Nicotinamide riboside NMN Congeners

By: Robert B. Login rloginconsulting.com

Recently I started following Prof. David Sinclair's advice. He is a tenured Harvard professor of genetics who is co-director of Harvard's Paul F. Glenn Center for Biology of Aging Research. He has written a book(Lifespan) on the subject of how to reverse aging and he can be found on You Tube explaining his findings. Could a scientist with such credentials be onto something? He also claims he knows how to restore sight to blind mice. Looking at his image on You Tube, he looks like a kid but claims to be in his fifties. Since I'm 78 I paid attention to this man! He tells you to take NMN(β-Nicotinamide Mononucleotide) supplements. So I started taking it (500mg) a day. I just started so apparently it takes a few weeks before you notice any effect.

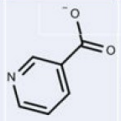
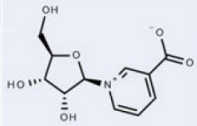
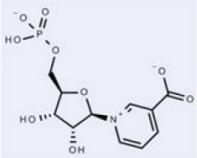
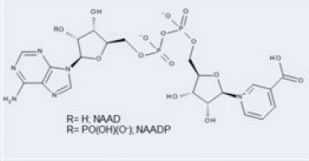
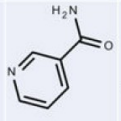
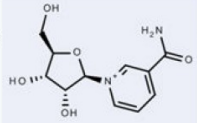
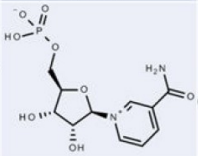
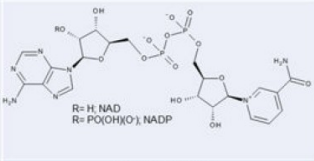
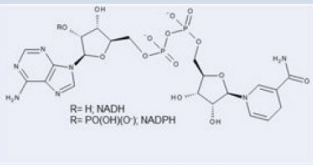
Mehmel, M., Jovanović, N., & Spitz, U. (2020). Nicotinamide riboside—the current State of research and therapeutic uses. *Nutrients*, *12*(6), 1616.

Igarashi, M., Miura, M., Nakagawa-Nagahama, Y., Yaku, K., Kashiwabara, K., Sawada, M., ... & Yamauchi, T. (2021). Chronic nicotinamide mononucleotide supplementation elevates blood nicotinamide adenine dinucleotide levels and alters muscle motility in healthy old men.

Looking at the structure of NMN, I thought about congeners. Because NMN is a safe natural chemical possibly this idea has been overlooked because such changes would then require extensive study to make sure such congeners were safe. To see if anything has been done, I started searching the patent literature. Sinclair has at least 60-70 patents, they are all based on nicotinamide ribosomes (N substituted pyridine derivatives.) I have to admit that I'm not a biochemist or a biologist and I don't understand all of the NMN technical literature, besides the patents are gigantic, some over 180 pages.

Chemical structures and abbreviations of the anabolites constituting the vitamin B3 metabolome

Anabolites of the vitamin B3 metabolome, precursor to the NAD(P)(H) pool

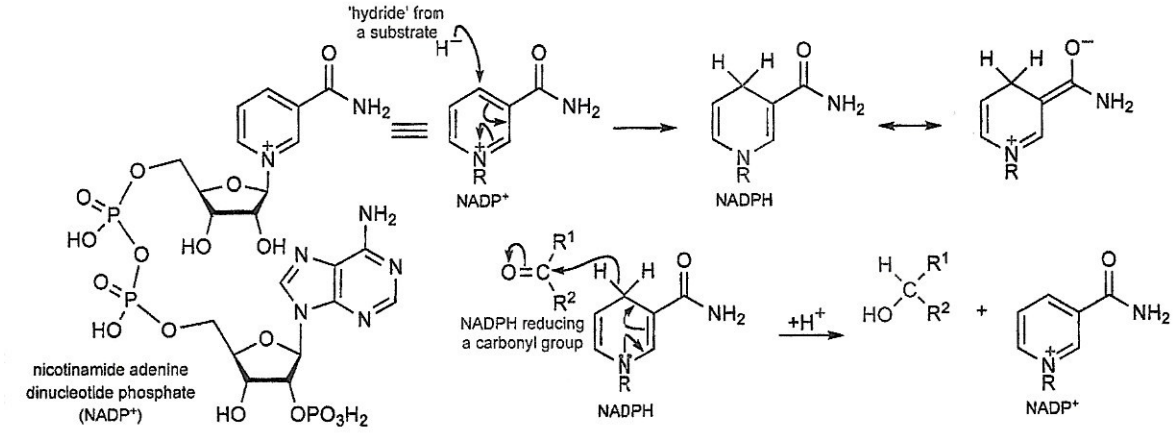
	Anabolic species				
VitaminB3	Nucleobase	Nucleoside	Nucleotide	Dinucleotide	Reduced dinucleotide
Niacin containing derivatives					
	NA	NAR	NAMN	NAAD, NAADP	
Nicotinamide containing derivatives					
	Nam	NR	NMN	NAD^+, NADP	NADH, NADPH

Abbreviations: NA, niacin/nicotinic acid; Nam, niacinamide/nicotinamide; NR, nicotinamide riboside; NAR, nicotinic acid riboside; NAMN, nicotinic acid mononucleotide; NMN, nicotinamide mononucleotide; NAAD, nicotinic acid adenine dinucleotide; NAADP*, nicotinic acid adenine dinucleotide phosphate; NAD^+, nicotinamide adenine dinucleotide; $NADP^+$, nicotinamide adenine dinucleotide phosphate; NADH, nicotinamide adenine dinucleotide reduced form; NADPH, nicotinamide adenine dinucleotide phosphate reduced form. *Generated via a yet unknown mechanism.

Makarov, M. V., Trammell, S. A., & Migaud, M. E. (2019). The chemistry of the vitamin B3 metabolome. *Biochemical Society Transactions*, *47*(1), 131-147.

32.2.1 Niacin (Vitamin B_3) and Nicotinamide Adenine Dinucleotide Phosphate ($NADP^+$)

Nicotinamide adenine dinucleotide phosphate ($NADP^+$) is a large complicated co-enzyme, but the significant part for its role in oxidation/reduction processes is the pyridinium ring – to understand the mechanism one can think of it as simply an *N*-alkyl pyridinium salt of nicotinamide. The positively charged nitrogen acts as an electron sink and allows this co-enzyme to accept two electrons and a proton, i.e. effectively, hydride. In line with typical pyridinium reactivity (8.12) the hydride adds at a γ-position, thus producing a 1,4-dihydropyridine (NADPH), the process being feasible because NADPH is a stabilised 1,4-dihydropyridine in which the ring nitrogen is conjugated to the carbonyl of the 3-substitutent (cf. Hantzsch synthesis products, 8.14.1.2). In the reverse sense, NADPH is a vital reducing agent in biosynthesis – it is nature's sodium borohydride. The rationale for the reverse process is the regain of aromaticity in the co-enzyme product – a pyridinium ion.

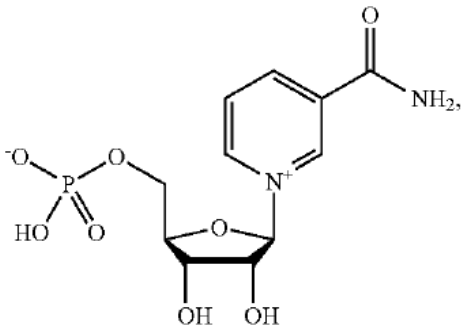


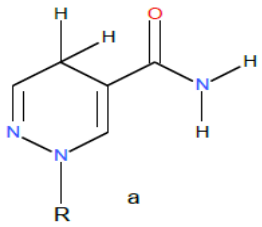
The role of a pyridinium ion and a 1,4-dihydropyridine in enzyme-catalysed oxidation and reduction processes

Joule, J., & Mills, K. (2010). Heterocyclic Chemistry, 5th (Ed.), A John Wiley & Sons Publication Ltd.

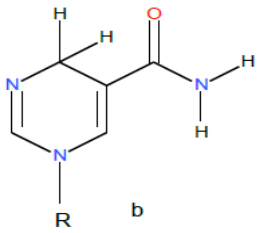
As an organic/polymer chemist, I decided to take a simplistic approach and suggest variations of the nicotinamide itself. I will suggest every possibility I could dream up. Structures that I think might work

[0063] "Nicotinamide Mononucleotide" (NMN), which corresponds to the following structure,





a



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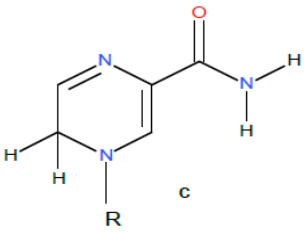

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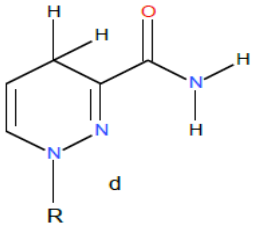

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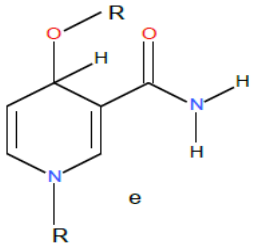

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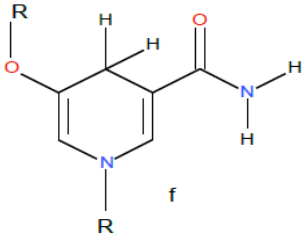

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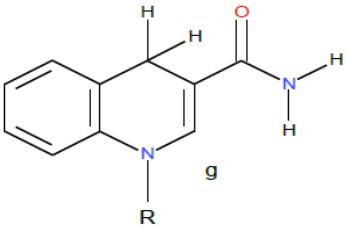
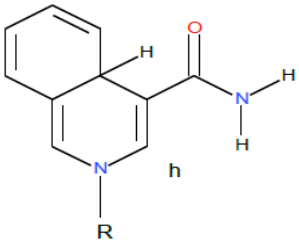
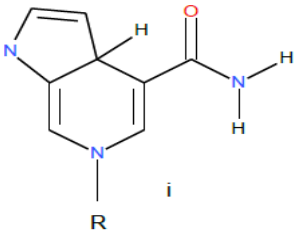


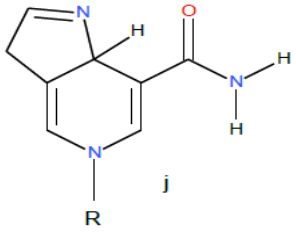
g



h



i



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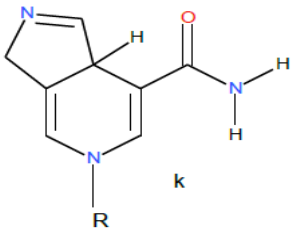

k

Scheme 1: A selection of intermediate structures that could be reducing agents. The pyridine nitrogen is derivatized with ribosome structures as in the above patents. Many more structures can be conceived of but the above make my point, is nicotinamide the only substructure that is biologically active for the intended application? Will any of the above structures act as reducing agents like NMN?
Structures h-k seem less likely because the structure eliminates aromaticity. G however looks OK.

(57) **ABSTRACT**

The invention relates to compositions of nicotinamide mononucleotide derivatives and their methods of use. The invention also relates to methods of preparing nicotinamide mononucleotide derivatives. The invention relates to pharmaceutical compositions and nutritional supplements containing a nicotinamide mononucleotide derivative. The invention relates to methods of using nicotinamide mononucleotide derivatives that promote the increase of intracellular levels of nicotinamide adenine dinucleotide (NAD+) in cells and tissues for treating diseases and improving cell and tissue survival.

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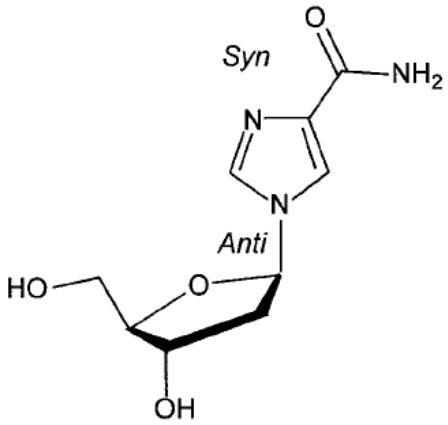
My point is that although I have searched, I failed to find other structures replacing the nicotinamide as far as Prof. Sinclair's applications and patents are concerned.

Five membered rings:



1-(24-Deoxy-b-D-ribofuranosyl)imidazole-4-carboxamide

Johnson, W. T., Zhang, P., & Bergstrom, D. E. (1997). The synthesis and stability of oligodeoxyribonucleotides

containing the deoxyadenosine mimic 1-(2′-deoxy-β-D-ribofuranosyl) imidazole-4-carboxamide.*Nucleic acids research*,*25*(3), 559-567.

Hoops, G. C., Zhang, P., Johnson, W. T., Paul, N., Bergstrom, D. E., & Davisson, V. J. (1997). Template directed incorporation of nucleotide mixtures using azole-nucleobase analogs. *Nucleic acids research*, *25*(24), 4866-4871.

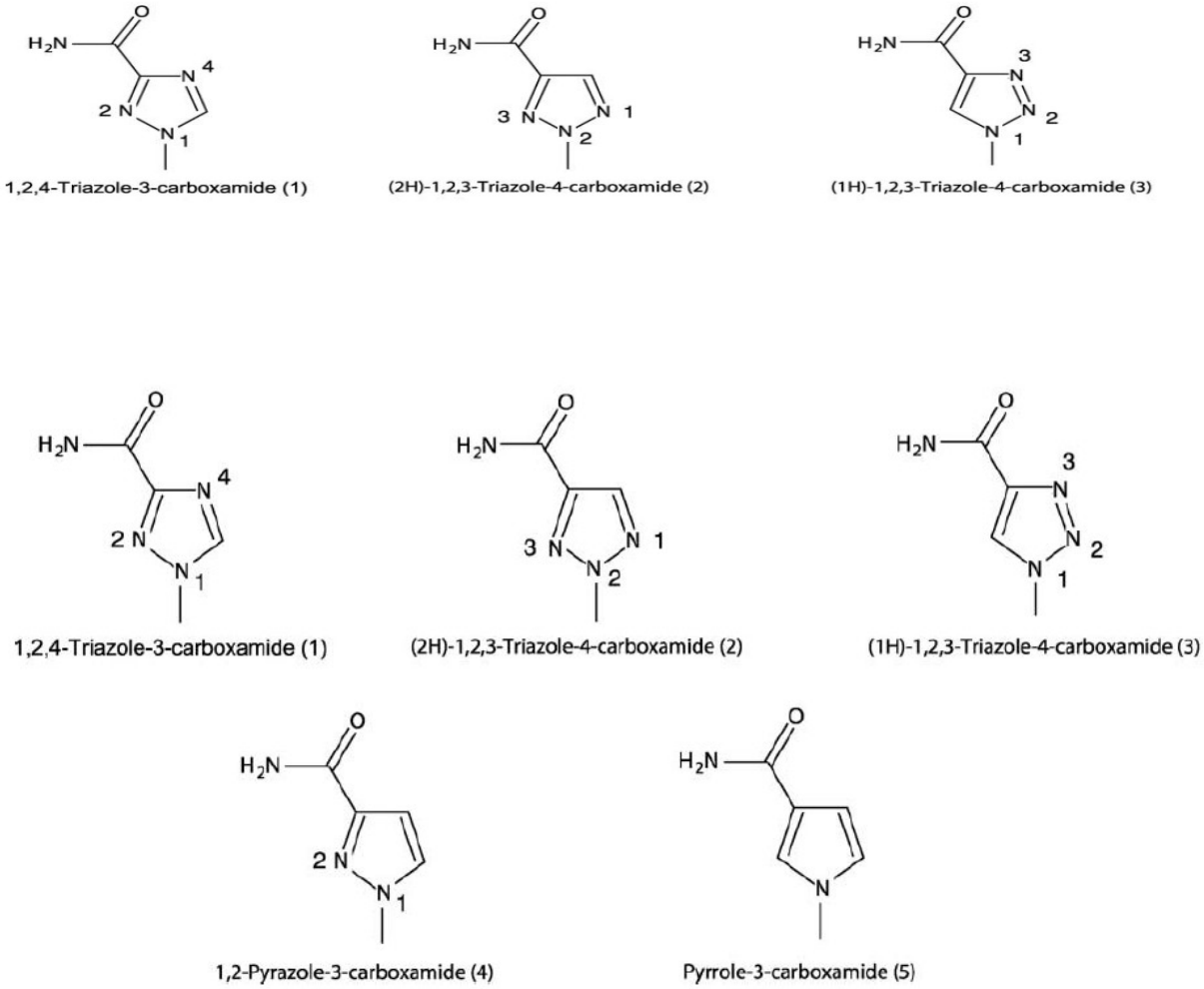


Figure 1. Model of the Azole Heterocycles Carboxamides as Nucleobase Pair Mimics
The key structural parameters in the context of duplex DNA are highlighted.

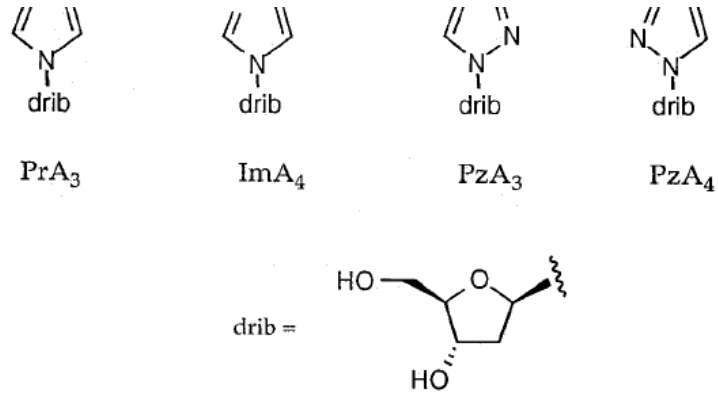
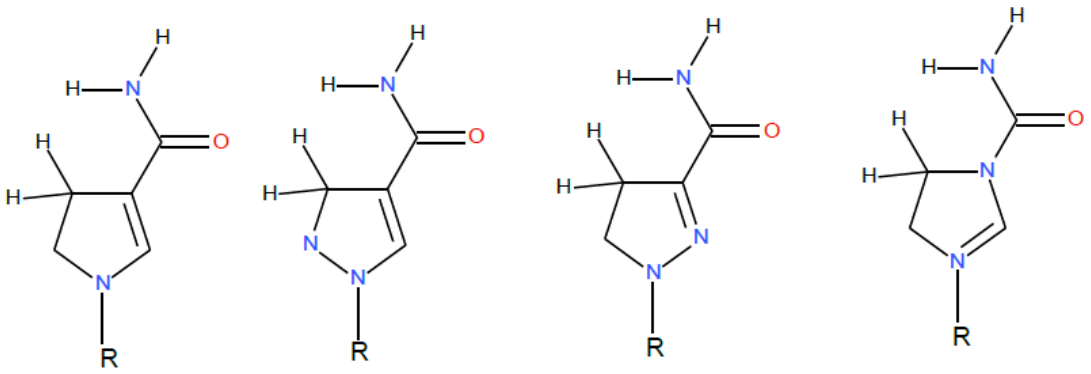


Figure 1. (**A**) Origin of the general structural subclass of azole nucleobases. (**B**) Structures of azole deoxyribonucleosides used in this study.

Paul, N., Nashine, V. C., Hoops, G., Zhang, P., Zhou, J., Bergstrom, D. E., & Davisson, V. J. (2003). DNA polymerase template interactions probed by degenerate isosteric nucleobase analogs. *Chemistry & biology*, *10*(9), 815-825.

The above are five membered cogeners of the nicotinamide of NMN. Coupled to the key NMN substituent riboses, will these cogeners work as superior NMN replacements?



Scheme 2: The first three look like they would work as reducing agents, the last one has a positive charge on nitrogen and might not work(?).

Thank you for your interest in this proposal.
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