P(O)Me$_2$-containing Building Blocks for Drug Design

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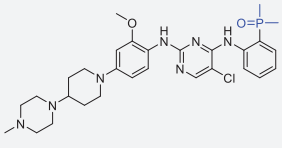
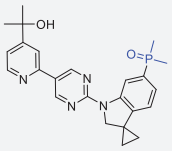
Introduction and Aim

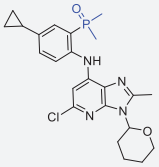
Phosphine oxides belong to a chemical class seldom employed in drug design. However, the FDA-approval of *Brigatinib* drug (ARIAD Pharm.) in 2017 may further inspire application of this unique functional group in medicinal chemistry. The highly ionic P=O bond imparts a number of important drug-like properties, including decreased lipophilicity, increased aqueous solubility, H-bond acceptor ability, and high metabolic stability. [1-3] Herein we have designed and synthesized a library of phosphine oxide derivatives for drug design.



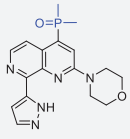
Anti-cancer drug **Brigatinib** (Alunbrig)
ARIAD Pharm.
2016



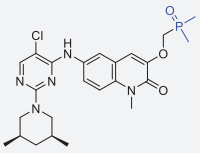
Phoshodiesterase inhibitor
WO2017/108203, A1
Grünenthal GmbH



TYK2 inhibitor
WO2018/075937, A1
Nimbus Lakshmi

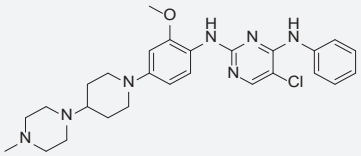


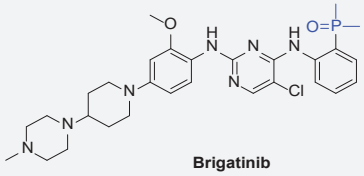
ATR kinase inhibitor
WO2018/153969, A1
Bayer Pharm.



BCL6 inhibitor
WO2018/108704, A1
Boehringer Ingelheim

Discovery of *Brigatinib*



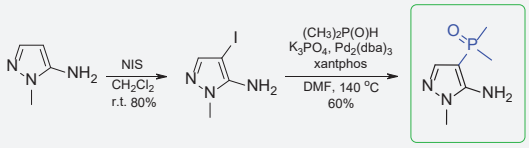


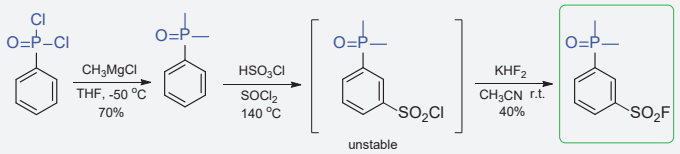
Brigatinib

P(O)Me$_2$-group:

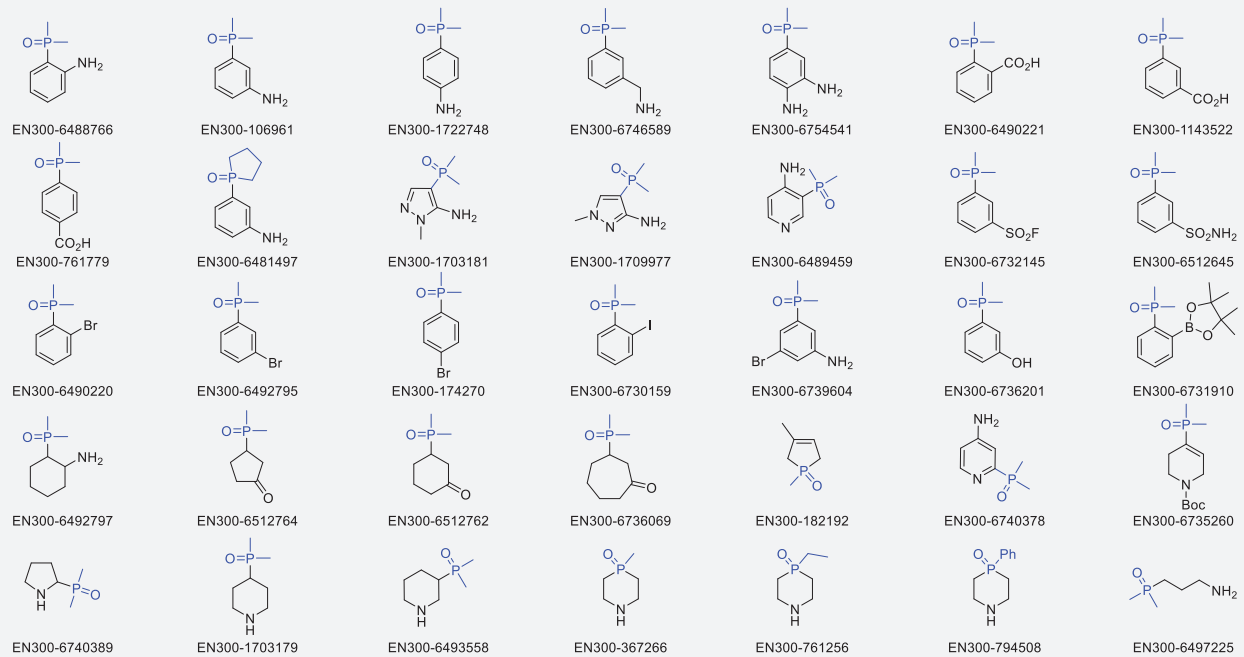
- chemically stable;
- metabolically stable;
- H-bond acceptor;
- increases solubility;
- decreases lipophilicity.

Synthesis





Results



References

1. W.-S. Huang et al. *J. Med. Chem.* **2016**, *59*, 4948.
2. A. A. Kamel. *International Journal of Chemical and Biomedical Science*, **2015**,*1*, 56.
3. V. Iaroshenko. *Organophosphorus Chemistry: From Molecules to Applications*, John Wiley & Sons, **2019**, 568.