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Novel cysteic acid s-amides substituted in the sulfonamide function. Synthesis and modifications

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In the present work we reported the synthesis of several analogues **5a-e** of cysteic acid S-amides with substituted sulfonamide function, where fully protected D,L-cysteic acid S-chlorides were treated with the required aliphatic amines to give a series of new derivatives which could be considered as structural sulfoanalogues of leucine, isoleucine and norleucine, respectively. We presented here new method for preparation of D,L-cysteic acid S-chlorides. Various modifications with N_{α}-, and C_{α}- protective groups useful in peptide synthesis have been successfully achieved. These novel compounds are of potential interest in structure-activity studies, easily applied in solid phase, as well as in conventional synthesis of biologically active peptides.

Keywords: Amino acids, Cysteic acid S-amides, Aliphatic amines, Alkaline protease, Antimetabolites

INTRODUCTION

Increasing the likelihood of a chance discovery, which is still a major route in drug development, it seems prudent to consider synthetic transformations of side-chain groups of the natural amino acids as an alternative strategy for the preparation of biologically active analogues and its incorporation in peptides. The relationship between the antagonist and the natural metabolite is one in which the β-carboxyl group of aspartic is replaced by the sulfo-group in the analogue. Accordingly, the sulfonamide or substituted sulfonamide derivatives of cysteic acid were obtained in the similar manner by different authors, [1-4] based on oxidative chlorination of the disulfide bond in the cystine molecule, followed by replacement of the chlorine atom in the sulfochloride by an amino group. Due to its structural similarity to asparagine, S-cysteine sulfonamide was suspected to have the ability to act as antagonist [5] and the early structure-activity relationship studies with the cysteic acid S-amide [6] aimed at developing inhibitors of L-asparagine synthetase and potential antitumor agents with substituted sulfonamide moiety [7,8]. It was found that they inhibit grouth of asparagine - dependant mutants of some microorganisms [9], exibit fairly wide range of other antibacterial activities as well as possess a low [10], or moderate antineoplastic activity [11]. However, very little was done for the application of the cysteic acid S-amide and its derivatives with substituted sulfonamide function, as structural sulfoanalogues of the appropriate natural amino acids in the peptide design [12]. The synthesis of sulfoanalogues of lysine [13] and arginine [14], as well as their incorporation in some model biologically active peptides have been achieved [15,16]. Most of the cysteine sulfonamide containing oligopeptides, synthesized by classical methods of peptide chemistry, displayed higher antibacterial activity than cysteine sulfonamide [11,17].

On the basis of the above data and continuing our research progr am on new nonproteinogenic acids, we considered to synthesize several new structurally related cysteic acid S-amides in order to verify whether such kind of substitution could improve the biological activity of this class of compounds.

In this paper we report the synthesis of the following new nonproteinogenic cysteic acid-S-amides: cysteic acid S-(N,N-dimethyl) amide **(5a)**, cysteic acid S-(N-methyl, N-ethyl) amide **(5b)**, cysteic acid S-(N-methyl) amide **(5c),** cysteic acid S-(N-ethyl) amide **(5d**), and cysteic acid S- (N-propyl) amide **(5e).** They could be considered as structural sulfoanalogues of the corresponding natural amino acids - leucine, isoleucine and norleucine, respectively and named as following - **sLeu, slle and sNIe** ($sNle_1$, $sNle_2$ and $sNle_3$) (Fig. 1.):

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EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus and are uncorrected. Elemental analysis was compatible for all new products synthesized. Electron spray mass spectra

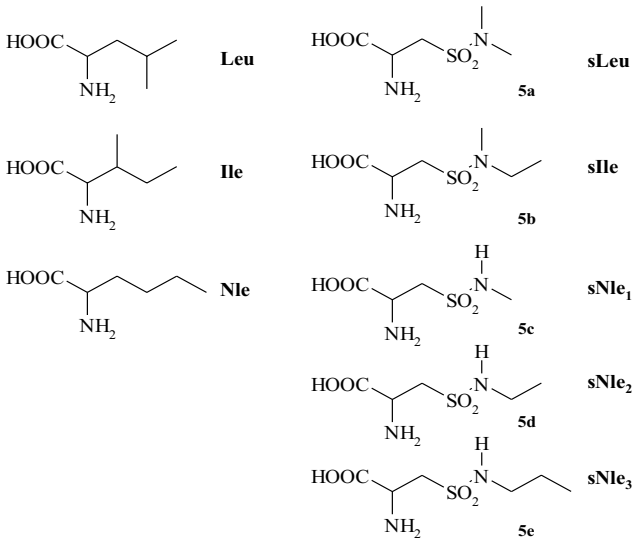

Fig. 1. Structures of the sulfoanalogues of natural amino acids Leu, Ile, Nle.

(ESMS) were done on a Vestec 201 single quadropole mass spectrometer using AcOH:H_2O:MeCN (4:46:50) as a solvent. ESMS spectra of the products were in agreement with the composition of each compound. Optical rotation was measured with a Perkin-Elmer polarimeter 241 (sodium lamp, 589nm). Thin-layer chromatography (TLC) was run on precoated silica gel plates (60F-254, Merck) with the following solvent systems : (a) 1-butanol : AcOH : H_2O (4:1:5), upper phase; (b) 1-butanol : AcOH : H_2O (4:1:1); (c) 1-butanol : AcOH : H_2O : pyridine (15:3:3:10); (d) chloroform : methanol (7:3); (e) l-butanol : AcOH : H_2O (2:1:1). Loads of 10-15 µg were applied and chromatograms were developed at a minimum length of 10 cm. Compounds were visualized by UV, ninhydrin as well as the chlorine gas procedure for the Rl-starch reagent. Analytical HPLC was performed on a Waters 810 instrument under the following conditions: gradient/solvent system A - 90:10 to 30:70 0,05% aqueous TFA : 0,05%TFA in MeCN, linear gradient over 60 min at l.0 ml/min and B: 60:40 to 15:85 H_2O/H_3PO_4 (pH 3): MeCN, linear gradient over 30 min at l.0 ml/min. In both cases a Mickrosorb C_{18} column (Rainin Instrument Co., Inc) was used. Overall yields are calculated from the starting amino acid.

General procedure for synthesis of fully protected cysteic acid S-amides(compounds 2a-e)

Nα-Z-D,L-cysteic acid S-chloride ethyl ester, **1** (3.49 g, l0 mmol) dissolved in 15 ml $CHCl_3$ was added dropwise to an ice-cold solution (DMF, 15 ml) of approptiate aliphatic amine (dimethylamine, methylethylamine, methylamine, ethylamine and propylamine) hydrochloride (30 mmol) previously converted to a free base by treatment with Et_3N (30 mmol). The mixture was stirred for 2-3 h at 0°C. After completion of the reaction (TLC-monitoring) the solvent was removed under reduced pressure, and the evaporated residue was precipitated twice from DMF/hot water and acetone light petroleum consecutively.

Enzymatic resolution of parent Nα-Z-D,L-cysteic acids S-amides ethyl esters (2a-e). Preparation of compounds 3a-e end 4a-e

The amino acid **2a-e** (10 mmol) was dissolved in a mixture of DMF (40 ml) and water (60ml) containing 30 mmol $NaHCO_3$. Alkaline protease from *Bacillus subtilis* DY strain (0.2 g) was added and the mixture was stirred for about 4 hours (TLC monitoring) at 37°C. After removal of the solvents under reduced pressure, water was added to the residue, pH was adjusted to 9 with 5% $NaHCO_3$, and the mixture was extracted with ethyl acetate (3 x 70 ml). The combined organic phases were washed with water, dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The isolated D-esters were crystallized from DMF/H_2O and/or recrystallized from $CHCl_3$/light petroleum. The aqueous phase was acidified with 5 % $NaHSO_4$ solution to pH 3 and extracted with ethyl acetate (3 x 70 ml). The combined organic phases were washed with water, dried with Na_2S0_4, and the solvent was evaporated under reduced pressure. The resulting L-enantiomers were crystallized from MeOH or 2-PrOH.

General procedure for removing of Na-Z-protective groups from L-enantiomers (4a-e). Preparation of compounds 5a-e

Nα-Z-L-cysteic acid S-[N-(R_1R_2)] amide (5 mmol) was hydrogenated on Pd/C in 4,4% formic acid/ MeOH (50 ml). After completion of the reduction (1 hour), the Pd was filtered off and the solution was concentrated under reduced pressure. The residue solidified upon consecutive treatment with MeOH and dry diethyl ether. The solid

products were obtained as white foams and were directly used for the next modifications.

General procedure for synthesis of Nα-substituted Boc-sulfonamide derivatives. Compounds 6a-e

Each of the solid products **5a-e** (10 mmol) was dissolved in a mixture of 2-PrOH (30 ml), water (10 ml) and Et_3N (4.2 ml, 30 mmol) with stirring. $(Boc)_2O$ (2.9 ml, 13 mmol) was added dropwise and kept stirring until completion of the reaction (12 hours, TLC monitoring). The organic solvent was evaporated under reduced pressure, and the cooled aqueous solution was acidified to pH 2 - 3 with 0,5% $NaHSO_4$. The resulting mixture was extracted with ethyl acetate (3 x 40 ml). The organic layers were combined, washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The products were recrystalized from DCM in a high purity.

Synthesis of methansulfonate of Z-Ser-OEt, 9

To stirred solution of Z-Ser-OEt (2.67 g, 10 mmol) in CH_2Cl_2 (20 ml) in the presence of DIPEA (1.9 ml, 11 mmol) was added at 0°C a solution of methanesulfonyl chloride (0.8 ml, 10.4 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred at room temperature for 20 minutes, then the solvent was evaporated under reduced pressure. The residue was treated with ethyl acetate (20 ml) and water (20 ml). The organic layer was separated, washed consecutivly with aqueous 5 % $NaHCO_3$ (3 x 10 ml) and brine (3 x 10 ml), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure to give **9** (3.1g, 91%) which then was used for the next steps without further purification.

Synthesis of fully protected cysteic acid, 10

Sodium sulfite (1.7 g, 13.5 mmol) was added to a solution of **9** (3.45 g, 9 mmol) in a mixture of water : dioxane (1:1, 20 ml) and the mixture was stirred at room temperature for 24 hours. Dioxane was evaporated under reduced pressure, aqueous solution was acidified to pH 3 and **10** was left to crystallize at 4°C. Product (**10**) was obtained in 2.94 g (89%).

Synthesis of sulfonyl chloride of N- and C-protected cysteic acid, 1

The $SOCl_2$ (1.4 ml, 19.4 mmol) was added slowly to CH_2Cl_2 (10 ml) at 0°C. The ice bath was removed and **10** (2.94 g, 8.8 mmol) in CH_2Cl_2 (10 ml) was added dropwise over one minute. The mixture was stirred for 1 hour at room temperature and then solvent was removed by evaporation under reduced pressure. Residue crystallized from absolute ethanol to give key intermediate, **1** (1.4 g, 45%).

RESULTS AND DISCUSSION

To our knowledge, until now only the single synthesis of L-cysteic acid S-(N,N-dimethyl) amide **(5a),** employing a similar approach to ours has been published [12]**.** On the other hand, our special interest concerns the synthesis of corresponding suitable protected sulfonamide derivatives (**4-7a-e,** Fig. 2), useful clues for the design of more potent and selective biologically active compounds.

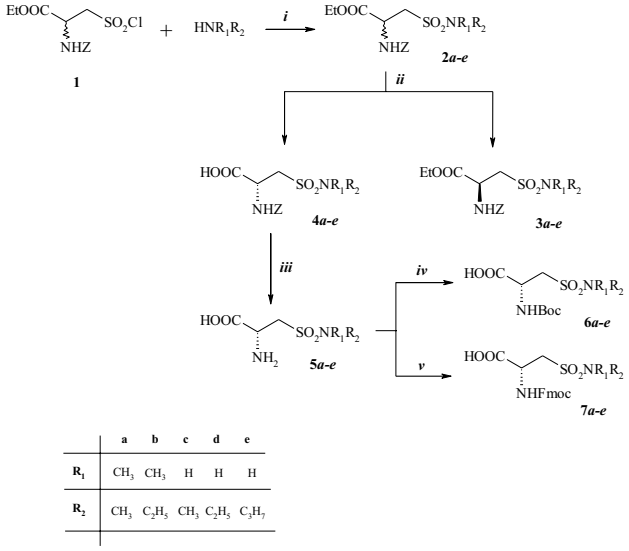

Fig. 2. Synthesis of protected sulfoanalogues. *Reagents and condition:* ***i***) $CHCl_3$/DMF/-5°C; ***ii***) *Bac. Subt.* DY/DMF-H_2O/$NaHCO_3$/37ºC;
iii) 10% Pd/C/MeOH/HCOOH; ***iv***) $(Boc)_2O$/i-PrOH-H_2O/5% Na_2CO_3; ***v***) Fmoc-OSu/Dioxan-H_2O/$NaHCO_3$.

The synthetic route chosen for preparation of the required compounds is illustrated in Fig. **2.** The key intermediate **1** was obtained according to the well-known procedures previously described [4,7], based on oxydative chlorination of the disulfide bond in the cysteic molecule, followed by replacement of the chlorine atom in the sulfochloride by an amino group. In addition we present also a new synthetic rout for preparation of the key initial compound – sulfonyl chloride of cysteic acid 1 (Fig. 3). On the first step mesylated N- and C-protected serine was obtained. Preparation of this compound was done in the presence of N,N-diisopropylethylamine (DIPEA) as a base in CH_2Cl_2. Methanesulfonyl

chloride was added to the reaction mixture at 0ºC and the process continue at room temperature for additional 20 minutes. Product was obtained easily by simple washing of its organic solution in very good yield of 91%. Next step of this synthetic scheme is preparation of N- and C-protected cysteic acid. It was made by reaction of methanesulfonate with sodium sulfite in water : dioxane mixture for 24 hours at room temperature. N- and C-protected cysteic acid was obtained in good yield (89%), after evaporation of dioxane and consecutive acidifying of the aqueous solution. Sulfonyl chloride **1** was synthesized in reaction of 10 with $SOCl_2$ with moderate yield of 45%.

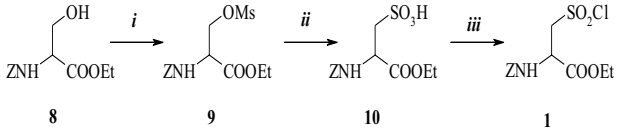

Fig. 3. Synthesis of sulfonylchloride. Reagents and condition: **i**) CH_3SO_2Cl/DIPEA/DMF; **ii**) Na_2SO_3/H_2O; **iii**) $SOCl_2/CH_2Cl_2$.

The experiments showed that stable cysteine sulfochloride derivatives could be obtained only if both the amino and the carboxy groups are blocked [6]. The synthesis of all compounds **l-7a-e** was accomplished in a similar manner as it is outlined in our initial studies [18]. The parent derivatives **2a-e** were afforded by simple condensation of the starting racemic compound N_α- carbobenzoxy-cysteic acid S-chloride ethyl ester with the desired aliphatic amine (dimethylamine, methylethylamine, methyl-, ethyl-, or propylamine). In all cases the sulfochloride/amine ratio was kept 1:3, the reaction was held at –5 to 0ºC, and was realized by drop wise adding of the solution of sulfochloride in $CHCl_3$ to the ice-cold stirred solution of the corresponding amine in DMF, previously converted to a free base by treatment with Et_3N. After completion of the condensation monitored by TLC, the obtained crude material was precipitated from DMF/hot water and recrystallized from ethyl acetate/light petroleum. These initial derivatives were obtained in yields ranging from 65 to 88%. Resolutions of the racemates **2a-e** was achieved using alkaline protease from *Bacillus subtilis DY* strain, whose applicability to selective hydrolysis of amino acid esters with L-configuration was shown in previous studies [19]. As well as the high level of enantiomeric discrimination involved with enzymatic processes, the work-up procedure after the use of protease is usually particularly straightforward since the unchanged D-amino acid derivatives **3a-e** can be extracted from the reaction mixture using a water-immiscible solvent, while the N_α-L-protected enantiomers **4a**-e – after acidifying the reaction mixture. In our present experiments we achieved good resolution of the racemic derivatives of di-substituted aliphatic amines **2a,b** defer from those of mono-substituted methyl, ethyl- and propylamine **2c-e**, where the yields of D-enantiomers **3c-e** were quite low – 20 to 25%.

The N_α-benzyloxycarbonyl protected L-enantiomers **4a**-e, recrystallized from appropriate alcohol in good yields (65 to 93%), were used for catalytic hydrogenation step in order to obtain the final L-cysteic acid S-amides **5a**-e. The Z-protecting group was removed by hydrogenolysis with 10% palladium on charcoal in methanol using formic acid as a hydrogen donor. Because of the S-content the reaction time was taken longer, up to 4 hours, determined by thin layer chromatographic analysis of samples taken at various times. The required S-cysteic acid sulfonamides **5a-e,** easily obtained as solids from aqueous ethanol directly were used for further modifications or purified finally by reversed phase MPLC (0-30% i-PrOH in 0,2% AcOH).

N_α-Boc-protected derivatives **6a-e** were obtained by treatment of the free L-enantiomers **5a-e** with $(Boc)_2O$ in misture of water/isopropanol and pH was adjusted to 7.5 - 8.0 with 5% Na_2CO_3. All of the obtained Boc-derivatives after recrystallization from appropriate alcohol were obtained in high yields (95 to 96%) and purity.

Cleavage of the Boc-protecting group was achieved using ethyl acetate saturated with anhydrous HCl (1.5-4N HCl/EtOAc) or TFA/anisole (9 : l) in 98% yield. Fmoc-OSu was chosen as the preferable reagent for the synthesis of the Fmoc-derivatives **7a-e** because its use results in reproducibly high yields under mild conditions. The optimum procedure was utilized a 10% excess of corresponding L-cysteic acid S-amide over Fmoc-OSu, a minimum volume of dioxane to aqueous phase (~ 1:10 by volume) and two fold excess of sodium carbonate over amino acid component. The reaction was most efficient when the reactants were stirred vigorously at room temperature. The preparation of Fmoc-cysteic acid S-amides was accomplished without serious side reactions, in 84 to 85% yields.

All newly reported cysteic acid S-amides and the corresponding derivatives were obtained chromatographically pure (TLC and HPLC) and identified by elemental analysis and electron spray mass spectra (ESMS). The chiral purity of the final compounds was verified also. The collected physico-chemical and analytical data of the described compounds are presented in Table 1.

Table 1. Analytical data of analogues 5a-e and derivatives

Comp. №	Yield [%]	M.p. [°C]	$[\alpha]_D^{20}$ (C=0.1, EtOH)	Elemental analysis % C Found/ Calc.	% H Found/ Calc.	% N Found/ Calc.	% S Found/ Calc.	ESMS (m/z) Found/ Calc.
2a	81	94- 96		50,03 / 50,27	6,11 / 6,19	26,32/ 26,78	9,03 / 8,95	358.2 / 358,419
3a	85	92- 93	+ 8,8	50,16 / 50,27	6,01 / 6,19	7,88/ 7,82	8,90 / 8,95	358.6 / 358,419
4a	91	103-104	-18,4	47,12 / 47,26	5,30 / 5,49	8,42/ 8,48	9,80 / 9,71	330.3 / 330,365
5a	95	157-160	-35,3	30,55 / 30,61	6,23 / 6,16	14,35/ 14,28	16,42 /16,34	195.9 / 196,221
6a	95	147-148	-15,8	40,30 / 40,53	6,72 / 6,80	9,33/ 9,45	10,88 /10,82	296.4 / 296,348
7a	84	133-134	-12,7	57,09 / 57,40	5,28 / 5,30	6,75/ 6,69	7,44 / 7,66	418.3 / 418,474
2b	88	85- 87		51,46 / 51,60	6,37 / 6,50	7,34 / 7,52	8,29 / 8,61	372.4 / 372,446
3b	80	83- 84	+ 7,7	51,53/ 51,60	6,38/ 6,50	7,63 / 7,52	8,60 / 8,61	372.5 / 372,446
4b	93	112-113	-20,2	48,41/ 48,83	5,55/ 5,85	8,03 / 8,13	9,17 / 9,31	344.3 / 344,392
5b	95	160-163	-37,1	34,33 / 34,28	6,80 / 6,71	13,43/13,32	15,34 /15,25	210,3 / 210,248
6b	93	140-142	-17,0	42,67/ 42,57	7,21 / 7,14	9,19 / 9,03	10,23 /10,33	310.4 / 310,375
7b	87	129-131	-14,6	58,43 / 58,46	5,66/ 5,37	6,27 / 6,49	7,19 / 7,43	431.3 / 431,482
2c	65	87- 90		48,76/ 48,83	5,81 / 5,85	8,20 / 8,13	9,35 / 9,31	344.3 / 344,382
3c	45	86- 88	+ 9,1	48,71/ 48,83	5,87 / 5,85	8,15 / 8,13	9,40 / 9,31	344.4 / 344,382
4c	65	113-115	-20,7	45,60/ 45,56	5,04 / 5,10	8,67 / 8,86	10,30 /10,14	316.2 / 316,328
5c	88	178-180	-35,6	26,47/ 26,37	5,66 / 5,53	15,33 / 15,38	17,71 /17,60	182.1 / 182,194
6c	91	149-151	-14,1	38,39/ 38,29	6,48 / 6,43	9,98 / 9,92	11,41/ 11,36	282.4 / 282,311
7c	82	140-142	-16,1	56,52/ 56,57	4,35 / 4,75	6,43 / 6,94	7,05 / 7,95	403.3 / 403,429
2d	54	89-92		49,76/ 50,27	6,71/ 6,19	7,20/ 7,82	8,35/ 8,94	358,42/ 358,408
3d	24	88-91	+8,9	50,71/ 50,27	6,71/ 6,19	7,20/ 7,82	8,35/ 8,94	358,42/ 358,408
4d	67	113-117	-21,7	45,36/ 47,27	5,40/ 5,49	8,17/ 8,48	9,30/ 9,70	330,4/ 330,354
5d	61	181-183	-36,6	29,82/ 30,61	5,74/ 6,16	14,93/14,28	16,87/16,34	195,0/ 196,221
6d	84	149-151	-14,5	39,33/ 40,52	7,11/ 6,80	9,39/ 9,49	10,42/10,81	297,1/ 296,454
7d	76	143-146	-17,1	58,11/ 57,52	4,88/ 5,07	7,06/ 6,74	6,90/ 7,68	416,7/ 417,572
2e	70	90-91		51,33/ 51,60	6,47 / 6,50	7,38 / 7,52	8,43 / 8,61	372.6 / 372,446
3e	51	93- 95	+ 9,1	51,33/ 51,60	6,47 / 6,50	7,38 / 7,52	8,43 / 8,61	372.3 / 372,446
4e	78	115-116	-21,8	48,74 / 48,83	5,69/ 5,85	8,17/ 8,13	9,23 / 9,31	344.3/ 344,392
5e	85	183-184	-38,7	34,32 / 34,28	6,85 / 6,71	13,13 /13,32	15,38 /15,25	210.3 / 210,248
6e	96	152-153	-14,7	42,66/ 42,57	7,18 / 7,14	9,23/ 9,03	10,02/ 10,33	310.4 / 310,375
7e	85	145-148	-18,6	58,49/ 58,46	5,45 / 5,37	6,38 / 6,49	7,51 / 7,43	431.5 / 431,482

In summary, a set of new chirally pure unusual amino acids, based on cysteic acid S-amide was synthesized. We have reported also, the new approach for synthesis of the lead compound **1**. According to our recent investigations these new members of cysteinsulfonamide family are promising candidates for studies on the

physiological roles of the corresponding natural amino acids – leucine, isoleucine and norleucine, as well as attractive peptide modifiers, useful clues for design of more potent and more selective biologically active compounds.

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НОВИ S-АМИДИ НА ЦИСТЕИНОВАТА КИСЕЛИНА, ЗАМЕСТЕНИ В СУЛФОНАМИДНАТА ГРУПА. СИНТЕЗ И МОДИФИКАЦИИ

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(Резюме)

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В настоящата работа представяме синтезата на поредица аналози 5a-e на S-амидите на цистеиновата киселина със заместена сулфонамидна група. Напълно защитените S-хлориди на D,L-цистеиновата киселина взаимодействат със съответните алифатни амини, при което се получава серия от нови производни, които могат да се приемат като структурни сулфо-аналози на левцин, изолевцин и норлевцин, съответно. Тук е представен и нов метод за получаване на S-хлориди на D,L-цистеиновата киселина. Успешно са направени модификации с различни Nα- и Cα-защитни групи за целите на пептидния синтез. Тези съединения са подходящи за изучаване на връзката структура – активност, тъй като могат лесно да се използват както при твърдофазен, така и при конвенционален синтез на биологично активни пептиди.