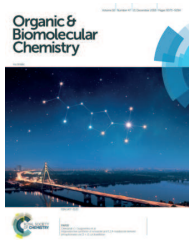


Isoxazole and 1,2,4-Oxadiazole-Derived Phosphonates via [3+2] Cycloaddition

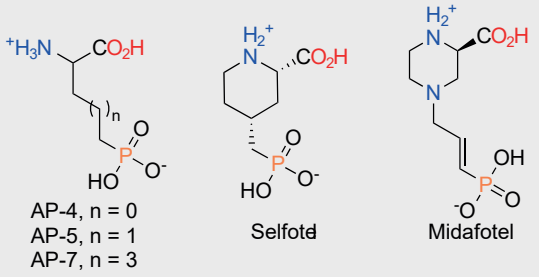
Bohdan A. Chalyk, Oleksandr O. Grygorenko, Sergey V. Ryabukhin, Dmitriy M. Volochnyuk

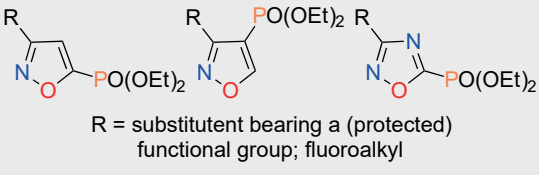
Introduction and Aim

Phosphorylation of amino acid side chains is one of the most important posttranslational modifications. It is not surprising therefore that phosphorylated amino acids have attracted much interest in medicinal chemistry. Several compounds of this class (*e.g.* AP-4, AP-5, AP-7, Selfotel, and Midafotel) were evaluated as NDMA receptor antagonists and have reached clinical trials.

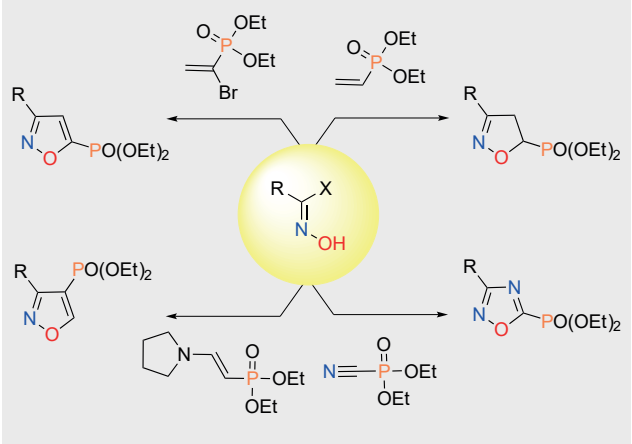
On the other hand, hydrophilic aromatic rings such as isoxazole or 1,2,4-oxadiazole follow requirements of hydrolytic stability; they introduce conformational restriction and can alter ADME properties of potential drug candidates. In fact, isoxazole ring is among top heterocycles used in medicinal chemistry.

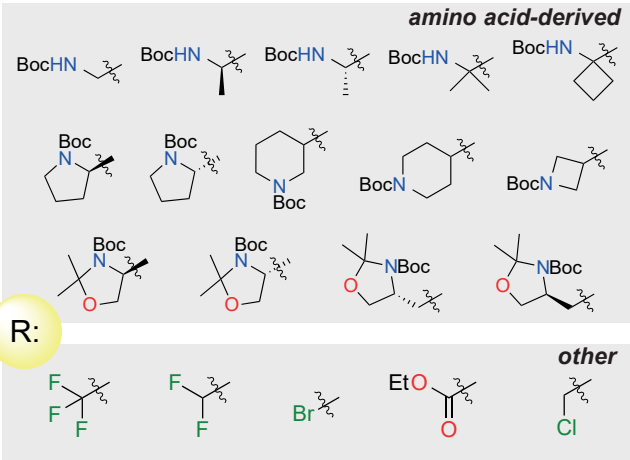
In this work, we describe methods for regioselective synthesis of isoxazole- or 1,2,4-oxadiazole-derived phosphonates bearing an additional functional or fluorinated group by [3+2] cycloadditions of phosporylated dipolarophiles and functionalized or fluorinated halogenoximes. The target compounds are promising building blocks for drug discovery which fully comply with the current lead-likeness criteria.



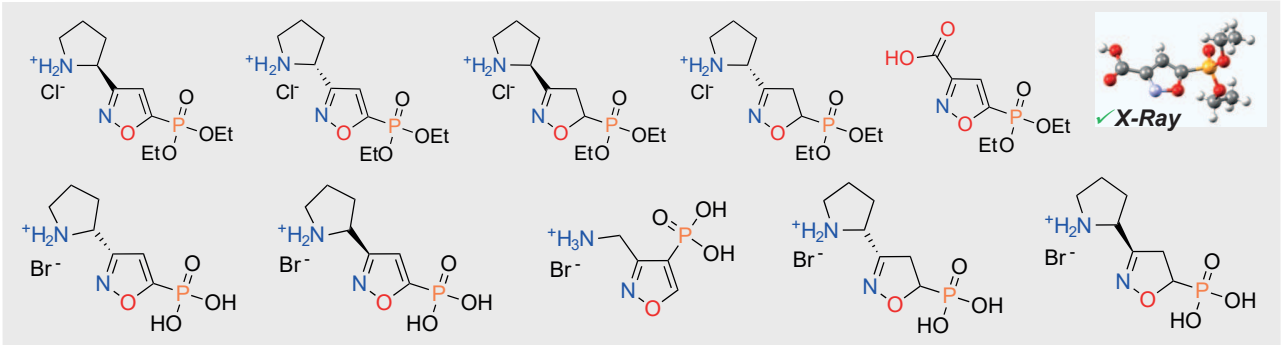


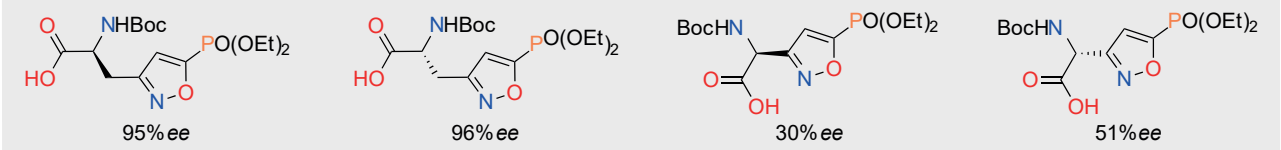
Scope and regioselectivity of the [3+2] cycloadditions





Phosphorylated isoxazolesand 1,2,4-oxadiazoles – advanced building blocks for drug discovery





Contacts

Dmitriy M. Volochnyuk, Dr. Sci., PhD, d.volochnyuk@enamine.net, d.volochyuk@gmail.com;
Sergey V. Ryabukhin, Prof. Dr. Sci, s.v.ryabukhin@gmail.com;
Enamine Ltd, 78 Chervonotkatska Str, 02660 Kyiv, Ukraine, www.enamine.net

References

1. Chalyk, B.; Sosedko, A.; Volochnyuk, D. M.; Tolmachev, A. A.; Gavrilenko, K.; Liashuk, O.; Grygorenko, O. O. Org. Biomol. Chem. 2018, 16, 9152–9164.
2. Chalyk, B. A.; Hrebeniuk, K. V.; Gavrilenko, K. S.; Shablykin, O. V.; Yanshyna, O. O.; Bash, D.; Mykhailiuk, P. K.; Liashuk, O. S.; Grygorenko, O. O. Eur. J. Org. Chem. 2018, 2753–2761.
3. Chalyk, B. A.; Hrebeniuk, K, V.; Gavrilenko, K. S.; Kulik, I. B.; Rozhenko, A. B.; Volochnyuk, D. M.; Liashuk, O. S.; Grygorenko, O. O. Eur. J. Org. Chem. 2018, 5585–5595.