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Synthesis of new *N*-glycosides based on Valproic acid analogs tetrazole derivatives

Nader Noroozi Pesyan[1] · Marziyeh Ebrahimi[1]

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Abstract New *N*-glycosides based on valproic acid analogs tetrazole derivatives were synthesized. The bis-tetrazole derived from 1,6-hexandiol was also connected to acetylated glucose and formed bis-*N*-glycoside. Structures characterizations have been performed using FT IR, ^{1}H and ^{13}C NMR spectroscopy.

Keywords Valproic acid · Antiepileptic · 5-(heptan-4-yl)-1*H*-tetrazole · Ethyl cyanoacetate · Tetrazole · *N*-glycoside

Introduction

Valproic acid (VPA **6**, in Fig. 1) has found clinical use as an anticonvulsant and mood-stabilizing drug, bipolar disorder, primarily in the treatment of epilepsy and prevention of migraine headaches. The acid, salt or mixture of the two (valproate semi-sodium) are marketed under a number of several trade names, including: Depakote, Convulex, Valparin, Epilim, Valpro, Stavzor and Vilapro. VPA is a branched side chain carboxylic acid, and it has eight carbon atoms. This compound is a slightly viscous, colorless to pale yellow, with a boiling point of 219.5 °C and its pKa is 4.6 [1]. VPA is also known as 2-propylpentanoic acid and *n*-dipropylacetic acid. It is effective to treat antiepileptic, and prophylaxis, neuropathic pain and migraine [2], use in several psychiatric disorders, a bipolar disorder [3–6], use in cancer, neuroprotection, and schizophrenia therapy [7–11].

Tetrazoles are aromatic heterocyclic compounds that have a 6π-electron system [12–15]. The free N–H bond of 5-substituted tetrazoles as tetrazolic acids is seen in two tautomeric forms [12–16], and also this group turns them into an acidic molecule in which the pK_{α} value is the same as its corresponding carboxylic acid [12]. Because of this extensive similarity, tetrazole ring is a suitable alternative for VPA in pharmaceutical compounds [17–20]. As in conventional papers listed, some of tetrazoles derivatives' applications are seen in the field of medicinal chemistry [19, 21, 22], agricultural [23, 24] and explosive materials [25].

Based on these concepts, we decided to synthesize the VPA derivatives based on tetrazole and coupled them to glucose for the synthesis of new *N*-glycosides. According to our search in the literature, there is no report of *N*-glycosides based on valproic acid analogs tetrazole derivatives.

Experimental

General

The drawing and nomination of compounds were done by ChemDraw Ultra 8.0 version software. Melting points were estimated with a digital melting point apparatus (electrothermal) and were uncorrected. The IR spectra were determined in the region 4000–400 cm^{-1} on a NEXUS 670 FT IR spectrometer by KBr pellets. The ^{1}H and ^{13}C NMR spectra were registered on Bruker 300 FT-NMR at 300 and 75 MHz, respectively (Urmia University, Urmia, Iran). The ^{1}H and ^{13}C NMR spectra were obtained on a

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✉ Nader Noroozi Pesyan
n.noroozi@urmia.ac.ir; nnp403@gmail.com

[1] Department of Organic Chemistry, Faculty of Chemistry, Urmia University, 57159 Urmia, Iran

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5-(Heptan-4-yl)-1*H*-tetrazole (**5a**) Valproic acid (**VPA, 6**)

Fig. 1 Formula structures of valproic acid (VPA **6**) and its tetrazole analog (**5a**)

solution in DMSO-d_6 and/or $CDCl_3$ as solvent using TMS as an internal standard. The data were reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, bs = broad singlet, coupling constant(s) in Hz, integration). The ^{1}H and ^{13}C NMR spectra were opened and analyzed via MestReC software from original spectra files. Alkyl halides, ethyl cyanoacetate, sodium azide and used solvents purchased from Merck and Aldrich without further purification.

2-Butyl-2-cyanohexanoic acid (3b)

Yield: 2.24 g (65%); brown viscous solid. FT IR (KBr, ν, cm^{-1}) 2400–3600 (OH), 2960, 2933, 2870 (CH-aliph.), 2253 (C≡N), 1728 (C=O), 1210 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.92 (t, 6H, $J = 6.9$ Hz, $2CH_3$), 1.26–1.37 (m, 4H), 1.59 (m, 4H), 1.79–2.00 (m, 4H), 8.95 (bs, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.6, 119.0, 50.4, 37.0, 27.5, 22.4, 13.7.

2-Butylhexanenitrile (4b)

Yield: 1 g (45%); brown viscous solid. FT IR (KBr, ν, cm^{-1}) 2943, 2870 (CH-aliph.), 2233 (C≡N); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.91 (m, 6H), 1.27–2.10 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 119.8, 37.0, 29.7, 27.5, 22.4, 13.7.

5-(Heptan-4-yl)-1H-tetrazole (5a)

Yield: 0.25 g (34%); pale yellow solid; M.p.: 184–187 °C. FT IR (KBr, ν, cm^{-1}) 2400–3500 (NH-tetrazole), 2959, 2930, 2871 (CH-aliph.), 1661 (C=N), 1462 (N=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.92 (t, 6H, $J = 6.9$ Hz, $2CH_3$), 1.26–1.47 (m, 6H), 1.53–1.64 (m, 2H), 2.12 (m, 1H), 5.47 (bs, 1H), 5.67 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 178.7, 46.8, 20.7, 14.9, 13.3.

5-(Nonan-5-yl)-1H-tetrazole (5b)

Yield: 0.33 g (38%); yellow viscous solid. FT IR (KBr, ν, cm^{-1}) 2400–3500 (NH-tetrazole), 2939, 2869 (CH-aliph.), 1663 (C=N), 1462 (N=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.83 (s, 6H, $J = 6.9$ Hz, $2CH_3$), 1.13–1.26 (m, 8H, $4CH_2$), 1.84–1.88 (m, 4H, $2CH_2$), 3.29 (quin, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.2, 36.3, 35.1, 34.0, 29.3, 22.4.

5-Butyl-1H-tetrazole (5d)

Yield: 0.35 g (57%); cream solid; M.p.: 60–61 °C. FT IR (KBr, ν, cm^{-1}) 2471–3420 (NH-tetrazole), 2963, 2939, 2875 (CH-aliph.);^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.93 (t, 3H, $J = 7.2$ Hz, $\mathbf{CH_3}$–CH_2–CH_2–CH_2–), 1.43 (sextet, 2H, CH_3–$\mathbf{CH_2}$–CH_2–CH_2–), 1.89 (quin, 2H, CH_3–CH_2–$\mathbf{CH_2}$–CH_2–), 3.16 (t, 2H, CH_3–CH_2–CH_2–$\mathbf{CH_2}$–), 15.91 (bs, 1H, tetrazole-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 157.0, 29.7, 23.1, 22.1, 13.5.

(2R,3R,4S,5R,6R)-2-(Acetoxymethyl)-6-(5-butyl-2H-tetrazol-2-yl) tetrahydro-2H-pyran-3,4,5-triyl triacetate (7d)

In a 25-mL round-bottomed flask equipped with a magnetically heater stirrer 5-*n*-butyl-1*H*-tetrazole **5d** (0.06 g, 0.5 mmol) was dissolved in 3 mL acetonitrile and then added K_2CO_3 (0.5 mmol) with 3 drops of DMF and stirring it during 1 h at room temperature. Afterward, dissolved (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-bromotetrahydro-2*H*-pyran-3,4,5-triyl triacetate **6** (0.24 g, 0.6 mmol) in acetonitrile was added dropwise into the reaction mixture, stirred for 16 h at room temperature, filtered off and evaporated. The residue was dissolved in 3 mL ethyl acetate and washed with distilled water (2 × 5 mL). The organic phase was dried with sodium sulfate, filtered off, and lastly, evaporated. The residue was purified by silica gel-coated plate, and the eluent solvent was the mixture of *n*-hexane: ethyl acetate/1: 1/V: V, (0.10 g, yield 45%).

Yellow solid, M.p.: 155–157 °C, FT IR (KBr, ν, cm^{-1}) 2956 (CH-aliph.), 1751 (C=O), 1437, 1376, 1229, 1046; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.98 (t, 3H, $J = 6.9$ Hz), 1.46 (sex, 2H, $J = 7.5$ Hz), 1.86 (s, 2H), 2.04, 2.08 (2 s, 12H), 2.96 (t, 3H, $J = 7.5$ Hz), 4.00–4.02 (m, 1H), 4.15–4.30 (m, 2H), 5.27 (t, 1H, $J = 9.9$ Hz), 5.43 (t, 1H, $J = 9.3$ Hz), 5.65 (t, 1H, $J = 9.3$ Hz), 5.82 (d, 1H, $J = 9.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.37, 170.03, 169.27, 168.65, 156.11, 83.71, 72.55, 69.47, 69.46, 67.38, 61.38, 28.92, 23.44, 22.22, 20.68, 20.61, 20.53, 20.18, 20.11 (an equilibrium of β-anomer).

(2R,3R,4S,5R,6R)-2-(Acetoxymethyl)-6-(5-(nonan-5-yl)-2H-tetrazol-2-yl) tetrahydro-2H-pyran-3,4,5-triyl triacetate (7b)

Yield: 0.09 g (35%); white solid; M.p.: 98–101 °C. FT IR (KBr, ν, cm^{-1}) 2944, 2872 (CH-aliph.), 1756 (C=O), 1446,

1376, 1228, 1037; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.82 (m, 2H), 1.22–1.39 (m, 2H), 1.77–1.81 (m, 2H), 1.99, 2.00, 2.06, 2.07 (4 s, 12H, $4CH_3CO$), 3.81–4.43 (m, 4H), 5.08–5.53 (m, 3H), 5.69 (d, 1H, J = 8.1 Hz), 6.30 (d, 1H, J = 3.3 Hz), 6.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 170.57, 170.11, 170.09, 169.38, 169.33, 168.92, 168.71 (C=O), 140.33, 138.12 (CN_4), 93.01, 92.35, 91.03, 90.47, 89.64, 75.95, 73.70, 73.44, 72.11, 71.45, 71.06, 70.90, 69.39, 68.97, 68.68, 68.34, 67.07, 66.90, 63.29, 61.49, 61.26, 59.64, 59.40, 23.21, 22.49, 22.07, 21.76, 20.73, 20.67, 19.30, 19.00, 18.00 (an equilibrium mixture of α and β-anomers).

1,6-Di(1H-tetrazol-5-yl)hexane (12d)

In a 25-mL round-bottomed flask equipped with a magnetically heater stirrer was dissolved octanedinitrile **11d** (0.6 g, 3.3 mmol) in 15 mL DMF, then adding sodium azide (0.43 g, 6.6 mmol) and ammonium chloride (0.35 g, 6.6 mmol) and refluxing at 120 °C for 6 days. The progression of the reaction was monitored by thin layer chromatography (TLC) by the eluent solvents of EtOAc; *n*-hexane; and EtOH (10: 3: 2, V: V: V). After the reaction completion, acidified by concentrated hydrochloric acid (6 M) with stirring, the tetrazole product precipitated, was washed by the mixture of water and EtOH and then dried.

Yield: 0.5 g (52%); pale yellow solid; M.p.: 164–168 °C. FT IR (KBr, ν, cm^{-1}) 2400–3127 (NH-tetrazole), 2864, 1730 (CH-aliph.), 1571, 1438, 1050; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.27 (m, 4H), 1.65 (m, 4H), 2.84 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 156.2 (CN_4H), 28.2 (–CH_2CH_2**C**H_2CN_4H), 27.2 (–CH_2**C**H-$_2CH_2CN_4H$), 23.0 (–**C**$H_2CH_2CH_2CN_4H$).

(2S,3S,4R,5S,6S)-2-(Acetoxymethyl)-6-(5-(6-(2-((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl) tetrahydro-2H-pyran-2-yl)-2H-tetrazol-5-yl) hexyl)-2H-tetrazol-2-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (13d)

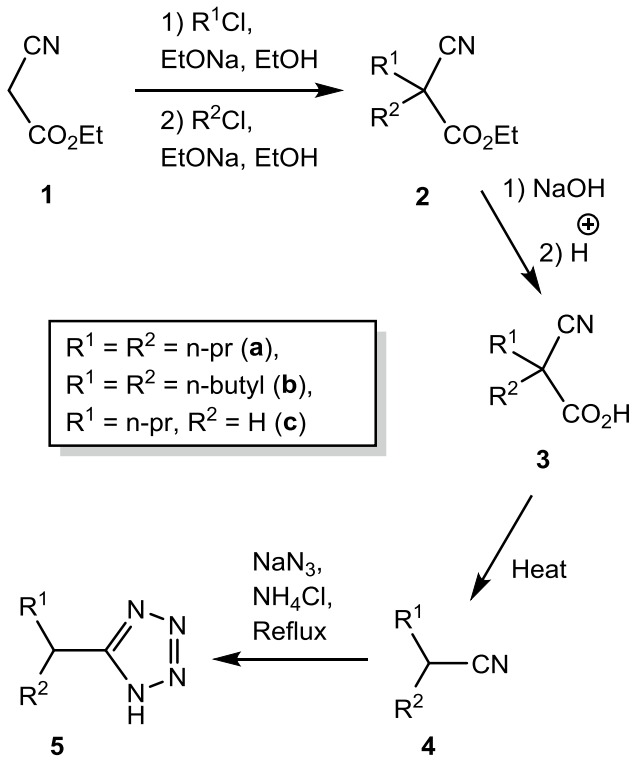
Yield: 0.21 g (58%); Pale yellow solid; M.p.: 90–92 °C. FT IR (KBr, ν, cm^{-1}) 2953 (CH-aliph.), 1748 (C=O), 1378, 1237, 1038; ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm) 1.30 (m, 2H), 1.80–1.96 (m, 6H), 2.00–2.07 (4 s, 24H, $4CH_3CO$–), 2.78, 2.82 (2 s, 2H), 4.06–4.15 (m, 4H), 4.22–4.31 (m, 4H), 4.44–4.47 (m, 1H), 5.02–5.22 (m, 4H), 5.36–5.54 (m, 3H), 5.90 (d, 1H, J = 8.4 Hz), 6.28 (d, 1H, J = 3.3 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm) 169.74, 169.41, 169.32, 168.47 ($4CH_3$**C**O–), 150.00 (**C**N_4), 91.45, 88.76, 71.66, 70.81, 69.53, 68.69, 67.59, 67.16, 65.86, 20.62, 19.67, 19.48, 19.20 (an equilibrium mixture of α- and β-anomers).

(2S,3R,4R,5S,6S)-2-(Hydroxymethyl)-6-(5-(6-(2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yl)-2H-tetrazol-5-yl) hexyl)-2H-tetrazol-2-yl)tetrahydro-2H-pyran-3,4,5-triol (14d)

Pale yellow solid; M.p.: 133–135 °C, FT IR (KBr, ν, cm^{-1}) 3424 (OH), 2923 (CH-aliph.), 1577, 1435, 1044; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.23 (m, 2H), 1.36 (q, 2H, J = 6.9 Hz), 1.60–1.70 (m, 2H), 2.92 (t, 2H, J = 8.7 Hz), 3.20–3.50 (m, 3H), 3.66 (d, 1H, J = 11.1 Hz), 3.83 (t, 1H, J = 8.1 Hz), 5.53 (d, 1H, J = 9.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 156.64, 81.40, 81.02, 78.27, 75.00, 73.00, 71.00, 29.50, 22.00, 13.00 (an equilibrium of α-anomer).

Results and discussion

This article describes the characterization and synthesis of VPA tetrazole analog derivatives, **5a** [26], with the inspiration of VPA (**6**) as an antiepileptic drug and then coupling them with pentaacetylated glucose for the synthesis of new type *N*-glycosides based on tetrazole. First, the twice alkylation of ethyl cyanoacetate (**1**) with the



Scheme 1 Synthesis of new tetrazole analogs (**5**)

same or different alkyl halides afforded 2,2-dialkylated ethyl cyanoacetates (**2**). The hydrolysis of **2** produced 2,2-dialkylated cyanoacetic acids (**3**) and following decarboxylation gave dialkylated acetonitriles (**4**). Finally, the cycloaddition reaction of **4** with sodium azide in the presence of a catalytic amount of ammonium chloride gave target tetrazoles (**5**) in DMF under reflux (Scheme 1).

For a demonstration of the hydrolysis of **2**, the IR spectra of **3** obviously show the peak of the carboxylic acid OH group at a frequency of 2400–3600 cm^{-1}. The stretching frequency of the nitrile group remained at 2253 cm^{-1} and indicated that the CN group did not hydrolyze. Decarboxylation of **3** to **4** was performed by the heating of **3** in toluene under reflux. The IR spectra of **4** show a peak at 2233 cm^{-1} that indicates the nitrile group and followed loss of carboxylic acid OH stretching frequency at 2400–3600 cm^{-1}. Representatively, for comparison, the IR spectra of compounds **2b**, **3b**, **4b** and **5b** are shown in Fig. 2 (see also experimental and supplementary material).

The ^{1}H NMR spectrum of **3b** showed that a triplet at δ 0.92 ppm corresponds to two equivalent methyl groups (6H), and three multiplets at δ 1.37 (4H), 1.59 (4H) and 1.79–2.00 ppm (4H) correspond to methylene groups, respectively. A broad peak at δ 8.95 ppm (1H)

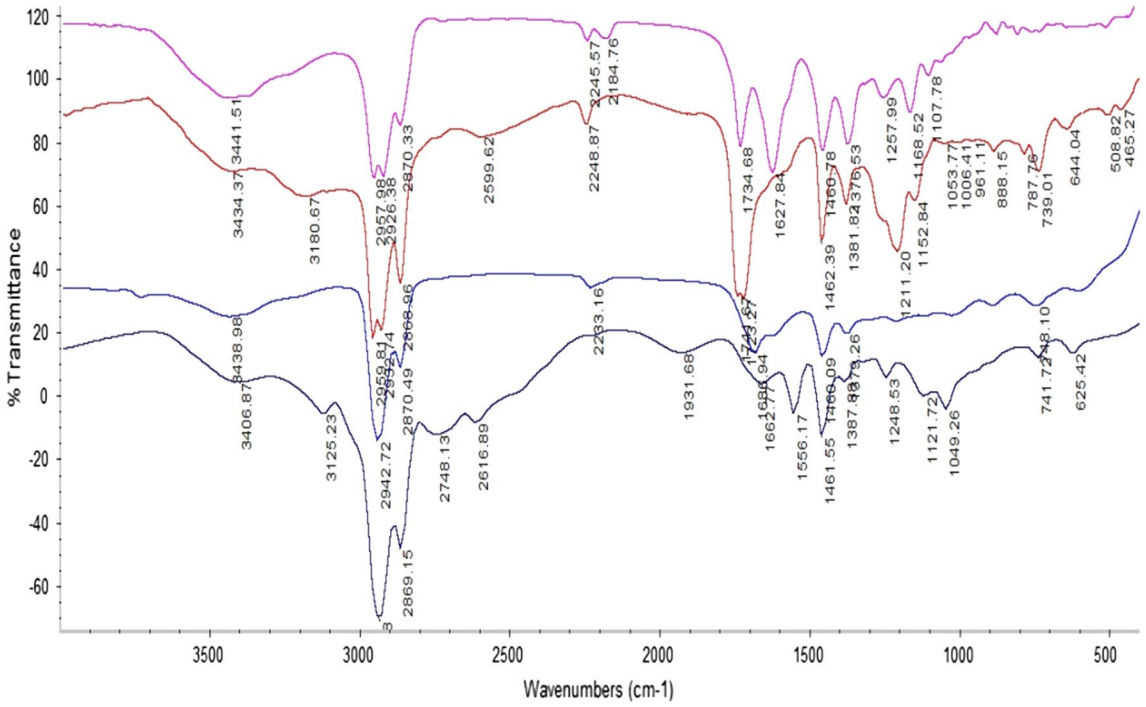
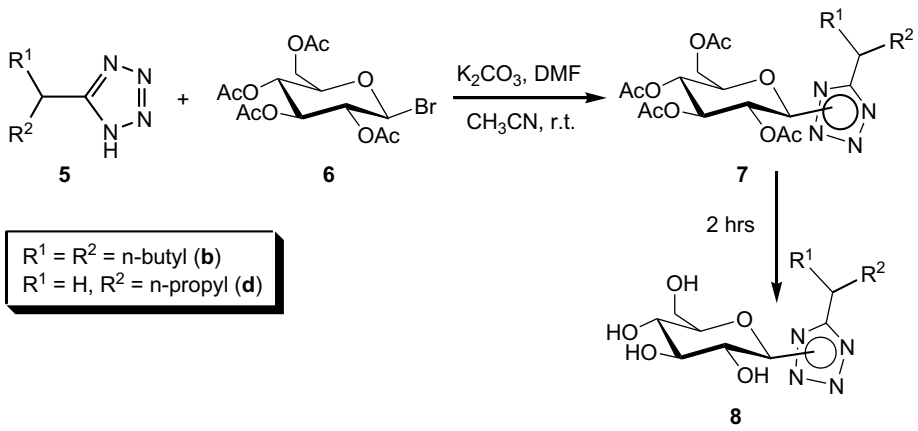


Fig. 2 IR spectra of compounds **2b** (*c pink solid line*), **3b** (*d red solid line*), **4b** (*a blue solid line*) and **5b** (*b violet solid line*)

Scheme 2 Coupling reaction of tetrazoles **5** with **6** for the synthesis of **8**



corresponds to acidic proton. The ^{13}C NMR spectrum of this compound showed seven distinct peaks that confirmed the assigned structure (see experimental and supplementary material).

For instance, the structure of **5b** was characterized by IR, ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **5b** consists of a triplet at δ 0.83 ppm, two multiplets at δ 1.13–1.26 and at δ 1.84–1.88 ppm corresponding to methyl and methylene groups and a quintet at δ 3.29 ppm for tertiary methine proton, respectively. The ^{13}C NMR spectrum is in good agreement with the molecular structure and shows six distinct peaks. Five peaks at δ 22.4, 29.3, 34.0, 35.1 and 36.3 ppm correspond to methyl, methylenes and methine groups on the chain, respectively. The peak at δ 160.2 ppm corresponds to tetrazole carbon atom (Experimental and supplementary material).

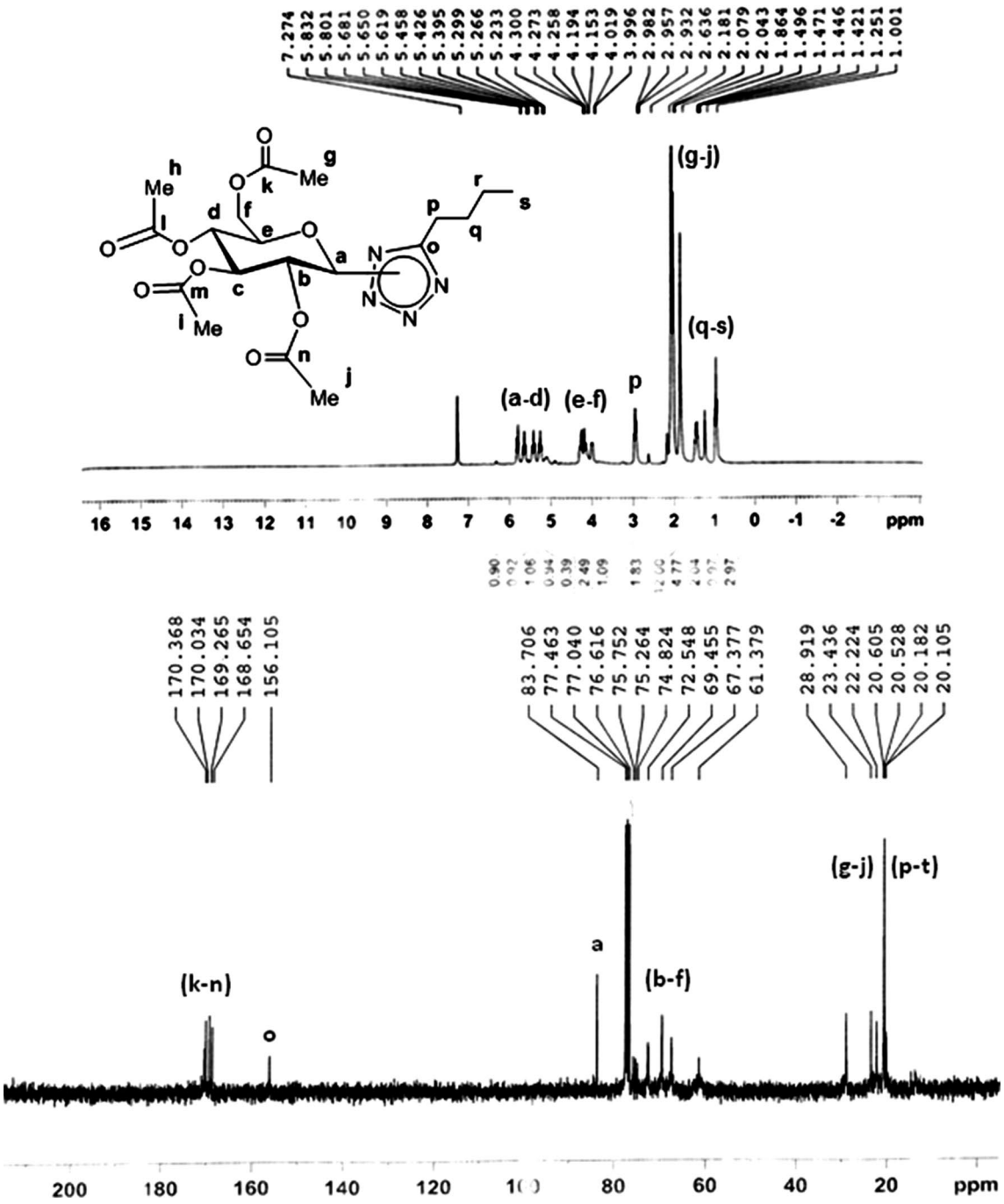
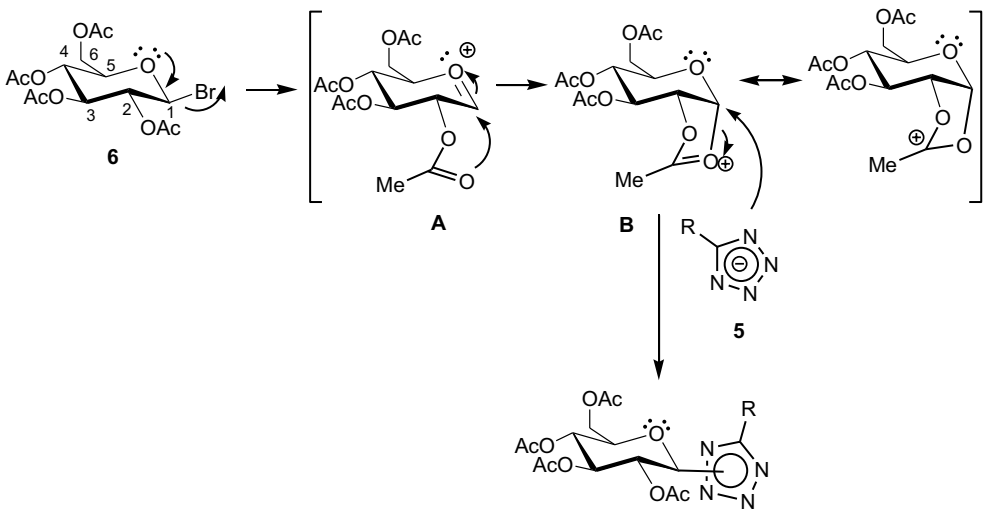


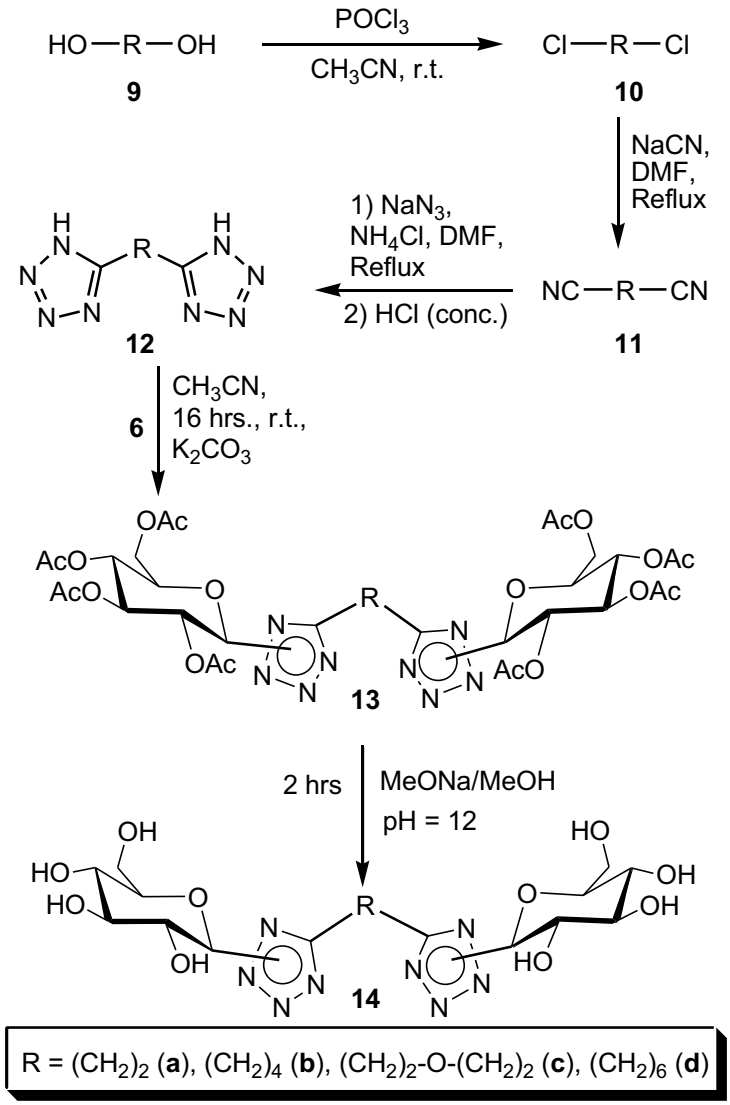
Fig. 3 Representatively, the ^{1}H (*top*) and ^{13}C NMR spectra of **7d** (*bottom*)

O-acetylation of D-glucose followed by bromination with HBr to obtain (2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-bromotetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**6**) has been reported previously [27]. We performed the coupling reaction of tetrazoles **5** with **6** for the synthesis of (**7**) as new compounds and are shown in Scheme 2. Representatively, the IR spectrum of **7d** showed no tetrazole NH stretching frequencies at the range of 2471–3420 cm^{-1}. Instead, the strong carbonyl stretching frequency at 1751 cm^{-1} appeared. The ^{1}H NMR spectrum of this compound showed a triplet at δ 0.98 ppm for the methyl group, a sextet at δ 1.46, a multiplet at δ 1.86 and a triplet at δ 2.96 ppm for diastereotopic methylene protons in aliphatic chain. Four methyl groups of acetoxy upon glucoside ring moiety appeared at δ 2.04 and 2.08 ppm with the integration of twelve protons (three of these methyl singlets were overlapped). A multiplet at δ 4.00–4.02 ppm corresponded to diastereotopic methylene protons (H_f) and H_e, two triplets at δ 5.43 and 5.65 ppm corresponded to H_b and H_d, a triplet at δ 5.27 corresponded to H_c and finally a doublet at δ 6.82 ppm corresponded to H_a (Fig. 3). In the ^{13}C NMR spectrum, the peaks at δ 170.37, 170.03, 169.27, 168.65 and 156.11 ppm corresponded to four carbonyl items and one tetrazole carbon atom, respectively. The ^{13}C NMR spectrum of this compound showed twenty distinct peaks that confirmed the assigned structure (Fig. 3). Other evidence for the formation of **7d** and **8d** (the existence and confirmation of the nitrogen atoms of tetrazole in this molecule) was performed by the Lassaigne's test [28–30] (appearance of Prussian blue color). Deprotection reaction of **7d** by sodium methoxide gave a good yield of **8d**. The ^{1}H NMR spectrum of **8d** showed the disappearance of methyl protons on acetyl groups upon glucose ring moiety. The ^{13}C NMR spectrum of this compound also showed the disappearance of carbonyl peaks at δ 170.37–168.65 ppm. These observations demonstrated the formation of **8d**. (see experimental and supplementary material). The reaction mechanism is according with Koenigs–Knorr [31] reaction and is shown in Scheme 3. At first a lone pair of oxygen atom **A** attacked to the C_1 of α or β anomer, and removed bromide ion out and then according by neighboring [32] acteyl group of C_2 in **A** was formed oxonium ion intermediate **B** by intramolecular reaction. The lone pair of nitrogen atom in tetrazole ring attacked to C_1, and new C–N bond was formed by nucleophilic substitution reaction.

We also examined and performed the conversion of some diols (**9**) to bis-tetrazoles (**12**). Only the following conversion of 1,6-hexanediol (**9d**) to **12d**, **13d** and **14d** was successful. No reason was offered for the unsuccessful reactions of **9a**–**9c**. Therefore, we chose **9d**, and it was converted to 1,6-dichlorohexane (**10d**) with excellent yield in the reaction with phosphoryl chloride in acetonitrile. The cyanation of **10d** yielded octanedinitrile (**11d**) followed by a cycloaddition reaction with sodium azide



Scheme 3 Mechanism of glycosylation reaction of tetrazole **5**



Scheme 4 Conversion of 1,6-hexanediol (**9d**) to 1,6-di(1*H*-tetrazol-5-yl)hexane (**12d**), followed by the synthesis of **13d** and **14d**

produced bis-tetrazole **12d** (Scheme 4). The IR spectra of compounds **9d**–**12d** are merged and showed these conversions successfully (Fig. 4). Obviously, in the conversion of diol **9d** to **10d**, the OH frequency stretching at 3455 cm^{-1} has disappeared (spectrum *b* in Fig. 4). In the conversion of **10d** to octanedinitrile **11d**, the CN frequency stretching at 2246 cm^{-1} has appeared (spectrum *c* in Fig. 4). In the cycloaddition reaction on nitrile groups in **11d** by sodium azide, the CN frequency stretching has disappeared; instead, tetrazole **12d** has formed and its tetrazole functional peak at 2470–3127 cm^{-1} has appeared (spectrum *d* in Fig. 4). These observations demonstrated the successful conversion of **9d** to **12d** and then to **13d**. The conversion of **13d** to **14d** was carried out in the presence of sodium methoxide at pH = 12 in 2 h (Scheme 4, see experimental). The IR spectrum of **14d** showed a sharp and broad absorption peak at 3424 cm^{-1} for hydroxyl groups, which indicated the deprotection reaction of these groups. In the IR spectrum of this compound, the loss of carbonyl frequency stretching also supported release of the hydroxyl groups. The ^{13}C NMR spectrum of **14d** also showed the loss of carbonyl peaks at δ 169.74, 169.41, 169.32 and 168.47 ppm; instead, the distinct peak of the tetrazole carbon atom is shown at 156.64 ppm (Fig. 5).

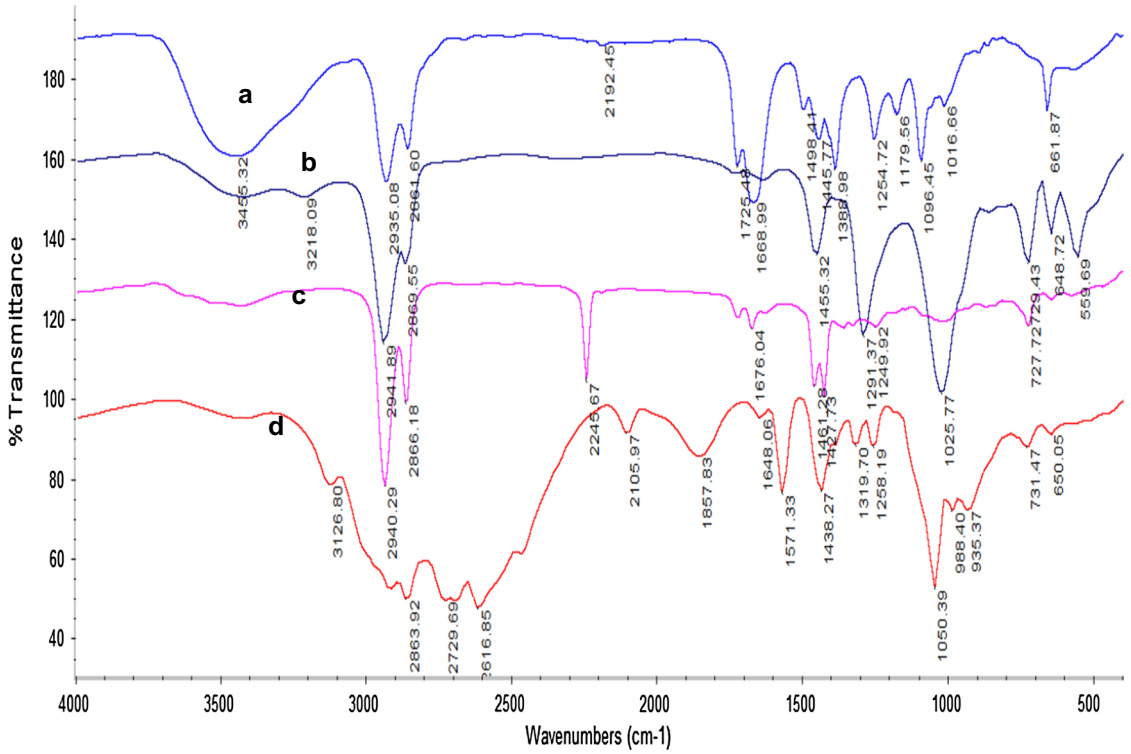


Fig. 4 IR spectra of compounds **9d** (*a blue solid line*), **10d** (*b green solid line*), **11d** (*c pink solid line*) and **12d** (*d red solid line*)

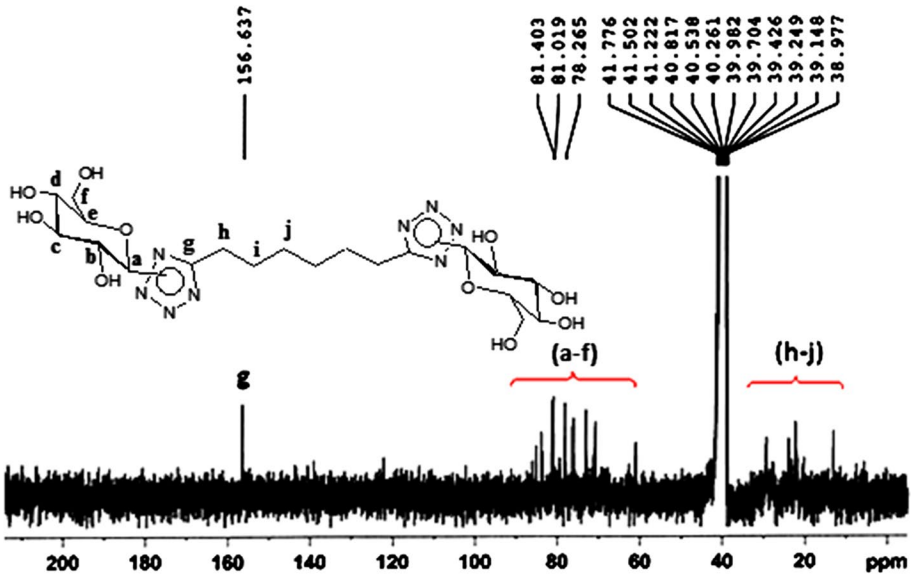


Fig. 5 ^{13}C NMR spectrum of compound **14d** in DMSO-d_6

Conclusion

The valproic acid analogs based on tetrazole and other 5-alkyl tetrazoles were synthesized and characterized by spectroscopic techniques. Bis-tetrazoles were also synthesized in good yield. Mono- and bis-tetrazoles were coupled with 1-bromo glucose pentaacetate, and the corresponding structures were characterized. The mono- and bis-tetrazoles, based on pentaacetylated glucose, were deprotected under basic media and newly obtained *N*-glycosides based on valproic acid analogs and other tetrazole derivatives.

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References

1. S. Budavari (ed.), *The Merck Index*, 12th edn. (Merck and Co, NJ, 1996), p. 1961
2. B.F.D. Bourgeois, Valproic acid—clinical efficacy and use in epilepsy, in *Antiepileptic Drugs*, ed. by R.H. Levy, R.H. Mattson, B.S. Meldrum, E. Perucca (Lippincot, Williams & Wilkins, Philadelphia, 2002), pp. 808–817
3. M.A. Rogawski, W. Loscher, Nat. Med. **10**, 685–692 (2004)
4. E. Spina, G. Perugi, Epileptic Disord. **6**, 57–75 (2004)
5. C.J. Landmark, Med. Sci. Mon. **13**(1), 1–7 (2007)
6. B. Anmann, H. Grünze, E. Vieta, M. Trimble, Clin. EEG Neurosci. **38**, 116–123 (2007)
7. H. Dou, K. Birusing, J. Faraei, S. Gorantla, L.Y. Poluektova, S.B. Maggirwar, S. Dewhurst, H.A. Gelbard, H.E. Gendelman, J. Neurosci. **23**, 9162–9170 (2003)
8. S. Eyal, B. Yagen, J. Shimshoni, M. Bialer, Biochem. Pharmacol. **69**, 1501–1508 (2005)
9. J. Ichikawa, Y.C. Chung, J. Dai, Y.H. Meltzer, Brain Res. **1052**, 56–62 (2005)
10. W.S. Yeow, M.F. Ziauddin, J.B. Maxhimer, S. Shamimi-Noori, A. Baras, A. Chua, D.S. Schrump, D.M. Nguyen, Br. J. Cancer **22**, 1436–1445 (2006)
11. I.A. Alsarra, M. Al-Omar, F. Belal, Profiles Drug Subst. Excip. Relat. Methodol. **32**, 209–240 (2005)
12. R.N. Butler, in *Comprehensive Heterocyclic Chemistry II*, ed. by A.R. Katritzky, C.W. Rees, E.F.V. Scriven (Pergamon Press, Oxford, **4**, 1996) pp. 621–678, 905–1006
13. R.E. Trifonov, V.A. Ostrovskii, Russ. J. Org. Chem. **42**, 1585–1605 (2006)
14. N. Sadlej-Sosnowska, J. Org. Chem. **66**, 8737–8743 (2001)
15. K. Jug, A.M. Köster, J. Am. Chem. Soc. **112**, 6772–6777 (1990)
16. R.N. Butler, V.C. Garvin, J. Chem. Soc. Perkin Trans. 1 **2**, 390–393 (1981)
17. T. Kimura, Y. Hamada, M. Stochaj, H. Ikari, A. Nagamine, H. Abdel-Rahman, N. Igawa, K. Hidaka, J.T. Nguyen, K. Saito, Y. Hayashi, Y. Kiso, Bioorg. Med. Chem. Lett. **16**, 2380–2386 (2006)
18. T. Pinter, S. Jana, R.J.M. Courtemanche, F. Hof, J. Org. Chem. **76**, 3733–3741 (2011)
19. R.J. Herr, Bioorg. Med. Chem. **10**, 3379–3393 (2002)
20. D. Moderhack, J. Prakt. Chem. **340**, 687–709 (1988)
21. H. Singh, A.S. Chawla, V.K. Kapoor, D. Paul, R.K. Malhotra, Prog. Med. Chem. **17**, 151–183 (1980)
22. V.A. Ostaraovskii, G.I. Koldoboskii, Chem. Hetrocycl. Comp. **28**, 626–631 (1992)
23. S.P. Cass, D. Borello-France, J.M. Furman, Am. J. Otol. **17**, 581–594 (1996)
24. I.C. Richards, P.S. Thomas, Pestic. Sci. **30**, 275–284 (1990)
25. M. Hiskey, D.E. Chavez, D.L. Naud, S.F. Son, H.L. Berghout, C.A. Bome, Proc. Int. Pyrotech. Semin. **27**, 3–14 (2000)
26. http://www.molbase.com/en/cas-85508-57-2.html Accessed: 4 Feb 2016
27. S.L. Warriner (ed.) Science of Synthesis: Houben-Weyl Methods of Molecular Transformations Vol, **29**, George Thieme Verlag KG, Stuttgart, Germany, 2007, and refs. therein
28. R.L. Schriner, R.C. Fusan, D.Y. Curtin, T.C. Morrill, *The Systematic Identification of Organic Compounds*, 6th edn. (Wiley, New York, 1980), p. 78
29. A.G. Sharpe, *The Chemistry of Cyano Complexes of the Transition Metals* (Academic Press, London, 1976)
30. R.P. Gower, I.P. Rhodes, J. Chem. Ed. **46**(9), 606–607 (1969)
31. Z. Wimmer, L. Pechova, D. Saman, Molecules **9**, 902–912 (2004)
32. T. Nukada, A. Berces, M.Z. Zgierski, D.M. Whitfield, J. Am. Chem. Soc. **120**, 13291–13295 (1998)