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Discovery of Potent Orally Active Protease-Activated Receptor 1 (PAR1) Antagonists Based on Andrographolide

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ABSTRACT: Protease-activated receptor-1 (PAR1), a G protein-coupled receptor, plays a critical role in thrombin-mediated platelet aggregation. It is regarded as a promising antithrombosis target that is unlikely to result in bleeding. Here, we describe the synthesis of a series of novel PAR1 antagonists by borrowing the chiral fragment of andrographolide, an easily accessible natural molecule from *Andrographis paniculata*, to produce natural product/synthesis hybrids. An *in vitro* PAR1 inhibition assay and an *in vivo* pharmacokinetic profile led to the identification of compound **39** as the best PAR1 inhibitor. The further *in vitro* and *ex vivo* anti-platelet aggregation assays of compound **39** indicated that compound **39** was a potent anti-platelet agent. In addition, this compound is metabolically stable, and displays a favorable pharmacokinetic profile with an elimination half-life of 3.1 h, which could be treated as a promising candidate for further clinical development.

KEYWORDS: Andrographolide analogs; protease-activated receptor-1; antagonists; orally active.

INTRODUCTION

Protease-activated receptor-1 (PAR1), a G-protein-coupled thrombin receptor, is the most potent cell surface inducer of platelet activation.[1,2] Mechanistically, thrombin activates PAR1 by cleaving its *N*-terminal ectodomain to reveal a new *N*-terminus, which serves as a tethered peptide ligand that binds to the heptahelical domain to trigger G protein activation and lead to the aggregation of platelets.[3,4] Given the critical role of PAR1, a PAR1 antagonist could be used as potent antiplatelet agent for the prevention of thrombosis and restenosis.[5-7] Additionally, because PAR1 antagonists target the cellular effector of thrombin, thrombin-mediated fibrin generation is not affected, and therefore normal hemostasis should be maintained when platelet activation is induced. Therefore, a PAR1 antagonist is likely to result in a lower risk of bleeding than conventional antithrombotic agents.[8,9]

Several novel PAR1 antagonists such as vorapaxar (SCH530348),[10,11] atopaxar (E5555),[12,13] SCH79797,[14-16] and others have been reported to have good efficacy in inhibiting the thrombin receptor (Fig. 1). So far, only vorapaxar, derived from the natural product himbacine, has been approved by the US Food and Drug Administration as the first-in-class anti-platelet drug targeting PAR1 to reduce the risk of recurrent cardiovascular events. It binds to PAR1 with high affinity, has good platelet inhibitory activity, and is rapidly absorbed via the gastrointestinal tract, with a terminal plasma half-life of 126 - 269 h.[17-19] The excellent anti-platelet activity of vorapaxar makes it an attractive molecule, and many series of its analogues were also reported to date. Based on the SAR analysis of vorapaxar as well as its analogues, it

was found that (3-fluorophenyl)pyridine-2-vinyl moiety is a critical pharmacophore for the PAR1 inhibitory activity by binding to the pocket of PAR1 involving residues Tyr 183, Leu 237, Phe 271, Leu 333 and Tyr 337.[20,21] In addition, the tricyclic ring of vorapaxar was also proved to be very important for the PAR1 inhibitory activity, and chemists invested considerable efforts and expense to synthesize this moiety,[22] because of its multi-chiral center. Recently, it was found that the tricyclic ring of vorapaxar could be simplified to bicyclic ring while maintaining the potent PAR1 inhibitory activity,[23,24] which provided new ways, and of course inspired us to design and synthesis of novel vorapaxar analogues targeting PAR1.

Natural products are considered to be one of the main sources of medicines, and their scaffolds have been well recognized as 'privileged' structures due to their chemical diversity, structural complexity and conformation immobilization.[25-28] An attractive concept of natural-product hybridization is becoming popular as an emerging structural modification tool to design novel and complex molecules.[29,30] The advantage of this concept over other approaches is the high diversity and the inherent biological activity of the hybrids.[31,32] By this means, it may be possible to improve the probability of finding new lead structures.[33] In addition, this concept could be used in the construction and preparation of complex molecules in a more convenient and efficient way.

Andrographolide, an easily accessible molecule isolated from the leaves of *Andrographis paniculata*, is an important active natural product (Fig. 2).[34,35] The two fused six-membered rings of andrographolide adopt the chair conformation and,

importantly, the stereostructure of this bicyclic ring is consistent with that of ring B and ring C of vorapaxar. This bicyclic ring could be "borrowed" to facilitate the efficient and rapid construction of vorapaxar analogues. Meanwhile, we found that there are two potential "hybrid points" at C-4 and C-9 of the andrographolide, which have the same conformation as that of C-9 of vorapaxar. Either of these two "hybrid points" could be converted to aldehyde group individually, and then be coupled with the (3-fluorophenyl)pyridine-2-vinyl phamacophore of vorapaxar, resulting in the formation of two novel series of analogues with a stereostructure consistent with that of vorapaxar (Fig. 2). The preliminary molecular modeling of these two series analogues was also performed, and it was found that these novel compounds could fit nicely to the vorapaxar binding pocket in PAR1, with the orientation similar to that of vorapaxar (Fig. S1).

In this study, based on the natural-product hybrid theory, the chiral fragment of andrographolide was combined with the (3-fluorophenyl)pyridine-2-vinyl pharmacophore, producing two series of novel vorapaxar analogues (series 1 and series 2), and the following *in vitro* PAR1 inhibitory assay resulted in the lead **13a** (Scheme 1). To optimize the drug-like properties beyond the basic PAR1 inhibitory activity, **13a** was further modified and ultimately resulted in compound **39**, which also exhibited *in vitro* and *ex vivo* anti-platelet activity, and could be considered as a candidate for further clinical development.

RESULTS AND DISCUSSION

Synthesis of Hybrid 13a and Its Derivatives (Series 1). The synthetic procedure

for hybrid **13a** and its derivatives (**12a-14b)** is shown in Scheme 1. The synthesis started with andrographolide (**5**), which was dehydrated with activated alumina in refluxing anhydrous pyridine to generate dehydroandrographolide **6** with a yield of 85 %. The double bond of compound **6** was cleaved with O_3 to give aldehyde **7**, which failed to react with the phosphonate **4a** by Horner-Wadsworth-Emmons reaction, presumably owing to the hydrogen bond between aldehyde group and beta-carbonyl group, which inactivated the aldehyde group. For this reason, the 8-*exo*-methylene group of compound **6** was selectively epoxidized through the *m*-CPBA-mediated Prilezhaev reaction to prevent the hydrogen bond from forming. To our delight, this reaction not only occurred preferentially at the 8-*exo*-methylene rather than the 11-ene but also formed an 8,19-epoxide ring stereoselectively from the less sterically hindered *β*-face to exclusively give 8*S*-epoxide **9**. The acetonide **10** was obtained by reaction with 2,2-dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate (PPTS). Double bond cleavage by ozonolysis gave aldehyde **11**, which was subjected to the Horner-Wadsworth-Emmons reaction using the phosphonates **4a** and **4b** to successfully yield the 3-fluorophenyl analog **12a** and 3-trifluoromethylphenyl analog **12b**, respectively. Phosphonate **4a** was synthesized in three steps from 2-methyl-5-hydroxypyridine **1** as shown in Scheme 1. Triflate formation followed by Suzuki coupling gave **3a** which was converted into **4a** via deprotonation followed by treatment with diethyl chlorophosphate, and **4b** was obtained using the same method.[36] The protecting group was then removed by hydrolysis with Amberlyst 15 to produce the diols **13a** and **13b**. The structure of **13a**

was also unequivocally determined by X-ray crystallographic analysis (Fig. S2). The double bonds were selectively reduced by titanocene dichloride and Mn in THF to give compounds **14a** and **14b**, respectively.

Synthesis of Hybrid 21 and the Derivatives (Series 2). The synthetic strategy above was mainly dependent on cleavage of the double bond of andrographolide to give an aldehyde group at C-9 point, which was then hybridized with the (3-fluorophenyl)pyridine-2-vinyl moiety of vorapaxar. All the key chiral carbon atoms in the two fused six-membered ring were the same as those of vorapaxar. Next, we intended to hybridize with the moiety of vorapaxar from the C-4 point of andrographolide by selectively oxidizing the primary hydroxyl group. Meanwhile, a five-membered lactone ring was also introduced for structural diversity, and the SAR was analyzed. As shown in Scheme 2, target compounds were synthesized starting from compound **10**, and the double bond was cleaved by ozonolysis to give aldehyde **11**, which was then oxidized to carboxylic acid **15** under the condition of $NaClO_2$-NaH_2PO_4 in isopentane. Titanocene-catalyzed reductive epoxide opening stereoselectively gave compound **17**. In this step, the intermediate **16** was only formed from the β-face of the B-ring because of the steric effect. Furthermore, a dehydration condensation reaction of compound **17** with DCC/DMAP in 1,4-Dioxane resulted in the formation of the five-membered lactone **18**. The protecting group was then removed by hydrolysis with Amberlyst 15 to produce diol **19**, which was selectively oxidized with the TEMPO-NCS system to give aldehyde **20**. Aldehyde **20** was coupled with phosphonate **4a** to give compound **21**. Unexpectedly, the target

compound **21** had four diastereoisomers (**21a - 21d**) which were then separated by HPLC, and their stereostructures were determined by HMBC and NOESY experiments (shown in Fig. S3). The structure of **21c** was also unequivocally determined by X-ray crystallographic analysis (Fig. S2). The process of the generation of the diastereoisomers most likely occurred through a reversible aldol reaction, and the proposed underlying mechanism is shown in Fig S4. Briefly, the beta-hydroxyl group was initially deprotonated under the basic condition, followed by electron transfer and cleavage of the covalent bond between C-3 and C-4, and the resulting dialdehyde then underwent an aldol reaction to yield the isomers. To study the effect of substitution on the hydroxyl at C-3, the resultant lactone **21** was subsequently derivatized with sulfonyl chloride, acetic anhydride, isocyanate, and butyric anhydride to produce the corresponding sulfonate, acetate, carbamate, and butyrate, respectively. All of the diastereoisomers were separated by HPLC, their PAR1 inhibition activities were evaluated, and the SAR was explored.

Identification of Lead Compound 13a. Twenty-one andrographolide analogs were initially obtained and subjected to a biological assay to determine their potency against PAR1 (Table 1). The PAR1 inhibitory effect of the test compounds was measured in 384-well plates by a functional calcium mobilization assay with the recombinant stable cell line HEK293-Gα15-PAR1 using haTRAP as the agonist. Vorapaxar was purchased from MedChemexpress (Princeton, USA), and served as the positive control.[37] In this assay, the highest concentration of tested drugs was set at 100 μM: compounds that did not show activity at this concentration were regarded

as inactive. The results showed that acetonides **12a** and **12b** were essentially inactive, with IC_{50} value more than 100 μM. To our surprise, when the acetonides were cleaved, the resulting compounds **13a** and **13b**, as well as their reductive products **14a** and **14b**, exhibited potent PAR1 inhibitory activities, with IC_{50} values ranging from 9.1 to 14 μM, which were obvious higher than vorapaxar (IC_{50} = 0.064 μM). Compounds **21a**, **24a**, **24b** and **24c** exhibited moderate PAR1 inhibitory activities with IC_{50} values ranging from 12 μM to 21 μM, while the other lactone derivatives (**21b**-**21d**, **22a**, **22c**, **23a**-**23c**, **24d** and **25a**, **25c**) were inactive. The results suggested that the substitution on the hydroxyl at C-3 with carbamate was preferable to the other substitutions. Additionally, the compounds hybridized with vorapaxar through selective oxidation of the primary hydroxyl group were less active than those hybridized through double bond cleavage of andrographolide. This could have been due to the steric effect of the lactone ring and changes in the conformation of two fused six-membered ring system. Given the increased lipophilicity that resulted from the CF_3-substituted moiety of **13b**, compound **13a** with the *m*-F-substituted diol was chosen as a candidate for further research on its drug-like properties.

It is well known that drug metabolism and pharmacokinetic (DMPK) studies have always played a critical role in helping to optimize the bioavailability and duration of action of new drugs and thereby increasing the success rate of drug development.[38,39] The application of DMPK principles to drug discovery is thus not a new concept.[40] Here, we applied concept to the new molecules as part of the lead optimization process.

First, the metabolite profiling of compound **13a** in rats was studied using liquid chromatography tandem high-resolution LTQ-Orbitrap mass spectrometry (LC-HRMS). As shown in Fig. 3A and S5A, the diol compound **13a** showed a poor metabolic stability in blood plasma, generating a considerable number of metabolites observed by LC-MS/MS analysis, and these metabolites were generated mainly by oxidation of hydroxyl group. The total concentration of the metabolites was much higher than that of the parent. Moreover, the plasma concentration of the major carboxylic acid metabolite (M0+O-2H), which was subsequently synthesized as compound **28** (Scheme 3), exceeded that of the parent by 3-fold. Therefore, the development of **13a** as a thrombin receptor antagonist was suspended and this prompted us to identify a replacement candidate for **13a** with an improved metabolic stability.

Optimization of 13a and Identification of 29. In this pursuit, we adopted two approaches for the optimization of **13a**. The first approach was to explore the metabolites. There have been several instances in the history of drug discovery research where a metabolite has served as an improved replacement for the initial drug candidate.[41,42] The second approach was to selectively block or modify the metabolically labile groups.[43,44] As shown in Scheme 3, the synthetic work of modification started with the diol compound **13a**, which was reduced by $LiAlH_4$ in Et_2O to give the epoxide ring-opened compound **26**. The aldehyde **27** was obtained by selective oxidation of primary hydroxyl group with the TEMPO-NCS system. The formed aldehyde **27** was further oxidized to a carboxyl group with $NaClO_2$-NaH_2PO_4

and isopentane, affording a carboxylic acid **28**, which was the main metabolite. Furthermore, we treated carboxylic acid **28** with CH_3I in DMF to obtain the methyl ester **29**. To study the effect of substitution on the hydroxyl at C-3, some derivatives of **29** were prepared as shown in Scheme 3 using procedures similar to the preparation of **23**-**25** described previously. Additionally, to block the metabolically labile hydroxyl group, the diol **13a** was also methylated using methyl iodide to give the ethers **31** and **32**. The attachment positions of the methyl substituents were determined using HMBC (Fig. S6). On the other hand, reductive amination of aldehyde **27** with ammonia and methylamine gave corresponding amines **33a** and **33b**, respectively.

The PAR1 inhibitory activity of each of these derivatives was then evaluated (Table 1). The derivatives **27**, **29**, **30b** and **31** showed potent activity. Among them, the aldehyde **27** exhibited the best PAR1 inhibitory activity with an IC_{50} value of 3.0 μM. Compound **29** (IC_{50} = 7.0 μM), with a methyl ester on C-9, also displayed potent PAR1 inhibitory activity. The derivatives **32**, **33a** and **33b** showed slightly diminished PAR1 inhibitory activity, with IC_{50} values of 14 μM, 23 μM and 17 μM, respectively. However, the epoxide ring-opened derivative **26** and carboxylic acid **28** displayed obviously decreased activity, with IC50 values of 55 and 29 μM, respectively. Compound **30b** with a carbamate on C-3 exhibited potent PAR1 inhibitory activity with IC_{50} value of 8.7 μM. Surprisingly, when the carbamate group was replaced by acetate or butyrate, the PAR1 inhibitory activities of the resulting compounds **30a** and **30c**, respectively, were totally lost, with IC_{50} values of more than 100 μM. Because of

aldehyde group in **27** was considered unstable in blood plasma, we chose methyl ester **29** as a candidate for further metabolic profiling (Fig. 3B). Unfortunately, the tested results showed that there was a relatively low plasma concentration for the parent (M1) and high plasma levels of metabolites (M1-CH_2) (**28**). As shown in Fig. S5B, the concentration of the M1-CH_2 metabolites was approximately 31 times higher ($AUC_{0-\infty}$ = 8412.70 h·μg/L) than that of its parent ($AUC_{0-\infty}$ = 268.93 h·μg/L). On this basis, an overwhelming majority of methyl ester **29** could be hydrolyzed and converted to carboxylic acid **28**, which in turn would be eliminated from the systemic circulation. It was therefore important to pay further attention to the generation of compounds that would increase metabolic stability and retain the desired activity against PAR1.

Further Optimization and Identification of 39. Based on the results described above, we attempted to further explore the C-4 and C-8 region of the bicyclic motif, which are known to undergo considerable *in vivo* metabolism. A series of novel derivatives was therefore designed and synthesized in which the metabolically labile primary hydroxyl and epoxy groups were replaced with the metabolically stable methyl group.

These syntheses, outlined in Scheme 4, started with aldehyde **27**. To improve the structural diversity and study the necessity of the pyridine ring, aldehyde **27** was oxidized with *m*-CPBA to give oxynitride. Through the reversible intramolecular aldol reaction as described above (Fig. S4), when the oxynitride was treated with basic conditions such as K_2CO_3, the configuration at C-9 was partially inverted to yield isomers **34** and **35**, the stereostructures of which were unambiguously

determined through X-ray crystallographic analysis (Fig. S2). The treatment of aldehyde **27** with 1.05 equiv of ethanedithiol and boron trifluoride etherate then gave the thioacetal **36**, which was further reduced with Raney nickel to generate compound **37**. When 3 equiv of ethanedithiol was used, dithioacetal **38** was obtained. In this step, the thioacetals **36** and **38** were only formed in a stereoselective manner from the *β*-face of the B-ring at C-8 due to a steric effect of the C-9 group. The stereostructure of compound **38** was determined by HMBC and NOESY experiments (Fig. S7). These results also suggested that the epoxy group is extremely active under boron trifluoride etherate conditions and can be easily hydrolyzed. The hydrolysate was then dehydrated to generate an aldehyde, which immediately reacted with ethanedithiol due to its lower steric factor than aldehyde group at C-4 (Fig. S8). Additionally, when excessive amounts of ethanedithiol were added, the aldehyde group at C-4 also reacted with ethanedithiol to generate thioacetals. Initially, the thioacetals were reduced by Raney nickel in ethyl alcohol or methanol, but the double bond was also easily reduced. We therefore investigated changing the solvent. To our surprise, when "hydrogen-free" acetone was used as solvent, a single product **39** was obtained. Subsequently, some derivatives of **39** were prepared as shown in Scheme 4 using procedures similar to the preparation of **22**-**25** as described previously. The sulfonyl group of **40a** was further eliminated to produce olefin **41**.

The PAR1 inhibitory activities of these newly synthesized derivatives were then tested. As shown in Table 1, compounds **37** and **39** showed excellent PAR1 inhibitory activity, with IC_{50} values of 1.5 and 1.1 μM, respectively, which were approximate

five-fold better than compound **29**. However, compounds **40a** and **40c** exhibited significantly decreased PAR1 inhibitory activity compared with compound **27**, with IC_{50} values of 87 μM and 32 μM, respectively. To our surprise, the rest of derivatives (**34**, **35**, **36**, **38**, **40b**, **40d**, **40e** and **41**) were inactive, with IC_{50} values of more than 100 μM.

Next, compound **39** was chosen for further metabolic profile research in rats. Representative EIC chromatograms of **39** and its metabolites are shown in Fig. 3C. A total of four primary metabolites were identified in rat plasma. More importantly, unlike compounds **13a** and **29**, the metabolically labile sites were blocked, and the main carboxylic acid metabolite was not observed. As shown in Fig. S5C, the total concentration of the metabolites was lower than the parent, and the main metabolite (M2+2O-2H) with NL = 1.36E5 only accounted for approximately 25 % of its parent (NL = 4.09E5), which suggested a good metabolic stability of compound **39**.

Effects of 39 on human platelet aggregation *in vitro*. Considering the potent PAR1 inhibitory activity and excellent metabolism profile of compound **39**, we further evaluated the inhibitory effects of **39** on human platelet aggregation induced by thrombin, TRAP, ADP, or collagen, using vorapaxar as the positive control. As shown in Fig. 4, **39** inhibited human platelet aggregation induced by thrombin (0.5 U/mL) or TRAP (15 μM) in a concentration-dependent manner, with IC_{50} values of 0.65 μM and 1.6 μM, respectively, and the IC_{50} values of vorapaxar were 0.081 μM and 0.031 μM, respectively (Table S1). Meanwhile, the platelet aggregation response following stimulation of human PRP with ADP (10 μM) and collagen (5 μg/mL), was

not affected by **39**, up to a concentration of 10 μM. These data demonstrated that compound **39** could selectively inhibit PAR1-mediated platelet aggregation.

Effects of 39 on *ex vivo* platelet aggregation in the guinea pig. Guinea pigs have been identified as the only small animal species expressing PAR1 on their platelets.[45-47] We therefore chose guinea pigs as an appropriate small animal model to evaluate PAR1-dependent responses in platelets. The research protocol complied strictly with the institutional guidelines of Animal Care and Use Committee at Shandong University. The guinea pigs were given compound **39** at a dosage of 10 or 30 mg/kg, vorapaxar 10 mg/kg, or vehicle orally, respectively. After 2 hours, the animals were anesthetized and blood was drawn from the vena cava. The inhibitory effects of **39** on *ex vivo* platelet aggregation induced by thrombin, TRAP, ADP, or collagen were then evaluated. It was found that compound **39** could significantly inhibit *ex vivo* platelet aggregation either induced by thrombin (1 U/mL) or TRAP (15 μM) at all doses tested (Table 2). At a dose of 10 mg/kg, however, platelet aggregation induced by thrombin and TRAP was not completely inhibited, and the inhibition was 66.9 % and 87.6 %, respectively. At a dose of 30 mg/kg, compound **39** showed an almost complete inhibition of platelet aggregation stimulated by thrombin and TRAP, and the inhibition was 99.8 % and 98.7 %, respectively. Even at 30 mg/kg, **39** did not inhibit platelet aggregation in response to ADP or collagen.

Pharmacokinetic Studies. Due to the reasonable activity against PAR1 and excellent metabolic stability of compound **39**, it was also subjected to a full rat pharmacokinetic assay. Male Wistar rats were intragastrically administered 5 mg/kg

or intravenously administered 1 mg/kg of the compound. The research protocol complied strictly with the institutional guidelines of Animal Care and Use Committee at Shandong University. The blood concentrations were measured over a 24 h period. The animals tolerated the treatment on the basis that no abnormalities in the animals' behavior were observed. As shown in table 3, compound **39** exhibited an excellent oral bioavailability of 52.5 % with an $AUC_{(0-\infty)}$ = 1450 h·μg/L. The oral C_{max} was 229 μg/L with a T_{max} of 2.5 h. The oral half-life was 3.1 h and mean residence time was 5.6 h. The compound showed a moderate volume of distribution (Vz = 20 L/kg) and a clearance of 4.5 L/h/kg. In summary, the compound **39** presented favorable pharmacokinetic properties.

SAR Analysis. Preliminary SAR conclusions were proposed on the basis of the results described above (Fig. 5). The C-8-epoxy group was less stable *in vivo* and the epoxide ring-opened compound showed weaker activity (compound **26**). Compounds **37** and **39**, in which a methyl moiety replaced the epoxy group, showed higher activity and good metabolic stability. The hydroxyl group at C-3 was important for the PAR1 inhibitory property. Except for the formation of a methyl ether, any changes of this group, e.g., its esterification or elimination, led to a decrease or completely loss of activity. Furthermore, bulky substitutions at C-3 and C-4, for example, a lactone or an ether ring, led to a decrease in activity. Compounds with a methyl group at C-4 exhibited the best potency and metabolic stability. Any other changes at this position either impacted the activity or decreased the stability *in vivo*. The stereochemistry at C-9 and the pyridine ring was critical, and minor changes could greatly impact the

activity. The reduction of the 11,12-double bond (compound **14a** and **14b**) had no significant effect on the activity. In the analogs that contained *m*-CF_3 or *m*-F on the aryl group, the activity was not affected.

Molecular Modeling Analysis. Subsequently, the excellent bioactivity of the andrographolide derivatives encouraged us to investigate the possible mechanism of action at the molecular level, and more specifically, the binding mode of active compound **39** to PAR1. Compound **39** was then docked into the vorapaxar-binding site on PAR1 using the GOLD (Genetic Optimization for Ligand Docking) program. The binding mode of compound **39** was studied further by energy minimization. In the resulting hypothetical structure (Fig. 6), compound **39** fit nicely in the active binding site, and aligned well with the native ligand vorapaxar. In addition, the bicyclic region of **39** binds to the extracellular loop region formed by residues His 336, Tyr 353, Tyr 350, Leu 258 and His 255, while the biaryl region binds to a hydrophobic pocket toward the trans-membrane region involving residues Leu 333, Tyr 183, Leu 237 and Phe 271. Moreover, the pyridine ring of compound **39** may form a strong hydrogen bond with residue Tyr 337, which is similar to the binding mode of vorapaxar.

CONCLUSION

Plant-derived natural products with unique skeletons and bioactivities provide considerable drug leads and candidates, thereby constituting a hotspot in the field of drug discovery. In this manuscript, we prepared two series of novel PAR1 inhibitors by “natural-product hybridization”, and “borrowed” the two fused six-membered ring

moiety from the natural product andrographolid, which led the discovery of the lead compound **13a**. The further structural optimization was guided by the metabolic stability evaluation and finally resulted in the most potent thrombin receptor antagonist **39**, which also displayed potent anti-platelet activity both *in vitro* and *ex vivo*. Although, there was an obvious anti-platelet potency gap between compound **39** and vorapaxar, the unique drug-likeness properties of **39** were underscored by its metabolic stability, excellent bioavailability and favorable pharmacokinetic profile. Importantly, with the help of the natural product skeleton, the synthetic route of compound **39** was relatively short and resulted in a high yield. Therefore, compound **39** could be obtained at low cost, which is an advantage in developing compound **39** as a PAR1 antagonist. Additionally, we also presented a model of these compounds docked to the PAR1 based on the X-ray crystal structure of vorapaxar bound to PAR1 and the model explains some of the SAR in this series. These studies suggest that compound **39** has a potential to be developed as a new generation of PAR1 antagonists.

EXPERIMENTAL SECTION

General Material and Methods. All commercially available reagents were used without further purification. Andrographolide was purchased from Shanghai Yulan, China. Anhydrous solvents were dried through routine protocols. All reactions were carried out under a nitrogen atmosphere in dry glassware with magnetic stirring. Column chromatography was carried out on 200-300 mesh silica gel (Qingdao Haiyang Chemical, China). Analytical TLC was carried out employing 0.25 mm

silicagel plates (GF254) and visualization under UV light. The NMR spectra were recorded on a Bruker 400 (^{1}H, 400 MHz; ^{13}C, 101 MHz) or Bruker 600 (^{1}H, 600 MHz; ^{13}C, 150 MHz) spectrometer. Chemical shifts were expressed in ppm and *J* values were given in Hz. High-resolution mass spectra were measured using a Thermo Fisher Finnigan LTQ Orbitrap Elite mass spectrometer. Ionization was achieved using the positive mode. The purity of the final compounds was verified using an HPLC system (Agilent Technologies 1200) equipped with a G1311A isopump, a G1322A degasser, and a G1315D DAD detector using an Eclipse XDB-C18 (150 mm × 4.6 mm, 5 μm). All compounds evaluated for biological effects were > 95 % pure.

6-Methylpyridin-3-yl trifluoromethanesulfonate (2). To a stirred solution of 6-methylpyridine-3-ol (2.18 g, 20 mM) in anhydrous CH_2Cl_2 (20 mL) under a nitrogen atmosphere at 0 °C, pyridine (2.5 mL, 30 mM) and trifluoromethanesulfone anhydride (4.1 mL, 24 mM) were slowly added. After stirring for 2 h at 0 °C, TLC analysis indicated the starting material had been consumed. Methanol (1 mL) and a saturated aqueous $NaHCO_3$ solution were then added to the mixture. The resulting mixture was extracted with CH_2Cl_2 and the extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure and then purified by flash chromatography to yield compound **2** (3.86 g, 80 %) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.4 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 2.61 (t, *J* = 2.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 145.2, 142.1, 129.3, 124.5, 123.7 (q, *J* = 123.7 Hz), 24.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.65. ESI-MS m/z 242 $[M + H]^+$.

5-(3-Fluorophenyl)-2-methylpyridine (3a). To a stirred solution of **2** (4.82 g, 20 mM) in anhydrous toluene (56 mL), K_2CO_3 (13.9 g, 100 mM), 3-trifluoromethylphenylboronic acid (4.5 g, 32 mM), EtOH (14 mL), H_2O (28 mL) and $Pd(PPH_3)_4$ (232 mg, 0.2 mM) were added. The mixture was heated in a closed pressure tube under N_2 at 120 °C for 16 h. After cooling to room temperature, the mixture was diluted with EtOAc, washed with 5 % NaOH and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography to yield compound **3a** as a yellow oil (3.80 g, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.2 Hz, 1H), 7.73 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.40 (td, *J* = 7.9, 5.9 Hz, 1H), 7.33 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.27 – 7.18 (m, 2H), 7.05 (tdd, *J* = 8.5, 2.5, 0.9 Hz, 1H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 162.1, 158.0, 147.5, 140.3 (d, *J* = 7.8 Hz), 134.8, 132.7 (d, *J* = 2.2 Hz), 130.7 (d, *J* = 8.4 Hz), 123.4, 122.7 (d, *J* = 2.9 Hz), 114.8, 114.6, 114.1, 113.9, 24.22. ESI-MS m/z 188 $[M + H]^+$.

2-Methyl-5-(3-(trifluoromethyl)phenyl)pyridine (3b). The general procedure for the synthesis of **3b** was similar to **3a** and resulted in a 78 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.1 Hz, 1H), 7.81 (m, 2H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 5.8 Hz, 1H), 2.64 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 147.6, 139.0, 135.1, 132.7, 131.9 (d, *J* = 32.5 Hz), 130.5, 129.8, 125.6 (d, *J* = 273.6 Hz), 124.73 (q, *J* = 3.8 Hz), 123.98 (q, *J* = 3.8 Hz), 123.6, 24.33.^{19}F NMR (376 MHz, $CDCl_3$) δ -62.69. ESI-MS m/z 238 $[M + H]^+$.

Diethyl ((5-(3-fluorophenyl)pyridin-2-yl)methyl)phosphonate (4a). A solution of compound **3a** (1.3 g, 5.5 mM) and diisopropylamine (924 µL, 6.6 mM) in anhydrous

THF (20 mL) under a nitrogen atmosphere at -78 °C was treated, dropwise, with n-BuLi (4.84 mL, 12.1 mM, 2.0 M in hexane) and the resulting mixture was left to stir at -78 °C for 20 min. Then, diethyl chlorophosphate (875 µL, 6.05 mM) was added. After an additional 20 min, the mixture was allowed to warm to room temperature and quenched with saturated NH_4Cl. The mixture was then extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product, which was purified by flash chromatography to yield compound **4a** as a yellow oil (1.5 g, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.3 Hz, 1H), 7.84 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.79 (s, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.48 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.10 (dq, *J* = 14.2, 7.1 Hz, 4H), 3.46 (d, *J* = 22.0 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6 (d, *J* = 8.5 Hz), 147.9 (d, *J* = 2.5 Hz), 138.5 (d, *J* = 1.3 Hz), 135.2 (d, *J* = 2.8 Hz), 133.6 (d, *J* = 3.4 Hz), 131.7 (d, *J* = 32.3 Hz), 130.4, 129.7, 125.4 (d, *J* = 272.7 Hz), 124.9 (q, *J* = 3.7 Hz), 124.4 (d, *J* = 4.9 Hz), 123.9 (q, *J* = 4.1 Hz), 62.4 (d, *J* = 6.6 Hz), 36.4 (d, *J* = 135.3 Hz), 35.76 (s), 16.5 (d, *J* = 6.0 Hz). ESI-MS m/z 324 $[M + H]^+$.

Diethyl ((5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)methyl)phosphonate (4b). The general procedure for the synthesis of **4b** was similar to **4a** and resulted in a 72 % yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 2.1 Hz, 1H), 7.86 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.80 (s, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.62 (dt, *J* = 15.4, 7.7 Hz, 1H), 7.50 (dd, *J* = 8.1, 1.9 Hz, 1H), 4.23 – 4.02 (m, 2H), 3.48 (d, *J* = 22.0 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7 (d, *J* = 8.5 Hz), 147.9

(d, J = 2.4 Hz), 138.6, 135.3 (d, J = 2.8 Hz), 133.8 (d, J = 3.3 Hz), 131.9 (d, J = 32.6 Hz), 130.5, 129.8, 125.5 (d, J = 273.5 Hz), 125.0 (q, J = 3.7 Hz), 124.5 (d, J = 4.9 Hz), 124.0 (q, J = 3.7 Hz), 62.5, 62.4, 37.2 (d, J = 135.8 Hz), 16.6, 16.5. ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.10 – 24.21 (m). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.70 (s). ESI-MS m/z 374 $[M + H]^+$.

3-((E)-2-((1R,4aS,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylenedecahydronaphthalen-1-yl)vinyl)furan-2(5H)-one (8). To a 100-mL flame-dried round-bottomed flask containing compound **5** (10 g, 28.6 mM) in anhydrous pyridine (40 mL), Al_2O_3 (3 g) was added. The mixture was heated to 115 °C and stirred for 5 h. After this time, TLC analysis indicated the consumption of the starting material. After filtration, the solvent was concentrated under reduced pressure to give a crude product, which was then purified by flash chromatography to yield compound **8** (7.6 g, 80 %) as a white solid, mp 205-207 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.65 (s, 1H), 6.74 (dd, J = 15.8, 10.1 Hz, 1H), 6.12 (d, J = 15.8 Hz, 1H), 5.05 (d, J = 4.9 Hz, 1H), 4.89 (s, 2H), 4.73 (s, 1H), 4.42 (s, 1H), 4.14 (dd, J = 7.4, 2.7 Hz, 1H), 3.84 (dd, J = 10.9, 2.6 Hz, 1H), 3.31 – 3.14 (m, 2H), 2.36 (d, J = 10.5 Hz, 2H), 2.01 – 1.95 (m, 1H), 1.72 (d, J = 13.0 Hz, 1H), 1.65 – 1.50 (m, 2H), 1.46 – 1.25 (m, 2H), 1.23 – 1.11 (m, 2H), 1.09 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.4, 148.9, 146.7, 134.3, 127.1, 121.2, 108.0, 78.6, 70.2, 62.7, 60.6, 53.7, 42.4, 38.3, 38.0, 36.2, 27.6, 23.2, 23.0, 15.4. ESI-MS m/z 333 $[M + H]^+$.

3-((E)-2-((1S,2S,4aS,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxiran]-1-yl)vinyl)furan-2(5H)-one (9). A

magnetically stirred solution of compound **8** (6.0 g, 18 mM) and K_2CO_3 (3.0 g, 21.6 mM) in anhydrous CH_2Cl_2 (100 mL) was maintained at 0 ºC under nitrogen. This mixture was treated, portion-wise, with *m*-CPBA (75 % pure, 5.0 g, 21.6 mM), and the resulting mixture was allowed to warm to room temperature for 3 h. After this time, TLC analysis indicated the consumption of the starting material. Then the mixture was diluted with CH_2Cl_2, washed with 5 % NaOH and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to produce a crude product. The crude residue was purified by column chromatography to give compound **9** (5.3 g, 85 %) as a white solid, mp 186-188 °C. ^{1}H NMR (400 MHz, Acetone) δ 7.48 (s, 1H), 6.49 (dd, *J* = 15.5, 9.9 Hz, 1H), 6.15 (d, *J* = 15.6 Hz, 1H), 4.84 (s, 2H), 4.53 (s, 1H), 4.15 (d, *J* = 10.8 Hz, 1H), 3.69 (s, 1H), 3.43 – 3.31 (m, 2H), 2.72 (d, *J* = 3.5 Hz, 1H), 2.51 (d, *J* = 4.5 Hz, 1H), 2.20 (d, *J* = 9.8 Hz, 1H), 1.93 – 1.52 (m, 6H), 1.48 – 1.38 (m, 2H), 1.23 (s, 3H), 1.20 – 1.17 (m, 1H), 0.99 (s, 3H).^{13}C NMR (101 MHz, Acetone) δ 173.0, 146.3, 131.7, 129.1, 124.9, 80.8, 70.8, 64.5, 60.1, 58.6, 55.2, 50.8, 43.7, 39.9, 39.1, 36.7, 28.5, 23.6, 22.3, 16.5. ESI-MS m/z 349 $[M + H]^+$.

3-((E)-2-((4aR,6aR,7S,8S,10aS,10bR)-3,3,6a,10b-Tetramethyloctahydro-1H,6H-spiro[naphtho[2,1-d][1,3]dioxine-8,2'-oxiran]-7-yl)vinyl)furan-2(5H)-one (10). A magnetically stirred solution of compound **9** (6.26 g, 18 mM) in anhydrous CH_2Cl_2 (100 mL) was maintained at 0 ºC under N_2 protection. Pyridinium p-toluenesulfonate (452 mg, 1.8 mM) and dimethoxypropane (15.5 mL, 126 mM) were added to the solution, and the resulting mixture was allowed to warm to room temperature for 3 h. After this time, TLC analysis indicated the consumption of starting material, and the

reaction was quenched with a 1 % $NaHCO_3$ solution. The resulting mixture was washed with water and brine, dried over $MgSO_4$ and filtered, after which the solvent was removed under reduced pressure to give the crude compound, which was purified by flash chromatography to obtain compound **10** (5.93 g, 85 %) as a white solid, mp 80-82 °C. ^{1}H NMR (400 MHz, Acetone) δ 7.49 (s, 1H), 6.54 (dd, *J* = 15.6, 9.9 Hz, 1H), 6.17 (d, *J* = 15.7 Hz, 1H), 4.85 (d, *J* = 1.4 Hz, 2H), 4.06 (d, *J* = 11.6 Hz, 1H), 3.45 (dd, *J* = 9.6, 4.3 Hz, 1H), 3.23 (d, *J* = 11.6 Hz, 1H), 2.73 (dd, *J* = 4.7, 1.6 Hz, 1H), 2.53 (d, *J* = 4.7 Hz, 1H), 2.26 (d, *J* = 9.9 Hz, 1H), 2.09 – 1.96 (m, 2H), 1.92 – 1.78 (m, 2H), 1.75 – 1.66 (m, 1H), 1.57 (dd, *J* = 12.9, 4.0 Hz, 1H), 1.52 – 1.40 (m, 2H), 1.38 (s, 3H), 1.28 (s, 3H), 1.26 – 1.24 (m, 1H), 1.23 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (101 MHz, Acetone) δ 172.9, 146.2, 131.5, 128.9, 125.0, 99.3, 77.7, 70.6, 64.1, 59.7, 58.5, 52.5, 50.8, 39.3, 38.3, 36.4, 28.0, 26.7, 26.0, 25.8, 21.4, 17.3. ESI-MS m/z 389 $[M + H]^+$.

5-(3-Fluorophenyl)-2-((E)-2-((4aR,6aR,7S,8S,10aS,10bR)-3,3,6a,10b-tetramethyloctahydro-1H,6H-spiro[naphtho[2,1-d][1,3]dioxine-8,2'-oxiran]-7-yl)vinyl)pyridine (12a). A solution of compound **10** (2.0 g, 5.15 mM) in CH_2Cl_2:MeOH (30 mL:30 mL) was maintained at -78 °C under N_2 protection. To this mixture, pyridine (3 mL) was added, and ozone was passed into the reaction mixture until a light blue color was obtained. TLC analysis indicated the consumption of starting material. N_2 was then bubbled through the solution to remove the excess ozone, and dimethyl sulfide (10 mL) was added. After 30 min, the -78 °C bath was allowed to warm to room temperature, and mixture was stirred for 10 min longer. The resulting mixture

was diluted with CH_2Cl_2, washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product. The crude residue was purified by flash chromatography to yield compound **11** (1.4 g, 88 %) which was unstable and was quickly used for the next step. To a stirred solution of compound **4a** (3.0 g, 9.1 mM) in dry THF (50 mL), under nitrogen atmosphere at 0 °C, n-BuLi (3.7 mL, 9.1 mM, 2.0 M in hexane) was added dropwise, and then the mixture was allowed to warm to room temperature for 15 min. Compound **11** (1.4 g, 4.55 mM) in dry THF (20 mL) was added dropwise to the mixture, and the solution was stirred for an additional 20 min. After this time, TLC analysis indicated that the starting material was consumed and then the resulting mixture was quenched with saturated NH_4Cl and extracted 3 times with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to give the crude product. The residue was subjected to chromatography on silica gel to yield compound **12a** (1.7 g, 78 %) as a white solid, mp 191-193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 2.1 Hz, 1H), 7.82 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.47 (td, *J* = 8.0, 5.9 Hz, 1H), 7.39 – 7.37 (m, 1H), 7.35 – 7.27 (m, 2H), 7.14 – 7.09 (m, 1H), 6.58 – 6.56 (m, 2H), 4.14 (d, *J* = 11.7 Hz, 1H), 3.54 (dd, *J* = 10.1, 4.4 Hz, 1H), 3.33 (d, *J* = 11.6 Hz, 1H), 2.96 (dd, *J* = 4.4, 1.5 Hz, 1H), 2.65 (d, *J* = 4.5 Hz, 1H), 2.46 – 2.44 (m, 1H), 2.15 – 1.96 (m, 2H), 1.94 – 1.86 (m, 1H), 1.83 – 1.75 (m, 1H), 1.73 – 1.59 (m, 2H), 1.57 (s, 1H), 1.55 – 1.52 (m, 1H), 1.49 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.30 – 1.26 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 162.2, 154.4, 148.0, 140.2, 135.0 (d, *J* = 23.4 Hz), 133.7, 130.8 (d, *J* = 8.4 Hz), 128.7, 122.6 (d, *J* = 2.8 Hz), 122.1,

114.9 (d, *J* = 21.1 Hz), 113.9 (d, *J* = 22.3 Hz), 98.9, 77.7, 63.7, 58.5, 58.4, 52.5, 51.2, 38.9, 37.7, 36.0, 35.7, 28.1, 26.6, 25.9, 25.3, 20.9, 17.0. ESI-HRMS (*m/z*): calcd for $C_{30}H_{37}FNO_3$ $[M + H]^+$, 478.2713; found, 478.2742.

2-((E)-2-((4aR,6aR,7S,10aS,10bR)-3,3,6a,10b-Tetramethyloctahydro-1H,6H-spiro[naphtho[2,1-d][1,3]dioxine-8,2'-oxiran]-7-yl)vinyl)-5-(3-(trifluoromethyl)phenyl)pyridine (12b). The general procedure for the synthesis of **12b** was similar to that used for **12a**, and produced a yield of 80 % as a white solid, mp 147-149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 6.47 (s, 2H), 4.02 (d, *J* = 11.5 Hz, 1H), 3.43 (dd, *J* = 9.8, 3.8 Hz, 1H), 3.22 (d, *J* = 11.7 Hz, 1H), 2.84 (d, *J* = 3.4 Hz, 1H), 2.53 (d, *J* = 4.0 Hz, 1H), 2.34 (d, *J* = 5.6 Hz, 1H), 2.05 – 1.84 (m, 2H), 1.78 (d, *J* = 13.9 Hz, 1H), 1.72 – 1.63 (m, 1H), 1.62 – 1.54 (m, 1H), 1.50 – 1.40 (m, 2H), 1.37 (s, 3H), 1.30 (d, *J* = 8.1 Hz, 3H), 1.27 – 1.17 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 147.9, 138.7, 135.0, 133.5, 131.9, 131.5, 130.3, 129.8, 125.5, 124.8, 123.8, 123.8, 122.8, 122.2, 98.9, 77.7, 63.7, 58.5, 58.5, 52.5, 51.3, 38.9, 37.7, 36.0, 35.7, 28.1, 26.6, 25.9, 25.3, 20.9, 17.0. ESI-HRMS (*m/z*): calcd for $C_{31}H_{39}F_3NO_3$ $[M + H]^+$, 530.2837; found, 530.2773.

(1S,2S,4aS,5R,6R,8aR)-1-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-5-(hydroxymethyl)-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxiran]-6-ol (13a). To a stirred solution of compound **12a** (500 mg, 1.05 mM) in anhydrous methanol (5 mL) Amberlyst 15 was added, and the mixture was stirred for two days at room temperature. After filtration and evaporation *in vacuo*, the crude compound **13a**

was obtained, which was then purified by flash chromatography to give compound **13a** (366 mg, 80 %) as a white solid, mp 207-209 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.1 Hz, 1H), 7.80 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.45 (td, *J* = 8.0, 5.9 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.31 – 7.23 (m, 2H), 7.14 – 7.06 (m, 1H), 6.57 – 6.42 (m, 2H), 4.27 (d, *J* = 10.6 Hz, 1H), 3.60 – 3.48 (m, 1H), 3.41 (t, *J* = 9.9 Hz, 1H), 3.21 (d, *J* = 7.6 Hz, 1H), 3.15 (d, *J* = 3.9 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.62 (d, *J* = 4.4 Hz, 1H), 2.38 (d, *J* = 9.0 Hz, 1H), 2.04 – 1.92 (m, 2H), 1.90 – 1.78 (m, 1H), 1.77 – 1.69 (m, 1H), 1.65 (dt, *J* = 13.6, 3.3 Hz, 1H), 1.59 – 1.47 (m, 2H), 1.32 (s, 3H), 1.26 – 1.17 (m, 2H), 1.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 162.2, 154.3, 147.8, 140.0, 135.0, 133.8, 130.79 (d, *J* = 8.4 Hz), 128.9, 122.64 (d, *J* = 2.8 Hz), 122.1, 115.0 (d, *J* = 21.1 Hz), 113.9 (d, *J* = 21.1 Hz), 80.7, 77.5, 77.2, 76.8, 64.2, 58.6, 58.5, 54.5, 51.1, 43.1, 39.3, 38.2, 35.8, 27.8, 22.9, 21.5, 16.3. ESI-HRMS (*m/z*): calcd for $C_{27}H_{33}FNO_3$ $[M + H]^+$, 438.2400; found, 438.2439.

(1S,2S,4aS,5R,6R,8aR)-5-(Hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydro-1H-spiro[naphthalene-2,2'-oxiran]-6-ol (13b). The general procedure for the synthesis of **13b** was similar to that used for **13a**, with a yield of 83 % as a white solid, mp 119-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 1.9 Hz, 1H), 7.83 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.80 (s, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.30 – 7.26 (m, 1H), 6.50 (dt, *J* = 15.3, 12.2 Hz, 2H), 4.27 (d, *J* = 10.7 Hz, 1H), 3.59 – 3.47 (m, 1H), 3.45 – 3.27 (m, 3H), 2.92 (d, *J* = 3.6 Hz, 1H), 2.62 (d, *J* = 4.3 Hz, 1H), 2.39 (d, *J* = 9.1 Hz, 1H), 2.00 – 1.93 (m, 2H), 1.88 – 1.79 (m, 1H), 1.78 – 1.69 (m, 1H), 1.69 – 1.60 (m,

1H), 1.58 – 1.47 (m, 2H), 1.32 (s, 3H), 1.27 – 1.23 (m, 1H), 1.23 – 1.19 (m, 1H), 1.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 147.9, 138.7, 135.1, 134.8, 133.7, 131.8 (q, *J* = 32.1 Hz), 130.3, 129.8, 129.2, 124.9 (q, *J* = 3.6 Hz), 124.2 (d, *J* = 273.6 Hz), 123.8 (q, *J* = 3.6 Hz), 122.2, 80.8, 64.3, 58.7, 58.5, 54.6, 51.1, 43.1, 39.3, 38.3, 35.9, 27.8, 23.0, 21.5, 16.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7. ESI-HRMS (*m/z*): calcd for $C_{28}H_{35}F_3NO_3$ $[M + H]^+$, 490.2524; found, 490.2559.

(1S,2S,4aS,5R,6R,8aR)-1-(2-(5-(3-Fluorophenyl)pyridin-2-yl)ethyl)-5-(hydroxymethyl)-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxiran]-6-ol (14a). Thoroughly deoxygenated THF (15 mL) was added to a mixture of Cp_2TiCl_2 (398 mg, 1.60 mM) and Mn (282 mg, 5.12 mM) under a N_2 atmosphere, and the suspension was stirred at room temperature until it turned lime green (after approximately 15 min). A solution of compound **13a** (277 mg, 0.64 mM) and H_2O (115 μL, 6.40 mM) in THF (1 mL) was added, and the mixture was stirred for 24 h, after which the reaction was quenched with a saturated solution of $KHSO_4$ and extracted with EtOAc. The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and concentrated. The residue was subjected to chromatography on silica gel to yield compound **14a** (208 mg, 75 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 2.0 Hz, 1H), 7.82 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.43 (td, *J* = 8.0, 6.0 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.08 (td, *J* = 8.3, 2.0 Hz, 1H), 4.09 (d, *J* = 11.2 Hz, 1H), 3.80 – 3.70 (m, 2H), 3.56 (d, *J* = 11.8 Hz, 1H), 3.48 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.18 – 3.07 (m, 2H), 2.98 (s, 2H), 2.58 (dd, *J* = 14.2, 11.7 Hz, 1H), 2.31 – 2.22 (m, 1H), 1.86 – 1.80 (m, 2H), 1.68 – 1.60 (m, 2H), 1.57 – 1.37 (m, 3H), 1.19 (s,

3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.91 – 0.86 (m, 1H), 0.78 – 0.69 (m, 1H), 0.49 (d, *J* = 5.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 162.2, 160.5, 147.1, 139.7, 139.6, 135.8, 133.6, 130.9, 130.8, 123.4, 122.7, 122.7, 115.2, 115.0, 114.1, 113.9, 80.7, 68.8, 64.2, 53.5, 43.2, 41.2, 38.6, 37.7, 32.2, 32.1, 29.3, 29.2, 25.4, 22.3, 21.6, 16.9. ESI-HRMS (*m/z*): calcd for $C_{27}H_{35}FNO_3$ $[M + H]^+$, 440.2556; found, 440.2592.

(1S,2S,4aS,5R,6R,8aR)-5-(Hydroxymethyl)-5,8a-dimethyl-1-(2-(5-(3-(trifluoro methyl)phenyl)pyridin-2-yl)ethyl)octahydro-1H-spiro[naphthalene-2,2'-oxiran]-6-ol (14b). The general procedure for the synthesis of **14b** was similar to that used for **14a** with a yield of 72 % as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 2.3 Hz, 1H), 7.85 (dd, J = 8.0, 2.3 Hz, 1H), 7.79 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 4.09 (d, J = 11.2 Hz, 1H), 3.84 – 3.66 (m, 2H), 3.57 (d, J = 11.8 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.21 – 3.08 (m, 2H), 2.83 (s, 2H), 2.60 (dd, J = 14.3, 11.6 Hz, 1H), 2.33 – 2.23 (m, 1H), 1.93 – 1.78 (m, 2H), 1.72 – 1.61 (m, 2H), 1.56 – 1.40 (m, 2H), 1.23 (d, J = 7.0 Hz, 1H), 1.19 (s, 3H), 0.93 (s, 3H), 0.83 – 0.72 (m, 2H), 0.49 (d, J = 5.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 147.2, 138.3, 135.9, 133.5, 131.9, 131.6, 130.3, 129.8, 125.4, 124.9, 124.9, 123.9, 123.9, 123.4, 122.7, 80.7, 68.8, 64.2, 53.6, 43.2, 41.2, 38.6, 37.7, 32.2, 32.1, 29.4, 29.2, 25.4, 22.3, 21.6, 16.9. ESI-HRMS (*m/z*): calcd for $C_{28}H_{35}F_3NO_3$ $[M + H]^+$, 490.2524; found, 490.2563.

(4aR,6aR,7S,8S,10aS,10bR)-3,3,6a,10b-Tetramethyloctahydro-1H,6H-spiro[naphtho[2,1-d][1,3]dioxine-8,2'-oxirane]-7-carboxylic acid (15). To a solution of compound **11** (3.08 g, 10.00 mM), isopentane (17.5 mL), t-BuOH (190 mL), and THF

(95 mL) in an ice bath, freshly prepared $NaClO_2$-NaH_2PO_4 buffer (10.56 g of $NaClO_2$ and 18.18 g of NaH_2PO_4 in 90 mL of water) was added dropwise. After 0.5 h, the reaction temperature was raised to room temperature and stirring was continued for 7 h. After this time, the reaction mixture was diluted with ethyl acetate, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The organic extracts were combined, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product. The crude product was used directly without further purification.

((4aR,6aR,7R,8S,10aS,10bR)-7-(Hydroperoxy-l2-methyl)-3,3,6a,10b-tetramethyldecahydro-1H-naphtho[2,1-d][1,3]dioxin-8-yl)methanol (17). The general procedure for the synthesis of **17** was similar to that used for **14a**, and the crude product was used directly without further purification.

(4aR,4bS,6aS,9aR,9bR,11aR)-2,2,4a,9b-Tetramethyldecahydro-4H-furo[3',4':5,6]naphtho[2,1-d][1,3]dioxin-9(4bH)-one (18). Compound **17** (500 mg, 1.53 mM) was dissolved in dry CH_2Cl_2 (100 mL). DCC (379 mg, 1.84 mM) and DMAP (38 mg, 0.31 mM) were added, and the mixture was stirred overnight at room temperature. After TLC analysis had indicated the consumption of starting material, the reaction was quenched with water. Then, CH_2Cl_2 was added to the mixture, which was then washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was used directly without further purification.

(3aS,5aS,6R,7R,9aR,9bR)-7-Hydroxy-6-(hydroxymethyl)-6,9a-dimethyldecahydronaphtho[1,2-c]furan-1(3H)-one (19). The general procedure for the synthesis of

19 was similar to that used for **13a**, and the crude product was used directly without further purification.

(3aS,5aS,6S,7R,9aR,9bR)-7-Hydroxy-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-6-carbaldehyde (20). To a solution of compound **19** (236 mg, 0.88 mM) in 15 mL of CH_2Cl_2 in an ice bath, TEMPO (28 mg, 0.18 mM), 15 mL of 0.05 M K_2CO_3 - 0.5 M $NaHCO_3$ buffer, TBAI (65 mg, 0.18 mmol) and NCS (235 mg, 1.76 mM) were added. The reaction mixture was then stirred vigorously for 7 h at room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was used directly without further purification.

(3aS,5aS,6S,7S,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-7-hydroxy-6,9a-dimethyldecahydronaphtho[1,2-c]furan-1(3H)-one (21a). The general procedure for the synthesis of **21a-d** was similar to that used for **12a**. Compound **21a** was a white solid, mp 85-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 1.9 Hz, 1H), 7.78 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.43 (td, *J* = 8.0, 5.9 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.28 – 7.22 (m, 1H), 7.12 – 7.04 (m, 1H), 6.54 (s, 2H), 4.08 (dd, *J* = 8.7, 4.2 Hz, 1H), 3.82 (d, *J* = 8.7 Hz, 1H), 3.66 (dd, *J* = 11.5, 4.4 Hz, 1H), 3.07 (td, *J* = 13.6, 4.0 Hz, 1H), 2.58 (ddd, *J* = 12.0, 10.2, 5.9 Hz, 1H), 2.19 (d, *J* = 5.9 Hz, 1H), 1.93 – 1.79 (m, 3H), 1.78 – 1.68 (m, 1H), 1.48 – 1.43 (m, 2H), 1.34 (dt, *J* = 13.6, 3.3 Hz, 1H), 1.31 – 1.21 (m, 2H), 1.17 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 163.4 (d, *J* = 246.5 Hz), 154.9, 147.7, 145.4, 139.9 (d, *J* = 7.7 Hz), 135.0, 133.7,

130.8 (d, *J* = 8.4 Hz), 130.1, 122.6 (d, *J* = 2.8 Hz), 121.3, 115.0 (d, *J* = 21.2 Hz), 113.9 (d, *J* = 22.2 Hz), 76.2, 70.8, 53.4, 46.6, 45.9, 35.1, 34.6, 31.5, 28.0, 25.4, 23.2, 21.5, 11.8. ESI-HRMS (*m/z*): calcd for $C_{27}H_{31}FNO_3$ $[M + H]^+$, 436.2243; found, 436.2282.

(3aS,5aS,6S,7R,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-7-hydroxy-6,9a-dimethyldecahydronaphtho[1,2-c]furan-1(3H)-one (21b). Compound **21b** was a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.1 Hz, 1H), 7.82 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.44 (td, *J* = 8.0, 5.9 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.30 – 7.23 (m, 1H), 7.09 (tdd, *J* = 8.4, 2.5, 0.9 Hz, 1H), 6.91 (d, *J* = 16.4 Hz, 1H), 6.51 (d, *J* = 16.4 Hz, 1H), 4.27 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.73 (dd, *J* = 11.0, 8.3 Hz, 1H), 3.62 (d, *J* = 2.9 Hz, 1H), 2.47 – 2.32 (m, 1H), 2.31 – 2.20 (m, 1H), 2.05 – 1.99 (m, 1H), 1.93 (d, *J* = 13.8 Hz, 1H), 1.85 (dd, *J* = 12.3, 2.4 Hz, 2H), 1.81 – 1.75 (m, 2H), 1.76 (s, 1H), 1.62 – 1.55 (m, 1H), 1.44 – 1.35 (m, 1H), 1.34 – 1.27 (m, 2H), 1.18 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 163.4 (d, *J* = 246.6 Hz), 155.1, 147.8, 145.2, 139.9 (d, *J* = 7.8 Hz), 135.2, 133.8, 130.8 (d, *J* = 8.5 Hz), 128.3, 122.6 (d, *J* = 2.9 Hz), 121.7, 115.1 (d, *J* = 21.0 Hz), 113.9 (d, *J* = 22.3 Hz), 74.9, 71.4, 57.4, 46.6, 44.3, 38.7, 35.5, 29.6, 28.7, 25.2, 22.5, 18.0, 16.4. ESI-HRMS (*m/z*): calcd for $C_{27}H_{31}FNO_3$ $[M + H]^+$, 436.2243; found, 436.2284.

(3aS,5aS,6R,7R,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-7-hydroxy-6,9a-dimethyldecahydronaphtho[1,2-c]furan-1(3H)-one (21c). Compound **21c** was a white solid, mp 139-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.1 Hz, 1H), 7.81 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.44 (td, *J* = 8.0, 5.9 Hz, 1H), 7.38 (dt, *J* = 8.0,

1.2 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.09 (tdd, *J* = 8.4, 2.5, 0.9 Hz, 1H), 6.65 – 6.47 (m, 2H), 4.28 (dd, *J* = 8.3, 6.7 Hz, 1H), 3.70 (dd, *J* = 11.0, 8.4 Hz, 1H), 3.56 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.57 (dt, *J* = 13.8, 3.4 Hz, 1H), 2.42 – 2.28 (m, 1H), 1.95 – 1.80 (m, 3H), 1.80 – 1.68 (m, 2H), 1.65 – 1.57 (m, 1H), 1.48 – 1.28 (m, 2H), 1.26 – 1.17 (m, 2H), 1.13 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 163.4 (d, *J* = 246.6 Hz), 154.6, 147.9, 145.1, 139.9 (d, *J* = 7.7 Hz), 135.1, 133.9, 130.8 (d, *J* = 8.5 Hz), 129.7, 122.6 (d, *J* = 2.8 Hz), 121.9, 115.0 (d, *J* = 21.1 Hz), 113.9 (d, *J* = 22.2 Hz), 76.6, 71.4, 57.6, 52.9, 46.6, 38.4, 35.2, 35.2, 28.5, 25.4, 22.8, 16.4, 11.4. ESI-HRMS (*m/z*): calcd for $C_{27}H_{31}FNO_3$ $[M + H]^+$, 436.2243; found, 436.2280.

(3aS,5aS,6R,7S,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-7-hydroxy-6,9a-dimethyldecahydronaphtho[1,2-c]furan-1(3H)-one (21d). Compound **21d** was a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.0 Hz, 1H), 7.82 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.43 (ddd, *J* = 9.8, 6.9, 4.8 Hz, 2H), 7.36 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.08 (tdd, *J* = 8.4, 2.5, 1.0 Hz, 1H), 6.90 (d, *J* = 16.5 Hz, 1H), 6.52 (d, *J* = 16.5 Hz, 1H), 4.09 (dd, *J* = 8.7, 4.3 Hz, 1H), 3.84 (d, *J* = 8.7 Hz, 1H), 3.59 (t, *J* = 2.6 Hz, 1H), 3.37 (td, *J* = 14.0, 3.9 Hz, 1H), 2.69 – 2.57 (m, 1H), 2.20 (d, *J* = 6.0 Hz, 1H), 2.07 (ddd, *J* = 14.4, 4.0, 2.3 Hz, 1H), 2.03 – 1.86 (m, 4H), 1.82 – 1.75 (m, 2H), 1.46 – 1.41 (m, 2H), 1.20 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 163.4 (d, *J* = 246.6 Hz), 155.4, 147.6, 144.8, 140.0 (d, *J* = 7.8 Hz), 135.1, 133.6, 130.8 (d, *J* = 8.4 Hz), 128.7, 122.7 (d, *J* = 2.8 Hz), 121.2, 115.0 (d, *J* = 21.2 Hz), 113.9 (d, *J* = 22.2 Hz), 74.9, 70.9, 53.6, 44.3, 40.2, 35.1, 34.8, 28.4, 26.1,

24.9, 23.3, 21.3, 18.7. ESI-HRMS (*m/z*): calcd for $C_{27}H_{31}FNO_3$ $[M + H]^+$, 436.2243; found, 436.2283.

(3aS,5aS,6S,7S,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-7-yl methanesulfonate (22a). To a solution of compound **21** (25 mg, 0.06 mM) in 4 mL of anhydrous CH_2Cl_2 under a nitrogen atmosphere at 0 °C, DMAP (7.3 mg, 0.06 mM) and methanesulfonyl chloride (9.3 μL, 0.12 mM) were added. The mixture was stirred overnight at room temperature, after which TLC analysis indicated the consumption of starting material. Next, 5 mL of water was added to the resulting solution, which was then extracted with CH_2Cl_2 (10 mL × 2). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated under vacuum to obtain the crude product, which was then separated by HPLC to give **22a** (8.8 mg, 30 %) and **22c** (8.2 mg, 28 %). Compound **22a** was a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.9 Hz, 1H), 7.83 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.44 (td, *J* = 8.0, 5.9 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.36 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.09 (tdd, *J* = 8.4, 2.5, 0.9 Hz, 1H), 6.63 – 6.51 (m, 2H), 4.61 (dd, *J* = 11.7, 4.6 Hz, 1H), 4.10 (dd, *J* = 8.8, 4.2 Hz, 1H), 3.84 (d, *J* = 8.8 Hz, 1H), 3.18 (td, *J* = 13.8, 3.9 Hz, 1H), 2.82 (s, 3H), 2.68 – 2.53 (m, 1H), 2.22 (d, *J* = 6.0 Hz, 1H), 2.14 (ddd, *J* = 17.2, 9.0, 3.8 Hz, 1H), 2.09 – 1.98 (m, 1H), 1.92 – 1.85 (m, 1H), 1.67 – 1.62 (m, 1H), 1.57 – 1.52 (m, 1H), 1.51 – 1.45 (m, 2H), 1.41 (dt, *J* = 14.0, 3.5 Hz, 1H), 1.35 – 1.26 (m, 2H), 1.22 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 163.4 (d, *J* = 246.7 Hz), 154.5, 147.9, 143.7, 139.8 (d, *J* = 7.7 Hz), 135.3, 134.0, 130.8 (d, *J* = 8.5 Hz), 130.3, 122.7 (d, *J* = 2.8 Hz), 121.5,

115.1 (d, J = 21.3 Hz), 113.9 (d, J = 22.2 Hz), 87.8, 70.8, 53.0, 46.2, 45.4, 38.7, 34.7, 34.6, 31.3, 27.8, 25.3, 23.0, 21.3, 12.6. ESI-HRMS (*m/z*): calcd for $C_{28}H_{33}FNO_5S$ [M + H]$^+$, 514.2019; found, 514.2055.

(3aS,5aS,6R,7R,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-7-yl methanesulfonate (22c). Compound **22c** was a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 8.1, 2.4 Hz, 1H), 7.44 (td, J = 8.0, 5.9 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.30 – 7.24 (m, 1H), 7.09 (tdd, J = 8.4, 2.5, 0.9 Hz, 1H), 6.63 – 6.49 (m, 2H), 4.56 (dd, J = 11.6, 5.1 Hz, 1H), 4.29 (dd, J = 8.3, 6.7 Hz, 1H), 3.73 (dd, J = 10.9, 8.4 Hz, 1H), 2.82 (s, 3H), 2.64 (dt, J = 14.1, 3.5 Hz, 1H), 2.44 – 2.29 (m, 1H), 2.17 – 2.01 (m, 2H), 1.94 (ddd, J = 12.2, 6.3, 3.3 Hz, 1H), 1.74 (d, J = 13.8 Hz, 1H), 1.70 – 1.63 (m, 1H), 1.49 – 1.35 (m, 2H), 1.29 – 1.24 (m, 2H), 1.23 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 163.4 (d, J = 246.8 Hz), 154.4, 148.0, 143.5, 139.8 (d, J = 7.8 Hz), 135.2, 134.1, 130.8 (d, J = 8.5 Hz), 130.1, 122.7 (d, J = 2.8 Hz), 121.9, 115.1 (d, J = 21.1 Hz), 113.9 (d, J = 22.3 Hz), 87.8, 71.3, 57.4, 53.3, 45.6, 39.0, 38.4, 35.1, 34.9, 28.4, 25.3, 22.6, 16.3, 12.2. ESI-HRMS (*m/z*): calcd for $C_{28}H_{33}FNO_5S$ [M + H]$^+$, 514.2019; found, 514.2059.

(3aS,5aS,6S,7S,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-7-yl acetate (23a). To a stirred solution of **21** (25 mg, 0.06 mM) in dry CH_2Cl_2 (3 mL) in an ice bath, DMAP (15 mg, 0.12 mM) and Ac_2O (12 μL, 0.12 mM) were added, and the reaction mixture was allowed to stir at room temperature overnight. After the TLC analysis had indicated

the consumption of starting material, the reaction was carefully quenched with water. Then, CH_2Cl_2 (20 mL) was poured into the mixture, which was then washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was separated by HPLC to give **23a** (4.7 mg, 18 %), **23b** (1.8 mg, 7 %) and **23c** (6.9 mg, 26 %). Compound **23a** was a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 2.0 Hz, 1H), 7.81 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.38 – 7.32 (m, 1H), 7.30 – 7.24 (m, 1H), 7.13 – 7.04 (m, 1H), 6.44 (q, *J* = 16.2 Hz, 2H), 5.02 – 4.86 (m, 1H), 4.09 (dd, *J* = 8.7, 4.2 Hz, 1H), 3.83 (d, *J* = 8.7 Hz, 1H), 3.26 – 3.07 (m, 1H), 2.59 (ddd, *J* = 11.9, 10.2, 5.8 Hz, 1H), 2.21 (d, *J* = 6.2 Hz, 1H), 1.92 (s, 3H), 1.90 – 1.77 (m, 3H), 1.55 – 1.41 (m, 3H), 1.36 (dt, *J* = 13.7, 3.3 Hz, 1H), 1.31 – 1.27 (m, 1H), 1.19 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 170.4, 163.4 (d, *J* = 246.5 Hz), 155.5, 147.5, 144.6, 140.0, 135.1, 133.7, 130.8 (d, *J* = 8.4 Hz), 129.6, 122.7 (d, *J* = 2.8 Hz), 120.6, 115.0 (d, *J* = 21.3 Hz), 113.9 (d, *J* = 22.2 Hz), 77.8, 70.8, 53.2, 46.1, 45.1, 35.0, 34.6, 31.4, 27.9, 23.4, 23.1, 21.3, 21.2, 12.9. ESI-HRMS (*m/z*): calcd for $C_{29}H_{33}FNO_4$ $[M + H]^+$, 478.2349; found, 478.2384.

(3aS,5aS,6S,7R,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-7-yl acetate (23b). Compound **23b** was a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.0 Hz, 1H), 7.82 (d, *J* = 5.0 Hz, 1H), 7.44 (td, *J* = 8.0, 6.0 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.09 (td, *J* = 8.3, 2.4 Hz, 1H), 6.74 (d, *J* = 13.9 Hz, 1H), 6.47 (d, *J* = 16.3 Hz, 1H), 4.80 (t, *J* = 2.5 Hz, 1H), 4.30 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.75 (dd, *J* = 11.0, 8.3 Hz, 1H), 2.47 – 2.37 (m, 1H), 2.33 (dt, *J* = 13.7, 3.2 Hz, 1H),

2.07 (s, 3H), 2.04 – 1.95 (m, 2H), 1.93 (d, *J* = 13.8 Hz, 1H), 1.82 – 1.76 (m, 2H), 1.38 – 1.28 (m, 4H), 1.24 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.6, 170.3, 164.2, 162.6, 130.9, 130.1, 122.7, 114.0, 113.8, 71.4, 57.4, 47.9, 38.6, 35.4, 30.3, 29.5, 28.5, 27.3, 22.8, 22.2, 21.5, 17.6, 16.3. ESI-HRMS (*m/z*): calcd for $C_{29}H_{33}FNO_4$ $[M + H]^+$, 478.2349; found, 478.2379.

(3aS,5aS,6R,7R,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-7-yl acetate (23c). Compound **23c** was a white solid, mp 161-163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.9 Hz, 1H), 7.80 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.44 (td, *J* = 8.0, 5.9 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.30 – 7.23 (m, 1H), 7.09 (tdd, *J* = 8.5, 2.5, 0.9 Hz, 1H), 6.48 (d, *J* = 16.1 Hz, 1H), 6.41 (d, *J* = 16.1 Hz, 1H), 4.94 – 4.76 (m, 1H), 4.29 (dd, *J* = 8.3, 6.7 Hz, 1H), 3.73 (dd, *J* = 11.0, 8.4 Hz, 1H), 2.59 (dt, *J* = 13.8, 3.4 Hz, 1H), 2.45 – 2.29 (m, 1H), 1.93 (s, 3H), 1.87 – 1.79 (m, 2H), 1.76 (d, *J* = 13.8 Hz, 1H), 1.68 – 1.62 (m, 1H), 1.48 – 1.35 (m, 2H), 1.29 – 1.22 (m, 3H), 1.20 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 170.6, 163.4 (d, *J* = 246.7 Hz), 155.2, 147.8, 144.4, 140.0, 135.1, 133.8, 130.8 (d, *J* = 8.4 Hz), 129.2, 122.7 (d, *J* = 2.8 Hz), 121.0, 115.0 (d, *J* = 21.1 Hz), 113.9 (d, *J* = 22.2 Hz), 78.0, 71.4, 57.5, 53.2, 45.2, 38.4, 35.1, 35.1, 28.4, 23.4, 22.5, 21.3, 16.4, 12.4. ESI-HRMS (*m/z*): calcd for $C_{29}H_{33}FNO_4$ $[M + H]^+$, 478.2349; found, 478.2381.

(3aS,5aS,6S,7S,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-7-yl carbamate (24a). Compound **21** (30 mg, 0.07 mM) was dissolved in anhydrous THF (3 mL), to which

trichloroacetyl isocyanate (17 μL, 0.14 mM) was added. The mixture was stirred overnight at room temperature, and the volatile substances were removed under reduced pressure. Methanol (4 mL), H_2O (0.2 mL) and K_2CO_3 (20 mg, 0.14 mM) were added to this solution. After completion of the reaction, the mixture was extracted with ethyl acetate and washed twice with a saturated aqueous sodium chloride solution. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated and separated by HPLC to give **24a** (12.0 mg, 36 %), **24b** (3.6 mg, 10 %), **24c** (12.3 mg, 37 %) and **24d** (4.8 mg, 14 %). Compound **24a** was a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 2.0 Hz, 1H), 7.79 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.42 (td, *J* = 8.0, 5.9 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.28 – 7.23 (m, 1H), 7.12 – 7.03 (m, 1H), 6.50 (d, *J* = 16.3 Hz, 1H), 6.43 (d, *J* = 16.3 Hz, 1H), 4.81 (dd, *J* = 11.8, 4.5 Hz, 1H), 4.51 (s, 2H), 4.08 (dd, *J* = 8.7, 4.3 Hz, 1H), 3.82 (d, *J* = 8.7 Hz, 1H), 3.16 (td, *J* = 13.7, 3.8 Hz, 1H), 2.58 (ddd, *J* = 11.9, 10.2, 5.8 Hz, 1H), 2.19 (d, *J* = 6.1 Hz, 1H), 1.92 – 1.83 (m, 3H), 1.81 – 1.73 (m, 1H), 1.53 – 1.45 (m, 2H), 1.35 (dt, *J* = 13.8, 3.3 Hz, 1H), 1.31 – 1.26 (m, 1H), 1.17 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 163.4 (d, *J* = 246.4 Hz), 156.4, 155.7, 147.6, 144.6, 140.1 (d, *J* = 7.7 Hz), 135.0, 133.5, 130.7 (d, *J* = 8.4 Hz), 129.7, 122.7 (d, *J* = 2.8 Hz), 120.6, 114.9 (d, *J* = 21.2 Hz), 113.9 (d, *J* = 22.1 Hz), 78.8, 70.7, 53.2, 46.0, 45.1, 35.0, 34.6, 31.4, 27.9, 23.6, 23.1, 21.1, 12.9. ESI-HRMS (*m/z*): calcd for $C_{28}H_{32}FN_2O_4$ $[M + H]^+$, 479.2301; found, 479.2332.

(3aS,5aS,6S,7R,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-7-yl carbamate (24b).

Compound **24b** was a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.1 Hz, 1H), 7.81 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.44 (td, *J* = 8.0, 6.0 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.09 (td, *J* = 8.3, 1.9 Hz, 1H), 6.76 (d, *J* = 16.4 Hz, 1H), 6.48 (d, *J* = 16.3 Hz, 1H), 4.66 (t, *J* = 2.4 Hz, 1H), 4.29 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.73 (dd, *J* = 11.0, 8.3 Hz, 1H), 2.45 – 2.36 (m, 1H), 2.33 (dt, *J* = 13.6, 3.2 Hz, 1H), 2.04 – 1.97 (m, 1H), 1.96 – 1.91 (m, 1H), 1.91 – 1.84 (m, 2H), 1.73 (dd, *J* = 12.4, 2.3 Hz, 2H), 1.65 – 1.60 (m, 2H), 1.41 – 1.35 (m, 1H), 1.30 (ddd, *J* = 24.5, 12.8, 3.4 Hz, 2H), 1.23 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.5, 163.4 (d, *J* = 246.5 Hz), 156.2, 155.2, 147.7, 143.1, 139.9, 135.2, 133.7, 130.8 (d, *J* = 8.6 Hz), 128.3, 122.6 (d, *J* = 3.1 Hz), 121.8, 115.0 (d, *J* = 21.5 Hz), 113.9 (d, *J* = 22.2 Hz), 77.9, 71.4, 57.4, 47.9, 42.9, 38.6, 35.4, 30.3, 28.6, 22.9, 22.2, 17.6, 16.3. ESI-HRMS (*m/z*): calcd for $C_{28}H_{32}FN_2O_4$ $[M + H]^+$, 479.2301; found, 479.2335.

(3aS,5aS,6R,7R,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-7-yl carbamate (24c). Compound **24c** was a white solid, mp 91-93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.0 Hz, 1H), 7.79 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.36 – 7.31 (m, 1H), 7.28 – 7.22 (m, 1H), 7.12 – 7.04 (m, 1H), 6.49 (d, *J* = 16.2 Hz, 1H), 6.44 (d, *J* = 16.2 Hz, 1H), 4.72 (dd, *J* = 11.7, 4.7 Hz, 1H), 4.55 (s, 2H), 4.28 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.72 (dd, *J* = 10.9, 8.4 Hz, 1H), 2.58 (dt, *J* = 13.8, 3.3 Hz, 1H), 2.44 – 2.26 (m, 1H), 1.95 – 1.86 (m, 3H), 1.75 (d, *J* = 13.8 Hz, 1H), 1.68 – 1.61 (m, 1H), 1.46 – 1.34 (m, 2H), 1.27 – 1.20 (m, 2H), 1.17 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 163.4 (d, *J* = 246.5 Hz), 156.4, 155.5, 147.7, 144.4, 140.0 (d, *J* = 7.7

Hz), 135.0, 133.6, 130.8 (d, J = 8.4 Hz), 129.4, 122.6 (d, J = 2.8 Hz), 121.0, 114.9 (d, J = 21.2 Hz), 113.9 (d, J = 22.2 Hz), 78.9, 71.4, 57.5, 53.2, 45.3, 38.4, 35.1, 35.1, 28.4, 23.6, 22.4, 16.3, 12.4. ESI-HRMS (*m/z*): calcd for $C_{28}H_{32}FN_2O_4$ $[M + H]^+$, 479.2301; found, 479.2336.

(3aS,5aS,6R,7S,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-7-yl carbamate (24d). Compound **24d** was a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, J = 2.1 Hz, 1H), 7.80 (dd, J = 8.2, 2.3 Hz, 1H), 7.43 (td, J = 8.0, 6.0 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.29 – 7.23 (m, 1H), 7.11 – 7.04 (m, 1H), 6.71 (d, J = 16.4 Hz, 1H), 6.50 (d, J = 16.4 Hz, 1H), 4.65 (s, 1H), 4.10 (dd, J = 8.8, 4.3 Hz, 1H), 3.85 (d, J = 8.8 Hz, 1H), 3.32 (td, J = 13.8, 4.1 Hz, 1H), 2.64 (td, J = 11.6, 5.8 Hz, 1H), 2.21 (d, J = 6.4 Hz, 1H), 2.02 – 1.93 (m, 2H), 1.92 – 1.87 (m, 2H), 1.78 (s, 2H), 1.48 – 1.35 (m, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 1.09 (dt, J = 13.6, 3.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.9, 163.4 (d, J = 246.4 Hz), 156.5, 155.4, 147.6, 143.0, 140.0, 135.1, 133.6, 130.8 (d, J = 8.6 Hz), 128.7, 122.7 (d, J = 3.1 Hz), 121.2, 114.9 (d, J = 21.3 Hz), 113.9 (d, J = 22.3 Hz), 77.5, 71.0, 53.6, 43.0, 41.3, 35.1, 34.8, 28.4, 26.9, 23.2, 22.8, 21.0, 18.2. ESI-HRMS (*m/z*): calcd for $C_{28}H_{32}FN_2O_4$ $[M + H]^+$, 479.2301; found, 479.2330.

(3aS,5aS,6S,7S,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-7-yl butyrate (25a). Compound **21** (25 mg, 0.06 mM) was dissolved in dry CH_2Cl_2 (3 mL), to which butyric anhydride (20 μL, 0.12 mM) and DMAP (15 mg, 0.12 mM) were added. The reaction

mixture was stirred overnight at room temperature. After TLC analysis indicated the consumption of starting material, the reaction was carefully quenched with water. Next, CH_2Cl_2 (20 mL) was poured into the mixture, which was then washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was separated using HPLC to give **25a** (1.9 mg, 6 %) and **25c** (7.0 mg, 29 %). Compound **25a** was a white solid, mp 131-133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 2.0 Hz, 1H), 7.81 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.08 (td, *J* = 8.3, 1.6 Hz, 1H), 6.48 (d, *J* = 16.3 Hz, 1H), 6.40 (d, *J* = 16.2 Hz, 1H), 5.04 – 4.86 (m, 1H), 4.09 (dd, *J* = 8.7, 4.2 Hz, 1H), 3.83 (d, *J* = 8.7 Hz, 1H), 3.29 – 3.08 (m, 1H), 2.67 – 2.49 (m, 1H), 2.20 (d, *J* = 6.1 Hz, 1H), 2.16 (t, *J* = 7.4 Hz, 2H), 1.85 – 1.79 (m, 2H), 1.68 (s, 2H), 1.55 – 1.45 (m, 4H), 1.38 – 1.32 (m, 1H), 1.31 – 1.27 (m, 1H), 1.19 (s, 6H), 0.77 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 172.9, 164.6, 162.2, 155.5, 147.5, 144.8, 135.1, 133.6, 130.8 (d, *J* = 8.4 Hz), 129.6, 122.7 (d, *J* = 2.8 Hz), 120.6, 115.0 (d, *J* = 21.1 Hz), 113.9 (d, *J* = 22.2 Hz), 77.4, 70.8, 53.2, 46.0, 45.2, 36.7, 35.0, 34.6, 31.4, 27.9, 23.5, 23.1, 21.2, 18.7, 13.7, 12.9. ESI-HRMS (*m/z*): calcd for $C_{31}H_{37}FNO_4$ $[M + H]^+$, 506.2662; found, 506.2697.

(3aS,5aS,6R,7R,9aR,9bR)-6-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6,9a-dimethyl-1-oxododecahydronaphtho[1,2-c]furan-7-yl butyrate (25c). Compound **25c** was a white solid, mp 149-151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.1 Hz, 1H), 7.80 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.43 (td, *J* = 8.0, 5.9 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.29 – 7.24 (m, 1H), 7.13 – 7.04 (m, 1H), 6.47 (d, *J* = 16.1 Hz, 1H), 6.41 (d, *J* =

16.1 Hz, 1H), 4.91 – 4.83 (m, 1H), 4.28 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.72 (dd, *J* = 10.9, 8.4 Hz, 1H), 2.59 (dt, *J* = 13.8, 3.3 Hz, 1H), 2.44 – 2.29 (m, 1H), 2.17 (t, *J* = 7.4 Hz, 2H), 1.96 – 1.88 (m, 1H), 1.85 – 1.74 (m, 3H), 1.70 - 1.62 (m, 2H), 1.56 – 1.47 (m, 2H), 1.47 – 1.35 (m, 2H), 1.28 (d, *J* = 2.3 Hz, 1H), 1.21 (s, 3H), 1.11 (s, 3H), 0.78 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 173.1, 164.6, 162.2, 155.2, 147.7, 144.5, 135.1, 133.7, 130.8 (d, *J* = 8.4 Hz), 129.3, 122.6 (d, *J* = 2.8 Hz), 121.0, 115.0 (d, *J* = 21.2 Hz), 113.9 (d, *J* = 22.2 Hz), 77.7, 71.4, 57.5, 53.2, 45.3, 38.4, 36.7, 35.2, 35.1, 28.4, 23.4, 22.5, 18.6, 16.4, 13.7, 12.4. ESI-HRMS (*m/z*): calcd for $C_{31}H_{37}FNO_4$ $[M + H]^+$, 506.2662; found, 506.2698.

(1R,2R,4aR,5S,6S,8aS)-5-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-1-(hydroxymethyl)-1,4a,6-trimethyldecahydronaphthalene-2,6-diol (26). $LiAlH_4$ (19 mg, 0.5 mM) and anhydrous diethyl ether (1.5 mL) were placed in a flame-dried 10 mL round bottomed flask under N_2 protection. Compound **13a** (50 mg, 0.11 mM) in anhydrous diethyl ether (2 mL) was added dropwise to the mixture and stirred for 0.5 h under reflux. After cooling to 0 ℃, the reaction was slowly quenched with H_2O. Then, the mixture was extracted with EtOAC, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product, which was purified by flash chromatography to give compound **26** (32.6 mg, 65 %) as a white solid, mp 200-202 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 1.9 Hz, 1H), 7.81 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.44 (td, *J* = 8.0, 5.9 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.13 – 7.04 (m, 1H), 6.84 (dd, *J* = 15.3, 10.4 Hz, 1H), 6.62 (d, *J* = 15.3 Hz, 1H), 4.84 (s, 1H), 4.19 (d, *J* = 11.1 Hz, 1H), 3.47 (dd, *J* = 11.6, 4.5

Hz, 1H), 3.36 (d, *J* = 11.0 Hz, 1H), 2.87 (d, *J* = 62.6 Hz, 2H), 2.08 – 1.91 (m, 3H), 1.85 – 1.79 (m, 2H), 1.73 – 1.67 (m, 1H), 1.60 – 1.46 (m, 2H), 1.41 – 1.32 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.09 (d, *J* = 1.9 Hz, 1H), 1.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (d, *J* = 246.6 Hz), 154.3, 148.0, 139.9 (d, *J* = 7.6 Hz), 135.1, 134.9, 134.0, 131.8, 130.8 (d, *J* = 8.5 Hz), 122.7 (d, *J* = 2.9 Hz), 121.9, 115.1 (d, *J* = 21.2 Hz), 113.9 (d, *J* = 22.1 Hz), 80.8, 72.2, 66.4, 64.3, 55.4, 43.1, 42.4, 39.0, 37.4, 27.7, 25.3, 22.7, 20.0, 16.8. ESI-HRMS (*m/z*): calcd for $C_{27}H_{35}FNO_3$ $[M + H]^+$, 440.2556; found, 440.2598.

(1S,2S,4aS,5S,6R,8aR)-1-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6-hydroxy-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxirane]-5-carbaldehyde (27). The general procedure for the synthesis of **27** was similar to that used for **20**, with a yield of 90 % as a white powder, mp 241-243 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.01 (s, 1H), 8.85 (d, *J* = 2.2 Hz, 1H), 8.06 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.67 – 7.45 (m, 4H), 7.31 – 7.18 (m, 1H), 6.57 – 6.38 (m, 2H), 5.15 (s, 1H), 3.36 (dd, *J* = 11.8, 4.8 Hz, 1H), 2.79 (d, *J* = 4.2 Hz, 1H), 2.54 (d, *J* = 4.5 Hz, 1H), 2.43 (d, *J* = 8.8 Hz, 1H), 2.06 – 1.69 (m, 4H), 1.60 – 1.44 (m, 1H), 1.44 – 1.22 (m, 4H), 1.13 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 207.7, 164.4, 162.0, 154.7, 147.8, 139.9 (d, *J* = 7.9 Hz), 135.1 (d, *J* = 22.2 Hz), 132.8 (d, *J* = 2.4 Hz), 131.6 (d, *J* = 8.6 Hz), 129.8, 123.2 (d, *J* = 2.5 Hz), 121.7, 115.2 (d, *J* = 21.2 Hz), 113.8 (d, *J* = 22.4 Hz), 75.5, 58.6, 56.9, 54.5, 53.1, 50.2, 39.3, 37.6, 35.4, 27.8, 22.0, 21.5, 16.2. ESI-HRMS (*m/z*): calcd for $C_{27}H_{31}FNO_3$ $[M + H]^+$, 436.2243; found, 436.2277.

(1S,2S,4aS,5S,6R,8aR)-1-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6-hydro

xy-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxirane]-5-carboxylic acid (28). The general procedure for the synthesis of **28** was similar to that used for **15**, with a yield of 82 % as a white solid, mp 240-242 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.41 (s, 1H), 8.84 (d, *J* = 2.0 Hz, 1H), 8.07 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.69 – 7.44 (m, 4H), 7.24 (td, *J* = 8.4, 1.6 Hz, 1H), 6.55 – 6.40 (m, 2H), 3.11 (dd, *J* = 11.8, 4.0 Hz, 1H), 2.81 (d, *J* = 4.2 Hz, 1H), 2.57 (d, *J* = 4.6 Hz, 1H), 2.36 (d, *J* = 7.6 Hz, 1H), 2.14 – 1.76 (m, 4H), 1.63 – 1.51 (m, 1H), 1.50 – 1.42 (m, 1H), 1.41 – 1.35 (m, 1H), 1.31 (s, 3H), 1.29 – 1.19 (m, 3H), 0.95 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 177.3, 164.0, 161.5, 154.2, 147.2, 139.32 (d, *J* = 8.0 Hz), 134.5(d, *J* = 69.5 Hz), 132.4, 131.1 (d, *J* = 8.6 Hz), 129.6, 122.7 (d, *J* = 2.5 Hz), 121.3, 114.7 (d, *J* = 21.1 Hz), 113.4 (d, *J* = 22.4 Hz), 76.7, 58.4, 57.4, 53.1, 49.6, 48.6, 38.3, 35.4, 27.7, 24.2, 22.7, 13.7. ESI-HRMS (*m/z*): calcd for $C_{27}H_{31}FNO_4$ $[M + H]^+$, 452.2192; found, 452.2225.

Methyl(1S,2S,4aS,5S,6R,8aR)-1-((E)-2-(5-(3-fluorophenyl)pyridin-2-yl)vinyl)-6-hydroxy-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxirane]-5-carboxylate (29). To a solution of compound **28** (20.0 mg, 0.05 mM) in 1.5 mL of DMF, anhydrous K_2CO_3 (15.3 mg, 0.11 mM) and MeI (13.7 μL, 0.22 mM) were added. The mixture was stirred for 4 h at room temperature. Next, 5 mL of water was added to the resulting solution, which was then extracted with EtOAc (10 mL × 2). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated under vacuum to obtain the crude product, which was then purified by flash chromatography to give compound **29** (20.4 mg, 99 %) as a white solid, mp 211-213 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.42 (td, *J* = 8.0, 6.0

Hz, 1H), 7.36 – 7.31 (m, 1H), 7.28 – 7.19 (m, 2H), 7.12 – 7.03 (m, 1H), 6.55 – 6.42 (m, 2H), 3.71 (s, 3H), 3.24 (d, *J* = 12.0 Hz, 1H), 3.16 (td, *J* = 11.8, 4.2 Hz, 1H), 2.91 (d, *J* = 4.1 Hz, 1H), 2.63 (d, *J* = 4.4 Hz, 1H), 2.38 (d, *J* = 9.0 Hz, 1H), 2.16 – 1.91 (m, 4H), 1.86 – 1.75 (m, 1H), 1.70 (dt, *J* = 13.7, 3.4 Hz, 1H), 1.54 – 1.48 (m, 1H), 1.46 (s, 3H), 1.31 – 1.19 (m, 2H), 0.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 164.6, 162.1, 154.2, 147.9, 140.1 (d, *J* = 7.1 Hz), 134.9 (d, *J* = 9.9 Hz), 133.7 (d, *J* = 1.4 Hz), 130.8 (d, *J* = 8.5 Hz), 128.4, 122.6 (d, *J* = 2.8 Hz), 122.3, 114.9 (d, *J* = 20.7 Hz), 113.9 (d, *J* = 22.2 Hz), 78.4, 58.5, 58.1, 54.8, 51.6, 50.7, 49.6, 39.8, 39.8, 35.9, 28.2, 24.0, 23.3, 13.8. ESI-HRMS (*m/z*): calcd for $C_{28}H_{33}FNO_4$ $[M + H]^+$, 466.2349; found, 466.2388.

Methyl(1S,2S,4aS,5S,6R,8aR)-6-acetoxy-1-((E)-2-(5-(3-fluorophenyl)pyridin-2-yl)vinyl)-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxirane]-5-carboxylate (30a). The general procedure for the synthesis of **30a** was similar to that used for **23** with a yield of 85 % as a white powder, mp 92-94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 1.8 Hz, 1H), 7.84 – 7.72 (m, 1H), 7.42 (dd, *J* = 14.0, 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.26 – 7.18 (m, 2H), 7.10 – 7.03 (m, 1H), 6.57 – 6.43 (m, 2H), 4.61 (dd, *J* = 12.1, 4.0 Hz, 1H), 3.71 (s, 3H), 2.90 (d, *J* = 3.9 Hz, 1H), 2.60 (d, *J* = 4.4 Hz, 1H), 2.47 – 2.31 (m, 2H), 2.14 – 2.07 (m, 1H), 2.06 (s, 3H), 1.95 (td, *J* = 13.3, 3.6 Hz, 1H), 1.75 – 1.70 (m, 2H), 1.54 – 1.47 (m, 1H), 1.40 – 1.31 (m, 2H), 1.29 (s, 3H), 1.24 (d, *J* = 7.1 Hz, 1H), 0.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 171.1, 164.6, 162.1, 154.2, 147.9, 140.0 (d, *J* = 7.9 Hz), 135.0, 133.8 (d, *J* = 1.8 Hz), 130.8 (d, *J* = 8.4 Hz), 128.4, 122.6 (d, *J* = 2.8 Hz), 122.4, 114.9 (d, *J* = 21.3 Hz), 113.9 (d, *J*

= 22.3 Hz), 79.2, 58.3, 54.6, 51.4, 50.9, 48.4, 39.6, 38.4, 35.7, 24.2, 24.1, 23.0, 21.4, 13.7. ESI-HRMS (*m/z*): calcd for $C_{30}H_{35}FNO_5$ $[M + H]^+$, 508.2455; found, 508.2489.

Methyl(1S,2S,4aS,5S,6R,8aR)-6-(carbamoyloxy)-1-((E)-2-(5-(3-fluorophenyl)pyridin-2-yl)vinyl)-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxirane]-5-carboxylate (30b). The general procedure for the synthesis of **30b** was similar to that used for **24** with a yield of 78 % as a white powder, mp 122-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.1 Hz, 1H), 7.77 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.41 (td, *J* = 8.0, 5.9 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.26 – 7.18 (m, 2H), 7.11 – 7.02 (m, 1H), 6.58 – 6.41 (m, 2H), 4.82 (s, 2H), 4.50 (dd, *J* = 12.2, 4.3 Hz, 1H), 3.69 (s, 3H), 2.90 (dd, *J* = 4.3, 1.4 Hz, 1H), 2.60 (d, *J* = 4.4 Hz, 1H), 2.46 – 2.34 (m, 2H), 2.14 – 2.05 (m, 1H), 2.00 – 1.89 (m, 2H), 1.81 – 1.65 (m, 3H), 1.50 (dt, *J* = 12.7, 3.2 Hz, 1H), 1.37 (dd, *J* = 12.4, 2.6 Hz, 1H), 1.33 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 164.6, 162.1, 157.0, 154.2, 147.9, 140.0 (d, *J* = 7.8 Hz), 135.0 (d, *J* = 4.6 Hz), 133.8 (d, *J* = 2,2 Hz), 130.7 (d, *J* = 8.4 Hz), 128.3, 122.6 (d, *J* = 2.8 Hz), 122.4, 114.9 (d, *J* = 21.2 Hz), 113.9 (d, *J* = 22.3 Hz), 79.9, 58.4, 58.3, 54.7, 51.4, 50.9, 48.8, 39.6, 38.5, 35.7, 24.5, 24.0, 23.0, 13.6. ESI-HRMS (*m/z*): calcd for $C_{29}H_{34}FN_2O_5$ $[M + H]^+$, 509.2407; found, 509.2445.

Methyl(1S,2S,4aS,5S,6R,8aR)-6-(butyryloxy)-1-((E)-2-(5-(3-fluorophenyl)pyridin-2-yl)vinyl)-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxirane]-5-carboxylate (30c). The general procedure for the synthesis of **30c** was similar to that used for **25** with a yield of 88 % as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.1 Hz, 1H), 7.78 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.47 – 7.38 (m, 1H), 7.34 (d, *J* =

7.8 Hz, 1H), 7.28 – 7.19 (m, 3H), 7.07 (td, *J* = 8.3, 2.4 Hz, 1H), 6.61 – 6.39 (m, 2H), 4.62 (dd, *J* = 12.2, 4.1 Hz, 1H), 3.71 (s, 3H), 2.91 (d, *J* = 3.4 Hz, 1H), 2.61 (d, *J* = 4.4 Hz, 1H), 2.42 – 2.27 (m, 4H), 2.16 – 2.06 (m, 1H), 1.96 (td, *J* = 13.2, 3.2 Hz, 1H), 1.83 – 1.58 (m, 6H), 1.51 (dt, *J* = 12.8, 3.0 Hz, 1H), 1.41 – 1.34 (m, 1H), 1.29 (s, 3H), 1.00 (s, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 173.6, 164.6, 162.2, 154.2, 147.8, 140.0 (d, *J* = 7.8 Hz), 135.0 (d, *J* = 21.3 Hz), 133.8 (d, *J* = 2.0 Hz), 130.8 (d, *J* = 8.4 Hz), 128.5, 122.7 (d, *J* = 2.8 Hz), 122.4, 115.0 (d, *J* = 21.4 Hz), 113.9 (d, *J* = 22.3 Hz), 78.9, 58.4, 54.7, 51.4, 51.0, 48.5, 39.6, 38.4, 36.7, 35.7, 24.3, 24.2, 23.0, 18.6, 13.8, 13.7. ESI-HRMS (*m/z*): calcd for $C_{32}H_{39}FNO_5$ $[M + H]^+$, 436.2768; found, 436.2808.

(1S,2S,4aS,5R,6R,8aR)-1-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-5-(methoxymethyl)-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxiran]-6-ol (31) and ((1S,2S,4aS,5R,6R,8aR)-1-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-6-methoxy-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxiran]-5-yl)methanol (32). To a 10-mL flame-dried round-bottomed flask containing compound **13a** (30 mg, 0.07 mM) in anhydrous THF (3 mL) under nitrogen protection, sodium hydride (60 % in mineral oil, 8.4 mg, 0.21 mM) was added, and the mixture was stirred for 30 min at room temperature. Then, CH_3I (21.8 μL, 0.35 mM) was added dropwise, and the mixture was stirred continuously for 5 h. After this time, TLC analysis indicated the consumption of starting material and the reaction was carefully quenched with water. The resulting mixture was extracted with CH_2Cl_2, and the extract was washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed under

reduced pressure to give the crude compound, which was purified by flash chromatography to obtain compound **31** (16.1 mg, 52 %) and compound **32** (10.5 mg, 34 %). Compound **31** was a white solid, mp 181-183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 1.7 Hz, 1H), 7.82 (d, *J* = 7.3 Hz, 1H), 7.43 (td, *J* = 7.9, 6.0 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.29 – 7.20 (m, 2H), 7.09 (td, *J* = 8.3, 1.8 Hz, 1H), 6.75 – 6.40 (m, 2H), 3.92 (d, *J* = 9.1 Hz, 1H), 3.86 (d, *J* = 7.2 Hz, 1H), 3.33 (s, 3H), 3.27 (d, *J* = 9.1 Hz, 1H), 2.94 (d, *J* = 3.6 Hz, 1H), 2.59 (d, *J* = 4.4 Hz, 1H), 2.38 (d, *J* = 9.0 Hz, 1H), 2.03 – 1.90 (m, 2H), 1.82 – 1.76 (m, 1H), 1.75 – 1.69 (m, 1H), 1.68 – 1.59 (m, 2H), 1.59 – 1.53 (m, 1H), 1.52 – 1.39 (m, 2H), 1.27 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 162.2, 133.9, 131.0, 130.9, 130.8, 129.0, 122.7, 122.6, 115.2, 114.0, 113.8, 80.0, 75.2, 59.6, 58.8, 58.5, 54.8, 51.1, 42.7, 39.4, 38.4, 35.8, 28.0, 23.4, 21.7, 16.4. ESI-HRMS (*m/z*): calcd for $C_{28}H_{35}FNO_3$ $[M + H]^+$, 452.2556; found, 452.2594. Compound **32** was a white solid, mp 175-177 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.78 (d, *J* = 7.4 Hz, 1H), 7.43 (dd, *J* = 14.0, 7.9 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.08 (td, *J* = 8.4, 2.0 Hz, 1H), 6.58 – 6.40 (m, 2H), 4.16 (d, *J* = 9.7 Hz, 1H), 3.38 (s, 3H), 3.31 – 3.23 (m, 2H), 2.99 (dd, *J* = 11.7, 4.1 Hz, 1H), 2.90 (d, *J* = 3.6 Hz, 1H), 2.60 (d, *J* = 4.4 Hz, 1H), 2.36 (d, *J* = 8.9 Hz, 1H), 2.04 – 1.90 (m, 4H), 1.69 (dt, *J* = 13.7, 3.3 Hz, 1H), 1.52 (ddd, *J* = 13.2, 10.9, 3.0 Hz, 2H), 1.25 (s, 3H), 1.22 – 1.19 (m, 1H), 1.13 (td, *J* = 13.7, 3.1 Hz, 1H), 1.02 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 162.5, 130.7, 130.6, 129.9, 129.9, 122.5, 122.5, 122.0, 114.9, 114.8, 113.9, 113.7, 90.4, 63.9, 58.5, 58.3, 57.7, 54.8, 51.0, 43.2, 39.1, 37.9, 35.7, 23.0, 21.9, 21.3, 16.1. ESI-HRMS (*m/z*): calcd for $C_{28}H_{35}FNO_3$ [M +

H]$^+$, 452.2556; found, 452.2593.

(1S,2S,4aS,5R,6R,8aR)-5-(Aminomethyl)-1-((E)-2-(5-(3-fluorophenyl)pyridin-2-yl)vinyl)-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxiran]-6-ol (33a). Compound **27** (20 mg, 0.05 mM) was dissolved in dry dichloroethane (1 mL), to which 7 M ammonia in methanol (66 μL, 5 mM) was added. The reaction mixture was stirred for 2 h at room temperature. After this time, TLC analysis indicated the consumption of starting material. Then, the flask was cooled on an ice bath and sodium cyanoborohydride (6 mg, 0.09 mM) was added. The mixture was acidified with acetic acid to pH 5 – 6 and allowed to stir at room temperature for an additional 2 h. After TLC analysis indicated the consumption of starting material, the reaction was carefully quenched with water. Next, CH_2Cl_2 (20 mL) was poured into the mixture, which was then washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give compound **33a** (16.4 mg, 82 %) as a white solid, mp 139-141 °C. ^{1}H NMR (400 MHz, MeOD) δ 8.73 (s, 1H), 8.10 – 7.95 (m, 1H), 7.53 (d, *J* = 8.2 Hz, 3H), 7.45 (d, *J* = 10.2 Hz, 1H), 7.21 – 7.11 (m, 1H), 6.64 – 6.43 (m, 2H), 3.71 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.59 (d, *J* = 11.0 Hz, 1H), 3.37 (d, *J* = 6.9 Hz, 1H), 2.99 (d, *J* = 3.1 Hz, 1H), 2.66 (d, *J* = 4.3 Hz, 1H), 2.45 (d, *J* = 8.4 Hz, 1H), 2.04 (td, *J* = 12.4, 4.3 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.76 – 1.63 (m, 3H), 1.60 – 1.52 (m, 2H), 1.51 – 1.44 (m, 1H), 1.36 – 1.22 (m, 3H), 1.16 (s, 3H), 0.79 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 164.8 (d, *J* = 245.0 Hz), 155.9, 148.0, 140.9 (d, *J* = 7.9 Hz), 136.8, 135.2, 135.2, 132.1 (d, *J* = 8.4 Hz), 131.3, 123.7 (d, *J* = 2.8 Hz), 123.0, 115.9 (d, *J* =

21.5 Hz), 114.5 (d, *J* = 22.7 Hz), 73.3, 66.7, 60.1, 51.9, 47.0, 43.8, 40.6, 39.3, 36.3, 27.5, 22.0, 16.3, 12.7. ESI-HRMS (*m/z*): calcd for $C_{27}H_{34}FN_2O_2$ $[M + H]^+$, 437.2560; found, 437.2438.

(1S,2S,4aS,5R,6R,8aR)-1-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-5,8a-dimethyl-5-((methylamino)methyl)octahydro-1H-spiro[naphthalene-2,2'-oxiran]-6-ol (33b). The general procedure for the synthesis of **33b** was similar to that used for **33a** as a white solid, mp 229-231 °C. ^{1}H NMR (400 MHz, MeOD) δ 8.71 (d, *J* = 1.9 Hz, 1H), 8.03 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.58 – 7.48 (m, 3H), 7.43 (d, *J* = 10.8 Hz, 1H), 7.20 – 7.10 (m, 1H), 6.58 – 6.41 (m, 2H), 3.49 (dd, *J* = 11.1, 5.0 Hz, 1H), 3.42 – 3.33 (m, 1H), 3.01 (d, *J* = 12.7 Hz, 1H), 2.96 (dd, *J* = 4.2, 1.3 Hz, 1H), 2.70 (s, 3H), 2.64 (d, *J* = 4.3 Hz, 1H), 2.43 (d, *J* = 9.3 Hz, 1H), 2.09 – 1.85 (m, 3H), 1.84 – 1.63 (m, 3H), 1.61 – 1.47 (m, 2H), 1.38 (d, *J* = 12.4 Hz, 1H), 1.33 (s, 3H), 1.31 – 1.24 (m, 1H), 1.08 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 164.8 (d, *J* = 245.0 Hz), 155.8, 148.1, 140.9 (d, *J* = 7.9 Hz), 136.8, 135.6, 135.3 (d, *J* = 2.1 Hz), 132.1 (d, *J* = 8.4 Hz), 130.6, 123.7 (d, *J* = 2.9 Hz), 123.1, 115.9 (d, *J* = 21.3 Hz), 114.6 (d, *J* = 22.7 Hz), 79.3, 59.5, 55.2, 53.0, 51.7, 49.3, 41.7, 40.2, 38.5, 36.4, 34.9, 27.9, 23.0, 22.2, 15.9. ESI-HRMS (*m/z*): calcd for $C_{28}H_{36}FN_2O_2$ $[M + H]^+$, 451.2716; found, 451.2752.

5-(3-Fluorophenyl)-2-((E)-2-((1S,2S,4aS,5S,6R,8aR)-5-formyl-6-hydroxy-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxiran]-1-yl)vinyl)pyridine 1-oxide (34) and 5-(3-Fluorophenyl)-2-((E)-2-((1S,2S,4aS,5R,6R,8aR)-5-formyl-6-hydroxy-5,8a-dimethyloctahydro-1H-spiro[naphthalene-2,2'-oxiran]-1-yl)vinyl)pyridine 1-oxide

(35). To a solution of compound **27** (30 mg, 0.07 mM) in dry CH_2Cl_2 (4 mL), Na_2HPO_4 (27 mg, 0.19 mM) and *m*-CPBA (42 mg, 0.17 mM) were added, and the mixture was then allowed to stir under reflux for 3 h. After cooling to room temperature, 20 mL of CH_2Cl_2 was added to the mixture, which was then washed with water and brine, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated *in vacuo* to give the crude product. The crude product was dissolved in methanol, to which was added K_2CO_3 (19.3 mg, 0.14 mM). The reaction mixture was stirred at room temperature for 3 d. Then, 20 mL of CH_2Cl_2 was poured into the mixture, which was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give compound **34** (7.5 mg, 23 %) and compound **35** (10.3 mg, 33 %). Compound **34** was a white solid, mp 192-194 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (d, *J* = 2.1 Hz, 1H), 8.45 (s, 1H), 7.49 – 7.34 (m, 3H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.22 (dt, *J* = 9.2, 2.0 Hz, 1H), 7.14 (td, *J* = 8.1, 2.2 Hz, 1H), 6.97 (d, *J* = 15.8 Hz, 1H), 6.56 (dd, *J* = 15.8, 9.8 Hz, 1H), 3.38 – 3.23 (m, 1H), 2.85 (dd, *J* = 4.2, 1.5 Hz, 1H), 2.64 (d, *J* = 4.2 Hz, 1H), 2.48 (d, *J* = 9.8 Hz, 1H), 2.24 – 2.11 (m, 1H), 2.05 – 1.78 (m, 6H), 1.67 (dt, *J* = 13.7, 3.2 Hz, 1H), 1.60 – 1.52 (m, 1H), 1.40 – 1.36 (m, 1H), 1.34 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5, 163.5 (d, *J* = 248.6 Hz), 145.5, 138.4, 137.5, 136.6, 132.4, 131.3 (d, *J* = 8.5 Hz), 127.0, 124.5, 124.2, 122.7 (d, *J* = 2.8 Hz), 116.4 (d, *J* = 21.2 Hz), 114.1 (d, *J* = 22.7 Hz), 77.5, 58.3, 58.2, 54.9, 52.9, 50.8, 39.9, 38.5, 35.7, 28.2, 21.7, 19.9, 15.2. ESI-HRMS (*m/z*): calcd for $C_{27}H_{31}FNO_4$ $[M + H]^+$, 452.2192; found, 452.2222. Compound **35** was a white solid, mp

231-233 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.41 (s, 1H), 7.46 – 7.35 (m, 3H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.22 (dt, *J* = 9.6, 2.0 Hz, 1H), 7.13 (td, *J* = 8.3, 2.1 Hz, 1H), 6.96 (d, *J* = 15.8 Hz, 1H), 6.61 (dd, *J* = 15.8, 9.8 Hz, 1H), 3.83 (dd, *J* = 11.1, 4.6 Hz, 1H), 2.90 – 2.81 (m, 1H), 2.61 (d, *J* = 4.3 Hz, 1H), 2.52 (d, *J* = 9.7 Hz, 1H), 2.04 – 1.95 (m, 2H), 1.79 – 1.71 (m, 1H), 1.70 – 1.60 (m, 4H), 1.57 – 1.51 (m, 2H), 1.47 – 1.35 (m, 3H), 1.35 – 1.32 (m, 1H), 1.19 (d, *J* = 11.8 Hz, 1H), 1.12 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.6, 163.5 (d, *J* = 247.7 Hz), 145.5, 138.4, 137.4 (d, *J* = 7.8 Hz), 136.6, 132. 6, 131.2 (d, *J* = 8.4 Hz), 126.9, 124.5 (d, *J* = 4.0 Hz), 122.7 (d, *J* = 2.9 Hz), 116.3 (d, *J* = 21.1 Hz), 114.1 (d, *J* = 22.7 Hz), 72.2, 62.9, 59.4, 58.4, 55.4, 51.0, 46.4, 38.8, 35.1, 26.3, 23.3, 16.0, 9.3. ESI-HRMS (*m/z*): calcd for $C_{27}H_{31}FNO_4$ $[M + H]^+$, 452.2192; found, 452.2229.

(1S,2R,4aS,5R,6S,8aS)-6-(1,3-Dithiolan-2-yl)-5-((E)-2-(5-(3-fluorophenyl)pyridin-2-yl)vinyl)-2-hydroxy-1,4a-dimethyldecahydronaphthalene-1-carbaldehyde (36). To a solution of compound **27** (20 mg, 0.05 mM) in dry CH_2Cl_2 (3 mL) under nitrogen protection, $BF_3{\cdot}Et_2O$ (6 μL, 0.05 mM) and 1,2-Ethanedithiol (4.6 μL, 0.06 mM) were added, and the mixture was stirred for 20 minutes at room temperature. After TLC analysis had indicated the consumption of starting material, the reaction was carefully quenched with water. Then CH_2Cl_2 (20 mL) was poured into the mixture, which was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give the thioacetal **36** (19.3 mg, 82 %) as a yellow solid, mp 234-236 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 2.2 Hz, 1H), 8.75 (d, *J* = 2.1 Hz, 1H), 7.79 (dd, *J* = 8.1, 2.3 Hz,

1H), 7.48 – 7.38 (m, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.07 (td, *J* = 8.3, 1.9 Hz, 1H), 6.66 – 6.49 (m, 2H), 4.77 (d, *J* = 3.0 Hz, 1H), 3.28 – 3.04 (m, 6H), 2.33 – 2.24 (m, 1H), 2.13 – 2.00 (m, 2H), 1.87 – 1.76 (m, 3H), 1.72 – 1.59 (m, 2H), 1.53 – 1.43 (m, 1H), 1.30 (s, 3H), 1.26 – 1.18 (m, 2H), 0.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9, 163.4 (d, *J* = 246.5 Hz), 154.4, 148.0, 140.0 (d, *J* = 7.8 Hz), 134.9, 133.9, 133.8 (d, *J* = 2.2 Hz), 133.4, 130.8 (d, *J* = 8.4 Hz), 122.6 (d, *J* = 2.8 Hz), 121.8, 114.9 (d, *J* = 21.2 Hz), 113.9 (d, *J* = 22.2 Hz), 77.4, 59.7, 57.4, 55.2, 52.9, 42.3, 39.3, 39.0, 38.6, 38.1, 28.3, 25.8, 21.0, 19.4, 14.7. ESI-HRMS (*m/z*): calcd for $C_{29}H_{35}FNO_2S_2$ $[M + H]^+$, 512.2049; found, 512.2085.

(1S,2R,4aS,5S,6R,8aS)-5-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-2-hydroxy-1,4a,6-trimethyldecahydronaphthalene-1-carbaldehyde (37). A solution of compound **36** (20 mg, 0.04 mM) in THF (3 mL) was added dropwise to a flask containing an excess amount of "hydrogen-free" Raney nickel (prepared by stirring Raney nickel in acetone at reflux for 20 min and then removing the solvent with a Pasteur pipette), and the resultant slurry was stirred vigorously for 20 minutes at room temperature. After completion, the reaction mixture was filtered through Celite using several THF washes to complete the transfer. The filtrate was then concentrated to produce the crude product, which was purified by flash chromatography to give compound **37** (12.0 mg, 73 %) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.82 (d, *J* = 2.2 Hz, 1H), 8.76 (d, *J* = 1.7 Hz, 1H), 7.79 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.43 (dd, *J* = 14.0, 7.8 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.12 – 7.05 (m, 1H), 6.53 (dd, *J* = 15.6, 9.8 Hz, 1H), 6.45 (d, *J* = 15.6 Hz,

1H), 3.31 – 3.16 (m, 1H), 3.08 (d, *J* = 10.5 Hz, 1H), 2.01 – 1.92 (m, 2H), 1.88 – 1.77 (m, 2H), 1.75 – 1.65 (m, 3H), 1.51 (t, *J* = 10.3 Hz, 1H), 1.30 (s, 3H), 1.22 – 1.17 (m, 2H), 1.05 (ddd, *J* = 16.0, 12.7, 3.7 Hz, 1H), 0.91 (s, 3H), 0.83 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.3, 163.4 (d, *J* = 246.5 Hz), 155.0, 148.0, 140.1, 136.1, 135.0, 133.5, 132.2, 130.8 (d, *J* = 8.4 Hz), 122.6 (d, *J* = 2.7 Hz), 121.3, 114.9 (d, *J* = 21.4 Hz), 113.9 (d, *J* = 22.2 Hz), 77.6, 62.0, 55.4, 52.9, 38.8, 37.9, 36.4, 31.2, 28.3, 21.8, 21.5, 19.4, 14.7. ESI-HRMS (*m/z*): calcd for $C_{27}H_{33}FNO_2$ $[M + H]^+$, 422.2451; found, 422.2487.

(1S,2R,4aS,5R,6R,8aS)-1,6-di(1,3-Dithiolan-2-yl)-5-((E)-2-(5-(3-fluorophenyl)pyridin-2-yl)vinyl)-1,4a-dimethyldecahydronaphthalen-2-ol (38). Compound **27** (50 mg, 0.12 mM) was dissolved in dry CH_2Cl_2 (3 mL), to which $BF_3{\cdot}Et_2O$ (37 μL, 0.30 mM) and 1,2-ethanedithiol (46 μL, 0.6 mM) were added under nitrogen protection, and the mixture was stirred overnight at room temperature. After TLC analysis had indicated the consumption of starting material, the reaction was carefully quenched with water. Then, CH_2Cl_2 (30 mL) was added to the mixture, which was subsequently washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give the thioacetal **38** (59.5 mg, 88 %) as a yellow power, mp 145-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.1 Hz, 1H), 7.80 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.43 (td, *J* = 8.0, 5.9 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.13 – 7.03 (m, 1H), 6.67 (dd, *J* = 15.5, 10.2 Hz, 1H), 6.54 (d, *J* = 15.5 Hz, 1H), 4.98 (s, 1H), 4.74 (d, *J* = 3.1 Hz, 1H), 3.46 (td, *J* = 10.2, 5.1 Hz, 1H), 3.30 – 2.86 (m, 8H), 2.34 (d, *J* = 7.0

Hz, 1H), 2.28 – 2.18 (m, 1H), 2.03 (tt, *J* = 11.5, 3.3 Hz, 1H), 1.87 (ddd, *J* = 16.4, 12.6, 3.3 Hz, 2H), 1.81 – 1.74 (m, 1H), 1.73 – 1.62 (m, 3H), 1.35 (dd, *J* = 12.4, 4.7 Hz, 1H), 1.30 (s, 3H), 1.19 (dd, *J* = 12.1, 3.0 Hz, 1H), 1.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ163.4 (d, *J* = 246.5 Hz), 154.6, 148.1, 140.1 (d, *J* = 7.7 Hz), 135.0, 134.2, 133.7, 133.2, 130.8 (d, *J* = 8.4 Hz), 122.7 (d, *J* = 2.8 Hz), 121.9, 114.9 (d, *J* = 21.1 Hz), 113.9 (d, *J* = 22.2 Hz), 81.5, 62.0, 58.0, 57.6, 57.5, 46.7, 42.8, 40.3, 39.3, 39.0, 38.2, 37.8, 37.4, 27.3, 26.7, 23.5, 20.0, 16.3. ESI-HRMS (*m/z*): calcd for $C_{31}H_{39}FNOS_4$ $[M + H]^+$, 588.1854; found, 588.1889.

(2R,4aS,5S,6R,8aS)-5-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-1,1,4a,6-tetramethyldecahydronaphthalen-2-ol (39). The general procedure for the synthesis of **39** was similar to that used for **37**, and resulted in a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.1 Hz, 1H), 7.78 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.43 (td, *J* = 7.9, 6.0 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 7.11 – 7.03 (m, 1H), 6.57 (dd, *J* = 15.6, 9.9 Hz, 1H), 6.43 (d, *J* = 15.6 Hz, 1H), 3.25 (dd, *J* = 11.2, 4.5 Hz, 1H), 1.90 (ddd, *J* = 13.0, 6.7, 3.7 Hz, 1H), 1.70 – 1.38 (m, 8H), 1.29 – 1.23 (m, 1H), 1.14 (td, *J* = 14.3, 5.9 Hz, 1H), 1.00 (s, 3H), 0.98 (s, 3H), 0.90 (dd, *J* = 12.3, 2.5 Hz, 1H), 0.82 (s, 3H), 0.79 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3 (d, *J* = 247.3 Hz), 155.2, 147.8, 140.1 (d, *J* = 7.8 Hz), 136.9, 134.7, 133.2 (d, *J* = 2.2 Hz), 131.5, 130.6 (d, *J* = 8.4 Hz), 122.5 (d, *J* = 2.8 Hz), 121.0, 114.7 (d, *J* = 21.1 Hz), 113.7 (d, *J* = 22.1 Hz), 79.1, 63.2, 53.9, 39.1, 38.7, 37.6, 36.2, 31.1, 28.3, 27.4, 21.6, 21.5, 15.6, 15.3. ESI-HRMS (*m/z*): calcd for $C_{27}H_{35}FNO$ $[M + H]^+$, 408.2658; found, 408.2697.

(2R,4aS,5S,6R,8aS)-5-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-1,1,4a,6-tetramethyldecahydronaphthalen-2-yl methanesulfonate (40a). The general procedure for the synthesis of **40a** was similar to that used for **22** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.0 Hz, 1H), 7.81 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.43 (td, *J* = 7.9, 6.0 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.12 – 7.05 (m, 1H), 6.61 (dd, *J* = 15.6, 10.0 Hz, 1H), 6.44 (d, *J* = 15.6 Hz, 1H), 4.37 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.01 (s, 3H), 1.95 – 1.85 (m, 3H), 1.69 – 1.61 (m, 3H), 1.51 – 1.42 (m, 2H), 1.24 (d, *J* = 4.8 Hz, 1H), 1.19 (dd, *J* = 13.5, 4.7 Hz, 1H), 1.04 (s, 3H), 1.02 (s, 3H), 0.99 (dd, *J* = 9.3, 3.1 Hz, 1H), 0.90 (s, 3H), 0.80 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 162.2, 154.8, 153.0, 147.6, 135.2, 133.5, 131.5, 130.8 (d, *J* = 8.4 Hz), 122.6 (d, *J* = 2.9 Hz), 121.5, 115.0 (d, *J* = 21.1 Hz), 113.9 (d, *J* = 22.1 Hz), 90.6, 63.1, 54.3, 39.0, 38.9, 38.5, 37.4, 36.1, 31.2, 28.5, 25.5, 21.6, 21.5, 16.6, 15.4. ESI-HRMS (*m/z*): calcd for $C_{28}H_{37}FNO_3S$ $[M + H]^+$, 486.2433; found, 486.2474.

(2R,4aS,5S,6R,8aS)-5-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-1,1,4a,6-tetramethyldecahydronaphthalen-2-yl acetate (40b). The general procedure for the synthesis of **40b** was similar to that used for **23** and resulted in a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.2 Hz, 1H), 7.79 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.43 (td, *J* = 7.9, 5.9 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.12 – 7.03 (m, 1H), 6.60 (dd, *J* = 15.6, 10.0 Hz, 1H), 6.43 (d, *J* = 15.6 Hz, 1H), 4.51 (dd, *J* = 10.6, 5.3 Hz, 1H), 2.04 (s, 3H), 1.90 (ddd, *J* = 12.1, 6.3, 3.1 Hz, 1H), 1.75 – 1.56 (m, 5H), 1.52 – 1.38 (m, 2H), 1.29 – 1.16 (m, 2H), 1.01 (s, 3H), 1.00

– 0.96 (m, 1H), 0.89 (s, 3H), 0.88 (s, 3H), 0.80 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 163.4 (d, J = 246.5 Hz), 155.1, 147.8, 140.1 (d, J = 7.5 Hz), 136.9, 135.0, 133.4, 131.5, 130.8 (d, J = 8.4 Hz), 122.6 (d, J = 2.8 Hz), 121.4, 114.9 (d, J = 21.1 Hz), 113.9 (d, J = 22.2 Hz), 81.1, 63.2, 54.1, 38.5, 38.1, 37.6, 36.2, 31.2, 28.3, 23.9, 21.6, 21.5, 16.9, 15.5. ESI-HRMS (*m/z*): calcd for $C_{29}H_{37}FNO_2$ $[M + H]^+$, 450.2764; found, 450.2801.

(2R,4aS,5S,6R,8aS)-5-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-1,1,4a,6-tetramethyldecahydronaphthalen-2-yl carbamate (40c). The general procedure for the synthesis of **40c** was similar to that used for **24** as a white solid, mp 89-91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 2.2 Hz, 1H), 7.79 (dd, J = 8.1, 1.6 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.07 (td, J = 8.1, 2.0 Hz, 1H), 6.60 (dd, J = 15.5, 10.0 Hz, 1H), 6.43 (d, J = 15.6 Hz, 1H), 4.62 (s, 2H), 4.39 (dd, J = 11.5, 4.6 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.74 – 1.57 (m, 5H), 1.44 (ddd, J = 16.5, 15.1, 7.0 Hz, 2H), 1.28 – 1.15 (m, 2H), 1.00 (s, 3H), 0.99 – 0.96 (m, 1H), 0.93 (s, 3H), 0.86 (s, 3H), 0.80 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ163.4 (d, J = 246.4 Hz), 157.2, 155.2, 147.9, 140.2, 136.9, 135.0, 133.4, 131.5, 130.7 (d, J = 8.5 Hz), 122.6 (d, J = 2.8 Hz), 121.4, 114.9 (d, J = 21.1 Hz), 113.9 (d, J = 22.2 Hz), 81.9, 63.2, 54.2, 38.5, 38.3, 37.6, 36.2, 31.3, 28.3, 24.2, 21.6, 21.5, 16.9, 15.5. ESI-HRMS (*m/z*): calcd for $C_{28}H_{36}FN_2O_2$ $[M + H]^+$, 451.2716; found, 451.2767.

(2R,4aS,5S,6S,8aS)-5-((E)-2-(5-(3-Fluorophenyl)pyridin-2-yl)vinyl)-1,1,4a,6-tetramethyldecahydronaphthalen-2-yl butyrate (40d). The general procedure for the

synthesis of **40d** was similar to that used for **25** and resulted in a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.82 (d, J = 5.8 Hz, 1H), 7.43 (dd, J = 14.0, 7.8 Hz, 1H), 7.34 (dd, J = 16.2, 7.7 Hz, 2H), 7.28 – 7.26 (m, 1H), 7.12 – 7.04 (m, 1H), 6.64 (s, 1H), 6.45 (d, J = 15.5 Hz, 1H), 4.53 (dd, J = 11.1, 4.7 Hz, 1H), 2.28 (t, J = 7.4 Hz, 2H), 2.01 (dd, J = 12.5, 6.6 Hz, 1H), 1.91 (dd, J = 13.3, 3.0 Hz, 1H), 1.69 – 1.63 (m, 4H), 1.52 – 1.41 (m, 3H), 1.35 – 1.30 (m, 2H), 1.21 (dd, J = 13.8, 4.5 Hz, 1H), 1.02 (s, 3H), 1.01 – 0.97 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H), 0.89 (s, 3H), 0.88 (s, 3H), 0.80 (d, J = 6.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.6, 164.2, 162.6, 159.0, 131.1, 130.9, 130.1, 122.7, 121.6, 114.0, 113.8, 80.7, 63.3, 54.2, 38.5, 38.2, 37.6, 36.9, 36.2, 31.3, 28.4, 24.0, 21.6, 21.5, 18.8, 17.0, 15.5, 13.9. ESI-HRMS (*m/z*): calcd for $C_{31}H_{41}FNO_2$ $[M + H]^+$, 478.3077; found, 478.3037.

Ethyl((2R,4aS,5S,6S,8aS)-5-((E)-2-(5-(3-fluorophenyl)pyridin-2-yl)vinyl)-1,1,4a ,6-tetramethyldecahydronaphthalen-2-yl) carbonate (40e). Compound **39** (28 mg, 0.07 mM) was dissolved in dry CH_2Cl_2 (3 mL), to which ethyl chloroformate (14 μL, 0.14 mM), triethylamine (15 μL, 0.10 mM) and DMAP (2 mg, 0.014 mM) were added. The reaction mixture was stirred overnight at room temperature. After this time, the reaction was quenched with water and then CH_2Cl_2 (20 mL) was poured into the mixture, which was subsequently washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give compound **40e** (2.7 mg, 8 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.1 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.43 (td, *J* = 7.9, 6.0 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 7.08 (td, *J* = 8.4, 1.8 Hz, 1H),

6.72 – 6.54 (m, 1H), 6.45 (d, *J* = 15.6 Hz, 1H), 4.36 (dd, *J* = 11.1, 5.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.27 – 2.19 (m, 2H), 2.02 (d, *J* = 6.6 Hz, 1H), 1.99 (d, *J* = 6.4 Hz, 1H), 1.91 (dd, *J* = 13.1, 3.0 Hz, 1H), 1.73 – 1.67 (m, 2H), 1.52 – 1.40 (m, 3H), 1.20 (dd, *J* = 13.6, 3.8 Hz, 1H), 1.02 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.6, 162.6, 155.4, 130.1, 130.0, 122.7, 114.0, 113.8, 85.2, 63.8, 54.1, 38.5, 38.4, 37.6, 36.2, 36.1, 31.2, 28.3, 23.9, 21.6, 21.4, 16.8, 15.5, 14.5. ESI-HRMS (*m/z*): calcd for $C_{30}H_{39}FNO_3$ $[M + H]^+$, 480.2869; found, 480.2828.

5-(3-Fluorophenyl)-2-((E)-2-((1S,2S,4aR,8aS)-2,5,5,8a-tetramethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-yl)vinyl)pyridine (41). Compound **40a** (50 mg, 0.11 mM) was dissolved in anhydrous DMF (3 mL), and the mixture was stirred at 80 °C overnight. After TLC analysis had indicated the consumption of starting material, the reaction was quenched with water. Then CH_2Cl_2 (20 mL) was poured into the mixture, which was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromotography to give compound **41** (40 mg, 99 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 1.7 Hz, 1H), 7.80 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.43 (td, *J* = 7.9, 6.0 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.30 – 7.24 (m, 1H), 7.08 (ddd, *J* = 8.2, 2.5, 1.7 Hz, 1H), 6.64 (dd, *J* = 15.7, 9.9 Hz, 1H), 6.47 (t, *J* = 14.0 Hz, 1H), 5.42 (ddd, *J* = 10.0, 5.5, 2.0 Hz, 1H), 5.36 (dd, *J* = 10.1, 2.1 Hz, 1H), 1.94 – 1.86 (m, 1H), 1.83 (d, *J* = 5.6 Hz, 1H), 1.72 – 1.68 (m, 1H), 1.68 – 1.62 (m, 1H), 1.59 – 1.53 (m, 1H), 1.51 – 1.45 (m, 1H), 1.30 – 1.26 (m, 1H), 1.11 (d, *J* = 7.2 Hz, 1H), 1.09 – 1.04 (m, 1H), 0.99 (s, 3H), 0.98 (s, 3H),

0.90 (s, 3H), 0.81 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 162.2, 155.4, 147.8, 138.0, 137.4, 134.9, 133.3, 131.3, 130.8, 130.7, 122.6, 122.6, 121.5, 121.1, 115.0, 114.7, 114.0, 113.8, 106.3, 62.2, 51.0, 40.3, 36.9, 36.2, 35.0, 31.9, 31.7, 23.5, 23.0, 21.7, 15.1. ESI-HRMS (*m/z*): calcd for $C_{27}H_{33}FN$ $[M + H]^+$, 390.2552; found, 390.2595.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures; spectral data for compounds; biological evaluation assay; crystallographic data; molecular formula strings (CSV).

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

PAR1, protease activated receptor-1; FLIPR, fluorometric imaging plate reader; PPTS,

pyridinium *p*-toluenesulfonate; SAR, structure-activity relationship; EIC, extracted ion chromatograms; DMPK, drug metabolism and pharmacokinetic; GOLD, genetic optimization for ligand docking; DCC, 1,3-dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; Tempo, tetramethylpiperdinyloxy free radical; TBAI, tetrabutylammonium iodide; NCS, N-chlorosuccinimide; *m*-CPBA, 3-chloroperbenzoic acid.

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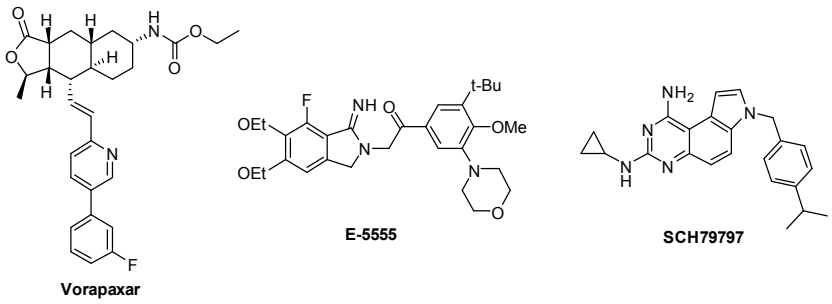


Figure 1. Structures of reported PAR1 antagonists.

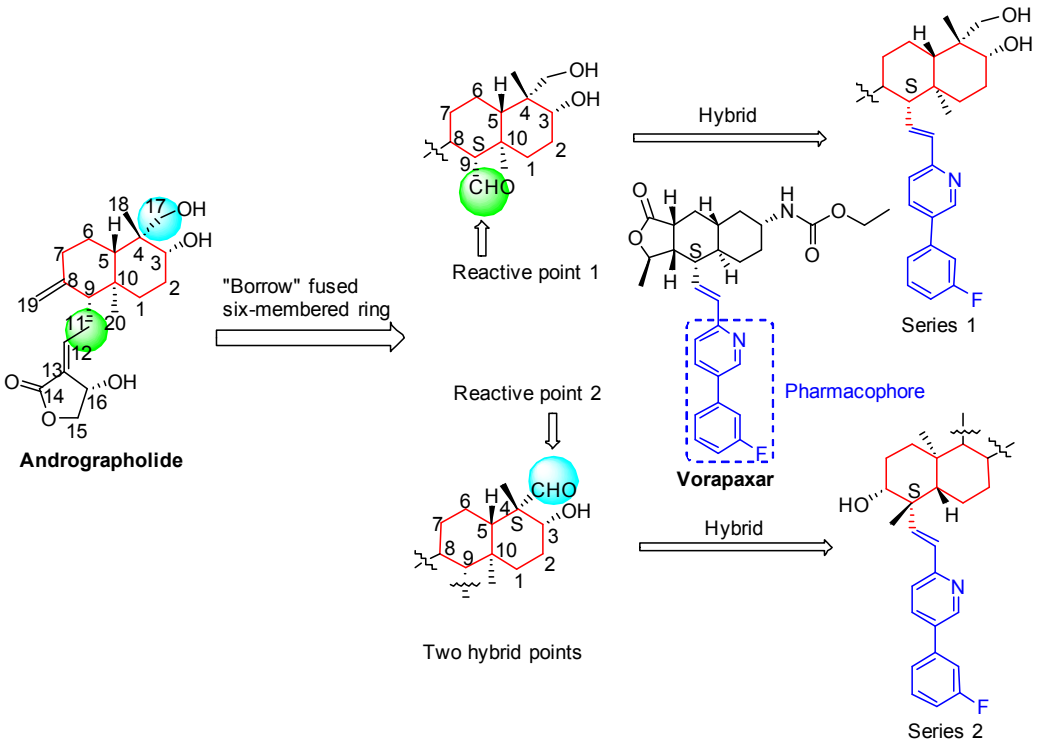
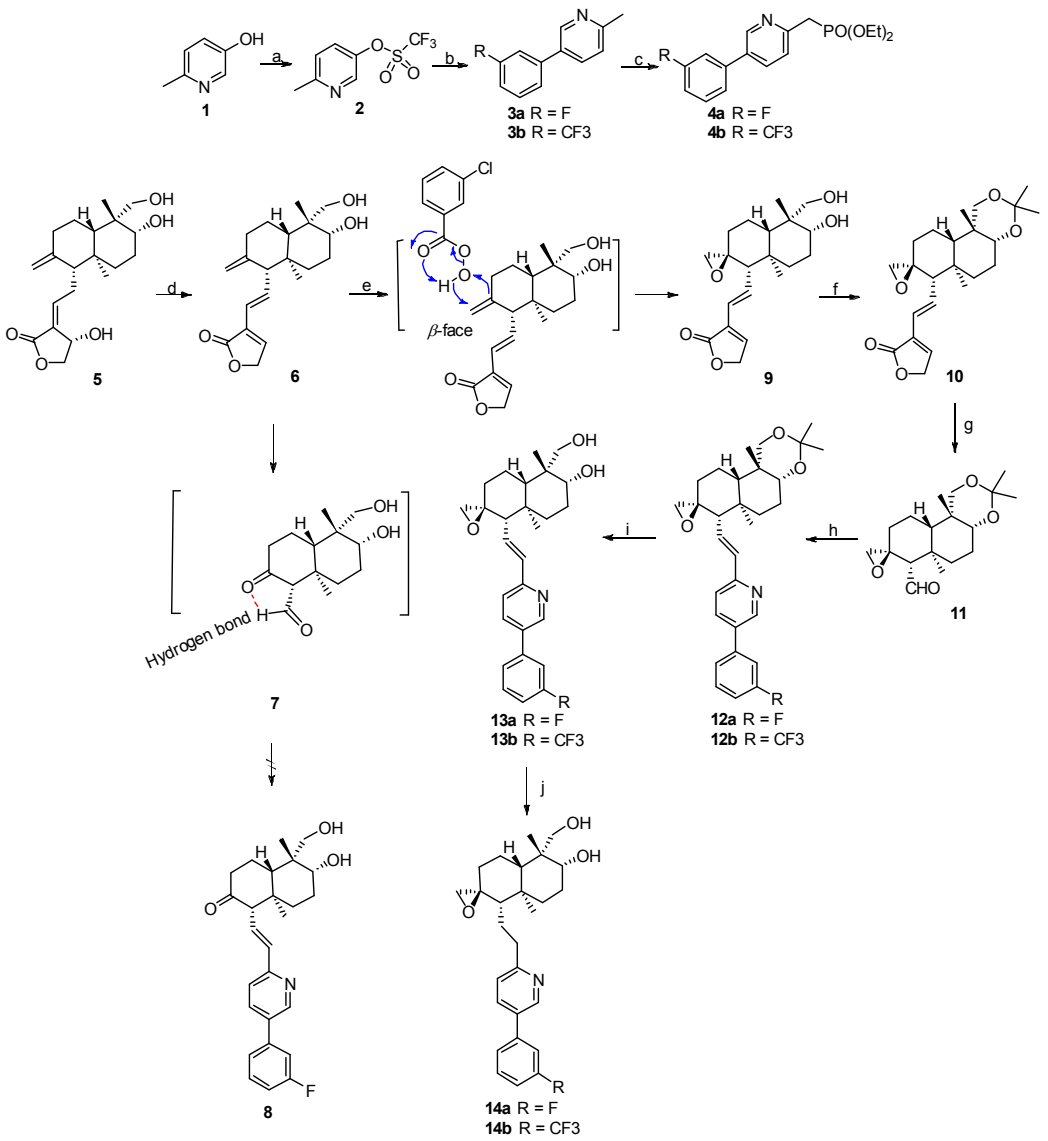


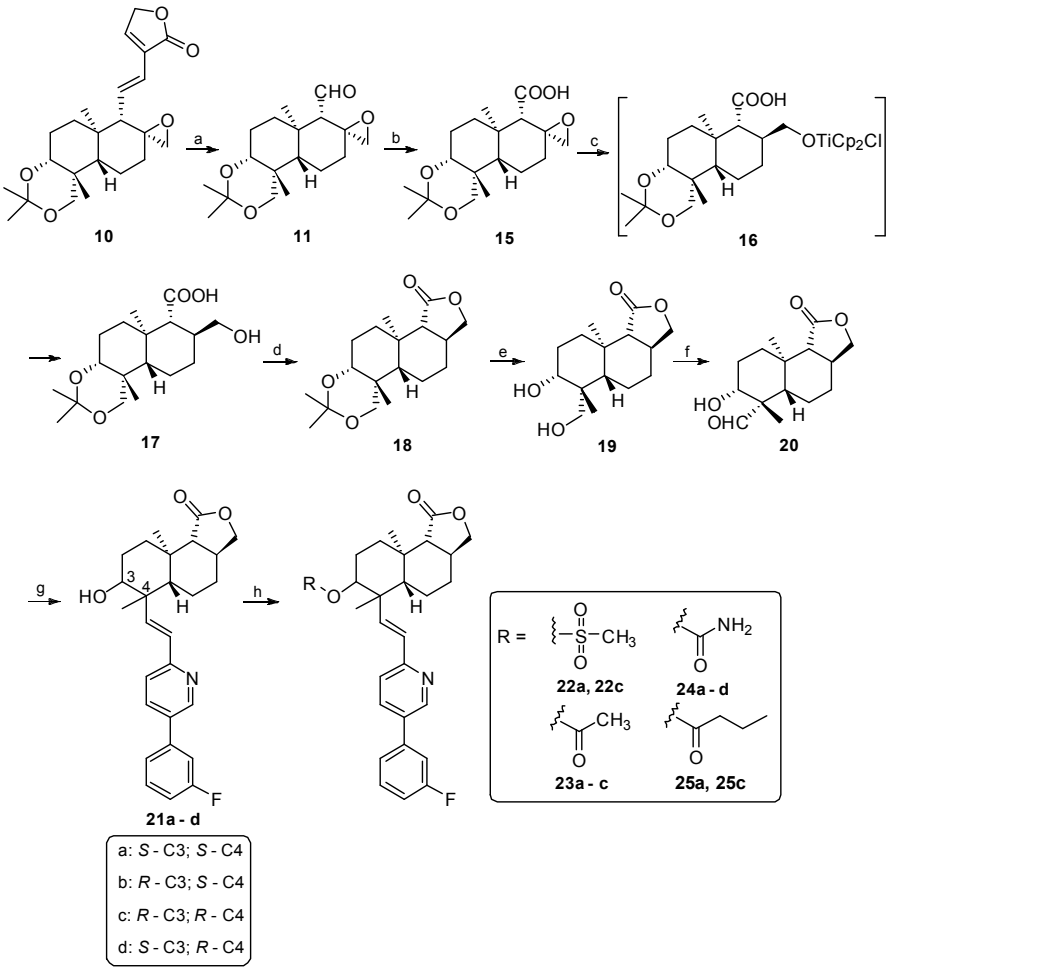
Figure 2. Design strategy for novel PAR1 antagonists.

Scheme 1. General procedure for synthesis of hybrid **13a** and its derivatives **12**, **14**.[a]



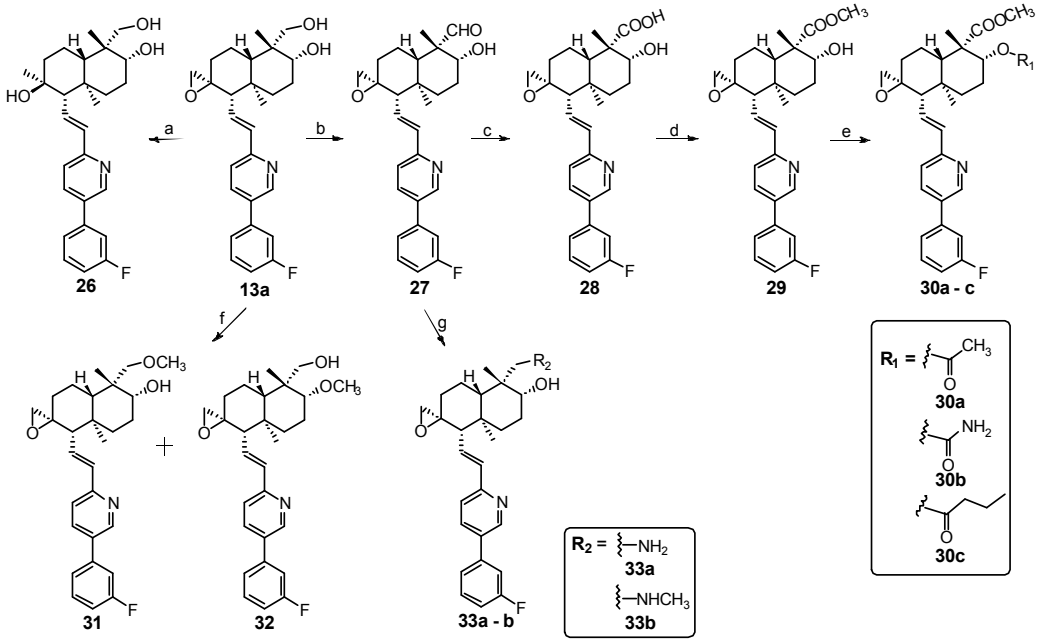
[a]Reagents and conditions: (a) Tf_2O, Pyridine; (b) $ArB(OH)_2$, EtOH, H_2O, $Pd(Ph_3P)_4$, Toluene; (c) Diisopropylamine, BuLi, $(EtO)_2POCl$; (d) Al_2O_3, Pyridine; (e) K_2CO_3, *m*-CPBA, DCM; (f) Dimethoxypropane, PPTS, CH_2Cl_2; (g) O_3, Me_2S; (h) BuLi, THF; (i) Amberlyst 15, MeOH; (j) Titanocene dichloride, Mn, THF, H_2O.

Scheme 2. General procedure for synthesis of hybrid **21** and the derivatives **22**-**25**. [a]



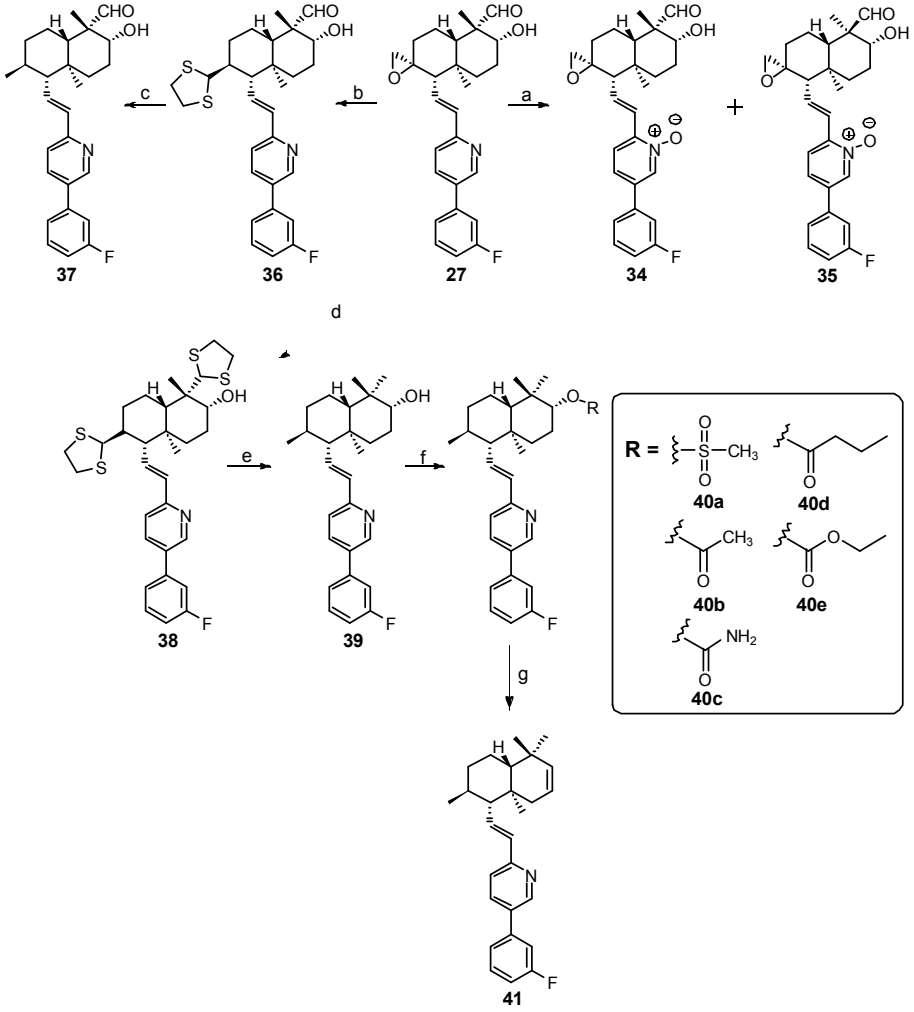
[a]Reagents and conditions: (a) O_3, Me_2S; (b) 2-Methylbutane, tert-Butanol, THF, $NaClO_2$-NaH_2PO_4; (c) Titanocene dichloride, Mn, THF, H_2O; (d) DCC, DMAP, 1,4-Dioxane; (e) Amberlyst 15, MeOH; (f) Tempo, TBAI, NCS, K_2CO_3-$NaHCO_3$, CH_2Cl_2; (g) BuLi, THF; (h) DMAP, CH_2Cl_2.

Scheme 3. General procedure for synthesis of compound **29** and the derivatives **26**-**28**, **30**-**33**. [a]



[a]Reagents and conditions: (a) $LiAlH_4$, Et_2O; (b) Tempo, TBAI, NCS, K_2CO_3-$NaHCO_3$, CH_2Cl_2; (c) 2-Methylbutane, tert-Butanol, THF, $NaClO_2$-NaH_2PO_4; (d) K_2CO_3, CH_3I, DMF; (e) DMAP, CH_2Cl_2; (f) NaH, CH_3I, THF; (g) Amine, $NaBHCN_3$, CH_3OH.

Scheme 4. General procedure for synthesis of compound **39** and the derivatives **34-38**, **40**, **41**. [a]



[a]Reagents and conditions: (a) 1) *m*-CPBA, NaH_2PO_4, CH_2Cl_2; 2) K_2CO_3-CH_3OH; (b) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$; CH_2Cl_2; (c) Raney Nickel, Acetone; (d) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$; CH_2Cl_2; (e) Raney Nickel, Acetone; (f) DMAP, CH_2Cl_2; (g) DMF, 80 °C.

Table 1. Inhibitory effect of compounds on the recombinant stable cell line HEK293-Gα15-PAR1.[a]

Compd	IC_{50}	Compd	IC_{50}	Compd	IC_{50}
Vorapaxar[b]	0.064 ± 0.013	**23c**	> 100	**32**	14 ± 3.0
12a	> 100	**24a**	20 ± 7.9	**33a**	23 ± 5.0
12b	> 100	**24b**	21 ± 5.8	**33b**	17 ± 6.4
13a	9.1 ± 1.6	**24c**	12 ± 3.2	**34**	> 100
13b	9.5 ± 2.4	**24d**	> 100	**35**	> 100
14a	14 ± 3.3	**25a**	> 100	**36**	> 100
14b	10 ± 1.7	**25c**	> 100	**37**	1.5 ± 0.6
21a	19 ± 3.1	**26**	55 ± 8.4	**38**	> 100
21b	> 100	**27**	3.0 ± 0.8	**39**	1.1 ± 0.4
21c	> 100	**28**	29 ± 5.6	**40a**	87 ± 7.8
21d	> 100	**29**	7.0 ± 2.3	**40b**	> 100
22a	> 100	**30a**	> 100	**40c**	32 ± 6.8
22c	> 100	**30b**	8.7 ± 2.2	**40d**	> 100
23a	> 100	**30c**	> 100	**40e**	> 100
23b	> 100	**31**	8.1 ± 1.9	**41**	> 100

[a]Results are expressed as IC_{50} values (μM), mean values based on three independent experiments, final top assay concentration is 100 μM. [b]Positive control.

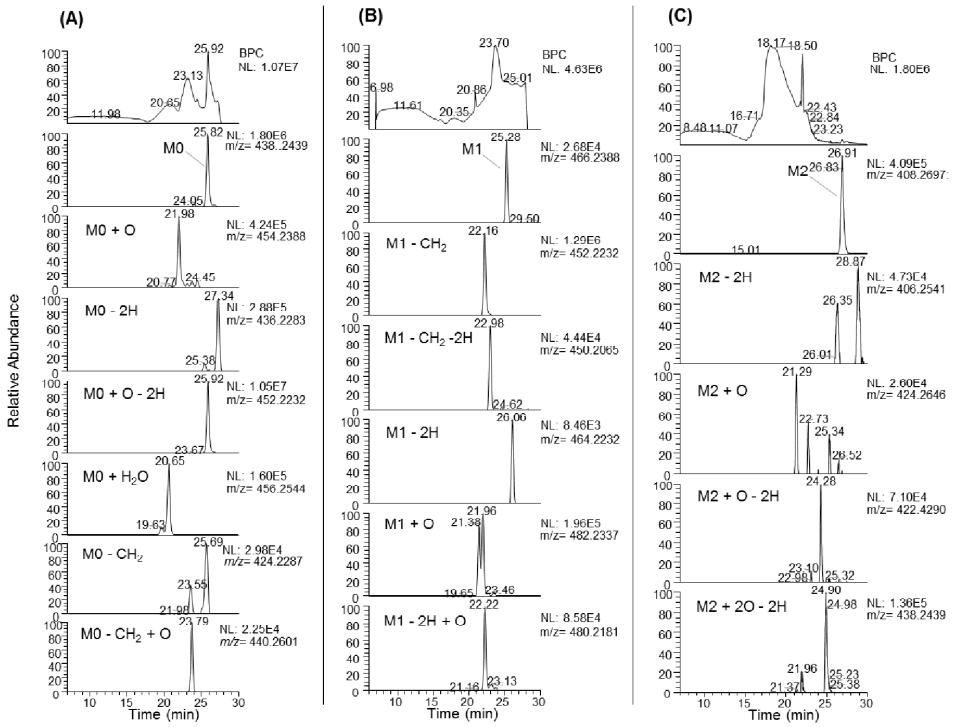


Figure 3. Representative extracted ion chromatograms (EICs) of (A) compound **13a** (M0) and its six metabolites detected in rat plasma at 3.0 h after an oral dose (10 mg/kg); (B) compound **29** (M1) and its five metabolites detected in rat plasma at 3.0 h after an oral dose (10 mg/kg); (C) compound **39** (M2) and its four metabolites detected in rat plasma at 3.0 h after an oral dose (5 mg/kg).

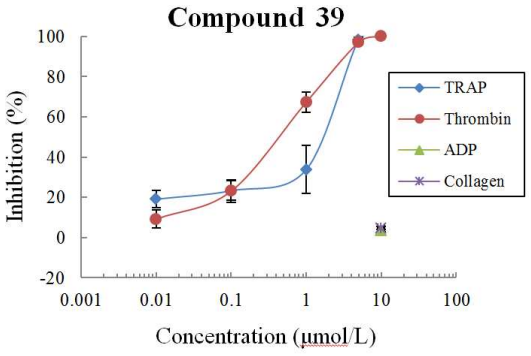


Figure 4. Inhibition of platelet aggregation *in vitro*. Effects of **39** on human platelet aggregation induced by 0.5 U/mL thrombin, 15 μM TRAP, 10 μM ADP or 5 μg/mL collagen. Thrombin-induced platelet aggregation was conducted in the presence of 1 mM GPRP-NH_2 to avoid fibrin polymerization. Each agonist was tested in three separated experiments. Each value was expressed as the median values ± standard deviation (SD). Mean IC_{50} values were determined from IC_{50} values generated from independent experiments.

Table 2. Inhibitory effects of **39** on *ex vivo* platelet aggregation in the guinea pig after oral administration for 2h at 10 and 30 mg/kg. (n = 5 for each group).[a]

Inducer	% Inhibition			
	Vehicle	**39**		Vorapaxar (10 mg/kg)
		10 mg/kg	30 mg/kg	
TRAP (15 μM)	0.0 ± 5.5	87.6 ± 5.1	98.7 ± 0.1	98.3 ± 0.1
Thrombin (1 U/mL)	0.0 ± 10	66.9 ± 6.8	99.8 ± 0.1	93.4 ± 5.9
ADP (10 μM)	0.0 ± 12	6.7 ± 5.4	4.5 ± 2.0	3.0 ± 2.4
Collagen (5 μg/mL)	0.0 ± 5.6	5.5 ± 4.8	6.8 ± 2.7	0.9 ± 3.5

[a]Estimates are presented as median values ± standard deviation (SD).

Table 3. Non-compartmental analysis of the main pharmacokinetic parameters for **39** after an oral and an intravenous administration (n = 6 for each group).[a]

Parameters	Intravenous Administration (1 mg/kg)	Oral Administration (5 mg/kg)
body-weight (g)	226 ± 5.4	224 ± 6.7
$AUC_{0-\infty}$ (h·μg/L)	552 ± 119	1450 ± 799
$AUMC_{0-\infty}$	1135 ± 367	8382 ± 5439
$MRT_{0-\infty}$ (h)	2.0 ± 0.3	5.6 ± 1.5
$VRT_{0-\infty}$ (h^2)	7.6 ± 1.4	25 ± 5.3
$t_{1/2,z}$ (h)	2.0 ± 0.2	3.1 ± 0.6
T_{max} (h)	0.02	2.5 ± 0.8
CLz (L/h/kg)	1.9 ± 0.5	4.5 ± 2.3
Vz (L/kg)	5.7 ± 2.1	20 ± 10
C_{max} (μg/L)	1732 ± 280	229 ± 135
F (%)[b]		52.5

[a]Estimates are presented as median values ± standard deviation (SD). [b]F (oral bioavailability) = $AUC_{0-\infty(i.g.)} \times 1/AUC_{0-\infty(i.v.)} \times 5 \times 100$ %.

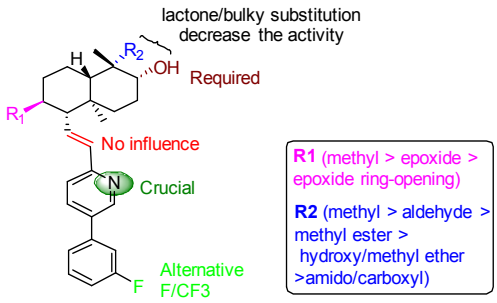


Figure 5. SAR summary of andrographolide-based derivatives.

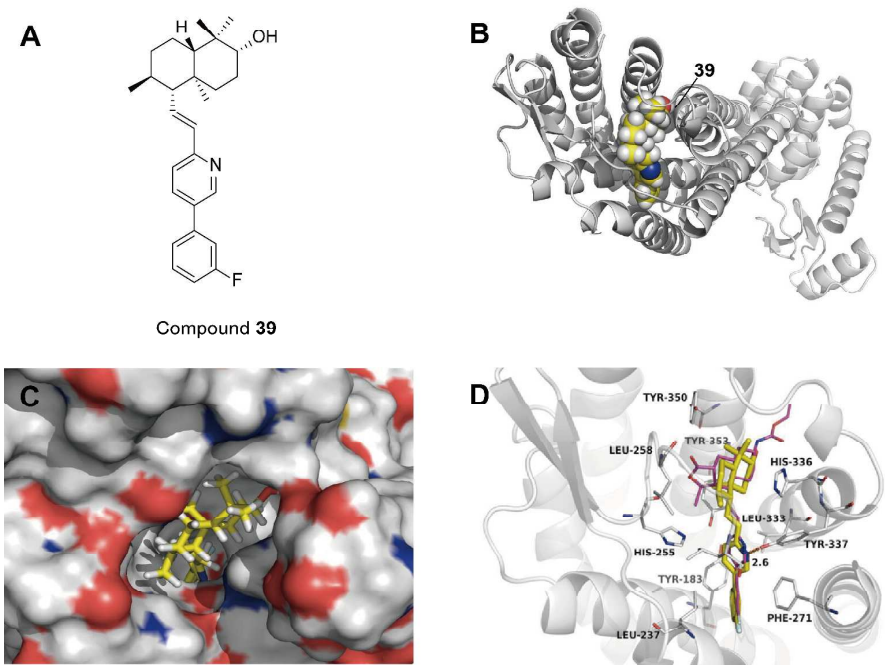


Figure 6. Molecular modeling of compound **39** with PAR1. (A) Chemical structure of compound **39**. (B) Overall view of the proposed binding mode of compound **39** with PAR1. Compound **39** is shown in a yellow sphere representation, and PAR1 is shown as a cartoon. (C) Proposed mode of compound **39** binding with PAR1 (surface). (D) Proposed mode of binding of compound **39** as a yellow stick model in the vorapaxar binding site (PDB code 3VW7). The native ligand, vorapaxar, is shown as a magenta thin stick model. Hydrogen bonds are shown as dotted orange lines, and the distance between the ligand and protein is less than 3 Å. The molecular modeling was performed using GOLD software.

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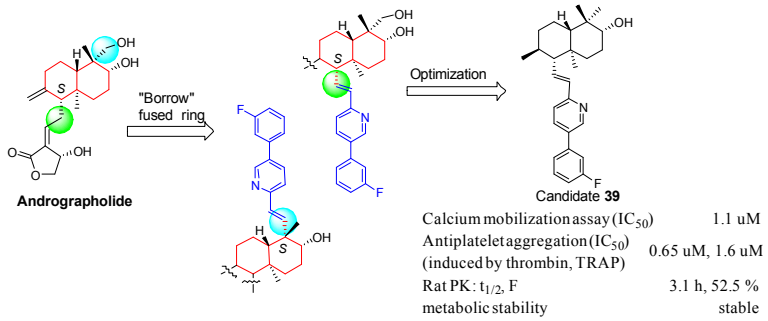

Calcium mobilization assay (IC_{50})	1.1 uM
Antiplatelet aggregation (IC_{50}) (induced by thrombin, TRAP)	0.65 uM, 1.6 uM
Rat PK: $t_{1/2}$, F	3.1 h, 52.5 %
metabolic stability	stable