Synthesis and Biological Evaluation of Novel Isopropanolamine Derivatives as Non-peptide Human Immunodeficiency Virus Protease Inhibitors

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Novel potential human immunodeficiency virus (HIV) protease inhibitors were designed by a combination of nelfinavir and amprenavir motifs. The designed compounds were prepared by a facile synthetic route and their stereochemistry was further confirmed by a stereospecific synthesis from commercially available (*S*)-2-oxiranylmethyl *m*-nitrobenzenesulfonate. All compounds were tested for their ability in inhibiting HIV type 1 protease activity with the published method of reference 19. Derivatives 1a—u exhibited moderate to significant inhibitory activities in preliminary bioassay. The best compound 1a has IC_{50} value of 0.02 μM, comparable to that of amprenavir. A docking study on compounds 1a—u was performed using the published X-ray crystal structure of HIV type 1 protease, all compounds bound to the HIV type 1 protease in an extended conformation and the scaffoldings of the binding conformations could be aligned quite well. Comparative molecular field analysis (CoMFA) study was performed to explore the specific contributions of electrostatic and steric effects in the binding of these new compounds to HIV type 1 protease and a predictive CoMFA model was built with thirteen compounds as training set. Test analysis of other five compounds as test set demonstrated that the CoMFA model has strong predictive ability to this series of compounds. It will be very useful to further optimize the designed inhibitors.

Key words isopropanolamine derivative; protease inhibitor; biological evaluation; docking study; predictive model

Discovery of highly active antiretroviral therapy (HAART) represents a significant advance in the management of acquired immune deficiency syndrome (AIDS).[1,2] As one of the crucial ingredients in HAART, protease inhibitors (PIs) play an important role in preventing the replication of human immunodeficiency virus (HIV). Although several HIV PIs have been used in clinical practice, emergence of viral resistance,[3,4] adverse side effects[5—10] and high costs of the production have limited their utilization. Development of novel HIV PIs against multi-drug resistant viral strains with unique profiles, is still urgently required for HAART.

It is proposed that non-peptidic HIV PIs bind to the enzyme active sites differently compared with the conventional peptidomimetic drugs, and the speed of emergence of drug-resistant strains would be slowed down due to the different binding mode.[11] As a bioisostere of peptide backbone, isopropanolamine was found to be a binding determinant by the structural analysis of peptidomimetic drugs.[12—14] Moreover, the decahydroisoquinoline moiety in nelfinavir and saquinavir would interact with the subsites of the enzyme and significantly affect the antiviral and pharmacokinetic properties of the hybrid compounds.[15,16] The methyl sulfonamide moiety of amprenavir has also been proved to be capable of efficiently interacting with both S1 and S2 enzyme pockets.[13] Therefore, we designed a series of hybrid molecules as non-peptidic HIV PIs by incorporating methyl sulfonamide moiety of amprenavir into hydroxyethyl decahydroisoquinoline backbone of nelfinavir (Fig. 1).

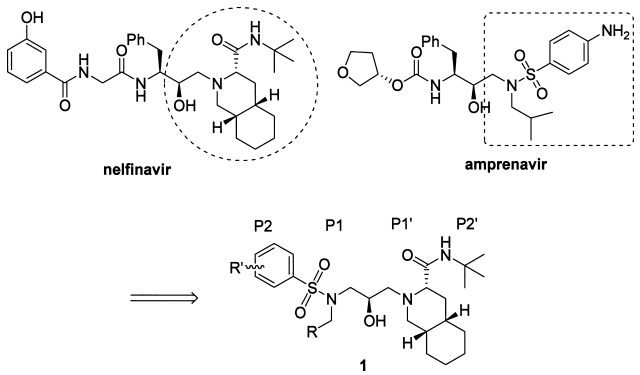
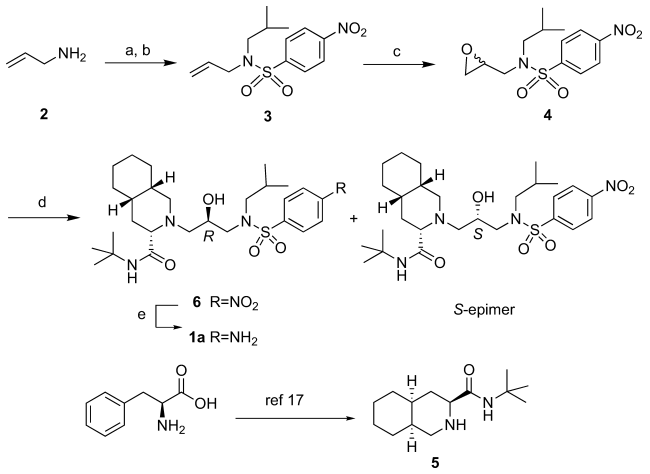


Fig. 1. Design of Derivatives **1** as New HIV PIs

Chemistry

The designed compounds were synthesized using the method as depicted in Chart 1. Reductive amination between allylamine **2** and isobutylaldehyde followed by sulfonylation with *p*-nitrobenzenesulfonyl chloride afforded the sulfon-



Reagents and conditions: a) isobutylaldehyde, anhydrous Na_2SO_4, CH_2Cl_2, $NaBH_4$; b) *p*-nitrobenzenesulfonyl chloride, TEA, CH_2Cl_2, 0 °C; c) *m*-CPBA, CH_2Cl_2, 50 °C; d) **5**, methanol, 50—60 °C; e) H_2, 10% Pd–C, methanol.

Chart 1. Synthesis of Compound **1a**

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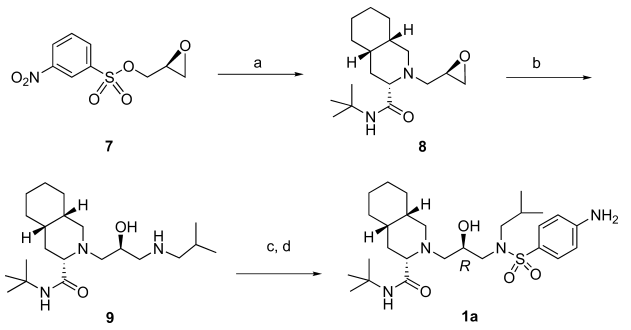
amide **3**. Epoxidation of the terminal double bond in compound **3** resulted in racemic epoxide **4**. The (3*S*)-decahydroisoquinoline-3-formamide **5** was prepared utilizing the method of Göhring.[17] Epoxide **4** was treated with amide **5** in methanol to provide a pair of separable diastereomers, **6** and its *S*-epimer, which could be easily separated by column chromatography in approximately a 1 : 1 ratio. The nitro group in **6** was further hydrogenated in the presence of 10% Pd–C to afford the desired compound **1a**. In addition, other designed compounds **1b**—**u** could be easily synthesized by the same method.

Stereochemistry of compound **1a** was further confirmed by a stereospecific synthesis from commercially available (*S*)-2-oxiranylmethyl *m*-nitrobenzenesulfonate **7** (Chart 2). First condensation with amide **5** yielded the desired epoxide **8**,[18] which is an important intermediate for the synthesis of enantiomerically isopropanolamine derivatives. Ring-opening of epoxide **8** with isobutylamine followed by subsequent sulfonylation of compound **9** with *p*-nitro benzenesulfonyl chloride and final reduction of the nitro group afforded the compound **1a**. The spectra data of compound **1a** obtained from this route were identical with that from Chart 1. Moreover, compounds **1b**—**u** also could be synthesized stereoselectively using the method from epoxide **8**.



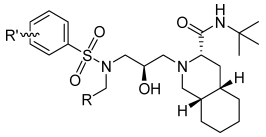
Reagents and conditions: a) **5**, iPr$_2$NEt, DMF, 60 °C; b) isobutylamine, methanol, 60 °C; c) *p*-nitrobenzenesulfonyl chloride, TEA, CH_2Cl_2, 0 °C; d) H_2, 10% Pd–C, methanol.

Chart 2. Stereospecific Synthesis of Compound **1a**

Biological Activity The synthesized compounds were assayed for inhibitory activities against the wild-type HIV type 1 protease enzyme using the published method[19] and the results were shown in Table 1. Amprenavir and indinavir were applied as reference compounds. The IC_{50} value of amprenavir was determined as 0.01 μM in this system.[20] In general, compounds **1a**—**u** exhibited moderate to significant inhibitory activities against HIV protease enzyme. When R group in **1** was changed from alkyl to aryl substituents, inhibitory activities dropped accordingly. For example derivatives **1a**, **1f** and **1j** were 4—100 times more potent than **1p** and **1t**. Moreover, investigation in R′ group indicated that *para*-amino substitution provided the best potency in each case. Derivatives **1a**, **1f**, **1p** and **1t** were more potent than their corresponding counterparts **1b**—**d**, **1e**, **1g**, **1h**, **1o**, **1q**, **1r**, **1s** and **1u** respectively, probably due to formation of the stronger hydrogen bond than that of the *para*-methoxy, *para*- or *meta*-nitro and *meta*-amino substituents. In particular, compound **1a** (IC_{50}=0.02 μM) was essentially comparable in potency to amprenavir (IC_{50}=0.01 μM).

Molecular Modeling A docking study was performed using the published X-ray crystal structure of HIV type 1 protease complexed with nelfinavir (PDB entry code: 1ohr)[21] as the template structure. The initial structures of compounds **1a**—**u** were generated by Sybyl and subsequently optimized

Table 1. Inhibitory Activities of Compounds **1a**—**u** to HIV-1 PR



Entry	R	R′	IC_{50} (μM)	Entry	R	R′	IC_{50} (μM)[a]
1a	*i*Pr	*p*-NH_2	0.02	**1l**		*p*-NO_2	33.16
1b	*i*Pr	*m*-NO_2	>200	**1m**		*m*-NO_2	29.85
1c	*i*Pr	*m*-NH_2	0.38	**1n**		*p*-OMe	19.73
1d	*i*Pr	*p*-OMe	13.83	**1o**		*p*-OMe	>200
1e	Et	*p*-NO_2	35.75	**1p**		*p*-NH_2	7.20
1f	Et	*p*-NH_2	0.47	**1q**		*m*-NH_2	10.39
1g	Et	*m*-NH_2	49.87	**1r**		*p*-OMe	42.43
1h	Et	*p*-OMe	14.80	**1s**		*p*-NO_2	37.10
1i	Cy	*p*-OMe	3.74	**1t**		*p*-NH_2	1.78
1j	Bn	*p*-NH_2	0.05	**1u**		*m*-NH_2	89.43
1k	Ph	*p*-OMe	4.88				

a) All IC_{50} values are measured based on serial dilutions of compound concentration, every inhibitory rate is the mean of three runs with the variation of the mean less than 20%.

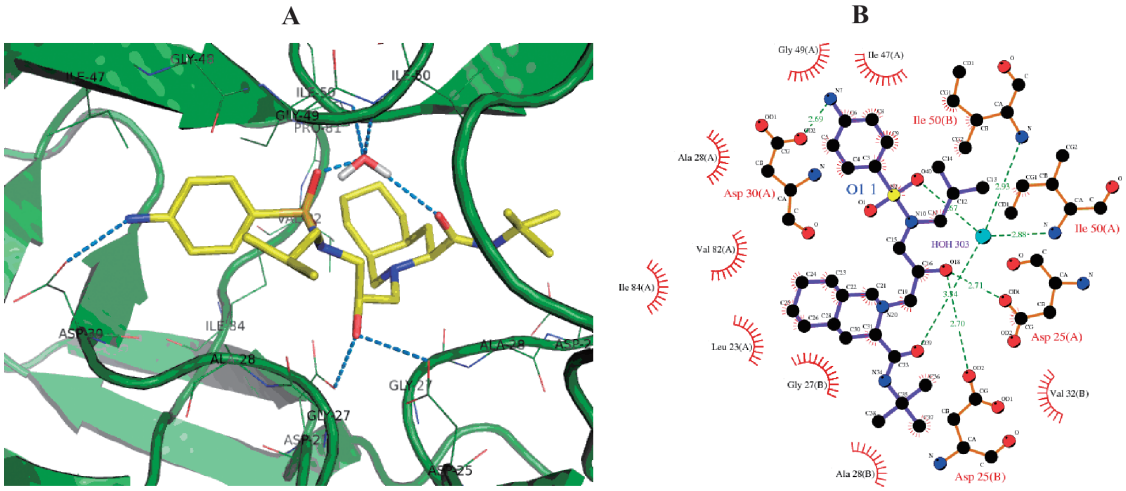


Fig. 2. Interactions between HIV Protease and Compound **1a** in the Docked Complex

(A) 3D representation. Enzyme is shown in cartoon style; the residues within 3 Å around **1a** are shown in line style; water and **1a** are shown in stick style; hydrogen bonds are represented as dashed lines. (B) 2D representation drawn by LIGPLOT. Dashed lines represent hydrogen bonds and spiked residues form hydrophobic contacts with the inhibitors.

using the Powell method with Tripos force field and Gasteiger–Hückel charges. In order to identify their binding conformations and positions, AutoDock 3.0.5 was used to dock these compounds to the enzyme, for which the Lamarckian genetic algorithm (LGA) was applied. The population size, the maximum number of energy evaluations, and docking runs was set to 120, 12000000, and 30, respectively.

To fully explore the specific contributions of electrostatic and steric effects in the binding of these new compounds to HIV type 1 protease and to build predictive quantitative structure–activity relationship (QSAR) models, comparative molecular field analysis (CoMFA) study was performed by using conformations and their alignment at the binding site, which resulted from the molecular docking. Steric and electrostatic interactions were calculated using a sp^3 carbon atom as steric probe and a +1 charge as electrostatic probe with Tripos force field. Regression analysis was performed using partial least square (PLS) algorithm. The final model was developed with the optimum number of components equal to that yielding the highest q^2.

Results and Discussion

All compounds bind to the HIV type 1 protease in an extended conformation and the scaffoldings of the binding conformations could be aligned quite well. A representative result is depicted in Fig. 2 using the structure of compound **1a**, which has the highest inhibitory activity. As the other compounds, **1a** has carbon-rich groups arrayed along either side, interacting with hydrophobic subsites of the pocket. The *tert*-butyl group is situated at the S2′ subsite of the binding pocket. The decahydroisoquinoline ring occupies the S1′ subsite. The *iso*-butyl moiety resides in the S3 subsite, and the *p*-amino-phenyl group occupies the S2 pocket, with amino group hydrogen bonding to ASP30 (2.69 Å). Besides these hydrophobic interactions, there are some typical hydrogen bonds also observed in the majority of HIV type 1 protease-derivatives **1a**—**u** complexes. With a network of hydrogen bonds, the central hydroxyl group binds to the catalytic aspartates (Asp 25 and Asp 25′, 2.70 Å and 2.71 Å) which are crucial to the enzyme's hydrolytic activity. The oxygen of the sulfonamide moiety and the carbonyl of the decahydroisoquinoline formamide moiety each accept a hydrogen bond from the "flap" water that stabilizing the complex by forming another two hydrogen bonds with the flexible flaps (Ile 50 and Ile 50′, 2.93 Å and 2.88 Å). The hydroxyl, amino and carbonyl groups in **1a** are all located in ideal positions and orientations, which was thought to maximize the hydrogen bond interactions with HIV protease. In comparison with nelfinavir, no new amino acid residues were found within a distance of forming additional hydrogen bonds which may indicate the huge rooms to optimize the designed molecular structure for potency improvement.

Table 2. Predicted Activities (PA) *vs.* Experimented Activities (EA, $-\log IC_{50}$) and Residues (Δ)

Compounds	EA	PA	Δ	Compounds	EA	PA	Δ
1a	7.72	7.81	0.09	**1l**	4.48	4.39	−0.09
1c	6.42	6.30	−0.12	**1m**	4.52	4.49	−0.03
1d	4.86	4.88	0.02	**1n**[a]	4.71	4.78	0.07
1e	4.45	4.52	0.07	**1p**	5.14	5.11	−0.03
1f	6.33	6.33	0.00	**1q**[a]	4.98	5.13	0.15
1g	4.30	4.52	0.22	**1r**	4.37	4.44	0.07
1i	5.43	5.37	−0.06	**1s**[a]	4.43	4.01	−0.42
1j	7.28	7.25	−0.03	**1t**[a]	5.75	5.54	−0.22
1k[a]	5.32	5.20	−0.13	**1u**	4.05	4.02	−0.03

a) Compounds in test set.

Thirteen compounds among the synthesized derivatives were used as training set to build QSAR model while five compounds constituted the test set for validation. A 6-component of CoMFA model was obtained with cross-validated q^2 of 0.557, conventional r^2 of 0.997, F value of 471, and standard error of 0.08, respectively. To test the reliability and predictive ability of the constructed model, the inhibitory activities of the five compounds in test set were predicted by it. Table 2 summarizes the correlation between experimental and predicted values of the eighteen studied compounds. The test analysis released r^2 of 0.809, demonstrating again that the CoMFA model is fairly reliable and has rather strong predictive ability to the series of isopropanolamine compounds,

and will be useful in further optimizing designed inhibitors.

Conclusion

In summary, a series of novel isopropanolamine derivatives were designed and synthesized as inhibitors of HIV protease. Derivatives **1a**—**u** displayed moderate to significant inhibitory activities. Among them, compound **1a** exhibited the best inhibitory activity, which is essentially equipotent to amprenavir and represents a promising platform for synthesizing potent inhibitors at low cost. Docking study of compounds **1a**—**u** was carried out for exploration of preliminary structure–activity relationship and predictive 3D-QSAR models were built for further optimization of the designed inhibitors. The test analysis on the eighteen studied compounds confirmed the reliability and predictive ability of the CoMFA model to the series of compounds.

Experimental

General All reaction solvents were dried and distilled before use. Other commercial reagents were used without further purification unless otherwise indicated. Melting points were obtained on a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on Gemini-300 spectrometers (300, 75.5 MHz, respectively). Optical rotations were measured on a Perkin-Elmer 241 MC. Mass spectrometry and high-resolution mass spectrometry (HR-MS) were recorded with Varian MAT-711 and MAT-95 spectrometers respectively. All compounds **1a**—**u** were determined to be >95% pure by HPLC analysis with two different eluent systems. The HPLC analysis was performed on an Agilent 1200 series LC system with a UV detector (λ) set at 254 nm, thermostat set at 25 °C, and a Zorbax Eclipse XDB-C18 column (4.6×150 mm, 80 Å) was used. The mobile phase of a binary gradient (50—100% B/20 min; solvent A, H_2O; solvent B, MeOH for method 1 or solvent A, H_2O, solvent B, CH_3CN for method 2) at a flow rate of 0.5 ml/min was used.

***N*-Allyl-*N*-isobutyl-4-nitrobenzenesulfonamide 3** Allylamine **2** (3.10 ml, 40 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise to a stirring solution of isobutylaldehyde (3.67 ml, 40 mmol) in CH_2Cl_2 (20 ml) at 0 °C. Then anhydrous sodium sulfate (5 g) was added. The mixture was allowed to warm up to room temperature for an additional 1 h, filtered and concentrated. To a solution of the residue in dry methanol (20 ml) was added sodium borohydride (1.67 g, 44 mmol) at 0 °C. The mixture was stirred for 1 h and then concentrated under reduced pressure. The residue was diluted with water (40 ml), extracted with ether (40 ml×3). The combined organic layer was washed with saturated aq. Na_2CO_3 (20 ml×3) and brine (20 ml×3) successively, dried over anhydrous magnesium sulfate. Filtration and concentration gave a colorless oil. To the solution of the crude oil in dry CH_2Cl_2 (30 ml) was added triethylamine (6.2 ml) and *p*-nitrobenzenesulfonyl chloride (8.88 g, 44 mmol) in dry CH_2Cl_2 (30 ml). The resulting mixture was stirred for 1 h. Concentration and purification by column chromatography (on silica gel, chloroform/petroleum ether/ethyl acetate: 60/35/5) gave **3** as a pale yellow solid. Recrystallization from ethyl acetate/hexane produced **3** as pale yellow needle crystal (5.13 g, yield 43%). mp 69—70.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.36 (2H, dt, J=9.0, 2.3 Hz), 8.00 (2H, dt, J=9.0, 2.2 Hz), 5.59—5.45 (1H, m), 5.19—5.12 (2H, m), 3.86 (2H, d, J=6.5 Hz), 2.96 (2H, d, J=7.6 Hz), 1.99—1.85 (1H, m), 0.90 (6H, d, J=6.6 Hz). *Anal.* Calcd for $C_{13}H_{18}N_2O_4S$: C, 52.33; H, 6.08; N, 9.39. Found: C, 52.27; H, 6.00; N, 9.29.

(±)-*N*-Isobutyl-4-nitro-*N*-(oxiran-2-ylmethyl)benzenesulfonamide 4 A mixture of **3** (4.47 g, 15 mmol) and *m*-CPBA (7.79 g, 45 mmol) in CH_2Cl_2 (150 ml) was stirred at 20—30 °C for 84 h, diluted with CH_2Cl_2 (150 ml), washed with saturated aq. $NaHSO_3$ (30 ml×3) and brine (30 ml×3) successively. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. Purification of the residue by column chromatography (on silica gel, petroleum ether/chloroform/ethyl acetate: 50/45/5) gave **4** as a pale yellow solid. Crystallization from ethyl acetate and hexane produced a white cottony crystal (4.23 g, yield 90%). mp 97—99 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.37 (2H, dt, J=8.6, 2.6 Hz), 8.02 (2H, dt, J=8.9, 2.5 Hz), 3.68 (1H, dd, J=15.2, 2.9 Hz), 3.12 (1H, dd, J=13.5, 8.0 Hz), 3.06—3.01 (1H, m), 2.97 (1H, dd, J=13.5, 7.2 Hz), 2.91 (1H, dd, J=15.2, 7.0 Hz), 2.79 (1H, t, J=4.6 Hz), 2.52 (1H, dd, J=4.5, 2.4 Hz), 2.06—1.92 (1H, m), 0.92 (6H, dd, J=16.5, 6.6 Hz). *Anal.* Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.65; H, 5.79; N, 8.80.

(3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyldecahydroisoquinoline-3-carboxamide 5 The compound **5** was prepared according to the procedure in reference 17. **5**: yield 58%. mp 111—113 °C. $[\alpha]_D^{20}$ −70 (c=1.00, MeOH). ^{1}H-NMR ($CDCl_3$): δ: 6.6 (1H, s, br), 3.06—3.02 (1H, m), 2.85—2.77 (2H, m), 1.85—1.17 (13H, m), 1.33 (9H, s).

(3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyl-2-[(*R*)-oxiran-2-ylmethyl]decahydroisoquinoline-3-carboxamide 8 A solution of (3*S*)-decahydroisoquinoline-3-formamide **5** (2.0 g, 8.4 mmol), (*S*)-2-oxiranylmethyl *m*-nitrobenzenesulfonate **7** (2.4 g, 9.3 mmol) and *i*Pr_2NEt (1.6 ml, 9.2 mmol) in DMF (40 ml) was stirred at 60 °C for 6 h under nitrogen atmosphere. The mixture was cooled to room temperature, diluted with water (50 ml) and saturated aq. $NaHCO_3$ (10 ml), extracted with ethyl acetate (100 ml×2). The combined organic layer was washed with water (50 ml×2) and brine (50 ml), dried over anhydrous sodium sulfate. Concentration and purification of the residue by column chromatography (on silica gel, petroleum ether/ethyl acetate: 4/1) furnished **8** as a colorless solid (2.0 g, yield 79%). $[\alpha]_D^{20}$ −147.2 (c=1.00, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 6.60 (1H, s), 2.87—3.02 (3H, m), 2.72—2.75 (1H, m), 2.63—2.66 (1H, m), 2.56—2.61 (1H, m), 2.21 (1H, dd, J=11.7, 3.3 Hz), 2.08 (1H, dd, J=14.4, 4.8 Hz), 1.16—1.80 (12H, m), 1.37 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 173.8, 69.5, 59.9, 56.4, 50.5×2, 44.1, 36.1, 33.1, 30.9, 30.8, 28.6×3, 26.3, 25.6, 20.3. ESI-MS m/z: 317 (M+Na). HR-MS m/z: 317.2215 (Calcd for $C_{17}H_{30}N_2O_2Na$: 317.2205).

(3*R*,4a*R*,8a*R*)-*N*-*tert*-Butyl-2-[(*R*)-2-hydroxy-3-(*N*-isobutyl-4-nitrophenylsulfonamido)propyl]decahydroisoquinoline-3-carboxamide 6 and Its *S*-Epimer from Expoxide 4 A mixture of **5** (1.91 g, 8.0 mmol) and epoxide **4** (0.63 g, 1.0 mmol) in dry methanol (30 ml) was heated to 50—60 °C with stirring for 12 h. The reacting mixture was concentrated and purified by column chromatography (on silica gel, chloroform/methanol: 99/1) to furnish product **6** (31%), further elution gave its *S*-epimer (33%).

6: Yield 31%. mp 188—192 °C (dec.). $[\alpha]_D^{20}$ −60.3 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3338, 2926, 2870, 1645, 1529, 1456, 1390, 1348, 1159, 1088, 1007. ^{1}H-NMR ($CDCl_3$) δ: 8.35 (2H, dt, J=8.9, 1.7 Hz), 7.99 (2H, dt, J=8.9, 2.0 Hz), 5.97 (1H, s), 3.91—3.86 (1H, m), 3.41 (1H, s), 3.22—2.93 (4H, m), 2.74 (1H, d, J=11.5 Hz), 2.65 (1H, dd, J=11.0, 2.9 Hz), 2.34 (1H, dd, J=12.7, 10.9 Hz), 2.20 (1H, dd, J=11.5, 3.4 Hz), 2.13 (1H, dd, J=12.8, 2.6 Hz), 2.00—1.14 (13H, m), 1.35 (9H, s), 0.87 (6H, dd, J=10.6, 6.6 Hz). *Anal.* Calcd for $C_{27}H_{44}N_4O_6S$: C, 58.67; H, 8.02; N, 10.14. Found: C, 58.76; H, 7.90; N, 10.19.

S-epimer of **6**: Yield 33%. mp 185—186.5 °C. $[\alpha]_D^{20}$ −72.9 (c=1.00, $CHCl_3$). IR (film) cm^{-1}: 3400, 3107, 2943, 2862, 1658, 1606, 1525, 1466, 1392, 1365 1348, 1315, 1192, 1159, 1109, 1090, 1005. ^{1}H-NMR ($CDCl_3$) δ: 8.35 (2H, dt, J=8.8, 2.0 Hz), 8.01 (2H, dt, J=8.5, 1.9 Hz), 5.76 (1H, s), 3.94—3.87 (1H, m), 3.38 (1H, dd, J=15.0, 2.0 Hz), 3.29 (1H, s, br), 3.10 (1H, dd, J=15.2, 9.5 Hz), 3.05 (2H, d, J=7.5 Hz), 2.81 (1H, dd, J=11.7, 1.8 Hz), 2.54 (1H, dd, J=10.7, 3.1 Hz), 2.39 (1H, dd, J=13.1, 7.6 Hz), 2.25 (1H, dd, J=11.6, 3.3 Hz), 2.19 (1H, dd, J=13.1, 5.1 Hz), 1.99—1.82 (2H, m), 1.80—1.20 (11H, m), 1.30 (9H, s), 0.90 (6H, t, J=7.1 Hz). *Anal.* Calcd for $C_{27}H_{44}N_4O_6S$: C, 58.67; H, 8.02; N, 10.14. Found: C, 58.79; H, 7.75; N, 10.12.

(3*R*,4a*R*,8a*R*)-*N*-*tert*-Butyl-2-[(*R*)-2-hydroxy-3-(*N*-isobutyl-4-nitrophenylsulfonamido)propyl]decahydroisoquinoline-3-carboxamide 6 from Epoxide 8 A mixture of epoxide **8** (200 mg, 0.68 mmol) and isobutylamine (0.09 ml, 0.68 mmol) in methanol (15 ml) was stirred for 3 h at 60 °C. The mixture was concentrated and the residue was dissolved in CH_2Cl_2 (10 ml). To the solution was added dropwise *p*-nitrobenzenesulfonyl chloride (230 mg, 1.0 mmol) in CH_2Cl_2 (5 ml) and triethylamine (0.15 ml, 1.1 mmol) at 0 °C. The mixture was allowed to warm up to room temperature for 2 h, then the solvent was removed. Purification of the residue by column chromatography (on silica gel, petroleum ether/ethyl acetate/CH_2Cl_2: 4/1/1) gave **6** as a white solid (53 mg, yield 13%).

(3*R*,4a*R*,8a*R*)-*N*-*tert*-Butyl-2-[(*R*)-2-hydroxy-3-(*N*-isobutyl-4-aminophenylsulfonamido)propyl]decahydroisoquinoline-3-carboxamide 1a A mixture of compound **6** (0.30 g, 0.54 mmol) and 10% Pd–C (60 mg) in dry methanol (20 ml) was hydrogenated for 16 h under hydrogen atmosphere. Removal of the catalyst, concentration of the filtrate and purification of the residue by column chromatography (on silica gel. chloroform/ethyl acetate: 9/1) gave **1a** as a white foam solid (0.26 g, yield 90%). $[\alpha]_D^{20}$ −80.3 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3462, 3373, 3242, 2926, 2866, 1666, 1597, 1518, 1504, 1456, 1392, 1365, 1315, 1228, 1148, 1092, 1001. ^{1}H-NMR ($CDCl_3$) δ: 7.57 (2H, dt, J=8.6, 2.2 Hz), 6.67 (2H, dt, J=8.7, 2.2 Hz), 5.95 (1H, s), 4.16 (2H, s), 4.01—3.94 (1H, m), 3.47 (1H, br s), 3.14 (1H, dd, J=14.9, 1.8 Hz), 3.02 (1H, dd, J=13.2, 8.4 Hz), 2.98—2.88 (2H, m), 2.82 (1H, dd, J=13.2, 6.3 Hz), 2.52 (1H, dd, J=10.5, 3.1 Hz), 2.38 (1H, dd, J=12.9, 8.1 Hz), 2.23—2.17 (2H, m), 1.94—1.06 (13H, m), 1.27 (9H, s), 0.93

(6H, dd, J=18.4, 6.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 173.5, 150.8, 129.4×2, 126.0, 114.0×2, 70.3, 68.1, 59.9, 59.3, 58.9, 55.0, 50.5, 35.6, 32.4, 30.6, 30.5, 25.6×3, 27.1, 26.2, 25.7, 20.4, 20.1, 19.8. EI-MS m/z: 521 (M^+-1), 422. HR-MS m/z: 521.3168 (Calcd for $C_{27}H_{45}N_4O_4S$: 521.3161).

The compounds **1b**, **1d**—**e**, **1h**—**i**, **1k**—**n**, **1r**, **1s** were synthesized by the similar procedure as described for the preparation of compound **6**.

1b: Yield 30%. $[\alpha]_D^{20}$ −84 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3425, 3392, 2929, 2862, 1660, 1533, 1350, 1163. ^{1}H-NMR ($CDCl_3$) δ: 8.68 (1H, s), 8.42 (1H, d, J=8.7 Hz), 8.15 (1H, d, J=7.8 Hz), 7.73 (1H, t, J=8.1 Hz), 5.73 (1H, s), 3.91—3.94 (1H, m), 3.39 (1H, d, J=15.0 Hz), 3.12—3.16 (1H, m), 3.07 (2H, d, J=7.5 Hz), 2.83 (1H, d, J=10.8 Hz), 2.54 (1H, dd, J=10.5, 2.7 Hz), 2.38—2.45 (1H, m), 2.17—2.29 (2H, m), 1.21—1.98 (14H, m), 1.29 (9H, s), 0.89—0.93 (6H, m). ^{13}C-NMR ($CDCl_3$) δ: 173.4, 148.3, 141.8, 132.8, 130.3, 126.9, 122.5, 70.3, 67.8, 59.9×2, 57.3, 53.7, 50.9, 35.9, 33.1, 30.7×2, 28.6×3, 26.8, 26.2, 25.8, 20.4, 19.9, 19.8. EI-MS m/z: 551 (M^+-1), 452 (100). HR-MS m/z: 552.2932 (Calcd for $C_{27}H_{44}N_4O_6S$ (M^+): 552.2982).

1d: Yield 17%. $[\alpha]_D^{20}$ −76 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3371, 2960, 2929, 2864, 1664, 1518, 1340, 1157. ^{1}H-NMR ($CDCl_3$) δ: 7.73 (2H, d, J=7.8 Hz), 6.96 (2H, d, J=7.8 Hz), 5.93 (1H, s), 3.96—3.98 (1H, m), 3.86 (3H, s), 3.19 (1H, d, J=15.0 Hz), 2.87—3.03 (4H, m), 2.51—2.54 (1H, d, J=8.4 Hz), 2.35—2.41 (1H, m), 2.00 (2H, d, J=12.0 Hz), 1.24—1.91 (14H, m), 1.27 (9H, s), 0.91 (6H, dd, J=12.6, 6.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 173.4, 163.0, 130.2, 129.5×2, 114.3×2, 70.3, 68.2, 59.9, 59.4, 58.8, 55.6, 54.9, 50.6, 35.7, 33.0, 30.7, 30.6, 28.6×3, 27.1, 26.2, 25.8, 20.4, 20.1, 19.8. EI-MS m/z: 536 (M^+-1), 437 (100); HR-MS m/z: 537.3266 (Calcd for $C_{28}H_{47}N_3O_5S$: 537.3236).

1e: Yield 35%. $[\alpha]_D^{20}$ −74 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3409, 2962, 2864, 1655, 1524, 1348, 1163. ^{1}H-NMR ($CDCl_3$) δ: 8.35 (2H, d, J=8.7 Hz), 8.02 (2H, d, J=8.7 Hz), 5.77 (1H, s), 3.90—3.97 (1H, m), 3.41 (1H, dd, J=15.0, 2.7 Hz), 3.20—3.26 (2H, m), 3.05—3.13 (1H, m), 2.85 (1H, dd, J=18.0, 2.7 Hz), 2.57 (1H, dd, J=10.5, 2.7 Hz), 2.42—2.49 (1H, m), 2.20—2.32 (2H, m), 1.21—1.93 (15H, m), 1.32 (9H, s), 0.87 (3H, t, J=7.5 Hz). ^{13}C-NMR ($CDCl_3$): δ 173.5, 149.9, 145.7, 128.4×2, 124.3×2, 70.2, 68.0, 59.9, 59.8, 52.9, 51.4, 50.9, 35.8, 33.1, 30.7, 29.6, 28.7×3, 26.1, 25.7, 21.6, 20.4, 11.0. EI-MS m/z: 537 (M−1), 438 (100). HR-MS m/z: 537.2737 (Calcd for $C_{26}H_{41}N_4O_6S$: 537.2747).

1h: Yield 34%. $[\alpha]_D^{20}$ −73.2 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3373, 2926, 1674, 1597, 1462, 1336, 1153. ^{1}H-NMR ($CDCl_3$): δ: 7.72 (2H, d, J=8.7 Hz), 6.95 (2H, d, J=9.0 Hz), 5.99 (1H, s), 3.93—3.97 (1H, m), 3.85 (3H, s), 3.03—3.27 (3H, m), 2.89—2.97 (2H, m), 2.51—2.55 (1H, m), 2.37—2.44 (1H, m), 2.15—2.23 (2H, m), 1.23—1.89 (14H, m), 1.28 (9H, s), 0.85 (3H, t, J=7.5 Hz). ^{13}C-NMR ($CDCl_3$): δ 173.5, 162.9, 130.6, 129.3×2, 114.2×2, 70.1, 68.3, 59.9, 59.3, 55.6, 53.6, 52.2, 50.5, 35.7, 33.0, 30.6, 30.5, 28.6×3, 26.2, 25.7, 21.8, 20.4, 11.1. ESI-MS m/z: 546 (M+Na); HR-MS m/z: 546.2977 (Calcd for $C_{27}H_{45}N_3O_5SNa$: 546.2978).

1i: Yield 29%. mp 179—180 °C. $[\alpha]_D^{20}$ −74.3 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3361, 2922, 2850, 1662, 1518, 1338, 1155. ^{1}H-NMR ($CDCl_3$) δ: 7.73 (2H, d, J=9.3 Hz), 6.97 (2H, d, J=9.0 Hz), 5.90 (1H, s), 3.91—3.99 (1H, m), 3.87 (3H, s), 2.87—3.21 (5H, m), 2.50—2.55 (1H, m), 2.35—2.42 (1H, m), 2.18—2.24 (2H, m), 1.15—1.83 (22H, m), 1.27 (9H, s), 0.85—0.93 (2H, m). ^{13}C-NMR ($CDCl_3$): δ 173.4, 162.9, 130.3, 129.4×2, 114.2×2, 77.2, 70.3, 68.0, 59.9, 59.4, 57.3, 55.6, 54.8, 50.6, 36.3, 35.7, 33.0, 30.9, 30.6×3, 28.6×3, 26.4, 26.1, 26.0, 25.7, 20.4. EI-MS m/z: 576 (M−1), 477 (100). HR-MS m/z: 577.3535 (Calcd for $C_{31}H_{51}N_3O_5S$: 577.3549).

1k: Yield 15%. mp 74—76 °C. $[\alpha]_D^{20}$ −60 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3379, 2926, 2860, 1660, 1498, 1259, 1153. ^{1}H-NMR ($CDCl_3$) δ: 7.77 (2H, d, J=9.0 Hz), 7.24—7.29 (5H, m), 6.97 (2H, d, J=9.0 Hz), 5.94 (1H, s), 4.42 (2H, dd, J=30.9, 14.7 Hz), 4.06—4.14 (1H, m), 3.86 (3H, s), 3.76—3.79 (1H, m), 3.29 (1H, d, J=12.3 Hz), 2.92—3.00 (1H, m), 2.62 (1H, d, J=12.0 Hz), 2.42 (1H, d, J=10.2 Hz), 2.25—2.29 (1H, m), 2.02—2.09 (4H, m), 1.24—1.76 (10H, m), 1.21 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 173.5, 163.0, 136.3, 131.0, 129.4×2, 128.7×2, 128.4×2, 127.9, 114.3×2, 69.9, 67.3, 60.0, 58.8, 55.6, 53.5, 52.8, 50.5, 35.5, 32.9, 30.6, 30.4, 28.6×3, 26.1, 25.6, 20.5. EI-MS m/z: 570 (M−1), 471 (100). HR-MS m/z: 570.3025 (Calcd for $C_{31}H_{44}N_3O_5S$: 570.3002).

1l: Yield 30%. mp 161—162 °C. $[\alpha]_D^{20}$ −80 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3386, 2926, 2862, 1660, 1529, 1350, 1161. ^{1}H-NMR ($CDCl_3$) δ: 8.37 (2H, d, J=8.7 Hz), 8.15 (1H, d, J=8.1 Hz), 8.07 (2H, d, J=9.0 Hz), 7.76 (1H, d, J=7.5 Hz), 7.51—7.56 (1H, m), 5.58 (1H, s), 4.64—4.79 (2H, m), 3.78—3.81 (1H, m), 3.48 (1H, dd, J=15.0, 1.8 Hz), 3.09—3.17 (1H, m), 2.51—2.59 (2H, m), 2.36—2.42 (1H, m), 2.25 (1H, dd, J=12.0, 3.0 Hz), 2.10—2.16 (1H, m), 1.83—1.91 (1H, m), 1.15—1.72 (13H, m), 1.27 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 173.7, 150.0, 148.4, 146.1, 138.4, 134.5, 129.8, 128.4×2, 124.4×2, 123.0, 122.9, 70.2, 67.8, 60.0×2, 51.7, 51.6, 50.9, 35.9, 33.0, 30.8, 30.6, 28.6×3, 26.1, 25.5, 20.3. ESI-MS m/z: 632 (M+1). HR-MS m/z: 632.2751 (Calcd for $C_{30}H_{42}N_5O_8S$: 632.2754).

1m: Yield 31%. mp 76—78 °C. $[\alpha]_D^{20}$ −76 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3385, 2928, 2860, 1660, 1533, 1352, 1163. ^{1}H-NMR ($CDCl_3$) δ: 8.69—8.70 (1H, m), 8.42—8.46 (1H, m), 8.12—8.20 (2H, m), 8.05—8.06 (1H, m), 7.71—7.76 (2H, m), 7.50—7.56 (1H, m), 5.61 (1H, s), 4.63—4.83 (2H, m), 3.82—3.85 (1H, m), 3.48 (1H, m), 3.13—3.21 (1H, m), 2.81—2.83 (1H, m), 2.62 (1H, dd, J=11.7, 2.7 Hz), 2.53 (1H, dd, J=11.4, 3.6 Hz), 2.36—2.43 (1H, m), 2.25 (1H, dd, J=11.7, 3.3 Hz), 2.14 (1H, dd, J=13.5, 8.4 Hz), 1.84—1.92 (1H, m), 1.60—1.76 (11H,m), 1.25 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 173.6, 148.4, 148.3, 142.5, 138.3, 134.5, 132.6, 130.5, 129.8, 127.1, 123.0×2, 122.4, 70.2, 68.0, 60.2, 59.8, 51.9, 51.7, 51.0, 35.9, 33.1, 30.8, 30.6, 28.6×3, 26.1, 25.6, 20.4. ESI-MS m/z: 632 (M+1). HR-MS m/z: 632.2781 (Calcd for $C_{30}H_{42}N_5O_8S$: 632.2754).

1n: Yield 37%. mp 111—112 °C. $[\alpha]_D^{20}$ −79 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3377, 2928, 2860, 1655, 1527, 1350, 1157. ^{1}H-NMR ($CDCl_3$) δ: 8.13 (1H, d, J=8.1 Hz), 8.01 (1H, s), 7.78 (2H, d, J=9.0 Hz), 7.24 (1H, d, J=8.7 Hz), 7.51 (1H, t, J=8.1 Hz), 6.99 (1H, d, J=9.0 Hz), 5.76 (1H, s), 4.59 (2H, d, J=4.2 Hz), 3.89 (3H, s), 3.44 (1H, dd, J=15.0, 2.4 Hz), 2.92—3.00 (1H, m), 2.65 (1H, dd, J=12.6, 2.4 Hz), 2.49 (1H, dd, J=13.8, 3.0 Hz), 2.33—2.39 (1H, m), 2.04—2.18 (2H, m), 1.19—1.83 (15H, m), 1.25 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 173.2, 163.2, 148.3, 139.1, 134.5, 130.9, 129.6, 129.3×2, 122.9, 122.7, 114.5×2, 70.2, 68.2, 60.0, 59.6, 55.7, 52.8, 52.6, 50.8, 35.7, 33.0, 30.6, 29.7, 28.6×3, 26.0, 25.6, 20.5. EI-MS m/z: 615 (M−1), 516 (100); HR-MS m/z: 615.2835 (Calcd for $C_{31}H_{43}N_4O_7S$: 615.2853).

1r: Yield 28%. mp 126—128 °C. $[\alpha]_D^{20}$ −79.2 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3383, 2941, 2864, 1657, 1491, 1325, 1254, 1155, 1095, 1026, 806. ^{1}H-NMR ($CDCl_3$) δ: 7.78 (2H, d, J=8.4 Hz), 6.99 (2H, d, J=9.0 Hz), 6.79 (1H, s), 6.71 (2H, s), 5.94 (2H, s), 4.26—4.38 (2H, m), 3.88 (3H, s), 3.80—3.82 (1H, m), 3.26—3.32 (1H, m), 3.93—3.01 (1H, m), 2.67—2.71 (1H, m), 2.46 (1H, dd, J=9.6, 3.3 Hz), 2.29—2.36 (1H, m), 2.04—2.13 (2H, m), 1.19—1.79 (14H, m), 1.25 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 173.5, 163.0, 148.1, 147.4, 131.1, 130.0, 129.4×2, 121.9, 114.3×2, 108.8, 108.2, 101.1, 69.9, 67.4, 60.1, 58.8, 55.6, 53.3, 52.7, 50.5, 35.5, 33.0, 30.6, 30.4, 28.6×3, 26.1, 25.7, 20.5. EI-MS m/z: 614 (M−1), 515 (100). HR-MS m/z: 614.2912 (Calcd for $C_{32}H_{44}N_3O_7S$: 614.2900).

1s: Yield 27%. mp 104—106 °C. $[\alpha]_D^{20}$ −62.3 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3332, 2926, 2864, 1649, 1531, 1350, 1159. ^{1}H-NMR ($CDCl_3$) δ: 8.34 (2H, d, J=8.7 Hz), 8.02 (2H, d, J=8.7 Hz), 6.77 (1H, s), 6.73 (2H, s), 5.94 (2H, s), 5.72 (1H, s), 4.37—4.51 (2H, m), 3.79—3.82 (1H, m), 3.40 (1H, dd, J=14.8, 2.9 Hz), 3.11—3.19 (1H, m), 2.64 (1H, dd, J=3.9, 0.9 Hz), 2.51 (1H, dd, J=10.2, 2.7 Hz), 2.34—2.41 (1H, m), 2.09—2.21 (2H, m), 1.33—1.92 (13H, m), 1.28 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 173.7, 149.8, 148.1, 147.6, 146.3, 129.2, 128.4×2, 124.2×2, 122.1, 108.8, 108.3, 101.2, 70.1, 67.4, 60.0, 59.6, 52.5, 51.8, 50.9, 35.8, 33.0, 30.6×2, 28.6×3, 26.1, 25.6, 20.5. EI-MS m/z: 629 (M−1), 530 (100). HR-MS m/z: 629.2652 (Calcd for $C_{32}H_{44}N_3O_7S$ (M−1): 629.2645).

The syntheses of compounds **1c**, **1f**, **1g**, **1j**, **1o**—**q**, **1t**—**u** were carried out by the similar procedure as described for the preparation of **1a**.

1c: Yield 84%. $[\alpha]_D^{20}$ −83 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3456, 3375, 2926, 1664, 1317, 1151. ^{1}H-NMR ($CDCl_3$) δ: 7.24—7.29 (1H, m), 7.13 (1H, d, J=7.5 Hz), 7.07 (1H, s), 6.84 (1H, d, J=8.1 Hz), 5.92 (1H, s), 3.92—3.98 (3H, m), 3.21 (1H, d, J=13.6 Hz), 2.85—3.10 (4H, m), 2.53 (1H, dd, J=10.2, 2.7 Hz), 2.36—2.43 (1H, m), 2.17—2.13 (2H, m), 1.25—1.93 (14H, m), 1.28 (9H, s), 0.94 (6H, dd, J=17.7, 6.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 173.5, 147.4, 139.1, 130.0, 118.9, 116.7, 113.0, 70.3, 68.2, 59.9, 59.4, 59.0, 55.1, 50.6, 35.7, 33.0, 30.7, 30.6, 28.6×3, 27.2, 26.2, 25.8, 20.4, 20.1, 19.8. EI-MS m/z: 521 (M−1), 422 (100). HR-MS m/z: 522.3238 (Calcd for $C_{27}H_{46}N_4O_4S$: 522.3240).

1f: Yield 86%. $[\alpha]_D^{20}$ −76.6 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3469, 3358, 3246, 2926, 2866, 1668, 1597, 1317, 1149. ^{1}H-NMR ($CDCl_3$) δ: 7.57 (2H, d, J=8.4 Hz), 6.67 (2H, d, J=8.7 Hz), 6.00 (1H, s), 4.16 (2H, s), 3.94—4.01 (1H, m), 2.89—3.22 (6H, m), 2.52—2.55 (1H, m), 2.38—2.45 (1H, m), 2.21 (2H, dd, J=12.0, 3.9 Hz), 1.25—1.88 (14H, m), 1.29 (9H, s), 0.88 (3H, t, J=6.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 173.6, 150.8, 129.3×2, 126.5, 114.0×2, 70.3, 68.4, 59.9, 59.3, 53.9, 52.5, 50.6, 35.7, 33.0, 30.7, 30.6, 28.6×3, 26.2, 25.8, 21.9, 20.5, 11.1. EI-MS m/z: 507 (M−1), 408 (100). HR-MS m/z: 507.3002 (Calcd for $C_{26}H_{43}N_4O_4S$: 507.3005).

1g: Yield 56%. mp 185—187 °C. $[\alpha]_D^{20}$ −70 (c=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3456, 3369, 2925, 1649, 1531, 1315, 1151. ^{1}H-NMR ($CDCl_3$) δ: 7.23—7.28 (1H, m), 7.13 (1H, d, J=7.2 Hz), 7.08—7.09 (1H, m), 6.82—6.85 (1H, m), 5.97 (1H, s), 3.91—3.99 (2H, m), 2.90—3.29 (5H, m), 2.53—2.57 (1H, m), 2.40—2.47 (1H, m), 2.19—2.27 (2H, m), 1.23—1.86 (16H, m), 1.30 (9H, m), 0.86—0.91 (3H, m); ^{13}C-NMR ($CDCl_3$) δ: 173.5, 147.4,

139.6, 130.0, 118.8, 116.6, 112.9, 70.2, 68.4, 59.9, 59.4, 53.9, 52.5, 50.6, 35.7, 33.0, 30.6×2, 28.6×3, 26.2, 25.8, 21.9, 20.5, 11.1. EI-MS *m/z*: 507 (M−1), 408 (100). HR-MS *m/z*: 507.3019 (Calcd for $C_{26}H_{43}N_4O_4S$: 507.3005).

1j: Yield 69%. mp 111—112 °C. $[\alpha]_D^{20}$ −77 (*c*=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3471, 3379, 2926, 2862, 1653, 1597, 1309, 1148. ^{1}H-NMR ($CDCl_3$) δ: 7.56 (2H, d, *J*=8.7 Hz), 7.15—7.32 (5H, m), 6.65 (2H, d, *J*=8.4 Hz), 5.98 (1H, s), 4.14 (1H, s), 3.91 (1H, s, br), 3.27—3.41 (4H, m), 2.87—2.99 (5H, m), 2.55 (1H, d, *J*=8.4 Hz), 2.40—2.47 (1H, m), 2.22 (1H, d, *J*=12.0 Hz), 1.25—1.87 (13H, m), 1.31 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 150.8, 150.0, 138.4, 129.4×2, 128.8×2, 128.6×2, 126.6, 114.1×2, 112.5, 70.2, 68.3, 59.8, 59.4, 54.2, 52.3, 50.7, 35.7, 35.5, 33.0, 30.6, 29.7, 28.7×3, 26.1, 25.9, 20.5. EI-MS *m/z*: 569 (M−1), 470 (100). HR-MS *m/z*: 570.3255 (Calcd for $C_{31}H_{46}N_4O_4S$: 570.3240).

1o: Yield 81%. mp 96—102 °C. $[\alpha]_D^{20}$ −69 (*c*=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3448, 3375, 2926, 2860, 1664, 1597, 1498, 1259, 1153. ^{1}H-NMR ($CDCl_3$) δ: 1.79 (2H, d, *J*=8.7 Hz), 7.06 (1H, t, *J*=7.8 Hz), 6.99 (2H, d, *J*=8.7 Hz), 6.22 (1H, s), 6.58 (2H, dd, *J*=7.5, 1.2 Hz), 5.99 (1H, s), 4.21—4.37 (2H, m), 3.88 (3H, s), 3.82—3.86 (1H, m), 3.26 (1H, dd, *J*=15.0, 2.7 Hz), 2.92—3.01 (1H, m), 2.71 (1H, dd, *J*=12.0, 2.4 Hz), 2.43—2.46 (1H, m), 2.30—2.37 (1H, m), 2.02—2.08 (2H, m), 1.17—1.78 (15H, m), 1.26 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 173.6, 163.0, 147.1, 137.3, 130.9, 129.6, 129.4×2, 118.3, 114.7×2, 114.3×2, 69.9, 67.6, 60.0, 58.8, 55.6, 53.7, 53.2, 50.5, 35.6, 33.0, 30.6, 30.4, 28.6×3, 26.1, 25.7, 20.6. ESI-MS *m/z*: 587.3 (M+1, 100), 486.4 (23). HR-MS *m/z*: 587.3285 (Calcd for $C_{31}H_{47}N_4O_5S$: 587.3267).

1p: Yield 49%. $[\alpha]_D^{20}$ −62.5 (*c*=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3450, 3365, 3238, 2926, 2860, 1662, 1597, 1313, 1149. ^{1}H-NMR ($CDCl_3$) δ: 7.63 (2H, d, *J*=8.7 Hz), 7.06—7.12 (1H, m), 6.69 (2H, d, *J*=9.0 Hz), 6.49—6.56 (3H, m), 6.03 (1H, s), 4.23—4.35 (2H, m), 4.15 (2H, s), 3.81—3.84 (1H, m), 3.24 (1H, dd, *J*=14.7, 3.0 Hz), 2.91—2.99 (1H, m), 2.79 (2H, s), 2.69 (1H, dd, *J*=12.3, 3.0 Hz), 2.41—2.45 (1H, m), 2.28—2.35 (1H, m), 2.01—2.10 (2H, m), 1.18—1.76 (13H, m), 1.25 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 173.7, 150.9, 147.1, 137.6, 129.6, 129.5×2, 126.9, 118.4, 114.7×2, 114.1×2, 69.9, 67.5, 60.0, 58.7, 53.9, 53.3, 50.5, 35.5, 32.9, 30.6, 30.4, 28.6×3, 26.1, 25.7, 20.6. ESI-MS *m/z*: 572 (M+1). HR-MS *m/z*: 572.3294 (Calcd for $C_{30}H_{46}N_5O_4S$: 572.3271).

1q: Yield 54%. $[\alpha]_D^{20}$ −71 (*c*=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3373, 2926, 2860, 1655, 1599, 1315, 1153, 773. ^{1}H-NMR ($CDCl_3$) δ: 7.03—7.30 (4H, m), 6.83—6.86 (1H, m), 6.54—6.60 (3H, m), 6.00 (1H, s), 4.23—4.40 (2H, m), 3.98 (2H, s), 3.81—3.83 (1H, m), 3.70 (2H, s), 3.25—3.31 (1H, m), 2.94—3.02 (1H, m), 2.69 (1H, dd, *J*=11.7, 2.1 Hz), 2.42—2.47 (1H, m), 2.29—2.36 (1H, m), 2.02—2.08 (2H, m), 1.23—1.82 (13H, m), 1.25 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 173.5, 147.5, 147.1, 139.9, 137.4, 130.1, 129.6, 118.9, 118.4, 116.7, 114.8×2, 113.0, 69.9, 67.4, 60.0, 58.8, 53.9, 53.2, 50.6, 35.5, 32.9, 30.6, 30.4, 28.6×3, 26.1, 25.7, 20.6. EI-MS *m/z*: 570 (M−1), 408 (100). HR-MS *m/z*: 571.3111 (Calcd for $C_{30}H_{44}N_5O_4S$: 571.3114).

1t: Yield 72%. $[\alpha]_D^{20}$ −79 (*c*=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3466, 3373, 3242, 2924, 2860, 1664, 1597, 1504, 1244, 1149. ^{1}H-NMR ($CDCl_3$) δ 7.58 (2H, d, *J*=3.0 Hz), 6.78 (1H, s), 6.65—6.70 (4H, m), 6.00 (1H, s), 5.91 (2H, s), 4.20—4.35 (2H, m), 4.30 (2H, s), 3.76—3.79 (1H, m), 3.24 (1H, dd, *J*=15.0, 2.7 Hz), 2.89—2.97 (2H, m), 2.66 (1H, d, *J*=11.4 Hz), 2.41—2.44 (1H, m), 2.26—2.33 (1H, m), 2.01—2.10 (2H, m), 1.17—1.76 (11H, m), 1.23 (9H, s). ^{13}C-NMR ($CDCl_3$): δ 173.7, 148.1, 147.4×2, 130.2, 129.4×2, 121.9, 114,1, 112.6, 108.9, 108.2×2, 101.2, 69.9, 67.2, 60.0, 58.8, 53.5, 52.9, 50.5, 35.5, 32.9, 30.6, 29.7, 28.6×3, 26.1, 25.7, 20.6. EI-MS *m/z*: 599 (M−1), 500 (100); HR-MS *m/z*: 600.3031 (Calcd for $C_{31}H_{44}N_4O_6S$: 600.2982).

1u: Yield 39%. mp 106—109 °C. $[\alpha]_D^{20}$ −62.9 (*c*=1.00, $CHCl_3$). IR (KBr) cm^{-1}: 3375, 2924, 2860, 1662, 1489, 1448, 1317, 1242, 1153, 1040. ^{1}H-NMR ($CDCl_3$) δ 7.58 (2H, d, *J*=9.0 Hz), 6.78 (1H, s), 6.65—6.70 (4H, m), 6.00 (1H, s), 5.91 (2H, s), 4.20—4.35 (2H, m), 4.30 (2H, s), 3.76—3.80 (1H, m,), 3.24 (1H, dd, *J*=11.7, 2.7 Hz), 2.89—2.97 (2H, m), 2.66 (1H, d, *J*=8.1 Hz), 2.41—2.44 (1H, m), 2.26—2.33 (1H, m), 2.01—2.10 (2H, m), 1.17—1.76 (12H, m), 1.23 (9H, s). ^{13}C-NMR ($CDCl_3$): δ 173.6, 148.1, 147.4, 140.1, 130.1, 130.0×2, 122.0, 118.9, 116.5, 112.9, 108.9, 108.2, 101.2, 69.8, 67.4, 60.0, 58.8, 53.5, 52.8, 50.6, 35.5, 32.9, 30.5, 30.4, 28.6×3, 26.1, 25.7, 20.6. ESI-MS *m/z*: 623 (M+Na); HR-MS *m/z*: 623.2898 (Calcd for $C_{31}H_{44}N_4O_6SNa$: 623.2879).

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