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The First Example of Glucose-containing Carbene Brønsted Acid Synthesis and Catalysis: Efficient Synthesis of Five Substituted Tetrahydropyridines

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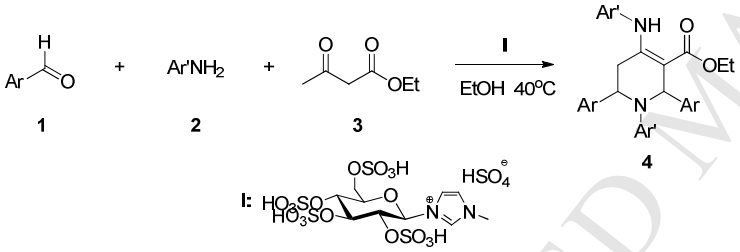

β-1-Imidazole-2,3,4,6-tetrasulfonic-D-glucopyranosyl bisulfate ([Bmim-G-$(SO_3H)_4$]$^+$[HSO_4]$^-$, **I**) was synthesized for the first time and used as an efficient catalyst to prepare five-substituted tetrahydropyridines via the three-component condensation of aromatic aldehyde, aromatic aniline and ethyl acetoacetate in ethanol at 40°C. Six bonds were cleaved while five new bonds and one new ring were formed in one-pot with water as the only one by-product in this highly atom-economic reaction. The work opens up a new and efficient synthesis and application of sugar-containing carbene Brønsted acid.

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ABSTRACT

β-1-Imidazole-2,3,4,6-tetrasulfonic-D-glucopyranosyl bisulfate ($[Bmim\text{-}G\text{-}(SO_3H)_4]^+[HSO_4]^-$, **I**) was synthesized for the first time and used as an efficient catalyst to prepare five-substituted tetrahydropyridines via the three-component condensation of aromatic aldehyde, aromatic aniline and ethyl acetoacetate in ethanol at 40°C. Six bonds were cleaved while five new bonds and one new ring were formed in one-pot with water as the only one by-product in this highly atom-economic reaction. The work opens up a new and efficient synthesis and application of sugar-containing carbene Brønsted acid.

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1. Introduction

Glucose is an important nature product bearing five hydroxyl groups. As a cheap and readily available substance, its physiological and pharmacological activity has been widely investigated.[1] However, its application in synthetic chemistry, especially as a catalyst, is relatively rare concerned. By far, it is mainly used as surfactant,[2] carrier to extract and separate protein from complex system[3] and substrate in asymmetric organic synthesis.[4] Although possessing five hydroxyl groups in its framework, glucose is not active enough to be an organocatalyst. Therefore, it should be functionalized and introduced active sites into its framework if we want to use it as catalyst or enhance its catalysis.

N-heterocyclic carbenes (NHCs) have become versatile neutral ligands for catalysis since 1991.[5] They also play important roles in catalysis[6] and biomedical applications[7] as well as other fields such as luminescent and functional materials applications.[8] Carbohydrate-containing metal NHC complexes such as Ag(I),[9-10] Ni(II),[11] Pd(II),[5] Pt(II),[12] Ru(III),[13] Ir(III)[11,14] and Rh(III)[14] have ever been synthesized and used as the efficient catalyst of organic reaction.[5,13,15]

The five-substituted tetrahydropyridines are widely distributed in many natural products, biologically active molecules and organic Finechemicals.[16] They are also the key structural units of many important synthetic bioactive molecules or drugs such as antibacterial,[17] anti-inflammation agent,[18] antineoplastic[19-20] and mental disorder drugs.[21]

Recently the researches on MCRs in which more than four components were used are of great important in organic chemistry due to their higher efficiency and atom economy and have already become a trend of organic chemistry. However, related researches are still not full enough to meet the demand of researches. Only several groups investigated these kind of MCRs. Bonfield et al. reported a six-compound to prepare isoindoline via tandem double A3-coupling and [2+2+2]-cyclo-addition reaction.[22] Brauch et al. have extended MCRs to seven components by taking advantage of the different chemoselectivities of the Ugi-Mumm and the Ugi-Smiles reaction.[23] Orru group developed a one-pot reaction of up to eight components that involves nine new bond formation and eleven points of diversity.[24] A key factor of a successful MCR is to choose an efficient and appropriate.

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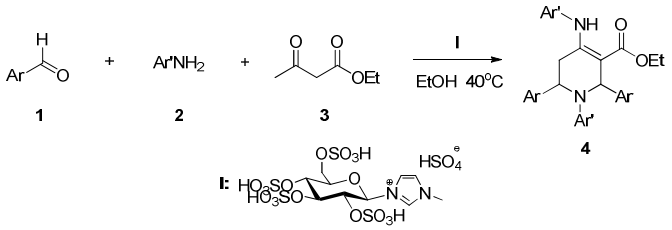
Glucose sulfonic acid (GSA), a sulfonic group functional glucose which is synthesized in our lab, is proved to be an efficient, inexpensive, non-toxic, non-metallic, readily available and environmentally benign catalyst to afford tetrahydrobenzo[α]xanthens and tetrahydrobenzo[α]acridines in water firstly in our previous work.[25]

To obtain these potential units in high the type and application of sugar-containing Brønsted acid, we herein introduced a carbene unit into the GSA framework to give a novel and efficient functional catalyst β-1-imidazole-2,3,4,6-tetrasulfonic-D-gluco-pyranosyl bisulfate ([Bmim-G-$(SO_3H)_4]^+[HSO_4]^-$, **I**) firstly. It's catalytic activity was then evaluated based on the three-component condensation of aromatic aldehyde (2 eq.), aromatic aniline (2 eq.), ethyl acetoacetate (1 eq.) in ethanol at 40°C to afford a series of five-substituted tetrahydropyridines efficiently (Scheme **1**).



Scheme 1. Synthesis of five-substituted tetrahydropyridines

2. Results and discussion

Firstly, the optimal reaction condition was tested based on the synthesis of **4a** (Table **1**). From Table **1**, this transformation could not run smoothly in the presence of catalysts such as TsOH, L-proline and Cl-SO_3H (Table **1**, Entries **1-3**). SSA could catalyze this reaction but with lower yield against **I** (Table **1**, Entries **4** and **5**, respectively), which indicated that strong acid condition was the key factor of this reaction. While increasing loading of **I** to 10 mol%, **4a** was afforded in 75% yield (Table **1**, Entry **5**), which showed the important role of catalyst concentration in the reaction. However, the yield decreased unexpectedly when the molar amount of catalyst was over 15 mol% (Table **1**, Entry **7**). A possible reason is that the starting material or the products had been destroyed when excess amount of **I** was added. Ethanol is the best solvent (Table **1**, Entries **7-11**) maybe due to its appropriate solubility and basicity. It seems that [BmIm][BF_4] ($pKa_{[BF4]-}$=0.5) is too alkaline to meet this reaction. It was also realized that the process was efficiently facilitated at 40°C (Table **1**, Entry **13**). However, elevating the temperature did not enhance the yields of products (Table **1**, Entry **12**).

Table 1 Synthesis of **4** under different conditions

Entry	Cat.	X / mol%	Solvent	T / °C	t / h	Yield / %[b]
1	L-proline	10	EtOH	60	15	Nr[c]
2	TsOH	10	EtOH	60	15	<5
3	Cl-SO_3H	10	EtOH	60	15	20
4	SSA[d]	10	EtOH	60	15	62
5	**I**	10	EtOH	60	15	75
6	**I**	5	EtOH	60	15	70
7	**I**	15	EtOH	60	15	65
8	---	---	[BMIM][BF_4]	60	15	16
9	**I**	10	[BMIM][BF_4]	60	15	24
10	**I**	10	H_2O	60	15	Nr[b]
11	**I**	10	DMF	60	15	Nr[b]
12	**I**	10	EtOH	60	15	70
13	**I**	10	EtOH	40	15	85
14	**I**	10	EtOH	30	15	30
15	**I**	10	EtOH	r.t	15	25
16	**I**	10	EtOH	40	10	85
17	**I**	10	EtOH	40	5	83

[a]All reactions were carried out in the scale of 2.0 mmol and in 2.0 mL of solvent. [b]Isolated yields. [c]not reacted. [d] Silica sulfuric acid.

To explore the application of this method, the scope of the substrates was evaluated with a variety of aromatic aldehydes and aromatic anilines (Table **2**). It showed that aromatic aldehydes and aromatic amine can afford moderate to high yield of product **4** and the product can be separated easily. The electric and effect and steric hindrance had no regular influence on the yields.

Table 2 Synthesis of **4** under optimum conditions[a]

Comp.	Ar	Ar[1]	Yield / %[b]	Mp/°C
4a	C_6H_5	4-$CH_3C_6H_4$	83	198-199
4b	3-FC_6H_4	4-$CH_3C_6H_4$	60	150-153
4c	4-FC_6H_4	4-$CH_3C_6H_4$	76	193-195
4d	4-ClC_6H_4	4-$CH_3C_6H_4$	83	233-236
4e	4-CNC_6H_4	4-$CH_3C_6H_4$	65	184-185
4f	4-OHC_6H_4	4-$CH_3C_6H_4$	53	218-220
4g	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	55	220-222
4h	2-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	71	166-168
4i	2,3-$(CH_3O)_2C_6H_3$	4-$CH_3C_6H_4$	70	222-224
4j	3,4,5-$(CH_3O)_3C_6H_2$	4-$CH_3C_6H_4$	80	171-172
4k	C_6H_5	4-$CH_3OC_6H_4$	77	196-197
4l	4-ClC_6H_4	4-$CH_3OC_6H_4$	71	187-189
4m	C_6H_5	4-ClC_6H_4	64	229-232
4n	3-FC_6H_4	4-ClC_6H_4	54	186-186
4o	4-FC_6H_4	4-ClC_6H_4	80	208-209
4p	C_6H_5	4-BrC_6H_4	76	230-231
4q	3-FC_6H_4	4-BrC_6H_4	55	193-194
4r	4-FC_6H_4	4-BrC_6H_4	60	195-200
4s	4-ClC_6H_4	4-BrC_6H_4	63	199-202
4t	C_6H_5	4-$NO_2C_6H_4$	70	250-252

[a] All reactions were carried out in the scale of 10 mol% of **I** in 2 mL ethanol at 40 °C, and starting materials (**1:2:3**=2.0:2.0:1.0 mmol) were completely consumed. [b] Isolated yield.

Alkyl aldehyde, alkyl amine or different beta-ketone esters (ethyl 3-oxo-3-phenylpropanoate) were used as substrates subsequently. However, the results indicated that alkyl-substituted aldehyde or amine could not react with other reactants to afford product **4**. Another aryl-substituted beta-ketone ester ethyl 3-oxo-3-phenylpropanoate could also not obtain the product like the result of most of literatures.[26]

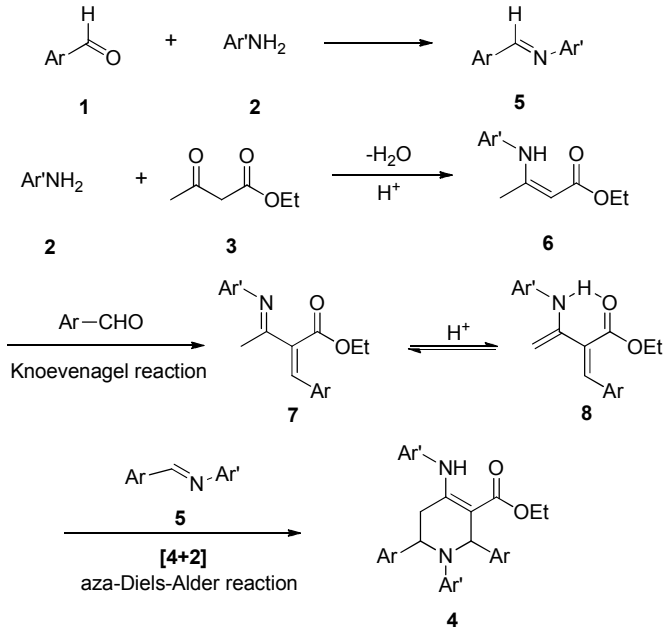
It is regret that no chiral product was detected which may be due to that chiral center of catalyst **I** was tightly wrapped by circumjacent sulfo groups. It also mentioned the necessity of further modification on sugar ring if we want to get an efficient asymmetric catalyst based on it.

The possible reaction mechanism was proposed in Scheme **4**. The reaction proceeds via initial formation of enamine **5** through condensation of aromatic aldehyde **1** and aromatic aniline **2**. Meanwhile, ethyl acetoacetate **3** condense with another aromatic aniline **2** to give enamine ester **6**. Subsequently, **6** react with another aromatic aldehyde **1** to give intermediate **7** by the Knoevenagel reaction. Intermediate **7** provide **8** via tautomerization, then **8** cyclize with **5** to give the expected **4** by an [**4**+**2**]-aza-Diels–Alder reaction. We supposed that the important role of ([Bmim-G']$^+HSO_4^-$) in this reaction is to provide an apropos acidity and supporting function.

3. Conclusion

In summary, we have developed a [Bmim-G']$^+HSO_4^-$-catalyzed three-component condensation for the construction of five-substituted tetrahydropyridines from commercially available

materials. ([Bmim-G']$^+$HSO$_4^-$) showed its important role in this interesting reaction. One ring of the fused-ring framework was constructed in one-pot. This method offers several advantages including cheap starting materials, low catalyst loading and no formation of by-products. In addition, there are several modifiable and coordinate sites in this framework, so the subsequent structural optimization should be possible.



Scheme 4. Proposed mechanisms

Acknowledgements

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General remarks

IR spectra were recorded with a Varian FTIR-Tensor-27 spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker DPX 400 spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Mass was determined by using a Bruker TOF-MS high resolution mass spectrometer. All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Organic solvents were dried and distilled prior to use.

The synthesis of ([Bmim-G']$^+$HSO$_4^-$)

A mixture of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (10 mmol) and N-methylimidazole (20 mmol) were dissolved in 1.0 mL of acetonitrile and then stirred at room temperature for 2h to give a white powder of β-1-imidazole-2,3,4,6-tetraacetyl-D-glucopyranoyl bromide which was collected by filtration and washed with cold acetone. After that, chlorosulfonic acid (20 mmol) was dropped into (5 mmol) at 0-5 °C under N_2 atmosphere, generated gas was absorbed by saturated NaOH solution. The mixture was stirred for 12 h at the same temperature to afford 2.5g of β-1-imidazole-2,3,4,6-tetrasulfonic-D-glucopyranosyl bisulfate (**1**) as yellow oil (78%). Because there was only two reactants β-1-imidazole-2,3,4,6-tetraacetyl-D-glucopyranoyl bromide and chlorosulfonic acid in the reaction system whose amount were calculated accurately, when these two reactants reacted completely there only the product **[Bmim-G']+HSO$_4^-$** itself in the system (HBr was removed out of the system by absorption via NaOH) and no further purification was necessary.

β-1-imidazole-2,3,4,6-tetraacetyl-D-glucopyranosyl bromide:

White solid; mp: 229-231 °C; IR (KBr) ν: 3077, 3046, 1750, 1539, 1264, 1224, 1210, 1103, 1047, 756, 617 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 1.91 (s, 3H), 1.98 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 3.88 (s, 3H), 4.13 (d, J =3.5 Hz, 2H), 4.31-4.41 (m, 1H), 5.25 (t, J=9.6 Hz), 5.55 (dd, J=6.3 and 2.2 Hz, 2H), 6.05 (d, J =8.4 Hz, 1H), 7.80 (s, 1H), 8.08 (s, 1H), 9.47 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.0, 169.5, 169.4, 169.0, 137.0, 124.5, 120.2, 83.2, 73.5, 71.5, 70.5, 67.2, 61.7, 36.3, 20.5, 20.4, 20.2, 20.1; HRMS (ESI) m/z: calc. for $C_{18}H_{25}N_2O_9$ [M-Br]$^+$, found (expected): 413.1573 (413.1560).

β-1-imidazole-2,3,4,6-tetrasulfonic-D-glucopyranosyl bisulfate (I):

Yellow oil; IR (KBr) ν: 3423, 2960, 1232, 1061, 1004, 885, 855; ^{1}H NMR (400 MHz, DMSO-d6) (δ, ppm): 3.03 (d, J=2.0 Hz, 1H), 3.09-3.18 (m, 1H), 3.24-3.28 (m, 1H), 3.34-3.39 (m, 1H), 3.57 (s, 1H), 3.75 (s, 3H), 4.01-4.12 (m, 1H), 5.25-5.53 (m, 1H), 7.55 (s, 1H), 7.71 (s, 1H), 9.14 (s, 1H), 9.77 (s, 5H). ^{13}C NMR (100 MHz, DMSO-d6): δ 170.0, 169.5, 169.4, 169.0, 137.0, 124.5, 120.2, 83.2, 73.5, 71.5, 70.5, 67.2, 61.7, 36.3, 20.5, 20.4, 20.2, 20.1; IR (KBr) ν: 3423, 2960, 1232, 1061, 1004, 885, 855.

General procedure for the Synthesis of five-substituted tetrahydropyridines derivatives 4

A mixture of aromatic aldehyde **1** (2.0 mmol), aniline **2** (2.0 mmol), ethyl acetoacetate **3** (1.0 mmol), ([Bmim-G']$^+$HSO$_4^-$) (10mol%) and EtOH (2.0 mL) was stirred at 40 °C for 10 hours until complete consumption of the starting material as monitored by TLC. After completion of the reaction, the mixture was diluted with water and the crude solid was filtered and washed with 95% EtOH. The solid residue was then recrystallized by 95% EtOH/DMF (1:4) to provide the pure product **4**.

The spectral data of new products are given below:

Ethyl4-(4-tolylamino)-1,2,5,6-tetrahydro-2,6-diphenyl-1-(4-tolylpyridine)-3-carboxylate (4a):

White solid. 83% yield. IR (KBr, ν, cm^{-1}): 3245, 3025, 2920, 1650, 1594, 1517, 1250; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.39 (t, J=7.0 Hz, 3H), 2.06 (s, 3H), 2.22 (s, 3H), 2.75 (dd, J=14.8 and 2.0 Hz, 1H), 2.88 (dd, J=15.6 and 8.4 Hz, 1H), 4.25-4.42 (m, 2H), 5.32 (brs, 1H), 6.24-6.33 (m, 5H), 6.81 (d, J=8.8 Hz, 2H), 6.96 (d, J=8.0 Hz, 2H), 7.15 (d, J=7.2 Hz, 2H), 7.28-7.31 (m, 8H), 10.18 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.3, 156.4, 144.9, 144.4, 143.1, 135.5, 135.2, 129.5, 129.4, 128.6, 128.2, 127.0, 126.7, 126.5, 126.2, 125.9, 125.0, 112.9, 97.7, 59.6, 58.2, 55.2, 33.6, 20.9, 20.1, 14.8; HRMS (ESI) m/z: calc. for $C_{34}H_{34}N_2O_2Na$ [M+Na]$^+$, found (expected): 525.2513 (525.2518).

Ethyl4-(4-tolylamino)-2,6-bis(3-fluorophenyl)-1,2,5,6-tetrahydro-1-4-tolylpyridine)-3-carboxylate (4b):

White solid. 60% yield. IR (KBr, ν, cm^{-1}): 3242, 2985, 2911, 2855, 1651, 1591, 1517, 1250; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (t, J=7.0 Hz, 3H), 2.07 (s, 3H), 2.23 (s, 3H), 2.75 (dd, J= 15.6 and 1.2 Hz, 1H), 2.93 (dd, J=15.6 and 5.6 Hz, 1H), 4.26-4.41 (m, 2H), 5.38 (brs, 1H), 6.25 (s, 1H), 6.31 (d, J=8.4 Hz, 2H), 6.38 (d, J=8.0 Hz, 2H), 6.84-6.88 (m, 3H), 6.95-7.06 (m, 6H), 7.17 (d, J=8.0 Hz, 1H), 7.30-7.39 (m, 2H), 10.20 (s, 1H);^{13}C NMR (100 MHz, CDCl$_3$): δ 168.0, 161.9, 161.8, 156.1, 144.3, 135.9, 135.0, 130.2, 130.1, 129.7, 129.5, 125.9, 125.7, 122.1, 122.0, 114.2, 114.0, 113.8, 113.6, 113.3, 113.1, 112.9, 97.0, 59.7, 57.6, 55.0, 33.4, 20.9, 20.1, 14.8; HRMS (ESI) m/z: calc. for $C_{34}H_{32}F_2N_2O_2Na$ [M+Na]$^+$, found (expected): 561.2347 (561.2330).

Ethyl4-(4-tolylamino)-2,6-bis(4-fluorophenyl)-1,2,5,6-tetrahydro-1-(4-tolylpyridine)-3-carboxylate (4c):

White solid. 76% yield. IR (KBr, ν, cm^{-1}): 3236, 2987, 2922, 1650, 1596, 1517, 1250; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (t, J=7.0 Hz, 3H), 2.07 (s, 3H), 2.23 (s, 3H), 2.72 (dd, J=15.2 and 1.2 Hz, 1H), 2.87 (dd, J=15.2 and 4.8 Hz, 1H), 4.24-4.40 (m, 2H), 5.33 (brs, 1H), 6.23 (s, 1H), 6.30 (d, J=8.8 Hz, 2H), 6.37 (d, J=8.4 Hz, 2H), 6.83 (d, J=8.4 Hz, 2H), 7.01 (d, J=8.0 Hz, 2H), 7.11-7.14 (m, 6H), 7.31-7.33 (m, 2H), 10.21 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.1, 156.2, 144.5, 139.8, 138.4, 135.8, 135.1, 129.5, 128.2, 128.1, 128.0, 127.9, 125.8, 125.6, 115.5, 115.3,115.0, 114.8, 113.0, 97.5, 59.7, 57.3, 54.7, 33.7, 20.9, 20.1, 14.8; HRMS (ESI) m/ z : calc. for $C_{34}H_{32}F_2N_2O_2Na$ [M+Na]$^+$, found (expected): 561.2(561.2330).

Ethyl4-(4-tolylamino)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydro-1-(4-tolylpyridine)-3-carboxylate (4d):

White solid. 83% yield. IR (KBr, ν, cm^{-1}): 3247, 2978, 2919, 1655, 1491, 1255; ^{1}HNMR (400 MHz, DMSO-d_6) δ 1.35 (t, J=7.0 Hz, 3H), 2.05 (s, 3H), 2.22 (s, 3H), 2.74 (dd, J=15.6 and 5.6 Hz, 1H), 2.90, 4.22-4.38 (m, 2H), 5.33 (brs, 1H), 6.19 (s, 1H), 6.27 (d, J=8.8 Hz, 2H), 6.38 (d, J=8.0 Hz, 2H), 6.82 (d, J=8.4 Hz, 2H), 7.00 (d, J =8.4 Hz, 2H), 7.10 (d, J=8.4 Hz, 2H), 7.31-7.36 (m, 6H), 10.19 (s, 1H); ^{13}C NMR (100 MHz, CDCl $_3$):

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δ 168.0, 156.2, 144.4, 142.8, 141.3, 135.9, 135.0, 132.8, 132.0, 129.6, 128.8, 128.4, 128.2, 128.1, 127.9, 125.9, 125.8, 113.0, 97.3, 59.3, 57.4, 54.9, 33.6, 21.0, 20.2, 14.8; HRMS (ESI) m/z: calc. for $C_{34}H_{32}Cl_2N_2O_2Na$ $[M+Na]^+$, found (expected): 593.1716 (593.1739).

Ethyl4-(4-tolylamino)-2,6-bis(4-cyanophenyl)-1,2,5,6-tetrahydro-1-(4-tolylpyridine)-3-carboxylate (4e):

White solid. 65% yield. IR (KBr, ν, cm^{-1}): 3357, 2979, 2923, 2227, 1653, 1602, 1517, 1250; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (t, J=7.2 Hz, 3H), 2.17 (s, 3H), 2.29 (s, 3H), 2.77 (s, 2H), 4.29-4.48 (m, 2H), 5.14(brs, 1H), 6.27-6.30 (m, 4H), 6.38 (s, 1H), 6.89 (d, J=8.0 Hz, 2H), 6.96 (d, J=7.6 Hz, 2H), 7.22 (d, J=7.6 Hz, 2H), 7.43 (d, J=7.6 Hz, 2H), 7.55-7.59 (m, 4H), 10.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 155.7, 143.8, 136.3, 132.5, 132.2, 132.0, 129.8, 129.7, 128.1, 127.7, 127.4, 127.3, 125.6, 119.1, 119.0, 118.7, 112.9, 111.2, 110.4, 96.5, 60.0, 57.6, 55.3, 33.4, 20.9, 20.1, 14.8; HRMS (ESI) m/z: calc. For $C_{36}H_{32}N_4O_2Na$ $[M+Na]^+$, found (expected): 553.2414(575.2423).

Ethyl4-(p-tolylamino)-1,2,5,6-tetrahydro-2,6-bis(4-hydroxyphenyl)-1-(4-tolylpyridine)-3-carboxylate (4f):

Yellow solid. 53% yield. IR (KBr, ν, cm^{-1}): 3026, 2917, 2860, 1607, 1577, 1505, 1287; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.07 (s, 6H), 2.10 (s, 3H), 2.29 (s, 4H), 4.76 (brs, 1H), 6.46 (m, 1H), 6.80 (d, J=8.4 Hz, 2H), 6.87 (d, J=8.4 Hz, 2H), 6.92 (d, J=8.4 Hz 2H), 7.10 (d, J=8.8 Hz 3H), 7.17 (d, J=8.4 Hz 3H), 7.75 (dd, J=8.4 and 2.4 Hz, 4H), 8.43 (s,1H), 9.77 (s,1H), 10.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 160.4, 159.2, 149.2, 145.8, 134.6, 132.1, 130.5, 129.6, 129.2, 128. 4, 127.5, 124.2, 120.7, 115.8, 115.6, 114.9, 114.1, 113.2, 52.6, 51.4, 30.6, 30.1, 20.5, 20.1, 19.9; HRMS (ESI) m/z: calc. for $C_{34}H_{34}N_2O_4Na$ $[M+Na]^+$, found (expected): 557.2413 (557.2416).

Ethyl4-(4-tolylamino)-1,2,5,6-tetrahydro-1,2,6-trip-tolylpyridine-3-carboxylate (4g):

White solid. 55% yield. IR (KBr, ν, cm^{-1}): 3236, 2979, 2919, 1651, 1596, 1515, 1254; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (t, J=7.2 Hz, 3H), 2.17 (s, 3H), 2.28 (s, 3H), 2.33 (s, 3H), 2.35 (s, 3H), 2.74 (dd, J=15.2 and 2.4 Hz, 1H), 2.83 (dd, J=15.2 and 5.6 Hz, 1H), 4.32-4.47 (m, 2H), 5.10 (brs, 1H), 6.19 (d, J=8.0 Hz, 2H), 6.38 (s, 1H), 6.45 (d, J=8.4 Hz, 2H), 6.89 (t, J=7.2 Hz, 4H), 7.09 (t, J=6.8 Hz, 6H), 7.24 (t, J=6.8 Hz, 2H), 10.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 156.5, 145.0, 141.5, 140.0, 13 6.5, 135.7, 135.4, 129.5, 129.4, 129.3, 128.9, 126.6, 126.4, 125.9, 124.9, 112.9, 97.9, 59.5, 58.0, 55.0, 33.6, 21.2, 21.1, 20.9, 20.2, 14.9; HRMS (ESI) m/z: calc. for $C_{36}H_{38}N_2O_2Na$ $[M+Na]^+$, found (expected): 553.2826 (553.2831).

Ethyl4-(4-tolylamino)-1,2,5,6-tetrahydro-2,6-bis(2-methoxyphenyl)-1-(4-tolylpyridine)-3-carboxylate (4h):

White solid. 71% yield. IR (KBr, ν, cm^{-1}): 3265, 2918, 2836, 1664, 1619, 1604, 1517, 1244;^{1}H NMR (400 MHz, $CHCl_3$) δ 1.41 (t, J= 7.2 Hz, 3H), 2.13 (s, 3H), 2.24 (s, 3H), 2.79 (dd, J = 15.6 and 5.6 Hz, 1H), 2.96 (dd, J=15.6 and 2.0 Hz, 1H), 3.60 (s, 3H), 3.82 (s, 3H), 4.23-4.44 (m, 2H), 5.38 (brs, 1H), 6.15 (d, J=8.4 Hz, 2H), 6.32 (d, J=8.4 Hz, 2H), 6.41 (s, 1H), 6.79-6.90 (m, 8H), 7.03 (d, J=6.8 Hz, 1H), 7.14-7.23 (m, 3H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 157.5, 156.1, 155.1, 144.8, 136.0, 134.7, 130.9, 129.8, 129.4, 129.1, 128.3, 127.9, 127.4, 126.0, 124.6, 120.7, 119.6, 112.6, 111.1, 109.8, 97.6, 59.3, 55.3, 54.8, 53.3, 53.2, 29.3, 20.8, 20.2, 14.9; HRMS (ESI) m/z: calc. for $C_{36}H_{38}N_2O_4Na$ $[M+Na]^+$, found (expected): 585.2716 (585.2729).

Ethyl4-(4-tolylamino)-1,2,5,6-tetrahydro-2-(2,3,4-trimethoxyphenyl)-6-(2,3-dimethoxypheny-1-(4-tolylpyridine)-3-carboxylate (4i):

White solid. 70% yield. IR (KBr, ν, cm^{-1}): 3245, 2940, 2829, 1646, 1597, 1517, 1477, 1233; ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.37 (t, J=7.0 Hz, 3H), 2.10 (s, 3H), 2.31 (s, 3H), 2.33 (s, 3H), 3.01 (dd, J=30.8 and 14.0 Hz, 1H), 3.21 (d, J=4.0 Hz, 1H), 3.63 (s, 3H), 3.89 (s, 3H), 3.98 (s, 3H), 4.20 (dd, J=14.0 and 6.8 Hz, 2H), 4.60 (brs, 1H), 5.23 (s, 1H), 6.39 (d, J=8.0 Hz, 2H), 6.61-6.67 (m, 4H), 6.80-7.00 (m, 4H), 7.05 (d, J=8.4 Hz, 2H), 7.12 (d, J=8.4 Hz, 2H), 10.22 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 170.2, 164.6, 159.0, 152.8, 152.5146.9, 146.2, 141.8, 136.7, 136.0, 135.0, 134.8, 133.8, 129.6, 128.6, 125.9, 125.8, 123.3,123.2, 119.8, 111.4, 110.7, 93.3, 60.1, 59.1, 58.8, 56.4, 55.6, 43.2, 28.8, 28.4, 20.9, 20.7, 14.7; HRMS (ESI) m/z: calc. for $C_{38}H_{42}N_2O_6Na$ $[M+Na]^+$, found (expected): 645.2886 (645.2941).

Ethyl4-(4-tolylamino)-1-(4-tolyl)-2,6-bis(3,4,5-trimethoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4j):

White solid. 80% yield. IR (KBr, ν, cm^{-1}): 3245, 2934, 2835, 1649, 1593, 1516, 1233; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (t, J=7.0 Hz, 3H), 2.08 (s, 3H), 2.24 (s, 3H), 2.72 (dd, J=14.4 and 4.4Hz, 1H), 2.94 (dd, J=15.6 and 5.6 Hz, 1H), 3.59 (s, 6H), 3.63 (s, 3H), 3.64 (s, 3H), 3.67 (s, 6H), 4.21-4.44 (m, 1H), 5.28 (brs, 1H), 6.19 (s, 1H), 6.30 (d, J=8.0 Hz 2H), 6.38 (d, J=8.8 Hz 2H), 6.43 (s, 2H), 6.56 (s, 2H), 6.86 (d, J=8.4 Hz, 2H), 6.98 (d, J=8.0 Hz, 2H), 10.19 (s, 1H); ^{13}CNMR (100 MHz, CDCl $_3$): δ 167.2, 155.9, 152.8, 152.7, 144.2, 140.3, 138.9, 136.2, 135.8, 135.1, 135.0, 129.3, 129.2, 125.5, 124.2, 112.3, 103.4, 103.1, 96.6, 60.0, 59.9, 56.5, 55.6, 55.5, 33.3, 20.4, 19.8, 14.8; HRMS (ESI) m/z: calc. for $C_{40}H_{46}N_2O_8Na$ $[M+Na]^+$, found (expected): 705.3188 (705.3152).

Ethyl4-(4-methoxyphenylamino)-1,2,5,6-tetrahydro-1-(4-methoxyphenyl)-2,6-diphenylpyridine-3-carboxylate (4k):

White solid. 77% yield. IR (KBr, ν, cm^{-1}): 3231, 2990, 2902, 1647, 1597, 1510, 1244; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (t, J=7.0 Hz, 3H), 2.65 (dd, J=15.2 and 1.6 Hz, 1H), 2.83 (dd, J=15.6 and 5.6 Hz, 1H), 3.55 (s, 3H), 3.69 (s, 3H), 4.26-4.36 (m, 2H), 5.26 (brs, 1H), 6.21 (s, 1H), 6.28-6.34 (dd, J=17.6 and 9.2 Hz, 4H), 6.63 (d, J=8.8 Hz, 2H), 6.70 (d, J=8.8 Hz, 2H), 7.13-7.30 (m, 10H), 10.09 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.3, 157.8, 156.8, 144.4, 143.6, 143.3, 141.6, 136.9, 128.6, 128.1, 127.9, 127.1, 126.8, 126.5, 126.2, 114.5, 114.1, 113.9, 97.3, 59.5, 58.3, 55.7, 55.6, 55.4, 33.6, 14.8; HRMS (ESI) m/z: calc. for $C_{34}H_{34}N_2O_4Na$ $[M+Na]^+$, found (expected): 557.2413 (557.2416).

Ethyl4-(4-methoxyphenylamino)-2,6-bis(4-chlorophenyl)-1,2,5,6–tetrahydro-1-(4-methoxyphenyl)pyridine-3-carboxylate (4l):

White solid. 71% yield. IR (KBr, ν, cm^{-1}): 3230, 2907, 2832, 1660, 1611, 1511, 1247; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (t, J=7.0 Hz, 3H), 2.65 (dd, J= 15.6 and 2.0 Hz, 1H), 2.85 (dd, J=16.0 and 5.6 Hz, 1H), 3.55 (s, 3H), 3.71 (s, 3H), 4.21-4.36 (m, 2H), 5.25 (brs, 1H), 6. 11 (s, 1H), 6.31 (d, J=9.2 Hz, 2H), 6.45 (d, J=8.8 Hz, 2H), 6.65 (d, J=9.2 Hz, 2H), 6.77 (d, J=8.8 Hz, 2H), 7.12 (d, J=8.4 Hz, 2H), 7.29-7.36 (m, 6H), 10.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 158.0, 156.5, 151.5, 142.8, 141.5, 141.0, 132.8, 132.0, 130.5, 128.7, 128.3, 128.0, 127.7, 114.7, 114.6, 114.1, 113.2, 96.7, 59.7, 57.4, 55.6, 55.4, 33.7, 14.8; HRMS (ESI) m/z: calc. for $C_{34}H_{32}Cl_2N_2O_4Na$ $[M+Na]^+$, found (expected): 625.1626 (625.1637).

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Ethyl4-(4-chlorophenylamino)-1-(4-chlorophenyl)-1,2,5,6-tetrahydro-2,6-diphenylpyridine-3-carboxylate (4m):

White solid. 64% yield. IR (KBr, ν, cm^{-1}): 3242, 2972, 2857, 1646, 1604, 1585, 1494, 1258; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (t, J=7.0 Hz, 3H), 2.76 (dd, J=15.2 and 4.0 Hz, 1H), 2.96 (dd, J=16.0 and 6.0 Hz, 1H), 4.24-4.44 (m, 2H), 5.39 (brs, 1H), 6.28 (s, 1H), 6.38-6.42 (m, 4H), 7.05 (d, J=9.2 Hz, 2H), 7.13 (d, J=6.8 Hz, 2H), 7.18-7.33 (m, 10H), 10.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 115.4, 145.5, 143.3, 142.3, 136.4, 131.4, 129.0, 128.8, 128.7, 128.4, 127.5, 127.0, 126.6, 126.5, 126.3, 121.3, 114.1, 98.7, 60.0, 58.3, 55.3, 33.5, 14.8; HRMS (ESI) m/z: calc. for $C_{32}H_{28}Cl_2N_2O_2Na$ $[M+Na]^+$, found (expected): 565.1420 (565.1426).

Ethyl4-(4-chlorophenylamino)-1-(4-chlorophenyl)-2,6-bis(3-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4n):

Yellow solid. 54% yield. IR (KBr, ν, cm^{-1}): 3241, 2981, 2858, 1647, 1607, 1494, 1260; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (t, J=7.0 Hz, 3H), 2.76 (dd, J= 15.6 and 1.6 Hz, 1H), 3.02 (dd, J=16.0 and 6.0 Hz, 1H), 4.26-4.44 (m, 2H), 5.44 (brs, 1H), 6.24 (s, 1H), 6.41 (d, J=8.8 Hz, 2H), 6.56 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.4 Hz, 1H), 6.93 (d, J=8.0 Hz, 1H), 7.05-7.10 (m, 5H), 7.18 (d, J=7.6 Hz, 1H), 7.24 (d, J=8.4 Hz, 2H), 7.31-7.41 (m, 2H), 10.19 (s, 1H); ^{13}C NMR(100 MHz, $CDCl_3$): δ 167.9, 161.9, 161.8, 155.1, 146.1, 145.0, 136.2, 131.7, 130.5, 130.4, 129.9, 129.8, 129.2, 128.9, 126.9, 121.9, 114.6, 114.4, 114.1, 113.8, 113.5, 113.3, 98.0, 60.1, 57.7, 55.1, 33.4, 14.7; HRMS (ESI) m/z: calc. for $C_{32}H_{26}Cl_2F_2N_2O_2Na$ $[M+Na]^+$, found (expected): 601.1189 (601.1237).

Ethyl4-(4-chlorophenylamino)-1-(4-chlorophenyl)-2,6-bis(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4o):

White solid. 80% yield. IR (KBr, ν, cm^{-1}): 3237, 3069, 2978, 1650, 1495, 1227; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (t, J=7.0 Hz, 3H), 2.76 (dd, J=15.6 and 4.0 Hz, 1H), 2.96 (dd, J=16.0 and 5.6 Hz, 1H), 4.25-4.41 (m, 2H), 5.39 (brs, 1H), 6.22 (s, 1H), 6.37 (d, J=8.8 Hz, 2H), 6.54 (d, J=8.8 Hz, 2H), 7.06-7.17 (m, 8H), 7.24 (d, J=8.8 Hz, 2H), 7.32-7.36 (m, 2H), 10.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 160.9, 160.4, 155.2, 145.2, 13 8.8, 137.6, 136.3, 131.6, 129.2, 128.9, 128.1, 128.0, 127.9, 127.8, 126.8, 121.7, 115.8, 115.6, 115.3, 115.1, 114.2, 98.6, 60.1, 57.4, 54.8, 33.7, 14.8; HRMS (ESI) m/z: calc. for $C_{32}H_{26}Cl_2F_2N_2O_2Na$ $[M+Na]^+$, found (expected): 601.1228 (601.1237).

Ethyl4-(4-bromophenylamino)-1-(4-bromophenyl)-1,2,5,6-tetrahydro-2,6-diphenylpyridine-3-carboxylate (4p):

White solid. 76% yield. IR (KBr, ν, cm^{-1}): 3241, 2973, 2834, 1646, 1602, 1491, 1225; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (t, J=7.0 Hz, 3H), 2.74 (dd, J=15.6 and 4.0 Hz, 1H), 2.96 (dd, J=16.0 and 5.6 Hz, 1H), 4.25-4.41 (m, 2H), 5.39 (brs, 1H), 6.22 (s, 1H), 6.37 (d, J=8.8 Hz, 2H), 6.54 (d, J=8.8 Hz, 2H), 7.06-7.17 (m, 10H), 7.25 (d, J=8.8 Hz, 2H), 7.32-7.36 (m, 2H), 10.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 155.2, 145.9, 143.1, 142.1, 136.9, 132.0, 131.6, 128.8, 128.4, 127.5, 127.2, 126.6, 126.4, 126.3, 119.1, 114.6, 108.4, 98.8, 59.9, 58.3, 55.2, 33.4, 14.8; HRMS (ESI) m/z: calc. for $C_{32}H_{28}Br_2N_2O_2Na$ $[M+Na]^+$, found (expected): 653.0405 (653.0415).

Ethyl4-(4-bromophenylamino)-1-(4-bromophenyl)-2,6-bis(3-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4q):

Yellow solid. 55% yield. IR (KBr, ν , cm^{-1}): 3242, 2977, 2859, 1647, 1590, 1488, 1260; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (t, J=7.0 Hz, 3H), 2.77 (dd, J=16.4 and 2.0 Hz, 1H), 3.04 (dd, J=16.0 and 5.6 Hz, 1H), 4.27-4.42 (m, 2H), 5.43 (brs, 1H), 6.23 (s, 1H), 6.35 (d, J=9.2 Hz, 2H), 6.50 (d, J=8.4 Hz, 2H), 6.88 (d, J=8.4 Hz, 1H), 6.95 (d, J=7.6 Hz, 1H), 7.05-7.09 (m, 3H), 7.18-7.22 (m, 3H), 7.30-7.43 (m, 4H),10.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 161.9, 161.8, 154.9, 145.4, 144.8, 136.7, 132.2, 131.8, 130.5, 130.0, 127.2, 122.0, 121.9, 119.4, 114.6, 113.8, 113.7, 113.6, 113.5, 113.3, 109.1, 98.2, 60.2, 57.6, 55.0, 33.4, 14.7; HRMS (ESI) m/z: calc. for $C_{32}H_{26}Br_2F_2N_2O_2Na$ $[M+Na]^+$, found (expected): 698.0229 (698.0227).

Ethyl4-(4-bromophenylamino)-1-(4-bromophenyl)-2,6-bis(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4r):

White solid. 60% yield. IR (KBr, ν, cm^{-1}): 3237, 2928, 2862, 1673, 1656, 1504, 1253; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (t, J=7.0 Hz, 3H), 2.77 (dd, J=14.4 and 4.0 Hz, 1H), 2.98 (dd, J=15.6 and 5.6 Hz, 1H), 4.21-4.42 (m, 2H), 5.40 (brs, 1H), 6.21 (s, 1H), 6.33 (d, J=9.2 Hz, 2H), 6.51 (d, J=8.8 Hz, 2H), 7.13-7.20 (m, 8H), 7.31-7.38 (m, 4H), 10.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 160.9, 160.4, 155.1, 145.6, 136.8, 132.1, 131.7, 128.1, 128.0, 127.9, 127.8, 127.1, 119.3, 115.8, 115.6, 115.3, 115.1, 114.7, 108.9, 98.7, 60.1, 57.4, 54.8, 33.7, 14.8; HRMS (ESI) m/z: calc. for $C_{32}H_{27}Br_2F_2N_2O_2$ $[M+H]^+$, found (expected): 667.0154 (667.0407).

Ethyl4-(4-bromophenylamino)-1-(4-bromophenyl)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4s):

White crystal. 63% yield. IR (KBr, ν, cm^{-1}): 3243, 2928, 1665, 1647, 1586, 1491, 1252; ^{1}HNMR (400 MHz, DMSO-d_6) δ 1.37 (t, J=7.2 Hz, 3H), 2.78 (dd, J= 14.4 and 4.0 Hz, 1H), 3.00 (dd, J=16.0 and 5.6 Hz, 1H), 4.25- 4.40 (m, 2H), 5.38 (brs, 1H), 6.21 (s, 1H), 6.31 (d, J=8.8 Hz, 2H), 6.54 (d, J=8.8 Hz, 2H), 7.11 (d, J=8.4 Hz, 2H), 7.19 (d, J=8.8 Hz, 2H), 7.32-7.40 (m, 8H), 10.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 155.0, 145.4, 141.6, 140.3, 136.7, 133.2, 132.5, 132.2, 131.8, 129.0, 128.6, 127.9, 127.7, 127.1, 119.4, 114.6, 109.1, 98.4, 60.1, 57.4, 54.9, 33.6, 14.8; HRMS (ESI) m/z: calc. for $C_{32}H_{26}Br_2Cl_2N_2O_2Na$ $[M+Na]^+$, found (expected): 698.9504 (698.9816).

Ethyl4-(4-nitrophenylamino)-1,2,5,6-tetrahydro-1-(4-nitrophenyl)-2,6-diphenylpyridine-3-carboxylate (4t):

Yellow solid. 70% yield. IR (KBr, ν , cm^{-1}): 3289, 2985, 1680, 1596, 1501, 1246; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (t, J=7.0 Hz, 3H), 2.87 (dd, J=14.4 and 4.0 Hz, 1H), 3.39 (dd, J=16.0 and 5.6 Hz, 1H), 4.10-4.23 (m, 2H), 4.48 (brs, 1H), 6.03 (dd, J=18.8 and 7.6 Hz, 3H), 6.61 (t, J=7.4 Hz, 2H), 6.67-6.70 (m, 1H), 6.74-6.78 (m, 1H), 6.83-6.89 (m, 4H), 7.03-7.07 (m, 2H), 7.42 (d, J=8.8 Hz, 2H), 8.15 (d, J=9.2 Hz, 2H), 8.42 (d, J=8.8 Hz, 2H), 10.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 157.0, 152.1, 146.9, 143.6, 141.4, 139.3, 136.7, 127.4, 126.9, 126.4, 126.2, 125.8, 125.2, 123.5, 115.8, 115.3, 103.5, 60.3, 52.3, 45.6, 38.5, 13.6; HRMS (ESI) m/z: calc. for $C_{32}H_{28}N_4O_6Na$ $[M+Na]^+$, found (expected): 587.1923 (587.1907).