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Synthesis of Nonracemic Tetrazole GABA Analogs

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Abstract—Nonracemic 3-substituted 4-(1*H*-tetrazol-1-yl)butanoic acids, analogs of the neurotropic drugs phenibut, tolibut, and baclofen, were synthesized by a three-component reaction of the *R*-isomers of the corresponding amino acids, triethyl orthoformate, and sodium azide. The key stage of the synthesis is the asymmetric addition of diethyl malonate to nitroalkenes, catalyzed by a Ni(II) complex of (S,S)-*N*,*N*'-dibenzylcyclohexane-1,2-diamine.

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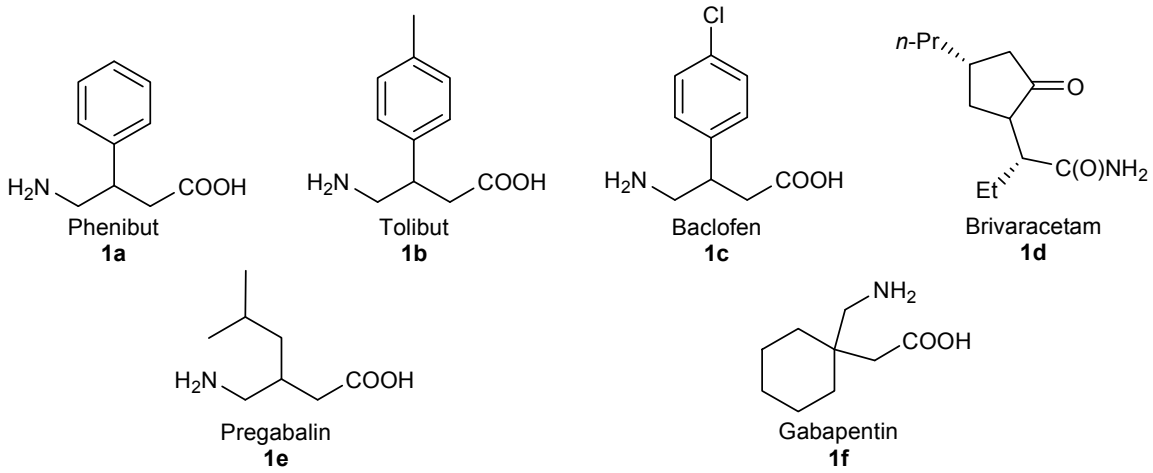
The chemical modification of biomolecules, including amino acids, by the introduction of the tetrazole fragment is a promising approach to drug design in medicinal chemistry [1–6]. The tetrazole fragments can impart to pharmaceutical preparations a higher metabolic stability and ability to penetrate biological membranes. The tetrazole fragments are frequently used as bioisosteres of carboxyls in biologically active compounds [7–9]. This approach was used to success in the design of drugs with improved pharmaceutical profiles, including antibacterial [10–12], antiviral [13–17], anticancer [18–21], and neurotropic agents [22–26].

Tetrazole analogs of amino acids attract attention of researchers focused on the design of new-generation drugs for curing CNS diseases [23–26].

The presently known tetrazole analogs of amino acids can be divided into four main groups: (i) tetrazole analogs of amino acids, where the tetrazole fragment plays the role of an isostere of the carboxyl group; (ii) derivatives, where the tetrazole fragment replaces the amino group; (iii) derivatives, where the tetrazole fragment is a structural unit of the substituent at the amino group; and (iv) tetrazole analogs of nonionogenic amino acids, in particular, γ-

Scheme 1.



aminobutyric acid (GABA) [27]. The latter group of compounds holds the greatest promise as potential neurotropic agents.

The modification of GABA, primarily via aliphatic, aromatic, or heterocyclic substitution in the *3*-position, as well as synthesis of cyclic GABA derivatives (pyrrolidin-2-ones) resulted in the development of highly efficient neurotropic drugs [28–32].

Phenibut **1a** [28] and Baclofen **1c** [29, 30], agonists of $GABA_B$ receptors, are presently successfully used in the therapy of asthenic and neurotic anxiety disorders, multiple sclerosis, strokes, traumatic brain injuries, meningitis, various spinal diseases, cerebral palsy, as well as in the complex therapy of alcoholism. Tolibut **1b** [31] exhibits analgesic and neuroprotective, but, however, has not still found application in clinical practice. The mentioned drugs also showed nootropic activity (Scheme 1).

The cyclic GABA analog brivaracetam {(2*S*)-2-[(4*R*)-2-oxo-4-propylpyrrolidin-1-yl]butanamide} **1d** [32] was approved by FDA in 2016 as an antiepileptic drug. This fact provides evidence for the relentless interest in GABA derivatives as broad-spectrum neurotropic agents and for the considerable promise of this line of research.

At the same time, at present the tetrazole derivatives of GABA and its analogs, where the tetrazole fragment acts as an isostere of carboxyl, is the only group of GABA derivatives well documented in terms of synthesis and biological activity. In particular, Yuan and Silverman reported the synthesis of 3-(1*H*-tetrazol-5-yl)propan-1-amine, an analog of unsubstituted GABA [24]. Isosteres of racemic pregabalin **1e** [25] and gabapentin **1f** [26] were also synthesized. These compounds present interest as anticonvulsants (Scheme 1).

The tetrazole analogs of 3-alkyl- and 3-aryl-substituted GABA analogs, including those neurotropic drugs, where the amino group is replaced by the tetrazole fragment, have scarcely been reported. At the same time, tetrazoles and amines have quite different acid–base properties (tetrazole is a fairly strong NH-acid) and the tetrazole nitrogen can be involved in multicenter intermolecular interactions with functional groups in the surrounding molecules, including enzyme active sites, and, as a result, the neurotropic activity profile of such tetrazole GABA analog may prove much different from that of the parent molecule.

Preliminary analysis of the available literature allows us to expect that some tetrazole GABA analogs will exhibit anxiolytic, nootropic, and antiepileptic activity.

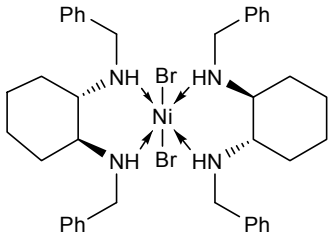
One more problem is that enantiomeric GABA analogs differ from each other in neurotropic activity. As known, the neurotropic activity is characteristic of the *R*-isomers of 3-aryl-substituted derivatives of GABA [33] and (*S*)-pregabalin [34]. This fact should be taken into account in the searching for potential drugs among tetrazole derivatives (in view of the present high international requirements to the enantiomeric purity of pharmaceutical substances).

The known methods of synthesis of enantiomerically pure 3-substituted GABA derivatives [35] generally make use of costly hydrogenation catalysts (platinum metal complexes) [36–38], organic catalysts [39], or chiral auxiliary groups at different stages of synthesis [40–43].

We earlier reported the synthesis of nonracemic 3-substituted GABA derivatives with the Ni(II)-catalyzed asymmetric Michael addition as the key stage [44]. Taking a step further in this approach, in the present work we have developed a simple and an efficient method of synthesis of nonracemic tetrazol-containing GABA derivatives.

Chiral nitro esters (*R*)-**5a–5c** were synthesized by the reaction of malonates **3a** and **3b** with nitroalkenes **2a–2c** in the presence of Ni(II) *N*,*N*′-dibezylcyclohexane-1,2-diamine complex **4** (Scheme 2).

Scheme 2.



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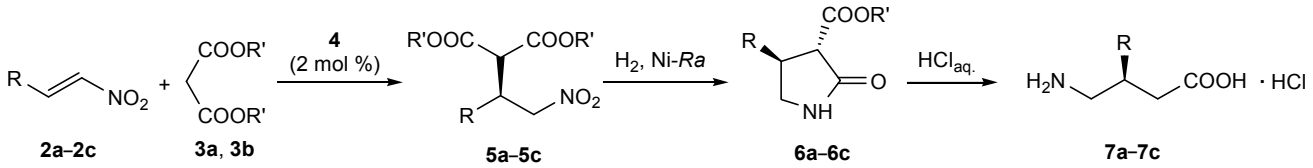
The subsequent reductive cyclization of nitro esters (*R*)-**5a–5c** and hydrolysis of the resulting pyrrolidones **6a–6c** afforded the hydrochlorides of corresponding amino acids **7a–7c** (Scheme 3).

The tetrazole derivatives were prepared using the three-component reaction of the amino acids, triethyl orthoformate, and sodium azide [45]. The efficiency of

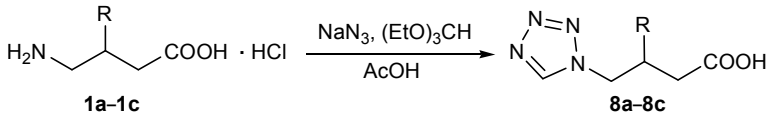
Scheme 3.



2a–2c **3a**, **3b** **5a–5c** **6a–6c** **7a–7c**

2, **7**, R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-ClC_6H_4 (**c**); **3**, R' = Et (**a**), Me (**b**); **5**, **6**, R = Ph, R' = Et (**a**); R = 4-MeC_6H_4, R' = Et (**b**); R = 4-ClC_6H_4, R' = Me (**c**).

Scheme 4.

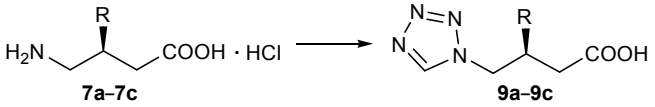


1a–1c **8a–8c**

this approach was previously demonstrated by Popova et al. [18] by the synthesis of the tetrazole derivative of racemic phenibut **7a**.

Taking into account the importance for neurotropic activity testing of comparable analysis of the respective properties of racemic mixtures and individual enantiomers, from amino acids **1a–1c** we prepared racemic tetrazole derivatives **8a–8c** (Scheme 4) and from corresponding nonracemic amino acids **7a–7c**, pure *R*-isomers **9a–9c** (Scheme 5).

Scheme 5.



7a–7c **9a–9c**

Thus, the three-component reaction of 3-substituted GABA derivatives, triethyl orthoformate, and sodium azide resulted in the synthesis of previously unknown nonracemic tetrazole (*R*)-phenibut, (*R*)-tolibut, and (*R*)-baclofen analogs **9a–9c**, which present interest as potential neurotropic agents.

EXPERIMENTAL

Elemental analysis was performed on a Euro-Vector EA 3000 analyzer. The IR spectra were obtained on a Shimadzu IRAffinity-1 instrument with a Specac Quest ATR accessory. The ^1H and ^{13}C NMR spectra were recorded on a Jeol JNM ECX -400 spectrometer [400 (^1H) and 100 (^{13}C) MHz, respectively]. The optical rotation angles were measured on a Rudolph Research Analytical Autopol V Plus automated polarimeter. The melting points were determined on an OptiMelt MPA 100 apparatus.

The HPLC analysis was performed using a Chiralpak AD-3 column; solvent system hexane–propan-2-one, 80 : 20, flow rate 1.2 mL/min; wavelength 210 nm).

Compounds **4** and **7a** were prepared as described in [46] and [47].

Diethyl (*R*)-2-[1-(4-methylphenyl)-2-nitroethyl]-malonate (5b). Complex **4**, 1.37 g (1.70 mmol), was added to a solution of 13.9 g (85.0 mmol) of reagent **2b** and 13.6 g (85.0 mmol) of diethyl malonate **3a** in 100 mL of toluene. The reaction mixture was stirred for 18 h at 25°C and then evaporated. The residue chromatographed on a silica gel column (eluent CCl_4).

HPLC analysis: t_r 9.5 (*R*-isomer), 24.3 min (*S*-isomer). Yield 23.7 g (86%), *ee* 95%, $[\alpha]_D^{22}$ –5.43 (*c* 2.5, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2982 w, 1732 vs, 1555 s, 1516 w, 1447 w, 1369 m, 1300 w, 1258 m, 1180 m, 1153 m, 1030 m, 818 m. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.02 t (3H, $C\underline{H}_3CH_2$, $^3J_{HH}$ 7.2 Hz), 1.22 t (3H, $C\underline{H}_3CH_2$, $^3J_{HH}$ 7.2 Hz), 2.27 s (3H, CH_3), 3.77 d [1H, $C\underline{H}(COOEt)_2$, $^3J_{HH}$ 9.6 Hz], 3.96 q (2H, $C\underline{H}_2CH_3$, $^3J_{HH}$ 6.8 Hz), 4.15–4.22 m (2H, $C\underline{H}_2CH_3$, 1H, $C\underline{H}CH_2NO_2$), 4.78–4.91 m (2H, CH_2NO_2), 7.09 m ($4H_{arom}$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.8 (CH_3), 14.1 (CH_3), 21.1 (CH_3, *p*-Tol), 42.7 ($\underline{C}HCH_2NO_2$), 55.1 [$\underline{C}H(COOEt)_2$], 61.9 ($\underline{C}H_2CH_3$), 62.2 ($\underline{C}H_2CH_3$), 76.5 ($\underline{C}H_2NO_2$), 127.9 ($2CH_{arom}$), 129.7 ($2CH_{arom}$), 133.2 (C), 138.1 (C), 167.0 (C=O), 167.6 (C=O). Found, %: C 59.55; H 6.51; N 4.38. $C_{16}H_{21}NO_6$. Calculated, %: C 59.43; H 6.55; N 4.33.

Dimethyl (*R*)-2-[1-(4-chlorophenyl)-2-nitroethyl]-malonate (5c). Complex **4**, 635 mg (0.780 mmol), was added to a solution of 7.22 g (39.3 mmol) of reagent **2c** and 5.19 g (39.3 mmol) of dimethyl malonate **3b** in 60 mL of toluene. The reaction mixture was stirred for

18 h at 25°C, left to stand for 12 h at room temperature, and then evaporated. The residue was recrystallized from propan-2-ol.

HPLC analysis: t_r 11.3 (*R*-isomer), 26.7 (*S*-isomer). Yield 8.68 g (72%), *ee* 95%, $[\alpha]_D^{20}$ –11.15 (*c* 2.5, $CHCl_3$), mp 94–96°C. IR spectrum, ν, cm^{-1}: 2960 (CH), 1747 (C=O), 1552, 1375 (NO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.57 s (3H, CH_3), 3.74 s (3H, CH_3), 3.80 d [1H, C<u>H</u>$(COOCH_3)_2$, $^3J_{HH}$ 8.9 Hz], 4.18–4.33 m (1H, C<u>H</u>CH_2NO_2), 4.80–4.91 m (2H, CH_2NO_2), 7.17 d (2H_{arom}, $^3J_{HH}$ 9.6 Hz), 7.27 d (2H_{arom}, $^3J_{HH}$ 9.6 Hz). ^{13}C NMR spectrum ($CDCl_3$) δ, ppm: 42.4 (<u>C</u>HCH_2), 53.0 ($COO\underline{C}H_3$), 53.2 ($COO\underline{C}H_3$), 54.4 [<u>C</u>H $(COOCH_3)_2$], 77.3 (<u>C</u>H_2NO_2), 129.3 (2CH_{arom}), 129.4 (2CH_{arom}), 134.5 (C_{arom}), 134.7 (C_{arom}), 166.1 (C=O), 167.7 (C=O). Found, %: C 49.39; H 4.51; N 4.47. $C_{13}H_{14}ClNO_6$. Calculated, %: C 49.46; H 4.47; N 4.44.

Ethyl (3*S*,4*R*)-4-(4-methylphenyl)-2-oxopyrrolidine-3-carboxylate (6b). A solution of 9.80 g (30.3 mmol) of compound **5b** in 50 mL of propan-2-ol was placed into an autoclave, and 1 g of Raney nickel was added. Hydrogenation was performed at a pressure of 40 atm at 50°C for 18 h. The reaction mixture was then evaporated, the residue was dissolved in toluene, and filtered through a bed of silica gel. The filtrate was evaporated in a vacuum, and the residue was recrystallized from cyclohexane. Yield 5.62 g (75%), $[\alpha]_D^{20}$ –113.3 (*c* 2.5, $CHCl_3$), mp 80–83°C. IR spectrum, ν, cm^{-1}: 3236 m, 2989 w, 2868 w, 1732 vs, 1705 vs, 1518 w, 1445 w, 1375 w, 1333 s, 1285 m, 1271 s, 1256 m, 1171 vs, 1117 m, 1053 m, 1020 s, 814 s, 719 s, 700 s, 687 s. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 t (3H, CH_3, $^3J_{HH}$ 9.6 Hz), 2.32 s (3H, CH_3, *p*-Tol), 3.38 d.d (1H, H^5, $^3J_{HH}$ 8.4, $^2J_{HH}$ 9.6 Hz), 3.52 d (1H, H^3, $^3J_{HH}$ 9.6 Hz), 3.76 d.d (1H, H^5, $^3J_{HH}$ 8.4, $^2J_{HH}$ 9.6 Hz), 4.03–4.09 m (1H, H^4), 4.18–4.26 m (2H, CH_2), 6.86 s (1H, NH), 7.11–7.14 m (4H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.2 (CH_3), 21.1 (CH_3, *p*-Tol), 44.4 (4-CH), 48.0 (5-CH_2) 55.4 (3-CH), 61.9 (CH_2), 127.0 (2CH_{arom}), 128.0 (2CH_{arom}), 136.8 (C_{arom}), 137.4 (C_{arom}), 169.3 (<u>C</u>OOEt), 172.9 (C=O). Found, %: C 67.95; H 6.99; N 5.72. $C_{14}H_{17}NO_3$. Calculated, %: C 68.00; H 6.93; N 5.66.

Methyl (3*S*,4*R*)-4-(4-chlorophenyl)-2-oxopyrrolidine-3-carboxylate (6c). A solution of 3.00 g (9.50 mmol) of compound **5c** in 50 mL of propan-2-ol was placed into an autoclave, and 0.5 g of Raney nickel was added. Hydrogenation was performed at a pressure of 40 atm at 50°C for 18 h. The reaction mixture was then evaporated, the residue was dissolved in toluene, and filtered through a bed of silica gel. The filtrate was evaporated in a vacuum, and the residue was recrystallized from ethanol. Yield 1.21 g (50%), $[\alpha]_D^{20}$ –124.4 (*c* 1.0, $CHCl_3$), mp 163–166°C. IR spectrum, ν, cm^{-1}: 3236 m, 2970 w, 2849 m, 2787 w, 1746 vs, 1717 vs, 1611 w, 1587 w, 1516 m, 1493 m, 1462 m, 1371 s, 1325 s, 1301 s, 1285 s, 1261 s, 1221 s, 1088 s, 1028 s, 1013 s, 991 s, 910 m, 851 m, 824 vs. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.36 s (3H, CH_3), 3.51 d (1H, 3-CH, $^3J_{HH}$ 9.6 Hz), 3.77–3.82 m (2H, C^5H_2), 4.05–4.12 m (1H, H^4), 6.94 s (1H, NH), 7.18 d (2H_{arom}, $^3J_{HH}$ 8.4 Hz), 7.30 d (2H_{arom}, $^3J_{HH}$ 8.4 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 47.7 (C^4H), 47.8 (C^5H_2), 53.1 (CH_3), 55.2 (C^3H), 128.5 (2CH_{arom}), 129.2 (2CH_{arom}), 133.7 (C_{arom}), 138.2 (C_{arom}), 169.4 (<u>C</u>OOMe), 172.4 (C=O). Found, %: C 56.76; H 4.82; N 5.57. $C_{12}H_{12}ClNO_3$. Calculated, %: C 56.82; H 4.77; N 5.52.

Compounds 7b and 7c (*general procedure*). To 19.8 mmol of compound **6b** and **6c** we added 110 mL of 6 M HCl, and the mixture was refluxed for 18 h. After cooling, the mixture was treated with ethyl acetate (4 × 30 mL). The aqueous layer was separated and evaporated in a vacuum.

(3*R*)-4-Amino-3-(4-methylphenyl)butanoic acid, hydrochloride (7b). Yield 4.2 g (90%), $[\alpha]_D^{20}$ –1.4 (*c* 2.5, H_2O), mp 173–175°C. IR spectrum, ν, cm^{-1}: 2924 s, 1711 s, 1562 m, 1503 s, 1404 s, 1254 m, 1192 vs, 1150 vs, 1063 w, 980 m, 829 m, 806 vs, 719 m, 654 s, 550 s, 521 s, 419 s. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.22 s (3H, CH_3), 2.46 d.d (1H, C<u>H</u>$_2$COOH, $^3J_{HH}$ 9.7, $^2J_{HH}$ 16.4 Hz), 2.81–2.89 m (1H, C<u>H</u>$_2NH_2$), 3.00–3.05 m (1H, C<u>H</u>$_2NH_2$), 3.28–3.35 m (1H, $CH_2C\underline{H}CH_2$), 7.09 d (2H_{arom}, $^3J_{HH}$ 8.0 Hz), 7.15 d (2H_{arom}, $^3J_{HH}$ 8.0 Hz), 8.3 br.s (3H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.2 (CH_3), 38.5 ($CH_2\underline{C}HCH_2$), 43.9 (CH_2NH_3), 128.2 (2CH), 129.7 (2CH_{arom}), 136.7 (C_{arom}), 137.9 (C_{arom}), 173.0 (C=O). Found, %: C 57.46; H 7.09; N 6.15. $C_{11}H_{16}ClNO_2$. Calculated, %: C 57.52; H 7.02; N 6.10.

(3*R*)-4-Amino-3-(4-chlorophenyl)butanoic acid, hydrochloride (7c). Yield 1.40 g (75%), $[\alpha]_D^{20}$ –1.3, mp 195–198°C. IR spectrum, ν, cm^{-1}: 2937 w, 1720 vs, 1573 w, 1504 m, 1492 s, 1414 s, 1404 s, 1269 w, 1201 s, 1179 vs, 1126 s, 1088 m, 1015 m, 947 m, 826 vs, 791 m, 654 m. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.50 d (1H, C<u>H</u>$_2$COOH, $^3J_{HH}$ 9.6 Hz), 2.85–2.94 m (2H, C<u>H</u>$_2NH_2$), 3.04–3.09 m (1H, C<u>H</u>$_2$COOH), 3.33

–3.40 m ($CH_2C\underline{H}CH_2$), 7.32 d ($4H_{arom}$, $^3J_{HH}$ 5.52 Hz), 7.18 s (2H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 38.3 ($\underline{C}H_2COOH$), 39.6 ($CH_2\underline{C}HCH_2$), 43.6 (CH_2NH_2), 129.0 (CCl), 130.4 ($2CH_{arom}$), 132.3 ($2CH_{arom}$), 139.8 (ArCH), 172.8 (C=O). Found, %: C 47.96; H 5.30; N 5.64. $C_{10}H_{13}Cl_2NO_2$. Calculated, %: C 48.02; H 5.24; N 5.60.

Acids 8a–8c and 9a–9c (*general procedure*). Triethyl orthoformate, 9.73 g (65.7 mmol), and then 1.71 g (26.3 mmol) of sodium azide were added to a stirred solution of the hydrochloride of amino acid **1a–1c** or **7a–7c**, 21.9 mmol, in 12 mL of acetic acid. The mixture was stirred for 7 h at 100°C and then evaporated in a vacuum. Water, 10 mL, was added to the residue and then solid NaOH to pH 9. After treatment with ethyl ether, the aqueous layer was separated and acidified with conc. HCl to pH 2. The precipitate that formed was filtered off and washed with 5 mL of water.

4-(1*H*-Tetrazol-1-yl)-3-phenylbutanoic acid (8a). Yield 1.58 g (31%), mp 114–117°C. IR spectrum, ν, cm^{-1}: 3126 m, 2929 m, 2601 w, 1707 vs, 1489 m, 1443 m, 1415 m, 1311 m, 1300 m, 1265 s, 1211 s, 1169 s, 1142 m, 1096 m, 980 m, 926 m, 899 m, 775 m, 733 s, 702 vs, 660 s. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.62–2.74 m (2H, $C\underline{H}_2COOH$), 3.61–3.68 m (1H, CH), 4.62–4.80 m (2H, $C\underline{H}_2NH_2$), 7.13–7.30 m ($5H_{arom}$), 9.07 s ($1H_{tetrazole}$), 12.24 br.s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 37.9 (CH), 42.4 ($\underline{C}H_2COOH$), 52.3 (CH_2NH_2), 127.7 (CH_{arom}), 128.2 ($2CH_{arom}$), 129.0 ($2CH_{arom}$), 140.3 (C_{arom}), 144.6 ($C_{tetrazole}$), 172.8 (C=O). Found, %: C 56.81; H 5.24; N 24.08. $C_{11}H_{12}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.12.

3-(4-Methylphenyl)-4-(1*H*-tetrazol-1-yl)butanoic acid (8b). Yield 1.56 g (29%), mp 140–142°C. IR spectrum, ν, cm^{-1}: 3169 w, 2993 m, 2927 m, 1717 vs, 1514 m, 1489 m, 1445 m, 1413 m, 1330 w, 1313 w, 1296 m, 1249 s, 1195 s, 1176 vs, 1099 vs, 974 s, 881 m, 868 m, 816 s, 760 w, 723 w, 665 s, 652 s, 640 m. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.17 s (3H, CH_3), 2.53–2.69 m (2H, $C\underline{H}_2COOH$), 3.52–3.60 m (1H, CH), 4.61–4.73 m (2H, $C\underline{H}_2NH_2$), 7.02 s (4H, $4CH_{arom}$), 9.07 s ($1H_{tetrazole}$), 12.18 br.s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.1 (CH_3), 38.1 (CH), 42.1 ($\underline{C}H_2COOH$), 52.3 (CH_2NH_2), 128.0 ($2CH_{arom}$), 129.5 ($2CH_{arom}$), 136.7 (C_{arom}), 137.2 (C_{arom}), 144.5 ($C_{tetrazole}$), 172.8 (C=O). Found, %: C 58.40; H 5.79; N 22.64. $C_{12}H_{14}N_4O_2$. Calculated, %: C 58.53; H 5.73; N 22.75.

4-(1*H*-Tetrazol-1-yl)-3-(4-chlorophenyl)butanoic acid (8c). Yield 2.16 g (37%), mp 145–147°C. IR spectrum, ν, cm^{-1}: 3134 w, 2930 m, 2596 w, 1700 vs, 1490 s, 1447 m, 1435 m, 1414 m, 1354 w, 1311 m, 1261 s, 1215 s, 1169 s, 1140 m, 1098 m, 1086 m, 1015 m, 982 m, 934 m, 897 m, 845 w, 825 vs, 754 s, 718 m, 658 m, 613 m. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.54–2.69 m (2H, $C\underline{H}_2COOH$), 3.51–3.59 m (1H, CH), 4.60–4.72 m (2H, $C\underline{H}_2NH_2$), 7.02 d (2H, $2CH_{arom}$, $^3J_{HH}$ 7.5 Hz), 7.61 d (2H, $2CH_{arom}$, $^3J_{HH}$ 7.5 Hz), 9.05 s ($1H_{tetrazole}$), 12.16 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 38.3 (CH), 42.0 ($\underline{C}H_2COOH$), 52.9 (CH_2NH_2), 128.7 ($2CH_{arom}$), 130.0 ($2CH_{arom}$), 133.1 (C_{arom}), 138.3 (C_{arom}), 144.4 ($C_{tetrazole}$), 174.3 (C=O). Found, %: C 49.45; H 4.20; N 20.92. $C_{11}H_{11}ClN_4O_2$. Calculated, %: C 49.54; H 4.16; N 21.01.

(3*R*)-4-(1*H*-Tetrazol-1-yl)-3-phenylbutanoic acid (9a). Yield 1.56 g (23%), mp 115–118°C, $[\alpha]_D^{20}$ +54.6 (*c* 1.0, MeOH). IR spectrum, ν, cm^{-1}: 3126 m, 2929 m, 2601 w, 1707 vs, 1489 m, 1443 m, 1415 m, 1311 m, 1300 m, 1265 s, 1211 s, 1169 s, 1142 m, 1096 m, 980 m, 926 m, 899 m, 775 m, 733 s, 702 vs, 660 s. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.65–2.69 m (2H, $C\underline{H}_2COOH$), 3.61 s (1H, CH), 4.68 s (2H, $C\underline{H}_2NH_2$), 7.14–7.27 m ($5H_{arom}$), 9.08 s ($1H_{tetrazole}$), 12.24 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 37.9 (CH), 42.4 ($\underline{C}H_2COOH$), 52.3 (CH_2NH_2), 127.7 (CH_{arom}), 128.2 ($2CH_{arom}$), 129.0 ($2CH_{arom}$), 140.3 (C_{arom}), 144.6 ($C_{tetrazole}$), 172.8 (C=O). Found, %: C 56.75; H 5.29; N 24.02. $C_{11}H_{12}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.12.

(3*R*)-3-(4-Methylphenyl)-4-(1*H*-tetrazol-1-yl)butanoic acid (9b). Yield 1.40 g (23%), mp 143–146°C, $[\alpha]_D^{20}$ +29.9 (*c* 1.0, MeOH). IR spectrum, ν, cm^{-1}: 3169 w, 2993 m, 2927 m, 1717 vs, 1514 m, 1489 m, 1445 m, 1413 m, 1330 w, 1313 w, 1296 m, 1249 s, 1195 s, 1176 vs, 1099 vs, 974 s, 881 m, 868 m, 816 s, 760 w, 723 w, 665 s, 652 s, 640 m. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.18 s (3H, CH_3), 2.56–2.71 m (2H, $C\underline{H}_2COOH$), 3.53–3.61 m (1H, CH), 4.61–4.73 m (2H, $C\underline{H}_2NH_2$), 7.01 s ($4H_{arom}$), 9.07 s ($1H_{tetrazole}$), 12.18 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.1 (CH_3), 38.1 (CH), 42.1 ($\underline{C}H_2COOH$), 52.4 (CH_2NH_2), 128.0 ($2CH_{arom}$), 129.6 ($2CH_{arom}$), 136.7 (C_{arom}), 137.2 (C_{arom}), 144.6 ($C_{tetrazole}$), 172.9 (C=O). Found, %: C 58.47; H 5.80; N 22.69. $C_{12}H_{14}N_4O_2$. Calculated, %: C 58.53; H 5.73; N 22.75.

(3*R*)-4-(1*H*-Tetrazol-1-yl)-3-(4-chlorophenyl)butanoic acid (9c). Yield 1.53 g (28%), $[\alpha]_D^{20}$ +51.0 (*c*

1.0, MeOH), mp 147–150°C. IR spectrum, ν, cm^{-1}: 3134 w, 2930 m, 2596 w, 1700 vs, 1490 s, 1447 m, 1435 m, 1414 m, 1354 w, 1311 m, 1261 s, 1215 s, 1169 s, 1140 m, 1098 m, 1086 m, 1015 m, 982 m, 934 m, 897 m, 845 w, 825 vs, 754 s, 718 m, 658 m, 613 m. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.56–2.71 m (2H, C$\underline{H}_2$COOH), 3.53–3.61 m (1H, CH), 4.61–4.73 m (2H, C$\underline{H}_2$NH$_2$), 7.05 d (2H$_{arom}$, $^3J_{HH}$ 7.5 Hz), 7.62 d (2H$_{arom}$, $^3J_{HH}$ 7.5 Hz), 9.07 s (1H$_{tetrazole}$), 12.18 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 38.2 (CH), 41.9 ($\underline{C}$H$_2$COOH), 52.8 (CH$_2$NH$_2$), 128.7 (2CH$_{arom}$), 129.9 (2CH$_{arom}$), 133.0 (C$_{arom}$), 138.2 (C$_{arom}$), 144.3 (C$_{tetrazole}$), 174.1 (C=O). Found, %: C 49.48; H 4.22; N 20.96. $C_{11}H_{11}ClN_4O_2$. Calculated, %: C 49.54; H 4.16; N 21.01.

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