MS7-02 **A Structure-Based Approach To Selective PI3Kbeta Inihibition.** Thomas Bertrand,[a] Jean-Pierre Marquette,[a] Andreas Karlsson[a], Nadine Michot[b], Angela Virone-Oddos[c] and Frank Halley[c] [a]*Structural Biology and Molecular Modeling, ,* [b]*Protein Production,* [c]*Oncology Drug Discovery, Sanofi, 13 Quai Jules Guesde, 94403 Vitry-sur-Seine France.*
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Most of the phosphoinositide-3 kinase (PI3K) kinase inhibitors currently in clinical trials for cancer treatment exhibit pan PI3K isoform profiles. Single PI3K isoforms differentially control tumorigenesis and PI3Kβ has emerged as the isoform involved in the tumorigenicity of PTEN-deficient tumors. Herein we describe the discovery and optimization of a new series of benzimidazole- and benzoxazole-pyrimidones as small molecular mass PI3Kβ-selective inhibitors [1]. Starting with compound **5** obtained from a one pot reaction *via* a novel intermediate **1**, medicinal chemistry optimization led to the discovery of compound **8**, which showed a significant activity and selectivity for PI3Kβ, and adequate *in vitro* pharmacokinetic properties. The X-Ray co-structure of compound **8** in PI3Kδ showed key interactions and structural features supporting the observed PI3Kβ isoform selectivity. Compound **8** achieved sustained target modulation and tumor growth delay at well tolerated doses when administered orally to SCID mice implanted with PTEN-deficient human tumor xenografts.

[1] Certal, V., Halley, F., Virone-Oddos, A., Delorme, C., Karlsson, A., Rak, A., Thompson, F., Filoche-Rommé, B., El-Ahmad, Y., Carry, J.C., Abecassis, P.Y., Lejeune, P., Vincent, L., Bonnevaux, H., Nicolas, J.P., Bertrand, T., Marquette, J.P., Michot, N., Benard, T., Below, P., Vade, I., Chatreaux, F., Lebourg, G., Pilorge, F., Angouillant-Boniface, O., Louboutin, A., Lengauer, C. & Schio, L. (2012). *J. Med. Chem.* In Press.

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MS7-03 **Starting Small and Getting Bigger: From Molecular Probes to Fragments and Leads.** A. Heine,[a] J. Behnen,[a] H. Köster,[a] T. Craan,[a] S. Brass,[a] G. Klebe[a]
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In addition to high-throughput screening and structure-based drug design, fragment- based approaches have recently become increasingly popular for lead development in pharmaceutical drug research. Here, a small but well selected library of low molecular weight compounds (< 300 Da) is screened by biophysical methods such as surface plasmon resonance (SPR), nuclear magnetic resonance (NMR) or X-ray crystallography. In this study, we started with even smaller, highly-soluble probe molecules, such as aniline, urea, N-methylurea, propanediol, bromophenol and phenol. These probe molecules were selected to experimentally map out protein binding pockets by detecting hot spots of binding with respect to hydrophobic and hydrophilic properties. As model protein the zinc protease thermolysin was selected. Subsequently, our studies were extended to additional proteins. The obtained crystal structures clearly show that the probe molecules could be located in these protein binding pockets. These probe molecules form similar interactions as larger ligands containing analogical chemical features and therefore are deemed suitable for hotspot detection. Next, the structure of PKA in complex with phenol was used as template for docking of a virtual in-house fragment library of about 4000 entries. With one promising candidate a crystal structure was subsequently determined. Using the structural information and the experimental hot spot analysis, a putative lead skeleton was obtained that was translated into a synthetically accessible compound class. During three rounds of lead optimization we achieved inhibitors with nanomolar affinity.

Keywords: probe molecules; fragments; drug design