Chapter 2
Pharmacology of TRP Channels

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Abstract TRP channels are a family of ion channels involved in a plethora of physiological sensory processes. Since their discovery they have attracted the attention of academic and non-academic laboratories with the aim of developing modulators that could be used as pharmacological tools for unveiling their physiological and pathological activities, and as therapeutic compounds for intervening in TRP dysfunction. Intriguingly, TRP pharmacology shows dispersed progress, with vast pharmacology developed for some members of the so-called thermoTRP channel subfamily (TRPV1, TRPV3, TRPM8 and TRPA1), and very little, for all other TRP channels. Pharmacologically, the most investigated TRP channel is undoubtedly TRPV1 for which a large number of agonists and antagonists with *in vitro* and *in vivo* activities have been characterized. Recent interest has grown for TRPV3, TRPM8 and TRPA1 because of their implication in several human pathologies and disorders. Similarly, the TRPM3 channel is emerging as important targets for pain transduction. With the development of novel screening methods, the focus is slowly changing to other TRP members for whom we do not have appropriate agonists or antagonists. These include the TRPC family, which has limited our understanding of their role in pathological processes and whether pharmacological intervention in these channels will have a therapeutic benefit. A bright future is anticipated for TRP pharmacology, with the discovery of selective and potent modulators for this important family of sensory channels.

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2.1 Introduction

TRP channels are a superfamily of ion channels that includes seven subfamilies, namely TRPC, TRPV, TRPP, TRPM, TRPA, TRPML, and TRPN. These channels perform a wide diversity of physiological functions and are present in many tissues, and almost all cell types. Most TRP channels are non-selective cation channels with low voltage dependence. TRP channels use a wide variety of activation and regulatory mechanisms and carry out functions as diverse as thermosensation, phototransduction, pheromone reception, magnesium homeostasis, and vascular tone regulation (Montell 1999) (see Chap. 4 by Bacigalupo et al. in this Book). Thus, these channels are considered molecular gateways in sensory and regulatory systems.

Structurally, TRP channels are tetrameric assemblies of basic subunits organized around a central aqueous pore. Akin to voltage-gated K^+ channels, each subunit is composed of a transmembrane region containing 6 transmembrane segments. The recent structural model derived from cryo-electron microscopic images has clearly shown this molecular analogy (Liao et al. 2013). All TRP channels display this core transmembrane region, and differ in the cytosolic N- and C-termini domains, which are involved in channel gating and mediating intracellular signaling. Indeed, most of TRP channels, if not all, are part of protein complexes known as signalplexes (Devesa et al. 2011; Fernandez-Carvajal et al. 2011; Ferrer-Montiel et al. 2012).

Some TRP channels have been involved in the pathophysiology of human diseases. This pathological contribution could be the result of channel mutations, giving rise to channelopathies (Devesa et al. 2011; Fernandez-Carvajal et al. 2011; Ferrer-Montiel et al. 2012), or the change in channel function due to alteration of the protein function and/or expression (Devesa et al. 2011; Fernandez-Carvajal et al. 2011; Ferrer-Montiel et al. 2012). The pivotal involvement in the etiology of pathological conditions has signaled members of this large channel family as druggable targets for therapeutic intervention, which has driven discovery programs in academic and non-academic institutions. This concerted effort has notably expanded the pharmacology of TRP channels, although, unfortunately, for a limited number of TRP members. For instance, large families of modulators have been obtained for TRPV1, TRPV3, TRPM8 and TRPA1, while the pharmacology of other TRP channels is still in its infancy. A plausible reason for the pharmacological progress in these channels is the availability of natural ligands present in food spices. Nonetheless, the development of combinatorial chemistry and the large diversity of vegetal and marine extracts, along with the development of high throughput electrophysiological assays for ion channels will expand the pharmacology of TRP channels to the entire family. Here, we briefly expose the pharmacological data for the most studied TRP channels, namely TRPV1, TRPM8 and TRPA1, and include the data accrued for TRPV2, TRPV4, TRPM3 and the TRPC5, most of them with an

important role in sensory transduction. We aim to illustrate the differential pharmacological progress in this exciting field and evidence a drift towards enhancing the pharmacology of other members, if not all, of this pivotal channel family.

2.2 TRPV1

TRP Vanillod 1, TRPV1, a non-selective $Ca2^{+}$ channel is a TRP channel activated by noxious temperatures (43 °C) acidic pH and vanilloid compounds, whose channel activity is highly potentiated by proalgesic mediators in response to inflammation, tissue injury and ischemia (Huang et al. 2006; Ueda et al. 2008). In addition, TRPV1 expression is markedly up-regulated under acute inflammatory conditions (Camprubi-Robles et al. 2009; Morenilla-Palao et al. 2004; Van Buren et al. 2005), and in human chronic pain states (Broad et al. 2008; Szallasi and Blumberg 2007). Consistent with a role in pain signaling, TRPV1 is highly expressed in C-type, peptidergic nociceptors in the peripheral nervous system. Thus, TRPV1 is considered a gateway for pain transduction, and a pivotal target for drug intervention in pain syndromes. In addition, due to a widespread tissue distribution of this TRP channel, it may be involved in the etiology of other human pathologies or disorders (Avelino et al. 2002; Inoue et al. 2002).

TRPV1 sensitization by inflammatory conditions is produced through two distinct, but complementary mechanisms, namely: (i) covalent modification of the channel by protein kinase A (PKA) and/or protein kinase C (PKC) phosphorylation (Bhave et al. 2003; Tominaga et al. 2001; Varga et al. 2006; Vellani et al. 2001); and, (ii) rapid recruitment of a vesicular population of TRPV1 channels to the neuronal surface through a $Ca2^{+}$ -dependent, SNARE-mediated exocytosis mechanism in response to pro-algesic agents (Camprubi-Robles et al. 2009; Zhang et al. 2005).

Pharmacologically, TRPV1 is primarily activated by a diverse collection of chemical ligands known as vanilloids (Caterina et al. 2000; Khairatkar-Joshi and Szallasi 2009) (Fig. 2.1). The most known agonist of TRPV1 is capsaicin, the pungent compound of chili peppers. Resiniferatoxin (RTX), a vanilloid from *Euphorbia resinifera*, is also a potent agonist of the receptor. Furthermore, TRPV1 may also be activated by non-vanilloid compounds, such as allicin, piperine, camphor, olvanil, 2-aminoethoxydiphenylborate (2-APB), and tarantula venom peptide toxins (Bohlen et al. 2010) (Table 2.1). In addition, there is a family of endogenous compounds, referred to as endovanilloids, that also act as agonists of TRPV1 (Van Der Stelt and Di 2004). These compounds may be divided into conjugates of biogenic amines [e.g., N-arachidonoylathanolamine (AEA, anandamide), N-arachidonoyldopamine (NADA), N-oleoylethanolamine (OLEA), N-arachidonolylserine, and various N-acyltaurines and N-acylsalsolinols (Appendino et al. 2008), and oxygenated eicosatetraenoic acids like the lipoxygenase products 5-, 12-, and 15-hydroperoxyeicosatetraenoic acids (5S-, 12S-, 15S-HPETE), their reduced hydroxyl analogs, prostaglandins, and leukotriene B4 (Ahern 2003; Huang et al. 2006; Wang et al. 2005) (Fig. 2.1).

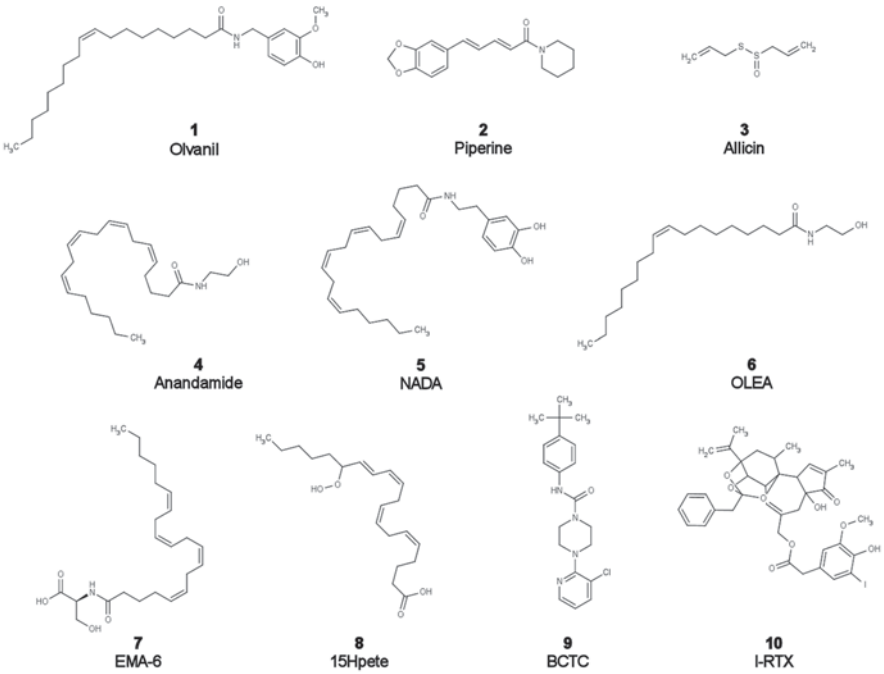

Fig. 2.1 Selected examples of activators (1–8) and inhibitors (9–10) of TRPV1. **1** Olvanil (CID 5311093). **2** Piperine (CID 638024). **3** Allicin (CID 65036). **4** Anandamide (CID 5281969). **5** NADA: N-arachidonoyl dopamine. (CID 5282105). **6** OLEA: N-oleoyl ethanolamine (CID 5283454). **7** EMA-6: N-arachidonoyl serine (CID 10596625). **8** 15-Hpete: 15-hydroperoxy eicosatetraenoic acid (CID 6437084). **9** BCTC (CID 9929425). **10** I-RTX: 5-iodoresiniferatoxin (CID 16219535)

As expected, the activation of TRPV1 in nociceptors with vanilloids causes a burning pain sensation and irritation. Paradoxically, capsaicin has been in use for many years as anti-nociceptive compound in peripheral neuropathies (e.g., post-herpetic neuralgia, neuropathy, mastectomy, amputation and skin cancer). Capsaicin is used as an analgesic, because in addition to activate the channel, it also induces its desensitization. Furthermore, the repetitive application of the vanilloid produces a rundown of channel activity known as tachyphylaxia that results in a strong anti-nociceptive effect (Knotkova et al. 2008). This analgesia may be accompanied by reversible and/or irreversible loss of the capsaicin sensitive C-fibers (Hiura 2000).

Although TRPV1 agonists may have some therapeutic application, their low in vivo activity, along with their poor bioavailability and secondary effects has limited their development as anti-nociceptives, and promoted the research into the design of potent antagonists that display higher therapeutic index. The efforts in developing TRPV1 antagonists have been concentrated in obtaining both competitive and non-competitive (including uncompetitive) inhibitors (Planells-Cases et al. 2003; Szallasi and Appendino 2004). Uncompetitive antagonists acting as open channel

blockers are activity-dependent blockers that preferentially bind to over-activated receptors, with minimal interaction with the physiologically working channels. Accordingly, they are supposed to display lower side-effects than conventional antagonists.

Among the competitive TRPV1 antagonists (Fig. 2.1), capsazepine was the first identified, although with poor in vivo activity (Bevan et al. 1992; Walker et al. 2003). A vanilloid with better therapeutic potential is 5-iodo-RTX, a potent TRPV1antagonist (IC_{50} = 3.9 nM) (McDonnell et al. 2002; Wahl et al. 2001). This compound produced notable analgesic activity in vivo and it is currently under clinical studies.

The family of competitive antagonists grew tremendously thanks to the contribution of pharmaceutical companies that established strong drug discovery programs for TRPV1 channels. As a result, ultra-high affinity synthetic antagonists were discovered for analgesic drug development. However, most of the clinical trials for these compounds had to be cancelled in Phase I because the indiscriminate blockade of TRPV1 channels with these compounds resulted in significant hyperthermia in humans, suggesting that this receptor also plays a pivotal role in core body temperature (Gavva et al. 2008).

The first non-competitive TRPV1 antagonist was the trinuclear polyamine complex, ruthenium red that was followed by arginine-rich peptides, and peptidomimetic compounds such as peptoids DD00069 and DD01050 (Garcia-Martinez et al. 2002, 2006). All these compounds resulted in unacceptable in vivo side effects and toxicity that prevented their clinical development. Recently, an uncompetitive antagonist, based in a triazine scaffold (triazine 8aA) that block TRPV1 channel by an activity-dependent mechanism was reported (Vidal-Mosquera et al. 2011). Triazine 8aA showed a strong voltage-dependent TRPV1 blockade by inhibiting at negative membrane potential, a hallmark of open-channel blockers. This compound holds promise for therapeutic development, although in vivo activity in pain models has not been yet reported.

Allosteric modulators of TRPV1 activity are another class of non-competitive antagonists. These compounds interfere with the allosteric mechanism that gates the channel. Structure-function analysis of TRPV1 channels demonstrated that the intracellular TRP domain, a highly conserved region adjacent to the receptor internal gate (Venkatachalam and Montell 2007), is essential for subunit tetramerization and allosteric activation (Garcia-Sanz et al. 2004, 2007). Thus, this protein interface could be used as an allosteric site to modulate channel function. Indeed, compound TRP-p5, a palmitoylated 13-mer peptide patterned after the N-terminus region of the TRP domain, displays in vitro and in vivo inhibitory activity (Valente et al. 2011). This finding is proof-of-concept that allosteric modulators such as TRPducins represent another family of non-competitive antagonists that could be developed therapeutically as anti-nociceptives.

A complementary approach to reduce the inflammatory sensitization of TRPV1 has been to interfere with the recruitment of the channel to the neuronal surface. This strategy has proven that blockers of neuronal exocytosis such as compound DD04107 display analgesic activity (Ponsati et al. 2012). In vitro experiments with DD04107 showed that it blocked the inflammatory over expression of TRPV1

channels to the plasma membrane (Camprubi-Robles et al. 2009). In vivo, this compound displays long-lasting anti-nociceptive activity against inflammatory and neuropathic pain, without apparent side effects, demonstrating that acting on the TRPV1 signalplex may be a valuable pharmacological strategy (Ponsati et al. 2012). This compound is being developed clinically.

2.3 TRPV2

At variance with TRPV1 channels, the pharmacology of its close homologue TRPV2 is still in its infancy (Peralvarez-Marin et al. 2013). This non-selective $Ca2^{+}$ channel is also present in the peripheral nervous system and co-localizes with TRPV1 in a subset of nociceptors (Liapi and Wood 2005). The physiological role of this TRP channel is yet elusive. Initially was considered a thermoTRP channel that activated at 52 °C, and also responded to hypotonicity (Caterina et al. 1999; Muraki et al. 2003). However, these are still highly debated functions (Park et al. 2011; Peralvarez-Marin et al. 2013), thus requiring further investigation, including the discovery of agonists and antagonists that could be used as pharmacological tools.

The identification of specific TRPV2 modulators is, surprisingly, inexistent, probably due to the species-specific pharmacology coupled with problems in developing stable recombinant cell lines due to cytotoxic effects of TRPV2 expression (Penna et al. 2006). Several chemical compounds have been shown to modulate TRPV2, however, virtually all of them are non-specific (Table 2.1 and Fig. 2.2). Indeed, TRPV2 is activated by general TRP channel agonists, such as 2-aminoethoxy-diphenyl borate (2-APB), probenecid, lysophospholipids, and cannabinoids (Juvin et al. 2007; Monet et al. 2009; Qin et al. 2008). However, the response to these ligands is low and variable and quite species-dependent (Neeper et al. 2007).

To date, only general blockers such as ruthenium red and trivalent cations ($La3^{+}$ and $Gn3^{+}$) (Table 2.1), have been described as blockers of TRPV2 (Leffler et al. 2007). In addition, the potassium channel blockers tetraethylamonium (TEA), 4-aminopyridine (4-AP), and 1-(2-(trifluoromethyl)phenyl)imidazole are also able to block TRPV2 currents (Vriens et al. 2009). Other reported inhibitors are SKF96365, amiloride, and Tranilast, an antiallergic drug (Juvin et al. 2007; Mihara et al. 2010) (Fig. 2.2).

2.4 TRPV3

TRPV3 is a non-selective $Ca2^{+}$ channel that plays a pivotal role in various physiological processes in the skin and hair follicles. This channel displays a moderate sequence homology to TRPV1. TRPV3 is mainly located in keratinocytes and epithelial cells (Nilius and Owsianik 2011; Valdes-Rodriguez et al. 2013), and marginally in sensory neurons (Nilius et al. 2014). This TRP channel is a polymodal receptor

Table 2.1 Representative modulators of depicted TRP channels

Ion channel	Activators	Representative blockers
TRPV1	Capsaicin, resiniferatoxin, olvanil, piperine, eugenol, camphor, 2-APB, allicin, anandamide, NADA, OLEA, N-arachidonolylserine 5S-, 12S-, 15S-HPETE, prostagalandine, leukotriene B4	Capsazepine, ruthenium red, DD01050, 5-iodo-RTX, Triazine 8aA, TRP-p5
TRPV2	2-APB, probenecid, lysophospholipids, cannabinoids	Ruthenium red, La^{3+}, Gn^{3+}, TEA, 4-aminopyridine, 1-(2-(trifluoromethyl)phenyl) imidazole, SKF96365, amiloride, Tranilast.
TRPV3	2-APB, 17(R)-resolvin D1, PIP_2, diphenylboronic anhydride, farnesyl pyrophosphate camphor, carvacrol, eugenol, menthol, thymol, borneol, cresol, carveol, gerianool, propofol, linalool, incensole, citral	Ruthenium red, icilin, isopentenyl pyrophosphate chromane-, fused pyrimidine-, fused pyrimidinones-, chromanone- and fused imidazole-derivatives
TRPV4	Endocannabinoids, arachidonic acid metabolites, nitric oxide, diaculglycerol, bisandrographolide A, 4αPDD phorbol derivatives, GSK1016790A, RN-1747	RN-1734
TRPC5	Thioredoxin, lysophosphatidylcholine, lanthanides, genistein, diadzein	SKF-96365, BTP-2, flufenamic acid, chlorpromazine, W-13, calmidazolium, W-7, 2-APB, ML-7, ML-9
TRPM3	Pregnenolone sulphate, dihydro-D-erythro-sphingosine, N,N-dimethyl-D-erythro-sphingosine, dihydropyridine nifedipine	2-APB, Gd^{3+}, rosiglitazone, troglitazone, mefenamic acid, cholesterol, naringenin, hesperetin
TRPM8	Menthol, icilin, geraniol, D3263	AMTB, JNJ41876666, BCTC, Thio-BCTC, clotrimazole, econazole, SKF-96365
TRPA1	Allyl isocyanate, cinnamaldehyde, allicin, nifedipine, chlorpromazine, auranofin, clotrimazole, clioquinol, apomorphine, glibenclamide, BCTC	HC-030031, GRC-17536, A-967079, piperazineurea, N-1-Alkyl-2-oxo-2-aryl amide, 1,8-cineole, chlorpromazine, toxin ProTx-I

activated by non-painful temperatures (Peier et al. 2002a; Smith et al. 2002; Xu et al. 2002), and chemical stimuli (Xu et al. 2006a), including natural irritants and synthetic ligands (Xu et al. 2006a), and endogenous compounds, some of them involved in the downstream inflammatory cascade (Doerner et al. 2011; Sherkheli et al. 2009). Stimulation of TRPV3 releases inflammatory mediators from keratinocytes including ATP, prostaglandin E2 and IL-1, which supports its contribution to pain transduction and inflammatory signaling. Indeed, in certain human disease states there are changes in the expression of TRPV3, such as an increase in painful breast tissue (Matta et al. 2008), or a decrease in keratinocytes in diabetic neuropathy (Facer et al. 2007).

Some evidence points to phosphatidyl inositol-4,5-bisphosphate and 17(R)-resolvin D1 as putative in vivo modulators of TRPV3 (Bang et al. 2012; Doerner et al. 2011) (Table 2.1). A role of 17(R)-resolvin D1 as potential analgesic mediated by TRPV3 has been described, although a direct evidence is still missing (Bang et al.

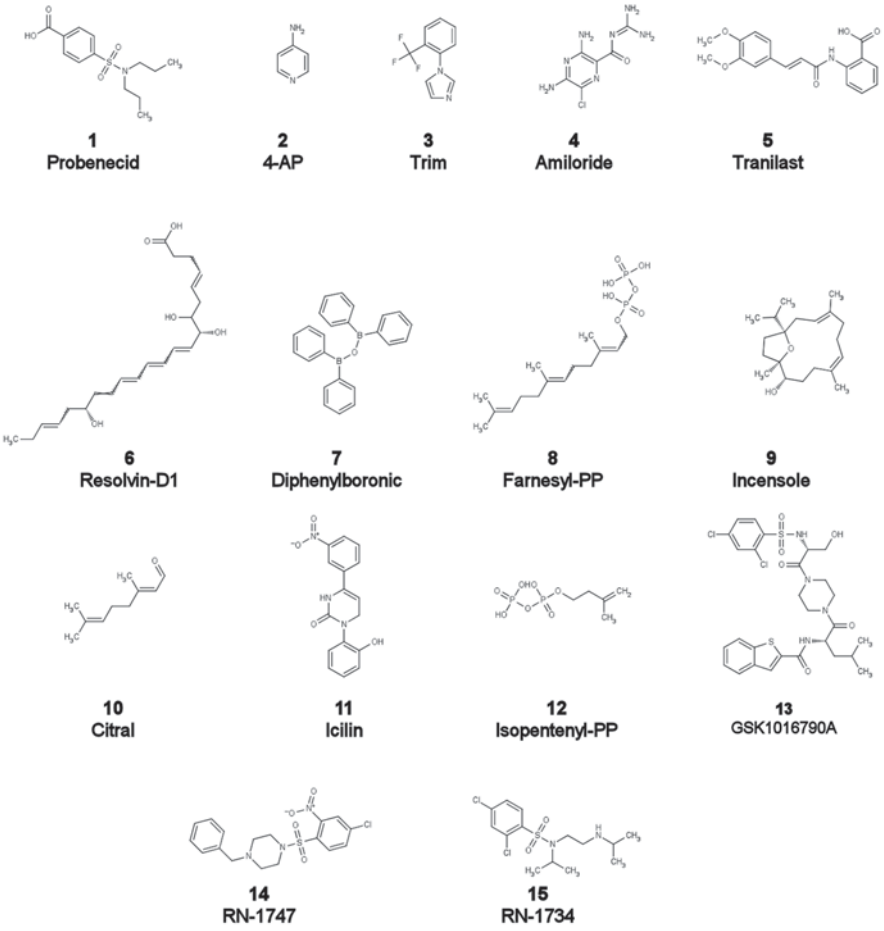

Fig. 2.2 Selected examples of TRPV2-4 effectors**.** TRPV2 activators (1) and inhibitors (2–5). TRPV3 activators (6–10) and inhibitors (11–12). TRPV4 activators (13–14) and inhibitors (15). **1** probenecid (CID 4911). **2** 4-AP: 4-aminopyridine (CID 1727). **3** Trim: 1-(2-(trifluoromethyl) phenyl) imidazole (CID 1359). **4** Amiloride (CID 16231). **5** Tranilast (CID 5282230). **6** Resolvin-D1: 17(R)-resolvin D1 (CID 71434077). **7** Diphenylboronic anhydride (CID 596810). **8** Farnesyl pyrophosphate (CID 44134714). **9** Incensole (CID 44583885). **10** Citral (CID 638011). **11** Icilin (CID 161930). **12** Isopentenyl pyrophosphate (CID 1195). **13** GSK1016790A (CID 23630424). **14** RN-1747 (CID 5068295). **15** RN-1734 (CID 3601086)

2012). Similarly, TRPV3 has been related with the production of nitric oxide via a nitrite independent pathway (Miyamoto et al. 2011). Furthermore, farnesyl pyrophosphate and isopentenyl pyrophosphate, intermediates of the melanovate pathway, are activator and inhibitor respectively, suggesting a fine-tuning of TRPV3

function (Bang et al. 2010; 2011). Alfa-hydroxy acids are proton donors commonly used in cosmetics to produce skin exfoliation mediated by TRPV3 activation (Cao et al. 2012).

The pharmacology of the TRPV family is far from simple, and TRPV3 is not an exception (Table 2.1 and Fig. 2.2). 2-APB also activates TRPV3 (Chung et al. 2004; Hu et al. 2004, 2009). Prolonged exposure of TRPV3 to 2-APB induced sensitization (Sherkheli et al. 2009). Structurally related 2-APB compounds such as diphenylboronic anhydride also act as potent TRPV3 agonists (Chung et al. 2005).

Natural aromatic monoterpenes, such as camphor, carvacrol, eugenol, menthol, thymol, as well as borneol, cresol, and others are an additional class of TRPV3 ligands (Moqrich et al. 2005; Vriens et al. 2009; Xu et al. 2006a). Camphor is a weak agonist for TRPV3 that activates currents only at concentrations of 10 mM. Carvacrol is responsible for arterial vasodilation by activating TRPV3 channels in the endothelium (Earley et al. 2010), which may account for some of their attributed cardioprotective effects. In addition to camphor and carvacrol, thymol and eugenol have also been shown to enhance the temperature response of TRPV3 (Macpherson et al. 2006; Xu et al. 2006a).

Non-aromatic monoterpenes such as carveol and derivatives (monocyclic), or gerianool, propofol and linalool (acyclic) display strong TRPV3 agonism (Vogt-Eisele et al. 2007). Incensole and incensole acetate are diterpenic cembrenoids found in incense (Boswellia papyrifera) potently activate TRPV3. The traditional use of these natural products is related to anti-inflammatory effects through the activation of TRPV3 in the skin. Interestingly, incensole acetate produces anxiolytic and antidepressive effects in mice (Moussaieff and Mechoulam 2009; Paul and Jauch 2012). Citral, a bioactive component of lemongrass is also an agonist of TRPV3 (Stotz et al. 2008), adding to the list of compounds acting on this channel (Fig. 2.2).

Cannabinoids such as cannabidiol or delta-9-tetrahydrocannabinol modulate nonspecifically TRPV3. Other derivatives such as cannabigerovarin or cannabigerolic desensitize TRPV3 (De Petrocellis et al. 2012). Active research is necessary in this field because, interestingly, the activation of TRPV3 by these compounds may contribute to their described in vivo activity (Anand 2003; Galeotti et al. 2001; Santos and Rao 2001; Umezu et al. 2001; Xu et al. 2005a).

TRPV3 antagonists include the non-specific ruthenium red, that blocks all TRPV family member at negative potentials (Vennekens et al. 2008). The compound icilin, which is a strong agonist of TRPM8 channel, is an inhibitor of TRPV3 at low doses (Sherkheli et al. 2012). Novel inhibitors are under study and have promising analgesic effects, which further suggests the involvement of TRPV3 in pain transduction (Reilly and Kym 2011). Several pharmaceutical industries have reported strong and selective TRPV3 antagonists including series of chromane-, fused pyrimidine-, fused pyrimidinones-, chromanone- and fused imidazole-derivatives (Ferrer-Montiel et al. 2012). Some of these antagonists are currently under clinical studies to treat human pain conditions.

2.5 TRPV4

Transient Receptor Potential Vanilloid 4 (TRPV4) a non-selective $Ca2^{+}$ channel is a homologue of the OSM-9 osmosensory channel first described in C. elegans. TRPV4 is activated by warm temperatures (27–35 °C) (Guler et al. 2002; Liedtke et al. 2000), and is sensitive to cell swelling and shear stress (Gao et al. 2003; Kohler et al. 2006; Loukin et al. 2010; Strotmann et al. 2000). Functions include temperature monitoring in skin keratinocytes, osmolarity sensing in the kidney (Pochynyuk et al. 2013), and shear stress detection in blood vessels, which indicates that TRPV4 functions as a putative mechanosensor (Nilius et al. 2003a, b), and is involved in nociception (Alessandri-Haber et al. 2005, 2006). It has been reported that TRPV4 may be activated by hypotonic solutions, and by mechanical forces in membrane patches (Loukin et al. 2009). TRPV4 may contribute to development of mechanical hyperalgesia after inflammation and injury (Alessandri-Haber et al. 2006). This channel is expressed in several tissues, including primary sensory neurons (Alvarez et al. 2006; Birder et al. 2007; Guler et al. 2002; Pochynyuk et al. 2013; Strotmann et al. 2000; Tabuchi et al. 2005; Watanabe et al. 2002b; Yang et al. 2006).

TRPV4 is activated by endogenous chemical ligands, such as endocannabinoids, arachidonic acid metabolites and nitric oxide (Birder et al. 2007) (Table 2.1 and Fig. 2.2). Phorbol esters that do not activate PKC, mediate TRPV4 heat responses (Watanabe et al. 2002a). TRPV4 sensitivity to osmotic and mechanical stimuli may depend on phospholipase A2 activation and the generation of arachidonic acid metabolites (Fernandes et al. 2008; Liedtke et al. 2000; Strotmann et al. 2000; Vriens et al. 2004). Furthermore, TRPV4 is activated by hypotonicity, diacylglycerol, and PKC-activating phorbol esters (Watanabe et al. 2002a, b, 2003).

Natural plant extracts (Klausen et al. 2009), bisandrographolide A (Smith et al. 2006) and synthetic compounds, such as a phorbol derivative (Birder et al. 2007), or GSK1016790A (Thorneloe et al. 2008) also activate TRPV4 channels. In addition, small molecules such as compound RN-1747 was also found to be a TRPV4 agonist (Vincent et al. 2009) (Table 2.1 and Fig. 2.2).

TRPV4 antagonism is being considered for inflammatory and neuropathic pain treatment (Vincent and Duncton 2011). However, selective TRPV4 antagonists have not been described appropriately. Ventilator-induced lung injury has emerged as a potential indicator for TRPV4 antagonists (Jin et al. 2011) (Table 2.1). The small molecule RN-1734 2,4-Dichloro-N-isopropyl-N-(2-isopropylaminoethyl)benzenesulfonamide was observed to inhibit ligand- and hypotonicity-activated TRPV4 (Vincent et al. 2009). In addition, the compound showed selective properties for TRPV4 over other TRPs such as TRPV1, TRPV3 and TRPM8, being a valuable pharmacological tool for TRPV4 studies (Vincent et al. 2009).

2.6 TRPC5

Several mammalian and Drosophila TRP canonical, TRPC proteins (TRPC1-7) have been identified (Plant and Schaefer 2003; Wes et al. 1995; Hardie and Minke 1995). All mammalian TRPCs seem to be enhanced with G-protein-coupled receptors and tyrosine kinases receptors (Montell 1999). The channels may be divided in three subgroups according to sequence homology: C1-C4-C5, C3-C6-C7, and C2 (Zufall et al. 2005). Particularly, TRPC5 is a functional plasma membrane ion channel (Beech 2007) activated by hypo-osmotic stimuli, which is dependent on phosphoinositides (Gomis et al. 2008). The inhibition of TRPC5 has been shown to suppress inflammatory pain induced by the component of the bee venom mellitin (Ding et al. 2011). Several studies support the conclusion that TRPC5 plays a role in growth cone extension and axonal guidance (Davare et al. 2009). A variety of other functions have been assigned to TRPC5, indicating a central role of this channel in physiology (Jiang et al. 2011; Nath et al. 2009; Premkumar and Abooj 2013; Wu et al. 2010; Wuensch et al. 2010; Xu et al. 2008), although the channel is not essential for life (Riccio et al. 2009).

TRPC5 modulation is not well known. A common stimulus for TRPC5 is the activation of G protein-coupled receptor. Many different receptors may be involved, including receptors for adenosine 5'-triphosphate, bradykinin, acetylcholine, histamine, prostaglandin E2, thrombin, uridine 5'-triphosphate, sphingosine-1-phosphate, glutamate and cholecystokinin (Meis et al. 2007; Riccio et al. 2009; Xu et al. 2006b; Zeng et al. 2004). TRPC5 is stimulated by activation of growth factor receptors (Bezzerides et al. 2004). TRPC5 is also a target for thioredoxin, an endogenous redox protein with established intracellular functions. Reduced thioredoxin activates TRPC5 expressed in secretory fibroblast-like synoviocytes when secreted extracellularly in patients with rheumatoid arthritis (Xu et al. 2008). Lysophosphatidylcholine has been identified as a TRPC5 activator (Flemming et al. 2006). Current data suggest a complex arrangement between TRPC5 activity and various lipid factors, supporting the hypothesis that a physiological function of TRPC5 channels is to act as lipid signal transducers.

An unusual feature of TRPC5 is its stimulation by external lanthanides (Jung et al. 2003; Schaefer et al. 2000; Xu et al. 2005b; Zeng et al. 2004). It was reported that ionic lead ($Pb2^{+}$) mimics the effect of lanthanides, leading to the hypothesis that TRPC5 may confer survival advantage by acting as a sensor of heavy metal ions (Sukumar and Beech 2010). Stimulation of TRPC5 by isoflavones like genistein or diadzein has also been reported (Wong et al. 2010) (Table 2.1, Fig. 2.3).

Although no specific or potent exogenous chemical inhibitors of TRPC5 are known, various chemicals have effects on TRPC5 function (Table 2.1). In many of these cases, it is not clear if the agent acts directly on the channel. TRPC5 has been reported to be inhibited by SKF-96365 (Okada et al. 1998), 3,5-bis(tri-fluoromethyl)pyrazole derivative BTP-2 (He et al. 2005; Kiyonaka et al. 2009), flufenamic acid (Lee et al. 2003b), W-13 or chlorpromazine (Shimizu et al. 2006), W-7 or calmidazolium (Kim et al. 2006), Pyr2, 2-APB (Xu et al. 2005b), and the myosin light chain kinase inhibitors ML-7 or ML-9 (Shimizu et al. 2006) (Fig. 2.3).

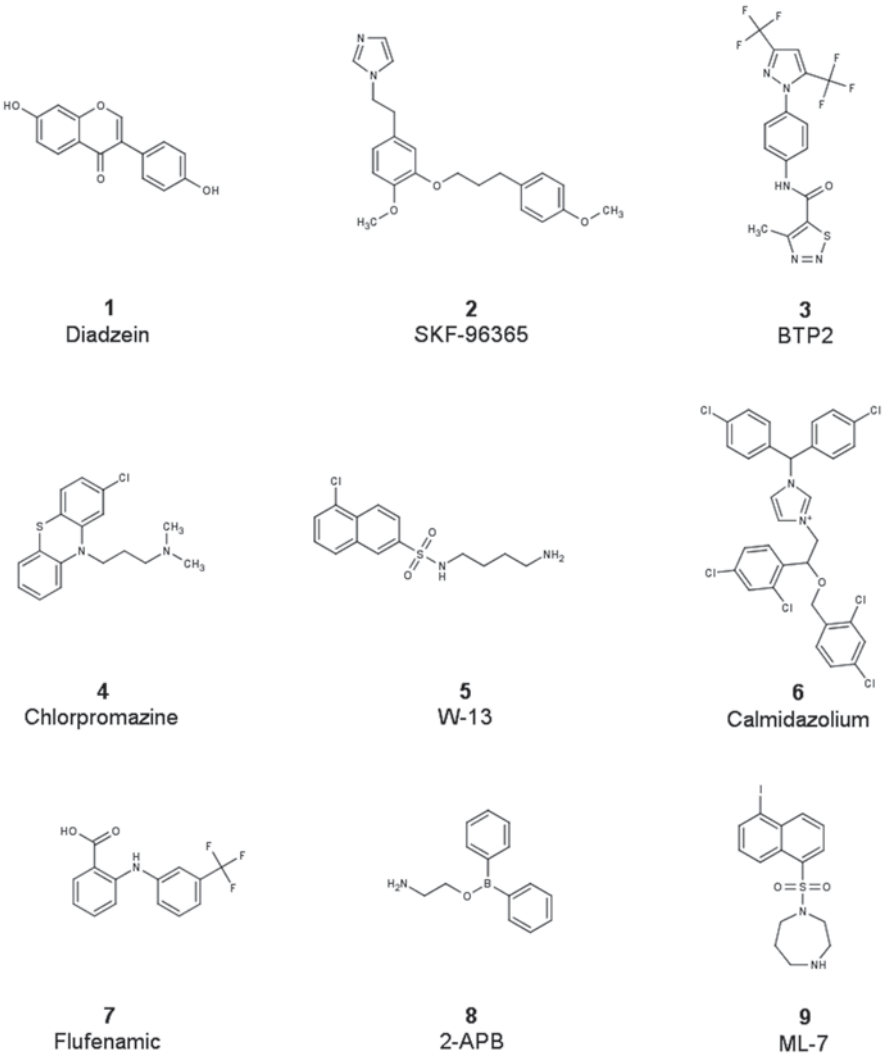

Fig. 2.3 Selected examples of activators (1) and inhibitors (2–9) of TRPC5. ***1*** Diadzein (CID 5281708). ***2*** SKF-96365 (CID 11957693). ***3*** BTP2 (CID 2455). ***4*** Flufenamic acid (CID 3371). ***5*** Chlorpromazine (CID 2726). ***6*** W-13 (CID 4299). ***7*** Calmidazolium (CID 644274). ***8*** 2-APB (CID 1598). ***9*** ML-7 (CID 4216)

2.7 TRPM3

TRPM3, TRP melastatin 3, non-selective $Ca2^{+}$ channel is one of the least investigated proteins of the TRP family of ion channels. In humans, it is highly expressed in the kidney (Grimm et al. 2003; Lee et al. 2003a), brain (Lee et al. 2003a; Oberwinkler 2007), sensory neurons, human pituitary (Fonfria et al. 2006), vascular smooth

muscle (Naylor et al. 2010) and pancreatic beta cells (Thiel et al. 2013; Wagner et al. 2008). However, its physiological role is still under investigation. Activation of TRPM3 has been linked to insulin secretion in pancreatic beta-cells (Wagner et al. 2008), to vascular smooth muscle cell contraction (Naylor et al. 2010), and to potentiating glutamatergic transmission in cerebellar Purkinje neurons of developing rats (Zamudio-Bulcock et al. 2011). A role in pain transduction has also been reported for TRPM3 (Vriens et al. 2011).

Recently, pharmacological investigations have been initiated in order to identify substances that influence TRPM3 channel activity. TRPM3 is rapidly and reversibly activated by extracellular pregnenolone sulphate, a neuroactive steroid. Application of pregnenolone sulphate led to a rapid calcium influx and enhanced insulin secretion from pancreatic islets (Wagner et al. 2008). Pregnenolone sulfate also activates TRPM3 channels in HEK293 cells, vascular smooth muscle cells, and synovial fibroblasts (Ciurtin et al. 2010; Klose et al. 2011; Majeed et al. 2012; Naylor et al. 2010), confirming the functional relevance of TRPM3 in contractile function. However, the concentration of pregnenolone sulfate required to stimulate TRPM3 channels is in the micromolar range, suggesting that pregnenolone sulfate is not a physiological agonist of TRPM3 and may have only pharmacological relevance. Moreover, the fact that TRPM3 deficient mice did not show alterations in resting blood glucose levels (Vriens et al. 2011) suggests that TRPM3 plays a marginal role in controlling β-cell functions.

Two structural analogs of sphingosine, dihydro-D-erythro-sphingosine and N, N-dimethyl-D-erythro-sphingosine, are able to activate TRPM3 (Grimm et al. 2005) (Table 2.1 and Fig. 2.4). Surprisingly, TRPM3 channels are also activated by the dihydropyridine nifedipine, an inhibitor of voltage-gated $Ca2^{+}$ channels, while the structurally related compounds nimodipine, nicardipine, and nitrendipine were inactive (Wagner et al. 2008).

As for many other members of the TRP ion channel family, 2-APB and $Gd3^{+}$ have been reported to inhibit $Ca2^{+}$ influx through TRPM3 channels (Grimm et al. 2003; Harteneck and Schultz 2007; Xu et al. 2005b). Other TRPM3 channel blockers described thus far include the antidiabetic PPARγ-agonists rosiglitazone and troglitazone (Majeed et al. 2012). Nonsteroidal anti-inflammatory drugs (NSAIDs) of the fenamate group, like mefenamic acid are able to selective block TRPM3-mediated $Ca2^{+}$ entry as well as insulin release (Klose et al. 2011). Cholesterol, the precursor metabolite of pregnenolone and progesterone, also prevents TRPM3 channel activation. (Naylor et al. 2010).

Recently, the screening of a compound library revealed that citrus fruit flavanones, such as naringenin and hesperetin, and fabacea secondary metabolites selectively inhibit TRPM3 channel activation with potencies ranged from upper nanomolar to lower micromolar concentrations (Straub et al. 2013) (Table 2.1).

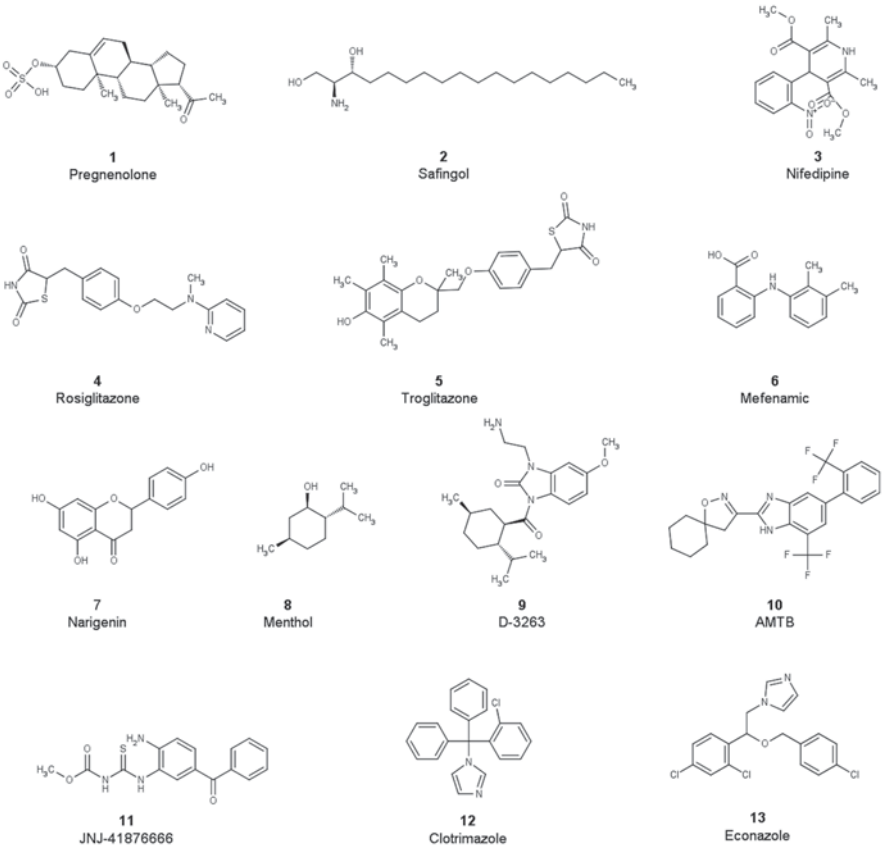

Fig. 2.4 Selected examples of TRPM3 and TRPM8 effectors. TRPM3 activators (1–3) and inhibitors (4–7). TRPM8 activators (8–9) and inhibitors (10–13). **1** Pregnenolone sulphate (CID 105074). **2** Safingol: Dihydro-D-erythro-sphingosine (CID 91486). **3** Nifedipine (CID 4485). **4** Rosiglitazone (CID 77999). **5** Troglitazone (CID 5591). **6** Mefenamic acid (CID 4044). **7** Naringenin (CID 932). **8** Menthol (CID 16666). **9** D-3263 (CID 44137358). **10** AMTB (CID 3036972). **11** JNJ-41876666: Johnson&Johnson patent. **12** Clotrimazole (CID 2812). **13** Econazole (CID 3198)

2.8 TRPM8

TRPM8 is a $Ca2^{+}$ permeable channel that was first identified in prostate cancer cells (Tsavaler et al. 2001; Bidaux et al. 2007), but also is present along the male urogenital tract (De Blas et al. 2009), artery myocytes (Johnson et al. 2009), and lung epithemium cells (Sabnis et al. 2008), although its role in many of these tissues still remains unclear. These channels are expressed in primary sensory neurons in skin and mucosae, with a physiological role in detecting low temperature signals (10–33 °C) (Babes et al. 2011), and in sensing cooling chemicals like menthol and icilin (McKemy et al. 2002; Peier et al. 2002) (Bharate and Bharate 2012; Chuang

et al. 2004). Under pathological conditions, there are increasing experimental evidences that confirm the anomalous over-expression of TRPM8 channels in sensory neurons after nerve injury or inflammation, as well as their involvement in cold allodynia and hyperalgesia (Kapoor 2012; Xing et al. 2007) (Abe et al. 2006; Ramachandran et al. 2013). The activation of TRPM8 also attenuates pain in certain acute and inflammatory pain states, mediating for instance the analgesic effects of menthol (Liu et al. 2013). Therefore, both TRPM8 agonists and antagonists could be valuable analgesic agents (Liu and Qin 2011; Maelkiae et al. 2011). TRPM8 channels are also expressed in corneal afferent neurons implicated in the regulation of ocular surface wetness, and in this respect TRPM8 modulators could have application in dry eye syndrome and excessive lacrimation dysfunction (Fernández-Peña and Viana 2013; Parra et al. 2010).

On the other hand, TRPM8 is abnormally over-expressed in androgen-sensitive prostate cancer (Gkika and Prevarskaya 2011; Tsavaler et al. 2001), breast cancer (Dhennin-Duthille et al. 2011; Ouadid-Ahidouch et al. 2012), skin melanoma cells (Yamamura et al. 2008), human pancreatic adenocarcinoma (Yee et al. 2010), oral scamous cell carcinoma (Okamoto et al. 2012), and osteosarcoma tissues and cell lines (Wang et al. 2014). Again, both agonists and antagonists of TRPM8 have proved to be valid as pharmacological tools for reducing growth and progression of neoplasias with intense expression of TRPM8 channels. Therefore, TRPM8 may also be considered an attractive target for therapeutic intervention in the search for new antitumor agents (Knowlton and McKemy 2011; Lehen'kyi and Prevarskaya 2011).

The crucial role of TRPM8 in the human pathologies is behind the intensive drug-discovery programs developed in recent years around this channel (with more than 25 patents filed since 2009). Among the antagonists, different families having benzotiophene, benzimidazole and arylglycine moieties as the central scaffold have been reported (Calvo et al. 2012; Matthews et al. 2012; Parks et al. 2011; Zhu et al. 2013). Some of these compounds showed excellent *in vitro* and *in vivo* profiles, including activity in animal models of inflammatory and neuropathic pain, thus emerging as strong candidates for future development (Table 2.1). The benzothiophene derivative JNJ41876666 has been used, along with other antagonist, AMTB, and RNAi to determine that the inhibition of either the expression or function of TRPM8 channels reduces the proliferation rate of prostate tumor cells, while no effect was observed in non-tumor cells (Valero et al. 2012).

The commercial antagonist N-(3-Aminopropyl)-2-[(3-methylphenyl)methoxy]-N-(2-thienylmethyl) benzamide hydrochloride AMTB has also served to suggest the potential of TRPM8 channel blocker as a new therapeutic opportunity for treating overactive bladder and painful bladder syndrome (Lashinger et al. 2008). Some tetrahydroquinoline and aza-analogues are TRPM8 antagonists, and a selected compound from this series reduced icilin-induced wet-dog shakes (WDS) in a dose dependent manner (Tamayo et al. 2012). Other chemotypes able to inhibit TRPM8 channels include the piperazine urea derivative BCTC, used to demonstrate that the menthol- and cold-induced allergic responses of mast cells are mediated by TRPM8 (Cho et al. 2010). A series of spiro-chromene-piperidines endowed with high po-

tency and favorable ADME properties are effective in rodent models of neuropathic pain (Chaudhari et al. 2013). SKF-96365 and the antifungic drugs clotrimazole and econazole are also effective blockers of TRPM8 (Madrid et al. 2006; Mälkiä et al. 2009 Meseguer et al. 2014; Table 2.1 and Fig. 2.4).

It has also been described that the Gαq protein, formed after activation of GPCRs, blocks TRPM8 activity by the direct formation of a complex with the channel (Zhang et al. 2012). This could indirectly arbitrate the inhibition of TRPM8 by the inflammatory mediators bradykinin and histamine in sensory nerves, and could open new strategies for modulating these channels, interfering within protein-protein interactions.

TRPM8 agonists are also therapeutically important for attenuating pain, and may induce apoptosis in TRPM8 expressing cancer cells (Maelkiae et al. 2011) (Table 2.1). The most remarkable result in this field refers to the ability of 3-(2-aminoethyl)-1(R)-[(2(S)-isopropyl-5(R)-methyl cyclohexanecarbonyl)]− 5-methoxy-1,3-dihydro-benzoimidazol-2-1 hydrochloride D3263 to inhibit the growth of TRPM8 expressing tumors. This new orally bioavailable chemical entity has already completed Phase I clinical trials in healthy individuals. The company also reported clinical studies on patients with advanced solid tumors, for which the preliminary results indicate disease stabilization after treatment. Some preclinical data also demonstrated the potential of D3263 to treat benign prostatic hyperplasia by itself or in combination with the synthetic 5α-reductase inhibitor finasteride.

2.9 TRPA1

Transient receptor potential ankyrin 1 (TRPA1) is a non-selective $Ca2^{+}$ channel characterized by a high number of ankyrin repeats (14) at the N-terminal domain (Andrade et al. 2012). This channel is activated by multiple stimuli, including temperature, acids, and numerous chemicals, like different noxious environmental and industrial pollutants, oxidant agents and bacterial endotoxins (Bandell et al. 2004; Bautista et al. 2005; Jordt et al. 2004; Levine and Alessandri-Haber 2007; Peterlin et al. 2007; Meseguer et al. 2014). Experimental evidence suggests that TRPA1 is activated by low temperatures, near the threshold of harmful cold for humans (Abrahamsen et al. 2008; del Camino et al. 2010; Karashima et al. 2009), although the categorization of TRPA1 as a cold thermosensor has been controversial.

TRPA1 receptors are vastly expressed in different unmyelinated sensory neurons (Story et al. 2003). They are also expressed in different organs, including the cardiovascular, gastrointestinal, and urinary systems (Andrade et al. 2012). TRPA1 co-localizes with TRPV1 channels at least in a subpopulation of C-type nociceptors (Fajardo et al. 2008). Akin to TRPV1, a number of studies have also established a crucial role of TRPA1 channels in neuronal and non-neuronal neuropathic pain (Barriere et al. 2012; Chen et al. 2011; Wei et al. 2010).

TRPA1 is also involved in respiratory reflexes due to inhaled pollutants (Bessac et al. 2009). These results suggest that the activation of this channel might con-

tribute to asthma and chronic obstructive pulmonary disease (Andre et al. 2008; Materazzi et al. 2010). TRPA1 is also activated by electrophilic products generated during oxidative processes, suggesting that these channels may act as sensors for the tissue damage during inflammatory processes (Taylor-Clark et al. 2008). Furthermore, TRPA1 channels have been identified as targets of allyl isocyanate, cinnamaldehyde, nifedipine, chlorpromazine, auranofin, as well as of clotrimazole, clioquinol, apomorphine, glibenclamide (Andrade et al. 2012; Babes et al. 2013), which provides some pharmacological basis for painful side effects of some of these drugs (Table 2.1 and Fig. 2.5).

The TRPA1 channel is considered a promising target for the development of new, clinically relevant drugs in different therapeutic areas (Baraldi et al. 2010). In this respect, the past few years have seen the emergence of novel TRPA1 antagonists, with more than 30 patents filed by different academic and non-academic institutions. Compounds claimed in these patents belong to different chemical

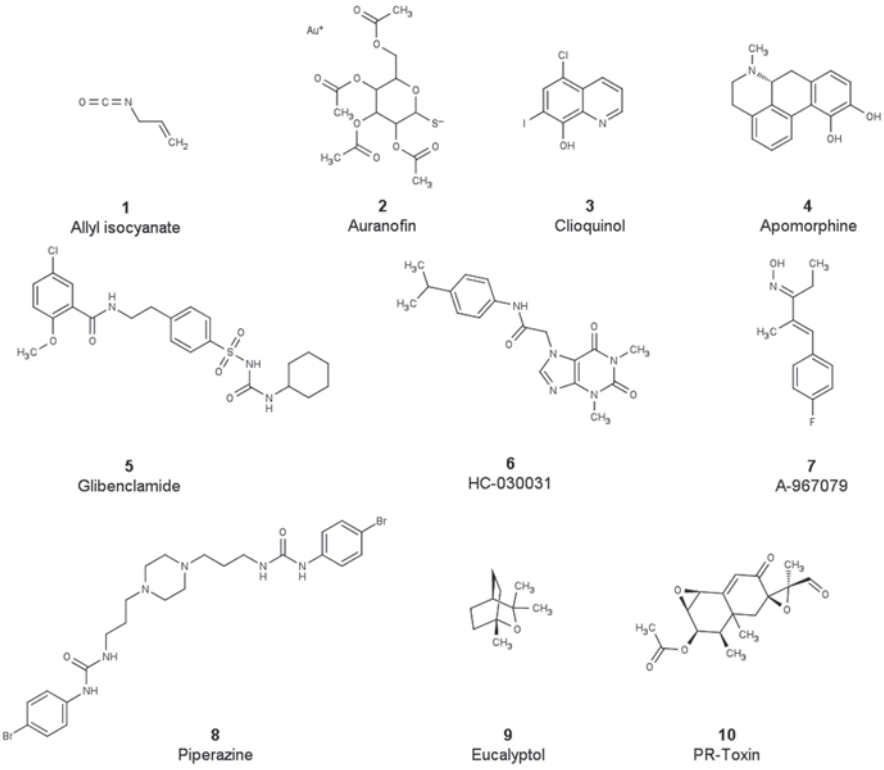

Fig. 2.5 Selected examples of activators (1–5) and inhibitors (6–10) of TRPA1. **1** Allyl isocyanate (CID15123). **2** Auranofin triethylphosphane (CID 24199313). **3** Clioquinol (CID 2788). **4** Apomorphine (CID 6005). **5** Glibenclamide (CID 3488). **6** HC-030031 (CID 1150897). **7** A-967079 (CID 42641861). **8** Piperazine urea (CID 96934). **9** Eucalyptol: 1,8-cineole (CID 2758). **10** PR-Toxin (CID 56844124)

families, but a number of them are related to fused pyrimidindione derivatives displaying efficacy in various models of pain (Table 2.1). Among the pyrimidindione antagonists, we can mention compound HC-030031 and its isobutyl analogue Chembridge-5861528, which are being profusely used as pharmacological tools for studying the implication of TRPA1 channels in pathophysiological pain, among other disorders (Koivisto et al. 2012; Meotti et al. 2013; Samer et al. 2008; Shigetomi et al. 2012). A small library of related pyrrolo[3,2-d]pyrimidinone derivatives with micromolar antagonist potencies was described (Baraldi et al. 2012). In addition, compound GRC-17536 has successfully completed Phase I clinical trials and, since 2012, is under Phase II studies in patients with painful diabetic neuropathy. Good efficacy was also observed when this selective compound was administered by the inhalation route, and a Phase IIa study is ongoing in people with refractory chronic cough.

The oxime derivative A-967079 is a TRPA1 antagonist that inhibits $Ca2^{+}$ influx through this channel at nanomolar concentrations, displayed moderate/good oral biovailability, and was active in models of inflammatory and neuropatic pain (Chen et al. 2011). Related analogues, showing either modest TRPA1 agonist or antagonist properties, have been described (DeFalco et al. 2010). Other chemotypes displaying potent TRPA1 antagonist properties include N-arylsufonyl-proline derivatives, piperazineurea, and N-1-Alkyl-2-oxo-2-aryl amide (Vallin et al. 2012). In addition, a series of 3-ylidenephtahlides and some leucettamol marine products were described to display a dual action, since they are able to activate the TRPA1 channel and to block the related cold sensor TRPM8 (Chianese et al. 2012; Ortar et al. 2013). On the contrary, the 1,8-cineole, an essential oil from eucalyptus, evoked inward currents through human TRPM8, but inhibited TRPA1 activation (Takaishi et al. 2012). BCTC, a good blocker of TRPM8 at micromolar concentrations is also a strong activator of TRPA1 at similar concentrations (Madrid et al. 2006) (Table 2.1 and Fig. 2.5). All these structures may be considered versatile templates towards novel TRP channel modulators.

Very recently, toxin ProTx-I was identified as a high-affinity TRPA1 antagonist. This Cys-rich peptide, isolated from the venom of the Peruvian green-velvet tarantula, also behave as an antagonist of voltage-gated sodium (NaV1.2) channels (Gui et al. 2014). However, mutations by Ala-scan indicated subtle differences in the structural requirements for binding to both ion channels. These findings open the possibility of using this peptide as the starting point for the development of new TRPA1 modulators. The use of ProTx-I, its mutants and the above indicated antagonists as pharmacological tools could certainly contribute to deepen our knowledge of TRPA1 function under physiological and pathological conditions, and to shed light on its gating mechanism.

2.10 Concluding Remarks

TRP channels pharmacology has been evolving a different pace for the members of this channel family, resulting in a plethora of modulators for few TRP proteins and a lack of ligands for the vast majority. However, technical advances in automated electrophysiology, along with an increase in the chemical diversity provided by synthetic and natural libraries most likely will change this conspicuous pharmacological unbalance. Furthermore, the discovery that allosteric modulators may be derived from the protein sequence will probably accelerate the discovery of TRP modulators. Moreover, the finding that TRP channel signalplexes are central to their function open new venues for drug intervention by targeting protein complexes involved in channel expression or signaling. Taken together, all these strategies will expand TRP pharmacology, even to previously considered non-druggable TRP channels.

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