SCIENCE FOR THE BENEFIT OF HUMANITY

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Novel Stable Phosphohistidine Analogues
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Technology Summary

Protein phosphorylation is one of the most common and well-studied post-translational modifications (PTMs) in biology, especially in the O-phosphorylation of serine, threonine, and tyrosine amino acid residues. Another biological PTM is the phosphorylation of histidine residues – this PTM is better understood in prokaryotes than eukaryotes, where a similar event takes place and appears to play an important role in signaling processes. The histone protein H4 is phosphorylated at two histidine residues, His18 and His75. The kinase responsible for this phosphorylation is 400 times more active in human hepatocellular carcinoma, and this increase in histidine kinase activity correlates with increased cell growth.

It is apparent that histidine phosphorylation of eukaryotes is a potentially untapped field of study, but the main challenge lies in the fact that the phosphorylated histidine (pHis) residue in eukaryotes is very unstable as it is easily hydrolyzed at acidic pH. In addition, the phosphorylation can take place at two atoms in the nitrogen ring in the histidine molecule, resulting in two possible isomers. Our scientists have made pHis analogues that are both non-hydrolyzable and non-isomerizable, and their current studies show that the pHis analogue can be incorporated into proteins, including peptide immunogens. These novel analogues are research tools that have the potential to be move this new field of research forward rapidly.

Advantage

- The pHis analogues are ideal reagents as they are stable and non-isomerizable.
- The pHis analogues can be used in solid-state peptide synthesis.
- Peptides containing the pHis analogue can be used as an immunogen to generate unique antibodies.

Area of Application

- These pHis analogues are powerful research tools to advance scientific understanding of the role of histidine phosphorylation in higher eukaryotes, including in signal transduction and cell growth.
- The analogues can be used to make haptens and immunogens to generate other research reagents to study phosphorylated histidine residues.

Stage of Development

- Early stage – the analogues have been incorporated in peptides used as an immunogen to create an antibody that recognizes a pHis epitope, and also in semi-synthesis of a histone protein.

Lead Inventor

Dr. Thomas W. Muir

Patent Information

- U.S. Patent 9,035,068 and other patent applications are pending.

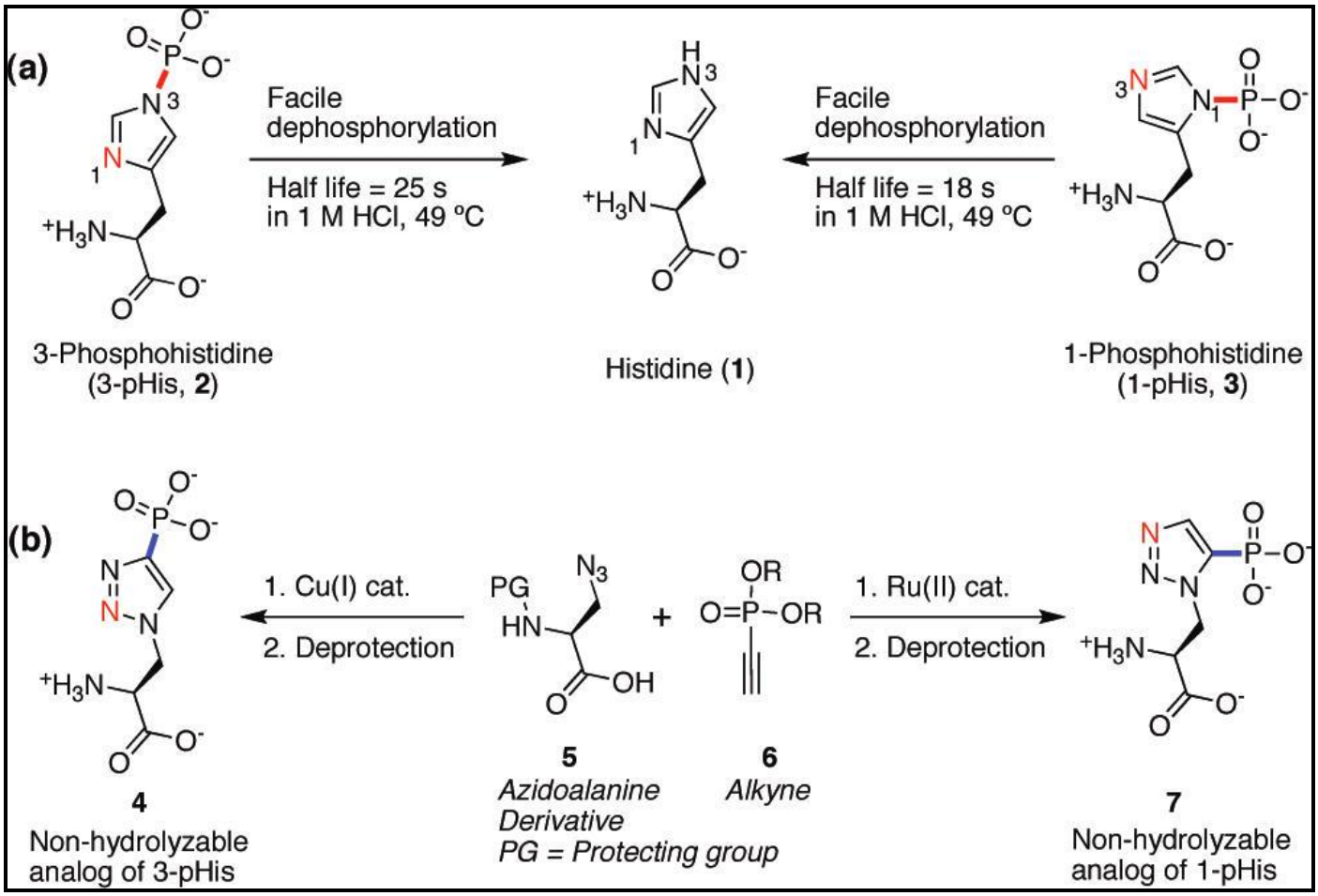
References

- Kee, *et al.* 2010. ***J. Am. Chem. Soc***, 132(41):14327-9
- Kee, et al. 2013. Nat. Chem. Biol. doi: 10.1038/nchembio.1259

STRUCTURE OF pHIS ANALOGUES

(a) Design of 3- and 1-pHis that undergoes facile hydrolysis under acidic conditions, making its detection and isolation from biological sources difficult.

(b) Stable analogues of 3-pHis and 1-pHis (isomer 4 and 7 respectively) where hydrolytically labile N_P bond is replaced by C_P bond.



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