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The synthesis of 5-substituted ring E analogs of methyllycaconitine via the Suzuki–Miyaura cross-coupling reaction

Junfeng Huang,[a] Crina M. Orac,[a] Susan McKay,[b] Dennis B. McKay[b] and Stephen C. Bergmeier[a,*]

[a]*Department of Chemistry and Biochemistry, Ohio University, Clippinger Laboratories, Athens, OH 45701, USA*
[b]*Division of Pharmacology, College of Pharmacy, Ohio State University, Columbus, OH 43210, USA*

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Abstract—Novel 3,5-disubstituted ring E analogs of methyllycaconitine were prepared and evaluated in nicotinic acetylcholine receptor binding assays. The desired analogs were prepared through the Suzuki–Miyaura cross-coupling reaction of methyl 5-bromo-nicotinate. The Suzuki–Miyaura cross-coupling reactions of pyridines with electron withdrawing substituents have not been extensively described previously.

1. Introduction

Methyllycaconitine (MLA, **1**) is a norditerpenoid alkaloid isolated from plants of the genera *Aconitum* and *Delphinium*.[1–3] MLA is the most potent nonpeptide nicotinic acetylcholine receptor (nAChR) antagonist known with selectivity for α7 nAChRs.[4–7] Significant work has been reported on the synthesis and pharmacological evaluation of analogs of MLA.[8] Briefly, the analogs of MLA that have been reported can be grouped into two major groups. The first major grouping is those that make minor (yet significant) modifications to the MLA skeleton or related natural products. Within this large group workers have found that the stereochemistry and substitution of the imide ring are vitally important to the affinity of MLA.[9–11] The identity and substitution of the hydroxyl group aree also important but variations in binding affinity are at most 20-fold. A second major group of MLA analogs is the synthetic ring deleted analogs of MLA. These include E-ring analogs,[12–17] A/E analogs,[18–23] A/E/F ring analogs,[24–26] A/B/E ring analogs,[27–31], and A/B/E/F ring analogs.[32] Of those syntheses that report pharmacological data it is clear that the necessary combination of structure and substitution to identify simpler yet potent and selective analogs of MLA have not been identified. Most of the reported compounds lack either potency or selectivity for the α7 nAChR.

Our own work in this area has been focused on the synthesis and evaluation of simplified analogs of MLA that contain only the E-ring of MLA. As shown in Figure 1 a deletion of all rings except the E-ring and the succinimidoanthranilate ester provides **2**. This structure is further simplified to structure **3**. We have prepared a number of analogs of this general structure with variation at both the R group and Ar group. Our initial lead compound (R = $CH_2CH_2CH_2Ph$, Ar = 2-(3-methylsuccinimide)C_6H_4) shows a relatively low affinity for the α7 nAChR (IC_{50} value, 177 μM).[14] These compounds also act as noncompetitive antagonists at the α3* nAChR.

2. Results and discussion

In an effort to continue to define the structural determinants of MLA nicotinic receptor interactions, we wished to provide additional conformational restriction to our previously reported ring E analogs. In addition to providing additional conformational restriction, we hoped to address additional MLA-like non-covalent contacts.

A slightly different dissection of MLA provides the ring deleted E-ring derivative **4** (Fig. 1). A further generalization of this structure provides the 3,5-disubstituted

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* Corresponding author. Tel.: +1 740 517 8462; fax: +1 740 593 0148; e-mail: bergmeis@ohio.edu

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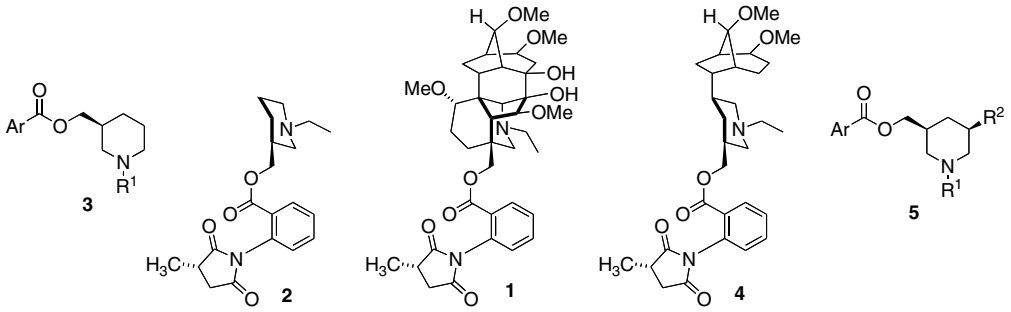


Figure 1. MLA, ring deleted compounds **2** and **4**, and simple ring E analog **3** and 3,5-disubstituted ring E analog **5**.

piperidine analog **5**. Based on previous work, we wished to examine a variety of groups at the Ar and R positions. Our hypothesis was that such an analog might have a more MLA-like pharmacological profile than **3** for two reasons. The first is that an overlay of a typical ring E analog of MLA with MLA requires that the ring E analog exist in a chair conformation with the ester in an equatorial position. Incorporation of the alkyl chain in the 5-position (e.g. **5**) should provide much more of the conformation in which both groups were in the equatorial conformation. A second rationale is that the 3,5-disubstituted analogs should more readily access non-covalent contacts similar to the B, C, and D rings of MLA.

A conformational analysis of an E-ring MLA analog **3** was carried out using Spartan. Empirical calculations were performed using the MMFF force field to investigate the equilibrium abundance of conformational forms for E-ring type analogs of MLA. Using the conformational structures generated in the Equilibrium Conformer calculations, a second set of calculations, Conformer Distribution, was performed using the MM/MMFF model.[33] The results of these calculations for compounds $\mathbf{3_{eq}}$ and $\mathbf{3_{ax}}$ show that the conformation $\mathbf{3_{ax}}$ is less stable than conformation $\mathbf{3_{eq}}$ by 2.223 kJ/mol (0.531 kcal/mol). Thus, 75% of E-ring analog molecules **3** have the ester group equatorial and 25% have the ester group axial, $\mathbf{3_{eq}/3_{ax}} = 3$. For structure **5** the di-axial conformation is less stable than the di-equatorial conformation by 17.002 kJ/mol (4.0633 kcal/mol). This difference in energy is translated into a higher abundance of the di-equatorial 3,5-disubstituted analogs over the di-axial conformer with a ratio of 913 (see Fig. 2).

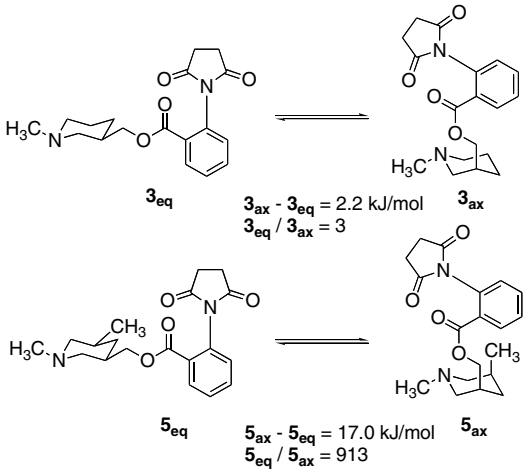
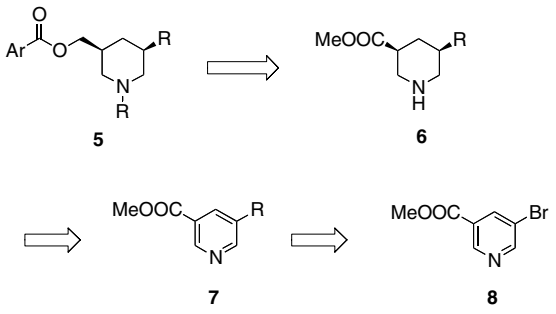


Figure 2. Conformational preferences of compounds **3** and **5**.



Scheme 1. Retrosynthetic plan for the synthesis of compound **5**.

Our synthetic plan hinges on the ability to carry out a cross-coupling reaction between methyl 5-bromo-nicotinate (**8**) and an organometallic reagent to provide **7** (Scheme 1). Catalytic hydrogenation of the resulting 3,5-disubstituted pyridine **7** should provide the *cis*-3,5-disubstituted piperidine ring system **6**.[34] Functional group modifications, esterification, and N-alkylation should then provide the desired 3,5-disubstituted ring E analogs of MLA.

Our initial plan was to use a Heck coupling to introduce an alkyl group at the 5-position of the nicotinic ester. This should be a versatile route to incorporate a wide variety of cyclic and acyclic groups at C-5. The Heck reaction of bromopyridines is known and generally proceeds in good yields.[35] Most of the pyridine substrates for the Heck reaction make use of pyridine ring systems that lack strongly electron withdrawing substituents. The reaction of **8** with cyclohexene and 1-hexene under either standard Heck conditions ($Pd(OAc)_2/NEt_3/P(o\text{-}tol)_3$ at 100 °C for 24 h)[36] or the Jeffery ligand-free conditions,[37] provided only starting materials.

We next examined the use of the Suzuki–Miyaura cross-coupling reaction in order to generate the requisite disubstituted pyridine **7**. Like the Heck reaction, the Suzuki–Miyaura reaction has been reported using 2- or 4-bromopyridine derivatives.[35,38] Pyridine is a π-electron deficient heterocycle in which the 2, 4, and 6 positions

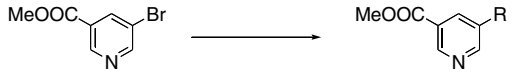
are more electron deficient thus making these position, more prone to nucleophilic attack. Intermediates in which the negative charge, developed during nucleophilic displacement, can be delocalized onto nitrogen are more stable relative to others. The same trend happens in palladium chemistry where the 2, 4, and 6 substituted halopyridines are more accessible to the oxidative addition to Pd (0). A large number of examples of the Suzuki–Miyaura coupling at the 2, 4, or 6-position of pyridine have been reported.

Compared with the number of Suzuki coupling reactions at the 2- and 4-position of a pyridine ring, the coupling reaction at the 3-position of pyridine is rarely reported. Only two examples of the Suzuki–Miyaura coupling in which the 3-position of the pyridine ring is substituted with an electron withdrawing substituent have been reported.[39,40] Both of these earlier examples made use of an aryl boronic acid as the organometallic reagent for the coupling reaction. No *B*-alkyl Suzuki coupling has been reported for 5-bromo-nicotinate. We wished to use a *B*-alkyl Suzuki–Miyaura reaction,[41] as this should provide a wide variety of substituted alkyl chains attached to the final piperidine molecule.

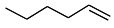
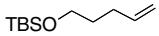
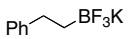
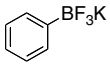
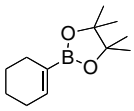
We first examined the *B*-alkyl Suzuki reaction conditions which had been reported for the synthesis of 3-alkylpyridines.[42,43] As outlined in Table 1, we have examined a series of reaction conditions in order to optimize the *B*-alkyl Suzuki–Miyaura cross-coupling reaction for ester **8**. The cross-coupling reaction of alkylborane reagents, generated by in situ hydroboration of 1-hexene, and **8** using $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as the base gave no product at room temperature. Changing the catalyst to $PdCl_2$(dppf) gave a very low yield (20%) at room temperature. Increasing the temperature to 90 °C improved the yield slightly but also generated significant amounts of by-products. Changing the base to K_3PO_4 also improved the yield marginally. However changing the DMF:THF ratio from 1:1 to 3:1 provided the greatest improvement yielding **7a** in 82% yield. Further increases in the amount of DMF did not lead to improved product yields. Carrying out the reaction in 100% DMF provided little to no product. Other solvents such as THF:H_2O, Et_3N, and MeOH provided either poorer yields or no product.

With an improved procedure in hand, we examined several additional alkenes as shown in Table 2. The silyl ether of 5-hexenol provided compound **7b** in 80% yield. Styrene and methylene cyclohexane provided poorer, but still acceptable yields of **7c** and **7d**, respectively. While the *B*-alkyl Suzuki reaction provides an excellent route to alkyl-substituted pyridines, this is of course limited to mono- or 1,1-disubstituted alkenes. We next wished to examine other boron reagents in an effort to prepare pyridines with a 2° alkyl or aryl attachment. Potassium trifluoroborate compounds have greater nucleophilicity than other organoboron compounds which facilitates the Suzuki coupling reaction.[44–46] The reaction of phenethyl potassium trifluoroborate and phenyl potassium trifluoroborate with pyridine **8** provided 5-substituted pyridines (**7c** and **7e**) in excellent yield. We have also examined a boronate ester in the

Table 2. Results of Suzuki couplings



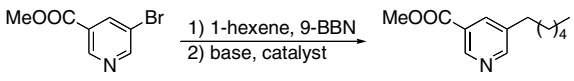
8 **7**

Coupling partner	Compound	Yield (%)
	**7a**	80[a]
	**7b**	80[a]
	**7c**	50[a]
	**7d**	65[a]
	**7c**	60[b]
	**7e**	85[b]
	**7f**	80[b]

[a] 9-BBN (2.0 equiv), 3 M K_3PO_4 (3.0 equiv), DMF:THF (3:1), 5 mol $PdCl_2$(dppf)CH_2Cl_2, 70 °C, 6 h.

[b] DMF:THF(3:1), $PdCl_2$(dppf)CH_2Cl_2 (5 mol%), K_3PO_4 (4 equiv), 70 °C, 6 h.

Table 1. Optimization of *B*-alkyl Suzuki couplings



8 **7a**

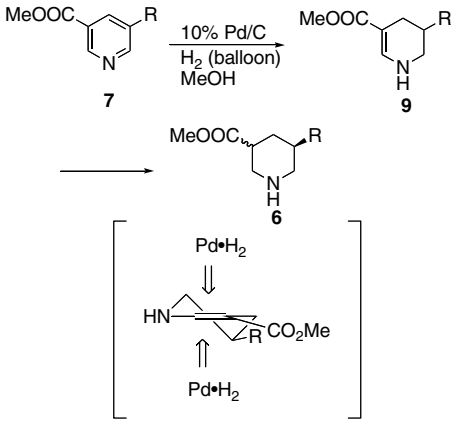
Entry	Solvent	Catalyst (5 mol%)	Base	Time (°C)	Yield (%)
1	DMF:THF (1:1)	$Pd(Ph_3P)_4$	K_2CO_3	12 h, rt	0
2	DMF:THF (1:1)	$PdCl_2$(dppf)	K_2CO_3	12 h, rt	21
3	DMF:THF (1:1)	$PdCl_2$(dppf)	K_2CO_3	12 h, 90	34
4	DMF:THF (1:1)	$PdCl_2$(dppf)	K_3PO_4	12 h, 90	48
5	DMF:THF (3:1)	$PdCl_2$(dppf)	K_3PO_4	6 h, 70	82
6	THF:H_2O	$PdCl_2$(dppf)	K_3PO_4	6 h, 70	43
7	Et_3N	$PdCl_2$(dppf)	Et3N	6 h, 70	0
8	MeOH	$PdCl_2$(dppf)	K_3PO_4	6 h, 70	0

reaction with **8**. Under the standard reaction conditions compound **7f** can be prepared in 80% yield.

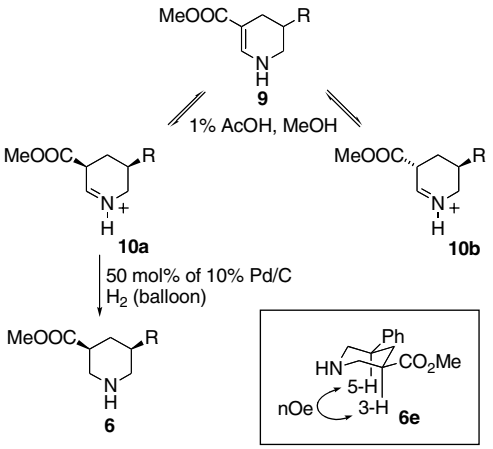
We next turned our attention to the reduction of the pyridine ring. The hydrogenation of pyridines is generally an efficient method to produce corresponding piperidine ring system. A key point however is the production of the *cis*-disubstituted piperidine ring system. We would expect that this would be the thermodynamically more stable compound with both substituents in an equatorial conformation. Usually the heterogeneous catalytic hydrogenation of pyridines is carried out in acid media using aqueous HCl or HOAc as the solvent, and requires high pressure. In most cases these conditions give *cis* products,[47–49] although two examples did note the formation of a poor *cis*:*trans* mixture.[34,50] We were concerned about the very acidic reaction conditions in that we hoped to prepare additional acid sensitive groups which would not survive such reaction conditions. We thus decided to examine alternate reduction conditions that did not require the use of HCl or HOAc as the solvent. We first examined a neutral hydrogentation using 10 mol% of 10% Pd/C in MeOH. The starting material was completely consumed in only 4 h but the expected product **6** was not observed. Instead the only product found was the enamine **9**. Increasing the reaction time to 24 h provided the same product. By increasing the amount of catalyst to 50 mol% the reaction did go to completion in 4 h providing **6** as a 1:1 mixture of the *cis*- and *trans*-diastereomers.

We rationalized this mixture of diastereomers as shown in Scheme 2. Both faces of the relatively flat enamine **9** can be readily approached by the catalyst leading to the observed mixture of isomers. We reasoned that under acidic conditions, if the enamine is formed it should readily form the iminium **10**. This iminium ion can readily equilibrate between the thermodynamically favored *cis*-isomer (**10a**) and the less favored *trans*-isomer (**10b**) under mildly acidic conditions. The more readily reduced iminium should then provide *cis*-isomer **6** as the sole or major product (see Scheme 3).

We found the hydrogenation of our 3,5-disubstituted pyridines **7** can be completed in 16 h to form piperidine



Scheme 2. Lack of diastereoselectivity under neutral hydrogenation conditions.



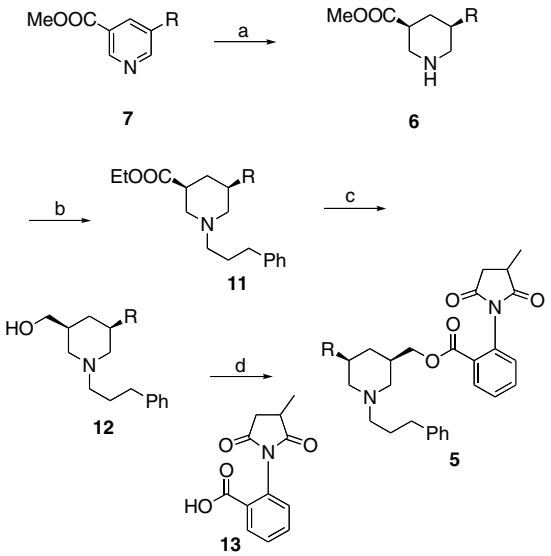
Scheme 3. Diastereoselective hydrogenation.

compounds **6** while loading 50 mol% of 10% Pd/C and using 1% HOAc in MeOH as the solvent (0.1 M). The ^{1}H NMR of the crude products showed that only one diastereomer was formed in the hydrogenation. We would expect that this single stereoisomer should be the *cis*-isomer.[48,49] An examination of the spectra reported in the literature provided little correlation with these compounds, however, NOESY spectra of **6e** does provide a clear crosspeak between H-5 and H-3, corroborating the cis assignment.

Compound **6** was not isolated but directly alkylated with 1-bromo-3-phenylpropane to generate compounds **11a**–**11f** in 60–70% overall yield. Not unexpectedly, the methyl ester was transesterified to the ethyl ester under these conditions. This was not a problem as compound **11** was then reduced with $LiAlH_4$ to the alcohol **12**. Again, this compound was not isolated but directly coupled to 2-(3′-methyl)succinimidoanthranilic acid (**13**)[51] to give the desired products **5** in generally good overall yields. Compound **5** is formed as a mixture of four diastereomers but we do not observe these diastereomers in the NMR, presumably due to the distance between the stereocenters on piperidine ring and the other stereocenter on the succinimide ring (see Scheme 4).

The MLA analogs were subsequently examined for their ability to displace [^{125}I]-α-bungarotoxin (α-Bgt) binding to α7 nicotinic receptors. Prior to pharmacological examination, all compounds were converted to their HCl salts by treatment with anhydrous HCl in EtOAc. Competition binding experiments were carried out using techniques previously described.[14] As shown in Table 3, unlike MLA, the disubstituted ring E analogs at a concentration of 10 μM showed little or no affinity for [^{125}I]-α-Bgt binding sites of α7 nicotinic receptors. While additional conformational restriction has been introduced into the E-ring, this alone is insufficient to impart affinity for the α7 nicotinic receptor.

We have shown previously that other ring E analogs of MLA inhibit nicotine-stimulated bovine adrenal neurosecretion.[14,16] Two of the analogs, **5a** and **5e**, are fairly potent inhibitors (IC_{50} values of 2–3 μM), while **5b**



Scheme 4. Reagents and conditions: (a) H_2, Pd/C; (b) K_2CO_3, $Ph(CH_2)_3Br$, **11a**, R = nC_6H_{13}, 70%, **11b**, R = $(CH_2)_5OTBS$, 60%, **11c**, R = CH_2CH_2Ph, 70%, **11d**, R = $CH_2(cC_6H_{11})$, 60%, **11e**, R = Ph, 65%, **11f**, R = cC_6H_{11}, 68%, all yields are for two steps; (c) $LiAlH_4$; (d) DCC, DMAP, **5a**, R = nC_6H_{13}, 70%, **5b**, R = $(CH_2)_5OTBS$, 65%, **5c**, R = CH_2CH_2Ph, 65%, **5d**, R = $CH_2(cC_6H_{11})$, 58%, **5e**, R = Ph, 60%, **5f**, R = cC_6H_{11}, 70%, all yields are for two steps.

Table 3. Effects of disubstituted E-ring analogs of MLA on α7 and α3β4 nAChR binding

Compound	α7 nAChR specific binding (% of control)[a]	α3β4 nAChR specific binding (% of control)[a]
5a	92.2% ± 9.5%	105.2% ± 8.1%
5b	88.8% ± 4.2%	118.5% ± 9.0%
5c	98.8% ± 7.5%	103.2% ± 15.3%
5d	92.6% ± 4.8%	ND[c]
5e	94.3% ± 7.3%	86.8% ± 9.3%
5f	103.3% ± 5.7%	ND[c]
MLA	7.5% ± 1.7%[b]	50.1% ± 1.5%[b]

[a] Competition binding experiments using [^{125}I]-α-Bgt (for α7 nAChR binding) or [^{3}H]epibatidine (for α3β4 nAChR binding) as the radiolabeled ligands were performed at fixed concentrations of each analog (10 μM); values represent means ± SEM, n = 4–7.

[b] Competition binding experiments were performed at a fixed MLA concentration of 1.0 μM.

[c] Not determined.

and **5c** are without effects when tested up to concentrations of 10 μM. These analogs have no significant effects on α3β4 nAChR binding (Table 3) using techniques previously described.[52]

3. Conclusions

We have tested the hypothesis that additional conformational restriction of ring E analogs of MLA would show affinity for α7 nAChR. These compounds failed to show any affinity for [^{125}I]-α-Bgt binding sites of α7 nicotinic acetylcholine receptor subtypes. While this turned out to be incorrect, this nonetheless provides important information regarding structure activity relationships of ring deleted analogs of MLA. In addition to the pharmacological findings, we have developed a general route to 3,5-*cis*-disubstituted piperidines. This general route involves the development of Suzuki–Miyaura cross-coupling conditions that allow for the synthesis of 3,5-disubstituted pyridine derivatives. This is significant in that no previous *B*-alkyl Suzuki–Miyaura reactions have been reported with pyridines substituted with electron withdrawing substituents. We have also found that milder hydrogenation conditions can provide the *cis*-disubstituted piperidines. This is an advance over previously reported hydrogenations of similar systems which observed a mixture of both *cis*- and *trans*-diastereomers.

4. Experimental

4.1. General

All reagents used were purchased from commercial sources or prepared according to standard literature methods using references given in the text and purified as necessary prior to use by standard literature procedures. THF and CH_2Cl_2 were dried using a Solv-Tek solvent purification system. Dry DMF was distilled from calcium hydride and degassed for 10 min prior to use. Column chromatography was performed using ICN silica gel 60A. Proton (^{1}H) and carbon (^{13}C) magnetic resonance spectra (NMR) were recorded on a Bruker 300 MHz Fourier transform spectrometer, and chemical shift is expressed in parts per million (δ) relative to tetramethylsilane (TMS, 0 ppm) as internal reference. All High Resolution Mass Spectra (HRMS) were acquired using positive electrospray ionization (ESI) at the Mass Spectrometry Center of the University of Tennessee.

4.2. General procedure for the *B*-alkyl-Suzuki coupling

To the alkene (1 mmol) in a dry flask at 0 °C under nitrogen was slowly added 9-BBN-H (0.5 M in THF, 4 mL, 2 mmol). The mixture was warmed to room temperature and stirred for 4 h. K_3PO_4 (3 M in H_2O, 1 mL, 3 mmol) was added slowly followed by the addition of methyl 5-bromo-nicotinate (1.1 mmol) in dry degassed DMF (12 mL) and finally $PdCl_2(dppf)CH_2Cl_2$ (42 mg, 5 mol%) under nitrogen. The reaction mixture was stirred for 6 h at 70 °C, cooled to room temperature, and then diluted with EtOAc and saturated $NaHCO_3$ solution. The aqueous layer was re-extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give crude products. In most cases, the product was contaminated by 9-BBN by-products which cannot be removed by flash column chromatography and can effect the following reactions. But they can be greatly reduced by dissolving crude products in THF (15 mL), followed by the addition of aqueous NaOH (15%, 1 mL) and H_2O_2 (30%, 2 mL), and the mixture was stirred for 1 h at 0 °C. The system was diluted with ethyl ether, washed with saturated $NaHCO_3$ solution, brine, dried ($MgSO_4$), concentrated, and purified by flash column chromatography, eluting with hexane–EtOAc (10:1) to afford the coupling compounds.

4.2.1. Methyl 5-(hexyl)-nicotinate (7a). Following the above general procedure, the reaction of 1-hexene (0.15 mL, 1.2 mmol) and methyl 5-bromo-nicotinate (286 mg, 1.33 mmol) afforded 212 mg **7a** (0.96 mmol, 80%) as a colorless oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.55 (s, 1H), 8.1 (s, 1H), 3.90 (s, 3H), 2.62 (t, J = 7.6 Hz, 2H), 1.80 (m, 2H), 1.52 (m, 2H), 1.21 (m, 4H), 0.85 (t, J = 2.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 153.3, 148.0, 138.1, 136.9, 125.8, 52.4, 36.3, 31.5, 30.9, 28.8, 22.6, 14.1; HRMS (ESI) $C_{13}H_{19}NO_2$ *m/z* calculated M+H$^+$ 222.1494, measured M+H$^+$ 222.1485 (4.0 ppm).

4.2.2. Methyl 5-(5-*tert*-butylmethylsilyl ether pentyl)-nicotinate (7b). Following the above general procedure, the reaction of *tert*-butyldimethyl(pent-4-enyloxy)silane (200 mg, 1 mmol) and methyl 5-bromo-nicotinate (238 mg, 1.1 mmol) afforded 270 mg **7b** (0.8 mmol, 80%) as a colorless oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.59 (s, 1H), 8.09 (s, 1H), 3.90 (s, 3H), 3.55 (t, J = 6.4, 2H), 2.62 (t, J = 7.6 Hz, 2H), 1.62 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 0.85 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 166.0, 153.6, 148.4, 137.7, 136.7, 125.6, 62.9, 52.3, 32.7, 32.5, 30.8, 25.9, 25.4, 18.3, −5.3; HRMS (ESI) $C_{18}H_{31}NO_3Si$ *m/z* calculated M+H$^+$ 338.2151, measured M+H$^+$ 338.2146 (1.5 ppm).

4.2.3. Methyl 5-(phenethyl)-nicotinate (7c). Following the above general procedure, the reaction of styrene (0.17 mL, 1.5 mmol) and methyl 5-bromo-nicotinate (356 mg, 1.65 mmol) afforded 181 mg **7e** (0.75 mmol, 50%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.55 (s, 1H), 8.11 (s, 1H), 7.15–7.35 (m, 5H), 3.96 (s, 3H), 2.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 153.7, 148.6, 140.4, 136.8, 136.7, 128.6, 128.4, 126.4, 125.7, 42.3, 37.2, 34.7; HRMS (ESI) $C_{15}H_{15}NO_2$ *m/z* calculated M+H$^+$ 242.1180, measured M+H$^+$ 242.1169 (4.5 ppm).

4.2.4. Methyl 5-(cyclohexylmethyl)-nicotinate (7d). Following the above general procedure, the reaction of methylenecyclohexane (0.17 mL, 1.4 mmol) and methyl 5-bromo-nicotinate (333 mg, 1.54 mmol) afforded 212 mg **7c** (0.91 mmol, 65%) as colorless oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.54 (s, 1H), 8.07 (s, 1H), 3.98 (s, 3H), 2.53 (d, J = 7.0, 2H), 1.89 (m, 1H), 1.71 (m, 5H), 1.24 (m, 2H), 1.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 154.2, 148.4, 137.3, 136.4, 125.6, 52.3, 40.7, 39.4, 32.9, 26.3, 26.1; HRMS (ESI) $C_{14}H_{19}NO_2$ *m/z* calculated M+H$^+$ 234.1494, measured M+H$^+$ 234.1486 (3.4 ppm).

4.3. General procedure for synthesis of 7c, 7e, and 7f

Methyl 5-bromo-nicotinate (1.1 mmol) was dissolved in degassed DMF–THF (3:1) (10 mL) under nitrogen, then trifluoroborate compound or boronic acid pinacolate (1 mmol) was added followed by the addition of K_3PO_4 (3 mmol, 637 mg) and $PdCl_2(dppf)CH_2Cl_2$ (42 mg, 5 mol%). The mixture was stirred for 6 h at 70 °C, cooled to room temperature, and then diluted with EtOAc and saturated $NaHCO_3$ solution. The aqueous layer was re-extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give crude products which were purified by flash column chromatography, eluting with hexane–EtOAc (10:1) to afford the coupling compounds.

4.3.1. Methyl 5-(phenethyl)-nicotinate (7c). Following the above general procedure, the reaction of potassium phenethyltrifluoroborate (320 mg, 1.5 mmol) and methyl 5-bromo-nicotinate (356 mg, 1.65 mmol) afforded 218 mg of **7e** (0.9 mmol, 60%) as a light yellow oil after purification by chromatography. Same analytical data as given previously.

4.3.2. Methyl 5-(phenyl)-nicotinate (7e). Following the above general procedure, the reaction of potassium phenyltrifluoroborate (276 mg, 1.5 mmol) and methyl 5-bromo-nicotinate (356 mg, 1.65 mmol) afforded 272 mg of **7f** (1.28 mmol, 85%) as a yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 9.01 (s, 1H), 8.50 (s, 1H), 7.40–7.72 (m, 5H), 4.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 136.6, 135.5, 129.3, 128.7, 127.2, 126.1, 52.6; HRMS (ESI) $C_{13}H_{11}NO_2$ *m/z* calculated M+H$^+$ 214.0868, measured M+H$^+$ 218.0870 (0.9 ppm).

4.3.3. Methyl 5-(cyclohexenyl)-nicotinate (7f). Following the above general procedure, the reaction of cyclohexene-1-boronic acid pinacol ester (312 mg, 1.5 mmol) and methyl 5-bromo-nicotinate (356 mg, 1.65 mmol) afforded 263 mg **7d** (0.75 mmol, 50%) as colorless oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.70 (s, 1H), 8.15 (s, 1H), 6.15 (s, 1H), 3.95 (s, 3H), 2.30 (m, 2H), 2.20 (m, 2H), 1.78 (m, 2H), 1.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 150.1, 148.5, 137.5, 132.9, 128.5, 125.4, 52.3, 26.9, 25.8, 22,6, 21.7; HRMS (ESI) $C_{13}H_{15}NO_2$ *m/z* calculated M+H$^+$ 218.1181, measured M+H$^+$ 218.1182 (0.5 ppm).

4.4. General procedure for the preparation of 11

The 3,5-disubstituted pyridines **7** were dissolved in 1% HOAc–MeOH (0.1 M) under nitrogen, then 10% Pd/C (50 mol%) was added carefully followed by the replacement of nitrogen with a balloon of hydrogen. The mixture was stirred for 6 h at room temperature under a balloon of hydrogen and then was filtered through Celite, which was subsequently washed with MeOH (20 mL). The solvent was removed under vacuum and gave the crude products that can be used directly in next step. The crude piperidine compounds **6** were then dissolved in EtOH (0.5 M) and then K_2CO_3 (400 mol%) was added followed by the addition of 1-bromo-3-phenylpropane (120 mol%). The mixture was stirred for 12 h at 85 °C, cooled to room temperature, and then diluted with EtOAc (50 mL). The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give crude products which can be purified by flash col-

umn chromatography, eluting with hexane–EtOAc (5:1) to afford the desired compound, **11**.

4.4.1. Ethyl 5-hexyl-1-(3-phenylpropyl)piperidine-3-carboxylate (11a). Following the above general procedure **7a** (332 mg, 1.5 mmol) was hydrogenated to provide 340 mg of crude **6a**. This material was used directly in the subsequent reaction to provide 377 mg of **11a** (1.05 mmol, 70%) as light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.30 (m, 5H), 4.10 (q, J = 7.2 Hz, 2H), 2.95 (m, 1H), 2.43–2.67 (m, 4H), 2.34 1(m, 1H), 2.24 (m, 2H), 2.1 (m, 1H), 1.70–1.97 (m, 4H), 1.10–1.30 (m, 14H), 0.87 (t, J = 4.5 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 142.4, 128.5, 128.2, 125.6, 60.3, 59.9, 58.0, 54.9, 39.5, 33.6, 33.5, 32.9, 31.8, 31.7, 29.5, 28.6, 26.9, 22.7, 14.2, 14.1; HRMS (ESI) $C_{23}H_{37}NO_2$ *m/z* calculated M+H$^+$ 360.2903, measured M+H$^+$ 360.2903 (0.0 ppm).

4.4.2. Ethyl 5-(5-*tert*-butylmethylsilyl ether pentyl)-1-(3-phenylpropyl)piperidine-3-carboxylate (11b). Following the above general procedure **7b** (610 mg, 1.81 mmol) was hydrogenated to provide 620 mg of crude **6b**. This material was used directly in the subsequent reaction to afford 512 mg of **11b** (1.09 mmol, 60%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.72 (m, 5H), 4.12 (q, J = 7.2 Hz, 2H), 3.55 (t, J = 6.6, 2H), 2.94 (m, 1H), 2.48–2.70 (m, 4H), 2.14–2.33 (m, 2H), 1.96 (m, 1H), 1.43–1.90 (m, 6H), 1.30–1.40 (m, 8H), 1.26 (t, J = 7.2, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 142.5, 128.5, 128.2, 125.6, 63.3, 60.3, 57.9, 55.0, 39.5, 33.7, 33.5, 33.0, 32.8, 31.7, 28.6, 27.4, 26.9, 25.9, 22.6, 14.2, −5.3; HRMS (ESI) $C_{28}H_{49}NO_3Si$ *m/z* calculated M+H$^+$ 476.3560, measured M+H$^+$ 476.3568 (1.7 ppm).

4.4.3. Ethyl 5-phenethyl-1-(3-phenylpropyl)piperidine-3-carboxylate (11c). Following the above general procedure **7c** (393 mg, 1.63 mmol) was hydrogenated to provide 400 mg of crude **6c**. This material was used directly in the subsequent reaction to afford 432 mg of **11c** (1.14 mmol, 70%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15–7.33 (m, 10H), 4.13 (q, J = 7.1 Hz, 2H), 2.93 (m, 1H), 2.52–2.72 (m, 6H), 2.21–2.40 (m, 2H), 1.72–2.14 (m, 4H), 1.50–1.67 (m, 5H), 1.23 (t, J = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 142.7, 142.4, 128.4, 128.3, 125.7, 63.7, 60.3, 57.8, 55.0, 39.5, 35.6, 33.5, 32.9, 31.7, 28.6, 14.3; HRMS (ESI) $C_{25}H_{33}NO_2$ *m/z* calculated M+H$^+$ 380.2590, measured M+H$^+$ 380.2580 (2.6 ppm).

4.4.4. Ethyl 5-(cyclohexylmethyl)-1-(3-phenylpropyl)piperidine-3-carboxylate (11d). Following the above general procedure **7d** (376 mg, 1.61 mmol) was hydrogenated to provide 383 mg of crude **6d**. This material was used directly in the subsequent reaction to afford 357 mg of **11d** (0.96 mmol, 60%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.22 (m, 5H), 4.11 (q, J = 7.2, 2H), 2.98 (m, 1H), 2.45–2.67 (m, 4H), 2.14–2.39 (m, 3H), 1.84–2.07 (m, 3H), 1.60–1.82 (m, 8H), 1.01–1.32 (m, 9H), 0.64–0.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 142.5, 128.5, 128.2, 125.6, 63.7, 60.3, 57.8, 54.9, 41.5, 39.6, 34.7, 33.5, 33.4, 33.3, 32.2, 30.3, 29.9, 28.6, 26.7, 26.4, 14.2; HRMS (ESI) $C_{24}H_{37}NO_2$ *m/z* calculated M+H$^+$ 372.2903, measured M+H$^+$ 372.2903 (0.0 ppm).

4.4.5. Ethyl 5-phenyl-1-(3-phenylpropyl)piperidine-3-carboxylate (11e). Following the above general procedure **7e** (271 mg, 1.27 mmol) was hydrogenated to provide 276 mg of crude **6e**. This material was used directly in the subsequent reaction to afford 290 mg of **11e** (0.82 mmol, 65%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09–7.19 (m, 10H), 4.12 (q, J = 7.12, 2H), 3.23 (m, 1H), 3.03–3.15 (m, 1H), 2.77–2.86 (m, 1H), 2.66–2.72 (m, 1H), 2.5–2.66 (m, 2H), 2.11–2.42 (m, 4H), 1.98 (s, 1H), 1.77 (m, J = 7.4, 2H), 1.52–1.68 (m, 1H), 1.22 (t, J = 7.12, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 144.4, 142.4, 128.5, 128.3, 128.2, 128.1, 127.4, 126.3, 125.6, 60.9, 60.4, 57.7, 54.4, 39.8, 39.2, 33.5, 32.3, 28.6, 14.3; HRMS (ESI) $C_{23}H_{29}NO_2$ *m/z* calculated M+H$^+$ 352.2277, measured M+H$^+$ 352.2261 (4.5 ppm).

4.4.6. Ethyl 5-cyclohexyl-1-(3-phenylpropyl)piperidine-3-carboxylate (11f). Following the above general procedure **7f** (373 mg, 1.7 mmol) was hydrogenated to provide 380 mg of crude **6f**. This material was used directly in the subsequent reaction to afford 411 mg of **11f** (1.15 mmol, 68%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–7.28 (m, 5H), 4.17 (q, J = 7.1, 2H), 3.04 (m, 1H), 2.53–2.73 (m, 4H), 2.32–2.43 (m, 1H), 2.14–2.30 (m, 2H), 1.93–2.08 (m, 2H), 1.52–1.86 (m, 8H), 1.10–1.33 (m, 8H), 0.84–1.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 141.9, 128.5, 128.2, 125.6, 63.7, 60.3, 58.0, 54.9, 39.8, 39.7, 38.3, 33.5, 32.3, 30.4, 28.9, 28.6, 26.5, 14.3; HRMS (ESI) $C_{23}H_{35}NO_2$ *m/z* calculated M+H$^+$ 358.2736, measured M+H$^+$ 358.2719 (4.5 ppm).

4.5. General procedure for the synthesis of 5

Compounds **11a**–**f** were dissolved in THF (0.1 M) under nitrogen and cooled to 0 °C. $LiAlH_4$ (200 mol%) was added carefully. The mixture was stirred for 12 h at room temperature, and then diluted with Et_2O and cooled to 0 °C. H_2O (80 μL) was added followed by the addition of 15% NaOH (80 μL) and H_2O (0.2 mL). The system was stirred for 2 h at room temperature and $MgSO_4$ was added. The mixture was filtered through Celite, which was subsequently washed with Et_2O (20 mL). The solvent was removed under vacuum and gave **12a**–**f** which were used directly in the next reaction. The crude reduction products, **12a**–**f**, were dissolved in CH_2Cl_2 (0.5 M) under nitrogen. DMAP (10 mol%) was added followed by the addition of 2-(3′-methyl)succinimidoanthranilic acid[51] (120 mol%). The mixture was cooled to 0 °C, and then DCC (130 mol%) was added. The mixture was stirred for 12 h at room temperature, and then the solvent was removed under vacuum. The residue was taken up in Et_2O ether (20 mL), and filtered through Celite. The clear solution was concentrated and gave the crude products which were purified by flash column chromatography,

eluting with hexane–EtOAc (3:1) to afford the desired compounds.

4.5.1. Succinimidoanthranilate ester 5a. Following the above general procedure **11a** (353 mg, 0.98 mmol) was reduced to provide crude **12a** (310 mg). This material was used directly in the subsequent coupling reaction to provide 366 mg of **5a** (0.68 mmol, 70%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.77, 1H), 7.56 (t, J = 7.68, 1H), 7.39 (t, J = 7.71, 1H), 7,03–7.30 (m, 6H), 4.21 (d, J = 6.98, 2H), 2.98 (m, 2H), 2.40–2.58 (m, 5H), 2.01–2.30 (m, 4H), 1.48–1.89 (m, 6H), 1.38–1.46 (m, 3H), 1.11–1.30 (m, 10H), 0.80 (t, J = 6.81, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 175.7, 164.4, 142.5, 133.2, 132.8, 131.5, 129.8, 129.2, 128.5, 128.2, 127.7, 125.6, 67.5, 59.8, 57.9, 56.1, 37.0, 35.3, 33.9, 33.6, 33.1, 32.5, 32.4, 31.9, 29.5, 28.7, 27.1, 24.9, 22.6, 16.4, 14.1; HRMS (ESI) $C_{33}H_{44}N_2O_4$ m/z calculated M+H$^+$ 533.3379, measured M+H$^+$ 533.3363 (3.0 ppm).

4.5.2. Succinimidoanthranilate ester 5b. Following the above general procedure **11b** (438 mg, 0.92 mmol) was reduced to provide crude **12b** (400 mg). This material was used directly in the subsequent coupling reaction to provide 386 mg of **5a** (0.6 mmol, 65%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.849 (s, 9H), 1.12–1.30 (m, 7H), 1.31–1.59 (m, 5H), 1.60–1.92 (m, 5H), 2.05–2.37 (m, 4H), 2.40–2.72 (m, 5H), 3.55 (m, 2H), 4.23 (t, J = 6.42, 2H), 4.23 (d, J = 7.0, 2H), 7.05–7.37 (m, 6H), 7.43 (t, J = 7.56, 1H), 7.62 (t, J = 7.56, 1H), 8.04 (d, J = 7.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 175.0, 163.6, 141.7, 132.4, 132.0, 130.7, 129.9, 129.4, 129.0, 128.5, 128.2, 127.7, 127.5, 124.8, 66.7, 62.5, 58.9, 57.2, 55.3, 36.2, 34.5, 33.1, 32.8, 32.3, 32.1, 31.7, 27.9, 26.2, 25.2, 25.3, 17.6, 15.6, −6.0; HRMS (ESI) $C_{38}H_{56}N_2O_5Si$ m/z calculated M+H$^+$ 649.4037, measured M+H$^+$ 649.4009 (4.3 ppm).

4.5.3. Succinimidoanthranilate ester 5c. Following the above general procedure **11c** (338 mg, 0.9 mmol) was reduced to provide crude **12c** (301 mg). This material was used directly in the subsequent coupling reaction to provide 320 mg of **5c** (0.58 mmol, 65%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.4, 1H), 7.57 (t, J = 7.65, 1H), 7.41 (t, J = 7.62, 1H), 7.08–7.38 (m, 11H), 4.19 (d, J = 6.99, 2H), 2.98 (m, 2H), 2.40–2.58 (m, 6H), 2.10–2.28 (m, 3H), 1.70–1.96 (m, 1H), 1.50–1.59 (m, 6H), 1.38 (m, 3H), 1.18–1.27 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 174.8, 163.4, 141.5, 132.3, 131.8, 130.5, 128.8, 128.3, 127.5, 127.3, 124.7, 66.4, 58.4, 56.9, 55.1, 36.0, 34.6, 34.3, 32.9, 32.5, 32.0, 31.2, 28.7, 27.7, 24.7, 23.9, 15.4; HRMS (ESI) $C_{35}H_{40}N_2O_4$ m/z calculated M+H$^+$ 553.3066, measured M+H$^+$ 553.3084 (3.3 ppm).

4.5.4. Succinimidoanthranilate ester 5d. Following the above general procedure **11d** (339 mg, 0.91 mmol) was reduced to provide crude **12d** (300 mg). This material was used directly in the subsequent coupling reaction to provide 288 mg of **5d** (0.53 mmol, 58%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.89, 1H), 7.57 (t, J = 7.65, 1H), 7.41 (t, J = 7.71, 1H), 7.05–7.25 (m, 6H), 4.22 (d, J = 6.98, 2H), 2.98 (m, 2H), 2.32–2.80 (m, 5H), 2.05–2.29 (m, 4H), 1.45–1.89 (m, 10H), 1.25–1.40 (m, 3H), 0.96–1.24 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 175.6, 164.5, 142.5, 133.2, 132.8, 131.5, 129.8, 129.2, 128.2, 125.6, 67.5, 60.2, 57.9, 55.9, 41.7, 37.0, 34.8, 33.7, 33.6, 33.1, 32.7, 29.7, 29.2, 28.7, 26.7, 26.4, 22.8, 16.6; HRMS (ESI) $C_{34}H_{44}N_2O_4$ m/z calculated M+H$^+$ 545.3379, measured M+H$^+$ 545.3369 (1.8 ppm).

4.5.5. Succinimidoanthranilate ester 5e. Following the above general procedure, **11e** (380 mg, 1.08 mmol) was reduced to provide crude **12e** (340 mg). This material was used directly in the subsequent coupling reaction to provide 402 mg of **5e** (0.76 mmol, 70%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 7.79, 1H), 7.65 (t, J = 7.70, 1H), 7.48 (t, J = 7.71, 1H), 7.17–7.29 (m, 6H), 4.27 (d, J = 6.98, 2H), 3.06 (m, 2H), 2.40–2.70 (m, 4H), 1.89–2.39 (m, 5H), 1.55–1.86 (m, 9H), 1.30–1.50 (m, 6H), 1.00–1.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 175.8, 164.4, 142.5, 133.2, 132.8, 131.5, 129.8, 129.2, 128.5, 128.4, 128.2, 126.0, 125.6, 67.4, 61.2, 58.2, 55.9, 39.9, 37.6, 37.0, 35.3, 33.9, 32.2, 30.6, 30.5, 29.7, 28.7, 26.6, 25.6, 24.9, 16.4; HRMS (ESI) $C_{33}H_{42}N_2O_4$ m/z calculated M+H$^+$ 531.3223, measured M+H$^+$ 531.3202 (4.0 ppm).

4.5.6. Succinimidoanthranilate ester 5f. Following the above general procedure, **11f** (320 mg, 0.9 mmol) was reduced to provide crude **12f** (276 mg). This material was used directly in the subsequent coupling reaction to provide 280 mg of **5f** (0.53 mmol, 60%) as a light yellow oil after purification by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.47, 1H), 7.56 (t, J = 7.71, 1H), 7.38 (t, J = 7.68, 1H), 7.04–7.25 (m, 11H), 4.38 (d, J = 6.99, 2H), 2.85–3.10 (m, 3H), 2.60–2.80 (m, 2H), 2.57 (t, J = 7.8, 2H), 1.50–1.79 (m, 4H), 1.26–1.37 (m, 3H), 1.10–1.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 175.8, 164.5, 144.4, 142.4, 133.2, 132.8, 131.5, 129.8, 129.2, 128.4, 128.4, 128.3, 127.6, 127.5, 126.3, 125.7, 66.9, 60.7, 57.9, 55.3, 49.2, 38.4, 37.0, 35.3, 33.9, 33.6, 28.6, 24.9, 16.4; HRMS (ESI) $C_{33}H_{36}N_2O_4$ m/z calculated M+H$^+$ 525.2743, measured M+H$^+$ 525.2718 (4.8 ppm).

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