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Synthesis of 12-quinoline substituted andrographolide derivatives and their preliminary evaluation as anti-aggregation drugs

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ABSTRACT

Based on the structure of the natural product andrographolide, a series of novel 12-quinoline substituted derivatives **9** were designed and synthesized. In preliminary biological evaluation, these synthesized compounds showed prominent anti-platelet aggregation activities in response to thrombin and adenosine diphosphate (ADP) agonists. Among them, compound **9o** (inhibition rate 55.73%, IC_{50} 0.36 μM/L) had the highest anti-platelet aggregation activity induced by ADP. Compound **9q** (inhibition rate 54.31%, IC_{50} 0.30 μM/L) showed the highest anti-platelet aggregation activity induced by thrombin. Most of the derivatives had no significant cytotoxicity. Our research results provide a novel candidate drug structure for anti-platelet aggregation and enrich the scope of application of andrographolide derivatives.

Keywords: 12-quinoline substituted andrographolide derivatives, ADP, andrographolide, anti-platelet aggregation, design, Inhibition rate, synthesis, Thrombin.

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Introduction

Natural products are endowed with various interesting pharmacophores and show various pharmacological activities.[1–3] Therefore, natural products are the source of many lead compounds in drug development. Andrographolide **1** (Fig. 1), a natural product from the aerial parts of *Andrographis paniculati* Nees with up to 2.0%,[4] shows rich biological activity such as anti-influenza virus,[5] anti-hepatotoxic,[6] anti-HIV,[7] anti-cancer,[8] anti-inflammatory[9] and anti-hyperglycaemic activities.[10] It is worth mentioning that, in our previous work, we reported firstly that andrographolide showed low anti-platelet aggregation activity due to its poor aqueous solubility. Owing to its high aqueous solubility, its sulfonate **2** (medicinal composition of Xiyanping) and succinate **3** (medicinal composition of Chuanhuning) (Fig. 1) had better anti-platelet aggregation activity, when adenosine diphosphate (ADP) was employed as inducer.[11–13] Quinoline derivatives also exhibit a wide spectrum of biological activities such as anti-malarial,[14] anti-bacterial,[15] anti-cancer,[16] anti-oxidant,[17] anti-tuberculous,[18] anti-parasitic,[19] and anti-platelet aggregation (methyl liensinine, rhynchophylline, berberine) activities.[20–22] Both andrographolide and quinoline are readily available pharmacophores and have been subjects in the search for new biologically active compounds. At the same time, there are practically no literature reports on anti-thrombotic or anti-platelet aggregation properties of hybrid derivatives with a combination of andrographolide and quinoline structures.

Thrombotic disease is a common and typical disease of cardiovascular disease, which seriously threatens human health and life quality.[23] Inhibition of platelet aggregation is one of the most direct and effective strategies for the treatment of thrombosis.[24–27] At present, there are quite a few kinds of anti-platelet aggregation drugs such as thromboxane A_2 (TXA_2) inhibitors (aspirin),[28] ADP induction inhibitors (clopidogrel),[29] phosphodiesterase (PDE) inhibitors (cilostazol),[30] 5-hydroxytryptamine receptor antagonists (sarpogrelate),[31] Ca^{2+} channel antagonists (flunarizine),[32–34] platelet membrane glycoproteins (GP) IIb/IIIa receptor inhibitors (tirofiban),[35] and the protease active receptor-1 (PAR-1)

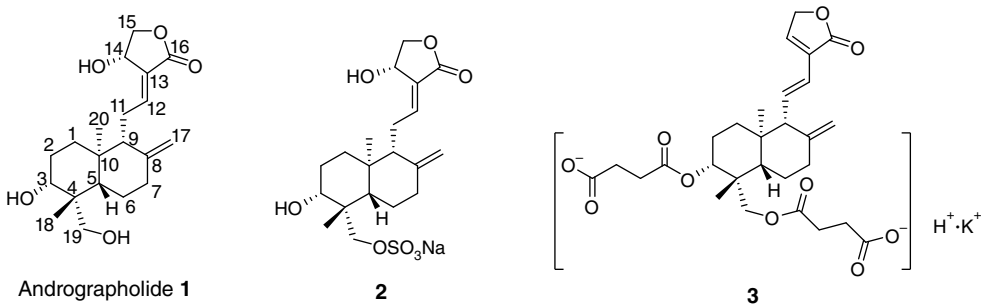


Fig. 1. The structure of andrographolide **1** and its sulfonate **2** and succinate **3**.

antagonist vorapaxar sulfate.[36,37] However, these drugs present many drawbacks in clinical treatment to some extent, such as excessive bleeding, allergic reactions, nausea, dyspnea, neutropenia, aplastic anaemia and thrombocytopenia.[38–43] Therefore, it has been a research focus to develop new skeleton compounds for inhibition of platelet aggregation in recent years.

The purpose of this work was to develop accessible and effective methods to construct compounds with novel high activity and no obvious cell toxicity platelet aggregation from andrographolide and quinolines.

Results and discussion

Synthesis

We successfully designed the synthetic route for the new skeleton compounds **9** with a combination of andrographolide and quinolines, shown in Scheme 1. Initially, andrographolide **1** underwent dehydration with activated aluminium oxide (neutral) to transform into dehydroandrographolide **4**.[44] Afterwards, the 3,19-OH groups of **4** were protected as isopropylidenes with 2,2-dimethoxypropane with pyridinium *p*-toluenesulfonate (PPTS) to yield **5**.[45] Compound **5** was degraded to key intermediate **6** by selective oxidation of the C-12,13 olefin bond with $KMnO_4$.[46] Compounds **8** were synthesized from key intermediate **6** by reacting with 2-methylquinolines **7** in the presence of $Fe(OAc)_2$/trifluoroacetic acid (TFA) and deprotection with AcOH.[47] To increase water solubility, two molecules of carboxylate were introduced into intermediates **8** to prepare a series of target derivatives **9** (12-quinoline substituted andrographolide derivatives).

Biological properties

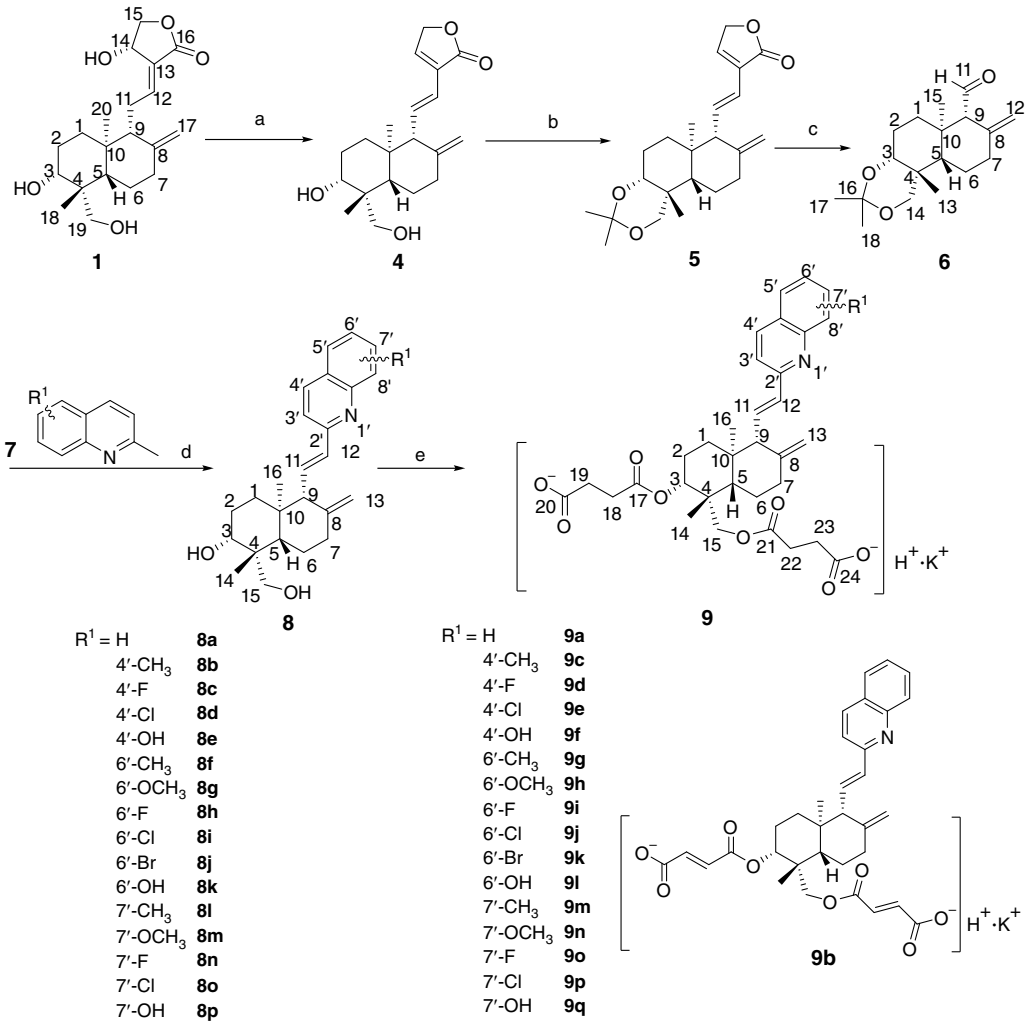
In preliminary screening, the 12-quinoline substituted andrographolide derivatives showed pronounced anti-platelet aggregation activities *in vitro* by turbidimetric test.[48] Thrombin and ADP were used as inducers for platelet aggregation. Vorapaxar sulfate and aspirin were selected as positive controls. The inhibition rate (IR) and IC_{50} of compounds **9** *in vitro* were calculated and are summarized in Table 1.

As shown in Table 1, compared with the positive control drugs vorapaxar sulfate and aspirin, both andrographolide (IR 23.53% for thrombin; IR 27.64% for ADP) and compound **8a** (IR 24.26% for thrombin; IR 22.79% for ADP) displayed low activities. However, compared with andrographolide and compound **8a**, compounds **2**, **3**, **9a** and **9b**, which contain sulfonate, succinate or maleate, exhibited better activities. The inhibition rate increased by 10–20%. This revealed that enhancing water solubility is beneficial to improving activity. Comparing compound **2** with **3**, or comparing **9a** with **9b**, we could confirm that succinic acid salinization could be the most beneficial to increase the activity of the derivatives. Therefore, in our current work, the derivatives were all succinated at 3,19-OH, shown in Scheme 1.

For thrombin as inducer, the IR of 4′-substituted quinoline derivates (**9c–9f**) was significantly lower than the 6′-substituted (**9g–9l**) and 7′-substituted (**9m–9q**) quinoline derivates, as well as for ADP as inducer. Comparing **9g–9l** with **9m–9q**, the activities of latter were higher than the former. For **9m–9q**, the order of inhibition rate for thrombin was **9q** (7′-OH) > **9o** (7′-F) > **9p** (7′-Cl) > **9m** (7′-CH_3) > **9n** (7′-OCH_3). Anti-platelet aggregation activities were higher slightly when electron-withdrawing groups (F, Cl) and hydroxyl were introduced. Among these, **9o** and **9q** showed superior platelet aggregation activities induced by thrombin. Especially, **9q** (IR 54.31%, IC_{50} 0.30 μM/L) was equivalent to the positive control drug vorapaxar sulfate. The order of IR for ADP was **9o** (7′-F) > **9p** (7′-Cl) > **9m** (7′-CH_3) > **9n** (7′-OCH_3) > **9q** (7′-OH). Also, **9o** and **9p**, which possess electron-withdrawing groups at 7′-C, showed superior platelet aggregation activities. Of these, **9o** (IR 55.73%, IC_{50} 0.36 μM/L) was equivalent to the positive control drug aspirin.

Cytotoxicity assay *in vitro*

Mouse fibroblast cells (L929) were used to evaluate the cell toxicity of target derivatives **9**. The relative survival rate is shown in Table 2 and Fig. 2. The results revealed that most compounds had no significant cytotoxicity. Among them, the survival rate of **9m**, **9o** and **9q** was higher than of aspirin at a dose of 10 μM/L.



Scheme 1. Synthetic route for compound **9**. Reagents and conditions: (a) activated alumina (neutral), anhydrous pyridine, 100°C, 12 h, 92% yield; (b) 2,2-dimethoxy propane, PPTS (cat.), toluene/dimethyl sulfoxide 7:3, reflux, 3 h, 90% yield; (c) $KMnO_4$, THF, −5°C; (d) $Fe(OAc)_2$, TFA (trifluoroacetic acid), toluene, N_2, 100°C, 24 h, then AcOH/H_2O 3:1, room temperature (rt), 2 h; (e) DMAP (4-dimethylaminopyridine), Et_3N, anhydride (succinic anhydride for **9a** and **9c**-**9q**, maleic anhydride for **9b**), CH_2Cl_2, rt, overnight, then $KHCO_3$.

Conclusion

Through our efforts, based on the structure of the natural product andrographolide, a series of 12-quinoline substituted derivatives were designed and synthesized. In preliminary biological evaluation, these compounds showed strong anti-platelet aggregation activities in response to thrombin and ADP agonists and no significant cytotoxicity. Among them, compound **9o** (IR 55.73%, IC_{50} 0.36 μM/L) had the highest anti-platelet aggregation activity induced by ADP. Compound **9q** (IR 54.31%, IC_{50} 0.30 μM/L) showed the highest anti-platelet aggregation activity induced by thrombin. In addition, both **9o** and **9q** had low cell toxicities at doses of 10 and 100 μM/L. The most active compounds were selected to be prepared for further studies such as bleeding time and mechanisms of action.

Experimental

General chemistry experimental

Infrared spectra were recorded on a Nicolet Avatar-370 spectrometer in KBr (ν in cm^{-1}). Melting points were measured on a Büchi B-540 capillary melting point apparatus and are uncorrected. Mass spectra (electrospray ionization mass spectrometry, ESI-MS) were obtained on a Thermo Finnigan LCQ-Advantage. High-resolution mass spectra (ESI-HRMS) were obtained on an Agilent 6210 time-of-flight (TOF) instrument.

Table 1. Inhibition rate (IR) and IC_{50} of target compounds **9** *in vitro*. Bold indicates highest activity.

Comp.	R[I]	Dose (μmol/L)	Thrombin (0.1 U/mL)		ADP (5 mM/L)	
			IR (%)[A]	IC_{50} (μM)[B]	IR (%)[A]	IC_{50} (μM)[B]
Vorapaxar sulfate	–	1.7	56.39 ± 0.14	0.18	33.87 ± 0.07	–
Aspirin	–	1.7	22.32 ± 0.25	–	54.03 ± 0.15	0.25
Andrographolide **1**	–	1.7	23.53 ± 0.21**	–	27.64 ± 0.11*	–
Andrographolide sulfonate **2**	–	1.7	31.34 ± 0.07*	–	40.85 ± 0.16**	0.76
Andrographolide succinate **3**	–	1.7	30.56 ± 0.12**	–	43.54 ± 0.13	0.72
12-Quinoline andrographolide **8a**	–	1.7	24.26 ± 0.10	–	22.79 ± 0.24*	–
9a	H	1.7	43.87 ± 0.14**	0.53	40.65 ± 0.17	0.86
9b[C]	H	1.7	34.75 ± 0.15**	–	36.71 ± 0.07	–
9c	4′-CH_3	1.7	29.57 ± 0.22	–	32.69 ± 0.15*	–
9d	4′-F	1.7	32.67 ± 0.21*	–	38.18 ± 0.11**	–
9e	4′-Cl	1.7	33.84 ± 0.17	–	35.23 ± 0.21	–
9f	4′-OH	1.7	35.83 ± 0.09**	–	41.25 ± 0.18**	0.75
9g	6′-CH_3	1.7	33.14 ± 0.05*	–	39.67 ± 0.06*	–
9h	6′-OCH_3	1.7	30.25 ± 0.06	–	29.13 ± 0.18	–
9i	6′-F	1.7	45.36 ± 0.13**	0.42	40.75 ± 0.09**	0.64
9j	6′-Cl	1.7	43.78 ± 0.26	0.48	37.61 ± 0.13	–
9k	6′-Br	1.7	40.49 ± 0.21*	0.51	36.47 ± 0.14	–
9l	6′-OH	1.7	41.38 ± 0.18	0.46	34.54 ± 0.21**	–
9m	7′-CH_3	1.7	38.14 ± 0.17	–	42.09 ± 0.13	0.68
9n	7′-OCH_3	1.7	32.49 ± 0.07*	–	36.05 ± 0.22*	–
9o	7′-F	1.7	47.63 ± 0.09	0.53	**55.73** ± 0.11*	**0.36**
9p	7′-Cl	1.7	42.47 ± 0.19	0.61	49.27 ± 0.14	0.63
9q	7′-OH	1.7	**54.31** ± 0.08**	**0.30**	32.49 ± 0.16	–

[A]Results are expressed as the mean ± s.e.; *$P < 0.05$ versus vorapaxar sulfate; **$P < 0.01$ versus vorapaxar sulfate.
[B]–, not tested.
[C]**9b** had maleate introduced at 3,15-OH.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury Plus-400 spectrometer (400 and 100 MHz) (δ in parts per million, J in hertz), using TMS as internal standard. Platelet aggregation rates were measured on an LG-PABER platelet aggregation apparatus (Beijing Shidi Scientific Instrument Co. Ltd, Beijing). All commercially available reagents and solvents were of analytical reagent grade and were used directly without further purification.

Synthesis of derivatives

Compound **4**: andrographolide **1** (100.00 g, 285.55 mmol) was dissolved in anhydrous pyridine (100 mL) and then activated alumina (neutral) (23.43 g, 228.42 mmol) was added. The mixture stirred at 100°C for ~12 h (reaction complete by TLC analysis). After cooling to room temperature, the reaction mixture was filtered and washed with CH_2Cl_2 (2 × 200 mL). The combined organic filtrate was concentrated under vacuum. The residue was purified by column chromatography (CH_2Cl_2/MeOH 20:1) and afforded product **4** dehydroandrographolide (69.82 g, 92.01%) as a white solid. Mp 203–204°C (lit.[49] 204–205°C). IR (KBr) ν_{max} 3526, 3480, 2973, 2935, 2855, 1805, 1635, 1447, 1386, 1346, 1271, 1222, 1102, 1036, 974, 891 cm^{-1}. ^{1}H NMR (600 MHz, [D6]DMSO) δ 7.67 (1H, s, 14-H), 6.73 (1H, dd, J = 6.6 Hz, J = 15.8 Hz, 11-H), 6.13 (1H, d, J = 15.8 Hz, 12-H), 5.06 (1H, brs, 3-OH), 4.90 (2H, s, 15-H), 4.74 (1H, s, 17-Ha), 4.43 (1H, s, 17-Hb), 4.17 (1H, brs, 19-OH), 4.11 (1H, d, J = 11.8 Hz, 19-Ha), 3.54 (1H, d, J = 11.8 Hz, 19-Hb), 3.26–3.24 (1H, m, 3-H), 2.49 (1H, d, J = 6.6 Hz, 9-H), 2.05–1.22 (9H, m, 1,2,5,6,7-H), 1.10 (3H, s, 18-H), 0.87 (3H, s, 20-H). ^{13}C NMR (100 MHz, [D6] DMSO) δ 173.2, 148.5, 138.8, 135.9, 131.5, 120.5, 110.1, 78.5, 71.0, 65.8, 61.2, 48.4, 43.2, 39.8, 36.8, 33.5, 28.3, 24.6, 19.6, 15.3 ppm.

Table 2. The relative survival rate of target compounds **9** *in vitro*. Bold indicates highest survival rates.

Compound	Dose (μM/L)	Survival rate (%)	Compound	Dose (μM/L)	Survival rate (%)
Blank group	–		**9h**	10	62.30
				100	45.67
Control group	–		**9i**	10	66.35
				100	47.39
Aspirin	10	71.02	**9j**	10	71.02
	100	52.31		100	45.67
9a	10	71.02	**9k**	10	75.26
	100	42.56		100	52.31
9b	10	62.30	**9l**	10	80.62
	100	42.56		100	50.87
9c	10	75.26	**9m**	**10**	**88.62**
	100	52.31		**100**	**62.30**
9d	10	80.62	**9n**	10	77.51
	100	53.64		100	64.33
9e	10	80.62	**9o**	**10**	**81.35**
	100	62.30		**100**	**64.33**
9f	10	72.38	**9p**	10	80.62
	100	42.56		100	59.46
9g	10	64.33	**9q**	**10**	**86.37**
	100	41.03		**100**	**62.30**

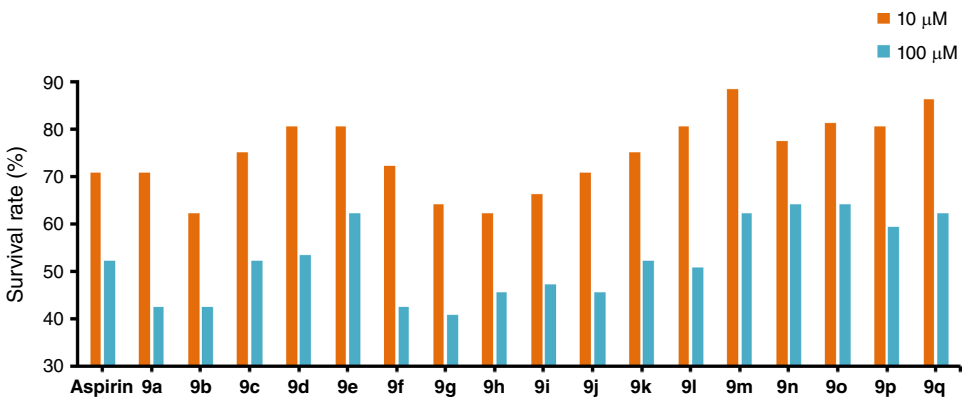


Fig. 2. The relative survival rate for target compounds **9** *in vitro*.

Compound **5**: dehydroandrographolide **4** (66.00 g, 198.68 mmol) was dissolved in a mixed solution of toluene and dimethyl sulfoxide (200 mL, 7:3) and then 2,2-dimethoxypropane (62.03 g, 595.85 mmol) and PPTS (cat.) (5.02 g, 20.05 mmol) were added. The mixture stirred at reflux for ~3–5 h (reaction complete by TLC analysis). After cooling to room temperature, water (200 mL) was added and the organic phase separated. Then, the aqueous phase was extracted with ethyl acetate (3 × 300 mL). The combined organic extract was washed with brine (3 × 200 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was washed with ether (2 × 100 mL) at 5°C and crystallized from ethanol to give compound **5** (3-((*E*)-2-((4a*R*,6a*R*,7*R*,10a*S*,10b*R*)-3,3,6*a*,10*b*-tetramethyl-8-methylenedecahydro-1*H*-naphtho[2,1-*d*][1,3]dioxin-7-yl)vinyl)furan-2(5*H*)-one) as a light yellow solid (65.82 g, yield 89.01%). Mp 167–168°C. IR (KBr) ν_{max} 2875,1808, 1645, 1449, 1385, 1377, 1343, 1274, 1234, 1113, 1023, 971, 892 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 7.64 (1H, s, 14-H), 6.53 (1H, dd, J = 6.6 Hz,

J = 15.7 Hz, 11-H), 6.16 (1H, d, J = 15.7 Hz, 12-H), 4.93 (2H, s, 15-H), 4.84 (1H, s, 17-Ha), 4.46 (1H, s, 17-Hb), 4.10 (1H, d, J = 11.7 Hz, 19-Ha), 3.52 (1H, d, J = 11.7 Hz, 19-Hb), 3.28–3.25 (1H, m, 3-H), 2.53 (1H, d, J = 6.6 Hz, 9-H), 2.07–1.28 (9H, m, 1,2,5,6,7-H), 1.23–1.22 (6H, m, 23,24-H), 1.09 (3H, s, 18-H), 0.91 (3H, s, 20-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 171.2, 140.2, 138.4, 136.2, 131.6, 120.2, 115.9, 110.0, 77.5, 71.2, 65.6, 61.3, 48.5, 43.1, 39.6, 36.7, 33.3, 31.3, 26.6, 26.5, 24.3, 16.6, 13.3 ppm. MS (ESI) m/z (%) 373.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{23}H_{33}O_4$ $[M + H]^+$ 373.2301, found 373.2309.

Compound **6:** compound **5** (62.00 g, 166.56 mmol) was dissolved in tetrahydrofuran (THF) (300 mL) and then $KMnO_4$ (52.60 g, 333.20 mmol) was added slowly at −5°C and the mixture stirred for 5 h until total consumption of compound **5**. Then, the mixture was stirred at reflux for ~3–5 h (reaction complete by TLC analysis). After reaction, the mixture was filtered and the solvent was removed under vacuum. Then, CH_2Cl_2 (3 × 200 mL) was poured into the residue and stirred strongly for 30 min. The combined CH_2Cl_2 extract was washed with brine (3 × 100 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (light petroleum/ethyl acetate 2:1) and afforded product **6** ((4a*R*,6a*R*,7*R*,10a*S*,10b*R*)-3,3,6*a*,10*b*-tetramethyl-8-methylenedecahydro-1*H*-naphtho[2,1-*d*][1,3]dioxine-7-carbaldehyde) (38.98 g, 80.10%) as a white solid. Mp 134 −135°C. IR (KBr) ν_{max} 2975, 2825, 2720, 1748, 1645, 1449, 1385, 1378, 1343, 1269, 1234, 1123, 1023, 971, 892 cm^{-1}. ^{1}H NMR (600 MHz, [D6]DMSO) δ 9.72 (1H, d, J = 2.4 Hz, 11-H), 5.25 (1H, s, 12-Ha), 5.14 (1H, s, 12-Hb), 4.10 (1H, d, J = 11.9 Hz, 14-Ha), 3.52 (1H, d, J = 11.9 Hz, 14-Hb), 3.07–3.05 (1H, m, 3-H), 2.93 (1H, d, J = 2.4 Hz, 9-H), 2.07–1.28 (9H, m, 1,2,5,6,7-H), 1.22–1.21 (6H, m, 17,18-H), 1.09 (3H, s, 13-H), 0.91 (3H, s, 15-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 205.1, 145.0, 115.8, 109.2, 77.6, 68.2, 65.6, 48.5, 43.1, 39.5, 36.7, 33.1, 31.3, 26.5, 26.4, 24.3, 15.6, 14.3 ppm. MS (ESI) m/z (%) 293.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{18}H_{29}O_3$ $[M + H]^+$ 293.2038, found 293.2048.

Compound **8** (**8a** is selected as an example): compound **6** (2.00 g, 6.84 mmol) was dissolved in dry toluene (20 mL) and then $Fe(OAc)_2$ (0.06 g, 0.34 mmol), 2-methylquinoline (1.16 g, 8.20 mmol) and TFA (0.08 g, 0.68 mmol) were added under N_2 at room temperature. The mixture was stirred at 100°C for 24 h until total consumption of compound **6**. The mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in a mixture of AcOH and H_2O (15 mL, 3:1) at room temperature for ~2 h. After reaction, sodium bicarbonate solution was added dropwise to neutralize the mixture. CH_2Cl_2 (3 × 40 mL) was poured into the mixture. The combined CH_2Cl_2 extract was washed with brine (3 × 30 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (CH_2Cl_2/MeOH 15:1) and afforded product **8a** ((1*R*,2*R*,4a*R*,5*R*,8a*S*)-1-(hydroxymethyl)-1,4*a*-dimethyl-6-methylene-5-((*E*)-2-(quinolin-2-yl)vinyl)decahydronaphthalen-2-ol) (77.52%, 2.00 g) as a pale yellow solid. Mp 220–221°C. IR (KBr) ν_{max} 3527, 3470, 3256, 3102, 2983, 2945, 2825, 1635, 1447, 1396, 1348, 1271, 1232, 1112, 1036, 975, 886 cm^{-1}. ^{1}H NMR (600 MHz, [D6]DMSO) δ 8.22–8.07 (1H, m, 4′-H), 8.08–7.83 (3H, m, 5′,7′,8′-H), 7.62–7.60 (1H, m, 6′-H), 7.37 (1H, d, J = 8.3 Hz, 3′-H), 6.68 (1H, dd, J = 6.8 Hz, J = 15.8 Hz, 11-H), 6.54 (1H, d, J = 15.8 Hz, 12-H), 5.03 (1H, s, 13-Ha), 4.87 (1H, s, 13-Hb), 3.68 (1H, brs, 15-OH), 3.59 (1H, brs, 3-OH), 3.50 (1H, d, J = 11.8 Hz, 15-Ha), 3.31 (1H, d, J = 11.8 Hz, 15-Hb), 3.17–3.14 (1H, m, 3-H), 2.76 (1H, d, J = 6.8 Hz, 9-H), 2.10–1.20 (9H, m, 1,2,5,6,7-H), 1.11 (3H, s, 14-H), 0.83 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 156.4, 148.8, 148.1, 136.5, 130.5, 128.8, 128.0, 126.9, 126.0, 125.8, 125.1, 118.5, 110.1, 78.5, 65.8, 61.9, 47.4, 43.3, 39.9, 36.7, 33.3, 27.9, 24.7, 19.4, 15.0 ppm. MS (ESI) m/z (%) 378.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{25}H_{32}NO_2$ $[M + H]^+$ 378.2433, found 378.2445.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-1-(Hydroxymethyl)-1,4*a*-dimethyl-6-methylene-5-((*E*)-2-(4-methylquinolin-2-yl)vinyl)decahydronaphthalen-2-ol **8b** (pale yellow solid, 74.25%, 1.99 g); mp 190–191°C. IR (KBr): ν_{max} 3527, 3453, 3104, 2973, 2945, 2925, 1635, 1447, 1363, 1343, 1276, 1230, 1037, 973, 893 cm^{-1}. ^{1}H NMR (600 MHz, [D6]DMSO) δ 8.10–7.74 (3H, m, 5′,7′,8′-H), 7.62–7.58 (1H, m, 6′-H), 7.17 (1H, s, 3′-H), 6.68 (1H, dd, J = 6.2 Hz, J = 15.7 Hz, 11-H), 6.55 (1H, d, J = 15.7 Hz, 12-H), 5.05 (1H, s, 13-Ha), 4.88 (1H, s, 13-Hb), 3.67 (1H, brs, 15-OH), 3.58 (1H, brs, 3-OH), 3.49 (1H, d, J = 11.8 Hz, 15-Ha), 3.32 (1H, d, J = 11.8 Hz, 15-Hb), 3.17–3.13 (1H, m, 3-H), 2.76 (1H, d, J = 6.2 Hz, 9-H), 2.61 (3H, s, 4′-CH_3), 2.10–1.18 (9H, m, 1,2,5,6,7-H), 1.08 (3H, s, 14-H), 0.80 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 157.4, 148.9, 146.8, 144.1, 130.5, 128.7, 128.2, 126.7, 126.0, 125.8, 125.2, 118.3, 109.1, 78.5, 65.8, 61.9, 47.4, 43.2, 39.8, 36.6, 33.2, 27.8, 24.8, 20.2, 19.6, 15.1 ppm. MS (ESI) m/z (%) 392.3 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{26}H_{34}NO_2$ $[M + H]^+$ 392.2589, found 392.2596.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-5-((*E*)-2-(4-Fluoroquinolin-2-yl)vinyl)-1-(hydroxymethyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-2-ol **8c** (yellow solid, 71.48%, 1.93 g); mp 210–211°C. IR (KBr) ν_{max} 3525, 3456, 3106, 2957, 2948, 2925, 1655, 1446, 1382, 1346, 1277, 1233, 1032, 975, 885 cm^{-1}. ^{1}H NMR (600 MHz, [D6]DMSO) δ 8.07–7.74 (4H, m, 5′,6′,7′,8′-H), 7.07–7.00 (1H, m, 3′-H), 6.65 (1H, dd, J = 6.2 Hz, J = 15.7 Hz, 11-H), 6.54 (1H, d, J = 15.7 Hz, 12-H), 5.05 (1H, s, 13-Ha), 4.87 (1H, s, 13-Hb), 3.65 (1H, brs, 15-OH), 3.54 (1H, brs, 3-OH), 3.43 (1H, d, J = 11.8 Hz, 15-Ha), 3.32 (1H, d, J = 11.8 Hz, 15-Hb), 3.15–3.11 (1H, m, 3-H), 2.78 (1H, d, J = 6.2 Hz, 9-H), 2.13–1.13 (9H, m, 1,2,5,6,7-H), 1.04 (3H, s, 14-H), 0.84 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 167.2 ($^1J_{CF}$ = 246.2 Hz), 156.4, 148.9, 148.5,

131.5, 129.0, 127.2, 125.7, 125.0, 120.8, 118.3 ($^2J_{CF}$ = 22.0 Hz), 109.1, 101.8 ($^2J_{CF}$ = 22.6 Hz), 78.7, 65.5, 61.6, 47.2, 43.3, 39.5, 36.3, 33.4, 27.3, 24.5, 19.1, 15.0 ppm. MS (ESI) *m/z* (%) 396.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{25}H_{31}FNO_2$ $[M + H]^+$ 396.2339, found 396.2348.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-5-((*E*)-2-(4-Chloroquinolin-2-yl)vinyl)-1-(hydroxymethyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-2-ol **8d** (pale yellow solid, 69.75%, 1.96 g); mp 215–216°C. IR (KBr) ν_{max} 3527, 3446, 3105, 2977, 2945, 2927, 1638, 1445, 1384, 1347, 1274, 1233, 1033, 974, 885 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 8.62–8.58 (1H, m, 5′-H), 8.10–7.74 (3H, m, 6′,7′,8′-H), 7.57 (1H, s, 3′-H), 6.64 (1H, dd, *J* = 6.2 Hz, *J* = 15.7 Hz, 11-H), 6.54 (1H, d, *J* = 15.7 Hz, 12-H), 5.05 (1H, s, 13-Ha), 4.84 (1H, s, 13-Hb), 3.63 (1H, brs, 15-OH), 3.55 (1H, brs, 3-OH), 3.42 (1H, d, *J* = 11.8 Hz, 15-Ha), 3.32 (1H, d, *J* = 11.8 Hz, 15-Hb), 3.16–3.10 (1H, m, 3-H), 2.79 (1H, d, *J* = 6.2 Hz, 9-H), 2.13–1.14 (9H, m, 1,2,5,6,7-H), 1.02 (3H, s, 14-H), 0.82 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 156.4, 148.9, 147.8, 143.4, 133.4, 129.1, 127.2, 126.7, 125.6, 125.1, 124.2, 118.1, 109.0, 78.8, 65.5, 62.3, 47.3, 43.3, 39.5, 36.4, 33.3, 27.4, 24.5, 19.3, 15.1 ppm. MS (ESI) *m/z* (%) 412.2 ($[M + H]^+$, $C_{25}H_{31}{}^{35}ClNO_2$, 100%), 414.2 ($[M + H]^+$, $C_{25}H_{31}{}^{37}ClNO_2$, 33%). HRMS (ESI) calcd for $C_{25}H_{31}{}^{35}ClNO_2$ $[M + H]^+$ 412.2043, found 412.2055; for $C_{25}H_{31}{}^{37}ClNO_2$ $[M + H]^+$ 414.2014, found 414.2023.

2-((*E*)-2-((1*R*,4*aS*,5*R*,6*R*,8*aR*)-6-Hydroxy-5-(hydroxymethyl)-5,8*a*-dimethyl-2-methylenedecahydronaphthalen-1-yl)vinyl) quinolin-4-ol **8e** (light yellow solid, 64.68%, 1.74 g); mp 195–196°C. IR (KBr) ν_{max} 3525, 3456, 3257, 3108, 2977, 2948, 2923, 1637, 1444, 1386, 1347, 1273, 1235, 1033, 975, 893 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 8.30–7.80 (3H, m, 5′,7′,8′-H), 7.72–7.59 (1H, m, 6′-H), 6.80 (1H, s, 3′-H), 6.65 (1H, dd, *J* = 6.2 Hz, *J* = 15.7 Hz, 11-H), 6.53 (1H, d, *J* = 15.7 Hz, 12-H), 5.35 (1H, brs, 4′-OH), 5.04 (1H, s, 13-Ha), 4.83 (1H, s, 13-Hb), 3.64 (1H, brs, 15-OH), 3.52 (1H, brs, 3-OH), 3.41 (1H, d, *J* = 11.8 Hz, 15-Ha), 3.34 (1H, d, *J* = 11.8 Hz, 15-Hb), 3.17–3.12 (1H, m, 3-H), 2.78 (1H, d, *J* = 6.2 Hz, 9-H), 2.12–1.19 (9H, m, 1,2,5,6,7-H), 1.06 (3H, s, 14-H), 0.90 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 166.3, 157.4, 149.2, 148.8, 130.8, 128.5, 127.1, 125.7, 125.2, 121.3, 117.3, 109.2, 102.4, 78.8, 65.4, 61.8, 47.6, 43.3, 39.4, 36.6, 33.3, 27.4, 24.4, 19.6, 15.0 ppm. MS (ESI) *m/z* (%) 394.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{25}H_{32}NO_3$ $[M + H]^+$ 394.2382, found 394.2392.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-1-(Hydroxymethyl)-1,4*a*-dimethyl-6-methylene-5-((*E*)-2-(6-methylquinolin-2-yl)vinyl)decahydronaphthalen-2-ol **8f** (yellow solid, 74.62%, 2.00 g); mp 201–202°C. IR (KBr) ν_{max} 3528, 3453, 3107, 2948, 2935, 1645, 1457, 1387, 1349, 1274, 1233, 1034, 973, 885 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 8.21 (1H, d, *J* = 8.3 Hz, 4′-H), 7.92 (1H, d, *J* = 8.3 Hz, 8′-H) 7.62–7.58 (2H, m, 5′,7′-H), 7.17 (1H, dd, *J* = 8.3 Hz, *J* = 4.3 Hz, 3′-H), 6.70 (1H, dd, *J* = 6.2 Hz, *J* = 15.7 Hz, 11-H), 6.55 (1H, d, *J* = 15.7 Hz, 12-H), 5.07 (1H, s, 13-Ha), 4.85 (1H, s, 13-Hb), 3.69 (1H, brs, 15-OH), 3.59 (1H, brs, 3-OH), 3.51 (1H, d, *J* = 11.8 Hz, 15-Ha), 3.31 (1H, d, *J* = 11.8 Hz, 15-Hb), 3.18–3.15 (1H, m, 3-H), 2.70 (1H, d, *J* = 6.2 Hz, 9-H), 2.34 (3H, s, 6′-CH_3), 2.13–1.18 (9H, m, 1,2,5,6,7-H), 1.12 (3H, s, 14-H), 0.86 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 155.4, 148.7, 146.2, 137.1, 135.8, 130.5, 128.2, 126.7, 126.2, 125.8, 125.2, 118.4, 109.3, 78.7, 65.5, 61.6, 47.5, 43.4, 39.6, 36.7, 33.3, 27.4, 24.6, 20.3, 19.7, 15.3 ppm. MS (ESI) *m/z* (%) 392.3 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{26}H_{34}NO_2$ $[M + H]^+$ 392.2589, found 392.2597.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-1-(Hydroxymethyl)-5-((*E*)-2-(6-methoxyquinolin-2-yl)vinyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-2-ol **8g** (pale yellow solid, 76.34%, 2.13 g); mp 206–207°C. IR (KBr) ν_{max} 3529, 3452, 3103, 2943, 2822, 1643, 1459, 1384, 1344, 1277, 1233, 1032, 972, 896 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 8.20–8.16 (1H, m, 4′-H), 7.78 (1H, d, *J* = 8.3 Hz, 8′-H), 7.39–7.32 (2H, m, 3′,7′-H), 7.17–7.09 (1H, m, 5′-H), 6.69 (1H, dd, *J* = 6.2 Hz, *J* = 15.7 Hz, 11-H), 6.54 (1H, d, *J* = 15.7 Hz, 12-H), 5.05 (1H, s, 13-Ha), 4.85 (1H, s, 13-Hb), 3.83 (3H, s, 6′-OCH_3), 3.67 (1H, brs, 15-OH), 3.58 (1H, brs, 3-OH), 3.50 (1H, d, *J* = 11.8 Hz, 15-Ha), 3.30 (1H, d, *J* = 11.8 Hz, 15-Hb), 3.17–3.14 (1H, m, 3-H), 2.77 (1H, d, *J* = 6.2 Hz, 9-H), 2.11–1.16 (9H, m, 1,2,5,6,7-H), 1.04 (3H, s, 14-H), 0.90 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 157.4, 154.7, 148.2, 143.1, 135.3, 130.4, 129.2, 125.5, 125.0, 122.5, 119.4, 109.2, 105.4, 78.9, 65.6, 61.3, 55.3, 47.4, 43.3, 39.3, 36.5, 33.3, 27.5, 24.7, 19.5, 15.1 ppm. MS (ESI) *m/z* (%) 408.3 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{26}H_{34}NO_3$ $[M + H]^+$ 408.2540, found 408.2549.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-5-((*E*)-2-(6-Fluoroquinolin-2-yl)vinyl)-1-(hydroxymethyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-2-ol **8h** (yellow solid, 66.66%, 1.80 g); mp 216–217°C. IR (KBr) ν_{max} 3535, 3458, 3107, 2943, 2922, 1644, 1454, 1384, 1345, 1273, 1235, 1033, 972, 883 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 8.26–8.20 (1H, m, 4′-H), 7.93 (1H, d, *J* = 8.3 Hz, 8′-H), 7.39–7.32 (3H, m, 3′,5′,7′-H), 6.67 (1H, dd, *J* = 6.2 Hz, *J* = 15.7 Hz, 11-H), 6.53 (1H, d, *J* = 15.7 Hz, 12-H), 5.03 (1H, s, 13-Ha), 4.84 (1H, s, 13-Hb), 3.63 (1H, brs, 15-OH), 3.51 (1H, brs, 3-OH), 3.52 (1H, d, *J* = 11.8 Hz, 15-Ha), 3.32 (1H, d, *J* = 11.8 Hz, 15-Hb), 3.15–3.12 (1H, m, 3-H), 2.79 (1H, d, *J* = 6.2 Hz, 9-H), 2.20–1.13 (9H, m, 1,2,5,6,7-H), 1.03 (3H, s, 14-H), 0.91 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 160.3 ($^1J_{CF}$ = 245.0 Hz), 155.4, 148.6, 147.1, 145.3, 135.9, 130.2, 125.6, 125.1, 121.5 ($^2J_{CF}$ = 21.2 Hz), 119.3, 109.5 ($^2J_{CF}$ = 21.3 Hz), 109.0, 78.7, 65.4, 62.3, 47.5, 43.1, 40.3, 36.2, 33.1, 27.2, 24.3, 19.3, 14.8 ppm. MS (ESI) *m/z* (%) 396.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{25}H_{31}FNO_2$ $[M + H]^+$ 396.2339, found 396.2349.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-5-((*E*)-2-(6-Chloroquinolin-2-yl)vinyl)-1-(hydroxymethyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-2-ol **8i** (yellow solid, 70.32%, 1.99 g); mp

218–219°C. IR (KBr) ν_{max} 3515, 3458, 3102, 2942, 2921, 1646, 1454, 1385, 1346, 1273, 1234, 1035, 994, 883 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 8.26–8.20 (1H, m, 4′-H), 8.10 (1H, d, J = 8.3 Hz, 8′-H), 7.82 (1H, d, J = 8.3 Hz, 7′-H), 7.39 (1H, d, J = 8.3 Hz, 3′-H), 7.17–7.08 (1H, m, 5′-H), 6.64 (1H, dd, J = 6.2 Hz, J = 15.7 Hz, 11-H), 6.53 (1H, d, J = 15.7 Hz, 12-H), 5.02 (1H, s, 13-Ha), 4.82 (1H, s, 13-Hb), 3.66 (1H, brs, 15-OH), 3.54 (1H, brs, 3-OH), 3.46 (1H, d, J = 11.8 Hz, 15-Ha), 3.25 (1H, d, J = 11.8 Hz, 15-Hb), 3.16–3.10 (1H, m, 3-H), 2.82 (1H, d, J = 6.2 Hz, 9-H), 2.13–1.14 (9H, m, 1,2,5,6,7-H), 1.02 (3H, s, 14-H), 0.91 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 156.4, 148.4, 146.1, 135.4, 132.0, 131.4, 130.2, 128.7, 125.6, 125.1, 123.5, 119.8, 109.3, 78.8, 65.5, 61.3, 47.4, 43.6, 39.4, 36.2, 33.3, 27.2, 24.5, 19.2, 15.0 ppm. MS (ESI) m/z (%) 412.2 ($[M + H]^+$, $C_{25}H_{31}{}^{35}ClNO_2$, 100%), 414.2 ($[M + H]^+$, $C_{25}H_{31}{}^{37}ClNO_2$, 33%). HRMS (ESI) calcd for $C_{25}H_{31}{}^{35}ClNO_2$ $[M + H]^+$: 412.2043, found 412.2057; for $C_{25}H_{31}{}^{37}ClNO_2$-$[M + H]^+$ 414.2014, found 414.2022.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-5-((*E*)-2-(6-Bromoquinolin-2-yl)vinyl)-1-(hydroxymethyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-2-ol **8j** (yellow solid, 65.18%, 2.04 g); mp 241–242°C. IR (KBr) ν_{max} 3534, 3437, 3101, 2945, 2926, 1646, 1457, 1383, 1346, 1276, 1231, 1031, 974, 882 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 8.28–8.01 (4H, m, 4′,5′,7′,8′-H), 7.44 (1H, d, J = 8.3 Hz, 3′-H), 6.68 (1H, dd, J = 6.2 Hz, J = 15.7 Hz, 11-H), 6.54 (1H, d, J = 15.7 Hz, 12-H), 5.04 (1H, s, 13-Ha), 4.85 (1H, s, 13-Hb), 3.65 (1H, brs, 15-OH), 3.56 (1H, brs, 3-OH), 3.50 (1H, d, J = 11.8 Hz, 15-Ha), 3.31 (1H, d, J = 11.8 Hz, 15-Hb), 3.18–3.12 (1H, m, 3-H), 2.83 (1H, d, J = 6.2 Hz, 9-H), 2.14–1.15 (9H, m, 1,2,5,6,7-H), 1.03 (3H, s, 14-H), 0.90 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 156.1, 148.8, 148.4, 135.3, 133.1, 132.4, 129.8, 128.7, 125.5, 125.1, 123.5, 120.8, 109.3, 78.7, 65.3, 61.2, 48.4, 43.7, 40.4, 36.7, 33.4, 27.6, 24.4, 19.7, 15.2 ppm. MS (ESI) m/z (%) 456.2 ($[M + H]^+$, $C_{25}H_{31}{}^{79}BrNO_2$, 100%), 458.2 ($[M + H]^+$, $C_{25}H_{31}{}^{81}BrNO_2$, 97%). HRMS (ESI) calcd for $C_{25}H_{31}{}^{79}BrNO_2$ $[M + H]^+$: 456.1538, found 456.1547; for $C_{25}H_{31}{}^{81}BrNO_2$ $[M + H]^+$ 458.1518, found 458.1527.

2-((*E*)-2-((1*R*,4*aS*,5*R*,6*R*,8*aR*)-6-Hydroxy-5-(hydroxymethyl)-5,8*a*-dimethyl-2-methylenedecahydronaphthalen-1-yl)vinyl) quinolin-6-ol **8k** (pale yellow solid, 57.62%, 1.55 g); mp 220–221°C. IR (KBr) ν_{max} 3532, 3464, 3105, 2946, 2924, 1643, 1452, 1385, 1346, 1273, 1235, 1032, 972, 885 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 8.06–8.00 (1H, m, 4′-H), 7.81 (1H, d, J = 8.3 Hz, 8′-H), 7.42–7.17 (3H, m, 3′,5′,7′-H), 6.68 (1H, dd, J = 6.2 Hz, J = 15.7 Hz, 11-H), 6.55 (1H, d, J = 15.7 Hz, 12-H), 5.35 (1H, s, 6′-OH), 5.05 (1H, s, 13-Ha), 4.84 (1H, s, 13-Hb), 3.64 (1H, brs, 15-OH), 3.55 (1H, brs, 3-OH), 3.43 (1H, d, J = 11.8 Hz, 15-Ha), 3.26 (1H, d, J = 11.8 Hz, 15-Hb), 3.17–3.13 (1H, m, 3-H), 2.84 (1H, d, J = 6.2 Hz, 9-H), 2.15–1.13 (9H, m, 1,2,5,6,7-H), 1.05 (3H, s, 14-H), 0.84 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 155.4, 154.1, 148.8, 143.1, 134.8, 130.2, 128.9, 125.6, 125.4, 125.0, 119.2, 111.3, 109.3, 78.7, 65.3, 61.7, 47.5, 43.6, 39.7, 36.5, 33.3, 27.4, 24.5, 19.3, 15.3 ppm. MS (ESI) m/z (%) 394.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{25}H_{32}NO_3$ $[M + H]^+$ 394.2382, found 394.2393.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-1-(Hydroxymethyl)-1,4*a*-dimethyl-6-methylene-5-((*E*)-2-(7-methylquinolin-2-yl)vinyl)decahydronaphthalen-2-ol **8l** (yellow solid, 75.37%, 2.02 g); mp 213–214°C. IR (KBr) ν_{max} 3538, 3446, 3107, 2952, 2942, 1654, 1453, 1386, 1350, 1264, 1230, 1044, 978, 887 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 8.21 (1H, d, J = 8.2 Hz, 4′-H), 7.92–7.58 (3H, m, 5′,6′,8′-H), 7.33 (1H, dd, J = 8.2 Hz, J = 4.3 Hz, 3′-H), 6.66 (1H, dd, J = 6.2 Hz, J = 15.7 Hz, 11-H), 6.53 (1H, d, J = 15.7 Hz, 12-H), 5.02 (1H, s, 13-Ha), 4.88 (1H, s, 13-Hb), 3.65 (1H, brs, 15-OH), 3.59 (1H, brs, 3-OH), 3.50 (1H, d, J = 11.6 Hz, 15-Ha), 3.31 (1H, d, J = 11.6 Hz, 15-Hb), 3.16–3.11 (1H, m, 3-H), 2.80 (1H, d, J = 6.2 Hz, 9-H), 2.34 (3H, s, 7′-CH_3), 2.12–1.17 (9H, m, 1,2,5,6,7-H), 1.09 (3H, s, 14-H), 0.92 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 156.2, 148.8, 146.4, 139.1, 136.0, 130.5, 128.2, 127.1, 126.2, 125.5, 125.0, 117.6, 109.2, 78.5, 65.3, 62.1, 46.5, 43.1, 40.3, 36.7, 33.1, 27.7, 24.6, 21.3, 19.5, 15.1 ppm. MS (ESI) m/z (%) 392.3 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{26}H_{34}NO_2$ $[M + H]^+$ 392.2589, found 392.2598.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-1-(Hydroxymethyl)-5-((*E*)-2-(7-methoxyquinolin-2-yl)vinyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-2-ol **8m** (pale yellow solid, 71.33%, 1.99 g); mp 232–233°C. IR (KBr) ν_{max} 3528, 3464, 3102, 2945, 2821, 1651, 1451, 1384, 1350, 1261, 1227, 1041, 975, 892 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 8.23 (1H, d, J = 8.2 Hz, 4′-H), 7.99–7.90 (1H, m, 5′-H), 7.35–7.22 (3H, m, 3′,6′,8′-H), 6.68 (1H, dd, J = 6.2 Hz, J = 15.7 Hz, 11-H), 6.54 (1H, d, J = 15.7 Hz, 12-H), 5.03 (1H, s, 13-Ha), 4.86 (1H, s, 13-Hb), 3.83 (1H, s, 7′-OCH_3), 3.64 (1H, brs, 15-OH), 3.58 (1H, brs, 3-OH), 3.47 (1H, d, J = 11.6 Hz, 15-Ha), 3.33 (1H, d, J = 11.6 Hz, 15-Hb), 3.14–3.10 (1H, m, 3-H), 2.83 (1H, d, J = 6.2 Hz, 9-H), 2.10–1.15 (9H, m, 1,2,5,6,7-H), 1.10 (3H, s, 14-H), 0.90 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 156.9, 151.2, 148.6, 147.4, 136.2, 129.5, 128.2, 125.5, 125.0, 117.6, 116.5, 109.2, 107.2, 78.7, 65.4, 62.5, 55.8, 46.5, 43.3, 40.3, 36.5, 33.4, 27.4, 24.3, 19.6, 15.0 ppm. MS (ESI) m/z (%) 408.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{26}H_{34}NO_3$ $[M + H]^+$ 408.2538, found 408.2548.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-5-((*E*)-2-(7-Fluoroquinolin-2-yl)vinyl)-1-(hydroxymethyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-2-ol **8n** (yellow solid, 67.77%, 1.83 g); mp 209–210°C. IR (KBr) ν_{max} 3531, 3462, 3111, 2912, 1658, 1454, 1389, 1353, 1265, 1232, 1042, 973, 893 cm^{-1}. ^1H NMR (600 MHz, [D6]DMSO) δ 8.23–8.05 (1H, m, 4′-H), 8.03–7.95 (1H, m, 5′-H), 7.76–7.69 (1H, m, 8′-H), 7.37 (1H, d, J = 8.3 Hz, 3′-H), 7.13–7.03 (1H, m, 6′-H), 6.68 (1H, dd, J = 6.2 Hz, J = 15.7 Hz, 11-H), 6.54 (1H, d, J = 15.7 Hz, 12-H), 5.04 (1H, s, 13-Ha), 4.88 (1H, s, 13-Hb), 3.63 (1H, brs, 15-OH), 3.57 (1H, brs, 3-OH), 3.46 (1H, d, J = 11.6 Hz, 15-Ha), 3.31 (1H, d, J = 11.6 Hz, 15-Hb),

3.15–3.10 (1H, m, 3-H), 2.83 (1H, d, J = 6.2 Hz, 9-H), 2.10–1.19 (9H, m, 1,2,5,6,7-H), 1.04 (3H, s, 14-H), 0.90 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 163.6 ($^{1}J_{CF}$ = 245.2 Hz), 157.2, 148.6, 147.4, 136.6, 130.5, 125.5, 125.0, 118.6, 116.8 ($^{2}J_{CF}$ = 21.2 Hz), 112.8 ($^{2}J_{CF}$ = 21.3 Hz), 109.1, 78.7, 65.4, 62.2, 47.5, 43.2, 40.4, 36.5, 33.3, 27.6, 24.5, 21.2, 19.3, 15.0 ppm. MS (ESI) *m/z* (%) 396.2 ([M + H]$^+$, 100%). HRMS (ESI) calcd for $C_{25}H_{31}FNO_2$ [M + H]$^+$ 396.2339, found 396.2351.

(1*R*,2*R*,4*aR*,5*R*,8*aS*)-5-((*E*)-2-(7-Chloroquinolin-2-yl)vinyl)-1-(hydroxymethyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-2-ol **8o** (pale yellow solid, 64.31%, 1.82 g); mp 196–197°C. IR (KBr) ν_{max} 3526, 3468, 3112, 2923, 1650, 1455, 1383, 1354, 1263, 1232, 1043, 975, 885 cm^{-1}. ^{1}H NMR (600 MHz, [D6]DMSO) δ 8.24–8.15 (2H, m, 4′,5′-H), 7.96–7.69 (2H, m, 6′,8′-H), 7.36 (1H, d, J = 8.3 Hz, 3′-H), 6.66 (1H, dd, J = 6.2 Hz, J = 15.7 Hz, 11-H), 6.56 (1H, d, J = 15.7 Hz, 12-H), 5.05 (1H, s, 13-Ha), 4.85 (1H, s, 13-Hb), 3.66 (1H, brs, 15-OH), 3.57 (1H, brs, 3-OH), 3.43 (1H, d, J = 11.6 Hz, 15-Ha), 3.33 (1H, d, J = 11.6 Hz, 15-Hb), 3.14–3.10 (1H, m, 3-H), 2.83 (1H, d, J = 6.2 Hz, 9-H), 2.10–1.15 (9H, m, 1,2,5,6,7-H), 1.02 (3H, s, 14-H), 0.85 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6]DMSO) δ 157.5, 148.8, 147.2, 136.3, 135.4, 129.5, 128.4, 126.1, 125.5, 125.3, 125.0, 118.9, 109.2, 78.8, 65.5, 62.3, 47.4, 43.3, 40.0, 36.4, 33.2, 27.7, 24.2, 19.3, 15.0 ppm. MS (ESI) *m/z* (%) 412.2 ([M + H]$^+$, $C_{25}H_{31}{}^{35}ClNO_2$, 100%), 414.2 ([M + H]$^+$, $C_{25}H_{31}{}^{37}ClNO_2$, 33%). HRMS (ESI) calcd for $C_{25}H_{31}{}^{35}ClNO_2$ [M + H]$^+$ 412.2043, found 412.2058; for $C_{25}H_{31}{}^{37}ClNO_2$ [M + H]$^+$ 414.2014, found 414.2026.

2-((*E*)-2-((1*R*,4*aS*,5*R*,6*R*,8*aR*)-6-Hydroxy-5-(hydroxymethyl)-5,8*a*-dimethyl-2-methylenedecahydronaphthalen-1-yl)vinyl) quinolin-7-ol **8p** (pale yellow solid, 58.74%, 1.58 g); mp 224–225°C. IR (KBr) ν_{max} 3535, 3446, 3254, 2914, 1651, 1455, 1381, 1354, 1261, 1235, 1042, 976, 888 cm^{-1}. ^{1}H NMR (600 MHz, [D6]DMSO) δ 8.24–8.13 (1H, m, 4′-H), 8.04–7.98 (1H, m, 5′-H), 7.33–7.12 (3H, m, 3′,6′,8′-H), 6.67 (1H, dd, J = 6.2 Hz, J = 15.7 Hz, 11-H), 6.55 (1H, d, J = 15.7 Hz, 12-H), 5.35 (1H, brs, 7′-OH), 5.02 (1H, s, 13-Ha), 4.87 (1H, s, 13-Hb), 3.66 (1H, brs, 15-OH), 3.57 (1H, brs, 3-OH), 3.50 (1H, d, J = 11.6 Hz, 15-Ha), 3.31 (1H, d, J = 11.6 Hz, 15-Hb), 3.17–3.11 (1H, m, 3-H), 2.82 (1H, d, J = 6.2 Hz, 9-H), 2.04–1.12 (9H, m, 1,2,5,6,7-H), 1.05 (3H, s, 14-H), 0.92 (3H, s, 16-H). ^{13}C NMR (100 MHz, [D6] DMSO) δ 158.3, 156.8, 151.1, 148.6, 136.2, 130.0, 125.5, 125.0, 123.3, 118.6, 116.3, 110.8, 109.2, 78.8, 65.5, 62.4, 47.4, 43.3, 40.1, 36.8, 33.5, 27.4, 24.7, 19.6, 15.1 ppm. MS (ESI) *m/z* (%) 394.2 ([M + H]$^+$, 100%). HRMS (ESI) calcd for $C_{25}H_{32}NO_3$ [M + H]$^+$ 394.2382, found 394.2393.

Compound **9** (**9a** is selected as an example): compound **8a** (1.50 g, 3.98 mmol) and succinic anhydride (1.19 g, 15.9 mmol) (for **9b**, maleic anhydride 1.56 g, 15.9 mmol) were dissolved in CH_2Cl_2 (30 mL). Then, DMAP (*N*,*N*-4-dimethylaminopyridine, 0.53 g, 4.38 mmol) and Et_3N (0.60 g, 5.97 mmol) were added under stirring. The mixture was stirred at room temperature overnight until no compound **8a** was detected by TLC. After reaction, hydrochloric acid (4 M) was added dropwise to neutralize the mixture. CH_2Cl_2 (3 × 30 mL) was poured into the mixture. The combined CH_2Cl_2 extract was washed with brine (3 × 30 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was dissolved in ethanol (10 mL) and then $KHCO_3$ saturated solution (1.1 equiv.) was slowly added, producing a large number of bubbles. The mixture changed gradually from clear to milky white and stirring was continued for 1 h until bubbling ceased. Last, the mixture was filtered, dried and crystallized from acetone to give potassium 4-(((1*R*,2*R*,4*aR*,5*R*,8*aS*)-2-(3-carboxypropanoyloxy)-1,4*a*-dimethyl-6-methylene-5-((*E*)-2-(quinolin-2-yl)vinyl) decahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9a** (1.54 g, yield 62.86%, purity 96.2%) as an off white solid. IR (KBr) ν_{max} 3412, 3080, 2938, 2851, 1753, 1720, 1636, 1575, 1447, 1384, 1346, 1277, 1235, 1114, 1037, 973, 892 cm^{-1}. ^{1}H NMR (600 MHz, D_2O) δ 8.24–8.17 (1H, m, 4′-H), 8.06 -7.80 (3H, m, 5′,7′,8′-H), 7.61–7.55 (1H, m, 6′-H), 7.34 (1H, d, J = 8.3 Hz, 3′-H), 6.67 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.54 (1H, d, J = 15.4 Hz, 12-H), 5.05 (1H, s, 13-Ha), 4.86 (1H, s, 13-Hb), 4.15 (1H, d, J = 11.8 Hz, 15-Ha), 4.01–3.95 (1H, m, 3-H), 3.83 (1H, d, J = 11.8 Hz, 15-Hb), 2.86–2.75 (9H, m, 9,18,19,22,23-H), 2.13–1.45 (9H, m, 1,2,5,6,7-H), 1.01 (3H, s, 14-H), 0.93 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.5, 176.1, 173.5, 173.1, 156.4, 148.8, 148.1, 136.5, 130.5, 128.8, 128.0, 126.9, 126.0, 125.8, 125.1, 118.5, 110.1, 75.5, 65.8, 61.9, 47.4, 43.3, 39.9, 36.7, 33.3, 32.6, 32.3, 32.0, 30.2, 27.9, 24.7, 21.9, 15.0 ppm. MS (ESI) *m/z* (%) 616.3 ([M + H]$^+$, 100%). HRMS (ESI) calcd for $C_{33}H_{39}NO_8K$ [M + H]$^+$ 616.3659, found 616.3667.

Potassium (*E*)-4-(((1*R*,2*R*,4*aR*,5*R*,8*aS*)-2-((*E*)-3-carboxyacryloyloxy)-1,4*a*-dimethyl-6-methylene-5-((*E*)-2-(quinolin-2-yl)vinyl)decahydronaphthalen-1-yl)methoxy)-4-oxobut-2-enoate **9b:** creamy white solid, 1.58 g, yield 65.02%, purity 96.8%. IR (KBr) ν_{max} 3422, 3084, 2934, 2853, 1753, 1634, 1575, 1446, 1383, 1343, 1275, 1233, 1114, 1032, 972, 891 cm^{-1}. ^{1}H NMR (600 MHz, D_2O) δ 8.25–8.19 (1H, m, 4′-H), 8.07–7.82 (3H, m, 5′,7′,8′-H), 7.63–7.52 (1H, m, 6′-H), 7.37–7.24 (3H, m, 19,23,3′-H), 6.65 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.53 (1H, d, J = 15.4 Hz, 12-H), 6.21–6.09 (2H, m, 18,22-H), 5.05 (1H, s, 13-Ha), 4.85 (1H, s, 13-Hb), 4.15 (1H, d, J = 11.8 Hz, 15-Ha), 4.00–3.94 (1H, m, 3-H), 3.82 (1H, d, J = 11.8 Hz, 15-Hb), 2.83–2.73 (1H, m, 9-H), 2.16–1.45 (9H, m, 1,2,5,6,7-H), 1.04 (3H, s, 14-H), 0.91 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 167.7, 167.1, 166.6, 166.1, 156.7, 148.6, 148.4, 139.7, 139.0, 136.4, 131.2, 131.1, 130.5, 128.6, 128.0, 126.7, 126.0, 125.4, 125.0, 118.6, 110.0, 75.7, 65.5, 62.3, 47.6, 43.3, 39.2, 36.4, 33.5, 27.6, 24.4, 21.7, 15.2 ppm. MS (ESI) *m/z* (%) 612.3 ([M + H]$^+$, 100%). HRMS (ESI) calcd for $C_{34}H_{41}NO_8K$ [M + H]$^+$ 612.3346, found 616.3359.

Potassium 4-(((1*R*,2*R*,4a*R*,5*R*,8a*S*)-2-(3-carboxypropanoyloxy)-1,4a-dimethyl-6-methylene-5-((*E*)-2-(4-methylquinolin-2-yl)vinyl)decahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9c:** creamy white solid, 1.58 g, yield 65.00%, purity 95.9%. IR (KBr) ν_{max} 3422, 3084, 3124, 2938, 2856, 1755, 1723, 1636, 1573, 1443, 1386, 1348, 1274, 1237, 1117, 1033, 973, 894 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ 8.20–7.84 (3H, m, 5′,7′,8′-H), 7.62–7.57 (1H, m, 6′-H), 7.15 (1H, s, 3′-H), 6.69 (1H, dd, J = 6.2 Hz, J = 15.7 Hz, 11-H), 6.65 (1H, d, J = 15.7 Hz, 12-H), 5.05 (1H, s, 13-Ha), 4.87 (1H, s, 13-Hb), 4.14 (1H, d, J = 11.8 Hz, 15-Ha), 4.00–3.93 (1H, m, 3-H), 3.85 (1H, d, J = 11.8 Hz, 15-Hb), 2.86–2.74 (9H, m, 9,18,19,22,23-H), 2.61 (3H, s, 4′-CH_3), 2.17–1.49 (9H, m, 1,2,5,6,7-H), 1.04 (3H, s, 14-H), 0.90 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.2, 176.0, 173.6, 173.4, 157.5, 148.6, 146.7, 144.6, 130.7, 128.4, 128.5, 126.3, 126.0, 125.5, 125.1, 118.2, 109.1, 75.5, 65.9, 61.4, 47.3, 43.4, 39.5, 36.3, 33.2, 32.3, 32.0, 31.8, 30.1, 27.2, 24.5, 21.7, 20.3, 15.1 ppm. MS (ESI) *m/z* (%) 630.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{24}H_{41}NO_8K[M + H]^+$ 630.2469, found 630.2483.

Potassium 4-(((1*R*,2*R*,4a*R*,5*R*,8a*S*)-2-(3-carboxypropanoyloxy)-5-((*E*)-2-(4-fluoroquinolin-2-yl)vinyl)-1,4a-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9d:** off white solid, 1.58 g, yield 62.70%, purity 96.8%. IR (KBr) ν_{max} 3418, 3081, 2933, 2854, 1757, 1722, 1634, 1576, 1444, 1387, 1346, 1274, 1237, 1114, 1036, 994, 886 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ 8.17–7.85 (4H, m, 5′,6′,7′,8′-H), 7.14 (1H, d, J = 4.3 Hz, 3′-H), 6.68 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.55 (1H, d, J = 15.4 Hz, 12-H), 5.04 (1H, s, 13-Ha), 4.84 (1H, s, 13-Hb), 4.16 (1H, d, J = 11.8 Hz, 15-Ha), 4.07–3.99 (1H, m, 3-H), 3.84 (1H, d, J = 11.8 Hz, 15-Hb), 2.83–2.72 (9H, m, 9,18,19,22,23-H), 2.15–1.46 (9H, m, 1,2,5,6,7-H), 1.04 (3H, s, 14-H), 0.87 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.6, 176.2, 173.4, 173.0, 167.3 ($^1J_{CF}$ = 245.2 Hz), 156.1, 148.8, 148.3, 131.7, 129.2, 127.3, 125.5, 125.0, 120.3, 118.4 ($^2J_{CF}$ = 23.0 Hz), 109.5, 101.4 ($^2J_{CF}$ = 22.5 Hz), 75.7, 65.4, 61.7, 47.4, 43.4, 39.6, 36.6, 33.3, 32.4, 32.0, 31.6, 30.2, 27.4, 24.4, 21.9, 15.2 ppm. MS (ESI) *m/z* (%) 634.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{33}H_{38}FNO_8K$ $[M + H]^+$ 634.2218, found 634.2229.

Potassium 4-(((1*R*,2*R*,4a*R*,5*R*,8a*S*)-2-(3-carboxypropanoyloxy)-5-((*E*)-2-(4-chloroquinolin-2-yl)vinyl)-1,4a-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9e:** off white solid, 1.55 g, yield 59.85%, purity 96.3%. IR (KBr) ν_{max} 3419, 3085, 2933, 2856, 1759, 1725, 1631, 1572, 1443, 1389, 1341, 1273, 1234, 1112, 1036, 973, 892 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ 8.64–8.55 (1H, m, 5′-H), 8.12–7.74 (3H, m, 6′,7′,8′-H), 7.54 (1H, s, 3′-H), 6.65 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.56 (1H, d, J = 15.4 Hz, 12-H), 5.04 (1H, s, 13-Ha), 4.86 (1H, s, 13-Hb), 4.16 (1H, d, J = 11.8 Hz, 15-Ha), 4.01–3.95 (1H, m, 3-H), 3.83 (1H, d, J = 11.8 Hz, 15-Hb), 2.82–2.75 (9H, m, 9,18,19,22,23-H), 2.13–1.45 (9H, m, 1,2,5,6,7-H), 1.03 (3H, s, 14-H), 0.89 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.5, 176.1, 173.5, 173.1, 156.4, 148.8, 148.1, 136.5, 130.5, 128.8, 128.0, 126.9, 126.0, 125.8, 125.1, 118.5, 110.1, 75.5, 65.8, 61.9, 47.4, 43.3, 39.9, 36.7, 33.3, 32.6, 32.3, 32.0, 30.2, 27.9, 24.7, 21.9, 15.0 ppm. MS (ESI) *m/z* (%) 650.2 ($[M + H]^+$, $C_{33}H_{38}{}^{35}ClNO_8K$, 100%), 652.2 ($[M + H]^+$, $C_{33}H_{38}{}^{37}ClNO_8K$, 33%). HRMS (ESI) calcd for $C_{33}H_{38}{}^{35}ClNO_8K$ $[M + H]^+$ 650.1970, found 650.1978; for $C_{33}H_{38}{}^{37}ClNO_8K$ $[M + H]^+$ 652.1941, found 652.1951.

Potassium 4-(((1*R*,2*R*,4a*R*,5*R*,8a*S*)-2-(3-carboxypropanoyloxy)-5-((*E*)-2-(4-hydroxyquinolin-2-yl)vinyl)-1,4a-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9f:** creamy white solid, 1.36 g, yield 54.18%, purity 95.8%. IR (KBr) ν_{max} 3478, 3392, 3082, 2948, 2854, 1756, 1723, 1638, 1572, 1442, 1386, 1342, 1272, 1232, 1116, 1034, 976, 893 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ 8.33–7.80 (3H, m, 5′,7′,8′-H), 7.72–7.54 (1H, m, 6′-H), 6.83 (1H, s, 3′-H), 6.64 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.53 (1H, d, J = 15.4 Hz, 12-H), 5.34 (1H, brs, 4′-OH), 5.04 (1H, s, 13-Ha), 4.85 (1H, s, 13-Hb), 4.16 (1H, d, J = 11.8 Hz, 15-Ha), 4.03–3.95 (1H, m, 3-H), 3.85 (1H, d, J = 11.8 Hz, 15-Hb), 2.82–2.73 (9H, m, 9,18,19,22,23-H), 2.16–1.42 (9H, m, 1,2,5,6,7-H), 1.04 (3H, s, 14-H), 0.85 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.6, 176.2, 173.7, 173.2, 166.8, 157.5, 149.1, 148.8, 130.3, 128.8, 127.2, 125.7, 125.1, 121.6, 117.6, 109.3, 102.6, 75.8, 65.6, 61.6, 47.4, 43.6, 39.7, 36.8, 33.3, 32.7, 32.3, 32.0, 30.6, 27.4, 24.4, 20.6, 15.4 ppm. MS (ESI) *m/z* (%) 632.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{33}H_{39}NO_9K$ $[M + H]^+$ 632.2310, found 632.2320.

Potassium 4-(((1*R*,2*R*,4a*R*,5*R*,8a*S*)-2-(3-carboxypropanoyloxy)-1,4a-dimethyl-6-methylene-5-((*E*)-2-(6-methylquinolin-2-yl)vinyl)decahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9g:** white solid, 1.60 g, yield 64.05%, purity 96.6%. IR (KBr) ν_{max} 3432, 3084, 2932, 2854, 1752, 1725, 1632, 1572, 1441, 1385, 1342, 1274, 1237, 1117, 1033, 973, 892 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ 8.23 (1H, d, J = 8.3 Hz, 4′-H), 7.96 (1H, d, J = 8.3 Hz, 8′-H) 7.62–7.53 (2H, m, 5′,7′-H), 7.14 (1H, dd, J = 8.3 Hz, J = 4.3 Hz, 3′-H), 6.68 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.58 (1H, d, J = 15.4 Hz, 12-H), 5.04 (1H, s, 13-Ha), 4.85 (1H, s, 13-Hb), 4.16 (1H, d, J = 11.8 Hz, 15-Ha), 4.01–3.96 (1H, m, 3-H), 3.85 (1H, d, J = 11.8 Hz, 15-Hb), 2.84–2.75 (9H, m, 9,18,19,22,23-H), 2.35 (3H, s, 6′-CH_3), 2.15–1.45 (9H, m, 1,2,5,6,7-H), 1.05 (3H, s, 14-H), 0.96 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.7, 176.1, 173.5, 173.0, 155.3, 148.8, 146.4, 137.3, 135.5, 130.5, 128.6, 126.4, 126.2, 125.6, 125.2, 118.7, 109.1, 75.7, 65.5, 61.6, 47.6, 43.3, 39.6, 36.5, 33.4, 32.6, 32.3, 31.6, 30.2, 27.5, 24.6, 21.5, 20.4, 15.3 ppm. MS (ESI) *m/z* (%) 630.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{34}H_{41}NO_8K$ $[M + H]^+$ 630.2469, found 630.2482.

Potassium 4-(((1*R*,2*R*,4a*R*,5*R*,8a*S*)-2-(3-carboxypropanoyloxy)-5-((*E*)-2-(6-methoxyquinolin-2-yl)vinyl)-1,4a-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9h:** white solid, 1.71 g, yield 64.04%, purity 96.2%. IR (KBr)

ν_{max} 3432, 3080, 2938, 2823, 1754, 1723, 1646, 1574, 1447, 1384, 1346, 1273, 1235, 1116, 1037, 973, 892 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ 8.20–8.16 (1H, m, 4′-H), 7.75 (1H, d, J = 8.3 Hz, 8′-H), 7.39–7.35 (2H, m, 3′,7′-H), 7.17–7.09 (1H, m, 5′-H), 6.66 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.56 (1H, d, J = 15.4 Hz, 12-H), 5.03 (1H, s, 13-Ha), 4.86 (1H, s, 13-Hb), 4.15 (1H, d, J = 11.8 Hz, 15-Ha), 4.05–3.95 (1H, m, 3-H), 3.89 (3H, s, 6′-OCH_3), 3.83 (1H, d, J = 11.8 Hz, 15-Hb), 2.88–2.75 (9H, m, 9,18,19,22,23-H), 2.13–1.46 (9H, m, 1,2,5,6,7-H), 1.06 (3H, s, 14-H), 0.90 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.7, 176.4, 173.4, 173.1, 157.4, 154.4, 148.6, 143.1, 135.4, 130.7, 129.4, 125.5, 125.1, 122.5, 119.4, 109.3, 105.4, 75.9, 65.6, 61.7, 55.3, 47.4, 43.3, 39.4, 36.5, 33.6, 32.6, 32.4, 32.1, 30.2, 27.5, 24.7, 21.0, 15.1 ppm. MS (ESI) *m/z* (%) 646.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{34}H_{41}NO_9K$ $[M + H]^+$ 646.2418, found 646.2432.

Potassium 4-(((1*R*,2*R*,4*aR*,5*R*,8*aS*)-2-(3-carboxypropanoyloxy)-5-((*E*)-2-(6-fluoroquinolin-2-yl)vinyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9i:** off white solid, 1.31 g, yield 51.98%, purity 97.2%. IR (KBr) ν_{max} 3417, 3084, 2938, 2856, 1753, 1724, 1636, 1578, 1447, 1384, 1346, 1277, 1235, 1114, 1034, 975, 892 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ 8.27–8.22 (1H, m, 4′-H), 7.96 (1H, d, J = 8.3 Hz, 8′-H), 7.39–7.37 (3H, m, 3′,5′,7′-H), 6.66 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.55 (1H, d, J = 15.4 Hz, 12-H), 5.05 (1H, s, 13-Ha), 4.84 (1H, s, 13-Hb), 4.15 (1H, d, J = 11.8 Hz, 15-Ha), 4.06–3.95 (1H, m, 3-H), 3.86 (1H, d, J = 11.8 Hz, 15-Hb), 2.82–2.78 (9H, m, 9,18,19,22,23-H), 2.16–1.45 (9H, m, 1,2,5,6,7-H), 1.04 (3H, s, 14-H), 0.87 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.6, 176.2, 173.5, 173.2, 160.6 ($^1J_{CF}$ = 244.8 Hz), 155.8, 148.6, 147.2, 145.3, 135.4, 130.2, 125.6, 125.3, 121.5 ($^2J_{CF}$ = 24.2 Hz), 119.3, 109.5 ($^2J_{CF}$ = 21.5 Hz), 109.1, 75.7, 65.4, 62.3, 47.7, 43.1, 40.3, 36.2, 33.6, 32.5, 32.3, 32.0, 30.3, 27.5, 24.3, 21.3, 14.8 ppm. MS (ESI) *m/z* (%) 634.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{33}H_{38}FNO_8K$ $[M + H]^+$ 634.2218, found 634.2231.

Potassium 4-(((1*R*,2*R*,4*aR*,5*R*,8*aS*)-2-(3-carboxypropanoyloxy)-5-((*E*)-2-(6-chloroquinolin-2-yl)vinyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9j:** offwhite solid, 1.47 g, yield 56.98%, purity 95.3%. IR (KBr) ν_{max} 3422, 3084, 2933, 2854, 1756, 1725, 1634, 1576, 1445, 1384, 1346, 1277, 1237, 1114, 1034, 973, 894 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ 8.27–8.20 (1H, m, 4′-H), 8.12 (1H, d, J = 8.3 Hz, 8′-H), 7.83 (1H, d, J = 8.3 Hz, 7′-H), 7.36 (1H, d, J = 8.3 Hz, 3′-H), 7.14–7.07 (1H, m, 5′-H), 6.68 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.52 (1H, d, J = 15.4 Hz, 12-H), 5.04 (1H, s, 13-Ha), 4.86 (1H, s, 13-Hb), 4.15 (1H, d, J = 11.8 Hz, 15-Ha), 4.05–3.92 (1H, m, 3-H), 3.82 (1H, d, J = 11.8 Hz, 15-Hb), 2.82–2.75 (9H, m, 9,18,19,22,23-H), 2.15–1.45 (9H, m, 1,2,5,6,7-H), 1.05 (3H, s, 14-H), 0.83 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.6, 176.2, 173.6, 173.2, 156.4, 148.6, 146.3, 135.4, 132.2, 131.4, 130.1, 128.7, 125.6, 125.3, 123.5, 119.2, 109.3, 75.8, 65.2, 61.7, 47.4, 43.3, 39.4, 36.1, 33.5, 32.6, 32.2, 32.0, 30.3, 27.2, 24.5, 21.2, 15.1 ppm. MS (ESI) *m/z* (%) 650.2 ($[M + H]^+$, $C_{33}H_{38}{}^{35}ClNO_8K$, 100%), 652.2 ($[M + H]^+$, $C_{33}H_{38}{}^{37}ClNO_8K$, 33%). HRMS (ESI) calcd for $C_{33}H_{38}{}^{35}ClNO_8K$ $[M + H]^+$ 650.1970, found 650.1978; for $C_{33}H_{38}{}^{37}ClNO_8K$ $[M + H]^+$ 652.1941, found 652.1951.

Potassium 4-(((1*R*,2*R*,4*aR*,5*R*,8*aS*)-5-((*E*)-2-(6-bromoquinolin-2-yl)vinyl)-2-(3-carboxypropanoyloxy)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9k:** off white solid, 1.41 g, yield 52.03%, purity 96.8%. IR (KBr) ν_{max} 3416, 3078, 2934, 2855, 1755, 1723, 1636, 1574, 1447, 1385, 1346, 1273, 1235, 1114, 1035, 973, 886 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ 8.28–8.05 (4H, m, 4′,5′,7′,8′-H), 7.46 (1H, d, J = 8.3 Hz, 3′-H), 6.63 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.51 (1H, d, J = 15.4 Hz, 12-H), 5.04 (1H, s, 13-Ha), 4.86 (1H, s, 13-Hb), 4.15 (1H, d, J = 11.8 Hz, 15-Ha), 4.06–3.95 (1H, m, 3-H), 3.83 (1H, d, J = 11.8 Hz, 15-Hb), 2.87–2.74 (9H, m, 9,18,19,22,23-H), 2.16–1.45 (9H, m, 1,2,5,6,7-H), 1.06 (3H, s, 14-H), 0.94 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.7, 176.3, 173.6, 173.3, 156.4, 148.5, 148.1, 135.3, 133.4, 132.1, 129.7, 128.5, 125.5, 125.2, 123.4, 120.3, 109.3, 75.7, 65.3, 61.2, 48.4, 43.7, 40.6, 36.7, 33.4, 32.7, 32.5, 32.0, 30.5, 27.6, 24.4, 20.7, 15.0 ppm. MS (ESI) *m/z* (%) 694.1 ($[M + H]^+$, $C_{33}H_{38}{}^{79}BrNO_8K$, 100%), 696.1 ($[M + H]^+$, $C_{33}H_{38}{}^{81}BrNO_8K$, 97%). HRMS (ESI) calcd for $C_{33}H_{38}{}^{79}BrNO_8K$ $[M + H]^+$ 694.1465, found 694.1475; for $C_{33}H_{38}{}^{81}BrNO_8K$ $[M + H]^+$ 696.1408, found 696.1418.

Potassium 4-(((1*R*,2*R*,4*aR*,5*R*,8*aS*)-2-(3-carboxypropanoyloxy)-5-((*E*)-2-(6-hydroxyquinolin-2-yl)vinyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9l:** creamy white solid, 1.36 g, yield 54.18%, purity 95.9%. IR (KBr) ν_{max} 3416, 3084, 2935, 2853, 1757, 1724, 1633, 1572, 1445, 1386, 1346, 1277, 1237, 1114, 1034, 973, 894 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ 8.08–8.02 (1H, m, 4′-H), 7.84 (1H, d, J = 8.3 Hz, 8′-H), 7.45–7.13 (3H, m, 3′,5′,7′-H), 6.68 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.55 (1H, d, J = 15.4 Hz, 12-H), 5.36 (1H, s, 6′-OH), 5.04 (1H, s, 13-Ha), 4.87 (1H, s, 13-Hb), 4.17 (1H, d, J = 11.8 Hz, 15-Ha), 4.07–3.95 (1H, m, 3-H), 3.85 (1H, d, J = 11.8 Hz, 15-Hb), 2.87–2.77 (9H, m, 9,18,19,22,23-H), 2.17–1.45 (9H, m, 1,2,5,6,7-H), 1.03 (3H, s, 14-H), 0.91 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.6, 176.4, 173.5, 173.3, 155.6, 154.2, 148.6, 143.2, 134.5, 130.6, 128.6, 125.6, 125.3, 125.0, 119.2, 111.4, 109.1, 75.7, 65.3, 61.5, 47.5, 43.2, 39.5, 36.5, 33.5, 32.6, 32.2, 32.0, 30.1, 27.4, 24.6, 20.3, 15.2 ppm. MS (ESI) *m/z* (%) 632.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{33}H_{39}NO_9K$ $[M + H]^+$ 632.2310, found 632.2322.

Potassium 4-(((1*R*,2*R*,4*aR*,5*R*,8*aS*)-2-(3-carboxypropanoyloxy)-1,4*a*-dimethyl-6-methylene-5-((*E*)-2-(7-methylquinolin-2-yl)vinyl)decahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9m:** white solid, 1.59 g, yield 63.60%, purity 97.9%. IR (KBr) ν_{max} 3421, 3084, 2933, 2852, 1753, 1722, 1633, 1572, 1444, 1385, 1344, 1274, 1233, 1116, 1035, 973, 892 cm^{-1}.

^{1}H NMR (600 MHz, D_2O) δ 8.23 (1H, d, J = 8.2 Hz, 4′-H), 7.90–7.58 (3H, m, 5′,6′,8′-H), 7.35 (1H, dd, J = 8.2 Hz, J = 4.3 Hz, 3′-H), 6.64 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.52 (1H, d, J = 15.4 Hz, 12-H), 5.04 (1H, s, 13-Ha), 4.85 (1H, s, 13-Hb), 4.17 (1H, d, J = 11.8 Hz, 15-Ha), 4.04–3.95 (1H, m, 3-H), 3.83 (1H, d, J = 11.8 Hz, 15-Hb), 2.83–2.75 (9H, m, 9,18,19,22,23-H), 2.35 (3H, s, 7′-CH_3), 2.17–1.46 (9H, m, 1,2,5,6,7-H), 1.04 (3H, s, 14-H), 0.87 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.7, 176.1, 173.4, 173.1, 156.5, 148.7, 146.4, 139.4, 136.2, 130.5, 128.3, 127.1, 126.4, 125.6, 125.2, 117.4, 109.1, 75.5, 65.3, 62.4, 46.6, 43.4, 40.2, 36.3, 33.6, 32.6, 32.2, 32.0, 30.2, 27.3, 24.6, 21.3, 20.5, 15.1 ppm. MS (ESI) m/z (%) 630.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{24}H_{41}NO_8K$ $[M + H]^+$ 630.2469, found 630.2480.

Potassium 4-(((1*R*,2*R*,4*aR*,5*R*,8*aS*)-2-(3-carboxypropanoyloxy)-5-((*E*)-2-(7-methoxyquinolin-2-yl)vinyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9n:** creamy white solid, 1.66 g, yield 66.00%, purity 96.7%. IR (KBr) ν_{max} 3419, 3086, 2933, 2854, 1756, 1723, 1635, 1575, 1447, 1386, 1342, 1273, 1235, 1116, 1034, 971, 892 cm^{-1}. ^{1}H NMR (600 MHz, D_2O) δ 8.26 (1H, d, J = 8.2 Hz, 4′-H), 7.95–7.90 (1H, m, 5′-H), 7.38–7.26 (3H, m, 3′,6′,8′-H), 6.67 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.55 (1H, d, J = 15.4 Hz, 12-H), 5.05 (1H, s, 13-Ha), 4.85 (1H, s, 13-Hb), 4.17 (1H, d, J = 11.8 Hz, 15-Ha), 4.06–3.95 (1H, m, 3-H), 3.86 (1H, s, 7′-OCH_3), 3.82 (1H, d, J = 11.8 Hz, 15-Hb), 2.88–2.75 (9H, m, 9,18,19,22,23-H), 2.16–1.45 (9H, m, 1,2,5,6,7-H), 1.04 (3H, s, 14-H), 0.93 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.5, 176.0, 173.2, 173.0, 156.5, 151.6, 148.3, 147.4, 136.5, 129.5, 128.7, 125.5, 125.1, 117.6, 116.5, 109.1, 107.4, 75.7, 65.4, 62.2, 55.4, 46.5, 43.3, 40.2, 36.6, 33.5, 32.7, 32.5, 32.0, 30.5, 27.4, 24.3, 20.6, 15.3 ppm. MS (ESI) m/z (%) 646.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{34}H_{41}NO_9K$ $[M + H]^+$ 646.2418, found 646.2429.

Potassium 4-(((1*R*,2*R*,4*aR*,5*R*,8*aS*)-2-(3-carboxypropanoyloxy)-5-((*E*)-2-(7-fluoroquinolin-2-yl)vinyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9o:** off white solid, 1.34 g, yield 53.17%, purity 96.7%. IR (KBr) ν_{max} 3432, 3084, 2938, 2854, 1753, 1725, 1633, 1575, 1444, 1384, 1346, 1275, 1235, 1114, 1036, 973, 892 cm^{-1}. ^{1}H NMR (600 MHz, D_2O) δ 8.25–8.12 (1H, m, 4′-H), 8.07–7.98 (1H, m, 5′-H), 7.76–7.64 (1H, m, 8′-H), 7.35 (1H, d, J = 8.3 Hz, 3′-H), 7.16–7.08 (1H, m, 6′-H), 6.63 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.51 (1H, d, J = 15.4 Hz, 12-H), 5.05 (1H, s, 13-Ha), 4.86 (1H, s, 13-Hb), 4.17 (1H, d, J = 11.8 Hz, 15-Ha), 4.05–3.95 (1H, m, 3-H), 3.86 (1H, d, J = 11.8 Hz, 15-Hb), 2.86–2.75 (9H, m, 9,18,19,22,23-H), 2.15–1.45 (9H, m, 1,2,5,6,7-H), 1.04 (3H, s, 14-H), 0.91 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.7, 176.2, 173.5, 173.0, 163.6 ($^1J_{CF}$ = 245.5 Hz), 157.2, 148.3, 147.4, 136.2, 130.3, 125.5, 125.1, 118.6, 116.3 ($^2J_{CF}$ = 22.2 Hz), 112.8 ($^2J_{CF}$ = 21.5 Hz), 109.5, 78.7, 65.4, 62.4, 47.5, 43.5, 40.4, 36.2, 33.3, 32.6, 32.3, 32.0, 30.1, 27.2, 24.5, 21.2, 20.1, 15.1 ppm. MS (ESI) m/z (%) 634.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{33}H_{38}FNO_8K$ $[M + H]^+$ 634.2218, found 634.2232.

Potassium 4-(((1*R*,2*R*,4*aR*,5*R*,8*aS*)-2-(3-carboxypropanoyloxy)-5-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9p:** off white solid, 1.42 g, yield 55.04%, purity 96.1%. IR (KBr) ν_{max} 3432, 3083, 2934, 2853, 1755, 1721, 1633, 1572, 1444, 1384, 1346, 1275, 1235, 1116, 1034, 973, 890 cm^{-1}. ^{1}H NMR (600 MHz, D_2O) δ 8.26–8.13 (2H, m, 4′,5′-H), 7.90–7.62 (2H, m, 6′,8′-H), 7.34 (1H, d, J = 8.3 Hz, 3′-H), 6.67 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.54 (1H, d, J = 15.4 Hz, 12-H), 5.05 (1H, s, 13-Ha), 4.85 (1H, s, 13-Hb), 4.17 (1H, d, J = 11.8 Hz, 15-Ha), 4.03–3.95 (1H, m, 3-H), 3.83 (1H, d, J = 11.8 Hz, 15-Hb), 2.84–2.75 (9H, m, 9,18,19,22,23-H), 2.13–1.45 (9H, m, 1,2,5,6,7-H), 1.03 (3H, s, 14-H), 0.91 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 177.6, 176.4, 173.5, 173.1, 157.6, 148.8, 147.2, 136.1, 135.4, 129.5, 128.4, 126.4, 125.5, 125.1, 124.8, 118.5, 109.1, 75.8, 65.5, 62.3, 47.4, 43.3, 40.0, 36.4, 33.2, 32.7, 32.4, 32.1, 30.2, 27.6, 24.2, 21.3, 15.1 ppm. MS (ESI) m/z (%) 650.2 ($[M + H]^+$, $C_{33}H_{38}{}^{35}ClNO_8K$, 100%), 652.2 ($[M + H]^+$, $C_{33}H_{38}{}^{37}ClNO_8K$, 33%). HRMS (ESI) calcd for $C_{33}H_{38}{}^{35}ClNO_8K$ $[M + H]^+$ 650.1970, found 650.1979; for $C_{33}H_{38}{}^{37}ClNO_8K$ $[M + H]^+$ 652.1941, found 652.1953.

Potassium 4-(((1*R*,2*R*,4*aR*,5*R*,8*aS*)-2-(3-carboxypropanoyloxy)-5-((*E*)-2-(7-hydroxyquinolin-2-yl)vinyl)-1,4*a*-dimethyl-6-methylenedecahydronaphthalen-1-yl)methoxy)-4-oxobutanoate **9q:** white solid, 1.46 g, yield 58.17%, purity 95.7%. IR (KBr) ν_{max} 3421, 3083, 2934, 2855, 1756, 1723, 1636, 1575, 1444, 1384, 1346, 1274, 1235, 1114, 1033, 973, 892 cm^{-1}. ^{1}H NMR (600 MHz, D_2O) δ 8.26–8.15 (1H, m, 4′-H), 8.04–7.96 (1H, m, 5′-H), 7.36–7.18 (3H, m, 3′,6′,8′-H), 6.67 (1H, dd, J = 6.2 Hz, J = 15.4 Hz, 11-H), 6.55 (1H, d, J = 15.4 Hz, 12-H), 5.35 (1H, brs, 7′-OH), 5.06 (1H, s, 13-Ha), 4.86 (1H, s, 13-Hb), 4.17 (1H, d, J = 11.8 Hz, 15-Ha), 4.01–3.95 (1H, m, 3-H), 3.86 (1H, d, J = 11.8 Hz, 15-Hb), 2.84–2.75 (9H, m, 9,18,19,22,23-H), 2.15–1.43 (9H, m, 1,2,5,6,7-H), 1.03 (3H, s, 14-H), 0.91 (3H, s, 16-H). ^{13}C NMR (100 MHz, D_2O) δ 176.6, 176.1, 173.7, 173.1, 158.5, 156.8, 151.5, 148.6, 136.2, 130.6, 125.5, 125.1, 123.3, 118.6, 116.4, 110.8, 109.1, 75.8, 65.5, 62.4, 47.4, 43.3, 40.3, 36.8, 33.5, 32.5, 32.3, 32.0, 30.3, 27.4, 24.7, 20.6, 15.1 ppm. MS (ESI) m/z (%) 632.2 ($[M + H]^+$, 100%). HRMS (ESI) calcd for $C_{33}H_{39}NO_9K$ $[M + H]^+$ 632.2310, found 632.2324.

Biological assays

The anti-platelet aggregation activities of **8a** and **9a–9q** were assessed using SD (Sprague Dawley) male rat arterial blood *in vitro*. Thrombin and ADP were used to induce platelet aggregation. Vorapaxar sulfate and aspirin were selected as positive controls. Fresh arterial blood was taken from the groin of SD male rats (180–220 g per rat) with 3.8% sodium

citrate as anticoagulant (9:1 by volume). Then, whole blood samples were centrifuged at 1000 rpm/min for 10 min at room temperature to give platelet-rich plasma (PRP-1). The residue continued to be centrifuged at 3000 rpm/min for 10 min at room temperature to prepare platelet-poor plasma (PPP). PPP was used as the blank control. The measurement range of the platelet aggregation apparatus was set according to the number of platelets of human blood. The number of platelets of human blood is (100–300) $\times 10^9\,L^{-1}$, but the number of platelets of rats is (600–1000) $\times 10^9\,L^{-1}$. In order to measure the platelet aggregation rate accurately, PPP was added to PRP to dilute the number of rat platelets to ~150 $\times 10^9\,L^{-1}$ (PRP-2).[50] The sample group solution (5 μL), with the target compound dissolved in normal saline (1.7 μmol/L) in advance, was added into PRP-2 (200 μL) and the mixture was incubated for 2 min, as well as positive controls. Normal saline (5 μL) was used as negative control with the procedure as above. Afterwards, adding 20 μL ADP (5 mM/L) or thrombin (0.1 U/mL) respectively induced platelet aggregation. IR was calculated with the formula IR = [1 − (SG/NC)] × 100% where SG and NC represent the platelet aggregation rates of sample group and negative control respectively.

Cytotoxicity assay *in vitro*

Mouse fibroblast cells (L929) were used to evaluate the cell toxicity of target derivatives **9** with Cell Counting Kit-8 (CCK-8) assays.[51] First, test compounds were dissolved and diluted to 10 and 100 μM/L with DMSO. Cells were added to 96-well microplates (1×10^4 cell/well) and then cultivated at 37°C in a humidified atmosphere of CO_2 (5%) for 24 h. Second, test compounds were added into the cells and incubation was continued at 37°C for 48 h. Third, the medium was removed and 100 μL of fresh complete medium of RPMI-1640 was added. CCK-8 solution was added to the microplates at 10 μL per well. Last, the absorbance of the test solution was measured at 450 nm on a Bio-Tek Flx800 fluorescence microplate reader. According to the formula to calculate relative survival rate: relative survival rate (%) = {[Abs(test cells) − Abs(blank cells)]/[Abs(controlled cells) − Abs(blank cells)]} × 100% (Abs, absorbance).

Statistical analysis

Results are presented as the means ± s.e. (SEM). Data were analyzed with one-way ANOVA (SPSS software) to measure statistical significance of the differences. The level of significance was considered at $P < 0.05$ and $P < 0.01$.

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Data availability. The data that support this study are available in the article.

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