Bergman Cyclization 1,8 Napthalimide derivatives

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After studying the Bergman cyclization(BC) and related cyclizations, now when I look at compounds that I'm interested in, I think about how or if the BC might be employed in their synthesis or application. For this reason I became interested in 1,8 napthalimide chemistry. I know from reading the literature concerning 1,8 Napthalimide derivatives that many are potent anticancer agents but can have toxicity problems.

Naphthalimides are aromatic heterocycles with profound biological significance and they serve as core scaffold for many anti-tumor, anti-inflammatory, antidepressant, antiprotozoal and antiviral compounds.[6] Planarity is the most important prerequisite for DNA intercalation and also facilitates embedding into DNA base pairs.[7] Owing to their tricyclic planar structure, naphthalimide is primarily responsible for its intercalation with DNA to perturb the cellular events, thereby prevents cancer cell divison.[8]

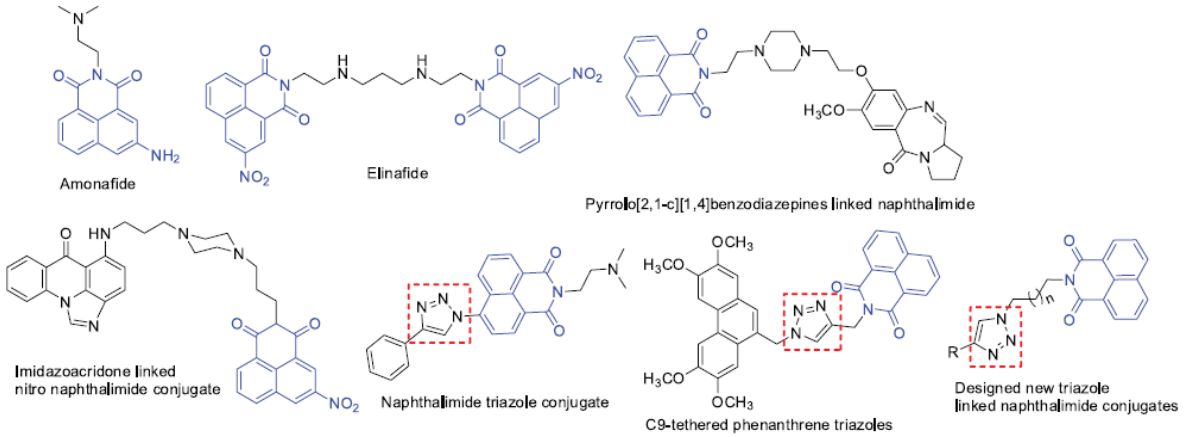
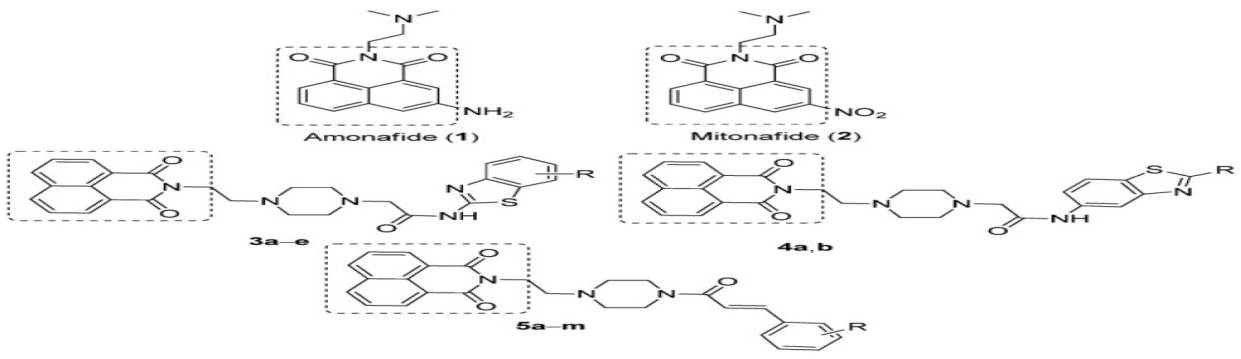


Figure 1. Structures of naphthalimide, triazole containing derivatives and newly designed 1,2,3-triazolo-naphthalimide conjugates.

Above from:

Shankaraiah, N., Kumar, N. P., Tokala, R., Gayatri, B. S., Talla, V., & Santos, L. S. (2019). Synthesis of New 1, 2, 3-Triazolo-naphthalimide/phthalimide Conjugates via 'Click'Reaction: DNA Intercalation and Cytotoxic Studies. *Journal of the Brazilian Chemical Society*, *30*(3), 454-461.



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Lead naphthalimides (1 and 2) and newly designed naphthalimide derivatives 3a–e, 4a,b and 5a–m.

A naphthalimide (NI) core is the most well-known unit that exhibits DNA-intercalating properties and topoisomerase II inhibition,[7] and considered as one of the most versatile fluorophore units owing to its unique photophysical properties.[8] These intercalators form and stabilize a ternary drug–DNA–topoisomerase complex and it has been proposed that these kinds of derivatives bind at the protein/DNA interface in such a way that the planar ring system intercalates into DNA, while the side chains would interact with the enzyme.[9] The well-known DNA-interactive agents such as amonafide (**1**) and mitonafide (**2**, Fig. 1) were the most potent naphthalimide-based topo-II inhibitors.[10–12] In particular, amonafide showed potent antitumor activity against advanced breast cancer, but apparently, its clinical development was regrettably terminated due to its poor therapeutic index or dose-limiting bone marrow toxicity.[13,14] Accordingly, extensive efforts including the modification of the side chain, the aromatic ring system, and the substituents on the ring have been attempted to search for more selective naphthalimide derivatives to improve the potency and reduce the adverse effects.[15,16] Braña *et al.* have designed and synthesized a

Above copied from:

Rao, N. S., Nagesh, N., Nayak, V. L., Sunkari, S., Tokala, R., Kiranmai, G., ... & Kamal, A. (2019). Design and synthesis of DNA-intercalative naphthalimide-benzothiazole/cinnamide derivatives: cytotoxicity evaluation and topoisomerase-IIα inhibition. *MedChemComm*, *10*(1), 72-79.

"It is thus no surprise that the 1,8-naphthalimide structure has made rapid development in applications for non-viral vectors, fluorescence probes, and anticancer agents in recent years."

Yong-Guang, G., Fen-Li, L., Patil, S., Di-Jie, L., Qadir, A., Lin, X., ... & Qian, A. R. (2019). 1, 8-Naphthalimide based multifunctional compounds as Cu2+ probes, lysosome staining agents and non-viral vectors. *Frontiers in chemistry*, *7*, 616.

Could BC be employed to prepare 1,8 Napthalimide derivatives that would be non-toxic but be converted to the active diradical intermediate in the cancer cell? I thought that the BC forms a transient biradical warhead that can abstract protons from DNA or topoisomerase II causing damage and apoptosis. Could said BC compound be both a damaging biradical and DNA intercalater, only doing its BC chemistry in the cancer cell. I even thought that the BC reaction could be photo-activated by a suitable light(laser).

Smith, A. R., & Iverson, B. (2017). NDI as a DNA Intercalator. *Naphthalenediimide and its Congeners*, 37-71.

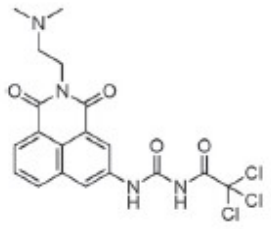
Bhattacharya, P., Basak, A., Campbell, A., & Alabugin, I. V. (2018). Photochemical activation of enediyne warheads: A potential tool for targeted antitumor therapy.*Molecular pharmaceutics*, *15*(3), 768-797.

Banerjee, S., Veale, E. B., Phelan, C. M., Murphy, S. A., Tocci, G. M., Gillespie, L. J., ... & Gunnlaugsson, T. (2013). Recent advances in the development of 1, 8-naphthalimide based DNA targeting binders, anticancer and fluorescent cellular imaging agents. *Chemical Society reviews*, *42*(4), 1601-1618.

Chen, J., Li, G., Liu, Q., Liang, Y., Liu, M., Wu, H., & Gao, W. (2019). A Photocleavable Amphiphilic Prodrug Self-Assembled Nanoparticles with Effective Anticancer Activity In Vitro. *Nanomaterials*, *9*(6), 860.

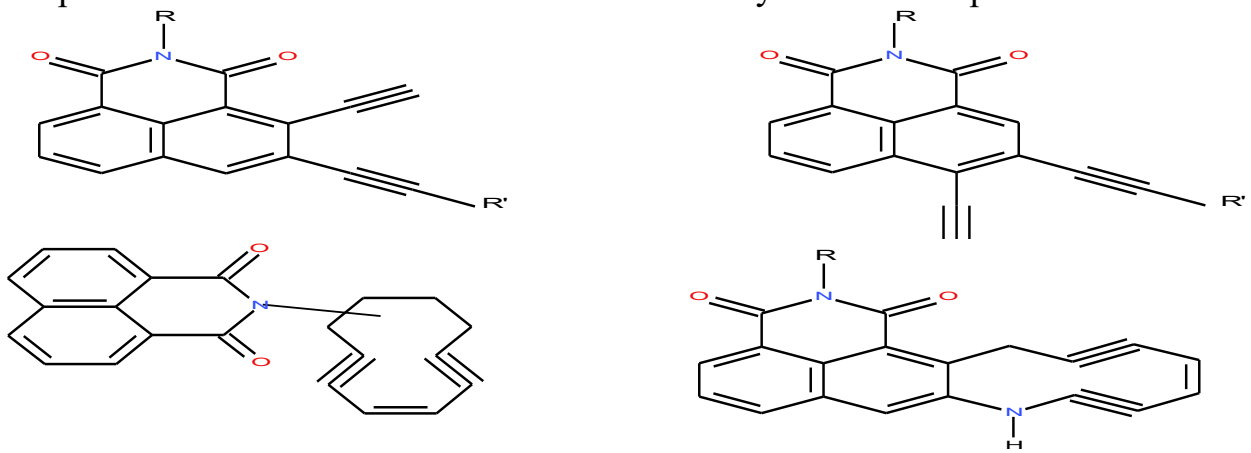
A straight forward approach would be to place the enediyne as a derivative of the napthalimides. The down side is that the toxicity of the naphthalimide might still be of concern; however, derivatives such as UNBS6152 exhibits workable toxicity and anti-cancer activity.

Ye, Y., Huang, S., & Wu, Y. (2019). UNBS5162 and amonafide inhibits tumor progression in human melanoma by the AKT/mTOR pathway. *Cancer management and research*,*11*, 2339.



UNBS5162 is the hydrolysis product of the above compound.

1,8- Napthalimide structures derivatised with an enediyne. For example:



Scheme 1: Although combining BC with 1,8-Napthalimide, I believe has not been proposed(I could not find this idea on a search of SciFinder or Google Scholar; however, the following ref. has similar ideas, Vinogradova, O. V., Balova, I. A., & Popik, V. V. (2011). Synthesis and reactivity of cinnoline-fused cyclic enediyne. *The Journal of organic chemistry*, *76*(16), 6937-6941.) and since 1,8-Napthalimides are DNA intercalaters, the BC diradical seems like a valuable warhead since it would be in close proximetry. It still contains the 1,8-Napthalimide structure that would attach it to cancer cell DNA. There are a large variety of enediynes that undergo the BC under various conditions. Some are illustrated in scheme 1. What I need to accomplish is an overview of BC chemistry so that the most likely enediyne candidates can be selected.

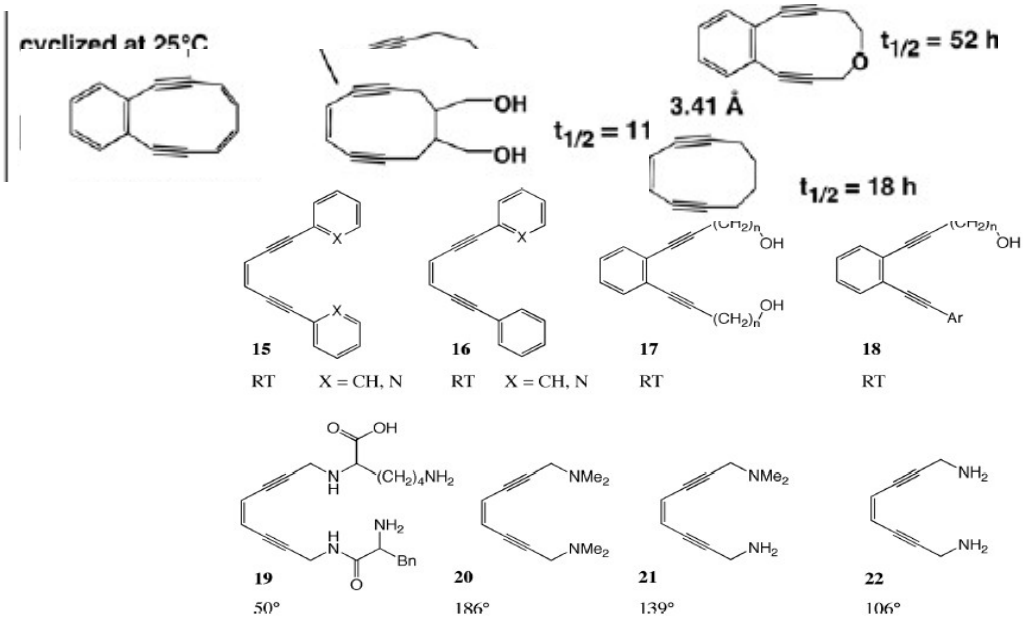


FIGURE 7 | Acyclic enediynes undergoing the Bergman cyclization at either room temperature (RT) or reduced temperature. Temperatures are in °C are given below formulas.

The above two charts afford examples of enediynes that will result in BC at around RT or body temperature or higher temperature conditions. Each could be attached to 1,8-Napthalimide in some way. However, this reference also reviews pH triggers that result in BC. Since cancer cells are acidic, these pH acidic triggers should work possibly avoiding toxicity issues in normal cells. Also see the following references for related chemistry:

Yang, W. Y., Roy, S., Phrathep, B., Rengert, Z., Kenworthy, R., Zorio, D. A., & Alabugin, I. V. (2011). Engineering pH-gated transitions for selective and efficient double-strand DNA photocleavage in hypoxic tumors. *Journal of medicinal chemistry*, *54*(24), 8501-8516.

Yang, W. Y., Breiner, B., Kovalenko, S. V., Ben, C., Singh, M., LeGrand, S. N., ... & Alabugin, I. V. (2009). C-lysine conjugates: pH-controlled light-activated reagents for efficient double-stranded DNA cleavage with implications for cancer therapy. *Journal of the American Chemical Society*, *131*(32), 11458-11470.

Breiner, B., Kaya, K., Roy, S., Yang, W. Y., & Alabugin, I. V. (2012). Hybrids of amino acids and acetylenic DNA-photocleavers: optimizing efficiency and selectivity for cancer phototherapy. *Organic & biomolecular chemistry*,*10*(20), 3974-3987. (note I have not been able to obtain this article)

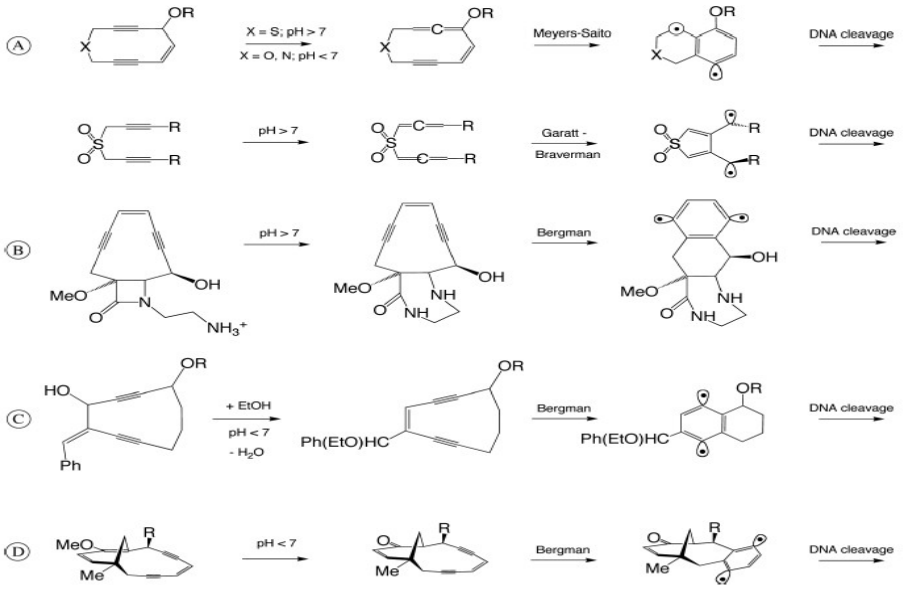
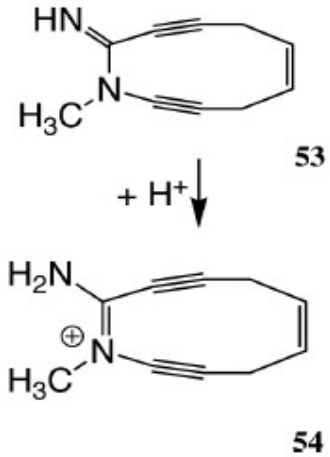


FIGURE 12 | Suggested strategies for biradical formation of an enediyne mimic or related compounds via a precursor at ambient conditions to yield DNA cleavage.

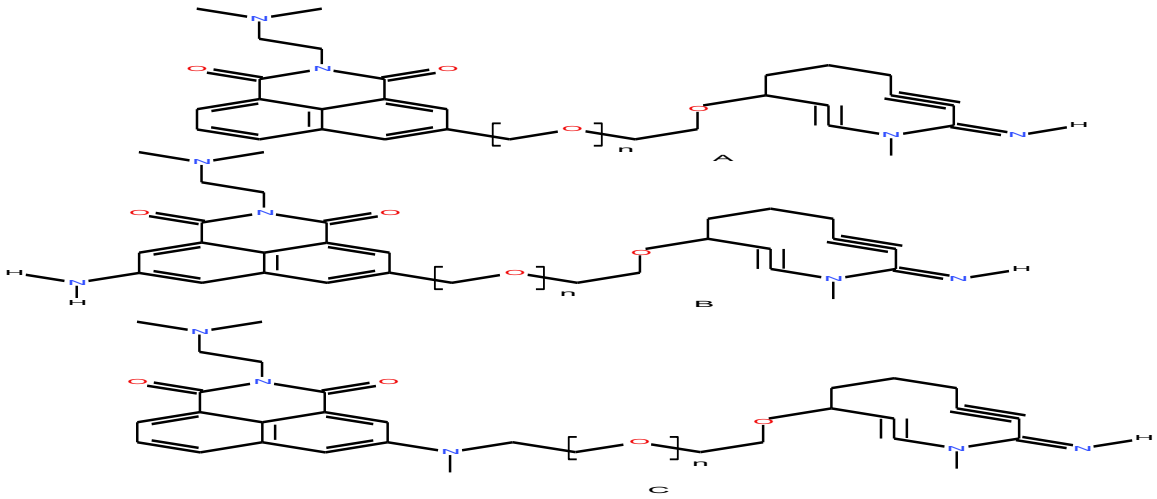


54 is now a reactive BC enediyne.

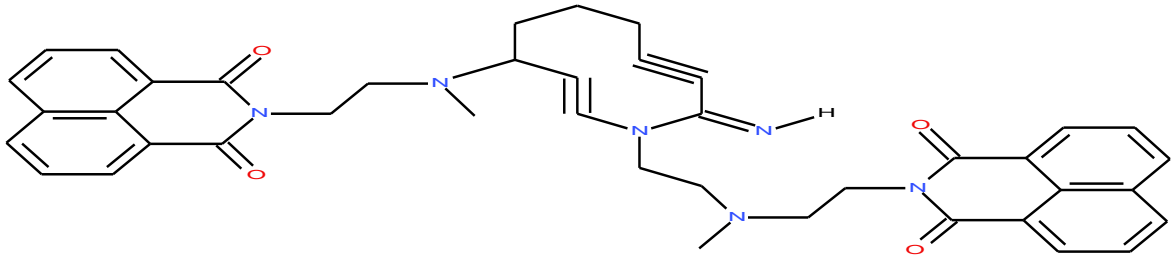
All of the above are from:

Kraka, E., & Cremer, D. (2014). Enediynes, enyne-allenes, their reactions, and beyond. *Wiley Interdisciplinary Reviews: Computational Molecular Science*, *4*(4), 285-324.

I propose that the R groups (scheme 1 above) can be some suitable derivative of 1,8 Naphthalimide. I could say that these as related to PROTACs(proteolysis targeting chimera) as they have a target DNA anchoring group connected to a BC warhead. I would think that the BC warhead should be close to the anchor 1,8 Naphthalimide so that one can attack the cancer cell DNA and the other a diradical, associated proteins. Proteins that are damaged are then destroyed by the ubiquitin-proteasome system.



Scheme 2: Three variations on possible conjugated types that require an acidic pH trigger.



Scheme 3: A dimer pH trigger example. This dimer should be water soluble after the amines are protonated. Note many other trigger chemistries can be considered. The above are just a few examples.

Not all enediynes would need a trigger as the BC can be relatively slow at body temperature for some of them, but active enough once some have been incorporated in a cancer cell. Please go to my web page(rloginconsulting.com) and download Bergman

Cyclization Thalidomide Precursors for a mini-review of BC chemistry.

There are many possible 1,8-Naphthalimide derivatives and several reviews are available. I could continue to apply the enediyne idea to most of them but I think I have shown enough to indicate how my proposal would work. Please look at this review:

Banerjee, S., Veale, E. B., Phelan, C. M., Murphy, S. A., Tocci, G. M., Gillespie, L. J., ... & Gunnlaugsson, T. (2013). Recent advances in the development of 1, 8-naphthalimide based DNA targeting binders, anticancer and fluorescent cellular imaging agents. *Chemical Society reviews*, *42*(4), 1601-1618.

My idea is to derivatise 1,8-napthalimides or derivatives thereof, coupled with enediynes such that said conjugated compounds would fatally damage cancer cell DNA and associated proteins.

Thank you for reading these proposals.
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