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TRPC channels: Structure, function, regulation and recent advances in small molecular probes

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Abstract

Transient receptor potential canonical (TRPC) channels constitute a group of receptor-operated calcium-permeable nonselective cation channels of the TRP superfamily. The seven mammalian TRPC members, which can be further divided into four subgroups (TRPC1, TRPC2, TRPC4/5, and TRPC3/6/7) based on their amino acid sequences and functional similarities, contribute to a broad spectrum of cellular functions and physiological roles. Studies have revealed complexity of their regulation involving several components of the phospholipase C pathway, G_i and G_o proteins, and internal Ca^{2+} stores. Recent advances in cryogenic electron microscopy have provided several high-resolution structures of TRPC channels. Growing evidence demonstrates the involvement of TRPC channels in diseases, particularly the link between genetic mutations of TRPC6 and familial

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Authors' statement

The literature on TRPC channels is very broad and large. Because of the space concern, scope restriction, and our intentional focus on the more recent development of the field, we are not able to include all the important studies on TRPC channels in the references. We apologize to investigators whose excellent work is not cited here.

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Declaration of Competing Interest

The authors claim no conflict of interest.

focal segmental glomerulosclerosis. Because TRPCs were discovered by the molecular identity first, their pharmacology had lagged behind. This is rapidly changing in recent years owning to great efforts from both academia and industry. A number of potent tool compounds from both synthetic and natural products that selective target different subtypes of TRPC channels have been discovered, including some preclinical drug candidates. This review will cover recent advancements in the understanding of TRPC channel regulation, structure, and discovery of novel TRPC small molecular probes over the past few years, with the goal of facilitating drug discovery for the study of TRPCs and therapeutic development.

Keywords

Calcium signaling; Drug discovery; Heterotrimeric G proteins; Nonselective cation channels; Phospholipase C; Receptor-operated channels

1. Introduction

1.1. The discovery and classification of TRPCs

The transient receptor potential (TRP) ion channels are named after the founding member of this superfamily that underlies the *trp* phenotype of the *Drosophila* phototransduction mutant that loses the sustained response to light stimulus (Cosens & Manning, 1969). Molecular cloning of the disrupted gene later revealed the encoded product to be a membrane protein that shares limited sequence homology with voltage-gated Na^+ and Ca^{2+} channels (Montell & Rubin, 1989; Wong et al., 1989). However, it was not until 1992 when the channel function of the fly TRP protein was first demonstrated (Hardie & Minke, 1992) and this was followed by reconstituting the ion channel function of a closely related *Drosophila* homology, TRP-Like (TRPL) (Phillips, Bull, & Kelly, 1992) in heterologous systems (Hu et al., 1994; Vaca, Sinkins, Hu, Kunze, & Schilling, 1994). In 1995, the first mammalian TRP homolog (TRPC1) was reported without functional demonstration (Wes et al., 1995; Zhu, Chu, Peyton, & Birnbaumer, 1995). In the following year, five more related mammalian sequences (TRPC2–6) were revealed with the functionality of TRPC1 and TRPC3 implicated in receptor- or store-operated Ca^{2+} entry (Zhu et al., 1996). Finally, the last member, TRPC7, was reported three years later (Okada et al., 1999). In the meantime, many distantly related TRP homologous were also uncovered between 1997 and 2003, expending the superfamily to 28 mammalian members and six subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPP (polycystin), and TRPML (mucolipin). In invertebrates, there is yet another subfamily, TRPN (*Drosophila* NOMPC), which has no mammalian members (Montell et al., 2002).

The TRP channels are mostly Ca^{2+}-permeable non-selective cation channels with few exceptions. For example, TRPV5 and TRPV6 are highly Ca^{2+} selective while TRPM4 and TRPM5 are Ca^{2+} impermeable. The majority of the TRP channels function at the plasma membrane (PM), but a few of them mainly work on membranes of intracellular organelles, such as endosomes and lysosomes (Dong et al., 2008; Dong et al., 2010). Unlike other TRP subfamilies, which were discovered based on functional screening or genetic linkage to disease, the mammalian TRPC members were identified strictly because of their sequence

homology with the prototypical *Drosophila* TRP and TRPL proteins and all of them share about 30–35% amino acid sequence identity with TRP and TRPL across almost the entire length, rather than in just limited regions. Therefore, functionally, the mammalian TRPC members are also similar to the *Drosophila* TRP and TRPL in that they are all activated downstream from receptors that signal through phospholipase C (PLC) (Trebak, Vazquez, Bird, & Putney Jr, 2003; Tian et al., 2014; Bavencoffe, Zhu, & Tian, 2017). However, unlike the restricted expression in photoreceptors of the insect channels, mammalian TRPC channels are widely expressed in numerous cell types of many different tissues, displaying tremendous diversity in expression patterns and functions.

Although TRPC channels had been considered as the top molecular candidates that mediate capacitative or store-operated Ca^{2+} entry in the early days. This idea has run out of fashion after the identification of STIM1 and Orai1 in 2005–2006 (Feske et al., 2006; Liou et al., 2005; Vig et al., 2006; Zhang et al., 2005; Zhang et al., 2006), which encode the sensor that detects Ca^{2+} depletion from the endoplasmic reticulum (ER) store and the PM channel that mediates the Ca^{2+}-release-activated Ca^{2+} (CRAC) current, respectively. Although evidence continues to accumulate for store-, or STIM-, or even Orai-operated or dependent TRPC channel function (see later), it is clear that TRPC proteins most likely do not participate in the formation of the highly Ca^{2+}-selective CRAC channel. Rather, these proteins form nonselective cation channels with variable Ca^{2+} permeabilities and complex regulatory mechanisms that allow them to sense changes in various aspects of PLC signaling, including but not limited to the filling state of the ER Ca^{2+} store. The activation of TRPC channels mainly leads to Na^{+} and Ca^{2+} influx, causing two major consequences: membrane depolarization and cytosolic Ca^{2+} concentration ($[Ca^{2+}]_c$) elevation, both having important impacts on cellular function. Based on sequence homology, the seven mammalian members of the TRPC subfamily (TRPC1–7) fall into four subgroups: TRPC1, TRPC2, TRPC4/5, and TRPC3/6/7. Since *TRPC2* is a pseudogene in humans, this review mainly focuses on recent studies of TRPC1, TRPC4/5 and TRPC3/6/7.

1.2. Tissue distribution and multimerization of TRPCs

Due to the lack of good quality antibodies, the tissue/cell type distributions of TRPC isoforms have mainly been examined based on mRNA (Fowler, Kyriaki, Ozkan, Phillips, & Cooper, 2007; Li, Xu, & Montell, 1999; Riccio et al., 2002). In addition, functional studies have yielded ample useful information about the contributions of individual TRPC isoforms in physiology and pathophysiology of certain tissue/cell types. These include studies using isoform specific *Trpc* knockout mice (Freichel et al., 2005), naturally occurring TRPC mutations in humans and rodents (Becker et al., 2009; Reiser et al., 2005; Winn et al., 2005), and some of the newly developed small molecular TRPC agonists and antagonists (Just et al., 2018; Seo et al., 2014; Yang et al., 2015; Zhou et al., 2017). Some of these studies will be discussed in greater details in the later part of this review. Here, we briefly summarize the findings from studying the expression of TRPC mRNAs, and in some cases proteins, as well as the interactions among different TRPC isoforms.

TRPC1 exhibits extensive expression in different tissues (Wes et al., 1995; Zhu et al., 1995). It is generally thought that TRPC1 may not form homomeric channels, but it serves as an

auxiliary subunit in heteromeric channels containing other TRPC subtypes (Lintschinger et al., 2000; Sours-Brothers, Ding, Graham, & Ma, 2009; Strübing, Krapivinsky, Krapivinsky, & Clapham, 2001), or even more distantly related TRPP2 (Tsiokas et al., 1999), TRPV4 (Ma et al., 2010), and TRPV6 (Schindl et al., 2012). Functionally, the best characterized effect of TRPC1 on the biophysical properties of the heteromeric channels is the marked reduction of the unitary conductance of TRPC4 and TRPC5, especially at negative potentials, which also leads to a change in the current-voltage (I-V) relationship when comparing between TRPC1-TRPC4/5 heteromers and TRPC4 (or C5) homomers (Strübing et al., 2001). In neurons, TRPC1 is often found to heteromultimerize with TRPC4, or TRPC4 and TRPC5 together (Bröker-Lai et al., 2017; Phelan et al., 2013; Stroh et al., 2012).

TRPC2 is found to be highly expressed in vomeronasal organs of rodents (Liman, Corey, & Dulac, 1999) and pivotal for sex discrimination and male-male aggression (Leypold et al., 2002; Stowers, Holy, Meister, Dulac, & Koentges, 2002). Its functions in erythroid cells (Chu et al., 2004) and sperm acrosome reaction during fertilization (Jungnickel, Marrero, Birnbaumer, Lémos, & Florman, 2001) in mice have also been reported. These functions are likely carried out by other genes in people since *TRPC2* is a pseudogene in humans (Zhu et al., 1996).

TRPC3 has been shown to be a multifunctional cellular sensor with a broad range of physiological/pathological functions. It is expressed in many tissues, but compared to brain, the expression levels are relatively low in peripheral tissues (Zhu et al., 1996). In the brain, TRPC3 is most prominently expressed in pituitary gland and Purkinje cells of the cerebellum (Hartmann et al., 2008; Riccio et al., 2002). TRPC3 expression has also been shown in heart (Goel, Zuo, Sinkins, & Schilling, 2007) and lungs of patients with idiopathic pulmonary arterial hypertension (IPAH) but not that of healthy individuals (Yu et al., 2004). TRPC3 is closely related to TRPC7 and to a lesser degree also TRPC6. These three subgroup members can form either homotetrameric channels or heterotetrameric channels by complexing among themselves in both native and heterologous expression systems (Trebak et al., 2003). It was shown that in rat brain synaptosomes, TRPC3 forms complexes with TRPC6 and C7 but not other TRPC members (Goel, Sinkins, & Schilling, 2002) and in heterologous systems, the expressed TRPC3 only interacts with TRPC6 and C7 but not TRPC1/C4/C5 (Hofmann, Schaefer, Schultz, & Gudermann, 2002). However, there is also evidence that TRPC3 forms a complex with TRPC1 (Liu, Bandyopadhyay, Singh, Groschner, & Ambudkar, 2005) or TRPC4 (Poteser et al., 2006). Therefore, the ability of TRPC3 to heteromerize with other TRPC members may be highly variable in different systems and under different conditions.

The mRNA of TRPC4 was found to be highly abundant in the corticolimbic regions of the brain (Fowler et al., 2007). In addition, it is also present in midbrain dopaminergic neurons of the ventral tegmental area and the substantia nigra (Illig, Varnell, Ostertag, Klipec, & Cooper, 2012). TRPC4 mRNA is also highly enriched in bones (Riccio et al., 2002). However, many of the well-characterized functions of TRPC4 are outside of these areas, suggesting broad expression and function (Fu, Gao, Shen, & Zhu, 2015; Mederos et al., 2018).

The mechanism of TRPC4 channel assembly had been studied using glutathione S-transferase pull-down, co-immunoprecipitation of expressed channel fragments and chimera with TRPC6 (Lepage et al., 2006). N- to N-terminal interactions at regions encompassing residues E87–H172 and D254–P304 and a N- to C-terminal interaction involving residues I627–S952 were identified. The multimerization of TRPC4 has also been studied using deletion mutations followed by patch-clamp recording to evaluate the channel function and Förster resonance energy transfer (FRET) to assess protein-protein interaction. It was found that the assembly of TRPC4 tetramers requires regions downstream of amino acid 99 (Ala) at the N-terminus and upstream of residue 730 (Gly) at the C-terminus (Myeong, Kwak, Hong, Jeon, & So, 2014). In addition, while the same N-terminal coiled-coil domain is crucial for heteromultimerization between TRPC1 and C4 or TRPC1 and C5, slightly different TRPC1 C-terminal regions are involved in the assembly with C4 and C5 (Myeong et al., 2016).

TRPC5 is mainly expressed in brain tissues (Fowler et al., 2007; Okada et al., 1998; Philipp et al., 1998; Riccio et al., 2002), where functions in neurite growth, neurotransmission and learning have been clearly indicated (Bröker-Lai et al., 2017; Greka, Navarro, Oancea, Duggan, & Clapham, 2003; Phelan et al., 2013; Riccio et al., 2009). In some cases, TRPC5 exhibits similar functions as TRPC1/C4 (Bröker-Lai et al., 2017; Riccio et al., 2009; Riccio et al., 2014), but in other cases, the functions appear to be distinct (Phelan et al., 2013; Stroh et al., 2012). Like in the case of TRPC4, despite the low transcript levels found in early studies, TRPC5 has also been implicated to play important functions in peripheral tissues, including kidney (Zhou et al., 2017), the cardiovascular system (Lau et al., 2016), and cancer (Ma et al., 2012). Particularly, TRPC5 was found to serve a key role in sensing pressure at the aortic baroreceptors and thereby help stabilize blood pressure (Lau et al., 2016). In carotid arteries, TRPC5 serves a pivotal role in endothelium-dependent contraction (Liang et al., 2019). Uniquely, TRPC5 has been shown to underlie the upregulation of chemotherapy-induced multidrug resistance by promoting expression of p-glycoprotein and ATP-binding cassette subfamily B member 1 (ABCB1) in different types of cancers (Ma et al., 2012; Wang et al., 2015). In addition, TRPC5 not only promotes the formation of extracellular vesicles from breast cancer cells but is also contained in these circulating vesicles, from which it invades nonresistant cells to confer chemoresistance by stimulating p-glycoprotein expression (Ma et al., 2014). Moreover, a role for TRPC5 in angiogenesis has also been recently reported (Zhu et al., 2019).

TRPC6 is highly expressed in placenta, heart, lung, pancreas, kidney, and many areas of the brain (Riccio et al., 2002). In the nervous system, TRPC6 exhibits wide expression in extrinsic fibers innervating intrinsic cardiac ganglia (Calupca, Locknar, & Parsons, 2002), olfactory epithelium neurons (Elsaesser, Montani, Tirindelli, & Paysan, 2005), retinal ganglion cells (Warren, Allen, Brown, & Robinson, 2006), and many regions of the brain, such as the cortex, hippocampus, substantia nigra, and cerebellum (Sun, Sukumaran, Bandyopadhyay, & Singh, 2014). In the kidney, TRPC6 is found in glomeruli, specific tubular cells of the cortex and both the outer and inner medulla, as well as podocytes (Goel, Sinkins, Zuo, Estacion, & Schilling, 2006). In the lung, it is found in human airway smooth muscle and both undifferentiated and differentiated bronchial epithelial cells (Corteling et al., 2004).

In mice, TRPC7 mRNA is highly abundant in the heart, lung, and eye and detectable at lower levels in the brain, spleen, and testis (Okada et al., 1999). In human samples, TRPC7 mRNA is prominently found in the kidney, pituitary gland, and multiple regions of the brain (Riccio et al., 2002). It has been common that results about TRPC mRNA expression from different studies do not match. This could result from differences in sample preparation, e. g. some of the human tissue samples were from tumor instead of normal tissues, methods used for mRNA detection, Northern blotting vs. RT-PCR, species and age differences, and etc.

2. Structure and functional regulation

2.1. High resolutions structures of TRPCs

High resolution structures of TRPCs were not available until 2018. Owning to the great advancement in single-particle cryogenic electron microscopy (cryo-EM) technology, high-resolution structures of many previously unattainable receptor classes, including that of TRPCs, have been resolved to near 3Å (Fig. 1). Compare to traditional X-ray crystallography, cryo-EM does not require crystallization and/or diffraction, and only a small amount of protein/protein complex is required. Therefore, structure determination of membrane proteins, particularly various ion channels, is greatly facilitated [see recent review by Groschner & Tiapko, 2018]. The current cryo-EM structures include homomeric TRPC3, TRPC4, TRPC5 and TRPC6 (Duan et al., 2019; Fan et al., 2018; Vinayagam et al., 2018; Duan et al., 2018; Tang et al., 2018; Azumaya, Sierra-Valdez, Cordero-Morales, & Nakagawa, 2018; Sierra-Valdez, Azumaya, Romero, Nakagawa, & Cordero-Morales, 2018). The overall architectures of these TRPCs are similar, all showing tetrameric structures with six transmembrane α helices in each subunit and the cytoplasmic N-termini surrounding the C-termini. The first four transmembrane α helices (S1–S4) form a voltage sensor-like domain similar to the voltage sensor domains of voltage-gated K^+, Na^+ and Ca^{2+} channels, and the last two α helices (S5–S6) form a structurally conserved ion conducting or pore domain common to all TRP channels, voltage-gated channels, inwardly rectifying K^+ channels, and bacterial K^+ and Na^+ channels. In the tetrameric structures, the voltage sensor-like domain of one protomer is domain-swapped to interact with the pore domain of the neighboring protomer and the four pore domains join at the center of the tetrameric complex to form the ion conducting pore. This arrangement is also very common in TRP channels and voltage-gated ion channels.

The ion conducting pore is formed by the S5 and S6 helices and an intervening pore (P) loop in a symmetric arrangement from all four protomers. The narrowest part or channel gate is found at the bundle near the C-terminal ends of the four S6 helices and for nearly all the TRPC structures, they include isoleucine (I), asparagine (N), and glutamine (Q) from the highly conserved sequence VLLNMLIAMXNXSXQ, except for TRPC3 in which L654 and I658, one residue before the commonly found I and N, respectively, were shown to form the most restricted path (Fan et al., 2018). The radiuses of the lower gates of the resolved TRPC structures are all <1 Å, indicating closed conformations. The narrowest part of the selectivity filter was formed by a conserved glycine, which is three residues apart from the glutamate (E630 in TRPC3 and E686 in TRPC6) situated in the entrance of the selectivity filter and shown for TRPC3 to be critical for the Ca^{2+} permeability of the channel (Poteser et al.,

2011). Interestingly, this residue is substituted by an asparagine in TRPC4 (N580) and TRPC5 (N584), for which TRPC5-N584 has been shown to be important for the Ca^{2+} permeability and Gd^{3+} sensitivity [Chen et al., 2017; Duan et al., 2019].

All TRPC structures contain a three helical region designated as pre-S1 elbow and pre-S1 helix before the transmembrane S1 helix (Fig. 1). This region is halfway embedded in the membrane, with its N-terminal end exposed to the cytoplasmic side to connect with a long stretch of tightly folded linker helices located at the proximal N-terminus of each protomer. Immediately before the linker helices are the four ankyrin-like repeats that form the outskirt of the cytoplasmic architecture, which completely surrounds the four helical bundle composed of the second C-terminal helix (CH2) as designated by some (Azumaya et al., 2018; Tang et al., 2018), which is also referred to coiled-coil (Duan et al., 2018; Duan et al., 2019) or pore helix (Fan et al., 2018) domains by other groups, from the four protomers running in parallel. The CH2 domain is preceded by CH1 (also known as connecting helix (Duan et al., 2018, Duan et al., 2019) or rib helix (Vinayagam et al., 2018)) via a short loop that crosses over the adjacent protomer such that the CH2 domain is in close contact with the ankyrin repeats of the same protomer. The knots at the crossovers and the four helical bundle formed by CH2 may help stabilize the tetrameric structure. On the other hand, the CH1 domain runs near perpendicularly (~100–120°) to CH2, but in parallel with the membrane, into a cavity between the linker helices and ankyrin repeats of a neighboring protomer. Separated by the linker helices, the CH1 domain also runs anti-parallelly with the TRP domain, a well-conserved region in all TRP channels thought to be critical for channel gating. Between the TRP and CH1 domain is a TRP re-entrant helix, which is halfway embedded into the membrane and in some cases looks more like a short open loop rather than a helix (Duan et al., 2019; Tang et al., 2018), and a stretch of unresolved region exposed to the cytoplasm (dashed lines in Fig. 1E, F).

The C-terminal end of the unresolved region and the beginning of CH1 contain the characteristic CIRB (Calmodulin and IP_3 Receptor Binding) motif found in all TRPC isoforms, including the invertebrate TRP and TRPL (Tang et al., 2001; Zhang et al., 2001). Interestingly, this motif also interacts with phosphoinositides and inositol polyphosphates (TRPC6) (Kwon, Hofmann, & Montell, 2007), $G\alpha_{i/o}$ proteins (TRPC4/5) (Jeon et al., 2012), and SEC14 and Spectrin Domain Containing 1 (SESTD1), a Ca^{2+}-dependent phospholipid/cytoskeleton-binding protein (TRPC4/5) (Miehe et al., 2010). The fact that it is exposed to the cytoplasmic environment gives the CIRB motif the opportunity to interact with different partners, making it a hotspot for regulation (Fig. 1A–D). As the major portion of the CIRB sequence is actually included in CH1, it is possible that the binding of CIRB motif by its protein partner presses the CH1 domain like a lever to cause conformation changes near the lower gate. Open structures and structures with CIRB motif binding partners will likely reveal important insights into how relative motions between CH1, TRP domain, and S4–S5 linker, which likely interacts with the TRP domain, are involved in TRPC channel gating. Notably, at the exposed side connected to the unresolved region, the CH1 domain begins ~3–4 residues (one turn) earlier in TRPC4/5 than in TRPC3/6 [compare Vinayagam et al., 2018; Duan et al., 2019; with Tang et al., 2018; Azumaya et al., 2018]. This may give rise to the wider overall shape of TRPC4/5 (100 to 105 Å in diameter) (Duan et al., 2018; Vinayagam

et al., 2018) and the skinner look of TRPC3/6 (75–85 Å in diameter) (Fan et al., 2018; Tang et al., 2018) (Fig. 1A, B).

The presence of the pre-S1 elbow and the TRP re-entrant helix makes TRPC structures resemble TRPMs and NOMPC more than TRPA and TRPVs (Jin et al., 2017; Guo et al., 2017; Autzen et al., 2017; Yin et al., 2017; Huang, Winkler, Sun, Lü, & Du, 2018; Wang et al., 2018). It was found that the pre-S1 elbow and pre-S1 helix pull the intracellular half of the S1 transmembrane helix away from the pore center, creating a window to expose the intracellular half of S4 helix and the S4–S5 linker to the lipid environment (Fan et al., 2018). This may be important for lipid gating. However, although densities for lipids were found in the TRPC3 structure, the resolution was not high enough to determine their identity (Fan et al., 2018). One of these lipids indeed interacts with pre-S1 elbow, S1, S4 and S4–S5 linker of TRPC3 and a mutation here (T561A on S4) has been reported to enhance TRPC3 channel function, causing cerebellar ataxia in mice (Becker et al., 2009). The second lipid was found to be wedged between the P loop and S6 of the neighboring protomer. Because G640 on S6, which interacts directly with the hydrocarbon tail of the lipid, was showed to be critical for lipid gating of TRPC3 (Lichtenegger et al., 2018), this site may be accessed by lipids from the extracellular side to activate the channel. Lipid densities were also found in other studies of TRPC structures and these were identified as cholesteryl hemisuccinate and phosphatidic acid (Duan et al., 2018; Tang et al., 2018; Vinayagam et al., 2018).

Unique to TRPC4 and C5 are the presence of an extracellular disulfide bond between two cysteines that are five residues apart located within the linker between S5 and the pore helix of the same protomer (Fig. 1C, E) and an intracellular cation (most likely Na^+) binding site formed by two residues (E417, Q420 of C4; E418, E421 of C5) at the last two helical turns of S2 and another two (N435, D438 of C4; N436, D439 of C5) at the beginning two helical turns of S3 (Fig. 2). While the disulfide bond has been shown to be pivotal for redox sensing of TRPC4 and C5 (Duan et al., 2018; Xu et al., 2008), the functional significance of the Na^+ binding site remains undefined. Ironically, in whole-cell voltage clamp recordings, TRPC4 and C5 have often exhibited larger inward currents when the cell was bathed in the Cs^+- than Na^+-based bath solutions (Jeon et al., 2008; Sung et al., 2011). This feature has been utilized to reveal constitutive channel activities that were otherwise undetectable in the normal Na^+-based physiological solution (Jeon et al., 2012; Jeon, Thakur, Tian, So, & Zhu, 2016). It may be possible that the Na^+ binding site mediates inhibition of TRPC4/5 by Na^+ flowed into the cell through the open channels.

Unique to TRPC3 and C6 is the extended S3 helix at the extracellular side, which extends about four helical turns longer than that of TRPC4 and C5 (Fig. 1B, D). This protrusion from the membrane surface may help support an extracellular pocket potentially targetable by small molecules (Fan et al., 2018; Tang et al., 2018). Clearly, much remained to be learned from these structures. It is anticipated that these high-resolution structures will greatly facilitate the study of structural and functional relationships of TRPCs and the development of drugs targeting these channels.

2.2. Mechanism of activation of TRPC channels

2.2.1. The PLC pathway

2.2.1.1. Diacylglycerols.: Like the prototypical *Drosophila* TRP and TRPL, mammalian TRPC channels have been shown to be activated downstream from receptors that signal through PLC (Liu & Montell, 2015; Tian et al., 2014; Trebak et al., 2003). This may occur through activation of $G_{q/11}$-coupled receptors and receptor tyrosine kinases. However, the PLC pathway consists of many steps or constituents, including hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) at the PM, production of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerols (DAG), activation of IP_3 receptors at the ER membrane, Ca^{2+} store depletion, and $[Ca^{2+}]_c$ increase. It has become clear that several of these steps are involved in TRPC channel gating (Fig. 3A). The first clue came from the study showing that both TRPC3 and C6 could be directly activated by diacylglycerols (Hofmann et al., 1999). Both the more natural 1-stearoyl-2-arachidonyl-sn-glycerol (SAG) and synthetic DAG analog 1-oleoyl-2-acetyl-sn-glycerol (OAG) were reported to be able to activate TRPC3 and C6 channels when applied either from the extracellular or cytoplasmic sides; however, they did not activate TRPC4 or C5 (Hofmann et al., 1999). Subsequently TRPC2 and TRPC7 were also shown to be activated by DAG (Lucas, Ukhanov, Leinders-Zufall, & Zufall, 2003; Okada et al., 1999). Only recently, it was shown that TRPC4/5 are also DAG-regulated channels, but the lipid sensitivity was masked by a multiple PDZ domain protein, Na^+/H^+ exchanger regulatory factor (NHERF) (Storch et al., 2017), which binds to the C-terminal ends for TRPC4/5 (Tang et al., 2000) (Fig. 3C). Upon removal of NHERF binding by phosphorylation of a threonine residue in the PDZ-binding motif of TRPC4/5 by protein kinase C, the DAG sensitivity appears, indicating a dynamic regulatory mechanism (Storch et al., 2017). Thus, DAGs appear to be direct activators of all mammalian TRPC channels.

However, comparing to receptor stimulation, DAGs, often by the use of OAG because of its easier access and better solubility in aqueous solutions than naturally occurring DAGs, do not appear to recapitulation all features of TRPC channel activation, at least in electrophysiological experiments (Albert & Large, 2003; Shi et al., 2004). The magnitude of OAG-evoked current tends to be smaller and the kinetics of its activation are slower than TRPC currents induced via receptor stimulation. Presumably, the solubility issue and side of application of the lipid, i. e. OAG is typically applied extracellularly but the endogenously produced DAGs should first appear in the inner leaflet of PM following the hydrolysis of PIP_2, could account for some of the differences between TRPC channel activation by OAG and receptor agonists. Recently, DAG photoswitches have been developed to allow equilibration of the lipids with the membrane in both leaflets before activation by light (Lichtenegger et al., 2018). This may help overcome some of the above issues. Combining mutagenesis and functional analysis using different DAG analogs including one of the DAG photoswithches, **OptoDArG** (Table 1), the authors demonstrated that DAG may gain access to the channel through a subunit-joining fenestration towards a conserved glycine residue behind the selectivity filter of TRPC3 (Lichtenegger et al., 2018).

2.2.1.2. IP_3 and IP_3 receptors.: On the other hand, numerous studies have shown the involvement of other constituents of the PLC pathway in TRPC channel activation. These

include IP_3, the other product of PIP_2 hydrolysis, which might enhance TRPC7 activation (Shi et al., 2004) or activate TRPC3 and C5 through IP_3 receptors (Kanki et al., 2001; Kiselyov et al., 1998). Indeed, IP_3 receptors were shown to be physically associated with TRPCs (Boulay et al., 1999; Kiselyov, Mignery, Zhu, & Muallem, 1999) and direct binding between the N-terminus of the IP_3 receptor and the C-terminal CIRB motif of the TRPC has been demonstrated for all three IP_3 receptors and all TRPC subtypes (Tang et al., 2001; Zhang et al., 2001) (Fig. 3C). Functionally, TRPC3, TRPC4, and endogenous TRPC1-containing channels were activated by IP_3 receptors but inhibited by Ca^{2+}-calmodulin (CaM), which competes with the IP_3 receptors for binding to the CIRB motif in a mutually exclusive manner (Kiselyov et al., 1998; Tang et al., 2001; Vaca & Sampieri, 2002; Zhang et al., 2001).

To make the matter more complicated, TRPC2, C3 and C5, but not C1, were reported to interact with Junctate (Fig. 3B), an ER transmembrane protein that also binds to IP_3 receptors (Stamboulian et al., 2005; Treves et al., 2004; Treves et al., 2010). Junctate has more recently been found in the complex where STIM1 interacts with Orai1 at the ER-PM junction (Srikanth et al., 2012), Intriguingly, the overexpression of junctate led to an increase in the number of ER-PM junctions that contained IP_3 receptors and TRPC3 and this effect was further enhanced by overexpressing TRPC3 (Treves et al., 2010). With the ability to sense Ca^{2+} contents in the ER lumen and to bridge ER-PM interactions, junctate is thus thought to be an important player in store-operated Ca^{2+} entry (Srikanth et al., 2012; Treves et al., 2004).

2.2.1.3. Protons.: The hydrolysis of PIP_2 by PLC also produces protons (H^+), which lead to local acidification at the cytoplasmic side of the PM. It was estimated that at the physiological pH of 7.2, the breakdown of each molecule of PIP_2 yields 0.8 proton (Huang et al., 2010). The effect of intracellular acidification has been studied in *Drosophila* photoreceptors for endogenous TRP and TRPL channels. For both, this often unappreciated by-product of PIP_2 hydrolysis was found to facilitate channel activation (Huang et al., 2010), although it was suggested in a later study that the acidification may exert its effect through a scaffolding protein, INAD, that holds PLC and TRP channels in a complex in the rhabdomere of the insect's photoreceptor (Liu et al., 2011). It was reported recently that the decrease of intracellular pH also facilitates activation of TRPC4 channels (Wang et al., 2018). Therefore, it is possible that H^+, as a product of PIP_2 hydrolysis and a general second messenger of PLC signaling, also contributes to activation of most, if not all, TRPC channels.

2.2.1.4. PIP_2.: Not only are the products of PLC activity but also the substrate, PIP_2, is important for TRPC channel gating. The effects of PIP_2 on TRPC activation are complex. On one hand, the channels may be somewhat inhibited by the basal levels of PIP_2, as well as its precursors, phosphatidylinositol 4-phosphate (PIP) and phosphatidylinositol (PI) on the PM. Thus, the breakdown of PIP_2 by PLC, which also lowers PIP and PI levels because of rapid conversions of PI to PIP and PIP to PIP_2 by kinases, should relieve the block and allow channel activation. On the other hand, some levels of PIP_2 may be needed to support TRPC channel activity, given that the production of DAG, IP_3 and H^+ is dependent on the substrate,

although this may not be the only reason for the PIP_2 dependence. It was shown that TRPC5 activation was enhanced by hydrolyzing PIP_2 with PLC or inhibiting the kinase that phosphorylates PIP to PIP_2 but suppressed by dephosphorylating PIP_2 to PIP via a phosphatase. However, direct application of PIP_2 to the cytoplasmic side of inside-out patches enhanced TRPC5 function (Trebak et al., 2009). In whole-cell recordings, infusing PIP_2 into the cell via the patch pipette, which would enhance the resting PIP_2 level, suppressed activation of TRPC4α, not TRPC4β, by receptor agonist (Otsuguro et al., 2008). Here, the β isoform lacks 84 amino acids at the C-terminus as compared to the full-length TRPC4α isoform because of an alternative intron acceptor site. Thus, a PIP_2-inhibitory site may be located within the 84 amino acids missing in TRPC4β. However, this apparently is not the only site and/or action of PIP_2, as the similar manipulation delayed desensitization of TRPC4β and TRPC5 currents (Kim et al., 2014; Kim, Kim, Jeon, Kim, & So, 2008). In experiments where endogenous PIP_2 levels were reduced by overexpressing constitutively active $G\alpha_q$ protein or phosphatase that dephosphorylates PIP_2 to PIP, the activation of TRPC4β was completely inhibited (Kim et al., 2014) and the G protein effect was rescued by intracellular dialysis of PIP_2 (Jeon et al., 2012), highlighting the dependence of TRPC4 activation on PIP_2.

More recently, it was shown that TRPC4 (both α and β isoforms) activation is absolutely dependent on PLCδ1 and $G_{i/o}$ protein signaling (Thakur et al., 2016). As such, PIP_2 serves not only as the substrate but also the membrane anchor of this PLC isozyme. It is worth pointing out that PLCδ1 may represent the prototypical PLC isozyme because it is the only family found in lower eukaryotes like yeast and slime molds (Meldrum, Parker, & Carozzi, 1991; Rhee & Bae, 1997). PLCδ1 is solely activated by Ca^{2+} while other mammalian PLC isozymes, which were likely evolved from PLCδ1, contain additional expanded domains for more specific regulations. Thus, it is possible that PLCβ's and PLCγ's contribute to TRPC4 activation because of their coupling to receptor signaling and their activation is propagated to PLCδ1 owning to $[Ca^{2+}]_c$ elevation. It is also interesting to note that in the same study by Thakur et al. (2016), manipulations that lowered PIP_2 levels in the cell also made it easier for TRPC4 to be activated by low concentrations of receptor agonist, again indicating a tonic inhibition by the phosphoinositide. The dual effects of PIP_2 on channel activation may explain the seemingly conflicting results found about carbacholevoked native TRPC4-like currents in ileal myocytes where intracellular dialysis of PIP_2 was reported to either accelerate (Otsuguro et al., 2008) or slow down current desensitization (Kim et al., 2008). Presumably, some variations in experimental conditions between the two studies, e. g. species used (guinea pigs *vs.* mice), sample preparations, compositions of the pipette and bath solutions, could impact the resting PIP_2 contents and/or state of the channel and thereby account for the different results.

For other TRPC channels, PIP_2 dependence has been reported for native channels in vascular smooth muscle cells likely composed of TRPC1/C5 heteromers, where TRPC1 appeared to confer the PIP_2 regulation (Shi et al., 2012). In heterologous systems, PIP_2 activated overexpressed TRPC6 and C7 in inside-out patches (Lemonnier, Trebak, & Putney Jr, 2008), but depleting PIP_2 in rabbit mesenteric artery smooth muscle cells augmented endogenous TRPC6-like activity (Albert, Saleh, & Large, 2008). With the use of membrane depolarization in whole-cell recordings to dephosphorylate PIP_2 through voltage-sensitive

phosphatases, PIP_2 was found to be essential in supporting TRPC3, C6, and C7 function, and the three TRPC members exhibited differences in the sensitivity to PIP_2 (Imai, Itsuki, Okamura, Inoue, & Mori, 2012). It was also shown that although both DAG and PIP_2 are important for the activation of TRPC6 and C7 channels, channel inactivation is correlated with the loss of PIP_2, but not DAG (Itsuki et al., 2014). In *Drosophila* photoreceptor cells, the light-induced activation of TRP and TRPL channels was mediated by phosphoinositide hydrolysis and intracellular pH decrease; however, direct application of PIP_2 to the cytoplasmic side of inside-out patches excised from insect S2 cells overexpressing TRPL also strongly increased channel function (Huang et al., 2010). Therefore, the phosphoinositides seem to exert complex effects on TRPC channels, including both facilitation and inhibition, as well as specific aspects of channel gating. The relative levels and number and positions of phosphates, i. e. PI, PIP, or PIP_2, as well as their cluster sizes and distribution patterns on PM, as they relate to TRPC channels, are all important questions that warrant further investigation.

2.2.1.5. Ca^{2+}.: The rise in $[Ca^{2+}]_c$ affects different TRPC subtypes differently. As a part of the PLC signaling, the Ca^{2+} signal first arises from IP_3-induced ER Ca^{2+} release; this probably provides the initial trigger to facilitate the activation of TRPC4 and C5. Then Ca^{2+} influx through the activated TRPC channels, as well as Orai channels that are activated as a result of ER Ca^{2+} store depletion (Cheng, Liu, Ong, & Ambudkar, 2008; Feske et al., 2006; Vig et al., 2006), may further enhance the TRPC activity. The effect of intracellular Ca^{2+} on TRPC4 and C5 activation had first been shown by whole-cell patch clamp recordings using the intracellular solutions that contained either EGTA or BAPTA as the Ca^{2+} buffer with the free $[Ca^{2+}]_c$ chelated at desired levels (Schaefer et al., 2000). Between the two Ca^{2+} chelators, EGTA binds to Ca^{2+} about 100–1000 times slower than BAPTA and therefore allows Ca^{2+} level near the source of Ca^{2+} generation (i. e. Ca^{2+}-permeable channels) to increase to a higher amplitude and to last for a longer time period than BAPTA. Thus, a comparison between results obtained with EGTA- *vs.* BAPTA-buffered solutions helps reveal the effect of near membrane Ca^{2+} dynamics on the channel, especially when Ca^{2+} entry serves a major role in channel activation and/or desensitization. On the other hand, the activation of TRPC4 and C5 is heavily influenced by extracellular Ca^{2+} (Jung et al., 2003). Thus, in experiments where Ca^{2+} effect was observed by changing Ca^{2+} levels in the bath solution, it is difficult to distinguish whether the side of action for Ca^{2+} is extracellular, representing a direct effect, or intracellular, which is secondary to Ca^{2+} entry via the open channels. The situation may be further complicated by the presence of additional Ca^{2+} entry mechanism, for instance, voltage-gated Ca^{2+} channels (VGCCs) and Orai channels (see later). By increasing $[Ca^{2+}]$ right underneath the PM, these channels also affect TRPC gating (Tian et al., 2014; Gross et al., 2009; Cheng et al., 2008).

Direct effect of intracellular Ca^{2+} has at least been demonstrated for heterologously expressed homomeric TRPC5 channels, where direct intracellular infusion of pipette solutions that contained higher than resting Ca^{2+} level (≥300 nM) or flash photolysis of preloaded caged Ca^{2+} triggered channel activation (Gross et al., 2009). In a separate study, the intracellular Ca^{2+} dependence of TRPC5 was studied in the context of stimulation of the co-expressed M1 muscarinic receptor. It was shown that 1 μM cytosolic Ca^{2+} was needed to

strongly potentiate the receptor-operated TRPC5 activation (Blair, Kaczmarek, & Clapham, 2009). For TRPC4β activated through the co-expressed μ opioid receptor (μOR), high cytosolic Ca^{2+} concentrations are also necessary, with an estimated EC_{50} of ~12 μM (Thakur et al., 2016). Thus, the sensitivity to Ca^{2+} appears to be different for TRPC4 and C5 and dependent on the mode of activation and other experimental conditions.

A CaM binding site downstream from the conserved CIRB motif has been reported to be critical for accelerating TRPC5 activation by Ca^{2+}-CaM (Ordaz et al., 2005). Multiple Ca^{2+}-CaM sites are also found at equivalent region of TRPC4α (Tang et al., 2001; Trost, Bergs, Himmerkus, & Flockerzi, 2001) despite sequence divergency in this area of TRPC4α and C5 (Zhu, 2005). However, since the area is excluded in TRPC4β, the Ca^{2+} dependence of TRPC4β activation must not be conferred by these binding sites. One possibility is that the Ca^{2+} dependence could be conferred by PLCδ1, the specific PLC isozyme required for the $G_{i/o}$-mediated TRPC4 activation (Thakur et al., 2016). Interestingly, the potentiation of TRPC6 activity by cytosolic Ca^{2+} was shown to be dependent on CaM-dependent kinase II (CaMKII) phosphorylation at Thr-487 (Shi et al., 2004; Shi et al., 2013). Furthermore, rapid translocation of TRPC5 from intracellular vesicles to PM in response to receptor stimulation has been observed (Bezzerides, Ramsey, Kotecha, Greka, & Clapham, 2004) and it may be quite common among TRPCs. This may also contribute to the Ca^{2+}-dependence of channel activation since membrane fusion is triggered by Ca^{2+}.

Ca^{2+} dependent inhibition has also been reported for TRPCs. Under similar experimental conditions, TRPC7 only displayed inhibition by Ca^{2+} whereas TRPC6 exhibited both potentiation and inhibition (Shi et al., 2004). Likewise, receptor agonist-evoked TRPC3 current was strongly inhibited by the rise in $[Ca^{2+}]_c$ (Thyagarajan et al., 2001). The mechanisms for the Ca^{2+}-dependent inhibition may involve both CaM-dependent and CaM-independent processes (Polat et al., 2019; Shi et al., 2004) with the IC_{50} of Ca^{2+} inhibition of TRPC7 being ~10 time lower than that of TRPC6. Single channel studies revealed that millimolar extracellular Ca^{2+} also suppressed the unitary conductance of TRPC6 and C7 at negative potentials, again with sensitivity higher for TRPC7 than C6 (Shi et al., 2004). A recent study indicates that CaM mediates Ca^{2+}-dependent inactivation of TRPC6 by altering the assembly of the C-terminal coiled-coil domain, where gain-of-function TRPC6 mutations have been found from patients with focal segmental glomerulosclerosis (FSGS) (Polat et al., 2019). For TRPC4 and C5, Ca^{2+} was shown to either inhibit channel activation or accelerate current inactivation at concentrations higher than that needed to support the channel opening (Gross et al., 2009; Ordaz et al., 2005; Thakur et al., 2016). While the activation of TRPC1 in human submandibular gland (HSG) cells is facilitated by Ca^{2+} influx mediated by Orai1-containing channels (Cheng et al., 2008), Ca^{2+} also inhibits TRPC1 function through CaM binding to a site at the very C-terminal end of TRPC1 protein (Singh, Liu, Tang, Zhu, & Ambudkar, 2002). Thus, for several TRPC subtypes, Ca^{2+} exert both stimulatory and inhibitory effects, utilizing diverse mechanisms including direct Ca^{2+} binding, PLCδ, CaM, CaMKII, and presumably others, such as vesicular trafficking. The resulting Ca^{2+} sensitivities differ greatly among different channels and experimental conditions, providing a delicate system to fine tune the channel function.

2.2.2. $G_{i/o}$ signaling—The pertussis toxin (PTX)-sensitive $G_{i/o}$ proteins exert a unique effect on the activation of TRPC4 and C5 (Fig. 3A). The knowledge on the involvement of $G_{i/o}$ protein signaling in receptor-operated activation of TRPC4-containing channels can be dated back to more than 20 years when the endogenous muscarinic cation current (mI_{CAT}) in intestinal smooth muscle cells were found to be codependent on both M_2 ($G_{i/o}$-coupled) and M_3 ($G_{q/11}$-coupled) muscarinic receptors (Zholos & Bolton, 1997). It was shown later that mI_{CAT} is mainly mediated by channels composed of TRPC4 (Tsvilovskyy et al., 2009). Importantly, mI_{CAT} was inhibited by the pre-treatment of cells with PTX (Pucovský, Zholos, & Bolton, 1998). Similarly, the PTX treatment also suppressed current development of heterologously expressed TRPC4 induced through intracellular infusion of GTPγS (Otsuguro et al., 2008). Furthermore, the knockdown of $G\alpha_{i1}$, but not that of $G\alpha_{q/11}$, in *Xenopus* oocytes strongly inhibited the activation of TRPC5 expressed in these cells (Tabata et al., 2002). In mammalian expression systems, the expressed TRPC5 was activated through stimulation with sphingosine-1-phosphate (S1P) or oxidized phospholipids and these activities were all inhibited by PTX (Al-Shawaf et al., 2010; Xu et al., 2006).

In principle, $G_{i/o}$ proteins could induce PLCβ activation through Gβγ dimers freed from the heterotrimeric complex as a part of G protein activation. However, an early study using pipette dialysis of antibodies against different G protein subunits showed that inhibiting $G\alpha_o$, rather than Gβ, suppressed the development of mI_{CAT} (Yan et al., 2003). Also, although TRPC4 and C5 are readily activated via stimulation of overexpressed $G_{q/11}$-coupled histamine and muscarinic receptors (Kim et al., 2014; Obukhov & Nowycky, 2004; Schaefer et al., 2000), stimulation of the endogenous muscarinic receptor (likely M_3) with carbachol in HEK293 cells overexpressing TRPC4 alone evoked very small, if any, current (Thakur et al., 2016). Intriguingly, the same manipulation effectively activated TRPC3, C5, C6, and C7 currents in the same expression system, as well as robust $[Ca^{2+}]_c$ increase through IP_3-mediated ER Ca^{2+} release in untransfected HEK293 cells, demonstrating efficient coupling to $G_{q/11}$-PLCβ. The discrepancy between endogenous and overexpressed receptors was resolved by pre-treating the cells with PTX, which abolished TRPC4α and TRPC4β activation by the overexpressed M_1, M_3, and M_5 receptors, suggesting that all of them were promiscuously coupled to $G_{i/o}$ proteins when overexpressed. Importantly, the PTX treatment also suppressed TRPC5 currents, evoked through either endogenous or overexpressed M_3 receptors, by at least 50% (Thakur et al., 2016) while having no effect on the activation of TRPC3, C6 and C7 (M. X. Zhu, unpublished observation). Also interesting is that when overexpressed in HEK293 cells, the $G_{i/o}$-coupled μOR activated PLC very poorly, but it mediated robust TRPC4 activation (Thakur et al., 2016). Therefore, the receptor-operated TRPC4 activation is not mediated through $G_{q/11}$-PLCβ or $G_{i/o}$-Gβγ-PLCβ signaling; rather it exhibits an absolute dependence on $G_{i/o}$ proteins. In this regard, TRPC5 is actually different from TRPC4 in that it may be activated by either $G_{q/11}$ or $G_{i/o}$.

The $G_{i/o}$-mediated TRPC5 activation has been suggested to occur through stimulation of Ca^{2+}-independent group 6 (GVI) phospholipase A_2 ($iPLA_2$) and the resultant production of lysophospholipids (AL-Shawaf et al., 2011). However, the iPLA2 inhibitor used in this study, bromoenol lactone, has been found to block TRPC5 channels independently of $iPLA_2$ (Chakraborty et al., 2011). In any case, lysophospholipids may have complex effects on

TRPC and other channels, as well as properties of the membrane from where these channels are recorded. Alternatively, Jeon and colleagues had examined the effects of different G protein subunits on TRPC4 and C5 activation through overexpression of Gβγ or constitutively active Gα mutants. They showed that coexpression of constitutively active $G\alpha_{i2}$, $G\alpha_{i3}$, or $G\alpha_{o}$, but not $G\alpha_{i1}$ or Gβγ, led to TRPC4 activation in the absence of any stimulus, with $G\alpha_{i2}$ being the most potent. For TRPC5, $G\alpha_{i3}$ may be more preferred (Jeon et al., 2012). With the combined approach of co-immunoprecipitation and functional evaluation of deletion mutants, the critical site of TRPC4 for $G\alpha_{i2}$ regulation was found to overlap with the CIRB motif (Jeon et al., 2012). Given that in the high resolution TRPC4 structures, the CIRB motif is largely exposed at the end of the extended lever formed by CH1 helix (see above), it is possible that the interaction with $G\alpha_{i/o}$ at this region induces an allosteric change that pulls the lower gate to open. Further evidence for the involvement of $G\alpha_{i/o}$-GTP, rather than Gβγ, in the receptor-operated activation of TRPC4 came from studying the effects of $G_{i/o}$-regulatory proteins that contain either GTPase-activating protein (GAP) or guanine-nucleotide-dissociation inhibitor (GDI) domains. It was shown that although $G_{i/o}$-mediated TRPC4 activation can be inhibited through both GAP and GDI functions of Regulators of G protein Signaling (RGS) proteins in an additive fashion, only the GAP, but not GDI, function can accelerate current desensitization (Jeon et al., 2016).

2.2.3. Store- or STIM-operated activation—Because of the history of mammalian TRPC discovery, a large volume of early studies were devoted to establishing the link between ER Ca^{2+} store depletion and TRPC channel activation. The concept of store-operated or capacitative Ca^{2+} entry was first proposed by James Putney Jr. over 30 years ago (Putney Jr., 1986), with the idea that in order for the cell to maintain its Ca^{2+} reserve, the loss of ER Ca^{2+} storage as a result of Ca^{2+} mobilization due to receptor activation should trigger a mechanism that brings Ca^{2+} into the cell from extracellular space. This mechanism requires the presence of a Ca^{2+}-permeable channel on the PM that opens in response to ER Ca^{2+} depletion. In subsequent years, several store- or receptor-operated ionic currents with varying properties were discovered in electrophysiological studies. Among them, the highly Ca^{2+} selective CRAC current (I_{CRAC}) first described in T-lymphocytes and mast cells, with single channel conductance too small to be detectable, was considered as the most typical store-operated channel (Hoth & Penner, 1992; Lewis & Cahalan, 1989). Although other channels have been described (Fasolato, Hoth, Matthews, & Penner, 1993; Vaca & Kunze, 1993), their ion selectivity, single channel conductance, and mode of activation tended to vary so much that no consensus could be drawn as to how to categorize them. Strictly speaking, store depletion is usually an inevitable component of PLC signaling. Thus, if a Ca^{2+}-permeable channel becomes activated as a result of PLC signaling, i. e. being receptor-operated, then it should be able to fulfill the role of store refilling. However, there have been growing appreciations of unique functions carried out by different Ca^{2+} entry pathways, including local Ca^{2+} signaling and temporal patterns (Berridge, 1995). Thus, having multiple and diverse channel types involved would be advantageous for signaling and cell function.

The original drive for the search of mammalian homologs of *Drosophila* TRP and TRPL indeed followed the hypothesis that store-operated Ca^{2+} entry might be mediated by such

channels, given the close similarity between the insect's phototransduction and mammalian PLC pathway (Hardie & Minke, 1993). Thus, the initial functional characterization of the newly identified TRPCs had always included a Ca^{2+}-free and Ca^{2+}-readdition protocol while changes in $[Ca^{2+}]_c$ were monitored by the pre-loaded fluorescence Ca^{2+} indicator dye, *e. g.* Fura-2 (Zhu et al., 1996; Zhu, Jiang, & Birnbaumer, 1998). Cells were stimulated with either a receptor agonist to trigger $G_{q/11}$-PLCβ signaling or thapsigargin (TG), an inhibitor of the sarco/endoplasmic reticulum ATPase (SERCA), to induce internal Ca^{2+} store depletion independently of receptor activation. While the receptor agonist had always elicited an increase in the extracellular Ca^{2+}-dependent $[Ca^{2+}]_c$ rise associated with TRPC overexpression, evidence for TG-induced activation was only obtained for TRPC1, C3, C4, and C5 (Liu et al., 2000; Philipp et al., 1996; Philipp et al., 1998; Thyagarajan et al., 2001; Zhu et al., 1996; Zhu et al., 1998), but not for TRPC6 and C7 (Boulay et al., 1997; Okada et al., 1999). For TRPC3 and C5, there are also reports suggesting the non-capacitative nature of the channels (Okada et al., 1998; Zhu et al., 1998).

Electrophysiological recording results have all agreed that the expressed TRPC channels do not recapitulate the key features of I_{CRAC}, especially with respect to ion selectivity and single channel conductance (Hurst, Zhu, Boulay, Birnbaumer, & Stefani, 1998; Liu et al., 2000; Okada et al., 1998; Zitt et al., 1996). Therefore, despite the numerous reports on the effects of knocking down or knocking out TRPC expression or using dominant negative TRPC constructs to suppress store-operated Ca^{2+} entry (Yuan et al., 2009), the contribution of TRPCs in this pathway remains controversial, although it is generally agreed that all TRPCs can function as receptor-operated Ca^{2+}-permeable nonselective cation channels. Possibility exists that store sensitivity may be acquired through heteromultimerization between different TRPC isoforms or a TRPC with other auxiliary proteins (Vazquez, Lievremont, St J Bird, & Putney, 2001; Zhu et al., 1998). However, even with TRPC heteromers, the biophysical properties are still quite different from that of the CRAC channel (Lintschinger et al., 2000; Strübing et al., 2001). Only in one example, successful heterologous reconstitution of a CRAC-like current was achieved using TRPC in combination with a low level of Orai1 overexpression (Liao et al., 2008).

The discovery of STIMs and Orai's had turned things around with the demonstration of I_{CRAC}-like current formed by the heterologously expressed Orai1 and ER Ca^{2+} store depletion sensed and conveyed to the PM by STIM1 (Feske et al., 2006; Liou et al., 2005; Roos et al., 2005; Vig et al., 2006). Growing evidence suggests that STIM1 not only interacts with Orai1, but also TRPCs and physical and/or functional interplays also occur between Orai1 and TRPCs. It is likely that at least some TRPC channels can be STIM-operated. It was reported that STIM1 can be physically associated with TRPC1, C2, C4, C5 (Huang et al., 2006; Lopez, Salido, Pariente, & Rosado, 2006) and C6 (Albarran et al., 2014; Boustany et al., 2010), but not C3 and C7, in response to Ca^{2+} store depletion at least in some cases. STIM1 can also mediate heteromultimerization between TRPC1 and C3, making the latter STIM1 dependent (Yuan, Zeng, Huang, Worley, & Muallem, 2007). For TRPC1, the interaction with STIM1 may involve coiled-coil regions at N- and C-terminal regions of the channel (Ong & Ambudkar, 2017) and the STIM-Orai1-activating region (SOAR) of STIM1 (Lee et al., 2014). Thus, the SOAR domain of STIM1 is equally important for activating Orai and TRPC channels. In the full-length STIM1, however, the

last two lysine residues may be especially critical for TRPC gating, as they form electrostatic interactions with the two conserved aspartates/glutamates (D639, D640 of TRPC1; E648, E649 of TRPC4) at TRPC C-terminus (Zeng et al., 2008), which are located right at the border of the TRP helix and TRP re-entrant as shown by the recent high resolution structures (Fig. 1A–D) (Duan et al., 2018; Tang et al., 2018; Vinayagam et al., 2018).

The ability of STIM1-SOAR domain to activate TRPC currents has been tested using excised inside-out patches, showing that the purified recombinant SOAR fragment directly activated single channel currents of TRPC1, C4 and C5, but not C3 and C6 (Asanov et al., 2015), despite the conservation of the two acidic residues in TRPC3 and C6 (Tang et al., 2018; Zeng et al., 2008). Combining the single channel recording technique with single molecule fluorescence imaging, the authors also demonstrated that two SOAR molecules are needed for one TRP tetramer and the activity was antagonized by four CaM molecules (Asanov et al., 2015).

Results of several studies support the idea that the interaction with STIM1 may switch the TRPC channel from store-independent to store-dependent gating (Asanov et al., 2015; Desai et al., 2015; Lee et al., 2014; Ong et al., 2007; Saul, Stanisz, Backes, Schwarz, & Hoth, 2014; Sundivakkam et al., 2012; Zeng et al., 2008). This might explain why in experiments with heterologous expression of TRPCs, which are typically carried out without co-expression of STIM1, the channels often behaved in a store-independent manner, with store-operation appearing only under strictly defined conditions (Philipp et al., 1998; Zhu et al., 1998). Therefore, as in the case of STIM1 gating Orai1, the stoichiometry between STIM1 and TRPC is also important for reconstituting store- or STIM1-operated TRPC channel gating (Fig. 3B). Plausibly, Orai1 and TRPCs may compete for binding to STIM1, and the outcome would determine whether the store-operated Ca^{2+} entry in the cell is carried out by CRAC channels formed by Orai1 or nonselective cation channels formed by TRPCs (de Souza, Ong, Liu, & Ambudkar, 2015; Desai et al., 2015; Lee et al., 2014; Saul et al., 2014).

The regulation by STIM1 sometimes may involve specific STIM1 isoforms or it may have additional consequences than channel gating. In human myotubes. a functional interaction between STIM1L (a splice variant of STIM1) and TRPC1/C4 promotes store-operated Ca^{2+} entry to enable fast repetitive Ca^{2+} transients and support myogenesis and muscle differentiation (Antigny et al., 2017). In the case of TRPC6, the interaction with STIM1 was reported to cause its translocation from PM to ER, reducing Ca^{2+} entry through the TRPC6-containing channels but increasing Ca^{2+} release from ER (Albarran et al., 2014).

Also, the relationship between Orai1 and TRPCs is not just competition. Orai1 may also be involved in the store-operated TRPC gating. With the endogenous Orai1 expression knocked down, both store-operated Ca^{2+} entry and TRPC1 currents were abolished and conversely, the overexpression of Orai1 augmented these activities (Cheng et al., 2008). The upregulation of Orai1 also enhanced store-operated Ca^{2+} entry through several other TRPC subtypes (Liao et al., 2007; Liao et al., 2008; Liao et al., 2009). It was proposed that Orai and TRPC proteins might co-assemble into a channel complex (Liao et al., 2008). Interestingly, the Ca^{2+} selectivity of an endogenous TRPC1/C4 channel was reduced by the

knockdown of Orai1 in endothelial cells, along with the decrease in store-operated currents (Cioffi et al., 2012). This implies a different mechanism from the one that assumes Orai and TRPC to form separate channels independently regulated by STIM. It has also been suggested that STIM, Orai, and TRPC may coexist in a complex named as “store-operated calcium influx complex (SOCIC)”, where channels composed of both TRPC and Orai and those made of either TRPC or Orai separately could assemble and disassemble dynamically in response to different scenarios of store depletion and/or receptor activation (Vaca, 2010). In injured medial and neointimal proliferative vascular smooth muscle cells prepared from carotid artery, the STIM-Orai-TRPC complex also includes Homer1, a scaffolding protein known to be involved in the assembly of SOCIC. It was shown that the knockdown of Homer1 suppressed not only store-operated Ca^{2+} entry, but also proliferation and migration of vascular smooth muscles cells as well as neointima formation (Jia, Rodriguez, Williams, & Yuan, 2017). However, in contractile vascular smooth muscle cells freshly isolated from mesenteric artery, store-operated Ca^{2+} entry required TRPC1 but not Orai1 (Shi et al., 2017).

Importantly, regardless of the modes of activation and channels involved, store-operated channel gating occurs at specialized PM domains, likely lipid rafts, through interaction with polymerized STIM1 situated on the ER membrane (Vaca, 2010), making them all STIM-regulated channels. As described above, the ER-PM junctions also contain junctate, capable of interacting with both STIM1-Orai1 complex (Srikanth et al., 2012) and IP_3 receptors / TRPCs (Stamboulian et al., 2005; Treves et al., 2004, 2010). On the other hand, in spite of the inter-dependence between TRPC and Orai proteins, ample studies have revealed distinct cellular and physiological functions between channels formed by Orai’s and TRPCs (Cheng, Ong, Liu, & Ambudkar, 2013; Ong, Jang, & Ambudkar, 2012). The interactions of TRPC, Orai and STIM proteins and their contributions to store- and receptor-operated Ca^{2+} entry will continue to be hot topics of future investigations.

3. Small molecular probes of TRPC

3.1. Physiological function and pathophysiological relevance

The TRPC channels have well-recognized roles in many cell signaling pathways that impact the function of diverse cells and tissues in physiology and diseases. Numerous studies have provided very rich information concerning the physiological significance and pathophysiological roles of individual TRPC isoforms. Many of these studies have been included in recent comprehensive review articles and book chapters that focus on specific organ/tissue system or disease, including cardiovascular system (Yue et al., 2015; Alonso-Carbajo et al., 2017; Xiao, Liu, Shen, Cao, & Li, 2017; Avila-Medina et al., 2018), with emphasis on vascular endothelial and smooth muscle cells (Beech, 2013; Earley & Brayden, 2015; Ampem et al., 2016; Grayson, Murphy, & Sandow, 2017), cardiac remodeling (Falcon et al., 2019), cardiac fibrosis (Numaga-Tomita et al., 2017), atrial fibrillation (Han & Li, 2018) and therapeutic angiogenesis (Moccia, Lucariello, & Guerra, 2018); skeletal muscles (Numaga-Tomita et al., 2019; Sauc & Frieden, 2017); lung and lung diseases (Smith, Ayon, Tang, Makino, & Yuan, 2016; Malczyk et al., 2017; Dietrich, Steinritz, & Gudermann, 2017); kidney and kidney diseases (Schlondorff, 2017; Staruschenko, Spires, & Palygin, 2019; Zhou & Greka, 2016); salivary gland physiology and dysfunction (Ambudkar, 2016),

reproduction and sperm function (Götz, Qiao, Beck, & Boehm, 2017; Kumar et al., 2018); immune system and inflammation (Ramirez et al., 2018); and many different aspects of nervous systems and neurological diseases, e. g. neurological functions (Sun et al., 2014); neurotransmission and hormone sensing (Kelly, Qiu, & Ronnekleiv, 2018) as well as glucose sensing (Fioramonti, Chrétien, Leloup, & Pénicaud, 2017) in the hypothalamus, neural development (Feng, He, Li, & Wang, 2015; Tai & Jia, 2017), neurological diseases especially neurodegeneration (Pchitskaya, Popugaeva, & Bezprozvanny, 2018; Secondo, Bagetta, & Amantea, 2018; Wang et al., 2017), Alzheimer's disease (Lu, He, & Wang, 2017); Parkinson's disease (Sukumaran, Sun, Schaar, Selvaraj, & Singh, 2017), seizure and excitotoxicity (Zheng & Phelan, 2014), stroke (Zhang & Liao, 2015), brain white matter function and ischemia (Cornillot, Giacco, & Hamilton, 2019), and neuropsychiatric diseases (Griesi-Oliveira, Suzuki, & Muotri, 2017; Zeng, Tian, & Xiao, 2016). The involvement of TRPC channels in cancer proliferation, invasion, and chemoresistance is also nicely covered in recent reviews [He & Ma, 2016; Gaunt, Vasudev, & Beech, 2016; Jardin & Rosado, 2016; Li & Ding, 2017; Zhan & Shi, 2017]. Readers are referred to these articles for details about TRPC channel contribution in various physiological systems and cell types and their relevance to different types of diseases. It is important to point out that one of the major caveats of many of the previous research on TRPC channels was the lack of good pharmacology. Therefore, the conclusions were mainly based on genetic evidence through phenotype analysis of naturally occurring mutations or gene knockout or knockdown, examining expression and sometimes using blockers that are unspecific. Clearly the genetic based approaches suffer from compensatory changes that may not directly reflect the TRPC function.

3.2. TRPC drug discovery

Given the relatively widespread expression of TRPC channels in many tissues, their contributions to store- and/or receptor-operated Ca^{2+} entry, and their implications in diverse physiological functions in a wide range of systems, TRPCs have gained attention as potential therapeutic targets for treating cardiovascular disorders, endocrine diseases, neurological disorders, chronic kidney disease, pain, cancer and several other pathological conditions. As pointed out before, mammalian TRPC channels are activated downstream from receptors that signal through the PLC pathway, which involves either $G_{q/11}$ proteins or receptor tyrosine kinases. Nearly all second messengers associated with the PLC pathway exert some roles in TRPC channel activation. For example, diacylglycerols (DAGs) may directly activate all TRPC channels, despite that for TRPC4/5, this requires specific conditions (Hofmann et al., 1999; Okada et al., 1999; Storch et al., 2017); IP_3 could activate TRPC3 and TRPC5 in an IP_3 receptor-dependent manner, via perhaps a direct interaction between the N-terminus of the IP_3 receptor and the CIRB motif of the TRPC (Kanki et al., 2001; Kiselyov et al., 1998; Tang et al., 2001; Zhang et al., 2001); elevation in $[Ca^{2+}]_c$ either directly activates or potentiates the activation of TRPC1, C4, C5, or C6 (Shi et al., 2004; Cheng et al., 2008; Blair et al., 2009; Gross et al., 2009; Tian et al., 2014; Thakur et al., 2016), but further increased $[Ca^{2+}]_c$ can also inhibit TRPC channel function (Ordaz et al., 2005; Shi et al., 2004; Singh et al., 2002; Thakur et al., 2016; Thyagarajan et al., 2001; Zhang et al., 2001). Moreover, the substrate of PLC, PIP_2, also exerts complex effects on TRPC channels, including both some levels of dependence on the presence of PIP_2 for

channel activation and also some inhibition by the lipid (Imai et al., 2012; Kim et al., 2008; Lemonnier et al., 2008; Otsuguro et al., 2008; Shi et al., 2012; Thakur et al., 2016). Among these factors, only DAGs have been exploited in drug development to create new analogs that activate TRPC3 channels (Lichtenegger et al., 2018; Tiapko, Bacsa, de la Cruz, Glasnov, & Groschner, 2016). Furthermore, the receptor-operated activation of TRPC4/5 channels also includes $G_{i/o}$-coupled receptors and the PTX-sensitive G_i and G_o proteins (Thakur et al., 2016).

Because the molecular identification of TRPC channels preceded their functional characterization, the pharmacology of TRPC channels had lagged behind, hindering the full understanding of their physiological and pathological contributions in native systems. In recent years, however, there has been an explosion of small molecular probes, including both natural and synthetic compounds, identified to exhibit specific activities on selective subtypes of TRPC channels, owning to the extraordinary efforts from both academic laboratories and pharmaceutical industry. To date, a series of validated TRPC probes have been developed to facilitate the exploration of the channels' function in various native systems and the potential of these nonselective cation channels as therapeutic targets through synthetic small molecule inhibitors or activators. Herein, we summarize these novel probes and discuss their impact in the context of cardiovascular, pulmonary, neurological, and renal diseases and cancer, attempting to delineate a framework for further exploration of TRPC-based therapies. The names, structures, and effective concentrations of these molecules are shown in Tables 1–4. To facilitate future studies, we highlight those with reasonably good selectivity on specific TRPC subtypes or subgroups and likelihood of direct actions on the channel function. Users are advised to examine the original publications (referenced in the tables) for details.

3.2.1. Modulators for cardiovascular disorders—In cardiovascular system, TRPC channels are directly or indirectly regulated by several endogenous factors involved in the pathogenesis of various cardiovascular disorders. Recent studies show that brain-derived neurotrophic factor (**BDNF**) protects against myocardial infarction through TRPC3/6 channels (Hang et al., 2015); prolonged activation of the exchange protein directly activated by cAMP (**EPAC**) causes upregulation in the expression of TRPC3 and TRPC4 proteins and enhanced store-operated Ca^{2+} entry in adult rat ventricular cardiomyocytes, which amounts to a proarrhythmic effect (Dominguez-Rodriguez et al., 2015); Transforming growth factor beta 1 (**TGFβ1**) induces upregulation of TRPC6 in vascular smooth muscle cells and in turn stress fiber formation that may underlie pathogenesis of vascular fibrosis (Park et al., 2017); lysophosphatidylcholine (**LPC**) activates TRPC6 channels in bovine aortic endothelial cells to inhibit endothelial cell migration and thereby delaying the healing of arterial injuries (Chaudhuri et al., 2008; Chaudhuri, Rosenbaum, Birnbaumer, & Graham, 2017). Other factors, such as atrial natriuretic peptide (**ANP**), **endoglin**, **MicroRNAs**, nitric oxide (**NO**) and **protein kinase G**, have also been shown to participate in various pathophysiological mechanisms by modulating TRPC channel function and/or expression [Chen et al., 2013; Feng, Xu, & Wang, 2018; Morine et al., 2016; Zhang et al., 2014].

In addition, several marketed drugs have recently been found to affect cardiovascular diseases by regulating function and/or expression of TRPC channels. For instance,

spironolactone, a mineralocorticoid receptor inhibitor, was reported to attenuate coronary TRPC expression under long-term usage in the model of metabolic syndrome, which may help reduce coronary pathology (Li et al., 2017). **Salvianolic acid B** was found to attenuate doxorubicin-induced ER stress by inhibiting TRPC3/6-mediated Ca^{2+} overload in cardiomyocytes (Chen et al., 2017). Similarly, **chlorogenic acid** was shown to protect endothelial cells against LPC injury by attenuating TRPC1 expression and thereby inhibiting atherosclerosis (Jung, Im, Song, & Bae, 2017). Moreover, **losartan** effectively prevented the downregulation in endothelial cells and upregulation in smooth muscle cells of TRPC1 and TRPC6 in thoracic aortas of sinoaortic denervation rats and thereby the vasomotor function impairment (Liang, Zhong, Miao, Wu, & Liu, 2018).

In view of the crucial role of TRPC channels in cardiovascular pathogenesis, development of new TRPC modulators is required. In many of the early studies, **SKF-96365** was used as a general TRPC channel antagonist, and therefore was also widely used in the study of cardiovascular disorders (Liu et al., 2016; Sabourin, Bartoli, Antigny, Gomez, & Benitah, 2016). Subsequently, **Pyr3**, a pyrazole compound that potently and selectively antagonizes TRPC3 (IC_{50} = 0.7 μM), was suggested to be of pharmaceutical potential in treating TRPC3-related diseases, like cardiac hypertrophy, and preventing stent-induced arterial remodeling (Kiyonaka et al., 2009; Koenig et al., 2013). However, because **Pyr3** inhibits TRPC3 and Orai channels with equal potency, structural analogs had been developed, with **Pyr10** showing about 18-fold selectivity for TRPC3 than Orai1 (Schleifer et al., 2012). **Pyr10** exhibited an IC_{50} of 0.72 μM at Ca^{2+} entry mediated by TRPC3 while at 10 μM, it only inhibited TRPC4, C5, and C6 by less than 50% (Schleifer et al., 2012). Moreover, the combined TRPC3 and TRPC6 blockade by selective TRPC3/6 antagonists (**GSK2332255B** and **GSK2833503A**, IC_{50}, 3–21 nM against TRPC3 and TRPC6) was shown to inhibit pathological cardiac hypertrophy (Seo et al., 2014). **GSK2332255B** and **GSK2833503A** display more than 100-fold selectivity over other calcium-permeable channels and 100-fold greater potency at TRPC3 compared with Pyr3. Moreover, they dose-dependently block cell hypertrophy signaling triggered by angiotensin II (Ang II) or endothelin-1 in neonatal and adult cardiac myocytes (Seo et al., 2014). Notably, the latest study has described a novel TRPC6-specific inhibitor (**BI 749327)** with IC_{50} of 13 nM and efficient oral bioavailability, which is able to protect cardiac function and reduce chamber dilation and fibrosis under abnormal hemodynamic stress. **BI 749327** is 85-fold more selective for TRPC6 than TRPC3 (IC_{50} = 1.1 μM) and 42-fold over TRPC7 (IC_{50} = 0.55 μM). **BI 749327** inhibited NFAT activation in HEK293T cells expressing wild-type or gain-of-function TRPC6 mutants, suppressed Ang II-induced expression of prohypertrophic genes in isolated myocytes, and improved heart function with reduced pathology in mice subjected to sustained pressure overload (Lin et al., 2019).

3.2.2. Modulators for pulmonary arterial hypertension (PAH)—Pulmonary circulation plays an essential role in gas exchange that supports all physiological activities. Dysfunction of pulmonary circulation often causes several progressive diseases such as pulmonary arterial hypertension (PAH) among others (Lambert et al., 2018). Ca^{2+} plays a key role in pulmonary circulation and TRPC channels contribute to the generation of Ca^{2+} signals in multiple lung tissues. Numerous studies have demonstrated the potential of

modulating TRPC channels in the treatment of PAH. Several endogenous and exogenous factors have been found to regulate TRPC channels in pulmonary arterial smooth muscle cells (PASMCs). Lipopolysaccharide (**LPS**) and bone morphogenetic protein 4 (**BMP4**), for example, induce PASMC proliferation through upregulation of expression of TRPC1, TRPC6, and perhaps also TRPC4 (Boucherat & Bonnet, 2015; Jiang et al., 2016; Wang et al., 2015; Zhang et al., 2014). On the other hand, **Guanabenz** (100 μM) has been shown to elicit Ca^{2+} influx in human airway epithelial cells independently of the α2-adrenoceptors, the drug's known clinic target. Based on the effects of isoform specific TRPC siRNAs, it was suggested that **guanabenz** may directly activate TRPC6, but not TRPC1. Subsequently, the $[Ca^{2+}]_c$ increase evoked by **guanabenz** causes activation of Ca^{2+}-activated Cl^- channels in these cells (Bertrand et al., 2015).

Because of the prominent expression of TRPC6 in lung tissues and its involvement in lung function and diseases, including hypoxic vasoconstriction, lung ischemia-reperfusion edema (LIRE) and idiopathic PAH (IPAH) (Weissmann et al., 2006; Weissmann et al., 2012; Yu et al., 2004), it would be highly desirable to verify the therapeutic value of inhibiting TRPC6 channels in lung diseases using pharmacological tools. A number of compounds, such as **SKF-96365**, **econazole**, **W7**, **compound 8009–5364, norgestimate,** and **sildenafil,** have been shown to inhibit TRPC6 through either direct or indirect mechanisms (Bon & Beech, 2013; Harteneck & Gollasch, 2011; Lu et al., 2010; Miehe et al., 2012; Urban, Hill, Wang, Kuebler, & Schaefer, 2012; Wang et al., 2013). However, limitations exist due to their low potency and poor selectivity. In addition, a series of **anilino-thiazoles** have been shown to inhibit TRPC3/6 channels with high potency (Washburn et al., 2013). Although their low oral bioavailability makes them poor candidates of chronic pharmacological studies, some of the analogs should still be excellent research tools for studying TRPC3 and C6 channels.

Recently, **SAR7334** was identified as a potent TRPC6 inhibitor (IC_{50} = 7.9 nM) from a series of aminoindanol derivatives. The compound exhibits reasonable selectivity for TRPC6 over TRPC3/7 channels (36–29 fold, IC_{50} = 282 nM for C3 and 226 nM for C7) and a good oral pharmacokinetic profile (Maier et al., 2015). In isolated perfused mouse lungs, **SAR7334** blocked acute hypoxic pulmonary vasoconstriction in a TRPC6-dependent fashion. Furthermore, a bicyclo[4.3.0]nonane derivative, **DS88790512**, has been reported to inhibit TRPC6 with an IC_{50} of 11 nM. This compound only weakly inhibited hERG and $hNa_V1.5$ channels at high micromolar concentrations and it displayed good oral bioavailability (Motoyama et al., 2018). However, the selectivity among TRPC channels is not known and no information is available about its therapeutic potentials. Larixyl *N*-methylcarbamate, **SH045**, derived from an abundant natural product, (+)-larixol, has also been shown to block TRPC6 channels expressed in cell lines at low nanomolar concentrations (IC_{50} = 5.8–62 nM depending on the assays used). The compound exhibited some selectivity over TRPC7 (~3.5 fold) and more so over TRPC3 (~13 fold). In rat PASMCs, **SH045** inhibited OAG-induced $[Ca^{2+}]_c$ increase with an IC_{50} of 340 nM, and in explanted mouse lungs, the treatment of **SH045** (5 μM) attenuated lung ischemia-reperfusion edema (LIRE) (Hafner et al., 2018). Likewise, **larixyl acetate**, which inhibited heterologously expressed TRPC6 with IC_{50} values of 0.1–0.6 μM and suppressed DAG-evoked native TRPC6-like Ca^{2+} signals in rat PASMCs, also prevented acute hypoxia-

induced vasoconstriction in isolated mouse lungs when applied at 5 μM (Urban et al., 2016). **Larixyl acetate** is one of the main ingredients of larch resin. The compound exhibited 12- and 5-fold selectivity for TRPC6 over TRPC3 and C7, respectively.

In addition, several marketed drugs have been shown to be potential inhibitors of TRPC6 and beneficial for PAH therapy. Sodium tanshinone IIA sulfonate (**STS**), a medicine with high efficiency on chronic hypoxic pulmonary hypertension, was recently recognized to have inhibitory effect on TRPC6 channels, and shown to suppress hypoxia-induced enhancement of store-operated Ca^{2+} entry in PASMCs (Wang et al., 2013; Jiang et al., 2016). Moreover, Topotecan (**TPT**), a topoisomerase inhibitor that is used to treat several cancers, was found to ameliorate the hypoxia-induced PAH by suppressing the upregulation in the expression of hypoxia-inducible factor 1α (HIF-1α) as well as TRPC1, C4, and C6 (Jiang et al., 2018). This effect required low concentrations of **TPT** (1–10 nM) and extended treatment time (≥24 h), which inhibited the proliferation of PASMCs.

3.2.3. Modulators for neurological disorders—Neurons exhibit the highest expression of various TRPC subtypes, as compared to other cell types, and this is even more true during the early developmental stage (Li et al., 1999). Essentially, any factor that triggers PLC activation can also activate the TRPC channels in neurons, meaning that many of the neurotransmitters and neuromodulators that signal through $G_{q/11}$ or tyrosine kinases, or even $G_{i/o}$ proteins if TRPC4/5 channels are involved (Jeon et al., 2012; Jeon et al., 2016; Thakur et al., 2016), may serve as endogenous triggers for TRPC channel activation, through which they may be linked to membrane excitability and Ca^{2+} signaling. For example, insulin and leptin can stimulate anorexigenic proopiomelanocortin neurons to participate in energy homeostasis through activation of TRPC channels (Qiu et al., 2014; Qiu, Wagner, Ronnekleiv, & Kelly, 2018). Several endogenous factors implicated in pathogenesis of neurological diseases may act through TRPC channels, including S1P, nerve growth factor, glutamate, serotonin and dopaminergic neurotoxins (Lepannetier et al., 2018; Shimizu et al., 2018; Shirakawa et al., 2017; Sukumaran, Sun, Antonson, & Singh, 2018; Yamamoto, Hatano, Sugai, & Kato, 2014).

A number of small molecular probes of TRPC channels have been found to be effective in animal models of neurological disorders. The first selective small molecular probe for TRPC4/5 channels, **ML204,** was identified out of a high-throughput screen effort. **ML204** blocked TRPC4 and C5 channels in both fluorescent Ca^{2+} and electrophysiological assays. It showed an IC_{50} of 0.96 μM for TRPC4β channels in the Ca^{2+} assay when the channel was activated via stimulation of μOR by the μ agonist, DAMGO. The IC_{50} was 2.6 μM in the electrophysiological assay (Miller et al., 2011). **ML204** has been a valuable probe since its discovery. In a rat visceral pain model induced by colonic exposure to mustard oil, oral feeding or intraperitoneal (i. p.) administration of **ML204** led to dose-dependent relief in pain, without any adverse cardiovascular or other side effects (Westlund et al., 2014). In addition, microinjection of **ML204** into amygdala of neuropathic pain rats suppressed mechanical hypersensitivity of the injured limb, as well as affective-like pain behavior, in a dose-dependent manner, without obvious side effects (Wei, Sagalajev, Yüzer, Koivisto, & Pertovaara, 2015). Furthermore, **ML204** blocked Ca^{2+} entry and cytotoxicity induced by maitotoxin in human neuronal stem cells (Boente-Juncal, Vale, Alfonso, & Botana, 2018),

although **maitotoxin** has been reported to evoke non-selective cation currents in mammalian cells and *Xenopus oocytes* in a manner that depends on the expression of TRPC1, but not TRPC4 (Brereton, Chen, Rychkov, Harland, & Barritt, 2001; Flores et al., 2017).

The same high throughput screen as above also identified **M084**, a 2-aminobenzimidazole derivative, as another TRPC4/5 inhibitor. Although not as potent as **ML204**, **M084** has better pharmacokinetic properties and provides an alternative structural scaffold for further development of more potent TRPC4/5-selective antagonists. **M084** has similar potency at TRPC4 and TRPC5 channels with IC_{50} values of 10.3 ± 0.5 and 8.2 ± 0.7 μM, respectively, when the channels were stimulated via activation of μOR. **M084** shows a weak inhibitory effect on TRPC3 with IC_{50} of ~50 μM (Zhu et al., 2015). Since TRPC4 and TRPC5 had been implicated in fear and anxiety-like behaviors (Riccio et al., 2009; Riccio et al., 2014), inhibiting these channels with the TRPC4/5 blocker might be antidepressant. Indeed, a single i. p. administration of **M084** in mice resulted in rapid antidepressant and anxiolytic-like effects, which are accompanied with increases in BDNF and phosphorylation of AKT and ERK in prefrontal cortex (Yang et al., 2015). More recently, a more potent TRPC4/5 antagonist, **HC-070**, which is structurally unrelated to **M084**, was also shown to have anxiolytic and antidepressant effects in mice upon oral dosing (Just et al., 2018). **HC-070** selectively inhibits TRPC4 and C5 channels with IC_{50} values of 46.0 ± 3.9 nM and 9.3 ± 0.9 nM, respectively, in the Ca^{2+} influx assay, and weakly inhibits TRPC3 (IC_{50} ~1 μM). It shows good pharmacokinetics and sufficient penetration to brain. In electrophysiological recordings, **HC-070** appears to show even higher potency than in the Ca^{2+} influx assay, yielding IC_{50} values close to or below 1 nM depending on the method of stimulation and the subtype and species of the channel examined. Some of these tests also included TRPC1 for probing the TRPC4–C1 or TRPC5–C1 heteromeric channels (Just et al., 2018). **HC-070** is a structural analog of **HC-608,** also known as **Pico145** and so named because it inhibits TRPC4/5 homomers or TRPC4/5 heteromers in complex with TRPC1 at picomolar concentrations (Rubaiy et al., 2017). In Ca^{2+} influx assay performed in parallel with **HC-070**, **HC-608** exhibited IC_{50} values of 32.5 ± 1.8 nM and 6.2 ± 0.5 nM, respectively, on TRPC4 and TRPC5 homomeric channels (Just et al., 2018). In the study that described **Pico145**, the compound inhibited homomeric TRPC4 or TRPC5, heteromeric TRPC4–C1 or TRPC5–C1, and endogenous TRPC4/5-like channels in cancer cell lines with IC_{50} values that ranged from 9 to 1300 pM, depending on the stimulation method, channel type and the functional assay (Ca^{2+} versus patch clamping) used. Interestingly, **Pico145** appears to be a competitive antagonist when the TRPC4 and TRPC5 channels are activated by **(−)-englerin A**, showing higher IC_{50} values as the concentration of **(−)-englerin A** increases (Rubaiy et al., 2017).

In an effort to determine the molecular target(s) of **ginger extract**, an analeptic in herbal medicine, for its antioxidant effects, TRPC5 was found to be inhibited by the extract and one of its pungent constituents, **[6]-shogaol**, which exhibited an IC_{50} of ~18.3 μM in the electrophysiological assay. Since TRPC5 channels are known to be activated by reactive oxygen species (**ROS**) and nitric oxide (**NO**) in central nervous system (CNS) neurons, the antioxidant effects of the **ginger extract** could be in part mediated by TRPC5 and this property may be applicable to the treatment of neurological diseases (Kim, Hong, Lee, Nam,

& Kim, 2016). More interestingly, **galangin**, a flavonol from galangal which is closely related to ginger, was shown to inhibit TRPC5 with an IC_{50} of 0.45 μM. Other structurally similar natural flavonols either inhibited (**kaempferol** and **quercetin**, IC_{50} of 3.9 μM and 6.5 μM, respectively), or weakly stimulated (**apigenin**), or had no effect (myricetin, apigenin and luteolin) on TRPC5. A synthetic derivative of galangin, **AM12**, inhibited TRPC5 with IC_{50} of 0.28 μM (Naylor et al., 2016). **AM12** can also inhibit TRPC4, but is very weak at the TRPC5–C1 heteromeric channels. Interestingly, **AM12** only inhibited TRPC5 when the channel was activated by Gd^{3+} or **(−)-englerin A**. With the stimulation by S1P or LPC, **AM12** acted more like allosteric activator and enhanced the TRPC5 current (Naylor et al., 2016).

TRPC6 has been shown to play roles in both neural development and neurodegeneration. A number of small molecular probes have shown their effects on brain function through acting at TRPC6 channels. Differing from TRPC4/5, the neuroprotective effect has often been associated with enhancing, rather than inhibiting, TRPC6 function. **Hyperforin**, an active component from Hypericum species including the medicinal plant, *Hypericum perforatum* (**HPer**), also known as St. John's wort, induces Ca^{2+} influx to neurons through TRPC6 channels, **Hyperforin** had been known to have an antidepressive effect with few side-effects through blocking serotonin and norepinephrine uptake via an indirect mechanism (Galeotti, 2017). It was proposed that the Na^+ currents generated by hyperforin activation of TRPC6 may dissipate the Na^+ gradients across the membrane and thereby suppress the neuronal amine uptake. Interestingly, despite the high homology, TRPC3 is not activated by **hyperforin** (Leuner et al., 2007). On the other hand, the roles of **hyperforin** and **HPer** on neurons may not always be dependent on TRPC6. It has been shown that hyperforin induces TRPC6-independent H^+ currents in several cell types and in artificial lipid bilayers not containing any proteins (Sell, Belkacemi, Flockerzi, & Beck, 2014). This latter effect suggests that hyperforin may act as a protonphore, which acidifies the cytoplasm in a voltage-dependent manner and in turn impairs neurotransmitter uptake through the PM Na^+/H^+ exchangers. In DRG neurons from rats that suffered spinal cord injury, **hyperforin** and **HPer** exerted protection through inhibition of TRPM2 and TRPV1 channels (Özdemir, Nazıroğlu, Şenol, & Ghazizadeh, 2016; Uslusoy, Nazıroğlu, & Çiğ, 2017). Despite these findings, **hyperforin** treatment alleviated the negative impacts of chronic unpredictable stress to rats on cognitive function, long-term potentiation of dentate gyrus, and dendrite morphology, including the length of dendrites, density of spines, and number of excitatory synapses; the same treatment of **hyperforin** also restored the expression of TRPC6 to normal in hippocampus, which were markedly reduced in rats subject to chronic stress (Liu, Liu, Qin, Zhu, & Yang, 2015). In rats subjected to middle cerebral artery occlusion to cause transient focal cerebral ischemia, intracerebroventricular injection of **hyperforin** at the onset of injury also mitigated brain damage and the neurological deficits, which were accompanied with the restoration of TRPC6 expression in hippocampus at 24 hr, but not 6 or 12 hr, after the ischemia reperfusion (Lin et al., 2013). Thus, the effect of hyperforin on TRPC6 may include both activation and expression.

Similarly, **calycosin**, as an antioxidant medicinal plant component, also exerts neuroprotective effects against cerebral ischemia by upregulating the expression of TRPC6

(Guo et al., 2017). For both **hyperforin** and **calycosin**, the neuroprotective actions include an inhibition of calpain-mediated degradation of TRPC6 and the restoration of CREB phosphorylation downstream of TRPC6-dependent activation of MAP kinase and CaMKIV pathways (Liu et al., 2015; Guo, Ma, et al., 2017). Moreover, **hyperforin** was reported to activate transcription factor AP-1 in HEK293 cells that stably expressed mouse TRPC6, but not the wild type HEK293 cells, an activity that was mimicked by another TRPC6 agonist, **OAG** (Thiel & Rossler, 2017). The TRPC6-dependent transcriptional regulation also includes c-Jun, c-Fos, with contributions from CREB and MAP kinases.

Furthermore, **tetrahydrohyperforin (IDN5706),** a derivative of hyperforin, was shown to be neuroprotective in the mouse model of Alzheimer's disease and able to overcome the inhibitory effect of Aβ oligomers on field excitatory postsynaptic potential in hippocampal slices (Montecinos-Oliva, Schüller, Parodi, Melo, & Inestrosa, 2014). **Tetrahydrohyperforin** is thought to act through TRPC3/6/7 and $[Ca^{2+}]_c$ elevation to exert its neuroprotective function as the compound shares the same structural moiety with **hyperforin**, **Hyp9** (2,4-diacylphloroglucinol) (Leuner et al., 2010), and **DAG** (Sawamura et al., 2016), with a potential pharmacophore of two hydrogen bond acceptors, one hydrogen bond donor, and an extended lipophilic contact surface.

Additionally, a group of piperazine-derived compounds, represented by **PPZ1** and **PPZ2,** were reported to activate TRPC3/6/7 channels and trigger Ca^{2+} signaling, which in turn resulted in neurotrophic effects such as promotion of neurite outgrowth and neuronal survival under serum-deprived conditions (Sawamura et al., 2016). **PPZ1** activated TRPC3, C6, and C7 channels with EC_{50} values of 57.0, 67.3, and 45.9 μM, respectively; **PPZ2** had EC_{50} values of 10.2, 8.4, and 2.9 μM, respectively. However, despite the apparent low potency, the piperazine compounds conferred neuroprotection at submicromolar concentrations of 3–300 nM. Higher concentrations of **PPZ2** was found to be toxic to neurons. The neuroprotective effect of the piperazine compounds also required MAP kinases, CaMKs, and CREB.

Other TRPC3/6/7 activators include a small 1,3-dihydro-2H-benzo [d]imidazol-2-one-based potent agonist (**GSK1702934A**), which has been briefly described in the abstract form by GlaxoSmithKline-US as a tool to directly activate TRPC3/6 channels independently of PLC signaling. **GSK1702934A** induces currents in HEK293 cells expressing human TRPC3 and C6 with EC_{50} values of 80 and 440 nM (patchclamp), respectively (Xu et al., 2013). The compound has been successfully used by others to activate TRPC3, C6, and C7 channels (Ding et al., 2018; Doleschal et al., 2015). An improved method in the synthesis of **GSK1702934A** and its structural analogs has been described (de la Cruz et al., 2017). Moreover, an azobenzene photoswitch moiety has been added to the main scaffold of GSK1702934A to create a light-sensitive TRPC agonist, **OptoBI-1**, which allows for photoactivation of TRPC3/6/7, but not TRPC4/5, channels. Interestingly, light treatment of hippocampal neurons exposed to **OptoBI-1** suppressed action potential firing elicited by current injection (Tiapko et al., 2019). Furthermore, the latest study has reported a positive allosteric TRPC6 modulator, **C20**, that selectively exaggerate TRPC6-dependent signals. Unlike OAG and many other TRPC3/6/7 drugs, **C20** acts at TRPC6 without affecting the closely related TRPC3 and C7. Detailed analysis revealed that **C20** rather functions as an

enhancer of TRPC6 activation than a direct activator by itself, showing its role as an allosteric regulator of TRPC6 that enables low basal concentration of DAG to elicit TRPC6 channel activation (Hafner, Urban, & Schaefer, 2019). Moreover, recent studies have reported that mycotoxins, such as **zeranol** and **aflatoxin B1**, induce COX-2 expression by mediating TRPC3 activation in the placental cells JEG-3. This poses a potential threat to pregnant women because TRPC3 is commonly expressed in the reproductive tissues in human and plays a critical role in the female reproductive processes (Zhu, Tan, & Leung, 2016; Zhu, Yao, & Leung, 2016). However, at this point, no information is available about how the above drugs affect neurons and neurological functions.

Indeed, it is not always beneficial to the neurological function to activate TRPC6 channels. For example, TRPC6 activation is involved in endothelial dysfunction in concussions, or mild, traumatic brain injury. With the treatment of **larixyl acetate,** which inhibits TRPC6 as described above, the damage on aortic endothelial cells was alleviated (Chen et al., 2019).

3.2.4. Modulators for kidney diseases—Growing evidence has implicated the role of TRPC channels in the kidney and the development of kidney diseases. Most prominently, mutations in TRPC6 are linked to familial focal segmental glomerulosclerosis (FSGS) (Reiser et al., 2005; Winn et al., 2005). While many of these mutations exhibit gain-of-function in channel activity, some of them also display loss-of-function phenotypes (Riehle et al., 2016). Thus, either too high or too low a TRPC6 channel activity seems to be detrimental to kidney function. The TRPC6 mutations mainly affect the filtering function of podocytes, where the slit diaphragm formed between feet or processes of the podocytes blocks the passage of large molecules, such as proteins, to the proximal tubule, but allows small molecules like glucose, ions, and water to go through. As a key component of the slit diaphragm, TRPC6 is critical for glomerular development, allowing the terminally differentiated podocytes to properly interface with glomerular capillaries (Liu et al., 2015). The mutations in TRPC6 disrupt the slit diaphragm formation, causing proteins to leak into the urine, i. e. proteinuria. Therefore, manipulation of the TRPC6 function should bring benefit to FSGS.

Intriguingly, TRPC5 has also been implicated in the pathogenesis of progressive kidney diseases, including FSGS (Schaldecker et al., 2013; Zhou et al., 2017). It was suggested that TRPC5 and TRPC6 may antagonize each other on regulating actin cytoskeleton, and thereby the contractility of podocytes, via Rac1 and RhoA, respectively (Greka & Mundel, 2011). The balance between podocyte TRPC5 and C6 activities then may be the most critical for glomerular filtration barrier function. However, the role of TRPC5 in renal function was recently challenged by another research group who examined TRPC5 gain-in-function mutant mice but found no increase in proteinuria even under conditions of kidney injury (Wang et al., 2018).

Based on the premise for TRPC5 to be involved in progressive kidney disease, a specific TRPC5 inhibitor, **AC1903**, (IC_{50} = 14.7 μM, by patch clamp recording) was developed. **AC1903** shares the benzimidazole backbone with **M084** (Zhu et al., 2015) and **clemizole** (Richter, Schaefer, & Hill, 2014a). It exerted a very weak effect on TRPC4 and no effect on TRPC6. In the rat model of FSGS, chronic administration of **AC1903** attenuated the severe

proteinuria and protected podocytes from damage. In the hypertensive proteinuric kidney disease model, **AC1903** also showed therapeutic benefit (Zhou et al., 2017). Another TRPC5 inhibitor, **GFB-887**, developed by a biotechnology company, Goldfinch Bio, was also claimed to suppress pathogenic podocyte motility and proteinuria in both a hypertension-induced FSGS rat model without altering blood pressure and a non-hypertensive FSGS model by puromycin aminonucleoside nephrosis. These results demonstrate a direct glomerular protection *in vivo* by **GFB-887** and the drug's potential in treating chronic kidney disease. **GFB-887** is described as a potent, selective and orally bioavailable small molecule TRPC5 antagonist; however, its structure has not been disclosed (Mundel et al., 2019).

For TRPC6, **20-hydroxyeicosatetraenoic acid** (**20-HETE**), a known agonist of TRPC6 channels (Basora, Boulay, Bilodeau, Rousseau, & Payet, 2003) and an agent that causes podocyte apoptosis (Eid et al., 2009), has been shown to activate TRPC6-like channels and increase TRPC6 surface abundance in cultured podocytes when applied exogenously. **20-HETE** is a metabolite of arachidonic acid and known to regulate glomerular function during tubuloglomerular feedback. This could represent an endogenous cue of regulating renal function through, at least in part, TRPC6 in podocytes. However, in the cultured podocytes, **20-HETE** does not appear to activate TRPC6 directly; the activation required ROS production and G proteins (Roshanravan, Kim, & Dryer, 2016). Consistent with the detrimental effect of TRPC6 overactivation on kidney, **(+)-conocarpan**, a benzofuran neolignane found in many medicinal plants, was shown to induce apoptosis of human proximal tubular epithelial (HK-2) cells through TRPC6, with accompanied $[Ca^{2+}]_c$ increase and caspase-3 activation. In whole-cell recordings, **(+)-conocarpan** evoked currents in TRPC6-expressing HEK293 cells with an EC_{50} of 6.01 μM (Yang et al., 2019). Because TRPC6 function is linked to NFAT activation through calcineurin, the calcineurin inhibitor, **FK506**, has been tested for its ability to ameliorate podocyte injury in the rat model of type 2 diabetic nephropathy. With the long-term (12 weeks) administration, **FK506** was found to mitigate many of the hallmarks of nephropathy and this was accompanied with attenuation of the upregulation of TRPC6 and NFAT expression found in untreated diabetic animals (Ma, Liu, Jiang, Yu, & Song, 2015). Additionally, an antidiabetic drug, **rosiglitazone (RSG)**, has been shown to inhibit the proliferation of rat glomerular mesangial cells (HBZY-1) induced by Ang II. Here, the drug was thought to activate PPAR-γ, which upregulates RGS4 expression and in turn reduces G_q signaling. The decreased G_q activity then results in lower activation of TRPC1 and TRPC6 by Ang II (Wei et al., 2017). Also acting through PPAR-γ, the protein kinase G activator, **sildenafil**, was shown to prevent proteinuria through suppressing the increase in the podocyte expression of TRPC6 in rats with nephropathy induced by adriamycin and mice suffering from renal injury due to hyperglycemia. The PPAR-γ activator, **pioglitazone**, had similar protective effects. In this case, PPAR-γ was thought to act at the TRPC6 promoter to suppress its expression (Sonneveld et al., 2017). However, in contrast to the above scenarios, downregulation of TRPC6 has been implicated in kidney injury associated with iatrogenic hyperinsulinemia due to long-term use of insulin to treat diabetes. The damage was found to be alleviated by **astragaloside IV**, a type of saponin from *Astragalus membranaceus* (Fisch) Bunge, which

also ameliorated the downregulation of TRPC6 expression seen in the iatrogenic hyperinsulinemia model (He et al., 2018).

Some of the direct antagonists of TRPC6, or of TRPC3/6/7, have also been tested for their effect on kidney or renal cells. For example, **BI 749327** was shown to dose dependently reduce renal fibrosis and changes in the gene expression pattern found in the mouse model of unilateral ureteral obstruction (Lin et al., 2019). **SAR7334** not only diminished TGFβ1-induced fibrogenesis of HK-2 cells (Zhou et al., 2018), but also protected renal proximal tubular cells from apoptotic death induced by oxidative stress (Hou et al., 2018). In a model of glomerular permeability response to the drop of oncotic pressure, **SAR7334** also attenuated the inhibitory action of Ang II on glomeruli volume increase (Ilatovskaya, Palygin, Levchenko, Endres, & Staruschenko, 2017). Additionally, two novel TRPC6 inhibitors isolated from *Ribes manshuricum*, **Ribemansides A and B**, which inhibited TRPC6 activity with IC_{50} values of 24.5 and 25.6 μM, respectively, were also shown to suppress TGF-β1-induced fibrogenesis in the HK-2 cells in a similar fashion as **SAR7334** (Zhou et al., 2018). Recently, BTDM was reported to be a potent inhibitor of TRPC3 (IC_{50} = 11 nM) and TRPC6 (IC_{50} = 10 nM), as well as some of the gain-of-function TRPC6 mutants found in FSGS; the compound directly binds to TRPC6 (Tang et al., 2018). However, the effects of this drug on kidney cells and kidney disease models have yet to be reported.

Collectively speaking, small molecular probes that inhibit TRPC5 or TRPC6 either directly or indirectly through downregulation of the channel's expression, function or its downstream signaling pathways have shown promising protective effects in kidney diseases. Further investigation into the roles of these channels in different renal cell types and pathogenesis of various renal diseases, as well as the effects of TRPC5 and C6 modulators on kidney dysfunction, will bring new insights into therapeutic development. In this context, the recently reported series of **pyrazolopyrimidines,** developed based on a lead compound identified using a cell-based high throughput screening assay against TRPC6, are worth noting. One of the modified analogs, **4n**, designed based on the lead compound, exhibits the most efficacious activation on TRPC3 (EC_{50} = 19 nM), followed by TRPC7 (EC_{50} = 90 nM) and TRPC6 (EC_{50} = 1.39 μM) (Qu et al., 2017). Further modifications of this series also gave rise to a potent partial agonist, **14a**, which essentially suppresses TRPC6 activity with an IC_{50} of 1 μM (Ding et al., 2018). Given that the agonists from this series activated native TRPC3/6 channels in rat glomerular mesangial cells (Qu et al., 2017), it is possible that this series of compounds may lead to more effective and specific TRPC modulators and contribute to the development of new treatments for renal diseases.

3.2.5. Modulators for cancers—TRPC channels have been implicated in the pathogenesis of various cancers [He & Ma, 2016; Gaunt et al., 2016; Jardin & Rosado, 2016; Li & Ding, 2017; Zhan & Shi, 2017]. These Ca^{2+}-permeable nonselective cation channels likely participate in tumor development to different extents by affecting cell metabolism, controlling cell proliferation, promoting angiogenesis, and supporting cell migration and invasion during tumor progression. One of the common effects that had been frequently seen for TRPC channels is the role on epithelial mesenchymal transition (EMT) (Ge et al., 2018; Xu et al., 2018; Xu, Liu, Li, Ma, & Zhang, 2017), but the underlying

mechanism remains to be elucidated. In addition, as described earlier, TRPC5 has been implicated in chemoresistance (Ma et al., 2012; Wang et al., 2015)

Although much evidence about the involvement of individual TRPC subtypes in various cancers have been obtained by the examination of mRNA and protein expression and gene silencing with siRNA, pharmacological evidence is also accumulating. Indeed, some TRPCs have been shown to be expressed at high levels in certain cancers and at particular stages of cancer progression, making them potential diagnostic markers (Jiang et al., 2013; Zeng, Yuan, Yang, Atkin, & Xu, 2013). Among these is TRPC4 in many renal cell carcinomas (Akbulut et al., 2015). Interestingly, a sesquiterpene agent, **(−)-englerin A**, a natural product obtained from *Phyllanthus engleri* and known to be highly toxic to renal cell carcinoma, has been found to be a highly selective and nanomolar-potent TRPC4 and C5 activator, with EC_{50} values of 11.2 nM and 7.6 nM, respectively (Akbulut et al., 2015). Although it was originally thought that **(−)-englerin A** inhibits proliferation of tumor cells that express high levels of TRPC4 or TRPC5 by promoting Ca^{2+} entry and causing intracellular Ca^{2+} overload, a more recently study suggests that **(−)-englerin A** may confer cancer cell cytotoxicity through sustained Na^{+} entry via activation of heteromeric TRPC1–C4 channels (Ludlow et al., 2017). **(−)-Englerin A** has been found to be extremely toxic *in vivo* due to its stability in the plasma (Carson et al., 2015), or it is rapidly metabolized to an inactive product, (−)-englerin B (Minard et al., 2018). Either will preclude its clinical use. Therefore, chemical synthesis of **(−)-englerin A** and its analogs has been undertaken in order to improve its bioavailability and better understand the mechanism of its action (Radtke et al., 2011). Similar to the situation for the **pyrazolopyrimidine** compounds described above, one of the analogs, **A54**, was found to reverse the action of the original compound. Instead of activation, **A54** inhibited **(−)-englerin A**-evoked $[Ca^{2+}]_c$ increase in A498 renal cell carcinoma with an IC_{50} of 62 nM in a competitive manner. It also strongly blocked **(−)-englerin A**-evoked currents of TRPC1–C4 heteromeric channels and TRPC5 homomeric channels, and weakly inhibited the activation of TRPC4 homomers. On the other hand, **A54** potentiated the activation of TRPC4 by S1P and that of TRPC5 by Gd^{3+}. These results indicate that minor modifications of the side chain in the compound can enable drastic changes in the outcome of the ligand binding (Rubaiy et al., 2018).

Similar to (−)-englerin A, another natural product, **Tonantzitlolone** (**TZL**), from Euphorbiaceae, also exerts cytotoxicity towards certain types of cancers including renal cell carcinoma lines. Although chemically distinct, **TZL** was shown to also activate TRPC4, C5, C1–C4 and C1–C5 heteromeric channels with EC_{50} values of 123 nM, 83 nM, 140 nM, and 61 nM, respectively. Moreover, the effects of **TZL** were reversible on wash-out and effectively inhibited by the TRPC1/4/5 inhibitor, **Pico145**. Therefore, **TZL** offers another option of achieving selective cytotoxicity against certain types of cancer cells through activating TRPC1/4/5 (Rubaiy et al., 2018).

To more specifically target TRPC5, **riluzole** has been identified as a selective TRPC5 agonist from a library of approved drugs and natural compounds. It was reported to activate TRPC5 with an EC_{50} of 9.2 ± 0.5 μM, independently of G protein signaling and PLC activity. Moreover, **riluzole** is able to activate both heterologously expressed TRPC5 in HEK293 cells and endogenous channels in U-87 glioblastoma cells (Richter, Schaefer, &

Hill, 2014b). However, riluzole is also known to inhibit voltage-gated Na^+ and Ca^{2+} channels and thereby attenuate neurotransmitter release (Bellingham, 2011). To validate the specificity of riluzole activation of TRPC5 in U-87 cells, the potent inhibitor of TRPC5, **clemizole hydrochloride**, was used. **Clemizole** inhibited TRPC5 with IC_{50} of about 1.0–1.3 μM, which is about 6-fold selective than TRPC4β (IC_{50} = 6.4 μM) and 9- to 10-fold selective than TRPC3 (IC_{50} = 9.1 μM) and TRPC6 (IC_{50} = 11.3 μM) (Richter et al., 2014a).

Additional TRPC5 activators include a benzothiadiazine derivative (**BTD**, EC_{50} = 1.4 μM) and **methylprednisolone** (EC_{50}, 12 μM). **Prednisolone** also acts as a weak activator of TRPC5 with an EC_{50} of 64 ± 15 μM (Beckmann et al., 2017). In addition, a structural analog of HC-070 and Pico145, **AM237**, was shown to specifically activate TRPC5 with EC_{50} values of 15–20 nM (Minard et al., 2019). The lack of stimulatory effect of these compounds on TRPC4 and TRPC1–C4 heteromers could make them good probes for distinguishing TRPC4 and TRPC5 channels in native systems. However, their effects on cancer have not been reported. In addition, not only did **AM237** show a decline in stimulating TRPC5 when used at high concentrations, but it also inhibited (−)-englerin A-induced activation of TRPC5, as well as TRPC4 and TRPC1–C4, channels, implicating complex gating effects (Minard et al., 2019).

Functional TRPC6 channels are found to be overexpressed in prostate, stomach, breast cancers, as well as neuroglia, as compared to the low or undetectable levels in the corresponding normal tissues. Recent studies have demonstrated $[Ca^{2+}]_c$ rise mediated via activation of α1-adrenoceptors in normal mesangial cells and prostate cancer cells, which elicits a proliferative signal, implicating the control in cell proliferation (Santoni et al., 2015). In prostate cancer mouse model of knock-In mouse adenocarcinoma prostate (KIMAP), dietary supplement of high Ca^{2+} accelerated the progression of prostate tumors in a manner that involves increasing the expression of calcium sensing receptor and TRPC6, an effect that was attenuated through dietary supplement of **Vitamin D3.** This effect of Ca^{2+} and its inhibition by **Vitamin D3** were also reproduced in cultured prostate cancer cell lines (Bernichtein et al., 2017). Additionally, **(−)-oleocanthal (OLCT)**, a phenolic compound from olive oil, was reported to inhibit the proliferation and migration of breast cancer cells, including triple negative breast cancer cells, via decreasing the expression of TRPC6 without having effects on non-tumoral breast cells (Diez-Bello et al., 2019). **Lovastatin**, through inhibition of cholesterol synthesis, also suppressed the expression of TRPC6 and thereby the proliferation of human B lymphoma Daudi cell. Here, the effect of cholesterol on TRPC6 expression required ROS production, as reducing ROS with **TEMPOL** or **apocynin** had similar effects as **lovastatin** (Song et al., 2014).

Direct TRPC3/6/7 antagonists have also shown effectiveness in suppressing cancer. Although not specific, **SKF-96365**, has been frequently shown to exert cytotoxic potential in several types of human cancers. For instance, **SKF-96365** was reported to induce cell cycle arrest in G2/M phase and inhibit the growth of gastric cancer cells through blocking TRPC6 (Cai et al., 2009); it was also shown to suppress the growth of glioblastoma cells by promoting the reverse mode of Na^+/Ca^{2+} exchangers and thereby increasing $[Ca^{2+}]_c$ (Song, Chen, & Yu, 2014); in B lymphoma Daudi cells; **SKF-96365** inhibited cell proliferation of human hepatocellular carcinoma cell lines, HepG2 and Huh7, suppressed TGFβ-induced

$[Ca^{2+}]_c$ elevation, cell migration and invasion, and the EMT (Xu et al., 2018). Moreover, the novel **pyrazolo[1,5-a] pyrimidine** TRPC6 antagonists, compound, **14a**, displayed a potent inhibitory effect on the growth of gastric cancer cells in culture and suppressed xenograft tumor formation in nude mice with excellent bioavailability. In the *in vitro* cytotoxicity assay, **14a** concentration-dependently inhibited the proliferation of gastric cancer cells, AGS and MKN45, with IC_{50} values of 17.1 and 18.5 μM, respectively, while exhibiting no cytotoxicity at HK-2 cells at a high concentration of 100 μM, indicating an excellent therapeutic potential against human gastric cancer (Ding et al., 2018).

At the time of this writing, the effects of many of the new TRPC modulators described above for other systems have not been described. Given the critical involvement of individual TRPC subtypes in different aspects of various cancers, it is anticipated that many of the novel TRPC probes will find their use in cancer therapies. Furthermore, microRNA (miRNA), endogenous single-stranded, noncoding RNA molecules, that modulate gene transcription and expression, have also been shown to affect TRPC channels. For example, miR-200b-3p inhibits TRPC6 in podocytes (Yin, Zhang, Li, Li, & Yang, 2018), miR-26a-5p suppresses the expression of TRPC3, which promotes the growth and invasion of melanoma (Gao, Zeng, Liu, Gao, & Liu, 2019). All these could potentially be targeted for therapeutic benefit.

4. Conclusion

The pivotal roles of TRPC channels in physiology and disease are only beginning to be more fully understood. TRPC channels are critically involved in normal physiological and pathophysiological responses in many systems including vasculature, nervous system, kidney, inflammation and immunity. These channels play important roles in various cellular functions through regulation of membrane potential and calcium signaling and they are under tight regulation by multiple mechanisms to allow them to function as sensors to different environmental cues. The recent development of a large collection of novel TRPC small molecular probes complements the traditional genetic approaches, which not only provides powerful tools for further understanding the physiological significance of TRPC channels and the mechanisms of their regulation, but also offers potential new strategies to devise clinic therapies to treat TRPC-associated diseases. Certainly, considerable work is still needed to more fully understand the structural, functional, and mechanistic aspects of TRPC channel biology. An improved understanding of the underlying mechanisms of TRPC regulation may assist in the identification of more selective pharmacological agonists and antagonists of TRPCs or interdependent channels and promote exciting opportunities to develop new therapies that prevent or treat TRPCs-related diseases. With the advancement of the cryo-EM technology and the vastly improved capability to obtain high-resolution structural information of these channels, it is expected that more efficient and selective tool compounds and highly effective drugs targeting TRPCs will be discovered at an accelerated rate.

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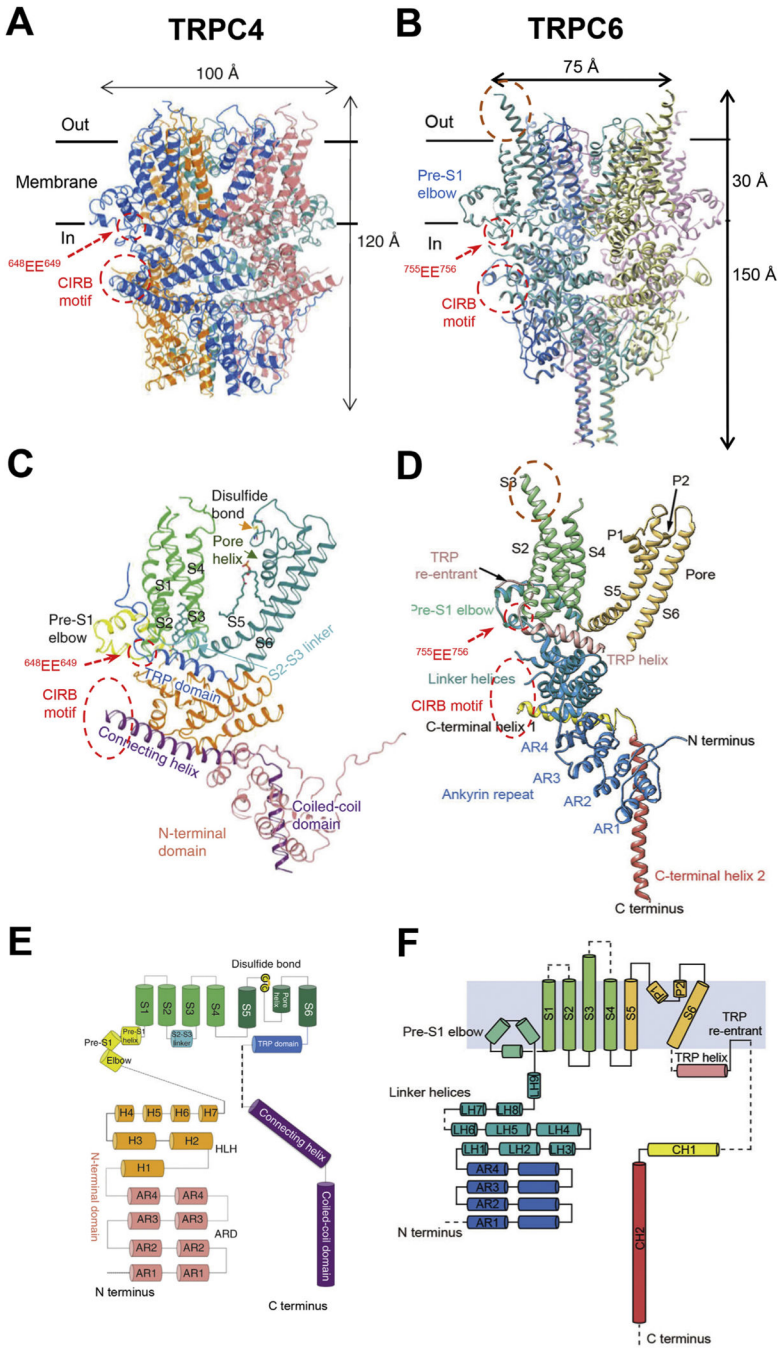


Fig. 1. Structures of TRPC channels.

A & B, cryo-EM structures of C terminus truncated mouse TRPC4 (aa 1–758) (**A**) and full-length human TRPC6 (aa 1–931) (**B**), as reported by Duan et al. (2018) and Tang et al. (2018), respectively. The transmembrane regions are defined by the horizontal black lines with the thickness of about 30 Å. Areas of the Calmodulin- and IP_3 receptor-binding (CIRB) motifs and the two conserved acidic residues (EE) critical for regulation by STIM1 are indicated by the dashed red circles. The extracellular protrusion of S3 transmembrane helix in TRPC6 is encircled by brown dashed line. Note the missing structures between the TRP

re-entrant loop and CIRB motif in both examples. **C & D**, ribbon diagrams of single subunits of TRPC4 (**C**) and TRPC6 (**D**). TRP domain (in **C**) is equivalent to TRP helix (in **D**); Connecting helix and coiled-coil domain (in **C**) are equivalent to C terminal helices 1 and 2 (in **D**), respectively. **E & F**, topology and domain organization of TRPC4 (**E**) and TRPC6 (**F**) single subunits. Cylinders indicate α helices; dashed lines highlight unresolved structures.

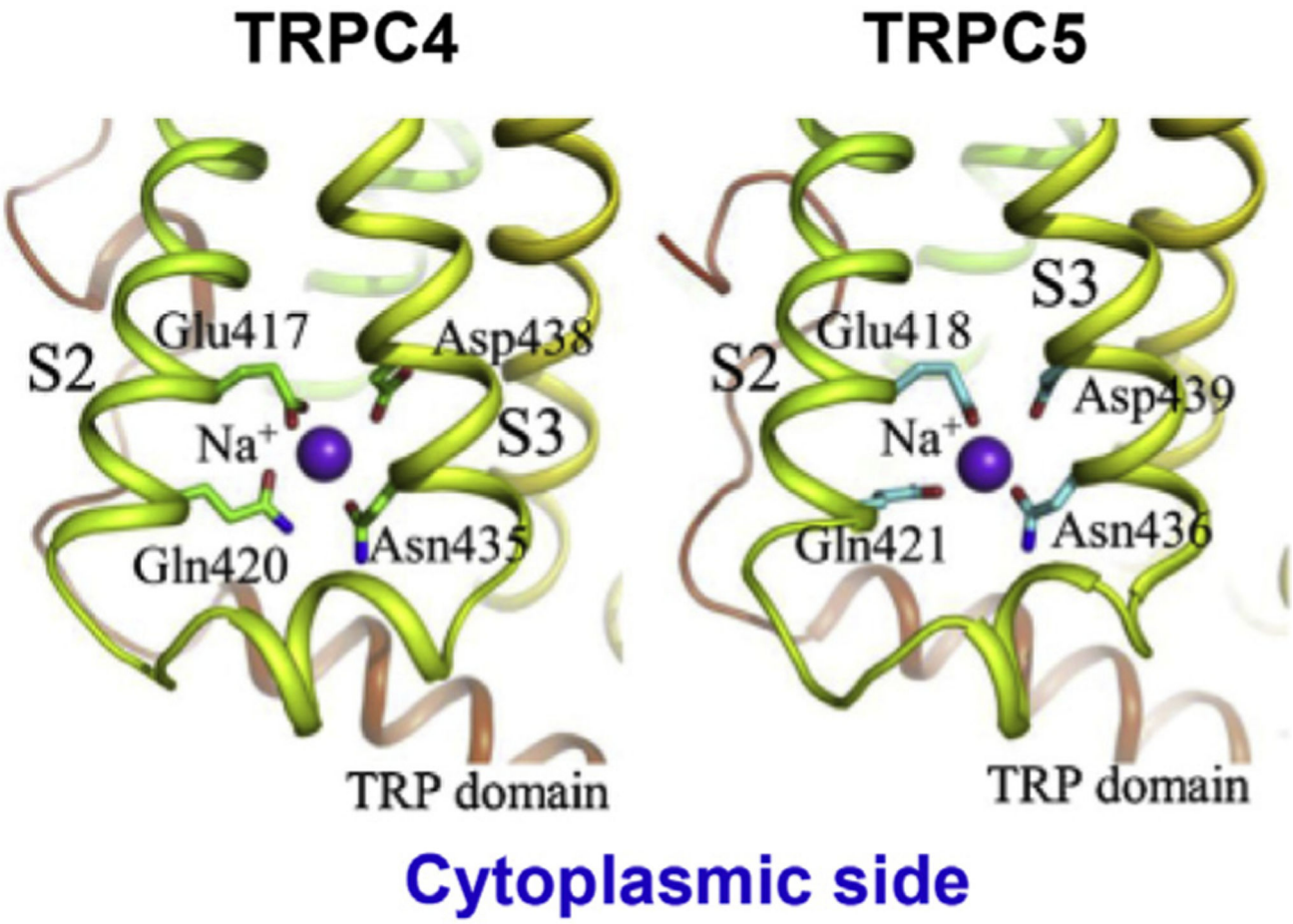


Fig. 2. Intracellular Na^+binding sites identified from TRPC4 (*left*) and TRPC5 (*right*) cryo-EM structures.

S2 and S3 depict the second and third transmembrane helices, respectively. Adopted from Li et al. (2019) with modifications.

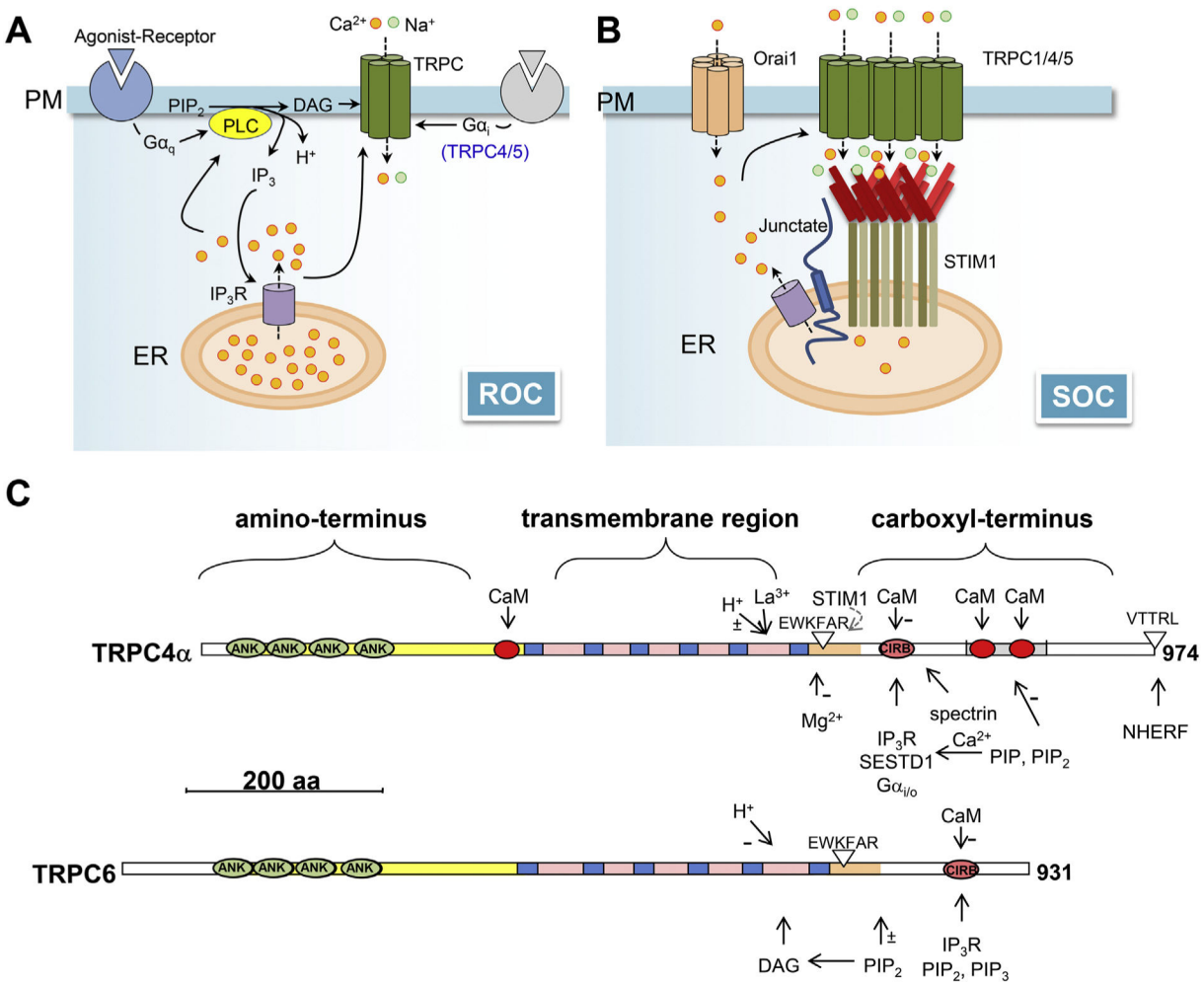


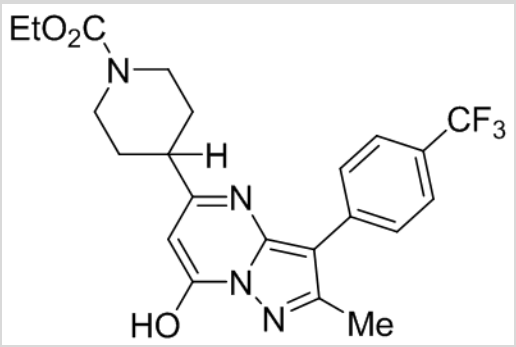
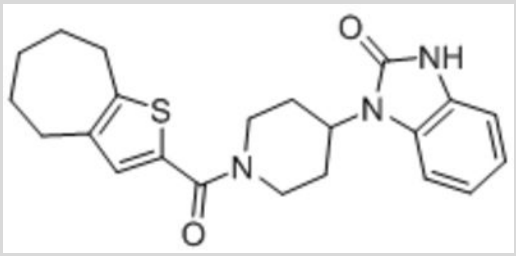
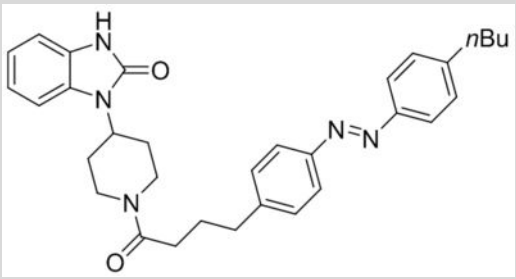
Fig. 3. Mechanism of activation of TRPC channels.

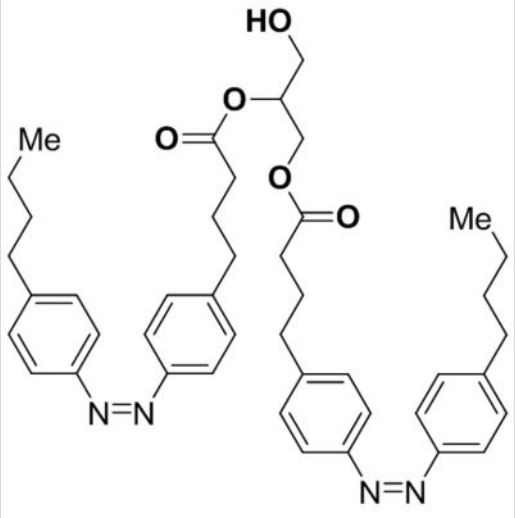
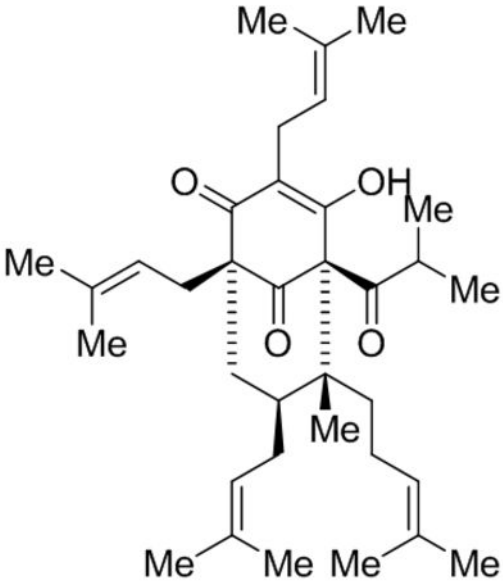
A, receptor-operated channel (ROC) activation of TRPCs. Independently of STIM1, receptor activation leads to PLC hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) and production of inositol 1,4,5-trisphosphate (IP_3), diacylglycerols (DAG), and protons (H^+). All of them have been implicated in the regulation of TRPC channel function. In addition, IP_3 activates IP_3 receptors (IP_3R) on the endoplasmic reticulum (ER) membrane to release stored Ca^{2+}, causing $[Ca^{2+}]_c$ to increase. Ca^{2+} regulates TRPC channels in both calmodulin (CaM)-dependent and -independent manners. Specifically for TRPC4 and C5, the activation of $G_{i/o}$ proteins also triggers channel activation in conjunction with PLC stimulation. **B**, store (or STIM)-operated channel (SOC) activation of TRPCs. TRPC1/4/5 have been shown to be directly activated by STIM1 (see text for details), which senses ER Ca^{2+} store depletion to oligomerize and move towards the plasma membrane (PM). This may be facilitated by junctate, which interacts with IP_3Rs, TRPCs, and STIM1, as well as by Ca^{2+} influx mediated by Orai1. **C**, linear representation of selected key structure features of TRPC4α (*upper*) and TRPC6 (*lower*). Ankyrin-like (ANK) repeats, transmembrane segments (blue boxes), and CaM-binding sites (red circles) are labeled. EWKFAR indicates the TRP motif. VTTRL indicates the PDZ-binding domain. Experimental evidence for some

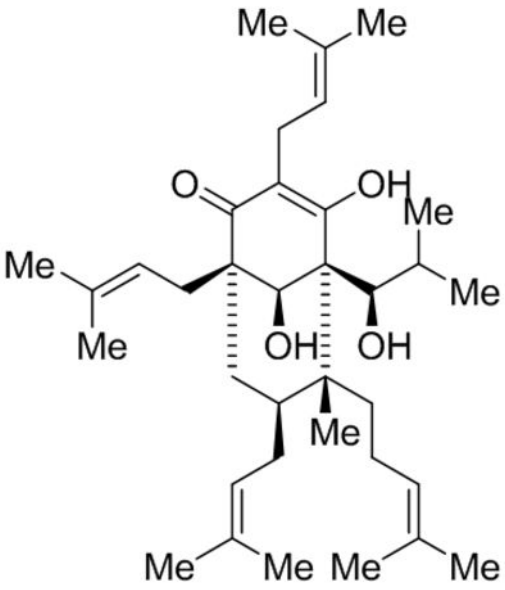
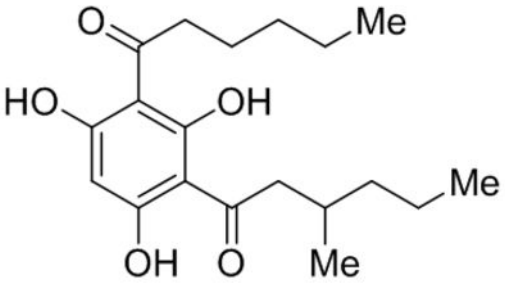
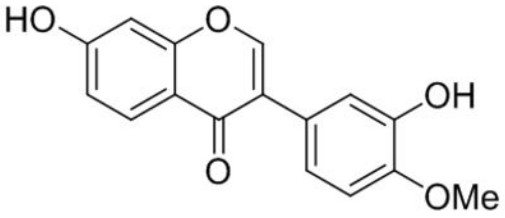
of the features indicated in TRPC4α has only been reported for TRPC5. −, experimental evidence exists for negative regulation; ±, experimental evidence exists for both positive and negative regulation. Binding motifs for NHERF (Tang et al., 2000), PIP_2 and PIP_3 (Kwon et al., 2007), SESTD1 (Miehe et al., 2010), $G_{i/o}α$-GTP (Jeon et al., 2012), STIM1 (Zeng et al., 2008), spectrin (Odell, Van Helden, & Scott, 2008), and Calmodulin- and IP_3 receptor-binding (CIRB) site (Zhang et al., 2001; Tang et al., 2001) are indicated.

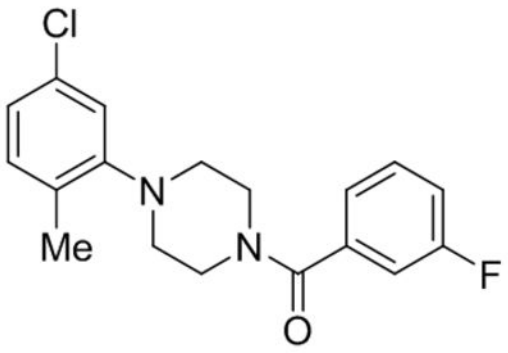
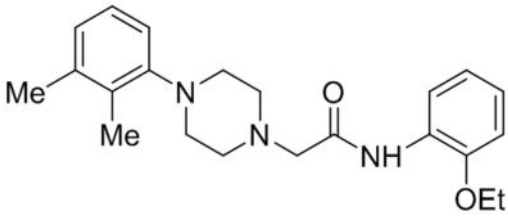
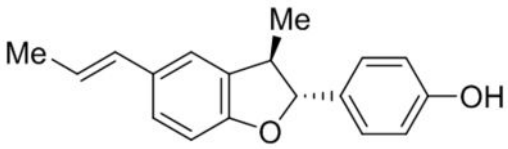
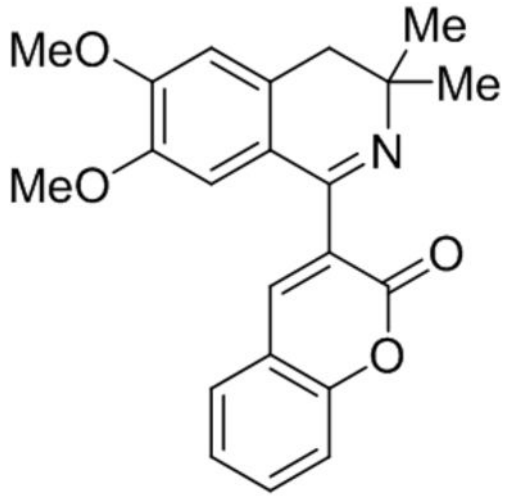
Table 1

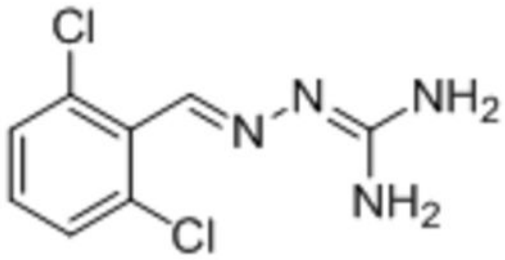
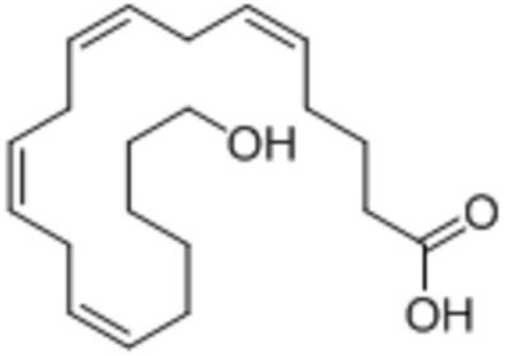
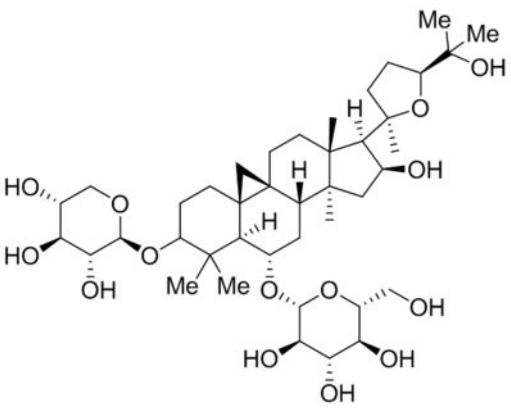
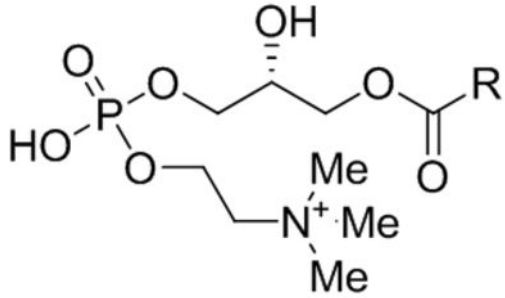
Small molecule TRPC3, C6, C7 agonists.

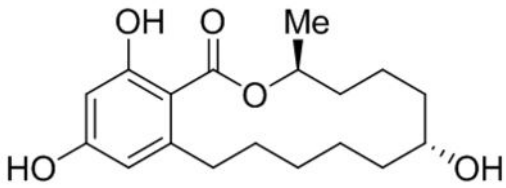
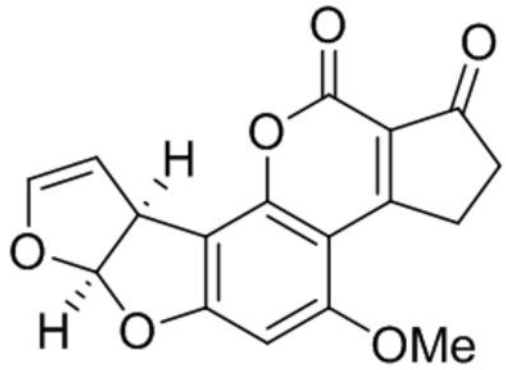
Name[a]	Structure	Target	Concentration or EC_{50}	Reference
Pyrazolopyrimidines 4n		TRPC3 TRPC6 TRPC7	EC_{50}, 19 nM EC_{50}, 1.39 μM EC_{50}, 90 nM	Qu et al., 2017
GSK1702934A		TRPC3 TRPC6	EC_{50}, 80 nM EC_{50}, 440 nM	Xu et al., 2013
OptoBI-1		TRPC3 TRPC6 TRPC7 photoswitch activation	Tested at 10–20 μM	Tiapko et al., 2019

Name[a]	Structure	Target	Concentration or EC_{50}	Reference
OptoDArG		TRPC3 TRPC6 photoswitch activation	Tested at 30 μM	Lichtenegger et al., 2018
Hyperforin (IDN5522)		TRPC6 activation and increasing expression	EC_{50}, 1.51 μM	Leuner et al., 2007; Leuner et al., 2010; Thiel & Rossler, 2017

Name[a]	Structure	Target	Concentration or EC_{50}	Reference
Tetrahydrohyperforin (IDN5706),		TRPC3 TRPC6 TRPC7	EC_{50}, 0.5 μg/mL (~1 μM)	Montecinos-Oliva et al., 2014
Hyp9		TRPC6	$EC_{50,}$ 1.26 μM	Leuner et al., 2010
Calycosin (CAL)		Upregulated TRPC6 expression	20 mg/kg body weight (*in vivo*), 60 μM (*in vitro*)	Guo et al., 2017a

Name[a]	Structure	Target	Concentration or EC_{50}	Reference
PPZ1		TRPC3 TRPC6 TRPC7	EC_{50}, 57 μM EC_{50}, 67.3 μM EC_{50}, 45.9 μM	Sawamura et al., 2016
PPZ2		TRPC3 TRPC6 TRPC7	EC_{50}, 10.2 μM EC_{50}, 8.4 μM EC_{50}, 2.9 μM	Sawamura et al., 2016
(+)-Conocarpan		TRPC6	EC, 6.01 μM	Yang et al., 2019
C20		Positive allosteric TRPC6 modulator	EC_{50}, 2.4 μM	Hafner et al., 2019

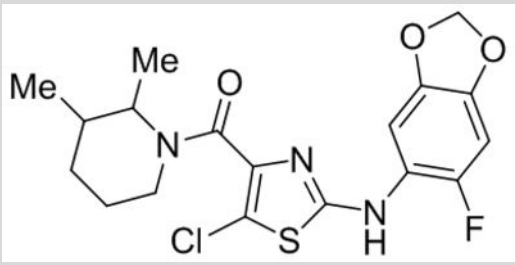
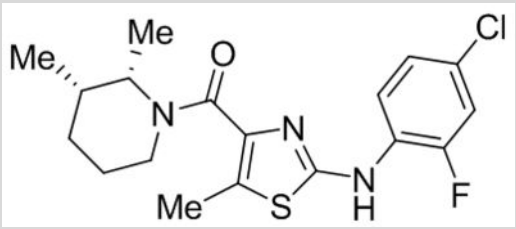
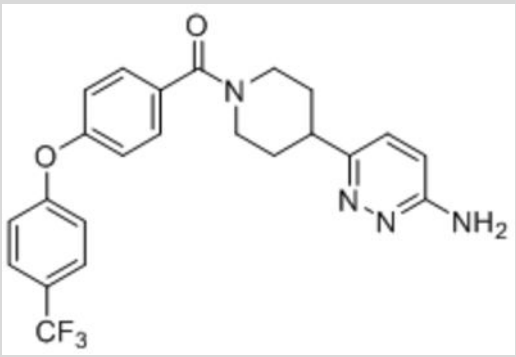
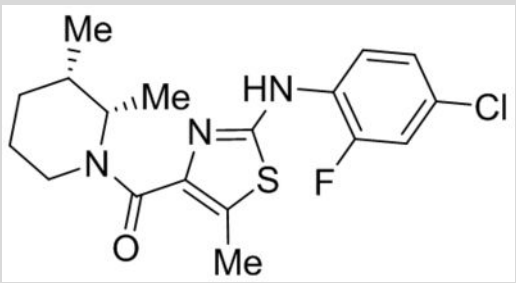
Name[a]	Structure	Target	Concentration or EC_{50}	Reference
Guanabenz		Activated TRPC6	EC_{50}, 100 μM	Bertrand et al., 2015
20-Hydroxyeicosa-tetraenoic acid (20-HETE)		Activated TRPC6 and increased surface expression	EC_{50}, 0.8 μM	Basora et al., 2003; Roshanravan et al., 2016
Astragaloside IV (AS-IV)		Prevented TRPC6 down regulation	2.5 mg/kg body weight/day (*in vivo*)	He et al., 2018
Lysophosphatidyl-choline (LysoPC)		Activated TRPC6	10 μM	Chaudhuri et al., 2008

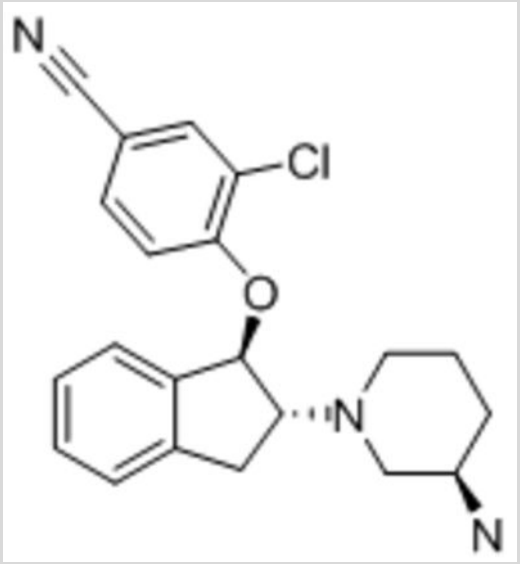
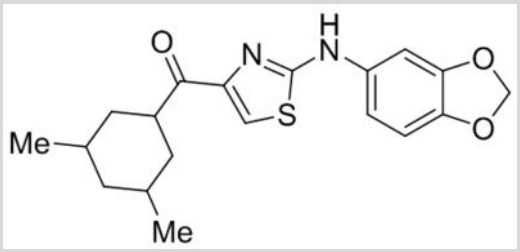
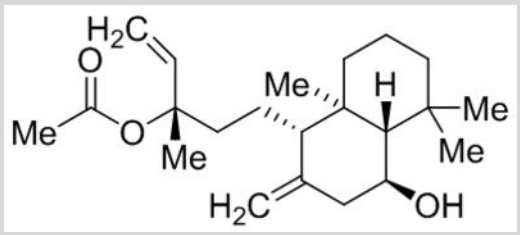
Name[a]	Structure	Target	Concentration or EC_{50}	Reference
Zeranol		Increased TRPC3 expression	10 nM	Zhu et al., 2016a
Aflatoxin B1		Increased TRPC3 expression	1 nM	Zhu et al., 2016b

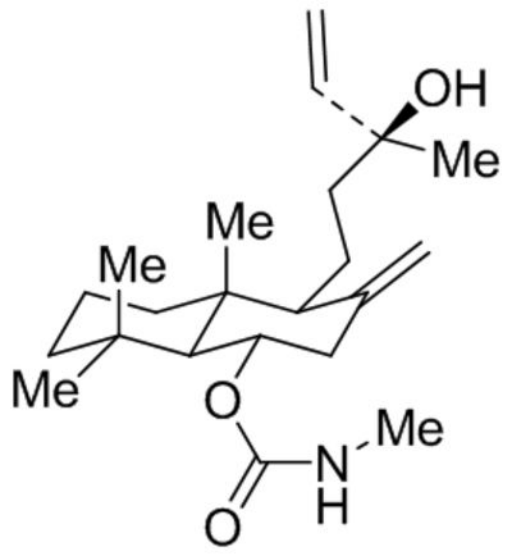
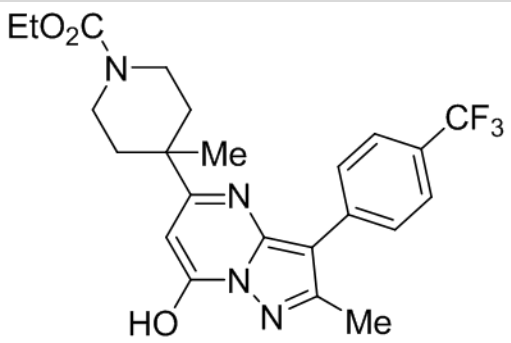
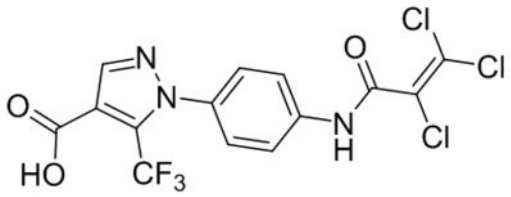
[a]Compounds with selectivity information and likelihood of direct interaction with the channel are highlighted in bold letters and shaded rows.

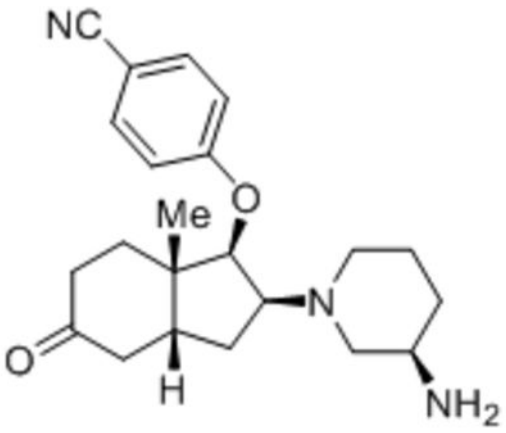
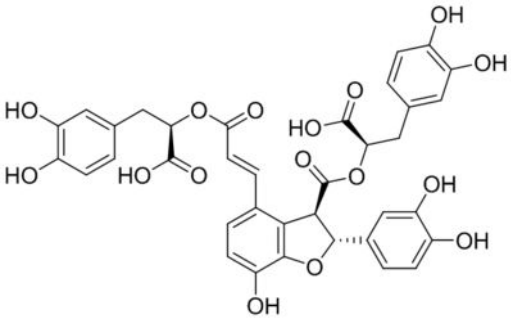
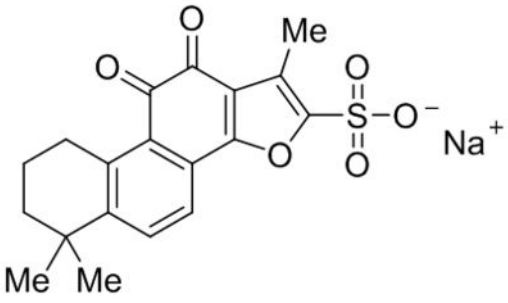
Table 2

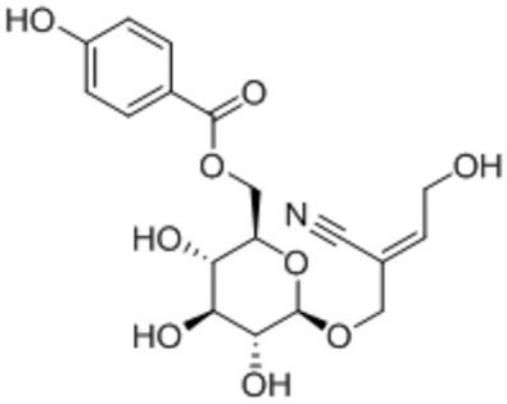
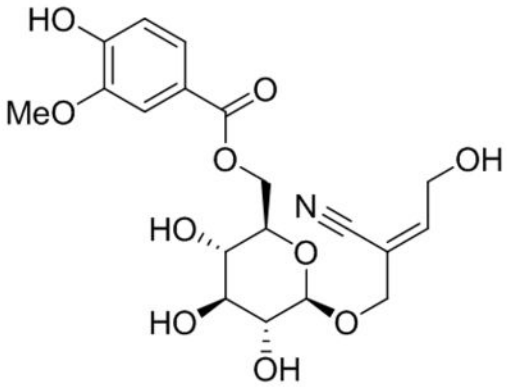
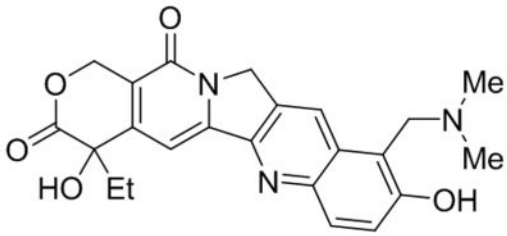
Small molecule TRPC3, C6, C7 antagonists.

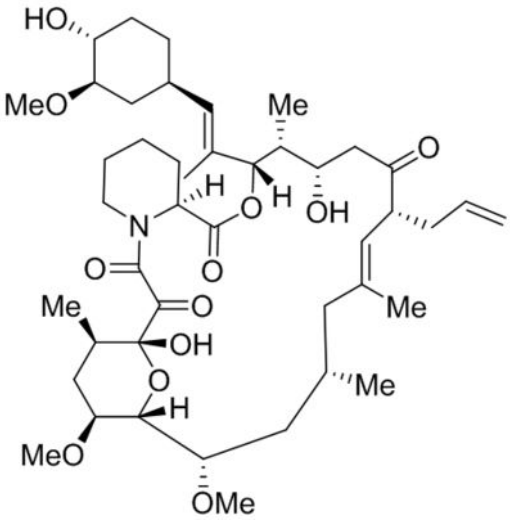
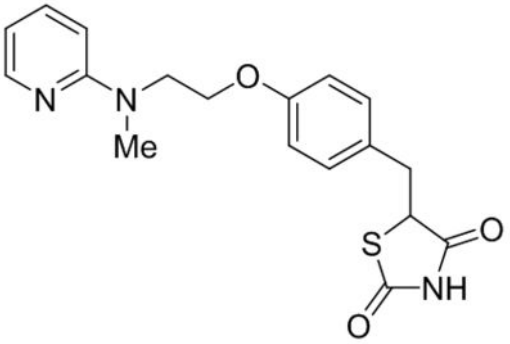
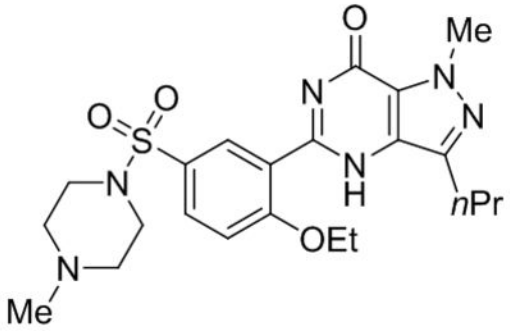
Name[a]	Structure	Target	Concentration or IC_{50}	Reference
GSK2332255B (GSK255B)		TRPC3 TRPC6	IC_{50}, 5 nM IC_{50}, 4 nM	Seo et al., 2014
GSK2833503A (GSK503A)		TRPC3 TRPC6	IC_{50}, 21 nM IC_{50}, 3 nM	Seo et al., 2014
BI 749327		TRPC3 TRPC6 TRPC7	IC_{50}, 1,100 nM IC_{50}, 13 nM IC_{50}, 550 nM	Lin et al., 2019
Anilino-thiazoles		TRPC3 TRPC6	100 nM 16 nM	Washburn et al., 2013

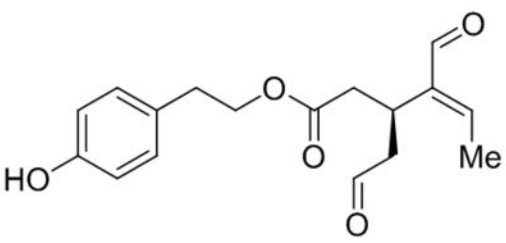
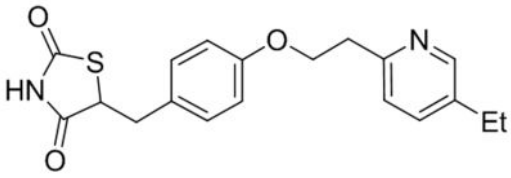
Name[a]	Structure	Target	Concentration or IC_{50}	Reference
SAR7334		TRPC3 TRPC6 TRPC7	IC_{50}, 282 nM IC_{50}, 7.9 nM IC_{50}, 226 nM	Maier, et al., 2015
BTDM		TRPC3 TRPC6	IC_{50}, 11 nM IC_{50}, 10 nM	Tang, et al., 2018
Larixyl acetate		TRPC3 TRPC6 TRPC7	12 fold > C6 IC_{50}, ~0.1 μM 5 fold > C6	Urban et al., 2016

Name[a]	Structure	Target	Concentration or IC_{50}	Reference
SH045		TRPC3 TRPC6 TRPC7	13 fold > C6 IC_{50}, ~5.8 nM 3.5 fold > C6	Hafner et al., 2018
Pyrazolopyrimidines 14a		TRPC6	IC_{50}, 1 μM	Ding et al., 2018
Pyr10		TRPC3 TRPC6	IC_{50}, 0.72 μM $IC_{50} \geq 10$ μM	Schleifer et al., 2012
Pyr3		TRPC3	IC_{50}, 0.7 μM	Kiyonaka et al., 2009; Koenig et al., 2013

Name[a]	Structure	Target	Concentration or IC_{50}	Reference
DS88790512		TRPC6	IC_{50}, 11 nM	Motoyama, et al., 2018
Salvianolic acid B		TRPC3 TRPC6	27.8 μM	Chen et al., 2017b
Sodium tanshinone IIA sulfonate (STS)		Attenuated TRPC6, C1 upregulation	12.5 μM	Wang et al., 2013a Jiang et al., 2016a.

Name[a]	Structure	Target	Concentration or IC_{50}	Reference
Ribemansides A		TRPC6	IC_{50}, 24.5 μM	Zhou et al., 2018
Ribemansides B		TRPC6	IC_{50}, 25.6 μM	Zhou et al., 2018
Topotecan (TPT),		Suppressed expression of TRPC6	1–10 nM	Jiang et al., 2018

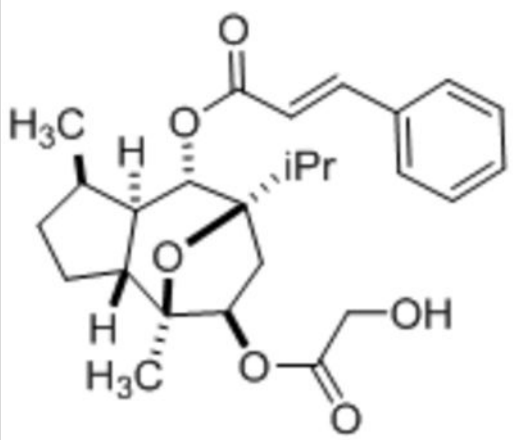
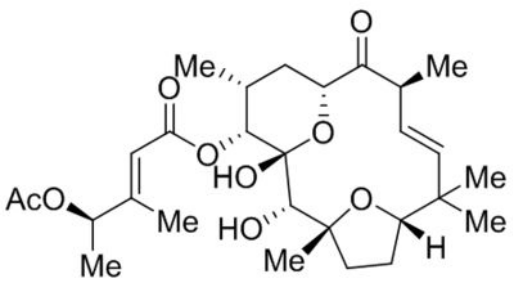
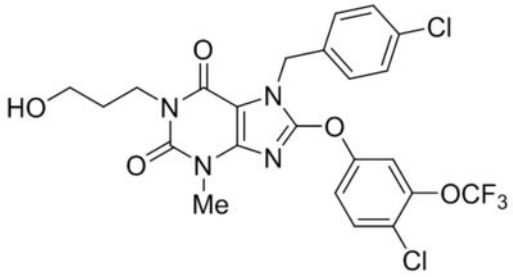
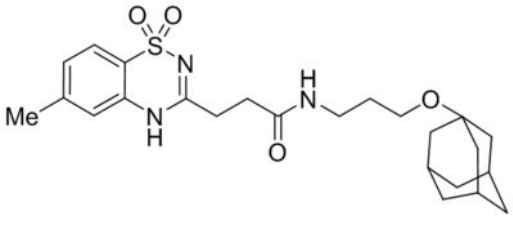
Name[a]	Structure	Target	Concentration or IC_{50}	Reference
FK506		Attenuated TRPC6 upregulation	6.2 μM	Ma et al., 2015
Rosiglitazone (RSG)		Reduced TRPC6, C1 activation	10 μM	Wei et al., 2017
Sildenafil		Suppressed TRPC6 expression	300 nM	Lu et al., 2010

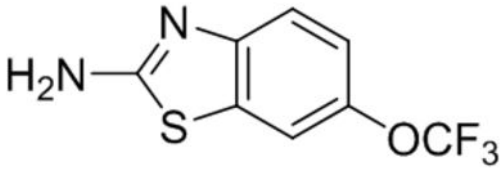
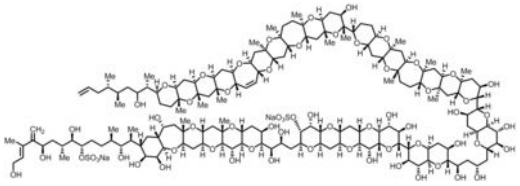
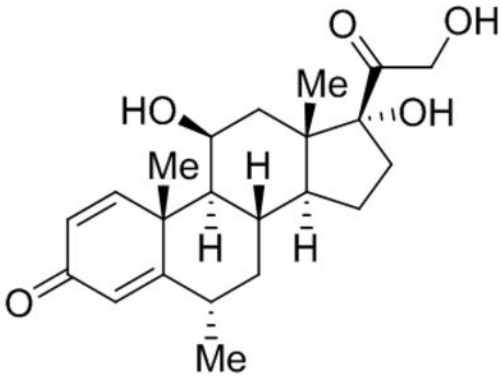
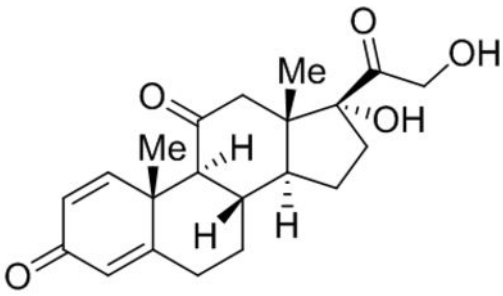
Name[a]	Structure	Target	Concentration or IC_{50}	Reference
(−)−Oleocanthal (OLCT)		Suppressed TRPC6 expression	10–20 μM	Diez-Bello, et al., 2019
Pioglitazone		Suppressed TRPC6 expression	12 mg/kg body weight (*in vivo*), 1 μM (*in vitro*)	Sonneveld et al., 2017

[a]Compounds with selectivity information and likelihood of direct interaction with the channel are highlighted in bold letters and shaded rows.

Table 3

Small molecule TRPC1, C4, C5 agonists.

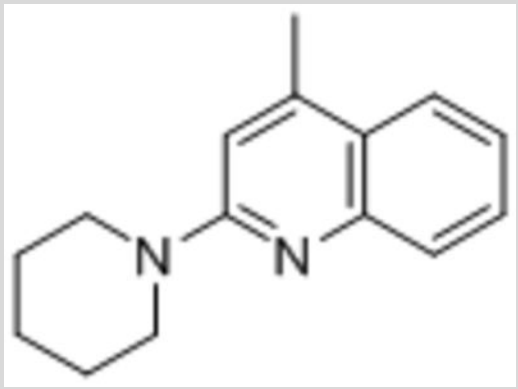
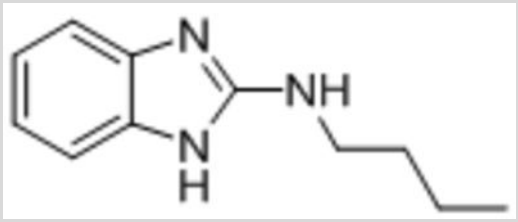
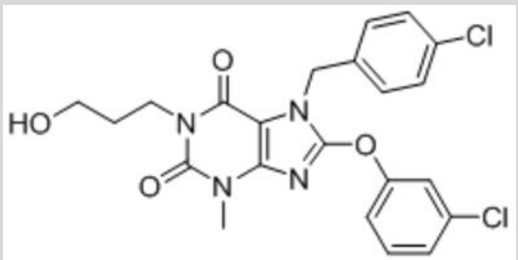
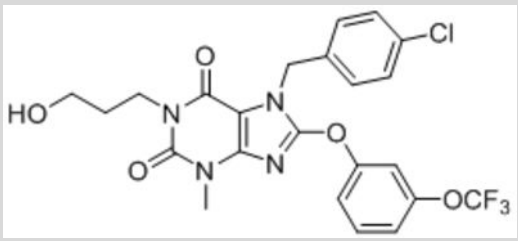
Name[a]	Structure	Target	Concentration or EC_{50}	Reference
(−)-Englerin A		TRPC4 TRPC5	EC_{50}, 11.2 nM EC_{50}, 7.6 nM	Akbulut et al., 2015
Tonantzitlolone (TZL),		TRPC4 TRPC5 TRPC1–C4 TRPC1–C5	EC_{50}, 123 nM EC_{50}, 83 nM EC_{50}, 140 nM EC_{50}, 61 nM	Rubaiy et al., 2018a
AM237		TRPC5	EC_{50}, 15–20 nM	Minard et al., 2019.
Benzothiadiazine derivative (BTD)		TRPC5	EC_{50}, 1.4 μM	Beckmann et al., 2017

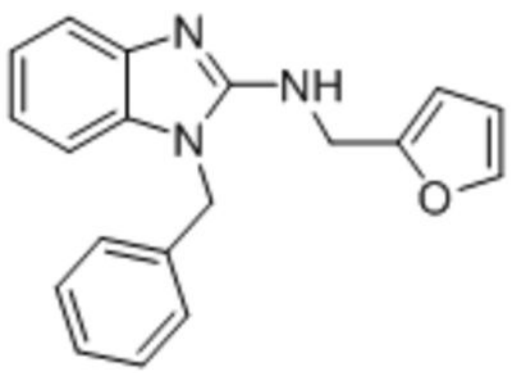
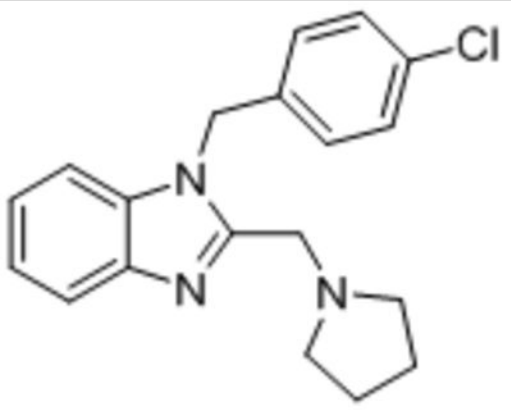
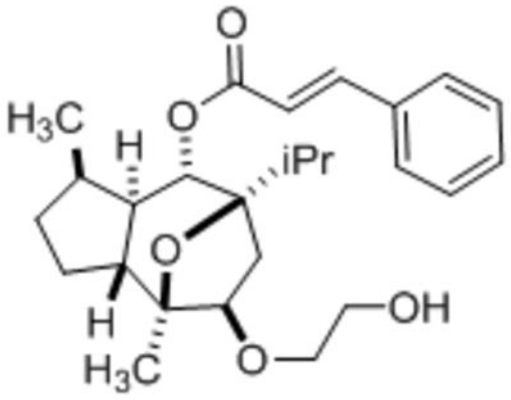
Name[a]	Structure	Target	Concentration or EC_{50}	Reference
Riluzole		TRPC5	EC_{50}, 9.2 μM,	Richter et al., 2014b
Maitotoxin		TRPC1	EC_{50}, 10 pM	Brereton et al., 2001; Flores, et al., 2017
Methyl-prednisolone		TRPC5	EC_{50}, 12 μM	Beckmann et al., 2017
Prednisolone		TRPC5	EC_{50}, 64 μM	Beckmann et al., 2017

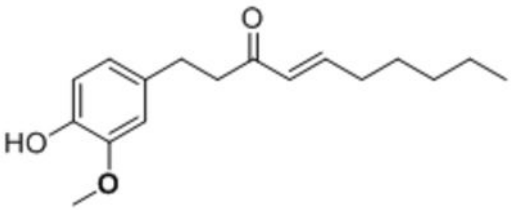
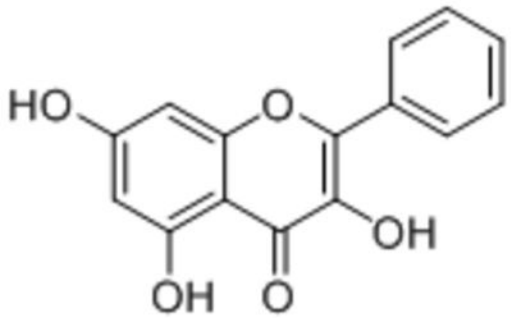
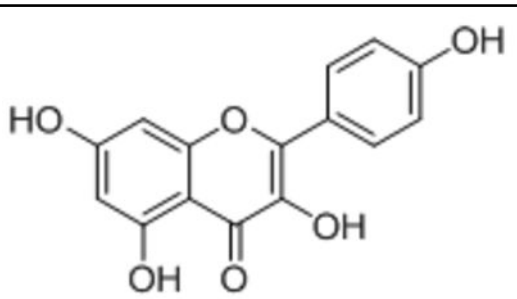
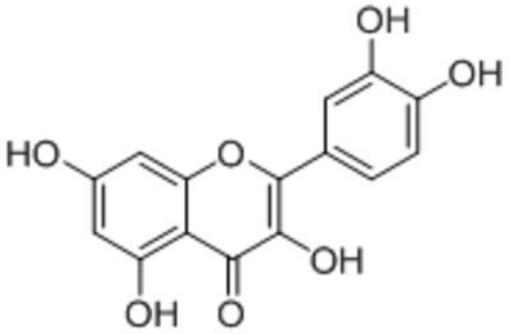
[a]Compounds with selectivity information and likelihood of direct interaction with the channel are highlighted in bold letters and shaded rows.

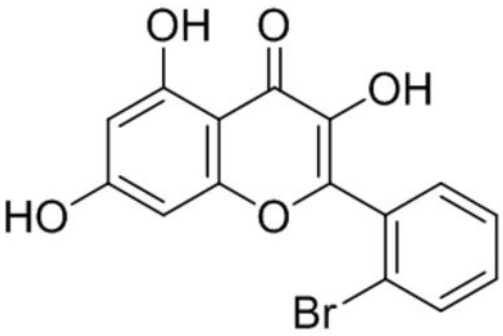
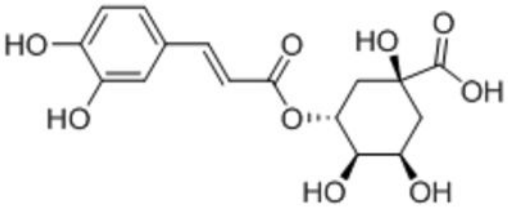
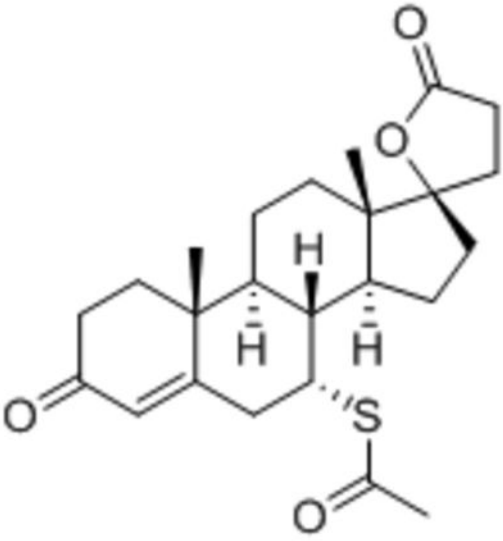
Table 4

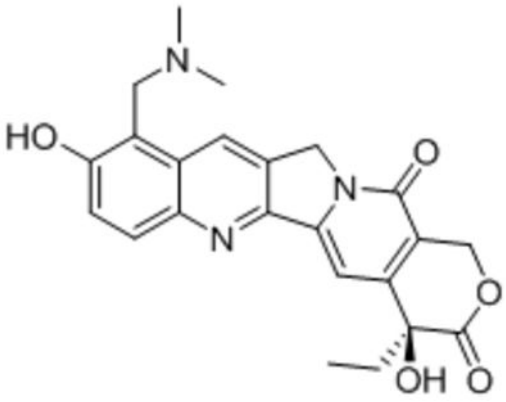
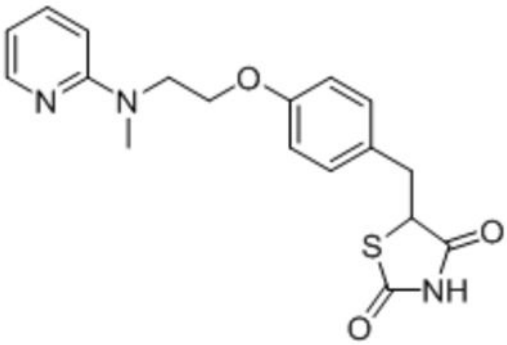
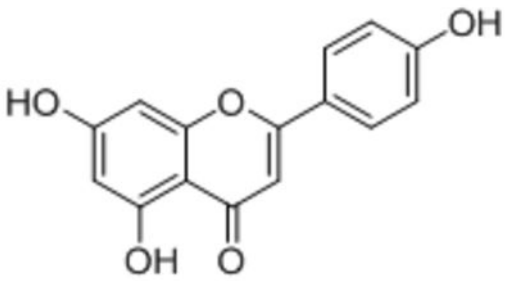
Small molecule TRPC1, C4, C5 antagonists.

Name[a]	Structure	Target	Concentration or IC_{50}	Reference
ML204		TRPC4 TRPC5	IC_{50}, 0.96 μM	Miller et al., 2011
M084		TRPC4 TRPC5	IC_{50}, 10.3 μM IC_{50}, 8.2 μM	Zhu et al., 2015
HC-070		TRPC4 TRPC5 TRPC4–C1 TRPC5–C1	IC_{50}, 46 nM IC_{50}, 9.3 nM	Just et al., 2018
HC-608 (Pico145)		TRPC4 TRPC5 TRPC4–C1 TRPC5–C1	IC_{50}, 32.5 nM IC_{50}, 6.2 nM 9 – 1,300 pM	Just et al., 2018; Rubaiy et al., 2017

Name[a]	Structure	Target	Concentration or IC_{50}	Reference
AC1903		TRPC5	IC_{50}, 14.7 μM	Zhou et al., 2017
Clemizole		TRPC4β TRPC5	IC_{50}, 6.4 μM IC_{50}, 1.0–1.3 μM	Richter et al., 2014a
GFB-887	Not disclosed	TRPC5	IC_{50}, 11 nM	Mundel et al., 2019
A54		A498 cells TRPC1–C4	IC_{50}, 62 nM	Rubaiy et al., 2018b

Name[a]	Structure	Target	Concentration or IC_{50}	Reference
[6]-shogaol		TRPC5	IC_{50}, 18.3 μM	Kim et al., 2016
Galangin		TRPC5	IC_{50}, 0.45 μM	Naylor et al., 2016
Kaempferol		TRPC5	IC_{50}, 3.9 μM	Naylor et al., 2016
Quercetin		TRPC5	IC_{50}, 6.5 μM	Naylor et al., 2016

Name[a]	Structure	Target	Concentration or IC_{50}	Reference
AM12		TRPC5 TRPC4	IC_{50}, 0.28 μM	Naylor et al., 2016
Chlorogenic acid (CGA)		Suppressed TRPC1 expression	300 μM	Jung et al., 2017
Spironolactone		Suppressed TRPC1, C6 expression	3 mg/kg body weight/day (*in vivo*)	Li et al., 2017

Name[a]	Structure	Target	Concentration or IC_{50}	Reference
Topotecan (TPT),		Suppressed expression of TRPC1, C4	IC_{50}, 1–10 nM	Jiang et al., 2018
Rosiglitazone (RSG)		Reduced TRPC1 activation	IC_{50}, 10 μM	Wei et al., 2017
Apigenin		TRPC5	IC_{50} >>10 μM	Naylor et al., 2016

[a]Compounds with selectivity information and likelihood of direct interaction with the channel are highlighted in bold letters and shaded rows.