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

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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 carbon-carbon double bond of the chiral ligands of square-planar 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-

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.

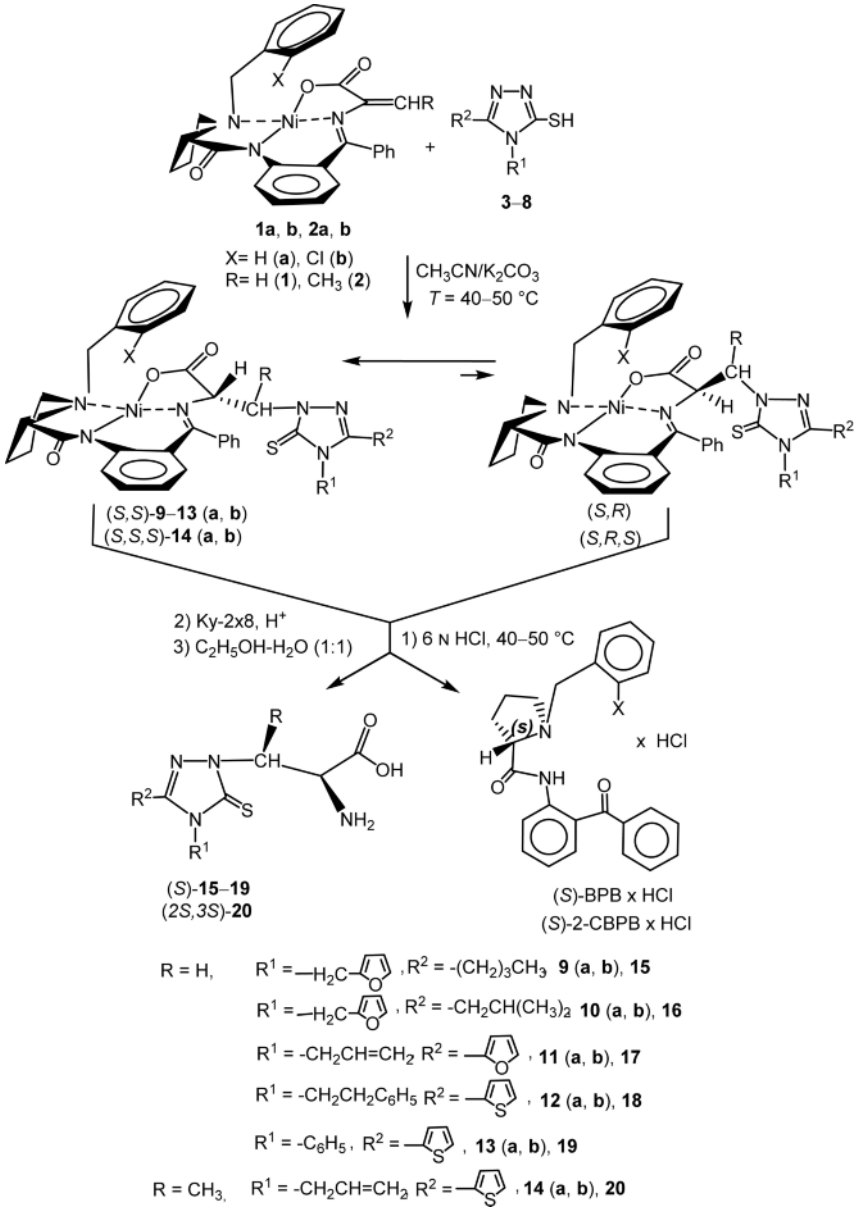
Results and Discussion

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)-4*H*-3-mercapto-1,2,4-triazole (**3**), 4-(fur-2-ylmethyl)-5-isobutyl-4*H*-3-mercapto-1,2,4-triazole (**4**), 4-allyl-5-(fur-2-yl)-4*H*-3-mercapto-1,2,4-triazole (**5**), 4-phenethyl-5-(thien-2-yl)-4*H*-3-mercapto-1,2,4-triazole (**6**), 4-phenyl-5-(thien-2-yl)-4*H*-3-mercapto-1,2,4-triazole (**7**), and 4-allyl-5-(thien-2-yl)-4*H*-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 K_2CO_3 at 50 °C. The course of the reaction was monitored by TLC (SiO_2). 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 × 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 CH_3CN/K_2CO_3 at 40 – 50 °C.

Initial complexes	**3** – **8**	**9** – **14**	*t* (min)	Yield[b] (**9** – **14**)	*de*[a] (**9** – **14**)	**15** – **20**	Yield[b] (**15** – **20**)
Ni^{II}-(*S*)-BPB-Δ-Ala (**1a**)	**3**	**9a**	100	71	94 (*S*,*S*)	**15**	52
Ni^{II}-(*S*)-2-CBPB-Δ-Ala (**1b**)	**3**	**9b**	120	75	98 (*S*,*S*)	**15**	53
Ni^{II}-(*S*)-BPB-Δ-Ala (**1a**)	**4**	**10a**	90	60	92 (*S*,*S*)	**16**	58
Ni^{II}-(*S*)-2-CBPB-Δ-Ala (**1b**)	**4**	**10b**	120	65	94 (*S*,*S*)	**16**	55
Ni^{II}-(*S*)-BPB-Δ-Ala (**1a**)	**5**	**11a**	120	71	88 (*S*,*S*)	**17**	54
Ni^{II}-(*S*)-2-CBPB-Δ-Ala (**1b**)	**5**	**11b**	150	73	96 (*S*,*S*)	**17**	51
Ni^{II}-(*S*)-BPB-Δ-Ala (**1a**)	**6**	**12a**	110	65	80 (*S*,*S*)	**18**	65
Ni^{II}-(*S*)-2-CBPB-Δ-Ala (**1b**)	**6**	**12b**	140	70	93 (*S*,*S*)	**18**	63
Ni^{II}-(*S*)-BPB-Δ-Ala (**1a**)	**7**	**13a**	180	70	74 (*S*,*S*)	**19**	70
Ni^{II}-(*S*)-2-CBPB-Δ-Ala (**1b**)	**7**	**13b**	210	62	95 (*S*,*S*)	**19**	66
Ni^{II}-(*S*)-BPB-Δ-Aba (2**a**)	**8**	**14a**	600	66	94 (*S*,*S*,*S*)	**20**	66
Ni^{II}-(*S*)-2-CBPB-Δ-Aba (**2b**)	**8**	**14b**	720	71	98 (*S*,*S*,*S*)	**20**	61

[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 *N*-benzylproline moiety.

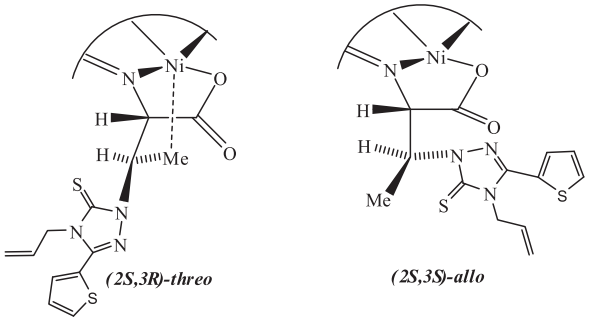


Fig. 1. Different steric location of the methyl group of the amino acid moiety in the two diastereomeric nickel complexes **14a**, **b**.

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 ^{1}H 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 *S*-benzyl-β-methylcysteine) that, in case of the (*2S,3S*)-*allo* absolute configuration of the amino acid moiety, the β-CH_3 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 CH_3 anisotropic cone of the Ni^{2+} ion in case of the (2*S*,3*R*)-*threo* 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. ^{1}H and ^{13}C NMR spectra were recorded on a Mercury-300 Varian spectrometer (300 and 75.4 MHz, respectively) in [D_6]DMSO-CCl_4 = 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 $NaH_2PO_4 \cdot 2H_2O$ 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 (SiO_2, $CHCl_3Me_2CO = 3 : 1$) 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 CH_3CN 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. – $[\alpha]_D^{20} = +2206.0°$ (c = 0.05; MeOH). – Analysis: found (%) C 62.85, H 5.51, N 11.41; calcd. for $C_{39}H_{40}N_6O_4SNi$ (%) C 62.68, H 5.36, N 11.25. – ^{1}H NMR ($CDCl_3$-$CCl_4 \sim 1 : 1$): $\delta = 0.90$ (3H, t, $J = 7.3$, CH_3), 1.36 (2H, qt, $J_1 = 7.3$, $J_2 = 7.1$, CH_2CH_3), 1.53 (2H, m, $CH_2C_2H_5$), 2.07 (1H, m, 5-CH_2, proline), 2.13 (1H, m, 4-CH_2, proline), 2.49 (1H, m, 3-CH_2, proline), 2.60 (2H, m, $CH_2C_3H_7$), 2.84 (1H, m, 3-CH_2, 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-CH_2, proline), 3.58 (1H, d, $J = 12.7$, CH_2-Ph), 3.71 (1H, m, 4-CH_2, 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, $J_1 = 13.7$, $J_2 = 6.3$, NCH_2CH), 4.93 (1H, dd, $J_1 = 13.7$, $J_2 = 6.8$, NCH_2CH), 5.09 (1H, d, $J = 15.7$, NCH_2-Furan), 5.22 (1H, d, $J = 15.7$, NCH_2-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, C_6H_4), 6.63 (1H, ddd, $J_1 = 8.2$, $J_2 = 6.9$, $J_3 = 1.3$, 4-CH, C_6H_4), 6.78 (1H, dt, $J_1 = 7.8$, $J_2 = 1.5$, 2-CH, C_6H_5), 7.27 (1H, dt, $J_1 = 7.4$, $J_2 = 1.8$, 2′-CH, C_6H_5), 7.33 (1H, d, $J = 1.8$, 5-CH_{furan}), 7.34 (2H, m, 3,5-CH, C_6H_5-CH_2), 7.45 (1H, tt, $J_1 = 7.5$, $J_2 = 1.4$, 4-CH, C_6H_5-CH_2), 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-CH_2), 8.25 (1H, dd, $J_1 = 8.7$, $J_2 = 1.3$, 2-CH, C_6H_4). – ^{13}C NMR ($CDCl_3$-$CCl_4 \sim 1 : 1$): $\delta = 13.92$ (CH_3), 22.37 (CH_2CH_3), 24.06 (4-CH_2, proline), 25.25 ($CH_2C_3H_7$), 27.71 ($CH_2C_2H_5$), 30.97 (3-CH_2, proline), 41.17 (NCH_2, furan), 52.06 (NCH_2CH), 57.35 (5-CH_2, proline), 63.12 (CH_2-Ph), 68.56 (NCH$_2$*CH*), 70.74 (2-CH, proline), 110.54 (3-CH_{furan}), 111.36 (4-CH_{furan}), 120.58 (4-CH, C_6H_4), 123.98 (2-CH, C_6H_4), 126.63, 127.77 (2′-CH_{Ph}), 128.25 (2-CH_{Ph}), 128.84 (4-CH_{Ph}), 129.06 (3,5-CH, CH_2-*Ph*), 129.08 (3′-CH_{Ph}), 129.17 (3-CH_{Ph}), 129.82 (4-CH, CH_2-*Ph*), 131.82 (2,6-CH, CH_2-*Ph*), 132.59 (3-CH, C_6H_4), 133.37, 133.73 (5-CH, C_6H_4), 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 °C. – $[\alpha]_D^{20} = +1955.2°$ (c = 0.25; MeOH). – Analysis: found (%) C 59.85, H 4.60, N 10.41; calcd. for $C_{39}H_{39}N_6O_4SNi$ (%) C 59.90, H 4.99, N 10.75. – ^{1}H NMR ($CDCl_3$-$CCl_4 \sim 1 : 1$): $\delta = 0.89$ (3H, t, $J = 7.2$, CH_3), 1.29 – 1.41 (2H, m, CH_2CH_3), 1.44 – 1,60 (2H, m, $CH_2C_2H_5$), 2.06 (1H, m, δ-H_a pro), 2.17 (1H, m, γ-H_a proline), 2.51 – 2.69 (3H, m, $CH_2C_3H_7$ 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-C_6H_4Cl), 4.41 (1H, d, $J = 12.9$, CH_2-C_6H_4Cl), 4.47 (1H, dd, $J_1 = 6.8$, $J_2 = 6.0$, NCHCH$_2$N), 4.71 (1H, dd, $J_1 = 13.8$, $J_2 = 6.0$, NCHCH_2N), 4.98 (1H, dd, $J_1 = 13.8$, $J_2 = 6.8$, NCHCH_2N), 5.09 (1H, d,) and 5.24 (1H, d, $J = 15.7$, NCH_2-furan), 6.30 (1H, dd, $J_1 = 3.1$, $J_2 = 1.8$, 4-CH_{furan}), 6.45 (1H, d, $J = 3.1$, 3-CH_{furan}), 6.58 (1H, dd, $J_1 = 8.2$, $J_2 = 2.0$, H-3 C_6H_4), 6.65 (1H, m, H-4 C_6H_4), 6.77 (1H, br.d, $J = 7.7$, H-2 C_6H_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, $J_1 = 7.7$, $J_2 = 1.9$, H-3 C_6H_4Cl). – ^{13}C NMR ($CDCl_3$-$CCl_4 \sim 1 : 1$): $\delta = 13.7$ (CH_3), 22.2 (CH_2, Bu), 23.8 (γ-C, proline), 25.1 (CH_2 Bu), 27.5 (CH_2 Bu), 30.6 (β-C, proline), 41.1 (CH_2-furan), 52.0 (NCH_2CHN), 57.4 (δ-C, proline), 59.8 ($CH_2C_6H_4Cl$), 68.5 (NCH$_2$*CH*N), 71.2 (α-C, proline), 110.4 and 111.1 (C-3,4 furan), 120.6 (C-4, C_6H_4), 123.7 (C-6, C_6H_4), 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, C_6H_4), 133.5, 133.7 (C-3, C_6H_4), 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. – $[\alpha]_D^{20} = +1892°$ (c = 0.05; CH_3OH). – Analysis: found (%) C 62.83, H 5.41, N 11.35; calcd. for $C_{39}H_{40}N_6O_4SNi$ (%) C 62.68, H 5.36, N 11.25. – ^{1}H NMR ($CDCl_3$): $\delta = 0.93$ (3H, d, $J = 6.6$, CH_3); 0.94 (3H, d, $J = 6.6$, CH_3); 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, $J_1 = 15.6$, $J_2 = 6.9$, CH_2 *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, $J_1 = 10.8$, $J_2 = 6.0$, α-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$_2$N); 4.39 (1H, d, $J = 12.7$, CH_2Ph.); 4.71 (1H, dd, $J_1 = 13.5$, $J_2 = 6.8$, CHCH_2); 4.90 (1H, dd, $J_1 = 13.5$, $J_2 = 7.2$, CHCH_2); 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 C_6H_4); 6.61 (1H, ddd, $J_1 = 8.2$, $J_2 = 6.8$, $J_3 = 1.1$, H-4 C_6H_4); 6.81 (1H, d.br., $J = 7.7$, H-2 C_6H_5);

7.12 (1H, ddd, $J_1 = 8.7$, $J_2 = 6.8$, $J_3 = 1.8$, H-5 C_6H_4); 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 C_6H_4); 7.31 (1H, dd, $J_1 = 1.9$, $J_2 = 0.8$, H-5 furan). – ^{13}C NMR ($CDCl_3$-CCl_4 ∼ 1 : 1): δ = 22.4 and 22.5 (CH_3), 23.9 (γ-C proline), 26.1 (CH *i*-Bu), 30.8 (β-C proline), 34.0 (CH_2 *i*-Bu), 41.0 (CH_2-furan); 51.6 (CH_2CH), 57.3 (δ-C proline), 62.9 (CH_2Ph), 68.0 ($CHCH_2$), 70.4 (α-C proline), 110.1 (C-3 furan); 111.1 (C-4 furan), 120.2 (C-4 C_6H_4), 123.8 (C-6 C_6H_4), 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 C_6H_4), 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. – $[\alpha]_D^{20} = +1943.2°$ (c = 0.25, CH_3OH). – Analysis: found (%) C 59.92, H 4,85, N 10,81; calcd. for $C_{39}H_{39}N_6O_4SNi$ (%) C 59.90, H 4.99, N 10.75. – ^{1}H NMR ($CDCl_3$): δ = 0.94 (3H, d, $J = 6.6$, CH_3), 0.95 (3H, d, $J = 6.6$, CH_3), 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, $J_1 = 15.6$, $J_2 = 6.9$, CH_2*i*-Bu), 2.50 (1H, dd, $J_1 = 15.6$, $J_2 = 7.1$, CH_2*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, $J_1 = 7.0$, $J_2 = 6.8$, $CHCH_2N$), 4.44 (1H, d, $J = 12.9$, $CH_2C_6H_4Cl$), 4.76 (1H, dd, $J_1 = 13.5$, $J_2 = 6.8$, CH_2CH), 4.83 (1H, dd, $J_1 = 13.5$, $J_2 = 7.0$, CH_2CH), 5.06 (1H, d, $J = 15.7$,CH_2-furan), 5.22 (1H, d, $J = 15.7$, CH_2-furan), 6.28 (1H, dd, $J_1 = 3.3$, $J_2 = 1.9$, H-4 furan), 6.57 (1H, dd, $J_1 = 8.2$, $J_2 = 1.8$, H-3 C_6H_4), 6.63 (1H, dd, $J_1 = 8.2$, $J_2 = 6.8$, $J_3 = 1.1$, H-4 C_6H_4), 6.80 (1H, d. br., $J = 7.7$, H-2 C_6H_5), 7.12 (1H, ddd, $J_1 = 8.7$, $J_2 = 6.8$, $J_3 = 1.8$, H-5 C_6H_4), 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 C_6H_5), 7.47 (1H, ddd, $J_1 = 8.8$, $J_2 = 7.6$, $J_3 = 1.4$, C_6H_4Cl), 7.54 (1H, ddd, $J_1 = 7.6$, $J_2 = 37.4$, $J_3 = 1.4$, C_6H_4Cl), 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). – ^{13}C NMR ($CDCl_3$-CCl_4 ∼ 1 : 1): δ = 22.7 (CH_3), 24.0 (γ-C proline), 26.3 (CH *i*-Bu), 30.8 (β-C proline), 34.3 (CH_2*i*-Bu), 41.2 (CH_2 furan), 51.8 (CH_2CH), 57.6 (δ-C proline), 59.7 ($CH_2C_6H_4Cl$), 68.3 ($CHCH_2$), 71.1 (α-C proline), 110.4 (C-3 furan), 111.4 (C-4 furan), 120.5 (C-4 C_6H_4), 124.0 (C-6 C_6H_4), 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 C_6H_4), 133.8 (CH), 134.4 (C-3 C_6H_4Cl), 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. – $[\alpha]_D^{20} = +840.0°$ (c = 0.05; MeOH). – Analysis: found (%) C 61.67, H 4.66, N 11.92; calcd. for $C_{37}H_{34}N_6NiO_4S$ (%) C 61.95, H 4.74, N 11.72. – ^{1}H NMR ($CDCl_3$-CCl_4 = 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_2CH), 4.91 (1H, dd, $J_1 = 13.7$, $J_2 = 6.2$, CH_2CH), 4.93 (2H, dt, $J_1 = 5.5$, $J_2 = 1.3$, CH_2All), 5.20 (1H, m, $=CH_2$), 5.21 (1H, m, $=CH_2$), 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 C_6H_4), 6.64 (1H, ddd, $J_1 = 8.3$, $J_2 = 6.4$, $J_3 = 1.1$, H-4 C_6H_4), 6.87(1H, d, $J = 3.5$, 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 C_6H_5), 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 C_6H_5), 8.27(1H, dd, $J_1 = 8.7$, $J_2 = 1.1$, H-6 C_6H_4). – ^{13}C NMR ($CDCl_3$-CCl_4 ∼ 1 : 1): δ = 24.1 (γ-C pro), 31.0 (β-C pro), 48.2 (CH_2 all), 52.1 (CH_2CH), 57.5(δ-C pro), 63.3 (CH_2 Ph), 68.4(CH), 70.7 (α-C pro), 112.2 (C-4 furan), 113.4 (C-5 furan), 119.1 (=CH_2), 120.7 (C-4 C_6H_4), 123.9(C-6 C_6H_4), 126.6 (CH), 128.4 (CH), 129.0 (C-3,5 C_6H_5 CH_2), 129.1 (CH), 129.1 (CH), 129.2 (CH), 129.9 (CH), 130.6 (=CH), 131.8 (C-2,6 $C_6H_5CH_2$), 132.7 (CH), 133.4 (C-3 C_6H_4), 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. – $[\alpha]_D^{20} = +876.0°$ (c = 0.05; MeOH). – Analysis: found (%) C 59.30, H 4.30, N 11.12; calcd. for $C_{37}H_{33}ClN_6NiO_4S$ (%) C 59.11, H 4.39, N 11.18. – ^{1}H NMR ($CDCl_3$-CCl_4 = 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, $J_1 = 10.5$, $J_2 = 6.6$, α-H pro), 3.48 (1H, m, γ-H pro), 3.57 (1H, m, δ-H pro), 3.85 (1H, d, $J = 12.9$, CH_2-Ar), 4.40 (1H, d, $J = 12.9$, CH_2-Ar), 4.48 (1H, t, $J = 6.2$, CH), 4.84 (2H, d, $J = 6.2$, $CHCH_2N$), 4.93 (2H, dt, $J_1 = 5.5$, $J_2 = 1.4$, NCH_2 Allyl), 5.20 (1H, m, $=CH_2$), 5.21 (1H, m, $=CH_2$), 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 C_6H_4), 6.66 (1H, ddd, $J_1 = 8.3$, $J_2 = 6.3$, $J_3 = 1.0$, H-4 C_6H_4), 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 ($CDCl_3$-$CCl_4 \sim 1:1$): $\delta = 23.9$ (γ-C pro), 30.8 (β-C pro), 48.3 (CH_2 Allyl), 52.1 (NCH_2 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 (=CH_2), 120.7 (C-4 C_6H_4), 123.8 (C-6 C_6H_4), 126.8 (C), 127.3 (CH), 127.7 (CH), 128.4 (CH), 129.2 (CH), 129.3 (CH), 130.5 (CH), 130.6 (CH), 130.6 (CH), 131.5 (CH), 132.8 (C-5 C_6H_4), 133.8 (CH), 133.9 (CH), 134.3 (C-3 C_6H_4 Cl), 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. – ^{1}H NMR ($CDCl_3$-$CCl_4 = 1:1$): $\delta = 2.02$ (2H, m, γ-H_a), 2.17 (δ-H_a Pro), 2.49 and 2.80 (1H and 1H, m, β-CH_2 Pro), 3.12 (2H, dd, $J_1 = 9.5$, $J_2 = 6.5$, $NCH_2CH_2C_6H_5$), 3.42 (1H, dd, $J_1 = 10.6$, $J_2 = 6.1$, α-H Pro), 3.58 (1H, d, $J = 12.7$, $NCH_2C_6H_5$), 3.58 (1H, m, δ-H_b Pro), 3.62 (1H, m, γ-H_b Pro), 4.38 (2H, dd, $J_1 = 10.0$, $J_2 = 6.3$, $NCH_2CH_2C_6H_5$), 4.41 (1H, d, $J = 12.7$, $NCH_2C_6H_5$), 4.52 (1H, t, $J = 6.3$, $NCHCH_2N$), 4.91 and 4.95 (1H and 1H, dd, $J_1 = 13.7$, $J_2 = 6.3$, $NCHCH_2N$), 6.61 (1H, m, H-3 C_6H_4), 6.65 (1H, m, H-4 C_6H_4), 7.05 (1H, m, H-2 C_6H_5), 7.11 (1H, dd, $J_1 = 5.1$, $J_2 = 3.7$, H-4 thiophene), 7.15 (1H, m, H-5 C_6H_4), 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 $NCH_2C_6H_5$), 8.26 (1H, d, $J = 8.6$, H-6 C_6H_4). – ^{13}C NMR ($CDCl_3$-$CCl_4 \sim 1:1$): $\delta = 24.1$ (γ-C Pro), 31.1 (β-C Pro), 34.2 (CH_2 Ph), 47.5 (NCH_2CH_2), 52.0 (NCH_2CH), 57.5 (δ-C Pro), 63.2 ($CH_2C_6H_5$), 68.4 (CH), 70.8 (α-C Pro), 120.7 (C-4 C_6H_4), 124.0 (C-6 C_6H_4), 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 C_6H_5), 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 °C. – $[\alpha]_D^{20} = +106.6$ ($c = 0.06$, MeOH). Analysis: found (%) C 60.50, H 4.50, N 10.50; calcd. for $C_{42}H_{36}ClN_6NiO_3S_2$ (%) C 60.64, H 4.33, N 10.11. – ^{1}H NMR ($CDCl_3$-$CCl_4 = 1:1$): $\delta = 2.06$ (1H, m, δ-H_a pro), 2.12 (1H, m, γ-H_a pro), 2.58 (1H), 3.00 (1H, m, β-CH_2 pro), 3.11 (2H, dd, $J_1 = 9.9$, $J_2 = 6.2$, $NCH_2CH_2C_6H_5$), 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, $J = 12.8$, $NCH_2C_6H_4Cl$), 4.38 (2H, m, $NCH_2CH_2C_6H_5$), 4.42 (1H, d, $J = 12.8$, $NCH_2C_6H_4Cl$), 4.51 (1H, t, $J = 6.3$, $NCHCH_2N$), 4.88 (1H), 4.90 (1H, dd, $J_1 = 13.8$, $J_2 = 6.3$ $NCHCH_2N$), 6.63 (1H, m, H-3 C_6H_4), 6.66 (1H, m, H-4 C_6H_4), 7.04 (1H, m, H-2 C_6H_5), 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 C_6H_4), 8.22 (1H, dd, $J_1 = 7.6$, $J_2 = 1.7$, H-3 C_6H_4Cl). – ^{13}C NMR ($CDCl_3$): $\delta = 23.9$ (γ-C pro), 30.8 (β-C pro), 34.0 (CH_2 Ph), 47.4 (NCH_2CH_2), 51.9 (NCH_2CH), 57.6 (δ-C pro), 59.8 ($CH_2C_6H_5$), 68.4 ($NCHCH_2N$), 71.1 (α-C pro), 120.6 (C-4 C_6H_4), 123.8 (C-6 C_6H_4), 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 C_6H_4), 133.7, 133.7 (C-3 C_6H_4), 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 °C. – $[\alpha]_D^{20} = +1316.25°$ ($c = 0.08$, CH_3OH). – Analysis: found (%) C 62.61, H 4.83, N 11.04; calcd. for $C_{40}H_{34}N_6O_3S_2Ni$ (%) C 62.44, H 4.42, N 10.93. – ^{1}H NMR ($CDCl_3$): $\delta = 1.98 – 2.14$ (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, $J = 12.5$, CH_2Ph), 3.57 – 3.69 (2H, m, γ, δ-H_6 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, $J_1 = 13.6$, $J_2 = 6.7$, $CHCH_2N$), 6.65 (2H, m, H-3,4 C_6H_4), 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 C_6H_5 (A)), 7.51 – 7.61 (4H, m, Ar), 8.07 (2H, m, H-2.6 C_6H_5 (B)), 8.26 (1H, d, $J = 8.6$, H-6, C_6H_4). – ^{13}C NMR ($CDCl_3$): $\delta = 24.1$ (γ-C pro), 31.1 (β-C pro), 52.0 (NCH_2CH), 57.7 (δ-C Pro), 63.4 (CH_2Ph), 68.2 ($CHCH_2N$), 70.8 (α-C pro), 120.7 (C-4 C_6H_4), 123.9 (C-6 C_6H_4), 126.5, 127.1, 127.5 (C-4 C_4H_3S), 127.6 (C-3 C_4H_3S), 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 C_6H_4), 135.1, 143.3, 145.4, 170.8, 172.5, 176.2, 180.3.

Complex ***13b***

Yield 63 %. M. p. 191 – 194 °C. – $[\alpha]_D^{20} = +1905.0°$ ($c = 0.06$, CH_3OH). – Analysis: found (%) C 59.59, H 4.16, N 10.38; calcd. for $C_{40}H_{33}N_6O_3S_2ClNi$ (%) C 59.75, H 4.14, N 10.45. – ^{1}H NMR ($CDCl_3$): $\delta = 2.01 – 2.12$ (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, $J = 13.7$, $CHCH_2N$), 6.63 – 6.70 (2H, m, H-3.4 C_6H_4), 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 C_6H_5 (A)), 7.52 – 7.59 (5H, m, Ar.), 8.15 (1H, dd, $J_1 = 8.6$, $J_2 = 1.1$, H-6 C_6H_4), 8.24 (1H, dd, $J_1 = 7.6$, $J_2 = 1.6$, Ar.). – ^{13}C NMR ($CDCl_3$): $\delta = 24.0$ (γ-C pro), 30.9 (β-C pro), 52.0(N*C*H$_2$CHN), 57.7 (δ-C pro), 59.9 (*C*H$_2$C$_6$H$_4$Cl), 68.3 (N*C*HCH$_2$N), 71.2 (α-C pro), 120.7 (C-4 C_6H_4), 123.8 (C-6 C_6H_4), 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 C_6H_4), 133.7, 133.8 (C-3 C_6H_4), 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 $C_{38}H_{36}N_6O_2S_2Ni$ (%) C 61.07, H 4.82, N 11.25. – $[\alpha]_D^{20} = +624.0$ ($c = 0.1$; CH_3OH). – ^{1}H NMR ($CDCl_3$): $\delta = 1.36$ (d, 3H, $J = 7.1$, CH_3), 1.57 (m, 1H, γ-H pro), 1.99 (ddd, 1H, $J_1 = 10.9$, $J_2 = 9.5$, $J_3 = 6.5$, δ-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, $J_1 = 10.1$, $J_2 = 6.5$, α-H pro), 3.39 (m, δ-H pro), 3.55 (d, 1H, $J = 12.7$, CH_2 Ph), 4.18 (d, 1H, $J = 4.2$, CH CH CH_3), 4.39 (d, 1H, $J = 12.7$, CH_2Ph), 4.90 (ddt, 1H, $J_1 = 16.3$, $J_2 = 4.8$, $J_3 = 1.7$, CH_2 all), 5.10 (ddt, 1H, $J_1 = 16.3$, $J_2 = 5.1$, $J_3 = 1.7$, CH_2 all), 5.25 (dm, 1H, $J = 17.3$, $=CH_2$), 5.35 (dm, 1H, $J = 10.4$, $=CH_2$), 5.52 (qd, 1H, $J_1 = 7.1$, $J_2 = 4.2$, CH CH CH_3), 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 C_6H_4), 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 C_4H_3S), 7.52 – 7.61 (m, 3H), 7.62 (dd, 1H, $J_1 = 3.7$, $J_2 = 1.0$, H-3 C_4H_3S), 7.70 (m, 1H, H-2, C_6H_5), 8.24 (dd, 1H, $J_1 = 7.6$, $J_2 = 1.7$, C_6H_4Cl), 8.32 (dd, 1H, $J_1 = 8.6$, $J_2 = 1.0$, H-6 C_6H_4).

Complex ***14b***

Yield: 71 %. M. p. 157 – 159 °C. Analysis: found (%) C 58.32, H 4.78, N 10.71; calcd. for $C_{38}H_{35}N_6O_2S_2ClNi$ (%) C 58.37, H 4.74, N 10.75. – $[\alpha]_D^{20} = +756.0$ ($c = 0.1$; CH_3OH). – ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.36$ (d, 3H, $J = 7.1$, CH_3), 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, $J = 12.9$, CH_2 C_6H_4Cl), 4.19 (d, 1H, $J = 4.1$, NCH), 4.43 (d, 1H, $J = 12.9$, CH_2 C_6H_4Cl), 4.90 (ddt, 1H), 5.10 (ddt, 1H, $J_1 = 16.2$, $J_2 = 5.2$, $J_3 = 1.7$ CH_2 all), 5.24 (dm, 1H, $J = 17.3$, $=CH_2$), 5.35 (dm, 1H, $J = 10.4$, $=CH_2$), 5.47 (qm, 1H, $J_1 = 7.1$, $J_2 = 4.1$, $CHCH_3$), 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 C_6H_4), 6.71 (dd, 1 H, $J_1 = 8.3$, $J_2 = 2.0$, H-3 C_6H_4), 7.12 – 7.19 (m, 3H, H-5 C_6H_4, H-4 C_4H_3S, H-4 Ph), 7.30 (m, 3H, H-3,5 Ph, H-2 C_6H_5), 7.52 (dd, 1H, $J_1 = 5.1$, $J_2 = 1.2$, H-5 C_4H_3S), 7.53 – 7.60 (m, 3H, H-3,4,5 C_6H_5), 7.62 (dd, 1H, $J_1 = 3.7$, $J_2 = 1.2$, H-3 C_4H_3S), 7.71 (m, 1H, H-2 C_6H_5), 7.94 (m, 2H, H-2,6 Ph), 8.46 (dd, 1H, $J_1 = 8.6$, $J_2 = 1.0$, H-6 C_6H_4).

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. – $[\alpha]_D^{20} = -9.40°$ ($c = 0.5$, 6 N HCl). – Analysis: found (%) C 51.94, H 6.19, N 17.36; calcd. for $C_{14}H_{20}N_4O_3S$ (%) C 51.85, H 6.17, N 17.28. – ^{1}H NMR (D_2O): $\delta = 0.97$ (3H, t, $J = 7.4$, CH_3), 1.45 (2H, q, $J = 7.4$, CH_2CH_3), 1.71 (2H, t, $J = 7.4$, $CH_2CH_2CH_3$), 2.88 (2H, t, $J = 7.4$, $CH_2CH_2CH_2CH_3$), 4.33 (1H, dd, $J_1 = 6.7$, $J_2 = 4.9$, NCH), 4.81 (2H, m, NCH_2), 5.38 (2H, s, NCH_2-furyl), 6.53 (1H, dd, $J_1 = 3.3$, $J_2 = 1.9$, 4H-furyl), 6.58 (1H, d, $J = 3.3$, 3H-furyl), 7.56 (1H, d, $J = 1.9$, 5H-furyl). – ^{13}C NMR ([D$_6$]DMSOCCl_4 = 1 : 3): $\delta = 13.5$ (CH_3), 21.8 (CH_2), 24.5 (CH_2), 27.4 (CH_2), 40.6 (NCH_2), 47.3 (NCH_2), 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 °C. – $[\alpha]_D^{20} = -5.4°$ ($c = 0.5$, 6 N HCl). Analysis: found (%) C 51.80, H 6.12, N 17.25; calcd. for $C_{14}H_{20}N_4SO_3$ (%) C 51.85, H 6.17, N 17.28. – ^{1}H NMR (D_2O+CF_3COOD): $\delta = 0.88$ (6H, d, $J = 6.6$, CH_3), 1.91 (1H, m, CH *i*-Bu), 2.62 (2H, d, $J = 7.2$, CH_2*i*-Bu), 4.62 (1H, dd, $J_1 = 5.6$, $J_2 = 5.0$, *CH*NH_2), 4.72 (1H, dd, $J_1 = 15.1$, $J_2 = 5.6$, NCH_2), 4.80 (1H, dd, $J_1 = 15.1$, $J_2 = 5.0$, NCH_2), 5.25 (2H, S, CH_2-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. – $[\alpha]_D^{20} = +3.60°$ ($c = 1$, 6 N HCl). Analysis: found (%) C 48.96, H 4.73, N 19.30; calcd. for $C_{12}H_{14}N_4O_3S$ (%) C 48.98, H 4.76, N 19.05. – ^{1}H NMR ([D$_6$]DMSO-CF_3COOD): $\delta = 4.45$ (1H, dd, $J_1 = 7.8$, $J_2 = 5.3$, CH), 4.57 (1H, dd, $J_1 = 14.2$, $J_2 = 7.8$, CH_2CH), 4.78 (1H, dd, $J_1 = 14.2$, $J_2 = 5.3$, CH_2CH), 4.88 (2H, dt, $J_1 = 5.3$, $J_2 = 1.6$, $NCH_2CH=$), 5.15 (1H, dq, $J_1 = 17.0$, $J_2 = 1.6$, $=CH_2$), 5.17 (1H, dq, $J_1 = 10.6$, $J_2 = 1.6$, $=CH_2$),

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 ([D$_6$]DMSO-CF$_3$COOD = 1 : 3): δ = 47.5 (CH_2 allyl), 47.7 (CH_2CH), 50.3 (CHCH$_2$), 111.8 (C-4 furan), 113.4 (C-3 furan), 117.9 (=CH$_2$), 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-triazol-1-yl)-α-alanine (**18**)*

Yield 65%. M. p. 198 – 199 °C. – $[\alpha]_D^{20} = -3.93°$ (c = 0.33, 6 N HCl). Analysis: found (%) C 54.12, H 4.79, N 14.91; calcd. for $C_{17}H_{18}N_4O_2S_2$ (%) C 54.55, H 4.81, N 14.97. – ^{1}H NMR ([D$_6$]DMSO-CF$_3$COOD): $\delta = 2.94 - 3.10$ (2H, m, CH$_2$CH$_2$Ph), 4.36 (2H, t, $J = 7.9$, NCH$_2$CH$_2$Ph), 4.42 (1H, dd, $J_1 = 7.6$, $J_2 = 5.3$, CH), 4.54 (1H, dd, $J_1 = 14.3$, $J_2 = 7.6$, NCH$_2$CH), 4.78(1H, dd, $J_1 = 14.3$, $J_2 = 5.3$, NCH$_2$CH), 7.16 – 7.33 (6H, m, C$_6$H$_5$, 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, NH$_2$HCl). – ^{13}C NMR (DMSO-CF$_3$COOD = 1 : 3): δ = 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. – $[\alpha]_D^{20} = -36.73°$ (c = 0.25, 6 N HCl). Analysis: found (%) C 52.10, H 4.18, N 16.15; calcd. for $C_{15}H_{14}N_4O_2S_2$ (%) C 52.02, H 4.05, N 16.18. – ^{1}H NMR ([D$_6$]DMSO): δ = 4.57 (1H, m, CH), 4.62 (1H, m, NCH$_2$), 4.83 (1H, dd, $J_1 = 13.4$, $J_2 = 3.9$, NCH$_2$), 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, C$_6$H$_5$), 7.60 – 7.66 (3H, m, C$_6$H$_5$), 7.74 (1H, dd, $J_1 = 5,0$, $J_2 = 1,1$, H-5, thiophene), 8.62 (3H, m, NH$_2$ HCl). – ^{13}C NMR ([D$_6$]DMSO): δ = 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. – $[\alpha]_D^{20} = -10.4°$ (c = 0.5, 6 N HCl). – ^{1}H NMR ([D$_6$]DMSO-CCl$_4$ + CF$_3$COOD): δ = 1.61 (d, 3H, $J = 7.0$, CH$_3$CH), 4.35 (d, 1H, $J = 5.6$, CHNH$_2$), 4.83 (br., 2H, CH$_2$ allyl), 5.14 (d, 1H, $J = 17.3$, =CH$_2$), 5.25 (d, 1H, $J = 10.4$, =CH$_2$), 5.48 (m, 1H, CH CH$_3$), 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 C$_4$H$_3$S), 7.58 (dd, 1H, $J_1 = 3.8$, $J_2 = 1.1$, H-3 C$_4$H$_3$S), 7.69 (dd, 1H, $J_1 = 5.0$, $J_2 = 1.1$, H-5 C$_4$H$_3$S). – ^{13}C NMR ([D$_6$]DMSO-CF$_3$COOD = 1 : 3): δ = 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.

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