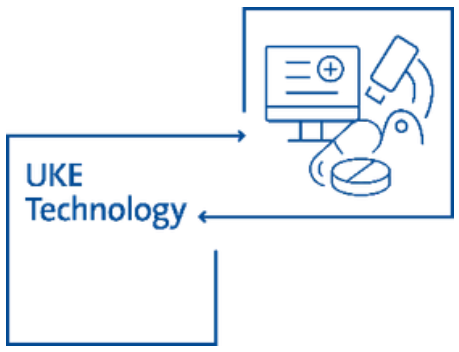
Breaking the Chain of Neurodegeneration: Next-Generation TRPM4 Antagonists



Background & Innovation

Neurodegenerative diseases such as **stroke, Alzheimer's disease, Parkinson's disease, ALS, and multiple sclerosis** remain difficult to treat, as current therapies largely address symptoms rather than preventing or reversing progressive neuronal loss. The **TRPM 4 ion channel** has emerged as a **key mediator of neuronal excitotoxicity** , a process that drives calcium overload and subsequent neuronal death.

This invention introduces a **new class of highly potent and selective TRPM 4** antagonists, the first with:

- **nanomolar IC 50 values**
- **low toxicity**
- **minimal off-target effects**

By targeting a newly identified binding site on TRPM4, these compounds provide **a novel therapeutic strategy** for preventing or slowing neurodegeneration in multiple CNS and immune-mediated diseases.

Technical Description

The compounds, derived from benzoxazole, anthranilic acid, thiadiazole, benzpyrimidine, and 5-(5-Isoxazolyl)-2-thiophenesulfonamide scaffolds, inhibit TRPM4-mediated sodium influx without disturbing calcium signaling or other ion channels.

Through electrophysiological and in vitro studies, the compounds demonstrated:

- **Specific TRPM 4 binding**
- **Reduction of neuronal excitotoxicity**
- **Protection of mitochondrial integrity**
- **Favorable ADMET and DMPK profiles**

This mechanism preserves neuronal function by stabilizing excitatory signaling while preventing cytotoxic overactivation, a downstream, safer intervention compared to glutamate- or NMDA-receptor–based strategies.

Competitive advantage

- **Highest potency** : IC50 values in the **nanomolar range** , surpassing glibenclamide and known TRPM4 inhibitors.
- **Superior selectivity** : Minimal off-target interaction across 44 safety-screened proteins.
- **Low toxicity and good bioavailability** : Confirmed *in vitro* and *in vivo* in murine models.
- **Broad therapeutic potential**: Applicable to **CNS, cardiac, and immune-mediated diseases** linked to TRPM4 dysregulation.
- **Validated mechanism**: Structural and electrophysiological data confirm a unique **TRPM 4 binding pocket** , supporting rational drug optimization

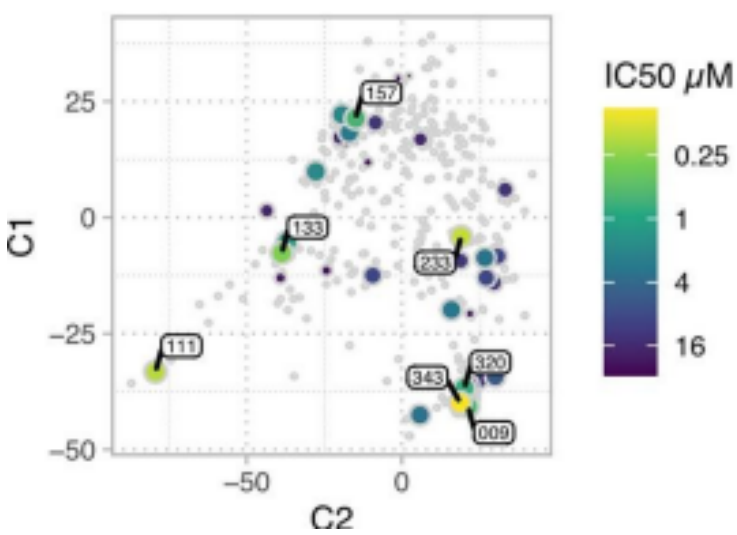


Figure 1: Multidimensional scaling (MDS) analysis presenting the distribution of 357 compounds identified during the high-throughput screening. The respective IC50 values determined by QPatch measurements are represented, with compounds exhibiting IC50 values below ≤1 µM highlighted.

FOCUS SECTORS

- Therapeutics
- Neurodegenerative & neuroinflammatory disorders
- Cardiac and immune - mediated diseases
- Pharmaceutical R&D
- Neuroprotective therapeutic

PROJECT KEY WORDS

- TRPM4 inhibition Neuroprotection
- Ion channel antagonist
- Excitotoxicity
- CNS drug discovery

DEVELOPMENT STATUS

- Lead compounds identified and validated
- *in vitro* and *in vivo* efficiency demonstrated

PATENT PROCEDURE STATUS

- PCT patent application

POTENTIAL FOR COOPERATION

- R&D Cooperation
- Licensing

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Last modified: 2026-04-28

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