Label-Free 7,000 Fragment Screening Using the Corning® Epic® System

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Fragment based drug discovery (FDD) covers a large chemical diversity in fewer numbers of compounds (ref. 1). We screened seven thousand compounds with an average molecular weight of 230 Da (Novartis, Basel, CH) at a final concentration of 520 µM.

Assay Flow:

1.Plate Activation

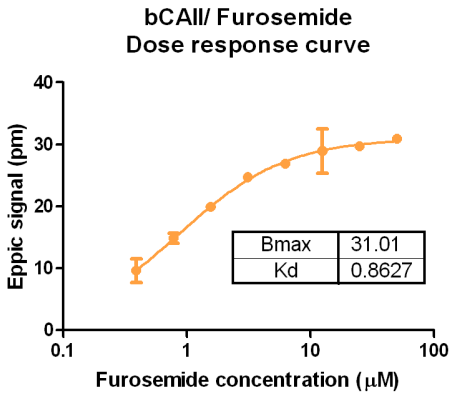
2.Protein Immobilization o/n @ 4°C 10 µl, 50 µg/ml

3.Plate blocking/washing and soaking

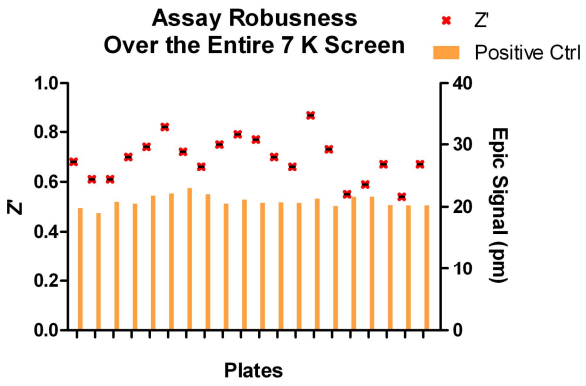
4.Baseline read

5.Compound reconstitution and addition (520 µM)

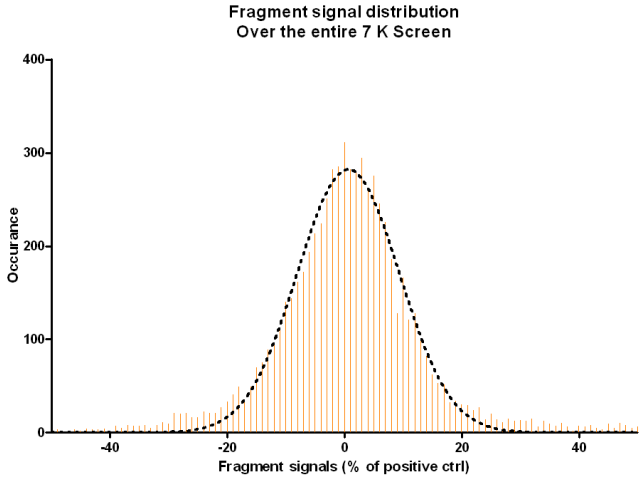
6.Final read



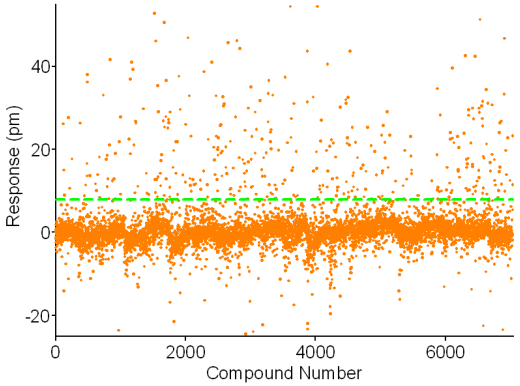
Positive control: The binding of furosemide to the bCAII is **specific and saturable**. Affinity (K_D) is in agreement with published data (ref. 2). **(suitable conditions for the screen**).



Assay Robustness: Over the 20 Epic microplates used for the 7 K screen, the positive control signal of 21 pm and the robustness, the **Z' factor, is ~ 0.7**.



The statistical distribution of the 7 k fragment signals is **very compact** and very well **centered close to zero**. Its shape fit perfectly with a Gaussian distribution with a R^2 of 0.98.



A majority of the compounds give a signal very close to zero. The threshold **(5MAD)** is represented by the green dashed line. It is clearly seen that the hits are well distributed along the 20 microplates of the screen, indicating that the hit distribution is not biased.

Hit rate: The hit rate for the seven thousand fragments screen is ~**6%** (in the expected range **at 500 µM**) (ref. 3).

Conclusions:

- The Epic System enables label-free biochemical assay for small molecules
- The results of this 7 k fragment screen demonstrate successfully a high assay robustness (average Z' of 0.7).
- Hit rate in agreement with expectations of this particular library (6%).
- Epic system combines the high sensitivity and the throughput, required for HTS Fragment based drug discovery process.

References:
1. **Carr RA, Congreve M, Murray CW and Rees DC** Fragment-based lead discovery: leads by design (2005) Drug Discov Today 14, **987-92**
2. **Myszka DG** Analysis of small-molecule interactions using Biacore S51 technology (2004) Analytical Biochem **329**, 316-323
3. **Erlanson DA and Jahnke W** The concept of Fragment-based Drug Discovery (2006) in Fragment-based Approaches in Drug Discovery Edited by Jahnke W and Erlanson DA, WILEY-VCH Verlag GmbH & Co. KGaA,Weinheim