Metal triflates catalyzed efficient synthesis of 3,4-dihydro-2*H*-1-benzopyrans

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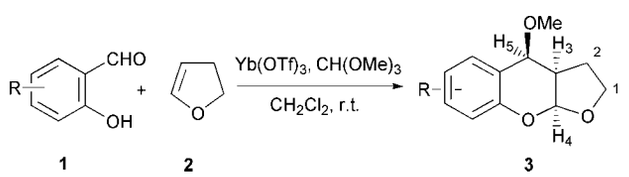
Ytterbium triflate efficiently catalyzes an unusual cyclization of *o*-hydroxybenzaldehydes with 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran in the presence of trimethyl orthoformate at ambient temperature to afford a new class of compounds, furo- and pyrano[2,3-*b*]benzopyrans in excellent yields with high diastereoselectivity. Also, *o*-hydroxybenzaldehydes reacted smoothly with acetophenones in the presence of a catalytic amount of scandium triflate under similar reaction conditions to give the corresponding 2,4-dialkoxy-2-aryl-3,4-dihydro-2*H*-1-benzopyrans in high yields.

2*H*-1-Benzopyrans (chromenes) and 3,4-dihydro-2*H*-1-benzopyrans (chromanes) are important classes of oxygenated heterocycles that have attracted much synthetic interest because of the biological activity of naturally occurring representatives.[1,2] 2-Substituted chromanes are particularly useful intermediates for the synthesis of naphthalene and phenanthrene derivatives.[3] In addition, 2-alkoxychromanes are versatile intermediates[4,5] for the synthesis of 2-oxoalkylchromanes, 2-cyanochromanes and 2-allylchromanes. Furthermore, the fused acetal moiety is an important structural subunit of a variety of biologically active natural products[6,7] such as aflatoxin, clerodin, asteltoxin, rhyacophiline, acmimycin and others. In particular, fused tetrahydropyrano[2,3-*b*]benzopyran derivatives are frequently found in naturally occurring bioactive molecules,[8] and direct methods for their synthesis are highly desired.[9,10] However, there are no reports on the synthesis of *cis*-fused furano- and pyranobenzopyrans from salicylaldehydes and cyclic enol ethers. Lanthanide triflates are unique Lewis acids that are currently of great research interest. They are quite stable to water and reusable as well as being highly efficient.[11] Therefore, lanthanide triflates are unique catalysts compared with conventional Lewis acids in several carbon–carbon bond-forming reactions and have found wide applications in organic synthesis.

Results and discussion

In continuation of our interest in the applications of metal triflates for various transformations,[12] we herein describe a new and efficient method for the synthesis of fused chromanes using a catalytic amount of ytterbium triflate. Treatment of salicylaldehyde with 2,3-dihydrofuran and trimethyl orthoformate in the presence of 5 mol% of $Yb(OTf)_3$ in dichloromethane at ambient temperature resulted in the formation of *cis*-fused furano[2,3-*b*]benzopyran in 92% yield (Scheme 1; Table 1, entry a).

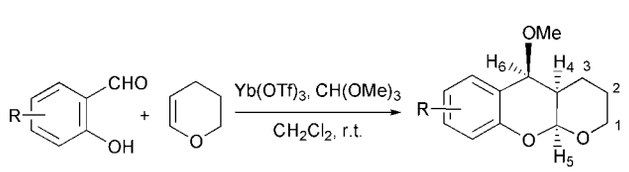
Similarly, several salicylaldehydes reacted well to give the corresponding fused acetals in excellent yields. In all cases, the reactions proceeded smoothly at ambient temperature with high selectivity. Only one diastereomer was obtained in each reaction, the structure of which was established by detailed NMR studies. The tetrahydropyran and tetrahydrofuran rings



Scheme 1 Non-systematic numbering for products **3**.

are *cis*-fused as depicted by the coupling constant of the proton at δ 5.84, J_{H3-H4} = 5.8 Hz, and the presence of a strong cross-peak between H3–H4 in the NOESY spectrum of the product **3a**. The coupling constant of the proton at δ 4.63, J_{H3-H5} = 5.5 Hz, and the presence of NOE cross-peaks between H3–H5 and H4–H5 indicate that these three protons are on the same side of the six-membered ring. A boat conformation of the ring was consistent with the experimental values of J_{H3-H4} and J_{H3-H5}, and the presence of an NOE cross-peak between the methoxy group and the aromatic proton (H-6) permitted the assignment of the protons in the phenyl ring, which is further supported by molecular mechanics calculations (Fig. 1).[13]

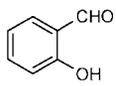
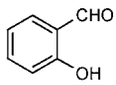
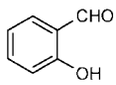
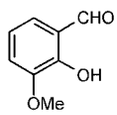
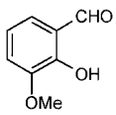
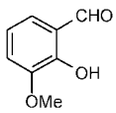
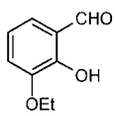
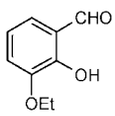
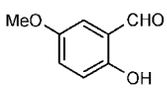
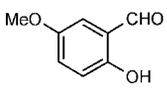
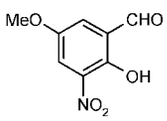
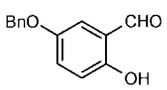
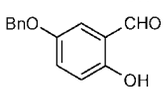
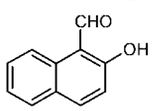
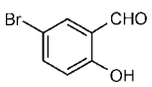
Further, the reaction of salicylaldehydes with 3,4-dihydro-2*H*-pyran under similar reaction conditions gave the corresponding pyrano[2,3-*b*]benzopyran derivatives in high yields (Scheme 2).



Scheme 2 Non-systematic numbering for products **3**.

The reaction is highly selective, and affords exclusively *cis*-fused acetals under the reaction conditions used. In the product **3b**, the two six-membered rings are *cis*-fused, consistent with a small coupling constant value J_{H4-H5} = 2.3 Hz, and strong NOESY cross-peak between H4 and H5. The coupling constant J_{H4-H6} = 5.5 Hz and H4–H6 cross-peaks in the NOESY spectrum shows that H4, H5 and H6 are on the same side of

Table 1 $Yb(OTf)_3$-catalyzed synthesis of furo- and pyranobenzopyrans[a]

Entry	*ortho*-Hydroxy aldehyde **1**	Enol ether **2**	Reaction time (*t*/h)	Yield (%)[b]
a			2.5	92
b			3.0	89
c			1.5	80
d			3.0	90
e			2.5	87
f			2.0	75
g			2.5	88
h			3.0	90
i			2.5	92
j			3.5	89
k			4.5	85
l			3.0	90
m			3.5	87
n			4.0	81
o			4.5	75

[a] All products were characterized by ^1H, ^{13}C NMR, IR and mass spectra. [b] Isolated and unoptimized yields.

the six-membered ring which takes a twist conformation. The other six-membered ring has a chair conformation ($^1C_4$) which is supported by the presence of NOEs the between $H1^{ax}$–$H3^{ax}$, $H2^{ax}$–H4 and $J_{H3ax–H4}$ = 12.4 Hz, $J_{H1ax–H2ax}$ = 11.3 Hz. The NOE cross-peak between the methoxy and aromatic proton (H-7) permitted the assignment of the aromatic protons (Fig. 2).

The reaction also proceeded smoothly with the dimethyl acetal of various salicyaldehydes and enol ethers in dichloromethane using 5 mol% $Yb(OTf)_3$ at ambient temperature. Other enol ethers, such as ethyl vinyl ether, worked well at 0 °C in the presence of 5 mol% $Yb(OTf)_3$ and trimethyl orthoformate in dichloromethane to afford the corresponding 2-ethoxy-4-methoxychromane in 80% yield with high selectivity (Scheme 3; Table 1, entry c).

In this product **3c**, the six membered ring behaved like the earlier products; the almost equal values of couplings $J_{H2a–H3}$ = 7.4 Hz and $J_{H2b–H3}$ = 5.9 Hz are consistent with a twist conform-

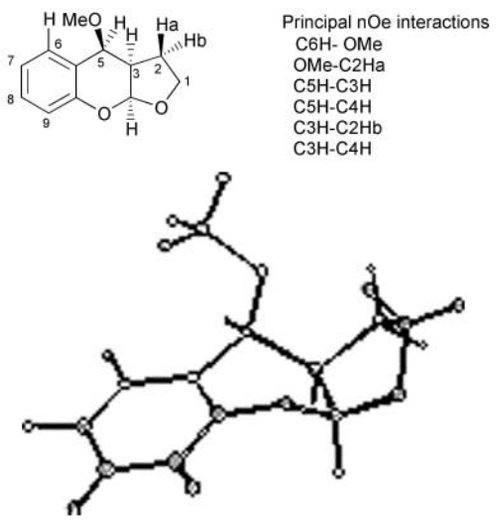


Fig. 1 Important NOE interactions and energy-minimized structure of **3a**. Non-systematic numbering.

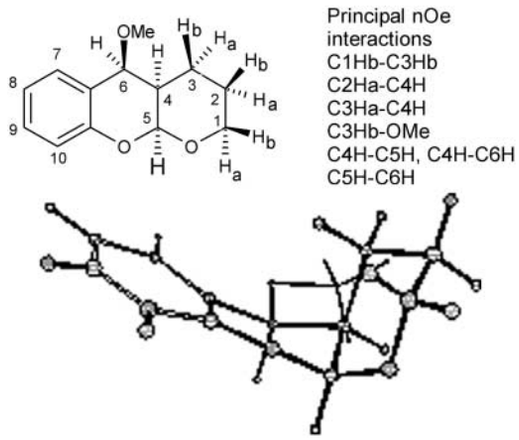
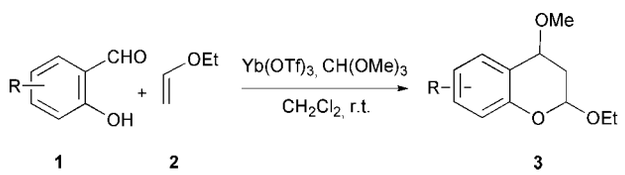


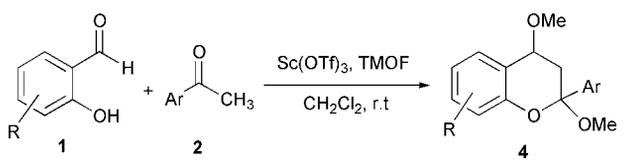
Fig. 2 Important NOE interactions and energy-minimized structure of **3b**. Non-systematic numbering.



Scheme 3

ation for the six-membered ring, which is further supported by molecular mechanics calculations (Fig. 3).

Several examples illustrating this novel and rapid procedure for the synthesis of fused chromanes are summarized in Table 1. Furthermore, the treatment of salicylaldehyde with acetophenone and trimethyl orthoformate in the presence of 5% $Sc(OTf)_3$ at ambient temperature resulted in the formation of 2,4-dimethoxy-2-phenylchromane in 85% yield (Scheme 4; Table 2, entry a).



Scheme 4

Several salicylaldehydes reacted well with acetophenones under the present rection conditions to afford the corresponding 2-alkoxychromanes in high yields. In all cases,

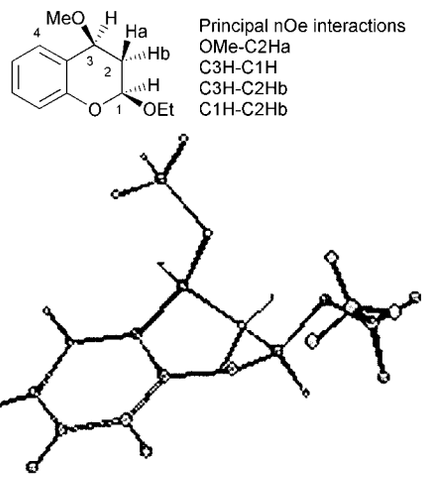
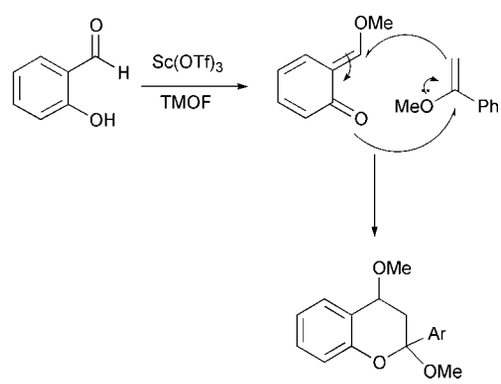


Fig. 3 Important NOE interactions and energy-minimized structure of **3c**. Non-systematic numbering.

the reactions proceeded smoothly at ambient temperature with high diastereoselectivity. Only a single diastereomer was obtained in each reaction, the structure of which was established by ^{1}H NMR studies. The assigned structure was further confirmed by direct comparison with literature data.[10] However, ketones such as cyclohexanone, cyclopentanone and tetralone did not yield any condensation products under these reaction conditions. The reaction was successful only with acetophenones and salicylaldehydes. Aliphatic aldehydes failed to react with acetophenones under the present reaction conditions. Several examples illustrating this new and novel method for the synthesis of 2-alkoxychromanes are listed in Table 2. This synthetic protocol utilizes readily available starting materials and a reusable catalyst, *i.e.*, scandium triflate. The reaction may proceed through the formation of *ortho*-quinonemethides generated *in situ* from salicylaldehydes and trimethyl orthoformate (TMOF) as shown in Scheme 5.

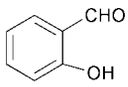
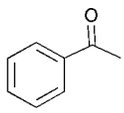
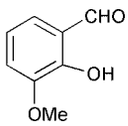
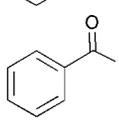
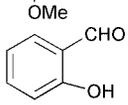
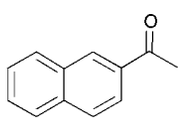
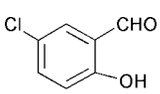
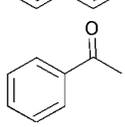
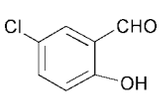
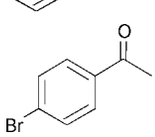
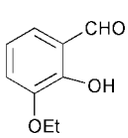
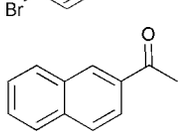
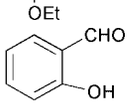
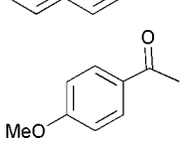
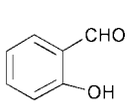
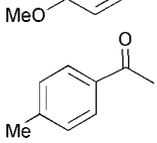
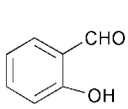
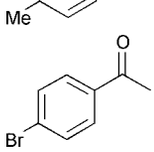
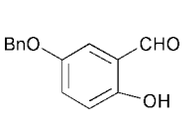
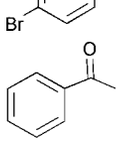
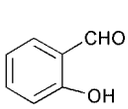
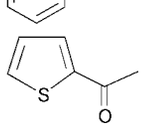
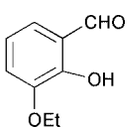
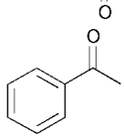
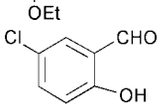
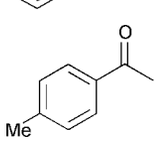
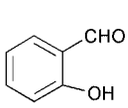
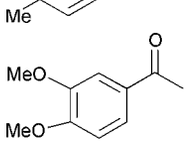
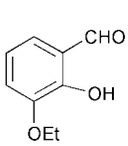
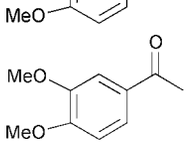


Scheme 5

The experimental procedure is very simple and the products are obtained in excellent yields with high diastereoselectivity. The reaction conditions are very mild and no side products or decomposition of the products are observed. The reactions are clean and are completed in a short reaction time. The catalyst was recovered from the aqueous layer during work-up and recycled in subsequent reactions without reduction in activity.

In summary, this paper describes a new method for the synthesis of fused chromanes from salicylaldehydes and enol ethers using a catalytic amount of $Yb(OTf)_3$. It also describes a method for the synthesis of 2,4-dimethoxy-2-arylchromanes by the cyclocondensation of salicylaldehydes with acetophenones using a catalytic amount of $Sc(OTf)_3$ under similar conditions. In addition to its efficiency, simplicity and milder reaction conditions, this method provides high yields of products with diastereoselectivity, which makes it a useful process for the synthesis of *cis*-fused chromanes and 2-alkoxychromanes.

Table 2 Sc(OTf)$_3$-catalyzed synthesis of 2,4-dialkoxy-2-arylchromanes[a]

Entry	*o*-Hydroxybenzaldehyde **1**	Aryl ketone **2**	Time (*t*/h)	Yield[b] (%)
a			6.5	85
b			5.0	81
c			9.0	78
d			8.0	85
e			7.5	88
f			9.5	75
g			7.0	80
h			6.5	84
i			8.0	76
j			6.5	80
k			7.0	85
l			8.0	77
m			7.5	82
n			9.0	75
o			9.5	73

[a] All products were characterized by ^{1}H NMR, IR and mass spectra. [b] Isolated and unoptimized yields.

Experimental

General

All melting points were determined using a Buchi R-535 apparatus. Proton magnetic resonance (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Gemini 200,500 MHz spectrometer. IR spectra were recorded on a Perkin-Elmer Infrared-683 spectrometer. Mass spectra were recorded on either a Finnigan-MAT1020B or Micro Mass VG70-70H. Elemental analysis was done on an Elementar Vario EL. Column chromatography was performed on silica gel (100–200 mesh); hexane was used as a co-eluent. Anhydrous sodium sulfate was used as drying agent for the organic extracts. Solvent removal was achieved by using a Buchi rotary evaporator.

I Preparation of *cis*-fused pyrano- and furanochromanes

A mixture of salicylaldehyde (5 mmol), trimethyl orthoformate (6 mmol) and Yb(OTf)$_3$ (5 mol% in dichloromethane; 10 mL) was stirred at ambient temperature for 10–15 min. Then a cyclic enol ether (7.5 mmol) was added slowly at 0 °C to the above mixture. The resulting reaction mixture was stirred at ambient temperature for an appropriate time. After complete conversion as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography on silica gel (Merck, 100–200 mesh; ethyl acetate–hexane, 1 : 9) to afford pure *cis*-fused acetal (Table 1, **3a**–**3o**).

Compound 3a. 4-Methoxy-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; 500 MHz) δ 1.70 (dddd, 1H, J = 7.2, 8.6, 9.2, 12.7 Hz), 1.93 (dddd, 1H, J = 5.0, 7.6, 9.2, 12.7 Hz), 3.17 (dt, 1H, J = 5.5, 5.8, 9.2 Hz), 3.60 (s, 3H), 3.80 (dt, 1H, J = 5.0, 8.5, 8.6 Hz), 3.85 (dt, 1H, J = 7.5, 7.6, 8.5 Hz), 4.63 (d, 1H, J = 5.5 Hz), 5.84 (d, 1H, J = 5.8 Hz), 6.88 (dd, 1H, H_9, J = 1.3, 8.0 Hz), 6.99 (dt, 1H, H_7, J = 1.3, 7.4 Hz), 7.18 (dt, 1H, H_8, J = 2.3, 7.9 Hz), 7.42 (td, 1H, H_6, J = 1.5, 7.5 Hz).

^{13}C NMR (proton decoupled ^{13}C in $CDCl_3$, at 50 MHz) δ 23.92, 42.29, 56.87, 68.18, 73.75, 102.26, 116.68, 121.56, 124.72, 125.46, 128.42, 152.15; EIMS: *m*/*z* 206 (M^+) [Calc. for $C_{12}H_{14}O_3$ (206.24): C, 69.89; H, 6.84. Found: C, 69.92; H, 6.87%].

Compound 3b. 5-Methoxy-3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; 500 MHz) δ 1.33 (m, 1H, H_{3ax}), 1.63 (m, 1H, H_{2eq}), 1.68 (m, 1H, H_{3eq}), 1.77 (m, 1H, H_{2ax}), 2.49 (dddd, 1H, J = 2.3, 3.8, 5.5, 12.4 Hz), 3.54 (s, 3H), 3.77 (dddd, 1H, H_{1eq}, J = 1.5, 4.8, 11.3 Hz), 4.02 (dt, 1H, H_{1ax}, J = 2.7, 11.3 Hz), 4.58 (d, 1H, J = 5.5 Hz), 5.48 (d, 1H, J = 2.3 Hz), 6.85 (dd, 1H, H_{10}, J = 1.3, 8.1 Hz), 6.93 (dt, 1H, H_8, J = 1.2, 7.4 Hz), 7.17 (dt, 1H, H_9 J = 1.6, 8.1 Hz), 7.40 (td, 1H, H_7, J = 1.5, 7.6 Hz); ^{13}C NMR (proton decoupled ^{13}C in $CDCl_3$; 50 MHz) δ 16.56, 23.99, 34.56, 56.58, 61.02, 75.70, 95.79, 115.66, 120.78, 121.34, 126.58, 151.86; EIMS: *m*/*z* 220 (M^+) [Calc. for $C_{13}H_{16}O_3$ (220.266): C, 70.89; H, 7.32. Found: C, 70.93; H, 7.35%].

Compound 3c. 2-Ethoxy-4-methoxychromane. Liquid, ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.1 Hz), 2.17 (dt, 1H, J = 6.9, 13.3 Hz), 2.37 (dddd, 1H, J = 2.7, 6.0, 13.3 Hz), 3.46 (s, 3H), 3.66 (dq, 1H, J = 7.1, 9.7 Hz), 3.99 (dq, 1H, J = 7.1, 9.7 Hz), 4.54 (dd, 1H, J = 6.0, 7.4 Hz), 5.21 (dd, 1H, J = 2.8, 6.9 Hz), 6.85 (dd, 1H, H_7, J = 1.3, 8.1 Hz), 6.95 (dt, 1H, H_5, J = 1.3, 7.5 Hz), 7.19 (dt, 1H, H_6, J = 1.9, 7.6 Hz), 7.36 (dd, 1H, H_4, J = 2.3, 7.6 Hz); ^{13}C NMR (proton decoupled ^{13}C in $CDCl_3$; 50 MHz) δ 14.97, 32.75, 55.68, 64.34, 71.79, 97.85, 116.88, 120.88, 123.20, 128.05, 129.08, 152.12; EIMS: *m*/*z* 208 (M^+) [Calc. for $C_{12}H_{16}O_3$ (208.255): C, 69.21; H, 7.74 Found: C, 69.25; H, 7.75%].

Compound 3d. 4,8-Dimethoxy-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; 500 MHz) δ 1.75 (dddd, 1H, J = 7.2, 8.6, 9.2, 12.7 Hz), 1.90 (dddd, 1H, J = 5.0, 7.6, 9.2, 12.7 Hz), 3.18 (dt, 1H, J = 5.5, 5.8, 9.2 Hz), 3.60 (s, 3H) 3.78 (dt, 1H, J = 5.0, 8.5, 8.6 Hz), 3.83 (dt, 1H, J = 7.5, 7.6, 8.5 Hz), 3.85 (s, 3H), 4.60 (d, 1H, J = 5.5 Hz), 5.85 (d, 1H, J = 5.8 Hz), 6.80 (d, 1H, H, J = 8.0 Hz), 6.90 (t, 1H, J = 7.4 Hz), 6.98 (d, 1H, J = 7.9 Hz); EIMS: *m*/*z* 236 (M^+) [Calc. for $C_{13}H_{16}O_4$ (236.265): C, 66.09; H, 6.83. Found: C, 66.12; H, 6.87%].

Compound 3e. 5,9-Dimethoxy-3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; 500 MHz) δ 1.35 (m, 1H, H_{3ax}), 1.65 (m, 1H, H_{2eq}), 1.67 (m, 1H, H_{3eq}), 1.78 (m, 1H, H_{2ax}), 2.45 (dddd, 1H, J = 2.3, 3.8, 5.5, 12.4 Hz), 3.54 (s, 3H), 3.75 (dddd, 1H, H_{1eq}, J = 1.5, 4.8, 11.3 Hz), 3.85 (s, 3H), 4.05 (dt, 1H, H_{1ax}, J = 2.7, 11.3 Hz), 4.58 (d, 1H, J = 5.5 Hz), 5.5 (d, 1H, J = 2.3 Hz), 6.78 (d, 1H, J = 8.1 Hz), 6.83 (t, 1H, J = 7.4 Hz), 6.98 (d, 1H, J = 8.1 Hz); EIMS: *m*/*z* 250 (M^+) [Calc. for $C_{14}H_{18}O_4$ (250.292): C, 67.18; H, 7.25. Found: C, 67.15; H, 7.28%].

Compound 3f. 2-Ethoxy-4,8-dimethoxychromane. Liquid, ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.1 Hz), 2.18 (dt, 1H, J = 6.9 and 13.3 Hz), 2.38 (dddd, 1H, J = 2.7, 6.0, 13.3), 3.45 (s, 3H), 3.68 (dq, 1H, J = 7.1, 9.7 Hz), 3.85 (s, 3H), 3.99 (dq, 1H, J = 7.1, 9.7 Hz), 4.55 (dd, 1H, J = 6.0, 7.4 Hz), 5.23 (dd, 1H, J = 2.8, 6.9 Hz), 6.80 (d, 1H, J = 8.0 Hz); 6.85 (t, 1H, J = 7.5 Hz), 6.98 (d, 1H, J = 8.0 Hz); EIMS: *m*/*z* 238 (M^+) [Calc. for $C_{13}H_{18}O_4$ (238.281): C, 65.53; H, 7.61. Found: C, 65.55; H, 7.63%].

Compound 3g. 8-Ethoxy-4-methoxy-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; 500 MHz), δ 1.40 (t, 3H, J = 6.8 Hz), 1.68 (dddd, 1H, J = 7.2, 8.6, 9.2, 12.7 Hz), 1.85 (dddd, 1H, J = 5.0, 7.6, 9.2, 12.7 Hz), 3.18 (dt, 1H, J = 5.5, 5.8, 9.2 Hz), 3.57 (s, 3H), 3.75 (dt, 1H, J = 5.0, 8.5, 8.6 Hz), 3.85 (dt, 1H, J = 7.5, 7.6, 8.5 Hz), 4.10 (q, 2H, J = 7.0 Hz), 4.58 (d, 1H, J = 5.5 Hz), 5.85 (d, 1H, J = 5.8 Hz), 6.78 (d, 1H, J = 8.0 Hz), 6.85 (t, 1H, J = 7.4 Hz), 7.0 (d, 1H, J = 7.9 Hz); EIMS: *m*/*z* 250 (M^+) [Calc. for $C_{14}H_{18}O_4$ (250.292): C, 67.18; H, 7.25. Found: C, 67.18; H, 7.24%].

Compound 3h. 9-Ethoxy-5-methoxy-3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; 500 MHz) δ 1.35 (m, 1H, H_{3ax}), 1.40 (t, 3H, J = 7.0 Hz), 1.62 (m, 1H, H_{2eq}), 1.70 (m, 1H, H_{3eq}), 1.75 (m, 1H, H_{2ax}), 2.45 (dddd, 1H, J = 2.3, 3.8, 5.5, 12.4 Hz), 3.55 (s, 3H), 3.78 (dddd, 1H, H_{1eq}, J = 1.5, 4.8, 11.3 Hz), 4.02 (dt, 1H, H_{1ax}, J = 2.7, 11.3 Hz), 4.10 (q, 2H, J = 6.9 Hz), 4.59 (d, 1H, J = 5.5 Hz), 5.48 (d, 1H, J = 2.3 Hz), 6.78 (d, 1H, J = 8.0 Hz), 6.83 (t, 1H, J = 7.5 Hz), 6.98 (d, 1H, J = 8.1 Hz); EIMS: *m*/*z* 264 (M^+) [Calc. for $C_{15}H_{20}O_4$ (264.319): C, 68.16; H, 7.63. Found: C, 68.19; H, 7.65%].

Compound 3i. 4,6-Dimethoxy-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; at 500 MHz) δ 1.65 (dddd, 1H, J = 7.2, 8.6, 9.2, 12.7 Hz), 1.87 (dddd, 1H, J = 5.0, 7.6, 9.2, 12.7 Hz), 3.18 (dt, 1H, J = 5.5, 5.8, 9.2 Hz), 3.58 (s, 3H), 3.70 (dt, 1H, J = 5.0, 8.5, 8.6 Hz), 3.78 (dt, 1H, J = 7.5, 7.6, 8.5 Hz), 3.80 (s, 3H), 4.50 (d, 1H, J = 5.5 Hz), 5.78 (d, 1H, J = 5.8 Hz), 6.70 (dd, 1H, J = 1.3, 8.0 Hz), 6.80 (d, 1H, J = 8.0 Hz), 6.95 (d, 1H, J = 2.3 Hz); EIMS: *m*/*z* 236 (M^+) [Calc. for $C_{13}H_{16}O_4$ (236.265): C, 66.09; H, 6.83. Found: C, 66.12; H, 6.87%].

Compound 3j. 5,7-Dimethoxy-3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; 500 MHz) δ 1.32 (m, 1H, H_{3ax}), 1.65 (m, 1H, H_{2eq}), 1.68 (m, 1H, H_{3eq}), 1.77 (m, 1H, H_{2ax}), 2.45 (dddd, 1H, J = 2.3, 3.8, 5.5, 12.4), 3.55 (s, 3H), 3.77 (dddd, 1H, H_{1eq}, J = 1.5, 4.8, 11.3 Hz), 3.80 (s, 3H),

4.0 (dt, 1H, H_{1ax}, J = 2.7, 11.3 Hz), 4.58 (d, 1H, J = 5.5 Hz), 5.40 (d, 1H, J = 2.3 Hz), 6.68 (dd, 1H, J = 1.3, 8.0 Hz), 6.80 (d, 1H, J = 8.0 Hz), 6.90 (d, 1H, J = 2.4 Hz); EIMS: *m/z* 250 (M^+) [Calc. for $C_{14}H_{18}O_4$ (250.292): C, 67.18; H, 7.25. Found: C, 67.15; H, 7.28%].

Compound 3k. 4,6-Dimethoxy-8-nitro-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; at 500 MHz) δ 1.68 (dddd, 1H, J = 7.2, 8.6, 9.2, 12.7 Hz), 1.90 (dddd, 1H, J = 5.0, 7.6, 9.2, 12.7 Hz), 3.18 (dt, 1H, J = 5.5, 5.8, 9.2 Hz), 3.59 (s, 3H), 3.78 (dt, 1H, J = 5.0, 8.5, 8.6 Hz), 3.80 (s, 3H), 3.85 (dt, 1H, J = 7.5, 7.6, 8.5 Hz), 4.62 (d, 1H, J = 5.5 Hz), 5.84 (d, 1H, J = 5.8 Hz), 7.18 (d, 1H, J = 2.3 Hz), 7.25 (d, 1H, J = 1.8 Hz); EIMS: *m/z* 281 (M^+) [Calc. for $C_{13}H_{15}NO_6$ (281.262): C, 55.52; H, 5.38; N, 4.98. Found: C, 55.50; H, 5.41; N, 4.80%].

Compound 3l. 6-Benzyloxy-4-methoxy-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; 500 MHz) δ 1.69 (dddd, 1H, J = 7.2, 8.6, 9.2, 12.7 Hz), 1.88 (dddd, 1H, J = 5.0, 7.6, 9.2, 12.7 Hz), 3.18 (dt, 1H, J = 5.5, 5.8, 9.2 Hz), 3.57 (s, 3H), 3.75 (dt, 1H, J = 5.0, 8.5, 8.6 Hz), 3.80 (dt, 1H, J = 7.5, 7.6, 8.5 Hz), 4.56 (d, 1H, J = 5.5 Hz), 5.0 (s, 2H), 5.80 (d, 1H, J = 5.8 Hz), 6.80 (m, 2H), 7.05 (d, 1H, J = 1.7 Hz), 7.32–7.45 (m, 5H); EIMS: *m/z* 312 (M^+) [Calc. for $C_{19}H_{20}O_4$ (312.363): C, 73.06; H, 6.45. Found: C, 73.10; H, 6.43%].

Compound 3m. 7-Benzyloxy-5-methoxy-3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; 500 MHz) δ 1.35 (m, 1H, H_{3ax}), 1.66 (m, 1H, H_{2eq}), 1.68 (m, 1H, H_{3eq}), 1.78 (m, 1H, H_{2ax}), 2.50 (dddd, 1H, J = 2.3, 3.8, 5.5, 12.4 Hz), 3.54 (s, 3H), 3.77 (dddd, 1H, H_{1eq}, J = 1.5, 4.8, 11.3 Hz), 4.05 (dt, 1H, H_{1ax}, J = 2.7, 11.3 Hz), 4.58 (d, 1H, J = 5.5 Hz), 5.48 (d, 1H, J = 2.3 Hz), 6.85 (m, 2H), 7.02 (d, 1H, J = 1.7 Hz), 7.35–7.48 (m 5H); EIMS: *m/z* 326 (M^+) [Calc. for $C_{20}H_{22}O_4$ (326.39): C, 73.6; H, 6.79. Found: C, 73.68; H, 6.81%].

Compound 3n. 11-Methoxy-9,10,10a,11-tetrahydro-7a*H*-benzo[*f*]furo[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; 500 MHz) δ 1.70 (dddd, 1H, J = 7.2, 8.6, 9.2, 12.7 Hz), 1.95 (dddd, 1H, J = 5.0, 7.6, 9.2, 12.7 Hz), 3.17 (dt, 1H, J = 5.5, 5.8, 9.2 Hz), 3.55 (s, 3H), 3.80 (dt, 1H, J = 5.0, 8.5, 8.6 Hz), 3.85 (dt, 1H, J = 7.5, 7.6, 8.5 Hz), 4.65 (d, 1H, J = 5.5 Hz), 5.80 (d, 1H, J = 5.8 Hz), 7.02 (d, 1H, J = 8.0 Hz), 7.30 (t, 1H, J = 7.5 Hz), 7.45 (t, 1H, J = 7.5 Hz), 7.70 (m, 2H), 7.88 (d, 1H, J = 8.0 Hz); EIMS: *m/z* 256 (M^+) [Calc. for $C_{16}H_{16}O_3$ (256.299): C, 74.98; H, 6.29. Found: C, 75.05; H, 6.30%].

Compound 3o. 6-Bromo-4-methoxy-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromene. Liquid, ^{1}H NMR ($CDCl_3$; at 500 MHz) δ 1.67 (dddd, 1H, J = 7.2, 8.6, 9.2, 12.7 Hz), 1.95 (dddd, 1H, J = 5.0, 7.6, 9.2, 12.7 Hz), 3.17 (dt, 1H, J = 5.5, 5.8, 9.2 Hz), 3.57 (s, 3H), 3.80 (dt, 1H, J = 5.0, 8.5, 8.6 Hz), 3.85 (dt, 1H, J = 7.5, 7.6, 8.5 Hz), 4.58 (d, 1H, J = 5.5 Hz), 5.80 (d, 1H, J = 5.8 Hz), 6.80 (dd, 1H, J = 1.3, 8.0 Hz), 7.10 (d, 1H, J = 7.9 Hz), 7.38 (d, 1H, J = 2.3 Hz); EIMS *m/z* 285 (M^+) [Calc. for $C_{12}H_{13}BrO_3$ (285.136): C, 50.55; H, 4.60; Br, 28.02. Found: C, 50.60; H, 4.57; Br, 28.10%].

II Preparation of 2,4-dimethoxy-2-arylchromanes

A mixture of a salicylaldehyde (2 mmol), an acetophenone (2 mmol), trimethyl orthoformate (5 mmol) and scandium triflate (5% w/w of aldehyde) in dichloromethane (10 mL) was stirred at ambient temperature for an appropriate time (Table 2). After complete conversion as indicated by TLC, the reaction mixture was quenched with water (15 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography on silica gel (Merck 100–200 mesh; ethyl acetate–hexane, 0.5 : 95) to afford pure 2,4-dimethoxy-2-phenylchromane (Table 2, **4a**–**4o**).

Compound 4a. 2,4-Dimethoxy-2-phenylchromane. Liquid, ^{1}H NMR ($CDCl_3$) δ 1.90 (dd, 1H, J = 12.5, 10.8 Hz), 2.68 (dd, 1H, J = 12.5, 6.0 Hz), 3.10 (s, 3H), 3.50 (s, 3H), 4.90 (dd, 1H, J = 10.8, 6.0 Hz), 6.98–7.08 (m, 2H), 7.18–7.30 (m, 1H), 7.38–7.60 (m, 4H), 7.65 (d, 2H, J = 8.0 Hz). EIMS: *m/z* 270 (M^+), 238, 207, 161, 121, 107, 77; IR (KBr) ν/cm^{-1} 3046, 2938, 2830, 1576, 1446, 1223, 1084, 1015, 930, 745 [Calc. for $C_{17}H_{18}O_3$ (270.326): C, 75.53; H, 6.71. Found: C, 75.70; H, 6.83%].

Compound 4b. 2,4,8-Trimethoxy-2-phenylchromane. Liquid, ^{1}H NMR ($CDCl_3$) δ 1.87 (dd, 1H, J = 12.7, 6.1 Hz), 2.67 (dd, 1H, J = 12.7, 10.6 Hz), 3.08 (s, 3H), 3.48 (s, 3H), 3.90 (s, 3H), 4.87 (dd, 1H, J = 10.6, 6.1 Hz), 5.85 (d, 1H, J = 8.0 Hz), 6.93 (t, 1H, J = 7.8 Hz), 7.10 (d, 1H, J = 8.0 Hz), 7.38–7.45 (m, 3H), 7.68 (d, 2H, J = 8.0 Hz); EIMS: *m/z* 300 (M^+), 237, 191, 151, 137, 105, 77; IR (KBr) ν/cm^{-1} 3053, 2853, 2830, 1584, 1476, 1353, 1261, 1076, 961, 730 [Calc. for $C_{18}H_{20}O_4$ (300.352): C, 71.98; H, 6.71. Found: C, 72.05; H, 6.79%].

Compound 4c. 2,4-Dimethoxy-2-(2-naphthyl)chromane. Liquid, ^{1}H NMR ($CDCl_3$) δ 1.98 (dd, 1H, J = 12.8, 10.5 Hz), 2.75 (dd, 1H, J = 12.8, 6.3 Hz), 3.09 (s, 3H), 3.47 (s, 3H), 4.90 (dd, 1H, J = 10.5, 6.3 Hz), 7.05 (t, 2H, J = 7.8 Hz), 7.10 (t, 1H, J = 7.8 Hz), 7.43–7.57 (m, 3H), 7.65 (d, 1H, J = 8.0 Hz), 7.83–7.97 (m, 3H), 8.15 (d, 1H, J = 1.8 Hz); EIMS: *m/z* 320 (M^+), 288, 257, 184, 155, 141, 119, 77, 43; IR (KBr) ν/cm^{-1} 3061, 2930, 2838, 1630, 1446, 1338, 1207, 1030, 907, 738 [Calc. for $C_{21}H_{20}O_3$ (320.386): C, 78.73; H, 6.29. Found: C, 78.77; H, 6.31%].

Compound 4d. 6-Chloro-2,4-dimethoxy-2-phenylchromane. Solid, mp 77–79 °C; ^{1}H NMR ($CDCl_3$) δ 1.80 (dd, 1H, J = 12.8, 10.7 Hz), 2.63 (dd, 1H, J = 12.8, 6.0 Hz), 3.05 (s, 3H), 3.45 (s, 3H), 4.80 (dd, 1H, J = 10.7, 6.0 Hz), 6.90 (d, 1H, J = 8.0 Hz), 7.18 (d, 1H, J = 8.0 Hz), 7.37–7.45 (m, 4H), 7.58 (d, 2H, J = 8 Hz); EIMS: *m/z* 304 (M^+), 272, 242, 195, 170, 155, 141, 105, 77, 43; IR (KBr) ν/cm^{-1} 3030, 3000, 2807, 1469, 1230, 1092, 1015, 900, 753 [Calc. for $C_{17}H_{17}ClO_3$ (304.771): C, 67.0; H, 5.62; Cl, 11.63. Found: C, 67.07; H, 5.68; Cl, 11.70%].

Compund 4e. 2-(4-Bromophenyl)-6-chloro-2,4-dimethoxychromane. Solid, mp 117–118 °C; ^{1}H NMR ($CDCl_3$) δ 1.78 (dd, 1H, J = 12.7, 10.8 Hz), 2.60 (dd, 1H, J = 12.7, 6.1 Hz), 3.03 (s, 3H), 3.48 (s, 3H), 4.78 (dd, 1H, J = 10.8, 6.1 Hz), 6.90 (d, 1H, J = 7.9 Hz), 7.18 (dd, 1H, J = 7.9, 2.7 Hz), 7.50–7.60 (m, 5H); EIMS: *m/z* 383 (M^+), 352, 321, 195, 155, 141, 102, 75, 43; IR (KBr) ν/cm^{-1} 2969, 2923, 2023, 1576, 1476, 1246, 1092, 1046, 915, 815 [Calc. for $C_{17}H_{16}BrClO_3$ (383.667): C, 53.22; H, 4.20; Br, 20.83; Cl, 9.24. Found: C, 53.25; H, 4.27; Br, 20.89; Cl, 9.28%].

Compund 4f. 8-Ethoxy-2,4-dimethoxy-2-(2-naphthyl)-chromane. Liquid, ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3H, J = 6.8 Hz), 1.98 (dd, 1H, J = 12.8, 10.9 Hz), 2.80 (dd, 1H, J = 12.8, 6.2 Hz), 3.17 (s, 3H), 3.48 (s, 3H), 4.20 (q, 2H, J = 6.8 Hz), 4.95 (dd, 1H, J = 10.9, 6.2 Hz), 6.90 (d, 1H, J = 8.0 Hz), 6.98 (t, 1H, J = 8.0 Hz), 7.18 (d, 1H, J = 8.0 Hz), 7.53–7.60 (m, 2H), 7.73 (d, 1H, J = 8.0 Hz), 7.85–7.98 (m, 3H), 8.20 (d, 1H, J = 1.8 Hz); EIMS: *m/z* 364 (M^+), 170, 155, 127, 101, 77, 43; IR (KBr) ν/cm^{-1} 3046, 2915, 2815, 1461, 1346, 1269, 1184, 1061, 1030, 815, 738 [Calc. for $C_{23}H_{24}O_4$ (364.439): C, 75.80; H, 6.64. Found: C, 76.05; H, 6.67%].

Compound 4g. 2,4-Dimethoxy-2-(4-methoxyphenyl)chromane. Liquid, ^{1}H NMR ($CDCl_3$) δ 1.80 (dd, 1H, J = 12.5, 10.5 Hz), 2.60 (dd, 1H, J = 12.5, 6.2 Hz), 3.02 (s, 3H), 3.45 (s, 3H), 3.80 (s, 3H), 4.80 (dd, 1H, J = 10.5, 6.2 Hz), 6.90–7.0 (m, 4H), 7.20 (t, 1H, J = 7.8 Hz), 7.43–7.57 (m, 3H); EIMS: *m/z* 300 (M^+),

272, 241, 167, 137, 109, 77, 43; IR (KBr) ν/cm^{-1} 3007, 2938, 2830, 2046, 1907, 1600, 1507, 1238, 1153, 1005, 892 [Calc. for $C_{18}H_{20}O_4$ (300.352): C, 71.98; H, 6.71. Found: C, 72.0; H, 6.75%].

Compound 4h. 2,4-Dimethoxy-2-(4-methylphenyl)chromane. Solid, mp 46–47 °C; ^{1}H NMR ($CDCl_3$) δ 1.90 (dd, 1H, J = 12.8, 11.0 Hz), 2.40 (s, 3H), 2.75 (dd, 1H, J = 12.8, 6.3 Hz), 3.10 (s, 3H), 3.50 (s, 3H), 4.90 (dd, 1H, J = 11.0, 6.3 Hz), 7.05 (t, 2H, J = 7.8 Hz), 7.25–7.38 (m, 3H), 7.50–7.60 (m, 3H); EIMS: m/z 284 (M^+), 254, 222, 162, 137, 108, 91, 77, 43; IR (KBr) ν/cm^{-1} 3030, 2923, 2815, 1576, 1446, 1307, 1238, 1092, 1015, 907, 753 [Calc. for $C_{18}H_{20}O_3$ (284.353): C, 76.03; H, 7.09. Found: C, 76.08; H, 7.15%].

Compound 4i. 2-(4-Bromophenyl)-2,4-dimethoxychromane. Liquid, ^{1}H NMR ($CDCl_3$) δ 1.80 (dd, 1H, J = 13.0, 10.8 Hz), 2.60 (dd, 1H, J = 13.0, 6.0 Hz), 3.05 (s, 3H), 3.43 (s, 3H), 4.80 (dd, 1H, J = 10.8, 6.0 Hz), 6.95–7.05 (m, 3H), 7.20 (t, 1H, J = 7.8 Hz), 7.40–7.55 (m, 4H); EIMS: m/z 350 (M^+), 322, 293, 204, 187, 158, 139, 109, 77, 43; IR (KBr) ν/cm^{-1} 3046, 2923, 2807, 1676, 1576, 1484, 1353, 1230, 1023, 900, 746 [Calc. for $C_{17}H_{17}BrO_3$ (349.222): C, 58.47; H, 4.91; Br, 22.88. Found: C, 58.5; H, 4.89; Br, 22.90%].

Compound 4j. 6-Benzyloxy-2,4-dimethoxy-2-phenylchromane. Liquid, ^{1}H NMR ($CDCl_3$) δ 1.90 (dd, 1H, J = 12.8, 11.0 Hz), 2.70 (dd, 1H, J = 12.8, 6.1 Hz), 3.10 (s, 3H), 3.50 (s, 3H), 4.85 (dd, 1H, J = 11.0, 6.1 Hz), 5.08 (s, 2H), 6.90–6.95 (m, 2H), 7.18 (d, 1H, J = 2.0 Hz), 7.38–7.60 (m, 8H), 7.65 (d, 2H, J = 8.0 Hz); EIMS: m/z 376 (M^+), 261, 139, 108, 79, 43; IR (KBr) ν/cm^{-1} 3015, 2923, 2830, 1607, 1484, 1200, 1146, 1015, 938, 700 [Calc. for $C_{24}H_{24}O_4$ (376.45): C, 76.57; H, 6.43. Found: C, 76.6; H, 6.51%].

Compound 4k. 2,4-Dimethoxy-2-(2-thienyl)chromane. Liquid, ^{1}H NMR ($CDCl_3$) δ 2.18 (dd, 1H, J = 12.9, 10.7 Hz), 2.80 (dd, 1H, J = 12.9, 6.2 Hz), 3.20 (s, 3H), 3.52 (s, 3H), 4.85 (dd, 1H, J = 10.7, 6.2 Hz), 6.98–7.10 (m, 3H), 7.20–7.30 (m, 2H), 7.35 (d, 1H, J = 8.0 Hz), 7.50 (d, 1H, J = 8.0 Hz); EIMS: m/z 276 (M^+), 244, 213, 136, 121, 107, 77, 65, 39; IR (KBr) ν/cm^{-1} 2969, 2930, 2807, 1576, 1446, 1346, 1200, 1146, 1084, 1030, 915 [Calc. for $C_{15}H_{16}O_3S$ (276.348): C, 65.19; H, 5.84; S, 11.60. Found: C, 65.23; H, 5.85; S, 11.63%].

Compound 4l. 8-Ethoxy-2,4-dimethoxy-2-phenylchromane. Solid, mp 83–86 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, 3H, J = 6.7 Hz), 1.90 (dd, 1H, J = 13.0, 11.0 Hz), 2.70 (dd, 1H, J = 13.0, 6.5 Hz), 3.02 (s, 3H), 3.40 (s, 3H), 4.10 (q, 2H, J = 6.7 Hz), 4.80 (dd, 1H, J = 11.0, 6.5 Hz), 6.85 (d, 1H, J = 8.1 Hz), 6.90 (t, 1H, J = 8.0 Hz), 7.05 (d, 1H, J = 8.1 Hz), 7.38–7.55 (m, 3H), 7.60 (d, 2H, J = 8.0 Hz); EIMS: m/z 314 (M^+), 282, 251, 165, 137, 120, 105, 91, 77, 51; IR (KBr) ν/cm^{-1} 3038, 2969, 2923, 2800, 1576, 1469, 1353, 1261, 1076, 1030, 892 [Calc. for $C_{19}H_{22}O_4$ (314.379): C, 72.59; H, 7.05. Found: C, 72.60; H, 7.10%].

Compound 4m. 6-Chloro-2,4-dimethoxy-2-(4-methylphenyl)-chromane. Liquid, ^{1}H NMR ($CDCl_3$) δ 1.78 (dd, 1H, J = 12.9, 10.7 Hz), 2.40 (s, 3H), 2.60 (dd, 1H, J = 12.9, 6.2 Hz), 3.05 (s, 3H), 3.45 (s, 3H), 4.80 (dd, 1H, J = 10.7, 6.2 Hz), 6.90 (d, 1H, J = 8.0 Hz), 7.18–7.25 (m, 3H), 7.37–7.48 (m, 3H); EIMS: m/z 318 (M^+), 286, 255, 195, 155, 133, 119, 91, 65, 35; IR (KBr) ν/cm^{-1} 3023, 2930, 2823, 1669, 1469, 1230, 1092, 1038, 907, 815, 753 [Calc. for $C_{18}H_{19}ClO_3$ (318.798): C, 67.82; H, 6.01; Cl, 11.12. Found: C, 67.85; H, 6.05; Cl, 11.17%].

Compound 4n. 2-(3,4-Dimethoxyphenyl)-2,4-dimethoxy-chromane. Liquid. ^{1}H NMR ($CDCl_3$) δ 1.85 (dd, 1H, J = 12.7, 10.5 Hz), 2.63 (dd, 1H, J = 12.7, 6.1 Hz), 3.18 (s, 3H), 3.48 (s, 3H), 3.95 (s, 6H), 4.85 (dd, 1H, J = 10.5, 6.1 Hz), 6.85–7.05 (m, 3H), 7.10–7.25 (m, 3H), 7.48 (d, 1H, J = 8.0 Hz); EIMS: m/z 330 (M^+), 299, 267, 196, 165, 141, 121, 69, 51, 43; IR (KBr) ν/cm^{-1} 3030, 2928, 2828, 1657, 1470, 1235, 1089, 1070, 1038, 905, 820, 750 [Calc. for $C_{19}H_{22}O_5$ (330.378): C, 69.08; H, 6.71. Found: C, 70.13; H, 6.75%].

Compound 4o. 2-(3,4-Dimethoxyphenyl)-8-ethoxy-2,4-dimeth-oxychromane. Liquid ^{1}H NMR ($CDCl_3$) δ 1.45 (t, 3H, J = 6.8 Hz), 1.83 (dd, 1H, J = 12.5, 10.7 Hz), 2.65 (dd, 1H, J = 12.5, 6.0 Hz), 3.15 (s, 3H), 3.48 (s, 3H), 3.90 (s, 6H), 4.18 (q, 2H, J = 6.8 Hz), 4.83 (dd, 1H, J = 10.7, 6.0 Hz), 6.83–6.98 (m, 3H), 7.10–7.20 (m, 2H), 7.58 (d, 1H, J = 8.1 Hz); EIMS: m/z 374 (M^+), 180, 165, 141, 137, 79, 69, 51, 43; IR (KBr) ν/cm^{-1} 3025, 2920, 2835, 1650, 1475, 1230, 1080, 1075, 1040, 902, 820, 740 [Calc. for $C_{21}H_{26}O_6$ (374.43): C, 67.36; H, 7.0. Found: C, 67.38; H, 7.05%].

III Molecular dynamics

Molecular dynamics calculations were carried out using Sybyl 6.7 program on a Silicon Graphics O2 work station. The Tripos force field with default parameters was used throughout the simulations. Minimizations were done first with steepest decent, followed by conjugate gradient methods for a maximum of 1000 iterations each. A 20 psec MD run at 300 K temperature was done and the conformations for each and every 500 fsec were sampled. The collected conformations were minimized using the above-mentioned procedure. Out of those 40 conformations one of the minimum-energy conformations which was consistent with NOE studies has been shown in the paper.

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