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Original article

Synthesis and antispasmodic activity of analogues of natural pterosins

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Abstract – The synthesis of an extensive range of analogues of natural pterosins using modified Heck coupling is reported. The smooth muscle relaxant activity of these compounds has been examimed. Several compounds with significant smooth muscle relaxant activity have been identified. © 1999 Éditions scientifiques et médicales Elsevier SAS

pterosins / indanones / indanes / smooth muscle relaxant activity

1. Introduction

As part of an ongoing study into the synthesis and smooth muscle relaxant activity of sesquiterpene indanones related to the pterosin family of fern metabolites [1], we have developed an improved synthetic route to pterosin Z (**1**) [2], a metabolite of *Pityrogramma* and *Pteris* species [3, 4]. More recently we have shown that (**1**) exhibits potent smooth muscle relaxant activity [5]. We now report on the synthesis and activity of a number of indane and indanone analogues of pterosins in which a variety of three carbon side chains replace the hydroxyethyl side chain of the natural pterosins.

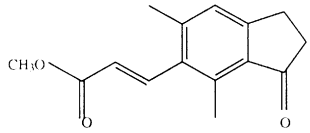
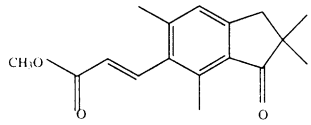
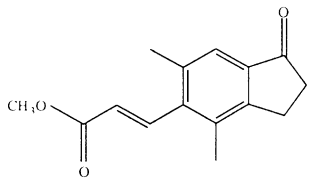
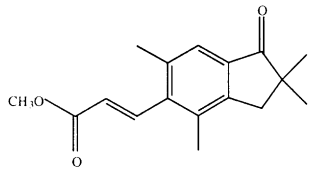
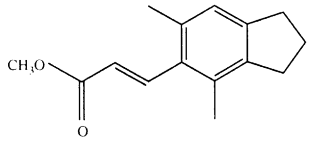
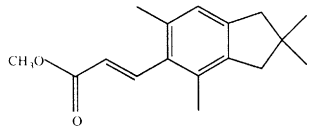
2. Chemistry

Palladium catalysed Heck coupling [6] was used in this study for attaching a three carbon side chain to a range of indanone nucleii to yield a series of pterosin analogues. Methylacrylate (**2**) was identified as a suitable three carbon unit for coupling with bromoindanes (**3–8**), key intermediates used in earlier pterosin synthetic studies [1, 2]. The regioselectivity of the site of arylation on the double bond of methylacrylate has been reported to occur exclusively at the terminal alkene position giving rise to a single structural isomer [6, 7]. Coupling of **2** with **3–8** was catalysed by palladium acetate in the presence of triphenylphosphine and triethylamine and was carried out at 100 °C in sealed ampoules (Expt. l). The lowest yields in the coupling reaction were consistently observed for the products **10**, **13** and **14** while the highest yields were observed for the isopterosin type structure **12**. The products of the initial coupling reactions **9–14** (*table I*) were characterised spectroscopically and in all cases were single geometric isomers. The ^{1}H-NMR spectrum of **10**, typical for the series, shows the presence of two sets of doublets downfield at 6.2 and 7.8 ppm, characteristic of the methylpropenoate side chain. The coupling constant of the doublets *J* (16 Hz) is characteristic of *trans* coupled protons and is observed for all compounds in the series. It is therefore confirmed that in the Heck coupling between methylacrylate and bromoindanes only the *E* isomer is formed.

Compounds **9–14** were subjected to a range of chemical reactions in which the methyl propenoate side chain was modified (*figure 1*) to give rise to a series of pterosin analogues **15–39** for which the change in smooth muscle relaxant activity could be measured relative to the change in structure. The structure of these compounds was established by spectroscopic means and the smooth muscle relaxant activity of **9–39** was measured using established methods.

*Correspondence and reprints

Table I. Yield and phsical data for compounds **9–14**.

Compound		Yield %	Melting point	M^+
9		60	86–87 °C	244.1100
10		45	93–94 °C	272.1407
11		61	124–125 °C	244.1100
12		73	oil	272.1413
13		45	47–48 °C	230.1307
14		41	oil	258.1620

3. Pharmacological results and discussion

Addition of calcium (2.5 mM) to guinea-pig ileum bathed in high potassium (45 mM), calcium-free Kreb's solution caused a contracture of the tissue which was sustained for a period greater than 40 min. The compounds (added cumulatively) caused a dose-dependant inhibition of calcium (2.5 mM) contractures of guinea-pig ileum (for examples see *figure 2*). The more potent compounds (**12**, **16, 20, 28** and **29**), with EC_{50} values ranging from 1.3×10^{-6} to 1.1×10^{-5} M, were more than 3 orders of magnitude less potent than the positive control, the calcium antagonist, nifedipine (*figure 2*) which had an EC_{50} value of $9.3 \pm 0.5 \times 10^{-9}$ M. Comparison of the activities of the compounds was made at a single concentration of 10^{-5} M, with inhibitory activity ranging from 20–75% (*figures 3–5*). In comparison, nifedipine, at a concentration of 10^{-8} M, inhibited calcium contractures by 48.1 ± 2.3%. The most potent smooth muscle relaxant (*figure 2*) is the diol **39**. The

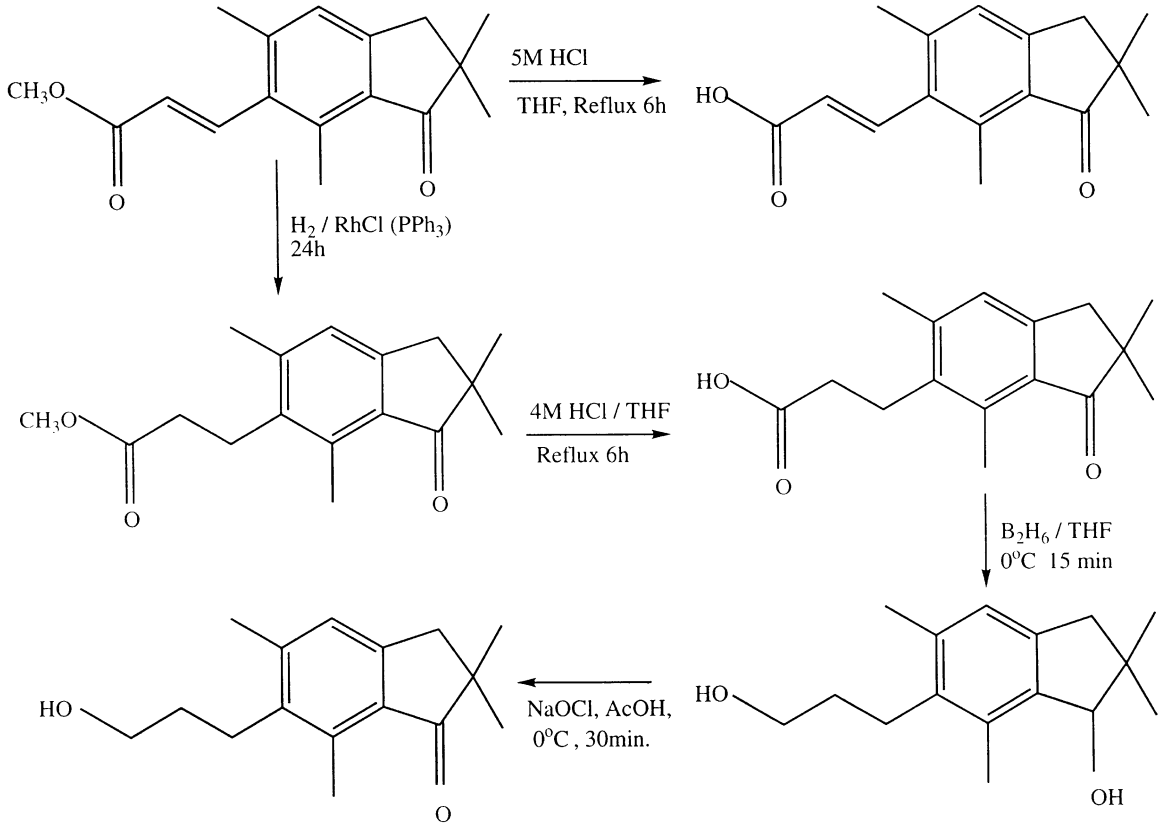
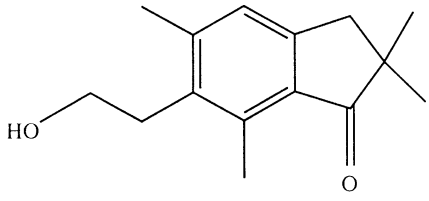


Figure 1. Example of reactions carried out to modify the methylpropenoate side chain of pterosins.

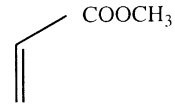
activity of this compound is statistically greater ($P < 0.05$) than that of its close analogue **29**. These two compounds (**29** and **39**) are structurally quite similar, having the three carbon side chain at the C-4 position and the aromatic methyl groups at the 3,5-positions. The next level of activity is shown by compounds **12**, **20** and **28**. These compounds are statistically ($P < 0.05$) less active than **29** and **39** but more active than **16** ($P < 0.05$).

No clear structure activity relationship is apparent from the results of the 30 compounds analysed in this study, although it does appear that an unsaturated three carbon side chain at the C-4 position coupled with aromatic methyls at the 3,5- positions with oxygenation at C-1 (isopterosin form) enhances activity relative to the positioning of the carbon side chain at the C-6 position combined with the aromatic methyl substitution at the 5,7- positions (pterosin form). The smooth muscle relaxant activity (*figure 2*) of the most active compound **39** in this study (EC_{50} $4.9 \pm 0.6 \times 10^{-6}$ M) is significantly lower ($P < 0.05$) than the activity we have recently reported for pterosin Z (**1**) (EC_{50} $1.3 \pm 0.1 \times 10^{-6}$ M) [5] and the fungal indane **40** (EC_{50} $2.9 \pm 1.6 \times 10^{-6}$ M) [1]. However, the structural modifications observed in this group of pterosin analogues has led to an increase in activity relative to the first reported naturally occurring smooth muscle relaxants, onitin (EC_{50} 1×10^{-4} M), onotisin (EC_{50} 2×10^{-3} M) and otninoside (EC_{50} 7×10^{-4}M) [8, 9].

Pterosins have been shown to inhibit contractile responses of guinea-pig ileum by both histamine and acetylcholine [8], together with barium and potassium [9], suggesting a mechanism of action involving interference with calcium handling in the smooth muscle cell. This conclusion is supported by the results of this study, showing that the compounds inhibit calcium contractures of potassium-depolarised smooth muscle. However it has not been determined at this time whether such interference with calcium handling involves inhibition of extracellular calcium influx through membrane channels or interference with the calcium/calmodulin cascade of reactions within the cell.



1



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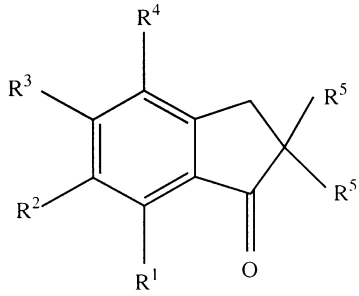
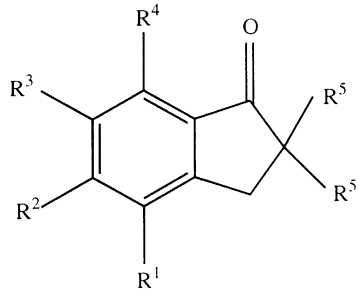


3-6

	R1	R2	R3	R4	R5
3	CH_3	Br	CH_3	H	H
4	CH_3	Br	CH_3	H	CH_3
5	H	CH_3	Br	CH_3	H
6	H	CH_3	Br	CH_3	CH_3
7	CH_3	Br	CH_3	H	H
8	CH_3	Br	CH_3	H	CH_3

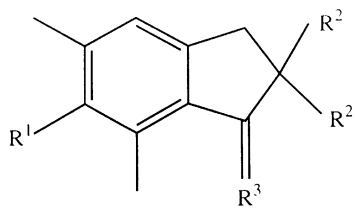


7,8

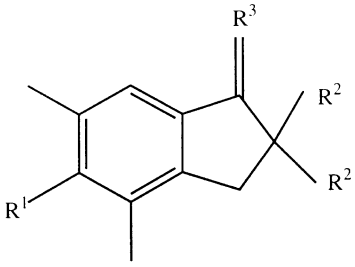
Figure 1. (Continued).

4. Experimental protocols

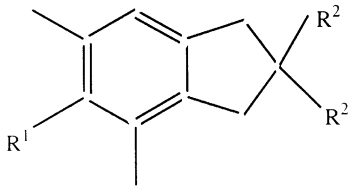
Melting points were determined on a Me-Opta hot stage and are uncorrected. Infra red spectra were recorded on a Nicolet 205 FT-IR. Ultraviolet spectra were recorded on a Varian Carey 3E UV-visible spectrophotometer. Mass spectra were determined at 70 eV on an AEI MS 30 instrument. ^{1}H-NMR spectra were recorded on a Bruker MSL 300 instrument at 300 MHz. ^{13}C-NMR were recorded at 75.47 MHz. Deuteriochloroform was used as



9 R^1= CH=CHCOOCH$_3$, R^2=H, R^3=O
15 R^1= CH=CHCOOH, R^2=H, R^3=O
16 R^1= $(CH_2)_2COOCH_3$, R^2=H, R^3=O
17 R^1= $(CH_2)_2COOH$, R^2=H, R^3=O
18 R^1= $(CH_2)_3OH$, R^2=H, R^3=HOH
10 R^1= CH=CHCOOCH$_3$, R^2=CH_3, R^3=O
19 R^1= CH=CHCOOH, R^2=CH_3, R^3=O
20 R^1= $(CH_2)_2COOCH_3$, R^2=CH_3, R^3=O
21 R^1= $(CH_2)_2COOH$,R^2=CH_3, R^3=O
22 R^1= $(CH_2)_3OH$,R^2=CH_3, R^3=O



11 R^1= CH=CHCOOCH$_3$, R^2=H, R^3=O
23 R^1= CH=CHCOOH, R^2=H, R^3=O
24 R^1= $(CH_2)_2COOCH_3$, R^2=H, R^3=O
25 R^1= $(CH_2)_2COOH$, R^2=H, R^3=O
26 R^1= $(CH_2)_3OH$, R^2=H, R^3=HOH
12 R^1= CH=CHCOOCH$_3$, R^2=CH_3, R^3=O
27 R^1= CH=CHCOOH, R^2=CH_3, R^3=O
28 R^1= $(CH_2)_2COOCH_3$, R^2=CH_3, R^3=O
29 R^1= $(CH_2)_2COOH$,R^2=CH_3, R^3=O
30 R^1= $(CH_2)_3OH$, R^2=CH_3, R^3=OH
39 R^1= $(CH_2)_3OH$, R^2=CH_3, R^3=O



13 R^1= CH=CHCOOCH$_3$, R^2=H
31 R^1= CH=CHCOOH, R^2=H
32 R^1= $(CH_2)_2COOCH_3$, R^2=H
33 R^1= $(CH_2)_2COOH$, R^2=H
34 R^1= $(CH_2)_3OH$, R^2=H
14 R^1= CH=CHCOOCH$_3$, R^2=CH_3
35 R^1= CH=CHCOOH, R^2=CH_3
36 R^1= $(CH_2)_2COOCH_3$, R^2=CH_3
37 R^1= $(CH_2)_2COOH$,R^2=CH_3
38 R^1= $(CH_2)_3OH$,R^2=CH_3
40 R^1= $(CH_2)_2OH$,R^2=CH_3

Figure 1. (Continued).

solvent with $SiMe_4$ as internal standard. TLC's were run on commercially pre-coated plates (Merck, Kieselgel $60F_{254}$). Merck Kieselgel 60 (9385) was used for column chromatography.

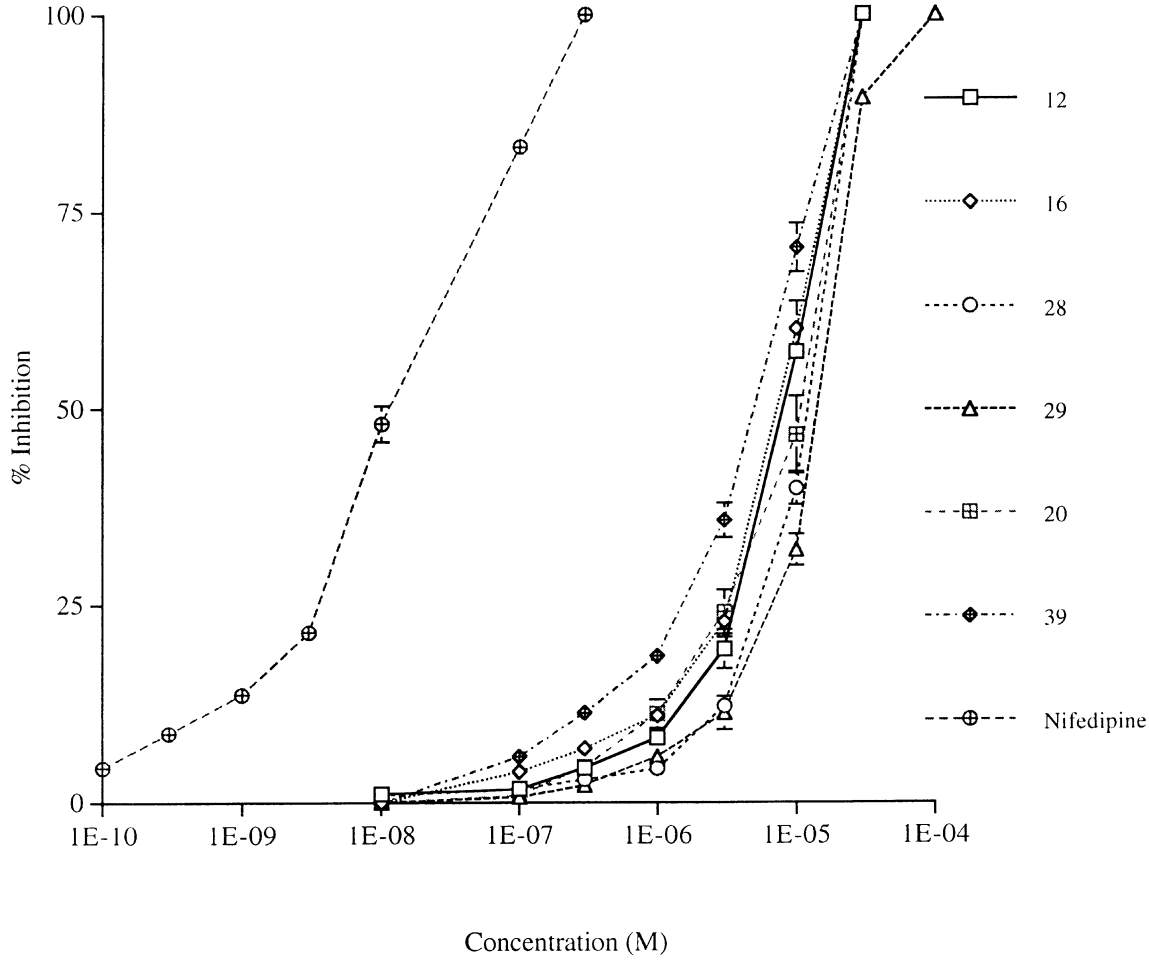


Figure 2. Effect of compounds 3×10^{-8}–3×10^{-5} M and Nifedipine, 1×10^{-10}–1×10^{-7} M (added cumulatively) on inhibition of calcium (2.5 mM) contractions of guinea-pig ileum suspended in high-potassium, calcium-free modified Kreb's solution. Values are expressed as means ± SEM, $n = 6$.

4.1. Synthesis of bromoindanones **3–8.** *As outlined in reference [1]*

4.1.1. General procedure for the coupling on methylacrylate (**2**) *with bromoindanones* (**3–8**) *to synthesise products* **9–14**

A solution of indanone (2 mmol), palladium acetate (0.11 mmol), triphenyl phosphine (0.21 mmol) and methylacrylate (**2**) (5 mmol) in triethylamine (10 mL) was sealed in a glass ampoule (25 mL). The ampoule was shaken until the mixture was homogeneous and was then heated under pressure 15 lbs/in^2 at 100 °C for 48 h. After cooling, the ampoule was broken and the reaction mixture was filtered and stirred on ice/HCl and extracted into EtOAc. The organic layer was washed, dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by column chromatography on silica gel (eluant: pet. ether:ethyl acetate, 9:1).

4.1.1.1. E-2,3-Dihydro-5,7-dimethyl-1H-inden-1-one-6-propenoic acid methyl ester (**9**)

Prepared by coupling 6-bromo-5,7-dimethyl-1H-indan-1-one [1] with methacrylate. White solid (59.5%), m.p. 86–87 °C (EtOH). Found M^+ 244.1109 ($C_{15}H_{16}O_3$ requires 244.1099). υ_{max} (KBr) 2 361, 1 707, 1 686 cm^{-1}; δ_H ($CDCl_3$): 2.41 (3H, s, CH_3), 2.62 (2H, t J 6.0 Hz,

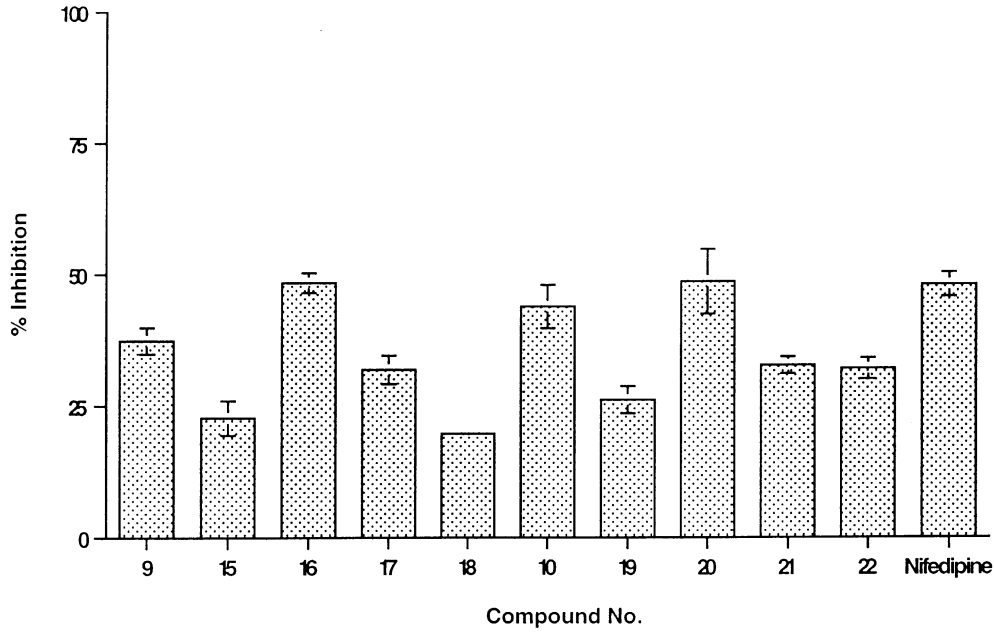


Figure 3. Effect of several compounds (1×10^{-5} M) and Nifedipine 1×10^{-8} M, on inhibition of calcium (2.5 mM) contractions of guinea-pig ileum suspended in high-potassium, calcium free modified Kreb's solution. Values are expressed as means ± SEM, $n = 6$.

CH_2), 2.65 (3H, s, CH_3), 3.08 (2H, t *J* 6.0 Hz, CH_2), 3.81 (3H, s, OCH_3), 6.23 (1H, d *J* 16.4 Hz), 6.96 (1H, s, Ar-H), 7.84 (1H, d *J* 16.4 Hz); δ_C 18.1(CH_3), 21.0 (CH_3), 25.94 (CH_2), 36.72 (CH_2), 51.72 (OCH_3), 122.1 (CH), 128.3 (CH), 129.0 (ArC), 133.1 (ArC), 139.6 (ArC), 140.2 (ArCH), 144.0 (ArC), 155.3 (ArC), 167.2 (CO), 207.0 (CO); m/z 244 (M^+, 100), 213 (59), 212 (66), 185 (58), 184 (40), 171 (43), 157 (32), 142 (66), 141 (44), 128 (30), 115 (25), 77 (19).

4.1.1.2. E-2,3-Dihydro-2,2,5,7-tetramethyl-1H-inden-1-one-6-propenoic acid methyl ester (**10**)

Prepared by coupling 6-bromo-2,3-dihydro-2,2,5,7-tetramethyl-1H-inden-1-one [1] with methacrylate. White crystals (46%), m.p. 93–94 °C (EtOH). Found M^+ 272.1416 ($C_{17}H_{20}O_3$ requires 272.1413); υ_{max} (KBr) 2 951, 1 712, 1 698 cm^{-1}; δ_H ($CDCl_3$) 1.19 (6H, s, 2×CH_3), 2.45 (3H, s, CH_3), 2.59 (3H, s, CH_3), 2.99 (2H, s, CH_2), 3.81 (3H, s, OCH_3), 6.23 (1H, d *J* 16.5 Hz), 7.01 (1H, s, Ar-H), 7.86 (1H, d *J* 16.4 Hz); δ_C 18.2 (CH_3), 21.0 (CH_3), 25.3 (2×CH_3), 43.1 (CH_2), 45.4 (C), 51.7(OCH_3), 122.0 (CH), 128.9 (ArC), 131.3(ArC), 132.5 (ArCH), 140.4 (ArCH), 141.2 (ArC), 144.0 (ArC), 152.3 (ArC), 167.2 (CO), 211.3 (CO); m/z 272 (M^+, 100), 257 (68) 211 (21), 213 (32), 195 (28), 170 (17), 128 (14).

4.1.1.3. E-2,3-Dihydro-4,6-dimethyl-1H-inden-1-one-5-propenoic acid methyl ester (**11**)

Prepared by coupling 5-bromo-2,3-dihydro-4,6-dimethyl-1H-inden-1-one [1] with methacrylate. White crystals (61%), m.p. 124–125 °C (EtOH). Found M^+ 244.1096 ($C_{15}H_{16}O_3$ requires 244.1099); υ_{max} (KBr) 2 955, 1 721, 1 704, 1 647cm^{-1}; δ_H ($CDCl_3$): 2.15 (3H, s, CH_3), 2.18 (3H, s, CH_3), 2.50 (2H, t *J* 5.5 Hz, CH_2), 2.83 (2H, t *J* 5.5 Hz, CH_2), 3.69 (3H, s, OCH_3), 5.91 (1H, d *J* 16.4 Hz), 7.31 (1H, s, ArH), 7.64 (1H, d *J* 16.4 Hz); δ_C 15.7 (CH_3), 20.6 (CH_3), 24.5 (CH_2), 35.9 (CH_2), 59.8 (OCH_3), 121.7 (CH), 124.8 (CH), 133.0 (ArC), 135.6 (ArC), 135.8 (ArC), 140.0 (ArC), 142.4 (ArCH), 151.9 (ArC), 166.0 (CO), 206.3 (CO); m/z 244 (M^+, 40), 229 (48), 213 (49), 212 (42), 184 (44), 171 (61), 143 (39), 142 (100), 141 (37), 128 (48), 115 (37).

4.1.1.4. E-2,3-Dihydro-2,2,4,6-tetramethyl-1H-inden-1-one-5-propenoic acid methyl ester (**12**)

Prepared by coupling 5-bromo-2,3-dihydro-2,2,4,6-tetramethyl-1H-indan-1-one [1] with methacrylate. Pale oil (72%). Found M^+ 272.1408 ($C_{17}H_{20}O_3$ requires 272.1413) υ_{max} (Film) 2 958, 1 714, 1 716, 1 644 cm^{-1}; δ_H ($CDCl_3$) 1.11 (6H, s, 2×CH_3), 2.18 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.77 (2H, s, CH_2), 3.72 (3H, s, OCH_3), 5.96

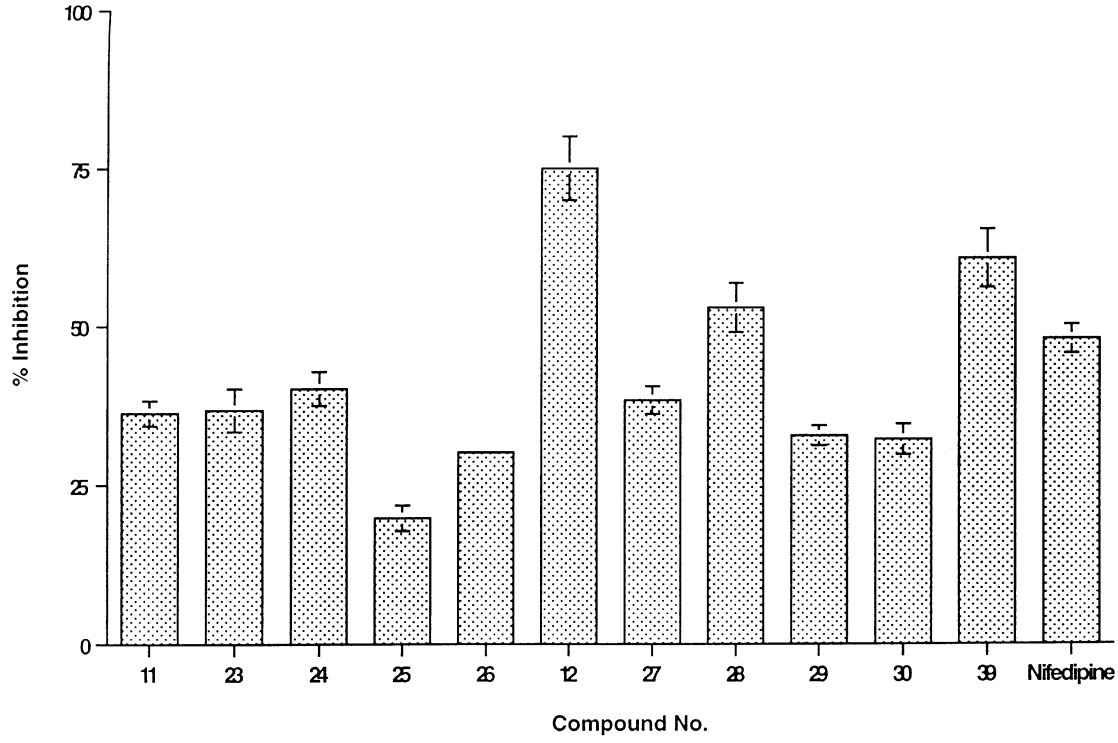


Figure 4. Effect of several compounds (1×10^{-5} M) and Nifedipine 1×10^{-8} M, on inhibition of calcium (2.5 mM) contractions of guinea-pig ileum suspended in high-potassium, calcium free modified Kreb's solution. Values are expressed as means ± SEM, $n = 6$.

(1H, d *J* 16.5 Hz), 7.32 (1H, s, ArH), 7.70 (1H, d *J* 16.5 Hz); δ_C 15.6 (CH_3), 20.6 (CH_3), 24.9 (2×CH_3), 41.7 (CH_2), 45.1 (C), 51.4 (OCH_3), 122.5 (CH), 124.7 (CH), 133.3 (ArC), 134.1 (ArC), 135.8 (ArC), 140.3 (ArC), 142.6 (ArCH), 149.0 (ArC), 166.1 (CO), 210.9 (CO); m/z 272 (M^+, 45), 258 (19), 257 (100), 241 (28), 240 (23), 225 (19), 213 (13), 197 (17), 153 (10), 128 (14), 77 (5).

4.1.1.5. E-2,3-Dihydro-2,4-dimethyl-1H-inden-3-propenoic acid methyl ester (**13**)

Prepared by coupling 3-bromo-2,3-dihydro-2,4-dimethyl-1H-inden [1] with methacrylate. White solid (45%), m.p. 47–48 °C (EtOH). Found M^+ 230.1300 ($C_{15}H_{18}O_2$ requires 230.1307); υ_{max} KBr 2 951, 1 721, 1 633, 1 161 cm^{-1}; δ_H ($CDCl_3$) 2.09 (2H, m *J* 7.5 Hz, CH_2), 2.29 (3H, s, CH_3), 2.34 (3H, s, CH_3), 2.86 (2H, t *J* 7.5 Hz, CH_2), 2.93 (2H, *J* 7.5 Hz, CH_2), 3.85 (3H, s, OCH_3), 6.06 (1H, d *J* 16.2 Hz, CH), 6.99 (1H, s, ArH), 7.90 (1H, d *J* 16.2 Hz); δ_C 17.4 (CH_3), 21.1 (CH_3), 24.6 (CH_2), 31.8 (CH_2), 33.1 (CH_2), 51.5 (OCH_3), 123.0 (CH), 123.9 (CH), 131.6 (ArC), 132.1 (ArC), 134.8 (ArC), 141.4 (ArC), 144.2 (ArCH), 144.4 (ArC), 167.2 (CO); m/z 230 (M^+, 67), 215 (39), 199 (100), 170 (67), 156 (19), 155 (57), 141 (15), 128 (23).

4.1.1.6. E-2,3-Dihydro-2,2,5,7-tetramethyl-1H-inden-6-propenoic acid methyl ester (**14**)

Prepared by coupling 6-bromo-2,3-dihydro-2,2,5,7-dimethyl-1H-inden [1] with methacrylate. Pale oil (41%). Found M^+ 258.1610 ($C_{17}H_{22}O_2$ requires 258.1602). υ_{max} (Film) 2 952, 1 723, 1 634 cm^{-1}; δ_H ($CDCl_3$): 1.16 (6H, s, 2×CH_3), 2.21 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.65 (2H, s, CH_2), 2.73 (2H, s, CH_2), 3.82 (3H, s, OCH_3), 6.04 (1H, d *J* 16.2 Hz, CH), 6.87 (1H, s, ArH), 7.90 (1H, t *J* 16.2 Hz, CH); δ_C 17.3 (CH_3), 20.3 (CH_3), 29.1 (2×CH_3), 39.2 (C), 45.8 (CH_2), 47.9 (CH_2), 51.5 (OCH_3), 124.2 (CH), 129.8 (CH), 131.6 (ArC), 134.8 (ArC), 135.4 (ArC), 140.6 (ArC), 142.8 (ArCH), 143.7 (ArC), 167.3 (CO); m/z 258 (M^+, 96), 243 (39), 228 (18), 227 (100), 212 (22), 211 (61), 199 (40), 197 (17), 171 (11), 157 (13), 153 (20), 143 (19), 128 (17).

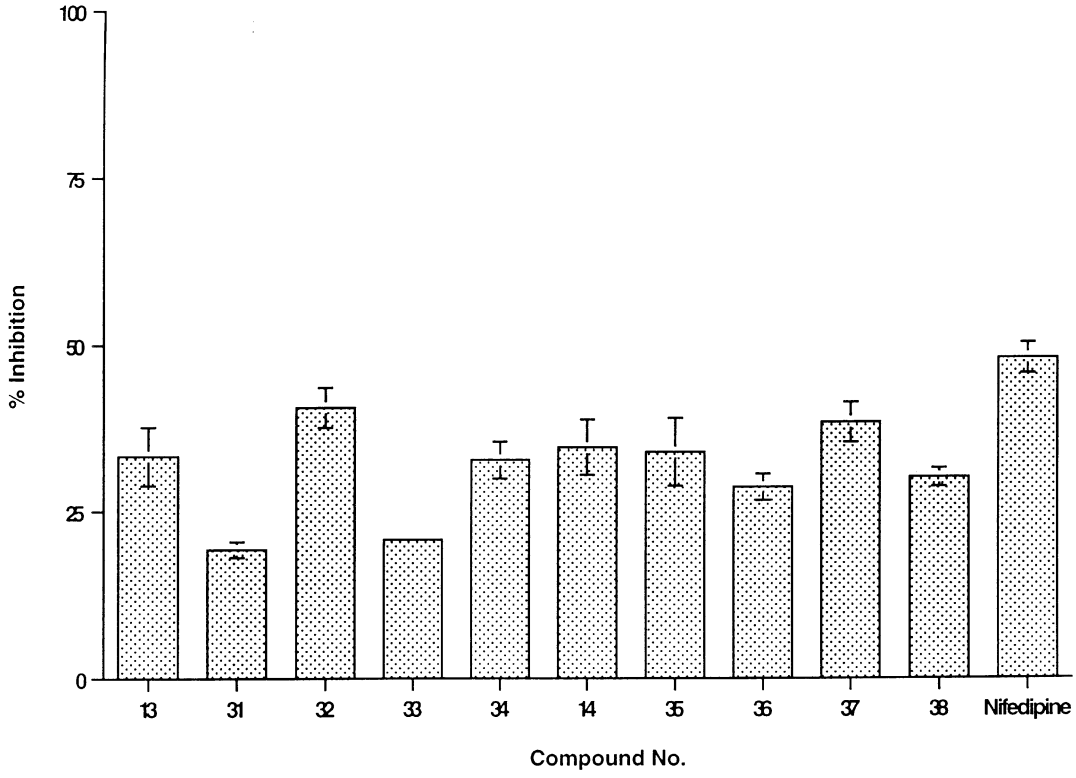


Figure 5. Effect of several compounds (1×10^{-5} M) and Nifedipine 1×10^{-8} M, on inhibition of calcium (2.5 mM) contractions of guinea-pig ileum suspended in high-potassium, calcium free modified Kreb's solution. Values are expressed as means ± SEM, $n = 6$.

4.1.2. General procedure for the preparation of propenoic acids (**15, 19, 23, 27, 31** *and* **35**)

A solution of propenoic acid methyl ester (2.25 mmol) in HCl (5 M, 15mL) and THF (15 mL) was refluxed for 6 h. After this time the THF was evaporated in vacuo. The aqueous residue was then diluted with H_2O (50 mL) and was extracted with EtOAc (2×30 mL). The organic layer was washed with 1 M NaOH (2×20 mL) and the aqueous layer retained. Following acidification with HCl the aqueous layer was extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate and evaporated off under vacuum to give a crude residue which was purified by recrystallisation to yield the propenoic acids.

4.1.2.1. E-2,3-Dihydro-5,7-dimethyl-1H-inden-1-one-6-propenoic acid (**15**)

Prepared from **9**. White crystalline powder, m.p. 219–220 °C. Found M^+ 230.0953 ($C_{14}H_{16}O_3$ requires 230.0943). υ_{max} (KBr) 3 500–3 200b, 1 725, 1 696 cm^{-1}; δ_H (DMSO-D_6), 2.41 (3H, s, CH_3), 2.51 (3H, s, CH_3), 2.59 (2H, t *J* 6 Hz, CH_2), 3.06 (2H, t *J* 6 Hz, CH_2), 6.27 (1H, d *J* 16 Hz, CH), 7.10 (1H, s, CH), 7.72 (1H, d *J* 16 Hz, CH); δ_C 17.7 (CH_3), 20.5 (CH_3), 25.5 (CH_2), 36.5 (CH_2), 123.6 (CH), 129.0 (C), 132.0 (C), 138.2 (CH), 139.1 (C), 140.2 (CH), 143.6 (C), 155.4 (C), 167.4 (CO), 206.5 (CO). m/z 230(M^+, 96), 215 (28), 212 (41), 186 (18), 185 (82), 184 (29), 171 (37), 157 (68), 156 (19), 143 (37), 128 (41).

4.1.2.2. E-2,3-Dihydro-2,2,5,7-tetramethyl-1H-inden-1-one-6-propenoic acid (**19**)

Prepared from **10**. Pale yellow needles (EtOH), m.p. 173–174 °C, yield 76%. Found M^+ 258.1245 ($C_{16}H_{18}O_3$ requires 258.1256). υ_{max} (KBr) 3 400–3 200b, 1 702, 1 679 cm^{-1}; δ_H ($CDCl_3$) 1.19 (6H, s, 2×CH_3), 2.45 (3H, s, CH_3), 2.59 (3H, s, CH_3), 3.01 (2H, s, CH_2), 6.23 (1H, d *J* 16 Hz, CH), 7.01 (1H, s, CH), 7.93 (1H, d *J* 16 Hz, CH); δ_C 18.2 (CH_3), 21.0 (CH_3), 25.3 (2×CH_3), 43.1 (CH_2), 45.4 (C), 121.9 (CH), 128.6 (C), 131.3 (C), 132.6

(CH), 139.1 (C), 140.7 (C), 141.8 (CH), 144.3 (C), 152.6 (C), 170.7 (CO), 211.6 (CO); MS(EI) m/z 258 (M^+, 82), 243 (91), 240 (12), 213 (38), 195 (31), 170 (15), 128 (16), 115 (10), 73 (13).

4.1.2.3. E-2,3-Dihydro-4,6-dimethyl-1H-inden-1-one-5-propenoic acid (**23**)

Prepared from **11**. White powder (EtOH), m.p. 225–226 °C yield 95%. Found M^+ 230.0934 ($C_{14}H_{14}O_3$ requires 230.0943). υ_{max} (KBr) 3 500–3 000b, 1 722, 1 711 cm^{-1}; δ_H (DMSO d_6) 2.28 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.63 (2H, t *J* 6 Hz, CH_2), 2.98 (2H, t *J* 6 Hz, CH_2), 6.09 (1H, d *J* 16 Hz, CH), 7.37 (1H, s, CH), 7.71 (1H, d *J* 16 Hz, CH), 12.73 (1H, s, COOH); δ_C 15.6 (CH_3), 20.6 (CH_3), 24.5 (CH_2), 36.0 (CH_2), 121.3 (CH), 126.4 (CH), 133.8 (C), 135.6 (C), 135.7 (C), 140.2 (C), 141.8 (CH), 152.4 (C), 166.9 (CO), 206.3 (CO); m/z 230 (M^+, 100), 215 (61), 212 (44), 184 (32), 171 (29), 143 (62), 142 (100), 141 (35), 128 (45), 91 (73), 77 (23).

4.1.2.4. E-2,3-Dihydro-2,2,4,6-tetramethyl-1H-inden-1-one-5-propenoic acid (**27**)

Prepared from **12**. White solid (EtOH), m.p. 181–182 °C yield 86%. Found M^+ 258.1227 ($C_{16}H_{18}O_3$ requires 258.1256). υ_{max} (KBr) 3 400–3 200b, 1 714, 1 702 cm^{-1}; δ_H ($CDCl_3$) 1.08 (6H, s, 2×CH_3), 2.16 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.75 (2H, s, CH_2), 5.94 (1H, d *J* 16 Hz, CH), 7.30 (1H, s, CH), 7.70 (1H, d *J* 16 Hz, CH); δ_C ($CDCl_3$) 15.7 (CH_3), 20.7 (CH_3), 25.0 (2×CH_3), 41.9 (CH_2), 45.4 (C), 122.7 (CH), 125.3 (CH), 133.6 (C), 134.1 (C), 136.1 (C), 140.7 (C), 143.5 (CH), 149.4 (C), 168.5 (CO), 211.9 (CO); m/z 258(M^+, 100), 244 (28), 243 (100), 240 (28), 153 (20), 128 (35), 115 (23), 77 (12).

4.1.2.5. E-2,3-Dihydro-5,7-dimethyl-1H-indene-6-propenoic acid (**31**)

Prepared from **13**. Pale oil, yield 64%. Found M^+ 216.1387 ($C_{14}H_{16}O_2$ requires 216.1146); υ_{max} (Film) 3 200–2 900, 1 693, 1 428 cm^{-1}; δ_H ($CDCl_3$) 2.05 (2H, m, CH_2), 2.25 (3H, s, CH_3), 2.31 (3H, s, CH_3), 2.83 (2H, t *J* 7.5 Hz, CH_2), 2.86 (2H, t *J* 7.5 Hz, CH_2), 6.01 (1H, d *J* 16 Hz, CH), 6.95 (1H, s, CH), 7.89 (1H, d *J* 16 Hz, CH); δ_C 17.4 (CH_3), 21.1 (CH_3), 24.5 (CH_2), 31.7 (CH_2), 33.1 (CH_2), 116.4 (CH), 123.8 (CH), 131.5 (C), 132.2 (C), 134.9 (C), 141.4 (C), 144.4 (CH), 145.2 (C), 169.0 (CO); m/z 216 (M^+, 100) 198 (29), 183 (42), 143 (44), 91 (10), 77 (17).

4.1.2.6. E-2,3-Dihydro-2,2,4,6-tetramethyl-1H-indene-5-propenoic acid (**35**)

Prepared from **14**. White solid (EtOH), m.p. 138–139 °C, yield 83%. Found M^+ 244.1459 ($C_{16}H_{18}O_2$ requires 244.1436). υ_{max} (KBr) 3 000b, 1 689 cm^{-1}; δ_H ($CDCl_3$) 1.17 (6H, s, 2×CH_3), 2.26 (3H, s, CH_3), 2.35 (3H, s, CH_3), 2.68 (2H, s, CH_2), 2.73 (2H, s, CH_2), 6.07 (1H, d *J* 16 Hz, CH), 6.92 (1H, s, CH), 8.01 (1H, d *J* 16 Hz, CH); δ_C 19.1 (CH_3), 20.3 (CH_3), 29.1 (2×CH_3), 39.4 (C), 45.7 (CH_2), 48.9 (CH_2) 124.4 (CH), 127.4 (C), 129.9 (CH), 132.6 (C), 136.0 (C), 140.8 (C), 143.2 (C), 144.9 (CH), 168.5 (CO); m/z 244 (M^+, 100), 229 (51), 226 (22), 199 (23), 185 (22), 183 (42), 171 (24), 157 (20), 143 (23), 128 (25), 91 (15), 77 (15).

4.1.3. General procedure for the preparation of propanoic acid methyl esters (**16, 20, 24, 28, 32** *and* **36**)

A solution of the corresponding propenoic acid methyl ester (2 mmol) in EtOH was stirred with H_2 under Wilkinson's catalyst [$RhCl(PPh_3)_3$] at room temperature for 24 h. On completion, the mixture was filtered and the EtOH was removed under vacuum. The residue was purified by column chromatography (eluant pet. ether-:ethyl acetate, 4:1) to yield the following:

4.1.3.1. 2,3-Dihydro-5,7-dimethyl-1H-inden-1-one-6-propanoic acid methyl ester (**16**)

Prepared by reduction of **15**. White solid (n-Hexane), m.p. 66–67 °C yield 86%. Found M^+ 246.1262 ($C_{15}H_{18}O_3$ requires 246.1256); υ_{max} (KBr) 1 738, 1 703, 1 438 cm^{-1}; δ_H ($CDCl_3$) 2.33 (3H, s, CH_3), 2.45 (2H, t *J* 8 Hz, CH_2), 2.51 (3H, s, CH_3), 2.61 (2H, t *J* 6 Hz, CH_2), 2.95 (2H, t *J* 8 Hz, CH_2), 2.97 (2H, t *J* 6 Hz, CH_2), 3.66 (3H, s, OCH_3), 6.89 (1H, s, CH); δ_C 17.7 (CH_3), 19.2 (CH_3), 23.8 (CH_2), 24.0 (CH_2), 33.0 (CH_2), 36.7 (CH_2), 51.6 (OCH_3), 131.8 (CH), 132.6 (C), 133.1 (C), 136.4 (C), 142.5 (C), 154.7 (C), 173.0 (CO), 210 (CO); m/z 246 (M^+, 88), 214 (74), 186 (19), 173 (100), 159 (43), 144 (40), 129 (35), 115 (24), 91 (17).

4.1.3.2. 2,3-Dihydro-2,2,4,6-tetramethyl-1H-indene-5-propanoic acid methyl ester (**20**)

Prepared by reduction of **19**. White solid (n-Hexane), m.p. 54–55 °C yield 92%. Found M^+ 274.1573 ($C_{17}H_{22}O_3$ requires 274.1569); υ_{max} (KBr) 1 731, 1 693, 1 441 cm^{-1}; δ_H ($CDCl_3$) 1.14 (6H, s, 2×CH_3), 2.30 (3H, s, CH_3), 2.42 (2H, t *J* 9 Hz, CH_2), 2.49 (3H, s, CH_3), 2.83 (2H, s, CH_2), 2.90 (2H, t *J* 9 Hz, CH_2), 3.62 (3H, s, OCH_3), 6.87 (1H, s, CH): δ_C 17.6 (CH_3), 19.2 (CH_3), 23.9 (CH_2), 25.4 (2×CH_3), 33.0 (CH_2), 41.0 (CH_2), 45.2 (C), 51.5 (OCH_3), 130.7 (C), 132.0 (CH), 133.1 (C), 137.1 (C), 142.5 (C), 151.5 (C), 172.82 (CO), 211.6

(CO); m/z 274(M^+, 100), 260 (17), 259 (97), 242 (27), 201 (56), 200 (29), 199 (23), 187 (14), 185 (21).

4.1.3.3. 2,3-Dihydro-4,6-dimethyl-1H-inden-1-one-5-propanoic acid methyl ester (**24**)

Prepared by reduction of **23**. White solid (n-Hexane), m.p. 97–98 °C, yield 86%. Found M^+ 245.1255 ($C_{15}H_{18}O_3$ requires 246.1256; υ_{max} (KBr) 1 738, 1 708 cm^{-1}. δ_H ($CDCl_3$) 2.26 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.40 (2H, t *J* 9 Hz, CH_2), 2.58 (2H, t *J* 6 Hz, CH_2), 2.92 (2H, t *J* 6 Hz, CH_2), 3.00 (2H, t *J* 9 Hz, CH_2), 3.67 (3H, s, OCH_3), 7.35 (1H, s, CH); δ_C 14.3 (CH_3), 19.9 (CH_3), 24.9 (CH_2), 25.2 (CH_2), 32.7 (CH_2), 36.2 (CH_2), 51.7 (OCH_3), 122.3 (CH), 133.6 (C), 134.8 (C), 135.8 (C), 144.2 (C), 152.6 (C), 172.8 (CO), 207.1 (CO); m/z 245 (M^+, 65), 214 (59), 186 (22), 173 (100), 159 (29), 144 (25), 128 (22), 115 (17), 91 (16).

4.1.3.4. 2,3-Dihydro-2,2,4,6-tetramethyl-1H-inden-1-one-5-propanoic acid methyl ester (**28**)

Prepared by reduction of **27**. Colourless oil yield 91%. Found M^+ 274.1570 ($C_{17}H_{22}O_3$ requires 274.1569). υ_{max} (KBr) 1 739, 1 711 cm^{-1}; δ_H ($CDCl_3$) 1.15 (6H, s, 2×CH_3), 2.23 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.40 (2H, t *J* 9 Hz, CH_2), 2.80 (2H, s, CH_2), 3.00 (2H, t *J* 9 Hz, CH_2), 3.66 (3H, s, OCH_3), 7.45 (1H, s, CH); δ_C 14.4 (CH_3), 19.9 (CH_3), 25.2 (2×CH_3), 25.3 (CH_2), 32.6 (CH_2), 42.1 (CH_2), 45.3 (C), 51.7 (OCH_3), 123.1 (CH), 133.0 (C), 133.5 (C), 136.0 (C), 144.5 (C), 149.6 (C), 172.9 (CO), 211.5 (CO); m/z 274 (M^+, 76), 260 (26), 259 (100), 227 (17), 201 (26), 187 (20), 128 (10).

4.1.3.5. 2,3-Dihydro-4,6-dimethyl-1H-indene-propanoic acid methyl ester (**32**)

Prepared by reduction of **31**. White solid (Pet. ether:ether), m.p. 42–43 °C, yield 83%. Found M^+ 232.1464 ($C_{15}H_{20}O_2$ requires 232.1463). υ_{max} (KBr) 2 952, 1 740, 1 194cm^{-1}. δ_H ($CDCl_3$) 2.09 (2H, quintet *J* 7 Hz, CH_2), 2.29 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.49 (2H, t *J* 9 Hz, CH_2), 2.91 (4H, 2×t *J* 7 Hz, 2×CH_2), 3.02 (2H, t *J* 9 Hz, CH_2), 3.76 (3H, s, OCH_3), 6.97 (1H, s, CH); δ_C 15.8 (CH_3), 19.9 (CH_3), 24.7 (CH_2), 24.9 (CH_2), 31.9 (CH_2), 32.9 (CH_2), 33.6 (CH_2), 51.5 (OCH_3), 123.8 (CH), 131.8 (C), 134.0 (C), 134.4 (C), 141.3 (C), 141.7 (C), 173.5 (CO); m/z 232 (M^+, 69), 217 (3), 160 (36), 159 (100), 146 (25), 149 (59), 128 (13).

4.1.3.6. 2,3-Dihydro-2,2,4,6-tetramethyl-1H-inden-1-one-5-propanoic acid methyl ester (**36**)

Prepared by reduction of **35**. Colourless oil, yield 87%. Found M^+ 260.1754 ($C_{17}H_{24}O_2$ requires 260.1776). υ_{max} (neat) 2 952, 1 742, 1 195cm^{-1}; δ_H ($CDCl_3$) 1.24 (6H, s, 2×CH_3), 2.23 (3H, s, CH_3), 2.35 (3H, s, CH_3), 2.52 (2H, t *J* 8 Hz, CH_2), 2.71 (2H, s, CH_2), 2.80 (2H, s, CH_2), 2.95 (2H, t *J* 8 Hz, CH_2), 3.76 (3H, s, OCH_3), 6.86 (1H, s, CH); δ_C 18.6 (CH_3), 18.7 (CH_3), 25.6 (CH_2), 29.3 (2×CH_3), 33.7 (CH_2), 39.2 (C), 46.3 (CH_2), 46.6 (CH_2), 51.5 (OCH_3), 129.5 (CH), 131.7 (C), 131.9 (C), 133.4 (C), 139.8 (C), 142.0 (C), 173.4 (CO); m/z 260 (M^+, 77), 245 (3), 228 (29), 187 (76), 173 (100), 141 (11).

4.1.4. General procedure for the preparation of propanoic acids (**17**, **21**, **25**, **29**, **33** *and* **37**)

A solution of the corresponding propanoic acid methyl ester (1.45mmol) in 4 M HCl (10 mL) and THF (20 mL) was refluxed for 6 h. On completion, the THF was removed under vacuum and the remaining mixture was poured onto iced water (50 mL). The aqueous mixture was extracted with EtOAc (2 × 50 mL). The organic layer was then washed with NaOH (2 × 20 mL) and the aqueous layer was acidified with HCl and extracted into EtOAc. The EtOAc was dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by recrystallisation to yield the following;

4.1.4.1 2,3-Dihydro-5,7-dimethyl-1H-inden-1-one-6-propanoic acid (**17**)

Prepared by HCl reflux from **16**. White solid (Pet. ether:ether), m.p. 154 °C, yield 88%. Found M^+ 232.1075 ($C_{14}H_{16}O_3$ requires 232.1099). υ_{max} (KBr) 3 300, 1 732, 1 162 cm^{-1}; δ_H ($CDCl_3$) 2.38 (3H, s, CH_3), 2.55 (2H, t *J* 6 Hz, CH_2), 2.57 (3H, s, CH_3), 2.67 (2H, t *J* 6 Hz, CH_2), 3.01 (2H, t *J* 8 Hz, CH_2), 3.04 (2H, t *J* 8 Hz, CH_2), 6.94 (1H, s, CH); δ_C 17.79 (CH_3), 19.25 (CH_3), 23.71 (CH_2), 24.07 (CH_2), 33.07 (CH_2), 36.80 (CH_2), 131.99 (CH), 132.76 (C), 133.06 (C), 136.72 (C), 142.66 (C), 154.85 (C), 177.84 (CO), 207.83 (CO). m/z 232 (M^+, 86), 214 (11), 173 (100), 159 (59), 149 (55), 144 (15), 128 (17), 91 (11), 71 (18).

4.1.4.2. 2,3-Dihydro-2,2,5,7-tetramethyl-1H-inden-1-one-6-propanoic acid (**21**)

Prepared by HCl reflux from **20**. White needles (EtOH), m.p. 84–86 °C, yield 70%. Found M^+ 260.1408 ($C_{16}H_{20}O_3$ requires 260.1412). υ_{max} (KBr) 3 400–2 800b, 1 737, 1 700 cm^{-1}. δ_H ($CDCl_3$); 1.20 (6H, s, 2×CH_3), 2.37 (3H, s, CH_3), 2.51 (2H, t *J* 8 Hz, CH_2), 2.57 (3H, s, CH_3), 2.89 (2H, s, CH_2), 2.97 (2H, t *J* 8 Hz, CH_2), 6.95 (1H, s, CH); δ_C 17.86 (CH_3), 19.35 (CH_3), 23.82 (CH_2), 25.47 (2×CH_3), 33.21 (CH_2), 41.17 (CH_2), 45.47 (C), 130.84 (C), 132.12 (CH), 132.91 (C), 137.36 (C), 142.83 (C), 151.81 (C), 178.42 (CO), 212.26 (CO). m/z 260 (M^+, 74), 246 (20), 245 (100), 187 (19), 185 (20), 157 (17), 143 (17), 128 (19), 91 (15), 77 (11).

4.1.4.3. 2,3-Dihydro-4,6-dimethyl-1H-inden-1-one-5-propanoic acid (**25**)

Prepared by HCl reflux from **24**. White needles (EtOH), m.p. 209–210 °C, yield 93%. Found M^+ 232.1102 ($C_{14}H_{16}O_3$ requires 232.1099). υ_{max} (KBr) 3 100–2 800b, 1 731, 1 178 cm^{-1}; δ_H ($CDCl_3$) 2.33 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.69 (2H, t *J* 8 Hz, CH_2), 2.68 (2H, t *J* 6 Hz, CH_3), 3.00 (2H, t *J* 6 Hz, CH_2), 3.09 (2H, t *J* 8 Hz, CH_2), 7.44 (1H, s, CH); δ_C 14.17 (CH_3), 19.76 (CH_3), 24.80 (CH_2), 24.84 (CH_2), 32.46 (CH_2), 36.06 (CH_2), 122.31 (CH), 133.45 (C), 134.68 (C), 135.70 (C), 143.90 (C), 152.90 (C), 177.25 (CO), 207.36 (CO); m/z 232 (M^+, 61), 173 (100), 172 (35), 160 (25), 159 (38), 129 (20), 128 (22), 115 (20), 91 (18), 77 (13).

4.1.4.4. 2,3-Dihydro-2,2,4,6-tetramethyl-1H-inden-1-one-5-propanoic acid (**29**)

White cubes (n-Hexane), m.p. 124–125 °C, yield 94%. Found M^+ 260.1405 ($C_{16}H_{20}O_3$ requires 260.1412). υ_{max} (KBr) 3 200, 1 709, 1 692 cm^{-1}; δ_H ($CDCl_3$) 1.19 (6H, s, 2×CH_3), 2.28 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.49 (2H, t *J* 8 Hz, CH_2), 2.84 (2H, s, CH_2), 3.06 (2H, t *J* 8 Hz, CH_2), 7.41 (1H, s, CH); δ_C 14.41 (CH_3), 19.92 (CH_3), 25.18 (CH_2), 25.26 (2×CH_3), 32.79 (CH_2), 42.26 (CH_2), 45.30 (C), 123.27 (CH), 133.10 (C), 133.59 (C), 136.09 (C), 144.50 (C), 149.75 (C), 177.41 (CO), 211.78 (CO); m/z 260 (M^+, 25), 245 (44), 149 (29), 139 (10), 125 (19), 119 (16), 97 (43), 77 (100).

4.1.4.5. 2,3-Dihydro-4,6-dimethyl-1H-inden-5-propanoic acid (**33**)

Prepared by HCl reflux from **32**. White solid (EtOH), m.p. 112 °C, yield 89%. Found M^+ 218.1302 ($C_{14}H_{18}O_2$ requires 218.1099). υ_{max} (KBr) 2 953, 1 699, 1 297 cm^{-1}; δ_H ($CDCl_3$) 2.10 (2H, quin *J* 7 Hz, CH_2), 2.31 (3H, s, CH_3), 2.38 (3H, s CH_3), 2.54 (2H, t *J* 9 Hz, 8 Hz, CH_2), 2.91 (4H, m, 2×CH_2), 3.05 (2H, t *J* 9 Hz, CH_2), 6.98 (1H, s, CH). δ_C 15.78 (CH_3), 19.92 (CH_3), 24.72 (2×CH_2), 31.96 (CH_2), 32.95 (CH_2) 33.64 (CH_2), 123.84 (CH), 131.82 (C), 134.00 (C), 134.17 (C), 141.40 (C), 141.79 (C), 179.12 (CO); m/z 218 (M^+, 59), 160 (28), 159 (100), 145 (44), 128 (14), 115 (10).

4.1.4.6. 2,3-Dihydro-2,2,4,6-tetramethyl-1H-indene-5-propanoic acid (**37**)

Prepared by HCl reflux from **36**. White cubes (EtOH), m.p. 63–64 °C, yield 86%. Found 246.1617 ($C_{16}H_{22}O_2$ requires 246.1620). υ_{max} (KBr) 3 200, 1 736, 1 170 cm^{-1}; δ_H ($CDCl_3$) 1.16 (6H, s, 2×CH_3), 2.16 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.48 (2H, t *J* 9 Hz, CH_2), 2.64 (2H, s, CH_2), 2.72 (2H, s, CH_2), 2.89 (2H, t *J* 9 Hz, CH_2), 6.80 (1H, s, CH); δ_C 18.67 (2×CH_3), 25.36 (CH_2), 29.28 (2×CH_3), 33.62 (CH_2), 39.21 (C), 46.28 (CH_2), 46.53 (CH_2), 129.46 (CH), 131.60 (C), 131.90 (C), 133.53 (C), 139.96 (C), 142.02 (C), 178.99 (CO); m/z 246 (M^+, 6), 228 (45), 187 (57), 186 (38), 185 (16), 173 (83), 85 (17), 72 (100).

4.1.5. General procedure for the preparation of 3′ hydroxypropyl derivatives (**18**, **26**, **30**, **34** *and* **38**)

Freshly generated diborane was introduced under N_2 to a solution of the appropriate propanoic acids (1.3 mmol) in dry THF (10 mL) at 0 °C. After 15 min EtOH was added and the solvents were removed under vacuum. The residue was purified by column chromatography (pet-ether, EtOAc; 9:1–7:3) to yield the corresponding alcohols.

4.1.5.1. (±)-2,3-Dihydro-6-(3′-hydroxypropyl)-5,7-dimethyl-1H-inden-1-ol (**18**)

Prepared by diborane reduction of **17**. White powder (n-hexane), m.p. 86 °C, yield 63%. Found M^+ 220.1457 ($C_{14}H_{20}O_2$ requires 220.1463). υ_{max} (KBr) 3 350b, 2 936, 1 465cm^{-1}; δ_H ($CDCl_3$) 1.74 (2H, m, CH_2), 2.08 (1H, m, CH), 2.30 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.39 (2H, m, CH), 2.65 (2H, t *J* 8 Hz, CH_2), 2.81 (1H, dq *J* 3,9 Hz, CH), 3.08 (1H, quin *J* 8 Hz, CH), 3.69 (2H, t *J* 6 Hz, CH_2), 5.28 (1H, dd *J* 2,7 Hz, CH), 6.87 (1H, s, CH); δ_C 17.8 (CH_3), 18.8 (CH_3), 26.2 (CH_2), 28.7 (CH_2), 32.2 (CH_2), 35.0 (CH_2), 62.7 (CH_2), 75.4 (CH), 130.5 (CH), 132.2 (C), 133.7 (C), 136.4 (C), 140.6 (C), 142.8 (C); m/z 220 (M^+, 50), 205 (26), 184 (26), 175 (30), 169 (36), 161 (41), 159 (39), 157 (100), 145 (35), 141 (24).

4.1.5.2. 2,3-Dihydro-6-(3′-hydroxypropyl)-2,2,5,7-tetramethyl-1H-inden-1-one (**22**)

$LiAlH_4$ (15 mg, 0.39 mmol) was added to a solution of **20** (200 mg, 0.73 mmol) in dry Et_2O (10 mL) and the mixture was stirred at 0 °C for 10min. The reaction mixture was poured onto ice/HCl and extracted with EtOAc. The organic layer was evaporated and the residue was purified by column chromatography on silica gel eluant (pet. ether:EtOAc, 7:3), followed by preparative TLC using the same developer to give **22** as a pale oil yield 45%. Found M^+ 246.1016 ($C_{16}H_{22}O_2$ requires 246.1614). υ_{max} (film) 3 400, 1 705, 1 465 cm^{-1}; δ_H ($CDCl_3$) 1.21 (6H, s, CH_3), 1.64 (2H, m, CH_2), 2.37 (3H, s, CH_3), 2.47 (2H, t *J* 8 Hz, CH_2), 2.57 (3H, s, CH_3), 2.89 (2H, s, CH_2), 4.06 (2H, t *J* 7, CH_2), 6.95 (1H, s, CH); δ_C 17.8 (CH_3), 19.3 (CH_3), 24.0 (CH_2), 25.5 (2×CH_3), 32.3 (CH_2), 41.1 (CH_2), 45.4 (C), 62.1 (CH_2), 131.0 (C), 132.0 (CH), 133.2 (C), 137.1 (C), 142.6 (C), 151.6 (C), 215.0 (C=O). 246 (M^+, 8), 245 (42), 201 (100), 200 (93).

4.1.5.3. (±)-2,3-Dihydro-5-(3′-hydroxypropyl)-4,6-dimethyl-1H-inden-1-ol (**26**)

Prepared by diborane reduction of **25**. Waxy solid (EtOH), yield 47%. M^+ 220.1431 ($C_{14}H_{20}O_2$ requires 220.1463). υ_{max} (KBr) 3 400b, 2 954, 1 457cm^{-1}; δ_H ($CDCl_3$) 1.68 (2H, m, CH_2), 1.71 (1H, m, CH), 2.09 (1H, m, CH), 2.24 (3H, s, CH_3), 2.35 (3H, s, CH_3), 2.70 (2H, t *J* 8 Hz, CH_2), 2.77 (1H, m, CH), 2.98 (1H, quin *J* 8 Hz, CH), 3.70 (2H, t *J* 9 Hz, CH_2), 4.89 (1H, dd *J* 4 Hz, 7 Hz, CH), 7.09 (1H, s, CH); δ_C 15.5 (CH_3), 20.1 (CH_3), 25.8 (CH_2), 29.4 (CH_2), 31.9 (CH_2), 32.2 (CH_2), 62.7 (CH_2OH), 83.4 (CH), 124.2 (CH), 131.9 (C), 134.3 (C), 138.6 (C), 139.9 (C), 140.9 (C); m/z 220 (M^+, 67), 175 (100), 169 (19), 160 (16), 131 (33), 115 (35), 91 (29).

4.1.5.4. (±)-2,3-Dihydro-5-(3′-hydroxypropyl)-2,2,4,6-tetramethyl-1H-inden-1-ol (**30**)

Prepared by diborane reduction of **29**. White needles (EtOH), m.p. 130–131 °C yield 85%. M^+ 248.1773 ($C_{16}H_{24}O_2$ requires 220.1776). υ_{max} (KBr) 3 600b, 1 464 cm^{-1}. δ_H (acetone D_6) 0.98 (3H, s, CH_3), 1.13 (3H, s, CH_3), 2.17 (3H, s, CH_3), 2.24 (3H, s, CH_2), 2.28 (3H, s, CH_3), 2.48 (1H, d *J* 15 Hz, CH), 2.66 (1H, d *J* 14 Hz, CH), 2.70 (2H, t *J* 8 Hz, CH_2), 2.90 (1H, bs, OH), 3.62 (2H, t *J* 7 Hz, CH_2), 3.97 (1H, d *J* 5 Hz, OH), 4.56 (1H, d *J* 5 Hz, CH), 6.94 (1H, s, CH); δ_C 15.4 (CH_3), 20.1 (CH_3), 25.9 (CH_2), 27.2 (CH_2), 32.1 (CH_2), 43.6 (C), 44.2 (CH_2), 62.6 (CH_2), 83.6 (CH), 123.8 (C), 132.0 (C), 134.4 (C), 138.3 (C), 138.7 (C), 141.4 (C); m/z 248 (M^+, 94), 247 (28), 233 (15), 203 (46), 189 (100), 186 (32), 171 (21), 91 (14).

4.1.5.5. 2,3-Dihydro-5-(3′-hydroxypropyl)-4,6-dimethyl-1H-indene (**34**)

Prepared by diborane reduction of **33**. White needles (EtOH), m.p. 51–52 °C yield 64%. Found M^+ 204.1508 ($C_{14}H_{20}O$ requires 204.1514). υ_{max} (KBr) 3 400b, 1 459cm^{-1}; δ_H ($CDCl_3$) 1.80 (1H, quin *J* 8 Hz, CH_2), 2.08 (2H, quin *J* 8 Hz, CH_2), 2.28 (3H, s, CH_3), 2.35 (3H, s, CH_3), 2.74 (2H, t *J* 8 Hz, CH_2), 2.90 (4H, 2×t *J* 8 Hz, 2×CH_2), 3.78 (2H, t *J* 8 Hz, CH_2), 6.96 (1H, s, CH); δ_C 15.8 (CH_3), 20.0 (CH_3), 24.7 (CH_2), 25.7 (CH_2), 32.0 (CH_2), 32.4 (CH_2), 32.9 (CH_2), 63.0 (CH_2), 123.7 (CH), 131.7 (C), 133.9 (C), 136.0 (C), 141.0 (C), 141.2 (C); m/z 204 (M^+, 61), 160 (39), 159 (100), 146 (19), 145 (28), 129 (11).

4.1.5.6. 2,3-Dihydro-5-(3′-hydroxypropyl)-2,2,4,6-tetramethyl-1H-indene (**38**)

Prepared by diborane reduction of **37**. Pale oil, yield 59%. Found M^+ 232.1785 ($C_{16}H_{24}O$ requires 232.1821). υ_{max} (film) 3 400b, 1 464 cm^{-1}. δ_H ($CDCl_3$) 1.18 (6H, s, 2×CH_3), 1.76 (2H, m, CH_2), 2.21 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.60 (2H, t *J* 7 Hz, CH_2), 2.66 (2H, s, CH_2), 2.72 (2H, s, CH_2), 3.76 (2H, t *J* 6 Hz, CH_2), 6.86 (1H, s, CH); δ_C 15.6 (CH_3), 18.6 (CH_3), 25.7 (CH_2), 29.2 (2×CH_3) 32.5 (CH_2), 39.1 (C), 46.3 (CH_2), 47.1 (CH_2), 62.8 (CH_2), 123.9 (CH), 129.3 (C), 131.8 (C), 132.4 (C), 139.6 (C), 140.3 (C); m/z 232 (M^+, 100), 187 (90), 173 (90), 159 (58), 128 (40).

4.1.5.7. 2,3-Dihydro-5-(3′-hydroxypropyl)-2,2,4,6-tetramethyl-1H-inden-1-one (**39**)

A solution of NaOCl (5 mL, 12.5% w/v) was added dropwise to a stirred solution of **30** (250 mg, 1 mmol) in glacial acetic acid (3 mL) at 0 °C. The reaction mixture was stirred for 30 min and was then poured onto ice and extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated under vacuo. The residue was purified by column chromatography on silica gel (eluant: pet. ether:EtOAc, 7:3) to yield **39** as a waxy solid yield 43%. Found M^+ 246.1599 ($C_{16}H_{22}O_2$ requires 246.1614). υ_{max} (KBr) 3 400b, 1 712 cm^{-1}; δ_H ($CDCl_3$) 1.23 (6H, s, 2×CH_3), 1.70 (2H, m, CH_2), 2.28 (3H, s, CH_3), 2.38 (3H, s, CH_3), 2.80 (2H, t *J* 8 Hz, CH_2), 2.86 (2H, s, CH_2), 3.77 (2H, t *J* 7 Hz, CH_2), 7.43 (1H, s, CH); δ_C 15.9 (CH_3), 20.0 (CH_3), 25.3 (2×CH_3), 25.8 (CH_2), 31.7 (CH_2), 43.6 (C), 44.2 (CH_2), 62.9 (CH_2), 123.0 (CH), 132.7 (C), 134.5 (C), 138.3 (C), 141.4 (C), 146.4 (C), 209.5 (C=O); m/z 246 (M^+, 73), 231 (40), 215 (100), 128 (22).

4.2. Pharmacological methods

Smooth muscle relaxant activity was assessed as described previously [1]. Guinea-pigs (250–400 g) of either sex were killed by cervical dislocation and exsanguination. The abdomen was opened by midline incision and the ileum removed. The tissue was stored at 4 °C in Kreb's solution (composition (mM): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $MgCl_2$ 1.15, NaH_2PO_4 1.17, $NaHCO_3$ 25, glucose 14.4). Segments of ileum 2.5 cm in length were suspended in a high potassium calcium-free modified Kreb's solution (composition (mM): NaCl 12.5, KCl 45, $MgCl_2$ 1.15, NaH_2PO_4 1.17, $NaHCO_3$ 25, glucose 11.1) at 37 °C, gassed with 95% O_2/5% CO_2 under a resting tension of 1.5 g, from Grass FT.03 transducers fitted with black springs to record contractions isometrically. Contractions were displayed on a Grass 79D oscillograph. Sustained (> 40 min) contactures were elicited by addition of CaCl solution sufficient to raise the calcium concentration in the bath to 2.5 mM. When contractures had reached a stable maximum, test compounds were administered at a single concentration of 1×10^{-5} M or in the case of sufficiently active compounds, they were added cumulatively (3×10^{-8}–3×10^{-5}M). Compounds

were dissolved in 0.5% ethanol, addition of which (0.1 mL) induced an inhibition of calcium contractions of approximately 14%. However, this inhibition was temporary, and contractions returned to control levels within 5 min. In contrast, the inhibitory effect of all compounds was sustained, and subsequently all responses were measured at least 10 min following addition of compound.

5. Statistics

Results are expressed as means ± SE, mean of % inhibition of calcium contractures at a single dose of 1×10^{-5} M. EC_{50} values were determined from the linear portion of individual dose/inhibition curves by regression analysis, and expressed as a mean ± SE, mean for each compound shown. Statistical analysis was performed using Students *t*-test for unpaired samples, with a probability value (*P*) of less than 0.05 being taken as significant. *n* denotes the number of preparations used in that series of experiments.

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