

Discovery of Eliquis®/Apixaban, a Novel Factor Xa Anticoagulant and Chan-Lam Coupling Reaction



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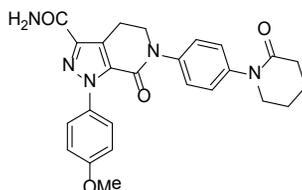
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Abstract:

Thrombosis is the leading cause of death in developed countries. There is a significant need for novel antithrombotics with an improved safety profile to replace Warfarin which has been in use for ~60 years and has significant bleeding issues. Factor Xa is at the junction of the intrinsic and extrinsic pathways of the coagulation cascade. Preclinical data has demonstrated that blocking FXa is an effective approach for anticoagulation with improved safety profile. Utilizing structure-based drug design tools, focused screening, and ADMET innovations, we at Bristol Myers Squibb had discovered a novel class of potent, selective and orally bioavailable Factor Xa inhibitors culminating in Eliquis®/Apixaban. Eliquis® was recently approved by FDA and named the “Best New Medicine of 2012” by Med Ad News. Eliquis® is currently a “block-buster” drug with annual sales of >\$5B. In 2015, the Eliquis discovery team received the American Chemical Society Heroes of Chemistry Award for a successful commercial product that benefits human well being.

During the optimization process, we have also discovered the powerful Chan-Lam Coupling reaction of copper promoted C-X bond cross-coupling via boronic acids, a complementary reaction to the Nobel prize Suzuki-Miyaura C-C bond Coupling reaction. In addition, at the molecular recognition frontier, we have pioneered the first rational use of halogen bonding in structure-based drug design.



Eliquis®/Apixaban

Keywords:

Factor Xa inhibitors, Eliquis®, apixaban, structure-based drug design, Chan-Lam reaction, halogen bonding.

References:

1. Discovery of 1-(4-Methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (Apixaban, BMS-562247), a Highly Potent, Selective, Efficacious, and Orally Bioavailable Inhibitor of Blood Coagulation Factor Xa." Pinto, D. J. P.; Orwat, M. J.; Koch, S.; Rossi, K. A.; Alexander, R. S.; Smallwood, A.; Wong, P. C.; Rendina, A. R.; Luetgen, J. M.; Knabb, R. M.; He, K.; Xin, B.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem.* 2007, 50, 5339-5356.
2. Copper-promoted Carbon-Heteroatom bond cross-coupling with boronic acids and derivatives. Qiao, J. X.; Lam, P. Y. S. *Syn.* 2011, 829-856.
3. Halogen bonding a world parallel to hydrogen-bonding Symposium in Organic Division, #58, ACS, August 16-20, 2009. Washington DC. Highlighted in C&E News, Sep 21, 2009, p39-42, "...to the best of our knowledge, this is the first successful use of halogen bonding in rational drug design..."

Biography:

Dr. Lam is a medicinal chemistry and drug discovery consultant. He currently collaborates with Blumberg scientists in terms of drug discovery and jointly supervises Blumberg chemistry postdocs and visiting scientists.

Dr. Lam has 30 years of extensive experience in innovation in structure-based drug design, ADME, focused libraries, molecular recognition and nucleic acid therapeutics to deliver biopharma clinical candidates with novel profiles. He is responsible for the discovery of a total of eight clinical candidates. At Bristol Myers Squibb, Dr. Lam was the group leader/co-inventor responsible for the discovery of Eliquis®/Apixaban, a novel Factor Xa anticoagulant recently launched on the market. Eliquis® is projected by analysts to be a transformational medicine with "block-buster" sales potential. Eliquis® was chosen as the "Best New Medicine of 2012" by Med Ad News. He and his team were awarded 2015 American Chemical Society Heroes of Chemistry Award for the discovery of Eliquis®. Dr. Lam is also the inventor of the novel cyclic urea class of HIV protease inhibitors that resulted in Mozenavir/DMP450. In Phase II clinical trial, Mozenavir was shown to be as efficacious as Merck's Crixivan, but without the lipodystrophy side effect of Crixivan.

Notes: