48% b)TBDMSOTf, 2,6-Lutidine, 75% c)Ph_3P, THF/H_2O, 77 % d) RSO_2Cl, Et_3N, 80% e) HF/pyridine, 90% f) LiOH, THF/H_2O, 10-50 %

Chart 2

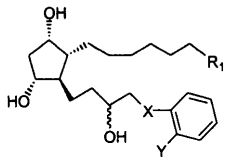
azide was reduced to the amine,[14] and then sulfonylated under standard conditions to provide the protected sulfonamide (**8**). The product was then desilylated to give the triol, which was saponified to provide the omega-chain sulfonamide (**9**).

Results and Discussion

The binding affinity at the human FP receptor for the C_1 sulfonamides is shown in Table 1. The compounds were evaluated for their ability to displace radiolabeled $PGF_{2\alpha}$ in membrane preparations isolated from COS-7 cells transiently transfected with hFP prostaglandin membrane. Data analysis was done on Graph Pad Prism (ver. 3.0) and the resulting IC_{50} values provide a measure of the relative affinity of the compounds for the hFP receptor in the presence of [^{3}H] $PGF_{2\alpha}$ (Fig. 2, see experimental section for details).

Several observations can be made based on the SAR of the sulfonamide substitution at C_1. For alkyl sulfonamides (**10**—

Table 1. Human FP Receptor Binding Data For C_1 Sulfonamides



Compd.	X	Y	R_1	IC_{50} hFP (nM)
1	Sulprostone		$C(O)NHSO_2CH_3$	—
10	S	H	$C(O)NHSO_2CH_3$	1400
11	NH	*o*-F	$C(O)NHSO_2CH_3$	2700
12	S	*o*-F	$C(O)NHSO_2CH_3$	1200
13	S	H	$C(O)NHSO_2CH_2CH_3$	1400
14	S	H	$C(O)NHSO_2CH(CH_3)_2$	1500
15	S	H	$C(O)NHSO_2Ph$	120
16	S	*o*-F	$C(O)NHSO_2Ph$	185
17	NH	*o*-F	$C(O)NHSO_2Ph$	550
18	S	*o*-F	$C(O)NHSO_2$·4-(Me)-Ph	$>10^4$
19	S	*o*-F	$C(O)NHSO_2$·4-(F)-Ph	1600

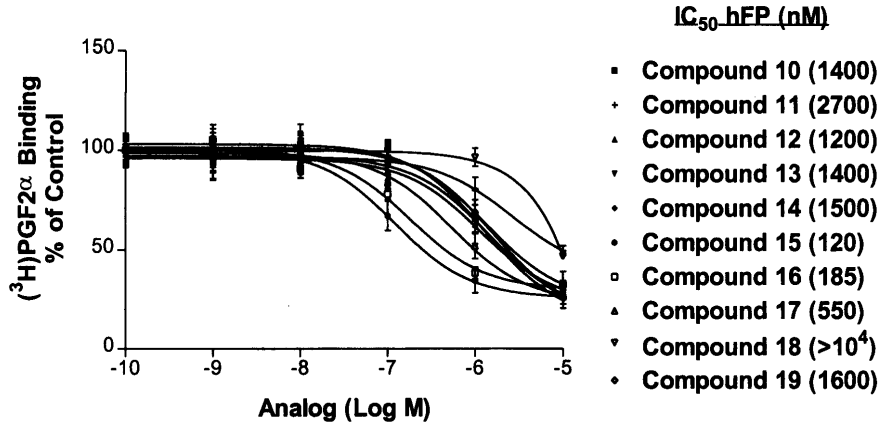


Fig. 2. Binding Affinity of Compounds **10**—**19** at the human FP Receptor

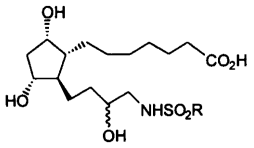
14), there seems to be only a slight apparent difference in binding affinity for the human FP receptor as the size of the alkyl group increases. When the alkyl group is replaced with an aryl group, however, a 10× increase in binding affinity is seen (**10** *vs.* **15**). This result suggests that the steric environment at the C_1 pocket in the human FP receptor can accommodate rather bulky substituents, and that binding affinity may be a function more of differences in sulfonamide acidity at C_1 (aromatic *vs.* aliphatic) rather than in the steric environment at the receptor binding site. This trend seemed to follow in comparing compounds (**11**) *vs.* (**17**) and (**12**) *vs.* (**16**). It is also interesting to note the loss of binding affinity in compound (**18**) (*p*-tolyl), in which the additional steric bulk of the *p*-methyl group may influence binding to a much greater degree, especially when compared to the analog (**19**) in which a fluorine atom (isosteric with H) is substituted at the same position. The phenyl sulfonamides (**15**) and (**16**) showed the best potency of all the compounds tested at 120 and 185 nM, respectively.

In the examples in which the sulfonamide was incorporated into the omega-chain of the prostaglandin, we saw a significant loss in binding affinity to the human FP receptor in all cases (Table 2). These results may be rationalized in terms of a putative human FP receptor model[8] in which the omega-tail of the ligand is residing in a hydrophobic cleft in the receptor populated with aromatic amino acid residues, resulting in a greater binding affinity for 13,14-dihydro $PGF_{1\alpha}$ analogs which possess aromatic rings in the "tail" position. In the case of ligands **20**—**24**, the incorporation of the more polar, hydrophilic sulfonamide moiety may result in a perturbation of binding at this site and loss of binding affinity.

Conclusions

We have designed and synthesized a novel series of sulfonamide analogs of the 13,14 dihydro $PGF_{1\alpha}$ skeleton and have evaluated them for the first time in a human FP receptor binding assay. We have found that when the sulfonamide substitution is at C_1, aryl sulfonamides provided better binding (nanomolar) than the alkyl counterparts (micromolar), suggesting that the steric environment of the C_1 pocket in the hFP receptor can accommodate rather large substituents, and that the p*K*a of the C_1 substituent may play a critical role in binding of the ligand to the receptor. In addition, we have also found that when the sulfonamide is incorporated into the C_{16}—C_{20} region (omega-tail) of the 13,14-dihydro $PGF_{1\alpha}$ prostaglandin skeleton, there is a substantial loss of binding at the human FP receptor, which is in keeping with our previously proposed receptor binding model for ligands of this type. As pharmacokinetics and metabolism have dramatic effects on prostaglandin efficacy *in vivo*, we are continuing to evaluate the potential stability and selectivity advantages of the most potent of these sulfonamide compounds in the ovariectomized rat model (OVX); the results of which will be reported in due course.

Table 2. Human FP Receptor Binding Data For Omega-Chain Sulfonamides



Compound	R	IC_{50} hFP (nM)
20	Ph	3800
21	*m*-F Ph	6700
22	2,4-difluoro Ph	$>10^4$
23	*p*-F Ph	$>10^4$
24	*o*-F Ph	$>10^4$

Experimental

General Methods: ^{1}H-NMR spectra were recorded on a Varian Unity Plus 300 MHz spectrometer and are referenced to either the deuteriochloroform singlet at 7.27 ppm or deuteriomethanol singlet at 4.87 ppm. ^{13}C spectra were obtained on a Varian Unity Plus 300 MHz spectrometer and are referenced at either the center line of the deuteriochloroform triplet at 77.0 ppm or the deuteriomethanol heptet at 49.15 ppm. Infrared absorption spectra were obtained on a Perkin-Elmer Model 197 spectrophotometer and are referenced to polystyrene (1601 cm^{-1}). Mass spectra were obtained on either a Fison Platform-II Quadrupole Mass Spectrometer or a Fison Trio2000 Quadrupole Mass Spectrometer. High Resolution Mass Spectra were obtained from the Procter & Gamble CRD Mass Spectrometry Lab (M. Lacey) or at the Nebraska Center for Mass Spectrometry. Elemental analysis were obtained from the Procter & Gamble EA Lab in Norwich, NY. Melting points were determined in open Pyrex capillary tubes on a Thomas-Hover Unimelt apparatus. Melting points and boiling points are uncorrected. All solvents were purchased anhydrous (Aldrich Chemical) and used without further purification. All air-sensitive reactions were performed under an anhydrous nitrogen atmosphere. Flash chromatography was performed on silica gel (70—230 mesh; Aldrich) or (230—400 mesh; Merck) as appropriate. Thin layer chromatography analysis was performed on glass mounted silica gel plates (200—300 mesh; Baker) and visualized using UV, 5% phosphomolybdic acid in EtOH, or ammonium molybdate/cerric sulfate in 10% aqueous H_2SO_4.

Radioligand Binding Assay COS-7 cells were transiently transfected with a hFP recombinant plasmid using LipofectAMINE Reagent. Forty-eight hours later, the transfected cells were washed with Hanks' Balanced Salt Solution (HBSS, without $CaCl_2$, $MgCl_2$, $MgSO_4$, or phenol red). The cells were detached with versene, and HBSS was added. The mixture was centrifuged at 200 ***g*** for 10 min, at 4 °C to pellet the cells. The pellet was re-suspended in phosphate-buffered saline–EDTA buffer (PBS; 1 mM EDTA; pH 7.4; 4 °C). The cells were disrupted by nitrogen cavitation (Parr model 4639), at 800 psi, for 15 min at 4 °C. The mixture was centrifuged at 1000 ***g*** for 10 min at 4 °C. The supernatant was centrifuged at 100000 ***g*** for 60 min at 4 °C. The pellet was resuspended to 1 mg protein/ml TME buffer (50 mM Tris; 10 mM $MgCl_2$; 1 mM EDTA; pH 6.0; 4 °C) based on protein levels measured using the Pierce BCA Protein Assay kit. The homogenate was mixed using a Kinematica Polytron for 10 s. The membrane preparations were then stored at −80 °C, until thawed for assay use.

The receptor competition binding assays were developed in a 96 well format. Each well (n=3) contained 100 μg of hFP membrane, 5 nM [^{3}H] $PGF_{2\alpha}$, and the various competing compounds in a total volume of 200 μl. The plates were incubated at 23 °C for 1 h. The incubation was terminated by rapid filtration using the Packard Filtermate 196 harvester through Packard UniFilter GF/B filters that were pre-wetted with TME buffer. The filter was washed four times with TME buffer. Packard Microscint 20, a high efficiency liquid scintillation cocktail, was added to the filter plate wells and the plates remained at room temperature for three hours prior to counting. The plates were read on the Packard TopCount Microplate Scintillation Counter.

General Procedure for Compounds 10—19: Synthesis of *N*-(7-{2-[4-(2-Fluoro-phenylsulfanyl)-3-hydroxy-butyl]-3,5-dihydroxy-cyclopentyl}-heptanoyl)-methanesulfonamide (12) To a solution of the tris-protected starting material (**3**) (X=S, Y=*o*-F) (1.89 g, 2.4 mol) in THF (15 ml) and H_2O (5 ml) at room temperature was added LiOH (1.5 eq) and the resulting mixture was stirred overnight. The reaction mixture was poured onto saturated citric acid solution, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×50 ml), and the organic layers were combined. The combined CH_2Cl_2 extracts were washed with saturated NaCl, dried with Na_2SO_4, concentrated, and purified by flash chromatography (95% CH_2Cl_2/MeOH) to afford 1.35 g (74%) of the free acid. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.05—0.10 (m, 18H), 0.90—0.93 (m, 27H), 1.14—1.83 (m, 17H), 2.10—2.19 (m, 1H), 2.31—2.37 (t, 2H, J=10.5 Hz), 2.94—3.08 (m, 2H), 3.80—3.84 (m, 2H), 4.08—4.09 (m, 1H), 7.03—7.09 (m, 2H), 7.18—7.25 (m, 1H), 7.39—7.44 (dt, 1H, J=1.5, 7.5 Hz); MS (+ES) *m/z* (relative intensity): 771 ($M+H^+$, 50), 788 ($M+NH_4^+$, 100).

A solution of the acid (X=S, Y=*o*-F) (0.3 mmol) in dry THF (3 ml) was added dropwise to as stirred solution of carbonyldiimidazole (0.33 mmol) in dry THF (2 ml) under nitrogen. The reaction was stirred 30 min at room temperature, refluxed 30 min, and then allowed to cool to room temperature again. The methanesulfonamide (0.3 mmol) was added in one portion and the reaction was stirred for 10 min before a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.3 mmol) in dry THF (2 ml) was added dropwise. The reaction was stirred overnight, then poured into 1 N HCl (50 ml). The aqueous layer was extracted with CH_2Cl_2 (3×50 ml), and the organic layers were combined. The organic layer was then washed (sat. $NaHCO_3$, then sat. NaCl), dried with Na_2SO_4 and concentrated. Purification *via* flash chromatography on SiO_2 (0.4%MeOH/CH_2Cl_2) gave 81 mg (32%) of product (**4**) (X=S, Y=*o*-F, R=CH_3) as an oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.03—0.06 (m, 18H), 0.88—0.89 (m, 27H), 1.23—1.76 (m, 17H), 2.03—2.16 (m, 1H), 2.31—2.26 (t, J=7.5 MHz, 2H), 2.92—3.05 (m, 2H), 3.31 (s, 3H), 3.76—3.78 (m, 2H), 4.05—4.06 (m, 1H), 7.03—7.11 (m, 2H), 7.18—7.29 (m, 1H), 7.37—7.42 (dt, J=1.5, 7.8 MHz, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: −4.8, −4.5, −4.4, −4.3, −4.2, −3.9, −3.8, −3.7, 18.1, 18.2, 24.7, 26.1, 26.6, 25.7, 27.6, 28.0, 29.4, 30.1, 33.4, 33.5, 36.7, 40.6, 41.7, 44.7, 48.1, 50.1, 50.3, 72.0, 72.1, 72.3, 76.9, 76.9, 77.3, 77.7, 115.7, 116.0, 123.9, 124.1, 124.6, 124.7, 128.3, 128.4, 132.2, 132.3, 159.9, 161.0, 163.2, 167.2, 172.5; ^{19}F-NMR ($CDCl_3$), 57.5, 57.5, 57.5, 57.582, 57.617; MS (+ES) *m/z* (relative intensity): 848 ($M+H^+$, 5), 865 ($M+NH_4^+$, 100).

A solution of protected sulfonamide (**4**) (0.197 mmol, 167 mg) in CH_3CN (2 ml) was treated with 0.3 ml HF/pyridine solution at 0 °C under nitrogen. The reaction was stirred at 0 °C for 5 h, then another 0.15 ml of HF/pyridine was added. The reaction was stirred at 0 °C for an additional 3 h. The reaction mixture was poured onto sat. $NaHCO_3$/CH_2Cl_2 solution, extracted with CH_2Cl_2 (3×50 ml), combined, and washed with sat. NaCl. After drying over Na_2SO_4 and concentrating, the residue was chromatographed on silica gel (95% CH_2Cl_2/MeOH) to give 75 mg (78%) of the final product, *N*-(7-{2-[4-(2-fluoro-phenylsulfanyl)-3-hydroxy-butyl]-3,5-dihydroxy-cyclopentyl}-heptanoyl)-methanesulfonamide (**12**). ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.33—1.92 (m, 21H), 2.29—2.34 (t, 2H), 2.86—2.93 (dd, J=8.2, 13.5 Hz, 1H), 3.07—3.12 (dd, J=3.3, 13.2 Hz, 1H), 3.27 (s, 3H), 3.68—3.69 (m, 1H), 3.96 (s, 1H), 4.16 (s, 1H), 7.03—7.13 (m, 2H), 7.21—7.26 (m, 1H), 7.40—7.46 (dt, J=1.8, 7.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) 24.5, 28.0, 28.7, 28.9, 29.5, 29.6, 30.12, 34.3, 34.5, 36.67, 41.6, 41.8, 42.7, 51.6, 52.6, 52.9, 70.1, 70.4, 74.6, 78.4, 78.7, 115.9, 116.2, 122.3, 122.5, 129.2, 129.3, 133.1, 160.2, 163.5, 173.5; ^{19}F-NMR ($CDCl_3$,) 57.9, 57.9, 57.8, 57.8, 57.8; MS (+AP) *m/z* (relative intensity) 505 ($M+H^+$, 5), 528 (M+Na, 20); HRMS Calcd for $C_{23}H_{36}O_6S_2NF$ ($M+H^+$): 506.2046. Found: 506.2052. Compounds **10**, **11** and **13—19** were prepared in a similar fashion:

N-(7-{2-[4-(2-Fluoro-phenylsulfanyl)-3-hydroxy-butyl]-3,5-dihydroxy-cyclopentyl}-heptanoyl)-benzenesulfonamide (**16**): 73% ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.21—1.87 (m, 22H), 2.19 (t, 2H, J=7.2 Hz), 2.86—2.93 (dd, 1H, J=8.1, 13.2 Hz), 3.69—3.70 (m, 1H), 3.97 (s, 1H), 4.16 (s, 1H), 7.02—7.11 (m, 2H), 7.10—7.26 (m, 1H), 7.02—7.11 (m, 2H), 7.19—7.26 (m, 1H), 7.39—7.44 (dt, J=1.8, 7.8 Hz), 7.48—7.51 (dd, J=7.2, 7.8 Hz, 2H), 7.58—7.63 (m, 1H), 8.03—8.06 (d, J=7.2 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: 24.4, 28.0, 28.6, 28.9, 29.4, 29.7, 30.2, 34.4, 34.5, 36.4, 41.6, 41.8, 42.7, 51.7, 52.6, 52.9, 70.1, 70.5, 74.6, 78.4, 78.7, 115.9, 116.2, 122.3, 122.5, 124.9, 128.4, 129.1, 133.1, 133.9, 139.1, 160.2, 163.5, 172.3; ^{19}F-NMR ($CDCl_3$) 57.9; MS (+AP) *m/z* (relative intensity): 567 ($M+H^+$, 20), 590 ($M+Na^+$, 40); HRMS Calcd for $C_{28}H_{38}O_6S_2NF$ ($M+Na^+$): 590.2022. Found: 590.2008.

N-(7-[3,5-Dihydroxy-2-(3-hydroxy-4-phenylsulfanyl-butyl)-cyclopentyl]-heptanoyl}-methanesulfonamide (**10**): 62% ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.28—1.88 (m, 18H), 2.31—2.36 (t, J=7.5 Hz, 2H), 2.90—2.96 (dd, 1H, J=8.4 Hz, 13.5 MHz), 3.12—3.17 (dd, 1H, J=2.7, 13.5 Hz), 3.27 (s, 3H), 3.67—3.79 (m, 1H), 3.99 (s, 1H), 4.18 (s, 1H), 7.22—7.24 (m, 1H), 7.28—7.33 (ddd, 2H, J=2.1, 6.9, 7.8 Hz), 7.38—7.41 (dd, 2H, J=1.8, 6.9 Hz); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: 24.5, 27.9, 28.7, 28.9, 29.4, 29.7, 30.3, 34.5, 34.6, 36.6, 41.6, 41.9, 42.3, 42.5, 42.7 51.8, 51.9 52.7, 53.0, 69.9, 70.3, 74.7, 78.4, 78.7, 126.1, 129.3, 130.1, 135.6, 173.4; MS (+ES) *m/z* (relative intensity): 470 (M^+-H_2O, 100), 488 ($M+H^+$, 40), 505 ($M+NH_4^+$, 50), 510 ($M+Na^+$, 30); HRMS Calcd for $C_{23}H_{37}O_6S_2N$ ($M+Na^+$): 510.1960. Found: 510.1985.

N-(7-[3,5-Dihydroxy-2-(3-hydroxy-4-phenylsulfanyl-butyl)-cyclopentyl]-heptanoyl}-benzenesulfonamide (**15**): 44% ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.23—1.89 (m, 27H), 2.20—2.25 (t, 2H, J=7.5 Hz), 2.89—2.97 (dd, 1H, J=8.4, 13.5 Hz), 3.11—3.17 (dd, 1H, J=3.3, 13.5 Hz), 3.74 (m, 1H), 3.99 (br s, 1H), 4.17 (br s, 1H), 7.18—7.22 (dd, 1H, J=7.2, 7.2 Hz), 7.26—7.31 (dd, 2H, J=7.2, 7.5 Hz), 7.36—7.39 (d, 2H, J=7.5 Hz), 7.49—7.54 (dd, 2H, J=7.5, 7.8 Hz), 7.59—7.64 (dd, 1H, J=7.2, 7.5 Hz), 8.05—8.07 (d, 2H, J=7.5 Hz), 9.99 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: 24.4, 28.049, 29.0, 29.8, 30.3, 34.5, 34.6, 36.4, 41.9, 42.2, 42.6, 42.7, 51.7, 51.8, 52.8, 53.0, 69.9, 70.3, 74.7, 78.5, 78.8, 126.8, 128.5, 129.2, 129.3, 130.0, 134.0, 135.6, 139.1, 171.9; MS (+ES) *m/z* (relative intensity): 567 ($M+NH_4^+$, 30); HRMS Calcd for $C_{28}H_{39}O_6S_2N$ ($M+Na^+$): 572.2117. Found: 572.2138.

N-(7-{2-[4-(2-Fluoro-phenylsulfanyl)-3-hydroxy-butyl]-3,5-dihydroxy-cyclopentyl}-heptanoyl)-4-methyl-benzenesulfonamide (**18**): 90% ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.21—1.87 (m, 22H), 2.18—2.23 (t, 2H, J=6.9 Hz), 2.39 (s, 3H), 2.87—2.94 (dd, 1H, J=8.1, 13.2 Hz), 3.05—3.11 (dd, 1H, J=3.6, 13.2 Hz), 3.69 (br s, 1H), 3.97 (br s, 1H), 4.14 (br s, 1H), 7.01—7.09 (m, 2H), 7.18—7.25 (m, 1H), 7.27—7.30 (d, 2H, J=8.1 Hz), 7.38—7.43 (t, 1H, J=7.5 Hz), 7.90—7.93 (d, 2H, J=8.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 21.9, 24.4, 28.1, 28.8, 28.9, 29.5, 30.1, 34.4, 36.4, 41.7, 42.6, 51.3, 52.6, 70.5, 74.5, 76.9, 77.4, 77.8, 78.5, 115.9, 116.2, 122.5, 122.7, 124.9, 125.0, 128.5, 129.1, 129.2, 129.8, 132.9, 136.2, 145.0, 160.2, 163.4, 172.3; MS (+ES) *m/z* (relative intensity): 546 (M^+-2H_2O, 40), 564 (M^+-H_2O, 90), 582 ($M+H^+$, 90), 599 ($M+NH_4^+$, 100); HRMS Calcd for $C_{29}H_{40}NO_6FS_2$ ($M+Na^+$): 604.2179. Found: 604.2186.

N-(7-{2-[4-(2-Fluoro-phenylsulfanyl)-3-hydroxy-butyl]-3,5-dihydroxy-cyclopentyl}-heptanoyl)-4-fluoro-benzenesulfonamide (**19**): 79% ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.21—1.87 (m, 22H), 2.20—2.25 (t, 2H, J=7.2 Hz), 2.87—2.94 (dd, 1H, J=7.8, 13.5 Hz), 3.06—3.12 (dd, 1H, J=3.6, 13.5 Hz), 3.70 (m, 1H), 3.98 (br s, 1H), 4.15 (br s, 1H), 7.01—7.09 (m, 2H), 7.15—7.26 (m, 3H), 7.39—7.43 (t, 1H, J=7.5 Hz), 8.05—8.10 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: 24.4, 28.1, 28.7, 28.9, 29.5, 30.1, 34.3, 36.4, 41.8, 42.6, 51.6, 52.6, 70.5, 74.6, 78.4, 115.9, 116.2, 116.3, 116.6, 122.4, 122.6, 124.9, 125.0, 129.2, 129.3, 131.5, 131.6, 132.9, 135.1, 160.2, 163.5, 164.2, 167.6, 172.3; MS (+ES) *m/z* (relative intensity): 550 (M^+-2H_2O, 25), 568 (M^+-H_2O, 50), 586 ($M+H^+$, 50), 603 ($M+NH_4^+$, 55), 608 ($M+Na^+$, 20); HRMS Calcd for $C_{28}H_{37}NO_6F_2S_2$ ($M+Na^+$): 608.1928. Found: 608.1947.

Propane-2-sulfonic acid {7-[3,5-dihydroxy-2-(3-hydroxy-4-phenylsulphanyl-butyl)-cyclopentyl]-heptanoyl}-amide (**14**): 69% ^{1}H-NMR ($CDCl_3$,

300 MHz) δ: 1.33—1.86 (m, 22H), 1.38 (S, 3H), 1.40 (S, 3H), 2.29—2.35 (t, 2H, J=7.2 Hz), 2.89—2.96 (dd, 1H, J=8.1, 13.5 Hz), 3.09—3.14 (dd, 1H, J=3.6, 13.5 Hz), 3.67—3.83 (m, 2H), 3.96 (bs, 1H), 4.15 (bs, 1H), 7.17 (m, 1H), 7.26—7.31 (overlapped dd, 2H, J=6.9, 8.1 Hz), 7.36—7.38 (d, 2H, J=7.5 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 16.1, 24.7, 28.1, 28.9, 29.0, 29.6, 29.7, 30.2, 34.5, 34.6, 36.7, 41.9, 42.1, 42.6, 42.7, 51.7, 52.7, 52.9, 53.8, 69.9, 70.3, 74.6, 78.5, 78.7, 126.7, 129.3, 129.9, 135.8, 173.3; MS (+AP) m/z (relative intensity): 462 (M^+-3H_2O, 50), 480 (M^+-2H_2O, 100), 497 (M^+-H_2O, 15), 515 ($M+H^+$, 20), HRMS Calcd for $C_{25}H_{41}NO_6S_2$ ($M+Na^+$): 538.2273. Found: 538.2268.

Ethanesulfonic acid {7-[3,5-dihydroxy-2-(3-hydroxy-4-phenylsulphanyl-butyl)-cyclopentyl]-heptanoyl}-amide (**13**): 82% ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.32—1.37 (t, 3H, J=7.2 Hz), 1.43—1.85 (m, 22H), 2.29—2.33 (t, 2H, J=6.9 Hz), 2.89—2.96 (dd, 1H, J=8.1, 13.5 Hz), 3.09—3.14 (dd, 1H, J=3.9, 13.5 Hz), 3.38—3.47 (q, 2H, J=7.2 Hz), 3.72—3.73 (m, 1H), 3.95 (bs, 1H), 4.14 (bs, 1H), 7.17—7.21 (dd, 1H, J=6.9, 7.5 Hz), 7.26—7.31 (overlapped dd, 2H, J=7.2, 7.8 Hz), 7.35—7.37 (d, 2H, J=7.5 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 8.1, 24.7, 28.1, 28.9, 29.0, 29.6, 29.7, 30.2, 34.5, 34.6, 36.6, 41.2, 42.1, 42.6, 42.7, 47.9, 51.6, 52.6, 52.9, 70.0, 70.3, 74.6, 78.4, 78.7, 126.7, 129.3, 129.9, 135.8, 173.4; MS (+AP) m/z (relative intensity): 448 (M^+-3H_2O, 40), 466 (M^+-2H_2O, 100), 524 ($M+Na^+$, 15); HRMS Calcd for $C_{24}H_{39}NO_6S_2$ ($M+Na^+$): 524.2117. Found: 524.2122.

N-(7-{2-[4-(2-Fluoro-phenylamino)-3-hydroxy-butyl]-3,5-dihydroxy-cyclopentyl}-heptanoyl)-benzenesulfonamide (**17**): 69% ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.17—1.79 (m, 22H), 2.07—2.14 (m, 1H), 2.16—2.27 (t, 2H, J=7.8 Hz), 3.03—3.10 (dd, 1H, J=7.5, 12.9 Hz), 3.24—3.29 (dd, 1H, J=4.2, 12.9 Hz), 3.76—3.89 (m, 2H), 4.08 (br s, 1H), 6.59 (m, 1H), 6.74—6.80 (overlapped dd, 1H, J=8.4, 8.8 Hz), 6.90—7.00 (m, 2H), 7.56—7.66 (overlapped dd, 2H, J=7.5, 8.1 Hz), 7.68—7.71 (m, 1H), 8.00—8.03 (dd, 2H, J=1.2, 7.2 Hz); ^{13}C-NMR (CD_3OD, 75 MHz) δ: 25.7, 28.9, 29.3, 29.4, 29.9, 30.0, 30.1, 30.7, 33.9, 34.1, 37.1, 43.9, 44.0, 50.6, 50.7, 51.1, 51.2, 52.4, 52.6, 71.3, 71.5, 73.6, 78.5, 113.6, 115.2, 115.4, 117.5, 117.6, 125.7, 129.1, 130.0, 134.8, 138.2, 138.5, 140.9, 174.0; MS (+AP) m/z (relative intensity): 551 ($M+H^+$, 100); HRMS Calcd for $C_{28}H_{39}O_6SN_2F$ ($M+H^+$): 551.2591. Found: 551.2581.

N-(7-{2-[4-(2-Fluoro-phenylamino)-3-hydroxy-butyl]-3,5-dihydroxy-cyclopentyl}-heptanoyl)-methanesulfonamide (**11**): 31% ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.37—1.79 (m, 22H), 2.09—2.18 (m, 1H), 2.29—2.34 (t, 2H, J=7.5 Hz), 3.04—3.11 (m, 1H), 3.19—3.33 (m, 1H), 3.24 (s, 3H), 3.79—3.88 (m, 2H), 4.11 (m, 1H), 6.57—6.64 (m, 1H), 6.76—6.82 (ddd, 1H, J=1.5, 7.8, 9 Hz), 6.92—7.01 (m, 2H); ^{13}C-NMR (CD_3OD, 75 MHz) δ: 25.7, 29.0, 29.4, 29.9, 30.1, 30.7, 33.9, 34.1, 37.2, 41.3, 43.9, 50.6, 50.7, 51.1, 51.2, 52.4, 52.6, 71.3, 71.5, 73.6, 78.5, 113.6, 115.1, 115.4, 117.5, 125.7, 151.6, 154.7, 175.3; MS (+AP) m/z (relative intensity): 489 ($M+H^+$, 100); HRMS Calcd for $C_{23}H_{37}O_6SN_2F$ ($M+H^+$): 489.2439. Found: 489.2450.

General Procedure for Compounds 20—24: Synthesis of 7-[2-(4-Benzenesulfonylamino-3-hydroxy-butyl)-3,5-dihydroxy-cylopentyl] heptanoic Acid (20) A solution of the epoxide (**6**) (0.39 mmol) and $Mg(ClO_4)_2$ (0.58 mmol) in CH_3CN (1 ml) was stirred until complete dissolution of the perchlorate salt was achieved. The resulting solution was treated, under N_2 with stirring, with the required amount of NaN_3 (0.58 mmol), at room temperature. The reaction was heated to 80 °C for 5 h and then cooled to room temperature. The reaction was diluted with water, extracted with Et_2O (3×30 ml), and the organic layers were combined. The organic layer was washed with sat. NaCl, dried (Na_2SO_4) and concentrated. After column chromatography on SiO_2 (10% EtOAc/Hexane), 108 mg (48%) of azide was recovered as a yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.02—0.08 (m, 12H), 0.88—0.89 (m, 18H), 1.20—1.80 (m, 18H), 2.09—2.19 (m, 1H), 2.29—2.34 (t, 2H, J=7.5 Hz), 3.23—3.39 (m, 2H), 3.68 (s, 3H), 3.74—3.81 (m, 2H), 4.04—4.07 (m, 1H); MS (+ES) m/z (relative intensity): 586 ($M+H^+$, 75), 603 ($M+NH_4^+$, 100). The azide was protected under standard conditions[12] to give product (**7**) before being reduced to the free amine.

To the solution of the azide (**7**) (0.16 mmol) in THF (3 ml), was added 3 drops of water. While stirring at room temperature, 84 mg triphenylphosphine (0.32 mmol) was added. The reaction was allowed to stir at room temperature under N_2 overnight. The solvent was then removed under vacuum and the residue chromatographed on SiO_2 (25% EtOAc/hexanes) to obtain 83 mg (77%) of the amine product as a yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.02—0.08 (m, 18H), 0.87—0.91 (m, 27H), 1.09—1.73 (m, 19H), 2.05—2.16 (m, 1H), 2.28—2.33 (t, 2H, J=7.8 Hz), 2.65—2.74 (m, 2H), 3.57—3.58 (m, 1H), 3.67 (s, 3H), 3.71—3.78 (m, 1H), 4.03—4.07 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: −4.5, 44.1, −3.9, −3.8, 18.1, 18.3, 25.2, 26.1, 27.1, 27.3, 27.6, 28.1, 29.5, 29.9, 32.1, 32.3, 34.3, 44.8, 47.9, 48.2, 50.1, 50.4, 51.6, 71.9, 74.3, 76.9, 77.1, 77.2, 77.3, 77.7; MS (+ES) m/z (relative intensity): 674 ($M+H^+$, 100).

A solution of the amine (0.18 mmol) in CH_2Cl_2 (2 ml) was cooled to 0 °C, and triethylamine (56 μl, 0.40 mmol) and benzenesulfonyl chloride (25 μl, 0.2 mmol) were added while stirring. The reaction was slowly warmed to room temperature and stirred overnight. Methylene chloride (20 ml) was added to the reaction mixture, and the solution was washed with sat. NaCl, and dried (Na_2SO_4). The solvent was concentrated and the resulting oil chromatographed on SiO_2 (30% EtOAc/hexanes) to provide 113 mg (77%) of the product (**8**). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: −0.04—0.04 (m, 18H), 0.83—0.89 (m, 27H), 1.09—1.78 (m, 18H), 2.06—2.15 (m ,1H), 2.29—2.34 (t, 2H, J=7.5 Hz), 2.91—2.96 (m, 2H), 3.67 (s, 3H), 3.69—3.70 (m, 1H), 4.04 (m, 1H), 4.65—4.68 (m, 1H), 7.50—7.62 (m, 3H), 7.85—7.87 (d, 1H, J=7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: −4.5, −4.3, −3.9, −3.8, −3.7, 18.1, 18.2, 18.3, 25.2, 26.0, 26.1, 26.9, 27.6, 28.0, 29.5, 29.9, 32.2, 32.3, 34.3, 44.7, 44.8, 48.2, 48.5, 49.9, 50.2, 51.7, 71.4, 71.7, 71.9, 76.9, 77.1, 77.3, 77.7, 127.3, 129.3, 132.8, 139.9, 174.6.

A solution of the protected sulfonamide (**8**) (0.14 mmol) in CH_3CN (1.5 ml) was cooled to 0 °C, and 0.14 ml (0.14 mmol) of HF/pyridine was added dropwise at 0 °C. The reaction was stirred at 0 °C overnight under N_2, then poured onto sat. $NaHCO_3$ solution. The solution was extracted with CH_2Cl_2 (3×50 ml), and the organic layers were combined and washed with sat. NaCl. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (4% MeOH/CH_2Cl_2) to yield 57 mg (88%) of product. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.15—1.81 (m, 20H), 1.90—1.91 (m, 1H), 2.279—2.329 (t, 2H, J=7.8 Hz), 2.81—2.88 (m, 1H), 3.01—3.08 (m, 1H), 3.66 (s, 3H), 3.69 (m, 1H), 3.91 (m, 1H), 4.13 (m, 1H), 5.98—6.05 (m, 1H), 7.48—7.59 (m, 3H), 7.84—7.88 (d, 2H, J=6.9 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 25.1, 28.2, 28.6, 28.7, 29.2, 29.7, 29.8, 32.6, 33.1, 34.3, 42.9, 48.9, 51.6, 51.8, 52.3, 70.6, 70.8, 74.0, 74.2, 78.1, 78.7, 127.2, 129.4, 132.9, 140.0, 174.8; MS (+ES) m/z (relative intensity): 436 ($M-2H_2O$, 60), 454 ($M-H_2O$, 20), 472 ($M+H^+$, 100).

A solution of the sulfonamide methyl ester (0.12 mmol) in THF (1.5 ml) and H_2O (0.5 ml) was treated with LiOH (20 mg, 0.48 mmol) at room temperature overnight under N_2. The solvent was removed under vacuum and the residue was chromatographed (10% MeOH/CH_2Cl_2) to give 7 mg (13%) of final product (**20**). ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.23—1.71 (m, 22H), 2.06—2.15 (m, 1H), 2.29—2.34 (t, 2H, J=6.9 Hz), 2.79—2.86 (dd, 1H, J=6.6, 12.9 Hz), 2.88—2.94 (dd, 1H, J=5.1, 12.9 Hz), 3.56—3.60 (m, 1H), 3.83 (m, 1H), 4.10 (m, 1H), 7.56—7.67 (m, 3H), 7.87—7.90 (m, 2H); MS (+ES) m/z (relative intensity): 404 ($M-3H_2O$, 20), 422 ($M-2H_2O$, 50), 440 ($M-H_2O$, 20), 458 ($M+H^+$, 100), 475 ($M+NH_4^+$, 60). Compounds **21**—**24** were prepared in a similar fashion.

7-{2-[4-(3-Fluoro-benzenesulfonylamino)-3-hydroxy-butyl]-3,5-dihydroxy-cyclopentyl} heptanoic acid (**21**): 33%; ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.24—1.72 (m, 22H), 2.06—2.15 (m, 1H), 2.75—2.33 (t, 2H, J=7.5 MHz), 2.83—2.98 (m, 2H), 3.59—3.87 (m, 1H), 3.83—3.87 (m, 1H), 4.11 (bs, 1H), 7.37—7.43 (m, 1H), 7.59—7.66 (m, 2H), 7.70—7.74 (dt, 1H, J=1.2, 7.8 MHz); ^{13}C-NMR (CD_3OD, 75 MHz) δ: 25.1, 27.9, 28.2, 28.5, 28.6, 29.1, 29.6, 32.1, 32.2, 34.3, 42.8, 50.0, 51.2, 51.3, 70.3, 70.6, 72.5, 77.3, 113.8, 114.1, 119.3, 119.6, 122.9, 131.2, 131.3, 143.1, 161.1, 164.4, 177.3; MS (+AP) m/z (relative intensity): 493.2 ($M+NH_4^+$, 55), 476.2 ($M+H^+$, 40), 440.2 ($M-2H_2O$, 100), 421.1 ($M-3H_2O$, 95); ^{19}F-NMR (CD_3OD): 51.1; HRMS Calcd for $(C_{22}H_{34}O_7NSF+H)^+$: 476.2118. Found: 476.2107.

7-{2-[4-(2,4-Fluoro-benzenesulfonylamino)-3-hydroxy-butyl]-3,5-dihydroxy-cyclopentyl} heptanoic acid (**22**): 48%; ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.20—1.71 (m, 22H), 2.06—2.15 (m, 1H), 2.27—2.32 (t, 2H, J=7.5 MHz), 2.89—2.96 (dd, 1H, J=6.9, 13.2 MHz), 2.98—3.04 (dd, 1H, J=5.1, 13.2 MHz), 3.58—3.60 (m, 1H), 3.81—3.86 (m, 1H), 4.10 (m, 1H), 7.12—7.27 (m, 2H), 7.91—7.99 (m, 1H); ^{13}C-NMR (CD_3OD, 75 MHz) δ: 25.0, 27.9, 28.1, 28.5, 28.7, 29.1, 29.6, 32.0, 32.2, 33.9, 42.8, 49.9, 51.2, 51.3, 70.3, 70.6, 72.4, 77.3, 105.1, 105.4, 105.8, 111.6, 111.8, 125.4, 131.9, 132.1, 158.1, 161.2, 164.2, 167.5, 176.7; MS (+ES) m/z (relative intensity): 511.1 ($M+Na^+$,100), 494.1 ($M+H^+$, 85); ^{19}F-NMR (CD_3OD): 56.1, 59.1; HRMS Calcd for $(C_{22}H_{33}O_7NSF_2+Na)^+$: 516.1834. Found: 516.1854.

7-{2-[4-(4-Fluoro-benzenesulfonylamino)-3-hydroxy-butyl]-3,5-dihydroxy-cyclopentyl} heptanoic acid (**23**): 57%; ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.24—1.72 (m, 22H), 2.07—2.16 (M, 1H), 2.28—2.33 (t, 2H, J=7.5 MHz), 2.81—2.96 (m, 2H), 3.58—3.63 (m, 1H), 3.84—3.85 (m, 1H), 4.11 (bs, 1H), 7.30—7.37 (m, 2H), 7.91—7.97 (m, 2H); ^{13}C-NMR (CD_3OD, 75 MHz) δ: 25.1, 27.9, 28.1, 28.2, 28.5, 28.7, 29.1, 29.6, 32.1, 32.2, 42.8, 49.9, 51.2, 51.3, 70.3, 70.6, 72.4, 77.3, 115.9, 116.2, 129.7, 129.9, 137.1, 163.5, 166.9, 177.1; MS (+AP) m/z (relative intensity): 498.3 ($M+Na^+$, 100), 440.4 ($M-2H_2O$, 85), 422.3 ($M-3H_2O$, 65); ^{19}F-NMR (CD_3OD): 52.1;

HRMS Calcd for $(C_{22}H_{34}O_7NSF+H)^+$: 476.2118. Found: 476.2135.

7-{2-[4-(2-Fluoro-benzenesulfonylamino)-3-hydroxy-butyl]-3,5-dihydroxy-cyclopentyl} heptanoic acid (**24**): 56%; ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.14—1.71 (m, 22H), 2.06—2.15 (m, 1H), 2.27—2.32 (t, 2H, J=7.2 MHz), 2.90—3.04 (m, 2H), 3.61 (m, 1H), 3.84 (M, 1H), 4.11 (s, 1H), 7.31—7.39 (m, 2H), 7.65—7.72 (m, 1H), 7.87—7.92 (overlapped dd, 1H, J=7.8, 8.4 MHz); ^{13}C-NMR (CD_3OD, 75 MHz) δ: 25.1, 27.9, 28.2, 28.5, 28.7, 29.1, 29.6, 30.0, 32.1, 34.3, 42.8, 50.0, 51.2, 51.3, 70.4, 70.6, 72.5, 77.3, 116.9, 117.1, 124.6, 130.1, 135.0, 135.2, 157.4, 160.8, 177.4; ^{19}F-NMR (CD_3OD) 51.1; MS (+AP) *m/z* (relative intensity): 493.1 ($M+NH_4^+$, 100), 475.1 ($M+H^+$, 25), 457.1 ($M-H_2O$, 17), 440.1 ($M-2H_2O$, 20), 421.1 ($M-3H_2O$, 19); HRMS Calcd for $(C_{22}H_{34}O_7NSF+Li)^+$: 4482.2200. Found: 482.2186.

References and Notes

1) *a*) Ueda K., Saito S., Nakano H., Aoshima M., Yokata M., Muraoka R., Iwaya T., *J. Pediatr.*, **97**, 834—836 (1980); *b*) Ueno K., Haba T., Woodbury D., Price P., Anderson R., Jee W. S. S., *Bone*, **6**, 79—86 (1985); *c*) Ma Y. F., Li X. J., Jee W. S. S., Mcosker J., Liang X. G., Setterberg R., Chow S. Y,. *ibid.*, **17**, 549—554 (1995); *d*) Jee W. S. S., Ma Y. F., *ibid.*, **21**, 297—304 (1997).
2) Jackson Roberts II, L., "Handbook of Eicosanoids: Prostaglandins and Related Lipids." ed. by Willis A. L., CRC Press, Inc., Boca Raton, Vol. 1, Part B., 1987, pp. 233—244.
3) *a*) Abramovitz M., Metters K. M., *Ann. Rep. Med Chem.*, **33**, 223—232 (1998); *b*) Ruel R., Lacombe P., Abramovitz M., Godbout C., Lamontagne S., Rochette C., Sawyer N., Stocco R., Tremblay N. M., Metters M., Labelle M., *Bioorganic Med. Chem. Lett.*, **9**, 2699—2704 (1999).
4) *a*) Hartke J. R., Lundy M. W., deLong M. A., WO 9912550, 1999; *Chem. Abstr.* **1999**, 194004; *b*) WO 9912895, 1999; *Chem Abstr.*, **1999**, 194115; *c*) Wos J. A., deLong M. A., Amburgey J. S., De B., Dai G., Wang Y., WO 9912897, 1999, *Chem. Abstr.*, **1999**, 194117.
5) *a*) Hartke J. R., Jankowsky M. L., deLong M. A., Soehner M. E., Jee W. S. S., Lundy M. W., *J. Bone and Min. Res.*, **14**, Suppl. 1, S207 (1999); *b*) deLong M. A., Hartke J. R., Jankowsky M. L., Soehner M. E., Wos J. A., Soper D. L., Lundy M. W., *ibid.*, **14**, Suppl. 1, S275 (1999).
6) *a*) Castaner J., *Drugs of the Future*, **3**, 59—61 (1978); *b*) Karim S. M. M., Choo H. T., Lim A. L., Ratnam S. S., *Prostaglandins*, **15**, 1063—1068 (1978); *c*) Krishna U., Ma H. K., Manuilova I., Hingorani V., Prasad R. N. V., Bygdeman M., Herczeg J., *Contraception*, **34**, 237—251 (1986); *d*) Schillinger E., Prior G., Speckenbach A., Wellershoff S., *Prostaglandins*, **18**, 293—302 (1979); *e*) Schaaf T. K., Hess H. J., *J. Med. Chem.*, **22**, 1340—1346 (1979); *f*) Schaaf T. K., Bindra J. S., Eggler J. F., Plattner J. J., Nelson A. J., Johnson M. R., Constantine J. W., Hess H. J., *J. Med. Chem.*, **24**, 1353—1359 (1981).
7) The binding affinity for Sulprostone at the murine FP receptor has been reported: Kiriyama M., Ushikubi F., Kobayashi T., Hirata M., Sugimoto Y., Narumiya S., *Br. J. Pharm.*, **122**, 217—224 (1997).
8) Wang Y., Wos J. A., Dirr M. A., Soper D. L., deLong M. A., Mieling G. E., De B., Amburgey J. S., Suchanek E. G., Taylor C. J., *J. Med. Chem.*, **43**, 945—952 (2000).
9) For a review see: Smith J. G., *Synthesis*, **1984**, 629—656 and references cited therein.
10) Drummond J. T., Johnson G., *Tetrahedron. Lett.*, **29**, 1653—1656 (1988).
11) The sulfonamides used in the condensation reaction were made by condensing NH_3 gas into a solution of the appropriate sulfonyl chloride (RSO_2Cl) in CH_2Cl_2. See: White E. H., Lim H. M., *J. Org. Chem.*, **52**, 2162—2166 (1987).
12) deLong M. A., Amburgey J., Taylor C., Wos J. A., Soper D. L., Wang Y. E., Hicks R., *Bioorganic Med. Chem. Lett.*, 2000, *Bioorganic Med. Chem. Lett.*, **10**, 1519—1522 (2000).
13) Corey E. J., Cho H., Rucker C., Hua D., *Tetrahedron Lett.*, **22**, 3455—3548 (1981).
14) Vaultier M., Knouzi N., Carrie R., *Tetrahedron Lett.*, **24**, 763 (1983).