# MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF COMPLEX MOLECULES

Dr. Jamsheena V.

Assistant Professor**,** PG Department of Chemistry,
KAHM Unity Women's College, Manjeri, Kerala- 672122, India
Email:jamshivkpt843@gmail.com

Organic synthesis is considered as a turning point of molecular science. Prof. K. C. Nicolaou from Rice University discussed the significance of organic synthesis in his several research articles. He stated in one of his research article "*One of the most vital and valued sub-disciplines of chemistry is the science of organic synthesis, without which much of science and industry would have remained paralyzed and sterile. This is the discipline that provides the myriad molecules from which emerge our most precious new material goods and gadgets, whether they are instruments to cure disease and promote wellness or tools that help us build machines, communicate, travel, and entertain ourselves, not to mention advance education and science, and achieve sustainability*". The development of sophisticated analytical and separation procedures necessitates the need for ideal synthesis. The target molecule should be assembled using easily available starting components in an easy, secure, cost-effective, and efficient process (Figure 1). In this context, multicomponent reactions (MCRs) satisfy majority of the criteria of ideal synthesis. MCRs are defined as reactions that involve three or more substrates and incorporate the majority of the substrate's atoms into the final product. Unlike multi-step total synthesis, MCRs produce the products in a single-pot operation with greater complexity and diversity (Figure 2). In MCRs, all the substrates react sequentially in a number of simple steps (the domino process) rather than all reacting at once to produce the final product.

 **ISBN:978-93-5701-222-5**

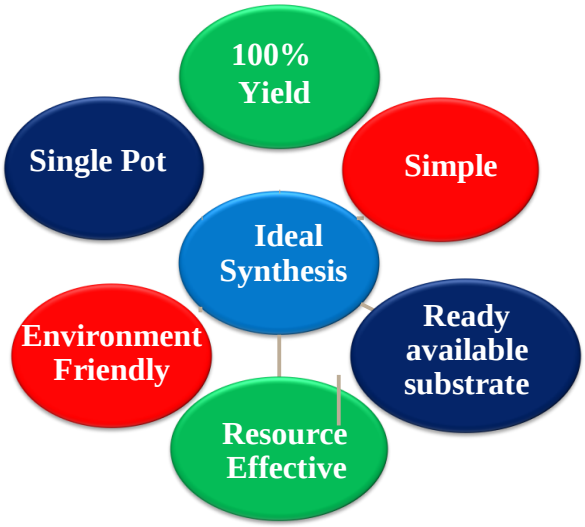



**Figure 1.** Criteria for ideal synthesis

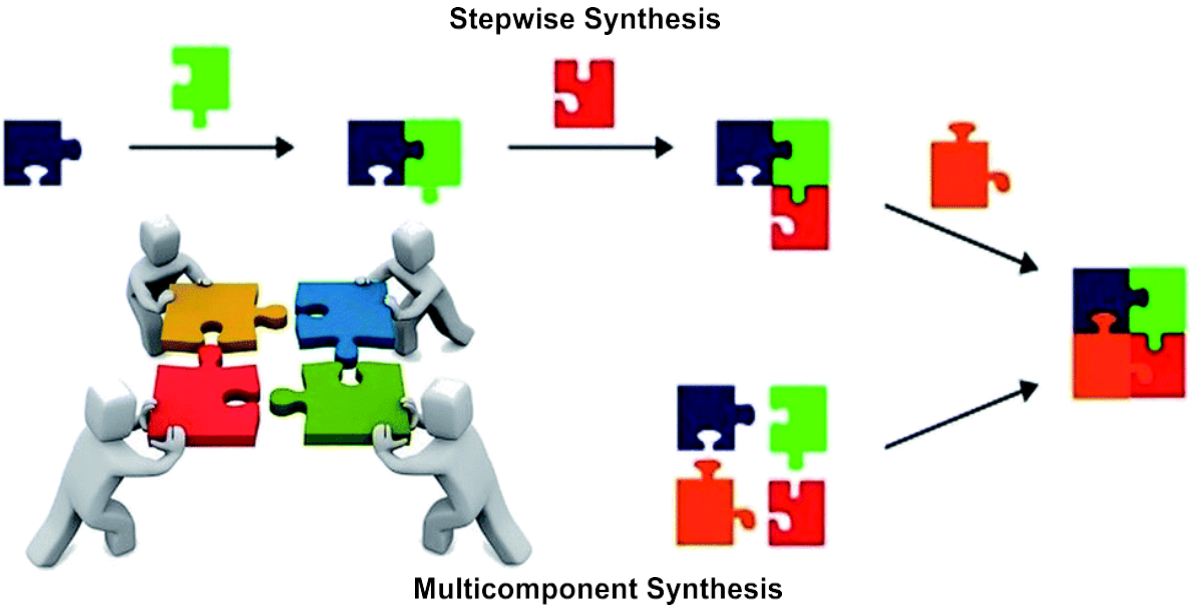



**Figure 2.** Stepwise linear synthesis *vs* multicomponent synthesis

**MCRs have so many advantages over conventional two-component reactions (2CRs) and multi-step total synthesis in contemporary organic synthesis.**

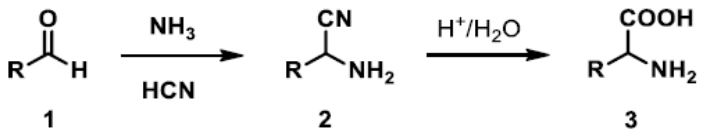
### 2.1. Advantages of MCRs:

- Multiple new bond forms in a single-pot operation


ISBN:978-93-5701-222-5

- No alteration to the reaction conditions or isolation of intermediates.
- Atom, energy, time and economic efficient
- Exhibits extensive substrate scope
- Highly sustainable and convergent
- Complexity and diversity oriented synthesis

Strecker developed α-amino acid **3** synthesis in 1850 by condensation of aldehyde **1**, ammonia and hydrogen cyanide.[6] The reaction proceeds via α-cyano amine intermediate **2** which upon hydrolysis generates α- amino acid **3 (Scheme 1)**. This reaction is considered as the first ever reported MCR. Twelve years ago, Gerhard and Laurent observed the formation of cyanohydrin imine as a poorly soluble compound from bitter almond oil and ammonia.




**Scheme 1.** Strecker synthesis of α-amino acid

## APPLICATIONS OF MCRs

The easily automated one-pot MCRs have found applications in various fields. Especially, the isocyanide based MCRs (IMCRs) were well explored and being employed in drug discovery, natural products synthesis, diversity-oriented synthesis (DOS) and material applications.

### MCRs in the synthesis of bioactive molecules

In the post-genomic era, medicinal chemistry added combinatorial synthesis and high-speed parallel synthesis in lead discovery and optimization in order to meet the vast need for diverse library of compounds by pharmaceutical industries. In this context, MCRs are considered as a powerful technology for the convergent synthesis of a diverse library of small molecule drugs. Utilizing MCR technology several protease inhibitors (e.g., serine, aspartyl, metallo and cysteine proteases), kinase inhibitors, phosphatase inhibitors, and G-protein coupled receptor ligands were synthesized (Figure 3).

 ISBN:978-93-5701-222-5

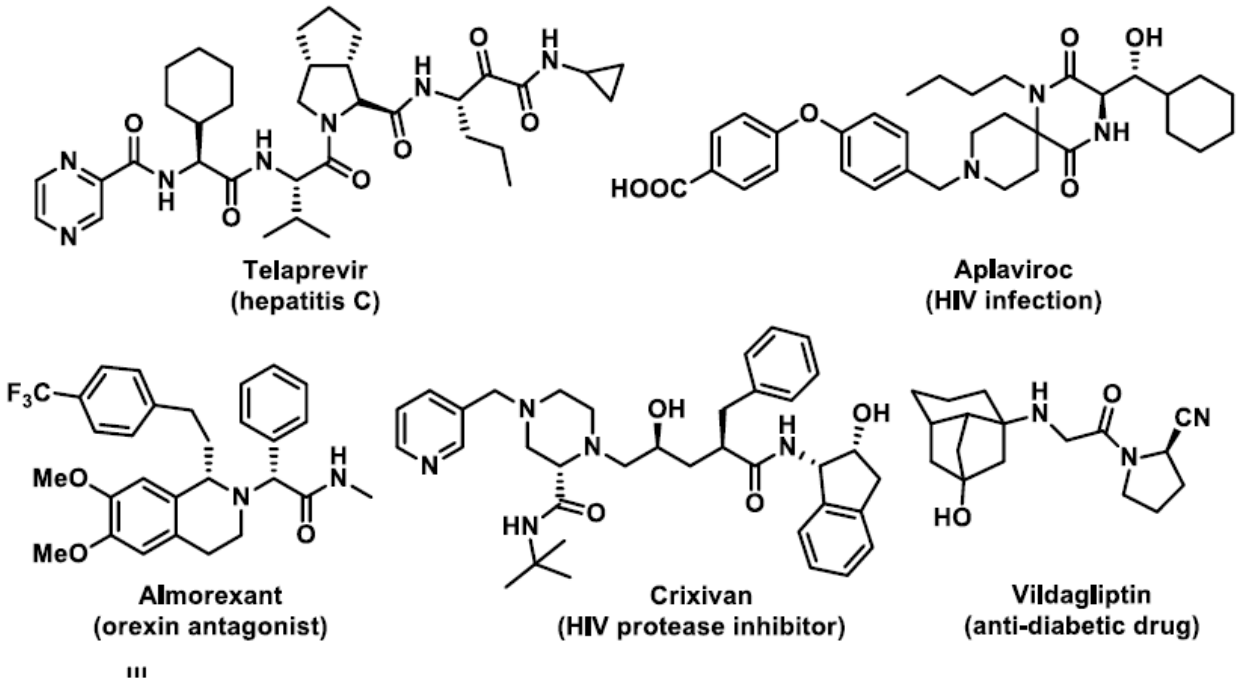
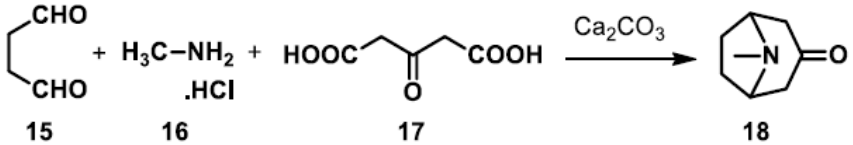



**Figure 3.** Selected examples of drugs synthesised through MCR

**MCRs in synthesis of natural products**

Initially, Robinson's synthesis of tropinone alkaloid by a double Mannich reaction **(Scheme 2)** laid the foundation for natural product synthesis using MCRs. Since then MCRs were underexploited in natural products synthesis for several decades, but recently MCRs experienced renaissance by the advent of combinatorial chemistry. Several complex natural products were synthesized by using MCRs as a key reaction strategy, and some of them are listed in the figure 4.




**Scheme 2. Robinson's synthesis of tropinone by a double Mannich-3CR**

 ISBN:978-93-5701-222-5

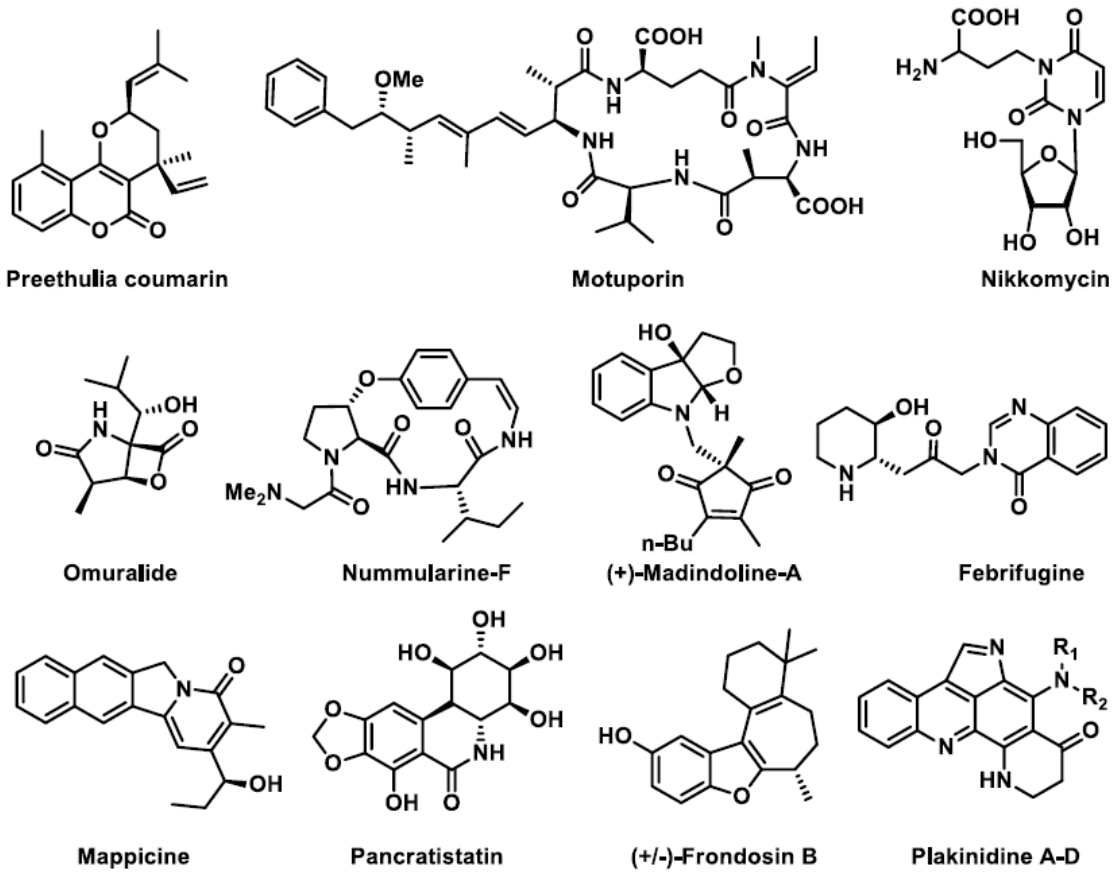



**Figure 4.** Targeted natural products using MCRs

MCR enable the facile, automated and high throughput generation of small organic molecules. The optimal MCR is sufficiently flexible that it can be employed to generate adducts bearing a variety of functional groups that may then be selectively paired to enable different cyclisation manifolds, thereby leading to diverse collection of products.

## References

1. Nicolaou, K. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 131.
2. Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657.
3. Wender, P. A. *Tetrahedron* **2013**, *69*, 7529.
4. Ugi, I.; Dömling, A.; Horl, W. *Endeavour* **1994**, *18*, 115.
5. (a) Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (c) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. - Eur. J.* **2000**, *6*, 3321. (d) de Graaff, C.; Ruijter,

 **ISBN:978-93-5701-222-5**

E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969. (e) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234.

6. Strecker, A. *Ann. Chem.* **1850**, *75*, 27.
7. Laurent, A.; Gerhardt, C. F. *Ann. Chem. Phys.* **1838**, *66*, 281.
8. Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085.
9. (a) Domling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083. (b) H. P. Isenring ; W. Hofhein; *Tetrahedron*, **1983**, *39*, 2591. (c) K. Rossen*, P.J. Pye*, L.M. DiMichelc, R.P. Volante and P.J. Reider, *Tetrahedron Letters*, **1998**, *39*, 6823-6826. (d) Marina Pedrola; Marta Jorba; Eda Jardas; Ferran Jardi; Ouldouz Ghashghaei; Miguel Viñas; Rodolfo Lavilla. *Front. Chem.* **2019**, *7*:475. (e) Lv, L.; Zheng, S.; Cai, X.; Chen, Z.; Zhu, Q.; Liu, S. *ACS Comb. Sci*. **2013**, *15*, 183−192. (f) Yihong Wan , Shengen Wu , Sichao Zheng, En Liang, Shuwen Liu, Xingang Yao, Qiuhua Zhu; *European Journal of Medicinal Chemistry* 200 (**2020**) 112318.
10. (a) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (b) Hall, D. G.; Rybak, T.; Verdelet, T. *Acc. Chem. Res.* **2016**, *49*, 2489. (c) Gao, X.; Hall, D. G. J. *Am. Chem. Soc.* **2005**, *127*, 1628. (d) Penner, M. N.; Rauniyar, V.; Kaspar, L.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216. (e) Hashimoto, S.; Katoh, S.; Kato, T.; Urabe, D.; Inoue, M. J. *Am. Chem. Soc.* **2017**, *139*, 16420. (f) Tingting Cao, Lei Zhu, Yu Lan**,** Jun Huang*****, Zhen Yang, *Org. Lett.* **2020**, *22*, 7, 2517.

 **ISBN:978-93-5701-222-5**