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Efficient synthesis of novel conjugated 1,3,4-oxadiazole-peptides

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Abstract

We were interested in the design and synthesis of novel bioisosteric analogues of leuprolide acetate containing oxadiazole moiety at *C*- or *N*-terminal of the peptide. An efficient approach for the synthesis of 2-amino-1,3,4-oxadiazoles through the reaction of hydrazide and ammonium thiocyanate and desulfurization reaction of the thiosemicarbazides via different coupling reagents was employed. These compounds are bioisosteres of the amide bond. Furthermore, the coupling of 2- amino-1,3,4- oxadiazoles at the *C*-terminal of leuprolide analogues was carried out, using coupling reagent in solution phase. On the other hand, the addition of 2- amino-1,3,4- oxadiazole to the *N*-terminal of the peptide sequence was done through the reaction of 2- amino- 1,3,4-oxadiazole with succinic anhydride that led to the formation of a carboxylic acid moiety. Addition of the synthesized oxadiazole containing carboxylic acid to the peptide sequence was made using coupling reagent and on the surface of the resin. The synthesized peptides containing oxadiazole moiety at the *C*- or *N*-terminal of the peptide sequence are peptidomimetics of leuprolide acetate. All of the synthesized peptides were purified using preparative HPLC and their structures were confirmed using HR-MS (ESI).

Keywords: 2-Amino-1,3,4-oxadiazoles, 2-Amino-1,3,4-oxadiazoles containing carboxylic acid, Peptidomimetic, Leuprolide acetate as anti-cancer peptide, Leuprolide acetate analogues

Dedicated to Prof. Norbert Sewald on the occasion of his birthday.

Introduction

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The resurgence of peptides as key compounds in a variety of fields ranging from drug discovery and chemical biology to medical applications has been made by improved methods for their synthesis.[1-5] Over the years, peptides have been evolving as promising therapeutic agents in the treatment of extended diseases such as cancer, diabetes and cardiovascular diseases. Meantime, the application of peptides in a variety of other therapeutic areas is growing rapidly.[6]

Despite the high potential of peptides as therapeutic agents, there are problems connected with the use of natural peptides, due to the low stability against proteolysis, resulting in a short duration of *in vivo* activity and rapid metabolism. [7]

Nevertheless, synthesizing of novel peptides with different modifications to improve their activities and overcome their limitations has been a big challenge for scientists. There are different approaches to improve the activity of peptides such as: a) cyclization of linear peptides, [8] b) chemical modifications including the incorporation of *D*-amino acids,[9] c) changing the sequence of the peptide,[10] d) synthesis of cyclopeptides or linear peptides containing bioactive heterocyclic backbones,[11] e) synthesis of pseudopeptides. [12]

Bioisosteres are chemical substituents that are used to replace some important functional groups such as: carboxylic acid, amide bond *etc.* affording similar biological properties. The reason behind using bioisosteres is to obtain new analogues with better properties. Such replacements are the toolbox of medicinal chemists to optimize their lead structures with respect to lipophilicity, solubility, activity, selectivity, absorption, metabolism, lack of toxic and other side effects. Amide isosteres are generally introduced to modulate polarity and bioavailability. [13]

Peptidomimetic approach contains the building block structures that can be used as bioisosteric replacement of the amide bond in the peptide backbone to generate compounds with improved pharmacokinetic profiles. In this approach, amide bond bioisosteres can affect the active conformation of the peptide. [14]

1,3,4-Oxadiazoles are known amide bioisosteres and have drawn attention in drug design. [15] 2-Amino-1,3,4-oxadiazoles also display a wide range of biological activities. [16] There are different reported approaches for the synthesis of oxadiazoles.[17] Efficient syntheses of 2,5-disubstituted 1,3,4-oxadiazoles from isothiocyanates and hydrazides through cyclodesulfurization in the presence of TBTU as an uronium coupling reagent was developed in our group.[18]

Studies of peptides (cyclic or linear) containing heterocycles within their backbones, have demonstrated that heterocyclic scaffolds can influence the conformational properties and

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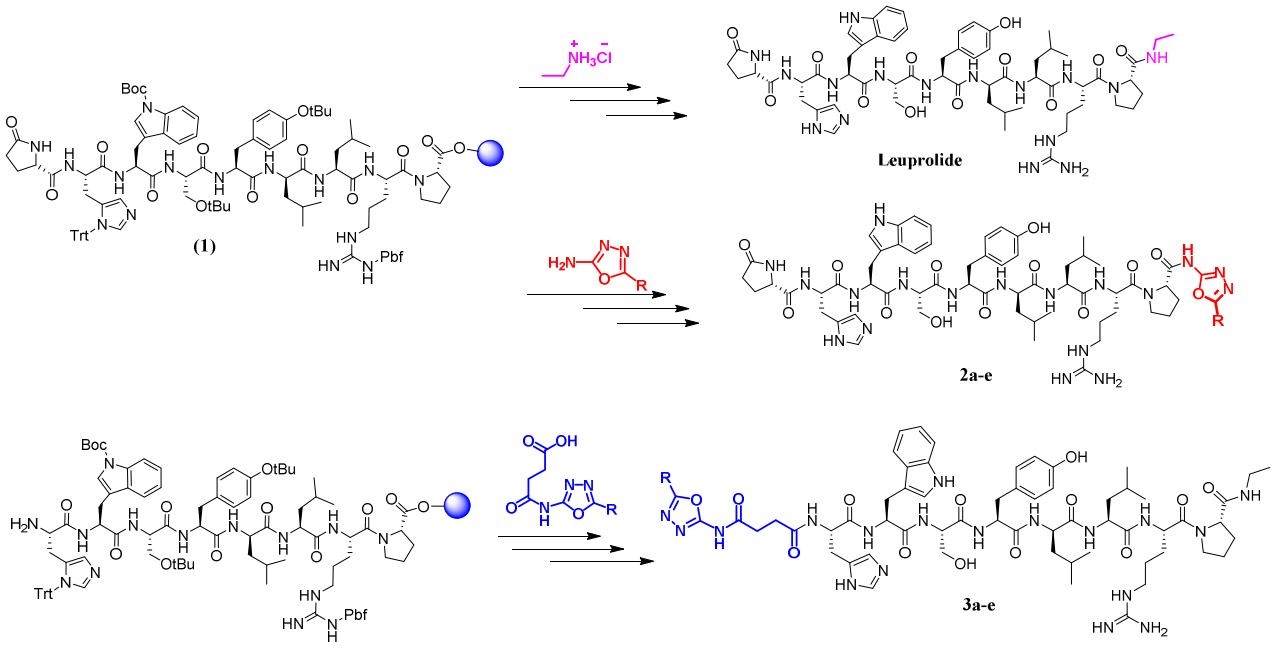
biological activity of the peptide.[19] Leuprolide acetate is a synthetic nonapeptide (Figure **1**) that is a potent gonadotropin-releasing hormone receptor (Gn-RH) agonist used for diverse clinical applications, including the treatment of prostate cancer. [20]

Pyr-His-Trp-Ser-Tyr-*D*-Leu-Leu-Arg-Pro-NH-Et

(Leuprolide)

Figure 1. The peptide sequence of leuprolide acetate

Herein, we report the synthesis of leuprolide acetate and their conjugated 1,3,4-oxadiazole-peptides at the *C*-or *N*-terminal of the peptide. Oxadiazole skeleton replaced the ethyl amide group at the *C*-terminal to access the conjugated 1,3,4-oxadiazole-peptides **(2a-e)**. On the other hand, 2-amino-1,3,4-oxadiazole was coupled to the *N*-terminal through modifying its amine group to a carboxylic acid moiety via reaction with succinic anhydride thus affording the conjugated 1,3,4-oxadiazole-peptides **(3a-e)** (Scheme **1**).



Scheme 1. Synthesis of leuprolide analogues containing oxadiazole moiety

Results and discussion:

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To achieve the conjugated oxadiazole-peptide, at first the linear protected peptide (Fmoc-His(Trt)-Trp(Boc)-Ser(*t*Bu) -Tyr(*t*Bu)-*D*-Leu-Leu-Arg(Pbf)-Pro-2-CTC) was synthesized on the surface of the 2-chloro-tritylchloride (2-CTC) resin through the standard solid phase peptide synthesis (SPPS) strategy. [21] At first, Fmoc-Pro-OH was added to the surface of resin using diisopropylethylamine (DIPEA) and after capping with acetic anhydride other Fmoc-protected amino acids were added to the peptide sequence using TBTU as coupling reagent and also HOBt was used to prevent racemization. Deprotection of the Fmoc group was achieved by treatment of the resin with 25% piperidine in DMF. After adding the nine amino acids, the desired fully protected nonapeptide on the surface of resin **1** was obtained. The nonapeptide on the surface of resin can be used to access leuprolide acetate and other targeted conjugated 1,3,4-oxadiazole-peptides. To access leuprolide acetate, the following steps were made a) the supported peptide **1** was cleaved using 1% TFA and compound **4** was formed. b) Then, ethylamidation was accomplished in solution phase using ethylammonium chloride and TBTU as coupling reagent in the presence of DIEA as base affording compound **5**. c) The final deprotection was done using reagent K (TFA/TES/Water 95:2.5:2.5). d) The purification of the peptide was done using preparative HPLC (Column C-18, Eurospher 100, 7 μm). The structure of the desired leuprolide acetate was approved using HR-MS (ESI). (Scheme **2**)

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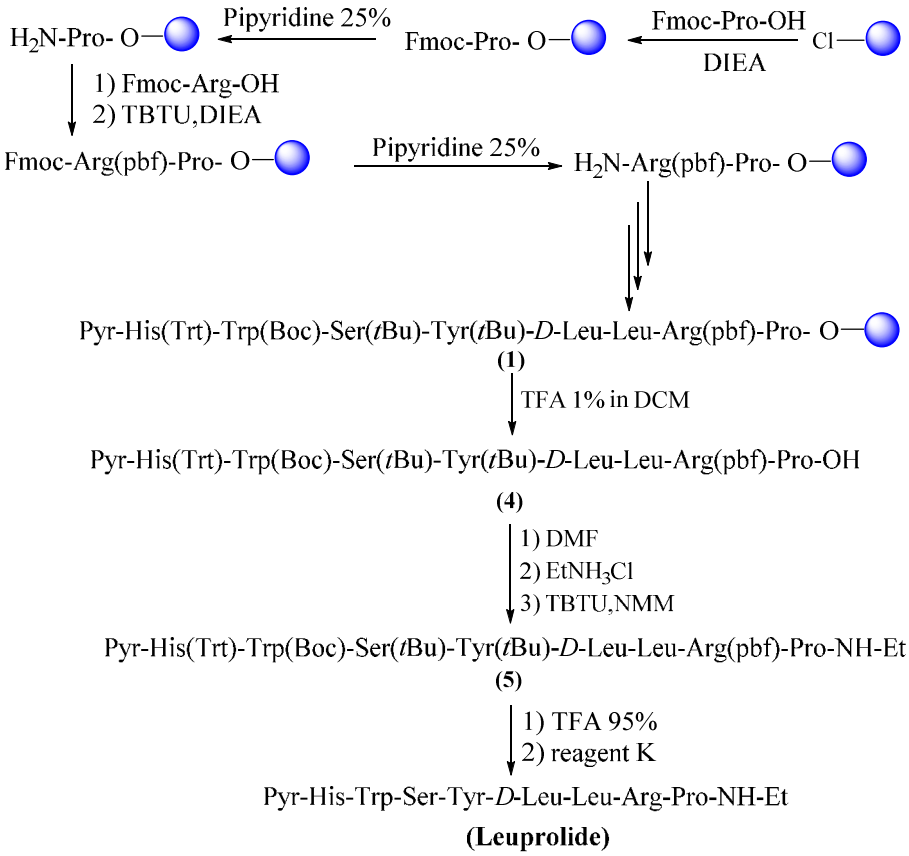
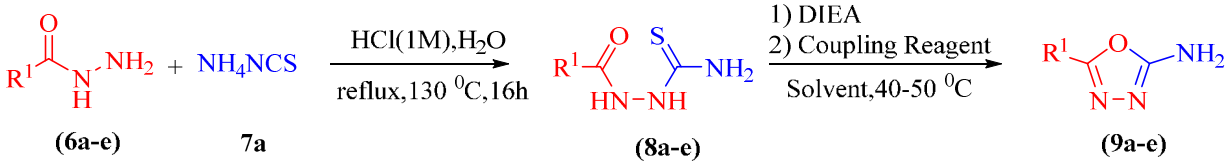


Scheme 2. General procedure for the synthesis of Leuprolide

To access the conjugated 1,3,4-oxadiazoles-peptide, protected nonapeptide **1** and 2-amino-1,3,4-oxadiazole can be used. There are extended methods for the synthesis of 2-amino-1,3,4-oxadiazoles but some of them have limitations such as byproduct formation, handling of harsh and toxic reagents and longtime reaction. [22] Recently, trimethylsilyl isothiocyanate (TMSNCS) was used as a suitable reagent for the synthesis of 2-amino-1,3,4-oxadiazoles through thiosemicarbazide. [23] Here, we present a practical method for the synthesis of 2-amino-1,3,4-oxadiazoles through the reaction of aryl hydrazides with ammonium thiocyanate instead of TMSNCS that led to the desired thiosemicarbazide intermediate **(8a-e)** and its cyclization accompanied by desulfurization was done using coupling reagents such as *N,N′*-diisopropylcarbodiimide (DIC) or TBTU to afford compounds **(9a-e)**. (Scheme **3**)



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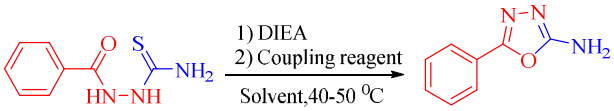
Scheme 3. Synthesis of (**9a-e**) through cyclization of thiosemicarbazide (**8a-e**) using coupling reagent

The aforementioned reaction was studied with different coupling reagents such as DCC, DIC, and TBTU. The optimized reaction condition with different solvents such as DMF, MeOH, and CH_3CN was studied. The best results were achieved using DIC in acetonitrile as solvent (Entry 6 in Table **1**).

Table 1. The optimization reaction condition for the synthesis of **9a**



8a **9a**

Entry	Coupling reagents	Solvent	Time (h)	Yield %
1	DIC	DMF	22	65
2	DCC	DMF	26	40
3	TBTU	DMF	14	65
4	TBTU	CH_3CN	24	-
5	TBTU	MeOH	24	-
6	**DIC**	**CH_3CN**	**24**	**70**
7	DIC	MeOH	24	Trace

The structure and yields of the synthesized 2-amino-1,3,4-oxadiazoles **(9a-e)** are shown in Figure **2**.

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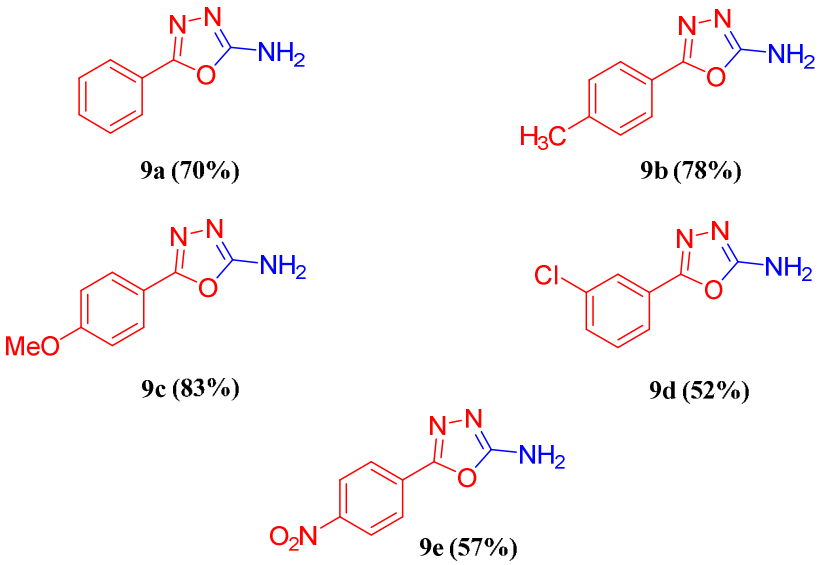
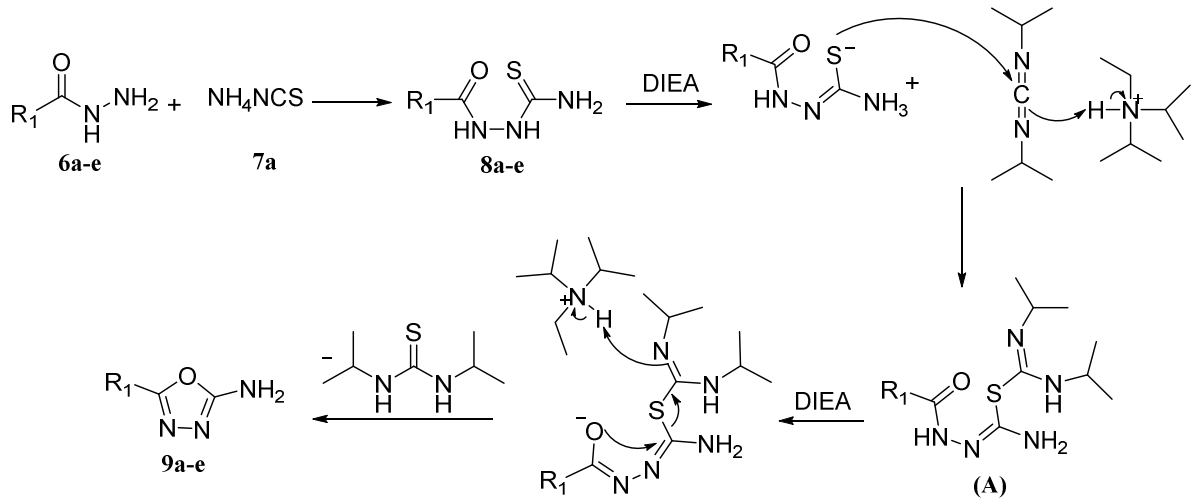


Figure 2. Structure of the synthesized 2-amino-1,3,4-oxadiazoles **9a-e**

The possible mechanism for the synthesis of 2-amino oxadiazoles **(9a-e)** is shown in Scheme 4. This conversion involves the initial nucleophilic addition reaction of the sulfur of thiosemicarbazide with the electrophilic center of the carbodiimide to form the desired intermediate **(A)**, then the subsequent cyclization of intermediate **(A)** followed by the elimination of the diisopropylthiourea group leads to the desired product (Scheme **4**).



Scheme 4. The proposed mechanism for the synthesis of 2-amino-1,3,4-oxadiazole **(9a-e)**

Meanwhile, in another try to synthesize 2-amino-1,3,4-oxadiazole **9f**, at first phenylalanine methyl ester hydrochloride was transformed to the Boc-phenylalanine methyl ester derivative and its further reaction with hydrazine hydrate led to Boc-phenylalanine hydrazide **6f** that was

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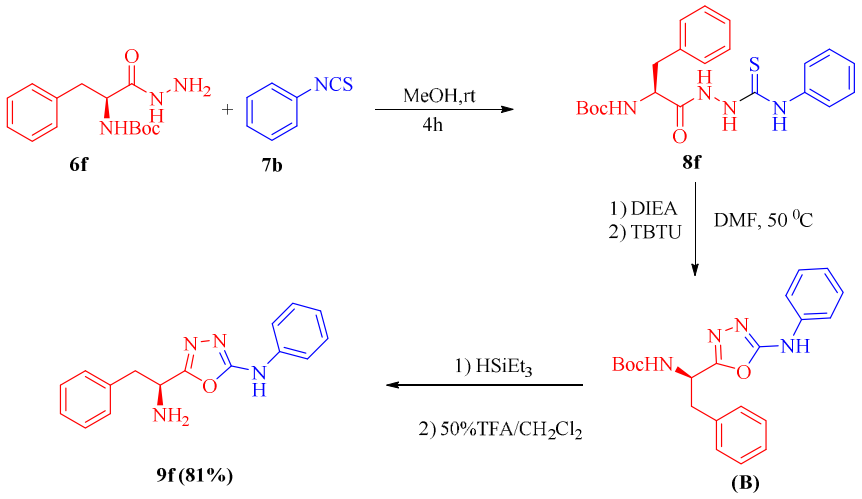
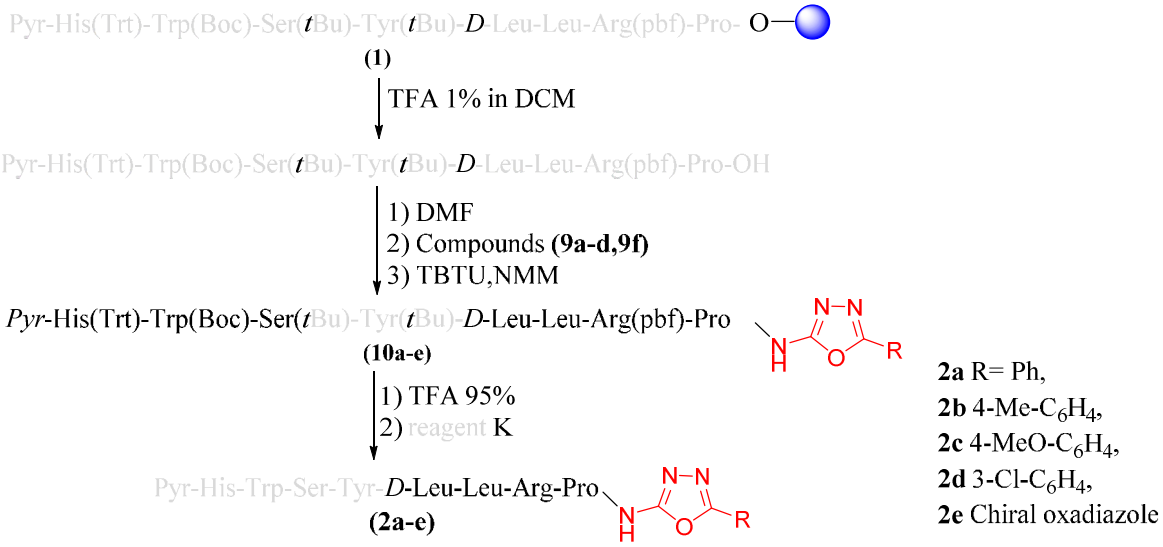
reacted with phenylisothiocyanate **7b** to give thiosemicarbazide **8f** the protected phenylalanine oxadiazole **(B)** was formed using TBTU in DMF, and after Boc deprotection with TFA (50%) chiral oxadiazole **9f** was obtained as shown in Scheme **5**. The selection of this approach was related to the solubility of the starting material **6f**.



Scheme 5. General method for the synthesis of compound **9f**

The protected peptide sequence **(1)** (Pyr-His(Trt)-Trp(Boc)-Ser(*t*Bu)-Tyr(*t*Bu)-*D*-Leu-Leu-Arg(Pbf)-Pro-O-2-CTC Resin) was synthesized using SPPS approach. After cleavage of the peptide from the resin surface, 2-amino oxadiazole derivatives **(9a-d,9f)** were added to the peptide sequence **1** at the *C*-terminal using TBTU as a coupling reagent in the presence of DIPEA (Scheme **6**).



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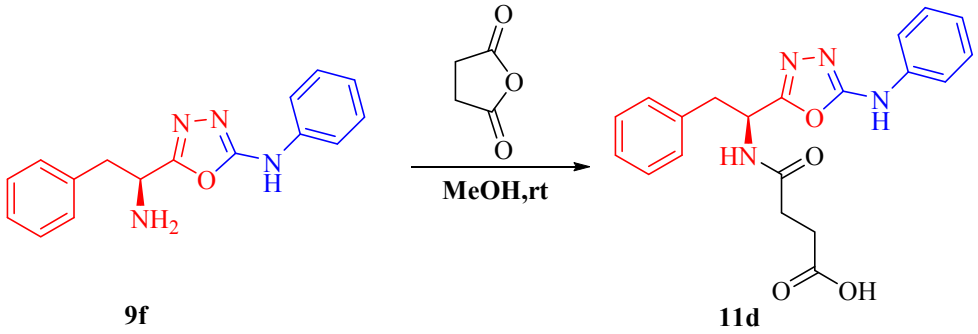
Scheme 6. Synthetic procedure for adding oxadiazole moiety to the *C*-terminal of peptide sequence

The structures of the synthesized peptide analogs were confirmed using high resolution mass spectrometry (HRMS-ESI). For example, the distinguished peak of compound **2e** of $[M+H]^+$ was 1444.7265 that confirmed the attachment of the peptide to the oxadiazole moiety.

On the other hand, adding the 2-amino-1,3,4-oxadiazole derivative to the peptide sequence at the *N*-terminal requires a carboxylic acid moiety. The reaction of the 2-amino-1,3,4-oxadiazole with succinic anhydride as a linker to form the desired carboxylic acid oxadiazole derivatives is used (Scheme **7**). [24] Figure **3** summarizes the obtained oxadiazole backbone containing carboxylic acid moiety **11a-e**.



9f **11d**

Scheme 7. Synthesis of oxadiazole backbone containing carboxylic acid **11d**

The structures of the synthesized compounds were confirmed using spectroscopic data that is enclosed in the supporting information.

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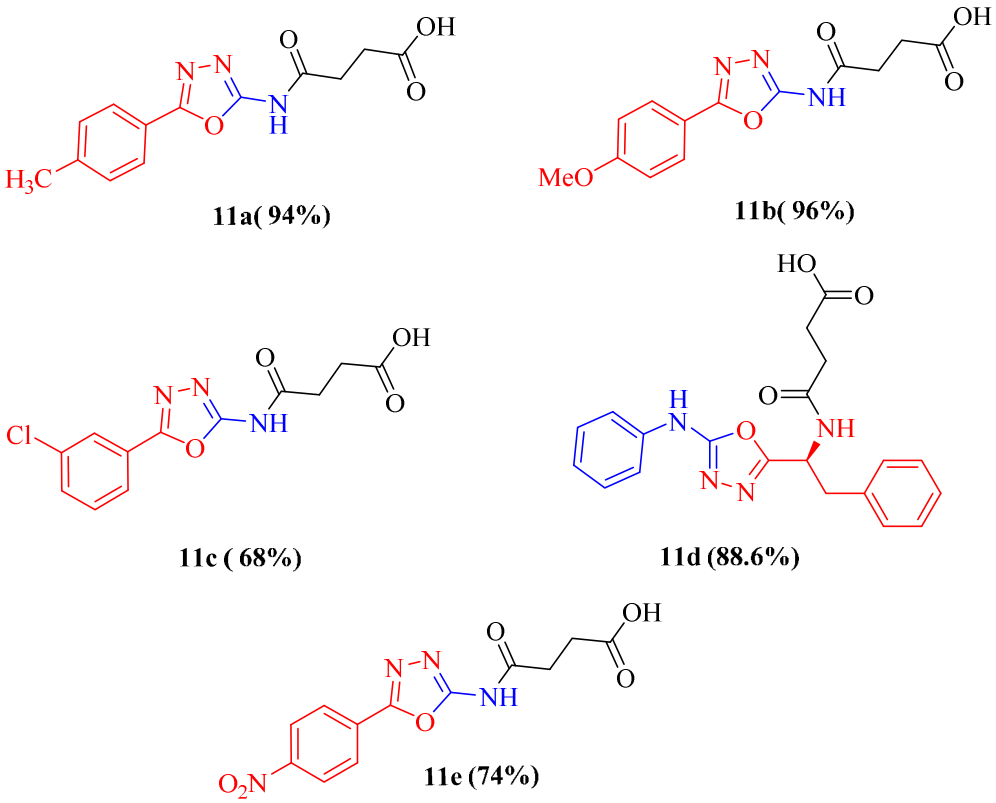

Figure 3. Structure of oxadiazole backbone containing carboxylic acid products **11a-e**

In another try, protected octapeptide (NH_2-His(Trt)-Trp(Boc)-Ser(*t*Bu)-Tyr(*t*Bu)-*D*-Leu-Leu-Arg(Pbf)-Pro-O-2-CTC resin) **13** was synthesized using SPPS approach, then oxadiazoles containing carboxylic acid moiety **11a-e** were added to the *N*-terminal of the peptide sequence using TBTU as coupling reagent in the presence of DIEA as base and finally after cleavage using 1% TFA the conjugated oxadiazole-octapeptides **14a-e** were formed. In this case, functionalized oxadiazole was attached to the *N*-terminal of the synthesized peptide instead of the pyroglutamic acid moiety. After the cleavage of the peptide analog from the resin, amidation of the *C*-terminal was achieved using ethylammonium chloride and also TBTU as coupling reagent in the presence of DIEA. Then final deprotection was done using reagent K and desired conjugated 1,3,4-oxidiazole-linker-peptides **3a-e** were formed. The procedure for the synthesis of the *N*-terminal oxadiaolyl-peptide analogs is shown in Scheme **8**.

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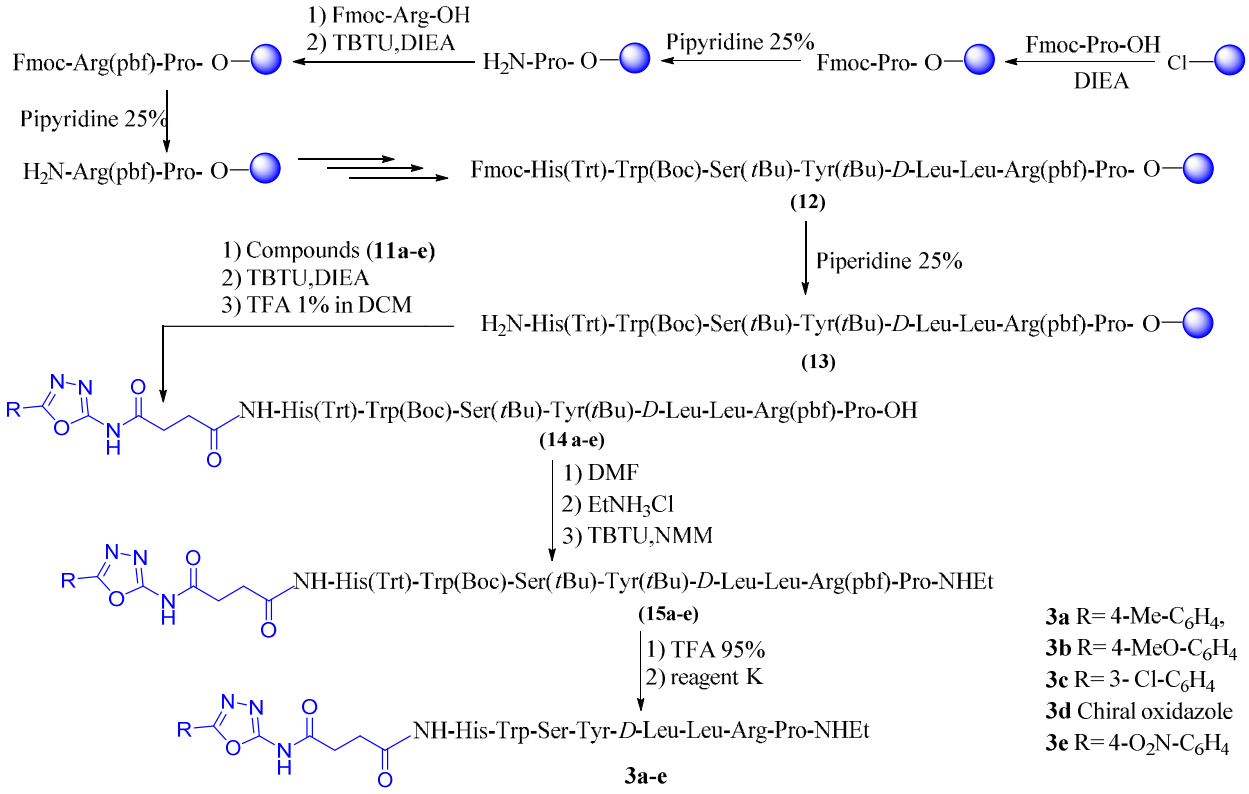

Scheme 8. Synthetic procedure for the synthesis of conjugated oxadiazole-octapeptide **3a-e**

The structures of the synthesized peptide analogues were confirmed using high resolution mass spectrometry HRMS (ESI). For example, the distinguished peak of compound **3d** of $[M+H]^+$ was 1460.75853 that confirm attaching of the peptide to the oxadiazole moiety.

In conclusion, we have described the design and synthesis of novel conjugated oxadiazolyl peptides, which represent the peptidomimetic structures of leuprolide acetate. We have established a strategy for the incorporation of the oxadiazolyl moiety onto the peptide backbone at *C*- or - *N* - terminal. Further studies to assemble the biological properties of the formed products are ongoing and will be reported in due course.

Experimental section:

General Information. Commercially available materials were used without further purification. 2-Cl-Trt resin and the amino acids were purchased from Iris. *N,N*-Diisopropylethylamine (DIEA) from Sigma-Aldrich. Organic Solvents (DMF, DCM, MeOH and CH_3CN) were purchased from Merck. RP-HPLC quality acetonitrile and water were used for RP-HPLC analyses and purification. Melting points were recorded using an electrothermal capillary melting point

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apparatus and were uncorrected. Fourier transform infrared (FT-IR) spectra were recorded as KBr pellets using an ABB FT-IR FTLA 2000 spectrophotometer. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on BRUKER NMR-Spectrometer. Chemical shifts were reported in parts per million (δ) using TMS as internal standard and DMSO (d_6) as the solvent, and coupling constants were expressed in Hertz. High resolution mass spectra were recorded on Mass-ESI-POS (Apex Qe-FT-ICR instrument) spectrometer.

Peptides were synthesized on an AAPTEC Focus-Xi instrument using standard Fmoc solid-phase peptide synthesis chemistry. The amino acids were used: Fmoc-Pro-OH, Fmoc-Arg(pbf)-OH, Fmoc-Leu-OH, Fmoc-*D*-Leu-OH, Fmoc-Tyr(*t*Bu)-OH, Fmoc-Ser(*t*Bu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-His(Trt)-OH, H-Pyr-OH

General procedure for the synthesis of thiosemicarbazide intermediate (8a-e):

To a solution of ammonium thiocyanate **7a** (0.19 g, 2.5 mmol) in water (2ml), hydrochloric acid 1M (2ml) was added. The reaction mixture was magnetically stirred at 110-130 °C for 45 min to in situ produce isothiocyanic acid intermediate. Then arylhydrazide (1 mmol) was added to the reaction mixture with continued stirring and heated for 5h. The progress of the reaction was monitored by TLC (*n*-hexane: EtOAc: MeOH 3:1:1). After the completion of the reaction, ice was added to reaction mixture and the resulting precipitate of thiosemicarbazide was collected by filtration, washed with water and dried.

2-Benzoylhydrazine-1-carbothioamide (8a):

mp: 179-181°C; IR (KBr, cm^{-1}) v = 1545, 1701, 3388,3526 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ(ppm) 3.35 (brs, NH_2, exchange with water), 7.42-7.68 (m, 5H, 3H-Ar, NH_2), 7.89 (d, 2H, J = 7.7, H-Ar), 9.34 (s, 1H, NH), 10.38 (s, 1H, NH); ^{13}C-NMR (75 MHz, DMSO-d_6): δ(ppm) 127.9, 128.2, 131.8, 132.5, 165.9, 182.1.

General procedure for the synthesis of 2-amino-oxadiazoles 9a-e:

A one-necked flask was charged with DIC (Coupling reagent) (0.24 ml, 1.5 mmol), thiosemicarbazide (1mmol), diisopropylethylamine (0.27 ml, 1.5 mmol) and CH_3CN (5 ml). The reaction mixture was stirred under reflux for 24h. The progress of the reaction was monitored by TLC (*n*-hexane: EtOAc 3:1). After completion of the reaction, the product was isolated by

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filtration and the precipitate was washed with MeOH then dried. For further purification, the product was recrystallized in EtOH to afford of desired products (**9a-e**) in 52%-83% yields.

5-phenyl-1,3,4-oxadiazol-2-amine (9a):

White powder (0.113 g, 0.7 mmol, yield 70%). mp: 242-243 °C; IR (KBr, cm^{-1}) v = 1680, 3196 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ(ppm) 7.25 (s, 2H, NH_2), 7.42-7.58 (m, 3H, H-Ar), 7.75-7.80 (m, 2H, H-Ar); ^{13}C-NMR (75 MHz, DMSO-d_6): δ(ppm) 124.4, 125.1, 129.2, 130.3, 157.3, 163.9.

General procedure for the synthesis of 1,3,4 –oxadizaole (11a-e) using succinic anhydride:

1 mmol of 2-amino oxadiazole **(9b-f)** and succinic anhydride (0.1 g, 1 mmol) were combined in MeOH (5 ml), in a 20-ml round-bottom flask at room temperature and stirred for 10 h. The progress of the reaction was monitored using TLC (*n*-Hexane: EtOAc 1:1). After completion the reaction, the solvent was evaporated under vacuum and the resultant precipitate was washed with diisopropylether and filtered. The yields of products (**11a-e**) were 68%-96%.

4-Oxo-4-((5-(p-tolyl)-1,3,4-oxadiazol-2-yl) amino) butanoic acid (11a):

White powder (0.259 g, 0.94 mmol, yield 94%). mp: 209-213 °C; IR (KBr, cm^{-1}) v = 1655, 1734, 3448 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ(ppm) = 2.34 (s, 3H, -CH_3), 2.46-2.49 (m, 4H, -CH_2), 7.12 (s, 1H, NH), 7.31 (d, 2H, J = 8.1 Hz, H-Ar), 7.67 (d, 2H, J = 8.1 Hz, H-Ar), 12.0 (brs, 1H, -COOH); ^{13}C-NMR (75 MHz, DMSO-d_6): δ(ppm) = 21.1, 28.5, 28.7, 121.7, 125.1, 129.8, 140.3, 157.5, 163.7, 172.7, 173.5.

General Method for the synthesis of leuprolide analogues (2a-e) by coupling oxadiazole (9a-d,9f) to the peptide sequence (4) at *C*-terminal:

To a solution of nonapeptide **(4)** (1.2 g, 0.64 mmol) in DMF (1.8 ml), NMM (0.39 ml, 3.2 mmol) was added and stirred for 15 min. Then TBTU (0.306 g, 0.96 mmol) was added and The reaction mixture was magnetically stirred for 30 min to activate the carboxylic acid group at *C*-terminal, after that 1.3 mmol of oxadiazole **(9a-d,9f)** was added to the reaction mixture. The mixture was stirred for 24 h at room temperature and the progress of reaction was monitored using TLC (EtOAc: MeOH: H2O 10:2:1). The desired C-terminal amidated unprotected nonapeptides **(10a-**

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e) was precipitated in water and dried. Final deprotection of the peptides **(10a-e)** was done by the same procedure mention previously to give leuprolide analogues **(2a-e)**, followed further purification was done using Prep-HPLC by the same procedure of purification.

(2a)

HPLC analysis found that peptide **(2a)** was obtained in 94%< purity (R_t: 45.497 min). mp: 107-110°C; HR-Mass (ESI): $C_{69}H_{92}N_{18}O_{13}$*m/z* = $[M+ (CH_3CN+H_2O) +H]^+$ Found 1434.6868, Calc. 1434.6867; $[M+ (CH_3CN+H_2O) +2H]^+/2$ Found 717.8472, Calc. 717.8472.

(2b)

HPLC analysis found that peptide **(2b)** was obtained in 96%< purity (R_t: 32.883 min). mp: 182-184°C; HR-Mass (ESI): $C_{66}H_{86}N_{18}O_{13}$*m/z* =$[M-C_8H_7N_2O+H]^+$ For Found 1196.6205, Calc. 1196.6203; $[M-C_8H_7N_2O +2H]^+/2$ Found 598.8142, Calc. 598.8143.

(2c)

HPLC analysis found that peptide **(2c)** was obtained in 95%< purity (R_t: 46.048 min). mp: 112-114 °C; HR-Mass (ESI): $C_{66}H_{86}N_{18}O_{14}$*m/z* = $[M+HOAc+H_2O+H]^+$ Found. 1434.6869, Calc. 1434.6871; $[M+HOAc+H_2O+2H]^+/2$ Found 717.8474, Calc. 717.8472.

(2d)

HPLC analysis found that peptide **(2d)** was obtained in 97%< purity (R_t: 32.258 min). mp: 214-218°C; HR-Mass (ESI): $C_{65}H_{83}ClN_{18}O_{13}$*m/z* =$[M-C_8H_4ClN_2O+H]^+$ Found 1182.6048, Calc. 1182.6050; $[M-C_8H_4ClN_2O +2H]^+/2$ Found 591.8063, Calc. 591.8065.

(2e)

HPLC analysis found that peptide **(2e)** was obtained in 96%< purity (R_t: 39.063 min). mp: 94-96°C; HR-Mass (ESI): $C_{73}H_{93}N_{19}O_{13}$*m/z* =$[M+H]^+$Found 1444.7265, Calc. 1444.7264; $[M+2H]/2^+$ Found 722.8669, Calc. 722.8668.

General procedure for the synthesis of leuprolide analogues (3a-e) by attaching functionalized oxadiazole 11a-e to the *N*-terminal of the peptidyl-resin sequence (12):

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After synthesis of the peptidyl-resin sequence **(12)** as mentioned previously, pyroglutamic acid was replaced with the functionalized oxadiazole **(11a-e)**. In this way at first deprotection of the Fmoc-His was made, and then a solution of oxadiazole **(11a-e)** (2 mmol), TBTU (0.64 g, 2.0 mmol), DIPEA (0.6 ml, 3.5 mmol) in 10 ml DMF was added to the resin-bound free amine **(13)** and shaken for 2 h at room temperature. Completion of the coupling was monitored by the Kaiser test. The resin was washed with DMF (3×10ml). Cleavage, ethyl amidation and final deprotection of the peptide were done by the same procedure mention previously to give leuprolide analogs **(3a-e)**, followed further purification was done using Prep-HPLC by the same procedure of purification.

(3a)

HPLC analysis found that peptide **(3a)** was obtained in 95%< purity (R_t: 34.77 min). mp: 142-145°C; HR-Mass (ESI): $C_{67}H_{90}N_{18}O_{13}$*m/z* = $[M\text{-}C_9H_7N_3O+H]^+$ Found 1185.6048, Calc. 1185.6049; $[M\text{-}C_9H_7N_3O+2H]^+/2$ Found 593.3061, Calc. 593.3062.

(3b)

HPLC analysis found that peptide **(3b)** was obtained in 96%< purity (R_t: 34.428 min). mp: 119-121°C; HR-Mass (ESI): $C_{67}H_{90}N_{18}O_{14}$*m/z* = $[M\text{-}C_8H_7N_2O+H]^+$Found 1212.6524, Calc. 1212.6525; $[M\text{-}C_8H_7N_2O+2H]^+/2$ Found 606.8296, Calc. 606.8295.

(3c)

HPLC analysis found that peptide **(3c)** was obtained in 94%< purity (R_t: 35.398 min). mp: 121-123°C; HR-Mass (ESI): $C_{66}H_{87}N_{18}ClO_{14}$*m/z* = $[M\text{-}C_8H_5ClN_3O+H]^+$ Found 1185.6050, Calc. 1185.6051; $[M\text{-}C_8H_5ClN_3O+2H]^+/2$ Found 593.3062, Calc. 593.3061.

(3d)

HPLC analysis found that peptide **(3d)** was obtained in 97%< purity (R_t: 43.682 min). mp: 104-106°C; HR-Mass (ESI): $C_{74}H_{97}N_{19}O_{13}$*m/z* =$[M+H]^+$Found 1460.7585, Calc. 1460.7585; $[M+2H]^+/2$ Found 730.8824, Calc. 730.8824.

(3e)

HPLC analysis found that peptide **(3e)** was obtained in 96%< purity (R_t: 35.988 min). mp: 108-110°C; HR-Mass (ESI): $C_{66}H_{87}N_{19}O_{15}$*m/z* = $[M\text{-}C_8H_5N_3O_3+H]^+$ Found 1185.6047, Calc. 1185.6046; $[M\text{-}C_8H_5N_3O_3+2H]^+/2$ Found 593.3061, Calc. 593.3060.

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Efficient synthesis of novel conjugated 1,3,4-oxadiazole-peptides

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Table of Content:

In this study, we developed an efficient approach for the synthesis of 2-amino-1,3,4-oxadiazoles that are bioisostere of amide functional group. The synthesized oxadiazoles were conjugated to octa-, and nonapeptides through *C*- or *N*- terminus as precursors of leuprolide acetate. The synthesized compounds are peptidomimetics of leuprolide acetate.