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Synthesis of Benzocyclohepta[*b*]indoles by Lewis Acid Catalyzed Annulation of Two 3-(1*H*-Isochromen-1-yl)-1*H*-indoles

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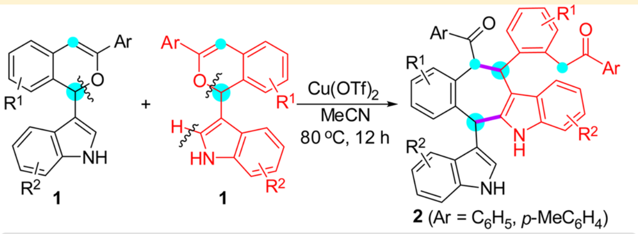
Ⓢ *Supporting Information*

ABSTRACT: A novel Lewis acid catalyzed annulation reaction has been established for the synthesis of benzocyclohepta[*b*]indoles. This method represents a new annulation strategy to a seven-membered carbocyclic ring system from two 3-(1*H*-isochromen-1-yl)-1*H*-indole molecules using Cu(OTf)$_2$ catalyst; moreover, the products, benzocyclohepta[*b*]indoles, can be used as the rapid mercuric ion colorimetric detection reagents.



- **New annulation strategy for constructing the cyclohepta[b]indole core, a seven-membered carbocyclic ring system**
- **13 examples, up to 75% yield**

■ INTRODUCTION

The seven-membered carbocyclic ring system is an important structural motif in many biologically active natural products and pharmaceutical molecules (Figure 1).[1] As a result, the efficient construction of seven-membered carbocyclic compounds has attracted much attention from both academia and industry, particularly with regard to the cycloaddition reaction.[2−5] Despite the impressive progress in this cycloaddition field, there have been much less abundant studies on the selective construction of the seven-membered carbocyclic ring system attributing the difficulty to enthalpic/entropic factors.[1−6] In this context, the [4 + 3] cycloaddition reaction, the annulation of an allyl cation with a four-atom π-system, has become an important methodology frequently utilized for the seven-membered carbocyclic ring synthesis purpose.[3−5] However, the majority of efforts[3,4] focused on the development of efficient routes to the formation of various oxallyl cation species since the group of Fort reported the first example of [4 + 3] cycloaddition of the oxallyl cation species, in situ generated from chlorodibenzyl ketone by 2,6-lutidin base, with furan.[4a] In 1994, the group of Trost found that trimethylenemethane equivalents could replace the oxallyl cation species to undergo the [4 + 3] cycloaddition reaction; however, this method suffered from the competing [3 + 2] reactions.[5] Thus, it is urgent and highly desirable to develop new annulation strategies involving new allyl cation species for more convenient and efficient preparation of the seven-membered carbocyclic rings.

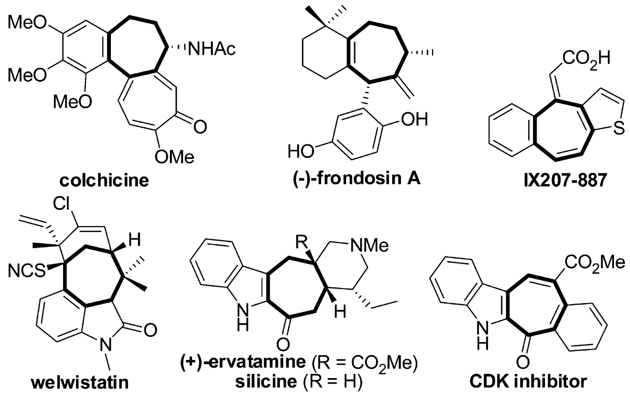
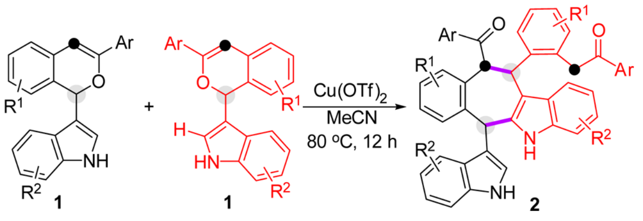


Figure 1. Examples of important seven-membered carbocyclic rings.

Herein, we report a new Lewis acid catalyzed annulation of 3-(1*H*-isochromen-1-yl)-1*H*-indoles for selective synthesis of benzocyclohepta[*b*]indoles, a new seven-membered carbocyclic ring system (Scheme 1).[4w,6] This annulation method is achieved by the reaction between two 3-(1*H*-isochromen-1-yl)-1*H*-indole molecules wherein one molecule is used as the four-atom π-system and another is the allyl cation resource. Notably, the products, benzocyclohepta[*b*]indoles, display

Scheme 1. Copper-Catalyzed Annulation Reaction



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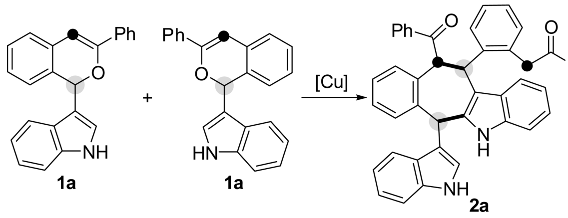
important biological activities[7] and can be used as the rapid mercuric ion colorimetric detection reagents.

■ RESULTS AND DISCUSSION

Our initial attempt with 3-(3-phenyl-1*H*-isochromen-1-yl)-1*H*-indole (**1a**) and 5 mol % of $Cu(OTf)_2$ in MeCN at room temperature for 48 h successfully underwent the annulation reaction to furnish the desired benzocyclohepta[*b*]indole product (**2a**) in 73% yield (entry 1 in Table 1), and the structure of product **2a** was unambiguously confirmed by the X-ray single-crystal diffraction analysis (see the Supporting Information). Inspired by the results, a number of other Cu catalysts, such as $CuCl_2$, $Cu(acac)_2$, $Cu(OAc)_2$, CuOTf, and CuI, were investigated (entries 2−6); however, the results demonstrated that they were less effective than $Cu(OTf)_2$. Three Lewis acids, $In(OTf)_3$, $Sc(OTf)_3$, and $Yb(OTf)_3$, were also tested: they all could effect the reaction, albeit lowering yield of product **2a** (entries 7−9). These results suggest that the real catalyst is a Lewis acid. Subsequently, a series of other solvents, including CH_2Cl_2, toluene, acetone, $MeNO_2$, and DMSO, were tested (entries 10−14). Screening revealed that solvents CH_2Cl_2, toluene, acetone, and $MeNO_2$ could effect the reaction, but they were less active than MeCN (entries 10−13). Surprisingly, DMSO completely suppressed the reaction and shifted the chemoselectivity toward to another ring rearrangement product, (5*H*-benzo[*b*]carbazol-6-yl)(phenyl)methanone (**3a**), albeit with a low yield (entry 14).[8] Interestingly, the higher reaction temperatures could improve the reaction rate (entries 15 and 16): results identical to those at room temperature could be achieved in 12 h when the reaction was carried out at either 80 or 100 °C. Among the amounts of $Cu(OTf)_2$ examined, the reaction at 5 mol % of $Cu(OTf)_2$ was viable (entries 1, 17, and 18). However, the reaction could not take place without any Lewis acids (entry 19). Finally, two Brøsted acids, TfOH and HOAc, were also tested (entries 20 and 21). TfOH could catalyze the reaction, albeit with a lower yield (entry 20). However, no reaction was observed in the presence of HOAc alone (entry 21).

Table 1. Screening Optimal Conditions[a]

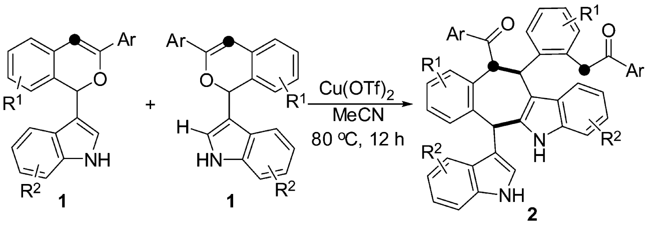


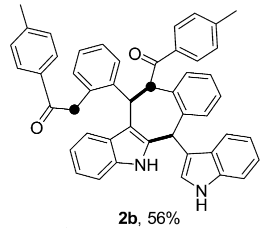
entry	[Cu] (mol %)	solvent	*T* (°C)	time (h)	yield (%)
1	$Cu(OTf)_2$ (5)	MeCN	rt	48	73
2	$CuCl_2$ (5)	MeCN	rt	48	17
3	$Cu(acac)_2$ (5)	MeCN	rt	48	9
4	$Cu(OAc)_2$ (5)	MeCN	rt	48	trace
5	CuOTf (5)	MeCN	rt	48	21
6	CuI (5)	MeCN	rt	48	trace
7	$In(OTf)_3$ (5)	MeCN	rt	48	48
8	$Sc(OTf)_3$ (5)	MeCN	rt	48	27
9	$Yb(OTf)_3$ (5)	MeCN	rt	48	63
10	$Cu(OTf)_2$ (5)	CH_2Cl_2	rt	48	42
11	$Cu(OTf)_2$ (5)	toluene	rt	48	25
12	$Cu(OTf)_2$ (5)	acetone	rt	48	34
13	$Cu(OTf)_2$ (5)	$MeNO_2$	rt	48	58
14[b]	$Cu(OTf)_2$ (5)	DMSO	rt	48	trace
15	$Cu(OTf)_2$ (5)	MeCN	80	12	73
16	$Cu(OTf)_2$ (5)	MeCN	100	12	74
17	$Cu(OTf)_2$ (10)	MeCN	80	12	75
18	$Cu(OTf)_2$ (2)	MeCN	80	12	38
19	—	MeCN	rt	48	0
20	TfOH (10)	MeCN	80	12	18
21	HOAc (10)	MeCN	80	12	trace

[a] Reaction conditions: **1a** (0.3 mmol), [Cu], and solvent (2 mL) under argon atmosphere. Some byproducts, including (5*H*-benzo[*b*]carbazol-6-yl)(phenyl)methanone (**3a**) and 2-(2-(di(1*H*-indol-3-yl)methyl)-phenyl)-1-phenylethanone (**4a**), were observed. [b] Only (5*H*-benzo-[*b*]carbazol-6-yl)(phenyl)methanone (**3a**) was isolated in 8% yields.

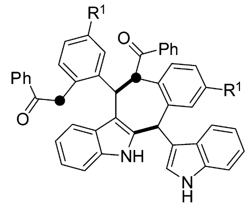
With the optimized conditions in hand, we then probed the scope of this annulation method with respect to 3-(1*H*-isochromen-1-yl)-1*H*-indoles (**1**) (Table 2). Initially, substrate **1b**, having a *p*-MeC_6H_4 group on the 3 position of the 1*H*-isochromen-1-yl moiety, was also viable for this annulation reaction, providing the desired product **2b** in 56% yield. Gratifyingly, the substitution effect on the aromatic ring of the 1*H*-isochromen-1-yl moiety was investigated (products **2c**−**g**). The results showed that several substituents, including Me, MeO, F, and Cl, were well-tolerated. For example, Me-substituted substrate **1c** underwent the reaction with $Cu(OTf)_2$

Table 2. Cu-Catalyzed Annulation of 3-(1*H*-Isochromen-1-yl)-1*H*-indoles (1)[a]

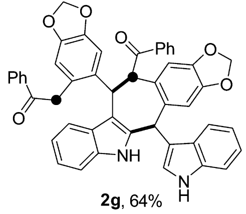




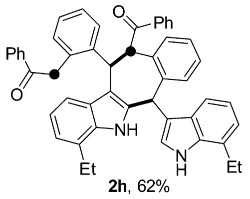
2b, 56%



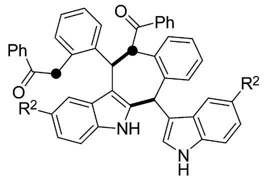
R¹ = Me, **2c**, 62%
R¹ = MeO, **2d**, 57%
R¹ = F, **2e**, 60%
R¹ = Cl, **2f**, 65%



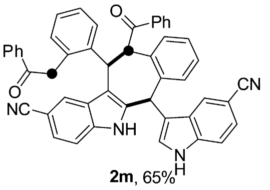
2g, 64%



2h, 62%



R² = Me, **2i**, 72%
R² = MeO, **2j**, 57%
R² = F, **2k**, 56%
R² = Br, **2l**, 71%



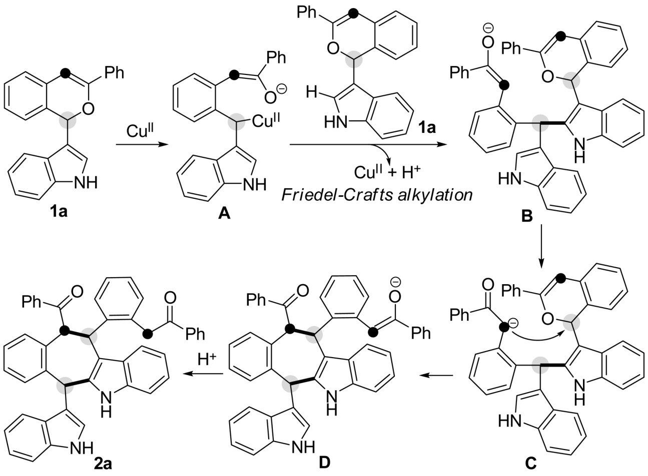
2m, 65%

[a] Reaction conditions: **1** (0.3 mmol), $Cu(OTf)_2$ (5 mol %), and MeCN (2 mL) at 80 °C under argon atmosphere for 12 h.

smoothly to afford the expected product **2c** in 62% yield. Substrates **1e** and **1f** with a F or a Cl group were found to be consistent with the optimal conditions leading to the corresponding products **2e** and **2f** in moderate yield. Treatment of heterocycle-containing substrate **1g** with $Cu(OTf)_2$ also afforded product **2g** in 64% yield. We were pleased to find that the annulation method could be applicable to a diverse range of substrates bearing substituents on the indole moiety. 7-Ethylindole **1h**, for instance, could be transferred into the desired benzocyclohepta[*b*]indole **2h** in 62% yield. To our delight, either electron-donating groups or electron-withdrawing substituents on the 5 position of the indole ring were suitable for the annulation reaction (products **2i−m**). Importantly, halogen groups, including F, Cl, and Br, were compatible with the optimal conditions, thereby facilitating additional modifications at the halogenated positions (products **2e**, **2f**, **2k**, and **2l**).

Consequently, a plausible mechanism outlined in Scheme 2 is proposed.[2−6] Initially, the insertion of the Cu^{II} species into the $C(sp^3)$−O bond of a molecule **1a** afforded intermediate **A**, followed by Friedel−Crafts alkylation of the 2 position of the indole moiety of another molecule **1a** with intermediate **A** yields intermediate **B**. Isomerization of intermediate **B** takes place easily leading to a carbon anion intermediate **C**. Subsequently, the carbon anion intermediate **C** undergoes intramolecular nucleophilic addition to generate intermediate **D**. Finally, isomerization of intermediate **D** offers the desired product **2a**.

Scheme 2. Possible Mechanism



We next turned our attention to apply the obtained products **2**. Generally, highly conjugated polyheterocyclic molecules have good fluorescence properties and can be used as the metal ion probes and functional materials.[9] As shown in Figure 2, 2 equiv of M^{n+} ion, including Ag^+, Ba^{2+}, Bi^{3+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Fe^{3+}, Hg^{2+}, Ni^{2+}, and Zn^{2+}, was added to the solution of product **2a** in CH_3CN/H_2O to test the changes of fluorescence emission intensity. Gratifyingly, four metal ions, Bi^{3+}, Cu^{2+}, Fe^{3+}, and Hg^{2+}, could quench the fluorescence completely, suggesting that product **2a** is a good probe for the four metal ions.

In particular, the color of the $Hg^{2+}(OAc)_2$/product **2a** solution was distinctly deepened at 50 °C for 8 min or at room temperature for 20 min (Figure 3), indicating that product **2a** can be used as the rapid mercuric ion colorimetric detection reagent.[10]

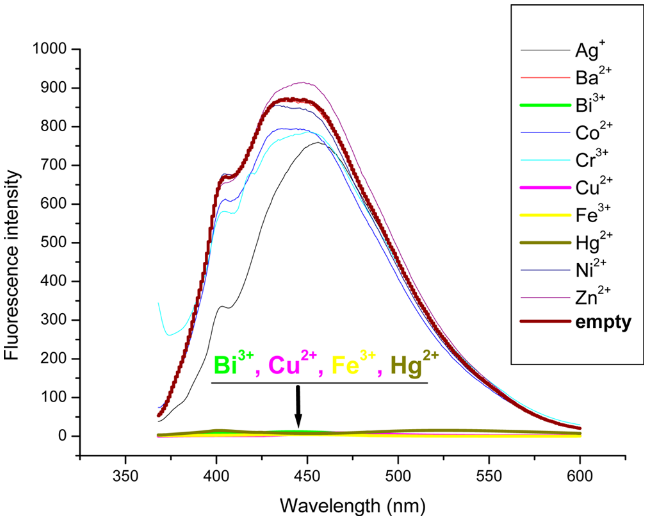
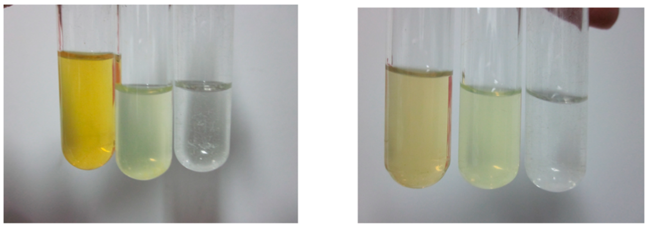


Figure 2. Fluorescence emission spectra of product **2a** in the absence/presence of metal ions: Ag^+, Ba^{2+}, Bi^{3+}, Co^+, Cr^{3+}, Cu^{2+}, Fe^{3+}, Hg^{2+}, Ni^{2+}, and Zn^{2+} in CH_3CN/H_2O (100:1): λ_{ex} = 358.0 nm, [**2a**] = 5 × 10^{-4} M and $[M^{n+}]$ = 1 × 10^{-3} M.



(a) At 50 °C for 8 min **(b) At rt for 20 min**

Figure 3. Use of product **2a** as a mercuric ion colorimetric detection reagent in CH_3CN/H_2O (100:1). Left: [**2a**] = 5 × 10^{-4} M and $[Hg^{2+}]$ = 1 × 10^{-3} M. Middle: $[Hg^{2+}]$ = 1 × 10^{-3} M. Right: [**2a**] = 5 × 10^{-4} M.

■ CONCLUSIONS

In summary, we have illustrated a new, efficient annulation protocol for the construction of the seven-membered carbocyclic ring system using $Cu(OTf)_2$ catalyst. This novel annulation strategy is atom-economic and employs two 3-(1*H*-isochromen-1-yl)-1*H*-indole molecules as the reaction partners: one molecule is played as the four-atom π-system and another is the allyl cation resource. Most importantly, the products, benzocyclohepta[*b*]indoles, were found to be potentially used as both some metal probes and the rapid mercuric ion colorimetric detection reagents.

■ EXPERIMENTAL SECTION

General Considerations. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 or acetone-d_6 on an NMR spectrometer using TMS as internal standard. LRMS was performed on a GC−MS instrument, and HRMS was measured on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry. Melting points are uncorrected.

Preparation of 3-(1*H*-Isochromen-1-yl)-1*H*-indoles (1). 3-(1*H*-Isochromen-1-yl)-1*H*-indoles (**1**) were prepared according to the known procedures.[8] Substrates **1a−e,h−i,l,m** are the known compounds.[8]

Typical Experimental Procedure for $Cu(OTf)_2$-Catalyzed Annulation of 3-(1*H*-Isochromen-1-yl)-1*H*-indoles (1). To a Schlenk tube were added 3-(1*H*-isochromen-1-yl)-1*H*-indoles **1** (0.3

mmol), $Cu(OTf)_2$ (10 mol %), and MeCN (2 mL). The tube was charged with argon and stirred at 80 °C for the indicated time until complete consumption of starting material as monitored by TLC analysis. After the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford the desired benzocyclohepta[*b*]indoles **2**.

Substrate ***1f:*** yellow solid (78%, 55.7 mg); mp 135.2−136.4 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.15 (s, 1H), 7.70 – 7.63 (m, 3H), 7.42−7.26 (m, 6H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 2H), 6.78 (s, 1H), 6.75 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 151.8, 136.7, 134.0, 132.3, 130.5, 130.2, 128.9, 128.4, 127.9, 125.9, 125.7, 125.3, 124.8,124.7, 121.5, 119.3, 119.2, 112.9, 111.9, 99.85, 73.0; IR (neat, cm^{-1}) 1266, 741, 704; HRMS (ESI) calcd for $C_{23}H_{17}ClNO$ (M + H)$^+$ 358.0993, found 358.0981.

Substrate ***1g:*** yellow solid (65%, 47.7 mg); mp 149.4−151.6 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.06 (s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.31−7.23 (m, 3H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.93 (s, 1H), 6.87 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 2H), 6.58 (s, 1H), 6.00 (d, *J* = 3.3 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.6, 146.9, 145.7, 136.7, 134.4, 128.3, 125.9, 125.8, 125.7, 124.4, 123.9, 121.4,119.4, 119.0, 113.7, 111.8, 105.9, 104.4, 100.9, 100.8, 73.3; IR (neat, cm^{-1}): 2229, 1971, 1714, 1363, 1223; HRMS (ESI) calcd for $C_{24}H_{18}NO_3$ (M + H)$^+$ 368.1281, found 368.1267.

Substrate ***1j:*** yellow solid (83%, 58.6); mp 98.1−99.3 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.92 (s, 1H), 7.69 (d, *J* = 7.4 Hz, 2H), 7.34−7.24 (m, 7H), 7.17 (t, *J* = 7 2H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 1.9 Hz, 1H), 6.77−6.72 (m, 3H), 3.73 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.3, 151.1, 134.4, 131.7, 131.4, 130.2, 128.6, 128.3, 128.0, 126.4, 126.1, 124.9, 124.7, 123.7, 113.7, 112.4, 111.5, 101.2, 100.7, 73.4, 55.3; IR (neat, cm^{-1}) 2998, 2152, 1713, 1363, 1223; HRMS (ESI) calcd for $C_{24}H_{20}NO_2$ (M + H)$^+$ 354.1489, found 354.1471.

Substrate ***1k:*** yellow solid (55%, 37.8 mg); mp 113.5−114.7 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.21 (s, 1H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.41−7.27 (m, 7H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 2.3 Hz, 1H), 7.00−6.94 (m, 2H), 6.76 (s, 1H), 6.73 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 156.3 (d, *J* = 230.5 Hz, 1C), 150.7, 133.7, 132.8, 130.8, 129.5, 128.2, 127.8, 127.6, 127.1, 126.0, 125.6 (d, *J* = 10.2 Hz, 1C), 124.3, 124.2, 123.2, 113.5 (d, *J* = 4.69 Hz, 1C), 112.3 (d, *J* = 9.54 Hz, 1C), 109.1 (d, *J* = 25.9 Hz, 1C), 103.5 (d, *J* = 23.4 Hz, 1C), 100.2, 72.7; IR (neat, cm^{-1}) 1676, 1487, 1279, 1051, 743; HRMS (ESI) calcd for $C_{23}H_{17}FNO$ (M + H)$^+$ 342.1289, found 342.1297.

Product ***2a:*** white solid (73%, 70.7 mg); mp 190.5−191.7 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.40 (s, 1H), 11.29 (s, 1H), 8.21 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 7.1 Hz, 1H), 7.67 (t, *J* = 7.1 Hz, 1H), 7.60−7.55 (m, 3H), 7.37−7.22 (m, 4H), 7.17−7.00 (m, 6H), 6.96−6.85 (m, 3H), 6.77−6.59 (m, 7H), 6.29 (d, *J* = 10.9 Hz, 1H), 5.82 (s, 1H), 5.03−5.02 (m, 2H), 4.81 (d, *J* = 11.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.9, 198.7, 144.2, 142.9, 137.4, 137.0, 136.8, 136.3, 135.7, 134.7, 134.2, 133.2, 132.8, 130.3, 129.6, 128.8, 128.5, 128.1, 127.7, 127.6, 127.2, 127.1, 126.5, 125.8, 125.6, 123.7, 121.4, 120.6, 119.7, 118.8, 118.2, 117.0, 112.0, 111.9, 110.6, 53.3, 44.0, 42.5, 41.1; IR (neat, cm^{-1}) 1679, 1446, 1271, 1220, 1001; HRMS (ESI) calcd for $C_{46}H_{35}N_2O_2$ (M + H)$^+$ 647.2693, found 647.2683.

Product ***2b:*** white solid (56%, 56.6 mg); mp 191.3−192.1 °C (uncorrected); ^{1}H NMR (500 MHz, acetone-d_6) δ 10.39 (brs, 1H), 10.29 (brs, 1H), 8.07−8.05 (m, 2H), 7.61−7.59 (m, 1H), 7.47−7.45 (m, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.19−7.15 (m, 1H), 7.12−6.98 (m, 7H), 6.87−6.81 (m, 2H), 6.76−6.66 (m, 6H), 6.56−6.43 (m, 4H), 6.32−6.24 (m, 2H), 5.73 (s, 1H), 5.07 (d, *J* = 16.4 Hz, 1H), 4.81 (d, *J* = 16.4 Hz, 1H), 4.80 (d, *J* = 11.0 Hz, 1H), 2.24 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (126 MHz, acetone-d_6) δ 200.36, 200.08, 145.21, 144.72, 144.27, 142.71, 139.18, 137.09, 136.91, 134.15, 132.75, 132.70, 131.38, 131.31, 130.87, 130.83, 130.47, 130.37, 130.35, 130.33, 130.26, 130.17, 130.14, 129.80, 129.25, 129.19, 128.69, 128.63, 127.91, 127.07, 123.34, 122.50, 121.87, 120.74, 120.23, 113.45, 113.28, 112.05, 53.48, 46.49, 44.26, 32.08, 22.33, 22.11; IR (neat, cm^{-1}) 3057, 2343, 1731, 1265, 1216; HRMS (ESI) calcd for $C_{48}H_{39}N_2O_2$ (M + H)$^+$ 675.3006, found 675.3020.

Product ***2c:*** white solid (62%, 62.7 mg); mp 195.5−196.8 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.32 (s, 1H), 11.25 (s, 1H), 8.20 (d, *J* = 7.2 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.59 (dd, *J* = 16.0 Hz, 8.1 Hz, 3H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.29−7.25(m, 2H), 7.14 (t, *J* = 7.7 Hz, 2H), 7.03 (d, *J* = 7.2 Hz, 2H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.89−6.82 (m, 4H), 6.81−6.73 (m, 4H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.60 (t, *J* = 7.5 Hz, 1H), 6.47 (d, *J* = 7.8 Hz, 1H), 6.22 (d, *J* = 11.1 Hz, 1H), 5.74 (s, 1H), 4.97−4.94 (m, 2H), 4.73 (d, *J* = 11.1 Hz, 1H), 2.18 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 204.4, 204.2, 146.8, 145.6, 143.3, 142.8, 142.6, 142.4, 142.1, 140.9, 140.8, 140.5, 140.3, 139.7, 138.1, 137.6, 135.7, 134.9, 134.2, 133.9, 133.8, 133.3, 133.2, 132.8, 132.4, 131.7, 128.9, 127.0, 126.9, 126.1, 125.6, 124.3, 123.8, 123.5, 118.3, 117.4, 117.0,115.6, 115.5, 49.6, 46.4, 41.2, 39.6, 27.6, 25.3; IR (neat, cm^{-1}) 3055, 2334, 1729, 1268, 1212; HRMS (ESI) calcd for $C_{48}H_{39}N_2O_2$ (M + H)$^+$ 675.3006, found 675.3012.

Product ***2d:*** white solid (57%, 60.4 mg); mp 250.4−251.6 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.39 (s, 1H), 11.35 (s, 1H), 8.18 (d, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.61−7.50 (m, 3H), 7.36−7.24 (m, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.08−6.91 (m, 5H), 6.90−6.76 (m, 6H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.61 (d, *J* = 7.3 Hz, 1H), 6.48−6.38 (m, 2H), 6.17 (d, *J* = 11.1 Hz, 1H), 5.73 (s, 1H), 4.95 (d, *J* = 16.3 Hz, 1H), 4.80 (d, *J* = 16.3 Hz, 1H), 4.72 (d, *J* = 11.1 Hz, 1H), 3.79 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 199.1, 198.9, 158.2, 157.5, 145.4, 144.2, 137.4, 137.1, 136.5, 135.6, 134.7, 133.1, 132.7, 131.1, 128.7, 128.6, 128.4, 128.2, 128.1, 127.7, 127.6, 126.1, 125.8, 123.3, 121.4, 120.6, 119.7, 119.6, 119.0, 118.2, 117.2, 115.8, 112.3, 112.0, 111.9, 111.8, 111.7,110.6, 55.2, 54.9, 52.5, 44.1, 41.7, 41.6; IR (neat, cm^{-1}) 1772, 1724, 1215, 1028, 745; HRMS (ESI) calcd for $C_{48}H_{39}N_2O_4$ (M + H)$^+$ 707.2904, found 707.2885.

Product ***2e:*** white solid (60%, 61.4 mg); mp 263.1−265.4 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.42 (s, 1H), 11.28 (s, 1H), 8.20 (d, *J* = 7.6 Hz, 2H), 7.81 (t, *J* = 7.0 Hz, 1H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.63−7.50 (m, 3H), 7.32−7.27 (m, 2H), 7.21−7.12 (m, 2H), 7.09 (s, 1H), 6.96 (d, *J* = 7.9 Hz, 4H), 6.87−6.79 (m, 4H), 6.68 (d, *J* = 7.7 Hz, 2H), 6.62 (d, *J* = 3.3 Hz, 2H), 6.47 (t, *J* = 7.3 Hz, 1H), 6.23 (d, *J* = 10.9 Hz, 1H), 5.84 (s, 1H), 5.05−4.94 (m, 2H), 4.82 (d, *J* = 11.0 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 204.4, 203.0, 167.2 (d, *J* = 243.6 Hz, 1C), 165.6 (d, *J* = 239.8 Hz, 1C), 145.2, 144.8, 144.7, 144.6, 143.0, 142.8, 142.1, 140.8, 140.5, 138.3, 138.0, 136.5, 135.2, 133.9, 133.8, 133.7, 133.4, 133.1, 131.5, 129.1, 127.1, 126.4, 125.3, 124.5, 124.0, 123.0, 122.2, 119.9, 118.6, 118.5, 118.3, 117.7, 117.2, 115.8, 58.6, 49.1, 47.3, 46.3; IR (neat, cm^{-1}) 3060, 1732, 1269, 742; HRMS (ESI) calcd for $C_{46}H_{33}F_2N_2O_2$ (M + H)$^+$ 683.2505, found 683.2538.

Product ***2f:*** white solid (65%, 69.6 mg); mp 171.3−172.5 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.51 (s, 1H), 11.43 (s, 1H), 8.20 (d, *J* = 7.5 Hz, 2H), 7.84 (s, 1H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.58 (m, 3H), 7.37−7.31 (m, 3H), 7.16−7.09 (m, 3H), 6.99 (d, *J* = 7.0 Hz, 2H), 6.95−6.88 (m, 6H), 6.76 (d, *J* = 7.5 Hz, 2H), 6.76−6.65 (m, 2H), 6.10 (d, *J* = 11.1 Hz, 1H), 5.82 (s, 1H), 5.04−4.91 (m, 2H), 4.84 (d, *J* = 11.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.5, 198.0, 146.0, 145.5, 137.3, 137.1, 136.2, 135.3, 134.8, 133.2, 133.0, 132.6, 131.9, 131.0, 129.2, 129.0, 128.8, 128.4, 128.2, 127.8, 127.6, 127.4, 127.3, 125.7, 125.6, 123.4, 121.6, 121.0, 119.3, 118.5, 116.3, 112.1, 111.3, 110.9, 52.6, 43.3, 41.5, 41.0; IR (neat, cm^{-1}) 1722, 1269, 1203, 744; HRMS (ESI) calcd for $C_{46}H_{33}{}^{35}Cl_2N_2O_2$ (M + H)$^+$ 715.1914, found 715.1885.

Product ***2g:*** white solid (64%, 70.5 mg); mp 230.2−232.4 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.35 (s, 1H), 11.31 (s, 1H), 8.18 (d, *J* = 7.3 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.60−7.51 (m, 3H), 7.37 (s, 1H), 7.33−7.26 (m, 2H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.03−6.92 (m, 4H), 6.89−6.61 (m, 8H), 6.57 (s, 1H), 6.33 (s, 1H), 6.09 (d, *J* = 11.0 Hz, 1H), 5.99 (d, *J* = 15.8 Hz, 2H), 5.67 (s, 2H), 4.88−4.86 (m, 2H), 4.71 (d, *J* = 11.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.9, 198.5, 146.3, 145.9, 145.5, 144.7, 137.4, 137.1, 137.0, 136.9, 136.3, 135.9, 134.6, 133.1, 132.9, 129.6, 128.7, 128.6, 128.4, 128.1, 128.0, 127.6, 127.0, 125.7, 123.4, 121.5, 120.6, 119.7, 119.6, 118.9, 118.2, 117.3, 111.9, 111.8, 110.6, 110.4, 107.3, 107.1, 101.2, 100.4, 52.6, 43.4, 42.1, 41.1; IR (neat, cm^{-1}) 1736, 1595, 1436, 1033, 742; HRMS (ESI) calcd for $C_{48}H_{35}N_2O_6$ (M + H)$^+$ 735.2490, found 735.2453.

*Product **2h**:* white solid (62%, 65.3 mg); mp 180.6−181.8 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.32 (s, 1H), 11.26 (s, 1H), 8.23 (d, J = 7.3 Hz, 2H), 7.76 (d, J = 7.3 Hz, 1H), 7.66 (t, J = 7.3 Hz, 1H), 7.58 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.29−7.22 (m, 2H), 7.14−7.02 (m, 5H), 6.98−6.89 (m, 2H), 6.85−6.77 (m, 6H), 6.72 (t, J = 7.5 Hz, 1H), 6.56 (t, J = 7.6 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 6.39 (d, J = 11.1 Hz, 1H), 5.95 (s, 1H), 5.06−5.02 (m, 2H), 4.83 (d, J = 11.1 Hz, 1H), 3.00 (q, J = 7.4 Hz, 2H), 2.88 (q, J = 7.4 Hz, 2H), 1.36 (t, J = 7.5 Hz, 3H), 1.30 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.9, 198.8, 144.3, 143.1, 137.4, 137.0, 136.4, 135.8, 135.5, 134.3, 133.5, 133.1, 132.8, 130.2, 129.6, 128.7, 128.5, 128.1, 128.0, 127.7, 127.6, 127.3, 127.2, 127.1, 126.5, 126.1, 125.9, 125.6, 123.3, 120.2, 119.4, 119.2, 118.5, 117.7, 117.5, 117.4, 112.4, 53.3, 43.9, 42.5, 41.2, 23.8, 23.6, 14.6, 14.2; IR (neat, cm^{-1}) 1763, 1730, 1268, 740; HRMS (ESI) calcd for $C_{50}H_{43}N_2O_2$ (M + H)$^+$ 703.3319, found 703.3309.

*Product **2i**:* white solid (72%, 72.8 mg); mp 189.6−190.8 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.19 (s, 1H), 11.13 (s, 1H), 8.20 (d, J = 7.4 Hz, 2H), 7.73 (d, J = 7.0 Hz, 1H), 7.67 (t, J = 7.3 Hz, 1H), 7.58 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 8.3 Hz, 1H), 7.34 (t, J = 7.0 Hz 1H), 7.27−7.21 (m, 2H), 7.15 (d, J = 8.1 Hz, 1H), 7.09 (d, J = 7.5 Hz, 2H), 7.04−6.97 (m, 3H), 6.90 (t, J = 7.25 Hz 1H), 6.81−6.68 (m, 7H), 6.42 (s, 1H), 6.27 (d, J = 11.1 Hz, 1H), 5.73 (s, 1H), 5.10 (d, J = 16.6 Hz, 1H), 4.92 (d, J = 16.8 Hz, 1H), 4.77 (d, J = 11.0 Hz, 1H), 2.14 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.8, 198.7, 144.3, 143.1, 137.4, 136.8, 136.3, 135.7, 135.4, 134.2, 133.2, 133.0, 132.8, 130.4, 129.5, 128.8, 128.6, 128.3, 128.1, 127.7, 127.6, 127.1, 127.0, 126.4, 126.1, 125.4, 123.7, 122.9, 122.1, 119.3, 119.2, 116.5, 111.6, 111.3, 110.2, 53.3, 44.1, 42.2, 41.0, 21.5, 21.0; IR (neat, cm^{-1})1734, 1270, 741, 703; HRMS (ESI) calcd for $C_{48}H_{39}N_2O_2$ (M + H)$^+$ 675.3006, found 675.2993.

*Product **2j**:* white solid (57%, 60.4 mg); mp 251.2−252.4 °C (uncorrected); ^{1}H NMR (500 MHz, acetone-d_6) δ 10.24 (s, 1H), 10.16 (s, 1H), 8.20 (d, J = 7.5 Hz, 2H), 7.65 (s, 1H), 7.52 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.35 (d, J = 8.8 Hz, 1H), 7.22 (s, 1H), 7.12−7.07 (m, 4H), 6.98 (s, 2H), 6.93 (d, J = 7.0 Hz, 1H), 6.80−6.68 (m, 6H), 6.56 (t, J = 7.6 Hz, 1H), 6.45 (d, J = 8.7 Hz, 1H), 6.33−6.28 (m, 2H), 6.17 (s, 1H), 5.68 (s, 1H), 5.12 (d, J = 16.1 Hz, 1H), 4.90 (d, J = 16.7 Hz, 1H), 4.75 (d, J = 10.1 Hz, 1H), 3.39 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.9, 198.7, 152.9, 152.6, 144.0, 142.9, 137.2, 136.9,136.5, 136.0, 134.6, 133.2, 132.8, 132.1, 129.9, 129.7, 129.5, 128.8, 128.4, 128.1,127.8, 127.6, 127.0, 126.5, 126.1, 125.5, 124.1, 116.7, 112.5, 111.8, 111.3, 111.0, 110.7,101.7, 54.9, 54.7, 53.2, 44.0, 42.4, 41.2; IR (neat, cm^{-1}) 1724, 1215, 1029, 745; HRMS (ESI) calcd for $C_{48}H_{39}N_2O_4$ (M + H)$^+$ 707.2904, found 707.2903.

*Product **2k**:* white solid (56%, 57.3 mg); mp 199.5−201.7 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.50 (s, 1H), 11.40 (s, 1H), 8.18 (d, J = 7.7 Hz, 2H), 7.77 (d, J = 6.9 Hz, 1H), 7.66 (t, J = 7.1 Hz, 1H), 7.59−7.54 (m, 3H), 7.37 (t, J = 7.8 Hz, 1H), 7.30−7.24 (m, 3H), 7.17 (s, 1H), 7.12 (t, J = 8.5 2H), 7.01−6.92 (m, 3H), 6.81−6.71 (m, 6H), 6.57 (d, J = 9.7 Hz, 1H), 6.35 (d, J = 10.2 Hz, 1H), 6.21 (d, J = 11.1 Hz, 1H), 5.76 (s, 1H), 5.08 (d, J = 16.8 Hz, 1H), 4.92 (d, J = 16.7 Hz, 1H), 4.72 (d, J = 11.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.7, 197.5, 155.4 (d, J = 229.9 Hz, 1C), 155.2 (d, J = 229.2 Hz, 1C), 142.5, 141.1, 136.3, 136.2, 135.6, 135.3, 133.3, 132.7, 132.1, 131.8, 130.3, 129.6, 128.6, 127.7, 127.3, 127.0, 126.8, 126.5, 126.4, 126.2, 126.0, 125.5, 124.7, 116.8, 115.9, 112.0 (d, J = 9.75 Hz, 1C), 111.2, 110.3 (d, J = 8.84 Hz, 1C), 108.5 (d, J = 26.1 Hz, 1C), 107.6 (d, J = 26.0 Hz, 1C), 103.6 (d, J = 23.6 Hz, 1C), 103.0 (d, J = 23.4 Hz, 1C), 52.1, 42.7, 41.3, 40.1; IR (neat, cm^{-1}) 2352, 1733, 1683, 1487, 1269; HRMS (ESI) calcd for $C_{46}H_{33}F_2N_2O_2$ (M + H)$^+$ 683.2505, found 683.2538.

*Product **2l**:* white solid (71%, 85.6 mg); mp 202.3−203.5 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.66 (s, 1H), 11.55 (s, 1H), 8.22 (d, J = 7.1 Hz, 2H), 7.57 (m, 3H), 7.39−7.24 (m, 6H), 7.21−7.04 (m, 6H), 6.99−6.72 (m, 8H), 6.19 (d, J = 10.0 Hz, 1H), 5.82 (s, 1H), 5.08 (d, J = 16.4 Hz, 1H), 4.96 (d, J = 16.3 Hz, 1H), 4.78 (d, J = 10.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.6, 198.3, 143.5, 142.5, 136.9, 136.6, 135.7, 135.3, 133.7, 133.4, 133.2, 132.9, 131.3, 130.5, 129.8, 129.7, 128.8, 128.6, 128.4, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.2, 126.7, 126.2, 125.9, 125.4, 124.0,123.5, 123.4, 122.0, 121.9, 121.1, 116.7, 114.0, 113.5, 112.5, 111.5, 111.1, 111.0, 53.3, 43.6, 42.3, 41.0; IR (neat, cm^{-1}) 1733, 1270, 1046, 741; HRMS (ESI) calcd for $C_{46}H_{33}{}^{79}Br_2N_2O_2$ (M + H)$^+$ 803.0903, found 803.0901.

*Product **2m**:* white solid (65%, 67.9 mg); mp 270.1−271.3 °C (uncorrected); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.07 (s, 1H), 11.94 (s, 1H), 8.20 (d, J = 7.2 Hz, 2H), 7.90 (d, J = 5.9 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.68−7.66 (m, 1H), 7.59 (t, J = 7.4 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.42 (s, 2H), 7.37−7.27 (m, 4H), 7.21−7.17 (m, 2H), 7.11 (s, 1H), 7.01−6.96 (m, 2H), 6.80−6.77 (m, 3H), 6.68 (d, J = 5.9 Hz, 2H), 6.15 (d, J = 10.6 Hz, 1H), 5.91 (s, 1H), 5.23 (d, J = 16.9 Hz, 1H), 4.91 (d, J = 17.1 Hz, 1H), 4.80 (d, J = 10.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.9, 198.2, 143.6, 143.3, 141.4, 141.3, 138.8, 137.7, 137.2, 136.7, 136.5, 136.3, 134.6, 133.3, 133.0, 131.1, 130.0, 123.0, 128.9, 128.3, 128.1, 127.7, 127.6, 127.2, 126.8, 126.1, 125.6, 125.4, 125.0, 124.1, 123.8, 120.6, 120.5, 117.6, 113.5, 113.4, 112.0, 101.0, 100.5, 53.3, 43.4, 42.4, 41.1; IR (neat, cm^{-1}) 1736, 1652, 1486, 1262, 1034; HRMS (ESI) calcd for $C_{48}H_{33}N_4O_2$ (M + H)$^+$ 697.2525, found 697.2598.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of spectra and X-ray single-crystal diffraction analysis of product (**2a**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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