SYNTHESIS OF 1,2,3-TRIAZOLE DERIVED POTENTIAL PEPTIDOMIMETICS

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ABSTRACT

In this study, synthesis of some new 1,2,3-triazole derived potential scaffold type peptidomimetics are described.

INTRODUCTION

Peptides are used very often for the development of new therapeutics. However since they have some disadvantages in the direct usage as drugs, they are modified into mimetics and these are called peptidomimetics which are derived from peptides by partly or completely removing the amide bonds while retaining essential amino acid side chains in a defined, spatial relationship (1-3). Peptidomimetics are usually prepared by the attachment of active amino acid side chains to a central core, these so called scaffold type peptidomimetics have usually two to eight amino acid residues on a central rigid core. Different type of central cores are described in the literature (1-3). Some heterocyclic rings are also chosen in some studies (4-7) because of their inflexible structures. Imidazol (8), pyrazole (9-10), 1,2,4-triazole (11-14) and tetrazol (15-17) derivatives are the examples of this kind of peptidomimetics.

Triazoles, like many other five membered heterocyclic compounds are used very often in the pharmacological and medicinal applications. Mainly there are two different methods to prepare 1,2,3-triazole derivatives; condensation of amine derivatives with α-diazo-1,3-dicarbonyl compounds (18,19) or condensation of acetylene compounds with azide derivatives (20).

RESULTS AND DISCUSSIONS

In this study, 16 new 1,2,3-triazole derived potential scaffold peptidomimetics were prepared. Our strategy for the synthesis, follows the "dendroid" approach (21,22). This strategy involves placement of mimetics of the key residues around a central core. This placement of mimetics might mimic β-turn form of a peptide. Such a system is shown in Scheme compound **5**.

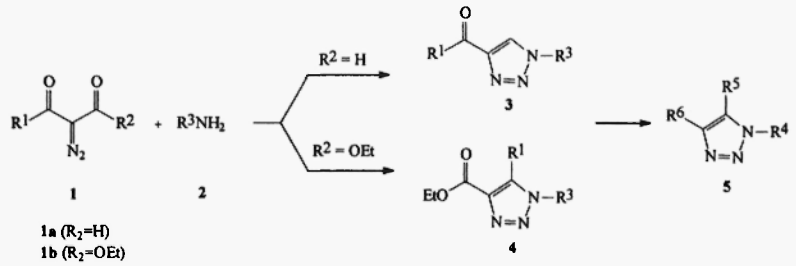
Since the 1,2,3-triazole ring has a rigid structure which can handle the amino acid side chains in a well defined direction and are potentially bioactive compounds, they were chosen for the peptidomimetic templates.

1,2,3-triazoles **3,4** were formed by the reaction of α-diazo-β-oxoaldehyde **1a** and α-diazo-β-oxoester **1b** derivatives with different amine compounds **2** and synthesized potential peptidomimetic precursors were derivatized to yield new potential peptidomimetics **5** (Scheme). Substituents of triazole compounds were chosen as amino acid side chains or their precursors. The results are summarized in Table 1.

α-Diazo-β-oxoaldehyde **1a** derivatives were synthesized by Vilsmeier-Haack formylation of 2-diazo-1-ethanone derivatives [23,24] and α-Diazo-β-oxoester compounds **1b** were synthesized by the diazo group transfer to the β-oxoester derivatives with tosylazide [23].

Some conformational flexibility is formed on the synthesised 1,2,3-triazoles by the aryl ether linkages. These linkages were introduced by high yielding etherifications under mild conditions following Williamson protocol.

In this study, acidic (-COOH), phenolic (-C_6H_4OH), alcoholic (-CH_2OH), basic (-$C(NH_2)$=NH) and lipophilic (-$CH(CH_3)_2$, -CH_3, -C_6H_5) groups were attached on the 1,2,3-triazole core unit. Tyrosine, is mimiced by *para*-substituted phenol; leucine, is mimiced by isopropyl group; serine, is mimiced by hydroxymethyl group; arginine, is mimiced by *para*- benzamidino group; phenyl alanine and alanine, are mimiced by phenyl and methyl groups; and glutamic acid and aspartic acid are mimiced by *para*-substituted benzoic acid.



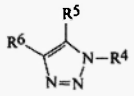
1 2 3 4 5

R^1, R^2, R^3, R^4, R^5,R^6 = Amino acid side chains or their precursors.

Scheme

In the future works, by the attachment of various amino acid side chains (R^4, R^5, R^6) in different combinations on our 1,2,3-triazole template, different potential peptidomimetics might be obtained for a chosen native peptide.

Table 1. 1,2,3-Triazole Templated Potential Peptidomimetics and potential Peptidomimetic Precursors.



5

	R^6	R^4	R^5	Yield (%)	Mp (^{0}C)
3a*	4-CH_3O-C_6H_4-C=O	4-HO-C_6H_4	H	60	216-221
3b*	C_6H_5-C=O	4-HO-C_6H_4	H	83	231-233
3c*	CH_3CH_2O-C=O	4-HO-C_6H_4	H	67	206-208
3d*	CH_3CH_2O-C=O	2-HO-C_6H_4	H	80	211.213
3e*	$(CH_3)_2CHCH_2$-C=O	4-HO-C_6H_4	H	65	185-188
3f*	$(CH_3)_2CH$-C=O	3-HO-4-COOH-C_6H_3	H	78	170 decomp.
3g*	4-$(CH_3)_2CHO$-C_6H_4-C=O	3-HO-4-COOH-C_6H_3	H	70	285-286
4a*	CH_3CH_2O-C=O	4-HO-C_6H_4	Me	68	178-179
4b*	HO-C=O	4-HO-C_6H_4	C_6H_5	65	124-126
5a*	$HOCH_2$	4-HO-C_6H_4	H	61	211-213
5b*	$HOCH_2$	4-(4-CH_3O-C_6H_4-CH_2O)-C_6H_4	H	72	153-157
5c*	$HOCH_2$	4-(4-CN-C_6H_4-CH_2O)-C_6H_4	H	80	159-162
5d*	$HOCH_2$	4-[4-(NH=(NH_2)C)-C_6H_4-CH_2O]-C_6H_4	H	55	233-234
5e*	$HOCH_2$	2-HO-C_6H_4	H	85	167-168
5f*	$HOCH_2$	2-(4-CH_3O-C_6H_4-CH_2O)-C_6H_4	H	70	136-137
5g*	C_6H_5-C=O	4-(4-CH_3O-C_6H_4-CH_2O)-C_6H_4	H	75	196-198

* These compounds are new.

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EXPERIMENTAL

Melting points were determined on a Electrothermal 9100 capillary melting point apparatus. Infrared spectra were obtained from films on sodium chloride discs for liquids or potassium bromide pellets for solids on a Jasco 5300 FT-IR recording spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker 250 MHz and are reported in δ units with tetramethylsilane as internal standard. Mass spectra VG-Zabspec (70 ev). ***General:*** All diazo compounds were prepared as described in (12,13). Spectroscopic datas of the synthesised compounds are shown in Table 2.

Synthesis of Compounds 3: 10 mmol **1a** was dissolved in 20 ml of EtOH, and a mixture of 10.1 mmol amine compound **2** and 10.1 mmol AcOH were added. The mixture was stirred at r.t. for 4 hr. During this time, the product precipitated and recyristallised from EtOH. The yields are given in Table.

Synthesis of Compounds 4: 30 mmol p-aminophenol was solved in min. amount of methanol and 60 mmol acetic acid was added. 10 mmol of diazo compound **1b** was added in this solution. The reaction mixture was refluxed for 12 hr. Then solvent was removed under reduced pressure and crude product was obtained. It was recrystallised from water in the presence of active coal.

Synthesis of 1-(p-hydroxyphenyl)-4-hydroxymethyl-1H-1,2,3-triazol (5a) and 1-(o-hydroxyphenyl)-4-hydroxymethyl-1H-1,2,3-triazol (5e): $LiAlH_4$ (137.3 mmol) is added in dry THF (75 ml). **3c** or **3d** (34,33 mmol) is solved in dry THF (100 ml) and added slowly to this mixture at rt. After stirring 30 min. at rt., mixture is refluxed for 8 hr. After cooling, excess $LiAlH_4$ is destroyed by the addition of ice-cold water. 20 ml of 5% H_2SO_4 is added and the mixture is extracted with ethyl acetate. Organic phase is washed with water and dried over sodium sulphate. Solvent is removed under reduced pressure and the residue is crystallized from ethanol.

Synthesis of 1-[4-(4-methoxybenzyloxy)phenyl]-4-hydroxymethyl-1H-1,2,3-triazol (5b), 1-[2-(4-methoxybenzyloxy)phenyl]-4-hydroxymethyl-1H-1,2,3-triazol (5f) and 1-[4-(4-methoxybenzyloxy)phenyl]-4-benzoyl-1H-1,2,3-triazol (5g): NaH (11.8 mmol) is added in a solution of phenol compound (**5a** or **5e** or **3b**) (11.8 mmol) in DMF (20 mL) under nitrogen atmosphere. After stirring for 10 min. a solution of p-methoxy benzylchloride (2.32 g, 11.8 mmol) in DMF (10 mL) is added to this mixture and stirred at room temperature for 4 hr. Water (200 mL) is added and precipated product is filtered. The product is crystallized from ethanol.

Synthesis of 1-[4-(4-cyanobenzyloxy)phenyl]-4-hydroxymethyl-1H-1,2,3-triazol (5c): .NaH (11 mmol) is added in a soln. of **5a** (10 mmol) in dry DMF (20 mL) under nitrogen atmosphere. After stirring for 10 min., a solution of p-cyano benzylbromide (10 mmol) in DMF (10 mL) is added and stirred at room temperature for 4 hr. Then water (200 mL) is added and precipated product is filtered. The product is crystallized from ethanol.

Synthesis of 1-[4-(4-amidinobenzyloxy)phenyl]-4-hydroxymethyl-1H-1,2,3-triazol acetic acid salt (5d): Hydrogen sulphide was bubled through a solution of the 1-[4-(4-cyanobenzyloxy)phenyl]-4-hydroxymethyl-1H-1,2,3-triazol (1.12 g), in pyridine-triethylamine (20 ml-2 ml) for 15 mins. at room temperature. After 24 h at room temperature in a stoppered flask, the reaction mixture was concentrated under a steady stream of nitrogen. The residue was diluted with ethyl acetate, washed with $KHSO_4$ and water, and dried over sodium sulphate. Concentration in vacuo afforted a quantitative yield of thioamide. (224-225° C decomposition.)

The thioamide (from previous reaction), was dissolved in a solution of acetone-iodomethane (30 ml-2 ml). The reaction mixture was warmed to achive reflux for 5 hours. Concentration in vacuo afforted the thioimidate as the HI salt. The raw mixture was used for the next step without further purification. (167-169 ° C decomposition.) A solution of the thioimidate (from previous reaction) and ammomium acetate (2 g) in methanol (150 ml) was warmed to achieve reflux for 8 h. After cooling to room temperature, the reaction mixture was concentrated under a steady stream of nitrogen, then acetone (200 ml) was added and precipitated product was filtrated.

Table 2. Spectroscopic datas of the synthesised compounds.

	H1-NMR (250 MHz) (DMSO-D6)	C13-NMR (63 MHz)	EI-MS (e/z)
3a	10.0 (s, O**H**); 9.3 (s, H-C(5)); 8.3 (s, 2 arom. H); 7.7 (s, 2 arom. H); 7.1 (s, 2 arom. H); 6.9 (s, 2 arom. H); 3.8 (s, OCH_3).	^{13}C-NMR (63 MHz): 159.71, 158.18, 147.32, 132.41, 129.10, 128.04, 127.21, 122.37, 115.97, 115.39, 113.83, 55.51.	294.8 (M^+)
3b	10.0 (s, OH); 9.3 (s, H-C(5)); 8.28-8.25 (m, 2 arom. H); 7.8-7.6 (m, 5 arom. H); 6.98-6.94 (m, 2 arom. H).	158.24, 146.87, 142.62, 136.51, 133.21, 129.89, 128.47, 128.00, 127.53, 122.43, 115.99	264.8 (M^+)
3c	10.0 (s, OH); 9.3 (s, H-C(5)); 7.7 (d, J= 8.8, 2 arom. H); 6.9 (d, J=8.8, 2 arom. H); 4.3 (q, J= 7.1, OCH_2); 1.3 (t, J= 7.1, CH_3)	160.14, 158.14, 139.40, 128.03, 126.77, 122.29, 115.94, 60.58, 14.10	232.8 (M^+)
3d	10.6 (s, OH); 9.0 (s, H-C(5)); 7.6-9.9 (4 arom. H); 4.3 (q, J= 7.1, OCH_2); 1.3 (t, J= 7.1, CH_3)	149.91, 148.80, 138.61, 130.73, 130.24, 125.38, 123.78, 119.41, 116.94, 60.55, 14.08	232.8 (M^+)
3e	10.0 (s, OH); 9.3 (s, H-C(5)); 7.7 (d, J=7.6, 2 arom. H); 6.9 (d, J=7.7, 2 arom. H); 2.9 (d, J=6.7, CH_2); 2.2 (m, CH); 0.9 (d, J=6.4, $(CH_3)_2$)	193.58, 158.17, 147.41, 128.05, 125.10, 122.31, 115.96, 47.80, 24.44, 22.34	244.9 (M^+)
3f	9.6 (s, H-C(5)); 8.0 (d, J= 8.1, 1 arom. H); 7.6 (d, J=8.9, 2 arom. H); 3.9 (broad, OH, COOH); 3.6 (m, $(CH_3)_2C$**H**); 1.2 (d, J=6.4)	197.31, 172.00, 170.94, 163.35, 161.84, 155.72, 146.48, 140.70, 132.13, 131.38, 126.13, 113.51, 110.80, 108.30, 106.17, 100.02, 98.45, 18.78, 18.28	275.0 (M^+)
3g	9.64 (s, H-C(5)); 8.3-7.1 (4 peak, 7 arom. H); 4.8 (septet, J= 5.8, OCH); 1.3 (d, J= 5.8, 6 H (CH_3))	182.87, 170.93, 161.88, 161.84, 147.57, 140.71, 132.53, 132.12, 128.52, 127.73, 115.04, 113.47, 110.86, 108.37, 69.71, 21.62	366.8 (M^+)
4a	10.1 (s, OH); 7.4 (d, J=8.64, 2 arom. H); 6.9 (d, J=8.64, 2 arom. H); 4.3 (q, J=7, OCH_2), 2.4 (s, CH_3(5)); 1.3 (t, J=7, CH_3**H**$_2$)	161.08, 158.67, 139.14, 135.40, 126.93, 126.41, 115.83, 66.93, 60.27, 25.03, 14.12, 9.59	247.0 (M^+)
4b	7.9 (d, J=7.5, 4 arom. H); 7.6 (d, J=6.76, 2 arom. H); 7.5 (d, J=7.18, 3 arom. H).	167.26, 161.84, 158.32, 132.80, 130.69, 130.28, 129.21, 128.88, 128.50, 127.91, 127.39, 126.91, 126.19, 115.51	281.0 (M^+)
5a	9.9 (s, -PhO**H**); 8.5 (s, H-C(5)); 7.6 (d, J=8.8, 2 arom. H); 6.9 (d, J=8.8, 2 arom. H); 5.2 (t, J=5.5, -CH_2O**H**); 4.6 (d, J=5.5, CH_2)	157.48, 148.61, 128.85, 121.69, 120.76, 115.90, 54.88	190.8 (M^+)
5b	8.5 (s, H-C(5)); 7.8 (d, J=8.7, 2 arom. H); 7.4 (d, J=8.3, 2 arom. H); 7.2 (d, J=8.7, 2 arom. H); 6.9 (d, J=8.3, 2 arom. H); 5.3 (t, J=5.1, OH); 5.1 (s, OCH_2); 4.6 (d, J=4.2, CH_2**H**OH); 3.7 (s, CH_3)	159.01, 158.16, 148.80, 130.18, 129.53, 129.39, 128.47, 121.59, 121.47, 120.87, 115.67, 113.78, 113.57, 69.30, 55.02, 54.91	310.7 (M^+)
5c	8.6 (s, H-C(5)); 7.9-7.8 (m, 4 arom. H); 7.7 (d, J=7.3, 2 arom. H); 7.2 (d, J=8.6, 2 arom. H); 5.3 (s, 3 H, CH_2+OH); 4.6 (s, CH_2)	157.70, 148.82, 142.46, 132.38, 130.52, 128.29, 128.02, 121.54, 120.87, 118.64, 115.71, 110.51, 68.52, 66.92, 54.89, 25.03	305.7 (M^+)
5d	8.6 (s, H-C(5)); 7.8 (d, J= 4.1, 2 arom. H); 7.7 (d, J=7.3, 2 arom. H); 7.2 (d, J=8.5, 2 arom. H); 6.1 (broad, OH, NH, NH_2, COOH); 5.3 (s, 2 H); 4.6 (s, 2H); 1.8 (s, CH_3COOH)	175.10, 165.75, 160.01, 157.75, 148.84, 144.70, 142.25, 132.40, 130.47, 128.62, 128.06, 127.87, 127.75, 127.65, 123.11, 121.55, 120.90, 116.16, 115.76, 110.51, 68.59, 54.88, 23.61	323.0 (M-acetic acid)
5e	10.5 (s, -PhO**H**), 8.3 (s, H-C(5)); 7.6-6.9 (4 arom. H); 5.2 (s, CH_2O**H**); 4.6 (d, J=4.2, -CH_2)	149.45, 147.61, 129.83, 124.95, 124.59, 124.11, 119.42, 116.95, 54.86	190.8 (M^+)
5f	8.3 (s, H-C(5)); 7.6-6.9 (m, 8 arom. H); 5.3 (t, J=5.4, OH); 5.1 (s, OCH_2); 4.6 (d, J=5.2, HO-CH_2); 3.7 (s, OCH_3).	158.95, 150.53, 147.67, 130.31, 129.08, 128.78, 128.08, 126.25, 125.72, 124.48, 121.02, 114.50, 113.78, 69.81, 54.98, 54.83	310.7 (M^+)
5g	9.5 (s, H-C(5)); 8.3-6.9 (13 arom. H); 5.1 (s, CH_2); 3.7 (s, CH_3)	185.02, 159.01, 158.80, 146.92, 136.47, 133.26, 129.89, 129.52, 129.33, 128.49, 128.35, 127.70, 122.24, 115.71, 113.77, 69.34, 55.01	385.0 (M^+)

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