Multiplecomponent Reactions (MCR) of Pyrrolidone and PVP Derivatives

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Low MW or oligomeric PVP's with appropriate end groups such as carboxylic, amine or carbonyl functionality can be employed in a variety of MCR reactions. Such three or four component reactions can be conducted with PVP in a variety of solvents even water. For example, Vazo 68 (a carboxylic acid derivative) can initiate NVP polymerization which would result in PVPs with two carboxylate end groups assuming that termination is by combination and not disproportionation. PVP can also be terminally derivatized on one end for example, with a compound (in excess) with the required functionality that readily forms an initiating radical in exchange with Vazo or other initiators(1).

MCR reactions can be employed to chain extend oligomeric PVP to higher MW, the advantage being that such coupling reactions can be designed to be not only degradable but have useful derivative structures that can be released upon hydrolysis. PVP although of remarkable biological compatibility, is not kidney excretable if the MW is too high(2-3). A version with useful degradable segments might eliminate this problem. This idea has been patented before but not with the simplicity of MCR chemistry(3-7).

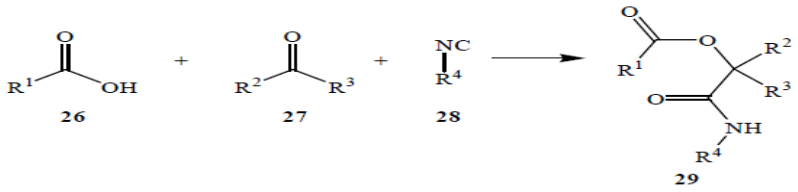
ABSTRACT(USP 4,254,239):

High molecular weight products based on N-vinylpyr rolidone, in which blocks of vinylpyrrolidone polymers or vinylpyrrolidone copolymers are linked by connect ing units carrying ester, amide, urethane or urea groups, as a result of which these high molecular weight prod ucts are biodegradable and may be used as plasma sub stitutes, and the plasma substitutes thus obtained.

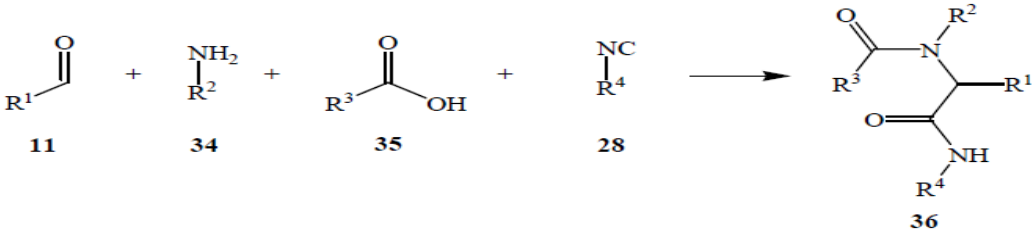
MCR reactions can also be employed to prepare medicinally active compounds that can be terminally attached to PVP. Such low MW PVP drug conjugates would benefit from the ability of PVP to transport these conjugates safely to biological targets and to be low

enough in MW to be easily excreted.

Multiplecomponent Reactions:

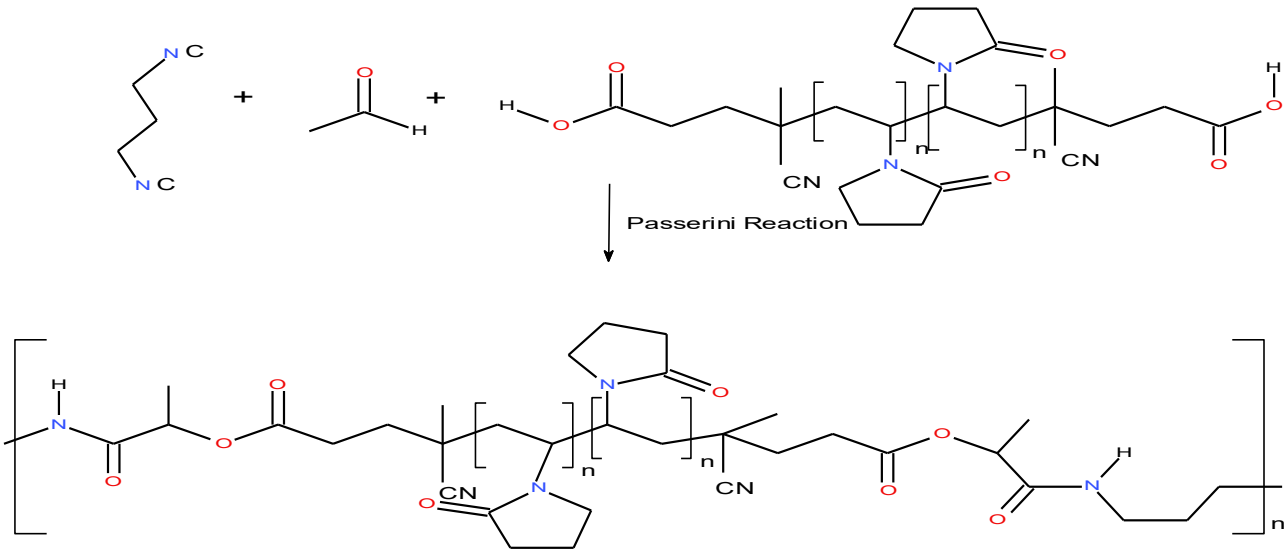


Scheme 11 Passerini 3-component reaction



Scheme 14 Ugi-four component reaction

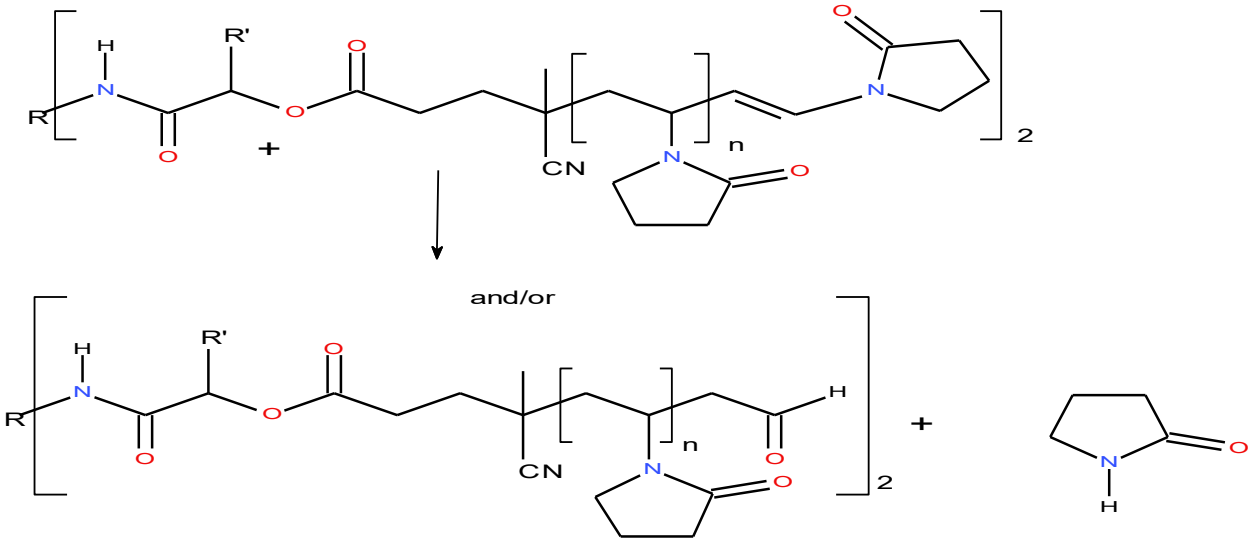
I am especially interested in the above two MCR's. There are others but the above have the most flexibility. Another reason I like these MCR's is because they are high yield reactions that take place under mild even low temperature conditions in a variety of solvents even water. Therefore, terminally functionized PVP can be one of the MCR components.



Scheme 1: NVP polymerized with Vazo 68 with bimolecular termination and chain

extended with a Passerini MCR(9-10). What is illustrated in scheme 1 uses simple Passerini components. Obviously, each reactant can be substituted with a wide varity of R groups to afford an amazing level of flexibility according to the required end use.

PVP is known to also terminate by disproportionation which results in it being derivatized at only one end. When polymerized in water, especially with the hydrogen peroxide, the terminus is an aldehyde. Therefore, the MCR reaction can employ the terminal aldehyde in said reactions.



Scheme 2: Alternative termination and subsequent Passerini MCR resulting in a dimer which can be further MCR chain extended through subsequent reaction with the terminal aldehyde.

PVP can be visualized terminally derivatized with aldehydes or ketones, primary or secondary amines or carboxylic acids or phenols etc. resulting in a vast library of potential Passirini, Ugi and other MCRs. Let me quote (11-12):

"they are atom economic, e.g. the majority if not all of the atoms of the starting materials are incorporated in the product; they are efficient, e.g. they efficiently yield the product since the product is formed in one-step instead of multiple sequential steps; they are convergent, e.g. several starting materials combine in one reaction to form the product; they exhibit a very high bond-forming-index (BFI), e.g. several non-hydrogen atom bonds are formed in one synthetic transformation. Therefore MCRs are often a useful alternative to sequential multistep synthesis."

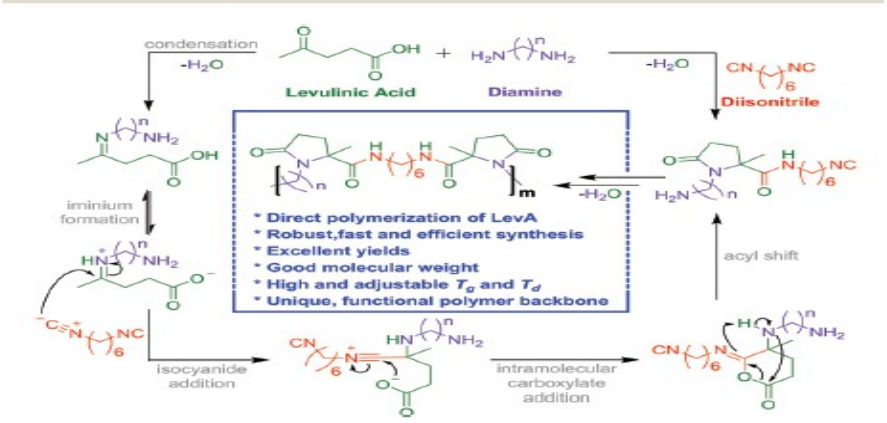
"Additionally, since MCRs are often highly
compatible with a range of unprotected orthogonal functional groups - on a second level -

the scaffold diversity of MCR can be greatly enhanced by the introduction of orthogonal functional groups into the primary MCR product and reacting them in subsequent transformations, e.g. ring forming reaction. This two layered strategy has been extremely fruitful in the past leading to a great manifold of scaffolds now routinely used in combinatorial and medicinal chemistry for drug discovery purposes."

MCR literature is vast, including several recent books (Zhu, Jieping, Qian Wang, and Meixiang Wang, eds. "*Multicomponent reactions in organic synthesis*.", John Wiley & Sons, 2014. and Zhu, Jieping, and Hugues Bienaymé, eds."*Multicomponent reactions*.", John Wiley & Sons, 2006.) ; therefore, rather than attempting to show examples of what can be attached to derivatized PVP, I suggest looking at these references. Many MCRs may not be designed as chain extenders of PVP but as methods to attach pro-drugs to PVP (conjugates) to take advantage of the ultra low toxicity that PVP would contribute, not to mention water solubility(13-15).

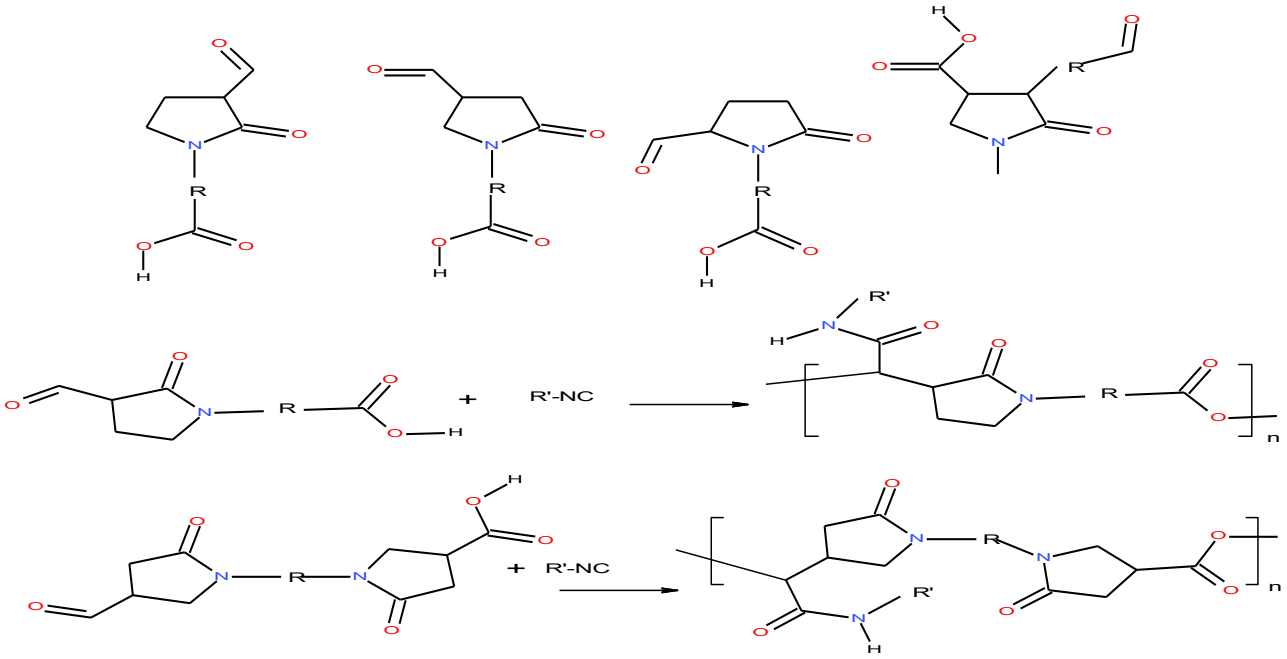
Lactam containing polymers:

PVP is not the only way that polylactams such as those based on pyrrolidone can be visualized. Manuel Hartweg and C. Remzi Becer (16) have prepared such polymers, for example:

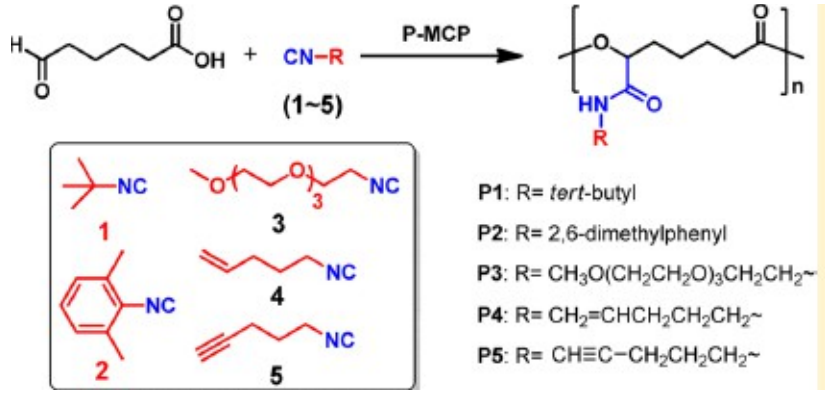


Scheme 1 Proposed mechanism for the Ugi-4C8C polymerization from LevA, diamines, and diisonitriles towards polyamides.

The interesting point is that the lactams are a result of the Ugi mechanism. The above might seem complicated but its just the mechanism. The actual Ugi is simply mixing the ingredients. The Passirini MCR might be more easily applied to lactam derivatives. For example:

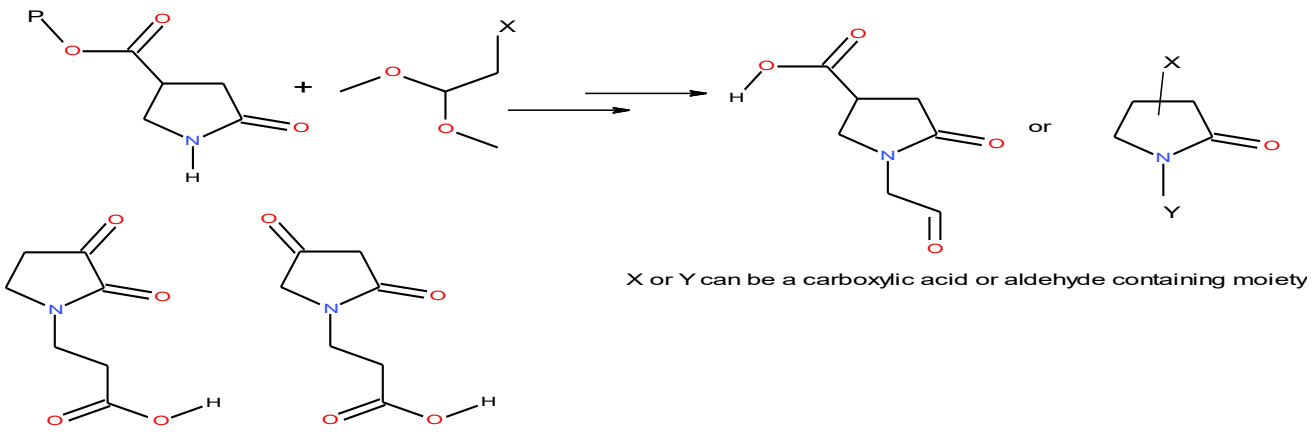


Scheme 3: Several aldehyde/carboxylate monomers are illustrated with two examples of their polymerization(17).

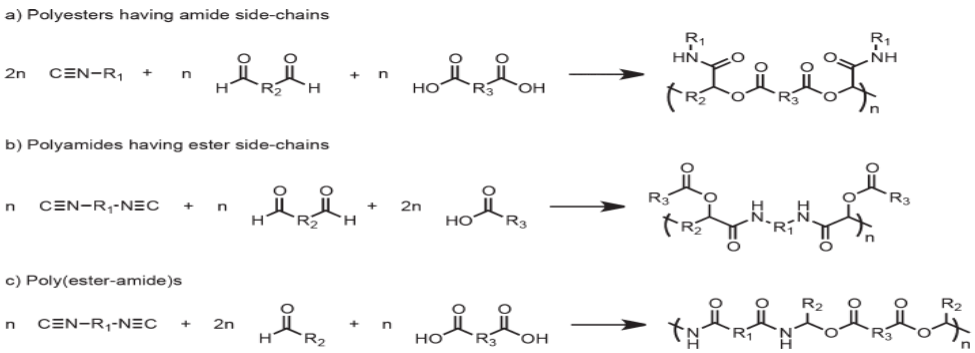


The simple and mild conditions of this high yield MCR is very interesting and applicable to scheme 3 (18).

Other monomer possibilities:

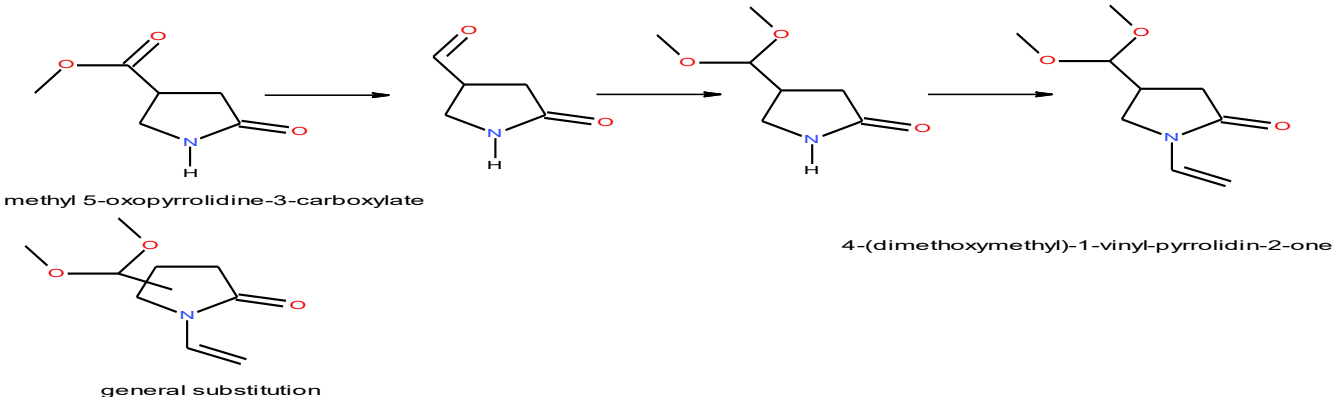


Scheme 4: P=carboxylic acid protecting group. Itaconic acid starting RM is highlighted but 3,4 and 5 positions on the lactam can be readily functionalized(19-23).



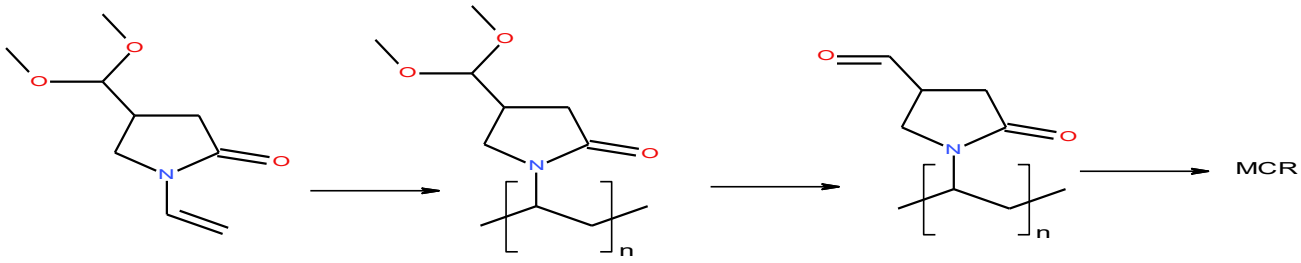
SCHEME 3 Structures of linear polymers obtained from various Passerini three-component polycondensation reactions.[4–6] The structures illustrate the controlled sequence in which the monomers are incorporated in the polymer chain.

The above shows the various approaches to three polymer possibilities. Although one can model the same polymerizations with lactam containing components, the goal would be to prepare lactam containing polymers that would be more useful in the same or similar applications as compared to PVP.



Scheme 5: Since a carboxylate group can occupy any of the 3-5 lactam

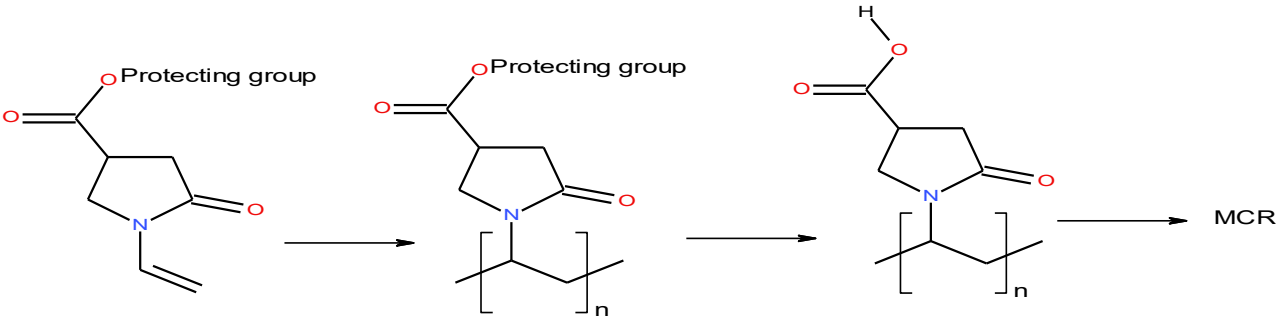
positions, the one illustrated is based on itaconic acid. Several methods are available to convert said carboxylates to aldehydes and to acetals. The acetal group is base stable and would be expected to survive vinylation. The resulting monomer would behave much like NVP and undergo the same homo & co-polymerizations



Scheme 6:

The unmasking of the acetal is simply accomplished in acidic solution and can be performed in the presence of Passerini or Ugi MCR components or done preliminary to the MCR reactions.

Instead of an aldehyde, the carboxylate can be also converted to the ketone and then the ketal which can be vinylated; should the ketone be required instead of the aldehyde.

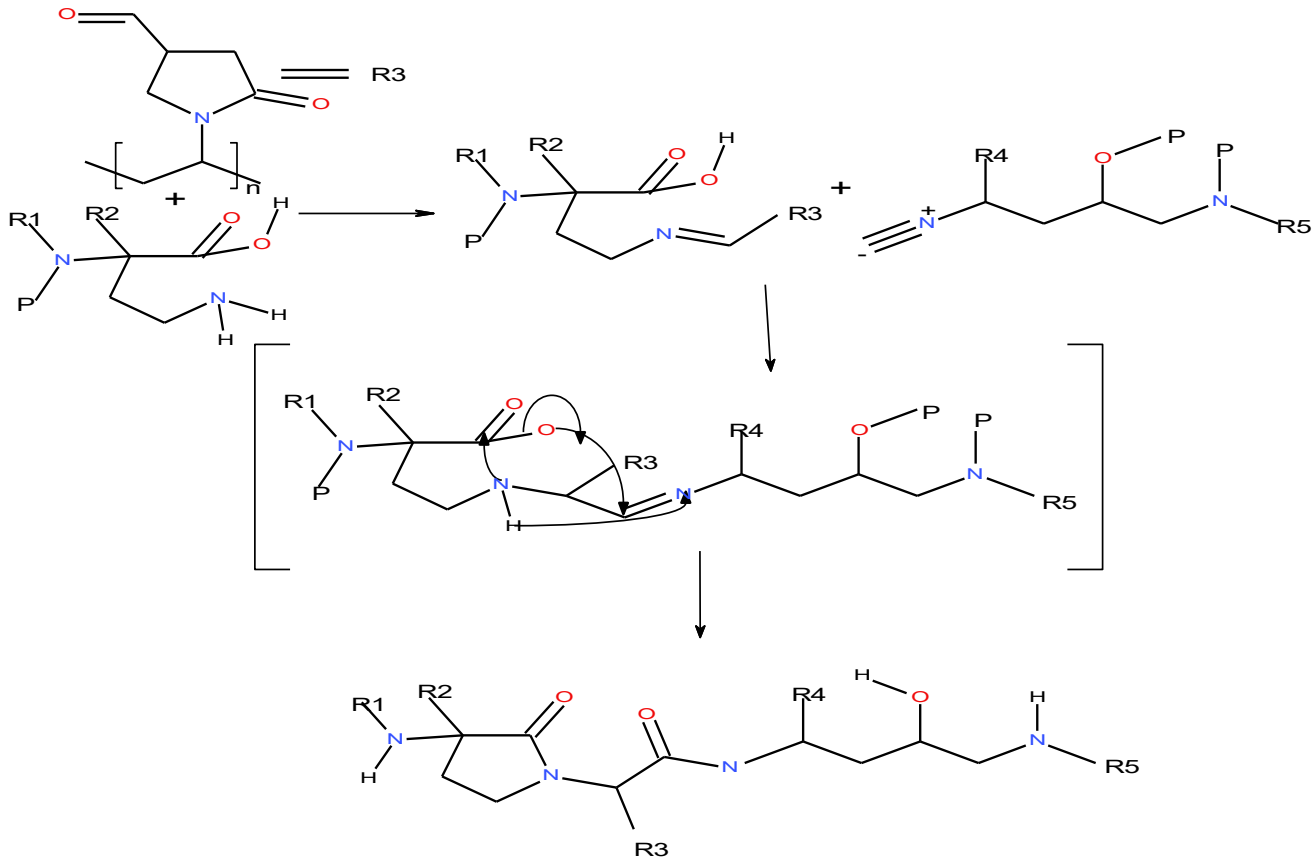


Scheme 7:

This would be the simplest method of producing a monomer that would participate in MCR reactions. In fact N-vinyl pyroglutamic acid is known but has very few references(24-25). The ester can be converted to an amide which can be rearranged to the amine, then the amine protected and the lactam then vinylated; therefore, derivatized NVP monomers with aldehyde, or ketone

or carboxylic acid or amine can be synthesized. In fact, as additives to PVP, more than one type of said monomers can be copolymerized with NVP or combinations of NVP and other monomers such as DMAEMA or vinyl acetate etc. to prepare terpolymers that can be cross-linked because two MCR components can be linked together.

There are obviously several additional ways to view this MCR chemistry. Many new drugs are being developed with MCR and if they can be linked to said derivatised PVP's which could be a method of safe drug delivery. Employing said monomers themselves, in various MCR drug or antibiotic type motifs would result in new monomers that could be polymerized in controlled radical polymerizations to benefit from these CRP procedures.

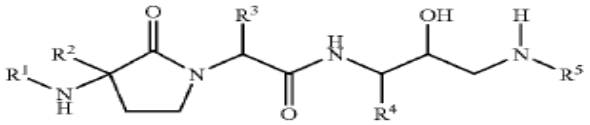


Scheme 8 P=protective moiety

Scheme 8 is an example of a patented (US 7,557,137 B2) Alzheimer drug that can be prepared by MCR and attached to an aldehyde (R3 with suitable cleavable functionality) containing PVP copolymers for delivery to targets.

(57) **ABSTRACT**

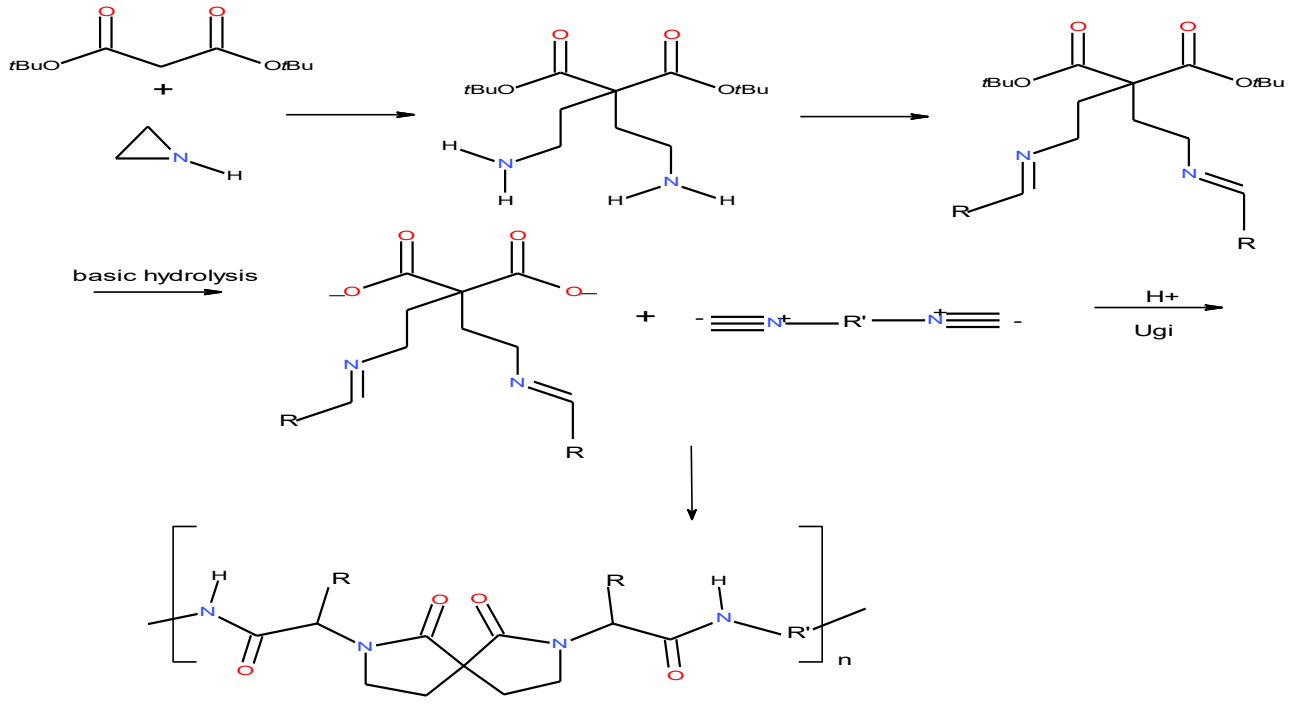
There is provided a series of novel substituted gamma-lactams of Formula (I)



(I)

wherein R^1, R^2, R^3, R^4 and R^5 are defined herein, their pharmaceutical compositions and methods of use. These novel compounds inhibit the processing of amyloid precursor protein (APP) by β-secretase and, more specifically, inhibit the production of Aβ-peptide. The present invention is directed to compounds useful in the treatment of neurological disorders related to β-amyloid production, such as Alzheimer's disease and other conditions affected by anti-amyloid activity.

Polymers can also be conceived with dimer pyrrolidones as described in a previous proposal (see rloginconsulting.com). Said dimers must first be hydrolyzed to dimers of aminobutyric acids. The following is another example of this Ugi polymerization:

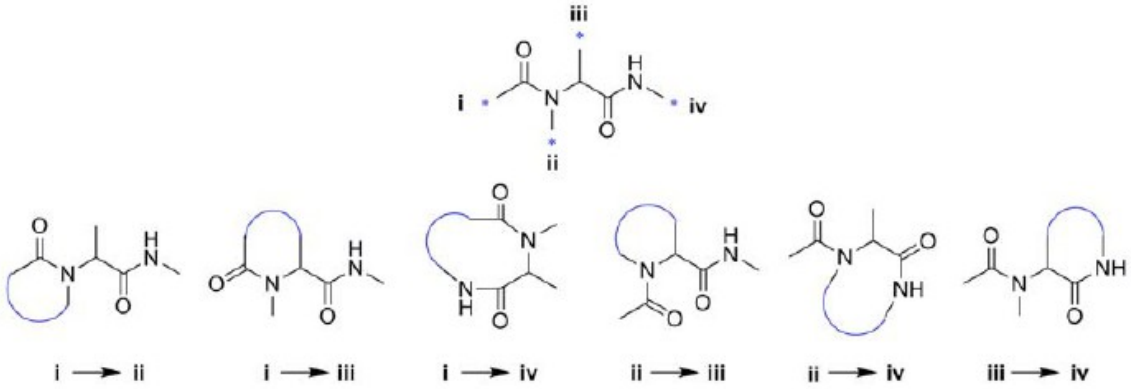


Scheme 9

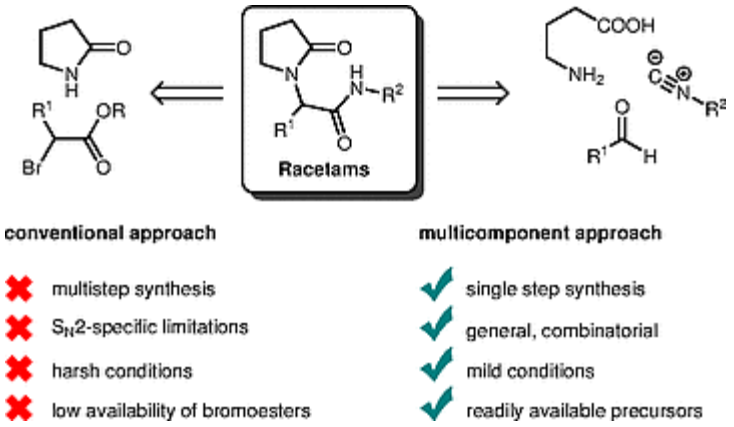
Obviously many variations of scheme 9 are possible.

The Ugi MCR is very applicable to synthesis of pyrrolidones by ring closure.

Scheme 8. Possible cyclic scaffolds available via post-modification of U-4CR

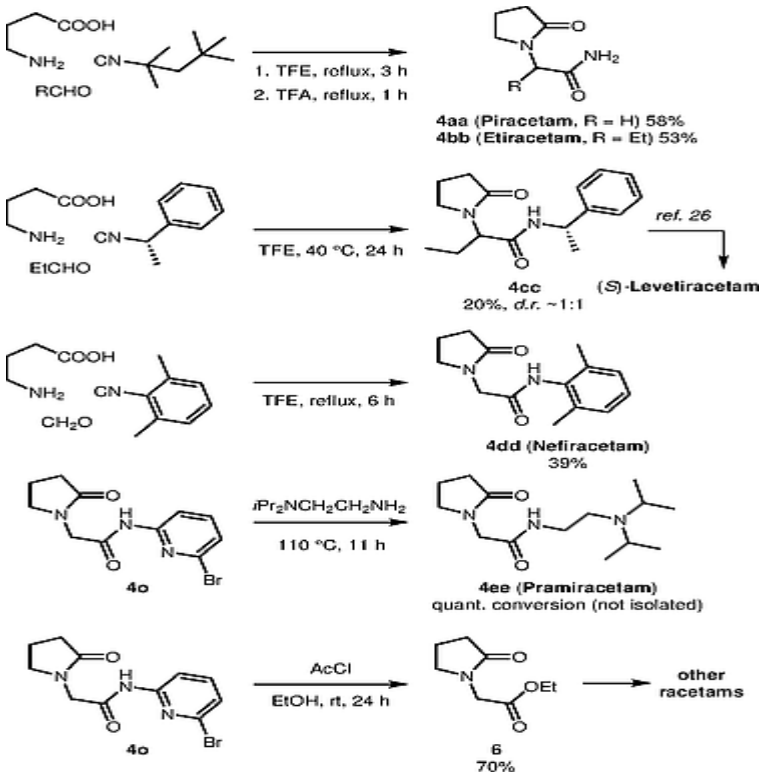


As can be seen, three pyrrolidone possibilities are i-ii; i-iii and iii-iv. This means that the indicated components must be either tethered together or have orthogonal moieties that can post react to form the pyrrolidone.



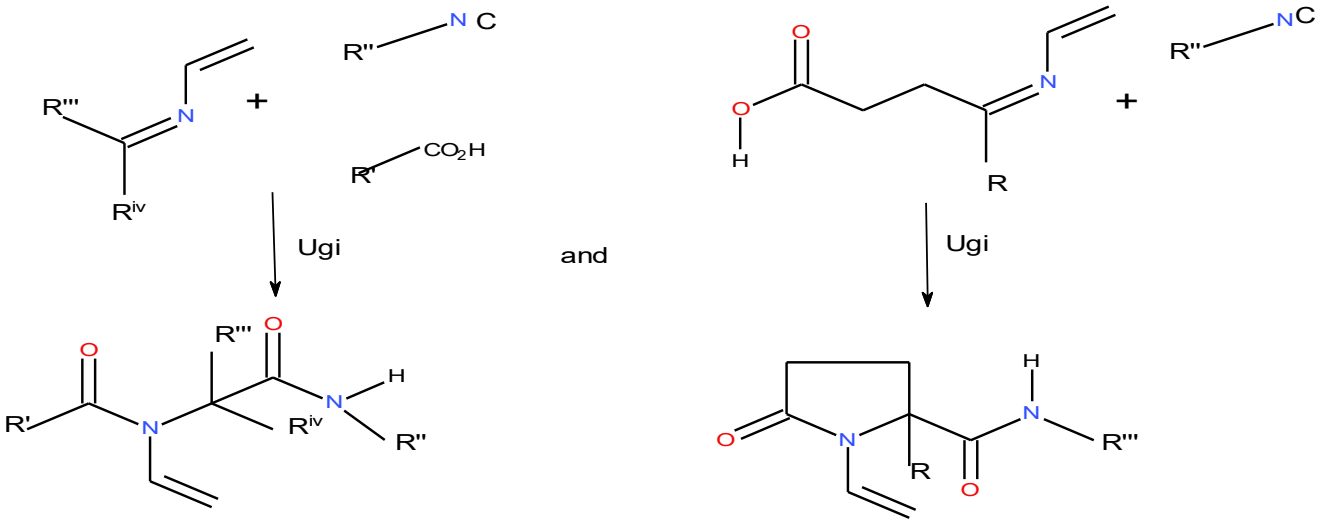
(26)

As can be seen this Ugi is an example of i-ii.



Synthesis of clinically important racetams(26)

As a final proposal I have a Ugi-4CR reaction that goes directly to an NVP monomer derivative.



Scheme 10

Scheme 10 is based on the well known 2-aza-butadiene type derivative(27-32). I have not found any references to this Ugi-4CR reaction and believe its original. The benefit of this reaction is the huge number of derivatives that can theoretically be possible. Each one would be a polymerizable monomer. This is not just limited to NVP's but to every possible vinyl amide availible by this reaction. Someone skilled in the Ugi art could come up with all kinds of valuable derivatives by functionalizing with

moieties that act as phophoresence markers, prodrugs that can be copolymerized with NVP for drug delivery, dyes or UV blockers, hair fixatives and conditioner functionality that can be copolymerized as a safe way to deliver such functions.

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Thanks for reading.
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