Mast cell stabilizing drugs inhibit the release of allergic mediators from mast cells and are used clinically to prevent allergic reactions to common allergens. Despite the relative success of the most commonly prescribed mast cell stabilizer, disodium cromoglycate, in use for the preventative treatment of bronchial asthma, allergic conjunctivitis and vernal keratoconjunctivitis, there still remains an urgent need to design new substances that are less expensive and require less frequent dosing schedules. In this regard, recent developments towards the discovery of the next generation of mast cell stabilizing drugs has included studies on substances isolated from natural sources, biological, newly synthesized compounds and drugs licensed for other indications. The diversity of natural products evaluated range from simple phenols, alkaloids, terpenes to simple amino acids. While in some cases their precise mode of action remains unknown it has nevertheless sparked interest in the development of synthetic derivatives with improved pharmacological properties. Within the purely synthetic class of inhibitors, particular attention has been devoted to the inhibition of important signalling molecules including spleen TK and JAK3. The statin class of cholesterol-lowering drugs as well as nilotinib, a TK inhibitor, are just some examples of clinically used drugs that have been evaluated for their anti-allergic properties. Here, we examine each approach under investigation, summarize the test data generated and offer suggestions for further preclinical evaluation before their therapeutic potential can be realized.

Abbreviations
AXE, *Amomum xanthiodes*; BEL, bromoenol lactone; BMMCs, bone marrow-derived cultured murine mast cells; CerK, ceramide kinase; CHMCs, cultured human mast cells; CMTs, chemically modified tetracyclines; DNP, dinitrophenyl; hCBMCs, human umbilical cord blood-derived cultured mast cells; iPLA2β, calcium-independent phospholipase A2; KL, c-kit ligand; PTL, parthenolide; RBL, rat basophilic leukaemia; SQLTs, sesquiterpene lactones; Syk, spleen TK; TGA, C70-tetraglycolic acid; TLCK, tosyl-L-lysine chloromethyl ketone; TPCK, Nα-tosyl-L-phenylalanine chloromethyl ketone

Introduction
Mast cells play a fundamental role in the occurrence of allergic diseases because of their hypersensitive response to otherwise innocuous substances that induces an allergic reaction. The allergic reaction begins with the interaction of allergen with polyvalent IgE-FcεRI complexes expressed on the surface of sensitized mast cells that causes receptor aggregation. A complex signalling cascade follows involving the activation of numerous signalling proteins such as spleen TK (Syk) and Lyn kinase, which in turn cause a series of downstream signal transduction events within the mast cell. Ultimately, this signal transduction process leads to calcium influx and release of preformed chemical mediators such as histamine from mast cells as well as the synthesis of lipid mediators such as PGs and LTs and the production of cytokines and chemokines. The actions of these mediators on their receptors and surrounding tissue as well as their recruitment of other immune cells are responsible for the early and late effects of an IgE-mediated allergic reaction. Mast cells are therefore central players in both the development and maintenance of allergic diseases and are subsequently considered an attractive therapeutic target in the treatment of allergic diseases such as asthma, allergic rhinitis and allergic conjunctivitis.

Mast cells play a prominent role in the immunopathology of the immediate-hypersensitivity reaction, which occurs in response to contact with certain allergens. Human
Mast cells are key effector cells in the occurrence and maintenance of an allergic reaction. Sensitized mast cells respond to the exposure of a foreign substance by orchestrating a complex downstream signalling cascade within the mast cell resulting in the release a variety of chemical mediators. The effect of these mediators on surrounding cells and tissues are what cause the symptoms and severity of an allergic reaction.

An allergic reaction may be prevented or attenuated by interfering with certain signalling molecules within the signalling cascade of the mast cell. A primary target of intracellular signalling upon mast cell activation is PLCγ1, which is recruited to the membrane where it is tyrosine phosphorylated by Syk and Bruton’s TK. PLCγ1 catalyses the breakdown of membrane phospholipid PIP2 to generate the second messengers inositol-1,4,5-triphosphate (IP3) and DAG (Suh et al., 2008). These signalling molecules are responsible for the activation of PKC isoforms and the release of calcium (Ca2+) from intracellular stores, respectively (Cho et al., 2004). This results in a transient rise in intracellular-free Ca2+, which triggers the entry of calcium from the extracellular environment. Degranulation and release of chemical mediators from the mast cell follows resulting in the onset of the allergic response. Agents that prevent mediator release from these cells are termed mast cell stabilizers with examples discovered over the last decade from natural, semi-synthetic and synthetic sources.

**Sources of mast cell stabilizers**

Nature has provided us with the basis of many medicines in clinical use today (Table 1). Indeed, the inspiration behind DSCG arises from the earlier data generated on Khellin, a plant-derived mast cell stabilizer from *Ammi visnaga*. In the first section of this review, emphasis will be placed on recent studies with natural products with particular emphasis placed on flavonoids/phenolics, terpenoids, alkaloids and biologics. The discussion will then focus on work conducted with synthetic mast cell stabilizers whose structure was inspired from studies on plant-derived materials. The final section of the review will focus on recent developments on rationally designed specific inhibitors as well as studies with proprietary medications for other indications that also have been shown to stabilize mast cells (Figure 1).

**Mast cell stabilizing agents from natural sources**

**Flavonoids.** Flavonoids can be subdivided into many different classes including flavones, flavonols, flavonones, isoflavones and flavonol-3-ols and anthocyanidins. Regardless of the individual subdivisions, all contain the benzo-γ-pyrone architecture and are classified according to the presence of different substituents on the rings and to the degree of saturation of the benzo-γ-pyrone ring. Within the flavone class, the most active mast cell stabilizers are luteolin, diosmetin and apigenin. Using anti-IgE to elicit degranulation, luteolin inhibited the release of histamine, LTs, PGs, and GM-CSF from human cultured mast cells (HCMCs) in a concentration-dependent manner (1–100 μM) (Kimata et al.,...
# Table 1

Naturally occurring mast cell stabilizers

<table>
<thead>
<tr>
<th>Source of MC stabilizers</th>
<th>Compound name</th>
<th>Mast cell population</th>
<th>Elicitor</th>
<th>In vivo evaluation</th>
<th>Reference</th>
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<td>Unspecified</td>
<td>Kimata et al., 2000b</td>
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<td></td>
<td></td>
<td>BMMCs</td>
<td>anti-IgE and IL-3</td>
<td></td>
<td>Kimata et al., 2000a</td>
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<td></td>
<td></td>
<td>Basophils</td>
<td>Antigen</td>
<td></td>
<td>Hirano et al., 2006</td>
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<tr>
<td></td>
<td></td>
<td>RBL-2H3</td>
<td></td>
<td></td>
<td>Mastuda et al., 2002</td>
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<td><strong>Diosmetin</strong></td>
<td>RBL-2H3</td>
<td>Antigen</td>
<td></td>
<td>Unspecified</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kimata et al., 2000a</td>
</tr>
<tr>
<td><strong>Quercetin</strong></td>
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<td>Anti-IgE, phorbol-12-myristate-13-acetate, calcium ionophore A23187 and PMACI</td>
<td></td>
<td>Unspecified</td>
<td>Park et al., 2008</td>
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<td>Park et al., 2007</td>
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<td></td>
<td>Lee et al., 2010</td>
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<td></td>
<td>Kempuraj et al., 2006</td>
</tr>
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<td><strong>Fisetin</strong></td>
<td>RBL-2H3</td>
<td>anti-IgE, PMACI</td>
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<td></td>
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<td>PMACI</td>
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<td>Park et al., 2007</td>
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<td><strong>Kaempferol</strong></td>
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<td>Park et al., 2008</td>
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<td>KL</td>
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<td>Son et al., 2005</td>
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<td>Compound 48/80</td>
<td>PCA reaction in rats</td>
<td>Li et al., 2005</td>
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<td>Compound 48/80</td>
<td>PCA reaction in mice</td>
<td>Choi and Yan, 2009c</td>
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<td>PMACI</td>
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<td><strong>Scaporone</strong></td>
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<td>anti-DNP IgE</td>
<td>PCA reaction in rats</td>
<td>Choi and Yan, 2009a</td>
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<td><strong>Artekeiskeanol A</strong></td>
<td>RBL-2H3 cells</td>
<td>Calcium ionophore A23187</td>
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<td>Hong et al., 2009</td>
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<td>Antigen</td>
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<td>KL</td>
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<td>anti-DNP IgE</td>
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<td>Choi and Yan, 2009b</td>
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<tr>
<td><strong>Magnolol and honokiol</strong></td>
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<td>IgE-antigen</td>
<td>PCA reaction in rats</td>
<td>Han et al., 2007</td>
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<td><strong>Resveratrol</strong></td>
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<td><strong>Polydatin</strong></td>
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<td>Anti-IgE</td>
<td>PCA reaction in mice</td>
<td>El-Agamy, 2012</td>
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<td><strong>Curcumin</strong></td>
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<td>Antigen</td>
<td>PCA reaction in mice</td>
<td>Lee et al., 2008</td>
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<td><strong>Mangostin-α, -β and -γ</strong></td>
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<td><strong>Parthenolide</strong></td>
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<td><strong>Sesquiterpene lactones (SQLTs)</strong></td>
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<td><strong>Amino acids</strong></td>
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<td>RPMCs and HMC-1 cells</td>
<td>Compound 48/80</td>
<td>PCA reaction in mice</td>
<td>Kim et al., 2011</td>
</tr>
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</table>
Luteolin also suppressed the production of proinflammatory cytokines TNF-α and IL-6 in bone marrow-derived cultured murine mast cells (BMMCs) (Kimata et al., 2000a). Luteolin and apigenin were strong inhibitors of production of IL-4 by purified basophils following combined challenge with anti-IgE and IL-3 (Hirano et al., 2006). Both luteolin and diosmetin showed potent inhibitory effects on the release of β-hexosaminidase from antigen-stimulated rat basophilic leukaemia (RBL)-2H3 cells with IC_{50} values of 3.0 μM and 2.1 μM, respectively. Additionally, these three flavones inhibited anti-IgE-mediated production of TNF-α and IL-4 from this cell line (Mastuda et al., 2002). The structure of the flavonols differs from the flavones by the presence of an additional hydroxy-substituent at position 3. Examples of flavonols, which have demonstrated anti-allergic activity include kaempferol, fisetin, quercetin and morin. Kaempferol, fisetin and quercetin inhibited anti-IgE, phorbol 12-myristate 13-acetate and calcium ionophore A23187 (PMACI)-induced histamine release in RBL-2H3 cells when evaluated at a relatively high concentration of 30 μM. Additionally, fisetin and quercetin decreased gene expression and production of proinflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-8 in PMACI-stimulated HMC-1 cells (Park et al., 2008). Fisetin was also shown to decrease gene expression of IL-4, inhibit the phosphorylation of p38 MAPK, ERK and JNK and suppress the activation of NF-κB (Park et al., 2007). Quercetin and kaempferol inhibited the secretion of mediators at concentrations of 1 and 10 μM from RBL-2H3 cells stimulated by anti-IgE antibodies and suppressed mRNA expression of CD23 and p38 MAPK activation in Caco-2 cells stimulated by IL-4 (Lee et al., 2010). These flavonols also significantly inhibited the release of histamine and cytokines; TNF-α, IL-6 and IL-8 from human umbilical cord blood-derived cultured mast cells (hCBMCs) activated by anti-IgE and decreased the elevation of intracellular Ca^{2+} in this cell line (Kempuraj et al., 2005). Quercetin has been shown to down-regulate the mRNA transcription of histidine decarboxylase in HMC-1 cells, an enzyme involved in the synthesis of histamine (Kempuraj et al., 2006). Morin prevented the degranulation and the production of cytokines such as TNF-α and IL-4 in both RBL-2H3 cells and BMMCs stimulated by antigen at low concentrations (1–10 μM). Morin demonstrated inhibition of activating phosphorylation of Syk. In vivo, this flavonol suppressed IgE-mediated passive cutaneous anaphylaxis (PCA) in mice almost completely at a dose of 100 mg·kg^{−1} (Kim et al., 2009). The isoflavone, genistein inhibited degranulation of HCMCs challenged with anti-IgE in a dose-dependent manner with inhibition of histamine release by 92% at concentration of 100 μg·mL^{−1}. Additionally, at this concentration, it inhibited phosphorylation of cellular proteins such as ERK-1 and ERK-2, which are involved in the downstream signalling cascade of activated mast cells (Suzuki et al., 1997). Similarly, genistein also inhibited histamine release and protein TK activation in BMMCs stimulated with antigen (Kawakami et al., 1992). The biflavone, ginkgetin, isolated from the leaves of Ginkgo biloba, demonstrated a dual COX-2/5-lipooxygenase inhibitory activity and was subsequently shown to inhibit the production of the de novo mediators, PGD_{2} and LTC_{4} in BMMCs stimulated with c-kit ligand (KL). Additionally, ginkgetin inhibited release of β-hexosaminidase from these cells stimulated with KL in a dose-dependent manner with IC_{50} value of 6.52 μM (Son et al., 2005).

Epigallocatechin gallate (EGCG), a constituent found in green tea is related to the flavonoid family, but differs from the core flavone and flavonol structure by the absence of the double bond and carbonyl group at positions 2–3 and 4, respectively. EGCG demonstrated anti-allergic activity in

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Figure 1
Sources of mast cell stabilizers. Significant data have been published on evaluating the mast cell stabilizing properties of natural products and their semi-synthetic derivatives, despite the fact that in many cases, their precise mechanism of action remains unknown. The data published on purely synthetic mast cell stabilizers have been more focussed on targeting specific events involved in the allergic cascade.
both in vitro and in vivo models. It significantly inhibited the release of compound 48/80-induced degranulation of histamine in rat peritoneal mast cells (RPMCs). EGCg also suppressed compound 48/80-induced PCA reaction in rats (Li et al., 2005). EGCg also inhibited antigen-induced degranulation and LTC₄ secretion in RBL-2H3 cells across a concentration range of 10–100 μM and has been shown to block store-operated Ca²⁺ entry of this cell line, which is the main route of calcium influx in mast cells that leads to the degranulation of allergic mediators (Inoue et al., 2010).

Silymarin is a mixture of polyphenolic flavonoids isolated from milk thistle (Silybum marianum) and is used primarily for its treatment of liver diseases such as hepatitis, cirrhosis and jaundice. One of its primary constituents, silybinin was shown to inhibit the release of histamine from RPMCs stimulated by compound 48/80 and anti-DNP as well as the secretion of proinflammatory cytokines such as TNF-α and IL-6 from anti-DNP induced degranulation of RPMCs in a dose-dependent manner (10–100 μM). In vivo, silybinin inhibited compound 48/80-induced PCA reaction, in mice dose-dependently (10–100 mg·kg⁻¹) (Choi and Yan, 2009c).

**Coumarins.** Several reports exist that describe the mast cell stabilizing properties of coumarins. Scopletin (6-methoxy-7-hydroxycoumarin), which has been isolated from several plant species including Erycibe obtusifolia Benth inhibited the production of proinflammatory cytokines including TNF-α, IL-6 and IL-8 from the HMC-1 following challenge with PMACl. These cytokines play a role in triggering and sustaining allergic inflammation. However, scopletin did not affect the release of histamine induced by agents from HMC-1 cells (Moon et al., 2007). Interestingly, scoporone, the methylated analogues of scopletin dose-dependently decreased histamine release from rat peritoneal mast cells stimulated by anti-DNP IgE at concentrations ranging from 25 to 100 μM. It also inhibited PCA reaction in rats dose-dependently at concentrations of 10, 25 and 50 mg·kg⁻¹. Scoporone also reduced the expression and secretion of proinflammatory cytokines such as TNF-α and IL-6 (Choi and Yan, 2009a).

The coumarin, artekeiskeanol A, isolated from Artemisia keskeana Miq. suppressed degranulation of RBL-2H3 cells induced by antigen and calcium ionophore A23187 in a concentration-dependent manner (10–100 μM). Artekeiskeanol A also suppressed the mRNA levels of proinflammatory cytokines TNF-α and IL-13 and phosphorylation of signalling kinases such as p38 MAPK and JNK, which are involved in downstream signalling events (Hong et al., 2009). Selinadin, a coumarin derived from Angelica keiskei attenuated the release of β-hexosaminidase from bone marrow-derived mast cells (BMMCs) stimulated by antigen and the production of proinflammatory mediators such as LT C₄ and TNF-α. Selinadin also decreased phosphorylation of PLCγ-1 and p38 MAPK, enzymes involved in the signalling pathway of degranulation (Kishiro et al., 2008). The furanocoumarin, 5-methoxy-8-(2-hydroxy-3-butoxy-3-methylbutyloxy)-psoralen, isolated from Angelica dahurica inhibited both COX-2 and 5-lipoxygenase activity and generation of the lipid mediators PGD₂ and LTC₄. This furanocoumarin also prevented degranulation of mice BMMCs activated with KL (Hua et al., 2008). Interestingly, cinnamic acid, which might be considered as a precursor to the coumarin structure, markedly suppressed antigen-stimulated degranulation of β-hexosaminidase from RBL-2H3 cells in a dose-dependent manner (10–100 μM) through inactivation of Syk and PLCγ pathways (Ninomiya et al., 2010). Thunberginols A and B are isocoumarin derivatives isolated from the processed leaves of Hydrangea macrophylla var. thunbergii, which have shown anti-allergic activity by inhibiting histamine release from RPMCs stimulated by calcium ionophore A23187 and antigen (Matsuda et al., 1999). Thunberginol B demonstrated potent activity by completely inhibiting degranulation against both elicitors at a concentration of 30 μM. They both also inhibited degranulation of RBL-2H3 cells stimulated by calcium ionophore and antigen as well as the release of cytokines TNF-α and IL-4 (Wang et al., 2007). Thunberginol B was also shown to inhibit mRNA expression of several cytokines including IL-2, IL-3, IL-4 and IL-13, TNF-α and granulocyte/macrophage colony-stimulating factor (GM-CSF) in RBL-2H3 cells stimulated by antigen (Matsuda et al., 2008).

Ellagic acid (2,3,7,8-tetrahydroxy[1]benzopyrano [5,4,3-c(de)l]benzopyran-5,10-dione) is a polyphenolic compound found in fruits and nuts such as raspberries, strawberries, walnuts, longan seeds, mango kernel and pomegranate, which has shown to attenuate anti-IgE-mediated allergic response in vitro and in vivo. Ellagic acid dose-dependently inhibited histamine release as well as the secretion of proinflammatory cytokines such as TNF-α and IL-6 from anti-DNP IgE induced degranulation of RPMCs across a concentration range of 50–200 μM. Ellagic acid attenuated anti-DNP IgE-mediated PCA in rats (Choi and Yan, 2009b).

**Phenols.** Magnolol and honokiol are phenolic structural isomers, isolated from the bark of Magnolia obovata that have shown to potently inhibit the degranulation of RBL-2H3 cells induced by IgE–antigen complex as well as the production of cytokines; IL-4 and TNF-α. Moreover, both compounds potently inhibited PCA reactions in mice induced by IgE–antigen complex dose-dependently at doses of 10 and 50 mg·kg⁻¹ (Han et al., 2007). Resveratrol, is a phytoalexin, stilbene polyphenolic compound found in grapes, berries and peanuts. It suppressed the expression of inflammatory cytokines such as TNF-α, IL-6 and IL-8 in PMACl-induced–HMC-1 cells and decreased the levels of intracellular Ca²⁺ (Kang et al., 2009). Likewise, the anti-allergic activity of polydatin, a resveratrol glucoside, significantly decreased FcεRI-mediated degranulation in IgE-sensitized RBL-2H3 cells in a dose-dependent manner (1–100 μM) and inhibited the IgE-dependent PCA reaction in mice (300 mg·kg⁻¹; El-Agamy, 2012). Curcumin is a polyphenolic compound found in Curcuma longa and related species. Curcumin has demonstrated anti-allergic activity in both in vitro and in vivo models. It significantly inhibited antigen-induced degranulation in a dose-dependent manner (1–10 μM) in both RBL-2H3 cells and BMMCs and moreover suppressed PCA reaction in mice at doses of 0.5–50 mg·kg⁻¹. Curcumin significantly inhibited the expression of mRNA for cytokines; IL-4 and TNF-α in a dose-dependent manner as well as their secretion in antigen-stimulated RBL-2H3 cells (Lee et al., 2008). The xanthones; mangostin-α, β and γ isolated from the pericarp of Garcinia mangostana L. inhibited the release of histamine from IgE-sensitized RBL-2H3 cells in response to antigen.
through suppression of the signalling transduction pathway involving Syk and PLCγ (Itoh et al., 2008).

Within the flavonoid, coumarin and phenolic classes, it is evident from studies conducted to date that the precise mechanism by which these substances stabilize mast cells remains largely unknown. As with most planar molecules, as in these series, it is perhaps conceivable that many processes in the allergic cascade are targeted. This point is reinforced by the broad spectrum of biological actions exhibited by these classes of compounds and from the evidence presented above where they show effects against many different cell populations. The hypothesis that truly selective inhibitors of a given molecular target can only be generated from three-dimensional molecules is perhaps reinforced by findings within these studies. Nevertheless, as the allergic cascade may involve several inflammatory pathways, the idea of designing anti-allergic substances with multiple mechanisms of actions may have potential advantageous therapeutically.

Terpenoids. Some recent examples of mast cell stabilizers from the terpenoid class include parthenolide (PTL), a sesquiterpene lactone isolated from the herb feverfew (Tanacetum parthenium), extracts from which exhibit anti-inflammatory properties and are used for the treatment of migraine (Murphy et al., 1988). PTL has also shown anti-allergic properties both in vitro and in vivo models. PTL inhibited antigen-IgE-induced degranulation of both RBL-2H3 cells and BMMCs at low concentrations (0.6–5 μM) and strongly inhibited PCA reaction in mice by approximately 90% at a concentration of 10 mg·kg⁻¹. PLT was also shown to strongly suppress IgE-antigen-induced cytoskeletal rearrangement in RBL-2H3 cells, which is considered a critical step for the degranulation process in mast cells (Miyata et al., 2008). Dehydroeleucodine, a sesquiterpene lactone isolated from Artemisia douglasiana Besser and xanthatin, a xanthanolide lactone isolated from Xanthium cavanillesii Schouw inhibited the release of the mediator serotonin from RPMCs induced by compound 48/80. Both substances showed more potent inhibitory activity than the established mast cell stabilizers, disodium cromoglycate and ketotifen (Penissi et al., 2009). Nine types of sesquiterpene lactones (SQTls) isolated from Eupatorium chinense L. suppressed the degranulation from antigen-stimulated RBL-2H3 cells and furthermore were shown to suppress the elevation of intracellular Ca²⁺. In vivo, the sesquiterpene lactones-rich extract potently inhibited PCA reaction induced by antigen–IgE complex in mice in a dose-dependent manner (Itoh et al., 2009). Monoterpenes including: borneol and camphene, terpene alcohol; linalool and sesquiterpene; nerolidol in the form of an extract of Amomum xanthiodes (AXE) showed good anti-allergic activity both in both in vitro and in vivo screens. AXE reduced histamine release from RPMCs stimulated by compound 48/80 in a dose-dependent manner and also reduced the level of intracellular Ca²⁺. AXE suppressed compound 48/80-induced PCA reaction in mice (Kim et al., 2007).

Alkaloids. Within the alkaloid class, sinomenine (SIN) (7,8-didehydro-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one), an alkaloid isolated from Sinomenium actum inhibited antigen-induced mast cell degranulation in RBL-2H3 cells in a dose-dependent manner from 0.5 to 2 mM. Similarly, SIN also inhibited the production of cytokines; IL-4 and TNF-α as well as the phosphorylation of various proteins involved in downstream signalling of activated mast cells such as Gab2 and p38 MAPK (Huang et al., 2008). Indoline (E,Z)-3-(3’,5’-dimethoxy-4-hydroxy-benzylidene)-2-indolindone, an alkaloid isolated from the medicinal plant Isatis tinctoria, demonstrated anti-allergic activity in vitro. Indoline-inhibited degranulation of BMMCs stimulated by antigen efficiently across a concentration range of 50–1000 nM. Indoline does not affect kinase activity directly downstream of FcεRI, but interrupts with granule exocytosis possibly by binding to proteins on the surface of granules such as soluble NSF (N-ethylmaleimide-sensitive factor) attachment protein receptors, which play an essential role in the exocytosis of mast cells (Kieler et al., 2010). Likewise, indoline inhibited compound 48/80-induced degranulation of RPMCs to a greater effect than that of the clinically used mast cell stabilizer, DSCG (Ruster et al., 2004). Xestospongin C is an alkaloid isolated from the sponge Xestospongia sp., which inhibited both antigen and thapsigargin induced degranulation of RBL-2H3 cells in a concentration-dependent manner (1–10 μM). It is suggested that xestospongin C exhibits its anti-allergic behaviour by crossing the mast cell membrane and blocking IP₃ receptors on the endoplasmic reticulum membrane. This action prevents Ca²⁺ store depletion and as a result inhibits the elevated levels of intracellular Ca²⁺ that is necessary for mast cell degranulation (Oka et al., 2002). Theanine is the major amino acid present in green tea. Recently, the anti-allergic activity of theanine has been elucidated in both in vitro and in vivo models. The amino acid inhibited compound 48/80-induced histamine release from both RPMCs and HMC-1 cells in a dose-dependent manner and showed significant activity at low concentration (1 μM). Additionally, theanine significantly suppressed the secretion of proinflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-8 by suppressing NF-κB activation in PMACI-stimulated HMC-1 cells. This activity was translated to the in vivo setting as theanine inhibited PCA reaction in mice at 1 mg·kg⁻¹ concentration. It is suggested that it acts as a mast cell stabilizer by preventing perturbation of the lipid bilayer of mast cells (Kim et al., 2011).

Biologics. Studies with biological inhibitors of mast cell degranulation have included the use of complement-derived peptide C3a. It was shown to inhibit degranulation of RBL-2H3 cells and BMMCs stimulated by antigen in a dose-dependent manner by interacting with the β-chain of FcεRI on mast cells. The binding of C3a to the mast cells caused a decrease in the proximity of IgE binding to FcεRI and as a result, suppressed the activating phosphorylation of TKs and the activity of PLCγ that are necessary for the signal transduction process involved in the degranulation of mast cells (Erdei et al., 1999). A complement peptide derived from C3a, namely C3a9 inhibited the immediate phase response of antigen-stimulated–RBL-2H3 cells by causing dissociation of TKs, Lyn and Fyn with FcεRI and the inactivation of downstream MAPK, p38 and ERK. C3a9 also inhibited late phase responses of stimulated BMMCs by suppressing the secretion of proinflammatory cytokines such as IL-6 and TNF-α (Petryer et al., 2008). Likewise, several other anti-allergic peptides have been identified, namely IVA, LSY, RVS, ETI, TDG, RVV
and GFW, which inhibited antigen-stimulated release of β-hexosaminidase from RBL-2H3 cells. These peptides decreased the influx of Ca\(^{2+}\) and the phosphorylation of Lyn, ERK and PKC (Kim et al., 2008). [Ala\(^{12}\)] mast cell degranulating (MCD) peptide effectively competes with IgE in the binding affinity to FcɛRI on mast cells and has consequently shown to inhibit antigen-stimulated mediator release in RBL-2H3 cells by 50% at 100 μM concentration (Buku et al., 2005). Subsequently, Buku et al., developed a range of modified peptide analogues of [Ala\(^{12}\)] MCD, which conserved the alanine residue in position 12. Analogue [Val\(^6\), Ala\(^{12}\)] MCD 7 is a potent inhibitor of IgE-mediated degranulation of RBL-2H3 cells causing almost complete inhibition at low concentrations (10 and 20 nM; Buku et al., 2008).

**Semi-synthetic inhibitors of mast cell degranulation**

Natures’ medicine cabinet has provided us and others with the inspiration to generate novel mast cell stabilizing compounds, stimulated by both simplicity of synthesis and observed biological effects in related systems (Figure 2). In this respect, initial studies focussed on analogues of the pterosins, which are indane sesquiterpenes from *Pteridium aquilinum* Kuhn var. *latiusculum* (Hikino et al., 1976). Of particular interest was the indaneone, pterosin Z, 1, (Farrell et al., 1996), a compound that exhibited potent smooth muscle relaxant activity by inhibiting calcium-induced contraction of guinea pig ileum (Sheridan et al., 1999). As calcium plays a central role in mast cell exocytosis, it was hypothesized that the pterosin indaneone family of compounds may also act as inhibitors of mast cell mediator release. Earlier investigations focused on the synthesis of analogues of this compound (Frankish et al., 2004). Within this series, the most active compound was the propanoic acid analogue 2, which demonstrated similar inhibition of compound 48/80-induced release from RPMC at 20 μM to DSCG. Encouraged by the somewhat fortuitous synthesis of and observation that dimer-type compounds containing the indane skeleton exhibited twofold superior activity to that of DSCG in mast cell assays, work commenced on building libraries of indane dimer-based compounds, which were not only investigated as mast cell stabilizers, but also as smooth muscle relaxants. Although preliminary findings indicated that no correlation existed between the structure and dual activity of these compounds, mast cell stabilizing compounds with superior activity to that of DSCG emerged from this study (Sheridan et al., 2009b). In later studies, diastereomers of a benzylated indanol dimer compound as exemplified by 3 and 4, which maintain the indanol and indenyl structural fragments were synthesized and shown to demonstrate dual mast cell stabilizing and anti-inflammatory effects in a range of *in vitro* and *in vivo* studies (Sheridan et al., 2009a). While the data generated on the indane dimer series of compounds was encouraging, further studies were conducted to elucidate the exact features in these structural types that were necessary for activity. Initial studies involved replacement of one of the indane units by a tetralin skeleton in the overall molecular framework of the compounds. Replacement of either the indanol or indenyl moiety of these diasteroisomers by the corresponding tetralol or dihydronaphthalene groups to give the benzylated dimer alcohols 5 and 6 resulted in these compounds exhibiting potent mass cell stabilizing activity against several elicitors including; compound 48/80 (5; IC\(_{50}\) 4.1 μM, 6; IC\(_{50}\) 7.7 μM), concanavalin A (5; IC\(_{50}\) 0.75 μM, 6; IC\(_{50}\) 3.6 μM) and calcium ionophore A23187 (5; IC\(_{50}\) 10 μM, 6; IC\(_{50}\) 4.7 μM), in the RPMC assay (Barlow et al., 2011a). Similarly, potent mast cell stabilizing activity was observed...
against compound 48/80-induced release (IC_{50} value of 3.3 μM) when the indanol core of 3 was deconstructed to give the naphthalenyl analogue 6 (Barlow et al., 2011a). Earlier concurrent studies also identified a series of aminoindanones, including 7, 8 and 9. The cyclopentyl aminoindanone 7 and the substituted 1- and 2-indanyl aminoindanones 6 and 9, respectively demonstrated substantial mast cell stabilizing activity in rodent models (Sheridan et al., 2008). As a branched series of compounds, the effect of ring expansion of the core indane skeleton(s) to tetralone on the pharmacological activity was investigated and shown in most cases to retain the activity of the indaneone series *in vitro* and *in vivo* (Barlow and Walsh, 2008; 2010). Like the aminoindanone congeners as exemplified by 8, both the allyl 9 and methyl 10, 11 derivatives in this series demonstrated excellent mast cell stabilizing ability when evaluated *in vitro* against compound 48/80-induced release from RPMC. Enlarging the ring further to give the benzosuberone series (7-membered B-ring) with the amino bearing a more bulky substituted benzyl group, either retained or enhanced the inhibition of mediator release from mast cells relative to 7 *in vitro* (Barlow et al., 2011b), as in good agreement with the individual stereoisomer of 12 (Byrne et al., 2011).

**Synthetic inhibitors of mast cell degranulation**

**Syk inhibitors.** Synthetic inhibitors of mast cell activation and degranulation include those that interfere with and inactivate signalling proteins and receptors required for the signal transduction of the allergic cascade (Table 2). As an example, Syk is an important mediator of immunoreceptor signalling in mast cells and other immune cells that cause inflammation. Activated Syk phosphorylates a variety of substrates including linker for activation of T cells (LAT), which orchestrates downstream signalling resulting in degranulation and cytokine gene transcription. Consequently, Syk is a potential target for the treatment of hypersensitivity reactions such as allergic rhinitis, asthma, urticaria and anaphylaxis. Studies by Mazuc et al. have shown that Compound 13 inhibited FcεRI-induced degranulation *in vitro* in RBL-2H3 cells and PCA reaction *in vivo*. It also impeded the interaction of Syk with other cellular signalling molecules by binding at the interface between two Src homology (SH2) domains and the interdomain A of Syk (Mazuc et al., 2008). Other Syk kinase inhibitors include a series of 2, 4-diaminopyrimidines, of which the title compound, R112 demonstrated potent inhibition of Syk kinase in *in vitro* studies. R112 completely and rapidly inhibited histamine release in allergen-induced basophils in addition to lipid mediator and cytokine production of cultured HMCs (HMCs) stimulated by allergen. The mechanism of action of R112 was confirmed to inactivate Syk, which consequently prevented the phosphorylation of LAT (Y191) and hence prevented its activation and the signalling cascade leading to degranulation (Rossi et al., 2006). In clinical trials, R112 rapidly ameliorated the symptoms of allergic rhinitis in hypersensitive individuals (Masuda and Schmitz, 2008). ER-27317, an acridone-related compound, inhibited mast cell response by preventing the phosphorylation and activation of Syk kinase. *In vitro*, ER-27317 inhibited degranulation in a dose-dependent manner in RBL-2H3 cells, RPMC and HMCs, all stimulated by antigen. Almost complete inhibition was demonstrated at a concentration of 30 μM in both rodent and human cell models. ER-27317 selectively interferes with FcεRy phospho-ITAM activation of Syk thus preventing the ensuing signalling cascade (Moriya et al., 1997). More recently, 3-buty1-1-chloro-8-(2-methoxycarbonyl) phenyl-5H-imidazo[1,5-b]isoquinolin-10-one (U63A05) dose- dependently inhibited degranulation of RBL-2H3 cells and BMMCs stimulated by antigen across a concentration range of 1–10 μM. This compound also suppressed the secretion of proinflammatory cytokines. U63A05 exerts it inhibitory effects on the activating phosphorylation of Syk, thereby preventing downstream activation of signalling molecules that lead to degranulation. *In vivo*, U63A05 suppressed antigen-stimulated PCA reaction in mice at doses ranging from 10 to 100 mg·kg⁻¹ (Kim do et al., 2011).

**JAK3 inhibitors.** JAK3 is a protein TK expressed in mast cells and plays a pivotal role in the FcεRI-mediated mast cell inflammatory response. JAK3 is activated by cytokines such as IL-2, IL-4, IL-7 and IL-9 upon mast cell activation. This causes phosphorylation and dimerization of STAT 5A for transcription of target genes involved in inflammation (D’Cruz and Uckun, 2007). A selective inhibitor of JAK3, 4-(4’-hydroxyphenyl)-amino-6,7-dimethoxyquinoxaline (WHI-131) inhibited calcium ionophore A23187-induced and IgE/antigen induced degranulation of RBL-2H3 cells in a concentration-dependent fashion from 1 to 30 μM. Additionally, WHI-131 prevented the release of the lipid mediator LTC₄ and the proinflammatory cytokine TNF-α. WHI-131 also prevented PCA reaction in mice by blocking degranulation *in vivo* (Malaviya et al., 1999). However, later studies indicated that degranulation of JAK3 deficient BMMCs from mice were inhibited by WHI-131 to the same extent as wild-type mice which implies that WHI-131 has other underlying mechanisms of mast cell stabilization (Linwong et al., 2005).

Astaurosporine-based compound entitled compound 32 was shown to potently inhibit JAK3-type signalling in different cell types. It inhibited the JAK3 enzyme in Jurkat cells as well as the activating phosphorylation of STAT5 in T cells. Additionally, it demonstrated potent activity in mast cells by inhibiting IgE/antigen-induced hexosaminidase release (IC₅₀ value of 55 nM) as well as the release of the proinflammatory cytokine TNF-α. *In vivo*, this compound reduced ovalbumin-induced IgE production by 70% (30 mg·kg⁻¹) in mice.

**Kit TK inhibitors.** The Kit ligand (stem cell factor) is essential for mast growth, differentiation, survival and enhances antigen-mediated mast cell degranulation. Therefore, inhibition of Kit is an attractive approach to prevent FcεRI-mediated allergic reactions. Hypothenemycin is a resoricylic acid lactone, which blocked Kit activation, inhibited degranulation of both HMCs and BMMCs as well as cytokine production at 10 μM. *In vivo*, hypothenemycin reduced PCA reaction in mice (500 μg·30 g⁻¹) (Jensen et al., 2008).

Midostaurin (PKC412) is a TK inhibitor that interacts with Kit on mast cells and is used in clinical trials to counteract the growth of neoplastic mast cells in mastocytosis. Midostaurin inhibited calcium ionophore A23187-induced degranulation of both the basophil and mast cell lines, KU812 and HMC-1.
<table>
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in a dose-dependent manner at low concentrations (1–1000 nM) (Krauth et al., 2009).

Mast cells are associated with stress-induced inflammatory skin disease such as psoriasis through involvement of substance P present in skin mast cells, which is an initiator of the stress response. CP99994 is a substance P NK-1 antagonist which prevented stress-induced response mast cell mediator release when Sprague-Dawley rats were treated peripherally at (1 and 2 mg·kg\(^{-1}\)) or i.c.v. (5, 10 and 20 μg). It is suggested that NK-1 antagonists may be used therapeutically to treat stress-induced inflammatory skin diseases (Erin et al., 2004).

Ceramide kinase (CerK) inhibition. CerK is an enzyme involved in the phosphorylation of ceramide, a precursor of sphingolipids found in the plasma membrane of cells, which is involved in differentiation and apoptosis of the cell. CerK was found to be involved in the activation of RBL-2H3 cells (Mitsutake et al., 2004). The CerK inhibitor, K1 dose-dependently (10–50 μM) suppressed degranulation of calcium ionophore A23187 induced BMMCs mediator release (Kumada et al., 2007).

Phosphodiesterases (PDEs) inhibition. PDEs are a family of 11 isoenzymes that hydrolyse cyclic nucleotides such as cAMP and cGMP to form inactive metabolites 5'-AMP and 5'-GMP, respectively. These are important secondary messengers involved in many biological processes such as the activation of PKA (a cAMP-dependent Ser/Thr kinase) and PKG (a cGMP-dependent Ser/Thr kinase). Inhibition of cAMP- or cGMP-dependent PDE has the effect of raising the intracellular levels of these nucleotides (Boswell-Smith et al., 2006). Inhibitors of PDEs have shown mast cell stabilizing properties (Weston et al., 1997). The PDE inhibitors of PDE 4, Ro 20–1724 and rolipram, dose-dependently (1–100 μM) inhibited histamine release from anti-IgE induced RPMCs and this inhibitory activity was enhanced when each of these PDE 4 inhibitors were combined with the PDE 3 inhibitor, siguazodan. The level of inhibition of rolipram at 10 μM was 29.4 ± 7.1% which, was elevated in the presence of 1 μM siguazodan to 49.5 ± 7.1% (Lau and Kam, 2005).

Miscellaneous inhibitors. Fullerenes present a carbon sphere structure with delocalised π molecular orbital electrons, which show unusual activity in electron transfer systems. By virtue of their unique properties, fullerene derivatives have been used to treat a range of diseases including types of cancer (Mroz et al., 2007) and neurodegenerative disease (Dugan et al., 1997). Recently, the water-soluble fullerene, C\(_{70}\)-tetracyglycolic acid (TGA) inhibited anti-IgE stimulated degranulation from human skin mast cells (10 μg·mL\(^{-1}\); % inhibition = 39.3 ± 9.2%) and peripheral blood basophils (5 μg·mL\(^{-1}\); % inhibition = 15.8 ± 4.2%). TGA-inhibited GMCSF cytokine production as well as the phosphorylation of mast cell signalling proteins such as ERK 1/2, p38 MAPK, LAT and PI3K, which are involved in the release of chemical mediators. This activity was translated in vivo where TGA suppressed PCA reaction in mice at a concentration of 100 ng. (Norton et al., 2010).

Vacuolin-1 is an inducer of large vacuole formation in various cell types. At a concentration of 10 μM, vacuolin-1 inhibited exocytosis of BMMCs stimulated with antigen, but did not inhibit exocytosis of RBL-2H3 cells under the same conditions. The early stages of mast cell activation such as phosphorylation of LAT, MAPK and ERK were not affected in stimulated BMMCs nor was F-actin polymerization, which is necessary for translocation of secretory granules in the later stages of exocytosis (Shailk et al., 2009).

Chemically modified tetracyclines (CMTs) have shown anti-inflammatory activity such as the inhibition of COX-2-mediated PGE\(_2\) production (Patel et al., 1999). Previously, CMT-3, also known as COL-3 had demonstrated promising anti-tumour activity (Lokeshwar et al., 2002) CMT-3 inhibited compound 48/80 stimulated-RPMCs and HuMCs dose-dependently. In RPMCs, the level of degranulation was reduced from 71.7 ± 4.2% to 28.7 ± 3.4% in the presence of 25 μM CMT-3. Similarly, CMT-3 also inhibited the secretion of cytokines TNF-α and IL-8 from HMC-1 cells and reduced the expression of TNF-α mRNA in these cells. Additionally, CMT-3 inhibited PKC activity with an IC\(_{50}\) value of 31 μM (Sandlet et al., 2005).

Orazipone (OR-1384) and its derivative OR-1958 are novel sulphydryl reactive anti-inflammatory compounds. In in vitro studies, these compounds affect mast cell functions, of which OR-1958 demonstrated the most effective anti-allergic activity. OR-1958 dose-dependently inhibited compound 48/80-induced histamine release from RPMCs with an inhibition value of 56 ± 10% at 20 μM and inhibited the expression of TNF-α mRNA in HMC-1 cells. Both OR-1958 and OR-1384 dose-dependently inhibited the production of TNF-α in HMC-1 cells stimulated by PMACI with IC\(_{50}\) values of 10 and 20 μM, respectively. It is suggested that these sulphydryl compounds exert their effects by inactivating thiol-containing molecules involved in the signal transduction process of activated mast cells (Vendelin et al., 2005).

In addition to inhibiting the release of the protease, tryp-tase, the protease inhibitors, N-α-tosyl-L-lysine chloromethyl ketone (TLCK) and N-p-tosyl-L-phenylalanine chloromethyl ketone (TPCK) have been shown to inhibit the release of histamine from both anti-IgE and calcium ionophore A23187-stimulated lung mast cells in a concentration-dependent manner. The maximum inhibition of histamine release induced by anti-IgE was approximately 40.7% with 100 μg·mL\(^{-1}\) TLCK and 40.2% with 80 μg·mL\(^{-1}\) TPCK (He and Xie, 2004). Later studies showed that TPCK (50 μM) almost completely suppressed degranulation of BMMCs co-stimulated with antigen and adenosine by inhibiting granule movement as well as the secretion of cytokine IL-13. In vivo, TPCK (30 mg·kg\(^{-1}\)) reduced PCA reaction in mice (Nunomura et al., 2008).

Bromoenol lactone (BEL) is a suicide-based irreversible inhibitor of calcium-independent PLA\(_2\) (iPLA\(_2\)) (Hazen et al., 1991). BEL demonstrated inhibition of exocytosis of both RBL-2H3 cells and BMMCs stimulated with either antigen, calcium ionophore A23187 or thapsigargin, with maximal inhibition of exocytosis at a concentration of 25 μM of BEL. The original hypothesis was that BEL prevented the calcium influx mediated by iPLA\(_2\) through SOCCS in these cells. However, BEL also inhibited exocytosis from permeabilized mast cells where Ca\(^{2+}\) entry mechanism was no longer relevant, which suggested that BEL interferes with events downstream of Ca\(^{2+}\) signalling, which are required for exocytosis (Fensome-Green et al., 2007).
Conclusions

Treatment of allergic diseases relies on clinically prescribed drug classes such as mast cell stabilizers and H1 antagonists, which control the symptoms associated with allergic diseases. Mast cell stabilizers act by stabilizing the mast cell upon allergen exposure to inhibit the release of chemical mediators while H1 antagonists antagonise histamine at the H1 receptor to eliminate the effects mediated by this biogenic amine released during an allergic reaction. Although the first generation mast cell stabilisers such as DSCG and nedocromil sodium effectively inhibit mast cell degranulation, the second-generation mast cell stabilisers typified by olopatadine and ketotifen additionally possess anti-histaminic properties which present anti-allergic agents with dual activity.

However, the number of anti-allergic agents is not limited to these drugs in clinical use. It is evident from the numerous reports outlined in this review that a broad range of compounds have been isolated from natural sources that demonstrate substantial anti-allergic activity in a panel of in vitro and in vivo screens. In some situations, their mechanism of action has been elucidated, while in many situations their activity is not solely limited to their effect on mast cells. Indeed, in many situations they, also target many inflammatory events, which may ultimately complement their effect on mast cell degranulation. Moreover, many of these anti-allergic agents are sourced from foodstuffs such as the flavonoid family which enter the body on a daily basis where they could potentially target activated mast cells and attenuate the mast cell response to allergens. The significance of these natural products may be further emphasized by the history of the natural mast cell stabilizer, Khellin, which subsequently led to the synthesis of the first established mast cell stabilizer, DSCG. Additionally, various biological agents such as natural and synthetic peptides have shown promising anti-allergic behaviour by blocking IgE/FcεRI binding or by interfering with the signalling pathway of the allergic response.

Also discussed here are several synthetic compounds that potently inhibit mast cell degranulation. A comprehensive understanding of the pathway involved in the allergic cascade is invaluable towards the design of novel, selective inhibitors of mast cell activation. Inactivation of signalling proteins such as Syk and JAK3 kinases, which play important roles in the signalling cascade of an allergic reaction, are just some of the molecular targets identified in the design of novel mast cell stabilizers. The development of new anti-allergic agents within our own research group and others has identified numerous, indane-, tetralin- and benzosuberone-based compounds that have demonstrated good inhibition of mast cell degranulation, although, in many cases their precise mode of action remains unanswered.

A diverse range of mast cell stabilizing compounds have been identified in the last decade from; natural, biological and synthetic sources to drugs already in clinical use for other indications. Although in many cases, the precise mode of action of these molecules is unclear, all of these substances have demonstrated mast cell stabilization activity and therefore may have potential therapeutic use in the treatment of allergic and related diseases where mast cells are intrinsically involved. However, owing to the heterogeneity of the mast cell, and their molecular targets, the real potential of any new mast cell stabilizer can only be realized once its properties are evaluated in an extended range of preclinical in vitro, ex vivo and in vivo models of efficacy and toxicity.

Old drugs with new uses as mast cell stabilizers. Statins are a class of hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors. This enzyme is essential for the biosynthesis of mevalonic acid, an essential precursor to isoprenoid compounds including cholesterol. Compounds from this series including cerivastatin, atorvastatin and fluvastatin have demonstrated anti-allergic activity. Cerivastatin and atorvastatin inhibited anti-IgE-induced histamine release from mature lung mast cells in a dose-dependent manner. The statin-induced changes in histamine release are expressed as a % of the histamine release induced by anti-IgE. The release of histamine was reduced from 100% to 40.2 ± 14.8% in the presence of 50 μM cerivastatin and reduced to 26.3 ± 13.5% in the presence of 50 μM atorvastatin. Additionally, these statins suppressed cytokine-dependent growth of normal mast cell progenitors in HMC-1 cells, which suggested that these statins are inhibitors of mast cell growth and function (Krauth et al., 2006). Fluvastatin inhibited degranulation of antigen-induced RBL-3H2 cells in a concentration-dependent manner (0.5–10 μM) without affecting cytosolic calcium levels or the granule content of these cells. It is suggested that the inhibitory action of fluvastatin may be mediated by the suppression of geranylgeranyl transferase via the depletion of intracellular mevalonic acid. This leads to the inactivation of small GTP-binding proteins involved in microtubule formation, which are important in the translocation of the granules in a calcium-independent manner (Fujimoto et al., 2009).

Nilotinib is a second-generation TK inhibitor that has been used for the treatment of BCR-ABL-positive chronic myelogenous leukemia. Recently, the anti-allergic effects of nilotinib have been reported. Administration of nilotinib prevented systematic anaphylaxis in mice mediated by compound 48/80 in a dose-dependent manner (5–50 mg·kg⁻¹) and significantly inhibited allergic paw edema in rats at concentrations of 25 and 50 mg·kg⁻¹. In addition, it dose-dependently (5–20 μM) reduced histamine release from RPMCs activated by either compound 48/80 or ovalbumin and attenuated the secretion of pro-inflammatory cytokines as well as TNF-α expression in the RPMCs (Yuan et al., 2012).

The mucolytic agent, ambroxol was shown to inhibit histamine release by more than 50% from human adenoidal mast cells (1000 μM) stimulated by concanavalin A and from skin mast cells (100 μM) stimulated by compound 48/80. Additionally ambroxol inhibited anti-IgE-induced release of histamine, LTC₄, IL-4 and IL-13 from basophils at a concentration of 100 μM (Gibbs et al., 1999).

The loop diuretic, frusemide, used in the treatment of congestive heart failure has been reported to prevent exercise-induced asthma. Frusemide dose-dependently inhibited histamine release from RPMCs within a concentration of 10⁻³–10⁻¹ M stimulated by a various secretagogues known to increase the concentration of intracellular calcium. Frusemide was shown to protect mast cells in a similar manner to DSCG (Stenton and Lau, 1996).
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Conflict of interest

None.

References


