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Diastereoselective Synthesis of Substituted Hexahydrobenzo[*de*]iso-chromans and their Evaluation as Antileishmanial activity

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Hexahydrobenzo[*de*]isochromanes and hexahydropyrano[3,4,5-*ij*]isoquinolines can be efficiently synthesized *via* Friedel Crafts and oxa Pictet-Spengler reaction of acrylyl enol ethers mediated by triflic acid in good yields. The reaction is highly stereoselective. Two of the hexahydrobenzo[*de*]isochromanes are found to have moderate antileishmanial activity.

Introduction

Heterocyclic structures are considered as prominent features in synthetic chemistry because of their existence in many natural products and biologically active molecules. Particularly, oxygen heterocyclic compounds fused with aromatic ring systems such as chromane[1] and isochromane[2] derivatives are reported to be biologically active. As for example excentricine, *N*-methyl excentricine isolated from *Stephania excentrica* and stephalooxocanine isolated from *Stephania cepharantha* are acetylcholesterase inhibitors.[3] Owing to their wide range of biological activities, synthesis of substituted isochromans have attracted the attention of the synthetic community and various methods have been developed for the functionalization of isochromane core in recent years.[4] Therefore, development of suitable methodology for the synthesis of substituted isochromans, in a single step, is most desirable. Friedel crafts[5] and Pictet-Spengler[6] reactions are two important C-C bond forming reactions and are demonstrated in the synthesis of structurally diverse molecules. Herein, we wish to disclose a methodology for the synthesis of hexahydrobenzo[*de*]isochromane from aryl and alkene substituted acrylyl enol ethers catalyzed by triflic acid. We

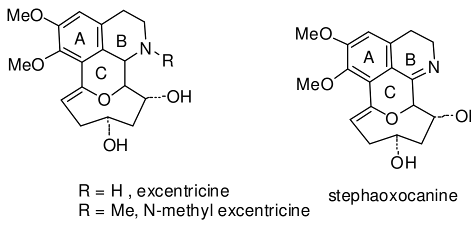
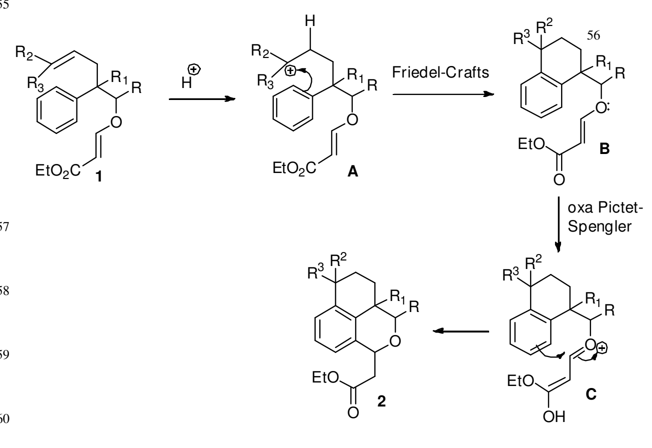


Fig. 1 Biologically important hexahydropyrano[3,4,5-ij]isoquinoline derivatives

envisioned that treatment of enol ether **1** with triflic acid would provide carbocation **A**, which after Friedel Crafts reaction will give enol ether **B**. The enol ether **B** will generate oxonium ion under acidic condition to facilitate the oxa Pictet-Spengler type reaction to give the tricyclic compound **2** (Scheme 1).

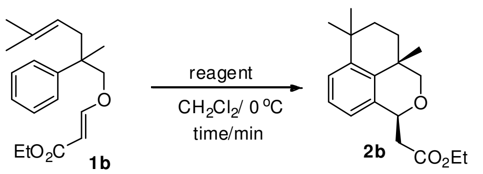
Scheme 1. Strategy for isochromane synthesis



Results and discussion

The reaction of (*E*)-ethyl 3-((5-methyl-2-phenylhex-4-en-1-yl)oxy)acrylate **1b** with triflic acid gave ethyl 2-((1*S**,3*aS**)-3a,6,6-trimethyl-1,3,3*a*,4,5,6- hexahydrobenzo[*de*]isochroman-1-yl)acetate **2b** in 75% yield. The reaction was also performed with different Bronsted and Lewis acids and the results are shown in Table 1. The reaction with 1.0 equivalent of $BF_3.OEt_2$, $In(OTf)_3$, $Sc(OTf)_2$, and $InCl_3$ produced no products, but starting material recovered in all the cases. On the other hand, TMSOTf, $FeCl_3$ and TsOH gave inseparable mixture of products (Table 1). The scope of the reaction is investigated by employing different types of substrates having aliphatic and aromatic substituents at different positions of the acrylyl enol ethers. It was observed from the Table 1 that, substrates having electron donating groups on the aromatic ring gave products in good yield. The reaction is highly diastereoselective and produced exclusively single diastereomers in most of the cases, and the stereochemistry of compounds is determined by 2-D nuclear Overhauser effect (NOESY). The products **2a**, **2h-j**, and **2m** where there is no bridgehead methyl group, the hydrogen at 3Ca-H and hydrogen at C1-H are in *cis* configuration, which is determined from the DEPT, HMQC and NOESY experiments of **2i**. It showed a clear characteristic NOE

Table 1 Optimization of the reaction condition



entry	reagent (equiv)	time/min	yield(%)^b
1	$BF_3 \cdot OEt_2$ (1.0)	30	--^{c}
2	$In(OTf)_3$ (1.0)	30	--^{c}
3	$Sc(OTf)_2$ 1.0)	30	--^{c}
4	$InCl_3$ (1.0)	30	--^{c}
5	TMSOTf (1.0)	30	--^{d}
6	$FeCl_3$ (1.0)	30	--^{d}
7	*p*-TsOH (1.0)	30	--^{d}
8	TfOH (1.0)	10	75
9	TfOH (10 mol%)	10	75

^{a}Reaction conditions: enol ether (1.0 mmol), solvent (2 mL) ^{b}Yield refers to isolated yield. ^{c}No reaction, starting material was recovered. ^{d}complex mixture.

correlation between the hydrogens 3Ca-H and C1-H (see SI). Similarly, compounds **2b**, **2k** and **2o** having bridgehead substituents show *cis* relationship between the substituents at C-1 and C-3a positions. It was confirmed by NOE experiment of the compound **2b**. On the other hand, stereochemistry of the products having substitutions at 1, 3, 3a and 6 positions is determined by NOE experiments of **2d**. In case of mono substitution at 6-position of the products, diastereomeric mixture with different ratios were obtained (entries 11-13, 15). The reaction is mild and substituents such as ester, ether, and halides are not affected in these reaction conditions.

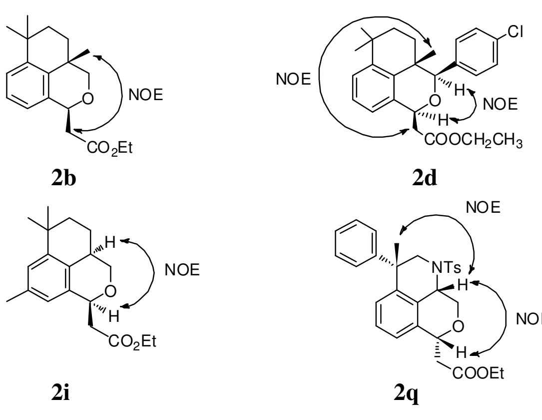
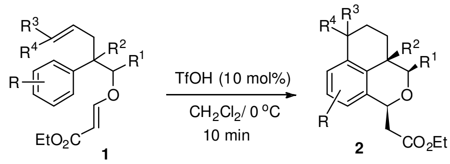
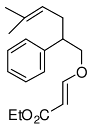
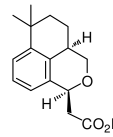
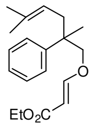
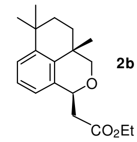
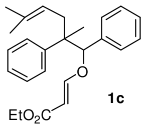
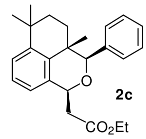
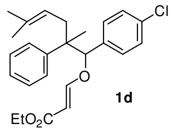
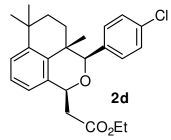
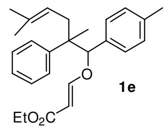
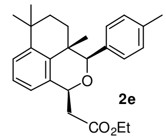
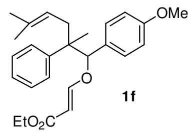
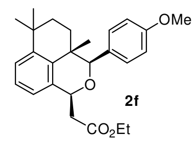
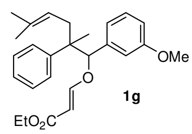
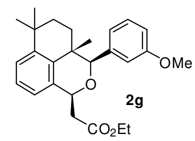
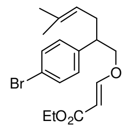
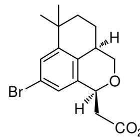


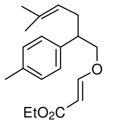
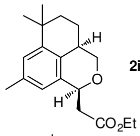
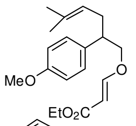
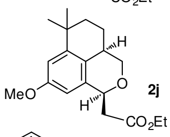
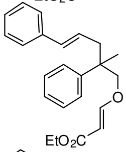
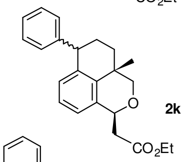
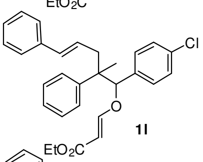
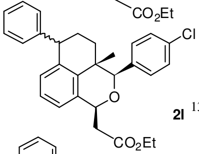
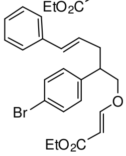
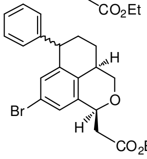
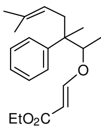
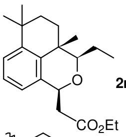
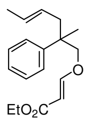
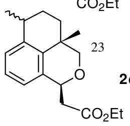
Figure 2. NOE of compounds 2b, 2d, 2i and 2q

After successful study of this methodology to the synthesis of hexahydrobenzo[*de*]isochromane, its application to the synthesis of hexahydropyrano[3,4,5-*ij*]isoquinoline was explored. The starting material enol ethers **1p-q** (Scheme 2) when treated with

Table 2. Synthesis of Hexahydrobenzo[*de*]isochromane



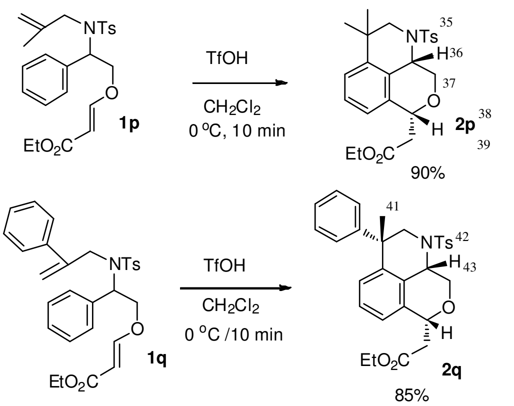
Sl.No.	Substrate **1**	Product **2**	Yield (%) ^{a}	d. r.^{b}
1	 **1a**	 **2a**	76	—
2	 **1b**	 **2b**	75	—
3	 **1c**	 **2c**	65	—
4	 **1d**	 **2d**	76	—
5	 **1e**	 **2e**	68	—
6	 **1f**	 **2f**	75	—
7	 **1g**	 **2g**	55	—
8	 **1h**	 **2h**	71	—

Sl.No.	Substrate **1**	Product **2**	Yield (%) [a]	d. r.[b]
9	 **1i**	 **2i**	62	—
10	 **1j**	 **2j**	74	—
11	 **1k**	 **2k**	70	3:1
12	 **1l**	 **2l**	75	4:1
13	 **1m**	 **2m**	71	8:1
14	 **1n**	 **2n**	73	—
15	 **1o**	 **2o**	57	8:5

[a]Yields refer to isolated yield. The compounds were characterized by IR, NMR and Mass spectrometry. [b]Ratio is determined by ^{1}H NMR.

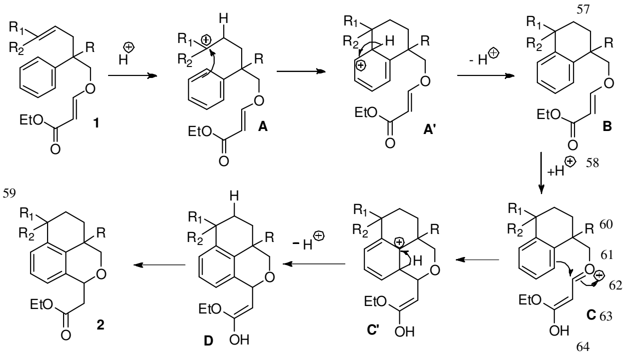
triflic acid under the same reaction conditions gave ethyl 2-((7*R**,9*aS**)-3,3-dimethyl-1-tosyl-1,2,3,7,9,9*a* hexahydro-pyrano[3,4,5-*ij*]isoquinolin-7-yl)acetate **2p** and ethyl2-((3*S**,7*R*,9*aS**)-3-methyl-3-phenyl-1-tosyl-1,2,3,7,9,9*a*-hexahydropyrano[3,4,5- *ij*]isoquinolin-7-yl)acetate **2q** in 90% and 85% yields, respectively (Scheme 2). The stereochemistry of **2p** and **2q** is determined by NOE experiment of **2q** (see SI).

Scheme 2. Synthesis of hexahydropyrano[3,4,5-*ij*]isoquinoline



The mechanism of formation of hexahydrobenzo[*de*]isochromans can be explained as follows. The enol ether **1** reacts with acid to form carbocation **A**, which after Friedel-Crafts reaction and subsequent elimination and addition of protons give oxocarbenium ion **C**. The oxocarbenium ion **C** is then attacked by aromatic ring *via* Pictet-Spengler type reaction to form hexahydrobenzo[*de*]isochromane **2** (Scheme 3).

Scheme 3 Plausible mechanism of the reaction



Evaluation of antileishmanial activity of 2f, 2j and 2p

Leishmania is a dimorphic protozoan parasite, which is responsible for self healing cutaneous leishmaniasis (CL) and life claiming visceral leishmaniasis (VL), commonly known as kala-

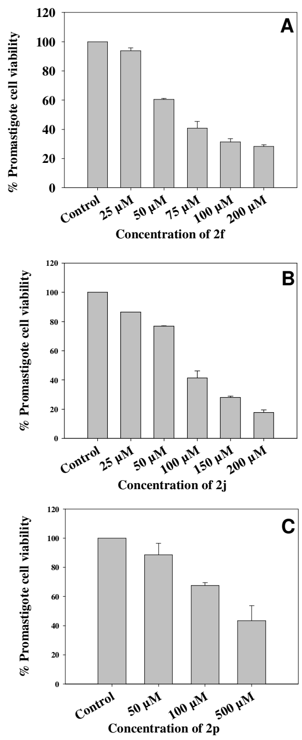


Figure 3. Antileishmanial effect of compounds (A), **2f** (B), **2j** and (C), **2p** on Leishmania donovani promastigote cells. The IC_{50} values were found out to be 72.5 µM, 98.75 µM and 440 µM, respectively.

azar in India.[7] Due to the high toxicity, high cost and drug resistance of available drugs, there is a need of synthesizing and evaluation of antileishmanial activity of new compounds.[8] We have already studied the antileishmanial activity of few oxabicyclo[3.3.1]nonanones and found promising result for one of the compounds.[9] Encouraged by these results we have undertaken to screen some tricyclic oxygen and nitrogen heterocycles fused with aromatic ring as these ring systems such as chromane[1] and isochromane[2] derivatives are reported to be biologically active. The three compounds were experimentally assessed for their anti- leishmanial activities. IC_{50} values for **2f**, **2j** and **2p** were found out to be 72.5 µM, 98.75 µM and 440 µM respectively. The compounds **2f** and **2h** were found to be most effective against *Leishmania donovani* promastigotes with moderate IC_{50} values, while compound **2p** was found to be least effective with a high IC_{50} value (**Figure 3**). This signifies that *Leishmania donovani* promastigotes are more sensitive to compounds **2f** and **2h** as compared to **2p**. However, the known potential antileishmanials like mliltefosine has an IC_{50} value of 25 µM. Thus there is need for further improvement in the efficacy of these compounds. This provides a novel chemical space for further modification for development of highly effective antileishmanial compounds.

Conclusions

In conclusion, we have developed a mild and efficient method for the synthesis of hexahydrobenzo[*de*]isochromane *via* Friedel Crafts and oxa Pictet-Spengler type reaction of enol ether in good yields. The same methodology can be used for the synthesis of hexahydropyrano[3,4,5-ij]isoquinoline. The reaction is highly diastereoselective and compatible to functional groups such as ester, halides and ether. This methodology would provide a tool to synthesize tricyclic heterocyclic compounds having a functional group at the bridgehead position. Two of the hexahydrobenzo[de]isochromanes **2f**, **2h** are found to have antileishmanial activity with IC_{50} values 72.5 µM and 98.75 µM, respectively.

Experimental section

General Information: General Information: All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 400 MHz) or ^{13}C (150 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer. The starting material enol ethers **1a-q** is prepared as per literature procedure (see SI).

(*E*)-Ethyl 3-((5-methyl-2-phenylhex-4-en-1-yl)oxy)acrylate (1a)

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.50; yield 225 mg, 78%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3 H), 1.54 (s, 3 H), 1.64 (s, 3 H), 2.26-2.33 (m, 1 H), 2.44- 2.52 (m, 1 H), 3.01 (quintet, *J* = 6.8 Hz, 1 H), 3.96 (d, *J* = 6.8 Hz, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 5.03 (t, *J* = 7.6 Hz, 1 H), 5.17 (d, *J* =12.4 Hz, 1 H), 7.18-7.21 (m, 2 H), 7.22-7.25 (m, 1 H) 7.28-7.32 (m, 2 H), 7.54 (d, *J* = 13.2 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl3) δ 14.5, 17.9, 25.9, 31.1, 45.5, 59.9, 74.2, 96.6, 121.3, 126.9, 128.0, 128.6, 134.0, 141.8, 162.5, 168.0; IR (KBr, neat) 2980, 2928, 1712, 1632, 1454, 1319, 1220, 1136, 1041, 770, 692 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{25}O_3$ $(M + H)^+$ 289.1798 found 289.1799.

(*E*)-Ethyl 3-((2,5-dimethyl-2-phenylhex-4-en-1-yl)oxy)acrylate (1b)

Pale yellow oil; R_f (hexane/ EtOAc, 24:1) 0.50; yield 242 mg, 80%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3 H), 1.35 (s, 3 H), 1.56 (s, 3 H), 1.63 (s, 3 H), 2.42 (d, *J* = 7.2 Hz, 2 H), 3.86 (d, *J* = 9.6 Hz, 1 H), 3.92 (d, *J* = 9.6 Hz, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 4.89 (t, *J* = 7.2 Hz, 1 H), 5.19 (d, *J* = 12.6 Hz, 1 H), 7.22 (t, *J* = 8.4 Hz, 1 H), 7.25-7.33 (m, 4 H), 7.57 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.6, 18.2, 22.9, 26.1, 37.2, 42.4, 60.0, 78.3, 96.5, 119.5, 126.4, 126.5, 128.5, 134.6, 144.9, 162.8, 168.0; IR (KBr, neat) 2977, 1709, 1625, 1444, 1326, 1220, 1133, 1048, 760, 685 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{27}O_3$ $(M + H)^+$ 303.1955 found 303.1956.

(*E*)-Ethyl 3-((2,5-dimethyl-1,2-diphenylhex-4-en-1-yl)oxy)acrylate (diastereomeric mixture, 4:3, 1c)

Pale yellow oil; R_f (hexane/ EtOAc, 24:1) 0.50; yield 306 mg, 81%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.2 Hz, 3 H, major), 1.98 (t, *J* = 7.2 Hz, 3 H, minor), 1.27 (s, 3 H, major), 1.29 (s, 3 H, minor), 1.56 (s, 3 H, major), 1.57 (s, 3 H, minor), 1.60 (s, 3 H), 2.45 (dd, *J* = 14.4 and 8.4 Hz, 2 H, minor), 2.61 (dd, *J* = 14.4 and 7.2 Hz, 2 H, major), 4.01-4.11 (m, 2 H), 4.81 (t, *J* = 7.2 Hz, 1 H, major), 4.87 (t, *J* = 7.2 Hz, 1 H, minor), 4.88 (s, 1 H, major), 4.95 (s, 1 H, minor), 5.11 (d, *J* = 12.6 Hz, 1 H, major), 5.15 (d, *J* = 12.0 Hz, 1 H, minor), 6.70 (d, *J* = 7.8 Hz, 2 H, minor), 6.81 (d, *J* = 7.2 Hz, 2 H, major), 7.08-7.26 (m, 8 H), 7.39 (d, *J* = 12.0 Hz, 1 H, major), 7.49 (d, *J* = 12.0 Hz, 1 H, minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 14.5, 18.3, 18.4, 18.8, 20.9, 26.0, 26.1, 36.3, 36.4, 46.5, 47.0, 59.8, 59.9, 91.0, 91.6, 98.4, 98.6, 119.8, 120.2, 126.5, 126.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.18, 128.2, 128.4, 133.8, 134.3, 135.6, 136.8, 142.8, 161.8, 162.0, 168.0; IR (KBr, neat) 2981, 2929, 1712, 1642, 1446, 1368, 1220, 1130, 1045, 779 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{31}O_3$ $(M + H)^+$ 379.2268 found 379.2265.

(*E*)-Ethyl 3-((1-(4-chlorophenyl)-2,5-dimethyl-2-phenylhex-4-en-1-yl)oxy)acrylate (diastereomeric mixture, 3:2, 1d)

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.50; yield 293 mg, 75%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 3 H, major), 1.21 (t, *J* = 7.2 Hz, 3 H, minor), 1.26 (s, 3 H, major), 1.27 (s, 3 H, minor), 1.57 (s, 3 H, minor), 1.58 (s, 3 H, major), 1.60 (s, 3 H, minor), 1.61 (s, 3 H, major), 2.49 (dd, *J* = 14.4 and 8.4 Hz, 2

H, minor), 2.60 (dd, *J* = 14.4 and 7.8 Hz, 2 H, major), 4.02-4.12 (m, 2 H), 4.79 (t, *J* = 7.2 Hz, 1 H, minor), 4.84 (s, 1 H, major), 4.89 (t, *J* = 7.2 Hz, 1 H, major), 4.92 (s, 1 H, minor), 5.09 (d, *J* = 12.6 Hz, 1 H, major), 5.13 (d, *J* = 12.6 Hz, 1 H, minor), 6.59 (d, *J* = 8.4 Hz, 2 H, minor), 6.70 (d, *J* = 8.4 Hz, 2 H, major), 7.06 (d, *J* = 8.4 Hz, 1 H), 7.10-7.14 (m, 2 H), 7.19-7.27 (m, 1 H), 7.37 (d, *J* = 12.6 Hz, 1 H, major), 7.48 (d, *J* = 12.6 Hz, 1 H, minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 18.4, 18.5, 21.1, 26.0, 26.1, 36.1, 36.5, 46.5, 47.0, 59.9, 60.1, 90.2, 90.8, 98.8, 98.9, 119.6, 119.9, 126.7, 126.8, 127.8, 127.9, 127.9, 128.0, 128.1, 128.3, 129.2, 129.7, 133.8, 134.0, 134.6, 135.4, 142.2, 142.3, 161.5, 161.7, 167.8; IR (KBr, neat) 2980, 2927, 1709, 1628, 1624, 1445, 1377, 1220, 1130, 1046, 760, 699 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{30}ClO_3$ $(M + H)^+$ 413.1878 found 413.1861.

(*E*)-Ethyl 3-((2,5-dimethyl-2-phenyl-1-(p-tolyl)hex-4-en-1-yl)oxy)acrylate (diasteromeric mixture, 4:3, 1e)

Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 294 mg, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 3 H, minor), 1.21 (t, *J* = 7.2 Hz, 3 H, major), 1.28 (s, 3 H, minor), 1.30 (s, 3 H, major), 1.57 (s, 3 H, minor), 1.58 (s, 3 H, major), 1.61 (s, 3 H), 2.25 (s, 3 H, major), 2.29 (s, 3 H, minor), 2.46 (dd, *J* = 14.4 and 8.4 Hz, 2 H, minor), 2.61-2.63 (m, 2 H, major), 4.04-4.10 (m, 2 H), 4.82 (t, *J* = 7.2 Hz, 1 H, major), 4.87 (s, 1 H, minor), 4.89 (t, *J* = 7.2 Hz, 1 H, minor), 4.93 (s, 1 H, major), 5.12 (d, *J* = 12.0 Hz, 1 H, minor), 5.16 (d, *J* = 12.6 Hz, 1 H, major), 6.61 (d, *J* = 7.8 Hz, 2 H, major), 6.71 (d, *J* = 7.8 Hz, 2 H, minor), 6.91 (d, *J* = 7.8 Hz, 2 H, minor), 6.98 (d, *J* = 7.8 Hz, 2 H, major), 7.15 (d, *J* = 7.8 Hz, 2 H), 7.20-7.36 (m, 1 H), 7.38 (d, *J* = 12.6 Hz, 1 H, major), 7.49 (d, *J* = 12.6 Hz, 1 H, minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 18.3, 18.4, 20.9, 21.2, 21.3, 26.0, 26.1, 36.3, 36.4, 46.5, 47.0, 59.8, 59.8, 91.0, 91.6, 98.3, 98.4, 119.9, 120.2, 126.4, 126.5, 127.8, 127.9, 128.0, 128.1, 128.2, 128.25, 128.3, 128.4, 128.5, 133.7, 133.8, 134.2, 137.5, 137.9, 142.8, 142.9, 161.9, 162.2, 168.0; IR (KBr, neat) 2978, 1707, 1622, 1444, 1220, 1130, 1038, 854, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{33}O_3$ $(M + H)^+$ 393.2424 found 393.2425.

(*E*)-Ethyl 3-((1-(4-methoxyphenyl)-2,5-dimethyl-2-phenylhex-4-en-1-yl)oxy)acrylate (diasteromeric mixture, 3:2, 1f)

Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 238 mg, 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 3 H, major), 1.20 (t, *J* = 7.2 Hz, 3 H, minor), 1.26 (s, 3 H, minor), 1.29 (s, 3 H, major), 1.55 (s, 3 H, minor), 1.56 (s, 3 H, major), 1.60 (s, 3 H, major), 1.61 (s, 3 H, minor), 2.44 (dd, *J* = 15.0 and 8.4 Hz, 2 H, minor), 2.56-2.66 (m, 2 H, major), 3.73 (s, 3 H, major), 3.76 (s, 3 H, minor), 4.03-4.10 (m, 2 H), 4.82 (t, *J* = 7.2 Hz, 1 H, major), 4.83 (s, 1 H, minor), 4.88 (t, *J* = 7.2 Hz, 1 H, minor), 4.90 (s, 1 H, major), 5.10 (d, *J* = 12.6 Hz, 1 H, minor), 5.15 (d, *J* = 12.6 Hz, 1 H, major), 6.61 (d, *J* = 7.2 Hz, 4 H, major), 6.71 (d, *J* = 7.8 Hz, 4 H, minor), 6.13 (d, *J* = 7.8 Hz, 1 H), 7.19-7.26 (m, 3 H), 7.35-7.40 (m, 1 H), 7.38 (d, *J* = 12.6 Hz, 1 H, minor), 7.48 (d, *J* = 12.6 Hz, 1 H, major); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 18.2, 18.3, 18.4, 18.9, 20.9, 26.0, 26.1, 36.3, 36.3, 46.6, 47.0, 55.1, 55.2, 59.7, 59.8, 90.7, 91.3, 98.3, 98.4, 112.9, 113.1, 119.8, 120.2, 126.4, 126.5, 127.8, 127.9, 128.0, 128.1, 128.3, 128.8, 129.1, 129.2, 129.6, 133.7, 134.2, 142.7, 142.8, 159.1, 159.4, 161.9, 162.1, 168.0; IR (KBr, neat) 2980, 2930, 1708, 1641, 1622, 1514, 1445, 1376, 1220, 1176, 1037, 830, 763, 685 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{18}NaO_5$ $(M + Na)^+$ 431.2193 found 431.2180.

(*E*)-Ethyl 3-((1-(3-methoxyphenyl)-2,5-dimethyl-2-phenylhex-4-en-1-yl)oxy)acrylate (diasteromeric mixture, 3:2, 1g)

Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 199 mg, 49 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.35 (m, 6 H), 1.57 (s, 6 H, major), 1.63 (s, 6 H, minor), 2.47 (dd, *J* =16.0 and 9.6 Hz, 1 H), 2.61 (d, *J* = 4.0 Hz, 1 H), 3.53 (s, 3 H, major), 3.56 (s, 3 H, minor), 4.04-4.17 (m, 2 H), 4.81 (t, *J* = 7.2 Hz, 1 H, major), 4.84 (s, 1 H, minor), 4.90 (t, *J* = 7.2 Hz, 1 H, minor), 4.92 (s, 1 H, major), 5.15 (d, *J* = 12.6 Hz, 1 H, minor), 5.16 (d, *J* = 12.0 Hz, 1 H, major), 6.10 (s, 1 H, major), 6.17 (s, 1 H, minor), 6.38 (d, *J* = 8.0 Hz, 1 H, major), 6.51 (d, *J* = 8.0 Hz, 1 H, minor), 6.69 (d, *J* = 8.0 Hz, 1 H), 6.75 (d, *J* = 8.0, 1 H), 7.03 (t, *J* = 8.0 Hz, 1 H), 7.10 (t, *J* = 8.0 Hz, 1 H, minor), 7.15 (d, *J* = 8.0 Hz, 1 H, major), 7.16-7.31(m, 3 H), 7.41 (d, *J* = 12 Hz, 1 H, minor), 7.50 (d, *J* = 12 Hz, 1 H, major); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.4, 14.5, 18.3, 18.4, 18.9, 21.2, 26.1, 26.2, 30.0, 36.5, 47.0, 58.2, 59.9, 60.0, 91.0, 91.4, 98.5, 98.6, 113.1, 113.4, 114.0, 114.3, 120.1, 120.4, 128.0, 128.2, 128.4, 133.9, 134.4, 138.3, 142.8, 142.8, 158.8, 159.0, 161.8, 162.1, 168.0. IR (KBr, neat) 2975, 2948, 1706, 1650, 1620, 1511, 1425, 1370, 1210, 1100, 1031, 755, 690 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{32}NaO_4$ $(M + Na)^+$ 431.2193 found 431.2195.

(*E*)-Ethyl 3-((2-(4-bromophenyl)-5-methylhex-4-en-1-yl)oxy)acrylate (1h)

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 275 mg, 71%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3 H), 1.54 (s, 3 H), 1.65 (s, 3 H), 2.26 (quint, *J* = 7.2 Hz, 1 H), 2.45 (quint, *J* = 7.2 Hz, 1 H), 2.95 (quint, *J* = 7.2 Hz, 1 H), 3.92-3.94 (m, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 4.98 (t, *J* = 7.8 Hz, 1 H), 5.16 (d, *J* = 12.6 Hz, 1 H), 7.06 (d, *J* = 7.8 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.52 (d, *J* = 13.2 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5,18.0, 25.9, 31.0, 45.1, 60.0, 73.9, 96.9, 120.8, 120.9, 129.8, 131.7, 134.4, 140.8, 162.3, 167.9; IR (KBr, neat) 2977, 2929, 1709, 1625, 1489, 1327, 1220, 1137, 1048, 821, 758, 685 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{23}BrO_3$ $(M + Na)^+$ 389.0723 found 389.0726.

(*E*)-Ethyl 3-((5-methyl-2-(*p*-tolyl)hex-4-en-1-yl)oxy)acrylate (1i)

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 211 mg, 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 1.57 (s, 3 H), 1.66 (s, 3 H), 2.29 (quint, *J* = 7.2 Hz, 1 H), 2.33 (s, 3 H), 2.48 (quint, *J* = 7.2 Hz, 1 H), 2.96 (quint, *J* = 7.2 Hz, 1 H), 3.95 (d, *J* = 6.0 Hz, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 5.04 (t, *J* = 7.2 Hz, 1 H), 5.18 (d, *J* = 12.6 Hz, 1 H), 7.08 (d, *J* =7.8 Hz, 2 H), 7.12 (d, *J* = 7.8 Hz, 2 H), 7.56 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 18.0, 21.2, 25.9, 31.1, 45.1, 59.9, 74.4, 96.6, 121.4, 127.8, 129.3, 133.8, 136.5, 138.7, 162.6, 168.0; IR (KBr, neat) 2977, 2928, 1710, 1625, 1447, 1325, 1219, , 1136, 1048, 816, 768 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{27}O_3$ $(M + H)^+$ 303.1955 found 303.1952.

(*E*)-Ethyl 3-((2-(4-methoxyphenyl)-5-methylhex-4-en-1-yl)oxy)acrylate (1j)

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 239 mg, 75%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3 H), 1.55 (s, 3 H), 1.65 (s, 3 H), 2.26 (quint, *J* = 7.2 Hz, 1 H), 2.46 (quint, *J* = 7.2 Hz, 1 H), 2.95 (quint, *J* = 7.2 Hz, 1 H), 3.79 (s, 3 H), 3.92 (d, *J* = 6.0 Hz, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 5.02 (t, *J* = 7.2 Hz, 1 H), 5.17 (d, *J* = 12.6 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 7.10 (d, *J* = 8.4 Hz, 2 H), 7.55 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 18.0, 25.9, 31.2, 44.7, 55.4, 59.9, 74.5, 96.6, 114.1, 121.4, 128.9, 133.7, 133.8, 158.6, 162.6, 168.0; IR (KBr, neat) 2928, 1710, 1625, 1463, 1325, 1220, 1136, 1040, 829, 772 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{27}O_4$ $(M + H)^+$ 319.1904 found 319.1907.

(*E*)-Ethyl 3-(((*E*)-2-methyl-2,5-diphenylpent-4-en-1-yl)oxy)acrylate (1k)

Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 245 mg, 70%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3 H), 1.42 (s, 3 H), 2.59 (dd, *J* = 14.0 and 14.0 Hz, 1 H), 2.70 (dd, *J* = 14.0 and 6.8 Hz, 1 H), 3.93 (dd, *J* = 12.8 and 9.6 Hz, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 5.20 (d, *J* = 12.8 Hz, 1 H), 5.91 (quint, *J* = 7.6 Hz, 1 H), 6.38 (d, *J* = 15.6 Hz, 1 H), 7.16-7.20 (m, 1 H), 7.20-7.25 (m, 5 H), 7.27-7.36 (m, 4 H), 7.59 (d, *J* = 13.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 22.9, 42.3, 42.5, 60.0, 78.4, 96.7, 125.7, 126.3, 126.5, 126.8, 127.4, 128.7, 133.5, 137.5, 144.3, 162.7, 168.0; IR (KBr, neat) 2975, 2928, 1707, 1629, 1455, 1399, 1210, 1132, 1040, 964, 770, 680 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{27}O_3$ $(M + H)^+$ 351.1955 found 351.1950.

(*E*)-Ethyl 3-(((*E*)-1-(4-chlorophenyl)-2-methyl-2,5-diphenylpent-4-en-1-yl)oxy)acrylate (diastereomerc ratio 2:1, 1l)

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 313 mg, 68%; ^1H NMR (400 MHz) δ 1.18-2.26 (m, 3 H, major & minor), 1.32 (s, 3 H, major), 1.34 (s, 3 H, minor), 2.56 (dd, *J* = 14.0 and 9.2 Hz, 1 H, minor), 2.71 (dd, *J* = 14.4 and 9.2 Hz, 1 H, major), 2.95 (ddd, *J* = 13.6, 5.6 and 4.8 Hz, 1 H, major & minor), 4.02-4.13 (m, 2 H, major & minor), 4.87 (s, 1 H, minor), 4.98 (s, 1 H, major), 5.12 (d, *J* = 12.4 Hz, 1 H, minor), 5.16 (d, *J* = 12.4 Hz, 1 H, major), 5.78-5.87 (m, 1 H, major), 5.89-5.95 (m, 1 H, minor), 6.40 (d, *J* =15.6 Hz, 1 H, major & minor), 6.63 (d, *J* = 8.8 Hz, 2 H, major), 6.73 (d, *J* = 8.8 Hz, 2 H, minor), 7.07-7.19 (m, 12 H, major & minor), 7.39 (d, *J* = 12.8 Hz, 1 H, minor), 7.49 (d, *J* = 12.4 Hz, 1 H, major); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 18.6, 21.3, 41.3, 42.1, 46.4, 46.9, 59.9, 60.0, 90.4, 90.7, 98.9, 99.1, 125.8, 126.1, 126.2, 126.3, 126.9, 127.0, 127.2, 127.3, 127.9, 128.0, 128.1, 128.4, 128.5, 128.6, 129.2, 129.7, 133.3, 133.7, 133.9, 135.1, 137.6, 141.8, 142.0, 161.3, 161.6, 167.7; IR (KBr, neat) 2979, 1707, 1642, 1492, 1321, 1220, 1131, 1048, 761, 686 cm^{-1}; HRMS (ESI) calcd. for $C_{29}H_{30}ClO_3$ $(M + H)^+$ 461.1878 found 461.1885.

(*E*)-Ethyl 3-(((*E*)-2-(4-bromophenyl)-5-phenylpent-4-en-1-yl)oxy)acrylate (1m)

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 298 mg, 72%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3 H), 2.54 (quint, *J* = 7.2 Hz, 1 H), 2.67 (quint, *J* = 7.6 Hz, 1 H), 3.11 (quint, *J* = 7.2 Hz, 1 H), 3.98 (d, *J* = 6.0 Hz, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 5.18 (d, *J* = 12.8 Hz, 1 H), 6.02 (quint, *J* = 7.6 Hz, 1 H), 6.38 (d, *J* = 15.6 Hz, 1 H), 7.10 (d, *J* = 8.4 Hz, 2 H), 7.18-7.21 (m, 1 H), 7.25-7.27 (m, 4 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 7.54 (d, *J* = 12.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 35.9, 45.0, 60.0, 73.8, 97.1, 121.1, 126.3, 126.7, 127.5, 128.7, 129.8, 131.9, 132.8, 137.3, 140.1, 162.2, 167.8; IR (KBr, neat) 2979, 2933, 1706, 1631, 1485, 1325, 1219, 1136, 1043, 963, 771, 683 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{24}BrO_3$ $(M + H)^+$ 415.0903 found 415.0900.

(*E*)-Ethyl 3-((4,7-dimethyl-4-phenyloct-6-en-3-yl)oxy)acrylate (diastereomeric ratio 3:1, 1n)

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 270 mg, 82%; ^1H NMR (600 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.2 Hz, 3 H, major), 0.97 (t, *J* = 7.2 Hz, 3 H, minor), 1.24-1.30 (m, 6 H), 1.31-1.41 (m, 2 H), 1.51 (s, 3 H), 1.59 (s, 3 H), 2.41 (d, *J* = 7.2 Hz, 2 H, major), 2.53 (d, *J* = 7.2 Hz, 2 H, minor), 3.52 (d, *J* = 9.6 Hz, 1 H, minor), 3.90 (d, *J* = 9.6 Hz, 1 H, major), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.71 (t, *J* = 6.6 Hz, 1 H, major), 4.85 (t, *J* = 6.6 Hz, 1 H, minor), 5.33 (d, *J* = 12.0 Hz, 1 H), 7.19-7.38 (m, 5 H, major, minor), 7.37 (d, *J* = 7.8 Hz, 1 H, minor) 7.55 (d, *J* = 8.0 Hz, 1 H, major); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 11.9, 14.6, 18.25, 18.3, 19.5, 23.8, 24.7, 26.0, 26.1, 36.6, 37.8, 46.8, 59.8, 81.3, 95.5, 96.5, 119.8, 120.8, 126.2, 126.4, 127.2, 127.6, 128.3, 128.4, 134.1, 144.2, 165.3, 168.7; IR (KBr, neat) 2974, 2926, 1706, 1635, 1455, 1378, 1233, 1133, 1045, 814, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{31}O_3$ $(M + H)^+$ 331.2268 found 331.2257.

(*E*)-Ethyl 3-(((*E*)-2-methyl-2-phenylhex-4-en-1-yl)oxy)acrylate (1o)

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 196 mg, 68%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.6 Hz, 3 H), 1.33 (s, 3 H), 1.59 (d, *J* = 6.8 Hz, 3 H), 2.37 (dd, *J* = 13.6 and Hz, 1 H), 2.47 (dd, *J* = 13.6 and 7.6 Hz, 1 H), 3.84 (d, *J* = 10.0 Hz, 1 H), 3.90 (d, *J* = 9.6 Hz, 1 H), 4.14 (q, *J* =7.2 Hz, 2 H), 5.11-5.16 (m, 1 H), 5.19 (d, *J* = 12.4 Hz, 1 H), 5.37-5.55 (m , 1 H), 7.18-7.24 (m, 1 H), 7.25 -7.39 (m, 4 H), 7.56 (d, *J* = 12.4 Hz, 1 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 18.2, 22.8, 41.9, 42.1, 59.9, 78.4, 96.5, 126.2, 126.5, 126.5, 128.5, 128.9, 144.7, 162.8, 168.1; IR (KBr, neat) 2926, 1708, 1630, 1454, 1323, 1205, 1131, 1042, 964, 749, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{25}O_3$ $(M + H)^+$ 28^9.1798 found 289.1790.

(*E*)-Ethyl 3-(2-(4-methyl-*N*-(2-methylallyl)phenylsulfonamido)-2-phenylethoxy)acrylate (1p)

Pale yellow oil; R_f (hexane/ EtOAc 17:3) 0.40; yield 244 mg, 55%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3 H), 1.56 (s, 3 H), 2.45 (s, 3 H), 3.35 (d, *J* = 16.0 Hz, 1 H), 3.84 (d, *J* = 16.0 Hz, 1 H), 4.14-4.19 (m, 3 H), 4.32-4.41 (m, 2 H), 4.77 (s, 1 H), 4.85 (s, 1 H), 5.20 (d, *J* = 12.8 Hz, 1 H), 7.02-7.04 (m, 2 H), 7.24-7.29 (m, 5 H), 7.45 (d, *J* = 12.8 Hz, 1 H), 7.68 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 20.0, 21.7, 51.5, 59.4, 60.1, 69.6, 97.4, 114.7, 127.7, 128.6, 128.7, 128.8, 129.7, 134.7, 137.9, 142.3, 143.7, 161.4, 167.7; IR (KBr, neat) 2920, 1725, 1632, 1443, 1219, 1039, 928, 772, 680 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{30}NO_5S$ (M + H)$^+$ 444.1839 found 444.1839.

(*E*)-Ethyl 3-(2-(4-methyl-*N*-(2-phenylallyl)phenylsulfonamido)-2-phenylethoxy)acrylate (1q)

Pale yellow oil; R_f (hexane/ EtOAc 17:3) 0.40; yield 288 mg, 57%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3 H), 2.44 (s, 3 H), 3.92 (d, *J* = 16.2 Hz, 1 H), 4.06 (dd, *J* = 10.2 and 3.6 Hz, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 4.28 (dd, *J* = 10.2 and 1.8 Hz, 1 H), 4.39 (d, *J* = 16.2 Hz, 1 H), 5.05 (d, *J* = 12.6 Hz, 1 H), 5.11 (s, 1 H), 5.18 (t, *J* = 7.2 Hz, 1 H), 5.34 (s, 1 H), 6.99 (d, *J* = 7.8 Hz, 2 H), 7.20-7.32 (m, 12 H), 7.60 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.6, 21.7, 49.6, 59.2, 60.1, 69.9, 97.4, 116.8, 126.8, 127.8, 128.3, 128.6 (2C), 128.7 (2C), 129.7, 134.6, 137.6, 138.7, 143.7, 144.5, 161.3, 167.7; IR (KBr, neat) 2931, 1707, 1632, 1332, 1145, 1042, 732 cm^{-1}; HRMS (ESI) calcd. for $C_{29}H_{32}NO_5S$ (M + H)$^+$ 506.1996 found 506.2000.

General Procedure for the Synthesis of cyclized product 2a-q:

To a solution of enol ether (1.0 mmol) in dry dichloromethane (1 mL) at 0 °C was added trifluoromethanesulfonic acid (10 mol%) under a N_2 atmosphere.. The reaction mixture was stirred for 10 minutes. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (EtOAc/hexane 24:1) as eluents. After the completion of the reaction, the solvent was removed on a rotary evaporator and quenched with a saturated solution of $NaHCO_3$ (2 mL). The product was extracted with ethyl acetate (10 mL) and then washed with brine solution (3 mL). The organic layer was dried (Na_2SO_4) and evaporated to give the crude product, which was purified by column chromatography over silica gel giving corresponding products **2a-q**.

Ethyl 2-((1*S,3*aR**)-6,6-dimethyl-1,3,3a,4,5,6-hexahydrobenzo[*de*]isochroman-1-yl)acetate (2a)**

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 219 mg, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.36 (s, 3 H), 1.65-1.71 (m, 2 H), 1.74- 1.77 (m, 2 H), 2.72 (dd, *J* = 15.2 and 9.2 Hz, 1 H), 2.88 (dd, *J* = 15.2 and 8.0 Hz, 1 H), 2.92 (dd, *J* = 12.0 and 7.2 Hz, 1 H), 3.36 (dd, *J* = 11.2 and 10.4 Hz, 1 H), 4.03 (dd, *J* = 10.4 and 4.8 Hz, 1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 5.31 (d, *J* = 6.8 Hz, 1 H), 6.87 (d, *J* = 7.2 Hz, 1 H), 6.17 (t, *J* = 7.6 Hz, 1 H), 7.24 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 21.6, 31.9. 32.8, 34.5, 36.6, 38.3, 43.3, 60.5, 69.6, 74.1, 122.8, 125.2, 126.2, 133.8, 135.1, 145.8, 171.3; IR (KBr, neat) 2926, 2858, 1735, 1445, 1373, 1220, 1180, 1029, 855, 761 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{25}O_3$ (M + H)$^+$ 289.1798 found 289.1799.

Ethyl 2-((1*S,3*aS**)-3a,6,6-trimethyl-1,3,3a,4,5,6-hexahydrobenzo[*de*]isochroman-1-yl)acetate (2b)**

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 227 mg, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.33 (s, 3 H), 1.38 (dt, *J* = 12.6 and 3.6 Hz, 1 H), 1.40 (s, 3 H), 1.50 (dt, *J* = 13.2 and 3.0 Hz, 1 H), 1.63 (dt, *J* = 13.8 and 3.0 Hz, 1 H), 2.11 (dt, *J* = 14.4 and 3.6 Hz, 1 H), 2.82 (dd, *J* = 15.0 and 9.6 Hz, 1 H), 2.94 (dd, *J* = 15.0 and 3.0 Hz, 1 H), 3.49 (d, *J* = 10.8, 1 H), 3.67 (d, *J* = 10.8, 1 H), 4.20-4.24 (m, 2 H), 5.32 (dd, *J* = 9.6 and 3.0 Hz, 1 H), 6.84 (d, *J* = 7.2 Hz, 1 H), 7.15 (t, *J* = 7.8 Hz, 1 H), 7.21 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.4, 27.1, 28.9, 32.4, 33.9, 34.0, 34.1, 34.6, 43.7, 60.8, 74.1, 75.3, 122.2, 125.9, 126.4, 134.6, 138.0, 144.3, 171.7; IR (KBr, neat) 2961, 2866, 1737, 1472, 1286, 1220, 1159, 1097, 1032, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{27}O_3$ (M + H)$^+$ 303.1955 found 303.1955.

Ethyl 2-((1*S,3*R**,3*aS**)-3a,6,6-trimethyl-3-phenyl-1,3,3a,4,5,6-hexahydrobenzo[*de*]iso-chroman-1-yl)acetate (2c)**

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 246 mg, 65%; ^{1}H NMR (600 MHz, CDCl3) δ 1.15 (s, 3 H), 1.24 (s, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.31 (dt, *J* = 15.0 and 7.2 Hz, 1 H), 1.37 (s, 3 H), 1.55 (dt, *J* = 13.8 and 3.0 Hz, 1 H), 1.68 (dt, *J* = 13.8 and 2.4 Hz, 1 H), 1.92 (dt, *J* = 14.4 and 2.4 Hz, 1 H), 2.93 (dd, *J* = 14.4 and 9.0 Hz, 1 H), 2.98 (dd, *J* = 14.4 and 3.6 Hz, 1 H), 4.16-4.20 (m, 1 H), 4.22-4.30 (m, 1 H), 4.52 (s, 1 H), 5.50 (dd, *J* = 9.6 and 4.2 Hz, 1 H), 6.91 (d, *J* = 7.2 Hz, 1 H), 7.20 (t, *J* = 7.8 Hz, 1 H), 7.26-7.29 (m, 2 H), 7.31 (t, *J* = 7.8 Hz, 2 H), 7.38 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 22.4, 29.7, 32.4. 33.8, 34.1, 34.3, 37.7, 44.3, 60.8, 74.7, 87.2, 122.4, 126.2, 126.5, 127.5, 128.2, 134.7, 135.6, 138.8, 139.0, 144.7, 171.6; IR (KBr, neat) 2960, 1717, 1622, 1447, 1369, 1220, 1123, 1094, 1029, 854, 165, 703 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{31}O_3$ (M + H)$^+$ 379.2268 found 379.2267.

Ethyl 2-((1*S,3*R**,3*aS**)-3-(4-chlorophenyl)-3a,6,6-trimethyl-1,3,3a,4,5,6-hexahydro-benzo[*de*]isochroman-1-yl)acetate (2d)**

Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 313 mg, 76%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.11 (s, 3 H), 1.23 (s, 3 H), 1.26-1.29 (m, 4 H), 1.37 (s, 3 H), 1.55 (dt, *J* = 13.8 and 3.0 Hz, 1 H), 1.65 (dt, *J* = 13.8 and 2.4 Hz, 1 H), 1.92 (dt, *J* = 13.8 and 2.4 Hz, 1 H), 2.91 (dd, *J* = 14.4 and 9.0 Hz, 1 H), 2.98 (dd, *J* = 14.4 and 3.6 Hz, 1 H), 4.16-4.20 (m, 1 H), 4.22-4.26 (m, 1 H), 4.49 (s, 1 H), 5.49 (dd, *J* = 9.6 and 3.6 Hz, 1 H), 6.91 (d, *J* = 7.8 Hz, 1 H), 7.20 (t, *J* = 7.8 Hz, 1 H) , 7.26-7.31 (m, 5 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 22.3, 29.7, 32.4. 33.8, 34.0, 34.3, 37.6, 44.2, 60.9, 74.8, 82.9, 122.4, 126.3, 126.6, 127.7, 129.5, 133.3, 134.5, 137.3, 138.7, 144.7, 171.5; IR (KBr, neat) 2929, 1734, 1448, 1375, 1220, 1168, 1088, 1028, 930, 771, 680 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{30}ClO_3$ (M + H)$^+$ 413.1878 found 413.1884.

Ethyl 2-((1*S,3*R**,3*aS**)-3a,6,6-trimethyl-3-(p-tolyl)-1,3,3a,4,5,6-hexahydro-benzo[*de*]iso-chroman-1-yl)acetate (2e)**

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 267 mg, 68%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.15 (s, 3 H), 1.23 (s, 3 H), 1.25-1.29 (m, 4 H), 1.37 (s, 3 H), 1.54 (dt, *J* = 10.8 and 3.0 Hz, 1 H), 1.66 (dt, *J* = 12.0 and 2.4 Hz, 1 H), 1.91 (dt, *J* = 13.8 and 1.8 Hz, 1 H), 2.35 (s, 3 H), 2.92 (dd, *J* = 14.4 and 9.0 Hz, 1 H), 2.97 (dd, *J* = 14.4 and 3.6 Hz, 1 H), 4.15-4.18 (m, 1 H), 4.19-4.25 (m, 1 H), 4.48 (s, 1 H), 5.49 (dd, *J* = 9.0 and 3.6 Hz , 1 H), 6.91 (d, *J* = 7.8 Hz, 1 H), 7.12 (d, *J* = 7.2 Hz, 2 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 7.25-7.26 (m, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 21.3, 22.4, 29.7, 32.4. 33.9, 34.1, 34.3, 37.7, 44.3, 60.8, 74.7, 83.3, 122.4, 126.2, 126.5, 128.1, 128.2, 134.7, 135.9, 137.1, 139.1, 144.7, 171.6; IR (KBr, neat) 2980, 2924, 1709, 1623, 1445, 1376, 1220, 1130, 1046, 944, 760, 699 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{33}O_3$ (M + H)$^+$ 393.2424 found 393.2427.

Ethyl 2-((1*S,3*R**,3a*S**)-3-(4-methoxyphenyl)-3a,6,6-trimethyl-1,3,3a,4,5,6-hexahydro-benzo[*de*]isochroman-1-yl)acetate (2f)**

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 306 mg, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.23 (s, 3 H), 1.23-1.29 (m, 4 H), 1.37 (s, 3 H), 1.54 (dt, *J* = 13.8 and 3.6 Hz, 1 H), 1.64 (dt, *J* = 13.8 and 3.0 Hz, 1 H), 1.92 (dt, *J* = 13.8 and 3.6 Hz, 1 H), 2.92 (dd, *J* = 14.4 and 9.0 Hz, 1 H), 2.97 (dd, *J* = 14.4 and 3.6 Hz, 1 H), 3.81 (s, 3 H), 4.17 (dd, *J* = 10.8 and 7.2 Hz, 1 H), 4.24 (dd, *J* = 10.8 and 7.2 Hz, 1 H), 4.47 (s, 1 H), 5.49 (dd, *J* = 9.0 and 3.6 Hz, 1 H), 6.86 (d, *J* = 6.6 Hz, 2 H), 6.90 (d, *J* = 7.8 Hz, 1 H), 7.18 (t, *J* =7.8 Hz, 1 H), 7.25 (d, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 9.0 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 22.3, 29.7, 32.4. 33.9, 34.0, 34.3, 37.7, 44.32, 55.42, 60.8, 74.7, 83.1, 113.0, 122.4, 126.2, 126.5, 129.2, 131.1, 134.7, 139.1, 144.7, 159.1, 171.6; IR (KBr, neat) 2960, 1735, 1613, 1514, 1370, 1220, 1123, 1035, 930, 759, 685 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{32}NaO_4$(M + Na)$^+$ 431.2193 found 431.2186.

Ethyl 2-((1*S,3*R**,3a*S**)-3-(3-methoxyphenyl)-3*a*,6,6-trimethyl-1,3,3*a*,4,5,6-hexahydrobenzo[*de*]isochromen-1-yl)acetate (2g)**

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 224 mg, 55%; ^{1}H NMR (600 MHz, $CDCl_3$)) δ 1.14 (s, 3 H), 1.23 (s, 3 H), 1.23-1.29 (m, 4 H), 1.37 (s, 3 H), 1.54 (dt, *J* = 14.0 and 4.0 Hz, 1 H), 1.64 (dt, *J* = 14.0 and 4.0 Hz, 1 H), 1.92 (dt, *J* = 14.0 and 4.0 Hz, 1 H), 2.92 (dd, *J* = 18.0 and 6.0 Hz, 1 H), 2.97 (dd, *J* = 12.0 and 6.0 Hz, 1 H), 3.81 (s, 3 H), 4.16-4.27 (m, 2 H), 4.47 (s, 1 H), 5.49 (dd, *J* = 12.0 and 6.0 Hz, 1 H), 6.86 (d, *J* = 7.2 Hz, 1 H), 6.91 (d, *J* = 7.2 Hz, 1 H), 6.95-6.96 (m, 2 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 7.23 (t, *J* = 8.0 Hz, 1 H), 7.27-7.29 (m, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 22.9, 29.9, 32.2, 33.9, 34.0, 34.1, 37.7, 44.3, 55.5, 60.8, 74.8, 83.4, 112.7, 114.3, 120.9, 122.4, 126.2, 126.5, 128.4, 134.5, 139.5, 140.5, 144.7, 159.1, 171.6. IR (KBr, neat) 2952, 1729, 1610, 1530, 1365, 1218, 1120, 1030, 925, 765, 690 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{32}NaO_4$ (M + Na)$^+$ 431.2193 found 431.2197.

Ethyl 2-((1*S,3a*R**)-8-bromo-6,6-dimethyl-1,3,3a,4,5,6-hexahydrobenzo[*de*]isochroman-1-yl)acetate (2h)**

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 260 mg, 71%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20 (s, 3 H), 1.23-1.29 (m, 4 H), 1.33 (s, 3 H), 1.66-1.69 (m, 1 H), 1.71- 1.76 (m, 2 H), 2.71 (dd, *J* = 15.6 and 9.0 Hz, 1 H), 2.80-2.85 (m, 2 H), 3.31 (t, *J* = 10.8 Hz, 1 H), 4.02 (dd, *J* = 10.8 and 4.8 Hz, 1 H), 4.17-4.20 (m, 2 H), 5.23 (dd, *J* = 9.0 and 3.0 Hz, 1 H), 7.0 (s, 1 H), 7.32 (d, *J* = 1.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.4, 21.7, 32.1, 33.0, 35.1, 36.7, 38.4, 43.3, 60.9, 69.8, 73.9, 120.5, 125.1, 128.7, 133.2, 137.9, 147.8, 171.2; IR (KBr, neat) 2961, 1736, 1445, 1371, 1220, 1108, 1028, 931, 855, 761, 685 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{23}NaBrO_3$ (M + Na)$^+$ 389..0723 found 389.0722.

Ethyl 2-((1*S,3a*R**)-6,6,8-trimethyl-1,3,3a,4,5,6-hexahydrobenzo[*de*]isochroman-1-yl)acetate (2i)**

Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 187 mg, 62%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (s, 3 H), 1.23-1.28 (m, 4 H), 1.35 (s, 3 H), 1.65-1.70 (m, 1 H), 1.72-1.75 (m, 2 H), 2.30 (s, 3 H), 2.71 (dd, *J* = 15.0 and 9.6 Hz, 1 H), 2.85-2.88 (m, 2 H), 3.32 (t, *J* = 10.8 Hz, 1 H), 4.02 (dd, *J* = 10.8 and 4.2 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz 2 H), 5.28 (dd, *J* = 10.2 and 7.2 Hz, 1 H), 6.70 (s, 1 H), 7.04 (s, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.4, 21.6, 22.0, 32.3, 33.1, 34.7, 36.7, 38.7, 43.7, 60.8, 70.0, 74.4, 122.9, 126.3, 131.2, 135.4, 135.8, 145.0, 171.7; IR (KBr, neat) 2925, 2858, 1736, 1612, 1465, 1374, 1220, 1168, 1109, 1031, 856, 772 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{27}O_3$ (M + H)$^+$ 303.1955 found 303.1955.

Ethyl 2-((1*S,3a*R**)-8-methoxy-6,6-dimethyl-1,3,3a,4,5,6-hexahydro-benzo[*de*]isochroman-1-yl)acetate (2j)**

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 235 mg, 74%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (s, 3 H), 1.22-1.29 (m, 4 H), 1.34 (s, 3 H), 1.62-1.67 (m, 1 H), 1.72- 1.75 (m, 2 H), 2.72 (t, *J* = 15.0 and 9.6 Hz, 1 H), 2.81-2.86 (m, 2 H), 3.31 (t, *J* = 10.2 Hz, 1 H), 3.77 (s, 3 H), 4.00 (dd, *J* = 10.8 and 4.8 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz 2 H), 5.26 (dd, *J* = 9.0 and 3.0 Hz, 1 H), 6.41 (d, *J* = 2.4 Hz, 1 H), 6.77 (d, *J* = 2.4 Hz, 1 H); ^{13}C NMR (150 MHz, CDCl3) δ 14.4, 22.0, 32.3, 33.0, 35.1, 36.4, 38.7, 43.6, 55.4, 60.9, 70.2, 74.4, 107.4, 111.6, 126.7, 136.8, 146.8, 158.2, 171.6; IR (KBr, neat) 2959, 2858, 1736, 1605, 1471, 1372, 1220, 1174, 1112, 1063, 854, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{27}O_4$(M + H)$^+$ 319.1904 found 319.1906.

Ethyl 2-((1*S,3a*S**)-3a-methyl-6-phenyl-1,3,3a,4,5,6-hexahydrobenzo[*de*]isochroman-1-yl)acetate (diastereomeric mixture, 3:1, 2k)**

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 245 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.32 (m, 4 H), 1.40 (s, 3 H, minor), 1.49 (s, 3 H, major), 1.52-1.59 (m, 2 H), 1.81-1.86 (m, 1 H, minor), 2.13-2.20 (m, 1 H, major), 2.56-2.61 (m, 1 H, minor), 2.81-2.89 (m, 1 H, major), 2.94-3.00 (m, 1 H), 3.55 (d, *J* = 10.4 Hz, 1 H, major), 3.59 (d, *J* = 10.8 Hz, 1 H, minor), 3.72 (d, *J* = 10.8 Hz, 1 H, major), 3.74 (d, *J* = 11.2 Hz, 1 H, minor), 4.06 (t, *J* = 9.2 Hz, 1 H), 4.20-4.26 (m, 2 H), 5.35 (dd, *J* = 9.0 and 3.0 Hz, 1 H, major), 5.37 (dd, *J* = 9.6 and 6.6 Hz, 1 H, minor), 6.69-6.73 (m, 1 H), 6.88 (m, 1 H), 6.95 (d, *J* = 6.8 Hz, 1

H), 6.97-7.04 (m, 1 H), 7.15-7.25 (m, 3 H), 7.29-7.33 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.4, 14.7, 26.9, 27.5, 27.6, 27.8, 29.0, 32.0, 33.7, 43.3, 43.4, 43.5, 46.7, 59.5, 60.9, 74.2, 75.3, 75.6, 122.5, 122.6, 126.1, 126.3, 126.4, 128.5, 128.7, 128.7, 128.8, 128.9, 134.7, 137.9, 138.1, 139.5, 148.0, 148.6, 171.7; IR (KBr, neat) 2926, 1736, 1449, 1220, 1096, 772, 702 cm-1; HRMS (ESI) calcd. for $C_{23}H_{27}O_3$ $(M + H)^+$ 351.1955 found 351.1953.

Ethyl 2-((1*S,3*R**,3*aS**)-3-(4-chlorophenyl)-3*a*-methyl-6-phenyl-1,3,3*a*,4,5,6-hexahydro-benzo[*de*]isochroman-1-yl)acetate (diastereomerc mixture, 4:1, 2l)**

Colourless oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 345 mg, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20-1.30 (m, 6 H), 1.32-1.36 (m, 1 H), 1.64-1.80 (m, 1 H), 1.93-2.05 (m, 1 H), 2.08-2.12 (m, 1 H), 2.93-2.96 (m, 1 H), 3.00-3.06 (m, 1 H), 4.06-4.26 (m, 3 H), 4.55 (s, 1 H, major), 4.60 (s, 1 H, minor), 5.53 (dd, J = 9.6 and 3.6 Hz, 1 H, major), 5.57 (dd, J = 9.0 and 3.6 Hz, 1 H, minor), 6.77 (d, J = 7.8 Hz, 1 H, major), 6.82 (d, J = 7.2 Hz, 1 H, minor), 6.93 (d, J = 7.8 Hz, 1 H, major), 6.97 (d, J = 7.8 Hz, 1 H, minor), 7.04-7.10 (m, 1 H), 7.18-7.33 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 22.2, 22.9, 27.1, 28.0, 29.0, 29.9, 32.1, 32.8, 37.4, 44.1, 46.6, 60.9, 74.8, 74,9, 82.9, 83.1, 122.8, 122.9, 126.4, 126.5, 127.7, 127.8, 128.5, 128.7, 128.8, 129.3, 129.5, 129.9, 133.4, 134.6, 137.2, 138.6, 140.1, 147.9, 171.5; IR (KBr, neat) 2979, 1733, 1444, 1371, 1220, 1036, 931, 854, 761, 685 cm^{-1}; HRMS (ESI) calcd. for $C_{29}H_{30}ClO_3$ $(M + H)^+$ 461.1878 found 461.1883.

Ethyl 2-((1*S,3*aR**)-8-bromo-6-phenyl-1,3,3*a*,4,5,6-hexahydrobenzo[*de*]isochroman-1-yl)acetate (diastereomeric mixture, 8:1, 2m)**

Pale yellow oil; R_f (hexane/ EtOAc 24:1) 0.48; yield 294 mg, 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.30 (m, 4 H), 1.59-1.63 (m, 1 H), 1.82-1.97 (m, 1 H), 2.21- 2.31 (m, 1 H), 2.62-2.83 (m, 1 H), 2.87-3.06 (m, 2 H), 3.40 (dt, J = 11.2 and 10.4 Hz, 1 H), 4.00-4.06 (m, 1 H), 4.08- 4.13 (m, 1 H), 4.19-4.24 (m, 2 H), 5.18-5.20 (m, 1 H, minor), 5.26-5.33 (m, 1 H, major), 6.87-6.96 (m, 2 H), 7.03-7.08 (s, 1 H), 7.15-7.22 (m, 2 H), 7.24-7.34 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 14.4, 22.9, 25.1, 32.2, 33.6, 34.0, 35.4, 43.2, 43.8, 61.0, 69.8, 69.9, 73.8, 73.9, 120.3, 120.5, 125.6, 125.64, 126.5, 126.8, 128.6, 128.7, 128.9, 129.0, 131.0, 131.3, 131.6, 134.4, 137.8, 137.9, 139.5, 140.7, 146.6, 147.2, 171.1, 171.2; IR (KBr, neat) 2929, 1736, 1619, 1447, 1372, 1220, 1163, 1094, 768, 685 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{24}BrO_3$ $(M + H)^+$ 415.0903 found 415.0894.

Ethyl 2-((1*S,3*R**,3*aS**)-3-ethyl-3a,6,6-trimethyl-1,3,3*a*,4,5,6-hexahydro-benzo[*de*]isochroman-1-yl)acetate (2n)**

Colourless oil, R_f (hexane/ EtOAc 24:1) 0.48; yield 241 mg, 73%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.04 (t, J = 7.2 Hz, 3 H), 1.17 (s, 3 H), 1.22-1.26 (m, 1 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.31-1.35 (m, 1 H), 1.37 (s, 3 H), 1.41 (s, 3 H), 1.50-1.55 (m, 1 H), 1.58 (dt, J = 13.8 and 3.0 Hz, 1 H), 1.71 (dt, J = 13.8 and 3.0 Hz, 1 H), 2.06 (dt, J = 13.8 and 3.0 Hz, 1 H), 2.78 (dd, J = 15.0 and 9.6 Hz, 1 H), 2.93 (dd, J = 15.6 and 3.0 Hz, 1 H), 3.56 (dd, J = 12.0 and 3.6 Hz, 1 H), 4.16-4.30 (m, 2 H), 5.19 (dd, J = 9.6 and 3.0 Hz, 1 H), 6.82 (d, J = 7.8 Hz, 1 H), 7.12 (t, J = 7.8 Hz, 1 H), 7.20 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7, 14.3, 20.6, 28.5, 32.2, 33.9, 34.3, 34.6, 37.3, 43.5, 60.8, 61.5, 68.4, 82.3, 121.8, 125.8, 125.9, 134.7, 136.2, 145.1, 171.8; IR (KBr, neat) 2927, 1738, 1637, 1372, 1220, 1127, 1038, 772 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{31}O_3$ $(M + H)^+$ 331.2268 found 331.2261.

Ethyl 2-((1*S,3*aS**)-3a,6-dimethyl-1,3,3*a*,4,5,6-hexahydrobenzo[*de*]isochroman-1-yl)acetate (diastereomerc ratio 8:5, 2o)**

Colourless oil; R_f (hexane/ EtOAc, 24:1) 0.48; yield 164 mg, 57%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.23 (d, J = 6.6 Hz, 3 H, major), 1.24 (d, J = 6.6 Hz, 3 H, minor), 1.27-39 (m, 6 H), 1.41-1.45 (m, 1 H), 1.47-1.55 (m, 1 H), 1.58-1.652 (m, 1 H, major), 1.77-1.84 (m 1 H, minor), 1.98-2.05 (m, 1 H, major), 2.25-2.33 (m, 1 H, minor), 2.65 (dt, J = 15.0 and 3.0 Hz, 1 H, major), 2.80-3.00 (m, 2 H), 3.02-3.05 (m, 1 H, minor), 3.45-3.70 (2 H), 4.17-4.26 (m, 2 H), 5.28-5.32 (m, 1 H, minor), 5.47-5.51 (m, 1 H, major), 6.81-6.86 (m, 1 H), 7.04-7.14 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 19.7, 25.1, 30.9, 33.6, 35.4, 36.2, 41.7, 42.1, 43.1, 43.8, 47.1, 61.0, 69.7, 69.8, 72.7, 73.8, 73.9, 120.3, 120.5, 126.4, 126.7, 128.6, 128.7, 134.5, 134.8, 137.8, 137.9, 146.6, 147.2, 171.1; IR (KBr, neat) 2927, 2855, 1734, 1621, 1451, 1372, 1286, 1163, 1095, 1028, 805, 848, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{25}O_3$ $(M + H)^+$ 289.1798 found 289.1795.

Ethyl 2-((7*R,9*aS**)-3,3-dimethyl-1-tosyl-1,2,3,7,9,9*a*-hexahydropyrano[3,4,5-*ij*]isoquinolin-7-yl)acetate (2p)**

Pale yellow oil; R_f (hexane/ EtOAc 17:3) 0.48; yield 399 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 3 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.35 (s, 3 H), 2.41 (s, 3 H), 2.66 (dd, J = 15.6 and 8.8 Hz, 1 H), 2.80 (dd, J = 15.2 and 3.2 Hz, 1 H), 3.16 (d, J = 12.4 Hz, 1 H), 3.41 (d, J = 12.0 Hz, 1 H), 3.54 (t, J = 10.4 Hz, 1 H), 4.15 (q, J = 7.2 Hz, 2 H), 4.34 (dd, J = 9.6 and 4.4 Hz, 1 H), 4.61 (dd, J = 10.4 and 4.0 Hz, 1 H), 5.22 (dd, J = 8.8 and 3.2 Hz, 1 H), 6.87-6.89 (m, 1 H), 7.18-7.22 (m, 2 H), 7.30 (d, J = 7.6 Hz, 2 H), 7.71 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 21.7, 27.3, 28.6, 36.0, 43.1, 53.9, 57.0, 61.0, 67.5, 74.0, 122.9, 123.9, 127.4, 127.6, 130.1, 135.5, 136.7, 143.4, 143.8, 171.1; IR (KBr, neat) 2971, 1734, 1447, 1337, 1220, 1160, 1103, 1036, 927, 771, 679 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{30}NO_5S$ $(M + H)^+$ 444.1839 found 444.1839.

Ethyl 2-((3*S,7*R**,9*aS**)-3-methyl-3-phenyl-1-tosyl-1,2,3,7,9,9*a*-hexahydropyrano[3,4,5-*ij*]isoquinolin-7-yl)acetate (2q)**

Pale yellow oil; R_f (hexane/ EtOAc 17:3) 0.48; yield 429 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3 H), 1.66 (s, 3 H), 2.40 (s, 3 H), 2.77 (dd, J = 15.6 and 8.4 Hz, 1 H), 2.86 (dd, J = 15.6 and 3.6 Hz, 1 H), 3.46 (d, J = 13.2 Hz, 1 H), 3.50 (d, J = 10.2 Hz, 1 H), 3.72 (d, J = 12.6 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 4.57 (dd, J = 10.2 and 4.2 Hz, 1 H), 4.69 (dd, J = 10.2 and 4.2

Hz, 1 H), 5.32 (dd, J = 8.4 and 3.6 Hz, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 6.94 (d, J = 7.8 Hz, 1 H), 7.11-7.15 (m, 3 H), 7.23 (d, J = 8.4 Hz, 2 H), 7.25 (d, J = 7.2 Hz, 1 H), 7.30 (t, J = 7.2 Hz, 2 H), 7.56 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 21.7, 25.4, 43.2, 44.2, 53.2, 56.7, 61.0, 67.2, 74.0, 123.2, 126.8, 126.9, 127.3, 127.4, 127.8, 128.4, 129.9, 130.8, 135.5, 137.7, 142.6, 143.7, 145.8, 171.1; IR (KBr, neat) 2925, 2854, 1735. 1624, 1468, 1332, 1158, 1090, 1026, 830, 767 cm^{-1}; HRMS (ESI) calcd. for $C_{29}H_{32}NO_5S$ $(M + H)^+$ 506.1996 found 506.1994.

Antileishmanial activity assay

Leishmania donovani (MHOM/IN/2010/BHU 1081) strain was obtained from Dr. Shyam Sundar, Banaras Hindu University, Varanasi and cultivated in M199 liquid media supplemented with 15% heat-inactivated fetal bovine serum (FBS), 100 U penicillin and 100 µg ml^{-1} streptomycin was used for assessing the anti-leishmanial activity of **2f**, **2j** and **2p**. The anti-leishmanial effect was checked using methods reported earlier.[9a,10,11] MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay was employed to check the antileishmanial efficacy of the compounds. Exponential phase promastigote cells (2.5 x 10^6) were seeded in a 96 well plate and treated with varying concentrations of compounds and incubated at 25°C for 24 hours. Cells were centrifuged and resuspended in MTT (0.5mg/ml) and again incubated at 25°C for 4 hours. Cells were again centrifuged and DMSO was added to dissolve the formazon pellet and absorbance taken at 570 nm. Miltefosine (IC_{50}-25 µM), a potent antileishmanial compound was used as a positive control.

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1 (a) I. B. Masesane and Z. Y. Desta, Beilstein *J. Org. Chem*. 2012, **8**, 2166-2175; (b) E. Corradini, P. Fogila, P . Giansanti, R. Gubbiotti, R. Samperi and A. Lagana, *Nat. Prod. Res*. 2011, **25**, 469-495; (c) R . Saxena,. V. Chandra, M. Manohar, K. Hajela, U. Debnath, Y. S. Prabhakar, K. S. Saini, R. Konwar, S. Kumar, K. Megu, B. G. Roy and A. Dwivedi, PLoS One 2013, **8**, e66246.

2 (a) E. C. Taylor and A. Weissberger, The Chemistry of Heterocyclic Compounds: John Wiley & Sons: New Work, 1981, 1990, 1995, Vol. **38**, Parts 1-3; (b) P. S. Charifson, *Drugs Future* 1989, **14**, 1179; (c) B. Hoffman, S. J. Cho, W. Zheng, S. Wyrick, D. E . Nichols, R. B. Mailman and A. Tropsha, *J. Med. Chem*. 1999, **42**, 3217-3226; (d) M. P DeNinno, R. Schoenleber, R. J. Perner, L. Lijewski, K. E. Asin, D. R.Britton, R. MacKenzie and J.W. Kebabian, *J. Med. Chem*. 1991, **34**, 2561-2569; (e) A. Evidente, B. Punzo, A. Andolifi, A. Berestetskiy and A. Motta, *J. Agric. Food. Chem*. 2009, **57**, 6656-6660.

3 (a) J. Z Deng, S. -X. Zhao and Z.-Ch. Miao, *Nat. Prod. Lett*. 1993, **2**, 283-286. (b) J. Z. Deng and S.-X. Zhao, *J. Nat. Prod*. 1997, **60**, 294-295. (c) D. A .Bianchi, G. S. Hirschmann, C. Theoduloz, A.B. J. Bracca and T. S. Kaufman, *Bioorg. Med. Chem. Lett.* 2005, **15**, 2711-2715.

4 (a) M. Sickert, H. Weinstabl, B. Peters, X. Hou and M. Lautens, *Angew. Chem. Int. Eds*. 2014, **53**, 5147-5151; (b) W. Muramatsu, K. Nakano and C.-J. Li, *Org. Lett*. 2013, **15**, 3650-3653; (c) Z. Meng, S. Sun, H. Yuan, H. Lou and L. Liu, *Angew. Chem. Int. Ed. Engl*. 2014, **53**, 543-547; (d) W. Muramatsu and K. Nakano, *Org. Lett*. 2014, **16**, 2042-2045; (e) X. Pan, Q. Hu, W. Chen, X. Liu, B. Sun, Z. Huang, Z. Zeng, L. Wang, D. Zhao, M. Ji, L. Liu, and H. Lou, *Tetrahedron* 2014, **70**, 3447-3451; (f) C. Huo, M. Wu, F. Chen, X. Jia, Y. Yuan and H. Xie, *Chem. Comuun*. 2015, **51**, 4708-4711; (g) W. Muramatsu and K. Nakano,. *Org. Lett*. 2015, **17**, 1549-1552.

5 (a) P. H. Gore, *Chem. Rev*. 1955, **55**, 229-281; (b) K. W. Anderson and J. J Tepe, *Tetrahedron* 2002, **58**, 8475-8481; (c) M. H. Sarvari and H. Sharghi, *Synthesis* 2004, 2165-2168; (d) F. Effenberger and G. Epple, *Angew. Chem. Int. Ed. Engl*. 1972, **11**, 300-301; (e) L . Boiaryna, M. S Azizi, A. E1. Bouakher,; B. Picard, C. Taillier, M. Othman, M. Trabelsi-Ayadi and V. Dalla, *Org. Lett*. 2015, **17**, 2130-2133; (f) K. Indukuri, R. Unnava, M. J. Deka and A. K . Saikia, *J. Org. Chem*. 2013, **78**, 10629-10641; (g) U. C. Reddy, S. Bondalapati and A. K. Saikia, *J. Org. Chem*. 2009, **74**, 2605-2608.

6 (a) E. D. Cox and J. M. Cook, *Chem. Rev*. 1995, **95**, 1797-1842; (b) E. L. Larghi and T. S. Kaufman, *Synthesis* 2006, 187-220; (c) J. Stöckigt, A.P. Antonchick, F.-R.Wu, H. Waldmann, *Angew. Chem. Int. Ed. Engl.* 2011, **50**, 8538-8564; (d) E. L. Larghi and T. S. Kaufman, *Eur. J. Org. Chem.* 2011, 5195-5231.

7 (a) H. W. Murray, J. D. Berman, C. R. Davies, N. G. Saravia, *Lancet* 2005, **366**, 1561-1577.

8 S. I. Croft, S. Sundar and A. H. Fairlamb, *Clin. Microbiol. Rev*. 2006, **19**, 111-126.

9 (a) P. Saudagar, P. Saha, A.K. Saikia and V. K. Dubey, *Eur. J. Pharma. Biopharma,* 2013, **85**, 569-577. (b) P. Saudagar, L. Mudavath, P. Saha, A. K. Saikia, S. Sundar, and V. K. Dubey, *Lett. Drug Design. Discovery*, 2014, **11**, 937-939.

10 A. K. Shukla, S. Patra and V. K. Dubey, *Mol Cell Biochem*. 2011, **352**, 261–270.

11 M. Das, P. Saudagar, S. Sundar and V. K. Dubey, *FEBS J*. 2013, **280**, 4807-4815.