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Synthesis of Potential Inhibitors of the Glycosphingolipid Biosynthesis

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Abstract: A synthesis of ceramide analogs **6** and **7** is reported here starting from L-cysteine. Alkylation of **2** and subsequent reduction of the intermediate formed ketone **3** afforded the diastereomeric alcohols **4**. Deprotection and acylation of **4** lead to the desired product **6** which is converted to the sulfonium salt **7**. Compound **6** is a powerful inhibitor of the glycosphingolipid biosynthesis.

Glycosphingolipids (GSL) are components of the plasma membrane of vertebrates. At the cell surface they form cell-typical patterns which undergo changes with cell growth, differentiation, upon viral transformation and oncogenesis.[1-6]

The biosynthesis of the GSL starts with the formation of ceramide (N-acylsphingosine, Figure 1) in the endoplasmic reticulum followed by step-wise glycosylation in the compartments of the Golgi apparatus which leads to the different GSL.[1,7,8]

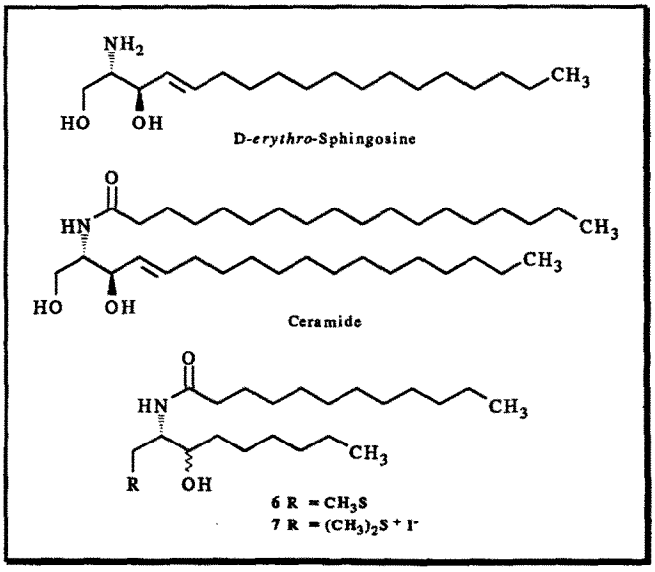


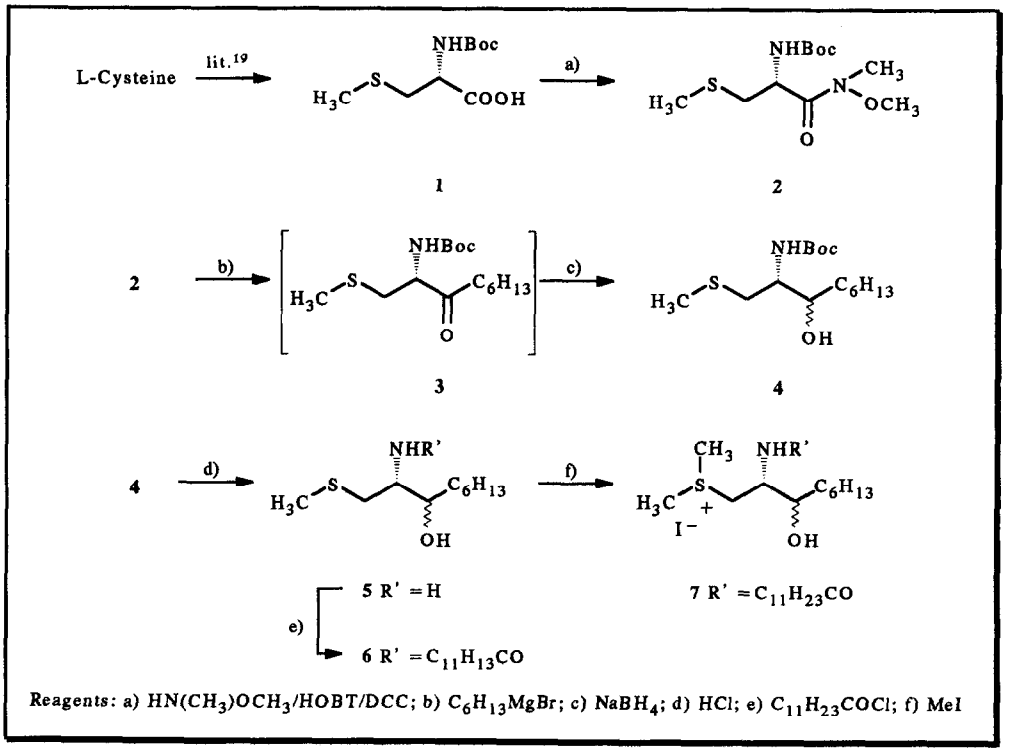
Figure 1

It is known that GSL interact with toxines, viruses and bacteria as well as membrane bound receptors and enzymes.[9] Recently sialyl Lewis x (SLe^x) determinants on GSL were found to be the ligands for the endothelial leukocyte adhesion molecule-1 (ELAM-1).[10]

The whole biological functions of GSL are poorly understood since (1) no genetic defects of eucaryotic GSL biosynthesis have been found, (2) no specific inhibitors of individual glycosylation steps are available.

Sphingoids themselves have been found to be inhibitors of protein kinase C.[11] Cycloserine,[12] β-fluoroalanine,[13] β-chloroalanine[13] and the sphingofungins[14] were reported as inhibitors of the serine palmitoyltransferase, the first enzyme of GSL-biosynthesis. *Radin et al.* reported that D-*threo*-1-phenyl-2-decanoylamino-3-morpholino-1-propanol inhibits glucosyl ceramide synthase forming glucosylceramide from ceramide and UDP-glucose.[15] Recently fumonisine B1, a mycotoxin of *Fusarium moniliforme*, has been found to inhibit dihydroceramide synthase.[16] Furthermore we found that exogenous sphingosines and azidosphingosine (2S,3R,4E-2-azido-octadec-4-ene-1,3-diol)[17] decreased serine palmitoyltransferase activity.[18,19]

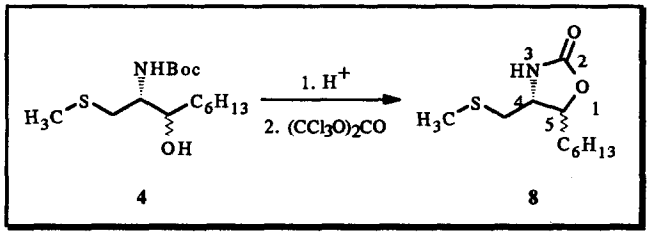
In this paper we describe the synthesis (Scheme 1) of **6** and **7** as structural analogs of ceramide. These compounds might be inhibitors of the glucosylceramide synthase. Compared to ceramide no further glycosylation at position 1 is possible. Moreover it is possible that **7** acts as a suicide inhibitor due to the alkylating properties of the sulfonium group.[20]



Scheme 1

Treatment of N-Boc-S-methyl-L-cysteine[21] **1** with N,O-dimethylhydroxylamine hydrochloride in the presence of hydroxybenzotriazole (HOBT), dicyclohexylcarbodiimide (DCC) and ethyldiisopropylamine according to *König* and *Geiger*[22] led to amide **2**. Alkylation with hexylmagnesium bromide following the procedure previously reported by *Nahm* and *Weinreb*[23] yielded ketone **3** (scheme 1) which was reduced without further purification by $NaBH_4$[24,25,26] forming the diastereomeric alcohols **4**. They were easily separated by column chromatography on silica gel. After removal of the Boc group with HCl gas in diethyl ether, subsequent acylation of the free amino group with lauroyl chloride in THF/50% NaOAc afforded the ceramide analogs **6**. They were converted into the corresponding sulfonium salts **7** by treatment with methyl iodide.

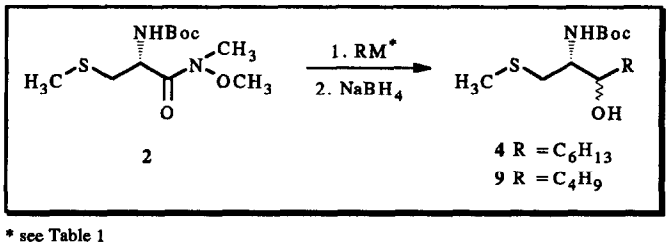
The relative configuration of the diastereomeric alcohols **4** was established after transformation into the corresponding oxazolidinones **8** (Scheme 2). Generally, the coupling constants of the *cis*-isomers (*erythro*) of such 4,5-disubstituted oxazolidinones are greater than those of the *trans*-isomer (*threo*).[27] Determined coupling constants $^3J_{H4,H5}$ showed that the reduction of ketone **3** with $NaBH_4$ predominantly led to the *erythro*-isomer with a coupling constant of 7.4 Hz whereas the *threo*-isomer showed a coupling constant of 5.1 Hz. This stereoselectivity observed was in agreement with the results reported in the literature.[24,25,26,28]



4 **8**

Scheme 2

The enantiomeric purity of the alcohols **4** was determined by the *Mosher* method.[29] In contrast to results of other authors[24,25,26,28] we observed a high degree of racemization during the formation of **4**. In order to suppress these racemization several reaction conditions as well as various organometallics R-M (R= n-Bu; M = MgBr, Li, $CeCl_2$) were tested in a model reaction (Scheme 3). As shown in Table 1 the best results were obtained using a 2.5 fold excess of alkyllithio compounds at low temperature. Further investigations on the described synthesis are in progress.



2

4 R = C_6H_{13}
9 R = C_4H_9

* see Table 1

Scheme 3

First biological experiments show that compound **6** is a potent inhibitor of the glycosphingolipid biosynthesis. The kind of inhibition is not yet known. The results will be reported elsewere.

Table 1: Addition of Organometallic Compounds to N-Methoxy-N-methylamide 2 and Subsequently Reduction with $NaBH_4$ (Scheme 3)

RM	T [°C]	equiv. RM	Product	Diastereomeric ratio	Racemi-zation [%]	Total yields [%]*
$n\text{-}C_6H_{13}MgBr$	- 30	5	4	8 : 2	40	40
$n\text{-}C_4H_9Li$	- 30	5	9	9 : 2	10	37
$n\text{-}C_4H_9CeCl_2$[30]	- 78	2	9	5 : 2	13	38
$n\text{-}C_4H_9Li$	- 78	2.5	9	5 : 2	<5	25

*Yields are not optimized

EXPERIMENTAL

Solvents were purified in the usual way. Water sensitive reactions were carried out in flame-dried glasware under argon. Tlc: Merck precoated tlc-plates, silica gel 60; detection by ninhydrin or a solution of 2.5 g phosphormolybdic acid, 1 g cerium-IV-sulfate tetrahydrate and 6 ml conc. sulfuric acid in 100 ml water, followed by heating.
Column chromatography: Merck silica gel 60, 43-60 mm.
^{1}H-NMR: Bruker, CR 200; chemical shifts (d) are indicated in ppm using TMS as internal standard.
HR-MS: A.E.I., Manchester, MS-50 (DE 180 °,70 eV).
Melting points were recorded on a Büchi capillary melting point apparatus and are uncorrected.

S-Methyl-N_α-(*tert.*-butyloxycarbonyl)-cysteine-N-methoxy-N-methylamide (2): The protected amino acid **1** (1.18 g, 5 mmol) and hydroxybenzotriazole (770 mg, 5.5 mmol) were dissolved in 100 ml tetrahydrofuran (THF) and cooled to 0 °C. Dicyclohexylcarbodiimide (1.14 g, 5.5 mmol) was added and the solution was stirred for 1h at 0 °C and for 1 h at room temperature followed by addition of N,O-dimethylhydroxylamine hydrochloride (Fluka, 540 mg, 5.5 mmol) and ethyldiisopropylamine (900 ml). After 12 h the reaction was complete. The precipitate was filtered off and washed with cold THF. The combined filtrates were evaporated in vacuo affording a yellow oil which was chromatographed on silica gel [n-hexane/ethyl acetate 4:1] yielded 1.1 g (78 %) 2 as an colourless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.38 (s, 3 H, $C(CH_3)_3$), 2.09 (s, 3 H, SCH_3), 2.67 (dd, J =14 Hz and 7 Hz, 1 H, H-b), 2.83 (dd, J = 14 Hz and 5.6 Hz, 1 H, H-b'), 3.18 (s, 3 H, N-CH_3), 3.73 (s, 3 H, OCH_3), 4.84 (m, 1 H, H-a), 5.34 (d, br., 1 H, NH).;Anal. Cald. (%) for $C_{11}H_{22}NO_4S$ (278.37): C 47.46 H 7.97 N 10.06; Found (%): C 47.21 H 7.91 N 10.12.

1-Methylthio-2-(N-*tert.*-butyloxycarbonyl)-amino-3-hydroxynonane (4): Amide **3** (4.68 g, 16.8 mmol) was dissolved under argon in 120 ml dry THF and cooled to - 23 °C. To this mixture 42 ml of a 2 M solution of hexylmagnesium bromide in diethyl ether (84 mmol) was added dropwise. After the reaction was complete [tlc, silica gel, n-hexane/ethyl acetate 4:1] the mixture was poured onto 100 ml of 1 M NaH_2PO_4 while stirring vigorously, and extracted with ethyl acetate (2 x 100 ml). The combined organic extracts were washed subsequently with 1 M NaH_2PO_4 (1 x 50 ml) and saturated NaCl (1 x 50 ml), dried over $MgSO_4$ and evaporated in vacuo. The residue was dissolved in 150 ml isopropyl alcohol and cooled to 0° C, sodium borohydride (165 mg, 50 mmol) was added and the mixture was stirred for 12 h at 0 °C. The reaction was quenched by adding 150 ml 1 N HCl dropwise. The resulting solution was extracted with ethyl acetate (3 x 50 ml) and the combined extracts were washed with saturated $NaHCO_3$ (2 x 50 ml) and saturated NaCl (1 x 50 ml), dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel [n-hexane/ethyl acetate 5:1] to separate the diastereomeric alcohols **4**.
threo-isomer: 420 mg (8 %); m.p. 60 - 62 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.89 (t, J = 7 Hz, 3 H), 1.2 - 1.6 (m, 19 H), 1.9 (s, br., 1 H), 2.19 (s, 1 H), 2.69 (m, 2 H), 3.66 (m, 1 H), 3.89 (m, 1 H), 4.95 (d, br., 1 H); Anal. Calcd. (%) for $C_{15}H_{31}NO_3S$ (305.48): C 58.98 H 10.23 N 4.59; Found (%): C 59.03 H 10.38 N 4.78.
erythro-isomer: 1.7 g (32 %); m.p. 89 - 91° C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.87 (t, J = 7 Hz, 3 H), 1.20 - 1.60 (m, 19 H), 2.1 (s, 3 H), 2.26 (s, br.,1 H), 2.60 - 2.80 (m, 2 H), 3.70 (m, 2 H), 4.97 (br., 1 H); Anal. Calcd. (%) for $C_{15}H_{31}NO_3S$ (305.48): C 58.98 H 10.23 N 4.59; Found (%): C 59.14 H 10.31 N 4.39.

2-Amino-1-methylthio-3-hydroxy-nonane hydrochloride (5): The protected alcohols **4** were dissolved in diethyl ether saturated with HCl gas and stirred for 4 h at room temperature. The reaction mixture was evaporated to dryness and the residue was recrystallized from ethanol/diethyl ether.

threo-isomer: 160 mg (98 %) from 205 mg (0.67 mmol) of *threo*-**4**; m.p. 71 - 72 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.88 (t, J = 6,8 Hz, 3 H), 1.20 - 1.70 (m, 10 H), 2.19 (s, 3 H), 2.88 (d, J = 7 Hz, 2 H), 3.49 (m, 1 H), 4.09 (s, br., 1 H), 4.22 (m, 1 H), 8.05 (m, 3 H); Anal. Calcd. (%) for $C_{10}H_{25}ClNOS$ (241.82): C 49.67, H 10.00, N 5.79,Found: C 49.58 H 10.15 N 5.84.
erythro-isomer: 386 mg (>98 %) from 500 mg (1.6 mmol) of *erythro*-**4**; m.p. 128 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.88 (t, J = 6,8 Hz, 3 H), 1.20 - 1.70 (m, 10 H), 2.08 (s, 3 H), 2.78 (dd, J = 4 Hz, J = 14 Hz, 1 H), 2.90 (dd, J = 14 Hz, 1 H), 3.44 (m, 1 H), 4.03 (s, br., 1 H), 4.22 (m, 1 H), 8.10 (m, 3 H); Anal. Calcd. (%) for $C_{10}H_{25}ClNOS$ (241.82): C 49.67, H 10.00, N 5.79; Found (%): C 48.87 H 9.71 N 5.25.

2-(N-Lauroyl)-amino-1-methylthio-3-hydroxy-nonane (**6**): The deprotected amino alcohols **5** were dissolved in a mixture of THF/50 % NaOAc and lauroyl chloride was added dropwise. After 2 h the reaction was complete. The organic layer was separated, washed with saturated NaCl, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel [n-hexane/ethyl acetate 2:1].
threo-isomer: 175 mg (70 %) from 154 mg (638 μmol) *threo*-**5** and 153 μl (638 μmol) lauroyl chloride; m.p. 48 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.88 (m, 6 H), 1.15 - 1.50 (m, 26 H), 1.52 - 1.67 (m, 2 H), 2.13 (s, 3 H, CH_3S), 2.19 (t, J = 7 Hz, 2 H), 2.38 (d, J = 4 Hz, 1 H), 2.65 (dd, J = 14 Hz, J = 6.2 Hz, 1 H), 2.73 (dd, J = 14 Hz, J = 7 Hz, 1 H), 3.87 - 4.06 (m, 2 H), 5.90 (d, J = 7 Hz, NH); Anal. Calcd. (%) for $C_{22}H_{45}NO_2S$ (387.66): C 68.16 H 11.70 N 3.61; Found (%): C 67.65, H 11.28, N 3.47.
erythro-isomer: 124 mg (83 %) from 93 mg (385 μmol) *erythro*-**5** and 96 μl (385 μmol) lauroyl chloride; mp. 87 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.89 (m, 6 H), 1.15 - 1.50 (m, 26 H), 1.52 - 1.70 (m, 2 H), 2.10(s, 3 H), 2.22 (t, J = 7 Hz, 2 H), 2.45 (s, br., 1 H), 2.67 (dd, J = 14 Hz, J = 8 Hz, 1 H), 2.78 (dd, J = 14 Hz, J = 4.2 Hz 1H), 3.68 (m, 1 H), 4.00 (m, 1 H), 5.97 (d, J = 7 Hz, 1 H, NH); Anal. Calcd. (%) for $C_{22}H_{45}NO_2S$ (387.66): C 68.16 H 11.70 N 3.61; Found (%): C 68.00 H 11.73, N 3.37.

1-Dimethylsulfonium-2-dodecanoylamino-3-hydroxy-nonane-iodide (**7**): The ceramide analoga **6** were dissolved in ethanol and methyl iodide (1 ml/ 200 μmol of **6**) was added. The reaction mixture was stirred for 24 h at 50 °C and evaporated to dryness. The residue was recrystallized from ethanol/diethyl ether.
threo-isomer: 200 mg (84 %) from 175 mg (451 μmol) *threo*-**6**; m.p. 112 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.86 (t, 6 H), 1.14 - 1.70 (m, 28 H), 2.33 (t, 2 H), 3.24 (s, 3 H), 3.27 (s, 3 H), 3.94 (m, 1 H), 4.22 (m, 3 H), 4.39 (m, 1 H), 7.22 (d, 1 H, NH); Anal. Calcd. (%) for $C_{23}H_{48}NO_2S$ (529.60): C 52.16 H 9.14 N 2.64; Found (%): C 51.75 H 9.10 N 2.89.
erythro-isomer: 124 mg (91 %) from 100 mg (260 μmol) *erythro*-**6**; m.p. 112 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.88 (t, 6 H), 1.15-1.40 (m, 24 H), 1.60 (m, 4 H), 2.33 (t, 2 H), 3.18 (s, 3 H), 3.27 (s, 3 H), 3.96 (m, 1 H), 4.02-4.30 (m, 4 H), 7.63 (d, 1 H, NH); Anal. Calcd. (%) for $C_{23}H_{48}NO_2S$ (529.60): C 52.16 H 9.14 N 2.64; Found (%): C 51.75 H 9.10 N 2.89.

Oxazolidinone (**8**): The aminoalcohols **5** (1 eq.) were dissolved in dichloromethane (10 ml/mmol) and triphosgene (0.3 eq.) and triethylamine (1 eq.) were added. After 1 h the reaction mixture was hydrolyzed with H_2O. The organic layer was separated and washed successively with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel [n-hexane/ethyl acetate 1:1].
threo-isomer: 54.6 mg (67 %) from 85 mg (0.35 mmol) *threo*-**5** as a pale yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.88 (t, J = 5.5 Hz, 3 H), 1.15 - 1.55 (m, 8 H) 1.60 - 1.80 (m, 2 H), 2.11 (s, 3 H), 2.61 (d, J = 6.6 Hz, 2H), 3.57 (dt, J = 6.6 Hz, $J_{4,5}$ = **5.1 Hz**, 1 H, H-4), 4.25 (m, 1 H, H-5), 6.45 (s, br., 1 H); HR-MS:calcd for $C_{11}H_{21}NO_2S$: 231.1293; found 231.1293 .
erythro-isomer: 173 mg (75 %) from 241 mg (1 mmol) *erythro*-**5** as a colourless oil.^{1}H-NMR (200 MHz, $CDCl_3$) δ = 0.88 (t, J = 5.5 Hz, 3 H), 1.20 - 1.40 (m, 5 H), 1.50 - 1.68 (m, 3 H), 1.70 - 1.80 (m, 2 H), 2.12 (s,3 H), 2.48 (dd, J = 14 Hz, J = 10.2 Hz, 1 H), 2.66 (dd, J = 4 Hz, J = 14 Hz, 1 H), 3.85 (ddd, J = 10.2 Hz, J = 4 Hz, $J_{4,5}$ = **7.4 Hz**, 1H, H-4), 4.61 (m, 1 H, H-5), 5.82 (s, br., 1 H); HR-MS: calcd for $C_{11}H_{21}NO_2S$: 231.1307, found: 231.1293

General Procedure for the Preparation of (**9**): N-Methoxy-N-methylamide **3** (650 mg, 2.3 mmol) was dissolved in 10 ml dry THF and cooled to the temperature given in Table 1. To this mixture was added the corresponding equivalents of organometallic compounds. After the reaction was complete [tlc, silica gel, n-hexane/ethyl acetate 4:1] the reaction mixture was treated in a similar manner described for the preparation of **4** using 23 mg (6.9 mmol) of sodium borohydride in 10 ml isopropyl alcohol for the reduction. The diastereomeric alcohols **9** were isolated by chromatography on silica gel [n-hexane/ethyl acetate 5:1]. Yields are given in Table 1.
threo-isomer: colourless oil; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, J = 7 Hz, 3 H), 1.20 - 1.60 (m, 15 H), 1.70 - 2.20 (br, OH), 2.13 (s, 3 H), 2.69 (m, 2 H), 3.66 (m, 1 H), 3.88 (m, 1 H), 4.98 (d, NH); Anal. Calcd. (%) for $C_{13}H_{27}NO_3S$ (277.45): C 56.28 H 9.81 N 5.05; Found (%): C 54.41 H 9.70 N 5.39.
erythro-isomer: m.p. 70 - 72 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, J = 7 Hz, 3H), 1.20 - 1.60 (m, 15 H), 2.00 - 2.20 (m, 4H), 2.71 (m, 2H), 3.70 (m, 1 H), 3.90 (m, 1 H), 4.97 (d, NH); Anal. Calcd. (%) for $C_{13}H_{27}NO_3S$ (277.45): C 56.28 H 9.81 N 5.05; Found (%): C 55.99 H 9.85 N 5.05.

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