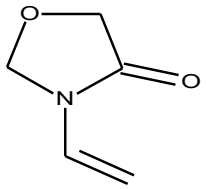
New Heterocyclic Monomers and Polymers

By Robert B Login

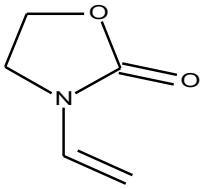
I find the ability to search the literature using Google very stimulating. Who would have thought that you could in a flash search all US patents, when I had to actually go to the patent office in the past to search by hand (and if you wanted copies they were $2 each!). This ability has allowed me to read about new discoveries, and I can't help having new ideas that might have commercial value. Since I spent a lot of time thinking about the pyrrolidone moiety when I worked for ISP, it is just natural for me to think of new related structures and several of the previous reports now on my web page (see: rloginconsulting.com) are also concerned with this very subject. I will elaborate on my new ideas in the following pages.

The fact that the five member pyrrolidone ring allows maximum overlap of the p-orbitals of the two resonance forms of the lactam suggests that this favorable overlap will also be evident in a variety of other five membered lactams. Chart 1 below illustrates some possibilities:

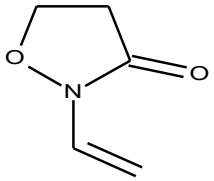
Vinyl Monomers



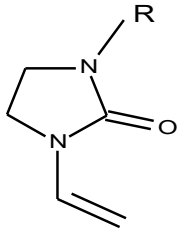
oxazolidin-4-one



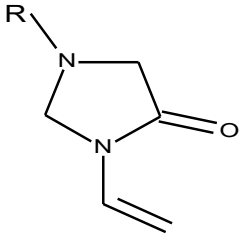
oxazolidin-2-one



isoxazolidin-3-one



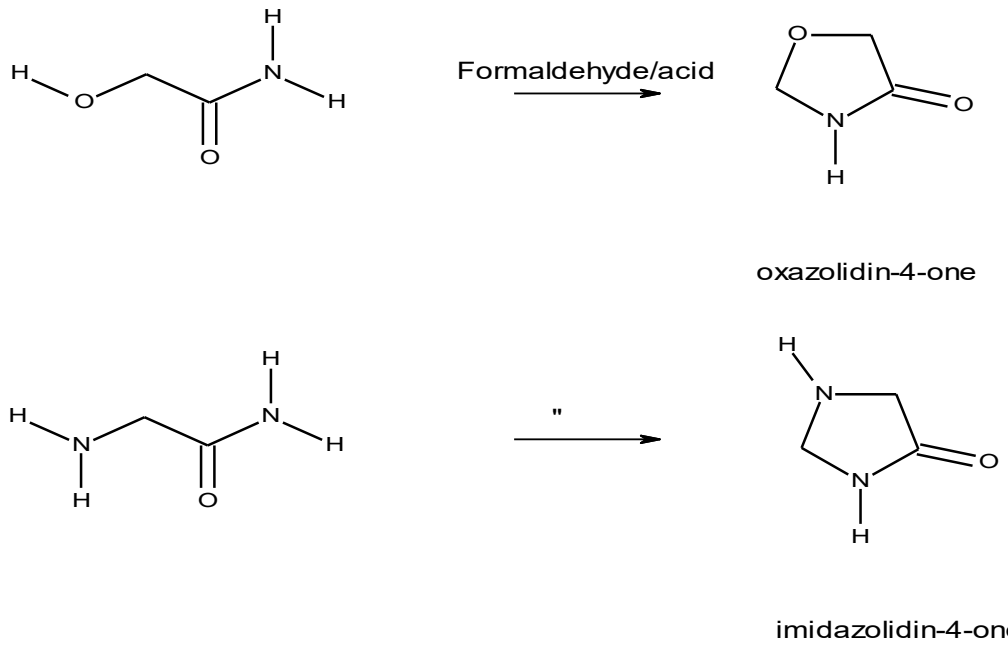
imidazolidin-2-one



imidazolidin-4-one

Of these five, the oxazolidin-2-ones and 4-ones and the imidazolidin-2-ones have been vinylated and polymerized as revealed in patents to Dow and BASF. The oxazolidin-2-one has a significant patent literature (USP 2,946,773 for example, assigned to Dow) but I believe it is no longer commercially available. Besides utility, the high cost of overcoming the regulatory hurdles might have killed this polymer. I however find this hard to believe, as Dow has enormous resources and the market for PVP is very lucrative. My suspicion is that it is hydrolytically unstable?

The isoxazolidin-3-one has a reference (EP 0224057A1 but nothing about the corresponding N-vinyl monomer) and would be worth checking out. Two of the above monomers are referred to as Seebach oxazolidinones and imidazolidinones and versions are of significant value for the synthesis of relatively pure amino acid stereoisomers (Handbook on Synthesis of Amino Acids; Oxford press 2010, pp532-566). Both can be prepared from lactic or glycine amides as follows:



Any aldehyde or ketone can be considered but formaldehyde is the simplest example. N-Vinyl Oxazolidin-4-one is known (USP 3,231,548 Dunn to UnionCarbide, 1966; however, no further information has been found) indicating that the lactam nitrogen as with pyrrolidone, is acidic and undergoes base catalyzed vinylation with acetylene (with regard to the imidazolidin-4-one amine, it would have to be protected during vinylation, however). Various additional vinylation synthesis methods are also possible if vinylation with acetylene is a problem and this goes also for the other monomers I will describe (see Kirsh, Water Soluble Poly-N-Vinylamides; Wiley, 1998).

In fact with the imidazolidin-4-one, if an R group is attached to the amine or amide nitrogen, and its an alkyl group in the surfactant range, interesting cationic surfactants or monomers can be visualized. An C8-20 aldehyde or ketone would also generate surface active imidazolidin-4-ones.

Another property of these structures (chart 1) is that it is possible under certain conditions to reverse ring formation with the release of the carbonyl compound. This is a complicated situation depending on pH, aqueous solubility, substituents etc. With this in mind a literature describing these heterocycles as pro-drugs is available (Euro JOC 14, 28376-2854, 2012 and Tetrahedron 62, 2006, 9883-9891). The idea is that the cyclic imidazolidin-4-one protects the amino acid amide from deactivation by enzymes but eventually hydrolyzes in-vivo revealing the active where it can do some good. However, no references to said polymeric versions of these compounds have been found. In any case, release of the carbonyl molecule from the polymer would be retarded as the reactions of polymers although the same as small molecules, is usually slower. This would allow the polymer the stability to reach its medical target before releasing the active(aka Pro-drugs). Carefully tailored copolymers can be designed to transport suitable reactive drugs to selected targets. This idea would also apply to said surfactants

(See: *Macromolecules* **2009**, *42*, 3-13 for a review of Polymer-Based Therapeutics). Chart 2 illustrates this idea showing three possible monomers (A,B&C) that would release the amino acid amide or amides or small peptides from polymers based on these monomers or in other words polymeric pro-drugs.

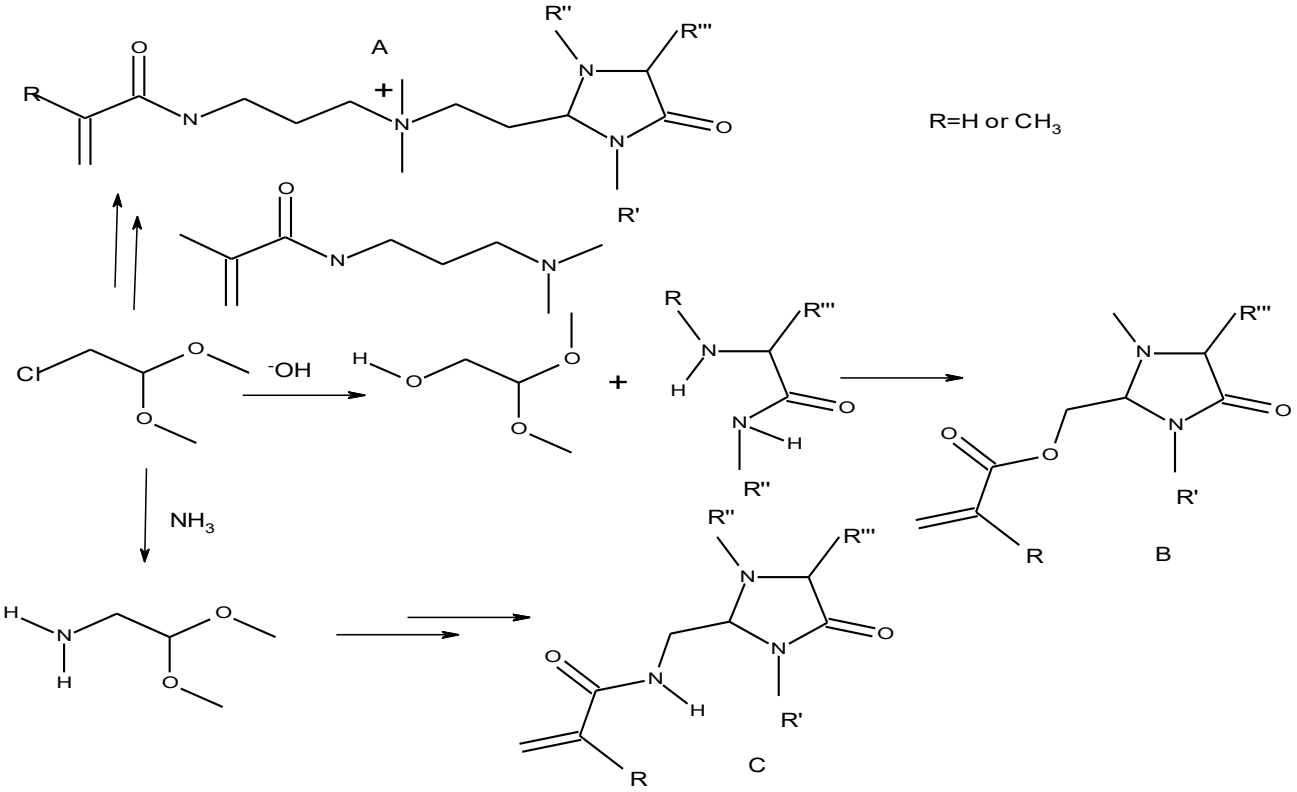


Chart 2

The advantage of these pyrrolidone analogs is that they are easily constructed from readily available natural products...lactic acid and amino acids. This then would be a "green" approach to a NVP replacement or complementary monomer or surfactant. Furthermore,the imidazolidinones based polymers because of the amine could be neutralized or quaternized to form cationic polymers before or after polymerization.

Another possibility is to employ various primary diamines. For example:

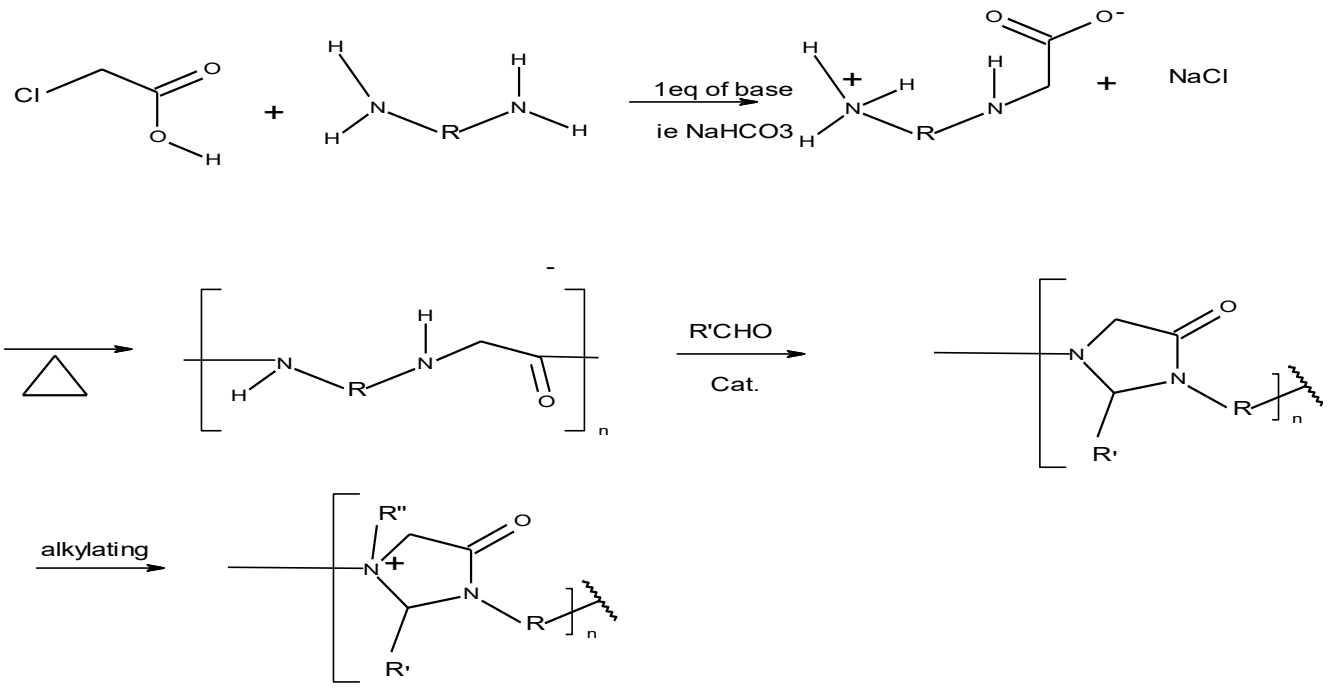


Chart 3

In the first step, one could also use the chloroacetic acid chloride and nylon 2 are known polymers; however, subsequent conversion to the imidazolidinone and quaternization is novel. In this scheme only readily available rm's are employed. An extensive series of derivatives can be visualized as the R groups can be readily varied. Polyimidazolidones would be very interesting as they are unknown and would have the possibility of unexpected chemistry and applications. Reversal of the reaction freeing the aldehyde is also possible here also.

Other monomers are shown in Chart 4:

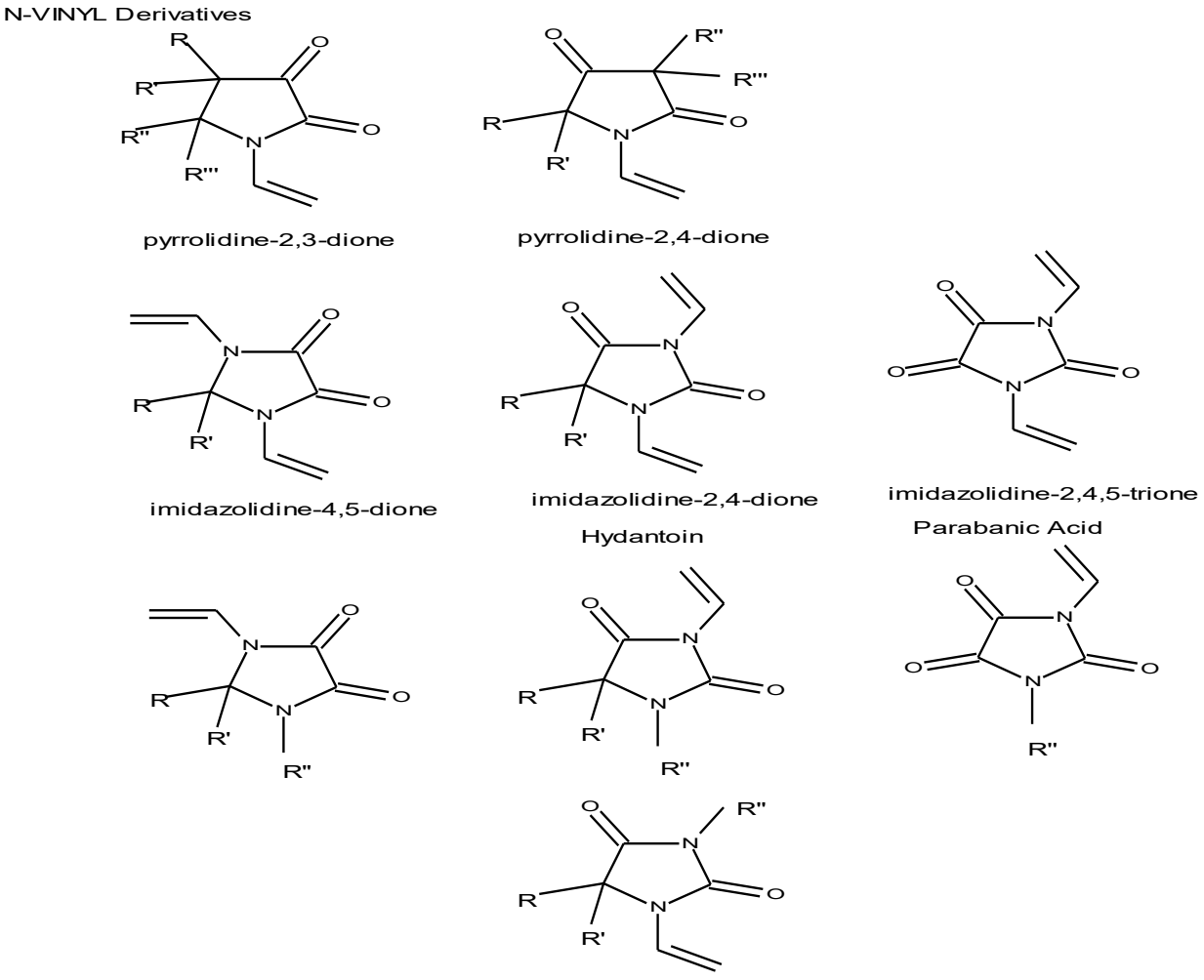


Chart 4. Listed below are references to N-vinyl derivatives of the above monomers:

1. Schulz, Rolf C., and H. Hartmann. *Angewandte Chemie International Edition in English* 1.4 (1962): 215-216.
2. Herzog et. al., USP 4,055,570, Oct. 25, 1977.
3. Zussman et. al. USP 4,091,223, May 23, 1978.
4. Jones, Brit 846,601, May 1958.
5. Zussman et. al. 4,091,223, May 23, 1978.
6. Gubitz, USP 3,197,477; Jul. 27, 1965.
7. Sun et al.US 6,768,009 B1 Jul. 27, 20043
8. Sun et al. US 7,084,208 B2 Aug. 1, 2006

The above heterocyclic diones and triones are additional examples of pyrrolidone analogs. Most of these are known heterocyclic compounds because of pharmaceutical activity; however, some literature (see above) to N-vinyl derivatives has been found. BASF (USP 3,933,766) employed the N,N'-divinylimidazolidone-2 for the proliferous polymerization of NVP. The hydantoin mono and divinyl monomer are known(ref 4-6). The first two in chart 2 would have to have the carbonyl groups protected with acetal or ketals or as acylated enols before the lactam could be vinylated.

Of the above references, 7 and 8 show many of these monomers for use in polymers for application to textiles. The polymers are readily converted to N-halamine structures on exposure to a halogen source such as commercially available chlorine bleach. The N-halamine derivatives exhibit potent antibacterial properties against microorganisms and these properties are durable and regenerable when bound to various textiles. The only examples are to vinyl hydantoin polymers even though a general structure in the patent specification could be interpreted as showing other five membered heterocycles.

The above divinyl examples would be expected to be cross-linkers and could be employed to form gels with several of said mono-vinyl monomers. In addition, these cross-linkers are critical to proliferous polymerization similar to PPVP technology; however, they could also undergo cyclopolymerization (Butler, ACS monograph 1982).

Although all of these monomers would be very interesting; I am especially intrigued by the tetramic acids (pyrrolidine-2,4-diones). For example:

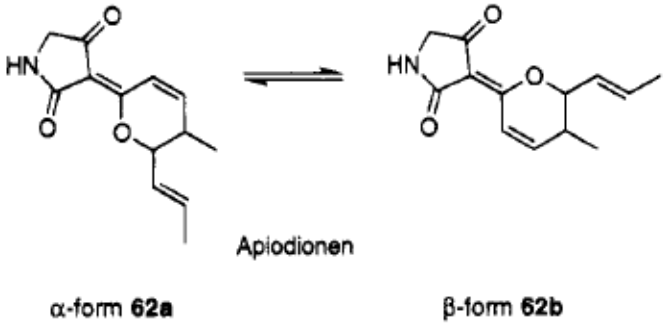
“2,4-Pyrrolidinedione derivatives, so-called tetramic acids, can serve as one of the basic building blocks for bio-active molecules found in a variety of natural products from marine organisms, fungi, and bacteria. Among these compounds, 3-acyl substituted

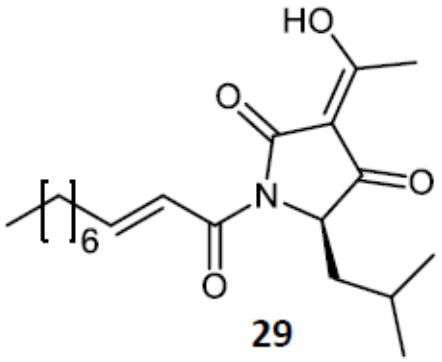
tetramic acids have proven particularly appealing to the medicinal community because of their remarkable potency such as antiviral and anti tumor activities (tenuazonic acid), herbicidal activity (macrocidin A), inhibitory activities against bacterial RNApolymerases(streptolydigin), anti-HIV activity (Sch 213766), and cytotoxicity (penicillenols A1,2). In particular, extensive research focused on streptolydigin, whose outstanding inhibitory activity against bacterial RNA polymerase has received particular attention over the past decade, provided an important stimulus for understanding mechanistic complexities of the biological events." (Sengoku et. al. J. Org. Chem. 2012, 77, 4391−4401.)

Many other references can be found concerning the tetramic acids; however, none have been found concerning the above vinyl lactam derivatives. If the corresponding polymer exhibited some of the above quoted biological properties and because of its size would be innocuous, then this would be a major discovery. The tetramic acids readily assume the enol form and can be easily acylated. Such acyl derivatives of the acrylates would be readily polymerized resulting like the said vinyl lactams in a plethora of polymers and copolymers. Would any of these resulting polymers have biological activity? (See Synthesis of Tetramic Acids and Investigation of their Biological Properties thesis of Catherine P. Katzka https://eldorado.tu-dortmund.de/handle/2003/22512).

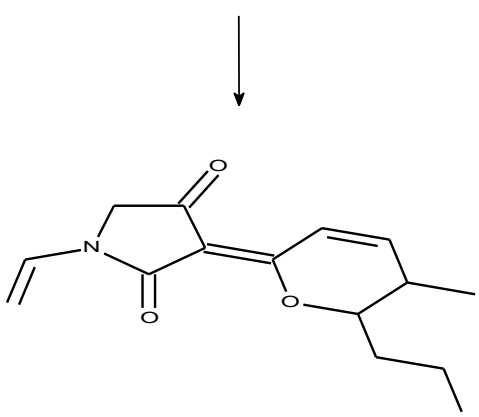
I would try as an approach, to keep those substituents that exhibit the desired biological activity. Such derivatives would still have to be polymerizable monomers. The R, R', R" and R"' groups would be those found in the natural product tetramic acids with the proviso that a vinyl lactam would replace the proton on that nitrogen with a polymerizable vinyl group. If the medicinal tetramic acid is blocked from being vinylated at the nitrogen lactam then if the tetramic acid contains hydroxyls and they could be acylated with (meth)acrylates (def. methacrylates or acrylates) then this would

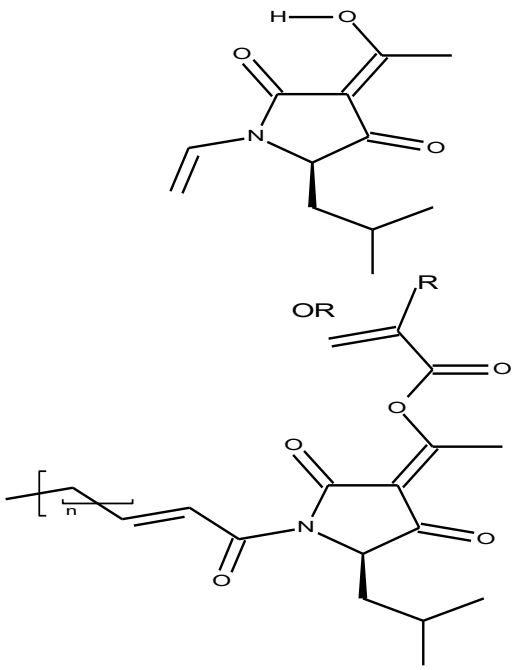
be another route to a polymerizable monomer. Not only can said monomers be homo-polymerized but they can be copolymerized with a wide variety of comonomers. The amount of the tetramic monomer needed for biological activity can be anywhere from 1-100% of said polymers. The following examples show this idea but are for illustration and are not to be considered limiting.





R-reutericyclin





I quote Prof Royles (Chem. Rev. 1995, 95, 1981-2001) ;

“The spectrum of biological activity displayed by tetramic acid-containing natural products is remarkable in its diversity; it includes potent antibiotic, antiviral and antiulcerative properties, cytotoxicity and mycotoxicity, the inhibition of tumors (in mice and humans) as well as fungicidal action. Other members of this class are responsible for the pigmentation of certain molds and sponges. Synthetic analogues of certain tetramic acids have been the subject of clinical investigations, particularly in the antibiotic area,...”

Royles' review affords a glimpse of the variety of tetramic acids known as of 1995.

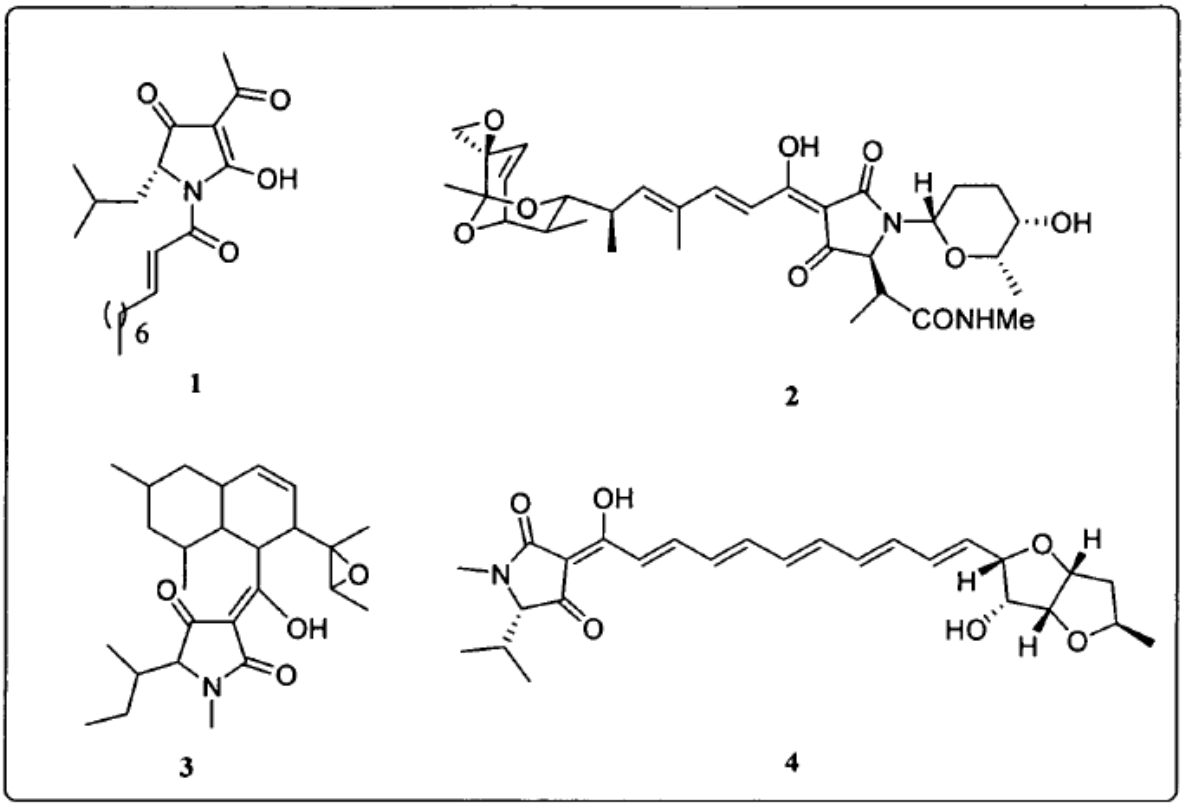


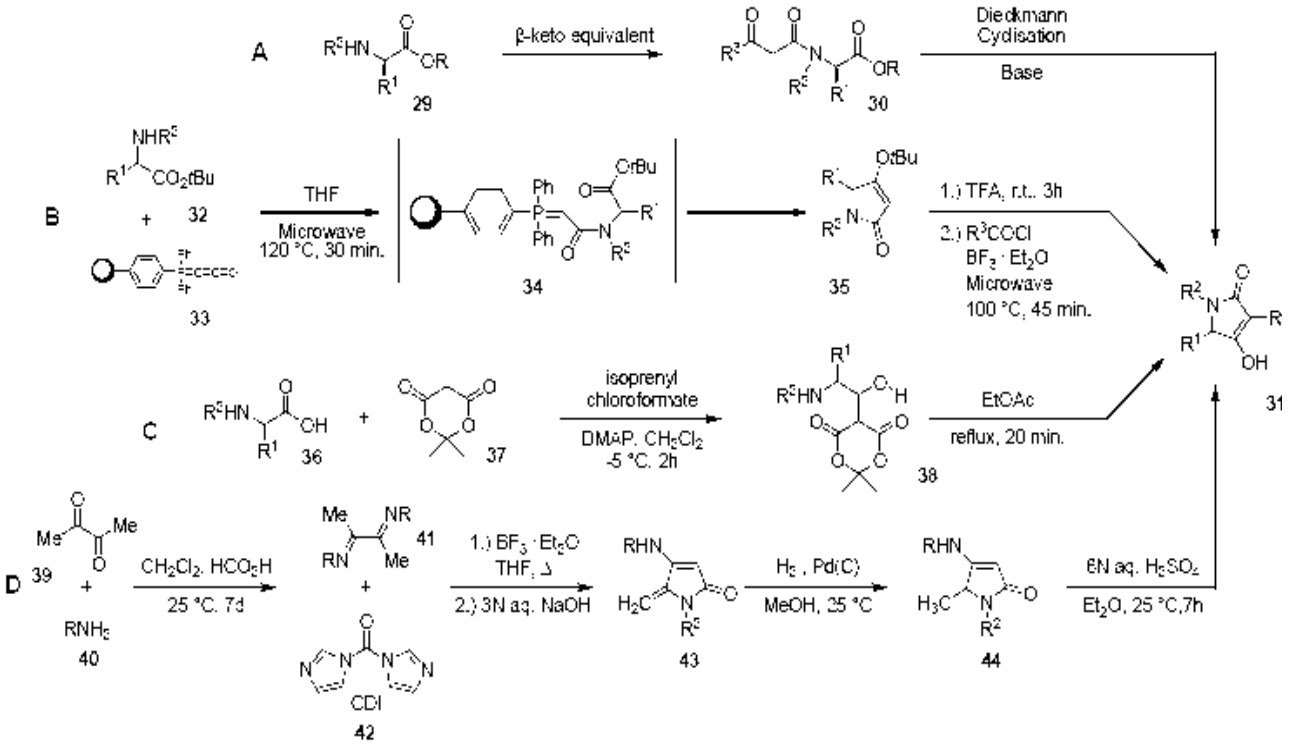
Figure 1

Fig. 1 shows the chemical structure of four naturally occurring tetramic acid derivatives having antibiotic activity. 1. reutericyclin, 2. streptolydigin, 3. PF1052, and 4. is erythroskyrine (Lee et. al. USP 8,552,208 B2, Oct. 8, 2013).

As can be seen there are hydroxyl groups that can be converted to (meth)acrylate ester monomers. I am aware that tethering to a polymer backbone can reduce biological activity; however, as topical skin treatments for example, such polymer-based tetramic structures would have long term activity unlike the easily removed monomeric analogs.

Except for the first two monomers in chart 4, the rest can be divinylated and polymerized with acids such as HBr under anhydrous conditions to form linear polymers stable under basic aqueous solution, only to fall apart when acidified. The resulting fragments would be innocuous and/or biodegradable (as discussed in a previous report on my web page).

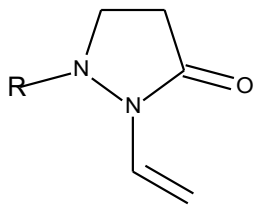
It is also possible that some of the said monomers are actually in the enol form because of conjugation with another carbonyl or the resulting possibility of aromaticity?
The tetramic acids can have the enol as a tuatomer which can be acylated with (meth)acrylate to form a polymerizeable monomer as previously mentioned.



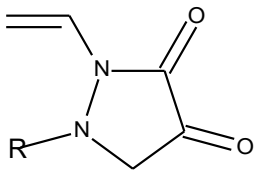
Scheme 3: Summary of recent solution-phase synthesis of tetramic acids.

General overview of tetramic acid synthesis:(From Catherine P. Katzka Dissertation)

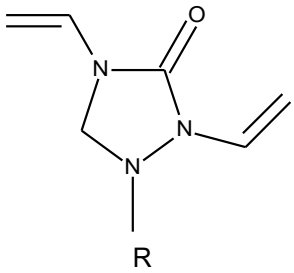
Chart 5 illustrates additional monomers wherein ring nitrogens are connected together.



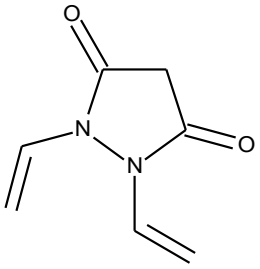
2-vinylpyrazolidin-3-one



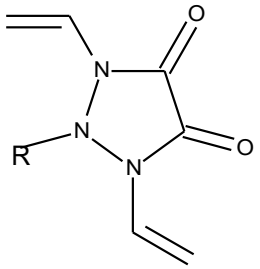
1-vinylpyrazolidine-3,4-dione



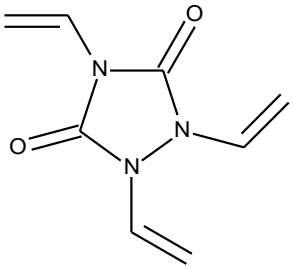
1,4-divinyl-1,2,4-triazolidin-3-one



1,2-divinylpyrazolidine-3,5-dione



1,3-divinyltriazolidine-4,5-dione

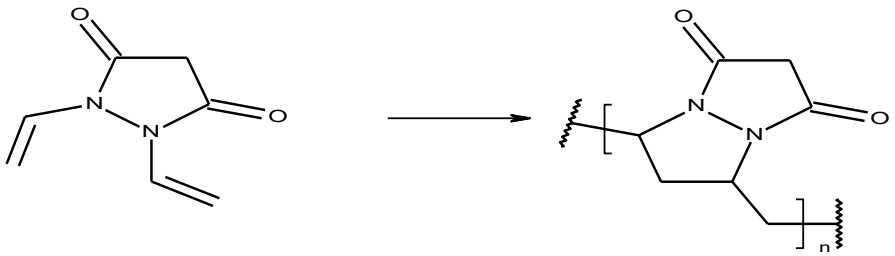


1,2,4-trivinyl-1,2,4-triazolidine-3,5-dione

Chart 5

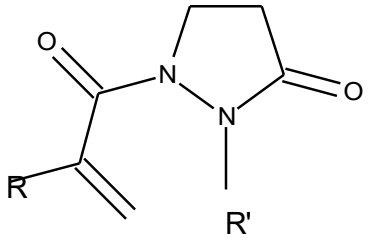
Amino ring atoms are not vinylated but depending on the method of vinylation of the lactam, they would have to be protected with an amide moiety like Boc or other types of amine protecting groups. Every lactam group is shown as being vinylated but partial vinylation where only one lactam is vinylated is also possible and the above structures are not meant to be limiting.

Those examples where the vinyl groups are adjacent to each other would be expected to undergo cyclopolymerization and the resulting bicyclic five membered ring repeat unit results in new valuable linear polymers.

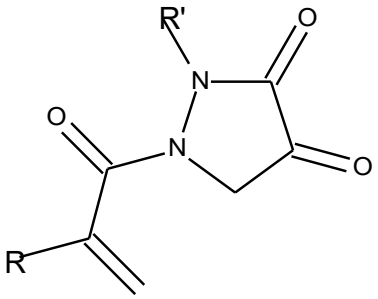


A literature search of these vinyl lactam structures failed to reveal any N-vinyl references (?). The literature concerning the heterocycles themselves, mainly describes pharmaceutical, herbicidal, photographic and dye structures and uses.

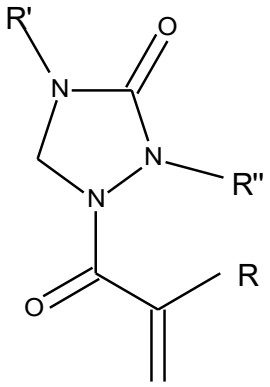
Although vinyl lactams would be closer to NVP, the (meth)acrylamides, easily synthesized from the ring amines and acid chlorides or esters, would also be interesting polymerizable monomers. For example:



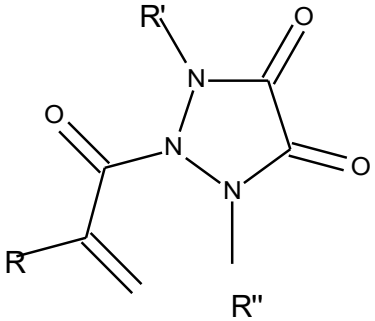
pyrazolidin-3-one



pyrazolidine-3,4-dione



1,2,4-triazolidin-3-one



triazolidine-4,5-dione

R=H or CH_3

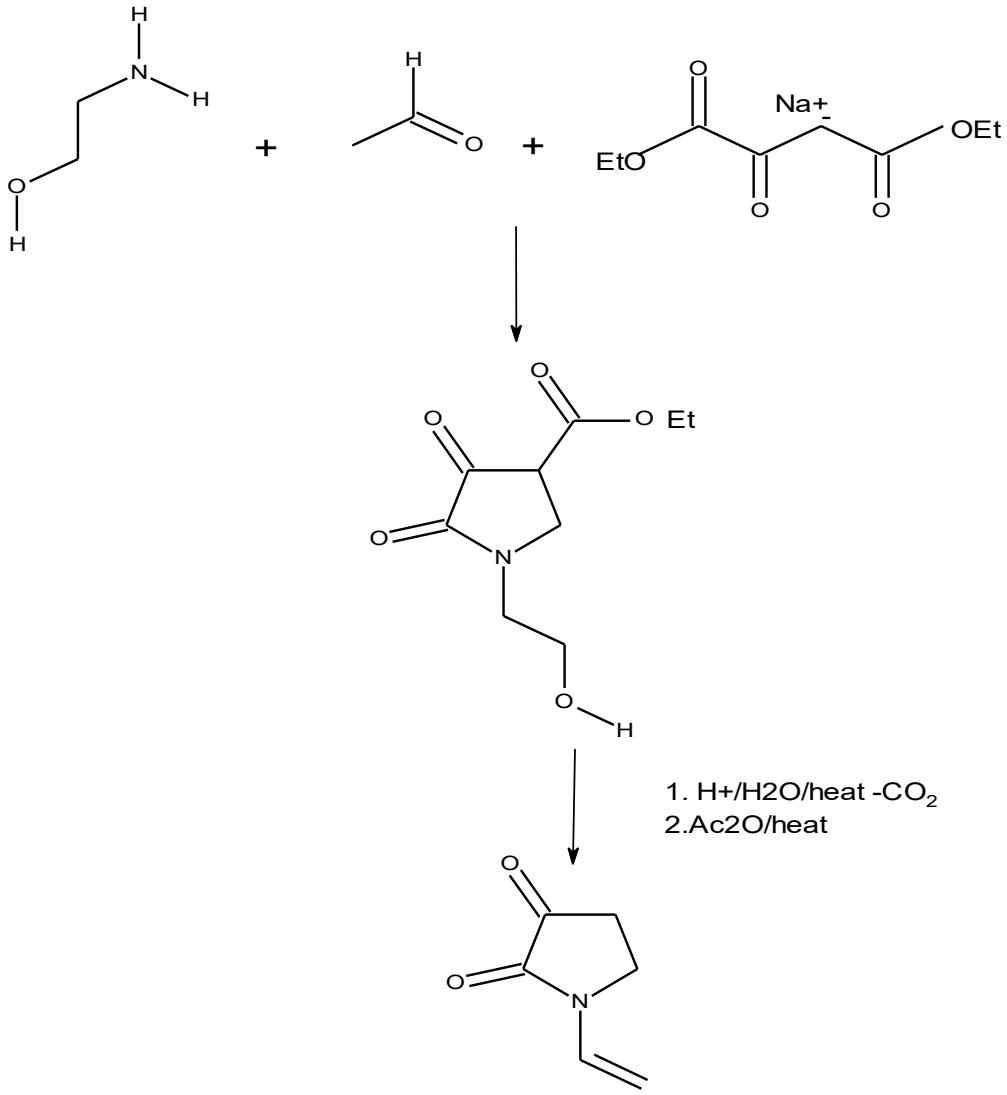
chart 6

Chart 6 shows some of these possibilities and is not meant to be limiting.

The obvious question to ask is what might be the utility of all of these new monomers? In polymer chemistry, the reactions of the repeat units are the same as those of similar small molecules. The difference can be rate of reaction due to steric hindrance. This is why the said polytetramic derivatives might be biologically active even in polymer scenarios? Several of the other monomers that have multiple lactam groups could produce polymers that are more potent complexers vs PVP because of greater polarity. In addition, those that contain amino groups would accentuate complexation of anionic or pseudo anionic target compounds because of their cationic nature. Therefor, the major application for these monomers as polymers is as complexing film formers. Premier amongst these possibilities is as superior iodine and hydrogen peroxide complexes for use as antibiotic film formers for the same applications as the PVP polymers. Besides improved activity in the various PVP applications, several of said monomers and their polymers can be prepared from readily available raw materials and may have an economic advantage. Several are “green” unlike PVP and this may become more and more important to end users.

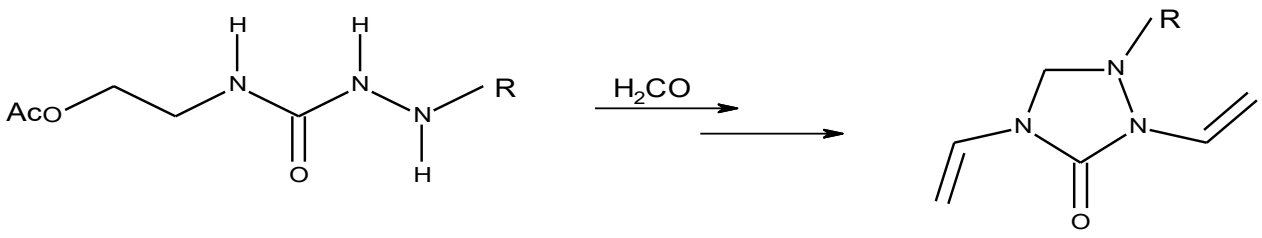
What follows are suggested synthesis of some of these monomers.

The hydantoins are readily prepared by the Bucherer-Bergs Reaction or from amino acids and potassium cyanate and HCl.



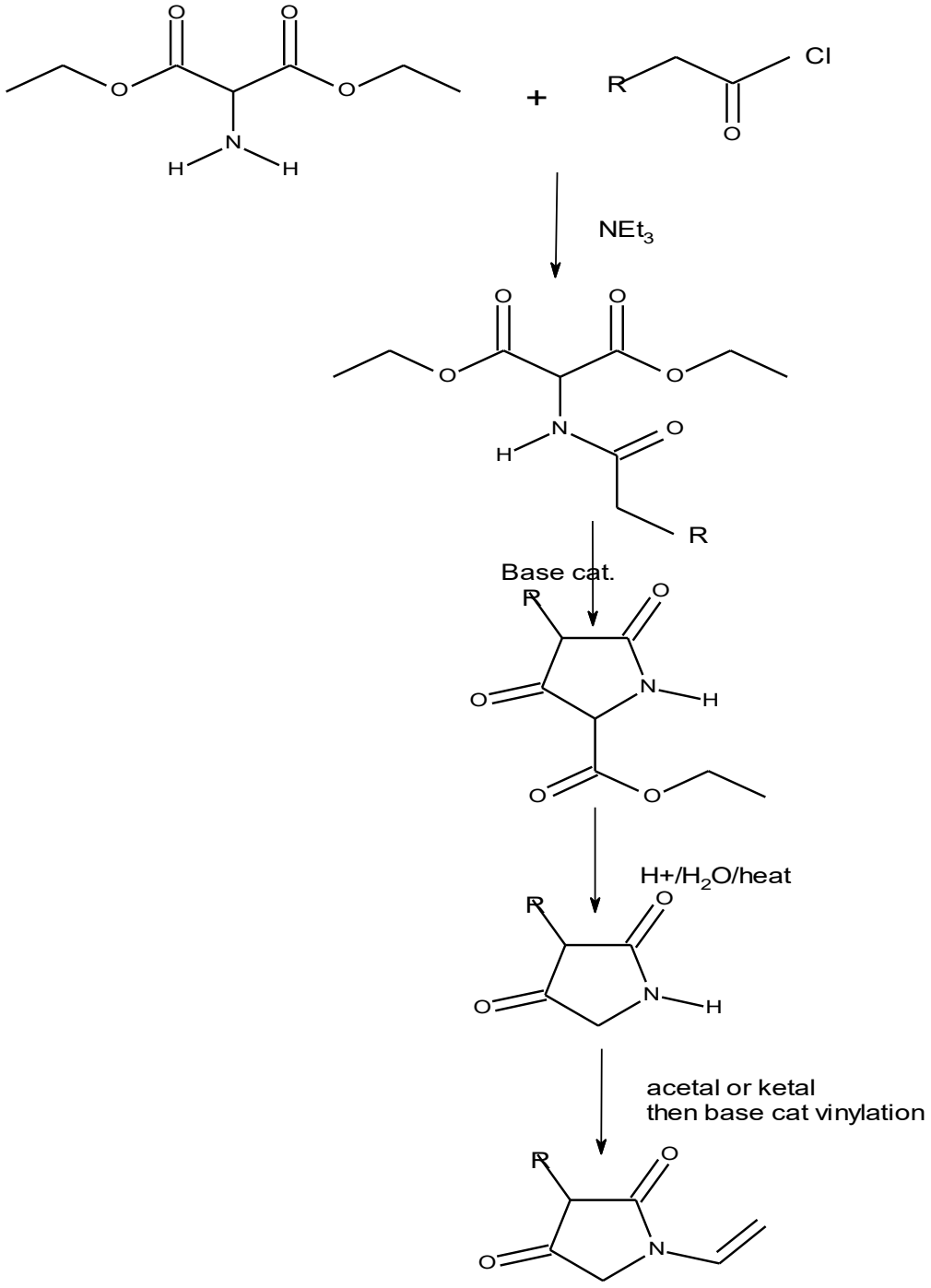
Hillebrand et. al. US 2008/0064736 A1 Mar. 13, 2008

How would homopolymers of this monomer perform? The key thing here is that the 3-one ketone would be available. It could be in the enol tautomer making the polymer more polar. It could be very reactive with alcohols as hemi and ketals would be possible. In other words, it would be a very good at hydrogen bonding. I would think that because of this hydrogen bonding ability, complexes with Iodine (HI3-) and hydrogen peroxide would be very feasible.



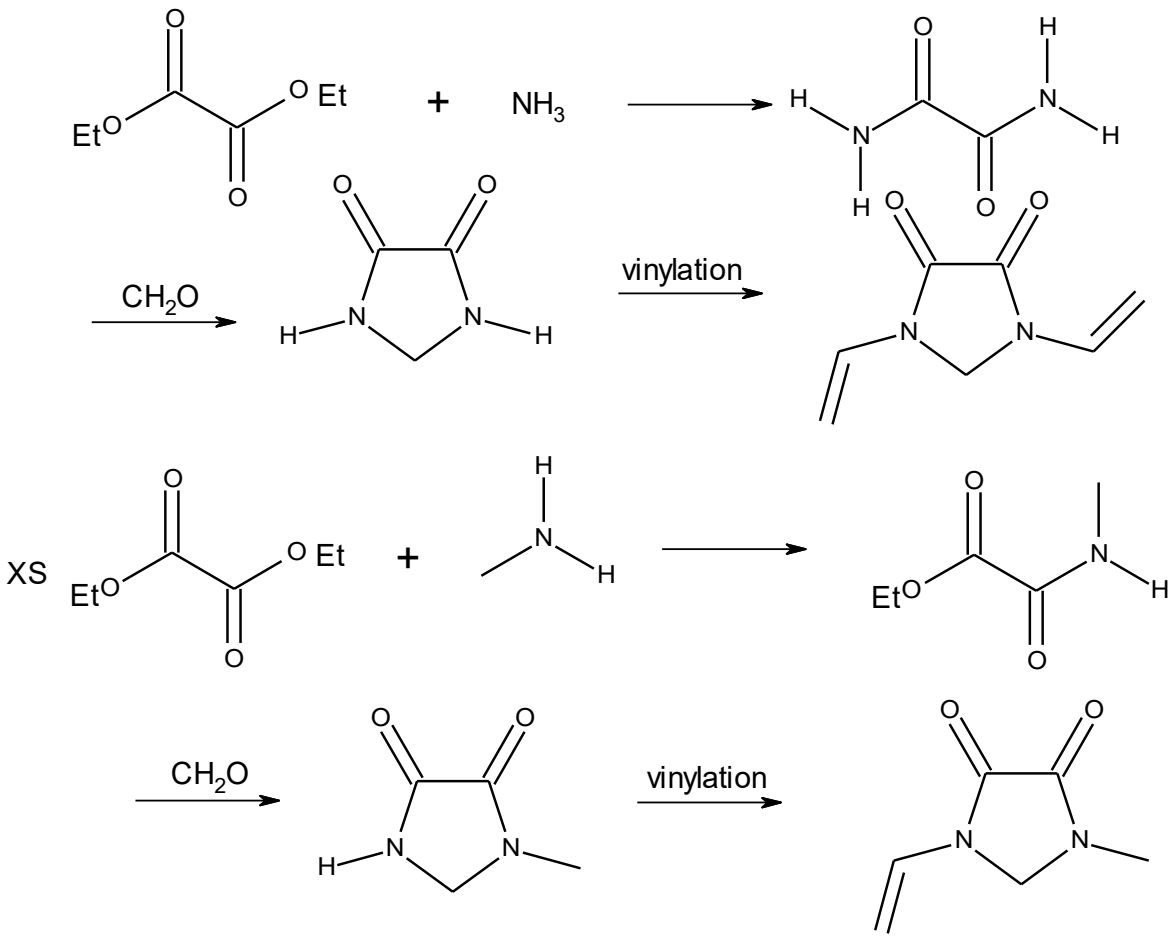
USP 3,922,162

This monomer would produce cross-linked polymers with a difference. The N-R group being an amine, it would confer amine chemistry and most prominent would be those reactions that produce cationic charge. You could form amine or cationic beads that would have ion exchange capability. As a secondary amine, said beads would react with or absorb a variety of acids and polyphenols.



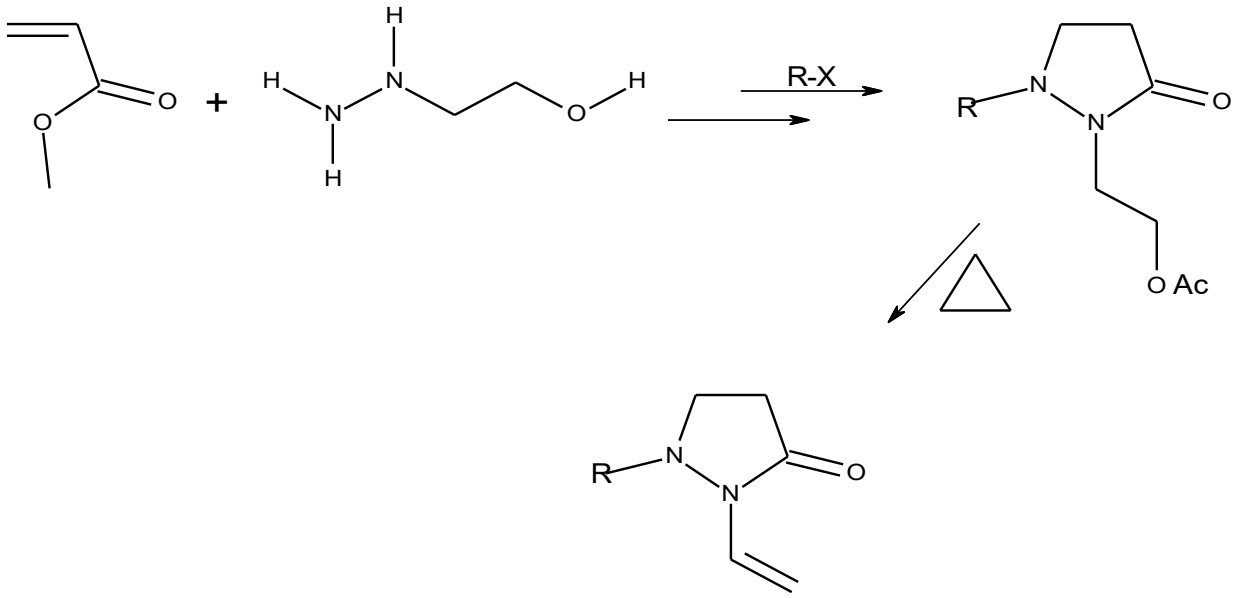
See Aissaui et. al. 2013/0237525 A1 Sep. 12, 2013.

This tetramic acid monomer is similar to the previous ketone containing monomer and would have similar properties. However, it would not readily be in the enol tautomer.



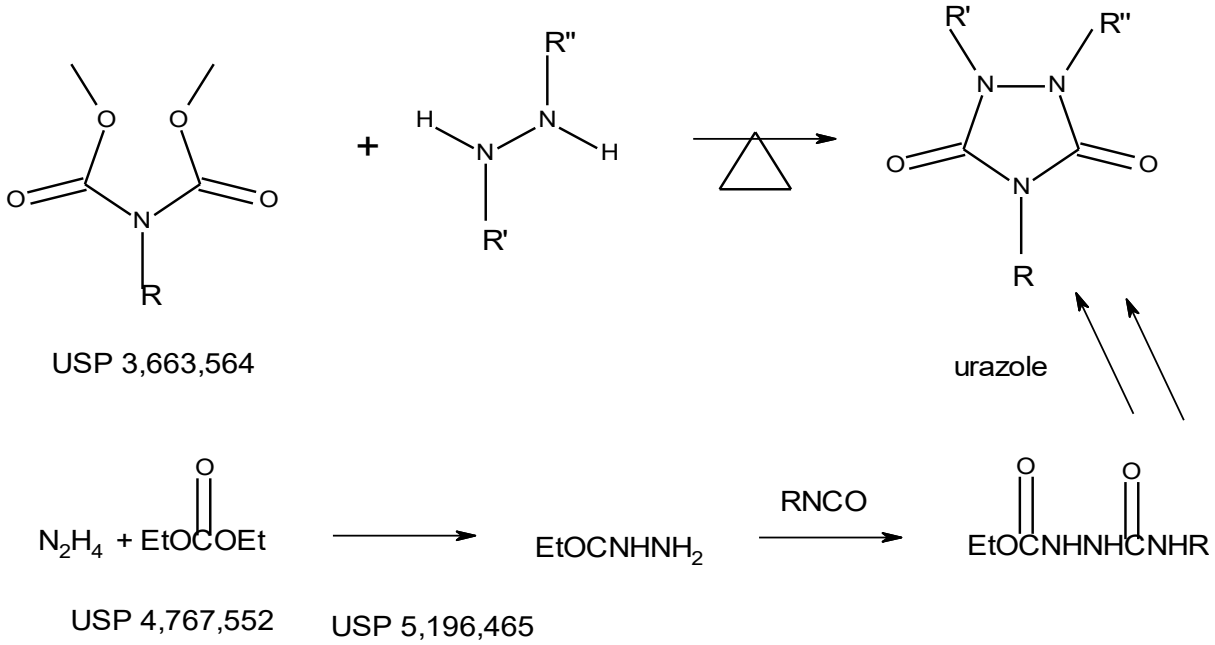
The above divinyl monomer would be a regular cross-linker but the mono-vinyl monomer would produce polymers in which a lactam would face away from the polymer backbone making it much more available for complexation and as an alkyl group like methyl, it would have solubility more like a polymeric version of NMP.

Instead of formaldehyde, a medicinally active carbonyl could be substituted, then this structure, under certain conditions of pH, such as the low pH found in and around tumors, would release said active.



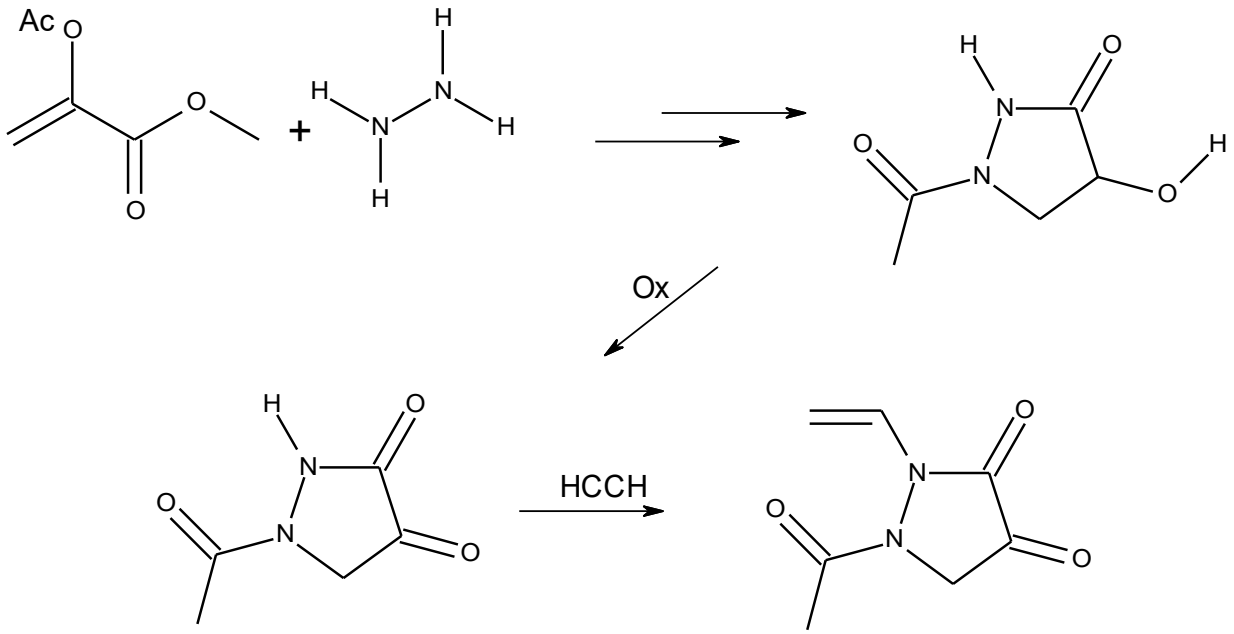
What I like about this monomer is the simplicity of its synthesis. It is prepared from very inexpensive rm's and would be inexpensive to manufacture. Once again it has an amine group but weaker than the previously mentioned amine containing heterocycles. However, in a polymer context said weaker amine would still improve complexation because the compounds like HI3-, hydrogen peroxide and polyphenols are acidic.

J. Org. ***Chem.,*** *Vol.* ***55,*** *No.* ***24,*** *1990 USP 3,178,441* and US 8,648,088



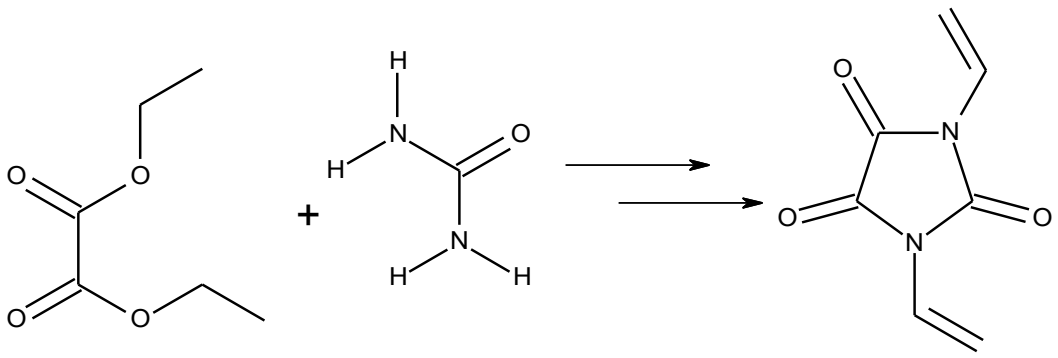
If the R group is hydroxyethyl then this is a synthethic route to a maleimide type N-vinyl

monomer that would form interesting linear polymers. The hydrazene derived nitrogens would complex with a variety of metal cations possibly generating transition metal catalysts with unique properties.



In the above a protecting group like Boc would probably be a better choice than the acetyl group. The starting acetoxy enol might not work as the oxygen would not accept a negative charge on that adjacent carbon; however, I'm not sure because a favored five membered ring is the result. I would try a much more electronegative group like trifluoromethyl acetate if it didn't work.

Removal of the amine protecting group, would reveal a weaker amine as its next to a electronegative lactam nitrogen but as mentioned before, its still an amine and would strongly interact with various acids like polyphenols.

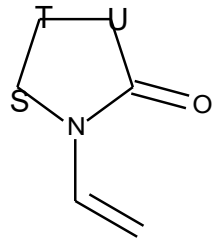


divinyl parabanic acid

The mono vinyl monomer starts with a substituted urea. This monomer would form highly polar polymers. Once again complexing with a wide variety of electron rich compound would be probable. The divinyl monomer could be employed to produce polar beads of all sizes from nano to macro depending on how polymerization is conducted.

I Claim:

1. Polymers and copolymers that can form useful complexes with iodine and hydrogen peroxide, based on five membered heterocyclic free radical polymerizable monomers comprising monomers of the following structure:



wherein:

S,T, and U are each independently selected from the group consisting of N(R), oxygen or C(R')(R") or C=O wherein:

R is selected from the groups consisting of C1-C20 alkyl, vinyl, C3-C7 alkenyl, C3-C7 cycloalkyl, -C(=O)CH=CH2, -C(=O)C(CH3)=CH2, -C(=O)C1-C7 alkyl, -C(=O)phenyl and

R' and R" are independently selected from the groups consisting of hydrogen, C1-20 alkyl, alkenyl, linear or branched or cyclic carbon hydrogen chains, or aromatic moieties, all optionally substituted with oxygen,or nitrogen containing moieties, pendant to or integral to, of said substituents.

2. The monomer of claim 1 wherein:

T and S are C(R')(R") and U is N(R).

3. The monomer of claim 1 wherein:

S and U are C(R')(R") and T is N(R).

4. The monomer of claim 1 wherein:

S and T are C(R')(R") and U is a carbonyl group.

5. The monomer of claim 1 wherein:

S and U are C(R')(R") and T is a carbonyl group.

6. The monomer of claim 1 wherein:

S is C(R')(R") and U is a carbonyl group and T is N(R).

7. The monomer of claim 1 wherein:

S is C(R')(R") and T is a carbonyl group and U is N(R).

8. The monomer of claim 1 wherein:

S is C(R')(R") and T is a carbonyl group and U is N(R) and V is N(R).

9. The monomer of claim 1 wherein:

S and T are carbonyl groups and U is N(R).

10. The monomer of claim 1 wherein:

T and U are C(R')(R") and S is N(R).

11. The monomer of claim 1 wherein:

T is C(R')(R") and S is N(R) and U is a carbonyl group and V is a vinyl group.

12. The monomer of claim 1 wherein:

T is C(R')(R") and S is N(R) and U is N(R).

13. The monomer of claim 1 wherein:

U is C(R')(R") and S is N(R) and T is a carbonyl group.

14. The monomer of claim 1 wherein:

S and T are N(R) and U is a carbonyl group.

15. The monomer of claim 1 wherein:

S and U are N(R) and T is a carbonyl group.

16. The copolymers prepared from the monomers of claim 1 wherein at least 10% of said monomers and the rest of the 90% are co-monomers selected from vinyl pyrrolidone, vinyl acetate, (meth)acrylate esters, (meth)acrylamides and so forth.

17. The polymers prepared from the monomers of claim 1 wherein said polymers are complexed with hydrogen peroxide in liquid or powdered form.

18. The polymers prepared from the monomers of claim 1 wherein said polymers are complexed with iodine.

19. The tetramic acid monomers of claim 1 wherein said R, R',R" and R"' are the same as the groups attached to the various known antibiotic active tetramic acid derivatives such as reutericyclin or streptolydigin or PF1052, or erythroskyrine, with the proviso that if the lactam is -NHCO- then the said lactam nitrogen is vinylated; if not, then a hydroxyl group is converted to a (meth)acrylate ester.

20. Polyimidazolidinones prepared from diamines and chloroacetic acid derivatives post converted to the imidazolidinone with the reaction of aldehydes or ketones with said nylon 2 polymers and optionally partially neutralized or quaternized to a cationic species.