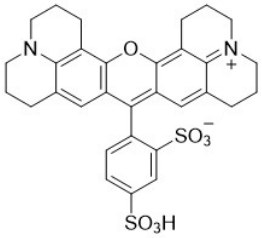
Astrocyte–specific targeting and kinase inhibition of the TNFR1 pathway

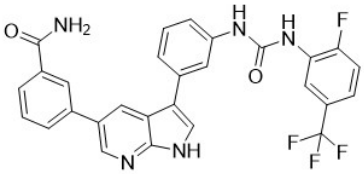
C. Schuppisser[1], R. De Ceglia[2], I. Zalachoras[2], A. Volterra[2]*, J. L. Reymond[1]*

[1]Department of Chemistry, Biochemistry and Pharmaceutical Sciences, University of Bern, Freiestrasse 3, 3012 Bern, Switzerland, [2]Department of Fundamental Neurosciences, University of Lausanne, Rue du Bugnon 9, 1005 Lausanne, Switzerland

Astrocytes, the most abundant subtype of glial cells, have important roles in metabolic support of the neurons i.e. regulation of blood flow, detoxification and clearance of synapses.[1] Additionally, astrocytes are active players in synaptic functions by releasing gliotransmitters as the cytokine TNFα. Therefore, the consequences of disruption of astrocytic supportive functions or gliotransmission could play a significant role in human neuronal diseases. TNFα transforms astrocytes into a neurotoxic phenotype and elevated levels of TNF are found in several human brain diseases including Alzheimer's, Parkinson's, Amyotrophic Lateral Sclerosis, trauma and stroke.[2]



(1)



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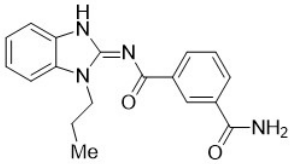

(3)

In this context, we aim to specifically inhibit upstream and downstream kinases of the TNFR1 pathway in astrocytes to gain insight in their function and for further physiological studies. Astrocytes can be specifically labelled by sulforhodamine 101 **(1)** via the thyroid hormone transporter OATP1C1.[3] Here we report the design, synthesis and cellular activity of linked sulforhodamines to RIPK1 **(2)** and TAK1 **(3)** inhibitors via cleavable and non-cleavable linkers.

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[2] Elena V. Mitroshina, Mariia Saviuk, Maria V. Vedunova, *Front. Aging Neurosci.*, **2023**, 14, 1016053.
[3] Christian Schnell, Ali Shahmoradi, Sven P. Wichert, Steffen Mayerl, Yohannes Hagos, Heike Heuer, Moritz J. Rossner, Swen Hülsmann, *Brain Struct. Funct.*, **2015**, 220, 193–203.