

# Aquaporin Inhibitors

Subjects: [Biochemistry & Molecular Biology](#) | [Cell Biology](#) | [Others](#)

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Aquaporins (AQPs) are water channel proteins that are essential to life, being expressed in all kingdoms. In humans, there are 13 AQPs, at least one of which is found in every organ system. The structural biology of the AQP family is well-established and many functions for AQPs have been reported in health and disease. AQP expression is linked to numerous pathologies including tumor metastasis, fluid dysregulation, and traumatic injury. The targeted modulation of AQPs therefore presents an opportunity to develop novel treatments for diverse conditions. Various techniques such as video microscopy, light scattering and fluorescence quenching have been used to test putative AQP inhibitors in both AQP-expressing mammalian cells and heterologous expression systems. The inherent variability within these methods has caused discrepancy and many molecules that are inhibitory in one experimental system (such as tetraethylammonium, acetazolamide, and anti-epileptic drugs) have no activity in others. Some heavy metal ions (that would not be suitable for therapeutic use) and the compound, TGN-020, have been shown to inhibit some AQPs. Clinical trials for neuromyelitis optica treatments using anti-AQP4 IgG are in progress. However, these antibodies have no effect on water transport. More research to standardize high-throughput assays is required to identify AQP modulators for which there is an urgent and unmet clinical need.

Aquaporin

AQP inhibitors

AQP modulators

AQPs in disease

TGN-020

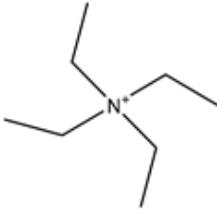
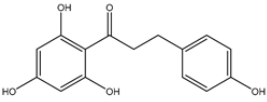
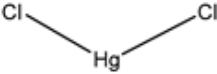
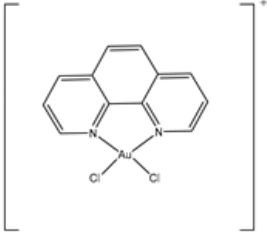
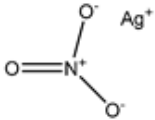
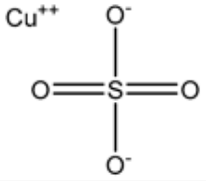
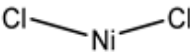
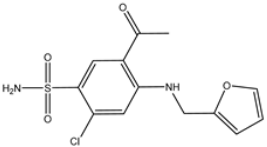
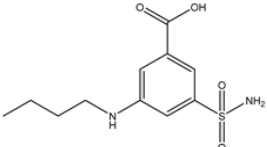
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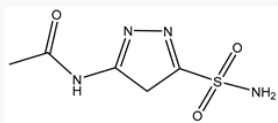
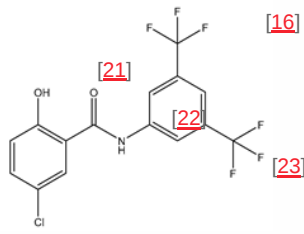
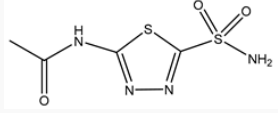
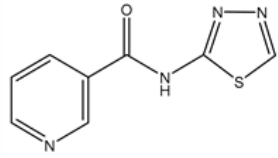
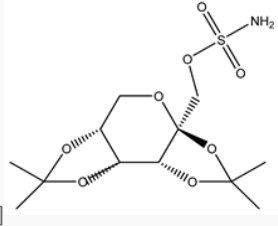
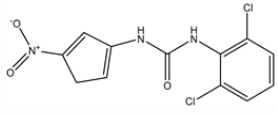
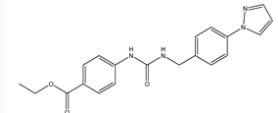
small molecule inhibitors

## 1. Aquaporin Inhibitors

Most of the molecules that are currently under investigation as aquaporin (AQP) inhibitors target AQPs 1, 2, 3 or 4. There are many patents, clinical trials, and studies on AQP up-regulators, modulators, and inhibitors. For the purposes of this review, only AQP inhibitors are considered (Table 1).

**Table 1.** Currently-available AQP inhibitors, their structures, the AQPs they inhibit (species are highlighted as h—human, m—mouse, and r—rat) and the conditions under which they were assayed.

Inhibitor	Conditions	AQPs Inhibited	Structure	References
Tetraethyl-ammonium	<i>Xenopus</i> oocytes 100 $\mu$ M	hAQP1		[1]
Phloretin	<i>Xenopus</i> oocytes 0.1 mM Proteoliposomes 0.5 mM	rAQP9 hAQP3		[2][3]
Mercury chloride	<i>Xenopus</i> oocytes 1 mM	hAQP1		[4][5]
AuPhen	Erythrocytes 50 $\mu$ M Adipocytes 15 $\mu$ M	hAQP3 hAQP7		[6][7]
Silver nitrate	Erythrocytes 10 $\mu$ M	hAQP3		[8]
Copper sulfate	Swan 71 cells 100 $\mu$ M	hAQP3		[9]
Nickel chloride	Human bronchial epithelium cells 1 mM	hAQP3		[10]
Furosemide	<i>Xenopus</i> oocytes 10 $\mu$ M	hAQP1		[11]
Bumetanide	<i>Xenopus</i> oocytes 100 $\mu$ M	rAQP4		[12]

Inhibitor	Conditions	AQPs Inhibited	Structure	References
<i>N</i> -(5-Sulfamoyl-1,3,4-thiadiazol-2-yl) acetamide	<i>Xenopus</i> oocytes 20 $\mu$ M [19] [20] [21]	hAQP4-M23		[13]
IMD-0354	Mice 0.76 mg/kg	mAQP4-M23		[16] [14] [21] [22] [23]
Acetazolamide	HEK293 cells 10 $\mu$ M	rAQP1 rAQP4		[15]
TGN-020	C57/BL6 male mice 200 mg/kg (23–28 g)	mAQP4		[16] [24]
Topiramate	<i>Xenopus</i> oocytes 20 $\mu$ M	rAQP4-M23		[17] [25]
DFP00173	Human erythrocytes 25 $\mu$ M [26]	hAQP3		[18]
Z433927330	Human erythrocytes 25 $\mu$ M [27]	mAQP7		[18] [28]

expressing rat AQP1, there was a 39% reduction in water permeability with 100  $\mu$ M acetazolamide compared to untreated rat AQP1 (using GFP fluorescence to measure swelling) [15]. However, acetazolamide appears to be unable to inhibit endogenous AQPs in human cells [29][30].

Anti-epileptic drugs (AEDs) have also been suggested as possible AQP inhibitors [17]. Their anti-epileptic action has been hypothesized take place through modulation of AQPs. Many AEDs such as topiramate, zonisamide, and lamotrigine are known to have a similar inhibitory effect to acetazolamide on carbonic anhydrase enzyme as well as an in silico predicted binding site on AQP4 that is similar to that hypothesized for acetazolamide [17]. AEDs had an inhibitory effect on AQP4 in *Xenopus* oocytes [17], however, this could not be reproduced in rat thyroid epithelial cells [20]. AEDs are thought to possibly have an inhibitory effect on AQP1, AQP4, and AQP5 [31]. However due to

their unconfirmed mechanisms of action and relatively non-specific action, there is no conclusive evidence showing that AEDs are effective and safe AQP inhibitors [32][33].

TGN-020 was shown in mouse models to significantly reduce AQP4-mediated edema following ischemia, but the molecule was administered before injury [16]. There was an approximately 10% reduction in brain volume [16]. Therapeutic administration must necessarily occur after a stroke, although a prophylactic treatment could be considered if the side effect profile of TGN-020 was acceptable. TGN-020 has since been tested on the same middle cerebral artery occlusion (MCAO) model and administered post-injury in mice. In a study using mouse models at a dose of 100 mg/kg, TGN-020 was administered 15 minutes post-ischemic injury and treated animals had better motor scores and less AQP4 expression around blood vessels when compared to untreated controls [34]. The half-maximal inhibitory concentration ( $IC_{50}$ ) of TGN-020 was  $3\mu\text{M}$  in *Xenopus* oocytes expressing human AQP4, but there is no evidence to show that TGN-020 is AQP4-specific [35].

Phloretin is a small molecule that acts as a non-specific aquaglyceroporin inhibitor. It has also been shown to inhibit the urea transporter, UT-A1, found in the kidney [36]. It has been speculated that the same mechanism underpinning urea inhibition is responsible for inhibition of the aquaglyceroporins, AQP3 and AQP9 [2][37]. Then 100  $\mu\text{M}$  of phloretin was used to inhibit AQP9 expressed in *Xenopus* oocytes, resulting in an 86% inhibition [2]. AQP3 glycerol permeability in proteoliposomes was inhibited by 500  $\mu\text{M}$  phloretin, producing 83% inhibition. Phloretin had no effect on control proteoliposomes which had a  $P_{\text{gly}}$  of  $\sim 2.8 \times 10^{-6}$  cm/s [3].

A recent study identified new inhibitors of the aquaglyceroporins, AQP3 and AQP7. The compound DFP00173 was able to inhibit the glycerol permeability of human erythrocytes with an  $IC_{50}$  of  $\sim 0.2\mu\text{M}$ . Compound Z433927330 reduced glycerol permeability with an  $IC_{50}$  of  $\sim 0.6\mu\text{M}$ . In a Chinese hamster ovary cell-line, compound DFP00173 was able to inhibit mouse AQP3 with an  $IC_{50}$  of  $\sim 0.1\mu\text{M}$  and was selective for AQP3 over AQP7 and AQP9. Compound Z433927330 was able to inhibit mouse AQP7 in the same cell-line with an  $IC_{50}$  of  $\sim 0.2\mu\text{M}$  and with selectivity for AQP7 over AQP3 and AQP9;  $IC_{50}$ s for this compound for mouse AQP3 and AQP9 were  $\sim 0.7\mu\text{M}$  and  $\sim 1.1\mu\text{M}$ , respectively [18].

## 1.2. Heavy Metal Ion Inhibitors

Heavy metal compounds have been used in cytotoxic treatments for many years, with the use of the platinum compound cisplatin being notable in cancer therapy. Many AQPs have been correlated with cancers, their presence influencing disease severity, increased local invasion, and the occurrence of metastasis [38]. AQP1 overexpression has been identified in brain, breast, lung, renal, cervical, ovarian, and colorectal cancers [39]. AQP3 overexpression has been found in skin, stomach, renal, liver, colorectal, lung, and cervical cancers [40]. AQP3 is highly expressed in skin carcinoma cells. The uptake of glycerol through AQP3 is thought to aid the growth of these cancer cells [38]. AQP4 overexpression is found in brain, lung, and thyroid cancers [41]. AQP5 overexpression has been found in breast, cervical, colorectal, liver, lung, pancreatic, ovarian, and esophageal cancers [42]. AQP7 and AQP8 overexpression are found in thyroid and cervical cancer, respectively [39]. AQP9 overexpression has been found in brain, liver, and ovarian cancers [43].

Nickel chloride has been shown to inhibit AQP3 overexpressed in human bronchial epithelium cells. Water permeability was reduced to approximately 60% in cells treated with 1 mM NiCl<sub>2</sub> compared to non-transfected control cells [10]. Mutational studies showed that the extracellular loop residues, Trp-128, Ser-152, and His-241, were all required for the observed inhibitory effect, but that further studies are required to confirm similar effects in other AQP3-expressing tissues such as the kidney [10]. Copper ions also inhibit AQP3 function and attempts to reduce the toxicity of copper compounds have been addressed by using nanoparticles for delivery [38]. Copper sulfate has been identified as an AQP3 inhibitor at 100 μM [9]. It is believed that copper ions act by binding the same three residues on the extracellular loops as nickel ions [44]. This inhibition mechanism is different from that of mercury ions, which bind to Cys-40 in AQP3 [44][45]. Copper compounds have been shown to specifically inhibit AQP3 and not AQP4, AQP5, or AQP1 [44], while other AQPs remain to be tested. Gold-based compounds have also been used as AQP3 inhibitors and have been shown to be effective. AQP3 is found in erythrocytes, alongside AQP1, however its role is mostly for glycerol rather than both water and glycerol permeability [6]. Erythrocytes showed a 90% decrease in glycerol permeability following treatment with 50 μM AuPhen. The binding of this gold compound is thought to be via Cys-40 and inhibition can be almost completely reversed by the addition of the reducing agent, 2-mercaptoethanol [6]. AuPhen and other Au(III) compounds such as Auphen were also compared with copper and platinum compounds as AQP3 inhibitors [7][46]. Due to their effective inhibition of glycerol transport in AQP3, they were tested on AQP7, another aquaglyceroporin. Initial results have demonstrated that 15 μM AuPhen inhibited water and glycerol transport through AQP7 [7]: there was a reduction in water permeability (63%) as well as glycerol permeability (79%). Adipocytes overexpressing hAQP7 were used and permeability was measured using loading with 5 μM of calcein-AM and hyperosmotic shock. In silico docking studies suggest that Auphen binds AQP7 through an interaction with Met-47 [47]. Silver has also been used as a possible AQP inhibitor and is found to produce a rapid and irreversible inhibition of AQP1 in erythrocytes [48]. It has been shown to be a much more potent inhibitor of AQP1 in erythrocytes than mercury, [48]. Silver nitrate and silver sulfadiazine were tested as inhibitors to prevent shrinking of human erythrocytes in hyperosmotic solutions. A dose-response curve was used to calculate an IC<sub>50</sub> of 3.9 μM and 1.24 μM and a 60% and 75% inhibition for silver nitrate and silver sulfadiazine, respectively. Gold and silver are thought to bind to sulfhydryl groups on cysteine residues of AQPs, but the complete mechanisms are not yet understood [6][7][48].

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