Available online on 15.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Unnatural Amino Acids (UAA'S): A Trendy Scaffold for Pharmaceutical Research

AS Bisht* & Divya Juyal

Himalayan Institute of Pharmacy & Research, Rajawala, dehradun Uttaralhnad, India-248007

ABSTRACT

Unnatural amino acids synthesis is a region of research that has gained a lot of interest in modern years. The accessibility of different synthetic routes for new unnatural amino acid derivatives and related compounds will be a critical point in the designning of novel molecules that impersonate the conformation of the natural, active peptides. These molecules (peptidomimetics) are specially designed to show the high receptor affinity and selectivity with enhanced bioavailability and metabolic stability of the drug molecule. Thus, this review focuses on detailed synthetic methods and analogues leading to synthesize variety of unnatural amino acids including various schemes that includes enantioselective synthesis and microwave-assisted synthesis also.

Keywords: Unnatural amino acids, peptidomimetics, enantioselective synthesis

Article Info: Received 07 June 2019; Review Completed 16 July 2019; Accepted 20 July 2019; Available online 15 August 2019

Cite this article as:

Bisht AS, Juyal D, Unnatural Amino Acids (UAA'S): A Trendy Scaffold for Pharmaceutical Research, Journal of Drug Delivery and Therapeutics. 2019; 9(4-s):601-609 **http://dx.doi.org/10.22270/jddt.v9i4-s.3210**

***Address for Correspondence:**

AS Bisht, Himalayan Institute of Pharmacy & Research, Rajawala, dehradun Uttaralhnad, India-248007

INTRODUCTION:

Development of new methods for the synthesis is currently attracting the organic chemists due to the discovery of many chemical entities with their varied biological activities. As it is already known, amino acids are the important biological molecules. They are the building blocks of proteins, and the twenty proteogenic L-amino acids (exception of glycine) are ubiquitous to all living organisms on earth.[1]

Unnatural amino acid (D-amino acids or amino acids with non-natural side chains) and their polymers that contain β- and γ-amino acids are known as "foldamers." These foldamers form long-lasting, predictable structures that are very stable and resistant to proteolytic degradation. They can be designed to interact with specific targets and have applications in medicine, materials and general healthcare.[2]

Unnatural amino acids play an important role in the design and synthesis of pharmacologically relevant molecules, peptidomimetics and enzyme inhibitors. [3,4] Aldehydes which are obtained from various natural amino acids leads to form a class of chiral synthons i,e peptides, that are useful in the synthesis of optically active biologically active compounds particularly in the synthesis of unnatural amino acids.[5]

Generally, Peptides act as carriers in a variety of metabolic functions in living organisms. They usually act as hormones, neurotransmitters, neuromodulators, paracrine factors, cytokines & antigens and mostly influences all fundamental physiological processes through inter/intra-cellular communication and/or by signal transduction mechanism through various types of receptor(s) [6,7]

Limitation(s) of natural peptides as drug candidates: [8]

Peptides are poor drug candidates due to their following limitations:

a) Characterized by fast hydrolytic cleavage

b) Poor penetration of membranes.

c) Rapid photolytic degradation.

d) Conformational instability.

e) Unfavorable pharmacokinetics

For above reasons many efforts have been done to find various ways to replace biologically active parts of peptides with non-peptide structures, which are termed as peptidomimetics. [9] One of the various strategies in the research for expansion of peptidomimetic agents is to incorporate unnatural amino acid and their derivatives, as they are conformationally restricted and non-proteinogenic amino acids in nature, having a potential to elucidate the bioactive conformation of peptides. It must be taken into consideration that there are only some amino acid analogs which facilitate restricted conformational flexibility without

much changing the stereo-electronic properties of the peptide [2].

Now days, designing and synthesis of novel unnatural amino acids in the field of pharmaceuticals is in demand and attract the imagination of many synthetic chemists because of their interesting folding properties. Thus, the present communication aims to present different ideas and approaches which deals with synthesis of unnatural amino acid. Our basic aim is to provide the reader a brief picture of work done till date in this exciting and not much known field of synthetic chemistry and pharmaceuticals.

Table1: summary of various synthetic methods and procedures in chronological order of their development.

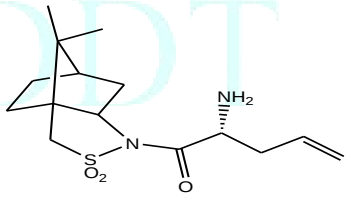
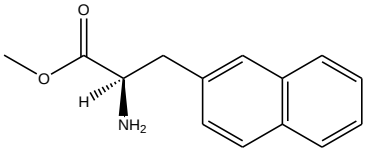
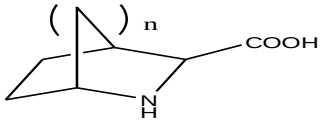
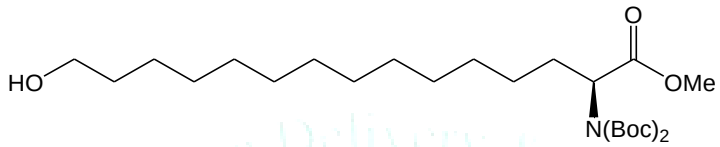
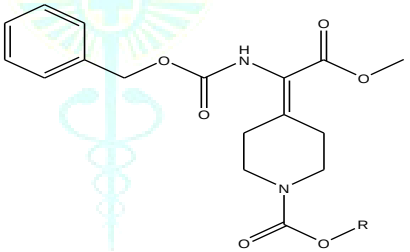
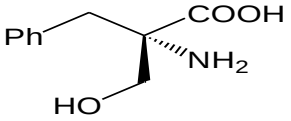
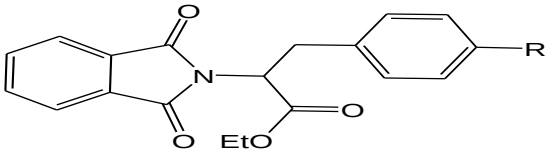
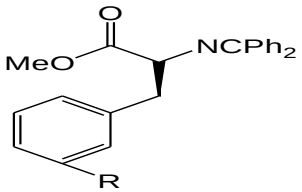
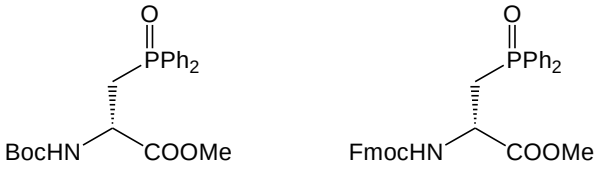
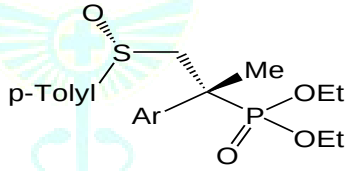
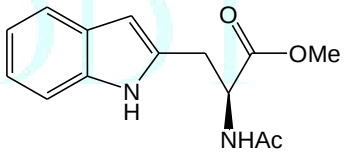
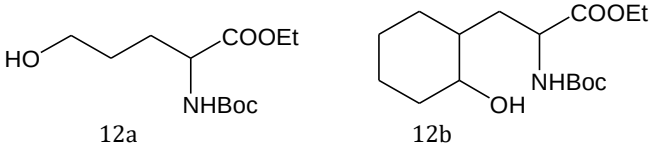
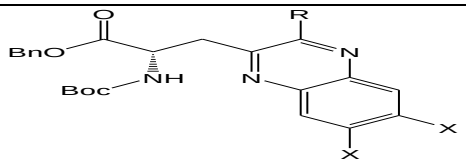
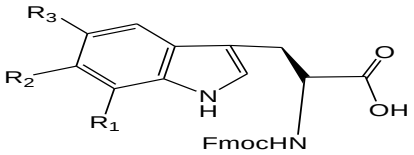
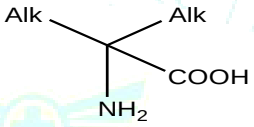
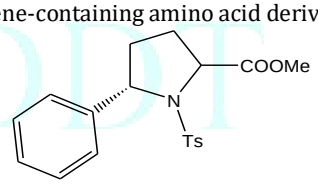
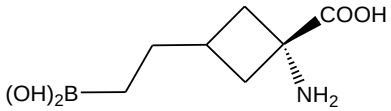
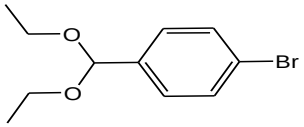
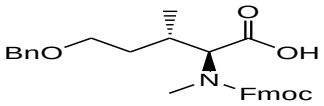
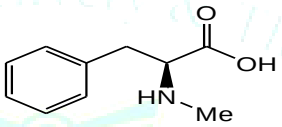
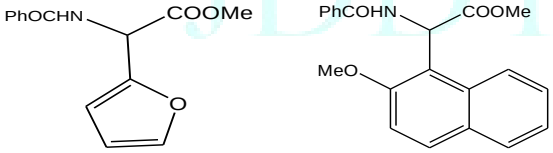
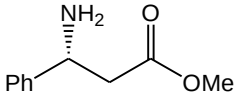
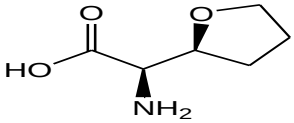
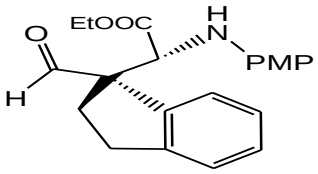
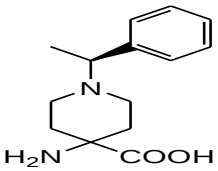
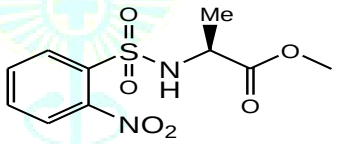
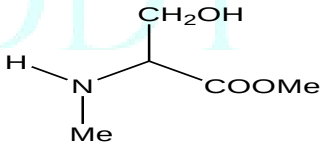
Year	Auther(s)	Description	Ref
1973	Eggelte TA *et al*.	Research showed reaction(s) of furan and maleic acid was carried out in several solvents. The *endo*-adduct was isolated and the structure established by its spectral properties and their conversion into compounds. The adducts of furan with fumaric acid, diethyl fumarate and diethyl maleate were reported.	[10]
1989	Bose AK *et al*.	Here morpholines were synthesized by an efficient molecular rearrangement of appropriate derivatives of α-hydroxy-β-lactams included optically active β-lactams prepared from homochiral Schiff bases.	[11]
1993	Varma RS *et al*.	The research focused on simple high-yielded method(s) for deprotection of acetylated phenols and alcohols which occurs under mild conditions on an alumina surface using microwave irradiation**.** Here, authors' reported a simplistic and trouble-free procedure to affect the deacetylation of a variety of such esters on neutral alumina under solvent-free reactions conditions which could be further accelerated safely by using an unmodified common household microwave oven.	[12]
1994	Crawford LA *et al*.	This communication discussed the synthesis of λ-aminobutyric acid in response to treatments reducing cytosolic *pH*. The proposal investigates by using isolated asparagus (*Asparagus sprengeri Regel*) mesophyll cells. The cell acidification was promoted by using hypoxia, H+/L-glutamic acid symport and addition of butyrate or other weak acids.	[13]
1994	Coles MP *et al.*	This communication deals with reaction of homochiral norbornene monomers which were derived from amino acids that undergo ring-opening metathesis polymerisation with [Mo(=CHCMe$_2$Ph)(=NC$_6$H$_3$Pri2-2,6)(OBut), to give homochiral polymers with narrow molecular mass distributions. Here, they described the synthesis of homochiral polymers derived from norbornenes functionalised with optically pure alanine ester residues.	[14]
1994	Ortiz AD *et al*.	They showed the reaction in microwave irradiation ketene acetals that undergo 1,3-dipolar and hetero- Diels-Alder cycloadditions within 5-12 min to give excellent yields of easily purified heterocyclic products.	[15]
1996	Hanessian *et al.*	Researcher(s) developed an enantiomerically selective synthesis of allyl containing amino acids (**1**). The starting sultam derivatives of *O*-benzyl glyoxylic acid oximes were reacted with allyl bromides in the presence of zinc in aqueous ammonium chloride. After selective cleavage of the N-O bond in the presence of Mo(CO)$_6$, the sultam auxiliary was removed by treatment with LiOH in THF/H$_2$O solution to afford the corresponding free allylglycine derivatives without any loss of stereochemical purity.  Fig. **1**	[16]
1996	Fuji *et al.*	Scientists performed a diastereoselective alkylation of the (*S*)-glycine equivalent**,** which includes axially chiral bi-naphthol (**2**) as an auxiliary, with several electrophiles yielding (*R)*-α-amino acid derivatives.  Fig. **2**	[17]
1996	Andersson *et al.*	Study described the preparation of the unnatural, bicyclic proline derivatives (3**a**) and (3**b**), along with their utility as chiral ligands in the copper-catalyzed enantioselective allylic oxidation of cyclohexene with *tert*-butyl perbenzoate.  n= 3a=1; 3b =2	[18]

		Fig. **3**	
1997	Ondrus V and Fisera L	Research proposed new routes for the synthesis of various novel chiral maleimides. The oxabicyclic anhydride, *exo*-Diels-Alder adduct of furan and maleic anhydride was used as a vehicle, which in turn reacted with hydrochlorides of amino acids in the presence of Et_3N with the release of furan to give the requisite novel chiral imides in good to moderate yields. The stereoselectivity of 1,3-dipolar cycloaddition of nitrile oxides with prepared chiral imides were also investigated.	**[19]**
1998	Sandhu S *et al.*	This communication tried to focus on how maleic and phthalic anhydride condensed with amino acids and alkylamines to undergo microwave irradiation technique. The reaction afforded N-substituted maleimides and phthalimides in excellent yields.	**[20]**
1998	Lectka T *et al.*	This communication reported, an operationally convenient and efficient, catalytic, enantioselective iminoene reaction of R-imino ester with various alkenes which were catalyzed by Lewis acid complex and show that the reaction could be a useful new pathway to get R-amino acid derivatives. They initiated the study with the reaction between R-imino ester and R-methylstyrene.	**[21]**
1998	Kokotos *et al.*	Chemist prepared enantiopure lipophilic α-amino (**4**) acids and also their other functionalized derivatives and some bis α-amino acids. The key intermediate was protected glutamic acid aldehyde which was utilized in a Wittig reaction with trityloxy alkylidene triphenylphosphoranes. After hydrogenation of the obtained β-hydroxy-α-amino acid was used as starting material in the synthesis of functionalized α-amino acids.  Fig. **4**	[22]
2001	Shieh *et al*	Study discussed a facile synthetic route to (*R*)-4 piperidinylglycine. It offers a promising alternative to the previously published 8-step synthesis for the same compound. The Cbzenamides **(5a)** and **(5b)** were prepared from commercially available *N*-Cbz-phosphonoglycine trimethyl ester and *N*Boc-4-piperidone using the Schmidt protocol.  **5a**=R=*t*-Bu; **5b**=R=*i*-Pr Fig. **5**	[23]
2001	Davis *et al.*	Scientest described an asymmetric synthesis which was reported with α-substituted serines (**6**) *via* the regioselective hydrogenolysis of 2-benzyloxyaziridine 2- carboxylate. The starting (2*S*, 3*S*) *N*-sulfinylaziridine carboxylate was treated with TFA to remove the *N* sulfinyl group without ring-opening.  Fig. **6**	[24]
2001	Li and Huang	Developed an interesting method for the synthesis of amino acid derivatives (**7a,7b,7c**) *via* carbon-carbon bond formation in water and air atmosphere. Rhodium-catalyzed (catalyst: $Rh_2(COD)_2Cl_2$) conjugated addition of ethyl alpha-phthalimido aminoacylate with various organotin reagents proceeded smoothly in water under ambient conditions and concurrent sonication to give the desired compounds.  R= 7a=Cl, 7b=Me, 7c= *t*-Bu Fig. **7**	[25]
2001	Park *et al.*	Described chiral auxiliary mediated stereoselective alkylation reaction of *N*'-[(*S*)-1'-phenylethyl]-*N*-(diphenylmethylene) glycinamide , using a phase transfer catalyst (PTC). **(8a,8b and 8c)**	[26]

		 R=8a=Cl; 8b=I; 8c= CH_2 Fig.8	
2001	Gilbertson *et al.*	Discussed incorporation of phosphine containing amino acids into rigid secondary structures such as α-helixes and ß-strands, that allows the generation of large libraries of bis- and monophosphine ligands for screening in asymmetric catalytic reactions. As because these ligands are produced by a solid phase approach, a wide variety of ligands with different structures and chiral environments can be made. **(9a,9b)**  Fig.9	**[27]**
2001	Ondrus V *et al.*	Showed a new route for the synthesis of novel chiral and achiral maleimides. A cheap and readily available *exo*-Diels-Alder adduct of furan and maleic anhydride reacted with amino acids in water that undergo classical heating or microwave irradiation with the release of furan to give maleimide products in good to excellent yields.	**[28]**
2001	Davis *et al.*	Reported the first example of asymmetric synthesis of α-alkyl-α-amino(arylmethyl)phosphonate derivatives (**10**) from enantiopure ketosulfinimines.  Fig.10	**[29]**
2002	Carlier *et al.*	Reported a catalytic asymmetric synthesis of Trp regioisomers (11) where the alanine unit is attached, not to C-3 of indole, but to C-2, C-4, C-5, C-6, or C-7. The most convenient catalyst was Burk DuPhos system, with the EtDuPhos ligand affording the greatest enantiomeric selectivity. The reactions were conducted in methanol, ethyl acetate, dichloromethane and acetone, all these solvents providing suitable reaction conditions.  Fig.11	[30]
2002	Kokotos G *et al.*	Described an efficient route for the synthesis of enantiopure unnatural α-amino acids and 2-amino alcohols. The synthesis was based on the Wittig-type olefination of 3-benzyloxy-2-(tertbutoxycarbonylamino) propanal with various ylides.	[31]
2003	Gallos *et al.*	Reported the synthesis of racemic nonproteinogenic alpha amino acids. Hetero Diels-Alder addition of a starting compound ethyl 2-nitrosoacrylate to electron rich alkenes such as enol esters, enamines and allylsilanes yields oxazines. The stereochemistry of the reaction is controlled by epimerization of the thermodynamically less stable isomer to the more stable one. (12a, 12b)  12a 12b Fig.12	[32]
2003	Wasserman *et al.*	Successfully showed the preparation of heterocyclic non-proteinogenic derivatives of α-amino acids (13a & 13b) by reacting alpha,beta-diketo nitrile with diamines and related dinucleophiles. alpha,beta -Diketo nitrile was prepared from mono Boc-protected amino dicarboxylic acid and phosphoranylidenacetonitrile, followed by ozonolysis of the obtained product at low temperature in CH_2Cl_2/MeOH.	[33]

		 13a R=OH; X=H 13b R=CN; X=Cl Fig.13	
2003	Gellerman *et al.*	Published a rapid synthesis of ring A-disubstituted, Fmoc and Boc protected *L*-tryptophan derivatives (**14a-d**)The synthesis starts from the appropriate 2,4- or 2,3 disubstituted phenylhydrazines and optically active *N,N*-diprotected *L*-glutamic a-aldehyde and it utilizes Fischer-indole synthesis as a key step affording the mixture of mono- Boc/di-Boc tryptophan esters.  **14a**=R1 = Me, R2 = H, R3 = Me **14b=** R1 = OMe, R2 = H, R3 = Me **14c=** R1 = H, R2 = Me, R3= Me **14d=** R1 = Et, R2 = H, R3 = Ph Fig.14	[34]
2003	Soloshonok *et al.*	Describe synthesis of sterically constrained α,α-symmetrically disubstituted α-amino acids. Showed interesting approach of dialkylating the Ni (II) complex of a glycine derivative resulted in symmetrical-α,α-amino acids. **15 (a-h)**  **Alk** = **a :** CH2-CH=CH2 **e :**(CH2)2CH3 **b:** CH2-C6H5 **f:** (CH2)3CH3 **c:** *trans* CH2-CH=CH-C6H5 **g :** CH3 **d:** CH2-CH3 **h :** (CH2)4CH3 Fig.15	**[35]**
2003	Rutjes *et al.*	Described an interesting approach to the synthesis of proline derivatives, by Pd- catalyzed *5-endo-dig* cyclization of lipophilic acetylene-containing amino acid derivatives. **16**  Fig.16	**[36], [37]**
2003 and 2004	Kabalka and coworkers	Successfully snthesized boronated novel 1-aminocyclobutane-1-carboxylic acid derivatives (ACBC). The skeleton was constructed by a [2+2] cycloaddition reaction. All presented boron-containing unnatural amino acids are currently being evaluated as potential agents for boron neutron capture therapy. **17**  Fig.17	**[38], [39]**
2004	Chang *et al.*	A novel class of pseudoaromatic amino acids, namely tetrahydroindazol-3-yl alanine and benzisoxazole-3- ylalanine derivatives, was reportedSequential acylation of cyclic 1,3-diketones or cyclic enamines by side chain carboxyl functionalities of appropriately protected aspartic or glutamic acids followed by regioselective cycloaddition with dinucleophiles such as hydrazine, *N*-benzylhydrazine and hydroxylamine, yielded various derivatives . These novel homochiral amino acids, offer unique opportunities, not only as structural surrogates of tryptophan, but also as novel amino acid building blocks for the design of molecular probes.	[40]
		The novel pyrrolidine-sulfonamide (**18)** has been prepared and used successfully to catalyze	

2004	Wang *et al.*	asymmetric Mannich-type reactions in DMSO between various ketones and PMP (*p*-methoxyphenol) alpha-imino ester. Other possible solvents were also explored and all could be employed in this reaction. The reaction is used to efficiently synthesize functionalized alpha-amino acid derivatives.  Fig.18	[41]
2004	Dondoni *et al*	Study shows a family of heterocyclic amino acids comprising highly functionalized ß-(2-pyridyl)- and ß-(4-pyridyl)-alanines and the corresponding *N*-oxide derivatives that have been developed by a convenient one-pot thermal Hantzsch-type cyclocondensation of aldehyde–ketoester enamine systems .	[42]
2004	De Riccardis *et al.*	Disclosed an asymmetric synthesis of N,O-diprotected (2*S*,3*S*)-*N*-methyl-delta hydroxyisoleucine,a building block required for the asymmetric synthesis of halipeptin A. **(19)**  Fig.19	**[43]**
2004	Esaki *et al.*	Described coupled enzymatic synthesis of *N*-methyl-*L*-phenyl alanine from phenylpyruvic acid and methylamine by using a novel enzyme *N*-methyl-*L*-amino acid dehydrogenase (NMAADH) from *Pseudomonas putida*, NADP+ and glucose dehydrogenase (GDH) from *Bacillus subtilis* as a co factor recycling system. **(20)**  Fig.20	**[44]**
2005	Garbay *et al*	Described an enantioselective synthesis of malonylphenylalanyl and malonylmethylphenylalanyl derivatives uses 4-bromobenzaldehyde diethyl acetal as a starting material and converts it to the corresponding products by a four step synthetic pathway as published	[45]
2005	Boto *et al*	In present communication arylglycine derivatives **21a and 21b** were prepared in one step, starting from readily available serine derivatives. The method involves treating the starting protected serine with iodine and DIB (di acetoxyiodo benzene) at room temperature. The reaction mixture was then cooled and BF_3 Et_2O, together with an excess of different nucleophiles, was added. These building blocks can be used to develop novel antineurodegenerative drugs, as they possess the ability to selectively modulate metabotropic glutamate receptors.  **21a** **21b** Fig.21	[46]
2005	Pedatella *et al.*	An orthogonally protected 2,3-amino acid **22** was reported. The starting enolates of *N,N*-dibenzylated ß^3-amino esters were treated with di *tert*- butyl azodicarboxylate (DBAD) to give *N`,N``*-di-Boc-2-hydrazino derivatives with excellent *anti* diastereomeric ratios.  Fig.22	[47]
2005	Pellicciari *et al.*	First time synthesized 2-(tetrahydrofuran-2-yl)glycine (**23**) is a conformationally constrained amino acid. The first enantiodivergent synthesis of all four possible 2-(tetrahydrofuran-2-yl) glycine stereoisomers was described. The key synthetic step is a highly stereo-controlled allylboration.  Fig.23	[48]
		A useful and fast microwave-assisted synthesis of α-nitro-α-amino esters **24** and the	

2005	Ballini *et al*	corresponding acids, under mild conditions and without solvent, was reported. The desired products were obtained *via* Michael addition from methyl *N*-(diphenylmethylene)-2,3 didehydroalaninate.  Fig.24	[49]
2005	Tanaka *et al.*	Prepared a new class of α-disubstituted α-amino acids **25** bearing a pendent chiral centre. Derivatives of 4-aminopiperidine-4-carboxylic acid are achiral α-amino acids bearing a nitrogen group. The focus on this amino acid has been due to the antimicrobial activity of its helical peptides.  Fig.25	**[50]**
2005	Takemoto *et al.*	Published a tandem reaction yielding dehydroamino acid derivatives. Afforded α-disubstituted amino acids *via* radical and anionic carbon–carbon bond-forming processes. The authors disclosed the reductive allylation reaction of *N*-phthaloyl dehydroalanine with allyl acetate which was accomplished by using Bu_3SnH and $Pd(PPh_3)_4$ yielding.	**[51]**
2005	Kessler *et al.*	Reported a three-step synthesis of N^{α}-methyl-N^{α}-(*o* nitrobenzenesulfonyl)-α-amino acids **26** without extensive purification. The procedure is based on previously known *N*-alkylation of N^{α}-arylsulfonylamino esters, which was improved by utilizing dimethyl sulfate and DBU as base.  Fig.26	**[52]**
2005	Konopelski *et al.*	Published a complementary method for the synthesis of optically pure *N*-methyl amino acids esters **27** that requires no protection of the functionalized amino acid side chain. The method comprises two consecutive reductive aminations, first with benzaldehyde, then with paraformaldehyde. An important feature of the reaction is that both sequences of imine formation and subsequent reduction were performed in the same flask and without isolation.  Fig.27	**[53]**
2005	Tandon *et al*	Presenting a series of (*S*)-*N*-(1,4-naphthoquinon-2-yl)-α-amino acid methyl esters. The reaction of 1,4-naphthoquinones and their bromo derivatives with enantiomerically pure *L*-amino acid methyl ester hydrochlorides produce *N*-modified-α-amino acid methyl esters	**[54]**
2007	Perdih A and Dolenc MS	This review focuses on the selected recent synthetic methodologies leading to unnatural amino acids including chiral catalysts that enabled enantioselective synthesis and microwave-assisted synthesis. It also focused on solid phase synthesis and construction of organometallic amino acids.	**[55]**
2007	Matthew JG *et al.*	The present communication shows an interesting topic of enantioselective organocatalysis. They discussed the impact of enamine, iminium, nucleophilic and bronsted acid catalysts in organic synthesis, and highlighted key strategic methods to assemble useful molecules with high enantiomeric purity.	**[56]**
2007	Corvo MC and Pereira MMA	Describes the synthesis of λ-amino acid analogues from natural α-amino acids by a radical pathway. They present a new λ-amino esters and amides preparation by a radical method. This was the first time that any radical species generated from natural α-amino acids and are used to synthesize λ-amino acid derivatives.	**[57]**
		The present study develops a convenient synthesis of amino acid methyl esters. All compounds are prepared in a good to excellent yields by room temperature reactions of	

2008	Sha Y and Li J	amino acids with methanol in the presence of trimethylchlorosilane. The method is not only compatible with natural amino acids, but also with other aromatic and aliphatic unnatural amino acids.	**[58]**
2008	Parra M *et al.*	Described an efficient synthesis of γ-amino acids and here attempts made to drive its enantioselectivity. The present communication describes a general procedure for the addition of dianions of carboxylic acids to bromoacetonitrile. This methodology, with saturated carboxylic acids, is a new approach to the synthesis of γ-aminoacids that are obtained with higher yields than those earlier described. Unfortunately, here poor yield resulted in their attempts which drive the enantioselectivity by chiral amide induction.	**[59]**
2009	Cobb AJA *et al.*	Presents an enantioselective intramolecular michael addition of nitronates onto conjugated esters for access to cyclic *γ*-amino acids with up to three stereocenters. They have shown the first use of bifunctional organocatalysis in the intramolecular michael addition of nitronates to conjugated esters. They have also demonstrated its utility in peptide chemistry, and mechanistic investigations of the reaction.	**[60]**
2011	Narsaiah AV *et al.*	The study describes the use of a catalyst named Amberlyst-15 which is an efficient, cost-effective and recyclable hetero generous solid acid catalyst for the synthesis of β-enaminones and β-enamino esters. The β-keto carbonyl compounds rapidly react with a variety of amines in the presence of Amberlyst-15 to produce beta-enamino compounds with excellent yields.	**[61]**
2012	R. Saladino *et al*.	In this review authors were tried to describe the recent advances in the amino acid side-chain transformations and backbone modifications by oxidative and fluorination procedures. They also emphasizes about how modified amino acids with enhanced biological activity, proteolitic stability and bioavailability are of increasing interest in protein design and engineering as drug candidates.	**[62]**
2012	Rudat J *et al.*	Presents a mini review on transaminases an enzyme for the synthesis of enantio-pure β-amino acids. This review gives an overview over microbial transaminases with activity towards β-amino acids and their substrate spectra. It also outlines current strategies for the screening of new biocatalysts. As optically pure β-amino acids constitute interesting building blocks for peptidomimetics and a great variety of pharmaceutically important compounds. Their efficient synthesis still poses a major challenge. Transaminases (also known as aminotransferases) possess a great potential for the synthesis of optically pure β-amino acids.	**[63]**
2012	Murthy LN *et al.*	Presents a brief review on synthesis and applications of β-enamino carbonyl compounds owing to the wide range applications in pharmaceuticals and as building blocks for the synthesis of a variety of heterocyclic compounds, β-amino esters, β-amino acids, β-amino alcohols, peptides and alkaloids. They developed a number of methods so far for the synthesis of these compounds.	**[64]**
2016	Lei Liu *et al*.	Reviewed surveys the recent advances of synthesis of chiral unnatural α-amino acids and peptides through palladium-catalyzed functionalization of un-activated C(sp_3)–H bonds. The review represents all the available methods for direct C–H functionalization of simple amino acids that represents one of the most attractive approaches because it exhibits good atom-economy and step-efficiency.	**[65]**

CONCLUSION:

Unnatural amino acids are of particularly interest for drug development and drug optimization. So there is growing interest for the synthesis of various unnatural amino acids and their derivatives as new medicines and other pharmaceuticals. Various organic chemist and researchers were develop different protocols but still there is a great need of a drug candidate which is more effective and more selective. Current review summarized various synthetic methods and procedures and their pharmaceutical uses. All mentioned research shows a remarkable creativity of those procedures and also involved in the design of novel unnatural amino acid and their derivatives. Without any doubt, it can be concluded that novel synthetic methodologies to construct various unnatural amino acids will continue to provide new ways for pharmaceutical drug design.

REFERENCES:

1. M. C. Rosen, "Asymmetric Synthesis of α-Amino Acids: New Twists on Old Ideas" *Mini reviews*, pp155, 2003
2. Samuel Gellma, "Efficient Method of Synthesizing Gamma Amino Acids for Applications in Medicine,Materials, Healthcare", *U.S. Patent* No. 8,269,039, 2012
3. Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed.* 1993, *32*, 1244.
4. Wang, L.; Schultz, P.G. *Chem. Commun*., 2002, *43*, 11623.
5. Garner, P.; Park, J.M. *Org. Synth.* 1992, *70*, 18.
6. *Burger's Medicinal Chemistry and Drug Discovery*, Volume *1*, Drug Discovery, 6th Ed., John Wiley & Sons: New York, 2005.
7. Bonner, G.G.; Davis, P.; Stropova, C.; Ferguson, R.; Yamamura, H.I.; Porreca, F.; Hruby, V.J. *Peptides*, 1997, *18*, 93.
8. Marshall, S.A.; Lazar, G.A.; Chirino, A.; Desjarlais, J.R. *Drug Discov. Today*, 2003, *8*, 212.
9. Adessi, C.; Soto, C. *Curr. Med. Chem.*, 2002, *9*, 963.
10. Eggelte T. A., Koning H. D., Huisman H. O.,"Diels-Alder reaction of furan with some dienophiles", *Tetrahedron* 1973,29,2491-2493.
11. Wagle D. R., Monteleone M. G., Krishnan L., Manhas M. S., Bose A. K.,"Novel synthesis of optically active morpholines" *J. Chem. Soc., Chem. Commun*, 1989,915-916.
12. Varma R. S., Varma M., Chatterjee A. K.,"Microwave-assisted deacetylation on alumina: a simple deprotection method" *J. Chem. Soc. Perkin Trans*., 1993,999-1000.
13. Crawford L. A., Bown A. W. , Breitkreuz K. E. , Cuine F. C., "The Synthesis of y-Aminobutyric Acid in Response to Treatments Reducing Cytosolic pH",*Plant Physiol.,* 1994,104,865-871.
14. Coles M. P., Gibson V. C., Mazzariol L., North M., Teasdale W. G., Williams C. M., Zamunerb D.,"Amino acid derived homochiral polymers *via* ring-opening metathesis polymerisation" *J. Chem. Soc., Chem. Commun*, 1994,2505-2506.

15. Ortiz A. D., Barra E. D., Hoz A., Prieto P., Moreno A.,"Cycloadditions of ketene acetals under microwave irradiation in solvent-free conditions" *J. Chem. Soc. Perkin Trans*., 1994, 3595-3578.
16. Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.*, 1996, *37*, 5273.
17. Tanaka, K.; Ahn, M.; Watanabe, Y.; Fuji, K. *Tetrahedron Asymmetry*, 1996, *7*, 1771.
18. Södergren, M.J.; Andersson P.G.; *Tetrahedron Lett.,* 1996, *37*, 7577.
19. Ondrus V., Fisera L.,"Synthesis and 1,3-dipolar cycloaddition reactions of chiral maleimides", *Molecules*, 1997,2,49–56.
20. Borah H. N., Boruah R. C., Sandhu J. S.,"Microwave-induced one-pot synthesis of N-carboxyalkyl Maleimides and Phthalimides" *J. Chem. Research (S)*,1998, 272-273.
21. Drury W. J., Ferraris D., Cox C., Young B., Lectka T.,"A novel synthesis of alpha-amino acid derivatives through catalytic, enantioselective ene reactions of alpha-imino esters" *J. Am. Chem. Soc.*, 1998, 120,11006-11007.
22. Padrón, J.M.; Kokotos, G.; Martín, T.; Markidis, T.; Gibbons, W.A.; Martín V.A. *Tetrahedron Asymmetry*, 1998*, 9*, 3381.
23. Shieh, W.-C.; Xue, S.; Reel, N.; Wu, R.; Fitt, R.; Repi , O. *Tetrahedron Asymmetry*, 2001, *12*, 2421.
24. Davis, F.A.; Zhang, Y.; Rao, A.; Zhang, Z. *Tetrahedron*, 2001*, 57*, 6345.
25. Huang, T.S.; Li, C. *J. Org. Lett.,* 2001*, 3* ,2037.
26. Kim, H.J.; Lee, S.; Park, Y.S. *Synlett,* 2001, *5*, 613.
27. Greenfield, S. J.; Gilbertson, S. R. *Synthesis,* 2001*, 10*, 2337-2340.
28. Ondrus V., Fisera L., Bradac V.,"On the use of water as a solvent - simple and short one- step synthesis of maleimides"*ARKIVOC*,2001,5,60-67.
29. Davis, F.A.; Lee, S.; Yan, H.; Titus, D.D. *Org. Lett.,* 2001, *3*, 1757.
30. Carlier, P.; Lam, P.C.H.; Wong, D.M. *J. Org. Chem.,* 2002, *67*, 6256.
31. Magrioti V., Antonopoulou G., Pantoleon E., Kokotos G.,"Synthesis of 2-amino alcohols and unnatural amino acids from serine" *ARKIVOC*, 2002,13,55-61.
32. Gallos, J.K.; Sarli, V. C.; Varvogli, A.C.; Papadoyanni, C.Z.; Papaspyrou, S.D.; Argyropoulos, N.G. *Tetrahedron*, 2003,*44*,3905.
33. Wasserman, H.H.; Long, Y.O.; Parr, J. *Tetrahedron Lett.*, 2003, *44*, 361.
34. Gorohovsky, S.; Meir, S.; Shkoulev, V.; Byk, G.; Gellerman, G. *Synlett*, 2003, 1411.
35. Ueki, H.; Ellis, T.K.; Collin, M.H.; Soloshonok, V.A. *Eur. J. Org.Chem.,* 2003, 1954.
36. Van Esseveldt, B.C.J.; van Delft, F.L.; Smits, J.M.M.; de Gelder, R.; Rutjes, F.P.J.T. *Synlett*, 2003, *15*, 2354-2358.
37. Van Esseveldt, B.C.J.; van Delft, F.L.; de Gelder, R; Rutjes, F.P.J.T. *Org. Lett.*, 2003, *5*, 1717.
38. Kabalka, G.W.; Yao, M.-L. *Synthesis*, 2003, 2890.
39. Kabalka, G.W.; Yao, M.-L. *J. Org. Chem.,* 2004, *69*, 8280.
40. Middleton, R.J.; Mellor, S.J.; Chhabra, S. R.; Bycroft, B. W.; Chan, W.C. *Tetrahedron Lett.,* 2004*, 45,* 123.
41. Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.,* 2004, *45,* 724.
42. Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. *Tetrahedron*, 2004*, 60*, 2311.
43. Izzo, I.; Avallone, E.; Della Corte, L.; Maulucci, N.; De Riccardis. *Tetrahedron Asymmetry,* 2004*, 14*, 1181.
44. Muramatsu, H.; Mihara, H.; Kakutani, R.; Yasuda, M.; Ueda, M.; Kurihara, T.; Esaki, N. *Tetrahedron Asymmetry,* 2004*, 15*, 2841.
45. Cheng, H.; Luzy, J.-P.; Garbay, C. *Tetrahedron Lett.*, 2005, *46*,3319.
46. Boto, A.; Hernandez, R.; Montoya, A.; Suarez, E. *Tetrahedron Lett.,* 2005, *43*, 8.
47. Capone, S.; Guaragna, A.; Palumbo, G.; Pedatella, S. *Tetrahedron*,2005*, 61,* 6575.
48. Jingersons, A.; Marinozzi, M.; Pellicciari, R.; *Tetrahedron*, 2005,*61*, 373.
49. Ballini, R.; Balsamini, C.; Bartoccini, F.; Gianotti, M.; Martinelli, C.; Savoretti, N. *Synthesis*, 2005*, 2*, 296.
50. Oba, M.; Tanaka, M.; Takano, Y.; Suemune, H. *Tetrahedron*, 2005, *61*, 593.
51. Miyabe, H.; Asada, R.; Takemoto, Y. *Tetrahedron*, 2005*, 61*, 385.
52. Biron, E.; Kessler, H. *J. Org. Chem.,* 2005, *70*, 5183.
53. White, K.N., Konopelski, J.P. *Org. Lett.,* 2005*, 7,* 4111.
54. Tandom, V.K.; Yadav, D.B.; Singh, R.V.; Chaturvedi, A.K.;Shukla, P.S. *Biorg. Med. Chem.*, 2005, *15*, 5324.
55. Perdih A., Dolenc S. M.,"Recent advances in the synthesis of unnatural alpha-amino acids" *Current Organic Chemistry*, 2007,11,801-832.
56. Matthew J. G., Johansson C. C. C., McNally A.,Vo N. T., "Enantioselective organocatalysis.," *Drug Discov. Today*, 2007,12,8–27.
57. Corvo M. C and Pereira M. M. A,"Synthesis of gamma-amino acid analogues from natural alpha-amino acids by a radical pathway", *Amino Acids*, 2007,32,243–246,.
58. Li J., Sha Y., "A convenient synthesis of amino acid methyl esters",*Molecules,*2008,13,1111-1119.
59. S. Gil, M. Parra, P. Rodríguez," An efficient synthesis of γ aminoacids and attempts to drive its enantioselectivity" *Molecules,* 2008,13, 716-728.
60. Nodes W. J., Nutt D. R., Chippindale A. M., and Cobb A. J. A.,"Enantioselective Intramolecular Michael Addition of Nitronates onto Conjugated Esters : Access to Cyclic γ -Amino Acids with up to Three Stereocenters," *J. Am. Chem. Soc*, pp. 2009,16016–16017.
61. Narsaiah A. V., Reddy A. R., Reddy B. V. S., Yadav J. S., "Amberlyst-15: An efficient, cost-Effective and recyclable hetero geneous solid acid catalyst for the synthesis of beta-enaminones and beta-enamino esters", *The Open Catalysis Journal,* 2011,4,43-46.
62. Saladino R., Bottaa G., Crucianelli M., "Advances in the synthesis of bioactive unnatural amino acids and peptides" *Mini-Reviews in Medicinal Chemistry,* 2012,12,277-300.
63. Rudat J., Brucher B. R., Syldatk C.,"Transaminases for the synthesis of enantiopure beta-amino acids" *AMB Express*, 2012,2,11.
64. Murthy L. N, Govindh B, Bhagavathula, S Diwakar, Yellajyosula, "A brief review on synthesis & applications of beta-enamino carbonyl compounds, *Org. Commun*. 2012,5(3),105-119,.
65. Xi Lu , Xiao B. , Shang R., Lei Liu, "Synthesis of unnatural amino acids through palladium catalyzed C(sp^3)–H functionalization" *Chinese Chemical Letters*, 2016,27,305–311.