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Synthesis and biological activity of C-7, C-9 and C-10 modified taxane analogues from 1-deoxybaccatin VI

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ABSTRACT

A series of C-7, C-9 and C-10 modified taxane analogues were synthesized and their *in vitro* anticancer activities against three human cancer cell lines: A-549 (human lung cancer cell line), MDA-MB-231 (human breast cancer cell line), A-549/T (human lung cancer resistant cell line) were studied. The novel 1-deoxybaccatin VI derivatives modified with carbonate group at C-9 and C-10 positions enable the behavior of these compounds to be evidently distinct from other similar compounds. The strong cytotoxicity in the three cell lines, especially in drug-resistant cell line, showed by the newly synthesized taxane analogues indicated them as potential lead compounds for anticancer drug design.

1. Introduction

Paclitaxel (PTX) **1**, a diterpenoid natural compound isolated from the stem bark of *Taxus brevifolia* (Pacific yew) in 1971,[1,2] and its derivative docetaxel **2** approved by FDA to treat breast cancer in 1996 are active against a number of cancer types including breast, lung, prostate, ovarian and some leukaemias,[3–5] due to their unique mechanism of action by bonding tubulin, promoting microtuble assembly and stabilizing microtubules,[6] which ultimately disrupts mitosis and causes cell death.[7–9] However, difficulties related to formulation and multiple drug resistance (MDR) limit the application of paclitaxel and its close analogue docetaxel in cancer treatments.[10] Therefore, it is essential to develop novel taxoid anticancer drugs with fewer side effects, superior pharmacological properties and improved activity against various classes of cancers.[11–13]

The bioactive conformation of paclitaxel is important since it could provide critical information that would allow the design of novel analogues with simpler structures and increased potency against cancers.[14] A series of analogues, which bear a 1,14-carbonate moiety, exhibited improved clinical properties such as oral bioavailability and broader spectrum of antitumor activity. Ortataxel **3** (Fig. 1) not only exhibited two orders of magnitude better cytotoxicity than paclitaxel against drug-resistant cells but also a significant improvement in water solubility, and it has been selected for clinical development.[15] In addition, it has been proposed that the ability of C-10 taxane analogues to overcome MDR *in vitro* is the result of reduced binding affinity for P-glycoprotein such as cabazitaxel **4**.[16] In 2002, C-9 and C-10 modified taxane analogues **5**, **6** and **7** were reported to be similar[17] and more potent than docetaxel, respectively.[18] These results suggest that substitutions at C7-C10 positions and carbonate group at C-1, C-14 positions may have profound influence on antitumor activity. Thus further exploration of the effects of carbonate group at C-9 and C-10 positions could be fruitful for the discovery of new candidates for drug development.

1-Deoxybaccatin VI (**8**), which is extracted from roots of *Taxus chinensis* in relatively high yield and reserves the essential pharmacophore, proves to be the valuable starting material for research.[19,20] As an ongoing part of our research on taxane analogues,[21,22] we developed a series of 1-deoxypaclitaxel analogues **16a-h** bearing different substituted groups at the C-3′-*N*-acyl position, C-7, C-9 and C-10 positions from 1-deoxybaccatin VI. The activities of these newly synthesized compounds against three cancer cell lines and cell survival data are also reported in this paper.

2. Results and discussion

2.1. Chemistry

As shown in Scheme 1, selective deacetylation of the C-7, C-9, C-10 and C-13 acetoxyl groups without concomitant deacylation of the C-2 and C-4 acyloxy groups of 1-deoxybaccatin VI **8** afforded **9**. Subsequent carbonation of the C-9 and C-10 hydroxyl groups using

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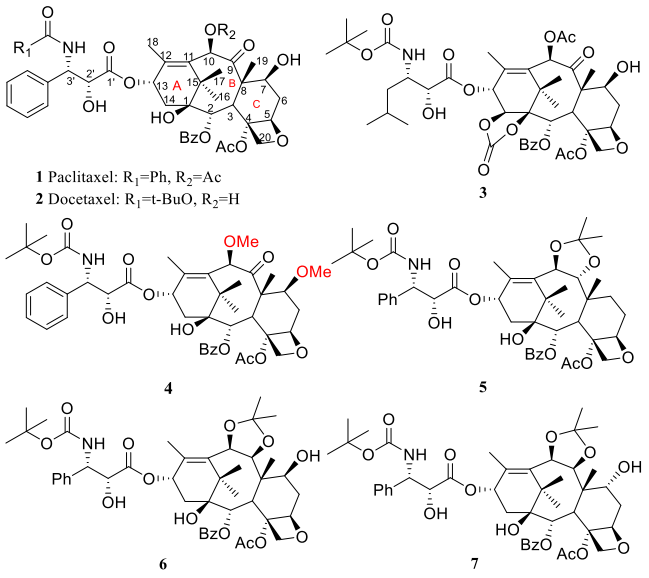
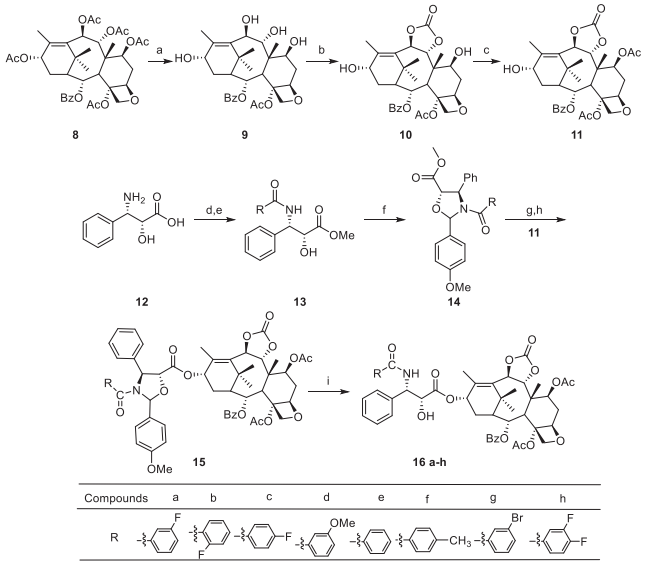


Fig. 1. Paclitaxel and paclitaxel analogues.



Scheme 1. Reagents and conditions: (a) $H_2NNH_2{\cdot}H_2O$, EtOH, rt, 40 h, 87%; (b) CDI, Et_3N, DCM/MeOH, rt, 6 h, 75%; (c) Ac_2O, DMAP, THF, rt, 1 h, 92% (**11**); (d) $SOCl_2$, MeOH, 0 ℃ to rt, overnight, 95%; (e) Carbonyl chloride, THF, sat. $NaHCO_3$, 0 ℃ to rt, 3 h, 85%-95%; (f) 4-Methoxybenzaldehyde dimethyl acetal, PPTS, toluene, 110 ℃, 80%-90%; (g) KOH, MeOH, rt, 2 h, 85%-95%; (h) EDC, DMAP, CH_2Cl_2, 50 ℃, 2 h, 85%-90%; (i) PTS, MeOH, rt, 5 h, 80%-85%.

carbonyldiimidazole (CDI) gave compound **10** due to the smaller stereo-hindrance effect on the C-9 and C-10 hydroxyl groups compared with C-7 and C-9 hydroxyl groups, in which only two hydroxyls remained at the C-7 and C-13 positions. The C-7 hydroxyl group of **10** is more active than C-13 hydroxyl group, which is distinctly different from the 9,10-O-isopropylidene derivative in which the C-13 hydroxyl group is more active than the C-7 hydroxyl group due to the huge stereo-hindrance effect on the C-7 hydroxyl group caused by the acetonide protection at the C-9 and C-10 positions.[23] Thus, the acetyl group was selectively introduced to C-7 position to afford **11** which can be coupled with paclitaxel side chains by the EDC-DMAP method in toluene.

As previously reported, paclitaxel side chains can be synthesized by different methods.[24–29] In this paper, we synthesized the oxazoline side chain precursor by using (*2R,3S*)-3-phenylisoserine **12** with natural configuration (Scheme 1).[29,30] Cyclic protection using 4-methoxy benzaldehyde dimethyl acetal in the presence of catalytic amount of pyridinium *para*-toluenesulfonate (PPTS) afforded **14a-h** in 80%-90% yields. Compounds **14a-h**, after saponification to the corresponding carboxylic acid without further purification, were then coupled with compound **11** in the presence of EDC and DMAP to smoothly provide the corresponding cyclic ester intermediates **15a-h** with good to excellent yield (85%-92%).[20,31] After hydrolysis of the acetonide protecting groups under p-toluenesulfonic acid, the final products **16a-h** were afforded (Scheme 1).

Table 1
Cytotoxicity (IC_{50} [a]) values for paclitaxel and its analogues **16a-h.**

Compound	IC_{50} ± SD (μM)		
	A549[b]	A549/T[c]	MDA-MB-231[d]
16a	0.068 ± 0.023	2.339 ± 0.338	0.183 ± 0.035
16b	0.115 ± 0.012	4.898 ± 1.006	0.182 ± 0.029
16c	0.133 ± 0.028	1.028 ± 0.069	0.209 ± 0.020
16d	0.069 ± 0.024	3.024 ± 0.053	0.068 ± 0.025
16e	0.022 ± 0.004	0.229 ± 0.057	0.124 ± 0.008
16f	0.062 ± 0.013	0.229 ± 0.035	0.119 ± 0.005
16 g	0.329 ± 0.003	2.885 ± 1.074	2.016 ± 0.369
16 h	0.408 ± 0.073	2.885 ± 0.069	1.950 ± 0.363
Paclitaxel	0.013 ± 0.003	1.584 ± 0.268	0.020 ± 0.001

[a] Cytotoxicity (IC_{50}) was assayed by CCK-8 method under growing human tumor cell lines were exposed for 72 h.
[b] Human lung cancer cell line.
[c] Human lung cancer resistant cell line.
[d] Human breast cancer cell line

2.2. Cytotoxicity assay

2.2.1. Cytotoxicity to A-549, A-549/T and MDA-MB-231

The newly synthesized compounds **16a-h** and paclitaxel were subsequently evaluated in cytotoxicity assays employing the A-549 (human lung cancer), MDA-MB-231 (human breast cancer), A549/T (human lung cancer resitent) cell line by CCK-8 method.[32] The inhibitory activities (IC_{50}) are summarized in Table 1.

As reported in Table 1, it was observed that most of compounds exhibited reduced cytotoxicities against A549 and MDA-MB-231 human cancer cell lines in comparison with paclitaxel. Among them, four compounds **16a**, **16d** and **16e-f** showed potent cytotoxicity with IC_{50} values in the range of 22–69 nM against A549 cell line and compound **16e** exhibited the highest cytotoxicity activity with IC_{50} of 22 nM. For MDA-MB-231 cell line, all compounds showed much weaker cytotoxicity activities than paclitaxel in this assay.

Although these new taxoids **16a-h** possess, in general, weaker cytotoxicities against A549 and MDA-MB-231 normal cancer cell lines than paclitaxel, it can be noted that compounds **16e** and **16f** exert remarkable cytotoxic effects against the drug-resistant human lung cancer cell line, A549/T, with IC_{50} values 7-fold lower than that of paclitaxel. The notable compound **16e** with benzoyl substituents at the C-3′-N shows the highest activity against both A549 and A549/T cell lines. In our previous investigation of 1-deoxypaclitaxel analogues, we discovered that compound **17** possessed a 10-fold reduced cytotoxicity against A 549 than paclitaxel,[19] by comparing both the structures of **16e** and **17** (Fig. 2), it is clear that a 9,10-O-isopropylidene group at the 9,10-positions markedly decreases cytotoxicity and the carbonate substituent at C-9,10 exerts a remarkable effect on the activity especially against the drug-resistant human lung cancer cell line, A549/T. Moreover, the 1-deoxypaclitaxel **18** synthesized from 1-deoxybaccatin VI exhibited comparable cytotoxicity to compound **17**. These results suggest that different substituents at C-9 and C-10 have great influences on the cytotoxicity.

The dose–response curves for paclitaxel and compounds **16a-h** are

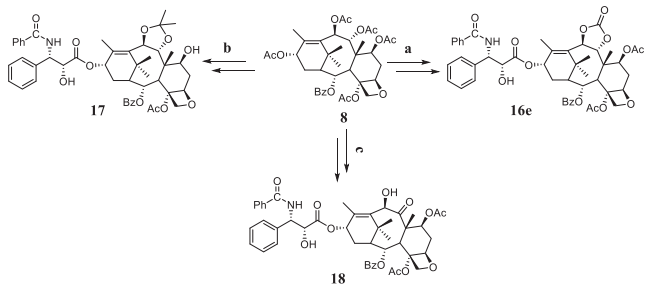


Fig. 2. Synthesis of compounds **16e** (Scheme 1), **17**[19] and **18** [21].

shown in Fig. 3. All exponentially growing human tumor cell lines exposed for 72 h to paclitaxel and the compounds formulated in DMSO solution (CCK-8 method) exhibited characteristic dose–response curves.[33–35] In A549 and MDA-MB-23 cell lines, all of the compounds exhibited weaker inhibition of cell survival than paclitaxel when the concentration was less than 0.1 μM. However, in A549/T cell lines, all of the compounds exhibited greater inhibition of cell survival than paclitaxel when the concentration was 0.01–0.1 μM, which implied that each of the compounds exhibited better efficacy than paclitaxel at this range of concentration. The superior cytotoxicity activity against A549/T of these compounds may be related to structural modifications at the C-7, C-9 and C-10 positions.

3. Conclusion

In summary, we have synthesized 1-deoxy taxane analogues from 1-deoxybaccatin VI and found that analogue **16e** based on the 9,10-carbonate taxane skeleton exhibits comparable cytotoxicity in A549 cell-based assay relative to paclitaxel and shows 7-fold more potent than paclitaxel in the A549/T assay. The new toxoids bearing different substituted groups at C-3′-N position showed degrees of cytotoxicity. Most of the compounds exhibited greater inhibition of cell survival than paclitaxel in 0.01–0.1 μM concentration in A549/T cell lines, indicating the advantage of introduction of carbonate group at the C-9 and C-10 positions. Further modifications of these structures with the aim of improving the potency *in vitro* as well as the efficacy *in vivo* are in progress.

4. Experimental section

4.1. General chemical procedures

Commercially available reagents were purchased and were used without further purification unless otherwise mentioned. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DM-500 MHz spectrometer at 500.134 MHz and 125.771 MHz, respectively, with TMS as an internal standard. Chemical shifts are reported in parts per million (ppm) and coupling constants (J) are reported in Hertz (Hz). Coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). Chemical shifts in $CDCl_3$ were reported in the scale relative to $CHCl_3$ (7.26 ppm) for ^{1}H NMR, and to $CDCl_3$ (77.16 ppm) for ^{13}C NMR, as internal references. Mass spectra were recorded on a Varian 320-MS TQ LC/MS in positive electrospray ionization (ESI) mode. 1-deoxybaccatin VI (**8**) was isolated according to literature procedures.

4.2. Synthetic procedures

4.2.1. Synthesis of compound 9

Compound **8** (2.0 g, 2.87 mol) was dissolved in 95% ethanol (140 mL) and treated with hydrazine hydrate (75 mL) at 26 ℃ for 12 h. After careful neutralization (1 N HCl, pH = 7), the mixture was extracted with EtOAc and worked up in the usual manner, then recrystallized from a mixture of methanol and water to yield **9** (1.4 g, 87%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.02 (d, J = 7.4 Hz, 2H), 7.69 (m, 1H), 7.58 (m, 2H), 6.27 (br, 1H), 6.08 (br,

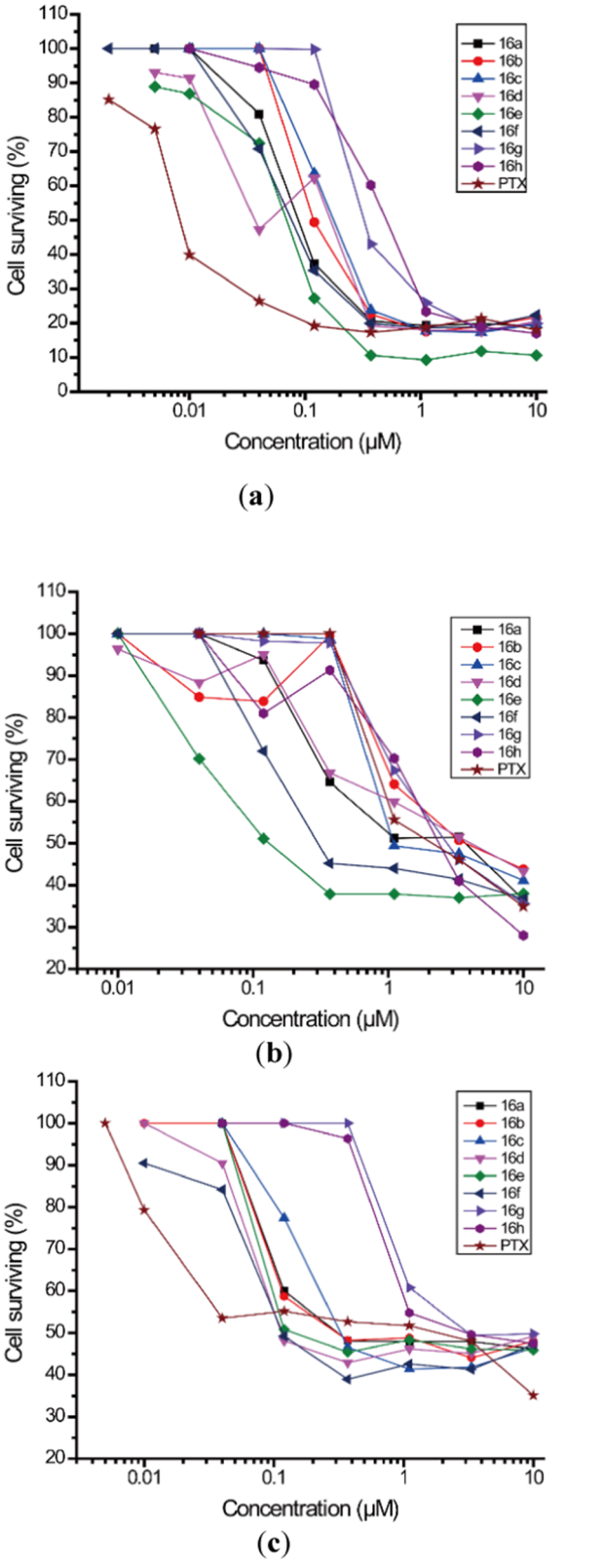


Fig. 3. Survival of three human tumor cell lines after exposure to compounds **16a-h** and paclitaxel for 72 h. (a) A-549 (human lung cancer) cell line; (b) A-549/T (human lung cancer resistant) cell line; (c) MDA-MB-231 (human breast cancer) cell line.

1H), 5.58 (dd, J = 4.4, 1.7 Hz, 1H), 4.99 (d, J = 4.6 Hz, 1H), 4.90 (d, J = 9.1 Hz, 1H), 4.68 (d, J = 10.4 Hz, 1H), 4.45–4.26 (m, 2H), 4.22 (t, J = 8.3 Hz, 1H), 4.15 (d, J = 8.0 Hz, 1H), 4.08–4.01 (br, 1H), 3.95 (d, J = 8.0 Hz, 1H), 2.87 (d, J = 5.3 Hz, 1H), 2.37–2.26 (m, 2H), 1.84 (s, 3H), 1.72 (dd, J = 8.7, 0.8 Hz, 1H), 1.67–1.64 (m, 2H), 1.59 (s, 6H), 1.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 169.5, 164.8, 138.4, 136.2, 134.0, 130.0, 129.7, 129.3, 83.7, 81.0, 78.9, 76.2, 73.4, 72.2, 70.8, 65.6, 47.6, 44.2, 43.8, 38.1, 37.8, 32.1, 30.3, 27.0, 23.0, 15.5, 13.0.

4.2.2. Synthesis of compound **10**

To a solution of 9 (530.8 mg, 1.0 mmol) in a mixture of CH_2Cl_2 (12 mL) and CH_3OH (0.5 mL) were added carbonyldiimidazole (162 mg, 4.0 mmol) followed by Et_3N (0.25 mL, 8 mmol), and the reaction mixture was vigorously stirred for 4 h at 50 ℃. The solution was filtered and evaporated to a white residue, which was recrystallized from acetonitrile, affording compound **10** (418.5 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.06 (d, J = 7.43 Hz, 2H), 7.62 (t, J = 7.40 Hz, 1H), 7.49 (t, J = 7.85 Hz, 2H), 5.74 (dd, J = 5.90, 2.40 Hz, 1H), 5.73 (d, J = 12.20 Hz, 1H), 5.24 (d, J = 12.20 Hz, 1H), 4.93 (d, J = 8.85 Hz, 1H), 4.66 (br, 1H), 4.37 (d, J = 8.35 Hz, 1H), 4.30 (td, J = 9.20 Hz, 3.80 Hz, 1H), 4.08 (d, J = 8.35 Hz, 1H), 2.69 (d, J = 5.45 Hz, 1H), 2.67–2.56 (m, 2H), 2.25 (s, 3H), 2.15 (d, J = 6.70, 1H), 2.08 (s, 3H), 2.00 (m, 1H), 1.88–1.82 (m, 1H), 1.75 (s, 3H), 1.71 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 171.8, 165.0, 134.1, 131.8, 129.9, 129.1, 126.9, 84.1, 83.9, 81.0, 78.0, 76.8, 71.4, 70.5, 69.0, 47.5, 42.6, 38.3, 36.7, 34.3, 31.7, 31.6, 26.8, 26.1, 22.3, 15.5, 13.9, 13.1.

4.2.3. Synthesis of compound **11**

To a stirred solution of **10** (53.0 mg, 0.10 mmol) and DMAP (48.9 mg, 0.4 mmol) in dry THF (8 mL) was added Ac_2O (0.08 mL, 0.4 mmol) dropwise. After stirred at 25 ℃ for 4 h, the reaction mixture was quenched with saturated aq. $NaHCO_3$, and then the solvent was evaporated under reduced pressure, followed by adding of EtOAc, the organic layer was washed by H_2O (3 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (eluent: EtOAc: hexane = 2: 1) to afford **11** as a white solid (50.8 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.07 (d, J = 7.43 Hz, 2H), 7.62 (t, J = 7.40 Hz, 1H), 7.49 (t, J = 7.85 Hz, 2H), 5.96 (d, J = 12.25 Hz, 1H), 5.70 (dd, J = 5.90, 2.40 Hz, 1H), 5.49 (t, J = 8.81 Hz, 1H), 5.10 (d, J = 12.25 Hz, 1H), 4.93 (d, J = 8.85 Hz, 1H), 4.66 (br, 1H), 4.37 (d, J = 8.35 Hz, 1H), 4.08 (d, J = 8.35 Hz, 1H), 2.75 (d, J = 5.45 Hz, 1H), 2.62–2.48 (m, 2H), 2.25(s, 3H), 2.16 (d, J = 6.70, 1H), 2.13 (s, 3H), 2.10 (s, 3H), 1.99–1.93 (m, 2H), 1.79 (s, 3H), 1.67 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.8, 171.1, 165.0, 134.1, 131.8, 129.9, 129.0, 126.8, 84.1, 83.9, 81.0, 78.0, 76.8, 71.4, 70.5, 69.0, 47.5, 42.6, 38.3, 36.7, 34.3, 31.7, 31.6, 26.8, 26.1, 22.3, 21.4, 15.5, 13.9, 13.1.

4.3. General procedure for synthesis of compounds **13a-h**

To a solution of (*2R,3S*)-3-Phenylisoserine **12** (100 mg, 0.52 mmol) in anhydrous MeOH (3 mL), thionyl chloride ($SOCl_2$, 0.05 mL, 0.79 mmol) was added drop-wise at 0 ℃. The reaction mixture was stirred overnight at room temperature and the reactionwas monitored by TLC. After the completion of the reaction, the reaction was quenched with $NaHCO_3$. The solution was evaporated under reduced pressure and diluted with H_2O. The water phasewas extracted with EtOAc three times, the combined organic solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure, resulting in an oil. To a solution of the resulting oil in a mixture of THF (10 mL) and saturated $NaHCO_3$ (10 mL), one of a series of different carbonyl chlorides (3 mmol) was added dropwise at 0 ℃, respectively. The whole mixture was stirred vigorously at room temperature for 3 h. The desired compound was extracted with EtOAc. The organic solution was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 1: 3), yielding a product **13a-h** (80%-90%).

4.3.1. Compound **13a**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.53 (d, J = 7.85 Hz, 2H), 7.48 (d, J = 5.90 Hz, 2H), 7.43–7.31 (m, 5H), 7.03 (br, 1H), 5.77 (dd, J = 5.80 Hz, 2.00 Hz, 1H), 4.77 (d, J = 2.61 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 171.7, 171.3, 165.5, 165.5, 164.9, 163.8, 158.8, 153.1, 143.1, 136.0, 131.9, 130.4, 128.8, 128.3, 127.3, 118.9, 73.5, 54.8, 47.5.

4.3.2. Compound **13b**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.96–7.90 (m, 1H), 7.52–7.46 (m, 5H), 7.33 (d, J = 7.36 Hz, 1H), 7.25–7.22 (m, 1H), 7.19–7.13 (m, 1H), 5.77 (dd, J = 5.76, 1.91 Hz, 1H), 4.72 (d, J = 2.58 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 171.3, 171.2, 164.9, 162.7, 161.8, 159.8, 153.1, 143.3, 133.7, 132.2, 131.9, 129.8, 128.8, 128.2, 127.3, 84.1, 73.9, 55.9, 47.5.

4.3.3. Compound **13c**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.80–7.76 (m, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 15.5 Hz, 2H), 7.31 (t, J = 15.0 Hz, 1H), 7.08 (t, J = 18.5 Hz, 2H), 5.74 (dd, J = 2.3, 2.5 Hz, 1H), 4.64 (d, J = 2.2 Hz, 1H), 4.60 (s, 1H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm:173.4, 166.0, 165.9, 163.9, 138.6, 130.2, 130.1, 129.6, 129.5, 128.8, 128.0, 126.9, 115.6, 73.3, 55.0, 53.2.

4.3.4. Compound **13d**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.76 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.38 (t, J = 15.4 Hz, 2H), 7.32 (t, J = 15.5 Hz, 1H), 6.94 (d, J = 8.4 Hz, 3H), 5.74 (d, J = 9.5 Hz, 1H), 4.65 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 173.4, 166.4, 162.7, 138.9, 129.8, 129.7, 128.9, 128.8, 128.5, 127.9, 126.9, 126.3, 113.8, 73.3, 55.4, 54.8, 53.3.

4.3.5. Compound **13e**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.77 (d, J = 7.45 Hz, 2H), 7.51 (t, J = 7.05 Hz, 1H), 7.44 (t, J = 7.45 Hz, 4H), 7.36 (t, J = 7.40 Hz, 2H), 7.31 (m, 1H), 7.03 (br, 1H), 5.75 (dd, J = 9.10, 1.70 Hz, 1H), 4.63 (br, 1H), 3.84 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 173.4, 166.8, 143.3, 138.2, 132.0, 129.1, 128.9, 128.4, 127.4, 127.1, 126.3, 113.8, 73.6, 54.8, 47.6.

4.3.6. Compound **13f**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.69 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 7 0.7 Hz, 2H), 7.39 (d, J = 15.5 Hz, 2H), 7.32 (t, J = 15.4 Hz, 1H), 7.25 (d, J = 7.5 Hz, 2H), 6.96 (br, 1H), 5.76 (dd, J = 5.8, 2.4 Hz, 1H), 4.66 (d, J = 5.2 Hz, 1H), 3.86 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm:173.5, 167.0, 142.3, 138.8, 131.2, 130.2, 129.3, 129.2, 128.7, 127.9, 127.2, 127.0, 73.3, 54.9, 53.2, 21.5.

4.3.7. Compound **13g**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.57 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 7.7 Hz, 2H), 7.39 (t, J = 15.5 Hz, 1H), 7.34–7.30 (m, 1H), 7.04 (d, J = 9.5 Hz, 1H), 5.72 (m, 1H), 4.65 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 173.3, 157.6, 147.4, 144.2, 138.6, 131.9, 130.4, 129.0, 128.9, 128.8, 128.0, 127.0, 114.9, 112.2, 55.1, 53.3.

4.3.8. Compound **13h**

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.57 (m, 1H), 7.44 (s, 1H), 7.38 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.26 (d, J = 7.1 Hz, 1H), 7.18–7.13 (m, 1H), 5.64 (d, J = 8.7 Hz, 1H), 4.57 (d, J = 2.0 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 173.2, 165.4, 161.0, 145.6, 140.9, 138.3, 133.2, 131.8, 131.3, 129.0, 128.7, 127.9, 127.0,

116.5, 109.3, 73.5, 55.7.

4.4. General procedure for synthesis of compounds **14a-h**

The resulting solid **13a-h** (1.0 mmol) and pyridinium p-toluenesulfonate (PPTS) (0.1 mmol) were dissolved in anhydrous toluene (8 mL), and 4-methoxybenzaldehyde dimethyl acetal (1.5 mmol) was subsequently added drop-wise under an argon atmosphere. Following 40 min of heating at reflux, the reaction mixture was allowed to cool to ambient temperature and was diluted with Et_2O. The organic layer was washed successively with water, saturated $NaHCO_3$, water and brine; the solution was dried over Na_2SO_4; and solvents were removed under reduced pressure. The resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 1: 4), yielding a product **14a-h** (80%-90%).

4.4.1. Compound **14a**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.53 (d, J = 7.85 Hz, 2H), 7.48 (d, J = 5.90 Hz, 2H), 7.43–7.31 (m, 5H), 7.30–7.21 (m, 4H), 7.03 (br, 1H), 5.89 (br, 1H), 5.77 (dd, J = 5.80, 2.00 Hz, 1H), 4.77 (d, J = 2.61 Hz, 1H), 3.85 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.7, 171.3, 165.5, 165.5, 164.9, 163.8, 158.8, 153.1, 143.1, 136.0, 131.9, 130.4, 129.2, 129.2, 128.8, 128.6, 128.3, 128.2, 127.3, 118.9, 73.5, 73.2, 54.8, 47.5.

4.4.2. Compound **14b**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.96–7.90 (m, 1H), 7.52–7.46 (m, 5H), 7.33 (d, J = 7.36 Hz, 1H), 7.25–7.22 (m, 3H), 7.19–7.13 (m, 3H), 5.89 (br, 1H), 5.77 (dd, J = 5.76, 1.91 Hz, 1H), 4.72 (d, J = 2.58 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 171.3, 171.2, 164.9, 162.7, 161.8, 159.8, 153.1, 143.3, 133.7, 132.2, 131.9, 129.8, 129.4, 129.2, 128.8, 128.6, 128.2, 128.1, 127.3, 84.1, 73.9, 73.4, 55.9, 47.5.

4.4.3. Compound **14c**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.80–7.76 (m, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 15.5 Hz, 2H), 7.31 (t, J = 15.0 Hz, 1H), 7,21–7.08 (m, 6H), 5.87(br, 1H), 5.74 (dd, J = 2.3, 2.5 Hz, 1H), 4.64 (d, J = 2.2 Hz, 1H), 4.60 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 173.4, 171.2, 166.0, 165.9, 163.9, 159.8, 153.1,138.6, 130.2, 130.1, 129.6, 129.5, 129.4, 129.3, 128.8, 128.0, 126.9, 115.6, 74.2, 73.3, 55.0, 53.2.

4.4.4. Compound **14d**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.76 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.38 (t, J = 15.4 Hz, 2H), 7.31–7.21 (m, 5H), 6.94 (d, J = 8.4 Hz, 3H), 5.94 (br, 1H), 5.74 (d, J = 9.5 Hz, 1H), 4.65 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 173.4, 166.4, 162.7, 138.9, 129.8, 129.7, 129.6, 129.5, 128.9, 128.8, 128.5, 128.7, 128.6, 127.9, 126.9, 126.3, 113.8, 74.3, 74.2, 55.4, 54.8, 53.3.

4.4.5. Compound **14e**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.35 (t, J = 7.30 Hz, 1H), 7.32–7.25 (m, 7H), 7.25–7.19 (m, 5H), 6.85 (br, 1H), 5.87 (br, 1H), 5.43 (br, 1H), 4.88 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 171.0, 166.4, 153.2, 143.3, 138.9, 132.1, 129.9, 128.9, 128.8, 128.4 128.0, 127.2, 127.1, 126.3, 113.5, 74.3, 55.5, 54.8, 52.7.

4.4.6. Compound **14f**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.69 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 7 0.7 Hz, 2H), 7.39 (d, J = 15.5 Hz, 2H), 7.32 (t, J = 15.4 Hz, 1H), 7.25 (d, J = 7.5 Hz, 2H), 6.96 (br, 1H), 5.76 (dd, J = 2.4, 2.4 Hz, 1H), 4.66 (d, J = 5.2 Hz, 1H), 3.86 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 173.5, 167.0, 142.3, 138.8, 131.2, 130.2, 129.8, 129.7, 129.3, 129.2, 128.7, 127.9, 127.2, 127.0, 74.5, 73.3, 54.9, 53.2, 21.5.

4.4.7. Compound **14 g**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.57 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 7.7 Hz, 2H), 7.39 (t, J = 15.5 Hz, 1H), 7.34–7.30 (m, 5H), 7.04 (d, J = 9.5 Hz, 1H), 5.89 (br, 1H), 5.72 (dd, J = 2.1, 2.1 Hz, 1H), 4.65 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 173.3, 157.6, 147.4, 144.2, 138.6, 129.4, 129.2, 129.0, 128.9, 128.8, 128.0, 127.2, 127.1, 127.0, 114.9, 112.2, 74.4, 55.1, 53.3.

4.4.8. Compound **14 h**

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.57 (m, 3H), 7.44 (s, 1H), 7.38 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.26 (d, J = 7.1 Hz, 1H), 7.18–7.13 (m, 3H), 5.94 (br, 1H). 5.64 (d, J = 8.7 Hz, 1H), 4.57 (d, J = 2.0 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 173.2, 165.4, 161.0, 145.6, 140.9, 138.3, 133.2, 131.8, 131.3, 129.4, 129.2, 129.0, 128.7, 128.7, 128.4, 127.9, 127.0, 116.5, 109.3, 74.5, 73.5, 55.7.

4.5. General procedure for synthesis of compounds **15a-h**

A solution of KOH (1.1 mmol) in water (4 mL) was added slowly at room temperature to a stirred solution of **14a-h** in MeOH (30 mL). The reaction mixturewas stirred for 2 h. After the completion of the reaction, MeOH was evaporated under reduced pressure. The residual mixture successively was diluted with water, washed with Et_2O, acidified with 1 N HCl, and extracted with EtOAc successively. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The resulting solid (2.0 mmol), compound **11** (1.0 mmol), EDC (2.0 mmol) and DMAP (1.0 mmol) were dissolved in an hydrous toluene (6.0 mL), and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with EtOAc and washed with saturated NH_4Cl, water, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 1: 3), yielding **15a-h** as a white solid (85%-90%).

4.5.1. Compound **15a**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppmδ ppm 8.04 (d, J = 8.05 Hz, 2H), 7.61 (t, J = 7.51 Hz, 1H), 7.47 (t, J = 7.85 Hz, 4H), 7.41–7.28 (m, 7H), 7.24–7.19 (m, 2H), 6.92–6.80 (br, 2H), 5.93 (t, J = 7.60 Hz, 1H), 5.87 (d, J = 12.25 Hz, 1H), 5.78 (dd, J = 6.05, 2.25 Hz, 1H), 5.45 (br, 1H), 5.39 (t, J = 8.90 Hz, 1H), 5.09 (d, J = 12.25 Hz, 1H), 4.91 (d, J = 8.60 Hz, 1H), 4.77 (d, J = 2.61 Hz, 1H), 4.36 (d, J = 8.45 Hz, 1H), 4.10 (d, J = 8.45 Hz, 1H), 3.83 (s, 3H), 2.66 (d, J = 6.00 Hz, 1H), 2.71–2.48 (m, 2H), 2.29 (s, 3H), 2.09 (s, 3H), 2.05 (d, J = 9.45, 1H), 2.01–1.94 (m, 1H), 1.80 (s, 3H), 1.73 (s, 3H), 1.71(s, 3H), 1.58–1.51 (m, 1H), 1.20 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.7, 171.3, 171.0, 165.5, 164.9, 143.1, 137.9, 136.0, 136.0, 134.0, 131.9, 130.4, 130.4, 129.8, 129.0, 128.8, 128.3, 127.3, 122.4, 122.4, 119.1, 118.9, 84.1, 83.8, 81.1, 78.0, 76.2, 73.5, 71.2, 70.4, 70.3, 47.5, 43.2, 42.6, 38.2, 34.3, 31.6, 26.7, 26.0, 22.6, 21.4, 15.6, 13.0.

4.5.2. Compound **15b**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.04 (d, J = 8.05 Hz, 2H), 7.62 (t, J = 7.97 Hz,1H), 7.55–7.45 (m, 5H), 7.41–7.34 (t, J = 7.03 Hz ,7H), 7.35–7.30 (m, 1H), 7.25–7.22 (m, 1H), 7.19–7.13 (m, 1H), 5.92 (t, J = 8.10 Hz, 1H), 5.91–5.87 (m, 1H), 5.86 (d, J = 12.20 Hz, 1H), 5.77 (dd, J = 5.76, 1.91 Hz, 1H), 5.45 (br, 1H), 5.39 (t, J = 9.08 Hz, 1H), 5.08 (d, J = 12.20 Hz, 1H), 4.90 (d, J = 8.60 Hz, 1H), 4.72 (d, J = 2.58 Hz, 1H), 4.36 (d, J = 8.45 Hz, 1H), 4.10 (d, J = 8.45 Hz, 1H), 3.85 (s, 3H), 2.72–2.65 (m, 1H), 2.67 (d, J = 5.98 Hz, 1H), 2.61–2.49 (m, 1H), 2.28 (s, 3H), 2.10 (s, 3H), 2.05 (d, J = 8.93, 1H), 2.01–1.94 (m, 2H), 1.80 (s, 3H), 1.73 (s, 3H), 1.71 (s, 3H), 1.55–1.49 (m, 1H), 1.18 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.3, 171.2, 171.0,

162.7, 161.8, 153.1, 143.3, 138.2, 134.0, 133.8, 133.7, 132.2, 130.9, 129.8, 129.0, 128.8, 128.2, 127.3, 84.1, 83.8, 81.2, 78.0, 76.2, 73.9, 71.3, 71.0, 70.5, 47.5, 43.2, 42.5, 38.2, 34.3, 31.9, 31.9, 31.6, 30.3, 26.8, 22.7, 22.5, 21.4, 15.6, 14.1, 13.0.

4.5.3. Compound **15c**

^{1}H NMR (500 MHz, $CDCl_3$) d (ppm): 8.05 (d, J = 8.0 Hz, 2H); 7.60 (t, J = 14.5 Hz, 1H), 7.47 (t, J = 16.5 Hz, 3H), 7.28–7.38 (m, 8H), 6.93–6.87 (m, 4H), 5.58 (br, 1H), 5.45 (br, 1H), 5.07 (d, J = 12.5 Hz, 2H), 5.04 (dd, J = 3.5, 2.4 Hz, 1H), 4.94 (br, 1H), 4.90 (d, J = 10.3 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.37–4.32 (m, 2H), 4.15–4.09 (m, 3H), 3.83 (s, 3H), 2.76 (d, J = 6.5 Hz, 1H), 2.66–2.59 (m, 1H), 2.53–2.45 (m, 1H), 2.01 (s, 3H), 1.99 (s, 3H), 1.85–1.88 (m, 1H), 1.84 (s, 3H), 1.71 (s, 3H), 1.66–1.70 (m, 1H), 1.56 (s, 3H), 1.55 (s, 3H), 1.28 (s, 3H).[13]C NMR (125 MHz, $CDCl_3$) d (ppm): 171.7, 171.3, 171.0, 165.7, 164.9, 153.1, 143.2, 138.1, 134.0, 131.9, 129.9, 129.8, 129.5, 129.4, 129.0, 128.8, 128.8, 128.3, 127.3, 115.9, 115.7, 84.1, 83.8, 81.1, 78.0, 76.2, 73.5, 71.2, 70.4, 70.3, 47.5, 43.2, 42.6, 38.2, 34.3, 31.6, 30.3, 26.7, 26.0, 22.6, 21.4, 15.6, 13.0.

4.5.4. Compound **15d**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.03 (d, J = 8.12 Hz, 2H), 7.64–7.60 (m, 1H), 7.50–7.46 (m, 4H), 7.40–7.28 (m, 8H), 7.06–7.02 (m, 1H), 5.93 (t, J = 7.60 Hz, 1H), 5.87 (d, J = 12.10 Hz, 1H), 5.80 (dd, J = 5.59, 2.20 Hz, 1H), 5.76 (dd, J = 5.86, 1.95 Hz, 1H), 5.45 (br, 1H), 5.39 (t, J = 8.58 Hz, 1H), 5.09 (d, J = 12.10 Hz, 1H), 4.90 (d, J = 8.60 Hz, 1H), 4.77 (d, J = 2.61 Hz, 1H), 4.35 (d, J = 8.45 Hz, 1H), 4.12 (d, J = 8.45 Hz, 1H), 3.85 (s, 3H), 2.67 (d, J = 6.00 Hz, 1H), 2.70–2.63 (m, 1H), 2.56–2.48 (m, 1H), 2.29 (s, 3H), 2.09 (s, 3H), 2.05 (d, J = 9.40 Hz, 1H), 2.00–1.94 (m, 1H), 1.80 (s, 3H), 1.75 (s, 3H), 1.70 (s, 3H), 1.58–1.51 (m, 1H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.7, 171.3, 170.9, 166.6, 164.9, 153.1, 138.1, 135.2, 134.0, 131.9, 129.8, 129.0, 128.8, 128.3, 127.3, 118.6, 118.0, 112.7, 84.1, 83.8, 81.1, 78.0, 76.2, 73.6, 71.2, 70.4, 70.3, 54.7, 47.5, 43.2, 42.6, 38.2, 34.3, 31.6, 26.7, 26.0, 22.6, 21.4, 15.6, 13.0.

4.5.5. Compound **15e**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.02 (d, J = 8.05 Hz, 2H), 7.61 (t, J = 7.51 Hz, 1H), 7.47 (t, J = 7.85 Hz, 4H), 7.41–7.30 (m, 8H), 7.24–7.19 (m, 2H), 6.92–6.81 (br, 2H), 6.18 (t, J = 7.60 Hz,1H), 6.03 (d, J = 12.30 Hz,1H), 5.78 (dd, J = 6.05, 2.25 Hz, 1H), 5.58 (br, 1H), 5.50 (t, J = 8.90 Hz,1H), 5.15 (d, J = 12.30 Hz, 1H), 4.93 (s, 1H), 4.88 (d, J = 8.50 Hz, 1H), 4.77 (d, J = 2.61 Hz, 1H), 4.32 (d, J = 8.40 Hz, 1H), 4.08 (d, J = 8.40 Hz, 1H), 3.83 (s, 3H), 2.72 (d, J = 6.00 Hz, 1H), 2.58–2.47 (m, 2H), 2.11 (s, 3H), 2.09 (s, 3H), 2.05 (d, J = 9.45 Hz, 1H), 2.00–1.94 (m, 2H), 1.80 (s, 3H), 1.76 (s, 3H), 1.51–1.58 (m, 5H), 1.43 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.8, 171.4, 171.0, 166.8, 165.0, 153.1, 143.3, 138.2, 134.1, 132.1, 132.0, 129.9, 128.9, 128.8, 127.4, 127.1, 118.6, 84.2, 83.9, 81.2, 78.1, 76.3, 73.6, 71.4, 70.5, 70.4, 47.6, 43.3, 42.7, 38.3, 34.4, 31.8, 26.8, 26.1, 22.7, 21.5, 15.7, 13.1.

4.5.6. Compound **15f**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.04 (d, J = 7.35 Hz, 2H), 7.68 (d, J = 8.11 Hz, 2H), 7.51–7.40 (m, 6H), 7.37 (t, J = 7.21 Hz, 2H), 7.34–7.20 (m, 6H), 5.92 (t, J = 8.25 Hz, 1H), 5.88 (d, J = 12.20 Hz,1H), 5.77 (dd, J = 6.05, 2.25 Hz, 1H), 5.56 (d, J = 9.60 Hz, 1H), 5.45 (br, 1H), 5.40 (t, J = 8.90 Hz,1H), 5.09 (d, J = 12.20 Hz, 1H), 4.91 (d, J = 8.65 Hz, 1H), 4.77 (s, 1H), 4.36 (d, J = 8.50 Hz, 1H), 4.10 (d, J = 8.50 Hz, 1H), 3.83 (s, 3H), 2.68 (d, J = 5.65 Hz, 1H), 2.73–2.64 (m, 1H), 2.56–2.46 (m, 1H), 2.38 (s, 3H), 2.29 (s, 3H), 2.09 (s, 3H), 2.05 (d, J = 9.45 Hz, 1H), 2.00–1.94 (m,1H), 1.80 (s, 3H), 1.75 (s, 3H), 1.70 (s, 3H), 1.58–1.51 (m, 1H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.8, 171.4, 171.0, 166.8, 165.0, 143.4, 138.4, 134.0, 131.9, 130.9, 129.5, 129.1, 128.3, 127.1, 84.2, 83.2, 78.4, 76.3, 73.7, 71.3, 70.5, 70.4, 60.5, 47.6, 43.3, 42.6, 38.3, 34.4, 31.7, 26.8, 26.1, 22.8, 22.6, 21.6, 21.5, 15.7, 14.3, 13.1.

4.5.7. Compound **15g**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.04 (d, J = 7.50 Hz, 2H), 7.92–7.68 (m, 3H), 7.65–7.60 (m, 2H), 7.51–7.45 (m, 4H), 7.38 (t, J = 7.10 Hz, 2H), 7.35–7.27 (m, 5H), 5.93 (t, J = 8.10 Hz, 1H), 5.87 (d, J = 12.20 Hz,1H), 5.81–5.75 (m, 2H), 5.45 (br, 1H), 5.39 (t, J = 8.50 Hz, 1H), 5.08 (d, J = 12.20 Hz, 1H), 4.90 (d, J = 8.60 Hz, 1H), 4.75 (s, 1H), 4.36 (d, J = 8.40 Hz, 1H), 4.10 (d, J = 8.40 Hz, 1H), 3.83 (s, 3H), 2.68 (d, J = 5.65 Hz, 1H), 2.70–2.62 (m, 1H), 2.55–2.47 (m, 1H), 2.28 (s, 3H), 2.08 (s, 3H), 2.05 (d, J = 9.45 Hz, 1H), 2.00–1.93 (m, 1H), 1.83 (s, 3H), 1.80 (s, 3H), 1.71 (s, 3H), 1.58–1.51 (m, 1H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.8, 171.3, 171.0, 165.4, 165.0, 143.2, 137.6, 135.8, 132.1, 130.5, 130.4, 129.9, 129.0, 128.9, 127.4, 125.6, 81.2, 83.9, 81.2, 78.1, 76.3, 73.5, 71.4, 70.5, 70.4, 60.5, 47.6, 43.3, 42.7, 38.3, 34.4, 31.8, 26.8, 26.1, 22.7, 21.5, 15.7, 14.3, 13.1.

4.5.8. Compound **15h**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.04 (d, J = 7.50 Hz, 2H), 7.69–7.62 (m, 3H), 7.65–7.60 (m, 2H), 7.50–7.45 (m, 5H), 7.38 (t, J = 7.06 Hz, 2H), 7.35–7.30 (m, 2H), 7.24–7.18 (m, 1H), 5.93 (t, J = 8.10 Hz, 1H), 5.86 (d, J = 12.20 Hz,1H), 5.81–5.75 (m, 2H), 5.45 (br, 1H), 5.38 (t, J = 8.85 Hz, 1H), 5.08 (d, J = 12.20 Hz, 1H), 4.90 (d, J = 8.60 Hz, 1H), 4.75 (s, 1H), 4.36 (d, J = 8.40 Hz, 1H), 4.21 (s, 1H), 4.10 (d, J = 8.40 Hz, 1H), 3.83 (s, 3H), 2.66 (d, J = 5.65 Hz, 1H), 2.70–2.61 (m, 1H), 2.55–2.47 (m, 1H), 2.28 (s, 3H), 2.09 (s, 3H), 2.05 (d, J = 9.45 Hz, 1H), 2.02–1.94 (m, 1H), 1.83 (s, 3H), 1.80 (s, 3H), 1.71(s, 6H), 1.58–1.51 (m, 1H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.7, 171.4, 171.1, 165.0, 164.7, 164.7, 153.8, 153.2, 143.1, 137.9, 134.1, 132.1, 130.9, 130.8, 129.9, 129.1, 129.0, 128.9, 128.5, 127.4, 123.5, 123.5, 117.8, 117.7, 117.2, 117.1, 84.2, 83.9, 81.3, 78.1, 76.3, 75.5, 71.3, 70.5, 70.4, 47.6, 43.3, 42.7, 38.3, 34.4, 31.7, 26.8, 26.1, 22.7, 21.1, 15.7, 14.2, 13.1.

4.6. General procedure for synthesis of compounds **16a-h**

The resulting solid **15a-h** (1.0 mmol) was dissolved in MeOH (5 mL) and p-toluenesulfonic acid (1.5 mmol) was added. After stirring for 2 h at 50 °C, the reaction mixture was diluted with EtOAc and washed three times with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 2: 3), and the unreacted minor diastereomer was discarded, yielding **16a-h** as a white powder (80%-85%).

4.6.1. Compound **16a**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.04 (d, J = 8.05 Hz, 2H), 7.61 (t, J = 7.40 Hz, 1H), 7.56–7.46 (m, 5H), 7.43–7.31 (m, 5H), 7.23–7.18 (m, 1H), 5.93 (t, J = 7.60 Hz, 1H), 5.87 (d, J = 12.25 Hz, 1H), 5.78 (dd, J = 6.05, 2.25 Hz, 1H), 5.39 (t, J = 8.90 Hz, 1H), 5.09 (d, J = 12.25 Hz, 1H), 4.91 (d, J = 8.60 Hz, 1H), 4.77 (d, J = 2.61 Hz, 1H), 4.36 (d, J = 8.45 Hz, 1H), 4.10 (d, J = 8.45 Hz, 1H), 2.66 (d, J = 6.00 Hz, 1H), 2.71–2.48 (m, 2H), 2.29 (s, 3H), 2.09 (s, 3H), 2.05 (d, J = 9.45 Hz, 1H), 2.01–1.94 (m, 1H), 1.80 (s, 3H), 1.73 (s, 3H), 1.71 (s, 3H), 1.58–1.51 (m, 1H), 1.20 (s, 3H). ^{19}F NMR (470 MHz, $CDCl_3$): δ ppm −111.3 (m, 1F). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.7, 171.3, 171.0, 165.5, 165.5, 164.9, 163.8, 158.8, 153.1, 143.1, 137.9, 136.0, 136.0, 134.0, 131.9, 130.4, 130.4, 129.8, 129.0, 128.8, 128.3, 127.3, 122.4, 122.4, 119.1, 118.9, 84.1, 83.8, 81.1, 78.0, 76.2, 73.5, 71.2, 70.4, 70.3, 54.8, 47.5, 43.2, 42.6, 38.2, 34.3, 31.6, 26.7, 26.0, 22.6, 21.4, 15.6, 13.0. HR-MS (ESI): calcd for $C_{48}H_{50}FNO_{14}$ ($[M + H]^+$): 884.3288, found: 884.3282.

4.6.2. Compound **16b**

^{1}H NMR (125 MHz, $CDCl_3$): δ ppm 8.07–8.02 (m, 2H), 7.92 (m,1H),

7.62 (t, J = 7.97 Hz, 1H), 7.55–7.45 (m, 5H), 7.41–7.34 (t, J = 7.03 Hz, 2H), 7.35–7.30 (m, 1H), 7.25–7.22 (m, 1H), 7.19–7.13 (m, 1H), 5.92 (t, J = 8.10 Hz, 1H), 5.91–5.87 (m, 1H), 5.86 (d, J = 12.20 Hz, 1H), 5.77 (dd, J = 5.76, 1.91 Hz, 1H), 5.39 (t, J = 9.08 Hz, 1H), 5.08 (d, J = 12.20 Hz, 1H), 4.90 (d, J = 8.60 Hz, 1H), 4.72 (d, J = 2.58 Hz, 1H), 4.36 (d, J = 8.45 Hz, 1H), 4.10 (d, J = 8.45 Hz, 1H), 2.72–2.65 (m, 1H), 2.67 (d, J = 5.98 Hz, 1H), 2.61–2.49 (m, 1H), 2.28 (s, 3H), 2.10 (s, 3H), 2.05 (d, J = 8.93 Hz, 1H), 2.01–1.94 (m, 2H), 1.80 (s, 3H), 1.73 (s, 3H), 1.71(s, 3H), 1.55–1.49 (m, 1H), 1.18 (s, 3H). ^{19}F NMR (470 MHz, $CDCl_3$): δ ppm −113.1 (m, 1F). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.3, 171.2, 171.0, 164.9, 162.7, 161.8, 159.8, 153.1, 143.3, 138.2, 134.0, 133.8, 133.7, 132.2, 131.9, 130.9, 129.9, 129.8, 129.0, 128.8, 128.2, 127.3, 84.1, 83.8, 81.2, 78.0, 76.2, 73.9, 71.3, 71.0, 70.5, 55.9, 47.5, 43.2, 42.5, 38.2, 34.3, 31.9, 31.9, 31.6, 30.3, 26.8, 22.7, 22.5, 21.4, 15.6, 14.1, 13.0. HR-MS (ESI): calcd for $C_{48}H_{50}FNO_{14}$ ([M + H]$^+$): 884.3288, found: 884.3273.

4.6.3. Compound **16c**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.06 (d, J = 8.60 Hz, 2H), 7.79 (m, 1H), 7.62 (t, J = 8.00 Hz ,1H), 7.50–7.45 (m, 4H), 7.41–7.39 (m, 2H), 7.33–7.28 (m, 2H), 7.12–7.06 (m, 2H), 5.93 (t, J = 7.60 Hz, 1H), 5.87 (d, J = 12.25 Hz, 1H), 5.78 (dd, J = 6.01, 2.24 Hz, 1H), 5.76 (dd, J = 5.85, 1.99 Hz, 1H), 5.39 (t, J = 8.87 Hz, 1H), 5.08 (d, J = 12.25 Hz, 1H), 4.90 (d, J = 8.60 Hz, 1H), 4.77 (d, J = 2.61 Hz, 1H), 4.35 (d, J = 8.43 Hz, 1H), 4.11 (d, J = 8.43 Hz, 1H), 2.65 (d, J = 6.00 Hz, 1H), 2.70–2.61 (m, 1H), 2.53–2.46 (m, 1H), 2.28 (s, 3H), 2.08 (s, 3H), 2.05 (d, J = 9.45 Hz, 1H), 2.01–1.94 (m, 1H), 1.80 (s, 3H), 1.73 (s, 3H), 1.71 (s, 3H), 1.57–1.50 (m, 1H), 1.18 (s, 3H). ^{19}F NMR (470 MHz, $CDCl_3$): δ ppm −107.2 (m, 1F). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.7, 171.3, 171.0, 166.0, 165.7, 164.9, 164.0, 153.1, 143.2, 138.1, 134.0, 131.9, 129.9, 129.9, 129.8, 129.5, 129.5, 129.4, 129.0, 128.8, 128.8, 128.3, 127.3, 115.9, 115.7, 84.1, 83.8, 81.1, 78.0, 76.2, 73.5, 71.2, 70.4, 70.3, 54.8, 47.5, 43.2, 42.6, 38.2, 34.3, 31.6, 30.3, 26.7, 26.0, 22.6, 21.4, 15.6, 13.0. HR-MS (ESI): calcd for $C_{48}H_{50}FNO_{14}$ ([M + H]$^+$): 884.3288, found: 884.3285.

4.6.4. Compound **16d**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.03 (d, J = 8.12 Hz, 2H), 7.64–7.60 (m, 1H), 7.50–7.46 (m, 4H), 7.40–7.28 (m, 6H), 7.06–7.02 (m, 1H), 5.94 (t, J = 7.60 Hz, 1H), 5.87 (d, J = 12.10 Hz, 1H), 5.80 (dd, J = 5.59, 2.20 Hz, 1H), 5.76 (dd, J = 5.86, 1.95 Hz, 1H), 5.39 (t, J = 8.58 Hz, 1H), 5.09 (d, J = 12.10 Hz, 1H), 4.90 (d, J = 8.60 Hz, 1H), 4.77 (d, J = 2.61 Hz, 1H), 4.35 (d, J = 8.45 Hz, 1H), 4.12 (d, J = 8.45 Hz, 1H), 3.81 (s, 3H), 2.67 (d, J = 6.00 Hz, 1H), 2.70–2.63 (m, 1H), 2.56–2.48 (m, 1H), 2.29 (s, 3H), 2.09 (s, 3H), 2.05 (d, J = 9.40 Hz, 1H), 2.00–1.94 (m, 1H), 1.80 (s, 3H), 1.75 (s, 3H), 1.70 (s, 3H), 1.58–1.51 (m, 1H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.7, 171.3, 170.9, 166.6, 164.9, 159.9, 153.1, 143.2, 138.1, 135.2, 134.0, 131.9, 129.8, 129.7, 129.0, 128.8, 128.8, 128.3, 127.3, 118.6, 118.0, 112.7, 84.1, 83.8, 81.1, 78.0, 76.2, 73.6, 71.2, 70.4, 70.3, 55.5, 54.7, 47.5, 43.2, 42.6, 38.2, 34.3, 31.6, 26.7, 26.0, 22.6, 21.4, 15.6, 13.0. HR-MS (ESI): calcd for $C_{49}H_{53}NO_{15}$ ([M + H]$^+$): 896.3488, found: 896.3483.

4.6.5. Compound **16e**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.04 (d, J = 8.05 Hz, 2H), 7.79 (d, J = 7.10 Hz, 2H), 7.62 (t, J = 7.45 Hz, 1H), 7.51–7.47 (m, 4H), 7.43 (t, J = 7.85 Hz, 2H), 7.38 (t, J = 7.11 Hz, 2H), 7.35–7.28 (m, 2H), 5.93 (t, J = 7.60 Hz,1H), 5.87 (d, J = 12.30 Hz,1H), 5.82 (dd, J = 6.05, 2.25 Hz, 1H), 5.77 (m, 1H), 5.40 (t, J = 8.90 Hz, 1H), 5.09 (d, J = 12.30 Hz, 1H), 4.91 (d, J = 8.50 Hz, 1H), 4.77 (d, J = 2.61 Hz, 1H), 4.36 (d, J = 8.40 Hz, 1H), 4.10 (d, J = 8.40 Hz, 1H), 2.67 (d, J = 6.00 Hz, 1H), 2.69–2.63 (m, 1H), 2.54–2.47 (m, 1H), 2.29 (s, 3H), 2.09 (s, 3H), 2.05 (d, J = 9.45 Hz, 1H), 2.00–1.94 (m, 2H), 1.84 (s, 3H), 1.74 (s, 3H), 1.71 (s, 3H), 1.51–1.58 (m, 5H), 1.19 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ ppm 171.8, 171.4, 171.0, 166.8, 165.0, 153.2, 143.3, 138.2, 134.1, 133.8, 132.1, 132.0, 129.9, 129.1, 128.9, 128.9, 128.4, 127.4, 127.1, 84.2, 83.9, 81.2, 78.1, 76.3, 73.6, 71.4, 70.5, 70.4, 54.8, 47.6, 43.3, 42.7, 38.3, 34.4, 31.8, 26.8, 26.1, 22.7, 21.5, 15.7, 13.1. HR-MS (ESI): calcd for $C_{48}H_{51}NO_{14}$ ([M + H]$^+$): 866.3382, found: 866.3383.

4.6.6. Compound **16f**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.04 (d, J = 7.35 Hz, 2H), 7.68 (d, J = 8.11 Hz, 2H), 7.51–7.46 (m, 3H), 7.37 (t, J = 7.21 Hz, 2H), 7.34–7.20 (m, 5H), 5.92 (t, J = 8.25 Hz,1H), 5.88 (d, J = 12.20 Hz,1H), 5.77 (dd, J = 6.05, 2.25 Hz, 1H), 5.56 (d, J = 9.60 Hz, 1H), 5.40 (t, J = 8.90 Hz, 1H), 5.09 (d, J = 12.20 Hz, 1H), 4.91 (d, J = 8.65 Hz, 1H), 4.77 (s, 1H), 4.36 (d, J = 8.50 Hz, 1H), 4.10 (d, J = 8.50 Hz, 1H), 2.68 (d, J = 5.65 Hz, 1H), 2.73–2.64 (m, 1H), 2.56–2.46 (m, 1H), 2.38 (s, 3H), 2.29 (s, 3H), 2.09 (s, 3H), 2.05 (d, J = 9.45, 1H), 2.00–1.94 (m, 1H), 1.80 (s, 3H), 1.75 (s, 3H), 1.70 (s, 3H), 1.58–1.51 (m,1H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.8, 171.4, 171.0, 166.8, 165.0, 153.2, 143.4, 142.6, 138.4, 134.0, 131.9, 130.9, 129.9, 129.5, 129.1, 128.3, 127.4, 127.1, 84.2, 83.2, 78.4, 76.3, 73.7, 71.3, 70.5, 70.4, 60.5, 54.7, 47.6, 43.3, 42.6, 38.3, 34.4, 31.7, 26.8, 26.1, 22.8, 22.6, 21.6, 21.5, 15.7, 14.3, 13.1. HR-MS (ESI): calcd for $C_{49}H_{53}NO_{14}$ ([M + H]$^+$): 880.3539, found: 880.3538.

4.6.7. Compound **16 g**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.04 (d, J = 7.50 Hz, 2H), 7.92 (s, 1H), 7.68 (d, J = 7.75 Hz, 1H), 7.65–7.60 (m, 2H), 7.51–7.45 (m, 4H), 7.38 (t, J = 7.10 Hz, 2H), 7.35–7.27 (m, 3H), 5.93 (t, J = 8.10 Hz, 1H), 5.87 (d, J = 12.20 Hz, 1H), 5.81–5.75 (m, 2H), 5.39 (t, J = 8.50 Hz, 1H), 5.08 (d, J = 12.20 Hz, 1H), 4.90 (d, J = 8.60 Hz, 1H), 4.75 (s, 1H), 4.36 (d, J = 8.40 Hz, 1H), 4.10 (d, J = 8.40 Hz, 1H), 2.68 (d, J = 5.65 Hz, 1H), 2.70–2.62 (m, 1H), 2.55–2.47 (m, 1H), 2.28 (s, 3H), 2.08 (s, 3H), 2.05 (d, J = 9.45 Hz, 1H), 2.00–1.93 (m, 1H), 1.83 (s, 3H), 1.80 (s, 3H), 1.71 (s, 3H), 1.58–1.51 (m, 1H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.8, 171.3, 171.0, 165.4, 165.0, 153.2, 143.2, 137.6, 135.8, 134.1, 132.1, 130.5, 130.4, 129.9, 129.1, 129.0, 128.9, 128.5, 127.4, 125.6, 81.2, 83.9, 81.2, 78.1, 76.3, 73.5, 71.4, 70.5, 70.4, 60.5, 54.9, 47.6, 43.3, 42.7, 38.3, 34.4, 31.8, 26.8, 26.1, 22.7, 21.5, 15.7, 14.3, 13.1. HR-MS (ESI): calcd for $C_{48}H_{50}BrNO_{14}$ ([M + H]$^+$): 944.2487, found: 944.2492.

4.6.8. Compound **16 h**

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.04 (d, J = 7.50 Hz, 2H), 7.69–7.65 (m, 1H), 7.65–7.60 (m, 2H), 7.50–7.44 (m, 4H), 7.38 (t, J = 7.06 Hz, 2H), 7.35–7.30 (m, 2H), 7.24–7.18 (m, 1H), 5.93 (t, J = 8.10 Hz, 1H), 5.86 (d, J = 12.20 Hz, 1H), 5.81–5.75 (m, 2H), 5.38 (t, J = 8.85 Hz, 1H), 5.08 (d, J = 12.20 Hz, 1H), 4.90 (d, J = 8.60 Hz, 1H), 4.75 (s, 1H), 4.36 (d, J = 8.40 Hz, 1H), 4.21 (s, 1H), 4.10 (d, J = 8.40 Hz, 1H), 2.66 (d, J = 5.65 Hz, 1H), 2.70–2.61 (m, 1H), 2.55–2.47 (m, 1H), 2.28 (s, 3H), 2.09 (s, 3H), 2.05 (d, J = 9.45 Hz, 1H), 2.02–1.94 (m, 1H), 1.83 (s, 3H), 1.80 (s, 3H), 1.71(s, 6H), 1.58–1.51 (m, 1H), 1.19 (s, 3H). ^{19}F NMR (470 MHz, $CDCl_3$): δ ppm −131.7 (m, 1F), −135.5 (m, 1F). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.7, 171.4, 171.1, 165.0, 164.7, 164.7, 153.9, 153.8, 153.2, 143.1, 137.9, 134.1, 132.1, 130.9, 130.9, 130.9, 129.9, 129.1, 129.0, 128.9, 128.5, 127.4, 123.5, 123.5, 123.5, 123.5, 117.8, 117.7, 117.2, 117.1, 84.2, 83.9, 81.3, 78.1, 76.3, 75.5, 71.3, 70.5, 70.4, 54.9, 47.6, 43.3, 42.7, 38.3, 34.4, 31.7, 26.8, 26.1, 22.7, 21.1, 15.7, 14.2, 13.1. HR-MS (ESI): calcd for $C_{48}H_{49}F_2NO_{14}$ ([M + H]$^+$): 902.3194, found: 902.3190.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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Appendix A. Supplementary material

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