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Resolution, absolute configuration and antifilarial activity of coumarinyl amino alcohols

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ABSTRACT

The resolution of racemic coumarinyl amino alcohols **5**–**10** was achieved by using the inexpensive and readily accessible chiral resolving agent *N*-carbethoxy-L-proline (*S*)-**11**. Direct esterification of *rac*-**5**–**10** with (*S*)-**11** furnished diastereomeric esters, which were easily separated by column chromatography. The obtained diastereomers yielded the desired enantiopure coumarinyl amino alcohols (*S*)-(+)-**5**–**10** and (*R*)-(−)-**5**–**10** in good yields with high enantiomeric excess on saponification. The absolute configurations were determined by X-ray crystal analysis and/or by comparison of the specific rotations. Furthermore, in in vitro antifilarial motility inhibition assays, enantiopure coumarins (*S*)-(+)-**9**, (*R*)-(−)-**9** and (*S*)-(+)-**10**, (*R*)-(−)-**10** were found to be less efficient in affecting the viability of macrofilariae of *Brugia malayi* than their racemic forms **9** and **10**, respectively, indicating the synergistic effect of the enantiomers in evoking antifilarial action.

1. Introduction

The wide use of enantiopure β-amino alcohols as chiral auxiliaries[1] and organocatalysts[2] in various synthetic transformations as well as reaction intermediates in the synthesis of variety of natural and synthetic medicines,[3] and unnatural amino acids has led to an upsurge in their synthetic demand. As a result, a number of synthetic methods have been developed for their synthesis including asymmetric reduction of α-amino carbonyl compounds[4] or α-hydroxy carbonyl compounds,[5] Sharpless asymmetric amino hydroxylation of olefins,[6] asymmetric hydroboration of enamines and enantioselective ring opening of epoxides.[7] The resolution of β-amino alcohols via formation of diastereomers is also one of the most efficient and widely used methods for the synthesis of optically active β-amino alcohols especially because of practical simplicity and low cost.[8] Enantiomerically pure tartaric acid,[9] *O*-acyl tartaric acid,[10] *O*-acyl mandelic acid,[11] chiral 1,1′-bi-2-naphthylphosphoric acid,[12] and boric acid and 1,1′-bi-2-naphthol[13] are some of the examples of resolving agents, which have been successfully employed for the resolution of amino alcohols. Over the past few decades, (*S*)-proline has also received considerable attention as a versatile resolving agent due to its low cost, low molecular weight, easy handling and easy availability. It has been successfully employed in the resolution of (±)-phenyl succinic acid,[14,15] 2,3-diphenylsuccinic acid,[16] 1,1′-binaphthols,[17] C_2-symmetric acyclic 1,3-diols[18] and 2,3-diphenyl butane-1,4-diol[19] and many others. However, to the best of our knowledge, its use in the resolution of vicinal amino alcohols has not been reported yet.

Herein we report our findings on the successful resolution of racemic coumarinyl amino alcohols **5**–**10** using (*S*)-proline ethyl ester (*S*)-**11** as a resolving agent. Furthermore, in our previous work we discovered that compounds **9** and **10** possess significant antifilarial activity against the micro- and macrofilariae of human filarial parasite, *Brugia malayi*.[20] It is well known that enantiomers generally show different pharmacokinetic and pharmacodynamic activities and sometimes it is seen that pharmaceutical activity generally resides predominantly with one isomer whereas the other enantiomer remains inactive or has some side effects.[21,22] Thus we also found it interesting to assess the antifilarial activity of individual enantiomers and report the results of in vitro antifilarial activities of these compounds. The in vitro antifilarial activities of *rac*-**5**–**7** are also reported for the first time herein.

2. Results and discussion

2.1. Chemistry

The racemic coumarinyl amino alcohols **5**–**10** were synthesized via regioselective nucleophilic opening of oxirane rings by selected

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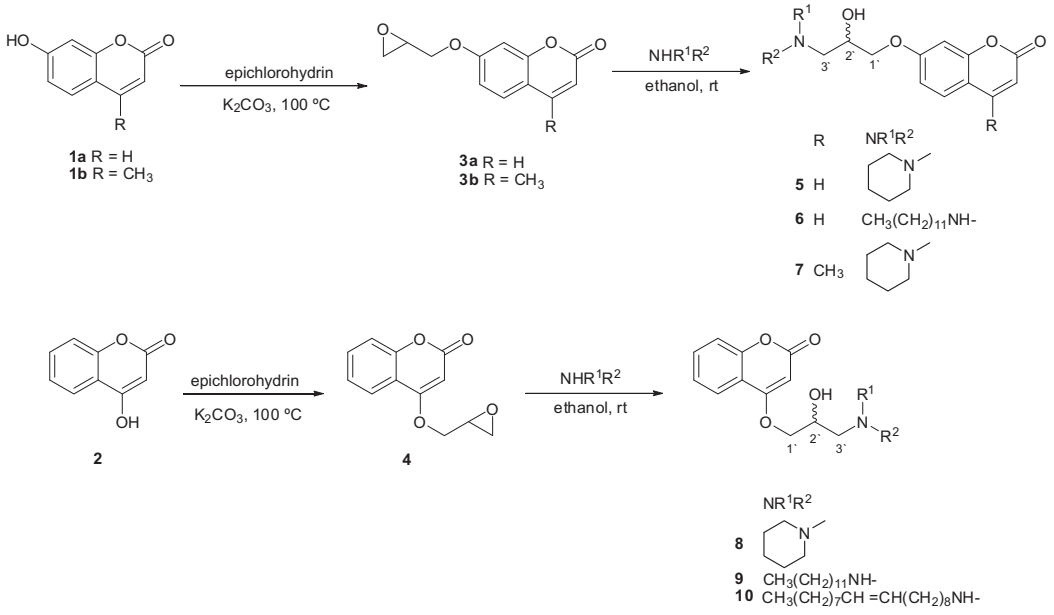
primary and secondary amines in the presence of K_2CO_3 (Scheme 1).[20,23] The structures of all these compounds were established on the basis of IR, ^1H and ^{13}C NMR and mass spectra data. Out of these compounds, only **5** and **6** were obtained as solids and only quality crystals of **5** could be obtained in acetone by slow evaporation of solvent for X-ray diffraction study. The crystallographic data of compound **5** are summarized in Table 1 and its X-ray structure is shown in Figure 1. The 2D packing structure of *rac*-**5**, as shown in Figure 2, establishes the existence of four intermolecular H-bonding interactions: (i) C(10)-H(10A)---O(4) with bond length of 2.31 Å (black), (ii) C(10)-H(10B)---O(2) with bond length of 2.57 Å (green), (iii) C(11)-H(11)---O(1) with bond length of 2.67 Å (red) and (iv) C(6)-H(6)---O(2) with bond length of 2.54 Å (blue).

With racemic compounds **5**–**10** in hand, we focused our attention on their resolution into their two enantiomeric constituents using commercially available (*S*)-proline as the resolving agent. (*S*)-Proline is insoluble in dichloromethane therefore we used its ethyl ester (*S*)-**11**, which was synthesized according to the literature.[18,24] Firstly, we attempted the resolution of compound **5**. The reaction of *rac*-**5** with (*S*)-**11** (1.25 equiv) in the presence of 1,3-dicyclohexylcarbodiimide (DCC, 1.25 equiv) and *N*,*N*′-dimethylaminopyridine (DMAP, 10 mol%) in dry dichloromethane at room temperature yielded a mixture of diastereomeric esters **12a** and **12b**. These diastereomers were easily separated by column chromatography using methanol-chloroform as eluent due to the marked difference in their R_f values. The less polar diastereomer **12a** (R_f 0.52; chloroform–methanol = 19:1), was eluted first followed by the elution of the more polar diastereomer **12b** (R_f 0.41; chloroform–methanol = 19:1) in 42% and 44% yield, respectively. After the separation, diastereomeric esters **12a** and **12b** were hydrolysed in the presence of methanolic KOH to afford enantiopure coumarinyl amino alcohols (*S*)-(+)-**5** and (*R*)-(−)-**5**, respectively, as colorless solids. The structures of these compounds were established on the basis of IR, ^1H and ^{13}C NMR, mass and 2D COSY spectra. It is worth mentioning that the spectroscopic spectra of both these enantiomers were found to be almost identical to that of their racemic form **5**. The enantiomeric excesses of the separated enantiomers (*S*)-(+)-**5** and (*R*)-(−)-**5** were determined to be 92% and 98.6% by HPLC with chiralpak AD-H column. The specific rotations of (*S*)-(+)-**5** and (*R*)-(−)-**5** were calculated as $[\alpha]_D^{25}$ = +10.6 (*c* 0.40, acetone) and $[\alpha]_D^{25}$ = −11.2 (*c* 0.40, acetone), respectively. Although we did not succeed in obtaining quality crystals of (*S*)-(+)-**5** for an X-ray diffraction study, crystals of (*R*)-(−)-**5** were obtained by recrystallization from acetone. The crystallographic data of (*R*)-(−)-**5** are summarized in Table 1 and its X-ray structure is shown in Figure 3. The absolute configuration of (*R*)-(−)-**5** was unambiguously determined by X-ray analysis as (*R*) using Flack parameter.[25] The absolute configuration of (*S*)-(+)-**5** was established to be (*S*) by comparison of the sign of its specific rotation to that of its opposite enantiomer (*R*)-(−)-**5**. The molecular packing structure of *R*-(−)-**5**, as depicted in Figure 4, is stabilized by three types of intermolecular H-bonding interactions: (i) C(10)-H(10A)---O(2) with bond length of 2.70 Å (green) and C(15)-H(15A)---O(2) with bond length of 2.71 Å (black), (ii) C(15)-H(15B)---O(1) with bond length of 2.64 Å (blue) and (iii) C(11)-H(11)---π interaction with bond length of 3.38 Å (red centroid).

Table 1
Crystallographic data collection and structural refinement information of *rac*-**5** and (*R*)-(−)-**5**

	rac-**5**	(*R*)-(−)-**5**
Formula empirical	$C_{17}H_{21}NO_4$	$C_{17}H_{21}NO_4$
Fw	303.35	303.35
Temp [K]	120	100(2)
λ [Å]	1.54184	1.54184
Crystal system	Monoclinic	Orthorhombic
Space group	P21/c	P212121
a [Å]	7.0002(3)	6.6770(2)
b [Å]	10.5240(4)	9.4799(2)
c [Å]	21.3883 (10)	23.9593
α [°]	90	90
β [°]	99.401(4)	90
γ [°]	90	90
V [Å^3]	1554.52 (12)	1516.56(7)
Z	4	4
Density [mg/m^3]	1.296	1.329
F(000)	648	648
Absolute structure parameter (Flack parameter)	—	0.01(3)



Scheme 1. Synthesis of racemic coumarinyl amino alcohols.

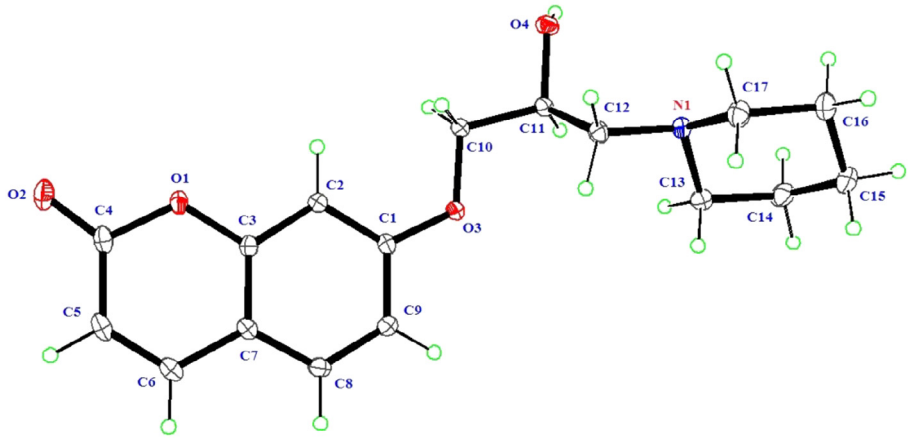


Figure 1. ORTEP plot of the X-ray structure of *rac*-**5** with 30% probability.

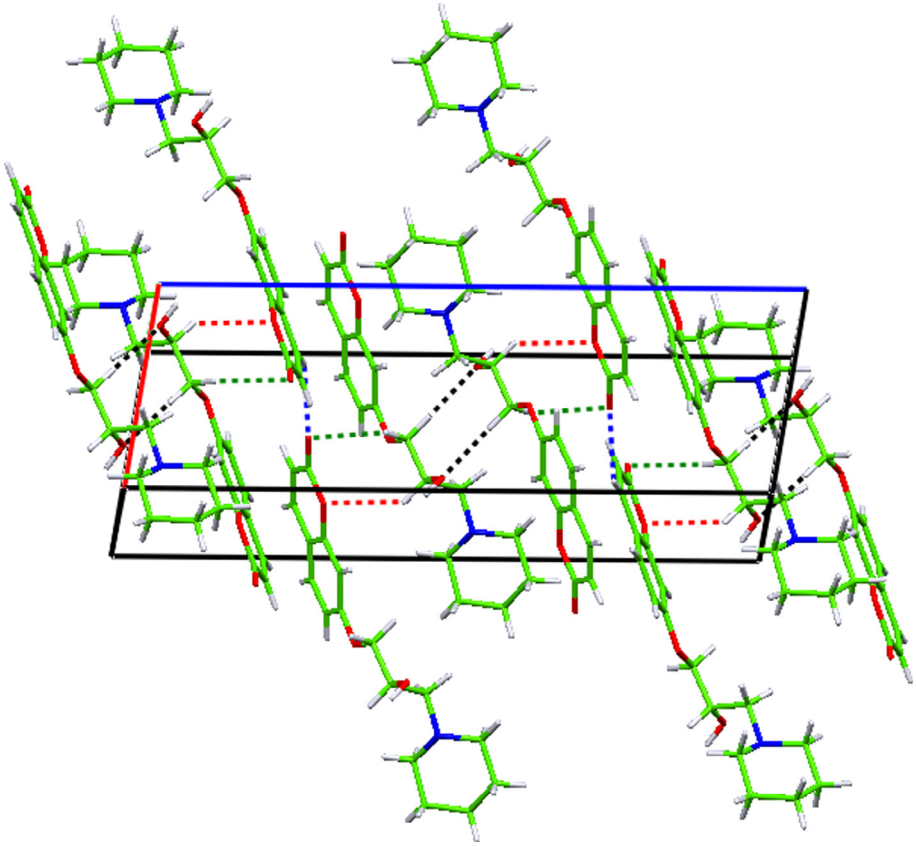


Figure 2. 2D packing diagram of *rac*-**5** viewed along b axis, showing Hydrogen-bonding interactions (dotted lines).

With the successful resolution of *rac*-**5**, we moved to the resolution of racemic compounds **6**–**10**. The esterification of compounds **6**–**10** with (*S*)-**11** as above in the presence of DCC and DMAP in dichloromethane at room temperature gave almost 1:1 diastereomeric mixtures of **13a**–**17a** and **13b**–**17b** with marked difference in their R_f values. These compounds were separated by column chromatography using methanol/chloroform as eluents as oils. Removal of the chiral auxiliary from diastereomers **13a**–**17a** and **13b**–**17b** on treatment with methanolic KOH gave optically active (+)-**6**–**10** and (−)-**6**–**10** coumarinyl amino alcohols, respectively, in good yields and with high enantiomeric purity (Schemes 2 and 3). The results are summarized in Table 2. Unfortunately, all of these enantiopure amino alcohols were obtained as colorless oil or as semi solid and therefore crystals of any of these compounds could not be obtained. The absolute configurations of these compounds were deduced by analogy with compounds (*S*)-(+)-**5** and (*R*)-(−)-**5.** The absolute configurations of coumarinyl amino alcohols (+)-**6**–**10**, which were obtained from less polar diastereomers **13a**–**17a** were assigned to be (*S*) while those of compounds (−)-**6**–**10** which were obtained from more polar diastereomeric esters **13b**–**17b** were assigned to be (*R*).

Next, in order to further corroborate the absolute configuration of the obtained products, we decided to synthesize enantiomerically pure (*S*)-**10** and (*R*)-**10** by an alternative route using

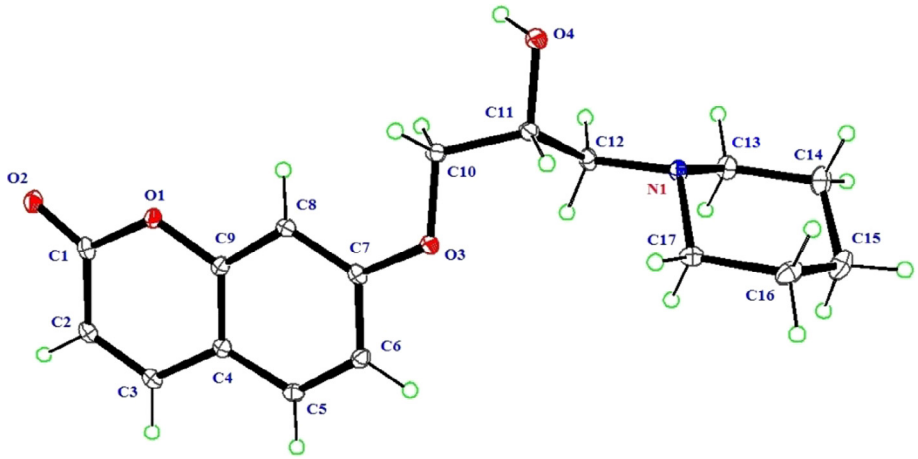


Figure 3. ORTEP plot of the X-ray structure of (*R*)-(−)-**5** with 30% probability.

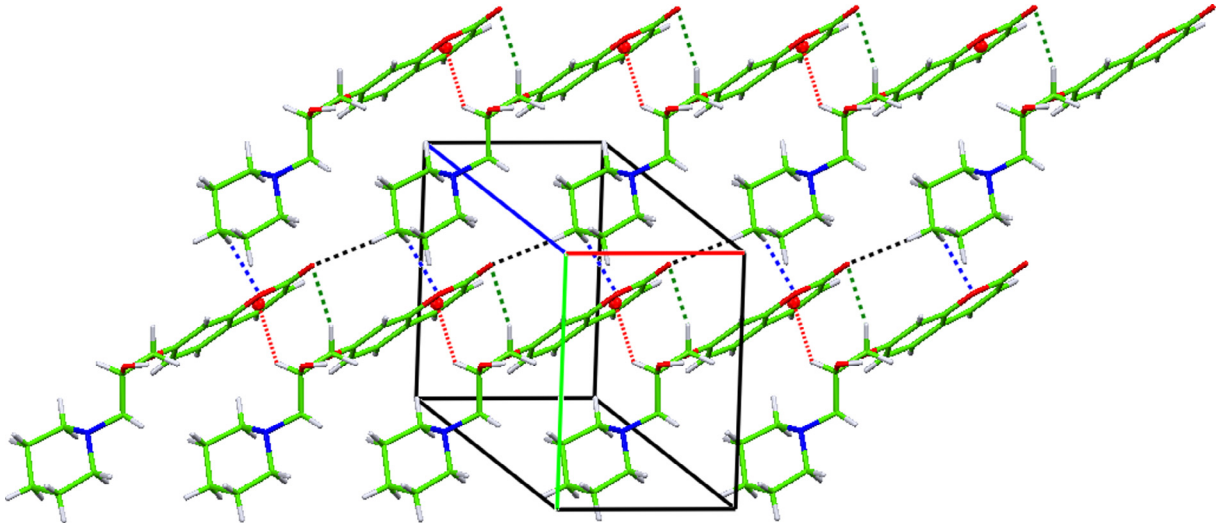
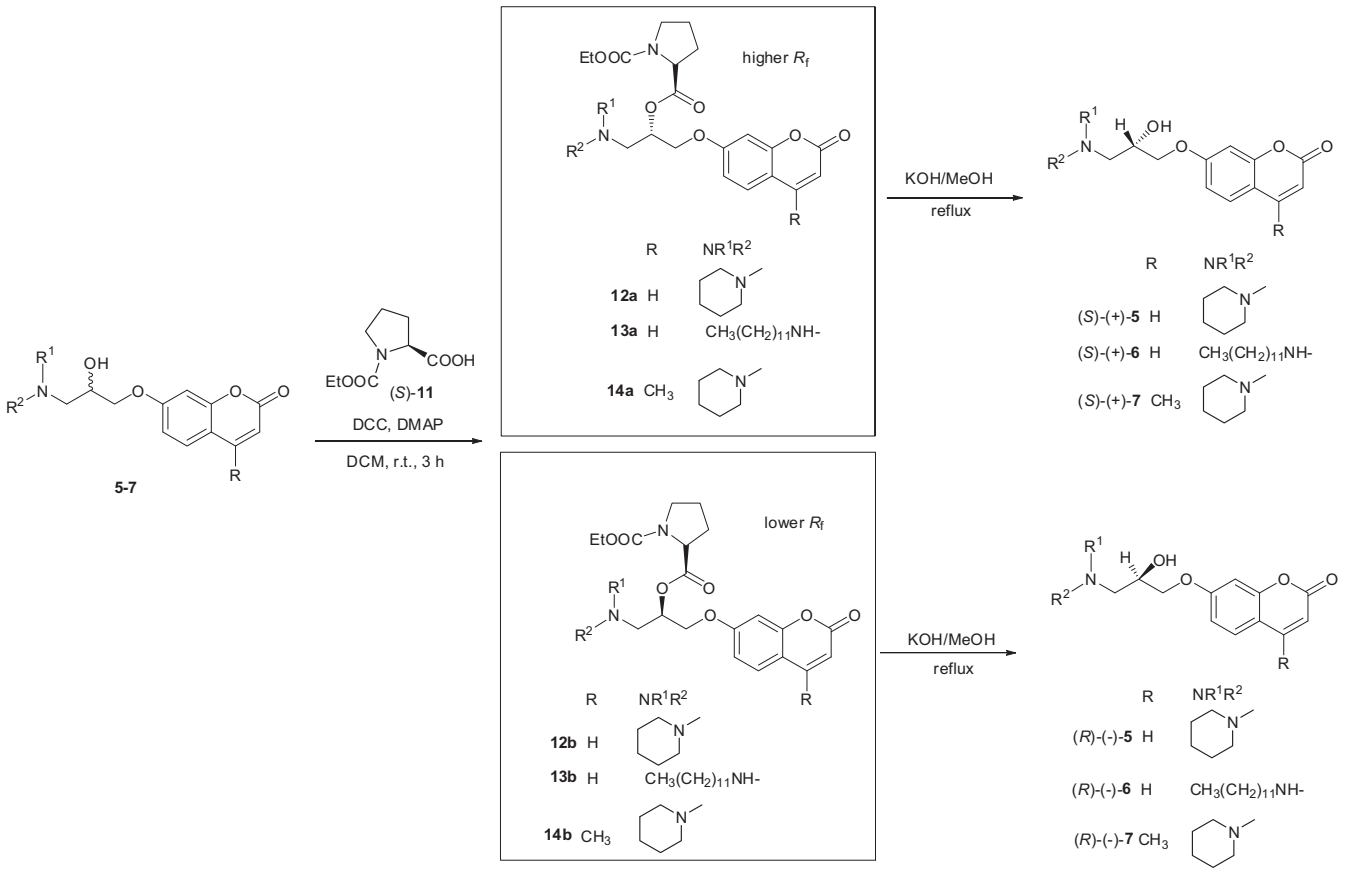


Figure 4. 2D packing diagram of (*R*)-(−)-**5** viewed along c axis, showing Hydogen-bonding and CH-π interactions (dotted lines).

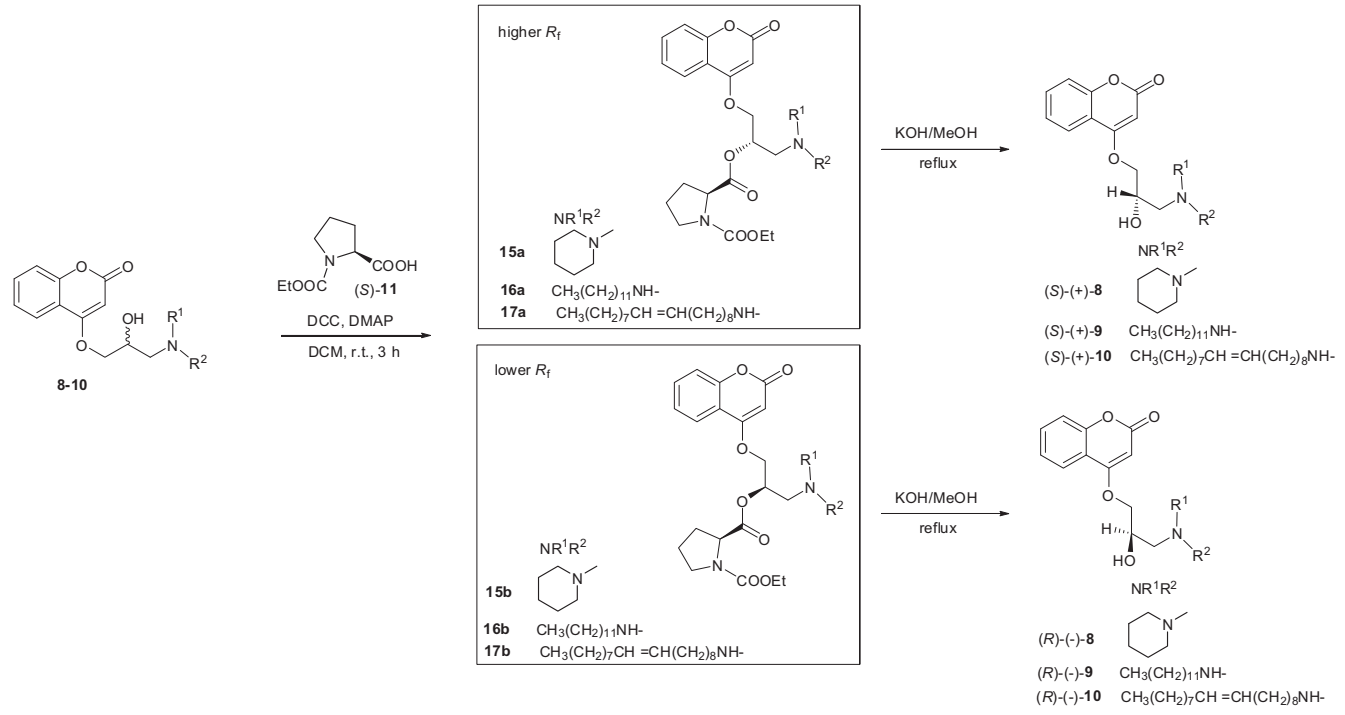
enantiopure epichlorohydrin (Scheme 4). Thus, 4-hydroxy-coumarin **2** upon reaction with enantiomerically pure (*R*)-(−)-epichlorohydrin in the presence of K_2CO_3 produced epoxide **18** with an (*S*)-stereochemistry $[\alpha]_D^{20}$ = +6.6 (*c* 0.50, acetone) while with enantiomerically pure (*S*)-(+)-epichlorohydrin gave epoxide **18** with an (*R*)-stereochemistry $[\alpha]_D^{20}$ = −6.3 (*c* 0.50, acetone). The absolute configurations of epoxides (*S*)-**18** and (*R*)-**18** were established on the basis of literature reports, which describe that the initial nucleophilic attack on chiral epichlorohydrin followed by extrusion of the leaving group under basic condition leads to an inversion of configuration of the product.[26,27] Epoxides (*S*)-**18** and (*R*)-**18**, when treated separately with oleyl amine produced enantiomerically pure (*S*)-**10** and (*R*)-**10** enantiomers, respectively. The specific rotations of these compounds, $[\alpha]_D^{20}$ = +5.3 (*c* 0.41, acetone) for (*S*)-**10** and $[\alpha]_D^{20}$ = −6.1 (*c* 0.42, acetone) for (*R*)-**10**, were found to be in good agreement with those of resolved products obtained earlier from *rac*-**10** (Table 2), our prior stereochemical assignments thus validating.

2.2. Antifilarial activity

In our previous work, we have reported the antifilarial activity of racemic 4-oxy coumarinyl amino alcohols.[20] The two compounds of this series *rac*-**9** and **10** demonstrated the best potency in vitro against both macro- and microfilariae of *B. malayi* in nanomolar range with high selectivity index. To examine the effect of stereogenic center at the 2′-position on the antifilarial activity profile of these compounds, we evaluated the in vitro antifilarial activity of (*S*)-(+)-**9** and **10** and (*R*)-(−)-**9** and **10** against the adult female worms of *B. malayi* using the motility assay according to the method of Nwaka et al.[28] using ivermectin as a standard antifilarial drug and diethylcarbamazine as a negative control, since it does not show any in vitro activity. Surprisingly, the results of the motility scores and the percent inhibition in MTT reduction by adult worms indicated the reduced activity of enantiopure compounds in comparison to their racemic forms (Table 3). While *rac*-**9** caused complete immobility of adult worms (100%) at very low concentration (1.25 μM), its enantiomeric components (*S*)-(+)-**9** and (*R*)-(−)-**9** showed only 75% and 70% inhibition in motility of adult worms, respectively, at a significantly higher concentration of 10 μM. Similarly, *rac*-**10** killed the adult worms at 0.312 μM while its enantiopure forms (*S*)-(+)-**10** and (*R*)-(−)-**10** required several times higher concentration (10 μM) to cause 80% and 75% inhibition in motility, respectively. The enantiomerically pure compounds also exerted lower inhibition in the MTT reduction potential of adult parasites



Scheme 2. Resolution of *rac*-**5**–**7** coumarinyl amino alcohols using (*S*)-**11.**

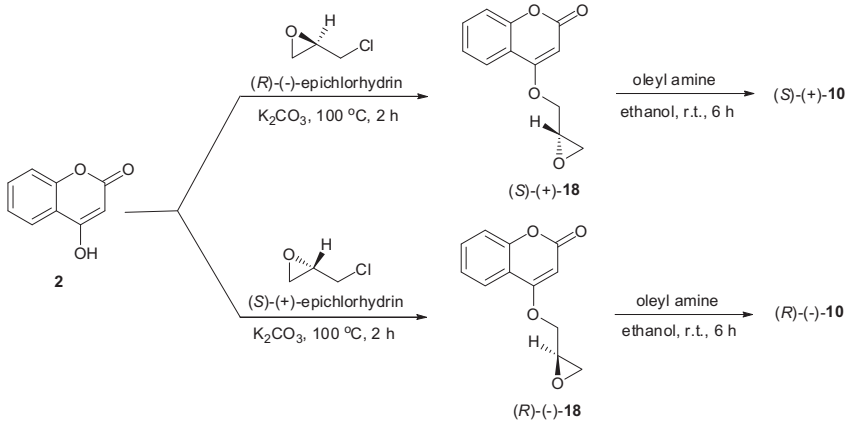


Scheme 3. Resolution of *rac*-**8**–**10** coumarinyl amino alcohols using (*S*)-**11.**

Table 2
Resolution of racemates **5**–**10**

Racemic Compds	Enantiomers	Yield (%)	ee (%)[a]	$[\alpha]_D$[b]
5	(*S*)-(+)-**5**	41	92.0	+10.6
	(*R*)-(−)-**5**	42	98.6	−11.2
6	(*S*)-(+)-**6**	35	n.d.	+8.7
	(*R*)-(−)-**6**	41	n.d.	−9.4
7	(*S*)-(+)-**7**	41	93.4	+9.6
	(*R*)-(−)-7	40	92.6	−8.9
8	(*S*)-(+)-**8**	43	96.4	+9.0
	(*R*)-(−)-**8**	44	95.2	−8.6
9	(*S*)-(+)-**9**	45	n.d.	+5.0
	(*R*)-(−)-**9**	43	n.d.	−4.7
10	(*S*)-(+)-**10**	44	92.4	+4.9
	(*R*)-(−)-**10**	42	91.8	−5.6

n.d. = not determined due to lack of compounds.
[a] Enantiomeric excesses were determined by HPCL with Chiralpak AD-H column.
[b] All specific rotation were measured in acetone at room temperature.



Scheme 4. Synthesis of enantiomerically pure (*S*)-**10** and (*R*)-**10.**

Table 3
In vitro motility scoring and MTT assay result of the compounds **5**–**7**, **9** and **10** and reference drug against adult worms of *B. malayi*.

Compound	Conc. (μM)	% Inhibition in *B. malayi* female adult worm motility	Motility score[a]	% Inhibition in MTT reduction
rac-**5**	20	95	1+	47.2
	10	90	1+	49.7
rac-**6**	20	90	1+	46.8
	10	85	1+	43.8
rac-**7**	20	75	1+	38.9
	10	70	2+	45.3
rac-**9**[b]	1.25	100	D	99.5
rac-**10**[b]	0.312	100	D	90.4
(*S*)-(+)-**9**	20	80	1+	38.9
	10	75	1+	45.3
(*S*)-(+)-**10**	20	90	1+	42.4
	10	80	1+	38.2
(*R*)-(−)-**9**	20	85	1+	46.2
	10	70	2+	42.3
(*R*)-(−)-**10**	20	85	1+	47.6
	10	75	1+	37.8
Ivermectin	8.9	100	D	61.2
Control 1	—	—	4+	—

[a] Motility scores: 4+ = 0%; 3+ = 1–49%; 2+ = 50–74%; 1+ = 75–99%; D = 100%.
[b] Data from Ref. 20.

[(*S*)-**9**,(*R*)-**9**:45.3%,42.3% and (*S*)-**10**,(*R*)-**10**:38.2%,37.8%] compared to their respective racemic forms (*rac*-**9**: 99.5% and *rac*-**10**: 90.4%). Thus, the antifilarial action of *rac*-**9** and **10** could be attributed to the combined effect of both enantiomers and it seems that on resolution the antifilarial properties are distributed between the two enantiomers resulting into much inferior activity compared to the racemates. Racemic compounds **5**–**7**, which were investigated for their antifilarial properties for the first time, caused 90%, 85% and 70% motility inhibition, respectively, leading to permanent paralysis in the adult parasites and inhibited MTT reduction potential of parasites in the range of 38.9–49.7%.

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3. Conclusion

In conclusion, we have developed a practical and efficient method for the resolution of *rac*-coumarinyl amino alcohols using (*S*)-proline ethyl ester as a chiral auxiliary. Enantiomers obtained after the resolution of their respective *rac*-aminoalcohols were characterized by IR, ^{1}H and ^{13}C NMR spectroscopy. The X-ray structure of the resolved enantiomer (−)-**5** confirmed the (*R*) stereochemistry of the compound. The results of the antifilarial motility assay indicate that the synergistic effects of both enantiomers are required to produce significant antifilarial action. This protocol could be extended to the resolution of other chemically and medicinally important amino alcohol derivatives. The studies related with the use of enantiopure coumarinyl amino alcohols as chiral auxiliaries as well as ligands for certain enantioselective reactions are currently under progress.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on JEOL 300 and at 500 MHz spectrometer with TMS as the internal standard. Chemical shifts are expressed in parts per million (ppm). The proton signals for residual non-deuterated solvents (δ 7.26 for $CDCl_3$) and carbon signals (δ 77.1 for $CDCl_3$) were used as an internal reference for ^{1}H and ^{13}C NMR spectra, respectively. Coupling constants are reported in Hertz. IR spectra were recorded on a JASCO FTIR 5300 in KBr from 400–4000 cm^{-1}. Analytical thin layer chromatography (TLC) was performed on Silica gel 60 F_{254} aluminium sheets precoated with a 0.25 mm thickness of silica gel. Melting points were determined on Buchi 510 apparatus by an open capillary method and are uncorrected. Enantiomeric excess (ee%) was determined on chiral HPLC system using Daicel Chiralpak AD-H column (*n*-hexane/isopropanol = 9:1; flow rate 1.0 mL min^{-1}) and UV detector working at 220 nm. Optical rotations were measured on Perkin–Elmer 241 polarimeter at 25 °C using sodium D light. All the materials were obtained from commercial suppliers (SRL, and Spectrochem Pvt. Ltd) and were used without further purification. Silica gel (60–120 mesh and 200–400 mesh) from commercial supplier Spectrochem Pvt. Ltd was used for column chromatography. ESI mass spectra were recorded using Quattro II (Micromass).

4.2. Preparation of the diastereomeric esters 12a–17a and 12b–17b

N-Carbethoxy-L-proline (*S*)-**11** (1.25 mmol) was dissolved in anhydrous dichloromethane (2 mL), then a solution of DCC (1.25 mmol) in anhydrous dichloromethane (2 mL) was added and the reaction mixture was stirred at room temperature for 1 h. To this reaction mixture, a solution of appropriate coumarinyl amino alcohol (1 mmol) in anhydrous dichloromethane (2 mL) and DMAP (10 mol %) was added. The progress of the reaction was monitored by TLC. After 2 h, the reaction mixture was diluted with CH_2Cl_2 and the solid that formed was filtered. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel (200–400 mesh) column chromatography using 1% MeOH in $CHCl_3$ as eluent to yield two diastereomeric products as viscous liquid.

4.2.1. (*S*)-1-Ethyl-2-[(*S*)-1-(2-oxo-2*H*-chromen-7-yl)oxy-3-(piperidin-1-yl)propan-2-yl]pyrrolidine-1,2-dicarboxylate 12a

Colorless oily liquid (42%); $[\alpha]_D^{20}$ = −9.3 (*c* 0.48, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 9.5 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 6.86 (m, 2H), 6.26 (d, *J* = 9.5 Hz, 1H), 5.38 (m, 1H), 4.25 (m, 2H), 4.15 (m, 3H), 3.49 (m, 2H), 2.55 (m, 2H), 2.44 (m, 4H), 2.25 (m, 2H), 2.0 (m, 2H), 1.53 (m, 4H), 1.41 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 161.8, 160.1, 155.7, 154.6, 143.4, 128.9, 113.5, 113.3, 112.9, 101.7, 70.0, 69.7, 68.6, 61.4, 59.2, 55.2, 46.8, 31.0, 26.1, 24.3, 23.4, 14.8; FT-IR (KBr) ν_{max}, cm^{-1}: 3417, 2931, 2874, 1729, 1690, 1614, 1508, 1232, 839. ESI-MS (*m*/*z*): 473 (M+H)$^+$.

4.2.2. (*S*)-2-[(*S*)-1-(Dodecylamino-3-(2-oxo-2*H*-chromen-7-yl)oxy-propan-2-yl]-1-ethyl pyrrolidine-1,2-dicarboxylate 13a

Colorless oily liquid (41%); $[\alpha]_D^{20}$ = −7.5 (*c* 0.56, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 9.5 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 6.85 (m, 2H), 6.26 (d, *J* = 9.5 Hz, 1H), 4.6 (m, 1H), 4.13 (m, 5H), 3.51 (m, 6H), 2.16 (m, 2H), 1.91 (m, 2H), 1.66 (m, 2H), 1.27 (m, 13H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 161.9, 161.1, 155.9, 154.5, 143.4, 129.0, 113.6, 113.4, 112.8, 101.9, 70.2, 69.8, 68.7, 61.5, 56.6, 52.0, 46.9, 31.9, 30.3, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 27.0, 26.9, 24.7, 22.7, 14.8, 14.2; FT-IR (KBr) ν_{max}, cm^{-1}:3429, 2925, 2855, 1728, 1712, 1614, 1508, 1232, 1119, 835. ESI-MS (*m*/*z*): 573 (M+H)$^+$.

4.2.3. (*S*)-1-Ethyl-2-[(*S*)-1-(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy-3-(piperidin-1-yl)propan-2-yl]pyrrolidine-1,2-dicarboxylate 14a

Colorless oily liquid (39%); $[\alpha]_D^{20}$ = −11.9 (*c* 0.34, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.5 Hz, 1H), 6.78 (m, 2H), 6.07 (s, 1H), 4.45 (m, 1H), 4.06 (m, 5H), 3.65 (m, 2H), 3.44 (m, 2H), 2.55 (m, 4H), 2.38 (s, 3H), 2.05 (m, 2H), 1.92 (m, 2H), 1.63 (m, 4H), 1.35 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 161.7, 161.2, 155.7, 154.0, 152.5, 113.8, 112.5, 112.2, 111.9, 101.9, 70.2, 68.5, 68.4, 61.3, 58.3, 55.2, 47.2, 31.7, 26.1, 25.3, 24.6, 18.7, 14.7; FT-IR (KBr) ν_{max}, cm^{-1}: 3425, 2926, 2854, 1730, 1704, 1625, 1567. ESI-MS (*m*/*z*): 487 (M+H)$^+$.

4.2.4. (*S*)-1-Ethyl-2-[(*R*)-1-(2-oxo-2*H*-chromen-7-yl-oxy)-3-(piperidin-1-yl)propan-2-yl]pyrrolidine-1,2-dicarboxylate 12b

Colorless oily liquid (44%); $[\alpha]_D^{20}$ = +8.7 (*c* 0.48, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 9.5 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 6.85 (m, 2H), 6.26 (d, *J* = 9.5 Hz, 1H), 5.38 (m, 1H), 4.25 (m, 2H), 4.15 (m, 3H), 3.51 (m, 2H), 2.56 (m, 2H), 2.47 (m, 4H), 2.24 (m, 2H), 2.04 (m, 2H), 1.53 (m, 4H), 1.42 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 161.8, 161.1, 155.9, 155.1, 143.3, 128.9, 113.5, 113.3, 112.9, 101.7, 70.0, 69.7, 68.6, 61.4, 59.2, 55.2, 55.1, 46.8, 31.0, 26.1, 24.3, 23.4, 14.8; FT-IR (KBr) ν_{max}, cm^{-1}: 3417, 2931, 2874, 1729, 1690, 1614, 1508, 1232, 1124, 839. ESI-MS (*m*/*z*): 473 (M+H)$^+$.

4.2.5. (*S*)-2-[(*R*)-1-Dodecylamino-3-(2-oxo-2*H*-chromen-7-yl-oxy)propan-2-yl]-1-ethyl pyrrolidine-1,2-dicarboxylate 13b

Colorless oily liquid (44%); $[\alpha]_D^{20}$ = +8.2 (*c* 0.52, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 9.5 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 6.86 (m, 2H), 6.26 (d, *J* = 9.5 Hz, 1H), 4.61 (m, 1H), 4.14 (m, 5H), 3.55 (m, 6H), 2.14 (m, 2H), 1.91 (m, 2H), 1.64 (m, 2H), 1.25 (m, 13H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.3, 161.7, 161.1, 155.3, 154.5, 143.3, 129.0, 113.6, 113.4, 112.9, 101.8, 70.0, 69.8, 68.7, 61.5, 56.6, 52.1, 46.8, 31.9, 30.4, 29.7, 29.6, 29.4, 29.3, 29.2, 26.9, 26.8, 24.8, 22.7, 22.7, 14.8, 14.2; FT-IR (KBr) ν_{max}, cm^{-1}: 3429, 2925, 2855, 1728, 1712, 1614, 1508, 1232, 1119, 835. ESI-MS (*m*/*z*): 573 (M+H)$^+$.

4.2.6. (*S*)-1-Ethyl-2-[(*R*)-1-(4-methyl-2-oxo-2*H*-chromen-7-yl-oxy)-3-(piperidin-1-yl)propan-2-yl]pyrrolidine-1,2-dicarboxylate 14b

Colorless oily liquid (44%); $[\alpha]_D^{20}$ = +11.8 (*c* 0.34, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.5 Hz, 1H), 6.76 (m, 2H), 6.07 (s, 1H), 4.45 (m, 1H), 4.06 (m, 5H), 3.65 (m, 2H), 3.44 (m, 2H), 2.55 (m, 4H), 2.38 (s, 3H), 2.07 (m, 2H), 1.90 (m, 2H), 1.63

(m, 4H), 1.35 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 161.6, 161.3, 155.8, 154.1, 152.5, 113.9, 112.5, 112.3, 111.9, 101.8, 70.3, 68.5, 68.3, 61.4, 58.2, 55.2, 55.1, 46.9, 31.1, 26.2, 25.3, 24.6, 18.7, 14.7; FT-IR (KBr) ν_{max}, cm^{-1}: 3431, 2926, 2854, 1730, 1626, 1568. ESI-MS (m/z): 487 (M+H)$^+$.

4.2.7. (*S*)-1-Ethyl-2-[(*S*)-1-(2-oxo-2*H*-chromen-4-yl-oxy)-3-(piperidin-1-yl)propan-2-yl]pyrrolidine-1,2-dicarboxylate 15a

Colorless oily liquid (40%); $[\alpha]_D^{20}$ = −9.5 (c 0.48, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, 1H, J = 7.5 Hz, 1H), 7.55 (m, 1H), 7.31 (m, 2H), 5.73 (s, 1H), 5.48 (m, 1H), 4.28 (m, 3H), 4.06 (m, 1H), 3.50 (m, 2H), 2.58 (m, 6H), 1.92 (m, 2H), 1.56 (m, 2H), 1.42 (m, 6H), 1.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 165.2, 161.8, 155.0, 153.3, 132.5, 123.9, 122.9, 116.8, 115.0, 90.7, 69.6, 69.3, 68.4, 61.3, 58.8, 55.2, 46.7, 31.0, 26.0, 24.2, 23.3, 14.6; FT-IR (KBr) ν_{max}, cm^{-1}: 3423, 2928, 1729, 1705, 1624, 1382, 1240. ESI-MS (m/z): 473 (M+H)$^+$.

4.2.8. (*S*)-2-[(*S*)-1-Dodecylamino-3-(2-oxo-2*H*-chromen-4-yl-oxy)propan-2-yl]-1-ethyl pyrrolidine-1,2-dicarboxylate 16a

Colorless oily liquid (40%); $[\alpha]_D^{20}$ = −9.0 (c 0.48, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, J = 7.5 Hz, 1H), 7.54 (m, 1H), 7.24 (m, 2H), 5.71 (s, 1H), 4.54 (m, 1H), 4.32 (m, 2H), 4.14 (m, 3H), 3.50 (m, 6H), 2.19 (m, 2H), 1.89 (m, 2H), 1.61 (m, 2H), 1.25 (m, 21H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 165.1, 161.4, 155.1, 153.3, 132.3, 123.9, 122.9, 116.8, 116.5, 90.9, 71.1, 70.4, 68.8, 61.4, 56.3, 48.9, 46.8, 31.9, 31.0, 30.3, 29.9, 29.7, 29.6, 29.4, 29.3, 26.8, 24.8, 22.7, 22.6, 14.7, 14.1; FT-IR (KBr) ν_{max}, cm^{-1}: 3432, 2926, 1727, 1705, 1625, 1241; ESI MS (m/z): 573 (M+H)$^+$.

4.2.9. (*S*)-1-Ethyl-2-[(*S*)-1-(octadec-9-en-1-ylamino)-3-(2-oxo-2*H*-chromen-4-yl-oxy)propan-2-yl] pyrrolidine-1,2-dicarboxylate 17a

Light yellow oily liquid (39%); $[\alpha]_D^{20}$ = −10.5 (c 0.4, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 7.2 Hz, 1H), 7.51 (m, 1H), 7.26 (m, 2H), 5.67 (s, 1H), 5.34 (m, 2H), 4.59 (m, 1H), 4.32 (m, 2H), 4.12 (m, 3H), 3.53 (m, 6H), 2.12 (m, 2H), 1.94 (m, 6H), 1.62 (m, 2H), 1.28 (m, 27H), 0.86 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 164.4, 161.2, 155.2, 153.4, 132.9, 130.0, 129.7, 124.7, 122.9, 117.5, 116.4, 91.1, 71.3, 70.1, 68.7, 61.3, 56.4, 49.9, 46.8, 31.9, 32.6, 30.3, 29.9, 29.8, 29.7, 29.6, 29.4, 29.3, 27.2, 26.9, 22.7, 22.7, 14.7, 14.1; FT-IR (KBr) ν_{max}, cm^{-1}: 3421, 2925, 2854, 1730, 1704, 1625, 1567, 1241, 1122, 770. ESI MS (m/z): 655 (M+H)$^+$.

4.2.10. (*S*)-1-Ethyl-2-[(*R*)-1-(2-oxo-2*H*-chromen-4-yl-oxy)-3-(piperidin-1-yl)propan-2-yl]pyrrolidine-1,2-dicarboxylate 15b

Colorless oily liquid (40%); $[\alpha]_D^{20}$ = +8.8 (c 0.48, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, 1H, J = 7.5 Hz, 1H), 7.55 (m, 1H), 7.31 (m, 2H), 5.73 (s,1H), 5.50 (m, 1H), 4.30 (m, 3H), 4.10 (m, 1H), 3.50 (m, 2H), 2.61 (m, 6H), 1.92 (m, 4H), 1.56 (m, 2H), 1.42 (m, 4H), 1.23 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 165.3, 162.0, 155.5, 153.4, 132.6, 124.0, 122.9, 116.8, 115.0, 90.8, 71.2, 69.6, 69.0, 61.4, 58.8, 55.3, 55.2, 46.7, 31.0, 26.0, 25.9, 24.3, 23.4, 14.7; FT-IR (KBr) ν_{max}, cm^{-1}: 3425, 2926, 1730, 1704, 1625, 1381, 1241. ESI-MS (m/z): 473 (M+H)$^+$.

4.2.11. (*S*)-2-[(*R*)-1-Dodecylamino-3-(2-oxo-2*H*-chromen-4-yl-oxy)propan-2-yl]1-ethyl pyrrolidine-1,2-dicarboxylate 16b

Colorless oily liquid (40%); $[\alpha]_D^{20}$ = +8.2 (c 0.52, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, J = 7.5 Hz, 1H), 7.54 (m, 1H), 7.27 (m, 2H), 5.75 (s, 1H), 4.54 (m, 1H), 4.29 (m, 2H), 4.14 (m, 3H), 3.48 (m, 6H), 2.17 (m, 2H), 1.93 (m, 2H), 1.54 (m, 2H), 1.25 (m, 13H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 165.1, 162.6, 155.2, 153.2, 132.5, 123.8, 122.8, 116.7, 115.4, 90.9, 70.7, 69.2, 68.1, 61.2, 56.4, 49.9, 46.7, 31.8, 30.2, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 26.8, 26.6, 22.6, 22.6, 14.6, 14.0; FT-IR (KBr) ν_{max}, cm^{-1}: 3432, 2926, 1727, 1705, 1625, 1241; ESI MS (m/z): 573 (M+H)$^+$.

4.2.12. (*S*)-1-Ethyl-2-[(*R*)-1-(octadec-9-en-1-ylamino)-3-(2-oxo-2*H*-chromen-4-yl-oxy)propan-2-yl]pyrrolidine-1,2-dicarboxylate 17b

Light yellow oily liquid (38%); $[\alpha]_D^{20}$ = +10.75 (c 0.4, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 7.2 Hz, 1H), 7.52 (m, 1H), 7.25 (m, 2H), 5.66 (s, 1H), 5.34 (m, 2H), 4.54 (m, 1H), 4.31 (m, 2H), 4.13 (m, 3H), 3.53 (m, 6H), 2.14 (m, 2H), 1.94 (m, 6H), 1.61 (m, 2H), 1.28 (m, 27H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 164.8, 161.1, 155.4, 153.4, 132.9, 130.0, 124.8, 122.9, 117.1, 116.6, 91.1, 71.4, 69.8, 68.9, 61.4, 56.4, 49.9, 46.8, 31.8, 32.7, 30.3, 29.9, 29.8, 29.7, 29.6, 29.4, 29.3, 27.2, 26.8, 24.4, 22.7, 14.7, 14.1; FT-IR (KBr) ν_{max}, cm^{-1}: 3422, 2925, 1730, 1704, 1625, 1241; ESI MS (m/z): 655 (M+H)$^+$.

4.3. General method for the hydrolysis of diastereomeric esters

The diastereomeric esters (0.5 mmol) were heated at reflux with 1 M KOH in methanol (10 mL) for 1 h. Excess solvent was removed under vacuum, after which water (10 mL) was added and the reaction mixture was extracted with chloroform. The extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (SiO_2) using 3% methanol in chloroform as eluent to afford the desired enantiopure compounds.

4.3.1. (*S*)-7-[2-Hydroxy-3-(piperidin-1-yl)propoxy]-2*H*-chromen-2-one (*S*)-(+)-5

(*S*)-(+)-**5** was prepared according to the above procedure starting from **12a** as off white solid. Mp.: 61–62 °C; $[\alpha]_D^{25}$ = +10.6 (c 0.40, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, J = 9.2 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 6.88 (dd, J = 8.6 and 2.3 Hz, 1H), 6.83 (s, 1H), 6.24 (d, J = 9.7 Hz, 1H), 4.10 (m, 1H), 4.01 (m, 2H), 2.64 (m, 2H), 2.49 (m, 2H), 2.40 (m, 2H), 1.60 (m, 4H), 1.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.1, 161.2, 155.8, 143.4, 128.8, 113.3, 113.0, 112.8, 101.7, 71.0, 65.1, 60.9, 54.8, 26.0, 24.2; FT-IR (KBr) ν_{max}, cm^{-1}: 3164, 2927, 1723, 1607, 1555, 1282. ESI-MS (m/z): 304 (M+H)$^+$.

4.3.2. (*S*)-7-(3-Dodecylamino-2-hydroxypropoxy)-2*H*-chromen-2-one (*S*)-(+)-6

(*S*)-(+)-**6** was prepared according to the above procedure starting from **13a** as off white semi solid. $[\alpha]_D^{20}$ = +8.7 (c 0.30, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 9.5 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 6.86 (dd, J = 8.5 and 3.0 Hz, 1H), 6.82 (s, 1H), 6.24 (d, J = 9.5 Hz, 1H), 4.13 (m, 1H), 4.03 (m, 2H), 3.15 (br s, 1H), 2.86 (m, 2H), 2.70 (m, 2H), 1.53 (m, 2H), 1.27 (m, 18H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.8, 161.1, 155.7, 143.3, 128.7, 113.2, 112.8, 112.7, 101.6, 70.8, 67.4, 51.3, 49.6, 31.8, 29.7, 29.6, 29.4, 29.3, 27.1, 22.6, 14.0. IR (cm^{-1}, KBr) ν_{max}: 3060, 2922, 1725, 1618, 1239; ESI-MS (m/z): 404 (M+H)$^+$.

4.3.3. (*S*)-7-[2-Hydroxy-3-(piperidin-1-yl)propoxy]-4-methyl-2*H*-chromen-2-one (*S*)-(+)-7

(*S*)-(+)-**7** was prepared according to the above procedure starting from **14a** as light yellow semi solid. $[\alpha]_D^{25}$ = +9.6 (c 0.28, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 8.6 Hz, 1H), 6.88 (dd, J = 8.6 and 2.3 Hz, 1H), 6.81 (d, J = 2.3 Hz, 1H), 6.11 (s, 1H), 4.11 (m, 1H), 4.01 (m, 2H), 2.63 (m, 2H), 2.90 (br s, 1H), 2.49 (m, 7H), 1.60 (m, 4H), 1.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8, 161.3, 155.2, 152.6, 125.6, 113.8, 112.6, 112.1, 101.7, 70.9, 65.1, 60.9, 54.7, 25.9, 24.1, 18.7; FT-IR (KBr) ν_{max}, cm^{-1}: 3424, 2933, 1723, 1614, 1266. ESI-MS (m/z): 318 (M+H)$^+$.

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4.3.4. (*R*)-7-[2-Hydroxy-3-(piperidin-1-yl)propoxy]-2*H*-chromen-2-one (*R*)-(−)-5

(*R*)-(−)-**5** was prepared according to the above procedure starting from **12b** as off white solid. Mp.: 62–63 °C; $[\alpha]_D^{25}$ = −11.2 (*c* 0.40, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 9.7 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 8.6 and 2.3 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.24 (d, *J* = 9.2 Hz, 1H), 4.11 (m, 1H), 4.01 (m, 2H), 3.20 (br s, 1H), 2.62 (m, 2H), 2.48 (m, 2H), 2.38 (m, 2H), 1.60 (m, 4H), 1.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.1, 161.2, 155.8, 143.4, 128.8, 113.3, 113.0, 112.8, 101.7, 71.0, 65.1, 60.8, 54.7, 26.0, 24.2; FT-IR (KBr) ν_{max}, cm^{-1}: 3166, 2928, 1726, 1608, 1230. ESI-MS (*m*/*z*): 304 (M+H)$^+$.

4.3.5. (*R*)-7-(3-Dodecylamino-2-hydroxypropoxy)-2*H*-chromen-2-one (*R*)-(−)-6

(*R*)-(−)-**6** was prepared according to the above procedure starting from **13b** as off white semi solid. $[\alpha]_D^{20}$ = −9.4 (*c* 0.30, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 9.5 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 6.85 (dd, *J* = 8.5 and 2.0 Hz, 1H), 6.81 (s, 1H), 6.24 (d, *J* = 9.5 Hz, 1H), 4.13 (m, 1H), 4.02 (m, 2H), 3.15 (br s, 1H), 2.86 (m, 2H), 2.69 (m, 2H), 1.53 (m, 2H), 1.26 (m, 18H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.9, 161.2, 155.8, 143.4, 128.8, 113.3, 112.9, 112.8, 101.7, 71.0, 67.5, 51.4, 49.7, 32.0, 29.8, 29.7, 29.5, 29.4, 27.2, 22.7, 14.2. IR (cm^{-1}, KBr) ν_{max}: 3059, 2921, 1725, 1618, 1239; ESI-MS (*m*/*z*): 404 (M+H)$^+$.

4.3.6. (*R*)-7-[2-hydroxy-3-(piperidin-1-yl)propoxy]-4-methyl-2*H*-chromen-2-one (*R*)-(−)-7

(*R*)-(−)-**7** was prepared according to the above procedure starting from **14b** as off light yellow semi solid. $[\alpha]_D^{25}$ = −8.9 (*c* 0.28, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.6 Hz, 1H), 6.86 (m, 2H), 6.12 (s, 1H), 4.15 (m, 1H), 4.02 (m, 2H), 2.68 (m, 2H), 2.50 (m, 4H), 2.38 (s, 3H), 1.63 (m, 4H), 1.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8, 161.5, 155.2, 152.6, 125.6, 113.8, 112.6, 112.4, 101.7, 70.9, 65.0, 60.9, 54.8, 25.8, 24.0, 18.7; FT-IR (KBr) ν_{max}, cm^{-1}: 3418, 2925, 1715, 1614, 1281. ESI-MS (*m*/*z*): 318 (M+H)$^+$.

4.3.7. (*S*)-4-[2-Hydroxy-3-(piperidin-1-yl)propoxy]-2*H*-chromen-2-one (*S*)-(+)-8

(*S*)-(+)-**8** was prepared according to the above procedure starting from **15a** as off white semi solid. $[\alpha]_D^{25}$ = +9.0 (*c* 0.20, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.53 (m, 1H), 7.27 (m, 2H), 5.68 (s, 1H), 4.22 (m, 1H), 4.10 (m, 2H), 3.01 (br s, 1H), 2.69 (m, 2H), 2.51 (m, 4H), 1.64 (m, 4H), 1.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 162.9, 153.3, 132.5, 123.9, 123.1, 116.8, 115.6, 90.8, 71.5, 64.6, 60.7, 54.7, 26.0, 25.8, 24.0; FT-IR (KBr) ν_{max}, cm^{-1}: 3455, 1722, 1619, 1565, 1238. ESI-MS (*m*/*z*): 304 (M+H)$^+$.

4.3.8. (*S*)-4-(3-Dodecylamino-2-hydroxypropoxy)-2*H*-chromen-2-one (*S*)-(+)-9

(*S*)-(+)-**9** was prepared according to the above procedure starting from **16a** as off white semi solid. $[\alpha]_D^{20}$ = +5.0 (*c* 0.4, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.5, 1H), 7.51 (m, 1H), 7.24 (m, 2H), 5.73 (s, 1H), 4.51 (m, 1H), 4.14 (m, 2H), 3.17 (m, 2H), 2.97 (m, 2H), 1.72 (m, 2H), 1.24 (m, 18H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 163.1, 153.2, 132.7, 124.1, 123.1, 116.8, 115.3, 90.9, 70.6, 65.2, 50.7, 48.9, 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 26.8, 26.7, 22.7, 14.1; FT-IR (KBr) ν_{max}, cm^{-1}: 3418, 2926, 1727, 1623, 1240; ESI-MS (*m*/*z*): 404 (M+H)$^+$.

4.3.9. (*S*)-4-[2-Hydroxy-3-(octadec-9-en-1-ylamino)propoxy]-2*H*-chromen-2-one (*S*)-(+)-10

(*S*)-(+)-**10** was prepared according to the above procedure starting from **17a** as light yellow semi solid. $[\alpha]_D^{25}$ = +4.9 (*c* 0.40, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.54 (m, 1H), 7.29 (m, 2H), 5.70 (s, 1H), 5.34 (m, 2H), 4.14 (m, 3H), 2.75 (m, 4H), 2.00 (m, 4H), 1.52 (m, 2H), 1.25 (m, 22H), 0.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 162.8, 153.2, 132.4, 129.8, 123.8, 122.9, 116.7, 115.5, 90.8, 90.6, 71.4, 67.1, 51.4, 49.7, 31.8, 29.6, 27.1, 22.6, 14.1; FT-IR (KBr) ν_{max}, cm^{-1}: 3472, 2922, 1735, 1627, 1247. ESI MS (*m*/*z*): 486 (M+H)$^+$.

4.3.10. (*R*)-4-[2-Hydroxy-3-(piperidin-1-yl)propoxy]-2*H*-chromen-2-one (*R*)-(−)-8

(*R*)-(−)-**8** was prepared according to the above procedure starting from **15b** as off white semi solid. $[\alpha]_D^{25}$ = −8.6 (*c* 0.20, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.8 Hz, 1H), 7.47 (m, 1H), 7.22 (m, 2H), 5.64 (s, 1H), 4.64 (m, 1H), 4.11 (m, 2H), 3.08 (m, 6H), 1.99 (m, 4H), 1.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 162.8, 153.1, 132.5, 123.9, 123.0, 116.6, 115.3, 90.8, 70.8, 63.9, 60.3, 54.7, 25.7, 24.0; FT-IR (KBr) ν_{max}, cm^{-1}: 3456, 2946, 1715, 1622, 1242; ESI MS (*m*/*z*): 304 (M+H)$^+$.

4.3.11. (*R*)-4-(3-Dodecylamino-2-hydroxypropoxy)-2*H*-chromen-2-one (*R*)-(−)-9

(*R*)-(−)-**9** was prepared according to the above procedure starting from **16b** as off white semi solid. $[\alpha]_D^{20}$ = −4.7 (*c* 0.40, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.5 Hz, 1H), 7.51 (m, 1H), 7.24 (m, 2H), 5.73 (s, 1H), 4.52 (m, 1H), 4.14 (m, 2H), 3.17 (m, 2H), 2.96 (m, 2H), 1.72 (m, 2H), 1.28 (m, 18H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 163.2, 153.1, 132.7, 124.2, 123.1, 116.7, 115.3, 90.9, 70.7, 65.2, 50.7, 48.8, 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 26.8, 26.6, 22.7, 14.1; FT-IR (KBr) ν_{max}, cm^{-1}: 3421, 2926, 1727, 1622, 1241; ESI-MS (*m*/*z*): 404 (M+H)$^+$.

4.3.12. (*R*)-4-[2-Hydroxy-3-(octadec-9-en-1-ylamino)propoxy]-2*H*-chromen-2-one (*R*)-(−)-10

(*R*)-(−)-**10** was prepared according to the above procedure starting from **17b** as light yellow semi solid. $[\alpha]_D^{25}$ = −5.6 (*c* 0.40, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.54 (m, 1H), 7.30 (m, 2H), 5.70 (s, 1H), 5.35 (m, 2H), 4.13 (m, 3H), 2.66 (m, 4H), 2.00 (m, 4H), 1.51 (m, 2H), 1.25 (m, 22H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 162.7, 153.2, 132.4, 129.9, 123.8, 122.9, 116.7, 115.5, 90.8, 71.4, 67.1, 51.3, 49.7, 32.5, 31.8, 29.9, 29.6, 29.2, 27.1, 22.6, 14.0; FT-IR (KBr) ν_{max}, cm^{-1}: 3345, 2921, 1735, 1626, 1249. ESI MS (*m*/*z*): 486 (M+H)$^+$.

4.4. Preparation of enantiopure coumarins (*S*)-10 and (*R*)-10

(*S*)-**18** was obtained from 4-hydroxycoumarin **2** (0.5 g, 3.08 mmol) and (*R*)-(−)-epichlorohydrin (1.14 g, 12.34 mmol) by the applying the same procedure as for the racemic compound.[20] Epoxide (*S*)-**18** (0.5 g 2.24 mmol) on reaction with oleyl amine (0.52 g, 2.75 mmol) in ethanol at room temperature resulted in the formation of enantiopure coumarinyl amino alcohol (*S*)-**10**, which was purified by column chromatography on silica gel using chloroform/methanol (97:3) as eluent. Off white semi solid; Yield: 71%.

An analogous method was applied for the synthesis of enantiopure (*R*)-**10** using and (*S*)-(+)-epichlorohydrin. Off white semi solid; Yield: 68%.

4.4.1. (*S*)-4-(Oxiranylmethoxy)-2*H*-chromen-2-one (*S*)-18

Off white solid (80%); mp 80–81 °C; $[\alpha]_D^{20}$ = +6.6 (*c* 0.50, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.5 Hz, 1H), 7.56 (m, 1H), 7.30 (m, 2H), 5.69 (s, 1H), 4.47 (d, *J* = 11.1 Hz, 1H), 4.02 (dd, *J* = 11.1 and 6.3 Hz, 1H), 3.46 (m, 1H), 2.99 (m, 1H), 2.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 162.5, 153.2, 132.5, 123.8, 123.1, 116.6, 115.3, 90.7, 69.7, 49.0, 44.3; FT-IR (KBr) ν_{max}, cm^{-1}: 1721, 1622, 1249, 1108, 760. ESI-MS (*m*/*z*): 219 (M+H)$^+$.

4.4.2. (*R*)-4-(Oxiranylmethoxy)-2*H*-chromen-2-one (*R*)-18

Off white solid (81%); mp 80–81 °C; $[\alpha]_D^{20} = -6.3$ (*c* 0.50, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.55 (m, 1H), 7.30 (m, 2H), 5.69 (s, 1H), 4.47 (dd, *J* = 11.1 and 2.4 Hz, 1H), 4.02 (dd, *J* = 11.1 and 6.3 Hz, 1H), 3.47 (m, 1H), 2.99 (m, 1H), 2.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 162.5, 153.2, 132.5, 123.9, 123.0, 116.6, 115.2, 90.9, 69.8, 49.1, 44.3; FT-IR (KBr) ν_{max}, cm^{-1}: 1723, 1621, 1239, 1108, 759. ESI-MS (*m*/*z*): 219 $(M+H)^+$.

4.5. X-ray crystallographic analysis

Crystallographic data for the structures reported herein have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publications. CCDC 1402654 for *rac*-**5** and CCDC 1499014 for (*R*)-(−)-**5** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.6. Antifilarial activity: in vitro assay

4.6.1. Sample preparation

A 1 mM stock solution of coumarin compound was prepared in DMSO (dimethyl sulfoxide).

4.6.2. Parasite isolation

B. malayi adult worms were isolated from the peritoneal cavity of jirds (*Meriones unguiculatus*) which were exposed to infective larvae (L3) of *B. malayi* recovered from experimentally infected mosquitoes, *Aedes aegypti*, approximately 100–150 days back.[29]

4.6.3. Primary in vitro screening

The efficacy of the coumarin compounds was assessed in vitro using live female adult *B. malayi* worms in motility and MTT [3-(4,5 dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide] reduction assays. The parasites were placed individually in the wells of a 48 well culture plate containing RPMI 1640 medium fortified with antibiotics (penicillin 100 units/mL, streptomycin sulfate 100 μg/mL, and neomycin mixture; Sigma, USA). Each well contained one female worm in 1 mL of the medium. The parasites were incubated at 37 °C for 5 continuous days in the presence of 10 μM concentration of each compound and the motility of parasites was monitored microscopically at regular time intervals. At the end of the experiment, adult parasites were transferred to a fresh drug free medium for one hour at 37 °C to observe reversal, if any, in the motility. The worms were later processed individually for MTT dye reduction assay as mentioned earlier[30] for checking their metabolic viability. Experiments were carried out in duplicate and degree of loss in motility as well as percent inhibition in MTT reduction in treated parasites over the untreated controls was assessed. Compounds causing complete irreversible immobility of adult worm along with ≥ 50% inhibition in MTT reduction was considered as macrofilaricidal.[30]

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.04.005.

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