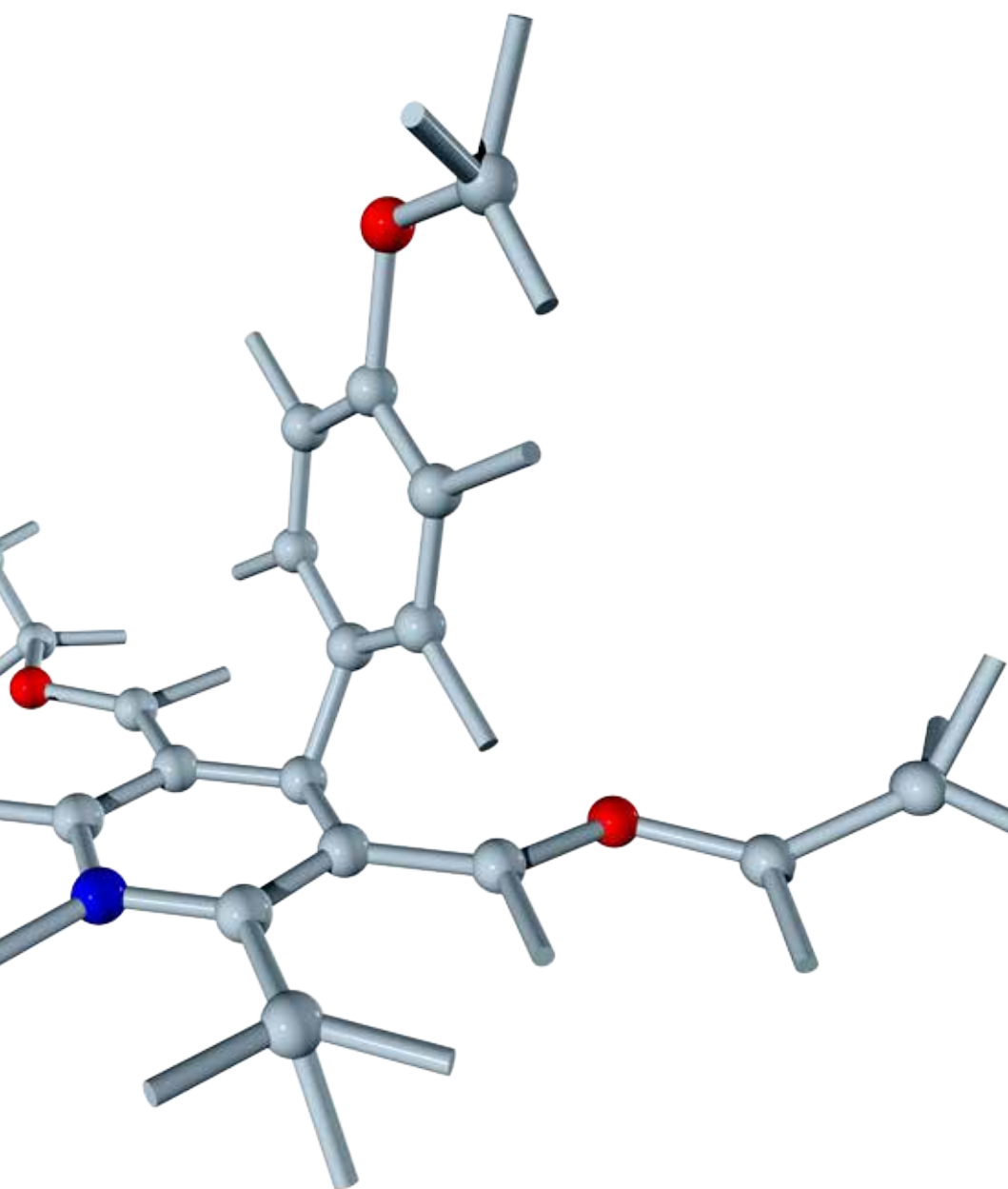




The Partner
of Choice
for Your Discovery
Programs



Axxam supports the discovery efforts of its partners by providing services, tool and solutions for the hit discovery process. A team of highly skilled scientists with a proven performance-driven attitude provides solutions for even the most challenging projects.

Compound Collection: AXX^{DIV2.0}

Axxam offers access to the new compound library AXX^{DIV2.0} for hit identification programs.

Comprising 240,000 compounds, the library is characterized by a high level of diversity and novelty. AXX^{DIV2.0} was developed by Axxam team of medicinal and computational chemists, and incorporates Axxam's extensive experience in HTS. Three library subsets designed for specific screening needs are available.



Subset	#Cmpds	Characteristics
Discovery	180.000	~10 analogues per scaffold to provide SAR information
Explorer	48.000	All singletons; suitable for exploring novel target space
Probe	12.000	Low MW; suitable as a starting point for further optimization

Assay Development

Axxam has extensive expertise in the development of functional cell-based assays and biochemical assays using a range of different technologies.

Assay are available for the following:

- GPCRs
- Ion Channels
- Receptor Tyrosine Kinases
- Transporters & Exchangers
- Cytokine Receptors
- Nuclear Hormone Receptors
- Enzymes (including recombinant protein expression and purification)
- Gene promoters
- Hormone secretion

Assays are developed using a range of different reporter genes and signal detection methods, to best adapt the assay to the final goal, including the identification of allosteric modulators and state-dependent blockers. The flexible and highly customized approach used by Axxam has yielded enhanced success rates in client discovery projects in particular for challenging targets.



The Assay Suite

Axxam offers a constantly growing number of optimised assays and cell lines. The Assay Suite contains more than 180 cell-based and 60 biochemical assays for key drug discovery targets. Different reporter genes and detection systems coupled to specific signalling cascades are used, and assays are optimized for the standard 384-well format. Clients have access to Axxam's Assay Suite by

- requesting compound profiling
- commissioning HTS campaigns conducted at Axxam
- purchasing cell lines or enzymes of interest

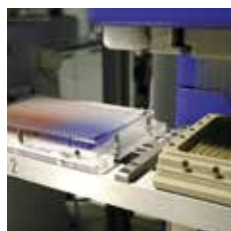


High Throughput Screening

Axxam has a long history and consolidated experience in High-Throughput Screening (HTS) using automated state-of-the-art screening stations designed to run biochemical and cell-based assays in 384 well format, using a broad range of detection technologies including luminescence, fluorescence, absorbance, HCS and radiometric readouts.

The most appropriate screening strategy is selected for any project according to the specific target features and characteristics to ensure the highest probability of success for the hit finding process.

Hit finding programs can be conducted using either customer's library (>1M) or Axxam's Compound Collection AXX^{DIV2.0}.



HTS services include

- Assay adaptation to the specific screening conditions
- Pilot screening performed on a sub-set of compounds
- Primary screening
- Data analysis for primary hit identification
- Hit-confirmation
- Activity determination (EC₅₀ /IC₅₀ determination)
- Preliminary SAR analysis

Hit Follow-up

Axxam's hit follow-up services provide solutions for addressing selectivity, specificity and safety liabilities. Having access to an extensive collection of assays in-house, Axxam can immediately support the drug discovery efforts of its clients. Each of the following activities can be accessed separately or as part of an integrated solution.

Dose-response analysis to determine potency (IC₅₀ and EC₅₀ values) and discriminate between orthosteric and allosteric modulators

Specificity profiling using orthogonal assay formats

Selectivity profiling against close homologues of the primary target

Proof of Concept studies in physiologically relevant orthogonal assays and cell types



Electrophysiology

Axxam offers both manual and automated patch-clamp facilities together with a deep understanding of ion channel biology and a long standing and recognized expertise in the field.

On the HEKA-based **manual patch-clamp** setup, a variety of protocols are available for both ligand and voltage-gated ion channels, as well as for transporters and exchangers. The platform is used during the assay development to validate cell lines and for analyzing the pharmacological and biophysical behavior of testing compounds, along with profiling programs.

The QPatch 16X-based **Automated Patch Clamp** unit allows:

- More than 300 data points per day
- Medium throughput screening for hit discovery, hit confirmation and cardiac safety
- Compound profiling on ready-to-use Axxam assays or on adapted client assays

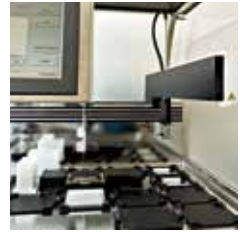


Cardiac Safety and Liability Profiling

A continuously growing panel of functional assays is available to address potential cardiac and safety liabilities. Compounds are tested in dose response curves and results are provided with quick turnaround.

Cardiac Safety Assays

- hERG (QPatch 16X)
- Nav1.5 (QPatch 16X)
- Kv1.5 (QPatch 16X)
- CaV1.2 (FLIPR assay)



Compound Management

Axxam offers a comprehensive solution for compound handling and storage.

Compound arrival, registration and handling is performed according to internal Standard Operating Procedures (SOPs) to guarantee:

- Integrity of the plates and the conservation status of the compounds
- Barcode acquisition and matching to the packing list sent by the provider
- Immediate plate storage in the most appropriate conditions
- Upload of the mapping data into Axxam's screening database (SB3)

Compound handling activities provided:

- Cherry picking of hits and custom libraries
- Plate copying, dilution preparation, screening-ready plates

Axxam uses a Brooks **Universal Labstore 600** (UL-600) to store up to 14,000 plates in a dry atmosphere at -20°C . **UL-600** offers strict monitoring of storage conditions, a redundant cooling system for maximum compound safety, and comprehensive tracking of plate locations.



Technologies and Platforms

Axxam researchers have developed innovative proprietary technologies and tools to successfully overcome the many challenges faced during the development of HTS assays for drug discovery programs. The following **proprietary technologies** are available from Axxam for licensing :

Photina® and **i-Photina®**: Ca^{2+} activated photoproteins optimized for the generation of HTS-assays for targets correlated to the intracellular increase of Ca^{2+} .

chAMPion technology: a universal GPCR reporter cell line capable of measuring the functional activation of any transfected GPCR, and a real time assay for cAMP and cGMP level variation.

In addition, other **novel technologies** and assay **platforms** have been developed or optimized by Axxam's researchers to further improve the performance of cell based assays:

- Use of gene editing technologies for cell-based assay generation
- Optogenetics: light-induced activation of Voltage gated ion channels
- Genetically encoded voltage sensors
- Odorant receptors platform
- Bitter receptors platform
- Metabolic platform: relevant cell based models
- Epigenetics: platform for compound testing
- Assays for Enzymatic Complexes constituted by multi-protein and/or multi-subunits



Working with Axxam

Key Advantages

- Over 10 years experience providing HTS services and assay development
- Over 180 functional cell-based and 60 biochemical assays developed or adapted to HTS
- Broad target experience, with particular expertise in ion channels and GPCRs
- New assays can be developed on-demand
- Most suitable assay technology for each target is selected
- Access to our new 240,000 compound AXX^{DIV2.0} library

**To learn more about our comprehensive
drug discovery services and products**

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