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# Modulators of TRPM7 and its potential as a drug target for brain tumours

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ABSTRACT

TRPM7 is a non-selective divalent cation channel with an alpha-kinase domain. Corresponding with its broad expression, TRPM7 has a role in a wide range of cell functions, including proliferation, migration, and survival. Growing evidence shows that TRPM7 is also aberrantly expressed in various cancers, including brain cancers. Because ion channels have widespread tissue distribution and result in extensive physiological consequences when dysfunctional, these proteins can be compelling drug targets. In fact, ion channels comprise the third-largest drug target type, following enzymes and receptors. Literature has shown that suppression of TRPM7 results in inhibition of migration, invasion, and proliferation in several human brain tumours. Therefore, TRPM7 presents a potential target for therapeutic brain tumour interventions. This article reviews current literature on TRPM7 as a potential drug target in the context of brain tumours and provides an overview of various selective and non-selective modulators of the channel relevant to pharmacology, oncology, and ion channel function.

## 1. Introduction

Brain tumours are a heterogeneous group of tumours that can be categorized as primary or metastatic and are further categorized based on the location, cell type, and degree of malignancy. There are more than 120 different types of brain tumours categorized by the World Health Organization (WHO) [1]. The WHO classification includes four grades of malignancy, where grade I tumours are least aggressive and grade IV are the most aggressive [2]. Glioblastoma (GBM), is the most aggressive and prevalent form of primary malignant brain tumour, constituting 14.6% of all brain and central nervous system (CNS) tumours, and 48% of malignant tumours [3]. Despite exhaustive treatments, the prognosis for malignant brain tumours remains poor. Following diagnosis, there is an expected five-year survival rate of 35.8% for any kind of malignant brain tumour, and 6.8% for glioblastoma patients [3]. Gliomas include all tumours that originated from a glial cell, such as astrocytoma, oligodendroglioma, ependymomas, and other mixed gliomas [4]. Due to the resilience and nature of primary brain tumours, treatments remain challenging. Typical treatments include temozolomide (TMZ) chemotherapy, radiation therapy (RT), and surgical resection [5]. Because current treatments are limited and hold potential for neurotoxic effects [6], research that advances new therapeutic modalities is needed, such as targeting ion channels via drug development.

*Abbreviations:* 2-APB, 2-aminoethyl diphenylborinate; 5-HPETE, 5-hydroperoxyeicosatetraenoic acid; 5-LO, 5-Lipoxygenase; ALDH, aldehyde dehydrogenase; Bcl-2, B-Cell lymphoma 2; CREB, cAMP response element-binding protein; CSC, cancer stem cells; eEF2-K, eukaryotic elongation factor 2 cognate kinase; EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; G-Rg3, ginsenoside Rg3; GBM, glioblastoma; GRB, growth factor receptor-bound protein; MHR, major homology region; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NM, nafamostat mesylate; OGD, oxygen-glucose deprivation; PDK, pyruvate dehydrogenase kinase; PGE2, prostaglandin $E_2$; PLC, phospholipase C; PPD, 20(S)-protopanaxadiol; PPT, 20(S)-protopanaxatriol; RhoA, ras homolog family member A; RT, radiation therapy; S1P, sphingosine-1-phosphate; SK, sphingosine kinase; SOCE, store operated calcium entry; SOS, son of sevenless; SPH, sphingosine; STAT3, signal transducer and activator of transcription 3; TMZ, temozolomide; TRP, transient receptor potential; TRPA, transient receptor potential ankyrin; TRPC, transient receptor potential canonical; TRPM, transient receptor potential melastatin; TRPML, transient receptor potential mucolipin; TRPP, transient receptor potential polycystin; TRPV, transient receptor potential vanilloid; WHO, World Health Organization.

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As the third most common drug target, following enzymes and receptors, ion channels hold therapeutic potential in the treatment of many pathological conditions [7]. Ion channels have become critical drug targets due to the ability to modulate an extensive spectrum of physiological processes where the dysfunction of which leads to numerous pathologies. Additionally, in recent literature, ion channels have emerged as important targets for cancer drug development and their expression levels have emerged as hallmarks of some cancers [8,9]. Ion channels have been implicated in key features of cancer including cell migration, invasion, and proliferation [10].

TRPM (transient receptor potential melastatin) is a subfamily of the TRP superfamily of ion channels that are ubiquitously expressed in tissue. TRPM7, the seventh TRPM member, is an ion channel physiologically permeable to $Zn^{2+}$, $Mg^{2+}$, and $Ca^{2+}$ and contains a cytosolic α-type serine/threonine protein kinase domain on its COOH-terminal [11]. Critical functions of TRPM7 include but are not limited to, magnesium homeostasis [11], brain ischemia [12], and neurotransmitter release [13]. While TRPM7 has already been implicated in breast [14], prostate [15], pancreatic cancer [16], and others, it has been shown to also be significantly upregulated in glioblastoma patients [17]. To provide a broader context for a review of the TRPM7 channel, this article will discuss the TRP channel family and TRPM subfamily before reviewing TRPM7 functions. We then discuss the range of small molecule modulators of TRPM7. Lastly, we will discuss the therapeutic potential of TRPM7 as a pharmacological target in brain tumours.

## 2. TRP superfamily

The first member of the TRP superfamily of ion channels was discovered in the fruit fly *Drosophila melanogaster*. Mutants of this gene manifested in visually impaired flies that responded transiently to a light stimulus compared to the wild type, measured using an electroretinogram [18]. Later in 1989, Montell and Rubin were able to identify the *trp* gene [19]. Since then, 28 polymodal ion channels were identified to be part of the diverse TRP superfamily [20]. Based on sequence homology, the TRP superfamily can be split into 6 subfamilies in mammals: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and TRPA (ankyrin). Broadly, TRP channels function as cation channels on the plasma membrane, are critical to the maintenance of ion homeostasis and can function as cell sensors [21]. TRP channels are ubiquitously expressed in the human body, and with widespread expression, it comes as no surprise that the TRP channels are also involved in a plethora of pathologies [21].

The general structure of TRP channels typically has six transmembrane segments labeled S1-S6 and a variety of different motifs on the intracellular carboxyl and amino termini [22]. For example, TRPM6 and 7 have a distinctive α-kinase domain, while TRPM2 has a NUDT9-H domain which acts as an ADP-ribose pyrophosphatase [23–26]. Other motifs and domains include calmodulin-binding sites, coiled coils, TRP motifs, and EF-hand motifs, among others [22]. Consequent to their diverse function and expression, TRP channels have also been found to be critical for cell functions associated with cancer hallmarks; for instance, TRP channels play a role in proliferation, migration, invasion, and various other characteristics of the development and progression of cancer [27].

In the context of brain tumours, various TRP channels have also been investigated for their potential roles in cancer progression and development, or as therapeutic targets. In 2015, Alptekin et al. investigated the gene expression of TRP channels in patients with GBM, quantified using qRT-PCR. Results showed that TRPV1, 2, TRPC1, 6, and TRPM2, 3, 7, 8 had significantly higher expression in glioblastoma patients [17]. It was also determined that the survival of patients corresponded TRP gene overexpression.

The TRPV subfamily of channels includes six members, namely TRPV1–6, all of which are $Ca^{2+}$-permeable. TRPV1 was first discovered in 1997 by Caterina et al. and has been found to be broadly expressed in the brain and has roles in various psychiatric and neuronal disorders [28,29]. Amantini et al. were able to show in 2007 that the expression of TRPV1 decreases with the severity of glial tumours; in fact, there was a complete loss of TRPV1 gene expression in 93% of grade IV glioblastomas [30]. Further, they show that activation with capsaicin, an agonist for TRPV1, could induce glioma cell apoptosis via activation of the p38 MAPK pathway [30]. While this suggests an association between TRPV1 and glioma, the profound downregulation with tumour progression presents a challenge for translating this knowledge into a therapeutic approach for glioblastoma [31]. In a similar fashion to TRPV1, TRPV2 was also found to be downregulated with the increase of histological grade of human glioma tissues [32]. Further, the overexpression of TRPV2 was found to inhibit glioblastoma stem-like cells (GSCs), reducing tumour diameter in mouse models [33]. As a drug target for gliomas, Nabissi et al. (2012) were able to demonstrate that cannabidiol, an agonist for TRPV2, sensitized glioblastoma to other chemotherapeutic agents like TMZ [34].

Within the TRPC subfamily, there are seven members, most of which function as non-selective cation channels. In the context of cancers, the TRPC subfamily is best known for its role in migration, more specifically axonal growth cone guidance [35]. Current literature suggests that TRPC1, 4, and 6, are implicated in glioma characteristics such as proliferation, angiogenesis, migration, invasion, and metabolism [36]. In 2010, Bomben et al. were able to show that the loss of TRPC1 function impairs tumour growth *in vivo* via a doxycycline-inducible shRNA knockdown [37]. Additionally, TRPC1 has been found to be implicated in angiogenesis [38], and migration [39]. TRPC6, as mentioned previously, is also upregulated in human glioma tissues [17], and has also been found to be implicated in glioma angiogenesis [40], invasion [41], and metabolism [42]. The TRPC subfamily of channels also holds therapeutic potential as a target for glioma but requires further investigation [36].

With the widespread expression and function of the TRP superfamily of channels comes high relevance in a variety of pathologies. In the context of brain tumours, most notably, both TRPV and TRPC hold relevance in the development of brain tumour therapeutics. However, one subfamily, that has yet to be discussed, has recently demonstrated the highest potential for brain tumour therapeutics: the TRPM subfamily.

## 3. TRPM subfamily

The TRPM (melastatin) subfamily is the most diverse and largest group within the TRP superfamily [43]. It consists of eight (TRPM1–8) plasma membrane ion channels that are dynamically expressed in various regions of the human body [43]. They are involved in numerous pathological and physiological functions, especially in cell development and ion homeostasis. The TRPM channels modulate these functions by contributing to cellular $Ca^{2+}$ signaling in response to lipids, second messengers, or ionic concentrations [44]. Most of the channels in this subfamily are nonselective, other than TRPM6 and TRPM7, which at physiologically relevant membrane potentials are divalent-selective. All TRPM channels are permeable to $Ca^{2+}$ except for TRPM4 and TRPM5, which are $Ca^{2+}$-activated monovalent cation channels that functionally conduct $Na^{+}$ ions. The general structure of TRPM channels consists of six transmembrane domains (S1–S6), with cytoplasmic COOH- and $NH_2$-termini. The $NH_2$-terminal contains four MHR (TRPM homology region) domains, while the COOH-terminal contains a coiled-coil domain [45]. The MHR domains consist of the MHR1/2, MHR3, and MHR4 and primarily function in channel assembly, as well as contributing to the structure as a whole [46]. Within the transmembrane domains, S5-S6 and the p loop form the pore domain, encapsulated within the S1-S4 domains [44]. The other side constitutes four cytosolic COOH-terminal domains, forming a vertical coiled-coil domain known as a “pole” and four helical “ribs” spanning horizontally [45,47].

As mentioned previously, several TRPM channels have been found to

be upregulated in the context of glioblastoma: TRPM2, 3, 7, and 8 [17]. In the context of brain tumours, TRPM2 has been investigated using the following compounds: $H_2O_2$ [48], curcumin [49], docetaxel and selenium [50], resveratrol and paclitaxel [51], and *Clostridium botulinum* neurotoxin A [52]. These experiments suggest TRPM2 as a therapeutic target via manipulation of its role in redox status management [53]. There is much less literature on TRPM3's role in brain tumours. Ying et al. showed in 2013 that the promoter for TRPM3 is downregulated in gliomas as it correlated with miR204 [54]. miR204 is expressed in intron 6 of the TRPM3 encoding gene and together have been implicated in the regulation of oncogenic autophagy [55]. TRPM8, showing the highest increase in expression in glioma patients, plays a role in proliferation, survival, apoptosis, and invasion of glioblastoma [56], as well as being necessary for radioresistance [57]. Despite the significant upregulation of TRPM8 in brain tumours, the literature has only recently shown investigations on TRPM8 as a potential therapeutic target for brain tumours, however TRPM8 inhibition has already been shown to affect the malignant characteristics of the bladder [58], prostate [59], pancreatic adenocarcinoma [60], melanoma [61], breast cancer [62], and osteosarcoma [63]. TRPM2 and TRPM3 hold an anti-tumourigenic protective role in glioma, and TRPM7 and 8 exacerbate glioma malignancy [64]. TRPM7's modulation of different molecular signals makes it a target to provide novel insights in developing new therapeutic treatments. Table 1 summarizes the TRPM subfamily of channels that have gained recognition as potential brain tumour therapeutic targets for their widespread functions in the cell, and expression profiles.

**Table 1**
Summary of TRPM channel expression and functions relating to potential brain tumour targeting.

| Channel | Defining structure | Modulators | Cellular effects in Glioma |
|---|---|---|---|
| TRPM2 | Nudix box motif | Activation: ADPR, NAD, $H_2O_2$, ROS, alloxan [65], cADPR, TNFα, $Zn^{2+}$, paclitaxel, resveratrol, docetaxel, selenium [53]<br>Inhibition: ACA, clotrimazole, econazole, flufenamic acid (FFA), compounds 7i and 8a, scalaradial, 2-aminoethoxydiphenyl borate (2-APB), AG490/555/556, curcumin, tat-M2NX, low extracellular pH and glutathione (GSH) [53] | Cell death |
| TRPM3 | | Activation: pregnenolone sulfate [66], CIM0216 [67]<br>Inhibition: mefenamic acid, primidone, flavanones (naringenin, eriodictyol, hesperetin, liquiritigenin, and isosakuranetin) [68] | Autophagy, Downregulated |
| TRPM7 | Serine/threonine kinase domain | Activation: naltriben [69], mibefradil, NNC 50–0396 [70], clozapine, A3 hydrochloride, proadifen, doxepin, U-73,343, metergoline, CGP-74514A, L-733,060, ST-148, A-77,636, desipramine, clemastine, sertraline, methiothepin, nortriptyline, loperamide, and prochlorperazine [69]<br>Inhibition: spermine [71], trivalent cations, 2-APB [72], sphingosine [73], carvacrol [74], nafamostat, MK886, AA861, NGDA, ginsenoside-rd and rg3, midazolam, waixenicin A, NS8593, FTY720, TG100–115, xyloketal B, CCT128930, ruthenium red, trivalent cations, CyPPA, dequalinium, SKA31, UCL1684, quinine, SKF-96,365 (Conflicting results), naproxen, ibuprofen, salicylate, aspirin [75] | Cell growth, invasion, differentiation, migration |
| TRPM8 | | Activation: menthol, icilin, D3263 [76]<br>Inhibition: AMTB, TC-I 2014, M8-B, PBMC, JNJ-39,267,631 [76] | Cell growth, migration, death and resistance |

## 4. TRPM7 channel

TRPM7, previously known as CHAK1 [77], TRP-PLIK [78], and LTRPC7 [24], is ubiquitously expressed, a chanzyme, and is permeable to $Ca^{2+}$, $Zn^{2+}$, and $Mg^{2+}$ [24,79]. The human TRPM7 gene is an 1863 amino acid protein located on chromosome 15 over 134.34 kb [80]. Like other TRP channels, TRPM7 is a tetrameric channel with six transmembrane domains having approximately 21 amino acids each, surrounded by a cytosolic amino ($NH_2$-) and carboxyl (COOH-) terminus (Fig. 1). Further, it has a coiled-coil domain which is suggested to aid in self-assembly [45,78]. To form the channel pore, TRPM7 proteins form a tetrameric complex. The channel pore lies between S5 and S6 and its permeability to divalent cations is dependent on glutamic acid at residue 1047 or 1052 [81]. TRPM7, along with its closest homologue TRPM6, has a dual function as a chanzyme associated with the COOH-terminal α-kinase domain [82, 83]. TRPM7's α-kinase domain primarily functions to phosphorylate serine/threonine residues. Substrates of the TRPM7 kinase include annexin 1 (Ser5) [84], histone H3 [85], RhoA [86], myosin IIA (Thr1800, Ser1803, Ser1808), IIB, and IIC [87], Smad2 (Ser465/467) [88], indirectly eukaryotic elongation factor 2 cognate kinase (eEF2-K) (Ser77) [89], tropomodulin 1 [90], and phospholipase Cγ2 (PLCγ2) (Ser1164, Thr1045) [91].

The primary role of TRPM7 is in the regulation of divalent cation homeostasis, specifically $Mg^{2+}$, $Zn^{2+}$, and $Ca^{2+}$. With its ubiquitous expression, TRPM7 is a critical component of cellular communication and function. It is especially critical in embryonic development, where the deletion of which is embryonic lethal in mice [92]. Other roles that TRPM7 functions in include immune responses [93], cell proliferation [14], cytoskeletal organization [87], and apoptosis [94]. Various experiments have shown that via PI3K/Akt and MAPK signaling pathways TRPM7 could mediate cell proliferation, and migration, critical to the progression of cancer [95]. TRPM7 was also found to regulate the Fas receptor critical for apoptotic signaling [94].

## 5. TRPM7 brain tumour signaling

The fundamental role of TRPM7 in cells is in the maintenance of $Mg^{2+}$, $Zn^{2+}$, and $Ca^{2+}$ divalent cation homeostasis. Reflective of such a critical role, $Mg^{2+}$, $Zn^{2+}$, and $Ca^{2+}$ regulate a variety of signaling molecules, act as cofactors to various enzymes, and are therefore by extension, modulated by TRPM7. The various signaling pathways modulated by TRPM7 have been extensively studied, showing that TRPM7 is critically involved in cancer proliferation, migration, and differentiation (Fig. 2) [96]. Therefore, the aberrant activity of TRPM7 would disrupt the homeostasis of $Mg^{2+}$ and $Ca^{2+}$, which can modulate epidermal growth factor (EGF) and other signaling pathways that result in the uncontrolled growth, proliferation, migration, and invasion characteristics of cancer cells [97]. Various studies further elucidated the mechanisms of TRPM7 in brain tumours. STAT3 and NF-κB signaling has been shown to have an important role in the regulation of Notch pathways in glioma cancer stem cells (CSC). CSCs are the source of several brain tumours and drive tumourigenesis [98]. Liu et al. used A172 glioblastoma cells and found that TRPM7 regulated proliferation and migration through the JAK2/STAT3 and/or Notch signaling pathways, as well as promoting ALDH, a marker for CSCs [99]. The PI3K/Akt signaling pathway is another critical pathway extensively implicated in cancer [100]. The receptor-tyrosine kinase (RTK)/PI3K/Akt/mTOR

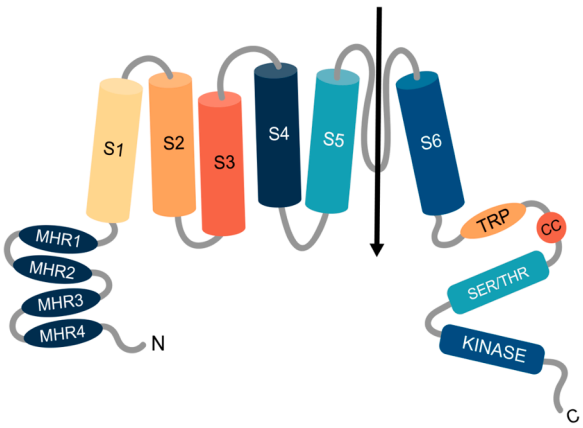


**Fig. 1.** Schematic diagram of the structure of TRPM7.
Illustrated here are 6 transmembrane domains, with 4 Melastatin homology domains on the $NH_2$-terminus. On the COOH-terminal there is a TRP motif, coiled-coil (CC) domain, serine/threonine (SER/THR) α-kinase domain, SER/THR rich domain. .

pathway is considered one of the most researched therapeutic targets for brain tumours [101]. The PI3K/Akt/RTK pathway regulates processes such as cell growth, cytoskeletal rearrangement, and proliferation. Typically seen in glioma is the overexpression of RTKs such as epidermal growth factor receptors (EGFR) [102]. Chen et al. saw a downregulation of p-Akt levels with the addition of xyloketal B, a TRPM7 inhibitor, implicating the PI3K/Akt pathway with the corresponding decreases in proliferation, migration, and invasion [103]. Naltriben, a TRPM7 activator, enhanced the MAPK/ERK signaling pathway produced an increase in migration, and invasion [104].

The kinase domain of TRPM7 also influences several critical molecules in cancer contexts, such as myosin IIA heavy chain, eukaryotic elongation factor 2 (eEF2), PLCγ2, SMAD2, annexin 1, and RhoA [105]. While the relationship between the TRPM7 kinase and brain tumours has not yet been extensively studied, the substrates of the kinase domain predict how it may contribute to cancer. Myosin IIA has been identified as a substrate of the TRPM7 kinase [87], where the channel interacts with the actomyosin protein complex, dependent on $[Ca^{2+}]_I$. In turn, this mediates actomyosin remodeling, cell adhesion, and migration. Additionally, the kinase phosphorylates the myosin IIA heavy chain leading to cytoskeletal remodeling [87]. eEF2 primarily functions to regulate protein synthesis and cell growth, and phosphorylation by eEF2-kinase (eEF2-k) at Thr56 leads to its inactivation. Perraud et al. investigated eEF2-k and determined that the TRPM7 kinase could phosphorylate the kinase at Ser77 dependent on $[Mg^{2+}]_E$ [89], acting as a $Mg^{2+}$ sensor, which is relevant since $Mg^{2+}$ is a key component for cell proliferation [106]. PLC enzymes are critical to cell proliferation and survival. Deason-Towne et al. found that the TRPM7 kinase phosphorylated PLCγ2 at Thr1045 and Ser1164 [91]. Like eEF2-k, phosphorylation is sensitive to $Mg^{2+}$ levels. Romagani et al. identified SMAD2 to be phosphorylated at Ser465/467 by the TRPM7 kinase [88]. Interestingly, however, Yu et al. found lower levels of phosphorylated SMAD2 in glioblastoma patients [107]. Annexin 1 is a $Ca^{2+}$ dependent phospholipid-binding protein that promotes membrane fusion [108]. Its relevance in cancer stems from its ability to inhibit the NF-κB signal transduction pathway, which is linked to proliferation in cancer cells [109]. Additionally, nuclear translocation of annexin 1 is required for

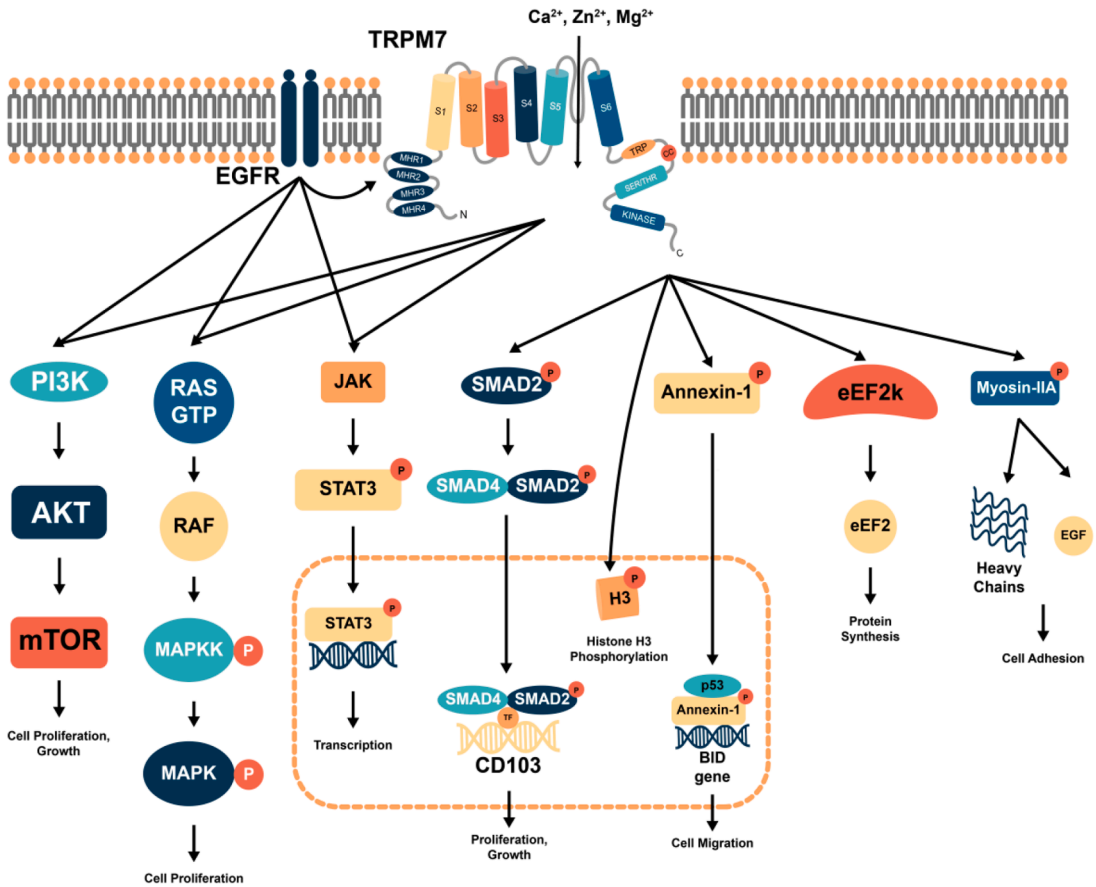


**Fig. 2.** Diagram of several main pathways of TRPM7 relevant to cancer.
Shown here is the structure of TRPM7, and the main related pathways known in various cancers. Illustrated here, pathways such as myosin IIA, eEF2k, annexin-1, SMAD2, JAK/STAT3, MAPK, PI3K along with their roles in cell function.

apoptosis [110] in the case of oxygen-glucose deprivation. Translocation into the nucleus requires TRPM7 kinase to phosphorylate annexin 1 [84]. Voringer et al. discovered TRPM7 kinase phosphorylates RhoA, affecting actin polymerization and MRTF-A-Filamin A complex formation [86]. Both of those are critical to cancer growth as demonstrated in hepatocellular carcinoma (HCC) cells. Inhibition of TRPM7 inactivated RhoA, leading to oncogene-induced senescence and decreased cell growth [86]. TRPM7 and its kinase have a wide range of substrates, affecting an extensive number of physiological processes, many of which are critical to cancer progression and other hallmark cancer characteristics. Understanding the pathways regulated by TRPM7 provides a more thorough outlook on the potential pathways affected by TRPM7 modulators discussed next.

## 6. TRPM7 in the brain tumours

### 6.1. Non-selective inhibitors

#### 6.1.1. 2-APB

2-Aminoethyl diphenylborinate (2-APB) is a lipophilic compound commonly used to study ion channels. Originally used as a blocker of inositol 1,4,5-trisphosphate ($Ins(1,4,5)P_3$) receptors, it was later found to be able to block potassium [111], gap junction connexin [112], and various TRP channels [113], as well as store-operated calcium entry (SOCE) [114]. Specifically, within the TRPM family, 2-APB has been found to inhibit TRPM2 [115], TRPM3 [116], and TRPM7 at micromolar concentrations [72]. 2-APB is a nonspecific inhibitor of TRPM7 with $IC_{50}$s in the 70–170 μM range [72,117]. The mechanism of inhibition is via cytoplasmic acidification, as studies that raised the pH of the internal solution negated the inhibitory effect of 2-APB. Where previously it was shown that TRPM7 also functions as a pH sensor and its activity is modulated by pH [118].

Since its initial use, 2-APB has become a widely implemented inhibitor for TRPM7 in a variety of cancer contexts. In breast cancer, Liu et al., were able to show that in HEK cells overexpressing TRPM7 (HEK-M7) inhibition with 2-APB inhibited cell proliferation, as significantly more cells were in the S phase rather than G0/G1, and this was not reflected in the wildtype [119]. Then, when tested in breast cancer cell lines MDA-MB-231, AU565, and T47D, the addition of 2-APB was able to suppress the viability of AU565, and T47D, likely attributed to the inability to leave the S phase [119]. Similar findings resulted in head and neck carcinoma cells, where the suppression of TRPM7 via 2-APB was able to inhibit the proliferation and growth of FaDu and SCC25 cells [120]. In brain tumours, 2-APB was used to inhibit TRPM7 in A172 cells and human glioma tissues. Leng et al. used both 2-APB and TRPM7 siRNA to inhibit TRPM7 channels and found both to show similar effects. 2-APB and TRPM7 siRNA significantly inhibited proliferation, invasion, and migration of A172 glioma cells [121]. Whole-cell patch-clamp recordings were used to confirm the presence of TRPM7 in A172 cells as well as the inhibitory effects of 2-APB [121]. The use of 2-APB confirmed the role of TRPM7 in oncogenesis and the proliferation of glioma cells while also identifying TRPM7 as a potential therapeutic target. While the literature regarding 2-APB and TRPM7 is plentiful due to its early discovery as an inhibitor, the use of 2-APB is advised against over newer and more specific inhibitors of TRPM7.

#### 6.1.2. Carvacrol

Carvacrol, (2-methyl-5-(1-methylethyl)-phenol) is a phenolic monoterpenoid and is sourced from essential oils derived from plants such as oregano (*Origanum vulgare*) and thyme (*Thymus vulgaris*). Carvacrol is used in isolated form commercially as a flavouring agent [122]. Biological activities include antioxidant, antibacterial, antifungal, anti-inflammatory, and anticarcinogenic properties [123]. It is a non-specific inhibitor of TRPM7 with an $IC_{50}$ of $561.3 \pm 22.2$ μM in U87 cells [124]. In 2009, Parnas et al. were able to show that carvacrol could inhibit TRPM7 channels, measured in whole-cell patch-clamp recordings, showing significant suppression of TRPM7 currents in HEK293 cells [74]. This was further supported by decreased vesicle release in GFP-tagged TRMP7 primary hippocampal CA1–CA3 neurons. Together, these findings prove that carvacrol inhibits TRPM7 function [74]. Carvacrol has since been used in various investigations targeting TRPM7 as a potential therapeutic target. Beneficial improvements from carvacrol in various pathologies have been identified, such as reducing proliferation, migration, and invasion in prostate cancer [125], protective effects in neonatal ischemia and hypoxia [126], and cell cycle regulation in breast cancer [127] and glioblastoma [124]. The mechanism of carvacrol on TRPM7 and its downstream signaling pathways are varied. In both the glioblastoma and prostate cancer studies, it was found that carvacrol inhibited TRPM7, and by extension inhibited p-ERK1/2 and p-AKT protein expression. As mentioned previously, the PI3K/AKT and MAPK pathways are critical to cancer growth, proliferation, migration, and invasion [124,125]. Increasing evidence shows that MAPK and increased activation of the PI3K/AKT are key components in tumourigenesis, and other hallmark cancer characteristics [128,129]. Interestingly, in neonatal hypoxic-ischemic brain carvacrol was able to restore the PI3K/AKT signaling pathway, and as mentioned previously to have a critical role in survival, therefore providing protective effects in cerebral ischemia [126].

Brain tumour experiments by Chen et al. identified carvacrol to have therapeutic potential in the treatment of glioblastoma via a mechanism involving TRPM7 [124]. First, experimenters were able to show that TRPM7 mRNA and protein were expressed higher in U87 compared to NHA, aligning with previous literature showing upregulation of TRPM7 in glioblastoma patients [17]. It had been previously shown that carvacrol could decrease N2a neuroblastoma cell proliferation [130], suggesting carvacrol to have slight chemoprotective effects, but at the time the mechanism of action was not identified. This was later supplemented by Chen et al. who were able to find that carvacrol suppresses PI3K/Akt and MEK/MAPK signaling pathways. As result, carvacrol was confirmed to act through TRPM7 in whole-cell patch-clamp recordings, decreased cell proliferation, migration, invasion, and induced apoptosis [124]. *In vivo*, carvacrol has shown protective effects in neonatal hypoxia [126], and its effects in brain tumour growth *in vivo* are currently being investigated in our lab.

#### 6.1.3. Xyloketal B

Xyloketal B is a marine compound isolated from the mangrove fungus *Xylaria* strain no. 2508 is located in the South China Sea. Xyloketal B and four other metabolites were isolated from the fungus via fermentation and all present as novel ketal compounds [131]. Later on, Lin et al. discovered two additional compounds creating the family of xyloketal A, B, C, D, E, F, G [132,133]. The structure of the xyloketal family includes 5,6-bicyclic acetal moieties around an aromatic center. It was first demonstrated that xyloketal B had protective effects against oxidized low-density lipoprotein (oxLDL) induced human umbilical vein endothelial cell (HUVEC) injury, where it was suggested that due to the hydroxy-phenol radical, xyloketal B had antioxidant properties [134]. With the treatment of xyloketal B, the oxLDL endothelial injury was greatly reduced, alongside a decrease in Bcl-2 expression. Aberrant regulation of Bcl-2 is characteristic of cancers as well as the development of resistance to chemotherapies [135]. Oxidative stress plays a crucial role in the carcinogenic process, and while the literature is relatively mixed on the role of antioxidants in cancer, some evidence suggests antioxidants to be able to reduce the malignancy of cancer [136]. Xyloketal B has also demonstrated neuroprotective effects neonatal hypoxic-ischemic brain injury. It had previously been shown that Xyloketal B could protect against oxygen-glucose deprivation (OGD) damage *in vitro* [137].

Despite its potential, xyloketal B has not been extensively tested in the context of cancers, as it has only been tested *in vitro* in glioblastoma cell lines. In relation to TRPM7, xyloketal B is a non-selective inhibitor with an $IC_{50}$ of $287.1 \pm 1.0$ μM. In the same study, Chen et al. were able

to show that xyloketal B reduced the cell viability, proliferation, and migration of glioblastoma cells, dependent on the PI3K/Akt and MEK/ERK signaling pathways [103]. The mechanisms were confirmed to involve TRPM7 using whole-cell patch-clamp experiments in HEK293 cell overexpressing TRPM7 channels. Here, the perfusion of xyloketal B was able to block the currents, significantly reducing the current density at 300 μM. U251 cell viability and proliferation were evaluated with the MTT assay, both showing significant inhibitory effects of xyloketal B. Migration, measured through a wound-healing assay, was also significantly inhibited with xyloketal B [103]. These results were compared to carvacrol, which showed similar effects. Finally, to determine signaling pathways to elucidate the mechanism, western blotting was carried out to show that xyloketal could suppress the PI3K/Akt and MEK/ERK pathways. The involvement of TRPM7 is further supported by the downregulation of the PI3K/Akt and MEK/ERK pathways with xyloketal B. These pathways are activated by receptor tyrosine kinases (RTKs) which in turn influence TRPM7 [96]. Despite the promising results *in vitro*, xyloketal B has not yet been investigated *in vivo* in brain tumours regardless of its therapeutic potential [138]. Research studying the pharmacokinetic properties of xyloketal B *in vivo* in rats suggested few side effects with administration, adding to its potential [139].

#### 6.1.4. Spermine

Spermine is a ubiquitously expressed polycationic alkylamine, first reported in 1678 by Leeuwenhoek, and is a derivative of putrescine [140]. Spermine plays an essential role in regulating translation and transcription, modulating kinases, nucleic acid stability, and overall growth and function of normal cells [141]. At a physiological pH, polyamines carry a positive charge, which allows for interactions with electrostatic and polyanionic macromolecules such as various nucleic acids, proteins, and a variety of ion channels [142]. Spermine was first identified as a non-specific inhibitor of TRPM7 channels in 2003, by Kozak et al., who found that spermine could block endogenous TRPM7 channel currents in rat basophilic leukemia (RBL) cells and Jurkat T cells [143] and heterologously expressed TRPM7 in CHO cells in a voltage-independent manner [71]. The mechanism of inhibition is described to not directly block the pore, did not rely on the kinase, and its potency corresponded with the charge [118]. More recent studies have shown that the substitution of Ser1107 of TRPM7 will decrease the inhibitory capabilities of spermine [144]. Ser1107 is described to have a role in inhibition from $Mg^{2+}$ [69], where the mechanism is suggested to be via electrostatic charge shielding around the negatively charged $PIP_2$ reducing $PIP_2$ hydrolysis by PLCs [145].

Spermine is a useful tool to confirm the roles of TRPM7 in various cancers [14]. However, in cancer contexts, the aberrant activity of polyamine metabolism results in elevated polyamine levels that contribute to tumour progression [146]. This makes spermine an unsuitable pharmacological tool to inhibit TRPM7 in the context of cancer therapeutics.

#### 6.1.5. Sphingosine/FTY720

Sphingosine (2-amino-4-octadecene-1,3-diol) (SPH) is part of a major class of cell membrane lipids, sphingolipids. It is an 18 carbon amino alcohol with an unsaturated alkyl chain and is the backbone of other sphingolipids [147]. Sphingosine is synthesized from palmitoyl CoA and serine and can be phosphorylated to sphingosine-1-phosphate (S1P) by sphingosine kinase 1 (SK1) and 2 (SK2) [148]. Sphingosine-1-phosphate (S1P) is a bioactive lipid involved in the modulation of several pathological and physiological processes [149]. Sphingolipids as a whole have been recognized for their regulation as second messengers of apoptosis. Sphingolipid ceramide and sphingosine are pro-apoptotic, while its phosphorylated form S1P is anti-apoptotic; acting as opposing pathways determining cell fate, a concept named the sphingolipid rheostat [150–152]. The sphingolipid rheostat is critical to cancer proliferation, metastasis, resistance, and angiogenesis, and thus is a focus of various therapeutic treatments for cancer [152].

FTY720 (2-amino-2-(2-[4-*octylphenyl*]ethyl)−1,3-propanediol), a structural analogue of sphingosine, also known as fingolimod, is an FDA approved immunomodulator currently used as a treatment for remitting multiple sclerosis [153,154]. First discovered in 1992, by Adachi et al., FTY720 was derived from ISP-1 (myriocin) and has since gained recognition as an antitumour agent [155]. FTY720 degrades and inhibits SK1, may also inhibit the PI3K/Akt/mTOR pathway, and therefore is highly relevant to cancers [156]. Several studies have been able to demonstrate FTY720's anticancer properties, such as breast cancer [157], prostate cancer [158], leukemia [159], bladder cancer [160], lung cancer [161], liver cancer [162], gastric cancer [163], colon cancer [164], ovarian cancer [165], pancreatic cancer [166], and glioblastoma [167].

Qin et al. were able to show in 2013 that SPH and FTY720 could potently inhibit TRPM7 by reducing the channel open probability [73]. In HEK293 cells overexpressing TRPM7, TRPM7 currents were inhibited by SPH ($IC_{50} = 0.59 \pm 0.02$ μM) and FTY720 ($IC_{50}$ of $0.72 \pm 0.04$ μM), but not their phosphorylated forms, S1P and FTY720-P [73]. In addition, in a kinase truncation mutant of TRPM7, experimenters were able to show that these substrates inhibited TRPM7 independently of its kinase. As briefly mentioned earlier, FTY720 has been used in brain tumour experiments, however, devoid of association with TRPM7. Estrada-Bernal et al. were able to show that FTY720 induced apoptosis in brain tumour stem cells (BTSCs) via inactivation of ERK MAP kinase, suggesting FTY720 to be a possible therapeutic agent in the treatment of GBM [167]. Wang et al. were also able to show that FTY720 induced apoptosis alongside inhibition of migration and invasion on U251MG and U87MG glioblastoma cell lines [168]. While sphingosine itself has not been used as a therapeutic agent for brain tumours, sphingosine metabolism has recently gained traction as a potential treatment [169]. Recent experiments have used FTY720 as an inhibitor of TRPM7 to prove its role in macrophage proliferation and polarization [170], and $Ca^{2+}$ transport in amelogenesis [171]. While FTY720 has shown *in vivo* efficacy and has reduced tumour growth in several mouse models of cancer, it has also slowed the growth of intracranial xenograft tumours in mice [167]. The potential of FTY720 has already been demonstrated in brain tumours, however, the involvement of TRPM7 requires further studies for confirmation.

#### 6.1.6. MK886/NDGA/AA861

Leukotrienes (LTs) are mediators of the inflammatory response, responsible for increased vascular permeability and phagocyte chemotaxis [172]. 5-Lipoxygenase (5-LO) is an enzyme that catalyzes arachidonic acid (AA) into 5-(*S*)-hydroperoxy eicosatetraenoic acid (5-HPETE) and leukotriene (LT) A4 [173]. $LTA_4$ is eventually converted into $LTB_4$, responsible as a chemoattractant for eosinophils, monocytes, and neutrophils. Beyond the inflammatory response, metabolites of 5-LO hold several roles in cell proliferation, invasion, and angiogenesis [174]. Chen et al. were able to demonstrate that 5-LO inhibitors NDGA (IC50 = 6.3 μM), MK886 (IC50 = 8.6 μM), and AA861 (IC50 = 6.0 μM) were also potent inhibitors of TRPM7 [175]. Further, inhibition of TRPM7 with these blockers reduced cell death via apoptosis [175]. The mechanism was shown to be independent of 5-LO as dsiRNA targeting 5-LO did not lower TRPM7 whole-cell currents measured through a voltage clamp [175]. The experiments by Chen et al. suggested using these inhibitors in the context of cerebral ischemia, where TRPM7 also plays a pivotal role [176]. However, 5-LO inhibitors have been recognized as a potential approach for cancer chemotherapy, as 5-LO also plays a crucial role in cancer, especially since the synthesis of LTs is suggested to promote carcinogenesis [174]. More specific to glioma, Ishii et al. suggested that inhibition of the 5-LO-$LTA_4$ hydrolase pathway suppressed proliferation in glioma cells [177]. While the exact interactions and role of TRPM7 and 5-LO are relatively unclear, inhibition of each seems to hold promise as therapeutic targets. To further support this conclusion, NDGA, MK886, and AA861 have also been tested on human gastric cell cancer, and its effects have been associated with

TRPM7 [178]. NDGA, MK886, and AA861 were all shown to reduce cell viability through MTT assays and TRPM7 inhibition was confirmed with electrophysiology showing significantly reduced TRPM7-like currents. Zileuton, another 5-LO inhibitor that does not inhibit TRPM7, did not show any significant changes in cell viability [178]. These results demonstrate the great potential of NDGA, MK886, and AA861 inhibiting TRPM7 as a potential pharmacological treatment for cancer. However, these modulators require more investigation into their effects *in vivo*, as the knowledge surrounding these compounds is relatively preliminary.

#### 6.1.7. NS8593

NS8593, N-[(1*R*)−1,2,3,4-*tetrahydronaphthalen*-1-*yl*]−1H-benzimidazol-2-amine, was originally synthesized as a potent selective inhibitory gating modifier of small-conductance $Ca^{2+}$-activated $K^{+}$ (SK) channels [179]. NS8593 has been found to be to have clinical potential as an antiarrhythmic agent, and its mechanisms fundamentally lie in decreasing the sensitivity of SK channels to free intracellular $Ca^{2+}$ [179,180]. Chubanov et al. were able to demonstrate that NS8593 could reversibly block endogenous TRPM7 currents in HEK293 cells [181]. Although SK channels and TRPM7 are genetically different, Chubanov et al., identified NS8593 as an inhibitor of both channels based on their similar drug-binding sites linked to divalent cation-dependent gating. NS8593 inhibition of TRPM7 is inversely dependent on $Mg^{2+}$, has an $IC_{50}$ of 1.6 μM in the absence of intracellular $Mg^{2+}$, was determined to function independently from the TRPM7 kinase, and interacts with the channel pore loop [181]. Since its initial discovery as a TRPM7 inhibitor, NS8593 has been used to reverse the increased invasion and migration of IL4 and IL10-treated microglia [182], inhibit MRTF-A nuclear localization and transcriptional activity via TRPM7 in HCC cells [86], negate proliferation and polarization of macrophage by inhibition of TRPM7 [170], increased tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) induced apoptosis and antiproliferative effects, as well as decrease colony formation in MDA-MB-231 breast cancer cells [183].

Tian et al. were able to show that both TRPM7 and prostaglandin E2 (PGE2) contributed to the proliferation and migration of human glioblastoma cells [184]. PGE2, a derivative of arachidonic acid activates GPCR subtypes called EP1, EP2, EP3, and EP4 [184]. PGE2 has been previously shown to enhance glioblastoma proliferation and survival via the Epithelial Growth Factor receptor (EGFR) and β-catenin [185]. In A172 glioblastoma cell lines, NS8593 was able to attenuate the PGE2 induced increases in migration, displaying similar results to TRPM7 shRNA [184]. Other studies have demonstrated that NS8593 can be well tolerated by a rat model of atrial fibrillation, showing promise in its potential *in vivo* studies and need for further research [186].

#### 6.1.8. Lidocaine

Lidocaine, an aminoethylamide, is one of the most commonly used local anesthetics for neuraxial, local, and topical anesthesia. It was first synthesized by Nils Löfgren and Bengt Lundquist in 1943 as a derivative of xylidine [187]. The mechanism of local anesthetics depends on blocking voltage-gated $Na^{+}$ channels and is clinically used for rapid pain suppression [188]. Leffler et al. first discovered in 2008 that TRPV1 to be activated by lidocaine [189]. Later, in 2015, Leng et al. discovered lidocaine's ability to inhibit TRPM7, with an $IC_{50}$ of 11.06 and 11.55 mM in HEK293 cells overexpressing TRPM7 and cortical mouse neurons respectively [190]. In whole-cell patch-clamp experiments, TRPM7 currents were inhibited by lidocaine in a dose-dependent manner, alongside QX-314, a derivative of lidocaine, and procaine [190]. While it had also been established that lidocaine itself could suppress cancer cell lines *in vitro,* [191,192] the mechanisms required further elucidation. In breast cancer, lidocaine was shown to reduce the viability, and migration in MDA-MB-231 cells, in a mechanism dependent on TRPM7. The role of TRPM7 was confirmed through whole-cell patch-clamp experiments, where TRPM7 was suppressed by lidocaine, as well as in a fluorescence quench assay to confirm the effect of lidocaine on TRPM7's function and found a similar $IC_{50}$ to Leng et al., of approximately 11 mM [193].

Leng et al. were able to investigate the effects of lidocaine on TRPM7 in C6 rat glioma and A172 glioblastoma cells [194]. After confirming the lidocaine's inhibition on TRPM7, lactate dehydrogenase (LDH) assays were performed to evaluate the effect of lidocaine on C6 and A172 cells, showing significant inhibition [194] and showing potential therapeutic applications for lidocaine and other anesthetics as well.

#### 6.1.9. Midazolam

Midazolam (8-chloro-6-(2-fluorophenyl)−1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine) is a common and short-acting benzodiazepine and has been used as an anticonvulsant, muscle relaxant, sedative, and sleep-inducing agent. Midazolam acts through modulating the $GABA_A$ receptor in the CNS. While it has been identified as an antitumour agent [195], it has also been shown to be cytotoxic to neuronal cells [196]. However, in a systematic review by Jiao et al., midazolam was identified to have a critical role in cancer cell death, as well as cell proliferation [195], and concluded that further experiments were required to study its effects and mechanisms. Dou et al., in 2013 identified midazolam as a TRPM7 inhibitor, and its inhibitory effects on cancer cell proliferation and growth were dependent on TRPM7 in FaDu human hypopharyngeal squamous cell carcinoma cells [197]. Results from MTT assays showed that midazolam treatment decreased cell proliferation and the effects of midazolam were independent of its benzodiazepine receptors (BR). As midazolam is a BR agonist, and BR activity could also inhibit nervous system activity. To demonstrate that midazolam was dependent on TRPM7 and not BR, experimenters used flumazenil and PK11195, inhibitors of central and peripheral type BR, respectively. Additionally RT-qPCR, the analysis showed that with increasing amounts of midazolam, mRNA levels of TRPM7 saw a corresponding decrease [197]. Interestingly, diazepam and clonazepam also showed inhibitory properties on FaDu cells, although whether the mechanism involved TRPM7 was not investigated.

With midazolam showing promise in FaDu cells, Chen et al. investigated its effects in T98-MG glioma cells [198]. In MGR2 cells, midazolam's $IC_{50}$ value was 112.3 and 75.1 μM for cell viability and proliferation, respectively. After confirming the expression of TRPM7 and upregulation of its mRNA in T98-MG cells, experimenters were able to demonstrate that midazolam could inhibit channel expression and function via RT-PCR and whole-cell recordings sequentially [198]. To further confirm the inhibitory capabilities of midazolam on TRPM7, Chen et al., used Fluo-4 AM-based $Ca^{2+}$ imaging to measure bradykinin (BK) induced $Ca^{2+}$ influx. With midazolam, TRPM7 channels showed no response to BK, proving the mechanism of midazolam is mediated through TRPM7's calcium activity. Finally, consistent with the previous experiment in FaDu cells, it was also shown that midazolam could inhibit proliferation in MGR2 cells [198]. These results highlight the potential of drug development of related compounds in targeting TRPM7 for chemotherapy.

#### 6.1.10. Nafamostat mesylate

Nafamostat mesylate (NM) (6′-amidino-2-naphthyl-4-guanidinobenzoate dihydrochloride), also known as FUT-175 is a synthetic serine protease inhibitor. First synthesized by Fujii et al., NM has been used to treat systematic inflammatory response syndrome, pancreatitis, inhibition of the complement system and coagulation cascade, and most recently SARS-CoV-2 [199,200]. Various studies have shown that NM can inhibit cell proliferation [201], invasion [202], and suppresses tumor growth *in vivo* [203]. The mechanism of NM's anticancer properties fundamentally lies in its inhibition of the canonical NF-κB pathway, suppressing the hallmark cancer characteristics. Chen et al. were able to show that NM could modulate TRPM7 depending on the concentration of extracellular divalent ions [204]. When $Ca^{2+}$ and $Mg^{2+}$ were at 1 mM, NM did not inhibit TRPM7, but in a divalent solution, the inhibitory capacity of NM increases substantially [204]. Surprisingly, in 2 mM $Ca^{2+}$ and 1 mM $Mg^{2+}$ NM induced inward currents seemingly

activating TRPM7, meaning at physiological concentrations, NM blocks and activates TRPM7 currents. Overall, NM was found to inhibit TRPM7 currents at $IC_{50}$ 617 μM at +100 mV and 514 μM at −100 mV.

While the mechanism and existing literature suggest that NM holds potential as a therapeutic agent against brain tumours, studies comparing several proteasome inhibitors found few changes to viability, migration, and invasion [205]. While other proteasome inhibitors reduced U87MG and LN229 glioblastoma cell line viability, NM showed no significant changes compared to the control. Suggesting that overall, NM and its association with TRPM7 is not relevant in the context of brain tumours.

#### 6.1.11. Ginsenoside Rg3 and Rd

Ginseng in the genus *Panax* and family *Aralliaceae* is a popular therapeutic agent used in Chinese medicine, whose pharmacologically active components are called ginsenosides [206]. Ginsenosides are triterpene saponins and are classified into two categories: 20(*S*)-protopanaxadiol (PPD) and 20(*S*)-protopanaxatriol (PPT) differing in a C6 carboxyl group in PPDs [207].

Ginsenoside Rd (G-Rd) is a relatively more active and efficient ginsenoside that has been recognized for its cardioprotective [208], neuroprotective [209], and anti-metastatic effects [210]. Zhang et al. were first able to show that G-Rd could significantly attenuate the increase of TRPM7 expression due to middle cerebral artery occlusion (MCAO) [211] suggesting that the neuroprotective effects of G-Rd could potentially be due to mediation of TRPM7 expression. These experiments were able to show that not only does G-Rd modulate TRPM7, but also initiated experiments investigating TRPM7's role in cerebral strokes [211]. The inhibition of TRPM7 by G-Rd was later confirmed via whole-cell voltage-clamp recordings of TRPM7-like currents in AGS, MCF-7, and HEK293 cells [212]. Experiments were further able to determine that G-Rd could inhibit proliferation and survival of AGS ($IC_{50}$ = 131.2 μM) and MCF-7 ($IC_{50}$ = 154.3 μM) cancer cell lines, as well as G-Rd induced cell death could be increased in the overexpression of TRPM7. Altogether this suggests that inhibition of TRPM7 via G-Rd could affect proliferation and survival in gastric and breast cancers [212]. G-Rd and its effects on TRPM7 have not been investigated in brain tumours, however, Gu et al. have demonstrated that G-Rd inhibited proliferation and increased apoptosis in U251 cells [213]. Whether this mechanism involves TRPM7 has not yet been explored.

Ginsenoside Rg3 (G-Rg3) is another ginsenoside that has shown antitumour [214] as well as neuroprotective [215], cardioprotective [216], and hepatoprotective [217] effects. Not only does G-Rg3 have antitumour effects, but it has also been recognized as a potential means of adjuvant therapy for cancer, significantly inhibiting angiogenesis in lung cancer ameliorating the treatment of chemotherapeutic agent gemcitabine [218]. While the effects of G-Rg3 have been identified, the underlying mechanisms have not yet been fully elucidated. Kim et al., in 2011 were able to identify that the mechanism of G-Rg3 induced apoptosis in AGS gastric cancer cell lines implicated TRPM7 [219]. After determining that G-Rg3 decreased AGS cell viability via MTT assays, whole-cell patch-clamp experiments determined that G-Rg3 blocked TRPM7 currents. This was further confirmed with RNA interference (RNAi) inhibition and tetracycline-induced increases in expression to suggest that TRPM7 expression correlates with increased rates of G-Rg3 induced cell death [219]. G-Rg3 has been shown to induce apoptosis on U87 glioblastoma cell lines via the MEK signaling pathway [220], however, the involvement of TRPM7 as a potential upstream regulator has not been confirmed.

Both G-Rd and G-Rg3 have demonstrated anti-cancer properties and thus have potential in cancer therapeutics. Suggesting the value of further developing these modulators in future research. As things currently stand, not enough is known about the relationship between G-Rd, G-Rg3, and TRPM7 to make any concrete evaluations.

#### 6.1.12. CCT128930

CCT128930 is a potent and selective AKT inhibitor, that has been investigated for its effects in various contexts including but not limited to human osteosarcoma, liver, and lung cancers. Aberrant signaling of the PI3K/Akt/mTOR signaling pathways is commonly found in cancer cells, and CCT128930 has helped induce apoptosis, inhibit proliferation, and induce G1 phase arrest [221,222]. Guan et al., in 2021 were able to identify CCT128930 as a novel potent inhibitor of TRPM7 in $Mg^{2+}$ and kinase-independent mechanisms in neuroblastoma SH-SY5Y cells. Whole-cell patch-clamp experiments showed that TRPM7 currents were almost completely inhibited with the addition of 10 μM CCT128930, with an $IC_{50}$ value of 0.83 ± 0.11 μM, which could be partially reversed [223]. Further, in terms of selectivity, CCT128930 does not inhibit TRPM6 and slightly inhibits TRPM8 currents, therefore preferentially inhibiting TRPM7. Through various mutations, the mechanism of CCT128930 was resolved to be based on a superficial part of the TRPM7 selectivity filter, and not on the kinase [223]. Since CCT128930 was only recently found to inhibit TRPM7, there have yet to be experiments investigating its therapeutic potential in relation to TRPM7.

### 6.2. Selective inhibitors

#### 6.2.1. Waixenicin A

Waixenicin A is a xenicane diterpenoid isolated from *Sarcothelia edmondsoni* (also known as *Anthelia edmondsoni*), a soft coral first investigated chemically by Coval and Scheuer in 1984 [224]. Zierler et al., determined in 2011 that waixenicin A could selectively inhibit TRPM7 by regulating the entry of divalent cations in a dose-dependent manner, with an $IC_{50}$ of 16 nM at physiological intracellular $Mg^{2+}$ levels [225]. Waixenicin A was identified as the active component of extracts of the soft coral by high throughput TRPM7 bioassay which measures [226] the fluorescence quench of Fura-2 with TRPM7 mediated $Mn^{2+}$ entry in HEK293 cells. Further, in TRPM7-K1648R, a kinase-inactive mutant, waixenicin A continued to inhibit TRPM7 currents, indicating that the mechanism of blockage might be independent of the kinase. When tested against other TRPM subfamily channels, Zierler et al., found that waixenicin A is selective to TRPM7, even over TRPM7's closest homolog, TRPM6 [225]. Since its discovery as a TRPM7 inhibitor, its specificity and potency have been recognized for its potential as a drug for various neurological disorders and diseases [227]. Waixenicin A has been used as a TRPM7 inhibitor in various pathological contexts such as neuronal outgrowth [228], store-operated calcium entry inhibition [229], anticancer [230,231], hyperglycemia [232], and hypoxic-ischemic encephalopathy [233].

In brain tumours, Visser et al. demonstrated that through TRPM7, waixenicin A increased formations of focal adhesions, and cell contraction in N1E-115 neuroblastoma cells [234]. Recently Wong et al. investigated the effects of waixenicin A inhibition of TRPM7 in glioblastoma *in vitro* and *in vivo*. *In vitro*, waixenicin A decreased viability, migration, and invasion in U251 or U87 cells, while downregulating Akt, cofilin, and Ki-67 *in vivo* [230]. In whole-cell patch-clamp experiments, it was confirmed that waixenicin A strongly inhibits TRPM7 and reduced channel expression. Overall, findings suggest that waixenicin A is an incredibly promising potential drug to treat glioblastoma and should be the focus in future research.

#### 6.2.2. TG100–115

TG100–115 is a PI3Kγ and δ-selective inhibitor originally used as a cardioprotective agent following myocardial infarction and a therapeutic agent for asthma and chronic obstructive pulmonary disease (COPD) [235,236]. Song et al. recently found TG100–115 to also be a potent inhibitor specific to the TRPM7 kinase with an $IC_{50}$ value of 2 μM and was tested in breast cancer cells [237]. However, it has been found to also inhibit the purified kinase domain of TRPM6 [238]. Song et al. were able to determine that TG100–115 acted specifically on the kinase by immunoblotting full-length CREB, a substrate of the TRPM7 kinase.

Here, the levels of phosphorylation at Ser133 significantly diminished with the addition of TG100–115 [237]. TG100–115 was then tested with MDA-MB-231 and MDA-MB-468, where it suppressed invasion and migration, where the results were compared to rottlerin, a nonselective TRPM7 kinase inhibitor. Interestingly, TG100–115 had mild effects on proliferation, only reducing cell proliferation by approximately 20%, 48 h after treatment [237]. TG100–115 has since been used to investigate neutrophil invasion [239], Schwann cell trans-dedifferentiation [240], and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) induced apoptosis in breast cancer [183]. While TG100–115 has not been tested in brain tumours yet, our group is currently investigating TG100–115 in U87 and U251 cell lines.

As reviewed here, this is a list of inhibitors that have currently been used in literature to inhibit TRPM7. This is not an extensive list as other inhibitors such as ruthenium red [241,242], trivalent cations [243], CyPPA, dequalinium, SKA31, UCL1684, quinine [181], naproxen, ibuprofen, salicylate, aspirin [75], and to differing results, SKF-96,365 [79,244]. The inhibitors not detailed are less mentioned in literature or have not been extensively tested as a potential drug therapy. Future research should consider the specific inhibitors of TRPM7 such as waixenicin A and TG100–115 to be valuable for further investigation. TRPM7 demonstrates a large variety of physiological functions, which are especially relevant in brain tumour contexts. Therefore, continued investigation into potential drug modulators provides a more specific treatment opportunity to better the prognosis of brain tumour outcomes.

### 6.3. Activators

#### 6.3.1. Naltriben

Naltriben mesylate is a phenanthrene opioid that functions as a δ opioid antagonist and was first synthesized by Sofuoglu et al. in 1991 and is the most frequently used and selective TRPM7 positive gating modulator in the literature, with an $EC_{50}$ of 20 μM [69,245]. Hofmann et al. screened for various activators using an aequorin bioluminescence-based assay and confirmed the activation of TRPM7 through whole-cell patch-clamp in TRPM7 recombinant HEK293 cells as well as endogenous TRPM7 in RBL-1 cells. Further, naltriben could attenuate inhibition by NS8593 and $[Mg^{2+}]_I$ and did not seem to have a stimulatory effect on TRPV1, TRPM2, and TRPM8 [69]. Once it had been established that naltriben could activate TRPM7 channels, it has been used extensively in TRPM7 related experiments influencing the channel's properties. The use of naltriben is immensely helpful in establishing the role of TRPM7 as well as attenuating the effects of various inhibitors. Naltriben has been used to elucidate the role of TRPM7 in embryo development [246], chondrogenesis [247], osteogenesis [248], $Mg^{2+}$ homeostasis [249], hypoxic ischemia [233] and glioblastoma [104].

Wong et al. investigated the effects of naltriben and TRPM7 in U87 cell lines. After confirming that naltriben increases endogenous TRPM7-like currents with whole-cell patch-clamp recordings, experimenters also used Fura-2 $Ca^{2+}$ imaging to measure a $Ca^{2+}$ influx with the application of naltriben [104]. MTT, invasion, and scratch wound assays showed that naltriben, reflective of TRPM7 inhibitors, increased migration, and invasion, but decreased viability, likely due to the increases of $Ca^{2+}$ influx. Since the addition of naltriben saw an increase in MAPK/ERK and MMP-2 signaling, it suggests the cascades' involvement.

#### 6.3.2. Mibefradil

Mibefradil is a Cav3 T-type voltage-gated calcium channel antagonist that was originally used as a treatment for hypertension and angina pectoris [250]. While originally approved by the FDA, it was later discontinued for its side effects and severe drug interactions [251]. Currently, mibefradil is more so used in the literature to investigate voltage-gated calcium channels. Schafer et al., discovered mibefradil to activate TRPM7 at physiological $[Mg^{2+}]_I$ levels, is dependent on $Mg^{2+}$ and has an $EC_{50}$ value of 53 ± 13 μM [70]. The experimenters propose two types of TRPM7 agonists, type one includes naltriben and activates TRPM7 independent of $[Mg^{2+}]_I$, while mibefradil is type two, meaning it acts dependently on $[Mg^{2+}]_I$ [70]. Mibefradil is also relatively specific to TRPM7 and does not affect TRPM3, TRPA1, or TRPV1 elucidated through aequorin-based $[Ca^{2+}]_I$ influx in HEK293 cells. Mibefradil has been used to investigate the relevance of TRPM7 in embryo development [252] and amelogenesis [171]. Outside the context of TRPM7, mibefradil has been identified to be potentially repurposed into an anticancer drug, as Cav3.2 T-type $Ca^{2+}$ channels are critical to the progression and regulation of cancer [253]. *In vitro*, Panner et al. were able to show that mibefradil could decrease proliferation levels in U87 and N1E-115 cells [254]. Interestingly, *in vivo*, Keir et al., demonstrated that mibefradil could slow the growth of xenograft GBM in mouse models [255]. Although these findings contradict the expected functions of TRPM7, TRPM7 was not studied in either of these experiments therefore further investigation into the mechanisms of mibefradil and TRPM7 are required.

There is a plethora of TRPM7 activators, covered here are the ones most frequently used; however, this list is by no means exhaustive. Other activators include: NNC 50–0396 [70], clozapine, A3 hydrochloride, proadifen, doxepin, U-73,343, metergoline, CGP-74514A, L-733,060, ST-148, A-77,636, desipramine, clemastine, sertraline, methiothepin, nortriptyline, loperamide, and prochlorperazine [69]. Although these have been measured to activate TRPM7, only the two compounds detailed above are more prevalently described in the literature. With TRPM7's widespread functions in physiology, there is an urgent need for pharmacological development in the modulation of the channel's function.

## 7. Future directions and conclusion

Brain tumour therapies have progressed significantly over the past decades; however, current treatments lack specificity and efficacy for ideal patient outcomes, therefore currently the prognosis remains poor for most brain tumours. Following enzymes and receptors, ion channels represent the third-largest class of drug target. TRPM7 is known for its ubiquitous expression and widespread roles in physiological processes and is especially relevant in cancer. TRPM7 is significantly upregulated in glioblastoma patients. Targeting ion channels like TRPM7 for drug development provides a potentially more specific therapy for treating brain tumours. Reviewed here are the different modulators of TRPM7 and their potential for brain tumour therapy. Many drugs have targeted TRPM7 and have shown promising results, proving the necessity of further extensive research targeting TRPM7 in a therapeutic context, while also elucidating the mechanisms of each modulator.

## Declaration of Competing Interest

The authors declare no conflict of interest.

## Author contributions

All authors listed made direct and substantial contribution to this manuscript.

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