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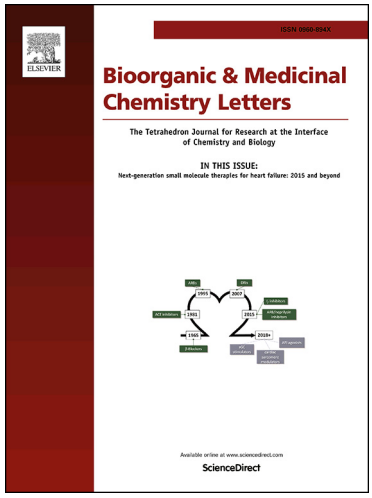

Discovery of a novel series of pyridine and pyrimidine carboxamides as potent and selective covalent inhibitors of Btk

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PII: S0960-894X(18)30775-3
DOI: https://doi.org/10.1016/j.bmcl.2018.09.033
Reference: BMCL 26054

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 4 June 2018
Revised Date: 22 September 2018
Accepted Date: 26 September 2018

Please cite this article as: Caldwell, R., Liu-Bujalski, L., Qiu, H., Mochalkin, I., Jones, R., Neagu, C., Goutopoulos, A., Grenningloh, R., Johnson, T., Sherer, B., Gardberg, A., Follis, A.V., Morandi, F., Head, J., Discovery of a novel series of pyridine and pyrimidine carboxamides as potent and selective covalent inhibitors of Btk, *Bioorganic & Medicinal Chemistry Letters* (2018), doi: https://doi.org/10.1016/j.bmcl.2018.09.033

Discovery of a novel series of pyridine and pyrimidine carboxamides as potent and selective covalent inhibitors of Btk.

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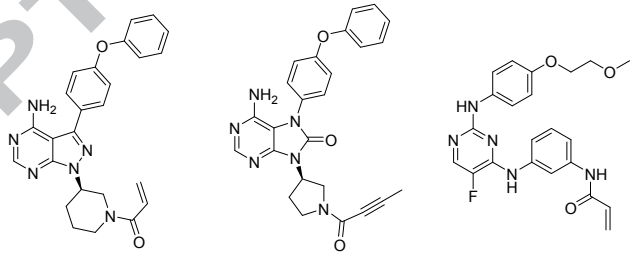
Keywords: Covalent, Irreversible, Btk inhibitor, Fragment

Bruton's Tyrosine Kinase (Btk) is a member of the Tec family of tyrosine kinases and is expressed in B cells, macrophages, neutrophils, and monocytes, but not T cells[1]. Btk activity is critical for B-cell receptor (BCR) signaling in B-cells and FCRγ signaling in myeloid cells[2, 3]. Several Btk inhibitors are currently in clinical development for the treatment of a range of B-cell malignancies[4], the most advanced of which, is the recently approved ibrutinib (Imbruvica).[5] Ibrutinib was shown clinically to mitigate multiple B-cell mediated forms of cancer including chronic lymphoid leukemia (CLL)[6], mantle-cell lymphoma (MCL)[7], and Waldenström's macroglobulinemia (WM)[8]. In addition, inhibition of Btk signaling in preclinical models of autoimmune diseases such as murine lupus[9] and rheumatoid arthritis[10] demonstrate Btk's utility as a target for the treatment of these diseases.

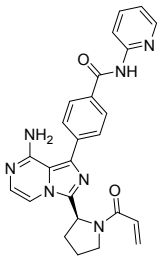
Ibrutinib and related compounds (Figure 1) target Btk specifically by formation of a covalent bond between the Cys481 residue of Btk and a chemically reactive warhead moiety, such as the acrylamide of ibrutinib and propargylamide of tirabrutinib **2**. Ibrutinib also binds covalently to several other kinases that possess a similarly accessible cysteine residue including Egfr, BrbB2, Itk, Jak3, Blk, Tec, and Bmx.[11, 12] Additionally, ibrutinib possess a promiscuous hinge binding moiety that enables the molecule to bind potently to other kinases that lack the cysteine residue (Lck, Lyn, Fyn, Src, Abl,[13, 14] and Flt3[15]) further contributing to the promiscuous kinase activity profile of the therapeutic. In addition to these undesirable off target effects, reports have also linked atrial fibrillation via inhibition of PI3k-Akt[16-18] cardiac signaling, as well other undesirable adverse effects such as drug-drug interaction with verapamil[19] to treatment with ibrutinib. Taken together, these data underscore the need to find new classes of covalent Btk inhibitors with improved selectivity and the potential to provide safer and more attractive treatment options for patents.



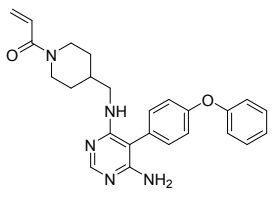
1 Ibrutinib

2 Tirabrutinib

3 Spebrutinib



4 Acalabrutinib



5 Evobrutinib