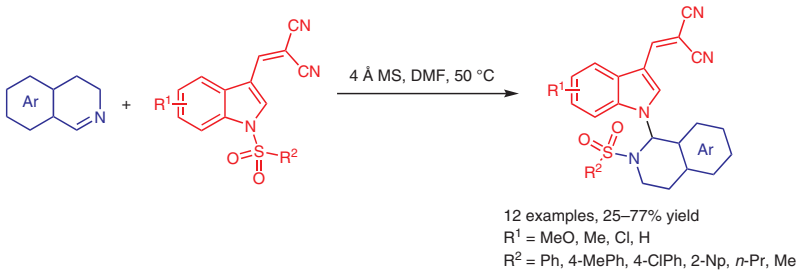
Synlett H.-L. Cui et al. Letter

Catalyst-Free Synthesis of Aminals from Indole-Derived α,α-Dicyanoolefins

Hai-Lei Cui *[a]
Yin Shi[a]
Hui-Qing Deng[a]
Jin-Ju Lei[a]
Xing-Jie Xu[a,b]
Xu Tian[b]
Jie Qiao[a]
Lin Zhou[a]

[a] Laboratory of Asymmetric Synthesis, Chongqing University of Arts and Sciences, 319 Honghe Ave., Yongchuan, Chongqing, 402160, P. R. of China
cuihailei616@163.com
[b] Key Laboratory of Molecular Target & Clinical Pharmacology, School of Pharmaceutical Sciences & the Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou, Guangdong 511436, P. R. of China



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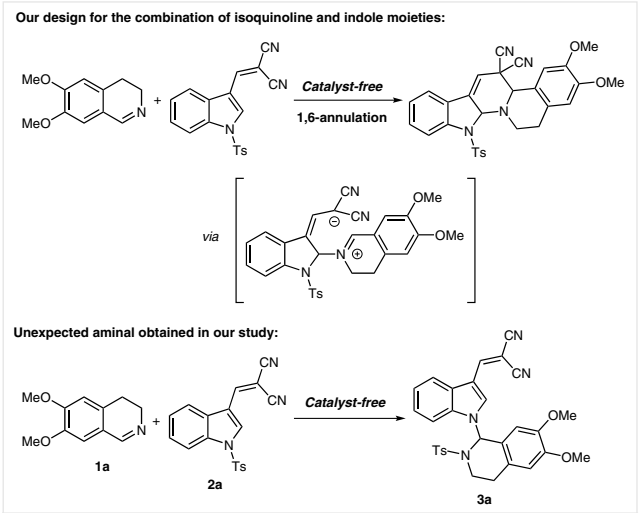
Abstract We have developed an efficient synthesis of indole fused aminals with nucleophilic imines and indole-derived α,α-dicyanoolefins via *N*-sulfonyl group transfer. The combination of two privileged frameworks, tetrahydroisoquinoline or tetrahydro-β-carboline and indole, can be realized by this approach to the construction of aminals. The synthetic application of this method was further demonstrated by the straightforward transformations into highly functionalized aminals possessing carbonyl groups through oxidative cleavage of the nitrile moiety.

Key words aminal, tetrahydroisoquinoline, tetrahydro-β-carboline, indole, α,α-dicyanoolefin

Indole and tetrahydroisoquinoline are both privileged frameworks that are widely present in numerous natural products and bioactive compounds.[1,2] As the combination of privileged scaffolds acts as a useful method for creating potential biological-related molecules for biomedical research and drug discovery,[3] the efficient construction of novel molecules combining privileged frameworks is a longstanding focus for us.[4] In our previous work, we have successfully incorporated tetrahydroisoquinoline into spirooxindole, delivering various functionalized tetrahydroisoquinoline fused spirooxindoles. Along this line, we envisioned that the synthesis of indole fused tetrahydroisoquinoline derivatives could be achieved by following an electrocyclization pathway.

Recently, 1,n-dipole based annulation has become a powerful strategy for the easy assembly of complex azacycles.[5,6] Inspired by pioneering reports,[5,6] we have developed several methods for the synthesis of nitrogen-containing molecules from readily available material through the formation of 1,n-dipoles as key intermediates.[4a,4b,4e,7] To search approaches for the easy construction of privileged scaffold incorporated molecules, we hypothesized that dihydroisoquinoline, as an electron-rich imine, may undergo 1,6-Michael addition with indole-derived electron-deficient olefin to deliver tetrahydroisoquinoline fused carboline derivatives (Scheme 1). However, instead of the desired carboline, an unexpected indole fused aminal was obtained. Pleasingly, it seems that indole-incorporated aminal is a key unit occurring in plenty of natural molecules and synthetic compounds possessing a wide range of activities.[8] For example, both natural (–)-Goniomitine and unnatural (+)-Goniomitine show antiproliferative activity; indole alkaloid Alsto-



Scheme 1 Our design for the combination of isoquinoline and indole moieties

scholarisine A, isolated from the leaves of Alstonia scholaris, exhibits significant ability to promote adult neural stem cells proliferation and differentiation at low concentrations (Figure 1). Thus, the synthesis of indole-incorporated aminals has attracted much attention from the field of synthetic chemistry and medicinal chemistry. A great number of elegant methods have been developed in this regard.[9,10,11] However, there is still a challenging task in the field of organic chemistry and medicinal chemistry to create more structurally diversified aminals and to develop novel methods for the combination of privileged frameworks from simple starting materials. Here, we report our development of the synthesis of aminals by combining both indole and tetrahydroisoquinoline scaffolds.

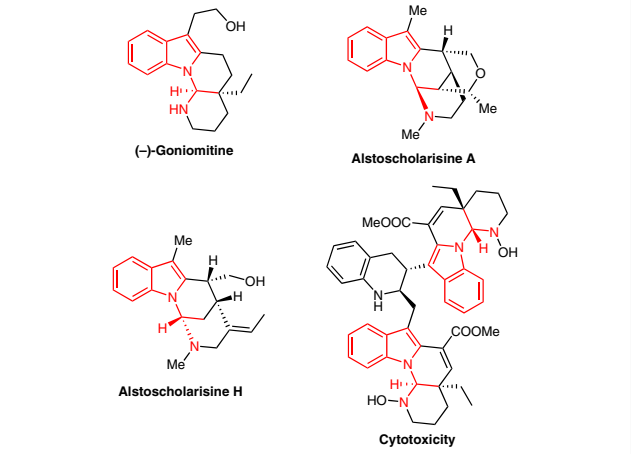
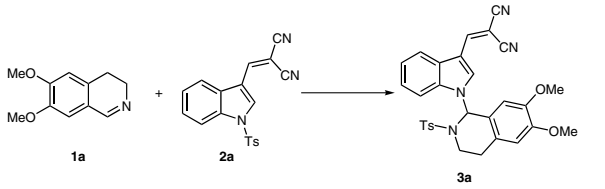


Figure 1 Representative examples of compounds possessing an indole-fused aminal moiety

We started our investigation with the catalyst-free reaction of dihydroisoquinoline **1a** and 2-((1-tosyl-1*H*-indol-3-yl)methylene)malononitrile (**2a**) at room temperature. Surprisingly, what we obtained was not the designed α-carboline derivative, but an indole fused aminal **3a** (46% yield, Table 1, entry 1). To develop a useful method for the straightforward construction of indole-incorporated aminals, we first optimized this reaction by screening the solvent. None of the other tested solvents (PhCl, MeOH, DCE, MeCN, DMSO, NMP) were effective, with only trace amounts of product being observed (entries 2–7). Lower temperature gave better yields; higher temperature led to the decomposition of starting material **2a** in the presence of nucleophilic imine **1a** (entry 8), while the reaction at 50 °C afforded better yield (65%; entry 9). Both using 4 Å MS as additive and increasing the amount of imine improved the yield (entries 10 and 11).

With the optimized reaction conditions in hand, we next examined the generality of this methodology. As shown in Scheme 2, indole derived dicyano olefins bearing

Table 1 Reaction Development[a]



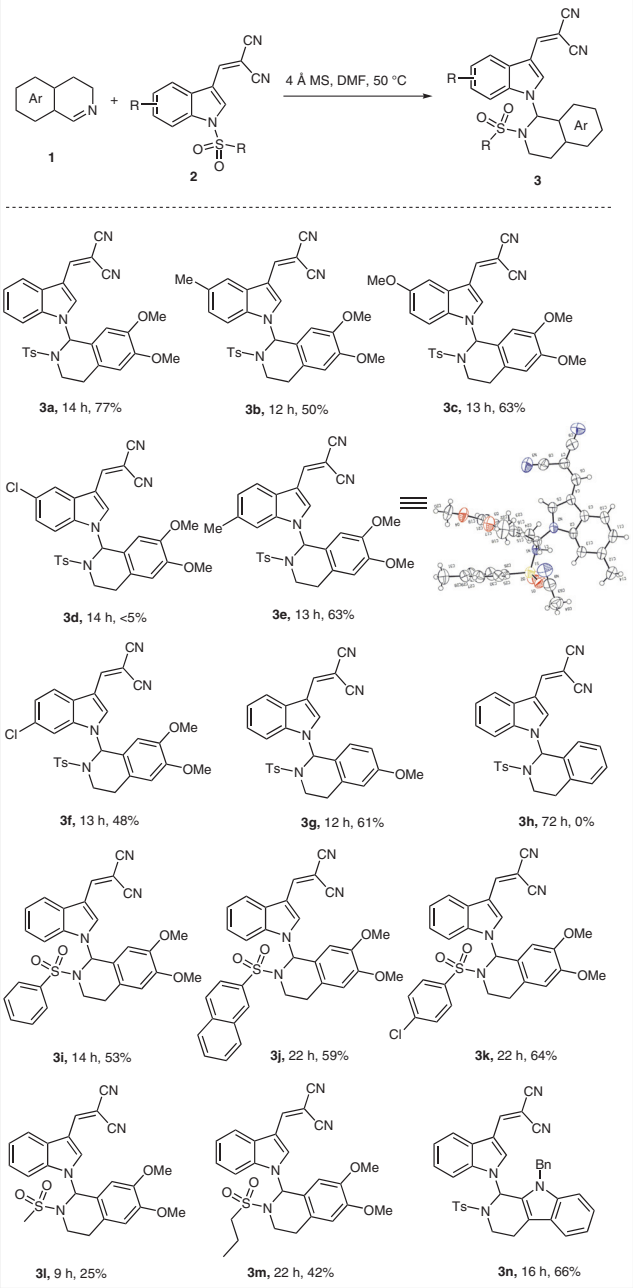
Entry	Ratio (**1a**/**2a**)	Solvent	*T* (°C)	*t* (h)	Yield (%)[b]
1	1.5:1	DMF	r.t.	143	46
2	1.5:1	PhCl	r.t.	161	<5
3	1.5:1	MeOH	r.t.	161	<5
4	1.5:1	DCE	r.t.	161	<5
5	1.5:1	MeCN	r.t.	161	<5
6	1.5:1	DMSO	r.t.	161	<10
7	1.5:1	NMP	r.t.	106	25
8	1.5:1	DMF	75	22	20
9	1.5:1	DMF	50	24	65
10[c]	1.5:1	DMF	50	24	70
11[c]	3:1	DMF	50	14	77

[a] *Reaction conditions*: **1a** (0.3 mmol), **2a** (0.1 mmol), solvent (0.5 mL).
[b] Isolated yield.
[c] 4 Å MS (100.0 mg) was added.

methyl or methoxy groups at the C-5 position reacted with imine **1a** to smoothly deliver **3b** and **3c** in 50% and 63% yields, respectively. In contrast, only a trace amount of **3d** was observed by ^{1}H NMR analysis of the crude material, suggesting that the electron-withdrawing substituent (Cl) had a significant effect on the reaction. Both electron-donating and electron-deficient groups substituted at the 6-position of the indole moiety were tolerated in this process, giving the corresponding products in 63% and 48% yield, respectively (**3e** and **3f**). The use of 6-methoxy-3,4-dihydroisoquinoline provided compound **3g** in 61% yield; no reaction occurred in the case of 3,4-dihydroisoquinoline as nucleophilic imine. These results suggest that electron-donating groups in the imines are critical for transfer of the sulfonyl group. The relative configuration of **3e** was confirmed by single-crystal X-ray analysis.[12]

Next, other types of sulfonyl groups were examined. Benzenesulfonyl, naphthalenesulfonyl, 4-chlorobenzensulfonyl, methanesulfonyl, and propane-1-sulfonyl groups were all tolerated in this process, affording the corresponding aminals in 25–64% yields (compounds **3i–m**). It is notable that tetrahydro-β-carboline could also be successfully employed in this approach, delivering indole-incorperated β-carboline **3n** in 66% yield.

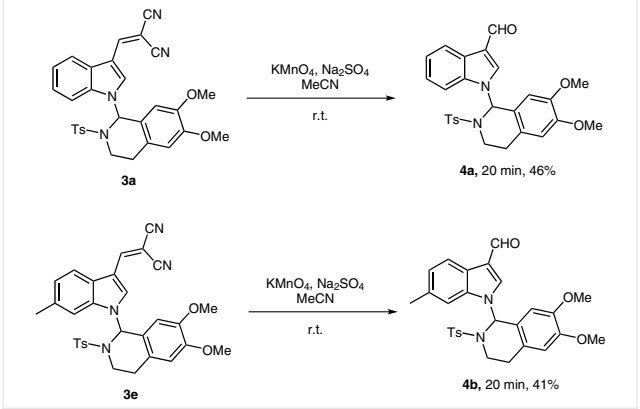
To demonstrate the application of indole-fused aminals, we further transformed the products into highly functionalized aldehydes by oxidative cleavage of the nitrile moiety



Scheme 2 Examination of substrate scope. *Reaction conditions*: **1a** (3 equiv, 0.3 mmol), **2a** (1 equiv, 0.1 mmol), 4 Å MS (100 mg), DMF (0.5 mL).

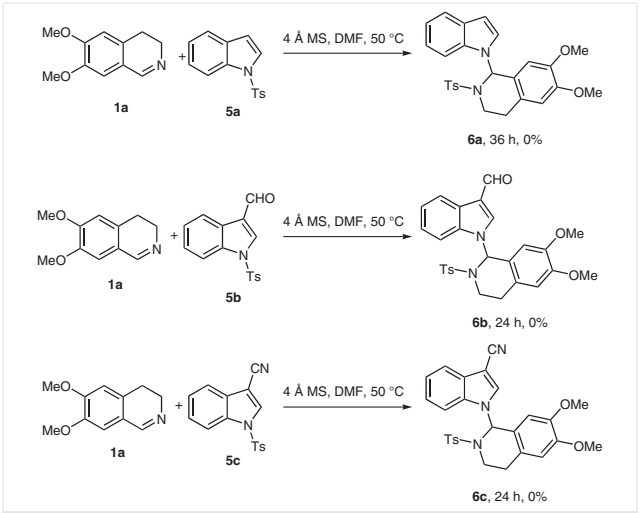
with $KMnO_4$.[13] As shown in Scheme 3, the desired aminals **4a** and **4b** could be afforded in 46% and 41% yields, respectively, by using a known procedure.

As shown in Scheme 4, further extensions of the substrate scope of the strategy for indole-fused aminals as well as control experiments were performed. Treatment of 1-tosyl-indole **5a**, 1-tosyl-indole-3-carbaldehyde **5b** and 1-tosyl-indole-3-carbonitrile **5c** under the standard conditions



Scheme 3 Transformations of aminals **3a** and **3e**

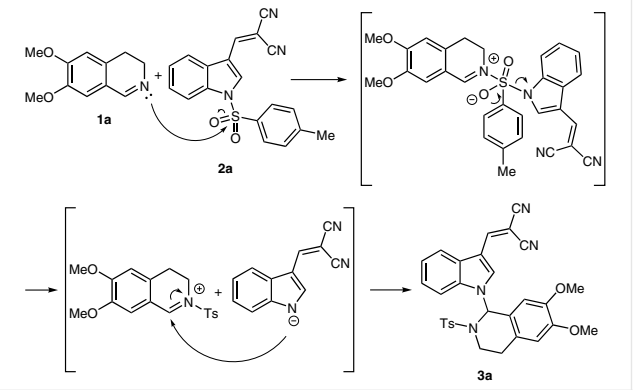
all failed to provide the desired indole fused aminals **6a–c**. The results suggest that dicyano groups act as activating groups and are essential for the improvement of electrophilic reactivity of the tosyl group.



Scheme 4 Further attempts to expand the substrate scope

Based on the obtained results, a possible mechanism was proposed for this reaction (Scheme 5). Indole derivative **2a** acts as sulfonylation reagent in this reaction, which can be attacked by the nucleophilic imine **1a**. Iminium ion would be formed and the final aza-Mannich reaction gives product **3a**.

In summary, we have developed a convenient synthesis of indole fused aminals with nucleophilic imines and indole derived dicyano olefins via *N*-sulfonyl group transfer.[14] The combination of two privileged frameworks, tetrahydroisoquinoline and indole, into aminals, can be realized by using this approach. The synthetic application of this methodology was further demonstrated by the straightforward transformations into highly functionalized indole-fused aminals.



Scheme 5 Proposed reaction pathway

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611940.

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(12) CCDC 1871844 for compound **3e**. See the Supporting Information for details.

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(14) **Synthesis of Compound 3; General Procedure:** A mixture of 3,4-dihydro-isoquinoline imine **1** (0.3 mmol), 2-((1-sulfonyl-1*H*-indol-3-yl)methylene)malononitrile **2** (0.1 mmol), 4 Å molecular sieves (100 mg) and DMF (0.5 mL) was stirred at 50 °C. Upon the consumption of **2** (monitored by TLC), the reaction was diluted with CH_2Cl_2 (3 mL) and washed with water (3 mL) and brine (3 mL). The organic layer was concentrated and purified by a silica gel flash chromatography (PE/EtOAc) to afford compound **3**.

Spectral Data for Selected Compounds

Compound 3a: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 43.3 mg (77%); yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.3 Hz, 1 H), 7.97 (s, 1 H), 7.93 (s, 1 H), 7.69 (d, *J* = 7.8 Hz, 1 H), 7.50–7.44 (m, 2 H), 7.41 (t, *J* = 7.2 Hz, 1 H), 7.34 (d, *J* = 8.3 Hz, 2 H), 7.02 (d, *J* = 8.0 Hz, 2 H), 6.60 (s, 1 H), 6.40 (s, 1 H), 3.99 (dd, *J* = 14.3, 5.1 Hz, 1 H), 3.87 (s, 3 H), 3.67 (s, 3 H), 3.36 (ddd, *J* = 14.4, 11.8, 5.1 Hz, 1 H), 2.84–2.68 (m, 2 H), 2.32 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.3, 149.8, 148.8, 144.0, 136.6, 136.3, 132.6, 129.5, 127.3, 127.0, 126.7, 125.2, 123.8, 120.9, 118.1, 114.9, 112.4, 111.3, 111.2, 109.5, 77.4, 65.5, 56.1, 56.0, 39.4, 26.4, 21.5; HRMS (ESI): *m*/*z* [M+H]$^+$ calcd. for $C_{30}H_{27}N_4O_4S^+$: 539.1748; found: 539.1743.

Compound 3b: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 28.1 mg (50%); yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 7.90 (s, 1 H), 7.88 (d, *J* = 8.4 Hz, 1 H), 7.47 (s, 1 H), 7.41 (s, 1 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 7.29 (s, 1 H), 7.03 (d, *J* = 8.1 Hz, 2 H), 6.59 (s, 1 H), 6.40 (s, 1 H), 3.98 (dd, *J* = 14.2, 5.1 Hz, 1 H), 3.87 (s, 3 H), 3.67 (s, 3 H), 3.35 (ddd, *J* = 14.4, 11.8, 5.0 Hz, 1 H), 2.85–2.67 (m, 2 H), 2.53 (s, 3 H), 2.33 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.2, 149.9, 148.7, 143.9, 136.3, 135.0, 133.7, 132.5, 129.5, 127.6, 127.0, 126.9, 126.8, 126.7, 121.0, 117.8, 115.0, 112.1, 111.2, 110.9, 109.5, 73.4, 65.5, 56.1, 56.0, 39.4, 26.5, 21.6, 21.5; HRMS (ESI): *m*/*z* [M+H]$^+$ calcd. for $C_{31}H_{29}N_4O_4S^+$: 553.1904; found: 553.1899.

Compound 3c: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 35.7 mg (63%); yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 3 H), 7.38–7.35 (m, 3 H), 7.11–7.04 (m, 4 H), 6.59 (s, 1 H), 6.41 (s, 1 H), 3.97 (dd, *J* = 14.5, 5.0 Hz, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.69 (s, 3 H), 3.33 (ddd, *J* = 14.4, 11.8, 5.0 Hz, 1 H), 2.78–2.33 (m, 2 H), 2.33 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 157.1, 150.3, 149.8, 148.8, 144.0, 136.4, 132.9, 131.5, 129.5, 128.4, 127.0, 126.8, 120.9, 115.1, 115.0, 114.8, 113.4, 111.3, 111.0, 109.6, 100.2, 73.1, 65.7, 56.1, 56.0, 55.9, 39.4, 26.4, 21.5; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd. for $C_{31}H_{28}N_4NaO_5S^+$: 591.1673; found: 591.1669.

Compound 3e: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 34.6 mg (63%); yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 4.8 Hz, 2 H), 7.82 (s, 1 H), 7.56 (d, *J* = 8.2 Hz, 1 H), 7.41 (s, 1 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 7.23 (d, *J* = 8.2 Hz, 1 H), 7.02 (d, *J* = 8.1 Hz, 2 H), 6.60 (s, 1 H), 6.39 (s, 1 H), 4.01 (dd, *J* = 14.4, 5.7 Hz, 1 H), 3.87 (s, 3 H), 3.67 (s, 3 H), 3.39–3.36 (m, 1 H), 2.90–2.65 (m, 2 H), 2.56 (s, 3 H), 2.32 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.2, 150.0, 148.7, 148.7, 143.9, 137.1, 136.4, 136.4, 135.4, 132.1, 129.5, 126.7, 125.5, 125.0, 121.1, 117.7, 115.0, 112.2, 111.2, 109.5, 73.6, 65.3, 56.1, 56.0, 39.5, 26.5, 22.7, 21.5; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd. for $C_{31}H_{28}N_4NaO_4S^+$: 575.1724; found: 575.1723.

Compound 3f: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 27.5 mg (48%); yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.95 (m, 2 H), 7.87 (s, 1 H), 7.59 (d, *J* = 8.5 Hz, 1 H), 7.40 (d, *J* = 8.3 Hz, 2 H), 7.38–7.33 (m, 2 H), 7.06 (d, *J* = 8.1 Hz, 2 H), 6.60 (s, 1 H), 6.38 (s, 1 H), 4.01 (dd, *J* = 14.4, 5.3 Hz, 1 H), 3.87 (s, 3 H), 3.69 (s, 3 H), 3.40–3.29 (m, 1 H), 2.85–2.67 (m, 2 H), 2.32 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.4, 149.5, 148.8, 144.1, 136.9, 136.3, 133.0, 131.2, 129.6, 127.1, 126.7, 125.7, 124.4, 120.5, 119.0, 114.6, 112.6, 111.3, 110.9, 109.5, 100.0, 75.2, 65.7, 56.2, 56.0, 39.5, 26.4, 21.5; HRMS (ESI): *m*/*z* [M+H_2O+H]$^+$ calcd. for $C_{30}H_{28}ClN_4O_5S^+$: 591.1463; found: 591.1467.

Compound 3g: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 30.7 mg (61%); yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.4 Hz, 1 H), 7.94 (s, 1 H), 7.90 (s, 1 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.48–7.44 (m, 2 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 6.99 (d, *J* = 8.0 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 6.74 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.68 (d, *J* = 2.0 Hz, 1 H), 4.06 (dd, *J* = 14.1, 4.6 Hz, 1 H), 3.79 (s, 3 H), 3.39 (ddd, *J* = 14.1, 11.8, 4.7 Hz, 1 H), 2.97–2.78 (m, 2 H), 2.31 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 160.2, 149.7, 143.9, 136.7, 136.3, 135.7, 132.4, 129.5, 128.9, 127.2, 126.6, 125.1, 123.7, 121.8, 118.0, 114.9, 114.4, 113.5, 112.3, 111.2, 73.8, 65.4, 55.4, 39.7, 27.7, 21.4; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd. for $C_{29}H_{24}N_4NaO_3S^+$: 531.1461; found: 531.1458.

Compound 3i: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 28.0 mg (53%); yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.0 Hz, 1 H), 7.98 (s, 1 H), 7.92 (s, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.47–7.40 (m, 4 H), 7.42–7.40 (m, 2 H), 7.22 (t, *J* = 7.6 Hz, 2 H), 6.59 (s, 1 H), 6.40 (s, 1 H), 4.08–3.98 (m, 1 H), 3.87 (s, 3 H), 3.67 (s, 3 H), 3.43–3.33 (m, 1 H), 2.79–2.78 (m, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.3, 149.9, 148.8, 139.3, 136.6, 132.9, 132.5, 128.9, 127.3, 126.9, 126.6, 125.2, 123.8, 120.9, 118.1, 114.9, 114.8, 112.4, 111.3, 111.2, 109.5, 74.2, 65.5, 56.1, 56.0, 39.5, 26.5; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd. for $C_{29}H_{24}N_4NaO_4S^+$: 547.1410; found: 547.1411.

Compound 3j: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 32.9 mg (59%); yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 1 H), 7.85 (s, 1 H), 7.81

(d, *J* = 8.4 Hz, 1 H), 7.71 (d, *J* = 8.8 Hz, 1 H), 7.66–7.61 (m, 2 H), 7.57–7.43 (m, 7 H), 7.40 (t, *J* = 7.2 Hz, 1 H), 6.58 (s, 1 H), 6.36 (s, 1 H), 4.25 (dd, *J* = 13.7, 4.8 Hz, 1 H), 3.83 (s, 3 H), 3.62 (s, 3 H), 3.46 (td, *J* = 13.6, 4.2 Hz, 1 H), 2.98–2.77 (m, 2 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 150.2, 149.1, 148.8, 136.8, 135.9, 134.6, 131.7, 131.7, 129.3, 129.2, 129.1, 127.9, 127.7, 127.4, 127.0, 126.9, 125.3, 123.7, 121.4, 121.4, 118.1, 114.8, 114.7, 112.0, 111.2, 109.3, 73.8, 65.3, 56.1, 56.0, 40.4, 27.5; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd. for $C_{33}H_{26}N_4NaO_4S^+$: 597.1567; found: 597.1561.

Compound 3k: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 35.4 mg (64%); yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.97 (m, 2 H), 7.93 (s, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.43–7.40 (m, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 6.62 (s, 1 H), 6.39 (s, 1 H), 4.05 (dd, *J* = 13.2, 5.2 Hz, 1 H), 3.89 (s, 3 H), 3.66 (s, 3 H), 3.44–3.36 (m, 1 H), 2.85–2.80 (m, 2 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 150.4, 149.7, 148.9, 139.6, 137.7, 136.6, 132.1, 129.1, 128.0, 127.2, 126.7, 125.3, 123.9, 120.8, 118.2, 114.9, 114.7, 112.1, 111.3, 111.2, 109.5, 65.4, 56.1, 56.0, 39.8, 29.7, 26.7; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd. for $C_{29}H_{23}ClN_4NaO_4S^+$: 581.1021; found: 581.1023.

Compound 3l: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 14.6 mg (25%); yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 8.01–7.99 (m, 2 H), 7.75 (d, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.36 (s, 1 H), 6.77 (s, 1 H), 6.42 (s, 1 H), 3.99 (dd, *J* = 14.0, 6.0 Hz, 1 H), 3.93 (s, 3 H), 3.69 (s, 3 H), 3.40 (td, *J* = 12.4, 4.4 Hz, 1 H), 3.25–3.16 (m, 1 H), 2.93 (dd, *J* = 12.8, 3.6 Hz, 1 H), 2.62 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 150.5, 150.0, 148.9, 136.4, 132.8, 127.5, 127.0, 125.3, 124.0, 120.6, 118.4, 114.9, 114.7, 112.3, 111.5, 111.2, 109.8, 74.9, 65.3, 56.1, 56.1, 40.2, 38.9, 27.1; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd. for $C_{24}H_{22}N_4NaO_4S^+$: 485.1254; found: 485.1249.

Compound 3m: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 20.0 mg (42%); yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 8.02 (s, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.37 (s, 1 H), 6.76 (s, 1 H), 6.39 (s, 1 H), 3.98 (dd, *J* = 14.0, 6.0 Hz, 1 H), 3.93 (s, 3 H), 3.68 (s, 3 H), 3.47–3.40 (m, 1 H), 3.23–3.14 (m, 1 H), 2.92 (dd, *J* = 16.4, 2.8 Hz, 1 H), 2.72–2.55 (m, 2 H), 1.75–1.56 (m, 2 H), 0.82 (t, *J* = 7.2 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 150.4, 150.0, 148.9, 136.4, 132.8, 127.4, 127.1, 125.1, 123.9, 120.9, 118.4, 114.9, 114.8, 112.3, 111.4, 111.2, 109.7, 74.8, 65.1, 56.1, 56.0, 55.2, 39.4, 27.5, 16.9, 12.9; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd. for $C_{26}H_{26}N_4NaO_4S^+$: 513.1567; found: 513.1563.

Compound 3n: Purified by flash column chromatography (PE/EtOAc, 4:1); Yield: 32.0 mg (66%); yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (s, 1 H), 7.85 (s, 1 H), 7.72 (s, 1 H), 7.58 (d, *J* = 4.8 Hz, 1 H), 7.56 (d, *J* = 4.4 Hz, 1 H), 7.50–7.42 (m, 2 H), 7.41–7.29 (m, 3 H), 7.24 (s, 1 H), 7.23–7.18 (m, 2 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.04 (t, *J* = 7.6 Hz, 2 H), 6.96 (d, *J* = 8.4 Hz, 2 H), 6.51 (d, *J* = 7.6 Hz, 2 H), 5.03 (d, *J* = 17.0 Hz, 1 H), 4.79 (d, *J* = 17.0 Hz, 1 H), 4.12 (dd, *J* = 14.7, 5.8 Hz, 1 H), 3.53–3.39 (m, 1 H), 2.91 (dd, *J* = 16.2, 4.1 Hz, 1 H), 2.73 (dd, *J* = 11.9, 5.6 Hz, 1 H), 2.26 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.8, 144.0, 138.2, 136.4, 136.0, 135.8, 129.5, 128.6, 127.7, 126.7, 126.0, 125.7, 125.3, 125.2, 124.2, 123.8, 120.4, 119.6, 118.1, 113.1, 112.1, 111.3, 109.7, 74.4, 61.6, 46.9, 39.9, 21.4, 20.2; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd. for $C_{37}H_{29}N_5NaO_2S^+$: 630.1934; found: 630.1943.