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Diastereoisomers of 2-benzyl-2, 3-dihydro-2-(1*H*-inden-2-yl)-1*H*-inden-1-ol: Potential anti-inflammatory agents

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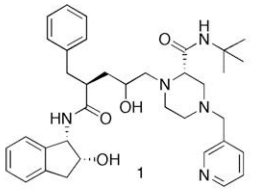
ABSTRACT

The synthesis and biological activity of the novel diastereoisomers of 2-benzyl-2,3-dihydro-2-(1*H*-inden-2-yl)-1*H*-inden-1-ol is reported. The 2,2-coupled indane dimers were synthesised by coupling of the silyl enol ether of 1-indanone with the dimethyl ketal of 2-indanone. The coupled product was directly alkylated to give the racemic ketone which was reduced to the diastereoisomeric alcohols. The alcohols were separated and their relative stereochemistry was established by X-ray crystallography. These molecules demonstrate significant anti-inflammatory activity in vivo and in vitro and may represent a new class of anti-inflammatory agent.

Introduction. Mast cells contain or may produce a wide range of pro-inflammatory mediators and will degranulate following both immunogenic (IgE) and non-immunogenic stimuli such as superoxides, complement, neuropeptides, and lipoproteins. In addition to histamine, mast cells may also release leukotrienes, and prostanoids, many inflammatory cytokines and chemokines as well as the protease enzymes, tryptase and chymase and many of these mediators are key agents in inflammation.[1] As a consequence of their 'sentinal' locations and their panoply of pro-inflammatory mediators, mast cells may play an active role in many inflammatory diseases, such as allergy, asthma, arthritis, atherosclerosis, pulmonary fibrosis, and parasitic diseases. Mast cells may also play a vital role in host defense against pathogens as part of the innate immune system since they express Toll-like receptors (TLR), and respond to TLR ligands such as LPS and peptidoglycan.[2,3]

The indane skeleton features in a range of molecules that display significant and diverse biological activity. The protease inhibitor Indinavir **1** (Crixivan) is used as a component of Highly Active Retroviral Therapy (HART) to treat HIV infection and AIDS.[4] Indacrinone **2** is a potent antidiuretic[5] while indanocine **3** demonstrates significant binding with microtubules.[6] For some time this research group has been working on a group of small biologically active indanes and their dimers. We have established that a number of simple indanes related to the pterosin group of natural products.[7–9] and their 1,2-coupled dimers[10,11] demonstrate smooth muscle relaxant activity and also inhibit histamine release from mast cells. The 1,2-coupled indane dimer **4** has shown significant inhibition of compound 48/80-stimulated histamine release from rat peritoneal mast cells together with moderate smooth muscle relaxation effects which suggested that this class of molecule had potential in the treatment of asthma and warranted further investigation.[11] More recently we have identified a second 1,2-coupled indane dimer **5** with significantly increased mast cell stabilisation activity. However, we did not succeed in our initial aim of combining bronchodilatory and mast cell stabilisation activity in a single molecule.[12]



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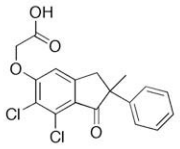

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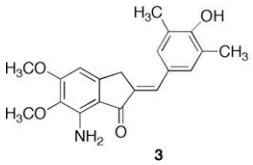

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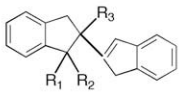

4 R1 = H, R2 = H, R3 = CH_3
5 R1 = H, R2 = OH, R3 = $CH_2CH{:}CHCH_2CH_3$

We have subsequently synthesized and evaluated the activity of related 2,2-coupled indane dimers. We now report on a pair of diastereoisomers (**6** and **7**) which demonstrate significant mast cell

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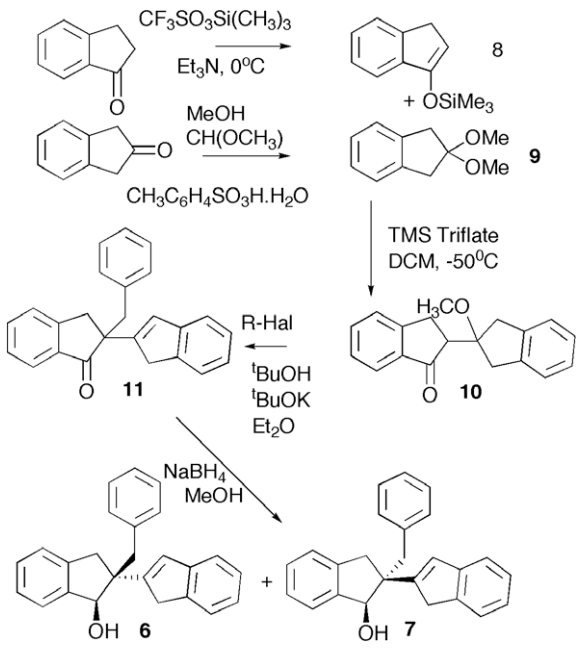
stabilisation and anti-inflammatory effects in a range of in vivo and in vitro screens. We feel that these diastereoisomers represents a potential new class of indane compounds with potential to treat a range of inflammatory conditions. The target 2,2-coupled indane dimers were synthesised as shown in Scheme 1.[13] The key intermediate to this class of dimer **11**, was prepared from **10** which was synthesised by coupling of the silyl enol ether of 1-indanone **8** with the dimethyl ketal of 2-indanone **9**. The coupled product **10** was alkylated to yield **11**. This route has been successfully used to synthesise a range of related dimers. Reduction of **11** yielded the diastereoisomers **6** and **7**. The relative stereochemistry of the pair of diastereoisomers was established by single crystal X-ray analysis of **6** as shown in Figure 1.[14]

Compounds **6** and 7 were evaluated for their smooth muscle relaxant activity, their ability to inhibit histamine release from rat peritoneal mast cells and to inhibit calcium ionophore A23187-stimulated β-hexosaminidase release from RBL-2H3 cells; these latter cells are a histamine-releasing cell line commonly used to model mast cell degranulation.[15] β-Hexosaminidase is released in parallel with histamine and both histamine and β-hexosaminidase release from rat peritoneal mast cells and RBL-2H3 cells, respectively, were used as markers for inhibition of release of inflammatory mediators from the mast cell. The compounds were also assessed for broad anti-inflammatory activity in vivo using the arachidonic mouse ear swelling test.

Smooth muscle relaxant activity was measured by inhibition of calcium contractures of potassium-depolarised isolated guinea-pig ileum.[16] Calcium (2.5 mM) induced a sustained contraction of guinea-pig ileum which was inhibited by 48.1 ± 2.3% by nifedipine (1×10^{-8} M). In contrast, **6** and **7** (1×10^{-5} M) inhibited contractures by 18.9 ± 2.16% and 36.37 ± 5.7%, respectively (Table 1). The difference between the two diastereoisomers was not statistically different ($P > 0.05$). It is unlikely that such a degree of smooth muscle relaxation would be clinically useful.

Following our original observation that similar compounds inhibited calcium contractions of smooth muscle, probably by inhibition of calcium handling in excitation–contraction coupling in smooth muscle cells[6] we had extended our studies to encompass a potential role in excitation–secretion coupling in secretory cells,



Scheme 1. Synthetic route to compounds **6** and **7**.

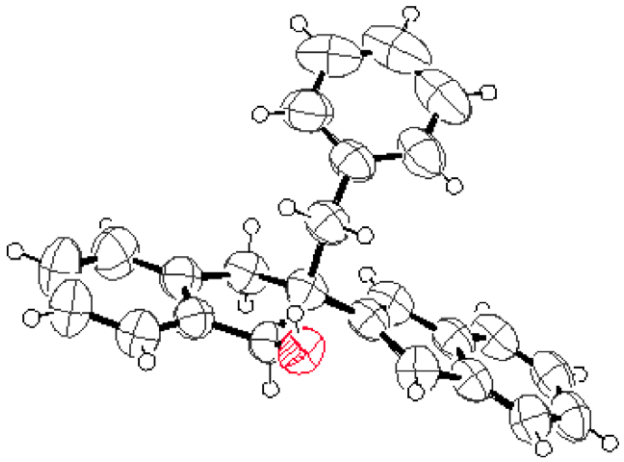


Figure 1. X-ray crystal structure and relative stereochemistry of **6**.

Table 1
Effect of nifedipine (1×10^{-8} M), and compounds **6** and **7** (1×10^{-5} M) on calcium-induced (2.5 mM) contractions of potassium-depolarised guinea-pig ileum

Treatment	Mean	SEM	*n*
Nifedipine	48.1	2.3	6
6	18.88	2.16	6
7	36.37	5.667	12

as histamine release inhibitors in rat peritoneal mast cells.[10] In addition, we have used the histamine-releasing rat cell line RBL-2H3 as a convenient alternative to rat peritoneal mast cells harvested by peritoneal lavage.

Histamine release[17] from rat peritoneal mast cells stimulated by compound 48/80 was inhibited by disodium cromoglycate by only approximately 11% (Table 2). However, **6** and **7** both inhibited histamine release in a much more potent manner, by 84% and 93% from 60.2 ± 5.0% for 48/80-stimulated release to 9.3 ± 1.3% and 4.1 ± 0.4%, respectively, the difference between the two not being statistically different ($P > 0.05$). Similarly, both **6** and **7** (10 μM) inhibited calcium ionophore A23187-stimulated β-hexosaminidase release from RBL-2H3 cells,[17–19] by approximately 45% and 40%, from a solvent (DMSO) control value of 35.2 ± 4.8% to 19.2 ± 3.2% and 21.0 ± 2.8%, respectively (Fig. 2). In comparison, quercetin (10 μM) inhibited enzyme release by approximately 70% to 11.0 ± 1.0% of the total as shown in Figure 3. Furthermore, such inhibition was dose-dependant; concentrations of both **6** (3–50 μM) and **7** (3–50 μM) gave a highly significant ($P < 0.0001$) linear trend, with maximum inhibition at 50 μM being 96% and 75%, from a solvent (DMSO) control value of 80.5 ± 9.4% to 20.1 ± 0.2% and 3.2 ± 0.4% for **6** and **7**, respectively, though there was no significant ($P > 0.05$) difference between **6** and **7** at this concentration.

These results suggest that both **6** and **7** are inhibitors of mediator release from RPMCs and RBL-2H3 cells. Furthermore, in the case of the latter, mediator release is dose-dependant. However,

Table 2
Histamine release from rat peritoneal mast cells stimulated by compound 48/80 (2 μg mL^{-1}) and the effect of DSCG (2×10^{-5} M) and compounds **6** and **7** (2×10^{-5} M)

Treatment	Mean	SEM	*n*
48/80 alone	60.23	4.984	15
DSCG	53.62	4.009	15
6	9.339	0.4251	5
7	4.138	1.316	5