Poly(Lenalidomides and Pomalidomides)

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For personal reasons I've become interested in multiple myeloma medicinals. Of the several now used, two are squarely in the realm of organic chemistry, Lenalidomide and Pomalidomide. I have reviewed their chemistry in a previous pdf and I refer you to that reference(rloginconsulting.com/joomla/images/SiteFiles/Patents/pheonix2.pdf). In the interim since that article, I have continued to think of what else might be suggested as far as analogs that might not have been previously considered. The following ideas are from an Organic/Polymer Chemists point of view.

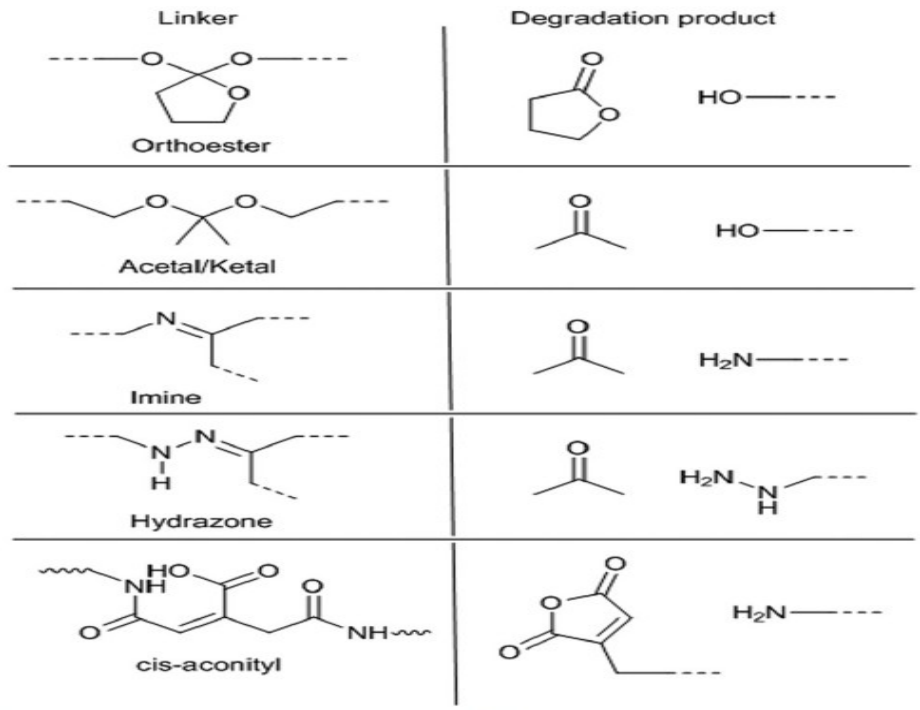


Fig. 2 Examples of acid-degradable bonds and their degradation products.

Binauld, S., & Stenzel, M. H. (2013). Acid-degradable polymers for drug delivery: a decade of innovation. *Chemical communications*, *49*(21), 2082-2102.

My thinking is to employ acid labile linkages to cross-link thalidomide analogs so that they would initially be nontoxic but in acidic cancer cells, would result in their hydrolysis to the active drug.

“The pH value of cancerous tissues is different from those of blood and healthy tissues [36,37]. Tumor cells have lower intracellular pH, with a pH value of 5.0–6.0 in endosomes and 4.0–5.0 in lysosomes [38], than a normal physiological environment.

The differences in pH values between normal and tumor tissues provide an effective strategy for targeted delivery of therapeutic drugs to tumor tissues and/or cancer cells by micelles. Endosomal pH sensitivity, in particular, has stood out as an effective approach for the intracellular release of payloads after the cellular uptake of micelles."

Pu, X., Zhao, L., Li, J., Song, R., Wang, Y., Yu, K., ... & Chang, S. (2019). A polymeric micelle with an endosomal pH-sensitivity for intracellular delivery and enhanced anti tumor efficacy of hydroxycamptothecin. *Acta biomaterialia*, *88*, 357-369.

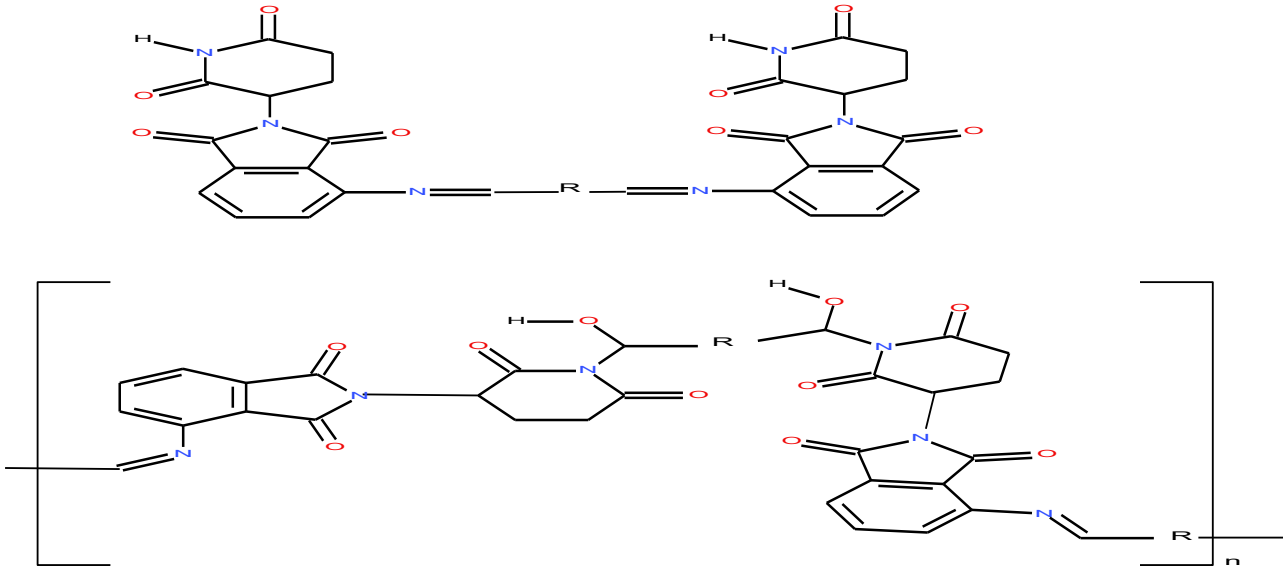
TABLE 1 pH in Various Biological Tissues[32]
Tissues and Cell Compartments pH
Blood 7.4
Tumor extracellular environment 6.5–7.2
Early endosome 6.0–6.5
Late endosome 5.0–6.0
Lysosome 4.5–5.0
Colon 7.0–7.5
Intestine 5–8
Stomach 1–3

Schmaljohann, D. (2006). Thermo-and pH-responsive polymers in drug delivery. *Advanced drug delivery reviews*, *58*(15), 1655-1670.

2.1.1.1. pH-Triggered Release: Acid-labile chemical bonds that are stable in the bloodstream (pH 7.4) but upon endocytic internalization are cleaved in the slightly acidic late endosomal (pH 5–6) and lysosomal (pH 4–5) environments, have been used to promote endolysosomal release.[30–32] Among the different pH sensitive linkers, which are available, such as acetal/ketal,[28–41] ortho ester,[30–32,42–44] imine,[30–32,36,45–48] oxime,[28,31,36,49–51] and maleic acid amide derivatives,[29,30,32,41,52–54] the hydrazone linker[28–32,36,41] is the most widely used.[31

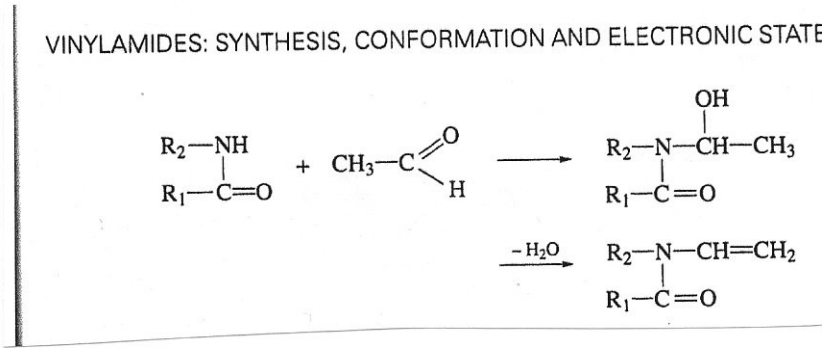
Battistella, C., & Klok, H. A. (2017). Controlling and Monitoring Intracellular Delivery of Anticancer Polymer Nanomedicines. *Macromolecular bioscience*, *17*(10), 1700022.

For simplicity in all of the following schemes, I will only show either the Lenalidomide or the Pomalidomide structure or vice versa with the other being understood.



Scheme 1: Dimer and polymeric imine ideas. The polymeric proposal prepared from dialdehydes must be cleavable under acidic cancer cell conditions. Acidic hydrolysis forms the active cancer drug. It is also possible for the condensation of aldehydes with imides would also lead to polymeric derivatives. All possibilities are acid labile and should work for this polymeric idea. A 1,4 benzene dialdehyde is a likely precursor but there is an enormous number of aldehydes described in the literature to choice from.

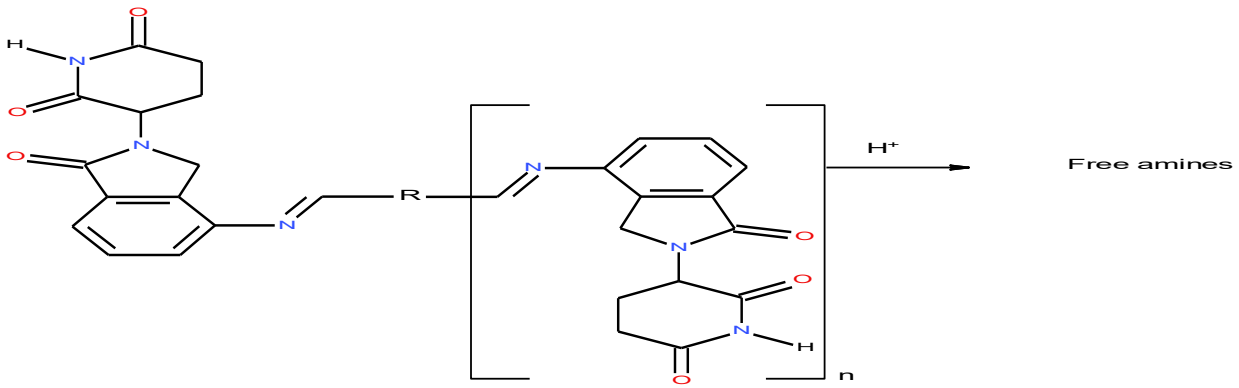
Kirsh, Y. E. (1998). *Water soluble poly-N-vinylamides: synthesis and physicochemical properties*. John Wiley & Sons. Shows examples of various amides reacted with aldehydes that I think would also work with imides. For example:



Qin, W., Long, S., Panunzio, M., & Biondi, S. (2013). Schiff bases: A short survey on an evergreen chemistry tool. *Molecules*, *18*(10), 12264-12289.

Xin, Y., & Yuan, J. (2012). Schiff's base as a stimuli-responsive linker in polymer chemistry. *Polymer Chemistry*, *3*(11), 3045-3055.

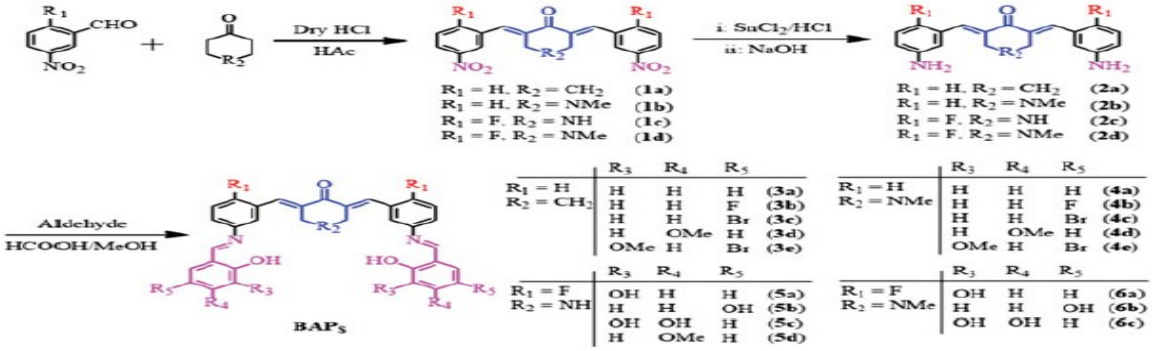
A possible problem with scheme 1 is aqueous solubility. In that case the R groups can be selected to remedy that problem.



Scheme 2: A dimer is simplest, but a trialdehyde or a polyaldehyde based imines can also be envisaged. The advantage of this idea is that the active amine would be revealed in the acidic cancer cell. But in the blood, as a dimer etc. they would not be toxic to

normal cells but because of cancer cell acidity the active would then be free to do its job. Only one possible syn/anti configuration is illustrated assuming its the most stable.

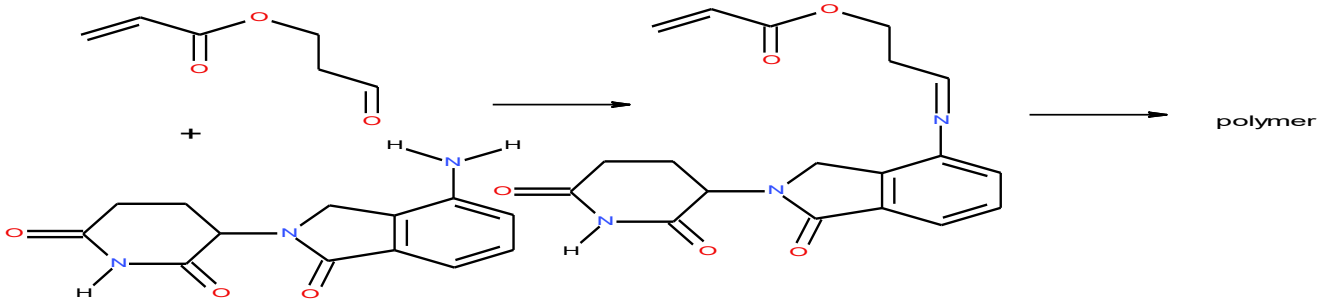
Example of Schiff-base from the literature:



Zhang, L., Chen, Q., Hou, G., Zhao, W., & Hou, Y. (2019). Hydroxyl-substituted double Schiff-base condensed 4-piperidone/cyclohexanones as potential anticancer agents with biological evaluation. *Journal of enzyme inhibition and medicinal chemistry*, *34*(1), 264-271.

Hejchman, E., Kruszewska, H., Maciejewska, D., Sowirka-Taciak, B., Tomczyk, M., Sztokfisz-Ignasiak, A., ... & Młynarczuk-Biały, I. (2019). Design, synthesis, and biological activity of Schiff bases bearing salicyl and 7-hydroxycoumarinyl moieties. *Monatshefte für Chemie-Chemical Monthly*, *150*(2), 255-266.

García, F., & Smulders, M. M. (2016). Dynamic covalent polymers. *Journal of Polymer Science Part A: Polymer Chemistry*, *54*(22), 3551-3577.



Scheme 3: Here an acrylic or acrylamide backbone polymer that could be injected or placed in tumors where acidity would free the active amine. If aqueous solubility is desired then ionic containing monomers and/or vinyl pyrrolidone can be copolymerized with the active imine precursor monomer, for example. Now I show only one type of monomer but any monomer that can sport an aldehyde could be tried. There is an enormous literature concerning these pH-responsive polymers as drug carriers.

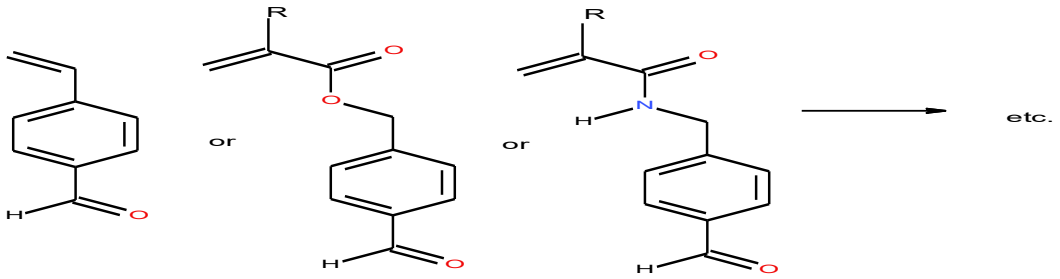
Ma, G., Li, D., Wang, J., Zhang, X., & Tang, H. (2014). Methoxy-Poly (ethylene glycol)-block-Poly (ε-caprolactone) Bearing Pendant Aldehyde Groups as pH-Responsive Drug Delivery Carrier. *Australian Journal of Chemistry*, *66*(12), 1576-1583.

Ekladious, I., Colson, Y. L., & Grinstaff, M. W. (2019). Polymer–drug conjugate therapeutics: advances, insights and

prospects. *Nature reviews Drug discovery*, *18*(4), 273-294.

Wu, W., Luo, L., Wang, Y., Wu, Q., Dai, H. B., Li, J. S., ... & Wang, G. X. (2018). Endogenous pH-responsive nanoparticles with programmable size changes for targeted tumor therapy and imaging applications. *Theranostics*, *8*(11), 3038.

Polymer-Drug Conjugates is another possibility. This technology has numerous references but fits my idea of employing imines of Lenalidomide and/of Pomalidomide in suggested structures.



Scheme 4: Benzaldehyde possibilities because benzaldehyde reacts more readily with aromatic amines to form Schiff bases; however, their Schiff bases are still reversible at acidic cancer pH.

I found one reference to Lenalidomide and pH release somewhat related to my proposals but not the same and not the same targets....http://rjptonline.org/HTML_Papers/Research%20Journal%20of%20Pharmacy%20and%20Technology__PID__2018-11-10-73.html Research J. Pharm. and Tech. 11(10): October 2018 (please if you know of pertinent references that I missed please let me know)

Additional references:

http://rloginconsulting.com/joomla/images/SiteFiles/Patents/patent%20app%202016%200355616.pdf

Pu, X., Zhao, L., Li, J., Song, R., Wang, Y., Yu, K., ... & Chang, S. (2019). A polymeric micelle with an endosomal pH-sensitivity for intracellular delivery and enhanced antitumor efficacy of hydroxycamptothecin. *Acta biomaterialia*, *88*, 357-369.

Wang, Z., Deng, X., Ding, J., Zhou, W., Zheng, X., & Tang, G. (2018). Mechanisms of drug release in pH-sensitive micelles for tumor targeted drug delivery system: A review. *International journal of pharmaceutics*, *535*(1-2), 253-260.

Thank you for reading these proposals.
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