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**Title**

Discovery of Small Molecule Inhibitors Using a Modern Screening Paradigm and High Throughput Chemistry

**Abstract**

In the realm of drug discovery, cycle time reduction to deliver the final clinical candidate for a program is highly sought after. Thus, there has been a growing interest in applying innovative high throughput chemistry capabilities to enable rapid data generation and decision making in a shortened timeframe for discovery programs. At Janssen, a collaborative working model amongst embedded parallel medicinal and project team chemists allowed for the rapid exploration and synthesis of final compounds to test against the Natural Killer Group 2D receptor (NKG2D). The initial small molecule leads were identified via two screening campaigns, a DNA-encoded library screen and a high throughput screen of the Janssen collection. Guided by co-crystallization of the leads with the NKG2D complex, the team pinpointed key hydrogen bonds and lipophilic interactions which led to the design and execution of multiple parallel libraries. These efforts allowed the team to expedite diverse SAR exploration resulting in improved biological activity against the target and identification of novel interactions with the protein. Overall, the application of high throughput capabilities via a fully collaborative model accelerated the Design-Make-Test-Analyze cycle and had a positive impact on the program objectives.