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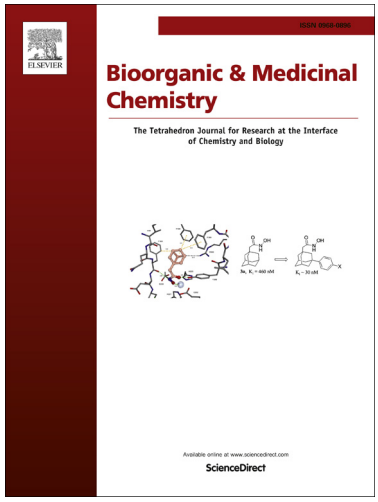

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PII: S0968-0896(14)00185-0
DOI: http://dx.doi.org/10.1016/j.bmc.2014.03.012
Reference: BMC 11459

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 20 January 2014
Revised Date: 7 March 2014
Accepted Date: 8 March 2014

Please cite this article as: Thuaud, F., Kojima, S., Hirai, G., Oonuma, K., Tsuchiya, A., Uchida, T., Tsuchimoto, T., Sodeoka, M., RE12 derivatives displaying *Vaccinia* H1-related phosphatase (VHR) inhibition in the presence of detergent and their anti-proliferative activity against HeLa cells, *Bioorganic & Medicinal Chemistry* (2014), doi: http://dx.doi.org/10.1016/j.bmc.2014.03.012

Graphical Abstract

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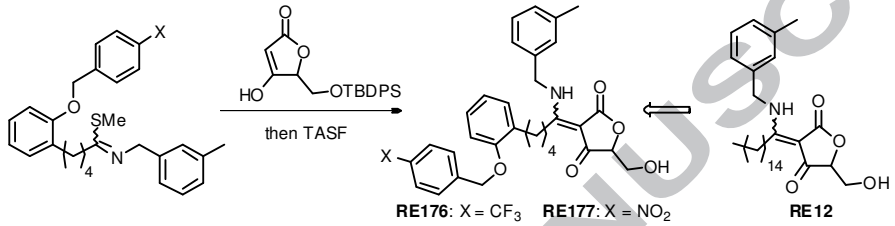

Bioorganic & Medicinal Chemistry
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Protein Phosphatase
Inhibitor
Enamine
Thioimidate
Detergent

ABSTRACT

New derivatives of *Vaccinia* H1-related phosphatase (VHR) inhibitor RE12 (**5**) were designed by replacing the long straight alkyl chain with other hydrophobic functionalities containing two aromatic rings, with the aim of obtaining potent, cell-active inhibitors. We established a direct coupling reaction between tetronic acid derivative and thioimidate to prepare the RE derivatives **6a~6i** efficiently. These compounds all showed VHR-inhibitory activity in the presence of 0.001% NP-40, whereas RE12 (**5**) was inactive under this condition, even at 100 μM. Further structure-activity studies focused on terminal substitution afforded trifluoromethyl derivative **6k** (RE176) and nitro derivative **6l** (RE177). The IC_{50} value of **6l** in the presence of NP-40 was almost equivalent to that of RE12 (**5**) in its absence. Compound **6k** (RE176) potently inhibited proliferation of HeLa cells.

1. Introduction

Protein phosphorylation is one of the most important post-translational modifications and has a key role in regulating cell growth and intracellular signaling pathways.[1] The activities of protein kinases and protein phosphatases (PPases) dynamically control the balance of phosphorylated and non-phosphorylated proteins in cells. Consequently, protein kinase inhibitors have been developed as therapeutic drug candidates.[2] On the other hand, PPases have been classified into protein serine/threonine phosphatases[3] (PPs) and protein tyrosine phosphatases (PTPs) on the basis of structure and substrate specificity.[4] Dual-specificity protein phosphatases (DSPs), which possess a similar active-site sequence and similar dephosphorylation mechanism to PTPs, can hydrolyze phosphate ester on both a tyrosine residue and either a serine or threonine residue located in the same protein.[5] *Vaccinia* H1-related phosphatase, VHR, is a member of the DSP family, and dephosphorylates mitogen-activated protein kinases (MAP kinases), extracellular signal-regulated kinases ERK1/2 and c-Jun N-terminal kinases JNK1/2.[6] Dephosphorylation of these MAP kinases by VHR, MAP kinase phosphatases (MKPs), or other atypical DSPs results in their inactivation. Although expression of VHR protein is not induced in response to activation of MAP kinases, unlike many MKPs, it was reported that the VHR protein level changes during cell cycle progression. In cells lacking VHR, cell cycle progression is blocked at the G1/S and G2/M transitions.[7] Moreover, protein levels of VHR were found to be upregulated in several cervical cancer cell lines, including human papillomavirus (HPV)-positive cell lines CaSki, HeLa, and SiHa, as well as HPV-negative cell lines HT3 and C33.[8] These findings suggested that small-molecular inhibitors of VHR would be not only novel drug candidates for cancer therapy, but also valuable tools to investigate the roles of VHR in cervical cancer cells and in cell cycle progression. However, creation of selective inhibitors of VHR is a demanding task because of the structural similarity of the active site residues among DSPs. Moreover, the active site of VHR has a shallower pocket compared to that of PTPs,[9] and this contributes to the difficulty.

Nevertheless, several VHR inhibitors have been found by screening of natural products or chemical libraries.[10] Among them, SA1 (**1**), which was reported by Tautz and co-workers, is one of the most potent, having an IC_{50} value of 18 nM (Figure 1).[11] Tautz *et al.* also reported that SA1 (**1**) and related molecule

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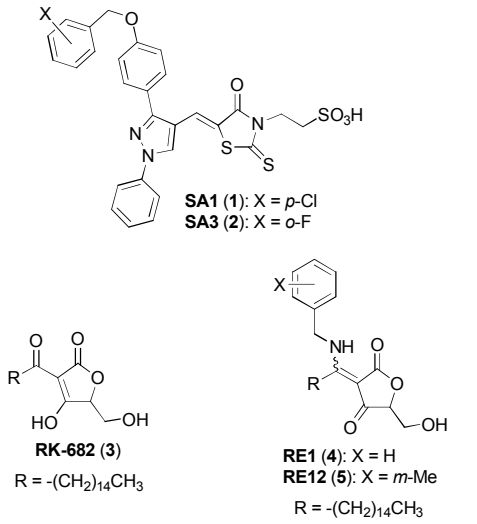


Figure 1. Structures of VHR inhibitors (**1**~**5**).

SA3 (**2**) inhibited proliferation of cervical cancer cells such as HeLa and CaSki. However, much higher concentrations of **1** or **2** compared to their IC_{50} values for VHR-inhibitory activity *in vitro* were required (approximately 50% inhibition of proliferation of HeLa cells by 20 μM **2**). Development of **2** led to the first crystallographic analysis of VHR protein bound with a small-molecular inhibitor. Compounds **1** and **2** possess a sulfonic acid moiety that interacts in a substrate (phosphate)-mimicking maner with the active site of VHR. Despite this role of sulfonic acid, its ionic nature at physiological *p*H may be unfavorable from the viewpoint of cell permeability, resulting the poor activity at the cell level. Other VHR inhibitors have similar problems. RK-682[12] (**3**) and its derivatives,[13] which possess a highly acidic 3-acyltetronic acid structure, showed potent inhibitory activity towards several PTPs and DSPs. However, again **3** was less effective at the cell level.[14] Thus, development of neutral derivatives is expected to be a fruitful approach developing cell-active VHR inhibitors.

Our previous investigations revealed that transformation of the 3-acyltetronic acid core structure of RK-682 (**3**) to the polarized but neutral enamine core structure (RE derivative) improved the cell permeability with retention of the VHR-inhibitory activity.[15] Namely, enamine derivatives RE1 (**4**) and RE12 (**5**) inhibited VHR activity *in vitro* and arrested cell cycle progression of NIH3T3 cells at the G1 phase. In addition, **4** and **5** inhibited dephosphorylation of ERKs and JNK1 in serum-stimulated NIH3T3 cells. In contrast, the parent compound **3** did not affect either cell cycle progression or dephosphorylation of MAP kinases. Moreover, **5** is highly selective for VHR, and it did not inhibit other PTPs and DSPs, such as CDC25s and several MKPs. However, there is still a room for improvement of the inhibitory activity at the cell level, because the cell cycle-arresting activity and inhibition of dephosphorylation of MAP kinases by **5** (50 μM) were only moderate. It is also noteworthy that the inhibitory activity in *in vitro* enzyme assay was reduced in the presence of detergent.[16] Although the molecular mechanisms of the reduced potency in the presence of detergent as well as in cells are not clear,[17-20] we speculate that the long hydrophobic alkyl chain in **4** or **5** might be a contributory factor. The long alkyl chain could contribute to poor solubility in aqueous media and non-specific hydrophobic interactions with unrelated proteins in cells. However, simple replacement of the long alkyl of **4** with a shorter one caused a drastic decrease of the VHR-inhibitory potency, suggesting the importance of hydrophobic interaction with VHR. Therefore, we envisioned that the inhibitory activity in the presence of detergent and at the cell level might be improved by replacement of the long alkyl chain with other hydrophobic substituents. Here we report the development of advanced derivatives of the previously reported VHR inhibitors.

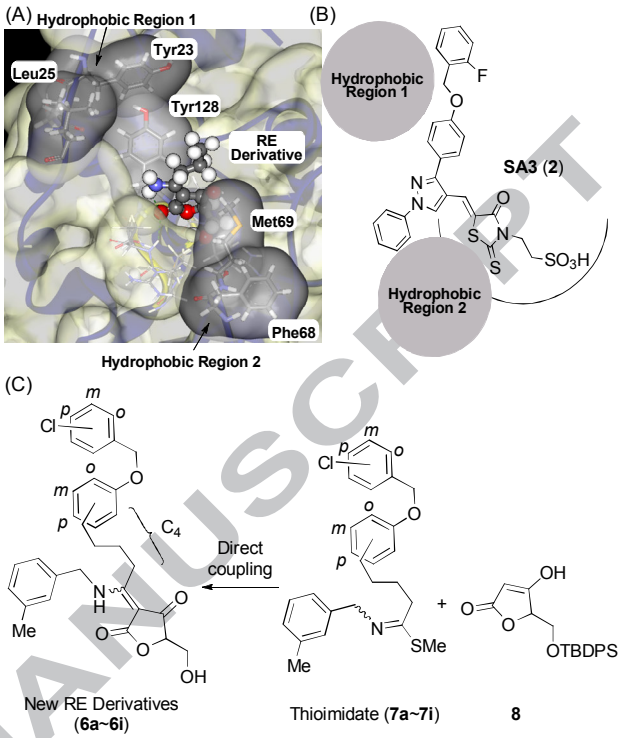
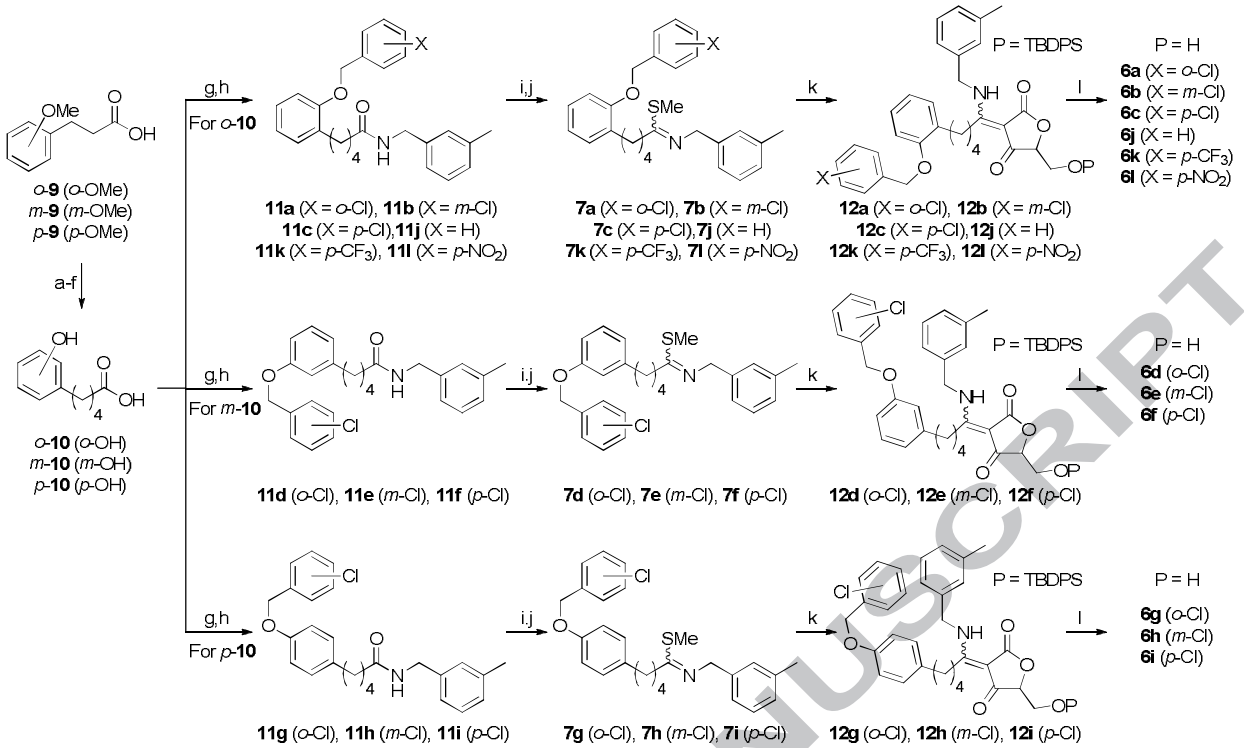


Figure 2. Design of new RE derivatives. (A) Molecular modeling of a short alkyl chain analogue of RE1 (**4**) without the benzyl group on nitrogen (ball-and-stick model) bound with VHR; (B) Schematic representation of the reported binding model of **2** with VHR; (C) Structure and synthetic plan of the new RE derivatives **6a~6i**.

2. Results and Discussion

2.1. Design and Synthetic Plan of New RE derivatives

We previously reported a binding model of RE derivatives with VHR,[15] which was constructed using Discovery Studio 1.1 and 1.2 (Accelrys, Figure 2A). The model with the *Z*-isomer of the RE derivative suggested that the long hydrophobic alkyl chain interacted with hydrophobic amino acid residues such as Tyr 23 and Leu 25 (hydrophobic region 1). We expected that it would be possible to replace a portion of the straight alkyl chain of **5** with less lipophilic aromatic substituents while retaining high affinity for VHR. The reported binding model constructed based on the crystal structure of VHR-**2** complex suggested that the *o*-fluorobenzyl phenyl ether moiety of **2** could interact with hydrophobic region 1 (Figure 2B). Since **1** was reported to show more potent inhibition than **2**, we decided to incorporate a cholorobenzyl phenyl ether moiety at the end of the alkyl chain. Another point to be considered was the length of the alkyl chain serving as a linker between the enamine core structure and the chlorobenzyl phenyl ether moiety. Eventually, we designed compounds **6** with a C4 linker (Figure 2C), which appeared to be suitable as judged from the binding model (Figure 2A). The substitution pattern of the benzyl ether and chloride on the terminal aromatic ring are expected to influence the interaction with hydrophobic amino acids. Thus we envisioned the synthesis and evaluation of all possible structural isomers of **6** (**6a~6i**). The ClogP value of the new RE derivatives **6** (6.65) indicated a moderate lipophilicity, lower than that of the parent compound **5** (ClogP of **5**: 8.65). We anticipated that the replacement of the



Scheme 1. Synthesis of new RE derivatives. Reagents and conditions: a) H_2SO_4, MeOH, reflux (*ortho*: 2.5 h, 97%, *meta*: 1 h, 96%, *para*: 3.5 h, 89%); b) DIBAL-H, THF, -78 °C (*ortho*: 3.5 h, 89%, *meta*: 1 h, quant., *para*: 2.5 h, quant.); c) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 30 min, then Et_3N, rt (*ortho*: 2.5 h, 95%, *meta*: 20 min, 90%, *para*: 20 min 95%); d) $MeOCOCH{=}PPh_3$, toluene, reflux (*ortho*: 10 min, 86%, *meta*: 20 min, 86%, *para*: 20 min, 95%); e) H_2 (balloon), Pd/C, EtOH, rt (*ortho*: 9 h, 98%, *meta*: 14 h, quant., *para*: 10 h, 99%); f) HBr, CH_3COOH, reflux (*ortho*: 26 h, 66%, *meta*: 44 h, 76%, *para*: 3 h, 50%); g) *m*-methylbenzylamine, EDC·HCl, DMAP, DMF, rt (for *o*-**10**: 7.5 h, 99%, for *m*-**10**: 11 h, 85%, for *p*-**10**: 8 h, quant.); h) *o*-chlorobenzyl bromide, *m*-chlorobenzyl bromide, *p*-chlorobenzyl bromide, benzyl bromide, *p*-trifluoromethylbenzyl bromide, or *p*-nitrobenzyl bromide, NaH, THF:DMF (5:1), rt (**11a**: 10 min, 87%, **11b**: 1.2 h, 75%, **11c**: 5 min, 84%, **11d**: 42 min, 44%, **11e**: 1 h, 41%, **11f**: 43 min, 52%, **11g**: 15 min, 74%, **11h**: 10 min, 84%, **11i**: 15 min, 75%, **11j**: 1 h, 74%, **11k**: 10 min, 94%, **11l**: 3 min, 85%); i) Lawesson's reagent, THF, reflux (for **11a**: 50 min, 93%, for **11b**: 30 min, 91%, for **11c**: 30 min, 87%, for **11d**: 15 min, quant., for **11e**: 15 min, 87%, for **11f**: 12 min, 91%, for **11g**: 20 min, 93%, for **11h**: 15 min, 98%, for **11i**: 2 min, 87%, for **11j**: 15 min, 96%, for **11k**: 22 min, 97%, for **11l**: 10 min, 99%); j) MeI, K_2CO_3, acetone, rt (**7a**: 15 h, 87%, **7b**: 9 h, 78%, **7c**: 12 h, 72%, **7d**: 5 h, 84%, **7e**: 7.5 h, 98%, **7f**: 6.5 h, quant., **7g**: 7 h, 88%, **7h**: 6 h, 65%, **7i**: 6 h, 77%, **7j**: 19 h, 64%, **7k**: 19 h, 82%, **7l**: 22 h, 91%); k) **8,** thioimidate **7** (1.4 equiv.), MS4A, CH_2Cl_2, rt, (**12a**: 30 h, 65%, **12b**: 30 h, 53%, **12c**: 30 h, 53%, **12d**: 24 h, 87%, **12e**: 48 h, 50%, **12f**: 32 h, 67%, **12g**: 30 h, 66%, **12h**: 30 h, 73%, **12i**: 31 h, 80%, **12j**: 20 h, 59%, **12k**: 20 h, 61%, **12l**: 20 h, 55%); l) $[(Me_2N)_3S]^+[F_2SiMe_3]^-$ (TASF), DMF, 0 °C (**6a**: 3.5 h, 61%, **6b**: 3.5 h, 58%, **6c**: 3.5 h, 62%, **6d**: 5 h, 67%, **6e**: 5 h, 61%, **6f**: 5 h, 72%, **6g**: 29 h, 70%, **6h**: 4.5 h, 64%, **6i**: 4.5 h, 70%, **6j**: 6 h, 78%, **6k**: 6 h, 72%, **6l**: 6 h, 82%).

substituent would maintain the hydrophobic interaction with the VHR surface and improve the inhibitory activity in the presence of detergent.

To synthesize **6a~6i** efficiently, we planned to establish a new synthetic route to RE derivatives with a variety of side chains. It was reported that enamines conjugated with two carbonyl groups could be constructed by mixing thioimidates with 1,3-dicarbonyl compounds such as 1,3-cyclohexanedione derivatives or Meldrum's acid under basic conditions.[21] Therefore we envisioned that direct coupling reaction of thioimidates (**7a~7i**) with the tetronic acid derivative **8** would provide the RE derivatives with various side chains.

*2.2. Synthesis of RE Derivatives (**6a~6i**)*

Synthesis of the new RE derivatives was commenced from commercially available *o*-, *m*-, or *p*-methoxyhydrocinnamic acids (*o*-**9**, *m*-**9**, and *p*-**9**, scheme 1). Conversion to carboxylic acid (*o*-**10**, *m*-**10**, and *p*-**10**) of methoxyhydrocinnamic acids **9** was achieved via a conventional 6-step sequence: methyl esterification, reduction to alcohol, oxidation to aldehyde, two-carbon elongation by Wittig reaction, hydrogenation of double bond, and de-methylation of methyl ester and methyl ether. Condensation of the carboxylic acids (*o*-**10**, *m*-**10**, and *p*-**10**) with *m*-methylbenzylamine was performed with EDC·HCl and DMAP to give the corresponding amide with a free phenol moiety. Then, alkylation with *o*-, *m*-, or *p*-chlorobenzyl bromide provided the 9 structural isomers of amides **11a~11i**. Treatment of **11a~11i** with Lawesson's reagent gave the corresponding thioamides, which were converted into methyl thioimidates **7a~7i** as mixtures of geometric isomers.

With the precursors of RE derivatives in hand, coupling reactions of methyl thioimidates with tetronic acid derivative **8** protected with a *t*-butyldiphenylsilyl group (TBDPS)[15] were investigated. Several model studies indicated that the desired enamine derivatives would be formed in moderate yields simply by mixing tetronic acid and an almost equal amount of thioimidate. Addition of silver nitrate or a catalytic amount of 4-dimethylaminopyridine slightly increased the yield of enamine derivative but 4 equivalents of thioimidate was necessary, because decomposition of thioimidate occurred as a competitive reaction. Instead, addition of molecular sieves 4A (MS4A) slightly improved the chemical yields without the need for an excess of thioimidate. Therefore we decided to use this condition. All the synthesized thioimidates **7a~7i** could be converted into the corresponding enamine derivatives **12a~12i** by treatment with tetronic acid **8** in the presence of MS4A (800 wt%) in CH_2Cl_2 at

room temperature. Finally, removal of the TBDPS group was performed with $[(Me_2N)_3S]^+[F_2SiMe_3]^-$ (TASF) to give the newly designed RE derivatives **6a~6i**.

*2.3. Inhibitory Activity of RE Derivatives **5** and **6a~6i** for VHR in the presence of NP-40*

Inhibitory activities of the synthesized compounds **6a~6i** towards VHR phosphatases were evaluated *in vitro*.[15] As described above, the inhibitory activity of RE derivatives towards DSPs was decreased in the presence of NP-40. In fact, RE12 (**5**) was inactive as a VHR inhibitor in the presence of 0.001% NP-40, even at 100 μM (Table 1). In contrast, all the new compounds showed VHR-inhibitory activity under the same condition, as expected. These results strongly indicated that substitution of the long hydrophobic methylene chain in **5** by aromatic groups was a successful strategy to overcome the drawback of the original RE12 (**5**). All structural isomers **6a~6i** showed moderate inhibition of VHR, but **6g** having *para*-substitution of the internal aromatic ring and *ortho*-substitution of the terminal aromatic ring was less potent than the other derivatives. Among the synthesized compounds **6a~6i**, **6c** showed the greatest inhibitory activity, although its potency was still only moderate.

Table 1. Inhibition of VHR activity in the presence of NP-40 (0.001%) and anti-proliferative activity towards HeLa cells of RE derivatives (**6a~6l**).

Compounds	Inhibition of VHR activity: IC_{50} values (SD) [μM]	Anti-proliferative activity for HeLa cells IC_{50} Values (SD) [μM]
5[a]	1.6 (0.2)	
5	>100	ND[b]
6a	18.8 (4.2)	ND[b]
6b	16.1 (1.3)	ND[b]
6c	***14.0 (0.5)***	ND[b]
6d	17.2 (1.2)	ND[b]
6e	18.3 (0.8)	ND[b]
6f	14.7 (1.0)	ND[b]
6g	28.8 (4.0)	ND[b]
6h	18.6 (1.3)	ND[b]
6i	19.1 (0.5)	ND[b]
6j	8.2 (1.5)	10.6 (0.2)
6k	***7.7 (2.0)***	***7.8 (0.5)***
6l	***4.6 (0.9)***	ND[b]

[a]The IC_{50} value was determined in the absence of NP-40 (reported in reference 15); [b]ND: not determined.

2.4. Effect of terminal substituents on VHR-inhibitory activity

We next investigated the effect of a terminal chlorine substituent on the inhibitory activity of **6c**. First we synthesized **6j** without any functionality on the terminal aromatic ring, using the procedure described above (Scheme 1). Interestingly, the VHR-inhibitory activity of **6j** was higher than that of **6a~6c** with the same substitution pattern in the internal aromatic ring (Table 1). This result suggested that chlorine atom on terminal aromatic ring in **6a~6c** decreased the inhibitory activity. Hence, we further examined compounds **6k** (ClogP = 6.8) with a trifluoromethyl group and **6l** (ClogP = 5.7) with a nitro group at the *para*-position of the terminal aromatic ring. Since these functionalities are larger than the chlorine atom and have different electronic and hydrophobic properties, we expected to obtain information concerning the effect of terminal substituents. The trifluoromethyl and nitro groups were compatible with the same synthetic procedure, and compounds **6k** and **6l** were synthesized without difficulty (Scheme 1). Evaluation of their inhibitory activity revealed that **6k** and **6l** were more potent VHR-inhibitors than chlorine derivative **6c** or non-substituted **6j** (Table 1). In paticular, polar nitro derivative **6l** showed a comparable IC_{50} value even in the presence of NP-40 to that of RE12 (**5**) in the absence of NP-40. These results strongly supported our hypothesis that the terminal substituent contributes to the interaction with VHR. Although the inhibitory potencies of **6k** and **6l** were decreased at a higher concentration of NP-40 (0.01%), their activities at the cell level was expected to be increased due to the improvement of their properties in solution.

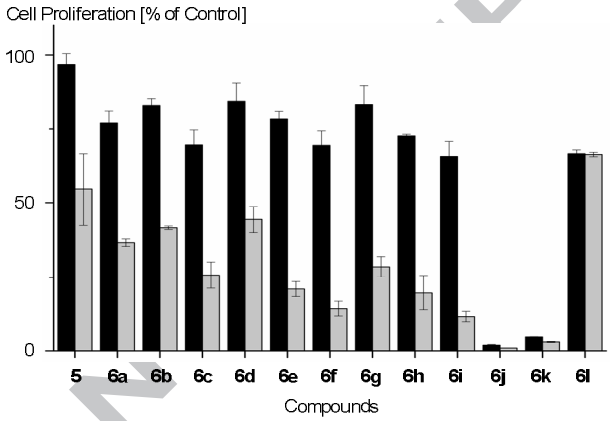


Figure 3. Anti-proliferative activity of RE derivatives (**6a~6l**) at 20 μM (black) and 30 μM (gray) against HeLa cells.

2.5. Inhibitory activity for the proliferation on HeLa cells

Since VHR is overexpressed in cervical cancer cells, VHR inhibitors might serve as anti-proliferative agents for these cell lines. Indeed, Tautz and co-workers reported that VHR inhibitors SA1 (**1**) and SA3 (**2**) inhibited the proliferation of HeLa and CaSki cells. Therefore, we evaluated the inhibitory effect of all the synthesized RE derivatives **5** and **6a~6l** on proliferation of HeLa cells. Unexpectedly, the original **5** and chloro derivatives **6a~6i** did not show significant inhibition at 20 μM though they showed moderate inhibition at 30 μM. The most potent VHR inhibitor **6l** showed weakest inhibition of HeLa cell proliferation at 30 μM. In contrast, non-substituted **6j** and trifluoromethyl derivative **6k** showed marked inhibition with IC_{50} values of 10.6 and 7.8 μM, respectively. These results indicated that replacement of the long hydrophobic alkyl chain in **5** with an aromatic substituent improved the inhibitory activity at the cell level. Compound **6k** (RE176) appears to be a good candidate as a next-generation VHR inhibitor effective at the cell level.

3. Conclusions

We synthesized a focused library of RE derivatives bearing enamine conjugated with two carbonyl groups as a core structure. Among them, two potent VHR inhibitors **6j** and **6k** effective at the cell level were found. Further structure-activity relationship studies and investigation of the biological activity of compound **6k** (RE176) at the cell level are under way.

4. Experimental

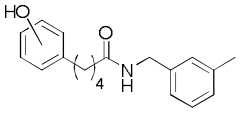
4.1. General

NMR spectra were recorded on a JEOL ECS400 or ECP500 spectrometer, or a Varian NMR System 500 spectrometer, operating at 400 or 500 MHz for ^{1}H-NMR and 100.4 or 125.8

MHz for ^{13}C-NMR. Chemical shifts were reported in the scale relative to $CHCl_3$ as an internal reference. IR spectra were measured on a Thermo Scientific Nicolet iS5 FT-IR with ZnSe iD3 ATR. EI-MS were taken on a JEOL JMS-HX/HX110. ESI-MS were taken on a JEOL JMS-T100LC. Column chromatography was performed with silica gel 60 (40-50 μm) purchased from KANTO CHEMICAL CO., INC. In general, reactions were carried out under a nitrogen atmosphere, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether, dichloromethane (CH_2Cl_2), *N,N*-dimethylformamide (DMF), toluene, and methanol were purified by a Glass Contour Solvent Dispensing System.

4.2. Synthesis of RE derivatives

*4.2.1. Representative procedure for transformation of **10** to **13***



o-**13** (*o*-OH), *m*-**13** (*m*-OH), *p*-**13** (*p*-Cl)

To a solution of *o*-**10** (915 mg, 4.71 mmol) in DMF (15.7 mL), 3-methylbenzylamine (701 μL, 5.65 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC: 1.20 g, 6.26 mmol) and *N,N*-dimethyl-4-aminopyridine (DMAP: 153 mg, 1.25 mmol) were added at 0 °C. The mixture was stirred for 7.5 h at room temperature, then water and ethyl acetate were added at 0 °C. The organic layer was separated and washed with water and brine. The combined aqueous layers were extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. Further purification was carried out by silica gel column chromatography (eluent: hexane/ethyl acetate = 1/1) to give *o*-**13** (1.38 g, 99%) as a pale yellow oil. IR (neat) 3296, 2943, 1643, 1608, 1593, 1535, 1456, 1240 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.65-1.78 (m, 4H), 2.30 (t, *J* = 6.8 Hz, 2H), 2.33 (s, 3H), 2.65 (brt, *J* = 7.2 Hz, 2H), 4.40 (d, *J* = 5.2 Hz, 2H), 5.74 (br, 1H), 5.98 (s, 1H), 6.78 (dd, *J* = 0.8 Hz, 7.6 Hz, 1H), 6.82 (td, *J* = 7.6 Hz, 0.8 Hz, 1H), 7.05-7.10 (m, 5H), 7.22 (brt, *J* = 7.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.4, 29.3, 29.5, 36.2, 43.6, 115.6, 120.0, 124.8, 127.0, 128.2, 128.4, 128.6 (2C), 130.0, 137.9, 138.4, 154.3, 173.7; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{19}H_{23}NO_2Na$, 297.1729; found, 297.1728.

m-**13** (65.3 mg, 85%): IR (neat) 3282, 2931, 1645, 1587, 1533, 1455, 1275, 1240, 1157 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.58-1.76 (m, 4H), 2.22 (t, *J* = 6.8 Hz, 2H), 2.33 (s, 3H), 2.58 (t, *J* = 7.2 Hz, 2H), 4.39 (d, *J* = 5.6 Hz, 2H), 5.61 (br, 1H), 5.69 (br, 1H), 6.64-6.68 (m, 2H), 6.71 (brd, *J* = 7.6 Hz, 1H), 7.04-7.14 (m, 4H), 7.22 (t, *J* = 7.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.2, 30.6, 35.3, 36.5, 43.7, 112.9, 115.4, 120.2, 124.8, 128.3, 128.6 (2C), 129.4, 137.8, 138.4, 143.7, 156.3, 173.4; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{19}H_{23}NO_2Na$, 297.1729; found, 297.1729.

p-**13** (905 mg, quant.): IR (neat) 3290,2925, 1641, 1612, 1541, 1514, 1446, 1230 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.57-1.73 (m, 4H), 2.30 (t, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 2.54 (t, *J* = 7.6 Hz, 2H), 4.39 (d, *J* = 5.6 Hz, 2H), 5.69 (br, 1H), 5.74 (br, 1H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 7.04-7.10 (m, 3H), 7.22 (t, *J* = 7.2 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.2, 25.2, 31.1, 34.6, 36.4, 43.5, 115.2 (2C), 124.7, 128.1, 128.4, 128.5, 129.1 (2C), 133.2, 137.7, 138.2, 154.5, 173.7; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{19}H_{23}NO_2Na$, 297.1729; found, 297.1728.

*4.2.2. Representative procedure for transformation of **13** to **11***

To a solution of **13a** (103 mg, 346 μmol) in THF (1.44 mL) and DMF (288 μL), *o*-chlorobenzyl bromide (67.4 μL, 519 μmol) and sodium hydride (NaH: 20.8 mg, 519 μmol) were added at 0 °C. The mixture was stirred for 10 min at room temperature, then water and ethyl acetate were added at 0 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo. Further purification was carried out by silica gel column chromatography (eluent: hexane/ethyl acetate = 3) to give **11a** (126.8 mg, 87%) as a colorless oil. IR (neat): 3292, 3062, 3022, 2941, 2862, 1645, 1550, 1493, 1454, 1240, 1059, 1047, 1034 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.60-1.78 (m, 4H), 2.22 (t, *J* = 7.6 Hz, 2H), 2.33 (s, 3H), 2.73 (brt, *J* = 7.2 Hz, 2H), 4.37 (d, *J* = 5.6 Hz, 2H), 5.15 (s, 2H), 5.63 (br, 1H), 6.91 (m, 2H), 7.03-7.09 (m, 3H), 7.15-7.31 (m, 5H), 7.39 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.55 (brd, *J* = 7.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.5, 29.5, 29.9, 36.5, 43.4, 67.0, 111.6, 120.9, 124.7, 126.9, 127.0, 128.1, 128.4, 128.5 (2C), 128.8, 129.2, 130.0, 130.9, 132.3, 135.0, 138.2, 138.3, 156.1, 172.8; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNO_2Na$, 421.1809; found, 421.1807.

11b (103 mg, 75%): IR (neat) 3294, 3062, 2924, 2860, 1643, 1549, 1493, 1454, 1433, 1240, 1115, 1051, 1030, 872 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.62-1.77 (m, 4H), 2.22 (t, *J* = 8.0 Hz, 2H), 2.32 (s, 3H), 2.70 (t, *J* = 6.8 Hz, 2H), 4.37 (d, *J* = 5.6 Hz, 2H), 5.02 (s, 2H), 5.60 (br, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.91 (brt, *J* = 7.2 Hz, 1H), 7.03-7.09 (m, 3H), 7.13-7.17 (m, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.26-7.31 (m, 3H), 7.41 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.5, 29.5, 29.8, 36.5, 43.4, 68.9, 111.5, 120.9, 124.7, 125.0, 126.9 (3C), 127.8, 128.1, 128.5 (2C), 129.8, 130.0, 130.9, 134.3, 138.2, 139.4, 156.1, 172.8; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNO_2Na$, 421.1809; found, 421.1808.

11c (129 mg, 84%): IR (neat) 3296, 3064, 3024, 2925, 2860, 1643, 1547, 1495, 1454, 1240, 1115, 1090, 1014, 810 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.62-1.75 (m, 4H), 2.20 (t, *J* = 7.2 Hz, 2H), 2.32 (s, 3H), 2.68 (t, *J* = 7.2 Hz, 2H), 4.37 (d, *J* = 5.2 Hz, 2H), 5.01 (s, 2H), 5.58 (br, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.90 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.03-7.10 (m, 3H), 7.13-7.17 (m, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.34 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.5, 29.5, 29.8, 36.6, 43.5, 69.1, 111.6, 120.9, 124.8, 127.0, 128.2, 128.4 (2C), 128.6 (2C), 128.7 (2C), 130.0, 130.9, 133.5, 135.9, 138.2, 138.4, 156.2, Signal of a carbon (*C*=O) was weak; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNO_2Na$, 421.1809; found, 421.1804.

11d (36.3 mg, 44%, impure): IR (neat) 3298, 3062, 3032, 2929, 2860, 1645, 1608, 1583, 1549, 1489, 1444, 1259, 1157, 1036 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.61-1.79 (m, 4H), 2.22 (t, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 2.62 (t, *J* = 7.2 Hz, 2H), 4.39 (d, *J* = 5.2 Hz, 2H), 5.15 (s, 2H), 5.62 (br, 1H), 6.78-6.81 (m, 3H), 7.05-7.09 (m, 3H), 7.17-7.23 (m, 2H), 7.25-7.31 (m, 2H), 7.38-7.41 (m, 1H), 7.55-7.57 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.3, 30.9, 35.6, 36.5, 43.5, 66.9, 111.8, 115.1, 121.3, 124.8, 126.9, 128.2, 128.5 (2C), 128.8, 128.9, 129.27, 129.30, 132.5, 134.8, 138.2, 138.3, 143.9, 158.5, 172.6; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNO_2Na$, 421.1809; found, 421.1807.

11e (26.6 mg, 41%): IR (neat) 3294, 3057, 3026, 2925, 2860, 1645, 1583, 1549, 1487, 1448, 1431, 1257, 1157, 1032, 876 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.61-1.75 (m, 4H), 2.22 (t, *J* = 7.6 Hz, 2H), 2.33 (s, 3H), 2.61 (t, *J* = 7.2 Hz, 2H), 4.39 (d, *J* = 5.2 Hz, 2H), 5.01 (s, 2H), 5.62 (br, 1H), 6.76-6.80 (m, 3H), 7.01-7.10 (m, 3H), 7.17-7.23 (m, 2H), 7.30 (m, 3H), 7.44 (br, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.3, 30.9, 35.6, 36.5, 43.5,

69.0, 111.8, 115.1, 131.3, 124.8, 125.3, 127.4, 128.0, 128.2, 128.6 (2C), 129.3, 129.8, 134.4, 138.2, 138.4, 139.2, 143.9, 158.5, 172.6; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNO_2Na$, 421.1809; found, 421.1810.

11f (31.5 mg, 52%, impure): IR (neat) 3290, 3068, 3030, 2924, 2860, 1643, 1601, 1583, 1543, 1491, 1448, 1255, 1155, 1093, 1030, 1014, 810 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.58-1.78 (m, 4H), 2.22 (t, *J* = 6.8 Hz, 2H), 2.33 (s, 3H), 2.60 (t, *J* = 7.2 Hz, 2H), 4.39 (d, *J* = 5.6 Hz, 2H), 5.01 (s, 2H), 5.64 (br, 1H), 6.74-6.82 (m, 3H), 7.03-7.09 (m, 3H), 7.16-7.23 (m, 2H), 7.32-7.40 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.3, 30.9, 35.7, 36.6, 43.6, 69.1, 111.8, 115.1, 121.3, 124.8, 128.2, 128.6 (2C), 128.7 (2C), 128.8 (2C), 129.3, 133.6, 135.6, 138.2, 138.4, 143.9, 158.6, 172.6; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNO_2Na$, 421.1809; found, 421.1803.

11g (101 mg, 74%): IR (neat) 3292, 3057, 3032, 2931, 2858, 1639, 1610, 1547, 1512, 1442, 1242, 1036 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.57-1.74 (m, 4H), 2.22 (t, *J* = 7.6 Hz, 2H), 2.33 (s, 3H), 2.58 (t, *J* = 7.2 Hz, 3H), 4.39 (d, *J* = 5.6 Hz, 2H), 5.14 (s, 2H), 5.64 (br, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.05-7.09 (m, 5H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.25-7.31 (m, 2H), 7.40 (dd, *J* = 1.6 Hz, 7.2 Hz, 1H), 7.56 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.2, 31.2, 34.7, 36.4, 43.4, 67.1, 114.6 (2C), 124.7, 126.8, 128.1, 128.5 (2C), 128.7, 128.8, 129.2 (3C), 132.4, 134.76, 134.83, 138.2 (2C), 156.6, 172.6; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNO_2Na$, 421.1809; found, 421.1805.

11h (99.3 mg, 84%): IR (neat) 3284, 3066, 3032, 2927, 2858, 1641, 1543, 1510, 1460, 1431, 1236, 1028, 825 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.58-1.72 (m, 4H), 2.20 (t, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 2.55 (t, *J* = 6.8 Hz, 2H), 4.37 (d, *J* = 5.6 Hz, 2H), 4.99 (s, 2H), 5.60 (br, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.02-7.09 (m, 5H), 7.20 (brt, *J* = 7.2 Hz, 1H), 7.28 (m, 3H), 7.42 (br, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.2, 31.2, 34.7, 36.4, 43.4, 69.1, 114.6 (2C), 124.7, 125.2, 127.3, 127.9, 128.1, 128.5 (2C), 129.3 (2C), 129.7, 134.3, 134.8, 138.2, 138.3, 139.2, 156.6, 172.6; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNO_2Na$, 421.1809; found, 421.1808.

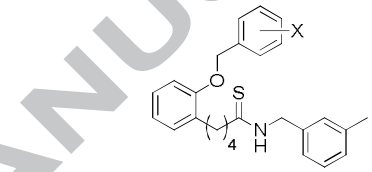
11i (83.1 mg, 75%): IR (neat) 3290, 3037, 2937, 2920, 2852, 1635, 1545, 1512, 1379, 1238, 1176, 1016, 876, 810 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59-1.72 (m, 4H), 2.20 (t, *J* = 7.6 Hz, 2H), 2.32 (s, 3H), 2.56 (t, *J* = 6.8 Hz, 2H), 4.38 (d, *J* = 6.0 Hz, 2H), 4.98 (s, 2H), 5.61 (br, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.02-7.09 (m, 5H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.34 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.3, 31.2, 34.7, 36.5, 43.5, 69.2, 114.6 (2C), 124.8, 128.2, 128.5 (2C), 128.6 (2C), 128.7 (2C), 129.3 (2C), 133.6, 134.7, 135.7, 138.2, 138.3, 156.6, 172.6; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNO_2Na$, 421.1809; found, 421.1805.

11j (56.2 mg, 74%): IR (neat) 3282, 3062, 3035, 2937, 2862, 1645, 1545, 1493, 1452, 1240, 1115, 1026 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.62-1.75 (m, 4H), 2.19 (t, *J* = 7.6 Hz, 2H), 2.32 (s, 3H), 2.69 (t, *J* = 6.8 Hz, 2H), 4.35 (d, *J* = 5.6 Hz, 2H), 5.05 (s, 2H), 5.52 (br, 1H), 6.87-6.92 (m, 2H), 7.01-7.09 (m, 3H), 7.13-7.23 (m, 3H), 7.28-7.31 (m, 1H), 7.35-7.42 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.4, 29.5, 29.8, 36.6, 43.5, 69.8, 111.6, 120.7, 124.8, 127.0, 127.1 (2C), 127.7, 128.2, 128.50 (2C), 128.53 (2C), 130.0, 130.9, 137.4, 138.26, 138.34, 156.5, Signal of a carbon (*C*=O) was weak; HRMS-EI (m/z): [M$^+$] calcd for $C_{26}H_{29}NO_2$, 387.2198; found, 387.2195.

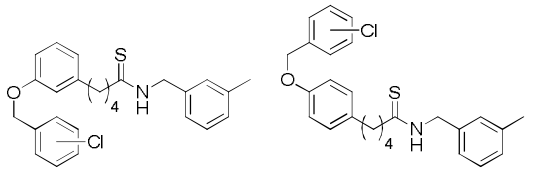
11k (80.8 mg, 94%): IR (neat) 3296, 3070, 3032, 2927, 2860, 1643, 1547, 1493, 1454, 1325, 1240, 1163, 1124, 1066, 1018, 823 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.63-1.77 (m, 4H), 2.22 (t, *J* = 7.2 Hz, 2H), 2.32 (s, 3H), 2.71 (t, *J* = 6.8 Hz, 2H), 4.38 (d, *J* = 5.6 Hz, 2H), 5.12 (s, 2H), 5.62 (br, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 7.03-7.09 (m, 3H), 7.13-7.17 (m, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.5, 29.5, 29.9, 36.6, 43.5, 68.9, 111.5, 121.0, 124.1 (q, *J* = 277.4 Hz), 124.8, 125.5 (q, *J* = 3.9 Hz, 2C), 126.99 (2C), 127.02, 128.2, 128.6 (2C), 129.9 (q, *J* = 32.8 Hz), 130.1, 130.9, 138.2, 138.4, 141.5, 156.1, 172.8; ^{19}F-NMR (376Hz, $CDCl_3$) δ -62.4 HRMS-EI (m/z): [M$^+$] calcd for $C_{27}H_{28}F_3NO_2$, 455.2072; found, 455.2072.

11l (74.3 mg, 85%): IR (neat) 3303, 3072, 2924, 2860, 1645, 1601, 1520, 1493, 1452, 1346, 1240, 1111, 1053, 854 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.64-1.78 (m, 4H), 2.23 (t, *J* = 7.6 Hz, 2H), 2.32 (s, 3H), 2.72 (t, *J* = 7.6 Hz, 2H), 4.38 (d, *J* = 5.6 Hz, 2H), 5.16 (s, 2H), 5.63 (br, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.93 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.03-7.09 (m, 3H), 7.13-7.22 (m, 3H), 7.59 (d, *J* = 8.8 Hz, 2H), 8.25 (d, *J* = 8.8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 25.5, 29.5, 29.9, 36.6, 43.5, 68.5, 111.4, 121.3, 123.8 (2C), 124.2, 124.8, 127.1, 127.3, 127.4 (2C), 128.2, 128.6 (2C), 130.2, 130.8, 138.2, 138.4, 144.8, 147.4, 155.8, Signal of a carbon (*C*=O) was weak; HRMS-EI (m/z): [M$^+$] calcd for $C_{26}H_{28}N_2O_4$, 432.2049; found, 432.2055.

*4.2.3. Representative procedure for transformation of **11** to **14***



14a (X = *o*-Cl), **14b** (X = *m*-Cl), **14c** (X = *p*-Cl)
14j (X = H), **14k** (X = *p*-CF_3), **14l** (X = *p*-NO_2)



14d (*o*-Cl), **14e** (*m*-Cl), **14f** (*p*-Cl) **14g** (*o*-Cl), **14h** (*m*-Cl), **14i** (*p*-Cl)

To a solution of **11a** (118 mg, 280 μmol) in THF, Lawesson's reagent (226 mg, 559 μmol) was added. The mixture was refluxed for 50 min and concentrated in vacuo. Further purification was carried out by silica gel column chromatography (eluent: hexane/ethyl acetate = 10/1) to give **14a** as a pale yellow oil. IR (neat) 3352, 3246, 3059, 3024, 2924, 2860, 1523, 1493, 1452, 1402, 1238, 1107, 1057, 1034 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.69 (m, 2H), 1.87 (m, 2H), 2.34 (s, 3H), 2.68 (t, *J* = 7.2 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 4.74 (d, *J* = 5.2 Hz, 2H), 5.12 (s, 2H), 6.87-6.92 (m, 2H), 7.07-7.18 (m, 5H), 7.23 (d, *J* = 7.2 Hz, 2H), 7.23 (br, 1H), 7.29 (td, *J* = 7.2 Hz, 1.6 Hz, 1H), 7.38 (dd, *J* = 1.6 Hz, 7.2 Hz, 1H), 7.53 (dd, *J* = 1.6 Hz, 7.2 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 29.0, 29.1, 29.8, 46.8, 50.2, 67.1, 111.7, 120.9, 125.2, 126.9, 127.0, 128.4, 128.7, 128.75, 128.80, 128.9, 129.2, 130.0, 130.8, 132.3, 134.9, 136.0, 138.6, 156.1, 205.3; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNOSNa$, 437.1580; found, 437.1576.

14b (96.3 mg, 91%, pale green oil): IR (neat) 3357, 3221, 3030, 2927, 2860, 1599, 1523, 1493, 1452, 1433, 1331, 1292, 1240, 1107, 1051, 960 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.67 (m, 2H), 1.86 (m, 2H), 2.34 (s, 3H), 2.68 (t, *J* = 8.3 Hz, 2H), 2.69 (t, *J* = 8.3 Hz, 2H), 4.74 (d, *J* = 5.2 Hz, 2H), 5.00 (s, 2H), 6.84 (d, *J* = 7.4 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 7.07-7.17 (m, 5H), 7.22 (br, 1H), 7.23-7.32 (m, 4H), 7.39 (br, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 29.1 (2C), 29.8, 46.8, 50.3, 69.0, 111.7, 121.0, 125.0, 125.3, 127.02, 127.05, 127.9, 128.77, 128.80, 129.0, 129.9, 130.1, 130.9, 134.3, 136.0, 138.6, 139.4, 156.1, 205.3; HRMS-

ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNOSNa$, 437.1580; found, 437.1575.

14c (117 mg, 87%, pale brown oil): IR (neat) 3356, 3232, 3033, 2924, 2860, 1601, 1493, 1452, 1406, 1331, 1238, 1105, 1053, 1014, 810 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.65 (m, 2H), 1.84 (m, 2H), 2.34 (s, 3H), 2.64 (t, *J* = 8.3 Hz, 2H), 2.68 (t, *J* = 8.3 Hz, 2H), 4.74 (d, *J* = 5.2 Hz, 2H), 4.99 (s, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.90 (t, *J* = 7.8 Hz, 1H), 7.07-7.17 (m, 5H), 7.20 (br, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.33 (br, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 29.0, 29.1, 29.7, 46.8, 50.2, 69.1, 111.7, 120.9, 125.2, 127.0, 128.4 (2C), 128.6 (2C), 128.7, 128.8, 129.0, 130.0, 130.8, 133.5, 135.7, 136.0, 138.6, 156.1, 205.3; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNOSNa$, 437.1580; found, 437.1575.

14d (20.1 mg, quant., white oil): IR (neat) 3344, 3230, 3033, 2931, 2858, 1583, 1525, 1489, 1444, 1402, 1331, 1257, 1157, 1059, 1045, 1034 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.67 (m, 2H), 1.85 (m, 2H), 2.34 (s, 3H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.7 Hz, 2H), 4.77 (d, *J* = 5.3 Hz, 2H), 5.15 (s, 2H), 6.77-6.81 (m, 3H), 7.09-7.31 (m, 7H), 7.24 (br, 1H), 7.39 (m, 1H), 7.56 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 29.0, 30.5, 35.6, 47.0, 50.4, 67.0, 111.9, 115.2, 121.3, 125.4, 126.9, 128.8, 128.87, 128.91 (2C), 129.1, 129.3, 129.4, 132.6, 134.8, 136.0, 138.8, 143.8, 158.6, 205.1; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNOSNa$, 437.1580; found, 437.1578.

14e (23.1 mg, 87%, white oil): IR (neat) 3348, 3236, 3033, 2925, 2860, 1583, 1525, 1489, 1448, 1433, 1404, 1331, 1259, 1157, 1095, 1078, 1043, 877 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.66 (m, 2H), 1.84 (m, 2H), 2.34 (s, 3H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 4.77 (d, *J* = 5.1 Hz, 2H), 5.01 (s, 2H), 6.74-6.79 (m, 3H), 7.08-7.31 (m, 8H), 7.24 (br, 1H), 7.43 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 28.9, 30.4, 35.6, 46.9, 50.4, 69.0, 111.9, 115.1, 121.3, 125.4 (2C), 127.4, 128.0, 128.86, 128.91, 129.1, 129.4, 129.8, 134.4, 136.0, 138.8, 139.2, 143.8, 158.5, 205.1; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNOSNa$, 437.1580; found, 437.1577.

14f (11.5 mg, 91%, colorless oil): IR (neat) 3236, 3041, 2927, 2856, 1601, 1493, 1448, 1408, 1333, 1259, 1157, 1093, 1045, 1016, 960, 810 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.66 (m, 2H), 1.84 (m, 2H), 2.34 (s, 3H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 4.77 (d, *J* = 5.1 Hz, 2H), 5.01 (s, 2H), 6.75-6.79 (m, 3H), 7.08-7.27 (m, 5H), 7.24 (br, 1H), 7.35 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 28.9, 30.5, 35.6, 46.9, 50.4, 69.1, 111.9, 115.1, 121.3, 125.4, 128.7 (2C), 128.8 (2C), 128.87, 128.92, 129.1, 129.3, 133.7, 135.6, 136.0, 138.8, 143.8, 158.6, 205.1; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNOSNa$, 437.1580; found, 437.1571.

14g (93.6 mg, 93%, pale yellow amorphous solid): IR (neat) 3348, 3232, 3028, 2922, 2856, 1610, 1510, 1442, 1402, 1238, 1176, 1034 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.64 (m, 2H), 1.84 (m, 2H), 2.354 (s, 3H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.68 (t, *J* = 8.0 Hz, 2H), 4.77 (d, *J* = 4.6 Hz, 2H), 5.13 (s, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.11-7.16 (m, 3H), 7.22 (br, 1H), 7.23-7.31 (m, 3H), 7.40 (m, 1H), 7.56 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 28.9, 30.8, 34.7, 46.9, 50.3, 67.1, 114.7 (2C), 125.3, 126.9, 128.7, 128.78, 128.83 (2C), 129.0, 129.3 (3C), 132.4, 134.7, 134.8, 136.0, 138.7, 156.6, 205.1; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNOSNa$, 437.1580; found, 437.1571.

14h (98.2 mg, 98%, pale yellow amorphous solid): IR (neat) 3359, 3226, 3030, 2924, 2856, 1608, 1510, 1458, 1433, 1402, 1331, 1298, 1236, 1176, 1105, 1036, 958 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.63 (m, 2H), 1.84 (m, 2H), 2.35 (s, 3H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 4.77 (d, *J* = 5.1 Hz, 2H), 5.00 (s, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.08-7.16 (m, 5H), 7.20 (br, 1H), 7.25 (t *J* = 7.4 Hz, 1H), 7.30 (br, 3H), 7.43 (br, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 28.9, 30.7, 34.6, 46.8, 50.2, 69.1, 114.6 (2C), 125.2 (2C), 127.3, 127.9, 128.7, 128.8, 129.0, 129.2 (2C), 129.7, 134.3, 134.7, 135.9, 138.6, 139.2, 156.6, 205.1; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNOSNa$, 437.1580; found, 437.1571.

14i (71.1 mg, 87%, white amorphous solid): IR (neat) 3213, 3051, 2929, 2854, 1599, 1510, 1460, 1396, 1335, 1298, 1246, 1174, 1105, 1014, 962, 812 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.63 (m, 2H), 1.84 (m, 2H), 2.35 (s, 3H), 2.58 (t, *J* = 8.0 Hz, 2H), 2.67 (t, *J* = 8.0 Hz, 2H), 4.77 (d, *J* = 4.6 Hz, 2H), 4.99 (s, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.08-7.16 (m, 3H), 7.21 (br, 1H), 7.25 (t *J* = 7.4 Hz, 1H), 7.35 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 28.9, 30.7, 34.6, 46.8, 50.3, 69.1, 114.6 (2C), 125.3, 128.6 (2C), 128.66 (2C), 128.76, 128.81 129.0, 129.2 (2C), 133.5, 134.6, 135.6, 135.9, 138.6, 156.6, 205.1; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{26}H_{28}ClNOSNa$, 437.1580; found, 437.1578.

14j (54.9 mg, 96%): IR (neat) 3363, 3230, 3033, 2924, 2860, 1601, 1523, 1493, 1452, 1397, 1333, 1290, 1240, 1188, 1134, 1109, 1051, 1026 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.67 (m, 2H), 1.84 (m, 2H), 2.34 (s, 3H), 2.65 (dd, *J* = 7.8 Hz, 7.4 Hz, 2H), 2.70 (dd, *J* = 7.8 Hz, 7.4 Hz, 2H), 4.72 (d, *J* = 5.1 Hz, 2H), 5.02 (s, 2H), 6.86-6.91 (m, 2H), 7.05-7.19 (m, 4H), 7.17 (br, 1H), 7.22-7.31 (m, 2H), 7.34-7.41 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 29.0, 29.1, 29.7, 46.8, 50.3, 70.0, 111.8, 120.8, 125.3, 127.0, 127.1 (2C), 127.8, 128.5 (2C), 128.77, 128.79, 129.0, 130.0, 130.9, 136.0, 137.3, 138.6, 156.4, 205.4; HRMS-EI (m/z): [M$^+$] calcd for $C_{26}H_{29}NOS$,403.1970; found, 403.1968.

14k (77.8 mg, 97%): IR (neat) 3240, 3028, 2931, 2862, 1601, 1523, 1493, 1454, 1404, 1325, 1242, 1165, 1124, 1066, 1018, 825 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.68 (m, 2H), 1.87 (m, 2H), 2.34 (s, 3H), 2.67 (dd, *J* = 7.8 Hz, 7.4 Hz, 2H), 2.72 (dd, *J* = 7.8 Hz, 7.4 Hz, 2H), 4.74 (d, *J* = 5.1 Hz, 2H), 5.10 (s, 2H), 6.87 (dd, *J* = 8.7 Hz, 0.9 Hz, 1H), 6.91 (td, *J* = 7.4 Hz, 0.9 Hz, 1H), 7.06-7.26 (m, 6H), 7.21 (br, 1H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 29.08, 29.14, 29.8, 46.9, 50.3, 69.0, 111.6, 121.1, 124.0 (q, *J* = 272.6 Hz), 125.3, 125.5 (q, *J* = 3.9 Hz, 2C), 127.0 (2C), 127.1, 128.79, 128.84, 129.0, 129.9 (q, *J* = 32.7 Hz), 130.1, 130.8, 136.0, 138.7, 141.4, 156.0, 205.3; ^{19}F-NMR (376Hz, $CDCl_3$) δ -62.4; HRMS-EI (m/z): [M$^+$] calcd for $C_{27}H_{28}F_3NOS$, 471.1844; found, 471.1836.

14l (74.2 mg, 99%): IR (neat) 3342, 3226, 3024, 2924, 2858, 1601, 1520, 1493, 1452, 1404, 1344, 1240, 1109, 1053, 839 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.67 (m, 2H), 1.86 (m, 2H), 2.32 (s, 3H), 2.66 (dd, *J* = 7.8 Hz, 7.4 Hz, 2H), 2.71 (dd, *J* = 7.8 Hz, 7.4 Hz, 2H), 4.73 (d, *J* = 4.6 Hz, 2H), 5.13 (s, 2H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.91 (td, *J* = 7.8 Hz, 0.9 Hz, 1H), 7.04-7.16 (m, 5H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.22 (br, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 8.23 (dt, *J* = 8.7 Hz, 2H), *J* = 1.6 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 29.1, 29.2, 29.9, 46.9, 50.3, 68.6, 111.5, 121.3, 123.8 (2C), 125.3, 127.1, 127.3 (2C), 128.80, 128.85, 129.0, 130.2, 130.8, 136.0, 138.7, 144.7, 147.4, 155.8, 205.2; HRMS-EI (m/z): [M$^+$] calcd for $C_{26}H_{28}N_2O_3S$, 448.1821; found, 448.1822.

*4.2.4. Representative procedure for transformation of **14** to **7***

To a solution of **14a** (112 mg, 256 μmol) in dry acetone (1.23 mL), potassium carbonate (70.9 mg, 513 μmol) and methyl iodide (48.0 μL, 769 μmol) were added. The mixture was stirred for 13.5 h, and further methyl iodide (32.0 μL, 514 μmol) was added. Stirring was continued for 1 h, and the reaction mixture

was filtered through Celite. Further purification was carried out by GPC (eluent: chloroform) to give **7a** (100 mg, 87%, 1:1 isomeric mixture) as a pale green oil. IR (neat) 3062, 3026, 2926, 2860, 1624, 1604, 1493, 1452, 1238, 1126, 1090, 1057, 1047, 1034 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.63-1.82 (m, 4H), 2.34 (s, 3H), 2.35 (s, 1.5H), 2.44 (s, 1.5H), 2.47 (dd, *J* = 8.3 Hz, 6.9 Hz, 1H), 2.63 (brdd, *J* = 7.4 Hz, 5.5 Hz, 1H), 2.73 (brdd, *J* = 8.3 Hz, 6.9 Hz, 1H), 2.76 (brdd, *J* = 7.4 Hz, 6.9 Hz, 1H), 4.49 (s, 1H), 4.58 (s, 1H), 5.16 (s, 1H), 5.17 (s, 1H), 6.88-6.95 (m, 2H), 7.05 (brd, *J* = 7.4 Hz, 1H), 7.12-7.32 (m, 7H), 7.40 (m, 1H), 7.57 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.7, 14.3, 21.42, 21.45, 27.1, 27.5, 29.4, 29.6, 30.0, 30.1, 34.2, 37.4, 54.4, 55.7, 67.0 (2C), 111.60, 111.64, 120.9 (2C), 124.3, 124.9, 126.92 (2C), 126.99, 127.1, 127.2, 127.4, 128.0, 128.17, 128.21, 128.3, 128.4, 128.6, 128.74, 128.77, 129.25, 129.28, 129.94, 129.99, 130.7, 131.0, 132.4 (2C), 135.06, 135.10, 137.8, 137.9, 140.40 (2C), 156.2 (2C), Signals of carbons (S*C*=N) were weak; HRMS-ESI (m/z): [M+H$^+$] calcd for $C_{27}H_{31}ClNOS$, 452.1809; found, 452.1807.

7b (76.8 mg, 78%, pale brown oil): IR (neat) 2924, 2860, 1624, 1601, 1493, 1454, 1431, 1290, 1240, 1095, 1051 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.60-1.79 (m, 4H), 2.32 (s, 1.5H), 2.33 (s, 1.5H), 2.34 (s, 1.5H), 2.42 (s, 1.5H), 2.46 (dd, *J* = 8.3 Hz, 6.9 Hz, 1H), 2.59 (brdd, *J* = 8.3 Hz, 6.0 Hz, 1H), 2.70 (brdd, *J* = 8.3 Hz, 6.9 Hz, 1H), 2.71 (brdd, *J* = 8.3 Hz, 6.9 Hz, 1H), 4.46 (s, 1H), 4.56 (s, 1H), 5.03 (s, 1H), 5.04 (s, 1H), 6.85 (brd, *J* = 7.8 Hz, 1H), 6.91 (m, 1H), 7.04 (brd, *J* = 7.4 Hz, 1H), 7.10-7.22 (m, 5H), 7.29 (m, 3H), 7.42 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.6, 14.2, 21.40, 21.43, 27.0, 27.4, 29.4, 29.6, 29.9, 30.1, 34.2, 37.5, 54.4, 55.9, 68.9 (2C), 111.48, 111.52, 120.9 (2C), 124.3, 124.8, 124.92, 124.96, 126.9, 127.0 (3C), 127.2, 127.3, 127.80, 127.82, 128.0, 128.12, 128.15, 128.5, 129.8 (2C), 129.97, 130.01, 130.7, 131.1, 134.35, 134.38, 137.7, 137.8, 139.47, 139.52, 140.0, 140.5, 156.2 (2C), 165.3, 168.3; HRMS-ESI (m/z): [M+H$^+$] calcd for $C_{27}H_{31}ClNOS$, 452.1809; found, 452.1808.

7c (85.4 mg, 72%, yellow oil): IR (neat) 2925, 2860, 1624, 1493, 1454, 1240, 1090, 1014, 810 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.62-1.78 (m, 4H), 2.32 (s, 1.5H), 2.33 (s, 1.5), 2.34 (s, 1.5H), 2.41 (s, 1.5H), 2.44 (dd, *J* = 8.3 Hz, 6.4 Hz, 1H), 2.57 (brdd, *J* = 7.4 Hz, 6.4 Hz, 1H), 2.68 (brdd, *J* = 7.4 Hz, 6.9 Hz, 1H), 2.70 (brdd, *J* = 8.3 Hz, 6.9 Hz, 1H), 4.46 (s, 1H), 4.56 (s, 1H), 5.02 (s, 1H), 5.03 (s, 1H), 6.86 (brd, *J* = 8.3 Hz, 1H), 6.90 (m, 1H), 7.04 (m, 1H), 7.11-7.23 (m, 5H), 7.34 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.6, 14.1, 21.38, 21.41, 27.0, 27.3, 29.4, 29.6, 29.87, 30.0, 34.2, 37.5, 54.4, 55.9, 68.92, 68.94, 111.43, 111.46, 120.8 (2C), 124.3, 124.8, 126.9, 127.0, 127.16, 127.24, 128.0, 128.1 (2C), 128.3 (2C), 128.4 (2C), 128.5, 128.59 (2C), 128.61 (2C), 129.89, 129.95, 130.6, 131.0, 133.37, 133.40, 135.8, 135.9, 137.7, 137.8, 140.0, 140.5, 156.16, 156.18, 165.1, 168.1; HRMS-ESI (m/z): [M+H$^+$] calcd for $C_{27}H_{31}ClNOS$, 452.1809; found, 452.1808.

7d (5.9 mg, 84%, colorless oil): IR (neat) 3033, 2925, 2860, 1626, 1610, 1489, 1446, 1261, 1157, 1059, 1047, 1036, 877 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59-1.79 (m, 4H), 2.34 (s, 3H), 2.35 (s, 1.5H), 2.45 (s, 1.5H), 2.47 (dd, *J* = 7.8 Hz, 7.4 Hz, 1H), 2.58-2.67 (m, 3H), 4.49 (s, 1H), 4.59 (s, 1H), 5.16 (s, 1H), 5.16 (s, 1H), 6.78-6.85 (m, 3H), 7.02-7.32 (m, 6H), 7.40 (brdd, *J* = 7.4 Hz, 2.3 Hz, 1H), 7.57 (brdd, *J* = 7.4 Hz, 2.3 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.7, 14.3, 21.4, 21.5, 26.8, 27.1, 30.7, 30.9, 34.1, 35.5, 35.7, 37.5, 54.5, 56.0, 67.0 (2C), 111.8, 112.0, 115.10, 115.12, 121.3 (2C), 124.3, 124.8, 126.9 (2C), 127.2, 127.3, 128.0, 128.18, 128.21, 128.6, 128.78, 128.80, 128.9 (2C), 129.3 (3C), 129.4, 132.5 (2C), 134.8, 134.9, 137.8, 137.9, 140.0, 140.5, 143.8, 144.1, 158.6 (2C), 165.0, 168.1; HRMS-ESI (m/z): [M+H$^+$] calcd for $C_{27}H_{31}ClNOS$, 452.1809; found, 452.1809.

7e (18.4 mg, 98%, colorless oil): IR (neat) 3028, 2927, 2858, 1608, 1583, 1487, 1450, 1431, 1259, 1157, 1095, 1080, 1043, 877 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59-1.78 (m, 4H), 2.34 (s, 3H), 2.35 (s, 1.5H), 2.45 (s, 1.5H), 2.47-2.49 (m, 1H), 2.58-2.67 (m, 3H), 4.48 (s, 1H), 4.58 (s, 1H), 5.01 (s, 1H), 5.02 (s, 1H), 6.76-6.83 (m, 3H), 7.05-7.25 (m, 5H), 7.30 (m, 3H), 7.45 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.7, 14.3, 21.4, 21.5, 26.8, 27.0, 30.7, 30.9, 34.1, 35.5, 35.7, 37.4, 54.5, 56.0, 69.0 (2C), 111.8, 111.9, 115.1 (2C), 121.4 (2C), 124.3, 124.8, 125.4 (2C), 127.2, 127.3, 127.4 (2C), 128.0 (2C), 128.19, 128.21, 128.57 (2C), 129.3, 129.4, 129.8 (2C), 134.4 (2C), 137.8, 137.9, 139.21, 139.24, 140.0, 140.5, 143.8, 144.1, 158.5 (2C), 165.0, 168.1; HRMS-ESI (m/z): [M+H$^+$] calcd for $C_{27}H_{31}ClNOS$, 452.1809; found, 452.1806.

7f (11.9 mg, quant., colorless oil): IR (neat) 3022, 2925, 2860, 1626, 1612, 1493, 1450, 1259, 1157, 1095, 1041, 1016, 810 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59-1.75 (m, 4H), 2.33 (s, 3H), 2.34 (s, 1.5H), 2.45 (s, 1.5H), 2.44-2.49 (m, 1H), 2.57-2.65 (m, 3H), 4.48 (s, 1H), 4.58 (s, 1H), 5.00 (s, 1H), 5.01 (s, 1H), 6.75-6.81 (m, 3H), 7.02-7.24 (m, 5H), 7.35 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.7, 14.3, 21.4, 21.5, 26.8, 27.1, 30.7, 30.9, 34.1, 35.5, 35.7, 37.5, 54.5, 56.0, 69.1 (2C), 111.8, 111.9, 115.1 (2C), 121.3 (2C), 124.3, 124.8, 127.25, 127.33, 128.0, 128.20, 128.22, 128.6, 128.7 (4C), 128.8 (4C), 129.3, 129.4, 133.6, 133.7, 135.6, 135.7, 137.85, 137.89, 140.0, 140.5, 143.8, 144.1, 158.57, 158.59, 165.0, 168.1; HRMS-ESI (m/z): [M+H$^+$] calcd for $C_{27}H_{31}ClNOS$, 452.1809; found, 452.1811.

7g (8.3 mg, 88%): IR (neat) 3030, 2927, 2856, 1624, 1612, 1510, 1442, 1240, 1176, 1034, 825 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59-1.77 (m, 4H), 2.34 (s, 3H), 2.35 (s, 1.5H), 2.45 (s, 1.5H), 2.45-2.49 (m, 1H), 2.55-2.64 (m, 3H), 4.49 (s, 1H), 4.58 (s, 1H), 5.15 (s, 2H), 6.88-6.92 (m, 2H), 7.02-7.31 (m, 8H), 7.40 (brdd, J = 7.4 Hz, 1.4 Hz, 1H), 7.56 (brd, *J* = 6.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.7, 14.3, 21.41, 21.45, 26.7, 27.0, 30.9, 31.3, 34.1, 34.6, 34.7, 37.3, 54.4, 55.7, 67.1 (2C), 114.66, 114.70, 124.3, 124.9, 126.9 (4C), 127.2, 127.4, 128.0, 128.17, 128.22, 128.6, 128.7 (2C), 128.8 (2C), 129.3 (6C), 132.5 (2C), 134.6 (2C), 134.9 (2C), 137.8, 137.9, 139.6, 140.4, 156.6, 156.7, 164.8, 170.3; HRMS-ESI (m/z): [M+H$^+$] calcd for $C_{27}H_{31}ClNOS$, 452.1809; found, 452.1809.

7h (64.6 mg, 65%, yellow oil): IR (neat) 3030, 2925, 2860, 1624, 1512, 1460, 1431, 1302, 1238, 1176, 1095, 1039, 827 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59-1.77 (m, 4H), 2.34 (s, 3H), 2.35 (s, 1.5H), 2.45 (s, 1.5H), 2.45-2.48 (m, 1H), 2.54-2.63 (m, 3H), 4.48 (s, 1H), 4.58 (s, 1H), 5.01 (s, 2H), 6.85-6.89 (m, 2H), 7.04-7.19 (m, 5H), 7.20 (td, *J* = 7.4 Hz, 1.8 Hz, 1H), 7.30 (brs, 3H), 7.44 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.7, 14.2, 21.40, 21.43, 26.7, 27.0, 30.9, 31.2, 34.1, 34.5, 34.7, 37.3, 54.4, 55.8, 69.1 (2C), 114.58, 114.62, 124.3, 124.8, 125.3 (2C), 127.2, 127.30 (2C), 127.34, 127.9 (2C), 128.0, 128.1, 128.2, 128.6, 129.3 (6C), 129.7 (2C), 134.4 (2C), 134.6, 134.9, 137.78, 137.83, 139.2, 139.3, 139.7, 140.4, 156.5, 156.6, 163.4, 168.3; HRMS-ESI (m/z): [M+H$^+$] calcd for $C_{27}H_{31}ClNOS$, 452.1809; found, 452.1809.

7i (56.0 mg, 77%, yellow oil): IR (neat) 3032, 2927, 2858, 1626, 1510, 1493, 1462, 1240, 1176, 1092, 1014, 812 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.58-1.74 (m, 4H), 2.33 (s, 3H), 2.34 (s, 1.5H), 2.45 (s, 1.5H), 2.45-2.48 (m, 1H), 2.54-2.61 (m, 3H), 4.49 (s, 1H), 4.58 (s, 1H), 5.00 (s, 2H), 6.84-6.88 (m, 2H), 7.03-7.19 (m, 5H), 7.21 (td, *J* = 7.8 Hz, 0.9 Hz, 1H), 7.35 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.7, 14.3, 21.42, 21.45, 26.7, 27.0, 31.0, 31.3, 34.1, 34.5, 34.7, 37.4, 54.4, 55.8, 69.2 (2C), 114.61 (2C), 114.64 (2C), 124.3, 124.9, 127.2, 127.4, 128.0, 128.16, 128.20, 128.6, 128.66 (4C), 128.69 (4C), 129.3 (4C), 133.6 (2C),

134.6, 134.9, 135.67, 135.69, 137.8, 137.9, 139.7, 140.4, 156.6, 156.7, Signals of carbons (S*C*=N) were weak; [M+H$^+$] calcd for $C_{27}H_{31}ClNOS$, 452.1809; found, 452.1808.

7j (36.0 mg, 64%): IR (neat) 3066, 3035, 2925, 2860, 1626, 1493, 1452, 1381, 1344, 1289, 1240, 1112, 1090, 1045, 1026, 856 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.61-1.78 (m, 4H), 2.33 (s, 1.5H), 2.34 (s, 1.5H), 2.36 (s, 1.5H), 2.40 (m, 1.5H), 2.45 (brdd, *J* = 7.8 Hz, 7.4 Hz, 1H), 2.61-2.74 (m, 3H), 4.49 (s, 1H), 4.57 (s, 1H), 5.06 (s, 1H), 5.08 (s, 1H), 6.87-6.92 (m, 2H), 7.05 (brd, *J* = 7.4 Hz, 1H), 7.11-7.20 (m, 4H), 7.21 (td, *J* = 7.4 Hz, 1.8Hz, 1H), 7.28-7.45 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.9, 14.3, 21.41, 21.45, 27.1, 27.5, 29.3, 29.6, 29.9, 30.0, 34.3, 37.3, 54.3, 55.4, 69.8 (2C), 111.55, 111.61, 120.7 (2C), 124.4, 125.0, 126.9, 127.0 (4C), 127.1 (2C), 127.3, 127.5, 127.69, 127.72, 128.1, 128.2, 128.3, 128.49 (4C), 128.54, 128.7, 129.88, 129.92, 130.7, 130.9, 137.38, 137.44, 137.8, 138.0, 156.5 (2C), Signals of carbons (S*C*=N) were weak; HRMS-EI (m/z): [M$^+$] calcd for $C_{27}H_{31}NOS$, 417.2126; found, 417.2107.

7k (61.7 mg, 82%): IR (neat) 3026, 2925, 2864, 1624, 1493, 1454, 1419, 1327, 1240, 1165, 1126, 1066, 1018, 825 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.62-1.81 (m, 4H), 2.32 (s, 1.5H), 2.34 (m, 3H), 2.42 (s, 1.5H), 2.47 (brdd, *J* = 8.3 Hz, 6.9 Hz, 1H), 2.62 (m, 1H), 2.71 (brdd, *J* = 7.4 Hz, 6.9 Hz, 1H), 2.73 (brdd, *J* = 7.4 Hz, 6.9 Hz, 1H), 4.48 (s, 1H), 4.58 (s, 1H), 5.12 (s, 1H), 5.13 (s, 1H), 6.86 (brd, *J* = 8.3 Hz, 1H), 6.92 (m, 1H), 7.05 (brd, *J* = 6.9 Hz, 1H), 7.10-7.23 (m, 5H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.7, 14.2, 21.40, 21.43, 27.1, 27.4, 29.4, 29.6, 29.9, 30.0, 34.2, 37.4, 54.4, 55.7, 68.90, 68.93, 111.44, 111.46, 121.0 (2C), 124.1 (m, 2C), 124.3, 124.9, 125.5 (m, 2C), 126.9 (4C), 127.0 (2C), 127.1 (2C), 127.3, 127.4, 128.0, 128.19, 128.22, 128.6, 129.9 (m, 2C), 130.0, 130.1, 130.7, 131.0 137.85, 137.91, 139.9, 140.4, 141.5 (2C), 156.08, 156.11, Signals of carbons (S*C*=N) were weak; ^{19}F-NMR (376Hz, $CDCl_3$) δ -62.42, -62.36; HRMS-EI (m/z): [M$^+$] calcd for $C_{28}H_{30}F_3NOS$, 485.2000; found, 485.2002.

7l (68.4 mg, 91%): IR (neat) 3014, 2925, 2860, 1624, 1608, 1522, 1493, 1452, 1346, 1240, 1111, 1055, 854 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.64-1.80 (m, 4H), 2.32 (s, 1.5H), 2.34 (m, 3H), 2.45 (s, 1.5H), 2.47 (brdd, *J* = 7.8 Hz, 6.9 Hz, 1H), 2.63 (m, 1H), 2.73 (brdd, *J* = 7.8 Hz, 6.9 Hz, 1H), 2.74 (brdd, *J* = 7.4 Hz, 6.9 Hz, 1H), 4.48 (s, 1H), 4.57 (s, 1H), 5.16 (s, 1H), 5.17 (s, 1H),6.83 (m, 1H), 6.94 (m, 1H), 7.05 (m, 1H), 7.10-7.23 (m, 5H), 7.59 (m, 2H), 8.24 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.7, 14.3, 21.38, 21.43, 27.0, 27.3, 29.4, 29.6, 29.9, 30.0, 34.2, 37.4, 54.4, 55.7, 68.49, 68.53, 111.4 (2C), 121.3 (2C), 123.76 (2C), 123.79 (2C), 124.3, 124.9, 127.0, 127.1, 127.2 (3C), 127.3 (2C), 127.4, 128.0, 128.18, 128.20, 128.6, 130.1, 130.2, 130.7, 131.0, 137.8, 137.9, 140.3 (2C), 144.8, 144.9, 147.4 (2C), 155.8 (2C), Signals of carbons (S*C*=N) were weak; HRMS-EI (m/z): [M$^+$] calcd for $C_{27}H_{30}N_2O_3S$, 462.1977; found, 462.1973.

*4.2.5. Representative procedure for transformation of **7** to **12***

To a mixture of **7a** and MS4A, a solution of **8** (15.0 mg, 33.2 μmol) in CH_2Cl_2 (205 μL) was added. The reaction mixture was stirred for 30 h and filtered through Celite. The filtrate was concentrated in vacuo. Further purification was carried out by silica gel column chromatography (eluent: hexane/ethyl acetate = 4) to give **12a** (11.1 mg, 65%, tautomeric mixture: 1.38:1 in $CDCl_3$) as a colorless oil. IR (neat) 3068, 2929, 2858, 1741, 1670, 1647, 1601, 1495, 1452, 1238, 1130, 1113, 1039 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 5.2H), 0.96 (s, 3.8H), 1.60-1.89 (m, 4H), 2.30 (s, 1.7H), 2.32 (s, 1.3H), 2.68-2.78 (m, 2H), 2.93-3.11 (m, 2H), 3.98-4.11 (m, 2H), 4.47-4.53 (m, 3H), 5.14 (brs, 2H), 6.88-7.00 (m, 4H), 7.11-7.30 (m, 6H), 7.33-7.43 (m, 7H), 7.54 (m, 1H), 7.62-7.69 (m, 4H), 10.4 (brm, 0.42H), 11.3 (brm, 0.58H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.3, 21.4, 26.51, 26.53, 27.1, 27.4, 27.48, 27.51, 29.6, 29.7, 29.9, 46.6, 46.9, 62.3, 62.5, 67.0, 81.2, 83.3, 91.3, 92.7, 111.6, 121.0, 124.0, 126.9, 127.0, 127.2, 127.6, 127.7, 128.4, 128.8, 129.0, 129.1, 129.2, 129.3, 129.6, 129.7, 130.0, 130.39, 130.43, 132.3, 132.4, 132.7, 132.95, 133.01, 135.0, 135.1, 135.5, 135.6, 139.0, 156.1, 171.4, 173.4, 174.1, 176.3, 193.0, 197.8; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{47}H_{50}ClNNaO_5Si$, 794.3039; found, 794.3036.

12b (9.9 mg, 53%, tautomeric mixture: 1.33:1 in $CDCl_3$): IR (neat) 3074, 2931, 2856, 1743, 1668, 1647, 1601, 1495, 1452, 1429, 1240, 1113, 1039 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 5.1H), 0.95 (s, 3.9H), 1.57-1.87 (m, 4H), 2.30 (s, 1.7H), 2.32 (s, 1.3H), 2.67-2.74 (m, 2H), 2.91-3.12 (m, 2H), 3.98-4.11 (m, 2H), 4.48-4.56 (m, 3H), 5.02 (brs, 0.9H), 5.03 (brs, 1.1H), 6.83-6.86 (m, 1H), 6.87-6.92 (m, 1H), 6.95-7.00 (m, 2H), 7.10-7.43 (m, 14H), 7.62-7.69 (m, 4H), 10.4 (brm, 0.43H), 11.3 (brm, 0.57H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.35, 21.38, 26.51, 26.54, 27.1, 27.4, 27.48, 27.52, 29.7, 29.8, 46.6, 46.9, 62.3, 62.5, 69.0, 81.3, 83.3, 91.3, 92.7, 111.6, 121.0, 124.0, 124.98, 125.02, 127.0, 127.1, 127.66, 127.69, 127.9, 129.06, 129.13, 129.6, 129.7, 129.8, 129.9, 130.1, 130.45, 130.50, 132.69, 132.74, 132.98, 133.03, 134.33, 134.35, 135.0, 135.1, 135.55, 135.64, 139.0, 139.5, 156.1, 171.5, 173.4, 174.1, 176.3, 193.1, 197.9; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{47}H_{50}ClNNaO_5Si$, 794.3039; found, 794.3035.

12c (50.4 mg, 53%, tautomeric mixture: 1.38:1 in $CDCl_3$): IR (neat) 3070, 2929, 2858, 1741, 1668, 1647, 1601, 1495, 1452, 1429, 1240, 1113, 1039, 810 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 5.2H), 0.95 (s, 3.8H), 1.59-1.84 (m, 4H), 2.31 (s, 1.7H), 2.33 (s, 1.3H), 2.63-2.74 (m, 2H), 2.91-3.10 (m, 2H), 3.98-4.14 (m, 2H), 4.48-4.53 (m, 3H), 5.01 (brs, 0.84H), 5.02 (brs, 1.2H), 6.83-6.92 (m, 2H), 6.95-7.01 (m, 2H), 7.10-7.26 (m, 4H), 7.29-7.43 (m, 10H), 7.63-7.70 (m, 4H), 10.4 (brm, 0.42H), 11.3 (brm, 0.58H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.35, 21.38, 26.51, 26.53, 27.1, 27.3, 27.45, 27.50, 29.7, 29.8, 46.6, 46.9, 62.3, 62.5, 69.0, 81.3, 83.3, 91.3, 92.8, 111.6, 120.9, 124.0, 127.1, 127.6, 127.7, 128.4, 128.6, 128.7, 129.07, 129.15, 129.6, 129.7, 129.98, 130.00, 130.41, 130.44, 132.7, 132.7, 132.97, 133.01, 133.5, 135.0, 135.1, 135.5, 135.6, 135.8, 139.0, 156.2, 171.5, 173.4, 174.0, 176.3, 193.1, 197.9; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{47}H_{50}ClNNaO_5Si$, 794.3039; found, 794.3040.

12d (5.5 mg, 87%, tautomeric mixture: 1.27:1 in $CDCl_3$): IR (neat) 3070, 2931, 2858, 1745, 1670, 1649, 1603, 1444, 1155, 1134, 1115, 1061, 1041 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 5.0H), 0.94 (s, 4.0H), 1.57-1.84 (m, 4H), 2.31 (s, 1.7H), 2.33 (s, 1.3H), 2.55-2.65 (m, 2H), 2.90-3.13 (m, 2H), 3.98-4.12 (m, 2H), 4.48-4.56 (m, 3H), 5.13 (br, 2H), 6.73-6.81 (m, 3H), 6.97-7.02 (m, 2H), 7.11-7.30 (m, 6H), 7.33-7.42 (m, 7H), 7.54-7.70 (m, 4H), 10.4 (brm, 0.44H), 11.3 (brm, 0.56H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.37, 21.40, 26.5, 26.6, 27.12, 27.14, 27.2, 27.5, 29.7, 31.10, 31.15, 35.3, 46.6, 46.9, 62.3, 62.5, 66.9, 81.3, 83.3, 91.4, 92.8, 112.0, 115.1, 121.27, 121.30, 124.0, 126.9, 127.68, 127.71, 128.8, 128.9, 129.1, 129.2, 129.3, 129.4, 129.66, 129.74, 132.5, 132.68, 132.71, 133.0, 133.1, 134.8, 135.0, 135.1, 135.56, 135.65, 139.0, 143.47, 143.51, 158.6, 171.5, 173.3, 174.0, 176.3, 193.2, 197.9; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{47}H_{50}ClNNaO_5Si$, 794.3039; found, 794.3052.

12e (5.9 mg, 50%, tautomeric mixture: 1.27:1 in $CDCl_3$): IR (neat) 3070, 3047, 2929, 2858, 1741, 1670, 1649, 1601, 1429, 1259, 1155, 1132, 1113, 1041 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 5.0H), 0.96 (s, 4.0H), 1.56-1.83 (m, 4H), 2.31 (s, 1.7H), 2.34 (s, 1.3H), 2.54-2.64 (m, 2H), 2.88-3.12 (m, 2H), 3.97-4.12 (m, 2H), 4.48-4.56 (m, 3H), 5.00 (br, 2H), 6.74-6.80 (m, 3H), 6.97-7.03 (m, 2H), 7.12-7.31 (m, 6H), 7.34-7.44 (m, 6H), 7.62-

7.70 (m, 4H), 10.4 (brm, 0.44H), 11.3 (brm, 0.56H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.38, 21.41, 26.5, 26.6, 27.11, 27.14, 27.2, 27.5, 29.7, 31.1, 31.2, 35.3, 46.6, 46.9, 62.3, 62.5, 69.0, 81.3, 83.3, 91.4, 92.8, 112.0, 112.1, 115.02, 115.04, 121.3, 124.0, 125.3, 125.4, 127.4, 127.69, 127.72, 128.0, 129.1, 129.2, 129.4, 129.66, 129.74, 129.8, 132.68, 132.71, 133.0, 133.1, 134.4, 135.0, 135.1, 135.57, 135.65, 139.1, 139.2, 143.49, 143.53, 158.6, 171.5, 173.3, 173.9, 176.3, 193.2, 197.9; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{47}H_{50}ClNNaO_5Si$, 794.3039; found, 794.3055.

12f (15.6 mg, 67%, tautomeric mixture: 1.44:1 in $CDCl_3$): IR (neat) 3051, 2929, 2856, 1741, 1668, 1647, 1601, 1493, 1448, 1429, 1408, 1259, 1132, 1113, 1041 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 5.3H), 0.96 (s, 3.7H), 1.57-1.83 (m, 4H), 2.31 (s, 1.8H), 2.34 (s, 1.2H), 2.54-2.63 (m, 2H), 2.90-3.12 (m, 2H), 3.98-4.15 (m, 2H), 4.47-4.56 (m, 3H), 4.99 (brs, 0.82H), 5.00 (brs, 1.2H), 6.74-6.79 (m, 3H), 6.98-7.03 (m, 2H), 7.1-7.26 (m, 3H), 7.34-7.43 (m, 10H), 7.63-7.7 (m, 4H), 10.4 (brm, 0.41H), 11.3 (brm, 0.59H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.38, 21.40, 26.5, 26.6, 27.1, 27.2, 27.5, 31.1, 31.2, 35.3, 46.6, 46.9, 62.3, 62.5, 69.0, 81.3, 83.3, 91.4, 92.8, 112.0, 112.1, 114.99, 115.03, 121.2, 124.0, 127.68, 127.71, 128.7, 128.8, 129.1, 129.2, 129.4, 129.66, 129.74, 132.66, 132.69, 133.0, 133.1, 133.6, 135.0, 135.1, 135.56, 135.64, 139.1, 143.46, 143.51, 158.6, 171.5, 173.3, 173.9, 176.3, 193.2, 197.9; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{47}H_{50}ClNNaO_5Si$, 794.3039; found, 794.3033.

12g (58.3 mg, 66%, tautomeric mixture: 1.33:1 in $CDCl_3$): IR (neat) 3070, 2929, 2856, 1741, 1668, 1647, 1601, 1510, 1442, 1429, 1238, 1130, 1113, 1038, 823 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 5.1H), 0.96 (s, 3.9H), 1.57-1.81 (m, 4H), 2.32 (s, 1.7H), 2.34 (s, 1.3H), 2.52-2.61 (m, 2H), 2.88-3.14 (m, 2H), 3.98-4.12 (m, 2H), 4.47-4.56 (m, 3H), 5.12 (br, 2H), 6.87-6.91 (m, 2H), 6.97-7.15 (m, 5H), 7.19-7.30 (m, 4H), 7.33-7.44 (m, 6H), 7.53-7.57 (m, 1H), 7.63-7.70 (m, 4H), 10.4 (brm, 0.43H), 11.3 (brm, 0.57H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.3, 21.4, 26.5, 26.5, 27.0, 27.1, 27.5, 31.38, 31.44, 34.4, 34.7, 46.6, 46.9, 62.2, 62.4, 67.1, 81.3, 83.3, 91.3, 92.8, 114.7, 124.0, 126.9, 127.58, 127.65, 127.7, 128.2, 128.5, 128.7 128.8, 129.06, 129.13, 129.3, 129.6, 129.7, 132.4, 132.6, 132.7, 132.9, 133.0, 134.27, 134.32, 134.8, 135.0, 135.1, 135.5, 135.6, 139.0, 156.7, 171.5, 173.3, 174.0, 176.2, 193.1, 197.9; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{47}H_{50}ClNNaO_5Si$, 794.3039; found, 794.3046.

12h (51.2 mg, 73%, tautomeric mixture: 1.38:1 in $CDCl_3$): IR (neat) 3032, 2929, 2856, 1741, 1668, 1647, 1601, 1510, 1429, 1238, 1132, 1113, 1039, 823 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 5.2H), 0.96 (s, 3.8H), 1.57-1.81 (m, 4H), 2.32 (s, 1.7H), 2.34 (s, 1.3H), 2.51-2.60 (m, 2H), 2.88-3.14 (m, 2H), 3.98-4.12 (m, 2H), 4.47-4.56 (m, 3H), 4.98 (brs, 2H), 6.84-6.88 (m, 2H), 6.98-7.09 (m, 4H), 7.12-7.15 (m, 1H), 7.20-7.25 (m, 1H), 7.28-7.31 (m, 3H), 7.33-7.44 (m, 7H), 7.63-7.69 (m, 4H), 10.4 (brm, 0.42H), 11.3 (brm, 0.58H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.36, 21.39, 26.52, 26.55, 27.07, 27.13, 27.2, 27.5, 31.4, 31.5, 34.4, 46.6, 46.9, 62.2, 62.5, 69.1, 81.3, 83.3, 91.4, 92.8, 114.7, 124.0, 125.28, 127.34, 127.59, 127.62, 127.67, 127.70, 128.0, 128.6, 129.1, 129.2, 129.28, 129.31, 129.6, 129.7, 129.8, 132.6, 132.7, 132.9, 133.0, 134.3, 134.39, 134.42, 135.0, 135.1, 135.5, 135.6, 139.0, 139.2, 156.7, 171.5, 173.3, 174.0, 176.3, 193.2, 197.9; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{47}H_{50}ClNNaO_5Si$, 794.3039; found, 794.3043.

12i (49.4 mg, 80%, tautomeric mixture: 1.38:1 in $CDCl_3$): IR (neat) 3030, 2929, 2858, 1741, 1668, 1645, 1601, 1510, 1238, 1132, 1113, 1039, 1014, 822 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 5.2H), 0.96 (s, 3.8H), 1.57-1.81 (m, 4H), 2.32 (s, 1.7H), 2.34 (s, 1.3H), 2.51-2.59 (m, 2H), 2.88-3.13 (m, 2H), 3.98-4.15 (m, 2H), 4.48-4.56 (m, 3H), 4.98 (br, 2H), 6.83-6.87 (m, 2H), 6.98-7.08 (m, 4H), 7.12-7.15 (m, 1H), 7.20-7.26 (m, 1H), 7.34-7.42 (m, 10H), 7.63-7.70 (m, 4H), 10.4 (brm, 0.42H), 11.3 (brm, 0.58H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.36, 21.39, 26.51, 26.54, 27.07, 27.12, 27.2, 27.5, 31.4, 31.5, 34.4, 46.6, 46.9, 62.2, 62.5, 69.2, 81.3, 83.3, 91.3, 92.8, 114.7, 124.0, 127.59, 127.62, 127.66, 127.69, 128.67, 128.69, 129.07, 129.15, 129.25, 129.29, 129.6, 129.7, 132.6, 132.7, 132.9, 133.0, 133.6, 134.26, 134.32, 135.0, 135.1, 135.5, 135.6, 139.0, 156.7, 171.5, 173.3, 174.0, 176.2, 193.2, 197.9; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{47}H_{50}ClNNaO_5Si$, 794.3039; found, 794.3045.

12j (24.9 mg, 59%, tautomeric mixture: 1.33:1 in $CDCl_3$): IR (neat) 3032, 2929, 2858, 1743, 1670, 1647, 1601, 1498, 1452, 1406, 1342, 1240, 1113, 1039, 924, 823 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 5.1H), 0.96 (s, 3.9H), 1.57-1.85 (m, 4H), 2.30 (s, 1.7H), 2.32 (s, 1.3H), 2.66-2.75 (m, 2H), 2.91-3.11 (m, 2H), 3.98-4.11 (m, 2H), 4.46-4.53 (m, 3H), 5.06 (br, 2H), 6.87-6.91 (m, 2H), 6.94-6.99 (m, 2H), 7.10-7.31 (m, 5H), 7.32-7.44 (m, 10H), 7.63-7.70 (m, 4H), 10.4 (brm, 0.43H), 11.3 (brm, 0.57H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.37, 21.39, 26.52, 26.55, 27.1, 27.3, 27.5, 29.7, 29.8, 46.6, 46.9, 62.3, 62.5, 69.8, 81.3, 83.3, 91.3, 92.7, 111.6, 120.7, 124.1, 127.05, 127.08, 127.67, 127.70, 127.8, 128.5, 129.06, 129.13, 129.6, 129.7, 129.9, 130.0, 130.4, 130.5, 132.70, 132.74, 132.98, 133.03, 135.0, 135.1, 135.56, 135.65, 137.4, 139.0, 156.5, 171.5, 173.5, 174.1, 176.3, 193.1, 197.9; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{47}H_{51}NO_5SiNa$, 760.3429; found, 760.3429.

12k (38.0 mg, 61%, tautomeric mixture: 1.38:1 in $CDCl_3$): IR (neat) 2931, 2860, 1741, 1670, 1649, 1601, 1493, 1454, 1429, 1325, 1242, 1165, 1124, 1113, 1066, 1039, 823 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 5.2H), 0.95 (s, 3.8H), 1.57-1.86 (m, 4H), 2.30 (s, 1.3H), 2.32 (s, 1.7H), 2.67-2.78 (m, 2H), 2.92-3.12 (m, 2H), 3.98-4.11 (m, 2H), 4.48-4.58 (m, 3H), 5.12 (br, 2H), 6.83-6.86 (m, 1H), 6.88-6.93 (m, 1H), 6.96-7.09 (m, 2H), 7.11-7.25 (m, 4H), 7.33-7.43 (m, 6H), 7.51-7.55 (m, 2H), 7.60-7.70 (m, 6H), 10.4 (brm, 0.42H), 11.3 (brm, 0.58H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.3, 21.4, 26.50, 26.53, 27.1, 27.4, 27.48, 27.54, 29.7, 29.8, 46.6, 46.9, 62.3, 62.5, 68.90, 68.93, 81.3, 83.3, 91.3, 92.8, 111.49, 111.52, 121.1, 124.0, 124.1 (m), 125.5 (m), 126.9, 126.98, 127.03, 127.2, 127.62, 127.66, 127.70, 128.6, 129.1, 129.2, 129.6 (m), 129.6, 129.7, 130.05, 130.08, 130.12, 130.39, 130.43, 132.6, 132.7, 132.96, 133.02, 135.0, 135.1, 135.53, 135.55, 135.64, 139.0, 141.4, 156.1, 171.5, 173.4, 174.0, 176.3, 193.1, 197.9; ^{19}F-NMR (376Hz, $CDCl_3$) δ -62.4; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{48}H_{50}F_3NO_5SiNa$, 828.3303; found, 828.3303.

12l (41.9 mg, 55%, tautomeric mixture: 1.44:1 in $CDCl_3$): IR (neat) 2934, 2855, 1740, 1668, 1647, 1601, 1521, 1494, 1428, 1346, 1300, 1241, 1134, 1112, 1089, 1041, 824 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 5.3H), 0.95 (s, 3.7H), 1.60-1.87 (m, 4H), 2.31 (s, 1.8H), 2.33 (s, 1.2H), 2.66-2.79 (m, 2H), 2.92-3.14 (m, 2H), 4.00-4.14 (m, 2H), 4.50-4.60 (m, 3H), 5.157 (br, 0.8H), 5.163 (br, 1.2H), 6.81-6.84 (m, 1H), 6.89-6.94 (m, 1H), 6.97-7.10 (m, 2H), 7.12-7.25 (m, 4H), 7.32-7.43 (m, 6H), 7.57-7.69 (m, 6H), 8.22-8.26 (m, 2H), 10.4 (brm, 0.41H), 11.3 (brm, 0.59H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.2, 21.35, 21.37, 26.49, 26.52, 27.1, 27.4, 27.5, 27.6, 29.7, 29.8, 29.9, 46.6, 46.9, 62.2, 62.5, 68.48, 68.53, 81.3, 83.3, 91.3, 92.8, 111.4, 111.5, 121.3, 123.8, 124.0, 127.19, 127.22, 127.3, 127.59, 127.65, 127.7, 129.1, 129.2, 129.59, 129.63, 129.7, 130.12, 130.15, 130.38, 130.42, 132.6, 132.7, 132.9, 133.0, 135.0, 135.1, 135.50, 135.53, 135.6, 139.0, 144.7, 147.39, 147.42, 155.78, 155.80, 171.5, 173.3, 173.9, 176.3, 193.1, 197.9; HRMS-ESI (m/z): [M+Na$^+$] calcd for $C_{47}H_{50}N_2O_7SiNa$, 805.3280; found, 805.3280.

*4.2.6. Representative procedure for transformation of **12** to **6***

To a solution of **12a** (10.0 mg, 12.9 μmol) in DMF (80 μL), a solution of TASF (4.3 mg, 15.5 μmol) in DMF (11.9 μL) was added at 0 °C. The mixture was stirred for 5 h, then a solution of phosphate buffer (*p*H 7.0) and ethyl acetate were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo (DMF was removed by azeotropic evaporation with toluene). Further purification was carried out by preparative thin layer chromatography (eluent: hexane/ethyl acetate = 1/4) and high-performance liquid chromatography (column: SenshuPak, PEGASIL Silica SP100, 10×250 mm, eluent: hexane/ethyl acetate = 1/2) to give **6a** (4.2 mg, 61%) as a white amorphous solid (tautomeric mixture: 1.38:1 in $CDCl_3$). IR (neat) 3444, 2930, 1736, 1645, 1600, 1494, 1442, 1407, 1343, 1238, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57-1.70 (m, 2H), 1.78-1.88 (m, 2H), 1.98 (brt, *J* = 6.9 Hz, 0.58H), 2.05 (brt, *J* = 6.9 Hz, 0.42H), 2.34 (br, 3H), 2.75 (brt, *J* = 7.4 Hz, 2H), 2.91-3.13 (m, 2H), 3.92-3.98 (m, 2H), 4.48 (br, 1.2H), 4.49 (br, 0.8H), 4.51 (brt, *J* = 4.1 Hz, 0.42H), 4.53 (brt, *J* = 4.1 Hz, 0.58H), 5.14 (br, 2H), 6.89-6.94 (m, 2H), 6.96-7.00 (m, 2H), 7.12-7.31 (m, 6H), 7.36-7.39 (m, 1H), 7.52-7.56 (m, 1H), 10.3 (br, 0.42H), 11.2 (br, 0.58H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 27.3, 27.4, 27.7, 29.7, 29.8, 29.9, 46.9, 47.2, 61.7, 61.8, 67.12, 67.14, 80.6, 82.3, 90.3, 91.8, 111.7, 121.0, 124.25, 124.34, 126.96, 127.03, 127.2, 127.9, 128.0, 128.5, 128.9, 129.1, 129.2, 129.3, 129.4, 130.1, 130.3, 130.4, 132.46, 132.51, 134.5, 134.6, 135.0, 139.1, 156.2, 171.1, 174.1, 174.6, 175.9, 193.2, 197.5; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{31}H_{32}ClNNaO_5$, 556.1861; found, 556.1860.

6b (3.3mg, 58%, tautomeric mixture: 1.27:1 in $CDCl_3$): IR (neat) 3445, 2930, 1738, 1646, 1600, 1495, 1453, 1408, 1344, 1239, 1113, 1085, 1048 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.53-1.71 (m, 2H), 1.76-1.86 (m, 2H), 1.97 (dd, *J* = 7.8 Hz, 6.0 Hz, 0.56H), 2.03 (dd, *J* = 7.4 Hz, 6.0 Hz, 0.44H), 2.339 (s, 1.3H), 2.342 (s, 1.7H), 2.73 (brt, *J* = 7.4 Hz, 2H), 2.91-3.14 (m, 2H), 3.90-4.00 (m, 2H), 4.49 (br, 1.1H), 4.50 (br, 0.9H), 4.51 (brt, *J* = 4.1 Hz, 0.44H), 4.54 (brt, *J* = 4.1 Hz, 0.56H), 5.03 (brs, 2H), 6.86 (brd, *J* = 7.8 Hz, 1H), 6.89-6.93 (m, 1H), 6.96-7.01 (m, 2H), 7.12-7.19 (m, 3H), 7.22-7.31 (m, 4H), 7.42 (brm, 1H), 10.3 (br, 0.44H), 11.2 (br, 0.56H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 27.27, 27.32, 27.4, 27.7, 29.76, 29.81, 46.9, 47.2, 61.7, 61.8, 69.0, 80.6, 82.3, 90.3, 91.8, 111.6, 121.0, 124.26, 124.34, 125.1, 127.0, 127.2, 127.9, 128.0, 129.1, 129.2, 129.3, 129.4, 129.86, 129.90, 130.1, 130.39, 130.4, 134.4, 134.5, 134.6, 139.1, 139.5, 156.2, 171.1, 174.0, 174.6, 175.8, 193.2, 197.5; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{31}H_{32}ClNNaO_5$, 556.1861; found, 556.1855.

6c (4.4 mg, 80%, tautomeric mixture: 1.44:1 in $CDCl_3$): IR (neat) 3392, 2930, 1738, 1644, 1600, 1494, 1452, 1409, 1343, 1239, 1086, 1049, 1015, 810 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.56-1.70 (m, 2H), 1.74-1.84 (m, 2H), 1.95-2.03 (m, 1H), 2.35 (br, 3H), 2.71 (brt, *J* = 7.4 Hz, 2H), 2.91-3.11 (m, 2H), 3.90-4.01 (m, 2H), 4.48 (br, 1.2H), 4.49 (br, 0.8H), 4.50 (brt, *J* = 4.6 Hz, 0.41H), 4.54 (brt, *J* = 4.1 Hz, 0.59H), 5.02 (s, 2H), 6.86 (brd, *J* = 8.3 Hz, 1H), 6.90 (brt, *J* = 7.4 Hz, 1H), 6.96-7.02 (m, 2H), 7.13-7.19 (m, 3H), 7.23-7.28 (m, 1H), 7.34 (brs, 4H), 10.3 (br, 0.41H), 11.2 (br, 0.59H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 27.2, 27.3, 27.3, 27.6, 29.61, 29.64, 29.7, 29.8, 46.8, 47.2, 61.6, 61.8, 69.1, 80.6, 82.4, 90.4, 91.9, 111.6, 121.0, 124.2, 124.3, 127.2, 127.9, 128.0, 128.5, 128.7, 129.16, 129.18, 129.36, 129.39, 130.0, 130.3, 130.4, 133.6, 134.5, 134.6, 135.8, 139.2, 156.3, 171.2, 174.0, 174.5, 175.9, 193.2, 197.5; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{31}H_{32}ClNNaO_5$, 556.1861; found, 556.1865.

6d (3.7 mg, 67%, tautomeric mixture: 1.38:1 in $CDCl_3$): IR (neat) 3390, 2937, 1736, 1645, 1600, 1506, 1443, 1407, 1344, 1258, 1157, 1089, 1035 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.52-1.69 (m, 2H), 1.75-1.84 (m, 2H), 1.99 (brt, *J* = 6.4 Hz, 0.58H), 2.05 (brt, *J* = 6.4 Hz, 0.42H), 2.35 (brs, 3H), 2.64 (brt, *J* = 7.8 Hz, 2H), 2.92-3.12 (m, 2H), 3.91-4.02 (m, 2H), 4.51 (br, 1.2H), 4.52 (br, 0.8H), 4.52 (brt, *J* = 4.1 Hz, 0.42H), 4.55 (brt, *J* = 4.1 Hz, 0.58H), 5.14 (s, 2H), 6.78-6.83 (m, 3H), 6.98-7.03 (m, 2H), 7.13-7.32 (m, 5H), 7.38-7.41 (m, 1H), 7.54-7.57 (m, 1H), 10.3 (br, 0.42H), 11.3 (br, 0.58H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 26.9, 27.0, 27.3, 27.6, 31.0, 35.2, 35.3, 46.9, 47.2, 61.6, 61.8, 70.0, 80.7, 82.5, 90.5, 91.9, 112.0, 112.1, 115.1, 115.2, 121.3, 124.2, 124.3, 126.9, 127.8, 128.0, 128.8, 128.9, 129.17, 129.19, 129.3, 129.4, 129.5, 132.6, 134.5, 134.6, 134.8, 139.2, 143.37, 143.41, 158.6, 171.2, 173.9, 174.4, 175.8, 193.3, 197.5; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{31}H_{32}ClNNaO_5$, 556.1861; found, 556.1865.

6e (3.6 mg, 61%, tautomeric mixture: 1.38:1 in $CDCl_3$): IR (neat) 3444, 2930, 1736, 1645, 1599, 1506, 1441, 1409, 1344, 1257, 1150, 1096, 1035 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.52-1.68 (m, 2H), 1.75-1.84 (m, 2H), 2.00 (brt, *J* = 6.4 Hz, 0.58H), 2.05 (brt, *J* = 6.9 Hz, 0.42H), 2.35 (s, 3H), 2.63 (t, *J* = 7.4 Hz, 2H), 2.93-3.12 (m, 2H), 4.51 (br, 1.2H), 4.52 (m, 1.2H), 4.55 (brt, *J* = 3.7 Hz, 0.58H), 5.01 (s, 2H), 6.77-6.81 (m, 3H), 6.98-7.04 (m, 2H), 7.13-7.26 (m, 3H), 7.30 (brs, 3H), 7.43 (brs, 1H), 10.3 (br, 0.42H), 11.2 (br, 0.58H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 26.9, 27.0, 27.2, 27.6, 31.0, 35.2, 46.9, 47.2, 61.6, 61.7, 69.0, 80.7, 82.5, 90.5, 91.9, 111.95, 112.03, 115.05, 115.11, 121.3, 124.2, 124.3, 125.4, 127.4, 127.8, 127.95, 128.01, 129.16, 129.19, 129.35, 129.39, 129.43, 129.44, 129.8, 134.4, 134.6, 139.1, 139.2, 143.36, 143.41, 158.5, 171.2, 173.8, 174.4, 175.8, 193.2, 197.5; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{31}H_{32}ClNNaO_5$, 556.1861; found, 556.1864.

6f (4.3 mg, 72%, tautomeric mixture: 1.44:1 in $CDCl_3$): IR (neat) 3445, 2932, 1736, 1645, 1600, 1494, 1446, 1408, 1343, 1258, 1156, 1087, 1034, 1016, 812 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.53-1.68 (m, 2H), 1.74-1.84 (m, 2H), 2.00 (brt, *J* = 6.4 Hz, 0.59H), 2.05 (brt, *J* = 6.9 Hz, 0.41H), 2.35 (s, 3H), 2.63 (brt, *J* = 7.4 Hz, 2H), 2.93-3.12 (m, 2H), 3.91-3.99 (m, 2H), 4.51 (br, 1.2H), 4.53 (m, 1.2H), 4.55 (brt, *J* = 4.1 Hz, 0.59H), 5.00 (brs, 2H), 6.76-6.80 (m, 3H), 6.99-7.04 (m, 2H), 7.14-7.21 (m, 2H), 7.24-7.29 (m, 1H), 7.35 (s, 4H), 10.3 (br, 0.41H), 11.3 (br, 0.59H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 26.9, 27.0, 27.2, 27.6, 30.9, 35.20, 35.24, 46.9, 47.2, 61.6, 61.7, 69.1, 80.7, 82.5, 90.5, 91.9, 112.0, 112.1, 115.07, 115.13, 121.2, 124.2, 124.3, 127.8, 128.0, 128.7, 128.8, 129.17, 129.20, 129.37, 129.40, 133.7, 134.5, 134.6, 135.6, 139.2, 143.36, 143.41, 158.6, 171.2, 173.9, 174.4, 175.8, 193.3, 197.5; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{31}H_{32}ClNNaO_5$, 556.1861; found, 556.1867.

6g (4.5 mg, 59%, tautomeric mixture: 1.38:1 in $CDCl_3$): IR (neat) 3391, 2924, 1736, 1644, 1598, 1509, 1442, 1408, 1343, 1237, 1177, 1085, 1033, 825 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.53-1.68 (m, 2H), 1.72-1.82 (m, 2H), 1.97-2.08 (m, 1H), 2.36 (brs, 3H), 2.60 (brt, *J* = 7.4 Hz, 2H), 2.92-3.13 (m, 2H), 3.91-4.03 (m, 2H), 4.51 (br, 1.2H), 4.52 (br, 1.2H), 4.55 (brt, *J* = 4.1 Hz, 0.59H), 5.13 (s, 2H), 6.88-6.92 (m, 2H), 6.98-7.04 (m, 2H), 7.07-7.11 (m, 2H), 7.13-7.18 (m, 1H), 7.23-7.31 (m, 3H), 7.37-7.41 (m, 1H), 7.54-7.58 (m, 1H), 10.3 (br, 0.42H), 11.3 (br, 0.58H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 26.9, 27.0, 27.3, 27.6, 31.3, 34.4, 46.9, 47.2, 61.6, 61.8, 67.1, 80.7, 82.5, 90.4, 91.9, 114.7, 124.2, 124.3, 126.9, 127.8, 127.9, 128.7, 128.9, 129.15, 129.18, 129.3, 129.4, 132.5, 134.19, 134.22, 134.5, 134.6, 134.8, 139.1, 156.7, 171.2, 173.9, 174.5, 175.8, 193.2, 197.5; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{31}H_{32}ClNNaO_5$, 556.1861; found, 556.1865.

6h (5.1 mg, 64%, tautomeric mixture: 1.44:1 in $CDCl_3$): IR (neat) 3441, 2930, 1736, 1645, 1600, 1510, 1437, 1408, 1344, 1237, 1084, 1032, 826 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.52-1.68 (m, 2H), 1.72-1.82 (m, 2H), 2.00-2.10 (m, 1H), 2.36 (brs, 3H), 2.59 (brt, *J* = 7.4 Hz, 2H), 2.91-3.13 (m, 2H), 3.94-4.00 (m, 2H), 4.51 (br, 1.2H), 4.52 (br, 1.2H), 4.55 (brt, *J* = 4.1 Hz, 0.59H), 5.00 (s, 2H), 6.85-6.89 (m, 2H), 6.98-7.04 (m, 2H), 7.06-7.11 (m, 2H), 7.13-7.18 (m, 1H), 7.24-7.28 (m, 1H), 7.28-7.31 (m, 3H), 7.43 (br, 1H), 10.3 (br, 0.41H), 11.3 (br, 0.59H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 26.9, 27.0, 27.3, 27.6, 31.3, 34.32, 34.35, 46.9, 47.2, 61.6, 61.7, 69.1, 80.7, 82.5, 90.4, 91.9, 114.7, 124.2, 124.3, 125.3, 127.4, 127.8, 127.9, 128.0, 129.1, 129.2, 129.3, 129.4, 129.8, 134.2, 134.3, 134.4, 134.5, 134.6, 139.16, 139.20, 156.7, 171.2, 173.9, 174.4, 175.8, 193.2, 197.5; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{31}H_{32}ClNNaO_5$, 556.1861; found, 556.1866.

6i (3.7 mg, 70%, tautomeric mixture: 1.44:1 in $CDCl_3$): IR (neat) 3452, 2929, 1736, 1644, 1599, 1510, 1440, 1408, 1344, 1238, 1091, 1033, 1015, 814 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.52-1.67 (m, 2H), 1.72-1.81 (m, 2H), 1.96-2.07 (m, 1H), 2.36 (brs, 3H), 2.59 (brt, *J* = 7.4 Hz, 2H), 2.92-3.13 (m, 2H), 3.93-4.00 (m, 2H), 4.51 (br, 1.2H), 4.53 (br, 1.2H), 4.55 (brt, *J* = 4.1 Hz, 0.59H), 4.99 (s, 2H), 6.85-6.89 (m, 2H), 6.96-7.04 (m, 2H), 6.98-7.04 (m, 2H), 7.05-7.10 (m, 1H), 7.24-7.29 (m, 1H), 7.35 (s, 4H), 10.3 (br, 0.41H), 11.3 (br, 0.59H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 26.96, 27.02, 27.3, 27.6, 31.3, 34.4, 46.9, 47.2, 61.6, 61.8, 69.2, 80.7, 82.4, 90.5, 91.9, 114.7, 124.2, 124.3, 127.8, 128.0, 128.7, 129.17, 129.19, 129.3, 129.36, 129.39, 133.7, 134.18, 134.22, 134.5, 134.6, 135.6, 139.2, 156.8, 171.2, 173.9, 174.5, 175.8, 193.3, 197.5; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{31}H_{32}ClNNaO_5$, 556.1861; found, 556.1867.

6j (11.4 mg, 78%, tautomeric mixture: 1.38:1 in $CDCl_3$): IR (neat) 3423, 2935, 2864, 1738, 1645, 1599, 1498, 1450, 1406, 1344, 1238, 1113, 1084, 1030 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.54-1.70 (m, 2H), 1.76-1.85 (m, 2H), 2.07 (brt, *J* = 6.9 Hz, 0.58H), 2.12 (brt, *J* = 6.9 Hz, 0.42H), 2.34 (brs, 3H), 2.72 (brt, *J* = 7.4 Hz, 2H), 2.90-3.11 (m, 2H), 3.91-4.00 (m, 2H), 4.45 (br, 0.8H), 4.46 (br, 1.2H), 4.50 (brt, *J* = 4.1 Hz, 0.42H), 4.53 (brt, *J* = 4.1 Hz, 0.58H), 5.06 (s, 2H), 6.87-6.92 (m, 2H), 6.94-7.00 (m, 2H), 7.12-7.19 (m, 3H), 7.21-7.25 (m, 1H), 7.27-7.32 (m, 1H), 7.34-7.43 (m, 4H), 10.3 (br, 0.42H), 11.2 (br, 0.58H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 27.2, 27.3, 27.6, 29.6, 29.7, 29.8, 46.8, 47.2, 61.6, 61.8, 69.8, 80.6, 82.4, 90.3, 91.8, 111.7, 120.8, 124.27, 124.34, 127.1, 127.2, 127.8, 127.9, 128.0, 128.5, 129.1, 129.2, 129.31, 129.35, 130.0, 130.36, 130.40, 134.5, 134.6, 137.3, 139.1, 156.5, 171.2, 174.1, 174.6, 175.9, 193.2, 197.5; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{31}H_{33}NO_5Na$, 522.2251; found, 522.2251.

6k (17.4 mg, 72%, tautomeric mixture: 1.44:1 in $CDCl_3$): IR (neat) 3423, 2929, 2864, 1738, 1645, 1601, 1493, 1452, 1412, 1325, 1240, 1163, 1120, 1066, 1018, 823 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.56-1.70 (m, 2H), 1.76-1.86 (m, 2H), 2.05-2.13 (m, 1H), 2.34 (brs, 3H), 2.73 (brt, *J* = 7.4 Hz, 2H), 2.92-3.14 (m, 2H), 3.90-4.01 (m, 2H), 4.50 (br, 1.2H), 4.51 (br, 1.2H), 4.53 (brt, *J* = 4.1 Hz, 0.59H), 4.53 (brt, *J* = 4.1 Hz, 0.58H), 5.12 (s, 2H), 6.86 (brd, *J* = 8.3 Hz, 1H), 6.92 (brt, *J* = 6.9 Hz, 1H), 6.96-7.02 (m, 2H), 7.12-7.20 (m, 3H), 7.22-7.27 (m, 1H), 7.54 (brd, *J* = 8.3 Hz, 2H), 7.64 (brd, *J* = 8.3 Hz, 2H), 10.3 (br, 0.41H), 11.2 (br, 0.59H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 27.3, 27.4, 27.6, 29.6, 29.8, 46.8, 47.2, 61.6, 61.7, 69.0, 80.7, 82.5, 90.4, 91.9, 111.6, 121.1, 124.1 (m), 124.2, 124.3, 125.5 (m), 127.0, 127.1, 127.2, 127.8, 127.9, 129.1, 129.2, 129.3, 129.4, 129.6 (m), 130.1, 130.3, 130.4, 134.5, 134.6, 139.2, 141.4, 156.1, 171.2, 174.0, 174.5, 175.9, 193.2, 197.5; ^{19}F-NMR (376Hz, $CDCl_3$) δ -62.4; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{32}H_{32}F_3NO_5Na$, 590.2125; found, 590.2125.

6l (22.7 mg, 82%, tautomeric mixture: 1.44:1 in $CDCl_3$): IR (neat) 3406, 2933, 2864, 1736, 1645, 1599, 1520, 1452, 1410, 1346, 1240, 1111, 1049, 825 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.57-1.70 (m, 2H), 1.78-1.87 (m, 2H), 2.07 (brt, *J* = 6.0 Hz, 1H), 2.35 (brs, 3H), 2.74 (brt, *J* = 7.4 Hz, 2H), 2.95-3.15 (m, 2H), 3.93-4.02 (m, 2H), 4.52 (br, 1.2H), 4.54 (br, 1.2H), 4.55 (brt, *J* = 4.1 Hz, 0.59H), 5.16 (s, 2H), 6.84 (brd, *J* = 8.7 Hz, 1H), 6.93 (brt, *J* = 7.4 Hz, 1H), 6.97-7.03 (m, 2H), 7.13-7.20 (m, 3H), 7.23-7.28 (m, 1H), 7.58-7.62 (m, 2H), 8.23-8.28 (m, 2H), 10.3 (br, 0.41H), 11.2 (br, 0.59H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 27.27, 27.32, 27.4, 27.7, 29.7, 29.8, 46.8, 47.2, 61.5, 61.6, 68.5, 68.6, 80.8, 82.6, 90.5, 91.9, 111.5, 121.3, 123.9, 124.16, 124.24, 127.2, 127.3, 127.4, 127.8, 127.9, 129.1, 129.2, 129.3, 129.4, 130.1, 130.3, 130.4, 134.4, 134.6, 139.2, 144.7, 147.5, 155.8, 171.2, 173.8, 174.4, 175.9, 193.2, 197.6; HRMS-ESI (m/z): [M+Na^+] calcd for $C_{31}H_{32}N_2O_7Na$, 567.2102; found, 567.2102.

4.2.7. Inhibitory activity for VHR

VHR activity was measured in a 96-well microtiter plate using O-methylfluorescein phosphate (OMFP) (Sigma, St. Louis, MO) as a substrate. Purified VHR (22 ng) was preincubated at 37 °C for 30 min in the reaction buffer (50 mM succinate, 1 mM EDTA, 150 mM NaCl, 1 mM dithiothreitol, pH 6.0, 0.001% NP-40) in the presence or absence of a test compound. Dephosphorylation reaction was started by addition of OMFP (10 μM). The mixture was incubated at 37 °C for 10 min. Fluorescence emission from the dephosphorylated product was measured with a SpectraMax M5 (Molecular Devices, Sunnyvale, CA) using a 485 nm excitation filter and 530 nm emission filter. The IC_{50} value for each cell line was determined from the sigmoid dose-response curve using the Origin8J program.

4.2.8. Anti-proliferative activity for HeLa cells

Proliferation of HeLa cells in the presence of RE derivatives was evaluated as follows. HeLa cells were plated at 3 x 10^3 cells/well in 96-well microtiter plates and treated with compounds at the indicated concentrations. After 48 h treatment, Alamar Blue™ (Invitrogen) was added to the wells, and the plate was incubated for 3 h at 37 °C under 5 % CO_2 in air. Fluorescence was measured with a SpectraMax M5 (Molecular Devices) using a 530 nm-excitation filter and a 590 nm-emission filter. The IC_{50} value for each cell line was determined from the sigmoid dose-response curve using the Origin8J program.

Acknowledgments

We thank the Collaboration Promotion Unit (RIKEN Global Research Cluster) for HRMS analysis and helpful discussions. This work was partially supported by Project Funding from RIKEN and a Grant-in Aid for Scientific Research on Innovative Area (Grant Number 24102534).

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Supplementary Material

^{1}H NMR, ^{13}C NMR, and data from biochemical and biological experiments.