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AN INTRODUCTION TO THE SYNTHETIC METHOD AND PHARAMCOLOGICAL ACITVITY OF UNUSUAL AMINO ACIDS: A REVIEW

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ABSTRACT

There have been various novel approaches for the development of unusual amino acids because of having the same groups as that of natural amino acids. The structural modification in the nucleus of certain heterocyclic compounds have been done for various opportunities, hence being non peptidogenic in nature they offer certain biological activities. The present article has discussed the importance of unusual amino acids, some natural existing unusual amino acids, and various methods for synthesizing the unusual amino acids.

KEYWORDS:- Unusual amino acids, non-peptidogenic, Synthetic methods.

Unusual amino acids

Amino acids

These are the compound containing carboxylic acid and amine moiety which are biologically important. These also acts as a building block for protein and play a very significant role physiological and metabolic role in living organism. There are 20 amino acid which are known as essential/standard amino acid.[1]

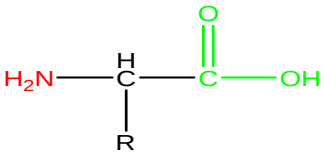


Fig. 1: An amino acid.

Role of amino acids

- Useful in the synthesis of proteins.
- Use in the synthesis of precursors in formation of molecules of secondary metabolism which participate in cell signaling, homeostatis regulation, gene expression, hormones synthesis and phosphorylation of protein.
- It also participate in certain physiological processes like atrophic conditions, cancer, skeletal function and sarcopenia.[2]
- It also provides raw material for different processes of cell like energy generation cell-wall synthesis, nitrogen metabolism, antibiotic production, intracellular communication.[3]

Classification of amino acids

Amino acids are divided into groups as acidic, basic and neutral amino acids. "Essential amino acids" are the types of amino acids that are not synthesized in the body and it is necessary to take these amino acids in diet.

These are:- Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Threonine, Tryptophan, Valine.

While there are some amino acids that are synthesized in the body and it is not necessary to take them in diet called "Non-essential amino acids".

The examples are:- Alanine, Asparagine, Aspartate, Cysteine, Glutamate, Glutamine, Glycine, Proline, Serine, Tyrosine, Arginine, Histidine.[4]

Table 1: List of amino acids with symbol.[5]

S. no.	Amino acid	Abbreviation
1	Alanine	Ala
2	Arginine	Arg
3	Asparagine	Asn
4	Aspartic acid	Asp
5	Cysteine	Cys
6	Glutamine	Gln
7	Glutamic acid	Glu
8	Glycine	Gly
9	Histidine	His
10	Isoleucine	Ile
11	Leucine	Leu
12	Lysine	Lys
13	Methionine	Met
14	Phenylalanine	Phe
15	Proline	Pro
16	Serine	Ser

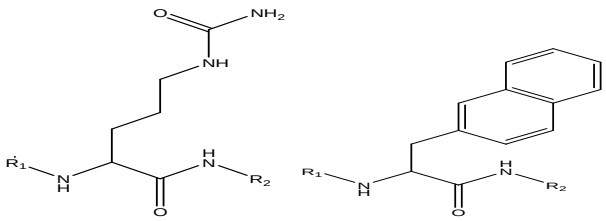
17	Threonine	Thr
18	Tryptophan	Trp
19	Tyrosine	Try
20	Valine	Val

Introduction: Unusual amino acid

Amino acids have always been fundamentally important in many areas of chemistry. Naturally, only 20 amino acids are utilized but slight modification of these amino acid has done a wonderful diversity on the basis of chemical structure and function. The number of non-proteogenic unusual amino acid is speedily increasing and the chances of drug, hormones, new enzymes derived from these are increasing rapidly.[6]

Biological importance of unusual amino acid

1. In the development of drug, unusual amino acids are used to increase the chemical, physical as well as pharmaceutical properties of the lead[7] For e.g.,



Citrulline Naphtylalanine

Fig. 2: Some unusual amino acids.

2. Unusual amino acids are becoming vital tool in discovery of drug and research. Because of their diversity in structure and versatile nature, the have been widely used as chiral building blocks and molecular scaffolds in construction of combinatorial libraries.[8]

3. These have found an increase in advantage as they offer much better stability, enhanced potency, better oral adsorption, improved tissue distribution, increase biological response selectivity. Thus, incorporation and modification has been interesting.

e.g. a cyclic tetrapeptid synthesized having some same biological activity as that of somatostatine, an important endogenous neurotransmitter.[9]

Naturally occurring unusual amino acids

Certains unusual amino acids are found to occur in the living system and known to perform specific functions:

- 4-hydroxyproline: Proline derivative which is formed by hydroxylation of 4th carbon, occurs in plant cell wall protein known as collagen which is an fibrous protein of connective tissues.
- 5-hydroxylysine: Lysine derivative and part of collagen protein and plant cell wall.
- Y-carboxyglutamate: Formed by the addition of carboxylate at y-carbon of glaumate. Occurs in protein involved in blood clotting such as prothrombin.
- 6-N-Methyllysine: Part of muscle protein, myosine that is involved in muscle contraction. It is formed by the methylation of lysine.
- Desmosine: Made by four lysine residues linked to central ring structure, occurs in fibrous protein elastin.

The others ones which exist are selenocysteine, pyroglutamic acid, phosphorylated amino acids, amino adipic acid.[10]

Methods of synthesizing variuous amino acids

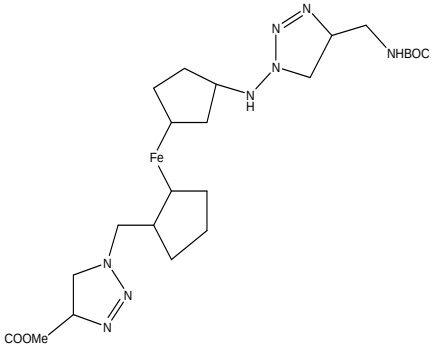
The synthesis of allows to generate novel types of peptides which are catalysts or carriers of biologically active residues with certain pharmacological properties. These method are via:-

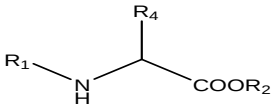
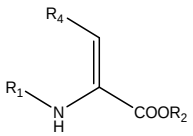
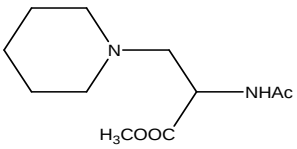
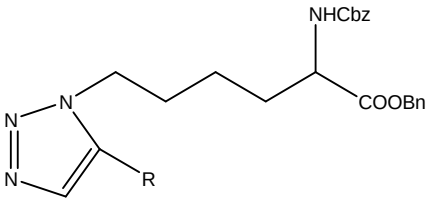
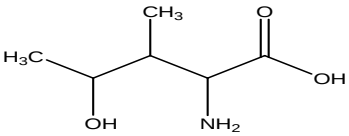
- Ezymatic resolution of racemates
- Use of chiral auxiliaries
- Introduction into biologically active peptides[11]

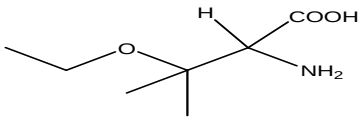
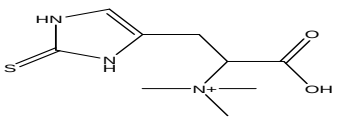
Table 2: Unusual amino acids.

S. no.	Title	Compound /Structure name	Abstract	Author & year
1	Synthesis, characterization and antibacterial property of novel triazole derivatives as unusual amino acids.	4- (acetic acid)-3(3-pyridyl)-5-thione-1,2,4-triazole, 4-(propionic acid)-3(3-pyridyl)-5-thione-1,2,4- triazole 4-(butanoic acid)-3(3-pyridyl)-5-thione-1,2,4-triazole	Excellent and broad bio-spectrum of triazole has lead to an attractive scope for the synthetic chemists for the introduction of structural modification in the nucleus so as to make access to new approaches and opportunities. A new technique	Joshi h[12] et al 2019

			for the incorporation of amino acids in the heterocyclic nucleus has been developed and hence the term to the resultant compounds can be given as unusual amino acid because of having the groups similar to amino acids but being nonpeptidogenic in nature. The name of the final compounds as unusual amino acids are 4-(acetic acid)-3(3-pyridyl)-5-thione-1,2,4-triazole, 4-(propionic acid)-3(3-pyridyl)-5-thione-1,2,4-triazole and 4-(butanoic acid)-3(3-pyridyl)-5-thione-1,2,4-triazole. The reaction and purity of the compounds is checked by tlc and melting point. The characterization of the compounds is performed by 1d-nmr and ir. The antibacterial activity is done on two strains of bacteria gram negative and gram positive.	

2	Click chemistry route to the synthesis of unusual amino acids, peptides, triazole-fused heterocyclic and pseudo disaccharides.	 1,1`-disubstituted ferrocenyl amino acid derivatives.	Conjugation of different molecule species using cu(i)-catalysed click reaction between azides and terminal alkynes. Method developed for synthesis of peptides and amino acid conjugated with carbohydrates ,thymidine, ferrocene.	S. Chandrasekaran[13] et al (2017)
3	N-substituted unusual amino acids as corrosion inhibitors:-n-acyl derivatives of unnatural amino acids with double bonds.	Och3c6h3ch=c(nh-coc6h5)-cooh	Corrosion inhibition efficiency of unusual phenyl alanine derivative were investigated in neutral aqueous solution. Influence of substituent in phenyl ring as well as of double bond was elucidated and explained. Effect of electrophilic or nucleophlic group in phenyl ring was demonstrate by efficacy and roughness parameter.	J.telegdi[14]et al (2016)
4	Scalable synthesis of the unusual amino acid segment of marine anti-inflammatory peptide-solomonamide a.	4-amino(2'amino-4'-hydroxy phenyl)-3,5-dihydroxy-2-methyl-6-oxo hexanoic acid.	Most abundantly available hexose sugar ,d-glucose has been converted to protect form, the unusual amino acid present in marine natural product solonamide a.	N kavitha[15] et al (2015)

5	Amino acid scaffolds bearing unnatural side chains:- an old idea generates new and versatile tool in life sciences.	 Side chain  Hydrogenation	Recent and innovative synthetic routes for the preparation of unusual amino acid had been discussed: Side chain modification Glycine equivalent Multicomponent reaction with imines.	A stevenazzi[16] et al (2015)
6	Diversity-oriented approach to unusual amino acid derivatives and heterocycles via methyl 2-acetamidoacrylate and its congeners.		Diverse approaches has been used to synthesize unusual amino acids like diel-alder reaction, heck coupling , suzuki –miyaura cross coupling , conjugate coupling, radical addition , cyclisation reaction.	S. Kotha[17] (2014)
7	(r)-alpha- amino adipic acid: a versatile precursor for the synthesis of d-amino acid.		A route for the synthesis of c-5-alkenyl and c-6-alkylidiene derivatives of (r)-pipecolic acid was described using (r)-alpha-amino adipic acid as pure starting material.	A. Sadiq[18] et al (2013)
8	Anti-hyperglycemic effect of an unusual amino acid(4-hydroxy isoleucine) in c57bl/ksj-db/db mice.	 4-hydroxyisoleucine	An unusual amnio acid isolated from trigonella foenum-g. Raecum seeds, in a well characterized model of type ii diabetes i.e.,	A.b. Singh[19] et al (2010)

			db/db mice. 4-hydroxyisoleucine, when given orally to these mice at 500mg/kg dose level, declined their elevated blood glucose, plasma insulin, triglyceride, total cholesterol, ldl-cholesterol level, indicating that 4-hydroxyisoleucine exhibit significant anti-diabetic potential.	
9	Unusual amino acid derivatives from the mushroom pleurocybella porrigen.		3 new amino acids derivatives were isolated from mushroom pleurocybella porrigens, structure determined by interpretation of spectroscopic data.	T.kawaguchi[20] et al
10	The unusual amino acid l-ergothioneine is a physiologic cytoprotectant.		Cells of et transporter were depleted in mammalian tissue. Cell lacking ett were susceptible to oxidative stress causing increase mitochondrial, dna damage, protein oxidation and lipid peroxidation.	B d paul[21] et al (2009)
11	Lc enantiomeric separation of unusual amino acid using cyclodextrin based stationary phases.	2,6 –dinitrophenyl-4-trifluoromethyl phenyl.	Mobile phase, ph effects, flow rates were optimized for each separation, limited to aqueous mobile	J w remsburg[22] (2007)

			phase. Highest selectivity came from alpha acetylated beta,2,6-dinitrophenyl-4-trifluoromethyl phenyl derivitised beta-cyclodextrin stationary phases. Amino acid containing 1,2,3,4 tetra hydroisoquinoline carboxylic acid structure showed great compatibility..	

CONCLUSION

The present study has provided the idea regarding the nature, introduction, chemistry, various synthetic method and literature review regarding unusual amino acids. Review also gives a basic idea that many of the unusual amino acids have been synthesized in the past for different biological activity such as antibacterial, anti inflammatory, physiologic cytoprotectant etc.

Hence the present review gives an overview of various methods which can be helpful for the chemist for further novel approaches on unusual amino acids for better medicinal compounds to increase the efficacy and safety of compound.

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