Asymmetric Synthesis of Enantiomerically Enriched α -Amino Acids Containing 2-Furyl- and 2-Thienyl-1,2,4-triazoles in the Side-Chain

Ashot S. Saghyan^{a,b}, Hayarpi M. Simonyan^b, Satenik G. Petrosyan^b, Anna F. Mkrtchyan^a, Lilit V. Khachatryan^b, Arpine V. Geolchanyan^{a,b}, Melanya A. Samvelyan^b, Tariel V. Ghochikyan^b, Nazken Kelzhanova^{c,d}, Amanzhan T. Saginavev^e, and Peter Langer^{c,d}

- ^a Scientific and Production Center "Armbiotechnology" of NAS RA, 14 Gyurjyan Str., 0056
- Yerevan, Armenia
 ^b Department of Pharmaceutical Chemistry, Yerevan State University, 1 A, Manoogian Str.,
- ^o Department of Pharmaceutical Chemistry, Yerevan State University, 1 A, Manoogian Str., 0025 Yerevan, Armenia
- ^c Institute of Chemistry, University of Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
- ^d Leibniz Institute of Catalysis at the University of Rostock e. V. (LIKAT), Albert-Einstein-Str. 29a, 18059 Rostock, Germany
- ^e Atyrau Institute of Oil and Gas, Atyrau, Republic of Kazakhstan

Reprint requests to Prof. Peter Langer. Fax: +381 4986412. E-mail: peter.langer@uni-rostock.de

Z. Naturforsch. **2014**, *69b*, 451–460 / DOI: 10.5560/ZNB.2014-3221 Received August 12, 2013

An efficient method for the asymmetric synthesis of α -amino acids, containing furyl- and thiophenyl-substituted triazoles in their side-chain, is reported. The strategy relies on Michael addition of 3,4,5-substituted 1,2,4-triazoles to the C=C bond of chiral Ni^{II} complexes containing the Schiff base formed from dehydroamino acids (dehydroalanine and (E + Z)-dehydroaminobutyric acid) and from chiral auxiliaries, *i. e.* (*S*)-2-*N*-(*N'*-benzylprolyl)aminobenzophenone and (*S*)-2-*N*-(*N'*-2-chlorobenzylprolyl) aminobenzophenone. The reactions proceeded with good to very good diastereoselectivity. Hydrolysis of the diastereomeric mixtures of metal complexes afforded the enantiomerically pure α -amino acids with high enantiomeric excess (*ee* > 98 %).

Key words: Asymmetric Synthesis, Amino Acids, Chiral Ni^{II} Complexes, Heterocycles

Introduction

Non-proteinogenic α -amino acids are constituents of many physiologically active peptides, antibiotics and other pharmacologically relevant molecules [1]. In this context, non-proteinogenic α -amino acids containing a heterocyclic side chain are of special interest because they combine the structural features of amino acids and of pharmacologically relevant heterocycles [2, 3]. This includes furans, thiophenes and triazoles which are all important constituents of many biologically and pharmacologically active drugs, such as antihyperglycemic [4], analgesic [4, 5], antiinflammatory [4, 6], antibacterial [4, 7], anticancer [8], antifungal [4], antitumoral [4], antiviral [4], and psychotropic agents [9]. For the last few decades a considerable amount of attention has been focused on the synthesis of furan and thiophene derivatives as well as on their screening for different pharmacological activities. Introduction of these heterocyclic moieties to the side-chain of optically active amino acids and peptides can result in potentially pharmacologically active molecules. In recent years, we have studied the asymmetric synthesis of optically active heterocyclic α -amino acids by conjugate addition of heterocyclic nucleophiles to the carboncarbon double bond of the chiral ligands of squareplanar Ni^{II} complexes. The ligands are Schiff bases formed by reaction of the chiral auxiliary (S)-2-N('benzylproline)aminobenzophenone (or its modified analogs) with dehydroalanine and dehydroaminobutyric acid [10-17]. In the present work, we report, for the first time, the asymmetric synthesis of a new class of enantiomerically enriched α -amino acids con-

© 2014 Verlag der Zeitschrift für Naturforschung, Tübingen · http://znaturforsch.com

taining furyl- and thienyl-substituted 1,2,4-triazoles in the side-chain. The products can be regarded as hybrids of the pharmacologically relevant subunits of α amino acids, 1,2,4-triazoles, furans, and thiophenes. The products have, to the best of our knowledge, not been previously prepared in enantiomerically pure form.

Results and Discussion

The chiral Ni^{II} complexes of the Schiff bases of dehydroalanine (Δ -Ala) and (E + Z)-dehydro-aminobutyric acid (Δ -Aba) with the chiral auxiliaries (S)-2-N-(N'-benzylprolyl)aminobenzophenone (Ni^{II}-(S)-BPB- Δ -Ala, **1a** and Ni^{II}-(S)-BPB- Δ -Aba, **2a**) and (S)-2-N-(N'-2-chloro-benzylprolyl)aminobenzophenone (Ni^{II}-(S)-2-CBPB- Δ -Ala, **1b** and Ni^{II}-(S)-2-CBPB- Δ -Ala, **2b**) were synthesized according to our procedure previously reported [18 - 20]. As heterocyclic nucleophiles. 5-butyl-4-(fur-2-ylmethyl)-4H-3-mercapto-1,2,4-triazole (3), 4-(fur-2-ylmethyl)-5-isobutyl-4H-3mercapto-1,2,4-triazole (4), 4-allyl-5-(fur-2-yl)-4H-3mercapto-1,2,4-triazole (5), 4-phenethyl-5-(thien-2-yl)-4H-3-mercapto-1,2,4-triazole (6), 4-phenyl-5-(thien-2-yl)-4H-3-mercapto-1,2,4-triazole (7), and 4allyl-5-(thien-2-yl)-4H-3-mercapto-1,2,4-triazole (8) were used. The addition of heterocyclic nucleophiles 3-8 to the chiral dehydroamino acid complexes 1a, b and 2a, b was carried out in MeCN in the presence of K₂CO₃ at 50 °C. The course of the reaction was monitored by TLC (SiO₂). The reactions of dehydroalanine complexes 1a and 1b afforded the nickel complexes 9a - 13a and 9b - 13b, respectively (Scheme 1, Table 1). All reactions proceeded with excellent diastereoselectivity in favor of the products containing an (S)-configurated newly generated chiral center. In case of the reactions of dehydroaminobutyric complexes 2a and 2b, the (2S,3S)-configurated complexes 14a and 14b were formed with excellent diastereoselectivity, respectively. All metal complexes were isolated in diastereomerically pure form (de > 98%) by chromatography and recrystallization, and their structure and absolute configuration were determined by spectroscopy. Isolation of the target amino acids was carried out by immediate decomposition of the diastereomeric mixture of complexes of addition products with hydrochloric acid in aqueous methanol. Amino acids 15-20 were isolated using a Ky-2 \times 8 cationic exchanger [10-21]. Amino acids 15-20 were crystallized from a mixture of water and

> Table 1. Results of the asymmetric addition of nucleophiles 3-8 to chiral complexes 1a, b and 2a, b in CH₃CN/K₂CO₃ at 40–50 °C.

Initial complexes	3-8	9–14	t (min)	Yield ^b (9-14)	<i>de</i> ^a (9-14)	15-20	$\begin{array}{c} \text{Yield}^{\text{b}} \\ (15-20) \end{array}$
				(S,S)			
Ni ^{II} -(S)-2-CBPB- Δ -Ala (1b)	3	9b	120	75	98	15	53
					(S,S)		
Ni ^{II} -(S)-BPB- Δ -Ala (1a)	4	10a	90	60	92	16	58
					(S,S)		
Ni ^{II} -(S)-2-CBPB- Δ -Ala (1b) Ni ^{II} -(S)-BPB- Δ -Ala (1a)	4	10b	120	65	94	16	55
	-		120		(S,S)		<i></i>
	5	11a	120	71	88	17	54
Ni ^{II} -(S)-2-CBPB- Δ -Ala (1b)	5	116	150	72	(3,3)	17	51
	5	110	150	15	90	17	51
Ni ^{II} -(S)-BPB- Δ -Ala (1a)	6	120	110	65	(3,3)	18	65
	U	12a	110	05	(5,5)	10	05
Ni ^{II} -(S)-2-CBPB- Δ -Ala (1b)	6	12b	140	70	93	18	63
	Ū		1.0	70	(S,S)	10	00
Ni ^{II} -(S)-BPB- Δ -Ala (1a)	7	13a	180	70	74	19	70
					(S,S)		
Ni ^{II} -(S)-2-CBPB- Δ -Ala (1b)	7	13b	210	62	95	19	66
					(S,S)		
Ni ^{II} -(S)-BPB- Δ -Aba (2 a)	8	14a	600	66	94	20	66
					(S, S, S)		
Ni^{II} -(S)-2-CBPB- Δ -Aba (2b)	8	14b	720	71	98	20	61
					(S, S, S)		

^a Diastereomeric excess (%) based on chiral HPLC (*ee* of **15–20** exceeded 98%); ^b chemical yield.



Scheme 1. Synthesis of complexes 9-14 and of amino acids 15-20.

ethanol (1:1). The optical purity of the synthesized amino acids was determined by chiral HPLC. The chiral auxiliaries (S)-BPB and (S)-2-CBPB were recovered in more than 95% yield with full retention of the optical purity, and they could be used again.

The conjugate addition of nucleophiles to the chlorinated nickel complexes 1b and 2b proceeded with higher diastereoselectivities as compared to the analogous reactions of the non-chlorinated nickel complexes **1a** and **2a**. In comparison to conjugate additions of simple aliphatic nucleophiles to nickel complexes, an increase of the reaction time is observed. This could be explained by the steric interaction between the heterocyclic nucleophiles and the phenyl group of the Nbenzylproline moiety.



Fig. 1. Different steric location of the methyl group of the amino acid moiety in the two diastereomeric nickel complexes **14a**, **b**.

The diastereomeric excess (de) of all metal complexes was determined by chiral HPLC analysis of the amino acids isolated by use of the ion-exchange method from the acid hydrolysates of the diastereomeric metal complexes (before chromatography). The relative configuration of the amino acid fragment of the diastereomeric complexes 9a, b-13a, b was determined based on the values of optical rotation (at 589 nm), and a comparison with similar complexes of α -amino acids [10-15]. The absolute configuration of the amino acid fragment of complex 14a, b was determined by ¹H NMR spectroscopy based on the values of the chemical shifts of the β -methyl protons. It was shown earlier for similar complexes (derived from α -aminobutyric acid and O-methylthreonine and Sbenzyl- β -methylcysteine) that, in case of the (2S,3S)allo absolute configuration of the amino acid moiety, the β -CH₃ protons resonate at relatively strong fields. In contrast, in case of (2S,3R)-configurated complexes, the protons appear at relatively weak fields [20, 21]. The shift of the methyl protons towards weak fields can be explained by location of the CH₃ anisotropic cone of the Ni²⁺ ion in case of the (2S,3R)-three configurated products (Fig. 1). In case of the nickel complexes 14a, b studied herein, a similar characteristic difference of the chemical shifts was observed for the signals of the β -methyl protons. Therefore, we conclude that 14a, b possess an (S)-anti or (2S,3S)-allo configuration of the amino acid moiety.

Conclusions

We have reported an efficient, highly selective method for the asymmetric synthesis of enantiomerically enriched α -amino acids containing furyl- and thienyl-substituted 1,2,4-triazoles in their side chain. The enantiomeric purity of the synthesized amino acids exceeded 98 % *ee*.

Experimental

Materials and methods

Silica gel L-40/100 was purchased from Merck (Germany); $(CH_2O)_n$, $CHCl_3$, $(CH_3CO)_2O$, CH_3COOH , $CH_3COOC_2H_5$, CH_3CN , Na_2CO_3 , NH_4OH , HCl, KOH, and 2-aminobenzophenone were purchased from Aldrich (USA). All solvents were freshly distilled. ¹H and ¹³C NMR spectra were recorded on a Mercury-300 Varian spectrometer (300 and 75.4 MHz, respectively) in [D₆]DMSO-CCl₄ = 1 : 3 (unless otherwise indicated). Chemical shift data δ are given in ppm, coupling constants *J* in Hz.

The enantiomeric purity of the amino acids was determined by HPLC on the chiral phase Diaspher-110-Chirasel-E-PA 6.0 mkm 4.0×250 mm, and a mixture of 20% of MeOH and of 80% of a 0.1 M aqueous solution of NaH₂PO₄·2H₂O was used as the eluent. The optical rotation was measured on a Perkin Elmer-341 polarimeter. It was previously shown in approximately 100 related reactions (ref. [10-21]), that the use of (S)-BPB as the chiral reagent induced asymmetric synthesis of (S)-amino acids, and the use of the (R)-BPB chiral reagent induced the asymmetric synthesis of (R)-amino acids. For the complexes, this was confirmed by the use of X-ray crystal structure analysis, ORD and CD, and for the final amino acids by application of the methods of X-ray crystal structure analysis, chiral HPLC and GLC. In all these cases it was proved by ORD and CD methods that under 589 nm wavelength the complexes of (S)-amino acids had a positive value of optical rotation, and the complexes of (R)-amino acids had a negative value of optical rotation. In the present article the values of optical rotation of all diastereomeric complexes synthesized under 589 nm wavelength have a positive value, which is an evidence of (S)-absolute configuration of the amino acid moiety derived from the major diastereomeric complexes. In contrast, in case of the minor complexes it is an evidence of (R)-absolute configuration. This was finally proved by chiral HPLC analysis of the isolated amino acids. For this, all racemic (S, R) mixtures were synthesized and analyzed, followed by the samples obtained by us. Racemate samples of all amino acids were obtained by the same method, *i. e.* by using similarly structured complexes of achiral N-(2-benzoylphenyl)pyridine-2-carboxamide (PBP) auxiliaries instead of the complex of an (S)-BPB chiral auxiliary, which resulted in racemate mixtures of amino acids. Therefore, according to the data of diastereomeric complexes of optical rotation under 589 nm wavelength and chiral HPLC analysis

of final amino acids, the (S, S)-absolute configuration of the major diastereomeric complexes and the (S)-absolute configuration of the isolated amino acids were established.

General method for the synthesis of 9-14(a, b)

To 0015 mol of complexes **1a**, **b** or **2a**, **b** in 20 mL of MeCN were added 0.045 mol of K_2CO_3 and 0.03 mol of nucleophiles **3**–**8** with stirring at 40–50 °C. The reaction was monitored by TLC (SiO₂, CHCl₃Me₂CO = 3 : 1) following the disappearance of the spot of the initial **1a**, **b** or **2a**, **b** complexes. Upon completion of the reaction, the mixture was filtered, the K_2CO_3 precipitate washed with CH₃CN and the solution evaporated to dryness. The diastereomeric mixture of complexes **9**–**14(a**, **b**) was crystallized from methanol.

Complex 9a

Yield 71 %. M. p. 140–141 °C. – $[\alpha]_{\rm D}^{20} = +2206.0^{\circ}$ (c = 0.05; MeOH). - Analysis: found (%) C 62.85, H 5.51, N 11.41; calcd. for C39H40N6O4SNi (%) C 62.68, H 5.36, N 11.25. – ¹H NMR (CDCl₃-CCl₄ ~ 1 : 1): $\delta = 0.90$ (3H, t, J = 7.3, CH₃), 1.36 (2H, qt, $J_1 = 7.3$, $J_2 = 7.1$, CH_2 CH₃), 1.53 (2H, m, CH₂C₂H₅), 2.07 (1H, m, 5-CH₂, proline), 2.13 (1H, m, 4-CH₂, proline), 2.49 (1H, m, 3-CH₂, proline), 2.60 (2H, M, CH₂C₃H₇), 2.84 (1H, m, 3-CH₂, proline), 3.41 (1H, dd, $J_1 = 10.7$, $J_2 = 6.1$, 2-CH, proline), 3.55 (1H, dd, $J_1 =$ 9.3, $J_2 = 6.8$, 5-CH₂, proline), 3.58 (1H, d, J = 12.7, CH₂-Ph), 3.71 (1H, m, 4-CH₂, proline), 4.40 (1H, d, J = 12.7, CH_2 -Ph), 4.44 (1H, dd, $J_1 = 6.8$, $J_2 = 6.3$, CH), 4.79 (1H, dd, *J*₁ = 13.7, *J*₂ = 6.3, NC*H*₂CH), 4.93 (1H, dd, *J*₁ = 13.7, J₂ = 6.8, NCH₂CH), 5.09 (1H, d, J = 15.7, NCH₂-Furan), 5.22 (1H, d, *J* = 15.7, NCH₂-Furan), 6.29 (1H, dd, *J*₁ = 3.3, $J_2 = 1.8, 4$ -CH_{furan}), 6.45 (1H, d, J = 3.3, 3-CH_{furan}), 6.55 (1H, dd, $J_1 = 8.2$, $J_2 = 1.2$, 5-CH, C₆H₄), 6.63 (1H, ddd, $J_1 = 8.2, J_2 = 6.9, J_3 = 1.3, 4$ -CH, C₆H₄), 6.78 (1H, dt, $J_1 =$ 7.8, $J_2 = 1.5$, 2-CH, C₆H₅), 7.27 (1H, dt, $J_1 = 7.4$, $J_2 = 1.8$, 2'-CH, C₆H₅), 7.33 (1H, d, J = 1.8, 5-CH_{furan}), 7.34 (2H, m, 3,5-CH, C_6H_5 -CH₂), 7.45 (1H, tt, $J_1 = 7.5$, $J_2 = 1.4$, 4-CH, C_6H_5 -CH₂), 7.52 (1H, td, $J_1 = 7.5, J_2 = 1.5, 3'$ -CH, C_6H_5), 8.02 (2H, m, 2,6-CH, C_6H_5 -CH₂), 8.25 (1H, dd, $J_1 = 8.7$, $J_2 = 1.3, 2$ -CH, C₆H₄). – ¹³C NMR (CDCl₃-CCl₄ ~ 1 : 1): $\delta = 13.92 (CH_3), 22.37 (CH_2CH_3), 24.06 (4-CH_2, proline),$ 25.25 (CH2C3H7), 27.71 (CH2C2H5), 30.97 (3-CH2, proline), 41.17 (NCH₂, furan), 52.06 (NCH₂CH), 57.35 (5-CH₂, proline), 63.12 (CH₂-Ph), 68.56 (NCH₂CH), 70.74 (2-CH, proline), 110.54 (3-CH_{furan}), 111.36 (4-CH_{furan}), 120.58 (4-CH, C₆H₄), 123.98 (2-CH, C₆H₄), 126.63, 127.77 (2'-CH_{Ph}), 128.25 (2-CH_{Ph}), 128.84 (4-CH_{Ph}), 129.06 (3,5-CH, CH₂-Ph), 129.08 (3'-CH_{Ph}), 129.17 (3-CH_{Ph}), 129.82 (4-CH, CH₂-Ph), 131.82 (2,6-CH, CH₂-Ph), 132.59 (3-CH, C₆H₄), 133.37, 133.73 (5-CH, C₆H₄), 133.81, 142.54 (5-CH_{furan}), 143.34, 148.12, 151.18, 168.90, 172.06, 176.13, 180.21.

Complex 9b

Yield 75 %. M. p. $127 - 125 \,^{\circ}\text{C}. - [\alpha]_{\text{D}}^{20} = +1955.2^{\circ} (c =$ 0.25; MeOH). - Analysis: found (%) C 59.85, H 4.60, N 10.41; calcd. for C39H39N6O4SNi (%) C 59.90, H 4.99, N 10.75. – ¹H NMR (CDCl₃-CCl₄ ~ 1 : 1): $\delta = 0.89$ (3H, t, J = 7.2, CH₃), 1.29-1.41 (2H, m, CH₂CH₃), 1.44-1,60 $(2H, m, CH_2C_2H_5), 2.06 (1H, m, \delta-H_a \text{ pro}), 2.17 (1H, m, \delta-H_a \text{$ γ -H_a proline), 2.51–2.69 (3H, m, CH₂C₃H₇ and β -H_a proline), 3.03 (1H, m, β -H_b pro), 3.45 (1H, m, δ -H_b proline), 3.50 (1H, dd, $J_1 = 10.8$, $J_2 = 6.7$, α -H proline), 3.68 (1H, m, γ -H_b proline), 3.83 (1H, d, J = 12.9, CH_2 -C₆H₄Cl), 4.41 (1H, d, J = 12.9, CH_2 -C₆H₄Cl), 4.47 (1H, dd, $J_1 = 6.8$, $J_2 = 6.0$, NCHCH₂N), 4.71 (1H, dd, $J_1 = 13.8$, $J_2 = 6.0$, NCH*CH*₂N), 4.98 (1H, dd, *J*₁ = 13.8, *J*₂ = 6.8, NCH*CH*₂N), 5.09 (1H, d,) and 5.24 (1H, d, J = 15.7, NCH₂-furan), 6.30 $(1H, dd, J_1 = 3.1, J_2 = 1.8, 4-CH_{furan}), 6.45 (1H, d, J = 3.1, J_2 = 1.8, 4-CH_{furan})$ 3-CH_{furan}), 6.58 (1H, dd, $J_1 = 8.2$, $J_2 = 2.0$, H-3 C₆H₄), $6.65 (1H, m, H-4 C_6 H_4), 6.77 (1H, br.d, J = 7.7, H-2 C_6 H_5),$ 7.10-7.20 (3H, m, Ar), 7.24-7.34 (4H, m, Ar), 7.41-7.53 $(2H, m, Ar), 8.10 (1H, d, J = 8.6, H-6 C_6H_4), 8.18 (1H, dd, H J_1 = 7.7, J_2 = 1.9, \text{H-3 C}_6\text{H}_4\text{Cl}). - {}^{13}\text{C} \text{NMR} (\text{CDCl}_3\text{-CCl}_4)$ ~ 1 : 1): δ = 13.7 (CH₃), 22.2 (CH₂, Bu), 23.8 (γ -C, proline), 25.1 (CH₂ Bu), 27.5 (CH₂ Bu), 30.6 (β-C, proline), 41.1 (CH₂-furan), 52.0 (NCH₂CHN), 57.4 (δ-C, proline), 59.8 (CH₂C₆H₄Cl), 68.5 (NCH₂CHN), 71.2 (α-C, proline), 110.4 and 111.1 (C-3,4 furan), 120.6 (C-4, C₆H₄), 123.7 (C-6, C₆H₄), 126.8, 127.1 (CH), 128.1 (CH), 128.7 (CH), 129.0 (CH), 129.7 (CH), 130.4 (CH), 130.5 (CH), 131.3, 132.5 (C-5, C₆H₄), 133.5, 133.7 (C-3, C₆H₄), 134.1, 135.8, 142.6 (C-5, furan), 142.9, 147.9, 151.3, 168.7, 172.1, 176.3, 179.3.

Complex 10a

Yield 65 %. M. p. 136–139 °C. – $[\alpha]_{\rm D}^{20} = +1892^{\circ}$ (c = 0.05; CH₃OH). - Analysis: found (%) C 62.83, H 5.41, N 11.35; calcd. for C₃₉H₄₀N₆O₄SNi (%) C 62.68, H 5.36, N 11.25. – ¹H NMR (CDCl₃): $\delta = 0.93$ (3H, d, J = 6.6, CH₃); 0.94 (3H, d, *J* = 6.6, CH₃); 1.95 (1H, m, CH *i*-Bu); 2.04 (1H, m, δ -H_a proline); 2.14 (1H, m, γ -H_a pro); 2.44 (1H, dd, $J_1 = 15.6$, $J_2 = 6.9$, CH₂ *i*-Bu); 2.49 (1H, dd, $J_1 = 15.6, J_2 = 7.1, CH_2 i$ -Bu); 2.48 (1H, m, β -H_a proline); 2.82 (1H, m, β -H_b proline); 3.39 (1H, dd, $J_1 = 10.8$, $J_2 = 6.0, \alpha$ -H proline); 3.55 (1H, m, δ -H_b proline); 3.57 (1H, d, J = 12.7, CH_2Ph); 3.75 (1H, m, γ -H_b pro); 4.38 $(1H, dd, J_1 = 7.2, J_2 = 6.8, CHCH_2N); 4.39 (1H, d, J =$ 12.7, CH_2 Ph.); 4.71 (1H, dd, $J_1 = 13.5$, $J_2 = 6.8$, CH CH_2); 4.90 (1H, dd, $J_1 = 13.5$, $J_2 = 7.2$, CHCH₂); 5.06 (1H, d, *J* = 15.7, *CH*₂-furan); 5.21 (1H, d, *J* = 15.7, *CH*₂-furan); 6.27 (1H, dd, $J_1 = 3.3$, $J_2 = 2.9$, H-4 furan); 6.41 (1H, dd, $J_1 = 3.3$, $J_2 = 0.8$, H-3 furan); 6.54 (1H, dd, $J_1 = 8.2$, $J_2 = 1.8$, H-3 C₆H₄); 6.61 (1H, ddd, $J_1 = 8.2$, $J_2 = 6.8$, $J_3 = 1.1$, H-4 C₆H₄); 6.81 (1H, d.br., J = 7.7, H-2 C₆H₅);

7.12 (1H, ddd, $J_1 = 8.7$, $J_2 = 6.8$, $J_3 = 1.8$, H-5 C₆H₄); 7.17 (1H, m, H-4 Ph); 7.21 – 7.37 (4H, m, H arom.); 7.43 – 7.56 (2H, m, H arom.); 7.99 (2H, m, H-2,6 Ph); 8.24 (1H, dd, $J_1 = 8.7$, $J_2 = 1.1$, H-6 C₆H₄); 7.31 (1H, dd, $J_1 = 1.9$, $J_2 = 0.8$, H-5 furan). – ¹³C NMR (CDCl₃-CCl₄ ~ 1 : 1): $\delta = 22.4$ and 22.5 (CH₃), 23.9 (γ -C proline), 26.1 (CH *i*-Bu), 30.8 (β -C proline), 34.0 (CH₂ *i*-Bu), 41.0 (CH₂-furan); 51.6 (CH₂CH), 57.3 (δ -C proline), 62.9 (CH₂Ph), 68.0 (CHCH₂), 70.4 (α -C proline), 110.1 (C-3 furan); 111.1 (C-4 furan), 120.2 (C-4 C₆H₄), 123.8 (C-6 C₆H₄), 126.2 (C*), 127.5 (CH), 128.0 (CH), 127.7 (CH), 128.8 (C-2.6 P?), 128.8 (CH), 129.0 (CH), 129.7 (CH), 131.6 (C-3.5 PH), 132.2 (C-5 furan), 133.4 (C-5 C₆H₄), 133.5 (C*), 142.2 (C*), 143.2 (C*), 148.0 (C*), 150.1 (C*), 168.4 (C*), 171.6 (C*), 175.4 (C*), 180.0 (C*):

Complex 10b

Yield 69 %. M. p. 147 – 148 °C. – $[\alpha]_{\rm D}^{20} = +1943.2^{\circ}$ (c = 0.25, CH₃OH). - Analysis: found (%) C 59.92, H 4,85, N 10,81; calcd. for C39H39N6O4SNi (%) C 59.90, H 4.99, N 10.75. $-{}^{1}$ H NMR (CDCl₃): $\delta = 0.94$ (3H, d, J = 6.6, CH₃), 0.95 (3H, d, J = 6.6, CH₃), 1.96 (1H, m, CH *i*-Bu), 2.06 (1H, m, δ -H_a proline), 2.18 (1H, m, γ -H_a pro), 2.45 (1H, dd, $J_1 = 15.6$, $J_2 = 6.9$, CH₂*i*-Bu), 2.50 (1H, dd, $J_1 = 15.6$, $J_2 = 7.1$, CH₂*i*-Bu), 2.58 (1H, m, β -H_a pro), 3.02 (1H, m, β -H_b pro), 3.47 (1H, dd, $J_1 = 10.8$, $J_2 = 6.6$, α -H proline), 3.52 (1H, m, δ -H_b Proline), 3.74 (1H, m, γ -Hb proline), 3.87 (1H, d, J = 12.9, $CH_2C_6H_4Cl$), 4.38 (1H, dd, $J_1 = 7.0$, $J_2 = 6.8$, CHCH₂N), 4.44 (1H, d, J = 12.9, CH₂C₆H₄Cl), 4.76 (1H, dd, $J_1 = 13.5$, $J_2 = 6.8$, CH_2 CH), 4.83 (1H, dd, $J_1 = 13.5, J_2 = 7.0, CH_2$ CH), 5.06 (1H, d, $J = 15.7, CH_2$ furan), 5.22 (1H, d, J = 15.7, CH₂-furan), 6.28 (1H, dd, J₁ = 3.3, $J_2 = 1.9$, H-4 furan), 6.57 (1H, dd, $J_1 = 8.2$, $J_2 = 1.8$, H-3 C₆H₄), 6.63 (1H, dd, $J_1 = 8.2$, $J_2 = 6.8$, $J_3 = 1.1$, H-4 C₆H₄), 6.80 (1H, d. br., J = 7.7, H-2 C₆H₅), 7.12 (1H, ddd, $J_1 = 8.7$, $J_2 = 6.8$, $J_3 = 1.8$, H-5 C₆H₄), 7.16 (1H, $ddd, J_1 = 7.7, J_2 = 7.7, J_3 = 1.8, C_6H_4Cl), 7.22 - 7.35$ (5H, m, H-5 furan, H-3,4,5,6 C₆H₅), 7.47 (1H, ddd, $J_1 = 8.8, J_2 =$ 7.6, $J_3 = 1.4$, C₆H₄Cl), 7.54 (1H, ddd, $J_1 = 7.6$, $J_2 = 37.4$, $J_3 = 1.4$, C₆H₄Cl), 8.16 (1H, dd, $J_1 = 8.7$, $J_2 = 1.1$, H-6 C_6H_4), 8.26 (1H, dd, $J_1 = 7.6$, $J_2 = 1.6$, H-3 C_6H_4Cl). – ¹³C NMR (CDCl₃-CCl₄ \sim 1 : 1): δ = 22.7 (CH₃), 24.0 (γ -C proline), 26.3 (CH *i*-Bu), 30.8 (β-C proline), 34.3 (CH₂*i*-Bu), 41.2 (CH₂ furan), 51.8 (CH₂CH), 57.6 (δ-C proline), 59.7 (CH₂C₆H₄Cl), 68.3 (CHCH₂), 71.1 (α-C proline), 110.4 (C-3 furan), 111.4 (C-4 furan), 120.5 (C-4 C₆H₄), 124.0 (C-6 C₆H₄), 126.7 (C*), 127.2 (CH), 127.8 (CH), 128.3 (CH), 129.0 (CH), 129.2 (CH), 129.8 (CH), 130.5 (CH), 130.5 (CH), 131.5 (C*), 132.5 (C-5 furan), 133.7 (C-5 C₆H₄), 133.8 (CH), 134.4 (C-3 C₆H₄Cl), 136 (C*), 142.3 (C*), 143.4 (C*), 148.2 (C*), 150.2 (C*), 168.7 (C*), 171.9 (C*), 175.5 (C*), 179.2 (C*).

Complex 11a

Yield 60 %. M. p. 230–232 °C. – $[\alpha]_D^{20} = +840.0^\circ$ (c = 0.05; MeOH). - Analysis: found (%) C 61.67, H 4.66, N 11.92; calcd. for C37H34N6NiO4S (%) C 61.95, H 4.74, N 11.72. – ¹H NMR (CDCl₃-CCl₄ = 1 : 1): δ = 1.98 (1H, m, γ -H_a pro), 2.04 (1H, m, δ -H_a pro), 2.46 (1H, m, β -H_a pro), 2.77(1H, m, β -H_b pro), 3.40 (1H, dd, $J_1 = 10.6$, $J_2 = 6.2$, α -H pro), 3.40 (1H, m, dd, $J_1 = 10.6$, $J_2 = 6.2$, α -H pro), 3.48 (1H, m, γ -H_b pro), 3.53 (1H, m, δ -H_b Pro), 3.56 (1H, $d,J = 12.6, CH_2C_6H_5), 4.38 (1H, d, J = 12.6, CH_2C_6H_5),$ 4.49 (1H, t, J = 6.2, CH), 4.84(1H, dd, $J_1 = 13.7$, $J_2 = 6.2$, CH_2 CH), 4.91 (1H, dd, $J_1 = 13.7$, $J_2 = 6.2$, CH₂CH), 4.93 (2H, dt, *J*₁ = 5.5, *J*₂ = 1.3, CH₂All), 5.20 (1H, m, = CH₂), 5.21 (1H, m, = CH₂), 5.90 (1H, ddt, $J_1 = 17.2$, $J_2 = 10.2$, $J_3 = 5.5, =$ CH), 6.55 (1H, dd, $J_1 = 3.5, J_2 = 1.8,$ H-4 furan), 6.60 (1H, dd, $J_1 = 8.3$, $J_2 = 2.2$, H-3 C₆H₄), 6.64 (1H, ddd, $J_1 = 8.3, J_2 = 6.4, J_3 = 1.1, H-4 C_6 H_4), 6.87(1H, d, J = 3.5, J_1 = 8.3, J_2 = 6.4, J_3 = 1.1, H-4 C_6 H_4)$ H-5 furan), 7.09-7.22 (3H, m, Ar), 7.27-7.37 (4H, m, Ar), 7.44 (1H, tt, $J_1 = 7.5$, $J_2 = 1.3$, H-4 C₆H₅), 7.53(1H, td, $J_1 = 7.6, J_2 = 1.4, Ar.$), 7.58 (1H, d, J = 1.8, H-3 furan), 8.02 (2H, m, H-2,6 C₆H₅), 8.27(1H, dd, $J_1 = 8.7$, $J_2 = 1.1$, H-6 C₆H₄). – ¹³C NMR (CDCl₃-CCl₄ \sim 1 : 1): δ = 24.1 (γ -C pro), 31.0 (β-C pro), 48.2 (CH₂ all), 52.1 (CH₂CH), 57.5(δ-C pro), 63.3 (CH₂ Ph), 68.4(CH), 70.7 (α-C pro), 112.2 (C-4 furan), 113.4 (C-5 furan), 119.1 (=CH₂), 120.7 (C-4 C₆H₄), 123.9(C-6 C₆H₄), 126.6 (CH), 128.4 (CH), 129.0 (C-3,5 C₆H₅ CH₂), 129.1 (CH), 129.1 (CH), 129.2 (CH), 129.9 (CH), 130.6 (=CH), 131.8 (C-2,6 C₆H₅CH₂), 132.7 (CH), 133.4 (C-3 C₆H₄), 133.8 (C), 133.9 (C), 140.9 (C), 143.4 (C), 144.6 (C-3 furan), 169.5 (C), 172.6 (C), 176.1 (C), 180.3 (C).

Complex 11b

Yield 62%. M. p. 234–236 °C. – $[\alpha]_{D}^{20} = +876.0^{\circ}$ (c = 0.05; MeOH). - Analysis: found (%) C 59.30, H 4.30, N 11.12; calcd. for C₃₇H₃₃ClN₆NiO₄S (%) C 59.11, H 4.39, N 11.18. – ¹H NMR (CDCl₃-CCl₄ = 1 : 1): δ = 2.06 (1H, m, δ -H pro), 2.06 (1H, m, γ -H pro), 2.56 (1H, m, β -H pro), 2.97 (1H, m, β -H pro), 3.48 (1H, dd, $J_1 = 10.5, J_2 = 6.6, \alpha$ -H pro), 3.48 (1H, m, γ-H pro), 3.57 (1H, m, δ-H pro), 3.85 (1H, d, J = 12.9, CH₂-Ar), 4.40 (1H, d, J = 12.9, CH₂-Ar), 4.48 (1H, t, *J* = 6.2, CH), 4.84 (2H, d, *J* = 6.2, CH*CH*₂N), 4.93 (2H, dt, $J_1 = 5.5$, $J_2 = 1.4$, NCH₂ Allyl), 5.20 (1H, $m_1 = CH_2$, 5.21 (1H, $m_2 = CH_2$), 5.90 (1H, ddt, $J_1 = 17.1$, $J_2 = 10.3, J_3 = 5.5, = CH$), 6.56 (1H, dd, $J_1 = 3.5, J_2 = 1.8$, H-4 furan), 6.62 (1H, dd, $J_1 = 8.3$, $J_2 = 2.4$, H-3 C₆H₄), 6.66 (1H, ddd, $J_1 = 8.3$, $J_2 = 6.3$, $J_3 = 1.0$, H-4 C₆H₄), 6.87 (1H,dd, $J_1 = 3.5$, $J_2 = 0.8$, H-5 furan), 7.09-7.19 $(3H, m, Ar), 7.25 - 7.36 (4H, m, Ar), 7.44 (1H, tt, J_1 = 7.5,$ $J_2 = 1.3$, Ar), 7.54 (1H, td, $J_1 = 7.5$, $J_2 = 1.3$, Ar), 7.58 (1H, dd, $J_1 = 1.8$, $J_2 = 0.8$, H-3 furan), 8.17 (1H, dd, $J_1 = 8.7$, $J_2 = 1.0, C_6H_4$), 8.23 (1H, dd, $J_1 = 7.6, J_2 = 1.6, C_6H_4Cl$).

 $-^{13}$ C NMR (CDCl₃-CCl₄ ~ 1 : 1): δ = 23.9 (γ-C pro), 30.8 (β-C pro), 48.3 (CH₂ Allyl), 52.1 (NCH₂ CH), 57.7 (δ-C Pro), 60.0 (*CH*₂ Ar), 68.4 (CH), 71.2 (α-C pro), 112.2 and 115.3 (C-4,5 furan), 119.2 (=CH₂), 120.7 (C-4 C₆H₄), 123.8 (C-6 C₆H₄), 126.8 (C), 127.3 (CH), 127.7 (CH), 128.4 (CH), 129.2 (CH), 129.3 (CH), 130.5 (CH), 130.6 (CH), 131.6 (CH), 131.5 (CH), 132.8 (C-5 C₆H₄), 133.8 (CH), 133.9 (CH), 134.3 (C-3 C₆H₄ CI), 136.0 (C), 140.9 (C), 142.5 (C), 143.3 (C), 144.5 (C), 169.4 (C), 172.6 (C), 176.0 (C), 179.4 (C).

Complex 12a

Yield 65 %. M. p. 248 – 250 °C. – $[\alpha]_D^{20} = +722.5$ (c = 0.04, MeOH). - Analysis: found (%) C 63.50, H 4.45, N 10.60; calcd. for $C_{42}H_{37}N_6NiO_3S_2$ (%) C 63.26, H 4.64, N 10.54. – ¹H NMR (CDCl₃-CCl₄ = 1 : 1): δ = 2.02 (2H, m, γ -H_a), 2.17 (δ -H_a Pro), 2.49 and 2.80 (1H and 1H, m, β -CH₂ Pro), 3.12 (2H, dd, $J_1 = 9.5$, $J_2 = 6.5$, NCH₂CH₂C₆H₅), 3.42 $(1H, dd, J_1 = 10.6, J_2 = 6.1, \alpha$ -H Pro), 3.58 (1H, d, J = 12.7, NCH₂C₆H₅), 3.58 (1H, m, δ -H_b Pro), 3.62 (1H, m, γ -H_b Pro), 4.38 (2H, dd, $J_1 = 10.0$, $J_2 = 6.3$, NCH₂CH₂C₆H₅), 4.41 (1H, d, J = 12.7, NCH₂C₆H₅), 4.52 (1H, t, J = 6.3, NCHCH₂N), 4.91 and 4.95 (1H and 1H, dd, $J_1 = 13.7$, $J_2 = 6.3$, NCH CH_2 N), 6.61 (1H, m, H-3 C₆H₄), 6.65 (1H, m, H-4 C₆H₄), 7.05 (1H, m, H-2 C₆H₅), 7.11 (1H, dd, $J_1 = 5.1, J_2 = 3.7, H-4$ thiophene), 7.15 (1H, m, H-5 C₆H₄), 7.20-7.38(1H, m, H-arom.), 7.45 (1H, m, H-arom.), 7.49 (1H, dd, $J_1 = 5.1$, $J_2 = 1.0$, H-5 thiophene), 7.54 (1H, m, H-arom.), 8.04 (2H, m, H-2,6 NCH₂ C_6H_5), 8.26 (1H, d, J =8.6, H-6 C₆H₄). – ¹³C NMR (CDCl₃-CCl₄ ~ 1 : 1): δ = 24.1 (γ-C Pro), 31.1 (β-C Pro), 34.2 (CH₂ Ph), 47.5 (NCH₂CH₂), 52.0 (NCH₂CH), 57.5 (δ-C Pro), 63.2 (CH₂C₆H₅), 68.4 (CH), 70.8 (a-C Pro), 120.7 (C-4 C₆H₄), 124.0 (C-6 C₆H₄), 126.5 (C), 136.6 (C), 127.2 (CH), 127.7 (C), 128.0 (CH), 128.3 (CH), 129.0, 129.1, 129.1, 129.2 (CH), 129.3, 129.4, 130.1, 131.8 (CH C₆H₅), 132.7, 133.4, 133.8, 137.2, 143.4, 145.4, 169.3, 172.4, 176.1, 180.3.

Complex 12b

Yield 70%. M. p. $250-252 \,^{\circ}$ C. $- [\alpha]_D^{20} = +106.6 (c = 0.06, MeOH).$ Analysis: found (%) C 60.50, H 4.50, N 10.50; calcd. for C₄₂H₃₆ClN₆NiO₃S₂ (%) C 60.64, H 4.33, N 10.11. $^{-1}$ H NMR (CDCl₃-CCl₄ = 1 : 1): δ = 2.06 (1H, m, δ -H_a pro), 2.12 (1H, m, γ -H_a pro), 2.58 (1H), 3.00 (1H, m, β -CH₂ pro), 3.11 (2H, dd, J_1 = 9.9, J_2 = 6.2, NCH₂CH₂C₆H₅), 3.49 (1H, dd, J_1 = 10.6, J_2 = 6.6, α -H Pro), 3.50 (1H, m, δ -H_b pro), 3.63 (1H, m, γ -H_b pro), 3.84 (1H, d, J = 12.8, NCH₂C₆H₄Cl), 4.51 (1H, t, J = 6.3, NCHCH₂N), 4.88 (1H), 4.90 (1H, dd, J_1 = 13.8, J_2 = 6.3 NCHCH₂N), 6.63 (1H, m, H-3 C₆H₄), 6.66 (1H, m, H-4 C₆H₄), 7.04 (1H, m, H-2 C₆H₅), 7.11 (1H, dd, J_1 = 5.1, J_2 = 3.7, H-4

thiophene), 7.11 – 7.36 (12H, m, H-arom), 7.45 (1H, m, H-arom), 7.49 (1H, dd, $J_1 = 5.1$, $J_2 = 1.1$, H-5 thiophene), 7.54 (1H, m, H-arom), 8.15 (1H, d, J = 8.6, H-6 C₆H₄), 8.22 (1H, dd, $J_1 = 7.6$, $J_2 = 1.7$, H-3 C₆H₄Cl). – ¹³C NMR (CDCl₃): $\delta = 23.9$ (γ -C pro), 30.8 (β -C pro), 34.0 (CH₂ Ph), 47.4 (NCH₂CH₂), 51.9 (NCH₂CH), 57.6 (δ -C pro), 59.8 (CH₂C₆H₅), 68.4 (NCHCH₂N), 71.1 (α -C pro), 120.6 (C-4 C₆H₄), 123.8 (C-6 C₆H₄), 126.3, 126.8, 127.1 (CH), 127.2 (CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 128.9 (C_{ortho} Ph), 129.0 (CH), 129.0 (C_{meta} Ph), 129.1 (CH), 129.2 (CH), 129.3 (CH), 130.0 (CH), 130.4 (CH), 130.5 (CH), 131.4, 132.6 (C-5 C₆H₄), 133.7, 133.7 (C-3 C₆H₄), 134.2 (CH), 135.9, 137.1, 143.1, 145.4, 169.2, 172.3, 176.0, 179.3.

Complex 13a

Yield 70%. M. p. $161 - 164 \,^{\circ}\text{C}. - [\alpha]_{\text{D}}^{20} = +1316.25^{\circ}$ (c = 0.08, CH₃OH). – Analysis: found (%) C 62.61, H 4.83, N 11.04; calcd. for C₄₀H₃₄N₆O₃S₂Ni (%) C 62.44, H 4.42, N 10.93. – ¹H NMR (CDCl₃): $\delta = 1.98 - 2.14$ (2H, m, γ , δ - H_a pro), 2.48 (1H, m, β - H_a pro), 2.79 (1H, m, β - H_b pro), 3.46 (1H, dd, $J_1 = 10.7$, $J_2 = 6.1$, α -H pro), 3.56 (1H, d, J = 12.5, CH₂Ph), 3.57-3.69 (2H, m, γ , δ -H₆ pro), 4.39 $(1H, d, J = 12.5, CH_2Ph), 4.56 (1H, dd, J_1 = 6.7, J_2 = 6.3,$ $CHCH_2N$), 4.88 (1H, dd, $J_1 = 13.6$, $J_2 = 6.3$, $CHCH_2N$), 5.04 (1H, dd, $J_1 = 13.6$, $J_2 = 6.7$, CHCH₂N), 6.65 (2H, m, H-3,4 C₆H₄), 6.74 (1H, dd, $J_1 = 03.8$, $J_2 = 1.1$, H-3 thiophene), 6.87 (1H, dd, J = 5.0 and 3.8, H-4, thiophene), 7.12-7.23 (3H, m, Ar.), 7.30-7.40 (8H, m, Ar.), 7.44 (1H, tt, 7.4 and J = 1.2, H-4 C₆H₅ (A)), 7.51-7.61 (4H, m, Ar), 8.07 (2H, m, H-2.6 C₆H₅ (B)), 8.26 (1H, d, J = 8.6, H-6, C₆H₄). – ¹³C NMR (CDCl₃): δ = 24.1 (γ -C pro), 31.1 (β-C pro), 52.0 (NCH₂CH), 57.7 (δ-C Pro), 63.4 (CH₂Ph), 68.2 (CHCH₂N), 70.8 (α-C pro), 120.7 (C-4 C₆H₄), 123.9 (C-6 C₆H₄), 126.5, 127.1, 127.5 (C-4 C₄H₃S), 127.6 (C-3 C₄H₃S), 128.2, 129.0, 129.1, 129.3, 130.0, 130.12, 130.5, 131.8 (C-2,6 Ph), 132.7, 133.8 (C-3 C₆H₄), 135.1, 143.3, 145.4, 170.8, 172.5, 176.2, 180.3.

Complex 13b

Yield 63%. M. p. $191-194 \,^{\circ}$ C. $- [\alpha]_{20}^{D} = +1905.0^{\circ}$ (c = 0.06, CH₃OH). – Analysis: found (%) C 59.59, H 4.16, N 10.38; calcd. for C₄₀H₃₃N₆O₃S₂ClNi (%) C 59.75, H 4.14, N 10.45. – ¹H NMR (CDCl₃): $\delta = 2.01-2.12$ (2H, m, γ , δ -H_a pro), 2.57 and 3.00 (1H, 1H, m, β -H pro), 3.52 (1H, dd, 10.7, $J_2 = 6.7$, α -H pro), 3.52 (1H, m, pro γ , δ -H_b pro), 3.65 (1H, m, pro γ , δ -H_b pro), 3.85 (1H, d, J = 12.8, $CH_2C_6H_4Cl$), 4.40 (1H, d, J = 12.8, $CH_2C_6H_4Cl$), 4.55 (1H, dd, $J_1 = 6.6$, $J_2 = 6.2$, $CHCH_2N$), 4.87 (1H, dd, $J_1 = 13.7$, $J_2 = 6.2$, $CHCH_2N$), 4.97 (1H, dd, J = 13.7, CHC H_2N), 6.63–6.70 (2H, m, H-3.4 C₆H₄), 6.75 (1H, dd, $J_1 = 3.8$, $J_2 = 1.1$, H-3, thiophene), 6.87 (1H, dd, $J_1 =$ 5.0, $J_2 = 3.8$, H-4, thiophene), 7.11–7.20 (3H, m, Ar.), 7.25 – 7.40(7H, m, Ar.), 7.44 (1H, tt, $J_1 = 7.4$, $J_2 = 1.1$, H-4 C₆H₅ (A)), 7.52 – 7.59 (5H, m, Ar.), 8.15 (1H, dd, $J_1 = 8.6$, $J_2 = 1.1$, H-6 C₆H₄), 8.24 (1H, dd, $J_1 = 7.6$, $J_2 = 1.6$, Ar.). – ¹³C NMR (CDCl₃): $\delta = 24.0$ (γ -C pro), 30.9 (β -C pro), 52.0(NCH₂CHN), 57.7 (δ -C pro), 59.9 (CH₂C₆H₄Cl), 68.3 (NCHCH₂N), 71.2 (α -C pro), 120.7 (C-4 C₆H₄), 123.8 (C-6 C₆H₄), 126.8, 127.0, 127.2 (CH), 127.6 (CH), 128.2 (CH), 129.0 (CH), 129.0 (CH), 129.0 (CH), 129.1 (CH), 129.2 (CH), 130.0 (CH), 130.1 (C_{ortho} Ph), 130.1 (CH), 130.5 (C_{meta} Ph), 130.6 (CH), 131.5, 132.7 (C-5 C₆H₄), 133.7, 133.8 (C-3 C₆H₄), 134.2 (CH), 135.0, 135.9, 143.2, 145.4, 170.7, 172.6, 176.2, 179.4.

Complex 14a

Yield 66 %. M. p. 148-150 °C. - Analysis: found (%) C 61.11, H 4.79, N 10.15; calcd. for C₃₈H₃₆N₆O₂S₂Ni (%) C 61.07, H 4.82, N 11.25. $- [\alpha]_D^{20} = +624.0$ (*c* = 0.1; CH₃OH). $- {}^{1}$ H NMR (CDCl₃): $\delta = 1.36$ (d, 3H, J = 7.1, CH₃), 1.57 (m, 1H, γ -H pro), 1.99 (ddd, 1H, $J_1 = 10.9$, $J_2 = 9.5, J_3 = 6.5, \delta$ -H pro), 2.28 (m, 1H, β -H pro), 2.52 (m, 1H, β-H pro), 2.59 (m, 1H, γ-H pro), 3.32 (dd, 1H, $J_1 = 10.1, J_2 = 6.5, \alpha$ -H pro), 3.39 (m, δ -H pro), 3.55 (d, 1H, J = 12.7, CH₂ Ph), 4.18 (d, 1H, J = 4.2, CH CH CH₃), 4.39 (d, 1H, J = 12.7, CH₂Ph), 4.90 (ddt, 1H, $J_1 = 16.3$, $J_2 = 4.8, J_3 = 1.7, CH_2 all$, 5.10 (ddt, 1H, $J_1 = 16.3, J_2 = 16.3, J_2 = 10.3, J_2$ $J_2 = 5.1, J_3 = 1.7, CH_2 all$, 5.25 (dm, 1H, $J = 17.3, = CH_2$), 5.35 (dm, 1H, J = 10.4, = CH₂), 5.52 (qd, 1H, $J_1 = 7.1$, $J_2 = 4.2$, CH CH CH₃), 6.04 (ddd, 1H, $J_1 = 17.3$, $J_2 = 10.4$, $J_3 = 5.2, J_4 = 4.8, = CH$), 6.66 (ddd, 1 H, $J_1 = 8.3, J_2 = 6.6$, $J_3 = 1.1$, H-4 C₆H₄), 6.71 (dd, 1 H, $J_1 = 8.3$, $J_2 = 2.0$, H-3 C_6H_4), 7.08–7.17 (m, 3H), 7.24 (td, 1H, $J_1 = 7.4$, $J_2 = 1.3$, C_6H_4Cl), 7.27–7.34 (m, 2H), 7.52 (dd, 1H, $J_1 = 5.1$, $J_2 =$ 1.0, H-5 C₄H₃S), 7.52 - 7.61 (m, 3H), 7.62 (dd, 1H, $J_1 = 3.7$, $J_2 = 1.0, \text{H-3} \text{ C}_4\text{H}_3\text{S}$), 7.70 (m, 1H, H-2, C₆H₅), 8.24 (dd, 1H, $J_1 = 7.6$, $J_2 = 1.7$, C₆H₄Cl), 8.32 (dd, 1H, $J_1 = 8.6$, $J_2 = 1.0, \text{H-6 C}_6\text{H}_4$).

Complex 14b

Yield: 71 %. M. p. 157 – 159 °C. Analysis: found (%) C 58.32, H 4.78, N 10.71; calcd. for $C_{38}H_{35}N_6O_2S_2CINi$ (%) C 58.37, H 4.74, N 10.75. – $[\alpha]_D^{20} = +756.0$ (c = 0.1; CH₃OH). – ¹H NMR ([D₆]DMSO): $\delta = 1.36$ (d, 3H, J = 7.1, CH₃), 1.64 (m, 1H, γ -H pro), 1.95 (m, 1H, δ -H pro), 2.38 (m, 1H, β -H pro), 2.66 (m, 1H, β -H pro), 2.71 (m, 1H, γ -H pro), 3.36 (m, 1H, δ -H pro), 3.39 (dd, 1H, $J_1 = 10.2$, $J_2 = 6.6$, α -H pro), 3.77 (d, 1H, J = 12.9, CH₂ C₆H₄Cl), 4.19 (d, 1H, J = 4.1, NCH), 4.43 (d, 1H, J = 12.9, CH₂ C₆H₄Cl), 4.90 (ddt, 1H), 5.10 (ddt, 1H, $J_1 = 16.2$, $J_2 = 5.2$, $J_3 = 1.7$ CH₂ all), 5.24 (dm, 1H, J = 17.3, $= CH_2$), 5.35 (dm, 1H, J =10.4, $= CH_2$), 5.47 (qm, 1H, $J_1 = 7.1$, $J_2 = 4.1$, CHCH₃), 6.04 (ddt, 1H, $J_1 = 17.3$, $J_2 = 10.4$, $J_3 = 5.2$, = CH), 6.66 (ddd, 1 H, $J_1 = 8.3$, $J_2 = 6.6$, $J_3 = 1.1$, H-4 C₆H₄), 6.71 (dd, 1 H, $J_1 = 8.3$, $J_2 = 2.0$, H-3 C₆H₄), 7.12–7.19 (m, 3H, H-5 C₆H₄, H-4 C₄H₃S, H-4 Ph), 7.30 (m, 3H, H-3,5 Ph, H-2 C₆H₅), 7.52 (dd, 1H, $J_1 = 5.1$, $J_2 = 1.2$, H-5 C₄H₃S), 7.53–7.60 (m, 3H, H-3,4,5 C₆H₅), 7.62 (dd, 1H, $J_1 = 3.7$, $J_2 = 1.2$, H-3 C₄H₃S), 7.71 (m, 1H, H-2 C₆H₅), 7.94 (m, 2H, H-2,6 Ph), 8.46 (dd, 1H, $J_1 = 8.6$, $J_2 = 1.0$, H-6 C₆H₄).

Isolation of the target amino acids 15-20

Decomposition of the diastereomeric complexes 9-14 (**a**, **b**) and isolation of the target α -amino acids 15-20 were carried out according to the earlier developed procedure [10-21].

(S)- β -(3-Butyl-4-(fur-2-ylmethyl)-5-thioxo-dihydro-1H-1,2,4-triazol-1-yl)- α -alanine (15)

Yield 52%. M. p. 229–230 °C. – $[\alpha]_D^{20} = -9.40^{\circ}$ (c = 0.5, 6 N HCl). – Analysis: found (%) C 51.94, H 6.19, N 17.36; calcd. for C₁₄H₂₀N₄O₃S (%) C 51.85, H 6.17, N 17.28. – ¹H NMR (D₂O): $\delta = 0.97$ (3H, t, J = 7.4, CH₃), 1.45 (2H, q, J = 7.4, CH₂CH₃), 1.71 (2H, t, J = 7.4, CH₂CH₂CH₃), 2.88 (2H, t, J = 7.4, CH₂CH₂CH₂CH₂), 2.88 (2H, t, J = 7.4, CH₂CH₂CH₂CH₂CH₃), 5.38 (2H, t, J = 3.3, 3H-furyl), 6.58 (1H, d, J = 3.3, 3H-furyl), 7.56 (1H, d, J = 1.9, 5H-furyl). – ¹³C NMR ([D₆]DMSOCCl₄ = 1 : 3): $\delta = 13.5$ (CH₃), 21.8 (CH₂), 24.5 (CH₂), 27.4 (CH₂), 40.6 (NCH₂), 47.3 (NCH₂), 50.4 (CH), 109.56 and 110.5 (C-3,4 furan), 142.5, 148.0, 151.7, 167.4 and 168.0 (C=S, C=O).

(S)- β -(4-(Fur-2-ylmethyl)-3-isobutyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)- α -alanine (**16**)

Yield 58 %. M. p. $224-226 \,^{\circ}$ C. $-[\alpha]_{D}^{20} = -5.4^{\circ} (c = 0.5, 6 \text{ N} \text{ HCl})$. Analysis: found (%) C 51.80, H 6.12, N 17.25; calcd. for C₁₄H₂₀N₄SO₃ (%) C 51.85, H 6.17, N 17.28. $^{-1}$ H NMR (D₂O+CF₃COOD): $\delta = 0.88$ (6H, d, J = 6.6, CH₃), 1.91 (1H, m, CH *i*-Bu), 2.62 (2H, d, J = 7.2, CH₂*i*-Bu), 4.62 (1H, dd, $J_1 = 5.6$, $J_2 = 5.0$, CHNH₂), 4.72 (1H, dd, $J_1 = 15.1$, $J_2 = 5.6$, NCH₂), 4.80 (1H, dd, $J_1 = 15.1$, $J_2 = 5.0$, NCH₂), 5.25 (2H, S, CH₂-furan), 6.39 (1H, dd, J = 1.9, H-4 furan), 6.43 (1H, dd, $J_1 = 3.2$, $J_2 = 0.8$, H-3 furan), 7.43 (1H, dd, $J_1 = 1.9$, $J_2 = 0.8$, H-5 furan).

(S)-β-(4-Allyl-3-(fur-2-yl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-α-alanine (17)

Yield 54%. M. p. 233–235 °C. – $[\alpha]_D^{20} = +3.60^\circ$ (c = 1, 6 N HCl). Analysis: found (%) C 48.96, H 4.73, N 19.30; calcd. for C₁₂H₁₄N₄O₃S (%) C 48.98, H 4.76, N 19.05. – ¹H NMR ([D₆]DMSO-CF₃COOD): $\delta = 4.45$ (1H, dd, $J_1 = 7.8$, $J_2 = 5.3$, CH), 4.57 (1H, dd, $J_1 = 14.2$, $J_2 = 7.8$, CH₂CH), 4.78 (1H, dd, $J_1 = 14.2$, $J_2 = 5.3$, CH₂CH), 4.88 (2H, dt, $J_1 = 5.3$, $J_2 = 1.6$, NCH₂CH=), 5.15 (1H, dq, $J_1 = 17.0$, $J_2 = 1.6$, = CH₂), 5.17 (1H, dq, $J_1 = 10.6$, $J_2 = 1.6$, = CH₂), 5.88 (1H, ddt, $J_1 = 17.0$, $J_2 = 10.6$, $J_3 = 5.3$, = CH), 6.61 (1H, dd, $J_1 = 3.5$, $J_2 = 1.8$, H-4 furan), 7.05 (1H, dd, $J_1 = 3.5$, $J_2 = 0.8$, H-5 furan), 7.75 (1H, dd, $J_1 = 1.8$, $J_2 = 0.8$, H-3 furan), $-^{13}$ C NMR ([D₆]DMSO-CF₃COOD = 1 : 3): $\delta = 47.5$ (CH₂ allyl), 47.7 (CH₂CH), 50.3 (CHCH₂), 111.8 (C-4 furan), 113.4 (C-3 furan), 117.9 (=CH₂), 130.8 (=CH), 139.8, 142.4, 145.1 (C-5 furan), 167.9, 168.0.

(S)- β -(4-Phenethyl-3-(thien-2-yl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazo-1-yl)- α -alanine (18)

Yield 65 %. M. p. 198–199 °C. – $[\alpha]_D^{20} = -3.93^\circ$ (c = 0.33, 6 N HCl). Analysis: found (%) C 54.12, H 4.79, N 14.91; calcd. for C₁₇H₁₈N₄O₂S₂ (%) C 54.55, H 4.81, N 14.97. – ¹H NMR ([D₆]DMSO-CF₃COOD): $\delta = 2.94-3.10$ (2H, m, CH₂CH₂Ph), 4.36 (2H, t, J = 7.9, NCH₂CH₂Ph), 4.42 (1H, dd, $J_1 = 7.6$, $J_2 = 5.3$, CH), 4.54 (1H, dd, $J_1 = 14.3$, $J_2 = 7.6$, NCH₂CH), 4.78(1H, dd, $J_1 = 14.3$, $J_2 = 5.3$, NCH₂CH), 7.16–7.33 (6H, m, C₆H₅, H, thiophene), 7.57 (1H, dd, $J_1 = 3.6$, $J_2 = 1.0$, H-3, thiophene), 7.89 (1H, dd, $J_1 = 5.1$, $J_2 = 1.0$, H-5, thiophene), 8.54 (3H, m, NH₂HCl). – ¹³C NMR (DMSO-CF₃COOD = 1 : 3): $\delta = 33.1$, 46.6, 47.5, 50.3, 125.3, 126.9, 128.4, 128.7 and 128.7 (C_{ortho} and C_{meta}), 130.0, 130.6, 137.2, 145.6, 167.6, 168.1.

(S)- β -(4-Phenyl-3-(thien-2-yl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)- α -alanine (19)

Yield 70%. M. p. 200–215 °C. – $[\alpha]_D^{20} = -36.73^\circ$ (*c* = 0.25, 6 N HCl). Analysis: found (%) C 52.10, H 4.18, N 16.15; calcd. for C₁₅H₁₄N₄O₂S₂ (%) C 52.02, H 4.05, N

16.18. $^{-1}$ H NMR ([D₆]DMSO): $\delta = 4.57$ (1H, m, CH), 4.62 (1H, m, NCH₂), 4.83 (1H, dd, $J_1 = 13.4$, $J_2 = 3.9$, NCH₂), 6.80 (1H, dd, $J_1 = 3,8$, $J_2 = 1,1$, H-3, thiophene), 7.04 (1H, dd, $J_1 = 5,0$, $J_2 = 3,8$, H-4, thiophene), 7.41 – 7.47 (2H, m, C₆H₅), 7.60 – 7.66 (3H, m, C₆H₅), 7.74 (1H, dd, $J_1 = 5,0$, $J_2 = 1,1$, H-5, thiophene), 8.62 (3H, m, NH₂ HCl). $^{-13}$ C NMR ([D₆]DMSO): $\delta = 47.7$, 50.4, 125.9, 127.7, 128.8 (C_{ortho}), 129.3 (C_{meta}), 129.8, 130.4, 130.4, 134.5, 145.3, 168.1, 168.7.

(2S,3S)- β -(3-(Thien-2-yl)-4-allyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)- α -amino-butyric acid (20)

Yield: 70%. M. p. 205–208 °C. – Analysis: found (%) C 48.20, H 4.98, N 17.2; calcd. for $C_{13}H_{16}N_4O_2S_2$ (%) C 48.15, H 4.93, N 17.28. – $[\alpha]_D^{20} = -10.4^{\circ}$ (c = 0.5, 6 N HCl). – ¹H NMR ([D₆]DMSO-CCl₄ + CF₃COOD): $\delta = 1.61$ (d, 3H, J = 7.0, CH₃CH), 4.35 (d, 1H, J = 5.6, CHNH₂), 4.83 (br., 2H, CH₂ allyl), 5.14 (d, 1H, J = 17.3, =CH₂), 5.25 (d, 1H, J = 10.4, =CH₂), 5.48 (m, 1H, CH CH₃), 5.95 (ddt, 1H, $J_1 = 17.3$, $J_2 = 10.4$, $J_3 = 4.8$, =CH), 7.18 (dd, 1H, $J_1 =$ 5.0, $J_2 = 10.4$, $J_3 = 3.8$, H-4 C₄H₃S), 7.58 (dd, 1H, $J_1 =$ 3.8, $J_2 = 1.1$, H-3 C₄H₃S), 7.69 (dd, 1H, $J_1 = 5.0$, $J_2 = 1.1$, H-5 C₄H₃S). – ¹³C NMR ([D₆]DMSO-CF₃COOD = 1 : 3): $\delta = 14.3$, 47.104, 52.750, 54.109, 117.7, 125.8, 127.7, 129.5, 129.5, 130.8, 145.6, 167.5, 167.9.

Acknowledgement

This work was supported by the Volkswagenstiftung, Project-ID Az 86 223.

- C. Cativiela, M. D. Díaz-de-Villegas, J. A. Gálvez, Y. Lapeña, *Tetrahedron* 1997, 53, 5891-5898.
- [2] J. V. Metzger, in *Comprehensive Heterocyclic Chemistry*, Vol. 6, (Eds.: A. R. Katritzky, C. W. Rees), Pergamon Press, Oxford **1984**, pp. 235–331.
- [3] R. L. N. Harris, J. Huppatz, Aust. J. Chem. 1977, 30, 2225-2240.
- [4] K. Manna, Y. K. Agrawal, Bioorg. Med. Chem. Lett. 2009, 19, 2688-2692.
- [5] W. W. Wardakhani, O. M. E. Abdel-Salem, G. A. Elmegeed, *Acta Pharm.* 2008, 58, 1–14.
- [6] P. R. Kumar, S. Raju, P. S. Goud, M. Sailaja, M. R. Sarma, G. O. Reddy, M. P. Kumar, V. V. R. M. Krishna Reddy, T. Suresh, P. Hegde, *Bioorg. Med. Chem.* 2004, *12*, 1221–1230.
- [7] M. R. P. Queiroz, I. C. F. R. Ferreira, Y. D. Gaetano, G. Kirsch, R. C. Calhelha, L. M. Estevinho, *Bioorg. Med. Chem.* 2006, 14, 6827–6831.

- [8] P. Thomson, M. A. Naylor, S. A. Everett, M. R. L. Stratford, G. Lewis, S. Hill, K. B. Patel, P. Wardman, P. D. Davis, *Mol. Cancer Therapeut.* 2006, *5*, 2886–2894.
- [9] E. Lukevits, L. Demicheva, *Chem. Heterocycl. Comp.* 1993, 29, 243–267.
- [10] A. S. Saghiyan, A. V. Geolchanyan, S. G. Petrosyan, T. V. Chochikyan, V. S. Haroutyunyan, A. A. Avetisyan, Yu. N. Belokon, K. Fisher, *Tetrahedron: Asymmetry* 2004, *15*, 705–711.
- [11] A. S. Saghiyan, A. V. Geolchanyan, L. L. Manasyan, G. M. Mkrtchyan, N. R. Martirosyan, S. A. Dadayan, T. V. Khochikyan, V. S. Harutyunyan, A. A. Avetisyan, V. I. Tararov, V. I. Maleev, Yu. N. Belokon, *Russ. Chem. Bull., Int. Ed.* 2004, *53*, 932–935.
- [12] A. S. Saghiyan, H. H. Hambardzumyan, L. L. Manasyan, A. A. Petrosyan, V. I. Maleev, A. S. Peregudov, *Synth. Commun.* 2005, *35*, 449–459.

- [13] A. S. Saghiyan, L. L. Manasyan, A. V. Geolchanyan, A. M. Hovhannisyan, T. V. Ghochikyan, V. S. Haroutunyan, A. A. Avetisyan, K. S. Mirzoyan, V. I. Maleev, V. N. Khrustalev, *Tetrahedron: Asymmetry* **2006**, *17*, 2743–2753.
- [14] A. S. Saghiyan, L. L. Manasyan, A. V. Geolchanyan, S. A. Dadayan, N. R. Martirosyan, S. M. Vardapetyan, T. V. Ghochikyan, V. S. Haroutunyan, A. A. Avetisyan, Yu. N. Belokon, *Chem. J. Arm.* **2003**, *56*, 64–71.
- [15] A. S. Saghyan, G. M. Mkrtchyan, A. S. Dadayan, S. G. Petrosyan, A. V. Geolchanyan, H. M. Simonyan, A. F. Mkrtchyan, S. Mkrtchyan, A. Gevorgyan, V. O. Iaroshenko, P. Langer, *Tetrahedron: Asymmetry* **2013**, 24, 229–232.
- [16] A. S. Saghyan, H. M. Simonyan, L. A. Stepanyan, S. G. Ghazaryan, A. V. Geolchanyan, L. L. Manasyan, V. T. Ghochikyan, T. V. Ghochikyan, N. A. Hovhannisyan,

A. Gevorgyan, V. O. Iaroshenko, P. Langer, *Tetrahedron: Asymmetry* **2012**, *23*, 891–897.

- Yu. N. Belokon, A. S. Saghiyan, S. M. Djamgaryan, B. I. Bakhmutov, V. M. Belikov, *Tetrahedron* 1988, 44, 5507-5514.
- [18] A. S. Saghiyan, A. S. Baghdasaryan, L. L. Manasyan, *Chem. J. Arm.* **2008**, *61*, 79–85.
- Yu. N. Belokon, A. S. Saghyan, S. M. Djamgaryan, V. I. Bakhmutov, S. V. Vitt, A. S. Batsanov, Yu.T. Struchkov, V. M. Belikov, J. Chem. Soc., Perkin Trans. 1 1990, 2301–2311.
- [20] Yu. N. Belokon, A. G. Bulychev, S. V. Vitt, Yu. T. Struchkov, A. S. Batsanov, T. V. Timofeeva, V. A. Tsyryapkin, M. G. Ryzhov, L. A. Lysova, J. Am. Chem. Soc. 1985, 107, 4252–4259.
- [21] A. S. Saghyan, L. L. Manasyan, S. A. Dadayan, S. G. Petrosyan, A. A. Petrosyan, V. I. Maleev, V. N. Khrustalev, *Russ. Chem. Bull.*, *Int. Ed.* **2006**, *55*, 442–450.