Mini Review
Volume 12:8, 2022

Medicinal Chemistry

ISSN: 2161-0444 Open Access

Recent Advancements in Medicinal Chemistry of Phosphotyrosine

Wael Ahmad Abu Dayyih*

Department of Pharmaceutical, Medicinal Chemistry and Pharmacognosy, Petra University, Jordan, Saudi Arabia

Abstract

Due to their ability to modify signalling pathways by binding to phospho-writers, erasers, and readers like proteins with SH2 and PTB domains, phosphotyrosine-containing compounds are the focus of considerable research. In order to research protein phosphorylation and dephosphorylation, phosphotyrosine derivatives are helpful chemical tools. As a result, they are appealing starting points for the creation of binding ligands, chemical probes to study biology, and inhibitor and degrader drug design. Physiologically stable phosphonate-based phosphotyrosine analogues are useful in a wide range of applications to overcome the enzymatic lability of the phosphate group.

Keywords: PTB • Drug • Inhibitor • Phosphotyrosine

Introduction

Crucial function in signal transmission, on/off control of enzyme activity, and activation or deactivation of gene transcription. Protein tyrosine phosphorylation is essential for controlling cell development, mitogenesis, metabolism, and apoptosis even though it occurs at a lower level than serine or threonine phosphorylation. 3 Protein tyrosine kinases (PTKs) phosphorylate tyrosine, proteins with pY-binding modules, such as Src homology 2 (SH2) or phosphotyrosine binding (PTB) domains, recognise pY residues, and protein tyrosine phosphatases remove a phosphate group from phosphotyrosine residues (PTPs). Numerous illnesses, including inflammation, diabetes, cancer, metabolic and autoimmune diseases, have been related to dysfunctions in each of these processes. The importance of protein tyrosine phosphorylation drives the development of pY-containing peptides and small-molecule derivatives that can mediate protein-protein interactions or serve as substrate/product mimics, thereby providing useful chemical tools to study the roles of individual proteins involved in signalling pathways or pathways contributing to diseases.Such compounds can also provide useful tools for biophysical protein characterization for monitoring protein stability, and for monitoring the effects of protein tyrosine phosphorylation Furthermore, the immobilisation of pY on an agarose gel has made it possible to isolate human immunoglobulin G (IgG)21 and pre-miRNA (MicroRNA)-29 from human plasma by replicating the actions of these molecules.

Literature Review

Phosphotyrosine-containing compounds are the subject of extensive research due to their capacity to alter signalling pathways by attaching to phospho-writers, erasers, and readers like proteins with SH2 and PTB domains. Phosphotyrosine derivatives are useful chemical tools to study protein phosphorylation and dephosphorylation. As a result, they are good beginning points for the design of inhibitor and degrader drugs as well as binding ligands, chemical probes, and biological assays. To get around the phosphate group's enzymatic lability, phosphonate-based phosphotyrosine analogues are effective in a variety of applications. This paper emphasises the expanded and improved synthetic toolbox, shows improvements over the previous ten years in the production of phosphotyrosine and its phosphonate-based derivatives, and illustrates uses in medicinal chemistry.

Phosphotyrosine building blocks and phosphotyrosine phosphonate-based mimics have been commercially available over the past ten years and are frequently used in the synthesis of peptides. Although this is a significant improvement over the previous decade, these chemicals are still quite expensive and mostly only useful for the solid phase peptide synthesis (SPPS). Because unprotected P-OH groups pose complications during the synthetic process, Fmoc-Tyr(PO3H2)-OH is currently only sometimes employed in peptide chemistry. These issues could be resolved by using bis-protected di-O-benzyl/methyl phosphotyrosine building blocks. However, it has been noted that piperidine during Fmoc-SPPS can remove methyl or benzyl groups in an unwanted manner.

Discussion

The oxidation of P(iii) to P(v), followed by phosphitylation utilising phosphoramidites and an activator, is the third most popular method for tyrosine phosphorylation (Scheme 1, path C). An established technique calls for the use of tetrazole as an activator and t-butyl hydroperoxide for oxidation. This technology has recently been successfully used to create probes for tracking PTP activity. To track the dephosphorylation of 3-nitrophosphotyrosine-containing peptides, van Ameijde et al. designed an assay. In this assay, phosphatase activity is determined by the formation of 3-nitrotyrosine residue, which can be detected by the particular, sequence-independent anti-nitrotyrosine antibody. Choi et al. proposed a different PTP activity probe, 1, based on a shift in fluorescence upon dephosphorylation.

Wu and colleagues revived the aminophosphoryl chloride strategy.GAP chemistry entails the introduction of special auxiliaries into the molecule to produce a compound with sufficient solubility. The chemical produced is poorly soluble in petroleum solvents and their cosolvents, but it is soluble in a number of solvents (often DCM, THF, and MeOH). Because of this, the desired product can be separated through straightforward filtration and washing. The proposed GAP idea enables solution phase peptide synthesis without the use of chromatography or recrystallization. Tyrosine was phosphorylated by 2-chloro-1,3-diphenyl-[1,3,2]diazaphospholidine 2-oxide in the presence of triethylamine in the recommended method.

Phosphotyrosine is a suitable functional group in the design of SH2, PTB, or

***Address for Correspondence:** Wael Ahmad Abu Dayyih, Department of Pharmaceutical, Medicinal Chemistry and Pharmacognosy, Petra University, Jordan, Saudi Arabia, E-mail: dayyihabu@gmail.com*

Date of Submission: 02 August, 2022, Manuscript No. mccr-79885; **Editor Assigned:** 04 August, 2022, PreQC No. P-79885; **Reviewed:** 16 August, 2022, QC No. Q-79885; **Revised:** 22 August, 2022, Manuscript No. R-79885; **Published:** 27 August, 2022, DOI: 10.37421/2161-0444.2022.12.635

PTP inhibitors due to the hydrolysis of the pY phosphate group by PTPs, which is an important step in cell signalling. In light of its structural characteristics and physicochemical properties, such as a similar pKa to pY and the presence of the methylene fluorine atoms, which may mimic the hydrogen bond interactions of phenolic oxygen with actinomycetes, non-hydrolysable pY mimetics are thus well-established and their synthesis has been reviewed.

Due to their ability to modify signalling pathways by binding to phospho-writers, erasers, and readers like proteins with SH2 and PTB domains, phosphotyrosine-containing compounds are the focus of considerable research. In order to research protein phosphorylation and dephosphorylation, phosphotyrosine derivatives are helpful chemical tools. As a result, they are appealing starting points for the creation of binding ligands, chemical probes to study biology, and inhibitor and degrader drug design. Physiologically stable phosphonate-based phosphotyrosine analogues are useful in a wide range of applications to overcome the enzymatic lability of the phosphate group. This study emphasises the enhanced and enlarged synthetic toolkit, highlights developments over the past ten years in the creation of phosphotyrosine and its phosphonate-based derivatives, and exhibits applications in medicinal chemistry [1-6].

Conclusion

Phosphate groups play a crucial role in a huge variety of biological activities. A protein's simple phosphorylation or dephosphorylation can have a variety of impacts on it, including changes to its biological function, how it interacts with other proteins, and where it is located within the cell. Several disorders, including cancer and diabetes, have been connected to abnormal levels of protein phosphorylation. As a result, proteins that recognise the phosphate moiety have gained interest as potential targets for new therapeutics. The majority of medicinal chemistry research focuses on the interactions of phosphorylated tyrosine residues, however phosphate groups also play important roles in sugars, nucleotides, DNA, and RNA, as well as lipid mediators like lysophosphatidic acid and serine or threonine residues.

The enzymatic lability and poor cellular bioavailability of this highly charged recognition element significantly restrict the use of the phosphate moiety as an inhibitor. By using groups with less charge that can yet interact favourably with the target protein in a manner similar to how the phosphate group does, together with a non-scissile bond, phosphate isosteres were created in an effort to overcome these problems. The highly successful fluoromethylenephosphonates are an example of a phosphate mimic that retains the phosphorus atom. Other phosphate mimics, however, lack the tetrahedral phosphate geometry and are built on the combination of one or more carboxylate groups, which typically lower the overall charge of the molecule.

Acknowledgement

None.

Conflict of Interest

There are no conflicts of interest by author.

References

1. Griffin, Julian L. and John P. Shockcor. "Metabolic profiles of cancer cells." *Nat Rev Cancer* 4 (2004): 551-561.
2. Yang, Weiwei and Zhimin Lu. "Pyruvate kinase M2 at a glance." *J Cell Sci* 128 (2015): 1655-1660.
3. Yang, Weiwei and Zhimin Lu. "Regulation and function of pyruvate kinase M2 in cancer." *Cancer Lett* 339 (2013): 153-158.
4. Chaneton, Barbara, Petra Hillmann, Liang Zheng and Agnes CL Martin, et al. "Serine is a natural ligand and allosteric activator of pyruvate kinase M2." *Nature* 491 (2012): 458-462.
5. Shi, Hua-shan, Dan Li, Jing Zhang and Yong-sheng Wang, et al. "Silencing of pkm2 increases the efficacy of docetaxel in human lung cancer xenografts in mice." *Cancer Sci* 101 (2010): 1447-1453.
6. Guo, Wenhao, Yu Zhang, Ting Chen and Yongsheng Wang, et al. "Efficacy of RNAi targeting of pyruvate kinase M2 combined with cisplatin in a lung cancer model." *J Cancer Res Clin Oncol* 137 (2011): 65-72.

How to cite this article: Abu Dayyih, Wael Ahmad Abu. "Recent Advancements in Medicinal Chemistry of Phosphotyrosine." J Med Chem 12 (2022): 635.