

Medicinal Chemistry Guidelines

All screeners will receive advice from the NSRB medicinal chemistry group on compounds that score as positives in their screen, but only a limited number of compounds can be carried forward for full structure-activity relationship (SAR) studies at the NSRB. Compound prioritization is generally based on that compound's biological activity and chemical properties. The NSRB Advisory Committee is responsible for selecting projects/compounds and setting priorities for the medicinal chemistry group. The Committee will be advised by NSRB staff in these decisions.

Initial Chemistry Analysis

After screening positives are identified and the Primary Screen Report is returned to the NSRB, the NSRB chemistry staff will provide screeners with a preliminary analysis of their screening positives, potentially including recommendations on cherry picks and commercially available compounds that may be of particular interest. Screeners are not obliged to cherry pick or order compounds based on the preliminary analysis, but screeners often find this information useful.

During secondary analysis, screeners should confirm that their cherry picks are active in the primary assay, and eliminate compounds that are obviously biologically uninteresting. Examples of obviously uninteresting hits are fluorescent compounds identified in a fluorescence-based assay, luciferase inhibitors, or promiscuously cytotoxic compounds identified in a cell-based assay. Compound solubility issues (e.g., compound precipitation) may also cause artifacts. Comparing data with other screen results should eliminate many false-positive compounds from consideration.

NSRB chemistry and biology staff are available to provide advice during secondary analysis.

Hit Validation

Before a structure-activity relationship (SAR) study can be initiated, screening positives must be confirmed and validated according to the following criteria:

- when resupplied directly by the vendor, the compound performs as well or better in the primary assay compared to the library sample.
- the compound shows a reasonable dose-response curve in the primary assay.
- the compound meets a minimum activity threshold (ideally, but not necessarily, in the range of $IC_{50} < 1 \mu M$ in pure-protein assays, and $EC_{50} < 10 \mu M$ in cell-based assays).

The NSRB chemistry group is available to advise screeners on experimental design and data analysis during the hit validation stage. To facilitate ongoing assessment of which compounds might be suitable for SAR analysis, screeners should keep the chemistry group informed of the progress of these studies.

SAR Studies

In the first phase of an SAR study, the NSRB chemistry group will attempt to identify commercially available compounds that are similar to the hit. Screeners should test the activity of these compounds and work with the chemistry group to analyze the resulting data. The Head of Medicinal Chemistry will then make a recommendation to the Advisory Committee about launching a full SAR study.

Approval of a full SAR study commits the NSRB to performing custom synthesis of analogs of hit compounds in order to develop lead compounds with enhanced biological activity and reduced cytotoxicity. Screeners will receive synthesized compounds from the chemistry group for testing in biological assays, and screeners will work closely with the chemistry group throughout the project. SAR analysis is a very resource-intensive undertaking for the NSRB, and we anticipate that only 20-25% of all screens will generate hits suitable for a full medicinal chemistry effort.

Contact Information

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