creoptix sensors

TechNote 3

Highly accurate resolution of fast off-rates to significantly reduce false-positives

Creoptix® WAVEsystem

In this TechNote we show how the WAVEsystem can be used to accurately measure fast off-rate kinetics of weakly binding molecules. Thanks to a cartridge design that enables ultra-fast transition times of 150 ms, low potency hits can now be easily spotted for more successful drug discovery

Summary

Weak binders such as those found in fragment-based screening libraries are typically ranked by affinity rather than kinetics. This is because standard instrumentation lacks the capacity to measure fast off-rates. However, measuring affinity rather than off-rates can generate large numbers of false positive results, extending workflows and incurring unnecessary costs.

Employing a proprietary Grating-Coupled Interferometry (GCI) technology, the Creoptix® WAVEsystem provides resolution of fast off-rates up to $10s^{-1}$. This enables accurate, early stage selection of true hits to greatly increase efficiencies.

By measuring the binding kinetics of methylsulfonamide to Carbonic Anhydrase II, we show that the Creoptix WAVEsystem achieves outstanding resolution at extremely fast off-rates, even for large target-to-analyte molecular weight ratios.

Table 1: Kinetic data compared to published data in Myszka, David G. "Analysis of small-molecule interactions using Biacore S51 technology." Analytical biochemistry 329.2 (2004): 316-323.

Kinetic Data			
Creoptix™ WAVE		Biacore™ S51	
k_{on} (M^{-1} s^{-1})	9.36 x 10^3	k_{on} (M^{-1} s^{-1})	8.05 x 10^3
k_{off} (s^{-1})	2.86	k_{off} (s^{-1})	2.21
K_D (uM)	306	K_D (uM)	274

Legend: (A) Sensorgram of methylsulfonamide (95.1 Da) binding to Carbonic Anhydrase II (29 kDa) immobilized by amine-coupling on a WAVEchip PCH at 8500 pg/mm² on flow cell 1. Dat was acquired at 40Hz with a flow rate of 200µl/min. (B) Zoom into the ssociation phase (left) and dissociation phase (right) with the respective residual distribution plots below showing the high and clear resolution of the kinetics.

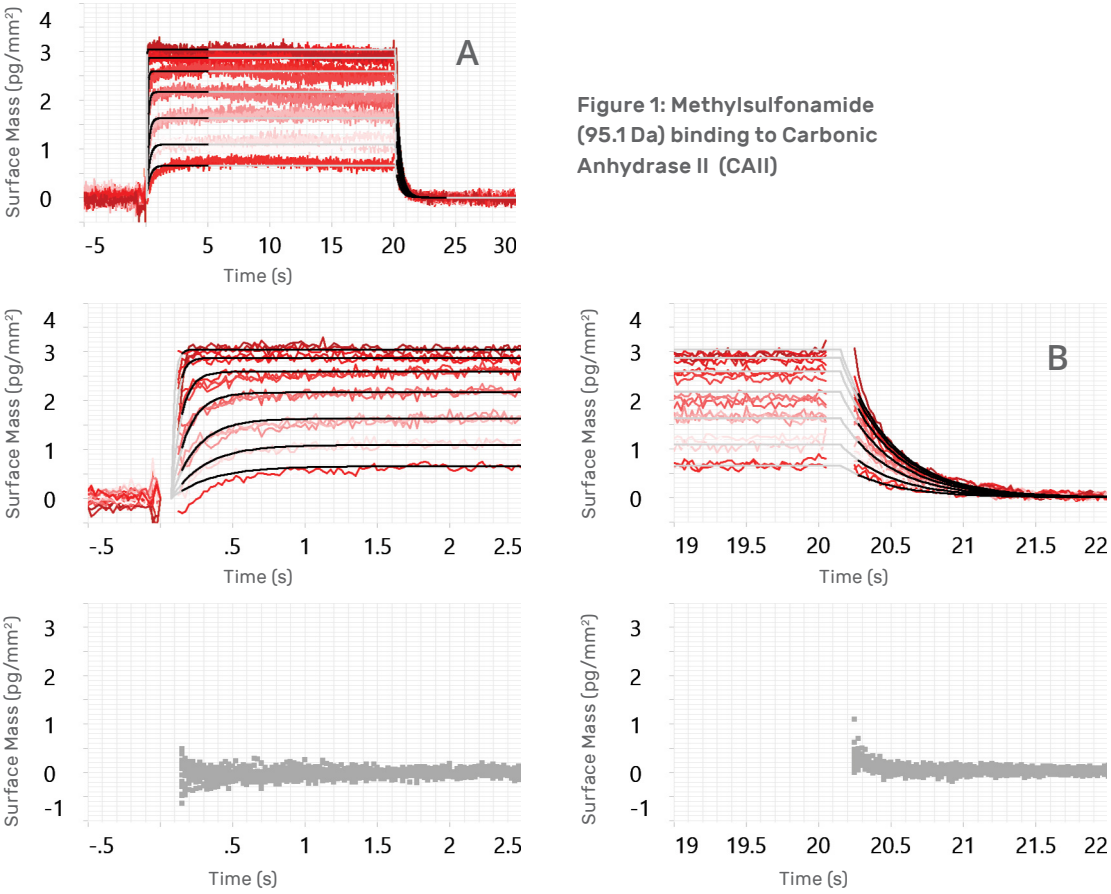

Figure 1: Methylsulfonamide (95.1 Da) binding to Carbonic Anhydrase II (CAII)

1 pg/mm² = 1 RU

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Keeping Kinetics Real

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