**Unnatural Amino Acids (UAA’s): A Review**

**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 (M. C. Rosen, 2003).

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 (Samuel Gellma,2012). Unnatural amino acids play an important role in the design and synthesis of pharmacologically relevant molecules, peptidomimetics and enzyme inhibitors (Giannis A. and Kolter T., 1993; Wang, L. and Schultz, 2002). 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.( Garner P. and Park J.M. 1993)

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) (Burger, 2005; Bonner GG et al.,1997)

**Limitation(s) of natural peptides as drug candidates**: (Marshall S.A et al., 2003)

Peptides are poor drug candidates due to their following limitations:

1. Characterized by fast hydrolytic cleavage
2. Poor penetration of membranes.
3. Rapid photolytic degradation.
4. Conformational instability.
5. 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 (Adessi C. and Soto C., 2002). 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 (Samuel Gellma,2012).

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.

**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 developed 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 in chronological order of their development. 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.

**Acknowledgements**

Authors are thankful to Himalayan Institute of Pharmacy & Research, Dehradun for providing infrastructure and facilities in department of Pharmacy.

**Disclosure Statement**

The authors report no conflict of interest.

**References:**

Adessi C, Soto C. 2002.Current Medicinal Chememistry. 9: 963.

Ballini R, Balsamini C, Bartoccini F, Gianotti M, Martinelli C, Savoretti N.2005.Synthesis,2: 296.

Biron E, Kessler H.2005. Journal of Organic Chemistry,70:5183.

Bonner GG, Davis P, Stropova C, Ferguson R, Yamamura HI, Porreca F, Hruby VJ. 1997. Peptides,18:93.

Borah HN, Boruah RC, Sandhu JS. 1998.Microwave-induced one-pot synthesis of N-carboxyalkyl Maleimides and Phthalimides, J. Chem. Research,1:272-273.

Boto A, Hernandez R, Montoya A, Suarez E.2005. Tetrahedron Lett.,43:8.

Burger's Medicinal Chemistry and Drug Discovery, 2005,1(6), John Wiley & Sons: New York.

Capone S, Guaragna A, Palumbo G, Pedatella S.2005. Tetrahedron,61:6575.

Carlier P, Lam PCH, Wong DM. 2002. J. Org. Chem.,67:6256.

Cheng H, Luzy JP, Garbay C. 2005. Tetrahedron Lett.,46:3319.

Coles MP, Gibson VC, Mazzariol L,North M, Teasdale WG, Williams CM, Zamunerb D. 1994. Amino acid derived homochiral polymers via ring-opening metathesis polymerization. J. Chem. Soc., Chem. Commun, 1:2505-2506.

Corvo MC and Pereira MMA. 2007. Synthesis of gamma-amino acid analogues from natural alpha-amino acids by a radical pathway. Amino Acids,32:243–246.

Crawford LA, Bown AW, Breitkreuz KE, Cuine FC. 1994. The Synthesis of y-Aminobutyric Acid in Response to Treatments Reducing Cytosolic pH”,Plant Physiol.,104:865-871.

Davis FA, Lee S, Yan H, Titus DD. 2001. Organic Letters,3:1757.

Davis FA, Zhang Y, Rao A, Zhang Z. 2001. Tetrahedron,57:6345.

Dondoni A, Massi A, Minghini E, Bertolasi V.2004.Tetrahedron,60:2311.

Drury WJ, Ferraris D, Cox C, Young B, Lectka T. 1998. A novel synthesis of alpha-amino acid derivatives through catalytic, enantioselective ene reactions of alpha-imino esters. J. Am. Chem. Soc.,120:11006-11007.

Eggelte TA, Koning HD, Huisman HO.1973. Diels-Alder reaction of furan with some dienophiles,Tetrahedron,29:2491-2493.

Gallos JK, Sarli VC, Varvogli AC, Papadoyanni CZ, Papaspyrou SD, Argyropoulos NG. 2003. Tetrahedron, 44:3905.

Garner P, Park JM.1992. Organic Synthesis, 70:18.

Giannis A, Kolter T, Angew. 1993. Chem., Int. Ed., 32:1244.

Gorohovsky S, Meir S, Shkoulev V, Byk G, Gellerman G. 2003. Synlett, 1:1411.

Greenfield SJ, Gilbertson SR. 2001. Synthesis,10: 2337-2340.

Hanessian S, Yang RY. 1996. Tetrahedron Lett., 37:5273.

Huang TS, Li CJ. 2001. Organic Letters.,3: 2037.

Izzo I, Avallone E, Della CL, Maulucci N, De Riccardis. 2004. Tetrahedron Asymmetry,14: 1181.

Jingersons A, Marinozzi M, Pellicciari R.2005. Tetrahedron,61:373.

Kabalka GW, Yao ML.2004. Journal of Organic Chemistry, 69: 8280.

Kabalka GW, Yao ML. 2003. Synthesis,1: 2890.

Kim HJ, Lee S, Park YS. 2001. Synlett, 5: 613.

Li J, Sha Y. 2008. A convenient synthesis of amino acid methyl esters, Molecules,13:1111-1119.

Rosen MC. 2003. Asymmetric Synthesis of α-Amino Acids: New Twists on Old Ideas, Mini reviews,1:155.

Magrioti V, Antonopoulou G, Pantoleon E, Kokotos G. 2002. Synthesis of 2-amino alcohols and unnatural amino acids from serine, ARKIVOC,13:55-61.

Marshall SA, Lazar GA, Chirino A, Desjarlais JR. 2003. Drug Discov. Today,8: 212.

Matthew JG, Johansson CCC, McNally AVN, 2007. Enantioselective organocatalysis, Drug Discov. Today,12:8–27.

Middleton RJ, Mellor SJ, Chhabra SR, Bycroft BW, Chan WC. 2004, Tetrahedron Lett.,45:123.

Miyabe H, Asada R, Takemoto Y. 2005. Tetrahedron,61:385.

Muramatsu H, Mihara H, Kakutani R, Yasuda M, Ueda M, Kurihara T, Esaki N. 2004. Tetrahedron Asymmetry,15:2841.

Murthy LN, Govindh B, Bhagavathula, S Diwakar, Yellajyosula. 2012. A brief review on synthesis & applications of beta-enamino carbonyl compounds, Org. Commun.,5(3):105-119.

Narsaiah AV, Reddy AR, Reddy BVS, Yadav JS. 2011. Amberlyst-15: An efficient, cost-Effective and recyclable heterogeneous solid acid catalyst for the synthesis of beta-enaminones and beta-enamino esters, The Open Catalysis Journal,4:43-46.

Nodes WJ, Nutt DR, Chippindale AM, and Cobb AJA. 2009. Enantioselective Intramolecular Michael Addition of Nitronates onto Conjugated Esters : Access to Cyclic γ -Amino Acids with up to Three Stereocenters, J. Am. Chem. Soc,1:16016–16017.

Oba M, Tanaka M, Takano Y, Suemune H.2005. Tetrahedron,61:593.

Ondrus V, Fisera L, Bradac V. 2001. On the use of water as a solvent - simple and short one- step synthesis of maleimides, ARKIVOC,5:60-67.

Ondrus V, Fisera L. 1997. Synthesis and 1,3-dipolar cycloaddition reactions of chiral maleimides, Molecules, 2: 49–56.

Ortiz AD, Barra ED, Hoz A, Prieto P, Moreno A. 1994 .Cycloadditions of ketene acetals under microwave irradiation in solvent-free conditions. J. Chem. Soc. Perkin Trans.,1: 3595-3578.

Padrón, JM, Kokotos G, Martín T, Markidis T, Gibbons WA, Martín VA.1998. Tetrahedron Asymmetry,9: 3381.

Perdih A, Dolenc SM. 2007. Recent advances in the synthesis of unnatural alpha-amino acids, Current Organic Chemistry,11: 801-832.

Rudat J, Brucher BR, Syldatk C. 2012. Transaminases for the synthesis of enantiopure beta-amino acids, AMB Express,2:11.

Gil S, Parra M, Rodríguez P. 2008. An efficient synthesis of γ aminoacids and attempts to drive its enantioselectivity. Molecules, 13: 716-728.

Saladino R, Bottaa G, Crucianelli M. 2012. Advances in the synthesis of bioactive unnatural amino acids and peptides, Mini-Reviews in Medicinal Chemistry,12:277-300.

Samuel G. 2012. Efficient Method of Synthesizing Gamma Amino Acids for Applications in Medicine,Materials, Healthcare. U.S. Patent No. 8: 269,039.

Shieh WC, Xue S, Reel N, Wu R, Fitt, R, Repi O. 2001. Tetrahedron Asymmetry. 12: 2421.

Södergren MJ, Andersson PG. 1996. Tetrahedron Lett., 37: 7577.

Tanaka K, Ahn M, Watanabe Y, Fuji K.1996. Tetrahedron Asymmetry,7:1771.

Tandom VK, Yadav DB, Singh RV, Chaturvedi AK, Shukla PS. 2005. Biorg. Med. Chem.,15: 5324.

Ueki H, Ellis TK, Collin MH, Soloshonok VA. 2003. Eur. J. Org.Chem.,1:1954.

Van Esseveldt BCJ, van Delft FL, de Gelder R, Rutjes FPJT. 2003. Org. Lett.,5:1717.

Van Esseveldt BCJ, van Delft FL, Smits JMM, de Gelder R, Rutjes FPJT.2003. Synlett,15:2354-2358.

Varma RS, Varma M, Chatterjee AK. 1993. Microwave-assisted deacetylation on alumina: a simple deprotection method. J. Chem. Soc. Perkin Trans.,1:999-1000.

Wagle DR, Monteleone MG, Krishnan L, Manhas MS, Bose AK. 1989. Novel synthesis of optically active morpholines. J. Chem. Soc. Chem. Commun,1:915-916.

Wang, L, Schultz PG. 2002. Chem. Commun.,43: 11623.

Wang W, Wang J, Li H. 2004. Tetrahedron Lett.,45:724.

Wasserman HH, Long YO, Parr J. 2003. Tetrahedron Lett., 44:361.

White KN, Konopelski JP. 2005. Org. Lett.,7: 4111.

Xi Lu , Xiao B , Shang R, Lei Liu.2016. Synthesis of unnatural amino acids through palladium catalyzed C(sp3)–H functionalization. Chinese Chemical Letters,27:305–311.