Design and synthesis of ring C opened analogues of α-santonin as potential anticancer agents

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Abstract:

Here we describe ring opening reaction of a novel halo triene derivative *viz.*, (3S, 5aS)-8-chloro-3a, 4, 5, 5a-tetrahydro-3, 5a, 9-trimethylnaphtho [1, 2-b] furan-2(3H)-one of α-santonin upon nucleophillic attack with alcohols. Halo-triene was synthesized from α-santonin upon reaction with vilsmeier reagent. The synthesised compounds from ring opening reaction were evaluated for anticancer activity against a panel of four human cancer cell lines (A-549, THP-1, HCT-15, and IMR-13). Most of the compounds exhibited promising anticancer activity against all cancer cells *in vitro*; however compound **3d** with benzyl substitution showed most potent anticancer activity with an IC_{50} value of 0.3 μM, 0.51 μM, 0.6 μM and 0.23 μM against A-549, THP-1, HCT- 116 and IMR-13 cell lines respectively.

Keywords: α-santonin, Vilsmeier reaction, aliphatic alcohols, cytotoxicity.

1. Introduction

Sesquiterpene lactones (SLs) are naturally occurring compounds known for their various biological activities such as anti-inflammatory (Hernández et al, 2007; Mazor et al, 2000), antimicrobial (Kuchkova et al, 2014), antiprotozoal (Trossini et al, 2014), and cytotoxic against different tumor cell lines (Zhang et al, 2005). In recent years, sesquiterpenes have attracted a great deal of interest due to their anticancer properties. Extensive work has been carried out to understand the molecular mechanisms and the potential chemo-preventive and chemo-therapeutic applications of sesquiterpeniods. Some of the sesquiterpene lactones have reached clinical trials because of their ability to selectively trigger cell death in cancer cells while sparing normal cells (Gershenzon et al, 2007; Zhou and Zhang, 2008; Jordan, 2006; Kawasaki et al, 2009; Crespo-Ortiz and Wei, 2012). The precise basis of their mechanism of action is still unclear; however many studies have demonstrated a strong correlation between the anti-tumor effect and anti-inflammatory responses of SLs (Dey et al, 2008; Jordan, 2007; Sarkar and Front, 2007; Zhang et al, 2005). Sesquiterpeniod lactones have been reported to selectively target the sarco/endoplasmic reticulum calcium ATPase pump (Denmeade and Isaacs, 2006), high iron content and cell surface transferrin receptors (Efferth, 2006; Nakase et al, 2009), NF-κB signalling (Hehner et al, 1999; Gopal et al, 2009), angiogenesis (Guzman et al, 2009), metastasis (Idris et al, 2009) and epigenetic mechanism (Gopal et al, 2007; Liu et

al, 2009) of tumour cells. Collectively these reports reveal a potential multifactorial effect of SLs in cancer cells.

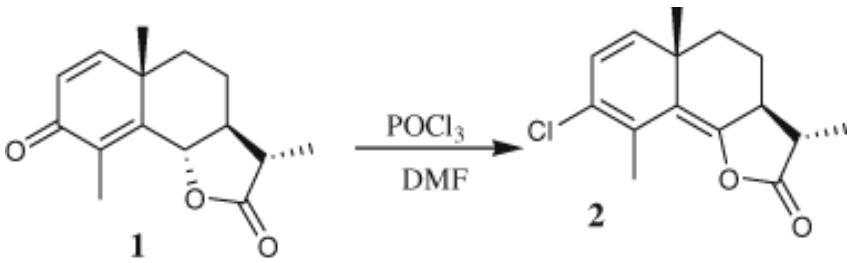
We studied α-santonin **1**, a promising sesquiterpeniod lactone, isolated from *Artemisia maritima*. α-Santonin has been reported to possess anti-parasitic, antipyretic and anti-inflammatory activities (Singh et al, 2001; Al-Harbi et al, 1994) . In addition to this, α-santonin being a highly functionalized and readily available compound has often been used as the starting material for the synthesis of more complex compounds with different skeletons. (Ando et al, 1987; Kawamato et al, 1996; Jenniskens et al, 1991). The derivatives of this natural product prepared through different synthetic routes have been reported active against various human cancer cell lines, many of them being highly potent showing activity in nanomolar range (Arantes et al, 2009, 2010). Recently, our research group found that spiro derivatives generated on lactone ring of α-santonin showed remarkable anticancer activity via down regulation of NF-kB (Khazir et al, 2013). The noble Diacetyl analogues formed by lactone ring opening of α-santonin have also been reported to show anti-leukemic activity by inducing HL-60 cell differentiation *via* down-regulation of NF-κB binding activity (Seung et al, 2008). As part of our continued interest in the design and synthesis of sesquiterpene lactones based anticancer agents (Khazir et al, 2013, 2014; Reddy et al, 2011) we here report the synthesis and cytotoxic activity of novel ring C opened derivatives of α-santonin. In previous studies ring C opening of α-santonin has been carried via hydrogenation of dienone ring however, we report a novel non catalysed route of lactone ring opening. In this study, α-santonin was first transformed into a novel halo-triene conjugated derivative upon reaction with Vilsmeier reagent. This triene derivative upon alcoholysis reaction resulted in the synthesis of novel biologically active ring C opened derivatives of α-santonin. A focussed library of novel compounds synthesised was subjected for anticancer activity against a panel of human cancer cell lines. From the IC_{50} values it appeared that most of the synthesised analogues showed better anticancer activity than the parent compound.

2. Results and Discussion

2.1 Chemistry

The Vilsmeier reagent is known to formylate substrates at active double bonds. However, in case of enonisable ketones it results in the formation of β-chloro substituted α-β unsaturated aldehydes. (Karlsson and Frejd , 1983; Weissenfels et al, 1997; Laurent and Wiechert, 1968) Interestingly, in α,β-unsaturated steroidal ketones, it results in the formation of a mixture of

β-chloro substituted α-β unsaturated aldehydes and halo-diene with latter as the major component (Laurent and Wiechert, 1968). α-Santonin on reaction with vilsmeier reagent was found to work similar to α,β-unsaturated steroidal ketones, but here instead of affording a mixture of products, we only achieved the halo-triene as the sole product (**Scheme 1**).



Scheme 1. Reaction of *α*-santonin with Vilsmeier reagent

Structure confirmation of compound **2** was done through various spectral analyses. Further the structure was also confirmed by X-ray crystallography as shown in **Fig 1.**

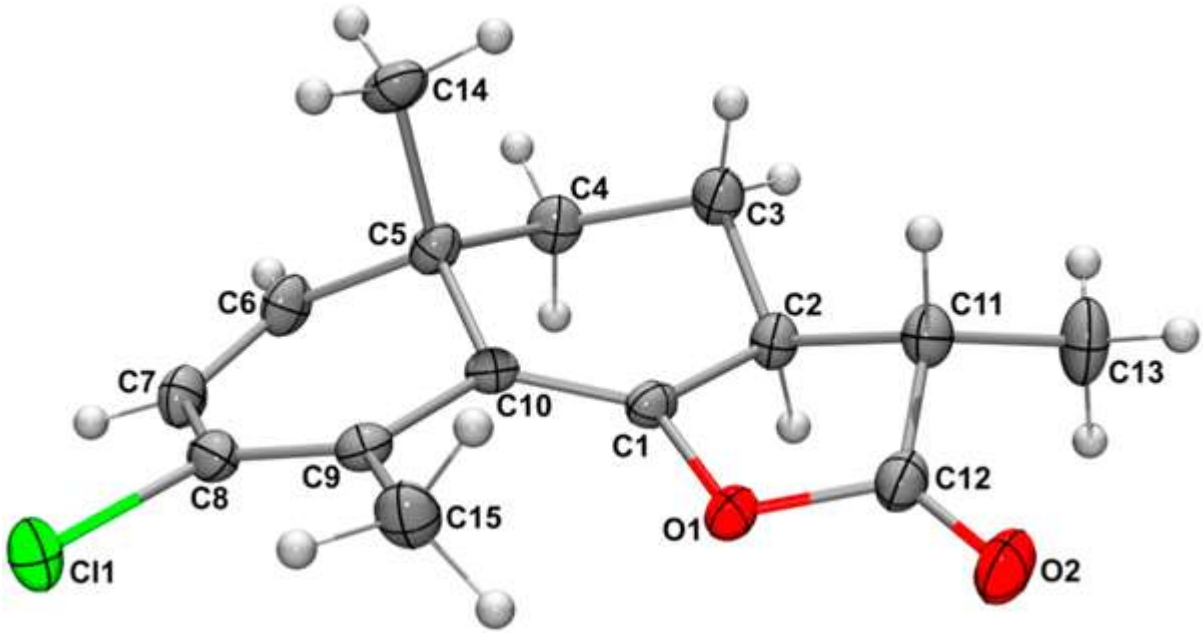


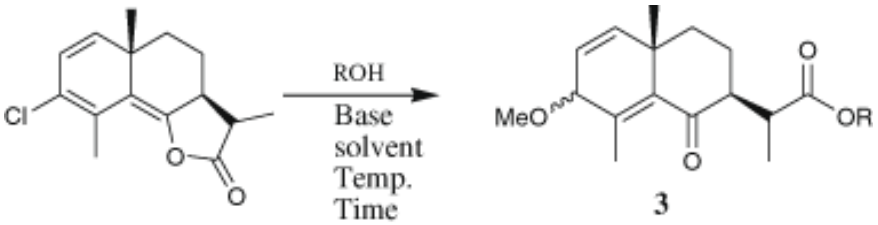
Fig. 1. Single X-ray crystal structure of (3S, 5aS)-8-chloro-3a, 4, 5, 5a-tetrahydro-3, 5a, 9-trimethylnaphtho [1, 2-b] furan-2(3H)-one (**2**)

Halo triene **2,** was further treated with different bases and various aliphatic nucleophiles such as alcohols, amines and thiols. The reaction was successful only with alcohols. Different bases like sodium acetate, *N*, *N*-diisopropylethylamine (DIEA), pyridine, pyrolidine and triethylamine were used to carry out the reaction. Significant product formation was only observed when using triethylamine (**Table 1**). The reaction was screened using a range of

primary, secondary and tertiary aliphatic amines, thiols and alcohols, however only primary aliphatic alcohols afforded the displaced products. Several different solvents were also screened but it was observed that solvent free conditions afford the best yields. Thus when compound **2** was treated with various aliphatic alcohols in presence of Et_3N and heated to 110^oC for 24 hours, the alcoholysis reaction took place, lactone ring was opened and ester derivatives (**Scheme 2, Table 2**) were formed. Most plausible mechanism for this reaction is given in **Fig 2.** Structure confirmation was done through various spectroscopic analyses.

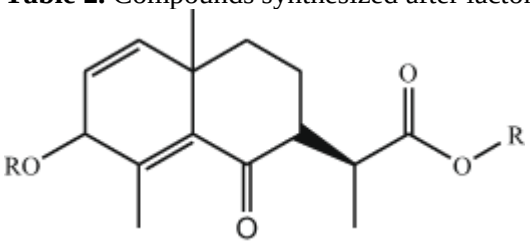
Table 1. Optimization of conditions for conversion of compound 2 to compound 3

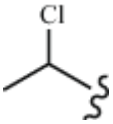
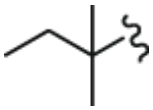
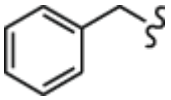
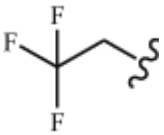
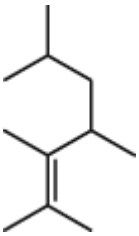
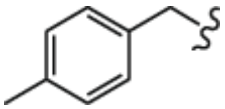
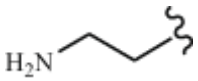
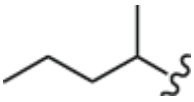
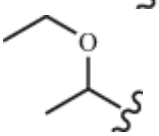
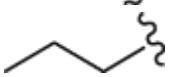
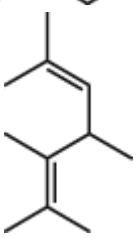
S.No	Base	Solvent	Nucleophile	Conditions	Yield (%)
1	DIPEA	CH_3CN, THF, DMF, MeOH	Pri, sec and tert-amine, thiols, pri, sec and tert-alcohol	rt-150 °C, 24 h	0
2	Pyridine	CH_3CN, THF, DMF, MeOH	Pri, sec and tert-amine, thiols, pri, sec and tert-alcohol	rt-150 °C, 24 h	0
3	K_2CO_3	CH_3CN, THF, DMF, MeOH	Pri, sec and tert-amine, thiols, pri, sec and tert-alcohol	rt-150 °C, 24 h	0
4	Pyrolidine	CH_3CN, THF, DMF, MeOH	Pri, sec and tert-amine, thiols, pri, sec and tert-alcohol	rt-150 °C, 24 h	0
5	Et_3N	CH_3CN, THF, DMF, MeOH	Pri, sec and tert-amine, thiols, pri, sec and tert-alcohol	rt-150 °C, 24 h	0
6	Et_3N	CH_3CN, THF, DMF, MeOH	Primary alcohols	rt-150 °C	30
7	Et_3N	No solvent	Primary alcohols	rt-110 °C	95

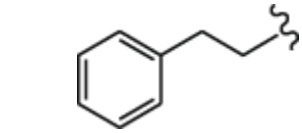
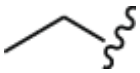


Scheme 2. Ring C opening alcoholysis reaction

Table 2. Compounds synthesized after lactone ring opening of Santonin



S. No	*R*	Yield (%)
3a		90
3b		87
3c		95
3d		95
3e		97
3f		86
3g		90
3h		90
3i		85
3j		85
3k		82
3l		90
3m		87

S. No	*R*	Yield (%)
3n		90
3o		87
3p		98
3q		98

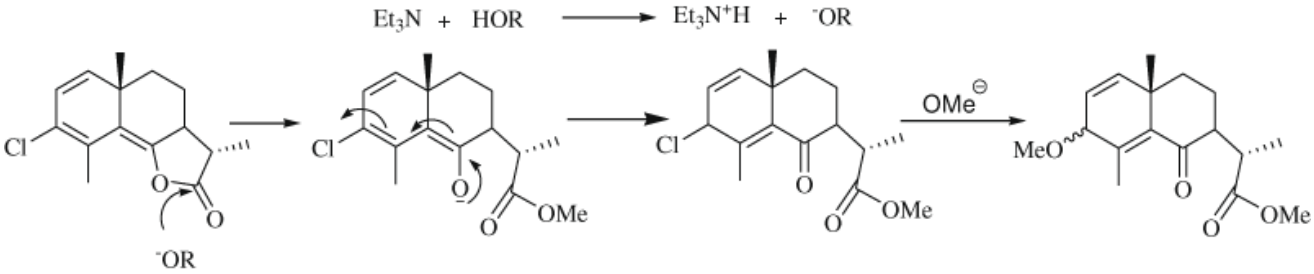


Fig. 2. Proposed mechanism for the formation of compound **3**

2.2 Anticancer activity

The *in vitro* antitumor activity of the newly synthesized compounds was evaluated against a panel of four human cancer cell lines, including A-549 (lung cancer line), THP-1(leukemia), HCT 116 (colon carcinoma cell), and IMR-32 (neuroblastoma). The inhibitory activities (IC_{50}) are summarized in **Table 3** and the well-known anticancer drug 5-fluorouracil was used as positive controls. From the screening results, it was observed that most of the synthesized compounds exhibited potent cytotoxic activities (IC_{50} < 10.0 μM) in comparison with the standard drugs used. Some compounds 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3l showed significantly higher cytotoxic activity against at least three human cancer cell lines with IC_{50} values below 10 μM. Compound **3d** showed promising anticancer activity on all four cancer cell lines with IC_{50} values of 0.3 μM, 0.51 μM, 0.6 μM and 0.23 μM against A-549, THP-1, HCT-116 and IMR-32 cell lines respectively. Compound **3g** showed good anticancer activity on three cancer cell lines with IC_{50} values of 0.033 μM, 0.8 μM and 0.16 μM against A-549, THP-1 and HCT-116 cell lines respectively. All the compounds showed potent activity against two cancer cell lines like leukemia and colon, while lesser activity was observed on lung cancer cell line.

Table 3. In vitro anticancer activity of synthesized compounds

Compound no	Lung A549	Leukemia THP-1	Colon HCT-15	Neuroblastoma IMR-32
3a	>50	7.96	2.21	3.36
3b	16.9	2.1	0.5	15
3c	14.2	5.6	1.2	2.4
3d	0.3	0.5	0.6	0.23
3e	>50	4.6	9.3	4.35
3f	18	13.2	6.8	12.4
3g	0.03	0.4	0.16	>50
3h	>50	5.4	1.28	2.5
3i	>50	0.82	7.8	3.4
3j	0.4	0.08	17	8.9
3k	>50	6.34	7.7	1.4
3l	0.12	0.7	0.66	>50
3m	15	18.7	18.9	40.5
3n	>50	3.8	40	8.2
3o	39	>50	>50	41
3p	27	>50	15	10
3q	26	13	35	29
2	29	38	21	50
1	36	42	29	45
5-Floro Uracil	4.9	1	6	4.5

2.3 Molecular docking

The compounds were subjected to molecular docking study to provide insights into the molecular binding modes of the molecules to assess the optimal orientation and binding abilities inside the receptor cavity of NF-kappa. For this purpose the AutoDock Tool (ADT) was used which is a program package of automated docking tools and is available on http://autodock.scripps.edu/. This program predicts how small molecules bind to a target protein or enzyme of known 3D-structure. The 3D crystal structure of NF-kappa (PDB ID: 1K3Z) (Malek et al, 2003) was collected from RCSB-Protein Data Bank (RCSB-PDB) based on resolution and date of deposition. The compounds were docked against the grid generated by AutoDock4.2 (Morris et al, 2009). The binding energy, intermolecular energy and unbound expanded energy of the ligands in the receptor site were calculated and are depicted in **Table 2.** For the most active compounds **3d** and **3g** the binding modes of the ligands in the receptor site are depicted in **Fig 3.**

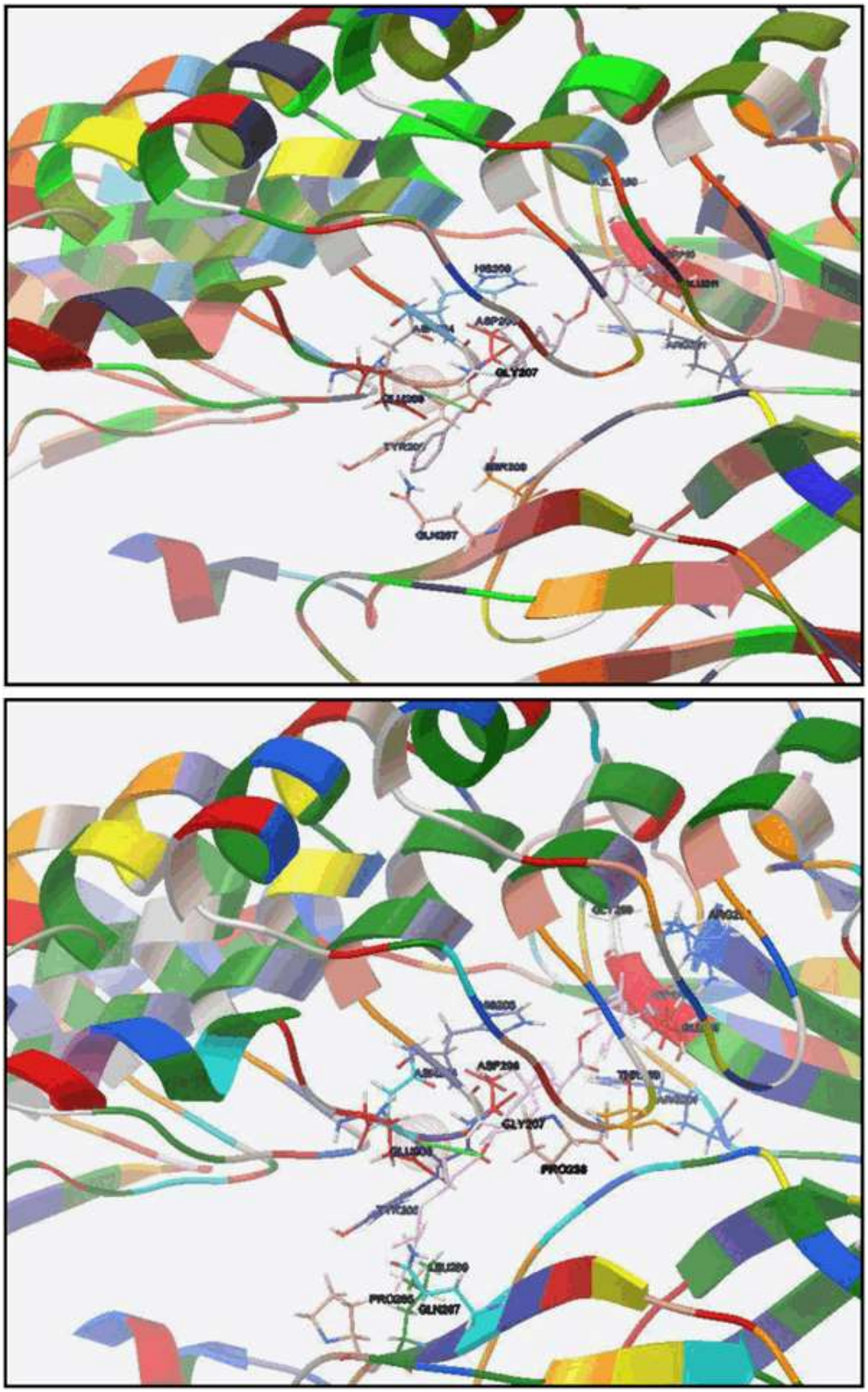


Fig. 3. Binding modes of most active compounds **a** 3d **b** 3g

3. Conclusion

In conclusion, halo-triene derivative of α-santonin was synthesised upon reaction with vilsmeier reagent. The later was then utilized for the synthesis of biologically active compounds via ring C opening on reaction with different aliphatic alcohols in the presence of Et_3N. Out of various nucleophiles used only primary alcohols were observed to give the desired products. A focussed library of ring C (lactone) opened derivatives were synthesised and evaluated for anticancer activity against a panel of four human cancer cell lines. Most of the tested compounds, showed better activity than the parent molecule and the standard drug 5-Fluoro uracil. The analogues **3d** and **3g** showed comparatively more potent activity than other derivatives. Compound **3d** with a benzyl substitution was found to be the most potent analogue. These results suggest that the esterified derivatives of α-santonin represent a promising new natural product based candidate which could be further developed into an anti-cancer agent (Table 4).

Table 4. Binding, intermolecular and unbound expanded energies of the compound synthesized

Compound no	Binding energy	Intermolecular energy	Unbound expanded energy
3a	−6.78	−7.92	−0.99
3b	−6.48	−9.23	−1.46
3c	−5.92	−8.85	−1.24
3d	−8.13	−10.52	−1.41
3e	−7.12	−8.91	−1.02
3f	−5.78	−8.77	−1.24
3g	−5.78	−10.55	−3.71
3h	−8.49	−10.88	−2.21
3i	−7.21	−8.93	−1.72
3j	−6.93	−9.91	−1.71
3k	−5.72	−8.71	−1.45
3l	−6.26	−9.24	−1.33
3m	−7.50	−10.48	−2.17
3n	−5.13	−8.72	−1.52
3o	−5.65	−8.36	−1.32
3p	−6.55	−7.72	−0.56
3q	−6.48	−8.27	−0.97

4. Experimental

Melting points were recorded on Buchi Melting point apparatus D-545. NMR spectra were recorded on Bruker DPX400 instrument in $CDCl_3$. Chemical shift values are reported in δ (ppm) and coupling constants in Hertz. Mass spectra were recorded on ESI-MS. The progress

of all reactions was monitored by TLC on 2-5 cm percolated silica gel 60 F_{254} plates of thickness 0.25mm (Merck). The chromatograms were visualized under UV 254-366 nm and iodine.

4.1 Synthesis of (3*S*, 3α*S*, 5α*S*)-8-Chloro-3,5α,9-trimethyl-3α, 4, 5, 5α-tetrahydro-3*H*-naptho [1,2-*β*] furan-2-one (2)

In a typical procedure to a solution of α-santonin (0.1 g, 1 mmol) in DMF (3 ml) was added $POCl_3$ (1.5 ml, 2 mmol) slowly and dropwise with vigorous stiring for about 15 minutes and then left at rt for 1 hour. Then reaction progress was monitored through TLC. Reaction was worked up with ether and water. Ether layer was extracted and evaporated to dryness. The crude product was subjected to column chromatography to afford pure product, whose structure was then elucidated as (3*S*, 3α*S*, 5α*S*)-8-Chloro-3,5α,9-trimethyl-3α, 4, 5, 5α-tetrahydro-3*H*-naptho [1,2-*β*] furan-2-one. (Yield 80%); Colourless solid; IR: (KBr, cm^{-1}): 712.30, 819.20, 1026.23, 1118.25, 1456.67, 1676.23, 1660.54, 1787.25, 2876.34, 2976.09, 3467.09; ^{1}H NMR (200 MHz, $CDCl_3$): 5.75 (d, 1H, *J*= 8.5 Hz, H-7), 5.62 (d, 1H, *J* = 8.5 Hz, H-6), 2.6-2.5 (m, 1H, H-2), 2.42 (m, 1H, H′-3), 1.95(s, 3H, H-9), 1.74 (m, 2H, H-3) 1.5 (s, 3H, H-5) 1.49 (m, 2H, H-4), 1.19 (d, 3H, *J* = 5.3 Hz, H′=4), ^{13}C (100 MHz, $CDCl_3$): 11.8(C-10), 14.5(C-14), 25.0(C-3), 28(C-11), 35.3(C-4), 37.7(C-5), 41.3(C-2), 41.8(C-12), 115.3(C-10), 127.4(C-7), 127.5(C-9), 132.6(C-8), 134.9(C-6),141.9(C-1), 171.0(C-13); GC MS: 264; Anal. Calcd for $C_{15}H_{17}ClO_2$: C, 68.05; H, 6.47 Found: C, 69.74; H, 6.21.

4.2 General Procedure for ring opening alcoholysis

In a typical procedure, to a solution of compound **2** (0.2 g, 1 mmol) in alcohol (10 ml) was added triethylamine (2 ml, 0.5 mmol) and then refluxed for 24 hrs.The reaction progress was checked through TLC. Then reaction mixture was extracted with EtOAc. The crude was then subjected to column chromatography to afford pure product. The structure of compound was confirmed through ^{1}H, ^{13}C and mass spectrometry.

Compound Characterisation

4.2.1. *1-Chloroethyl 2-(7-(1-chloroethoxy)-1, 2,3,4,4α,7-hexahydro-4α,8-dimethyl-7-oxo nap hthalene-2-yl) propanoate* (3a)

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 90%); mp: 178-179 ^{o}C; $[\alpha]_D^{25}$ -120 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}): 712.30, 819.20, 1026.23, 1118.25, 1456.67, 1676.23, 1660.54, 1787.25, 2876.34, 2976.09,

3467.09; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70-6.50 (m, 1H, H-7), 5.70-5.62 (m, 1H, H-6), 5.30 (q, 1H, *J* = 4.5 Hz, H=3′), 4.30 (q, 1H, *J* = 3.7 Hz, H-1″), 4.21(m, 1 H, H-8), 3.74-3.40 (m, 1H, H-2), 2.90 (m, 1H, H-1′), 2.10 (s, 3H, H-12 (CH_3), 1.74 (d, 4H, *J* = 7.8 Hz, H-3, H-4 (CH_2-CH_2), 1.56(d, 3H, *J* = 5.8Hz, H-2″(CH_3), 1.33 (d, 3H, *J* = 5.4 Hz, H-5′), 0.91 (m, 3H, H-11), 0.50 (m, 1H); ^{13}C (100 MHz, $CDCl_3$): 19.3(C-12, C-5″), 23.9(C-3, C-4′), 24.5(C-2″), 29.6 (C-11), 37.3(C-4), 37.6(C-1′), 40.7(C-5), 50.4(C-2), 65.4(C-8), 73.6(C-3′), 72.5(C-1″), 129.5(C-7), 130.3(C-6), 142.0(C-9), 143.3(C-10), 178.2(C-2′), 187.2(C-1); ESI- MS: 388 ; Anal. Calcd for $C_{19}H_{26}Cl_2O_4$: C, 58.62; H, 6.73 Found: C, 58.40; H, 6.57

4.2.2. *2-Methylpentan-2-yl 2-(7-(2-methylpentan-2-yloxy)-1, 2, 3, 4, 4α, 7-hexahydro-4α, 8-dimethyl -1-oxonaphthalen-2-yl) propanoate* (3b)

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 87%); mp: 154-155 ^{o}C; $[\alpha]_D^{25}$ -85 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}): 720.30, 810.14, 1025.98, 1128.30, 1465.43, 1687.87, 1669.34, 1768.65, 2856.54, 2990.09, 3443.24; ^{1}H NMR (400 MHz, $CDCl_3$); *δ* 6.90-5.50 (m, 2H, H-6, H-7), 3.51 (d, 1H, *J* = 7.8 Hz, H-8), 2.48-2.46 (m, 2H, H-2, H-1′), 1.53 (s, 3H, H-12(CH_3), 1.49 (t, 2H, *J* = 4.5 Hz, H-4 (CH_2) 1.49-1.45 (m, 10H, H-3(CH_2), H-4(CH_2), H-7′(CH_3), H-8′(CH_3), 1.38 (t, 2H, *J* = 4.2 Hz, H-2′), 1.36-1.30 (m, 7H, H-11(CH_3), H-5′(CH_2), H-3″(CH_2), 1.26(s, 6H, H-5″(CH_3), H-6″(CH_3), 1.24 (d, 3H, *J* = 2.1Hz, H-9′), 0.95 (t, 6H, *J* = 4.6 Hz, H-4″(CH_3), H-6′(CH_3); ^{13}C (100 MHz, $CDCl_3$): 10.7(C-12), 14.4(C-4″, C-7′), 15.3(C-6′), 16.8(C-5′, C-3″), 22.4(C-3), 26.7(C-7′, C-8′), 28.9(C-5″, C-6″), 29.3(C-11), 31.0(C-5), 37.5(C-4), 38.1(C-1′), 39.0(C-2′), 40.5(C-4″), 52.1(C-2), 67.9(C-1″), 70.0(C-8), 72.1(C-3′), 125.1(C-6), 131.5(C-7), 135.6(C-9), 137.3(C-10), 173.4(C-2′), 187.3(C-1) ; ESI-MS: 432; Anal. Calcd for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25 Found: C, 74.50; H, 10.14.

4.2.3. *3-Chloropropyl 2-(7-(3-chloropropoxy)-1, 2, 3, 4, 4α, 7-hexahydro-4α, 8-dimethyl-1-oxonaphthalen-2-yl)propanoate* (3c)

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 95%); mp: 176 ^{o}C; $[\alpha]_D^{25}$ -65 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}): 710.00, 823.15, 1023.20, 1123.26, 1457.57, 1667.45, 1656.24, 1780.35, 2865.14, 2970.89, 3433.29; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.8 (d, 1H, *J* = 10.1Hz, H-7), δ 6.40 (d, 1H, *J* = 10.1Hz, H-6), 4.23(m, 1H, H-8), 4.43 (m, 2H, H-3′(COO-CH_2), 3.80-3.73 (m, 2H, H-1″(O-CH_2), 3.70-3.65 (m, 4H, H-5′ (CH_2), H-3″ (CH_2), 2.90-2.83 (m, 1H, H-2), 2.71(m, 1H, H-1′), 2.50 (d, 3H, *J* = 5.1 Hz, H-6′), 2.40 (s, 3H, H-11), 2.00 (q, 4H, *J* = 8.4 Hz, H-3(CH_2), H-4(CH_2), 1.90 (m, 3H,

H-11),1.30 (m, 4H, H-4(CH_2), H-2″(CH_2); ^{13}C (100 MHz, $CDCl_3$):13.8 (C-12), 14.1(C-6′), 22.9 (C-3), 25.2 (C-11), 27.2 (C-4′), 29.6(C-5), 31.6(C-2″), 39.1(C-4), 39.5(C-1′), 41.2(C-3″), 42.0(C-5′), 52.3(C-2), 64.0(C-3′), 67.1(C-1″), 68.5(C-8), 129.9(C-7), 131.4(C-6), 133.6(C-9), 138.5(C-10), 176.2(C-2′), 187.3(C-1); ESI- MS : 416; Anal. Calcd for $C_{21}H_{30}Cl_2O_4$: C, 60.43; H, 7.26 Found: C, 60.37; H, 7.22

4.2.4. *Benzyl 2-(7-(benzyloxy)-1, 2, 3, 4, 4α, 7-hexahydro-4α,8-dimethyl-1-oxonaphthalen-2-yl) propanoate* (3d)

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 95%); mp: 153 ^{o}C; $[\alpha]_D^{25}$ -43 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}): 717.87, 820.97, 1032.11, 1143.32, 1454.53, 1668.32, 1678.09, 1775.23, 2854.32, 2967.32, 3430.97; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.30 (m, 10H, (protons of two benzene rings), 6.80-6.40 (m, 2H, H-6, H-7), 5.10 (m, 2H, H-4′(CH_2), 4.60-4.30 (m, 2H, H-1″(CH_2),4-20(m, 1H, H-8), 2.90-2.85 (m, 1H, H-2), 2.00-1.97 (m, 1H, H-1′), 1.70 (d, 5H, *J* = 2.4 Hz, H-12(CH_3), H-3(CH_2), 1.50 (s, 3H, H-11), 1.30 (d, 3H, *J* = 4.0 Hz, H-10′), 1.10 (m, 2H, H-3(CH_2); ^{13}C (100 MHz, $CDCl_3$): 15.0(C-12), 23.8(C-10′), 24.5(C-3), 25.1(C-11), 29.6(C-5), 37.3(C-4), 38.7(C-1′), 54.3(C-2), 66.1(C-3′), 73.5(C-1″), 127.4(C-3″, C-7″), 128.1(C-5′, C-9′), 128.3(C-4″, C-6″),129.0(C-7′, C-5″) 129.7(C-6′, C-8′), 130.0(C-6), 130.7(C-7, C-7″), 136.1(C-4′), 138.2(C-2″), 139.8(C-9) 141.8(C-10),175.8(C-2′), 187.6(C-1); ESI- MS: 444; Anal. Calcd for $C_{29}H_{32}O_4$: C, 78.37; H, 7.26 Found: C, 78.29; H, 7.21

4.2.5. 2*, 2, 2-Trifluoroethyl 2-(7-(2, 2, 2-trifluoroethoxy)-1, 2, 3, 4, 4α, 7-hexahydro-4α, 8-dimethyl-1-oxonaphthalen-2-yl)propanoate* (3e)

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 97%); mp: 87-88 ^{o}C; $[\alpha]_D^{25}$ -73 (*c* 0.5, $CHCl_3$) IR: (KBr, cm^{-1}): 705.56, 815.45, 1045.34, 1124.32, 1456.54, 1665.34, 1678.23, 1778.67, 2856.43, 2967.56, 3430.76; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (d, 1H, *J* = 9.4 Hz, H-7), 5.53 (d, 1H, *J* = 9.4 Hz, H-6), 4.64-4.60 (m, 2H, H-3′(CH_2), 4.20 (m, 1H, H-8), 3.80-3.75 (m, 2H, H-1″(CH_2), 2.50-2.45 (m, 1H, H-2), 2.40-2.37 (m, 1H, H-1′), 1.90 (s, 3H, H-12 (CH_3), 1.35 (t, 2H, *J* = 4.5 Hz, H-3(CH_2), 1.33 (s, 3H, H-11(CH_3), 1.23 (t, 2H, *J* = 3.2 Hz, H-4(CH_2), 1.15 (d, 3H, *J* = 2.1 Hz, H-5′); ^{13}C (100 MHz, $CDC1_3$): 16.90 (C-11), 17.7(C-5′), 19.3(C-3), 24.3(C-11), 26.7(C-5), 29.6(C-4), 31.5(C-1′), 41.2(C-2), 60.5(C-8), 63.1(C-3″), 70.6(C-2′), 124.8(C-4′), 133.4(C-4″), 174.5(C-2′), 187.3(C-2″): ESI- MS: 428; Anal. Calcd for $C_{19}H_{22}F_6O_4$: C, 53.27; H, 5.20 Found: C, 53.20; H, 5.17.

4.2.6. ***Pentyl 2-(1, 2, 3, 4, 4α, 7-hexahydro-4α, 8-dimethyl-1-oxo-7-(pentyloxy)naphthalen-2-yl) propanoate*** **(3f)**

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 86%); mp: 90-91 ^{o}C; $[\alpha]_D^{25}$ -116 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}); 709.87, 819.87, 1022.67, 1110.34, 1454.34, 1656.25, 1656.78, 1767.54, 2876.34, 2967.76, 3456.00; ^{1}H NMR (400MHz, $CDCl_3$): δ 6.34-6.28 (m, 2H, H-6, H-7), 4.12 (m, 1H, H-8), 3.50 (m, 2H, H-3′(CH_2), 3.35 (m, 2H, H-1″(CH_2), 2.50-2.47 (m, 1H, H-2), 2.35-2.30 (m, 1H, H-1′), 1.57-1.50 (m, 4H, H-2 (CH_2), H-5′ CH_2), 1.46-1.40 (m, 3H, H-12(CH_3), 1.35 (s, 3H, H-11(CH_3), 1.33-1.28 (m, 8H, H-2″ (CH_2), H-3″ (CH_2), H-5′ (CH_2), H-5(CH_2), 1.24 (d, 3H, *J* = 3.2 Hz, H-8′(CH_3), 1.10 (m, 4H, H-4″ (CH_2), H-6′ (CH_2), 0.95 (t, 6H, *J* = 4.2 Hz, H-5″(CH_3), H-7′(CH_3); ^{13}C (100 MHz, $CDCl_3$):10.7(C-12), 13.8(C-5″, C-7′), 14.1(C-8′), 16.5(C-6′), 19.4(C-4″), 19.8(C-5′), 27.9(C-11, C-3″), 31.2(C-2″), 32.7(C-4), 37.6(C-1′), 38.7(C-4′), 39.5(C-5), 55.4(C-2), 65.3(C-3′), 70.4(C-8), 70.6(C-1″), 128.4(C-6), 131.3(C-7), 135.3(C-9), 155.4(C-10), 173.1(C-2′), 187.2(C-1); ESI-MS: 404; Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.22; H, 9.97. Found: C, 74.16; H, 9.65.

4.2.7. ***3, 6, 7-Trimethyloct-6-enyl 2-(7-(3,6,7-trimethyloct-6-enyloxy)-1, 2, 3, 4, 4α, 7-hexahydro-4α, 8-dimethyl-1-oxonaphthalen-2-yl)propanoate*** **(3g)**

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 90%); mp: 76-77 ^{o}C; $[\alpha]_D^{25}$ -110 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}): 723.30, 811.56, 1027.87, 1113.43, 1467.72, 1668.09, 1675.39, 1764.19, 2804,23, 2932.31, 3456.33; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, 1H, *J* = 9.4 Hz, H-6), 6.50 (d, 1H, *J* = 9.7 Hz, H-7), 5.24 (t, 2H, *J* = 6.75 Hz, H-8′, H-6″), 4.22 (m, 1H, H-8), 3.41(t, 2H, *J* = 7.8 Hz, H-3′ (CH_2), 3.37 (t, 2H, *J* = 4.9 Hz, H-1″(CH_2), 2.95-2.90 (m, 2H, H-2, H-1′), 2.80-2.78 (m, 2H, H-3′(CH_2), 2.30 (s, 3H, H-12), 2.20 (d, 5H, *J* = 3.9 Hz, H-11(CH_3), H-3(CH_2), 2.13 (d, 6H, *J* = 2.1 Hz, H-2″(CH_2), H-4′(CH_2), H-4(CH_2), 2.00 (m, 3H, H-13′(CH_3), 1.90 (m, 12H, H-8′′(CH_3), H-9′′(CH_3), H-10′(CH_3), H-11′(CH_3), 1.80 (d, 4H, *J* = 4.9 Hz, H-5′′(CH_2), H-7′(CH_2), 1.53 (q, 2H, *J* = 5.6 Hz, H-3′′, H-5′), 1.15 (m, 4H, H-4′′(CH_2), H-6′(CH_2), 0.91 (d, 6H, *J* = 5.4 Hz, H-10′′(CH_3), H-12′(CH_3); ^{13}C (100 MHz, $CDCl_3$): 14.5 (C-12), 17.1(C-13′), 17.6 (C-11′, C-8″), 19.3 (C-12′, C-10″), 24.9 (C-7′, C-5″), 25.1(C-8″, C-10′), 25.3(C-3), 25.7(C-11), 29.4 (C-3″,C-5′) 29.6(C-5), 35.4(C-1′), 36.9(C-4′), 39.1(C-4, C-2″), 39.6(C-4″, C-6′), 50.5(C-2), 60.1(C-1), 63.1(C-3), 70.1(C-8), 126.1(C-6), 126.5(C-7), 131.5(C-9), 131.7(C-10), 135.8 (C-6″. C-8′), 135.9(C-7″. C-9′), 173.2(C-2′), 187.9(C-1) ; ESI- MS: 540; Anal. Calcd for $C_{35}H_{56}O_4$: C, 77.93; H, 10.54 Found: C, 77.58; H, 10.15.

4.2.8. 4-Methyl (*benzyl 2-(7-(benzyloxy)-1, 2, 3, 4, 4α, 7-hexahydro-4α,8-dimethyl-1-oxonaphthalen-2-yl) propanoate* (3h)

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 90%); mp: 85-86 ^{o}C; $[\alpha]_D^{25}$ -97 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}): 706.34, 812.23, 1034.23, 1145.54, 1451.65, 1654.32, 1692.35, 1784.12, 2800.12, 2945.23, 3452.87; ^{1}H NMR (400MHz, $CDCl_3$): δ 7.32 (d, 4H, *J* = 8.6 Hz, H-3″, H-7″, H-5′, H-9′), 6.95 (d, 4H, *J* = 8.5 Hz, H-4″, H-6″, H-6′, H-8′), 5.85 (d, 1H, *J* = 9.7 Hz, H-6), 5.55 (d, 1H, *J* = 9.7 Hz, H-7), 5.00 (s, 2H, H-3′(CH_2), 4.63 (s, 2H, H-1″(CH_2), 4.21(m, 1H, H-8), 2.75-2.70 (m, 2H, H-2, H-1′), 2.10 (s, 6H, H-8″ (CH_3), H-10′(CH_3), 1.95 (s, 3H, H-12(CH_3), 1.65 (d, 2H, *J* = 10.4 Hz, H-3(CH_2), 1.34-1.28 (m, 2H, H-4(CH_2), 1.22 (d, 3H, *J* = 6.9 Hz, H-11″(CH_3), 0.95 (s, 3H, H-11′(CH_3); ^{13}C (100 MHz, $CDCl_3$): 11.0(C-12), 16.7(C-11′), 19.5 (C-3), 27.8(C-11), 30.3(C-5), 32.3(C-8″, C-10′), 37.2(C-4), 39.0(C-1′), 51.3(C-2), 65.3(C-3′), 70.2(C-8), 72.3(C-1″), 125.7(C-3″, C-7″), 125.8 (C-5′, C-9′), 127.6 (C-4″, C-6″), 127.7(C-6′, C-7′), 129.3(C-6), 129.7(C-7), 131.8(C-9), 132.2(C-10), 134.0(C-2″), 134.6(C-4′), 171.8(C-2′), 185.9(C-1); ESI- MS: 472; Anal. Calcd for $C_{31}H_{36}O_4$: C, 78.78; H, 7.68. Found: C, 78.61; H, 7.65.

4.2.9. *2-Aminoethyl 2-(7-(2-aminoethoxy)-1, 2, 3, 4, 4α, 7-hexahydro-4α, 8-dimethyl-1-oxo nap hthalen-2-yl)propanoate* (3i)

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 80%); mp: 85 ^{o}C; $[\alpha]_D^{25}$ -117 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}); 698.23, 778.90, 1042.12, 1139.06, 1456.23, 1653.21, 1678.90, 1767.90, 2812.14, 2956.09, 3440.00; ^{1}H NMR (400 MHz, $CDCl_3$); δ 6.34-6.28 (m, 2H, H-6, H-7), 4.85 (t, 2H, *J* = 5.8 Hz, H-3′(CH_2), 4.20 (m, 1H, H-8), 3.64 (t, 2H, *J* = 4.7 Hz, H-1″), 2.95 (m, 2H, H-2′, H-1), 2.48 (m, 2H, H-2″(CH_2), 2.46-2.40 (m, 2H, H-4′), 2.00 (s, 3H, H-12(CH_3), 1.74 (d, 3H, *J* = 4.8 Hz, H-5′(CH_3), 1.38-1.35 (m, 4H, H-3(CH_2), H-4(CH_2), 1.30 (s, 3H, H-11(CH_3); ^{13}C (100 MHz, $CDCl_3$):10.7(C-12), 15.1(C-4′), 19.4(C-3), 27.9(C-11), 30.6(C-5), 38.2(C-4), 39.5(C-1′), 40.7(C-2″), 42.2(C-4′), 54.3(C-2), 66.7(C-1″), 70.1(C-3′), 71.2(C-8), 128.4(C-6), 131.3(C-7), 135.4(C-9), 142.3(C-10), 173.3(C-2′), 187.2(C-1); ESI-MS: 350; Anal. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.39. Found: C, 65.05; H, 8.32.

4.2.10. ***Pentan-2-yl 2-(1, 2, 3, 4, 4α, 7-hexahydro-4α, 8-dimethyl-1-oxo-7-(pentan-2-yloxy) nap hthalen-2-yl)propanoate*** **(3j)**

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 85%); mp: 120-121 ^{o}C; $[\alpha]_D^{25}$ 86 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}); 696.78, 754.32, 1032.21, 1135.98, 1443.09, 1645.85, 1665.25, 1756.90, 2810.43, 2956.00, 3434.67; ^{1}H NMR (400 MHz, $CDCl_3$); δ 6.90-5.50 (m, 2H, H-6, H-7), 4.30 (q, 1H, *J* = 4.8 Hz, H-3′), 3.51 (m, 1H, H-8), 3.10 (q, 1H, *J* = 3.4 Hz, H-1″), 2.48-2.46 (m, 2H, H-2, H-1′), 1.53-1.50 (m, 6H, H-7′(CH_3), H-12(CH_3), 1.45-1.38 (m, 8H, H-3(CH_2), H-4(CH_2), H-2″(CH_2), H-4′(CH_2), 1.33 (m, 7H, H-11(CH_3), H-3″(CH_2), H-5′(CH_2), 1.24(d, 3H, *J* = 2.1Hz, H-5″(CH_3), 0.95 (t, 6H, *J* = 4.6 Hz, H-4″(CH_3), H-6′(CH_3), 0.90 (d, 3H, *J* = 3.4 Hz, H-8′); ^{13}C (100 MHz, $CDCl_3$): 10.7(C-12), 14.4(C-8′), 15.3(C-5″), 16.8(C-4″), 19.0 (C-7′), 19.3(C-11), 20.1(C-6′), 22.4(C-3, C-5′), 26.7(C-3″), 29.3(C-6), 37.5(C-4), 38.1(C-1′), 40.5(C-2″), 67.9(C-1″), 72.1(C-8,C-3′), 130.1(C-6), 131.5(C-7), 135.6(C-9), 137.3(C-10), 173.4(C-2′), 187.3(C-1) ; ESI-MS: 405; Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.22; H, 9.97 Found: C, 74.50; H, 9.54.

4.2.11. ***2-Ethoxyethyl 2-(7-(2-ethoxyethoxy)-1, 2, 3, 4, 4α, 7-hexahydro-4α, 8-dimethyl-1-oxonaph thalen-2-yl)propanoate*** **(3k)**

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 82%); mp: 87-88 ^{o}C; $[\alpha]_D^{25}$ -125 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}); 705.21, 773.12, 1053.23, 1154.21, 1408.65, 1665.87, 1679.89, 1743.30, 2815.65, 2950.80, 3434.98; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40-5.70(m, 2H, H-6, H-7), 4.85 (t, 1H, *J* = 9.7 Hz, H-3′), 4.65 (t, 1H, *J* = 4.8 Hz, H-1″), 4.21(m, 1H, H-8), 3.54-3.50 (q, 4H, *J* = 6.7 Hz, H-2″ (CH_2), H-4′(CH_2), 2.54(m, 2H, H-2, H-1′), 1.90 (s, 3H, H-12(CH_3), 1.41-1.38 (m, 7H, H-3 (CH_2), H-4 (CH_2), H-6′ (CH_3), 1.35(m, 3H, H-11(CH_3), 1.30 (d, 3H, *J* = 6.5 Hz, H-4″(CH_3), 1.24 (d, 3H, *J* = 3.5 Hz, H-7′(CH_3), 0.95 (t, 6H, *J* = 2.4 Hz, H-5′(CH_3), H-3″ (CH_3); ^{13}C (100 MHz, $CDCl_3$):10.7(C-12), 15.2(C-5′), 15.5(C-3″), 16.7(C-7′), 19.4(C-5′), 20.5(C-4″), 22.4(C-3), 27.9(C-11), 29.0(C-5), 38.7(C-4), 39.5(C-1′), 51.2(C-2), 65.0(C-2″), 67.6(C-4′), 70.4(C-8), 90.6 (C-1″), 95.4(C-3′), 128.4(C-6), 131.3(C-7), 135.6(C-9), 140.4(C-10), 173.1(C-2′), 187.2 (C-1); ESI-MS: 408; Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.08. Found: C, 67.60; H, 8.02.

4.2.12. ***Butyl 2-(7-butoxy-1, 2, 3, 4, 4α, 7-hexahydro-4α, 8-dimethyl-1-oxonaphthalen-2-yl) propanoate*****(3l)**

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 90%); mp: 92-93 ^{o}C; $[\alpha]_D^{25}$ -78 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}); 715.21, 767.10, 1065.20, 1153.25, 1416.43, 1656.76, 1675.78, 1740.31, 2821.60, 2953.86, 3439.98; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40-5.84 (m, 2H, H-6, H-7), 4.21(m, 1H, H-8), 4.05 (t, 2H, *J* = 5.6 Hz, H-3′(CH_2), 2.48-2.46 (m, 2H, H-2, H-1″), 1.90 (s, 3H, H-12(CH_3), 1.57-1.53 (m, 2H, H-4′(CH_2), 1.46(m, 2H, H-2″(CH_2), 1.41-1.38 (m, 7H, H-3(CH_2), H-4(CH_2), H-11(CH_3), 1.33-1.30 (m, 4H, H-3″ (CH_2), H-4′(CH_2), 1.20 (d, 3H, *J* = 1.4 Hz, H-7′(CH_3), 0.95 (t, 6H, *J* = 2.4 Hz, H-6′ (CH_3), H-4″(CH_3); ^{13}C (100 MHz, $CDCl_3$):10.7(C-12), 13.8(C-6′), 15.2(C-7′), 15.5(C-4″), 16.7(C-5′), 19.4(C-3″), 27.9(C-3), 29.0(C-11), 30.3(C-5), 31.2(C-2″), 32.5(C-4′), 37.6(C-4), 38.7(C-1′), 51.2(C-2), 65.0(C-1″), 67.6(C-3′), 70.4(C-8), 128.4(C-6), 131.3(C-7), 135.4(C-9), 142.3(C-10), 173.1(C-2′), 187.2 (C-1); ESI-MS: 377; Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.28; H, 9.45.

4.2.13. ***(E)-3,7-dimethylocta-2,6-dienyl 2-(1-((E)-3,1-dimethylocta-2,6-dienyloxy)-1,2,3,4,4 α,7-hexahydro-4α, 8-dimethyl-1-oxonaphthalen-2-yl)propanoate*** **(3m)**

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 87%); mp: 68-69 ^{o}C; $[\alpha]_D^{25}$ -130 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}); 706.34, 812.23, 1034.23, 1145.54, 1451.65, 1654.32, 1692.35, 1784.12, 2800.12, 2945.23, 3452.87; ^{1}H NMR (400 MHz, $CDCl_3$); δ 6.28-5.70 (m, 2H, H-6, H-7), 5.45 (t, 2H, *J* = 6.6 Hz, H-6′, H-4″), 4.62 (d, 2H, *J* = 7.0 Hz), 4.56 (t, 2H, *J* = 3.1 Hz, H-3′(CH_2), 4.20(m, 1H, H-8), 3.54 (t, 2H, *J* = 7.8 Hz, H-1″(CH_2), 2.30-2.46 (m, 2H, H-2, H-1′), 2.63 (d, 4H, *J* = 4.2 Hz, H-5″(CH_2), H-7′(CH_2), 2.10-2.00 (t, 4H, *J* = 6.5 Hz, H-2″(CH_2), H-4′(CH_2), 1.90 (s, 3H, H-12(CH_3), 1.71-1.65 (m, 24H, H-10′(CH_3), H-11′(CH_3), H-12′(CH_3), H-13′(CH_3), H-8″(CH_3), H-9″(CH_3), H-10″(CH_3), H-11″(CH_3), 1.40 (m, 7H, H-3(CH_2), H-4(CH_2), H-14(CH_3), 1.24 (d, 3H, *J* = 3.8 Hz, H-11(CH_3); ^{13}C (100 MHz, $CDCl_3$); 10.2(C-12), 14.2(C-14′), 16.4(C-10″, C-12′), 19.1(C-10′, C-11′, C-8″, C-9″), 21.2 (C-3), 23.7(C-13′), 24.5(C-11″), 27.0(C-11), 31.3(C-5), 33.2 (C-5″, C-7′), 37.0(C-2″), 37.7(C-4′), 38.1(C-4), 38.2(C-1′), 50.1(C-2), 61.2(C-1″), 65.4(C-3′), 70.4(C-8), 123.1(C-4″), 125.4(C-6′), 125.7(C-6″, C-8′), 127.8(C-7″, C-9′), 127.8(C-6), 128.0(C-7), 135.3(C-3″, C-5′, C-9), 140.6(C-10), 175.3(C-2′), 186.9(C-1); ESI- MS: 564; Anal. Calcd for $C_{37}H_{56}O_4$: C, 78.68; H, 9.99. Found: C, 78.54; H, 9.72.

4.2.14. ***Phenethyl 2-(1 ,2, 3, 4, 4α, 7-hexahydro-4α,8-dimethyl-1-oxo-7-(phenethyloxy) naphtha len-2-yl)propanoate*** **(3n)**

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 90%); mp: 85-86 ^{o}C; $[\alpha]_D^{25}$ -105 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}); 696.78, 754.32, 1032.21, 1135.98, 1443.09, 1645.85, 1665.25, 1756.90, 2810.43, 2956.00, 3434.67; ^{1}H NMR (200 MHz, $CDCl_3$); δ 7.30-7.00 (m, 10H, H-4″, H-5″, H-6″, H-7″, H-8″, H-6′, H-7′, H-8′, H-9′, H-10′), 5.75-5.50 (m, 2H, H-6, H-7), 4.20(m, 1H, H-8), 4.30 (t, 2H, *J* = 6.0 Hz, H-3′(CH_2), 3.73 (t, 2H, *J* = 3.4 Hz, H-1″(CH_2), 2.80 (t, 2H, *J* = 5.3 Hz, H-4′), 2.70 (t, 2H, *J* = 2.4 Hz, H-2″), 2.50-2.45 (m, 2H, H-2, H-1′), 1.90 (s, 3H, H-12(CH_3), 1.50-1.35 (m, 7H, H-3(CH_2), H-4(CH_2), H-11(CH_3), 1.20 (d, 3H, *J* = 4.8 Hz, H-11′(CH_3); ^{13}C (100 MHz, $CDCl_3$): 11.0 (C-12), 17.4(C-11′), 22.0(C-3), 27.9(C-11), 30.3(C-5), 35.3(C-2″), 37.3(C-4′), 38.6(C-4, C-1′), 50.0(C-2), 64.4(C-1″), 75.5(C-8), 82.3(C-1′), 126.0(C-6″), 126.8(C-8′), 127.8(C-4″, C-8″, C-6′, C-10′), 128.8(C-5″, C-7″, C-7′, C-9′), 129.2(C-6), 130.3(C-7), 135.2(C-9), 137.7(C-10), 139.0(C-3″), 139.9(C-5′), 172.4(C-2′), 186.0(C-1); ESI- MS: 472; Anal. Calcd for $C_{31}H_{36}O_4$: C, 78.78; H, 7.68 Found: C, 78.65; H, 7.57.

4.2.15. ***Nonyl 2-(7-(decyloxy)-1,2,3,4,4α,7-hexahydro-4α,8-dimethyl-1-oxonaphthalen-2-yl) pro panoate*** **(3o)**

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 87%); mp: 57-58 ^{o}C; $[\alpha]_D^{25}$ -118 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}); 710.00, 823.15, 1023.20, 1123.26, 1457.57, 1667.45, 1656.24, 1780.35, 2865.14, 2970.89, 3433.29; ^{1}H NMR (400 MHz, $CDCl_3$); δ 5.75-5.50 (m, 2H, H-6, H-7), 4.30 (t, 2H, *J* = 3.1 Hz, H-3′(CH_2), 4.20 (m, 1H, H-8), 4.00 (t, 2H, *J* = 2.6 Hz, H-1″(CH_2), 2.75-2.50 (m, 2H, H-2, H-1′), 1.80 (s, 3H, H-12 (CH_3), 1.53-1.40 (m, 8H, H-3(CH_2), H-4(CH_2), H-2″(CH_2), H-4′(CH_2), 1.34-1.25 (m, 24H, H-3(CH_2), H-4(CH_2), H-5(CH_2), H-6(CH_2), H-7(CH_2), H-8(CH_2), H-5(CH_2), H-6(CH_2), H-7(CH_2), H-8(CH_2), H-9(CH_2), H-10(CH_2),1.20 (s, 3H, H-11(CH_3), 1.10 (d, 3H, *J* = 4.5Hz, H-12′), 0.91 (t, 6H, *J* = 3.1 Hz, H-9″(CH_3), H-11′(CH_3); ^{13}C (100 MHz, $CDCl_3$); 10.2(C-12), 11.0(C-12′), 15.4(C-11′, C-9″), 19.8(C-10′, C-8″), 22.2(C-3), 27.4(C-11), 28.0(C-7″, C-6″, C-5″, C-4″, C-9′, C-8′, C-7′, C-6′), 29.0(C-3″, C-5′), 29.5(C-2″), 29.6(C-4′), 30.5(C-5), 37.5(C-4), 38.2(C-1′), 65.4(C-1″), 70.6(C-3′), 71.0(C-8), 127.4(C-6), 128.4(C-7), 135.2(C-9), 140.4(C-10), 172.7(C-2′), 187.9(C-1), ESI- MS ; 516: Anal. Calcd for $C_{33}H_{56}O_4$: C, 76.67; H, 10.92 Found: C, 76.52; H, 10.65.

4.2.16. ***Methyl 2-(1,2,3,4,4α,7-hexahydro-7-methoxy-4α,8-dimethyl-1-oxonaphthalen-2-yl)pro panoate*** **(3p)**

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 98%); mp: 67-68 ^{o}C; $[\alpha]_D^{25}$ -123 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}); 712.30, 819.20, 1026.23, 1118.25, 1456.67, 1676.23, 1660.54, 1787.25, 2876.34, 2976.09, 3467.09; ^{1}H NMR (400 MHz, $CDCl_3$); 5.85-5.75 (m, 2H, H-6, H-7), 4.24 (m, 1H, H-8), 3.74 (s, 3H, H-3′(OCH_3), 3.21 (d, 3H, *J* = 12.6 Hz, H-1″(OCH_3), 2.80-2.70 (m, 2H, H-2, H-1′), 1.84 (m, 3H, H-12(CH_3), 1.40-1.30(m, 4H, H-3(CH_2), H-4(CH_2) 1.23 (d, 3H, *J* = 6.3 Hz, H-4′(CH_3), *δ* 0.91 (d, 3H, *J* = 6.5 Hz, H-11(CH_3); ^{13}C (100 MHz, $CDCl_3$); 14.1 (C-12),16.6 (C-4′), 20.8 (C-3), 27.5 (C-11), 30.4 (C-5), 37.4 (C-4), 37.5,(C-1′), 50.4(C-1), 52.6(C-1″), 57.9(C-3′), 72.6(C-8), 128.5(C-6), 134.1(C-7), 138.4(C-9), 143.2(C-10), 176.5(C-2′), 187.4(C-1); ESI- MS: 292; Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27 Found: C, 69.74; H, 8.21.

4.2.17. ***Ethyl 2-(7-ethoxy-1, 2, 3, 4, 4α, 7-hexahydro-4α, 8-dimethyl-1-oxonaphthalen-2-yl)pro panoate*** **(3q)**

Gummy solid (This compound was prepared according to the general procedure given in section 4.2 with yield 98%); mp: 56-57^{o}C; $[\alpha]_D^{25}$ -87 (*c* 0.5, $CHCl_3$); IR: (KBr, cm^{-1}); 724.35, 813.34, 1020.98, 1132.30, 1457.43, 1670.97, 1665.34, 1767.65, 2867.54, 2987.09, 3433.24; ^{1}H NMR (400 MHz, $CDCl_3$); *δ* 5.75 (d, 1H, *J* = 9.6 Hz, H-6), 5.63 (d, 1H, *J* = 9.5 Hz, H-7), 4.41 (s, 1H, H-8), 4.22 (m, 2H, H-3′(CH_2), 3.54 (m, 2H, H-1″(CH_2), 2.73 (q, 2H, *J* = 8 Hz, H-2, H-1′), 1.84 (d, 3H, *J* = 4 Hz, H-12(CH_3),1.32 (m, 10H, H-3(CH_2), H-4(CH_2), H-11(CH_3), H-4′(CH_3), 1.24(d, 3H, *J* = 4.4 Hz, H-5′(CH_3), 0.90 (t, 3H, *J* = 3.7 Hz, H-3″(CH_3) ; ^{13}C (100 MHz, $CDCl_3$); 15.6(C-12, C-3″), 16.6(C-5′, C-4′), 22.7(C-3), 31.4(C-5), 37.4(C-4), 38.8(C-1′), 50.7(C-2), 54.3(C-1″), 72.3(C-8), 73.4(C-3′), 130.2(C-6), 131.0(C-7), 141.4(C-9), 142.6(C-10), 176.1(C-2′), 205.8(C-1); ESI MS: 320; Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81 Found: C, 71.05; H, 8.60.

4.3 X-Ray crystallography

Data were collected on a Bruker D8 Venture kappa-geometry diffractomter, fitted with twin IμS sources and a Photon 100 CMOS detector, using Cu Kα radiation and Bruker *APEX*2 control software. The data were processed using Bruker *SAINT* and corrected for absorption, by the multi-scan method, and scaled using Bruker *SADABS*. The structure was solved by intrinsic-phasing using Bruker *SHELXTS* and refined using Bruker *SHELXTL* and *SHELXL*-

2013. Graphics were generated using *OTEP*-3 *for windows* and *POV-RAY* and publication material was produced using *SHELXL*-2013 and *PLATO* (Vinutha et al, 2013). For further details see the supplementary information.

4.4 Anticancer activity

The effect of lactone opened derivatives of α-santonin on the growth of cancer cell lines was evaluated according to the procedure adopted by the National Cancer Institute for *in vitro* anticancer drug screening that uses the protein-binding dye Sulphorhodamine B to estimate cell growth. Briefly, cells in their log phase of growth were harvested, counted and seeded (104 cells/well in 100 mL medium) in 96-well microtitre plates. After 24 h of incubation at 37^{o}C and 5% CO_2 to allow cell attachment, cultures were treated with varying concentrations (0.1-10 μM) of test samples made with 1:10 serial dilutions. Four replicate wells were set up for each experimental condition. Test samples were left in contact with the cells for 48 h under same conditions. Thereafter cells were fixed with 50% chilled TCA and kept at 4^{o}C for 1 h, washed and air-dried. Cells were stained with Sulphorhodamine B dye. The adsorbed dye was dissolved in tris-buffer and the plates were gently shaken for 10 min on a mechanical shaker. The optical density (OD) was recorded on ELISA reader at 540 nm. The cell growth was calculated by subtracting mean OD value of the respective blank from the mean OD value of experimental set. Percentage of growth in the presence of test material was calculated considering the growth in the absence of any test material as 100% and the results are reported in terms of IC_{50} values.

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SUPPLEMENTRY INFORMATION S1

X-Ray data of (3*S*, 3α*S*, 5α*S*)-8-Chloro-3, 5α, 9-trimethyl-3α, 4, 5, 5α-tetrahydro-3*H*-naptho [1, 2-*β*]furan-2-one (coded as compound 2)

Crystal data and structure refinement for compound 2.

Identification code	2	
Empirical formula	$C_{15}H_{17}ClO_2$	
Formula weight	264.73	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	*a* = 8.0644(3) Å	□□= 90°.
	b = 10.6099(3) Å	□□= 90°.
	c = 15.8443(5) Å	□ = 90°.
Volume	1355.68(8) Å^3	
Z	4	
Density (calculated)	1.297 Mg/m^3	
Absorption coefficient	2.422 mm^{-1}	
F(000)	560	
Crystal size	0.362 x 0.333 x 0.137 mm^3	
θ range for data collection	5.017 to 77.367°.	
Index ranges	-9<=h<=10, -13<=k<=12, -20<=l<=19	
Reflections collected	10602	
Independent reflections	2776 [*R*(int) = 0.0295]	
Completeness to θ = 67.679°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7542 and 0.5490	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2776 / 0 / 214	
Goodness-of-fit on F^2	1.091	
Final *R* indices [$I>2\sigma(I)$]	*R*1 = 0.0314, *wR*2 = 0.0781	
R indices (all data)	*R*1 = 0.0320, *wR*2 = 0.0786	
Absolute structure parameter	0.044(5)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.348 and -0.163 e.Å^{-3}	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound 2. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	-1989(1)	10275(1)	6714(1)	29(1)
O(1)	271(2)	5490(1)	6078(1)	25(1)
O(2)	13(2)	3389(2)	6024(1)	37(1)
C(1)	1583(2)	6350(2)	6067(1)	21(1)
C(2)	3093(3)	5683(2)	5744(1)	23(1)
C(3)	4671(3)	6365(2)	5989(1)	26(1)
C(4)	4421(3)	7764(2)	5806(1)	25(1)
C(5)	3017(2)	8354(2)	6333(1)	21(1)
C(6)	2624(3)	9662(2)	6001(1)	26(1)
C(7)	1118(3)	10153(2)	6084(1)	25(1)
C(8)	-201(3)	9407(2)	6461(1)	22(1)
C(9)	-118(2)	8159(2)	6592(1)	20(1)
C(10)	1445(2)	7550(2)	6318(1)	19(1)
C(11)	2787(3)	4349(2)	6069(1)	25(1)
C(12)	909(3)	4280(2)	6053(1)	26(1)
C(13)	3638(4)	3269(2)	5620(2)	38(1)
C(14)	3575(3)	8520(2)	7264(1)	28(1)
C(15)	-1473(3)	7385(2)	6982(1)	27(1)

Bond lengths [Å] and angles [°] for 2.

Cl(1)-C(8)	1.757(2)	C(15)-H(15A)	0.97(3)
O(1)-C(12)	1.383(2)	C(15)-H(15B)	0.93(3)
O(1)-C(1)	1.398(2)	C(15)-H(15C)	0.96(3)
O(2)-C(12)	1.192(3)		
C(1)-C(10)	1.338(3)	C(12)-O(1)-C(1)	108.86(15)
C(1)-C(2)	1.498(3)	C(10)-C(1)-O(1)	123.68(17)
C(2)-C(3)	1.515(3)	C(10)-C(1)-C(2)	128.18(18)
C(2)-C(11)	1.526(3)	O(1)-C(1)-C(2)	108.14(15)
C(2)-H(2)	0.99(2)	C(1)-C(2)-C(3)	111.73(15)
C(3)-C(4)	1.525(3)	C(1)-C(2)-C(11)	101.09(16)
C(3)-H(3A)	0.98(3)	C(3)-C(2)-C(11)	119.51(18)
C(3)-H(3B)	0.97(3)	C(1)-C(2)-H(2)	107.4(16)
C(4)-C(5)	1.540(3)	C(3)-C(2)-H(2)	109.9(16)
C(4)-H(4A)	0.95(3)	C(11)-C(2)-H(2)	106.3(15)
C(4)-H(4B)	0.97(3)	C(2)-C(3)-C(4)	107.75(17)
C(5)-C(6)	1.517(3)	C(2)-C(3)-H(3A)	108.8(17)
C(5)-C(10)	1.528(3)	C(4)-C(3)-H(3A)	111.4(16)
C(5)-C(14)	1.552(3)	C(2)-C(3)-H(3B)	109.1(17)
C(6)-C(7)	1.328(3)	C(4)-C(3)-H(3B)	115.1(16)
C(6)-H(6)	0.91(3)	H(3A)-C(3)-H(3B)	105(2)
C(7)-C(8)	1.455(3)	C(3)-C(4)-C(5)	112.93(16)
C(7)-H(7)	0.89(3)	C(3)-C(4)-H(4A)	112.1(17)
C(8)-C(9)	1.342(3)	C(5)-C(4)-H(4A)	107.1(16)
C(9)-C(10)	1.482(3)	C(3)-C(4)-H(4B)	108.2(15)
C(9)-C(15)	1.500(3)	C(5)-C(4)-H(4B)	110.0(17)
C(11)-C(13)	1.513(3)	H(4A)-C(4)-H(4B)	106(2)
C(11)-C(12)	1.516(3)	C(6)-C(5)-C(10)	109.38(16)
C(11)-H(11)	0.98(3)	C(6)-C(5)-C(4)	109.69(16)
C(13)-H(13A)	0.91(4)	C(10)-C(5)-C(4)	111.96(15)
C(13)-H(13B)	0.97(4)	C(6)-C(5)-C(14)	106.66(16)
C(13)-H(13C)	0.95(4)	C(10)-C(5)-C(14)	108.60(15)
C(14)-H(14A)	0.92(3)	C(4)-C(5)-C(14)	110.40(17)
C(14)-H(14B)	0.92(3)	C(7)-C(6)-C(5)	121.02(18)
C(14)-H(14C)	0.97(3)	C(7)-C(6)-H(6)	122.9(17)

C(5)-C(6)-H(6)	115.9(17)	O(2)-C(12)-C(11)	130.1(2)
C(6)-C(7)-C(8)	119.71(18)	O(1)-C(12)-C(11)	109.09(17)
C(6)-C(7)-H(7)	123.6(19)	C(11)-C(13)-H(13A)	110(2)
C(8)-C(7)-H(7)	116.6(19)	C(11)-C(13)-H(13B)	114(2)
C(9)-C(8)-C(7)	124.37(19)	H(13A)-C(13)-H(13B)	106(3)
C(9)-C(8)-Cl(1)	121.50(16)	C(11)-C(13)-H(13C)	111(2)
C(7)-C(8)-Cl(1)	114.11(14)	H(13A)-C(13)-H(13C)	112(3)
C(8)-C(9)-C(10)	115.27(17)	H(13B)-C(13)-H(13C)	104(3)
C(8)-C(9)-C(15)	124.60(19)	C(5)-C(14)-H(14A)	109.8(19)
C(10)-C(9)-C(15)	120.12(17)	C(5)-C(14)-H(14B)	113.4(19)
C(1)-C(10)-C(9)	124.93(17)	H(14A)-C(14)-H(14B)	106(2)
C(1)-C(10)-C(5)	117.84(17)	C(5)-C(14)-H(14C)	112.3(17)
C(9)-C(10)-C(5)	117.22(15)	H(14A)-C(14)-H(14C)	109(3)
C(13)-C(11)-C(12)	114.12(19)	H(14B)-C(14)-H(14C)	106(3)
C(13)-C(11)-C(2)	118.08(18)	C(9)-C(15)-H(15A)	112.5(18)
C(12)-C(11)-C(2)	101.52(17)	C(9)-C(15)-H(15B)	113.6(18)
C(13)-C(11)-H(11)	110.7(15)	H(15A)-C(15)-H(15B)	108(3)
C(12)-C(11)-H(11)	103.0(16)	C(9)-C(15)-H(15C)	108.0(19)
C(2)-C(11)-H(11)	108.0(15)	H(15A)-C(15)-H(15C)	110(2)
O(2)-C(12)-O(1)	120.8(2)	H(15B)-C(15)-H(15C)	105(3)

Anisotropic displacement parameters ($Å^2$x 10^3) for compound 2. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	29(1)	24(1)	35(1)	-1(1)	5(1)	6(1)
O(1)	23(1)	18(1)	35(1)	-3(1)	-4(1)	-3(1)
O(2)	37(1)	19(1)	54(1)	-3(1)	-2(1)	-7(1)
C(1)	21(1)	19(1)	22(1)	2(1)	-3(1)	-4(1)
C(2)	26(1)	18(1)	26(1)	-2(1)	1(1)	0(1)
C(3)	22(1)	22(1)	34(1)	-2(1)	3(1)	-1(1)
C(4)	21(1)	23(1)	32(1)	-1(1)	6(1)	-4(1)
C(5)	20(1)	19(1)	24(1)	-2(1)	1(1)	-3(1)
C(6)	28(1)	19(1)	31(1)	-2(1)	4(1)	-7(1)
C(7)	32(1)	16(1)	27(1)	1(1)	1(1)	-2(1)
C(8)	22(1)	23(1)	23(1)	-2(1)	-1(1)	2(1)
C(9)	21(1)	21(1)	19(1)	-2(1)	-2(1)	-2(1)
C(10)	20(1)	19(1)	18(1)	1(1)	-2(1)	-2(1)
C(11)	29(1)	19(1)	27(1)	0(1)	2(1)	-1(1)
C(12)	33(1)	17(1)	27(1)	-2(1)	-2(1)	-1(1)
C(13)	44(1)	19(1)	50(1)	-3(1)	12(1)	3(1)
C(14)	24(1)	31(1)	30(1)	-6(1)	-3(1)	-6(1)
C(15)	21(1)	25(1)	37(1)	0(1)	3(1)	-1(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound 2.

	x	y	z	U(eq)
H(2)	3000(30)	5640(20)	5123(16)	28
H(3A)	5600(40)	6020(30)	5659(16)	31
H(3B)	4940(40)	6160(30)	6569(17)	31
H(4A)	5400(40)	8240(30)	5912(16)	30
H(4B)	4180(40)	7860(20)	5206(17)	30
H(6)	3500(40)	10100(20)	5784(16)	31
H(7)	860(40)	10930(30)	5933(16)	30
H(11)	3040(30)	4330(20)	6675(16)	30
H(13A)	3270(50)	3210(30)	5080(20)	56
H(13B)	3420(50)	2450(30)	5870(20)	56
H(13C)	4810(50)	3350(30)	5650(20)	56
H(14A)	4450(40)	9070(30)	7291(19)	42
H(14B)	2770(40)	8850(30)	7605(19)	42
H(14C)	3900(40)	7720(30)	7523(18)	42
H(15A)	-1970(40)	6810(30)	6583(18)	41
H(15B)	-2320(40)	7870(30)	7223(18)	41
H(15C)	-1010(40)	6920(30)	7445(19)	41

Torsion angles [°] for compound 2

C(12)-O(1)-C(1)-C(10)	-160.56(18)	C(2)-C(1)-C(10)-C(9)	176.98(17)
C(12)-O(1)-C(1)-C(2)	18.8(2)	O(1)-C(1)-C(10)-C(5)	175.48(16)
C(10)-C(1)-C(2)-C(3)	19.3(3)	C(2)-C(1)-C(10)-C(5)	-3.8(3)
O(1)-C(1)-C(2)-C(3)	-160.09(16)	C(8)-C(9)-C(10)-C(1)	-151.62(18)
C(10)-C(1)-C(2)-C(11)	147.46(19)	C(15)-C(9)-C(10)-C(1)	28.1(3)
O(1)-C(1)-C(2)-C(11)	-31.89(19)	C(8)-C(9)-C(10)-C(5)	29.1(2)
C(1)-C(2)-C(3)-C(4)	-46.0(2)	C(15)-C(9)-C(10)-C(5)	-151.19(17)
C(11)-C(2)-C(3)-C(4)	-163.57(17)	C(6)-C(5)-C(10)-C(1)	138.96(17)
C(2)-C(3)-C(4)-C(5)	62.6(2)	C(4)-C(5)-C(10)-C(1)	17.2(2)
C(3)-C(4)-C(5)-C(6)	-169.22(17)	C(14)-C(5)-C(10)-C(1)	-105.00(19)
C(3)-C(4)-C(5)-C(10)	-47.6(2)	C(6)-C(5)-C(10)-C(9)	-41.7(2)
C(3)-C(4)-C(5)-C(14)	73.5(2)	C(4)-C(5)-C(10)-C(9)	-163.53(15)
C(10)-C(5)-C(6)-C(7)	28.8(2)	C(14)-C(5)-C(10)-C(9)	74.3(2)
C(4)-C(5)-C(6)-C(7)	151.93(19)	C(1)-C(2)-C(11)-C(13)	156.8(2)
C(14)-C(5)-C(6)-C(7)	-88.5(2)	C(3)-C(2)-C(11)-C(13)	-80.2(3)
C(5)-C(6)-C(7)-C(8)	-3.1(3)	C(1)-C(2)-C(11)-C(12)	31.28(19)
C(6)-C(7)-C(8)-C(9)	-13.5(3)	C(3)-C(2)-C(11)-C(12)	154.27(18)
C(6)-C(7)-C(8)-Cl(1)	168.29(15)	C(1)-O(1)-C(12)-O(2)	-177.1(2)
C(7)-C(8)-C(9)-C(10)	-0.4(3)	C(1)-O(1)-C(12)-C(11)	2.9(2)
Cl(1)-C(8)-C(9)-C(10)	177.74(13)	C(13)-C(11)-C(12)-O(2)	29.4(3)
C(7)-C(8)-C(9)-C(15)	179.94(18)	C(2)-C(11)-C(12)-O(2)	157.6(2)
Cl(1)-C(8)-C(9)-C(15)	-1.9(3)	C(13)-C(11)-C(12)-O(1)	-150.52(17)
O(1)-C(1)-C(10)-C(9)	-3.8(3)	C(2)-C(11)-C(12)-O(1)	-22.4(2)