

Synthesis and Bioactive Investigation of Amino Acids Fused 1,3,4-Oxadiazole Derivatives as Unnatural Amino Acids

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ABSTRACT

Background: In present study 1,3,4-oxadiazole was attempted to synthesize from nicotinic acid and further their amino acid derivatives were formed. Amino acids play a significant role in biological system. Only 20 amino acids are naturally used, yet even little changes to these amino acids can produce an amazing diversity in terms of their chemical structure and function. Unnatural amino acids can be used to develop novel drugs, novel hormones, and novel enzymes. **Materials and Methods:** Derivatives were tried to synthesize from two methods, conventional as well as new microwave method in order to find out highest yielding method. Microwave method also referred to as "green chemistry" because it uses no external energy sources to produce any harmful fumes, gases, or heat. **Results:** "Method B" i.e., microwave used method found to be produce high yield. Amino acids which are fused to 1,3,4-oxadiazole were said to be unnatural amino acids. The compound(s) were analyzed using UV, IR and NMR spectral data. Synthesized compound(s) were experienced for *in vitro* free radical scavenging activity by DPPH and found to have promising activity. **Conclusion:** Synthesis of unnatural amino acids is an area for new research that has gained an attention now days. Study provides a facile route for preparation of Unnatural amino acids with derivatives and for its similar compound(s). The results could be a crucial study in the designing of novel therapeutic drugs in future.

Keywords: 1,3,4-oxadiazole, Unnatural amino acids, Microwave synthesis, Scavenging activity, Amino acids, DPPH.

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INTRODUCTION

Most of the heterocyclic compounds are those having five and six member rings that have heteroatom such as O, N, S, B, Si, P etc. Heterocyclic compound(s) always had been in consideration in medicinal chemist due to its broad-spectrum pharmacological activities. One such heterocyclic compound is oxadiazole nucleus. A heterocyclic moiety with two nitrogen (N) and one oxygen (O) atoms in a ring is called an oxadiazole.¹ As variety of chemical reactions that 1, 3, and 4-oxadiazole molecules can experience, it made them very useful for searching of molecule altogether its high advantaged structure having enormous biological potential.² Heterocyclic ring fusion frequently produced molecules with a broad range of biological activities.³

It has been reported that 1,3,4-oxadiazole has a variety of biological and pharmacological properties, including Anti-bacterial,⁴⁻⁷ Analgesic and Anti-inflammatory activity,⁸⁻¹¹ Anti-tumor,¹²⁻¹⁴ Anti-fungal,¹⁵⁻¹⁷ Anti-oxidant,^{18,19} Anti-microbial,^{20,21} Anti-convulsant,²² Ant-tubercular.²³

Due to the discovery of several chemical entities with a wide range of biological activities, organic chemists are increasingly interested in developing new methods for synthesis.²⁴ Here use of technique to isosteric substitute of different amino acids in order to synthesize 1,3,4-oxadiazole to combine their pharmacological and biological effects. This experiment facilitates the synthesis of compounds with the assumption that incorporation of amino acids with oxadiazole scaffold will give new compounds that may also called as unnatural amino acids.

"Foldamers" are recognized are the polymers of unnatural amino acids (amino acids with unnatural side chains) and their polymers that contain amino acids. They have uses in medicine, materials, and general healthcare and are created to act on specific targets.²⁵

Unnatural amino acids are crucial for the design and manufacturing of pharmacologically active drugs.^{26,27}



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Biological Importance of Unnatural Amino Acid

May be use in Drug Development Process, UAA's are used to increase the physicochemical as well as pharmacodynamic properties of the drug.²⁸

Unnatural amino acids are becoming new tool in discovery of drug and research. Because of their diversity in structure and versatile in nature, used as chiral building blocks in of combinatorial libraries.²⁹

They are very advantageous as they offer much better stability, enhanced potency, better oral adsorption, improved tissue distribution, increase biological response selectivity. Thus, its incorporation with some modification could be interesting.³⁰

Because of their intriguing folding properties, unique unnatural amino acids are now in demand and capture the imagination of many synthetic chemists in the pharmaceutical industry. The current communication is having an objective to present the designing and synthesis of Unnatural amino acids. The goal is to provide a reader a brief overview of types of synthesis while revealing a little-known area of unnatural amino acids.

Since DPPH is a persistent free radical, it has frequently been used to assess the antioxidants' capacity to scavenge free radicals. As DPPH forms a non-radical state, the approach relies on reducing DPPH in a methanolic solution in the presence of antioxidants that donate hydrogen. The outcomes are, purple to yellow color change that can be observed with a spectrometer at 517 nm, purple color lost is observed.

MATERIALS AND METHODS

Experimental

The solvents employed in the processes were first tried to distil, and all of the compound(s) utilized in the investigation were of Laboratory Grade (LR). The open capillary method was used to calculate the physical data, including melting points. On silica gel TLC plates, the homogeneity of produced substances was evaluated. All compounds were subjected to Thin Layer Chromatography (TLC), which was periodically recorded and discovered to differ from the starting substance. The mechanistic technique was used to synthesis all the compounds in accordance with the earlier scheme design (Figure 1), and they were all examined for *in vitro* free radical scavenging activity using DPPH (1,1-diphenyl-2-picrylhydrazide). For the reaction, a domestic microwave oven (IFB) was employed. Compounds' maximum concentrations were measured using an Elico SL210 UV spectrophotometer. Through, KBr disc approach, IR spectra were recorded using a Thermo-Nicolet IR 200 spectrophotometer. The ¹H-NMR spectra of derivatives were recorded by using a 400 MHz Bruker Advance II NMR Spectrometer.

Synthetic procedure

Synthesis of 2-amino-5-aryl-1,3,4-oxadiazole (1): A blend of semi carbazide (0.01 mol), nicotinic acid (0.01 mol) and con. sulfuric acid (10 drops) was refluxed till the compound formed by checking the TLC time to time. Once the compound formed it was transferred onto the crushed ice. The separated solid was filtered, done water washing and recrystallized with suitable solvent to get the product.^{31,32}

Synthesis of derivatives (1A to 1E): All the compounds from 1A to 1E were synthesized by two methods for getting and comparing yield. Form compounds A-E different amino acids were used, shown in Table 1.³³

Method A (Conventional Method): The combination of compound (1) (0.01 mol) and amino acid (1Aa to 1Ae) (0.01 mol) in 50 mL water stirred and subjected under reflux till compound formed by checking the TLC time to time. When the compound supposed to be formed the reaction was discontinued to heat more. Remained water in the reaction was evaporated by distillation with toluene and the residue was triturated with acetone until it solidified. Filtered and recrystallized with suitable solvent to get the compound.

Method B (Microwave method): The combination of synthesized compound (1) (0.01 mol) and amino acid (1Aa to 1Ae) (0.01 mol) in 25 mL water in a 100 mL open Erlenmeyer flask and irradiated carefully in domestic microwave with power 500 W for 5 min (5 X 60 sec) till the compound formed by checking the TLC after every 60 sec. Remained water was evaporated by distillation with toluene and the residue was triturated with acetone until it solidified. Filtered and recrystallized with suitable solvent to get the compound.

2-amino-5-aryl-1,3,4-oxadiazole (1): Mol. Formula: C₇H₆N₄O, M. Wt.: 162.15, yield: 9.1 g (Method B), M.P: 150-155. λ_{max} (methanol): 222 nm; IR (KBr) cm⁻¹: 3309 (CH- aromatic in pyridine), 1551(C=C and C=N ring in pyridine), 706 (C-H(out of plane in pyridine), 1298 (C-C Str), 3383 (N-H Str), 3368 (N-N Str), 1648 (C=N Str), 1592 (C-O Str), ¹H NMR: δ 1.0-4.1 (s 2H aromatic C-NH), 7.97-7.75 (s 1H CH), 8.55-8.59 (m 2H N-CH).

Compound 1A (S-isoleucine): Mol. Formula: C₁₃H₁₇N₅O₂, M. Wt.: 275.31, yield: 2.4 g (Method B), M.P: 180-185. λ_{max} (methanol): 298 nm; IR (KBr) cm⁻¹: 2962 (CH-aromatic in pyridine), 1562 (C=C and C=N- Str ring in pyridine), 706 (C-H Str out of plane in pyridine), 2538 and 1503 (Str O-H and C=O(COOH)), 3372 (N-H Str), 2877 (Str C-H in CH₃), 1417 (C-H in CH₂), 1596 (C-N Str), 1134 (C-C Str), 1108 (CHCOOH, C₂H₅ str), 1596 (N-N Str), ¹H NMR: δ 2.54-3.99 (d 2H -CHCOOH), 0.82-1.94 (m 9H C₄H₉), 7.30 (s 1H -NH), 7.85-9.00 (s 4H pyridine).

Compound 1B (S-alanine): Mol. Formula: C₁₀H₁₁N₅O₂, M. Wt.: 233.23, yield: 2.3 g (Method B), M.P: 185-190. λ_{max} (methanol): 242 nm; IR (KBr) cm⁻¹: 3074 (Str CH-aromatic in pyridine), 1594

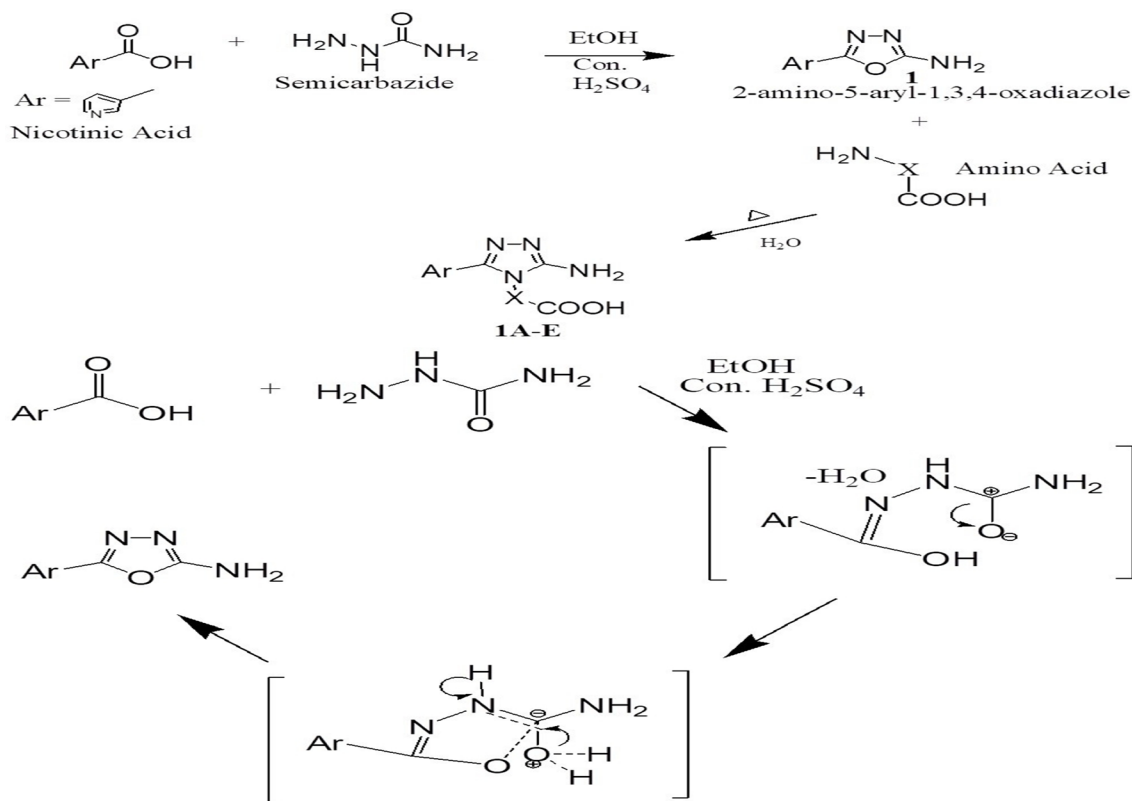


Figure 1: Possible mechanism and Synthesis of 1,3,4-oxadiazole derivative and incorporation of amino acid.

Table 1: Various amino acids fused derivatives.

Compound	Amino acid Used
1A	S-isoleucine
1B	S-alanine
1C	S-tryptophane
1D	2-aminoacetic acid
1E	3-amino propanoic acid

(C=C and C=N Str ring in pyridine), 706 (C-H Str out of plane in pyridine), 2806 and 1622 (Str O-H and C=O(COOH)), 2985 (Str N-H), 2806 (Str C-H in CH₃), 1458 (Str C-H in CH₂), 855 (C-N Str), 1309 (Str C-C in CH₂COOH), 1551 (Str N-N), ¹H NMR: δ 1.91-2.50 (d 2H -CHCOOH), 3.40-3.77 (s 3H -CH₃), 7.35 (s 1H -NH), 7.86-9.00 (s 4H pyridine).

Compound 1C (S-tryptophane): Mol. Formula: C₁₉H₁₉N₅O₄, M. Wt.: 381.39, yield: 2.2 g (Method B), M.P.: 190-192. λ_{max} (methanol): 239 nm; IR (KBr) cm⁻¹: 3048 (CH- Str aromatic in pyridine), 1458 (C=C and C=N Str ring in pyridine), 743 (C-H Str out of plane in pyridine), 2527 and 1559 (O-H and C=O Str in COOH), 3402 (Str N-H), 2966 (Str C-H), 847 (Str in C-N), 1659 (Str C=N(indole)), 1112 (Str C-C in CH₂COOH), 1585 (Str N-N), ¹H NMR: δ 7.03 (s 1H -NH), 11.13 (s 1H -COOH), 2.51-3.92 (m 3H CH,CH₂), 6.93-7.93 (s 5H Indole), 7.61-9.02 (s 4H pyridine).

Compound 1D (2-aminoacetic acid): Mol. Formula: C₉H₉N₅O₂, M. Wt.: 219.2, yield: 2.8 g (Method B), M.P.: 175-180. λ_{max}

(methanol): 249 nm; IR (KBr) cm⁻¹: 3022 (Str CH aromatic in pyridine), 1439 (Str C=C and C=N ring in pyridine), 687 (Str C-H out of plane in pyridine), 3007 and 1499 (Str O-H and C=O in COOH), 3096 (Str N-H), 2873 (Str C-H in CH₃), 1048 (Str C-N), 1391 (Str C-C in CH₂COOH), 1518 (Str N-N), ¹H NMR: δ 2.50-2.51 (d 3H CHCOOH), 3.58 (s 1H -H), 7.26 (s 1H -NH), 7.26-9.04 (s 4H pyridine).

Compound 1E (3-aminopropanoic acid): Mol. Formula: C₁₃H₁₅N₅O₃, M. Wt.: 289.29, yield: 2.5 g (Method B), M.P.: 180-182. λ_{max} (methanol): 254 nm; IR (KBr) cm⁻¹: 2966 (Str CH aromatic in pyridine), 1555 (Str C=C and C=N ring in pyridine), 706 (Str C-H out of plane in pyridine), 2571 and 1585 (O-H and C=O in COOH), 3379 (Str N-H), 2880 (Str C-H in CH₃), 1417 (C-H in CH), 1383 (Str C-H in CH), 844 (Str C-N), 1339 (Str C-C in CHCOOH), 2929 (Str N-N), ¹H NMR: δ 1.91-2.50 (d 2H -CHCOOH), 3.40-3.77 (s 3H -CH₃), 7.35 (s 1H -NH), 7.86-9.00 (s 4H pyridine).

Free radical scavenging assays: Diphenyl-picrylhydrazyl radical scavenging (DPPH) assay, developed by Liyana-Pathirana and Shahidi in 2005, was used to calculate the impact of standard medication and produced compound(s) on the DPPH radical. 1 mL of a chemical in methanol containing 0.02-0.1 mg of the sample was combined with 1 mL of a solution of 0.135 mM DPPH in methanol. After completely overtaxing the produced solution and leaving it in the dark for 30 min, it was measured at 517 nm using ascorbic acid as a reference.³⁴

RESULTS

Compound 1 was synthesized from conventional method, whereas compounds 1A, 1B, 1C, 1D, 1E were synthesized by two methods Method A and Method B, which gives different yields, comparison of yields was shown in Figure 2. Reaction completion time done by checking the reaction mixture after every 15 min for method A and after 60 sec for method B through TLC analysis and the gap was maintained and found suitable, details are shown in Table 2.

All synthesized compound(s) were subjected to 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, where standard was taken as Ascorbic acid. Solvent used as methanol. Standard DPPH solution was taken as 0.135 mM solution. All sample stock

solutions were prepared 0.1 mg/mL solution. Absorbance of control was taken 0.603. All compounds showed promising assay activity shown in Table 3. Compound 1, 1A and 1B found to be best.

DISCUSSION

In this study synthesis of unnatural amino acids were done and the derivatives were analyzed for their yield as well as for their potential. In living things, amino acids carry out a wide range

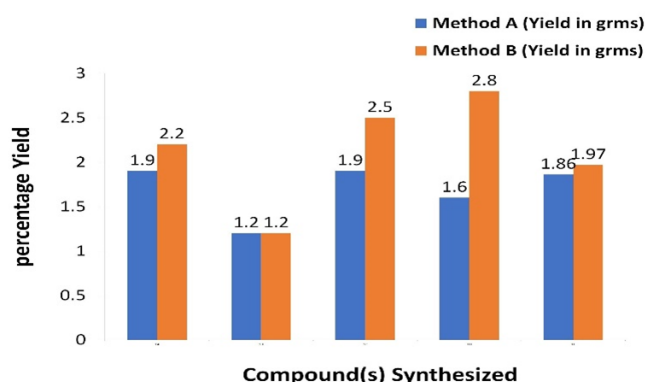


Figure 2: Comparison of yields of compounds from 1A to 1E through Method A and Method B.

Table 2: Reaction completion time.

Compound(s)	Reaction completion time*	
1	45-50 min (reflux)	
	Method A (conventional)	Method B (Microwave)
1Aa	1.50 Hr	500 W (5X60 Sec)
1Ab	1.30 Hr	500 W (5X60 Sec)
1Ac	2.00 Hr	500 W (5X60 Sec)
1Ad	2.00 Hr	500 W (5X60 Sec)
1Ae	1.15 Hr	500 W (5X60 Sec)

Table 3: Showing *in vitro* DPPH assay activity.

Concentrations	0.02	0.04	0.06	0.08	0.1
Ascorbic acid	74.62%	77.94%	81.09%	83.58%	80.76%
Compound 1	54.39%	62.68%	67.49%	78.10%	86.40%
Compound 1Aa	47.76%	54.72%	66.99%	76.45%	84.57%
Compound 1Ab	30.34%	60.86%	78.44%	79.93%	84.24%
Compound 1Ac	18.24%	24.37%	53.39%	79.60%	81.75%
Compound 1Ad	40.29%	58.37%	61.52%	67.82%	75.12%
Compound 1Ae	22.88%	38.14%	45.27%	46.10%	54.39%

of tasks. They function as neurotransmitters, neuromodulators, hormones, cytokines, and antigens, and they have an impact on nearly all-important physiological processes through intra- and intercellular communication through signal transduction by numerous kinds of receptors.^{35,36} Due to their limitations, which include quick photolytic breakdown, low membrane penetration, and fast hydrolytic cleavage, amino acids are typically poor therapeutic candidates.³⁷ For these reasons, a lot of work has gone into figuring out how to substitute amino acids with other structural moieties without breakdown and cleavage, known as "Unnatural amino acids".³⁸ An effective bio-isosteric methodology is one of the potential development methods for these drugs. Amino acids with limited conformation that are not proteinogenic may generate the bioactive molecules.^{35,39}

The present study attempts to synthesize 1,3,4-oxadiazole and its various amino acid derivatives as unnatural amino acids and tested for *in vitro* free radical scavenging activity by using DPPH assay method. Total six new compounds were prepared, compounds 1A to 1E were prepared by two methods, Method A and Method B. Method A was the conventional method which was found to be time taking whereas Method B was Microwave method, which was quick and high yield was found.

CONCLUSION

Modern technologies like microwave-assisted synthesis are suitable in addition to traditional chemical synthesis methods. The above mention methods guarantee the production of unnatural amino acids with an improved yield. Structure of all compound(s) was characterized by IR, NMR and UV analysis. The compounds were evaluated for the activity by known standard method against standard compound. Without a doubt, this is a novel synthetic method for constructing unnatural amino acids using oxadiazoles, which will continue to open up new possibilities for peptidomimetic and, consequently, drug design. Compounds will further test for antimicrobial and hepatoprotective activity potentials in future.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

UAA's: Unnatural Amino Acids; **UV:** Ultraviolet; **IR:** Infra-Red; **NMR:** Nuclear Magnetic Resonance; **DPPH:** 2,2-diphenyl-1-picrylhyrazyl; **nm:** Nanometer; **TLC:** Thin Layer Chromatography; **KBr:** Potassium Bromide; **MHz:** Megahertz; **DMSO:** Dimethyl-sulfoxide; **mL:** Mili Liter; **mM:** Mili Molar; **Abs:** Absorption; **Str:** Stretching.

SUMMARY

In this study, the synthesis of 1,3,4-oxadiazole compounds was attempted using nicotinic acid, followed by the formation of amino acid derivatives. Amino acids are vital in biological systems, with only 20 naturally occurring variants. However, even slight modifications to these amino acids can result in a wide array of chemical structures and functions. Unnatural amino acids hold promise for the development of new drugs, hormones, and enzymes. The microwave method, also known as "green synthesis," yielded the highest results. The amino acids integrated with 1,3,4-oxadiazole were considered unnatural. This study highlights the growing interest in the synthesis of unnatural amino acids and offers a straightforward method for preparing these derivatives and related compounds. The findings could be instrumental in the development of novel therapeutic drugs in the future.

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