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Anti-AIDS agents 86. Synthesis and anti-HIV evaluation of 2',3'-seco-3'-nor DCP and DCK analogues

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Abstract

In a continuing study of novel anti-HIV agents with drug-like structures and properties, 30 1'-*O*-, 1'-*S*-, 4'-*O*- and 4'-substituted-2',3'-seco-3'-nor DCP and DCK analogues (**8–37**) were designed and synthesized. All newly synthesized seco-compounds were screened against HIV-1_{NL4-3} and a multiple reverse transcriptase (RT) inhibitor-resistant (RTMDR) strain in the TZM-bl cell line, using seco-DCK (**7**) and 2-ethyl-DCP (**4**) as controls. Several compounds (**14**, **18**, **19**, **22–24**, and **32**) exhibited potent anti-HIV activity with EC₅₀ values ranging from 0.93 to 1.93 μM and therapeutic index (TI) values ranging from 20 to 39. 1'-*O*-Isopropoxy-2',3'-seco-3'-nor-DCP (**12**) showed the greatest potency among the newly synthesized compounds with EC₅₀ values of 0.47 and 0.88 μM, and TI of 96 and 51, respectively, against HIV-1_{NL4-3} and RTMDR strains. The seco-compounds exhibited better chemical stability in acidic conditions compared with DCP and DCK compounds. Overall, the results suggested that seco-DCP analogues with simplified structures may be more favorable for development as novel anti-HIV candidates.

Keywords

2', 3'-Seco-3'-nor-DCPs; Anti-HIV activity; Structure–activity relationship (SAR)

1. Introduction

Acquired immunodeficiency syndrome (AIDS), one of the most devastating diseases currently affecting mankind, is caused by infection with the human immunodeficiency virus (HIV). Although there are over 30 clinically used drugs [1], the fast emergence of drug resistance and toxicity problems due to long-term use and drug-drug interactions have

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limited their long-term drug effectiveness. Therefore, studies aimed at the discovery of new anti-viral agents with novel structures or targets are still needed.

In our prior research, 3'*R*,4'*R*-di-*O*-(−)-camphanoyl-(+)-cis-khellactone (DCK, **1**) and 4-methyl-DCK (**2**) exhibited high potency against HIV-1 replication in H9 lymphocytes (Figure 1) [2, 3]. Subsequently, diverse DCK analogues were designed and synthesized by modifications of DCK, particularly different coumarin substituents, ring isomers, and bioisosteric replacements [4–10]. Most of the new compounds showed promising *in vitro* inhibitory activity in anti-HIV replication assays, and a preliminary structure-activity relationship (SAR) was established. However, the problems of poor water solubility, low bioavailability and reduced potency against multiple reverse transcriptase (RT) inhibitor-resistant (RTMDR) strains have obstructed the further development of DCKs. Subsequently, 4*H*-chromone-4-one (DCP, **3**) derivatives, which are positional isomers of DCK, were designed and synthesized [11, 12]. Among them, 2-ethyl DCP (**4**), 5-methyl-2-ethyl DCP (**5**), and 2,5-dimethyl DCP (**6**) not only exhibited high activity against wild-type HIV isolates, but also retained potency against RTMDR-1 (Figure 1).

These favorable results led us to investigate whether the integrity of the tricyclic system (ring-A, -B and -C) was essential for the anti-HIV activity. While ring-A opened DCK analogues did not exhibit antiviral activity, ring-C opened DCK analogues (seco-DCKs) were active. In fact, compared with **2**, seco-DCK analogue **7** showed better anti-HIV activity and increased sensitivity against RTMDR in anti-HIV replication assays using HIV-1_{IIIIB} in MT-2 cell lines, as well as HIV-1_{NL4-3} and RTMDR in MT-4 lymphocytes [13]. The seco-DCKs have a simplified skeleton, fewer hydrogen-bond acceptors and lower log P values, resulting in increased water solubility and better pharmacokinetic properties compared with DCKs. Our success with seco-DCKs prompted us to make corresponding modifications on DCP analogues in our search for new desirable anti-HIV inhibitors with better drug-like properties and inhibitory activity against RTMDR. Herein, we report the design, synthesis, biological evaluation and chemical stability of novel 2',3'-seco-3'-nor DCP (**8–31**, **33–37**) and DCK (**32**) analogues (Figures 2–4).

2. Design

Previous research suggested that a 4'-camphanoyl moiety is preferred for anti-HIV activity of DCK/DCP analogues. Therefore, in our current study, we first retained the 4'-camphanoyl ester substitution, while focusing on diverse substituents at the 1'-*O* position of the new ring-C opened seco-DCP products. Eight 2',3'-seco-3'-nor-2-ethyl DCP analogues (**8–15**) with different aliphatic groups, such as methyl, ethyl, isopropyl, isobutyl, and 2- α -bromoethyl, at the 1'-*O* position were synthesized. Aromatic and heterocyclic moieties, which were not introduced at the 1'-*O* position in our prior seco-DCK study, were also incorporated to examine the effects of 1'-*O*-aryl rings with electron-donating or -withdrawing groups and 1'-*O*-heterocyclic substituents on the antiviral replication activity of new compounds (**16–28**). In addition, because an ether bond usually has better chemical stability than an ester bond, the 4'-camphanoyl ester [-O(C=O)- linkage] was replaced with a 4'-camphanol ether [-O-CH₂- linkage] with the aim of slowing down possible metabolism at this position. Accordingly, three 4'-camphanol ethers of 2',3'-seco-3'-nor-2-ethyl-DCPs (**29–31**) were generated. Prior research on bioisosteric replacement showed that some 1-thia and/or 1'-thia DCKs exhibited comparable or better activity against HIV replication compared with 1-oxa and/or 1'-oxa DCKs. Consequently, we synthesized 1'-thia-2',3'-seco-3'-nor-4-methyl-DCK (**32**) and 1'-thia-2',3'-seco-3'-nor-2-ethyl-DCP (**33**) to verify if seco-series showed a similar trend. Finally, we replaced the 4'-*O*-camphanoyl ester with piperidinyl oxalamide moieties, and synthesized four 4'-(*N*'-substituted piperidin-1-yl)-2',3'-seco-3'-nor DCP analogues (**34–**

37). All new compounds were evaluated in an antiviral replication assay against wild-type virus, and 15 compounds were also assayed against RTMDR virus.

3. Chemistry

Scheme 1 shows the synthesis of 1'-*O*-alkyl-2',3'-seco-3'-nor DCPs (**8–15**). Commercially available 2,4-dihydroxy-3-methylacetophenone (**38**) was selectively protected as the 4-methoxymethyl (MOM) ether (**39**), followed by condensation with ethyl propionate to afford **40**, which was further reacted with concentrated hydrochloric acid in EtOH to provide bicyclic compound **41**. Four 7-alkoxy ethers (**42a–d**) were synthesized by alkylation of **41** with corresponding bromides, and subsequent treatment with *N*-bromosuccinimide provided 8-bromomethylmonobromides (**43a–d**) and 2- α -bromoethyl-8-bromomethyldibromides (**44e–h**). A mixture of the mono- and di-bromides was first heated at reflux in a solution of NaOAc/Ac₂O and then hydrolyzed with 2N HCl in EtOH to produce 8-hydroxymethyl compounds (**45a–d**) and 2- α -bromoethyl-8-hydroxymethyl compounds (**46e–h**), respectively. Subsequently, the desired esters **8–15** were prepared by esterification of **45a–d** and **46e–h** with camphanoyl chloride in DMAP and CH₂Cl₂ at room temperature.

The synthesis of 1'-*O*-aryl or -heterocyclic substituted 2',3'-seco-3'-nor-2-ethyl-DCPs (**16–28**) is depicted in Scheme 2. To avoid the reaction of the 7-OH group of **41** with NBS, the MOM ether **47** was prepared and subsequently brominated with NBS to yield the 8-bromomethyl compound **48**, which was then treated as described above to afford **49**. Thirteen 7-aromatic and -heterocyclic substituted ethers (**50a–m**) were prepared by alkylation of **49** with corresponding bromides in DMF in the presence of K₂CO₃ at room temperature. Compounds **50a–m** were then converted into the target compounds (**16–28**) by acylation with camphanoyl chloride.

As shown in Scheme 3, etherification of 7-alkyloxy-8-bromomethyl-2-ethyl-4*H*-chromen-4-ones (**43a–c**) with camphanol in toluene in presence of NaH afforded the three respective 4'-camphanol ether 2',3'-seco-3'-nor-2-ethyl-DCPs (**29–31**). Four 4'-(*N'*-substituted piperidin-1-yl)-2',3'-seco-3'-nor DCP analogues (**34–37**) were obtained from the amidation of **43b** with the corresponding *N'*-substituted piperidine in THF in presence of DMAP at room temperature.

The syntheses of 1'-thia-2',3'-seco-3'-nor-4-methyl-DCK (**32**) and 1'-thia-2',3'-seco-3'-nor-2-ethyl-DCP (**33**) are depicted in Schemes 4 and 5, respectively. For **33**, the mono-acetylation of commercially available resorcinol (**60**) in an HOAc solution containing zinc chloride gave **61**. 2-Ethyl-7-hydroxy-4*H*-chromen-4-one (**64**) was then obtained from **61** via three steps, 4-OH protection with MOMCl (**62**), condensation with ethyl propionate (**63**), and ring-A closure. Compounds **52** (Scheme 4) and **65** (Scheme 5) were obtained by Duff formylation of **51** and **64**, respectively, with hexamethylenamine in acetic acid solution. Because hydrogen bonding between the 7-hydroxy and 8-formyl groups could possibly interfere with the conversion of the 7-OH to 7-SH, the 8-formyl moiety in **52** and **65** was first protected as a cyclic acetal in intermediates **53** and **66** by reaction with ethylene glycol in the presence of *p*-toluenesulfonic acid in benzene under reflux-dehydration conditions. Subsequently, the 7-hydroxy compounds (**53** and **66**) were converted to the 7-mercapto compounds (**56** and **69**) in three steps, acylation with dimethylthiocarbamoyl chloride (**54** and **67**), Newman-Kwart rearrangement (**55** and **68**), and basic hydrolysis. The alkylation of **56** and **69** with isopropyl bromide yielded **57** and **70**. Finally, target compounds **32** and **33** were prepared from **57** and **70** by the following reaction sequence, deprotection of the 8-acetal in 1N HCl, reduction of **58** and **71** with NaBH₄ in MeOH, and esterification of **60** and **72** with camphanoyl chloride.

4. Results and discussion

All 30 newly synthesized seco-DCK and DCP analogues (**8–37**) were evaluated for *in vitro* suppression of HIV-1_{NL4-3} replication in a single cycle infection assay using the TZM-bl cell line with both 2-ethyl-DCP (**4**) and seco-DCK (**7**) as positive controls. Moreover, compounds **8–15**, **29–31**, and **34–37** were also screened for antiviral activity against HIV-1 RTMDR. The data are summarized in Tables 1 and 2.

As shown in Table 1, compounds **8–15** exhibited varying degrees of potency against wild-type HIV-1_{NL4-3}. Based on the size of the alkyl group at the 1'-*O* position, the rank order of antiviral activity was methyl < ethyl < isobutyl < isopropyl. 1'-*O*-Isopropyl substituted **12** showed the best antiviral activity against both HIV-1_{NL4-3} and RTMDR with EC₅₀ values of 0.47 and 0.88 μM, and TI of 96 and 51, respectively, which were generally comparable or better, particularly against RTMDR, than those of prior hits **7** (EC₅₀ 0.5 and 1.89 μM; TI 34.54 and 9.13, respectively) and **4** (EC₅₀ 0.12 and 0.20 μM, TI 118.75 and 71.25, respectively). Compounds **12** and **14** (1'-*O*-isobutyl-2',3'-seco-3'-nor-2-ethyl-DCP) had comparable anti-RTMDR potencies (EC₅₀ 0.88 and 0.94 μM, respectively), which were two-fold better than that of **7**. Compounds with a bromine on the 2-ethyl group (**9**, **11**, **13**, and **15**) exhibited much lower anti-HIV activity compared with the corresponding non-brominated compounds (**8**, **10**, **12**, and **14**). This finding suggested that a 2-*α*-bromoethyl group was unfavorable. Overall, the results suggested that the size of an isopropyl group at the 1'-*O* position was more suitable to fit within the binding pocket of wild-type virus, while both isopropyl and isobutyl may fit into the slightly changed binding pocket of the RTMDR strain, due to possible mutations near the interaction site.

The three novel 4'-camphanol ether seco-DCP analogues (**29–31**) exhibited better inhibition activity against drug-resistant RTMDR than wild-type HIV-1_{NL4-3}. 1'-*O*-Isopropyl-4'-camphanol ether **31** exhibited the best potency against RTMDR (EC₅₀ 1.49 μM, TI 31.45). However, the 4'-camphanol ether compounds (**29–31**) were less potent than their corresponding 4'-camphanoyl ester analogues (**8**, **10**, **12**, respectively). The four compounds (**34–37**) with a piperidinyl group rather than a camphanoyl ester or camphanol ether at the 4'-position showed decreased or completely abolished inhibitory activity against HIV, further confirming our prior finding that a 4'-camphanoyl group is very important for enhanced anti-HIV activity in the DCK/DCP series.

The anti-HIV-1_{NL4-3} results for 1'-*O*-aryl and -heterocyclic 2',3'-seco-3'-nor-2-ethyl-DCPs (**16–28**) and 1'-thia compounds (**32** and **33**) are shown in Table 2. Among these analogues, 1'-*O*-3-methoxycarbonylbenzyl-2',3'-seco-3'-nor-2-ethyl-DCP (**23**) (EC₅₀ 0.93 μM, TI 39.20) and the positive control (**7**) (EC₅₀ 0.5 μM, TI 34.54) exhibited comparable potency. 1'-*O*-Pyrid-3-yl-methyl, -pyrid-4-yl-methyl, 1'-*O*-3-cyanobenzyl, 1'-*O*-3-methoxybenzyl, and 1'-*O*-3-methylbenzyl analogues (**18**, **19**, **21**, **22**, and **24**, respectively) also showed moderate anti-HIV inhibitory activity with EC₅₀ values ranging from 1.26 to 2.41 μM. The significantly reduced potency of **17**, which contains a 1'-*O*-pyrid-2-yl-methyl substituent, compared with **18** and **19** suggested that a nitrogen atom at the 2-position of the aromatic ring is detrimental to the antiviral activity. Compounds **25** and **26** with 1'-*O*-3,5-dimethoxybenzyl and 1'-*O*-3-trifluoromethoxybenzyl substituents exhibited very weak anti-HIV activity, while compounds **16**, **20**, **27**, and **28** with 1'-*O*- γ -butyrolactone, 1'-*O*-3-trifluoromethylbenzyl, 1'-*O*-2-bromo-5-methoxybenzyl, and 1'-*O*-2-nitro-4,5-dimethoxybenzyl substituents lost all activity. These results indicated that the 1'-*O*-substituents have a significant impact on the analogues' antiviral activity. The 1'-*O* position in the seco-compounds, which corresponds to the 2'-position of DCK and DCP analogues, should be interacting with the viral binding target, as consistent with our previous study in the DCK series. Finally, compound **32** (1'-thia-seco-DCK) showed moderate antiviral

activity (EC_{50} 1.53 μ M, TI 21.32), while **33** (1'-thia-seco-DCP) was more active (EC_{50} 0.56 μ M, TI 11.25). Comparing the sulfur compounds with their oxygen counterparts, **32** was less potent than **12**, while **33** was equipotent with **7**.

Chemically, the seco-DCK/DCP analogues have lower molecular weights and should have reduced spatial strain, because they contain only one rather than two adjacent, extremely bulky cis-3',4'-camphanoyl esters as found in the DCK and DCP series. Hypothetically, these changes could improve the chemical stability of the molecules and their drug-like properties. Consequently, the chemical stability of 4-Me-DCK (**2**), seco-DCK (**7**), 1'-thia-seco-DCK (**32**), 2-ethyl-DCP (**4**), and seco-DCP (**12**) were tested under acidic conditions with HPLC monitoring. The preliminary results are listed in Table 3. The results showed that, after 30 min, only 64% of compound **2** was detectable, while 77% of **7** and 96% of **32** were intact. Compound **12**, which exhibited the greatest antiviral activity among the newly synthesized seco-DCK/DCP analogues, also showed the best chemical stability in this study (100% intact after 30 min). Overall, the seco-series of compounds showed good stability in acidic conditions, indicating that they should remain stable in the stomach *via* oral administration.

5. Conclusions

In conclusion, most of the new 2',3'-seco-3'-nor-2-ethyl-DCP analogues showed potent to moderate anti-HIV activity, and compounds **12** and **14** also showed promising activity against RTMDR. In addition, the chemical stability of seco-DCKs and seco-DCPs was improved in comparison with DCK and DCP analogues. Preliminary SAR conclusions were as follows, a) integrity of the ring-C is not essential for DCK and DCP analogues, and aliphatic alkyl substituents at 1'-*O*-position are better than aryl or heterocyclic groups, with isopropyl substitution being the most favorable for anti-HIV potency; b) converting the 4'-camphanoyl ester into a camphanol ether resulted in some potency decrease, but compounds remained more selective against RTMDR; c) 4'-camphanoyl is the most preferred moiety for anti-HIV activity of DCK and DCP analogues; and d) sulfur rather than oxygen at the 1'-position led to similar or slightly reduced anti-HIV activity.

6. Experimental

Melting points were measured with a Fisher Johns melting apparatus without correction. The proton nuclear magnetic resonance (1H NMR) spectra were measured on a Bruker-DPX 400 MHz spectrometer and 300 MHz Varian Gemini 2000 spectrometer using TMS as internal standard. The solvent used was $CDCl_3$ unless indicated. Mass spectra were measured with HP5973N analytical mass spectrometers. High resolution mass spectra (HRMS) were measured on a Shimadzu LCMSIT-TOF with ESI interface. HPLC purity determinations were conducted using a Shimadzu LCMS-2010 with a Grace Alltima 2.1 \times 150 mm HP C18 3 μ M column and Shimadzu SPD-M20A detector at 254 nm wavelength. HPLC purity analyses were determined by using two different solvent conditions. The first was 70% MeCN as solvent A and 30% H_2O as solvent B with 0.2 mL/min flow rate; the second was 70% MeOH as solvent A and 30% H_2O as solvent B with 0.1 mL/min flow rate. The HPLC model was an isocratic system. All target compounds had purity greater than 95%. Commercially available silica gel H was used for column chromatography. Thin-layer chromatography (TLC) was performed on PLC silica gel 60 F254 plates.

6.1. Synthesis of 1'-alkoxy-seco-DCPs (8–15)

6.1.1. 1-(2-Hydroxy-4-(methoxymethoxy)-3-methylphenyl)ethanone (**39**)—

Chloromethyl methyl ether (9.14 mL, 120 mmol) was added dropwise into a mixture of **38** (10.0 g, 60.2 mmol) and potassium carbonate (20.8 g, 150 mmol) in anhydrous acetone (60

mL) in an ice-bath. The reaction mixture was then allowed to warm to room temperature and stirred for 1.5 h. The mixture was then filtered, and the filtrate was dissolved in brine and extracted with EtOAc (35 mL). The organic layer was dried *in vacuo* to provide **39** (13.9 g) as brown oil: 91% yield. $^1\text{H NMR}$ δ : 2.14 (3H, s, 3-CH₃), 2.56 (3H, s, 1-COCH₃), 3.50 (3H, s, 4-OCH₂OCH₃), 5.27 (2H, s, 4-OCH₂OCH₃), 6.65 (1H, d, $J = 8.7$ Hz, 6-H), 7.57 (1H, d, $J = 8.7$ Hz, 5-H), 12.80 (1H, s, 2-OH). ESI-MS m/z 209 ($M^+ - 1$).

6.1.2. 2-Ethyl-7-hydroxy-8-methyl-4H-chromen-4-one (41)—Sodium hydride (60% in mineral oil, 9.52 g/15.9 g, 397 mmol) was added slowly to a mixture of **39** (13.9 mg, 66.1 mmol) and ethyl propionate (19.0 mL, 165 mmol) in absolute THF under nitrogen. Then, the mixture was warmed to reflux temperature for 2 h, cooled and neutralized to pH 8 with 37% HCl (25 mL). Water (60 mL) was added and the mixture was extracted with EtOAc (4 \times 30 mL). The organic layer was collected and evaporated *in vacuo* to yield **40** as dark oil. This crude product and 37% HCl (3 mL) were dissolved in EtOH (60 mL) and refluxed for 45 min to give **41**, which was used in the next reaction without further purification. mp 223–224 °C. $^1\text{H NMR}$ (DMSO, δ): 1.23 (3H, t, $J = 7.2$ Hz, 2-CH₂CH₃), 2.20 (3H, s, 8-CH₃), 2.65 (2H, q, $J = 7.2$ Hz, 2-CH₂CH₃), 6.06 (1H, s, 3-H), 6.98 (1H, d, $J = 8.7$ Hz, 6-H), 7.68 (1H, d, $J = 8.7$ Hz, 5-H). ESI-MS m/z 203 ($M^+ - 1$).

6.1.3. Synthesis of 2-ethyl-7-alkoxychromones (42a–d)—A mixture of **41** (1 equiv), K₂CO₃ (3 equiv), and halogenated compounds (2 equiv) in DMF (5 mL) was stirred for 45 min at room temperature. After filtering the mixture and removing the solvent *in vacuo*, the residue was purified by column chromatography (eluent: hexane/EtOAc 95:5) to afford the desired compounds (**42a–d**) as white solids in 73–82% yields.

6.1.3.1. 2-Ethyl-7-methoxy-8-methyl-4H-chromen-4-one (42a): 75% yield, mp 104–106 °C. $^1\text{H NMR}$ δ : 1.32 (3H, t, $J = 7.5$ Hz, 2-CH₂CH₃), 2.30 (3H, s, 8-CH₃), 2.68 (2H, q, $J = 7.5$ Hz, 2-CH₂CH₃), 3.95 (3H, s, 7-OCH₃), 6.11 (1H, s, 3-H), 6.96 (1H, d, $J = 9.0$ Hz, 6-H), 8.10 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 219 ($M^+ + 1$).

6.1.3.2. 7-Ethoxy-2-ethyl-8-methyl-4H-chromen-4-one (42b): 73% yield, mp 85–87 °C. $^1\text{H NMR}$ δ : 1.33 (3H, t, $J = 7.5$ Hz, 2-CH₂CH₃), 1.48 (3H, t, $J = 7.2$ Hz, 7-OCH₂CH₃), 2.31 (3H, s, 8-CH₃), 2.68 (2H, q, $J = 7.5$ Hz, 2-CH₂CH₃), 4.17 (2H, q, $J = 7.2$ Hz, 7-OCH₂CH₃), 6.11 (1H, s, 3-H), 6.93 (1H, d, $J = 9.0$ Hz, 6-H), 8.01 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 233 ($M^+ + 1$).

6.1.3.3. 2-Ethyl-7-isopropoxy-8-methyl-4H-chromen-4-one (42c): 79% yield, mp 99–101 °C. $^1\text{H NMR}$ δ : 1.33 (3H, t, $J = 6.9$ Hz, 2-CH₂CH₃), 1.38 (6H, d, $J = 6.0$ Hz, 7-OCH(CH₃)₂), 2.29 (3H, s, 8-CH₃), 2.68 (2H, q, $J = 6.9$ Hz, 2-CH₂CH₃), 4.70 (1H, m, $J = 6.0$ Hz, 7-OCH(CH₃)₂), 6.11 (1H, s, 3-H), 6.95 (1H, d, $J = 9.0$ Hz, 6-H), 8.01 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 247 ($M^+ + 1$).

6.1.3.4. 2-Ethyl-7-isobutoxy-8-methyl-4H-chromen-4-one (42d): 82% yield, mp 61–62 °C. $^1\text{H NMR}$ δ : 1.07 (6H, d, $J = 6.6$ Hz, 7-OCH₂CH(CH₃)₂), 1.33 (3H, t, $J = 7.2$ Hz, 2-CH₂CH₃), 2.16 (1H, m, $J = 6.6$ Hz, 7-OCH₂CH(CH₃)₂), 2.32 (3H, s, 8-CH₃), 2.68 (2H, q, $J = 7.2$ Hz, 2-CH₂CH₃), 3.86 (2H, d, $J = 6.6$ Hz, 7-OCH₂CH(CH₃)₂), 6.11 (1H, s, 3-H), 6.93 (1H, d, $J = 9.0$ Hz, 6-H), 8.01 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 261 ($M^+ + 1$).

6.1.4. Synthesis of bromides (43a–d and 44e–h)—A mixture of **42a–d** (1 equiv) and NBS (1.2 equiv) in CCl₄ was refluxed for 16 h. After filtration and removal of the solvent, the residue was purified by column chromatography with a gradient eluent of CH₂Cl₂/

MeOH 40:1 to 30:1 to afford pure **43a–d** and **44e–h** in yields of 40–78% and 11–15%, respectively.

6.1.4.1. 8-(Bromomethyl)-2-ethyl-7-methoxy-4H-chromen-4-one (43a): 40% yield (starting with 300 mg of **42a**): mp 162–164 °C. $^1\text{H NMR } \delta$: 1.36 (3H, t, $J = 7.5$ Hz, $2\text{-CH}_2\text{CH}_3$), 2.72 (2H, q, $J = 7.5$ Hz, $2\text{-CH}_2\text{CH}_3$), 4.03 (3H, s, 7-OCH₃), 4.78 (2H, s, 8-CH₂Br), 6.15 (1H, s, 3-H), 6.99 (1H, d, $J = 9.0$ Hz, 6-H), 8.16 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 297 ($\text{M}^+ + 1$).

6.1.4.2. 8-(Bromomethyl)-7-ethoxy-2-ethyl-4H-chromen-4-one (43b): 58% yield (starting with 880 mg of **42b**): mp 114–116 °C. $^1\text{H NMR } \delta$: 1.36 (3H, t, $J = 7.8$ Hz, $2\text{-CH}_2\text{CH}_3$), 1.52 (3H, t, $J = 6.9$ Hz, 7-OCH₂CH₃), 2.72 (2H, q, $J = 7.8$ Hz, $2\text{-CH}_2\text{CH}_3$), 4.25 (2H, q, $J = 6.9$ Hz, 7-OCH₂CH₃), 4.79 (2H, s, 8-CH₂Br), 6.14 (1H, s, 3-H), 6.96 (1H, d, $J = 9.0$ Hz, 6-H), 8.13 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 311 ($\text{M}^+ + 1$).

6.1.4.3. 8-(Bromomethyl)-2-ethyl-7-isopropoxy-4H-chromen-4-one (43c): 45% yield (starting with 1.2 g of **42c**): mp 66–68 °C. $^1\text{H NMR } \delta$: 1.36 (3H, t, $J = 7.8$ Hz, $2\text{-CH}_2\text{CH}_3$), 1.44 (6H, d, $J = 6.0$ Hz, 7-OCH(CH₃)₂), 2.71 (2H, q, $J = 7.8$ Hz, $2\text{-CH}_2\text{CH}_3$), 4.72–4.81 (3H, m, $J = 6.0$ Hz, 7-OCH(CH₃)₂ & 8-CH₂Br), 6.14 (1H, s, 3-H), 6.96 (1H, d, $J = 9.0$ Hz, 6-H), 8.12 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 325 ($\text{M}^+ + 1$).

6.1.4.4. 8-(Bromomethyl)-2-ethyl-7-isobutoxy-4H-chromen-4-one (43d): 78% yield (starting with 200 mg of **42d**): mp 91–93 °C. $^1\text{H NMR } \delta$: 1.25 (6H, d, $J = 6.6$ Hz, 7-OCH₂CH(CH₃)₂), 1.50 (3H, t, $J = 7.5$ Hz, $2\text{-CH}_2\text{CH}_3$), 2.35 (1H, m, $J = 6.6$ Hz, 7-OCH₂CH(CH₃)₂), 2.85 (2H, t, $J = 7.5$ Hz, $2\text{-CH}_2\text{CH}_3$), 4.07 (2H, d, $J = 6.6$ Hz, 7-OCH₂CH(CH₃)₂), 4.93 (2H, s, 8-CH₂Br), 6.28 (1H, s, 3-H), 7.09 (1H, d, $J = 9.0$ Hz, 6-H), 8.27 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 339 ($\text{M}^+ + 1$).

6.1.4.5. 2-(1-Bromoethyl)-8-(bromomethyl)-7-methoxy-4H-chromen-4-one (44e): 14% yield (starting with 300 mg of **42a**): mp 153–156 °C. $^1\text{H NMR } \delta$: 2.09 (3H, d, $J = 7.2$ Hz, 2-CHBrCH₃), 4.04 (3H, s, 7-OCH₃), 4.81 (2H, s, 8-CH₂Br), 4.94 (1H, q, $J = 7.2$ Hz, 2-CHBrCH₃), 6.33 (1H, s, 3-H), 7.02 (1H, d, $J = 9.0$ Hz, 6-H), 8.16 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 377 (100).

6.1.4.6. 2-(1-Bromoethyl)-8-(bromomethyl)-7-ethoxy-4H-chromen-4-one (44f): 15% yield (starting with 880 mg of **42b**): mp 138–140 °C. $^1\text{H NMR } \delta$: 1.53 (3H, t, $J = 6.9$ Hz, 7-OCH₂CH₃), 2.09 (3H, d, $J = 7.2$ Hz, 2-CHBrCH₃), 4.26 (2H, q, $J = 6.9$ Hz, 7-OCH₂CH₃), 4.82 (2H, s, 8-CH₂Br), 4.95 (1H, q, $J = 7.2$ Hz, 2-CHBrCH₃), 6.33 (1H, s, 3-H), 6.99 (1H, d, $J = 9.0$ Hz, 6-H), 8.12 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 384 (100).

6.1.4.7. 2-(1-Bromoethyl)-8-(bromomethyl)-7-isopropoxy-4H-chromen-4-one (44g): 15% yield (starting with 1.2 g of **42c**): mp 95–97 °C. $^1\text{H NMR } \delta$: 1.45 (6H, d, $J = 6.0$ Hz, 7-OCH(CH₃)₂), 2.85 (3H, d, $J = 6.9$ Hz, 2-CHBrCH₃), 4.80 (3H, m, $J = 6.0$ Hz, 7-OCH(CH₃)₂ & 8-CH₂Br), 4.94 (1H, q, $J = 6.9$ Hz, 2-CHBrCH₃), 6.32 (1H, s, 3-H), 7.00 (1H, d, $J = 9.0$ Hz, 6-H), 8.12 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 405 (100).

6.1.4.8. 2-(1-Bromoethyl)-8-(bromomethyl)-7-isobutoxy-4H-chromen-4-one (44h): 11% yield (starting with 200 mg of **42d**): mp 108–109 °C. $^1\text{H NMR } \delta$: 1.11 (6H, d, $J = 6.6$ Hz, 7-OCH₂CH(CH₃)₂), 2.09 (3H, d, $J = 6.9$ Hz, 2-CHBrCH₃), 2.22 (1H, m, $J = 6.6$ Hz, 7-OCH₂CH(CH₃)₂), 3.95 (2H, d, $J = 6.6$ Hz, 7-OCH₂CH(CH₃)₂), 4.83 (2H, s, 8-CH₂Br), 4.94 (1H, q, $J = 6.9$ Hz, 2-CHBrCH₃), 6.33 (1H, s, 3-H), 7.0 (1H, d, $J = 9.0$ Hz, 6-H), 8.12 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 412 (100).

6.1.5. Synthesis of 8-hydroxymethyl compounds (45a–d and 46e–h)—A mixture of the above bromides [**43a–d** or **44e–h** (1 equiv)] and NaOAc (10 equiv) in acetic anhydride (5 mL) was refluxed for 2 h and progress was monitored by TLC (CH₂Cl₂/MeOH 20:1). After removal of solvent *in vacuo*, EtOH (5 mL) and 2N HCl (2 mL) were added, and the mixture refluxed for 2 h. After the solvent was removed *in vacuo*, the crude product was purified by column chromatography (eluent: CH₂Cl₂/MeOH 99:1) to give **45a–d** and **46e–h**.

6.1.5.1. 2-Ethyl-8-(hydroxymethyl)-7-methoxy-4H-chromen-4-one (45a): 87% yield (starting with 300 mg of **43a**): mp 139–140 °C. ¹H NMR δ: 1.32 (3H, t, *J* = 7.5 Hz, 2-CH₂CH₃), 2.34 (1H, s, 8-CH₂OH), 2.69 (2H, q, *J* = 7.5 Hz, 2-CH₂CH₃), 4.01 (3H, s, 7-OCH₃), 4.97 (2H, s, 8-CH₂OH), 6.13 (1H, s, 3-H), 7.02 (1H, d, *J* = 9.0 Hz, 6-H), 8.17 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 235 (M⁺+1).

6.1.5.2. 7-Ethoxy-2-ethyl-8-(hydroxymethyl)-4H-chromen-4-one (45b): 42% yield (starting with 140 mg of **43b**): mp 100–102 °C. ¹H NMR δ: 1.32 (3H, t, *J* = 7.2 Hz, 2-CH₂CH₃), 1.51 (3H, t, *J* = 6.9 Hz, 7-OCH₂CH₃), 2.44 (1H, s, 8-CH₂OH), 2.68 (2H, q, *J* = 7.2 Hz, 2-CH₂CH₃), 4.24 (2H, q, *J* = 6.9 Hz, 7-OCH₂CH₃), 4.98 (2H, s, 8-CH₂OH), 6.12 (1H, s, 3-H), 7.0 (1H, d, *J* = 9.0 Hz, 6-H), 8.13 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 249 (M⁺+1).

6.1.5.3. 2-Ethyl-8-(hydroxymethyl)-7-isopropoxy-4H-chromen-4-one (45c): 35% yield (starting with 120 mg of **43c**): mp 114–116 °C. ¹H NMR δ: 1.32 (3H, t, *J* = 6.9 Hz, 2-CH₂CH₃), 1.43 (6H, d, *J* = 6.0 Hz, 7-OCH(CH₃)₂), 2.48 (1H, t, *J* = 6.4 Hz, 8-CH₂OH), 2.68 (2H, q, *J* = 6.9 Hz, 2-CH₂CH₃), 4.78 (1H, m, *J* = 6.0 Hz, 7-OCH(CH₃)₂), 4.96 (2H, d, *J* = 6.4 Hz, 8-CH₂OH), 6.12 (1H, s, 3-H), 7.0 (1H, d, *J* = 9.3 Hz, 6-H), 8.12 (1H, d, *J* = 9.3 Hz, 5-H). ESI-MS *m/z* 263 (M⁺+1).

6.1.5.4. 2-Ethyl-8-(hydroxymethyl)-7-isobutoxy-4H-chromen-4-one (45d): 58% yield (starting with 200 mg of **43d**): mp 120–122 °C. ¹H NMR δ: 1.08 (6H, d, *J* = 6.6 Hz, 7-OCH₂CH(CH₃)₂), 1.32 (3H, t, *J* = 7.2 Hz, 2-CH₂CH₃), 2.19 (1H, m, *J* = 6.6 Hz, 7-OCH₂CH(CH₃)₂), 2.35 (1H, s, 8-CH₂OH), 2.68 (2H, q, *J* = 7.2 Hz, 2-CH₂CH₃), 3.93 (2H, d, *J* = 6.6 Hz, 7-OCH₂CH(CH₃)₂), 4.98 (2H, s, 8-CH₂OH), 6.13 (1H, s, 3-H), 6.99 (1H, d, *J* = 9.0 Hz, 6-H), 8.13 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 277 (M⁺+1).

6.1.5.5. 2-(1-Bromoethyl)-8-(hydroxymethyl)-7-methoxy-4H-chromen-4-one (46e): 38% yield (starting with 100 mg of **44e**): colorless oil. ¹H NMR δ: 1.97 (3H, d, *J* = 6.9 Hz, 2-CHBrCH₃), 2.37 (1H, s, 8-CH₂OH), 4.01 (3H, s, 7-OCH₃), 4.90 (1H, q, *J* = 6.9 Hz, 2-CHBrCH₃), 5.01 (2H, s, 8-CH₂OH), 6.33 (1H, s, 3-H), 7.05 (1H, d, *J* = 9.0 Hz, 6-H), 8.16 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 313 (M⁺+1).

6.1.5.6. 2-(1-Bromoethyl)-7-ethoxy-8-(hydroxymethyl)-4H-chromen-4-one (46f): 34% yield (starting with 90 mg of **44f**): colorless oil. ¹H NMR δ: 1.50 (3H, t, *J* = 7.2 Hz, 7-OCH₂CH₃), 1.97 (3H, d, *J* = 6.9 Hz, 2-CHBrCH₃), 2.27 (1H, s, 8-CH₂OH), 4.25 (2H, q, *J* = 7.2 Hz, 7-OCH₂CH₃), 4.95 (1H, q, *J* = 6.9 Hz, 2-CHBrCH₃), 5.01 (2H, s, 8-CH₂OH), 6.33 (1H, s, 3-H), 7.02 (1H, d, *J* = 8.7 Hz, 6-H), 8.14 (1H, d, *J* = 8.7 Hz, 5-H). ESI-MS *m/z* 327 (M⁺+1).

6.1.5.7. 2-(1-Bromoethyl)-8-(hydroxymethyl)-7-isopropoxy-4H-chromen-4-one (46g): 24% yield (starting with 120 mg of **44g**): mp 63–65 °C. ¹H NMR δ: 1.39 (6H, d, *J* = 6.0 Hz, 7-OCH(CH₃)₂), 1.97 (3H, d, *J* = 6.9 Hz, 2-CHBrCH₃), 2.47 (1H, s, 8-CH₂OH), 4.80 (1H, m, *J* = 6.0 Hz, 7-OCH(CH₃)₂), 4.91 (1H, q, *J* = 6.9 Hz, 2-CHBrCH₃), 4.99 (2H, s, 8-

CH_2OH), 6.33 (1H, s, 3-H), 7.02 (1H, d, $J = 9.3$ Hz, 6-H), 8.12 (1H, d, $J = 9.3$ Hz, 5-H). ESI-MS m/z 341 ($\text{M}^+ + 1$).

6.1.5.8. 2-(1-Bromoethyl)-8-(hydroxymethyl)-7-isobutoxy-4H-chromen-4-one (46h):

14% yield (starting with 200 mg of **44h**): mp 116–118 °C. ^1H NMR δ : 1.07 (6H, d, $J = 6.6$ Hz, 7- $\text{OCH}_2\text{CH}(\text{CH}_3)_2$), 1.58 (3H, d, $J = 6.6$ Hz, 2- CHBrCH_3), 2.18 (1H, m, $J = 6.6$ Hz, 7- $\text{OCH}_2\text{CH}(\text{CH}_3)_2$), 3.10 (1H, s, 8- CH_2OH), 3.93 (2H, d, $J = 6.6$ Hz, 7- $\text{OCH}_2\text{CH}(\text{CH}_3)_2$), 4.70 (1H, q, $J = 6.6$ Hz, 2- CHBrCH_3), 5.49 (2H, s, $J = 15.3$ Hz, 8- CH_2OH), 6.34 (1H, s, 3-H), 7.0 (1H, d, $J = 9.0$ Hz, 6-H), 8.17 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 355 ($\text{M}^+ + 1$).

6.1.6. Synthesis of 1'-alkoxy-seco-DCPs (8–15)—The substituted 8-hydroxymethylchromone (**45a–d** or **46e–h**, 1 equiv), *S*-(–)-camphanic chloride (2.5 equiv), and DMAP (6 equiv) were stirred in CH_2Cl_2 (3 mL) for 1 h at room temperature, monitored by TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20:1). At completion, the mixture was concentrated and the residue was purified by column chromatography with an eluent of hexane/EtOAc 3:1 to afford eight target compounds (**8–15**).

6.1.6.1. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-methoxy-4H-chromen-4-one (8): 78% yield (starting with 32 mg of **45a**): mp 164–165 °C. ^1H NMR δ 0.92, 1.00, 1.10 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.31 (3H, t, $J = 7.8$ Hz, 2- CH_2CH_3), 1.61–2.46 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 2.66 (2H, q, $J = 7.8$ Hz, 2- CH_2CH_3), 3.97 (3H, s, 7- OCH_3), 5.54 (2H, t, $J = 11.4$ Hz, 4'- CH_2O -), 6.14 (1H, s, 3-H), 7.02 (1H, d, $J = 9.0$ Hz, 6-H), 8.22 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 415 ($\text{M}^+ + 1$).

6.1.6.2. 2-(1-Bromoethyl)-4'-((-)-camphanoyloxymethyl)-7-methoxy-4H-chromen-4-one (9): 77% yield (starting with 33 mg of **46e**): mp 211–213 °C. ^1H NMR δ 0.92, 1.01, 1.09 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.62–2.43 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 1.88 (3H, d, $J = 6.9$ Hz, 2- CHBrCH_3), 3.99 (3H, s, 7- OCH_3), 4.84 (1H, q, $J = 6.9$ Hz, 2- CHBrCH_3), 5.57 (2H, m, 4'- CH_2O -), 6.36 (1H, s, 3-H), 7.05 (1H, d, $J = 9.0$ Hz, 6-H), 8.23 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 493 ($\text{M}^+ + 1$).

6.1.6.3. 4'-((-)-Camphanoyloxymethyl)-7-ethoxy-2-ethyl-4H-chromen-4-one (10): 77% yield (starting with 24 mg of **45b**): mp 117–118 °C. ^1H NMR δ 0.93, 1.01, 1.10 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.31 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 1.46 (3H, t, $J = 6.9$ Hz, 7- OCH_2CH_3), 1.64–2.46 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 2.66 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 4.21 (2H, q, $J = 6.9$ Hz, 7- OCH_2CH_3), 5.54 (2H, t, $J = 11.4$ Hz, 4'- CH_2O -), 6.14 (1H, s, 3-H), 6.99 (1H, d, $J = 9.0$ Hz, 6-H), 8.20 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 429 ($\text{M}^+ + 1$).

6.1.6.4. 2-(1-Bromoethyl)-4'-((-)-camphanoyloxymethyl)-7-ethoxy-4H-chromen-4-one (11): 58% yield (starting with 19 mg of **46f**): mp 151–152 °C. ^1H NMR δ 0.93, 1.02, 1.09 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.47 (3H, t, $J = 6.9$ Hz, 7- OCH_2CH_3), 1.62–2.43 (7H, m, camphanoyl- $\text{CH}_2 \times 2$ and 2- CHBrCH_3), 4.23 (2H, q, $J = 6.9$ Hz, 7- OCH_2CH_3), 4.88 (1H, q, 2- CHBrCH_3), 5.58 (2H, m, 4'- CH_2O -), 6.35 (1H, d, $J = 8.4$ Hz, 3-H), 7.02 (1H, d, $J = 9.0$ Hz, 6-H), 8.20 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 507 ($\text{M}^+ + 1$).

6.1.6.5. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-isopropoxy-4H-chromen-4-one (12): 70% yield (starting with 38 mg of **45c**): mp 168–169 °C. ^1H NMR δ 0.94, 1.01, 1.10 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.30 (3H, t, $J = 7.2$ Hz, 2- CH_2CH_3), 1.39 (6H, d, $J = 6.0$ Hz, 7- $\text{OCH}(\text{CH}_3)_2$), 1.63–2.45 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 2.66 (2H, q, $J = 7.2$ Hz, 2- CH_2CH_3), 4.76 (2H, m, $J = 6.0$ Hz, 7- $\text{OCH}(\text{CH}_3)_2$), 5.53 (2H, t, $J = 11.4$ Hz, 4'- CH_2O -), 6.14 (1H, s, 3-H), 7.0 (1H, d, $J = 9.0$ Hz, 6-H), 8.20 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 443 ($\text{M}^+ + 1$).

6.1.6.6. 2-(1-Bromoethyl)-4'-((-)-camphanoyloxymethyl)-7-isopropoxy-4H-chromen-4-one (13): 92% yield (starting with 40 mg of **46g**): mp 50–52 °C. ¹H NMR δ 0.94, 1.01, 1.09 (9H, s, camphanoyl-CH₃ × 3), 1.40 (6H, d, *J* = 6.0 Hz, 7-OCH(CH₃)₂), 1.62–2.43 (7H, m, camphanoyl-CH₂ × 2 and 2-CHBrCH₃), 4.78 (1H, m, *J* = 6.0 Hz, 7-OCH(CH₃)₂), 4.88 (1H, m, 2-CHBrCH₃), 5.55 (2H, m, 4'-CH₂O-), 6.33 (1H, d, *J* = 7.5 Hz, 3-H), 7.02 (1H, d, *J* = 9.0 Hz, 6-H), 8.20 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 521 (M⁺+1).

6.1.6.7. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-isobutoxy-4H-chromen-4-one (14): 85% yield (starting with 30 mg of **45d**): mp 161–162 °C. ¹H NMR δ 0.92, 0.99, 1.04 (9H, s, camphanoyl-CH₃ × 3), 1.07 (6H, d, *J* = 6.9 Hz, 7-OCH₂CH(CH₃)₂), 1.31 (3H, t, *J* = 7.5 Hz, 2-CH₂CH₃), 1.60–2.45 (5H, m, camphanoyl-CH₂ × 2 & 7-OCH₂CH(CH₃)₂), 2.67 (2H, q, *J* = 7.5 Hz, 2-CH₂CH₃), 3.89 (2H, d, *J* = 6.9 Hz, 7-OCH₂CH(CH₃)₂), 5.56 (2H, t, *J* = 17.4 Hz, 4'-CH₂O-), 6.14 (1H, s, 3-H), 7.0 (1H, d, *J* = 9.0 Hz, 6-pH), 8.20 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 457 (M⁺+1).

6.1.6.8. 2-(1-Bromoethyl)-4'-((-)-camphanoyloxymethyl)-7-isobutoxy-4H-chromen-4-one (15): 92% yield (starting with 23 mg of **46h**): colorless oil. ¹H NMR δ 0.98, 1.05, 1.08 (9H, s, camphanoyl-CH₃ × 3), 1.12 (6H, d, *J* = 6.9 Hz, 7-OCH₂CH(CH₃)₂), 1.68 (3H, d, *J* = 6.9 Hz, 2-CHBrCH₃), 1.93–2.48 (5H, m, camphanoyl-CH₂ × 2 & 7-OCH₂CH(CH₃)₂), 3.91 (2H, d, *J* = 6.6 Hz, 7-OCH₂CH(CH₃)₂), 5.40 (2H, s, 4'-CH₂O-), 5.86 (1H, q, *J* = 6.9 Hz, 2-CHBrCH₃), 6.33 (1H, s, 3-H), 7.02 (1H, d, *J* = 9.3 Hz, 6-H), 8.18 (1H, d, *J* = 9.3 Hz, 5-H). ESI-MS *m/z* 535 (M⁺+1).

6.2. Synthesis of 1'-aryloxy-seco-DCPs (16–28)

6.2.1. 2-Ethyl-7-(methoxymethoxy)-8-methyl-4H-chromen-4-one (47)—The procedure was the same as that used for the preparation of **39**. 60% yield [starting from 3.0 g of **41**, but using DMF (20 mL) instead of acetone (60 mL)]: mp 93–94 °C. ¹H NMR δ 1.33 (3H, d, *J* = 7.2 Hz, 2-CH₂CH₃), 2.34 (3H, s, 8-CH₃), 2.68 (2H, q, *J* = 7.2 Hz, 2-CH₂CH₃), 3.51 (3H, s, 7-OCH₂OCH₃), 5.31 (2H, s, 7-OCH₂OCH₃), 6.13 (1H, s, 3-H), 7.15 (1H, d, *J* = 9.0 Hz, 6-H), 8.01 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 203 (M⁺-45).

6.2.2. 8-(Bromomethyl)-2-ethyl-7-(methoxymethoxy)-4H-chromen-4-one (48)—The procedure was the same as that used for the preparation of **43**. 39% yield (starting from 1.5 g of **47**): mp 61–64 °C. ¹H NMR δ 1.36 (3H, t, *J* = 7.5 Hz, 2-CH₂CH₃), 2.72 (2H, q, *J* = 7.5 Hz, 2-CH₂CH₃), 3.55 (3H, s, 7-OCH₂OCH₃), 4.80 (2H, s, 8-CH₂Br), 5.39 (2H, s, 7-OCH₂OCH₃), 6.16 (1H, s, 3-H), 7.18 (1H, d, *J* = 9.0 Hz, 6-H), 8.13 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 327 (M⁺+1).

6.2.3. 2-Ethyl-7-hydroxy-8-(hydroxymethyl)-4H-chromen-4-one (49)—The procedure was the same as that used for the preparation of **45**. 50% yield (starting from 100 mg of **48**): mp 147–148 °C. ¹H NMR δ 1.57 (3H, t, *J* = 7.8 Hz, 2-CH₂CH₃), 2.98 (2H, q, *J* = 7.8 Hz, 2-CH₂CH₃), 4.86 (2H, s, 8-CH₂OH), 6.38 (1H, s, 3-H), 7.18 (1H, d, *J* = 9.0 Hz, 6-H), 8.14 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 243 (M⁺+Na).

6.2.4. Synthesis of 7-aryloxy-substituted-8-(hydroxymethyl)-4H-chromen-4-one (50a–m)—The procedure was identical to that used in the preparation of **42a–b**.

6.2.4.1. 2-Ethyl-8-(hydroxymethyl)-7-(2-oxo-tetrahydrofuran-3-yloxy)-4H-chromen-4-one (50a): 70% yield (starting from 30 mg of **49**): mp 210–212 °C. ¹H NMR (CDCl₃ + CD₃OD) δ 1.33 (3H, t, *J* = 7.8 Hz, 2-CH₂CH₃), 2.54 (2H, m, *J* = 9.0 Hz, furanone 3-H₂), 2.72 (2H, q, *J* = 7.8 Hz, 2-CH₂CH₃), 2.92 (1H, br s, 8-OCH₂OH), 4.45, 4.62 (2H, m, *J*_J=9.0 Hz, furanone 4-H₂), 4.94 (1H, s, 8-CH₂OH), 5.24 (1H, t, *J*=9.0 Hz, furanone 2-H), 6.19 (1H,

s, 3-H), 7.17 (1H, d, $J = 9.0$ Hz, 6-H), 8.14 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 327 ($M^+ + Na$).

6.2.4.2. 2-Ethyl-8-(hydroxymethyl)-7-(pyridin-2-ylmethoxy)-4H-chromen-4-one (50b):

30% yield (starting from 38 mg of **49**): colorless oil. 1H NMR δ 1.36 (3H, t, $J = 7.8$ Hz, 2- CH_2CH_3), 2.20 (1H, br s, 8- CH_2OH), 2.75 (2H, q, $J = 7.8$ Hz, 2- CH_2CH_3), 5.02 (2H, d, $J = 6.9$ Hz, 8- CH_2OH), 5.39 (2H, s, 7- OCH_2-), 6.17 (1H, s, 3-H), 7.10 (1H, d, $J = 9.0$ Hz, 6-H), 7.37 (1H, m, $J = 7.2$ Hz, pyridine H), 7.55, 7.84 (2H, d, $J = 7.8$ Hz, pyridine H), 8.10 (1H, d, $J = 9.0$ Hz, 5-H), 8.60 (1H, m, $J = 7.8$ Hz, pyridine H). ESI-MS m/z 334 ($M^+ + Na$).

6.2.4.3. 2-Ethyl-8-(hydroxymethyl)-7-(pyridin-3-ylmethoxy)-4H-chromen-4-one (50c):

38% yield (starting from 30 mg of **49**): mp 115–116 °C. 1H NMR δ 1.33 (3H, t, $J = 7.8$ Hz, 2- CH_2CH_3), 2.40 (1H, br s, 8- CH_2OH), 2.70 (2H, q, $J = 7.8$ Hz, 2- CH_2CH_3), 5.00 (2H, s, 8- CH_2OH), 5.27 (2H, s, 7- OCH_2-), 6.14 (1H, s, 3-H), 7.07 (1H, d, $J = 9.0$ Hz, 6-H), 7.37 (1H, q, $J = 7.2$ Hz, pyridine H), 7.81 (1H, d, $J = 7.8$ Hz, pyridine H), 8.15 (1H, d, $J = 9.0$ Hz, 5-H), 8.62 (1H, d, $J = 7.8$ Hz, pyridine H), 8.72 (1H, s, pyridine H). ESI-MS m/z 334 ($M^+ + Na$).

6.2.4.4. 2-Ethyl-8-(hydroxymethyl)-7-(pyridin-4-ylmethoxy)-4H-chromen-4-one (50d):

33% yield (starting from 30 mg of **49**): mp 171–172 °C. 1H NMR δ 1.33 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 2.47 (1H, br s, 8- CH_2OH), 2.70 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 5.06 (2H, d, $J = 6.3$ Hz, 8- CH_2OH), 5.28 (2H, s, 7- OCH_2-), 6.14 (1H, s, 3-H), 6.99 (1H, d, $J = 9.0$ Hz, 6-H), 7.37 (2H, d, $J = 5.4$ Hz, pyridine H), 8.14 (1H, d, $J = 9.0$ Hz, 5-H), 8.64 (2H, d, $J = 4.8$ Hz, pyridine H). ESI-MS m/z 312 ($M^+ + H$).

6.2.4.5. 2-Ethyl-8-(hydroxymethyl)-7-(3-(trifluoromethyl)benzyloxy)-4H-chromen-4-one (50e):

29% yield (starting from 22 mg of **49**): mp 171–172 °C. 1H NMR δ 1.32 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 2.32 (1H, br s, 8- CH_2OH), 2.69 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 5.02 (2H, s, 8- CH_2OH), 5.30 (2H, s, 7- OCH_2-), 6.13 (1H, s, 3-H), 7.04 (1H, d, $J = 9.0$ Hz, 6-H), 7.53–7.71 (4H, m, aromatic H), 8.14 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 377 ($M^+ - H$).

6.2.4.6. 3-((2-Ethyl-8-(hydroxymethyl)-4-oxo-4H-chromen-7-yloxy)methyl)benzointrile (50f):

44% yield (starting from 24 mg of **49**): mp 201–202 °C. 1H NMR δ 1.35 (3H, t, $J = 7.8$ Hz, 2- CH_2CH_3), 2.74 (2H, q, $J = 7.8$ Hz, 2- CH_2CH_3), 5.00 (2H, s, 8- CH_2OH), 5.31 (2H, s, 7- OCH_2-), 6.17 (1H, s, 3-H), 7.06 (1H, d, $J = 9.0$ Hz, 6-H), 7.56 (1H, t, $J = 7.8$ Hz, aromatic H), 7.68 (1H, d, $J = 7.8$ Hz, aromatic H), 7.74 (1H, d, $J = 7.8$ Hz, aromatic H), 7.81 (1H, s, aromatic H), 8.12 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 334 ($M^+ - H$).

6.2.4.7. 2-Ethyl-8-(hydroxymethyl)-7-(3-methoxybenzyloxy)-4H-chromen-4-one (50g):

34% yield (starting from 30 mg of **49**): mp 108–110 °C. 1H NMR δ 1.33 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 2.38 (1H, br s, 8- CH_2OH), 2.68 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 3.83 (3H, s, phenyl OCH_3), 5.01 (2H, s, 8- CH_2OH), 5.23 (2H, s, 7- OCH_2-), 6.13 (1H, s, 3-H), 6.89–7.00 (3H, m, aromatic H), 7.05 (1H, d, $J = 9.0$ Hz, 6-H), 7.33 (1H, t, $J = 8.1$ Hz, aromatic H), 8.12 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 339 ($M^+ - H$).

6.2.4.8. Methyl-3-(2-ethyl-8-(hydroxymethyl)-4-oxo-4H-chromen-7-yloxy)benzoate (50h):

40% yield (starting from 30 mg of **49**): mp 153–155 °C. 1H NMR δ 1.32 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 2.33 (1H, br s, 8- CH_2OH), 2.69 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 3.94 (3H, s, phenyl OCH_3), 5.03 (2H, s, 8- CH_2OH), 5.30 (2H, s, 7- OCH_2-), 6.13 (1H, s, 3-H), 7.05 (1H, d, $J = 9.0$ Hz, 6-H), 7.51 (1H, t, $J = 7.8$ Hz, aromatic H), 7.65 (1H, d, $J = 7.8$ Hz, aromatic H), 8.05 (1H, d, $J = 7.8$ Hz, aromatic H), 8.12 (1H, s, aromatic H), 8.14 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 367 ($M^+ - H$).

6.2.4.9. 2-Ethyl-8-(hydroxymethyl)-7-(3-methylbenzyloxy)-4H-chromen-4-one (50i):

48% yield (starting from 30 mg of **49**): mp 147–149 °C. $^1\text{H NMR}$ δ 1.32 (3H, t, $J = 7.8$ Hz, 2- CH_2CH_3), 2.36 (1H, br s, 8- CH_2OH), 2.39 (3H, s, phenyl CH_3), 2.68 (2H, q, $J = 7.8$ Hz, 2- CH_2CH_3), 5.00 (2H, br s, 8- CH_2OH), 5.22 (2H, s, 7- OCH_2 -), 6.13 (1H, s, 3-H), 7.07 (1H, d, $J = 9.0$ Hz, 6-H), 7.12–7.34 (4H, m, aromatic H), 8.14 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 323 ($\text{M}^+ - \text{H}$).

6.2.4.10. 7-(3,5-Dimethoxybenzyloxy)-2-ethyl-8-(hydroxymethyl)-4H-chromen-4-one (50j):

44% yield (starting from 30 mg of **49**): mp 154–155 °C. $^1\text{H NMR}$ δ 1.32 (3H, t, $J = 7.8$ Hz, 2- CH_2CH_3), 2.37 (1H, t, $J = 6.9$ Hz, 8- CH_2OH), 2.68 (2H, q, $J = 7.8$ Hz, 2- CH_2CH_3), 3.81 (6H, s, $2 \times \text{OCH}_3$), 5.01 (2H, d, $J = 6.9$ Hz, 8- CH_2OH), 5.20 (2H, s, 7- OCH_2 -), 6.13 (1H, s, 3-H), 6.44 (1H, t, $J = 2.4$ Hz, aromatic H), 6.57 (2H, d, $J = 2.4$ Hz, aromatic H), 7.04 (1H, d, $J = 9.0$ Hz, 6-H), 8.13 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 369 ($\text{M}^+ - \text{H}$).

6.2.4.11. 2-Ethyl-8-(hydroxymethyl)-7-((3-trifluoromethoxy)benzyloxy)-4H-chromen-4-one (50k):

73% yield (starting from 30 mg of **49**): mp 109–110 °C. $^1\text{H NMR}$ δ 1.33 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 2.29 (1H, t, $J = 6.6$ Hz, 8- CH_2OH), 2.69 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 5.02 (2H, d, $J = 6.6$ Hz, 8- CH_2OH), 5.27 (2H, s, 7- OCH_2 -), 6.14 (1H, s, 3-H), 7.03 (1H, d, $J = 9.0$ Hz, 6-H), 7.23 (1H, d, $J = 7.8$ Hz, aromatic H), 7.31 (1H, s, aromatic H), 7.38 (1H, d, $J = 7.8$ Hz, aromatic H), 7.46 (1H, t, $J = 7.8$ Hz, aromatic H), 8.15 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 393 ($\text{M}^+ - \text{H}$).

6.2.4.12. 7-(2-Bromo-5-methoxybenzyloxy)-2-ethyl-8-(hydroxymethyl)-4H-chromen-4-one (50l):

39% yield (starting from 30 mg of **49**): mp 132–134 °C. $^1\text{H NMR}$ δ 1.32 (3H, t, $J = 7.8$ Hz, 2- CH_2CH_3), 1.83 (1H, br s, 8- CH_2OH), 2.69 (2H, q, $J = 7.8$ Hz, 2- CH_2CH_3), 3.81 (3H, s, OCH_3), 5.02 (2H, s, 8- CH_2OH), 5.26 (2H, s, 7- OCH_2 -), 6.13 (1H, s, 3-H), 6.80 (1H, dd, $J_1 = 9.0$ Hz, $J_2 = 3.3$ Hz, aromatic H), 7.04 (1H, s, aromatic H), 7.07 (1H, d, $J = 9.0$ Hz, aromatic H), 7.51 (1H, d, $J = 8.7$ Hz, 6-H), 8.14 (1H, d, $J = 8.7$ Hz, 5-H). ESI-MS m/z 441 ($\text{M}^+ + \text{Na}$).

6.2.4.13. 7-(4,5-Dimethoxy-2-nitrobenzyloxy)-2-ethyl-8-(hydroxymethyl)-4H-chromen-4-one (50m):

76% yield (starting from 30 mg of **49**): mp 222–224 °C. $^1\text{H NMR}$ δ 1.34 (3H, t, $J = 7.8$ Hz, 2- CH_2CH_3), 2.18 (1H, t, $J = 6.0$ Hz, 8- CH_2OH), 2.70 (2H, q, $J = 7.8$ Hz, 2- CH_2CH_3), 3.99 (6H, s, $2 \times \text{OCH}_3$), 5.07 (2H, d, $J = 6.0$ Hz, 8- CH_2OH), 5.68 (2H, s, 7- OCH_2 -), 6.15 (1H, s, 3-H), 7.07 (1H, d, $J = 8.7$ Hz, 6-H), 7.37 (1H, s, aromatic H), 7.80 (1H, s, aromatic H), 8.16 (1H, d, $J = 8.7$ Hz, 5-H). ESI-MS m/z 438 ($\text{M}^+ + \text{Na}$).

6.2.5. Synthesis of 1'-aryloxy-substituted-seco-DCPs (16–28)—The procedure was the same as that used for the preparation of **8–15**.

6.2.5.1. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-(2-oxo-tetrahydrofuran-3-yloxy)-4H-chromen-4-one (16):

37% yield, white solid (starting from 29 mg of **50a**): mp 211–212 °C. $^1\text{H NMR}$ δ 0.88, 0.99, 1.07 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.32 (3H, t, $J = 7.8$ Hz, 2- CH_2CH_3), 1.68, 1.90, 2.00, 2.39 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 2.68 (2H, q, $J = 7.8$ Hz, 2- CH_2CH_3), 2.83 (2H, m, furanone 3- H_2); 4.42, 4.58 (2H, m, $J_1 = 6.6$ Hz, $J_2 = 1.5$ Hz, furanone 4- H_2), 5.19 (1H, t, $J = 7.8$ Hz, furanone 2-H), 5.58 (2H, m, $J = 7.5$ Hz, 4'- CH_2 -), 6.16 (1H, s, 3-H), 7.21 (1H, dd, $J_1 = 9.0$ Hz, $J_2 = 3.3$ Hz, 6-H), 8.22 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 507 ($\text{M}^+ + \text{Na}$).

6.2.5.2. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-(pyridin-2-ylmethoxy)-4H-chromen-4-one (17):

44% yield, white solid (starting from 16 mg of **50b**): mp 169–170

°C. $^1\text{H NMR}$ δ 0.86, 0.97, 1.08 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.32 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 1.66, 1.87, 2.01, 2.34 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 2.68 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 5.39 (2H, s, 7-O CH_2 -), 5.66 (2H, s, 4'- CH_2 -), 6.15 (1H, s, 3-H), 7.05 (1H, d, $J = 9.0$ Hz, 6-H), 7.26, 7.55 (2H, m, $J = 7.8$ Hz, pyridine H), 7.78 (1H, m, $J_1=7.8$ Hz, $J_2=1.8$ Hz, pyridine H), 8.18 (1H, d, $J = 9.0$ Hz, 5-H), 8.61 (1H, m, $J = 7.8$ Hz, pyridine H). ESI-MS m/z 514 ($\text{M}^+\text{+Na}$).

6.2.5.3. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-(pyridin-3-ylmethoxy)-4H-chromen-4-one (18): 83% yield, white solid (starting from 16 mg of **50c**): mp 166–167 °C. $^1\text{H NMR}$ δ 0.81, 0.95, 1.08 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.32 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 1.66, 1.87, 2.01, 2.34 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 2.67 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 5.27 (2H, s, 7-O CH_2 -), 5.57 (2H, q, $J = 11.4$ Hz, 4'- CH_2 -), 6.16 (1H, s, 3-H), 7.08 (1H, d, $J = 8.7$ Hz, 6-H), 7.39 (1H, dd, $J_1=7.8$ Hz, $J_2=4.8$ Hz, pyridine H), 7.84 (1H, d, $J = 7.8$ Hz, pyridine H), 8.23 (1H, d, $J = 8.7$ Hz, 5-H), 7.78 (1H, dd, $J_1=6.3$ Hz, $J_2=1.8$ Hz, pyridine H), 8.69 (1H, d, $J = 1.2$ Hz, pyridine H). ESI-MS m/z 492 ($\text{M}^+\text{+H}$).

6.2.5.4. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-(pyridin-4-ylmethoxy)-4H-chromen-4-one (19): 90% yield, white solid (starting from 14 mg of **50d**): mp 162–163 °C. $^1\text{H NMR}$ δ 0.84, 0.97, 1.08 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.33 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 1.66, 1.87, 2.01, 2.39 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 2.68 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 5.28 (2H, s, 7-O CH_2 -), 5.64 (2H, q, $J = 11.4$ Hz, 4'- CH_2 -), 6.16 (1H, s, 3-H), 7.00 (1H, d, $J = 9.0$ Hz, 6-H), 7.38 (2H, d, $J = 6.0$ Hz, pyridine H), 8.21 (1H, d, $J = 9.0$ Hz, 5-H), 8.65 (2H, d, $J = 6.0$ Hz, pyridine H). ESI-MS m/z 492 ($\text{M}^+\text{+H}$).

6.2.5.5. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-(3-(trifluoromethyl)benzyloxy)-4H-chromen-4-one (20): 74% yield, white solid (starting from 11 mg of **50e**): mp 156–157 °C. $^1\text{H NMR}$ δ 0.81, 0.94, 1.07 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.32 (3H, t, $J = 7.8$ Hz, 2- CH_2CH_3), 1.66, 1.86, 1.98, 2.35 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 2.70 (2H, q, $J = 7.8$ Hz, 2- CH_2CH_3), 5.29 (2H, s, 7-O CH_2 -), 5.60 (2H, q, $J = 11.4$ Hz, 4'- CH_2 -), 6.16 (1H, s, 3-H), 7.05 (1H, d, $J = 9.0$ Hz, 6-H), 7.54–7.69 (4H, m, aromatic H), 8.22 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 559 ($\text{M}^+\text{+H}$).

6.2.5.6. 4'-((-)-Camphanoyloxymethyl)-7-(3-cyanobenzyloxy)-2-ethyl-4H-chromen-4-one (21): 65% yield, white solid (starting from 16 mg of **50f**): mp 175–176 °C. $^1\text{H NMR}$ δ 0.84, 0.98, 1.08 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.32 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 1.67, 1.90, 1.99, 2.40 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 2.70 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 5.28 (2H, s, 7-O CH_2 -), 5.61 (2H, q, $J = 11.4$ Hz, 4'- CH_2 -), 6.16 (1H, s, 3-H), 7.02 (1H, d, $J = 9.0$ Hz, 6-H), 7.54–7.75 (4H, m, aromatic H), 8.22 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 516 ($\text{M}^+\text{+H}$).

6.2.5.7. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-(3-methoxybenzyloxy)-4H-chromen-4-one (22): 57% yield, white solid (starting from 16 mg of **50g**): mp 126–127 °C. $^1\text{H NMR}$ δ 0.83, 0.94, 1.07 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.32 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 1.67, 1.87, 1.98, 2.37 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 2.69 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 5.23 (2H, s, 7-O CH_2 -), 3.82 (3H, s, OCH_3), 5.60 (2H, q, $J = 11.4$ Hz, 4'- CH_2 -), 6.14 (1H, s, 3-H), 6.87, 6.97 (2H, dd, $J_1=8.1$ Hz, $J_2=2.1$ Hz, aromatic H), 7.00 (1H, s, aromatic H), 7.05 (1H, d, $J = 9.0$ Hz, 6-H), 7.31 (1H, t, $J = 8.1$ Hz, aromatic H), 8.18 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 543 ($\text{M}^+\text{+Na}$).

6.2.5.8. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-(3-methoxycarbonylbenzyloxy)-4H-chromen-4-one (23): 97% yield, white solid (starting from 20 mg of **50h**): mp 190–191 °C. $^1\text{H NMR}$ δ 0.82, 0.94, 1.07 (9H, s, camphanoyl- $\text{CH}_3 \times 3$), 1.31 (3H, t, $J = 7.8$ Hz, 2- CH_2CH_3), 1.66, 1.87, 1.99, 2.37 (4H, m, camphanoyl- $\text{CH}_2 \times 2$), 2.67 (2H, q, $J = 7.8$ Hz, 2-

CH_2CH_3), 3.94 (3H, s, $-\text{OCOCH}_3$), 5.29 (2H, s, 7-OCH₂-), 5.60 (2H, q, $J = 11.7$ Hz, 4'-CH₂O-), 6.15 (1H, s, 3-H), 7.05 (1H, d, $J = 9.0$ Hz, 6-H), 7.51, 7.67, 8.03 (3H, d, $J = 7.8$ Hz, aromatic H), 8.09 (1H, s, aromatic H), 8.21 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 571 (M^+Na).

6.2.5.9. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-(3-methylbenzyloxy)-4H-chromen-4-one (24): 64% yield, white solid (starting from 21 mg of **50i**): mp 172–173 °C. ¹H NMR δ 0.83, 0.94, 1.07 (9H, s, camphanoyl-CH₃ × 3), 1.31 (3H, t, $J = 7.8$ Hz, 2-CH₂CH₃), 1.66, 1.87, 1.98, 2.37 (4H, m, camphanoyl-CH₂ × 2), 2.37 (3H, s, CH₃ on phenyl), 2.67 (2H, q, $J = 7.8$ Hz, 2-CH₂CH₃), 5.22 (2H, s, 7-OCH₂-), 5.59 (2H, q, $J = 11.1$ Hz, 4'-CH₂O-), 6.14 (1H, s, 3-H), 7.06 (1H, d, $J = 9.0$ Hz, 6-H), 7.14–7.31 (4H, m, aromatic H), 8.19 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 527 (M^+Na).

6.2.5.10. 4'-((-)-Camphanoyloxymethyl)-7-(3,5-dimethoxybenzyloxy)-2-ethyl-4H-chromen-4-one (25): 65% yield, white solid (starting from 30 mg of **50j**): mp 159–160 °C. ¹H NMR δ 0.84, 0.95, 1.07 (9H, s, camphanoyl-CH₃ × 3), 1.31 (3H, t, $J = 7.5$ Hz, 2-CH₂CH₃), 1.66, 1.87, 1.99, 2.37 (4H, m, camphanoyl-CH₂ × 2), 2.67 (2H, q, $J = 7.5$ Hz, 2-CH₂CH₃), 3.80 (6H, s, 2 × CH₃ on phenyl), 5.19 (2H, s, 7-OCH₂-), 5.60 (2H, q, $J = 11.4$ Hz, 4'-CH₂O-), 6.15 (1H, s, 3-H), 6.42 (1H, d, $J = 2.4$ Hz, aromatic H), 6.56 (2H, d, $J = 8.4$ Hz, aromatic H), 7.04 (1H, d, $J = 9.0$ Hz, 6-H), 8.18 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 573 (M^+Na).

6.2.5.11. 4'-((-)-Camphanoyloxymethyl)-2-ethyl-7-(3-trifluoromethoxybenzyloxy)-4H-chromen-4-one (26): 79% yield, white solid (starting from 39 mg of **50k**): mp 133–134 °C. ¹H NMR δ 0.82, 0.95, 1.07 (9H, s, camphanoyl-CH₃ × 3), 1.32 (3H, t, $J = 7.5$ Hz, 2-CH₂CH₃), 1.66, 1.87, 1.99, 2.37 (4H, m, camphanoyl-CH₂ × 2), 2.67 (2H, q, $J = 7.5$ Hz, 2-CH₂CH₃), 5.26 (2H, s, 7-OCH₂-), 5.60 (2H, q, $J = 11.1$ Hz, 4'-CH₂O-), 6.15 (1H, s, 3-H), 7.04 (1H, d, $J = 9.0$ Hz, 6-H), 7.22, 7.39 (2H, d, $J = 7.8$ Hz, aromatic H), 7.29 (1H, s, aromatic H), 7.46 (1H, t, $J = 7.8$ Hz, aromatic H), 8.21 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 597 (M^+Na).

6.2.5.12. 7-(2-Bromo-5-methoxybenzyloxy)-4'-((-)-camphanoyloxymethyl)-2-ethyl-4H-chromen-4-one (27): 54% yield, white solid (starting from 22 mg of **50l**): mp 158–159 °C. ¹H NMR δ 0.85, 0.95, 1.07 (9H, s, camphanoyl-CH₃ × 3), 1.32 (3H, t, $J = 7.5$ Hz, 2-CH₂CH₃), 1.66, 1.87, 1.99, 2.37 (4H, m, camphanoyl-CH₂ × 2), 2.67 (2H, q, $J = 7.5$ Hz, 2-CH₂CH₃), 3.80 (3H, s, CH₃ on phenyl), 5.25 (2H, s, 7-OCH₂-), 5.63 (2H, q, $J = 11.7$ Hz, 4'-CH₂O-), 6.16 (1H, s, 3-H), 6.77 (1H, dd, $J_1 = 8.7$ Hz, $J_2 = 3.0$ Hz, aromatic H), 7.05 (1H, d, $J = 9.0$ Hz, 6-H), 7.08 (1H, d, $J = 3.0$ Hz, aromatic H), 7.48 (1H, d, $J = 8.7$ Hz, aromatic H), 8.22 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 623 (M^+Na).

6.2.5.13. 4'-((-)-Camphanoyloxymethyl)-7-(4,5-dimethoxy-2-nitrobenzyloxy)-2-ethyl-4H-chromen-4-one (28): 79% yield, light yellow solid (starting from 43 mg of **50m**): mp 211–212 °C. ¹H NMR δ 0.81, 0.94, 1.06 (9H, s, camphanoyl-CH₃ × 3), 1.34 (3H, t, $J = 7.5$ Hz, 2-CH₂CH₃), 1.66, 1.87, 1.96, 2.37 (4H, m, camphanoyl-CH₂ × 2), 2.69 (2H, q, $J = 7.5$ Hz, 2-CH₂CH₃), 4.00 (6H, s, 2 × OCH₃), 5.66 (4H, s, 7-OCH₂- & 4'-CH₂O-), 6.17 (1H, s, 3-H), 7.09 (1H, d, $J = 9.0$ Hz, 6-H), 7.37 (1H, s, aromatic H), 7.81 (1H, s, aromatic H), 8.24 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 618 (M^+Na).

6.3. Synthesis of 4'-camphanol-seco-DCPs (29–31)

A mixture of **43a-c** (1 equiv), camphanol (1.2 equiv), and NaH (6 equiv) in toluene (6 mL) was stirred for 4 h at room temperature and monitored by TLC (CH₂Cl₂/MeOH 20:1). Ice-water (10 mL) was then added to stop the reaction. Following extraction with EtOAc (10

mL × 3), the organic layer was dried over Na₂SO₄. After removal of solvent *in vacuo*, the residue was purified by PTLC (eluent: CH₂Cl₂/MeOH 40:1 and 20:1) to give **29–31**.

6.3.1. 2-Ethyl-7-methoxy-8-(((4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptan-1-yl)methoxy)methyl)-4H-chromen-4-one (29)—12% yield, white solid (starting from 50 mg of **43a**): mp 127–128 °C. ¹H NMR δ 0.87 (6H, s, camphanol-CH₃ × 2), 1.07 (3H, s, camphanol-CH₃), 1.32 (3H, t, *J* = 7.5 Hz, 2-CH₂CH₃), 1.58–2.10 (4H, m, camphanol-CH₂ × 2), 2.68 (2H, q, *J* = 7.5 Hz, 2-CH₂CH₃), 3.84 (2H, q, *J* = 11.4 Hz, camphanol-CH₂), 3.97 (3H, s, 7-OCH₃), 4.86 (2H, q, *J*₁=11.4 Hz, *J*₂=13.8 Hz, 4'-CH₂O-), 6.14 (1H, s, 3-H), 7.02 (1H, d, *J* = 9.0 Hz, 6-H), 8.18 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 423 (M⁺+Na).

6.3.2. 2-Ethyl-7-ethoxy-8-(((4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptan-1-yl)methoxy)methyl)-4H-chromen-4-one (30)—9% yield, white solid (starting from 100 mg of **43b**): mp 60–62 °C. ¹H NMR δ 0.87 (6H, s, camphanol-CH₃ × 2), 1.07 (3H, s, camphanol-CH₃), 1.32 (3H, t, *J* = 7.5 Hz, 2-CH₂CH₃), 1.48 (3H, t, *J* = 6.9 Hz, 7-OCH₂CH₃), 1.61–2.04 (4H, m, camphanol-CH₂ × 2), 2.67 (2H, q, *J* = 7.5 Hz, 2-CH₂CH₃), 3.80 (2H, q, *J* = 13.8 Hz, camphanol-CH₂), 4.20 (2H, q, *J* = 6.9 Hz, 7-OCH₂CH₃), 4.87 (2H, q, *J*₁=10.5 Hz, *J*₂=24 Hz, 4'-CH₂O-), 6.13 (1H, s, 3-H), 6.99 (1H, d, *J* = 9.0 Hz, 6-H), 8.16 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 437 (M⁺+Na).

6.3.3. 2-Ethyl-7-isopropoxy-8-(((4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptan-1-yl)methoxy)methyl)-4H-chromen-4-one (31)—5% yield, colorless oil (starting from 200 mg of **43c**). ¹H NMR δ 0.87 (6H, s, camphanol-CH₃ × 2), 1.06 (3H, s, camphanol-CH₃), 1.32 (3H, t, *J* = 7.2 Hz, 2-CH₂CH₃), 1.40 (6H, d, *J* = 6.0 Hz, 7-OCH(CH₃)₂), 1.57–2.03 (4H, m, camphanol-CH₂ × 2), 2.67 (2H, q, *J* = 7.2 Hz, 2-CH₂CH₃), 3.78 (2H, q, *J* = 14.4 Hz, camphanol-CH₂), 4.74 (1H, m, *J* = 6.0 Hz, 7-OCH(CH₃)₂), 4.84 (2H, q, *J*₁=11.4 Hz, *J*₂=10.8 Hz, 4'-CH₂O-), 6.13 (1H, s, 3-H), 7.0 (1H, d, *J* = 9.0 Hz, 6-H), 8.13 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 429 (M⁺+1).

6.4. Synthesis of 4'-piperidinyl oxalamide-seco-DCPs (34–37)—A mixture of **43b** (1 equiv), piperidinyl oxalamide (1.2 equiv), and DMAP (2.5 equiv) in THF (5 mL) was stirred for 24 h at room temperature and monitored by TLC (CH₂Cl₂/MeOH 20:1). After removal of solvent *in vacuo*, the residue was purified by column chromatography (eluent: CH₂Cl₂/MeOH 99:1) to give **34–37**.

6.4.1. 7-Ethoxy-2-ethyl-8-((4-(2-oxo-2-(2-thienyl)acetyl)piperazin-1-yl)methyl)-4H-chromen-4-one (34)—27% yield, white solid (starting from 50 mg of **43b**): mp 62–64 °C. ¹H NMR δ 1.31 (3H, t, *J* = 7.5 Hz, 2-CH₂CH₃), 1.46 (3H, t, *J* = 6.9 Hz, 7-OCH₂CH₃), 2.58 (2H, t, *J* = 5.1 Hz, piperazine H₂), 2.66 (4H, m, 2-CH₂CH₃ & piperazine H₂), 3.44, 3.72 (4H, t, *J* = 5.1 Hz, piperazine H₂ × 2), 3.87 (2H, s, 8-CH₂-), 4.17 (2H, q, *J* = 6.9 Hz, 7-OCH₂CH₃), 6.12 (1H, s, 3-H), 6.98 (1H, d, *J* = 9.0 Hz, 6-H), 7.18, 7.80 (3H, d, *J* = 3.9 Hz, thiophene H), 8.12 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 455 (M⁺+1).

6.4.2. 7-Ethoxy-2-ethyl-8-((4-(2-oxo-2-phenylacetyl)piperazin-1-yl)methyl)-4H-chromen-4-one (35)—11% yield, white solid (starting from 50 mg of **43b**): mp 61–62 °C. ¹H NMR δ 1.31 (3H, t, *J* = 7.5 Hz, 2-CH₂CH₃), 1.45 (3H, t, *J* = 7.2 Hz, 7-OCH₂CH₃), 2.53 (2H, t, *J* = 5.1 Hz, piperazine H₂), 2.64 (2H, q, *J* = 7.5 Hz, 2-CH₂CH₃), 2.68, 3.33, 3.75 (6H, t, *J* = 5.1 Hz, piperazine H₂ × 3), 3.87 (2H, s, 8-CH₂-), 4.17 (2H, q, *J* = 7.2 Hz, 7-OCH₂CH₃), 6.12 (1H, s, 3-H), 6.98 (1H, d, *J* = 9.0 Hz, 6-H), 7.51 (2H, t, *J* = 7.8 Hz, aromatic H), 7.65 (1H, t, *J* = 6.6 Hz, aromatic H), 7.94 (1H, d, *J* = 7.4 Hz, aromatic H), 8.13 (1H, d, *J* = 9.0 Hz, 5-H). ESI-MS *m/z* 449 (M⁺+1).

6.4.3. 7-Ethoxy-2-ethyl-8-((4-(2-oxo-3-phenylpropanoyl)piperazin-1-yl)methyl)-4H-chromen-4-one (36)—10% yield, white solid (starting from 50 mg of **43b**): mp 54–56 °C. $^1\text{H NMR}$ δ 1.30 (3H, t, $J = 7.2$ Hz, 2- CH_2CH_3), 1.45 (3H, t, $J = 6.9$ Hz, 7- OCH_2CH_3), 2.06, 2.44, 3.08, 3.52 (8H, t, $J = 5.1$ Hz, piperazine $\text{H}_2 \times 4$), 2.63 (2H, q, $J = 7.2$ Hz, 2- CH_2CH_3), 3.78 (2H, s, 8- CH_2 -), 4.02 (2H, s, - $\text{CH}_2\text{-C}_6\text{H}_5$), 4.16 (2H, q, $J = 6.9$ Hz, 7- OCH_2CH_3), 6.13 (1H, s, 3-H), 6.97 (1H, d, $J = 9.0$ Hz, 6-H), 7.17–7.27 (1H \times 5, m, $J_1 = 7.2$ Hz, $J_2 = 6.6$ Hz, aromatic H), 8.13 (1H, d, $J = 9.0$ Hz, 5-H). ESI-MS m/z 463 (M^+H).

6.4.4. 4'-((4-(2-(1H-Indol-3-yl)-2-oxoacetyl)piperazin-1-yl)methyl)-2-ethyl-7-ethoxy-4H-chromen-4-one (37)—29% yield, white solid (starting from 50 mg of **43b**): mp 122–124 °C. $^1\text{H NMR}$ δ 1.30 (3H, t, $J = 7.5$ Hz, 2- CH_2CH_3), 1.44 (3H, t, $J = 6.9$ Hz, 7- OCH_2CH_3), 2.53, 2.66, 3.48, 3.73 (8H, t, $J = 5.1$ Hz, piperazine $\text{H}_2 \times 4$), 2.64 (2H, q, $J = 7.5$ Hz, 2- CH_2CH_3), 3.90 (2H, s, 8- CH_2 -), 4.15 (2H, q, $J = 6.9$ Hz, 7- OCH_2CH_3), 6.12 (1H, s, 3-H), 6.97 (1H, d, $J = 9.0$ Hz, 6-H), 7.24–7.41 (3H, m, aromatic H), 7.85 (1H, br s, aromatic H), 8.13 (1H, d, $J = 9.0$ Hz, 5-H), 8.31 (1H, br s, pyrrole H), 10.09 (1H, br s, pyrrole NH). ESI-MS m/z 488 (M^+H).

6.5. Synthesis of 1'-thia -seco-DCK (32)

6.5.1. 7-Hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde (52)—A reaction mixture of **51** (20.0 g, 114 mmol) and hexamethylenetetramine (40.0 g, 285 mmol) in HOAc (150 mL) was stirred for 5.5 h at 80–90 °C. Aq. HCl (300 mL, conc. HCl/ H_2O 84:100, v/v) was then added, and the reaction mixture was stirred for 0.5 h at 70 °C. After cooling, the reaction mixture was poured into ice-water (1.5 L) and extracted with EtOAc (500 mL \times 3). The combined organic fraction was dried over Na_2SO_4 , and the solvent was removed *in vacuo*. The residue was recrystallized from EtOAc to provide **52** as a light yellow solid (2.4 g, 11% yield): mp 120–122 °C.

6.5.2. 8-(1,3-Dioxolan-2-yl)-7-hydroxy-4-methyl-2H-chromene-2-one (53)—A mixture of **52** (2.13 g, 10.4 mmol), ethane-1,2-diol (3.0 mL) and *p*-toluenesulfonic acid (120 mg) in toluene (25 mL) was refluxed for 2 h with removal of water by a water separator. After removing solvent *in vacuo*, the residue was dissolved in CH_2Cl_2 and filtered. The filtrate was washed with saturated NaHCO_3 , and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **53** as a yellow solid (1.96 g, 76% yield): mp 215–217 °C. $^1\text{H NMR}$ δ 2.39 (3H, s, 4- CH_3), 4.11–4.61 (4H, m, 2 \times CH_2 of 1,3-dioxolane), 6.12 (1H, s, 3-H), 6.39 (1H, s, 8- CH -), 6.84 (1H, d, $J = 9.1$ Hz, 6-H), 7.50 (1H, d, $J = 9.1$ Hz, 5-H).

6.5.3. O-(8-(1,3-Dioxolan-2-yl)-4-methyl-2-oxo-2H-chromen-7-yl)-N,N-dimethylcarbamothioate (54)—Compound **53** (1.50 g, 6.05 mmol) and KOH (2.0 g, 36 mmol) were dissolved in MeOH (30 mL) and reacted with dimethylthiocarbamoyl chloride (2.5 g, 20 mmol) for 3 h at rt. The mixture was poured into saturated NH_4Cl (150 mL) and filtered to afford crude product, which was purified by column chromatography (eluent: petroleum ether/EtOAc 4:1) to give **54** as a white solid (667 mg, 33% yield): mp 190–192 °C. $^1\text{H NMR}$ δ 2.36 (3H, s, 4- CH_3), 3.38, 3.47 (6H, s, - $\text{N}(\text{CH}_3)_2$), 4.05–4.40 (4H, m, 2 \times CH_2 of 1,3-dioxolane), 6.27 (2H, s, 3-H & 8- CH -), 7.02 (1H, d, $J = 8.6$ Hz, 6-H), 7.62 (1H, d, $J = 8.6$ Hz, 5-H). ESI-MS m/z 336 ($\text{M}+\text{H}$).

6.5.4. S-(8-(1,3-Dioxolan-2-yl)-4-methyl-2-oxo-2H-chromen-7-yl)-N,N-dimethylcarbamothioate (55)—Compound **54** (1.50 g, 5.70 mmol) was heated to 200 °C with stirring for 1 h. The crude product was purified by column chromatography (eluent: petroleum ether/EtOAc 4:1) to give **55** as light yellow crystals (235 mg, 47% yield): mp 138–140 °C. $^1\text{H NMR}$ δ 2.42 (3H, s, 4- CH_3), 3.08 (6H, s, - $\text{N}(\text{CH}_3)_2$), 4.05–4.48 (4H, m,

2×CH₂ of 1,3-dioxolane), 6.36 (1H, s, 3-H), 6.65 (1H, s, 8-CH-), 7.46 (1H, d, *J* = 8.29 Hz, 6-H), 7.59 (1H, d, *J* = 8.29 Hz, 5-H). ESI-MS *m/z* 336 (M+H).

6.5.5. 7-(Isopropylthio)-4-methyl-2-oxo-2H-chromene-8-carbaldehyde (58)—

Under nitrogen and in the dark, compound **55** (200 mg, 0.6 mmol) was hydrolyzed in the presence of KOH (500 mg) in MeOH (20 mL) for 2 h at reflux temperature. At completion, 2-bromopropane (2.0 mL) was added, and the reaction continued for another 30 min. The reaction solution was then poured into cool 1N HCl (100 mL) and filtered to give **58** as a light yellow solid (12 mg, 8% yield): mp 159–162 °C. ¹H NMR δ 1.44 (6H, d, *J* = 6.7 Hz, 7-SCH(CH₃)₂), 2.45 (3H, s, 4-CH₃), 3.62 (1H, m, *J* = 6.7 Hz, 7-SCH(CH₃)₂), 6.15 (1H, s, 3-H), 7.30 (1H, d, *J* = 9.0 Hz, 6-H), 7.67 (1H, d, *J* = 9.0 Hz, 5-H), 10.84 (1H, s, 8-CHO). ESI-MS *m/z* 263 (M+H).

6.5.6. 4'-((-)-Camphanoyloxymethyl)-7-(isopropylthio)-4-methyl-2H-chromen-2-one (32)—

A mixture of **58** (9 mg, 0.034 mmol) and NaBH₄ (3 mg) in MeOH (2 mL) was stirred for 1 h at room temperature, then acidified to pH 3–4 with 1N HCl and extracted with CH₂Cl₂ (10 mL×3). The organic layer was dried over anhydrous Na₂SO₄, and most of the solvent was removed under reduced pressure to give crude **59**. Then, **32** was synthesized following the same synthetic procedure as for **16–28**, but starting from **59**. 52% yield, White solid: mp 146–147 °C. ¹H NMR δ × 3, 1.34 (6H, d, *J* = 6.7 Hz, 1.00, 1.05, 1.09 (9H, s, camphanoyl-CH₃), 1.67–2.46 (4H, m, camphanoyl-CH₂ × 2), 2.47 (3H, s, 4-CH₃), 3.57 (1H, m, *J* = 6.7 Hz, 7-SCH(CH₃)₂), 5.65 (2H, s, 4'-CH₂O-), 6.27 (1H, s, 3-H), 7.36 (1H, d, *J* = 8.4 Hz, 6-H), 7.57 (1H, d, *J* = 8.4 Hz, 5-H). ESI-MS *m/z* 445 (M+H).

6.6. Synthesis of 1'-thia-seco-DCP (33)

6.6.1. 2-Ethyl-7-hydroxy-4H-chromen-4-one (64)—The procedure was the same as that used for the preparation of **41**. 52% yield, white crystals (starting from 10 g of **60**): mp 188–189 °C.

6.6.2. 2-Ethyl-7-hydroxy-4-oxo-4H-chromen-8-carbaldehyde (65)—The procedure was the same as that used for the preparation of **52**. 44% yield, white crystals (starting from 650 mg of **64**): mp 179–181 °C.

6.6.3. O-(8-(1,3-Dioxolan-2-yl)-2-ethyl-4-oxo-4H-chromen-7-yl)-N,N-dimethylcarbamothioate (67)—Compound **66** was prepared by the same procedure as used for the preparation of **52**. However, due to its instability, **66** was not purified, but was reacted directly with dimethylthiocarbonyl chloride (1.0 g, 8.09 mmol) to give compound **67** following the same method used for the synthesis of **54**. 31% yield, white solid (starting from 600 mg of **66**): mp 132–134 °C. ¹H NMR δ 1.31 (3H, t, *J* = 7.43 Hz, 2-CH₂CH₃), 2.66 (2H, q, *J* = 7.43 Hz, 2-CH₂CH₃), 3.43 (6H, s, -N(CH₃)₂), 4.08, 4.24 (4H, m, 2 × CH₂ of 1,3-dioxolane), 6.19 (1H, s, 3-H), 6.35 (1H, s, 8-CH-), 7.06 (2H, d, *J* = 8.6 Hz, 6-H), 8.22 (2H, d, *J* = 8.6 Hz, 5-H). ESI-MS *m/z* 350 (M+H).

6.6.4. S-(8-(1,3-Dioxolan-2-yl)-2-ethyl-4-oxo-4H-chromen-7-yl)-N,N-dimethylcarbamothioate (68)—The procedure was the same as that used for the preparation of **55**. 34% yield, light yellow solid (starting from 450 mg of **67**): mp 132–135 °C. ¹H NMR δ 1.32 (3H, t, *J* = 7.4 Hz, 2-CH₂CH₃), 2.66 (2H, q, *J* = 7.4 Hz, 2-CH₂CH₃), 3.13 (6H, s, -N(CH₃)₂), 4.08, 4.27 (4H, m, 2×CH₂ of 1,3-dioxolane), 6.21 (1H, s, 3-H), 6.59 (1H, s, 8-CH-), 7.52 (1H, d, *J* = 8.6 Hz, 6-H), 8.20 (2H, d, *J* = 8.6 Hz, 5-H). ESI-MS *m/z* 350 (M+H).

6.6.5. 2-Ethyl-7-(isopropylthio)-4-oxo-4H-chromene-8-carbaldehyde (71)—The procedure was the same as that used for the preparation of **58**. 52% yield, light yellow solid (starting from 70 mg of **68**): mp 152–154 °C. ¹H NMR δ 1.32 (3H, t, *J* = 7.3 Hz, 2-CH₂CH₃), 1.45 (6H, d, *J* = 6.7 Hz, 7-SCH(CH₃)₂), 2.72 (2H, q, *J* = 7.3 Hz, 2-CH₂CH₃), 3.67 (1H, m, *J* = 6.7 Hz, 7-SCH(CH₃)₂), 6.23 (1H, s, 3-CH), 7.40 (1H, d, *J* = 9.0 Hz, 6-H), 8.24 (1H, d, *J* = 9.0 Hz, 5-H), 10.81 (1H, s, 8-CHO). ESI-MS *m/z* 277 (M+H).

6.6.6. 4'-((-)-Camphanoyloxymethyl)-7-(isopropylthio)-2-ethyl-4H-chromene-2-one (33)—The procedure was the same as that used for the preparation of **32**. 48% yield, white solid (starting from 27 mg of **71**): mp 92–94 °C. ¹H NMR δ 0.95, 1.05, 1.00, 1.09 (9H, s, camphanoyl-CH₃ × 3), 1.31 (3H, t, *J* = 7.3 Hz, 2-CH₂CH₃), 1.35 (6H, d, *J* = 6.7 Hz, 7-SCH(CH₃)₂), 1.89–2.40 (4H, m, camphanoyl-CH₂ × 2), 2.67 (2H, q, *J* = 7.3 Hz, 2-CH₂CH₃), 3.62 (1H, m, *J* = 6.7 Hz, 7-SCH(CH₃)₂), 5.66 (2H, s, 4'-CH₂O-), 6.18 (1H, s, 3-H), 7.42 (1H, d, *J* = 8.6 Hz, 6-H), 8.14 (1H, d, *J* = 8.6 Hz, 5-H). ESI-MS *m/z* 459 (M+H).

6.7. HIV-1 infectivity assay

Anti-HIV-1 activity was measured as reductions in Luc reporter gene expression after a single round of virus infection of TZM-bl cells. HIV-1 at 200 TCID₅₀ and various dilutions of test samples (eight dilutions, fourfold stepwise) were mixed in a total volume of 100 μL growth medium in 96-well black solid plates (Corning-Costar). After 48-h incubation, culture medium was removed from each well and 100 μL of Bright Glo luciferase reagent was added to each culture well. The luciferase activity in the assay wells was measured using a Victor 2 luminometer. The 50% inhibitory dose (EC₅₀) was defined as the sample concentration that caused a 50% reduction in Relative Luminescence Units (RLU) compared to virus control wells after subtraction of background RLU.

6.8. Cytotoxicity assay

Compounds were tested for cytotoxicity against TZM-bl cells. The cells at 1 × 10⁵ cells/mL were added to each well in a 96-well plate in the presence of various concentrations of the tested compounds for an indicated period parallel to the antiviral assays. Cell viability was determined by using a Promega cytotoxicity assay kit, CellTiter-Glo® Luminescent Cell Viability Assay, following the manufacturer's instruction. The drug concentration that resulted in a 50% decrease in viable cells was defined as the IC₅₀ of the compound.

6.9. Chemical stability analysis

Each tested compound (1 mg) was dissolved in MeOH (0.5 mL) in centrifuge tubes. After adding 1% HCl (0.2 mL) into the tubes, each mixture was shaken at room temperature. The amount of compound in acidic solution was measured by HPLC (Column: Hypersil ODS2 5μm, 4.6 mm G250 mm; a mobile phase of 30% water and 70% MeOH) at 1 min and 30 min.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Kilmarx PH. *Curr Opin HIV AIDS*. 2009; 4:240–246. [PubMed: 19532059]
2. Huang L, Kashiwada Y, Cosentino LM, Fan S, Chen CH, McPhail AT, Fujioka T, Mihashi K, Lee KH. *J Med Chem*. 1994; 37:3947–3955. [PubMed: 7525962]
3. Xie L, Takeuchi Y, Cosentino LM, Lee KH. *J Med Chem*. 1999; 42:2662–2672. [PubMed: 10411486]
4. Yang ZY, Xia Y, Xia P, Brossi A, Cosentino LM, Lee KH. *Bioorg Med Chem Lett*. 2000; 10:1003–1005. [PubMed: 10843202]
5. Chen Y, Zhang Q, Zhang B, Xia P, Xia Y, Yang ZY, Kilgore N, Wild C, Morris-Natschke SL, Lee KH. *Bioorg Med Chem*. 2004; 12:6383–6387. [PubMed: 15556756]
6. Xia P, Yin ZJ, Chen Y, Zhang Q, Zhang B, Xia Y, Yang ZY, Kilgore N, Wild C, Morris-Natschke SL, Lee KH. *Bioorg Med Chem Lett*. 2004; 14:3341–3343. [PubMed: 15149703]
7. Xie L, Yu D, Wild C, Allaway G, Turpin J, Smith PC, Lee KH. *J Med Chem*. 2004; 47:756–760. [PubMed: 14736256]
8. Zhang Q, Chen Y, Xia P, Xia Y, Yang ZY, Yu D, Morris-Natschke SL, Lee KH. *Bioorg Med Chem Lett*. 2004; 14:5855–5857. [PubMed: 15501055]
9. Wang Y, Huang SX, Xia P, Xia Y, Yang ZY, Kilgore N, Morris-Natschke SL, Lee KH. *Bioorg Med Chem Lett*. 2007; 17:4316–4319. [PubMed: 17533128]
10. Xu SQ, Yan X, Chen Y, Xia P, Qian K, Yu D, Xia Y, Yang ZY, Morris-Natschke SL, Lee KH. *Bioorg Med Chem*. 2010; 18:7203–7211. [PubMed: 20846868]
11. Yu D, Brossi A, Kilgore N, Wild C, Allaway G, Lee KH. *Bioorg Med Chem Lett*. 2003; 13:1575–1576. [PubMed: 12699758]
12. Zhou T, Shi Q, Chen CH, Zhu H, Huang L, Ho P, Lee KH. *Bioorg Med Chem*. 2010; 18:6678–6689. [PubMed: 20728367]
13. Tang J, Qian K, Zhang BN, Chen Y, Xia P, Yu D, Xia Y, Yang ZY, Chen CH, Morris-Natschke SL, Lee KH. *Bioorg Med Chem*. 2010; 18:4363–4373. [PubMed: 20537902]

Research Highlights

- Thirty 2',3'-seco-3'-nor DCP and DCK analogs (**8–37**) were designed and synthesized.
- Several seco-compounds showed potent anti-HIV activity against HIV-1_{NL4-3} and RTMDR strains.
- 1'-*O*-Isopropoxy-2',3'-seco-3'-nor-DCP (**12**) showed the greatest potency among the newly synthesized compounds.
- The seco-analogues exhibited better chemical stability in acidic conditions than DCP/DCK compounds.
- Seco-DCP analogues may be favorable for development as novel anti-HIV candidates.

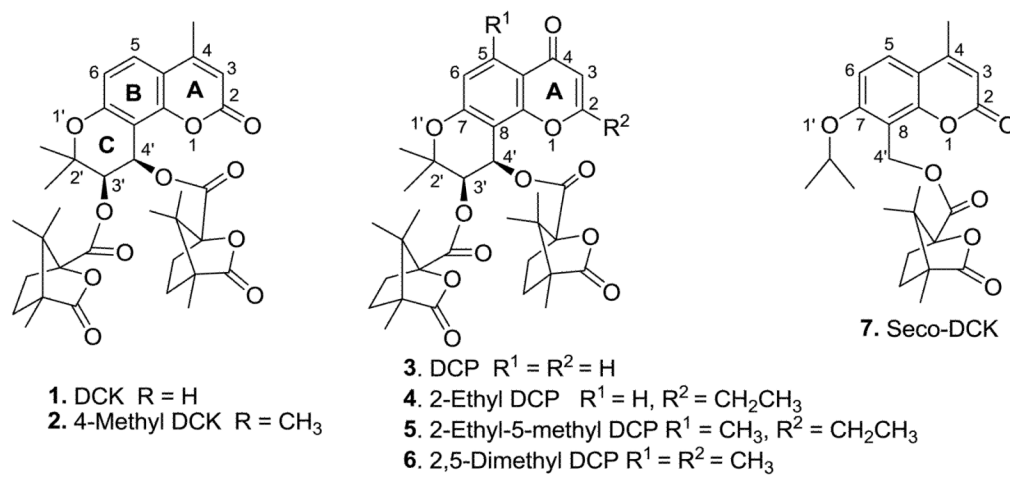


Figure 1.
DCK & DCP analogues and seco-DCK

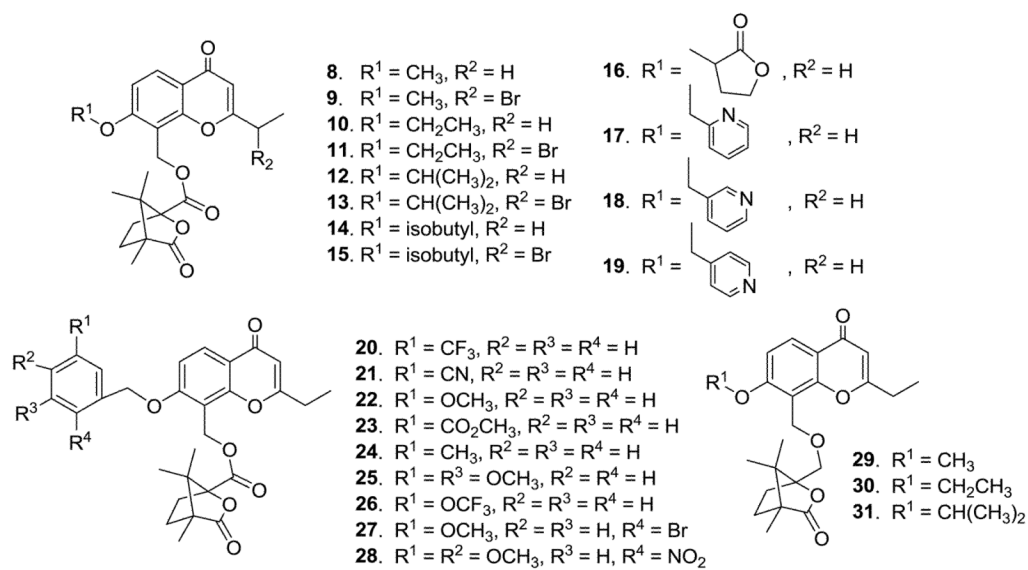


Figure 2.
Newly designed 1'-*O*-substituted 2',3'-seco-3'-nor-DCP analogues (**8–31**)

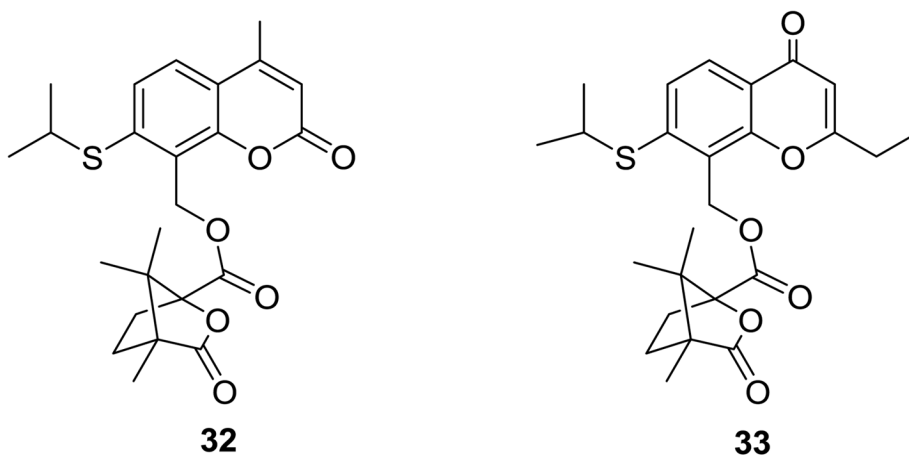


Figure 3. Newly designed 1'-thia-2',3'-seco-3'-nor-DCK (**32**) and -DCP (**33**) analogues

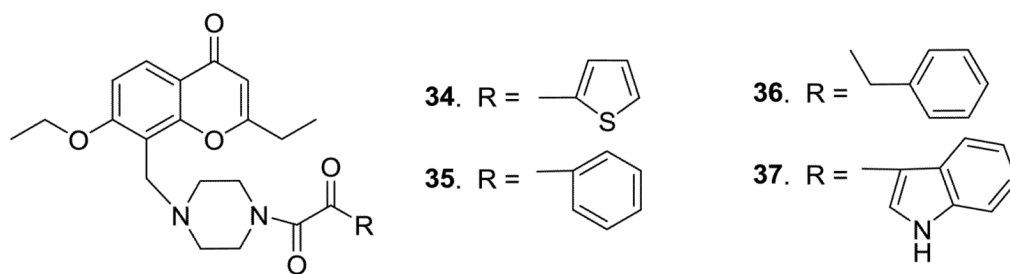
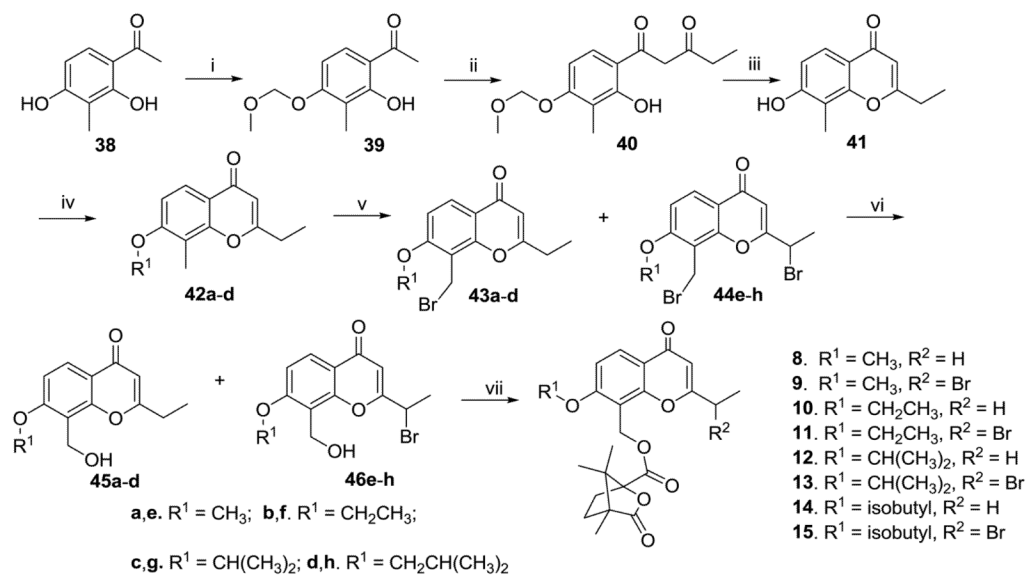
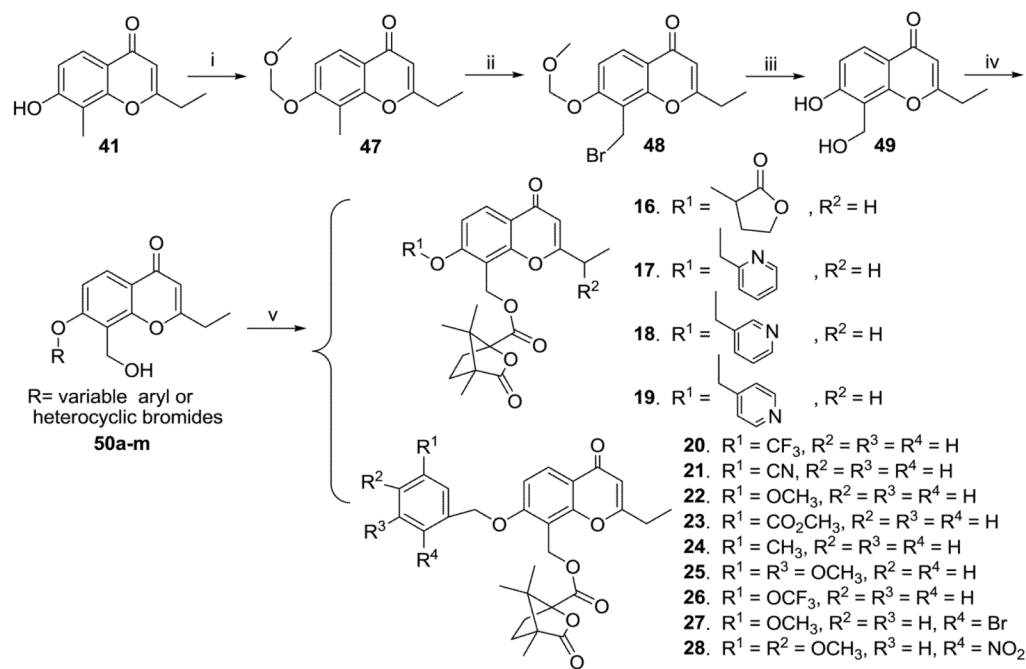


Figure 4. Newly designed 4'-(N'-substituted piperidin-1-yl)-2',3'-seco-3'-nor-DCP analogues (**34–37**)

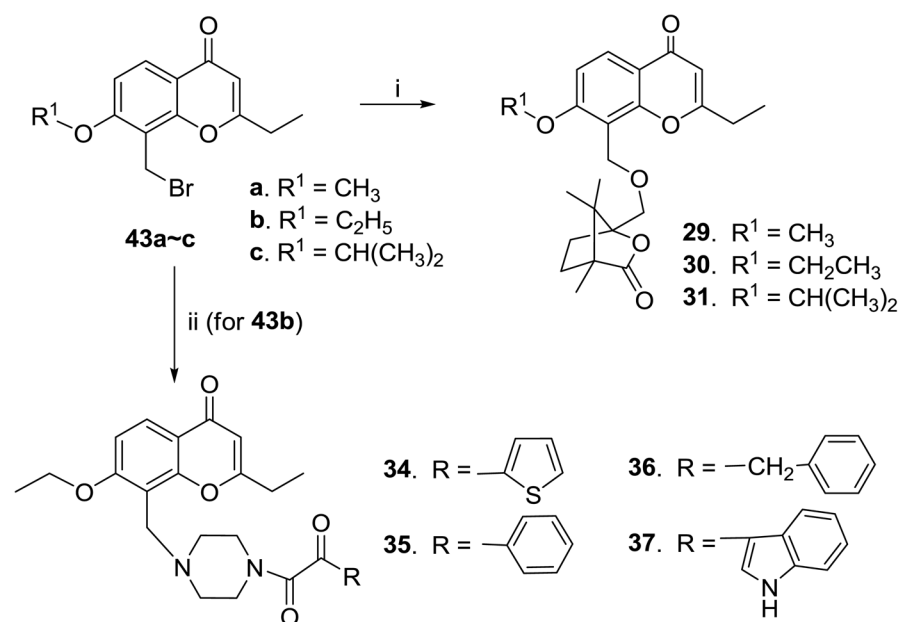
**Scheme 1.**

The synthetic routes to 1'-O-alkyl-2',3'-seco-3'-nor-DCPs (**8–15**). Reagents and conditions:

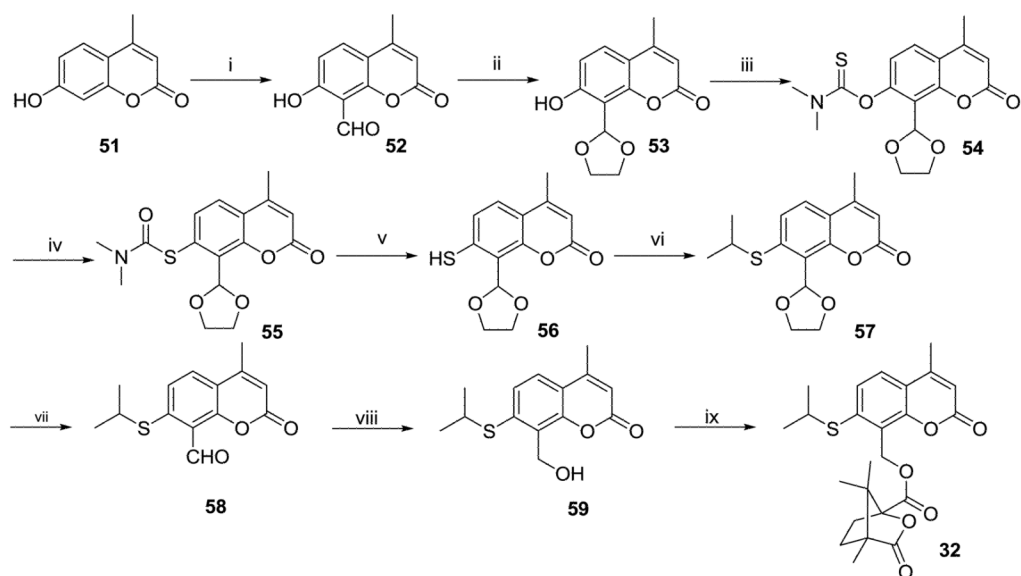
(i). chloromethyl methyl ether/ K_2CO_3 /acetone/rt; (ii). ethyl propionate/ NaH /THF/reflux;
 (iii). conc. HCl /EtOH/reflux; (iv). variable bromides/ K_2CO_3 /DMF; (v). 1.2 equiv. NBS / CCl_4 /reflux;
 (vi). a. $\text{NaOAc}/\text{Ac}_2\text{O}$ /reflux; b. 2N HCl /EtOH/reflux; (vii). camphanoyl chloride/ $\text{DMAP}/\text{CH}_2\text{Cl}_2$ /rt.

**Scheme 2.**

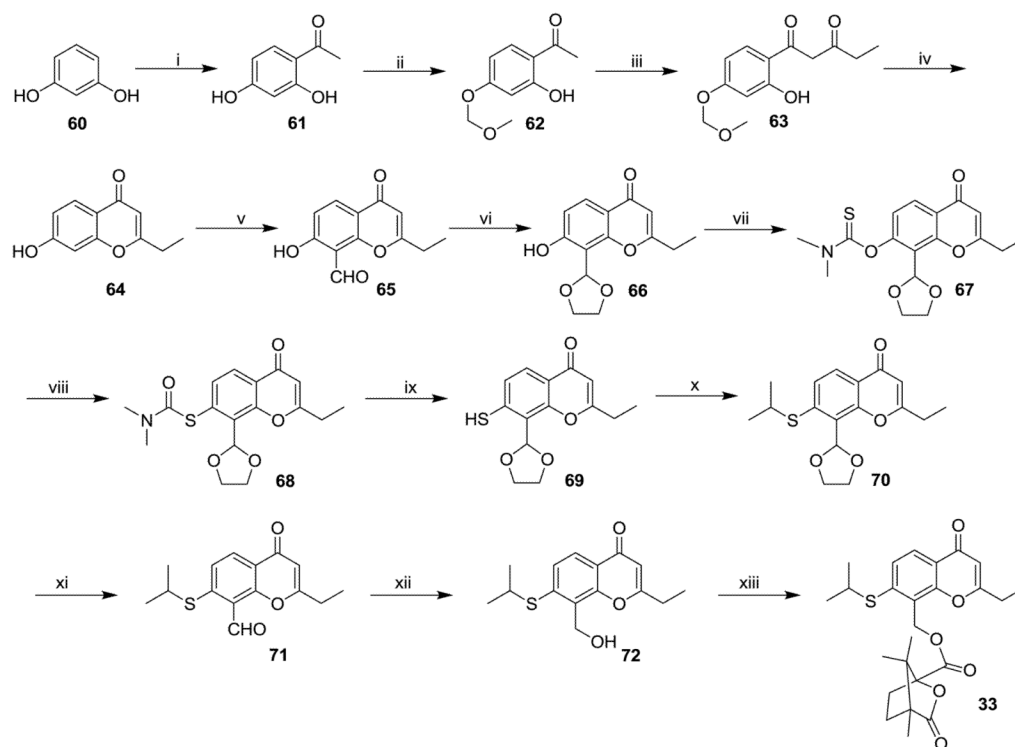
The synthesis of 1'-*O*-aryl or heterocyclic substituted 2',3'-seco-3'-nor-2-ethyl-DCPs (**16–28**). Reaction Conditions: (i). chloromethyl methyl ether/ K_2CO_3 /DMF/rt; (ii). 1.2 equiv. NBS/ CCl_4 /reflux; (iii). a. NaOAc/ Ac_2O /reflux; b. 2N HCl/EtOH/reflux; (iv). variable bromides/ K_2CO_3 /DMF/rt; (v). camphanoyl chloride/DMAP/ CH_2Cl_2 /rt.

**Scheme 3.**

The synthetic routes to 4'-camphanol ethers of 2',3'-seco-3'-nor-2-ethyl-DCPs (**29–31**) and 4'-(N'-substituted piperidin-1-yl)-2',3'-seco-3'-nor-DCP analogues (**36–39**). Reaction Conditions: (i). camphanol/NaH/toluene/rt; (ii). variable N'-substituted piperidines/DMAP/THF/rt.

**Scheme 4.**

The synthetic route to 1'-thia-2',3'-seco-3'-nor-4-methyl-DCK (**32**). Reaction Conditions: (i). hexamethylenamine/HOAc; (ii). HOCH₂CH₂OH/p-TSA/benzene/reflux; (iii). dimethylthiocarbonyl chloride/DMF/K₂CO₃; (iv). heat at 195–205 °C; (v). KOH/MeOH; (vi). isopropyl bromide/KOH/DMF; (vii). 1N HCl; (viii). NaBH₄/MeOH; (ix). camphanoyl chloride/DMAP/CH₂Cl₂

**Scheme 5.**

The synthesis of 1'-thia-2',3'-seco-3'-nor-2-ethyl-DCP (**33**). Reaction Conditions: (i). HOAc/ ZnCl_2 /reflux; (ii). chloromethyl methyl ether/ K_2CO_3 /acetone/ice-water bath; (iii). ethyl propionate/ NaH /THF/reflux; (iv). conc. HCl/EtOH/reflux; (v). a. urotropin/HOAc/reflux; b. HCl/reflux; (vi). ethylene glycol/benzene/*p*-TSA- H_2O /reflux; (vii). dimethylthiocarbamoyl chloride/ K_2CO_3 /MeOH; (viii). N_2 /220 °C; (ix). K_2CO_3 /MeOH/reflux; (x). 2-bromopropane; (xi). 1N HCl; (xii). NaBH_4 /MeOH; (xiii). camphanoyl chloride/DMAP/ CH_2Cl_2 .

Table 1

Anti-HIV-1_{NL4-3} and HIV-1 RTMDR results of seco-DCP analogues (8–15, 29–31, and 34–37) in TZM-bl cells^a

Compd	CC ₅₀ (μM)	HIV-1 _{NL4-3}			RTMDR		
		EC ₅₀ (μM)	TI	EC ₅₀ (μM)	TI	TI	
8	>48.29	27.45	>1.76	7.91	>6.11	>6.11	
9	>40.64	30.69	>1.32	9.70	>4.19	>4.19	
10	>46.68	3.69	>12.6	2.26	>20.5	>20.5	
11	23.14	16.67	1.39	5.18	4.47	4.47	
12	>45.23	0.47	>95.95	0.88	>51.37	>51.37	
13	16.94	2.24	7.55	1.52	11.12	11.12	
14	37.08	1.11	33.0	0.94	39.5	39.5	
15	>37.35	31.28	>1.33	25.90	>1.44	>1.44	
29	>50	>50	NS	23.3	>2.14	>2.14	
30	36.72	18.36	2	9.28	3.96	3.96	
31	>47	2.5	>18.75	1.49	>31.45	>31.45	
34	>22.00	>22.00	NS	16.94	1.30	1.30	
35	>22.30	16.72	>1.33	16.28	>1.37	>1.37	
36	>21.62	19.03	>1.14	16.0	>1.36	>1.36	
37	>20.51	>20.51	NS	>20.51	NS	NS	
4	14.25	0.12	118.75	0.20	71.25	71.25	
7	17.27	0.5	34.54	1.89	9.13	9.13	

^a All data presented in this table were averaged from at least three independent experiments. Cytotoxicity was determined using a Promega CytoTox-Glo assay kit.

NS: no suppression at the highest tested concentration (20 μM).

Table 2Anti-HIV-1_{NL4-3} data of seco-DCP and -DCK analogues (**16–28**, **32**, and **33**) in TZM-bl cells ^a

Compd	CC ₅₀ (μM)	HIV-1 _{NL4-3}	
		EC ₅₀ (μM)	TI
16	-	-	NS
17	>40.69	11.00	3.70
18	>40.69	1.26	32.29
19	>40.69	1.93	21.08
20			NS
21	>38.79	2.41	>16.09
22	>38.42	1.63	23.57
23	>36.46	0.93	39.20
24	>39.64	1.92	20.65
25	>36.32	22.18	1.64
26	>34.81	18.45	1.87
27	-	-	NS
28	-	-	NS
32	32.62	1.53	21.32
33	6.3	0.56	11.25
4	14.25	0.12	118.75
7	17.27	0.5	34.54

^aAll data presented in this table were averaged from at least three independent experiments. Cytotoxicity was determined using a Promega CytoTox-GloTM assay kit. NS: no suppression at the highest tested concentration (20 μM).

Table 3

Chemical stability of 4-Me-DCK (**2**), seco-DCK (**7**), 1'-thia-seco-DCK (**32**), 2-ethyl-DCP (**4**), and seco-DCP (**12**) in acidic conditions ^a

	Purity (area %)	
	Reaction Time = 1 min	Reaction Time = 30 min
2	100%	64%
7	100%	77%
32	100%	96%
4	100%	91%
12	100%	100%

^aCondition: 1% HCl/MeOH/rt; Compound purity: peak area percentage by HPLC determination.