An Efficient Method for Solution-Phase Parallel Synthesis of 2-Quinoxalinol Salen Schiff-Base Ligands

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A solution-phase parallel method for the synthesis of 2-quinoxalinol salen ligands was designed and optimized. The synthesis begins with commercially available 1,5-difluoro-2, 4-dinitrobenzene (DFDNB) and employs a sequence of five straightforward and high-yielding reaction steps. Simple laboratory techniques with low sensitivity to water or air for solution-phase parallel reactions were coupled with convenient workup and purification procedures to give high-purity and yield a small ligand library of 20 compounds. The final step, a Schiff-base condensation of an aldehyde with the diaminoquinoxaline results in a new category of ligands for metal coordination or of potential bioactivity, based on the skeleton 2,2′-(1*E*,1′*E*)-(quinoxaline-6,7-diylbis(azan-1-yl-1-ylidene))bis(methan-1-yl-1-ylidene)diphenol. The approach described here is easily adaptable for parallel synthesis of a larger library.

Introduction

Salen ligands and the related salenophene ligands have been of interest to a wide variety of chemists. In particular, these have been investigated in a variety of applications because of their ease of preparation and their ability to form stable metal complexes. For example, copper(I) salen complexes have been investigated as antitumor agents and found to be more bioactive than the currently available metal-based antitumor drug cisplatin.[1] Ruthenium salen complexes have been studied as protein kinase inhibitors mimicking organic indolocarbazoles.[2] Salen or salenophene ligands and their complexes have also been applied as catalysts in a variety of processes as Cu, Mn, or Ru complexes including as catalytic scavengers of hydrogen peroxide and cytoprotective agents,[3] in the catalytic oxidation of secondary amines,[4] as enantioselective catalysts for asymmetric epoxidation of unfunctionalized olefins,[5,6] or most commonly, as catalysts for ring-opening metathesis.[7−9] As catalysts, these have proven quite useful, in particular, when incorporated into solid supports[10,11] and for chiral or stereoselective reaction catalysis.[12−23]

In this article, we combine the salen coordination framework with a second set of ligand building blocks to modify the ligand properties to our specific applications of interest. Derivatives of 2-quinoxalinols are key intermediates as bioactive agents in agriculture;[24] they also have been used in dyes[25] and have been key pharmaceutical or medicinal intermediates.[26,27] Synthetic methods for the parallel synthesis of the 2-quinoxalinols have been previously reported.[26−28] These factors have served to peak our interest in combining these two systems for the preparation of a new series of 2-quinoxalinol salen framework ligands based on a Schiff base synthesis. The development of preparative methods using solution-phase parallel synthesis is not only feasible but also desirable in the development of a new series of metal-complexing agents that could be screened for bioactivity or used in the development of new catalysts, metal selective sensors, or sensing materials, through the incorporation of a unique coordination site and a quinoxaline that should have high UV and fluorescent activity. The solution-phase combinatorial approach allows for the preparation of

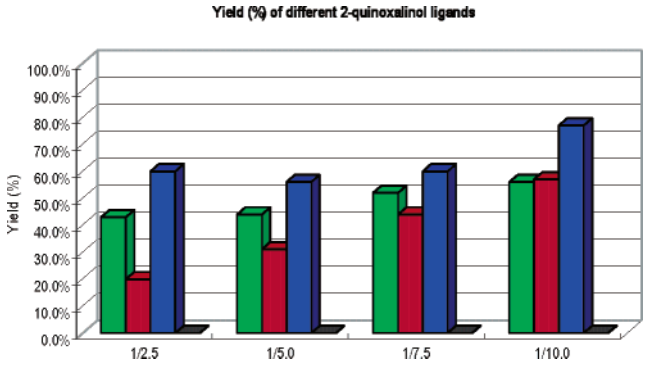

Figure 1. Ratio of diamino-2quinoxalinol to salicylaldehyde in the preparation of four quinoxalinol-salen ligands.

Table 1. Results of Diamino-2-quinoxalinols

No.	Compound	R_1	Purity (%)[a]	R_t (min)	Yield (%)[b]	mp (°C)
1	4a		99	3.46	97	261.4~263.5
2	4b		99	3.53	90	234.5~244.5
3	4c		99	3.18	99	249.5~250.3
4	4d		99	3.47	68	>300

[a] Identified by HPLC; R_t is retention time. [b] One-step yield of Pd−C reduction.

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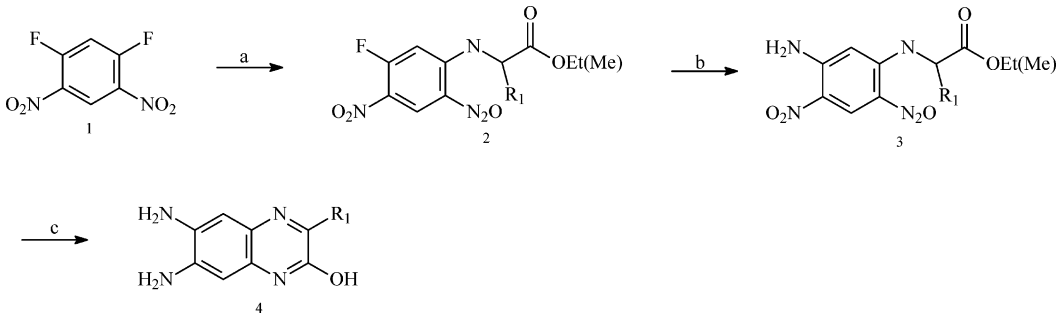
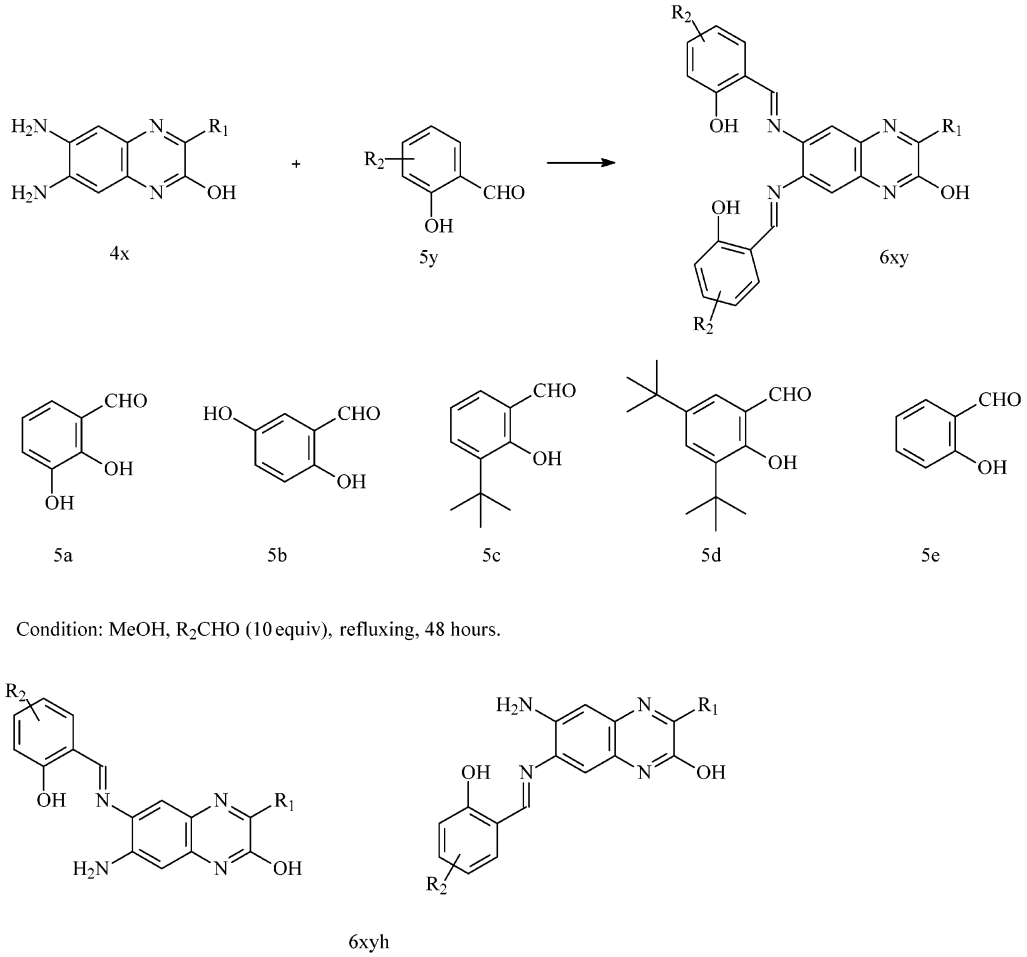
Scheme 1. Reaction Route for Synthesis of Diamino-2-quinoxalinol



[a] THF, amino acid, 1 equiv, DIEPA. [b] $NH_3 \cdot H_2O$, THF. [c] PdC, $HCOONH_4$, EtOH 95%, N_2.

Scheme 2. Reaction for Synthesis of Library of 2-Quinoxalinol Ligands



Condition: MeOH, R_2CHO (10 equiv), refluxing, 48 hours.

a series of ligands with a variety of substitution patterns that will allow us to investigate a variety of applications in a variety of solvents.

Previously, no quinoxaline Schiff base ligands like these have been reported, perhaps because of the difficulty in the preparation of the required diaminoquinoxaline intermediate. In addition, the typical Schiff base methods of preparation vary widely or require additional catalysts because of steric constraints. Both problems restrict the development of a synthetic library.[29−32] Here, we describe the optimization of the reaction conditions for such a library using four different kinds of reactions. Finally, a simple, solution-phase parallel method for the synthesis of 2-quinoxalinonl salen ligands and a preparative library for a series of these ligands were achieved.

Results and Discussion

Our synthesis begins with the preparation of the 2-quinoxalinol precursor. Previously, Liu and co-workers reported the solution-phase parallel synthesis of a series of diamino-2-quinoxalinol derivatives.[26,27,33] Based on this previous work, we have further simplified and optimized the method for the synthesis of diamino-2-quinoxalinols. Here, the scavenger resins used in the previous investigations have been replaced with 2 equiv of DIPEA (diisopropylethylamine) to remove the produced HF and HCl on the amino acid methyl group in the first step (Scheme 1). Ammonium hydroxide in water (3 equiv) was employed in the substitution of the second fluorine (step 2, Scheme 1). In this way, the intermediate (**3**) does not require additional

Table 2. Results of 2-Quinoxalinol Schiff-Base Ligands Library

No.	Product	R_1	R_2	Purity (%)[a]	Yield (%)[b]	mp (°C)
1	6aa		3-OH	>90	50	251.0[c]
2	6ab		5-OH	>95	41	246.0[c]
3	6ac		3-*tert*-butyl	>95	55	271.0-273.5
4	6ad		3,5-Di-*tert*-butyl	>99	56	279.1-280.1
5	6ae		H	>99	77	264.1-266.1
6	6ba		3-OH	>90	64	>300.0
7	6bb		5-OH	>95	44	221.5[c]
8	6bc		3-*tert*-butyl	>99	56	285.1-286.1
9	6bd		3,5-Di-*tert*-butyl	>99	55	280.0-281.0
10	6be		H	>90	70	288.5-289.3
11	6ca		3-OH	>95	50	260.0-261.5
12	6cb		5-OH	>90	67	290.5[c]
13	6cc		3-*tert*-butyl	>95	52	285.1-286.7
14	6cd		3,5-Di-*tert*-butyl	>99	57	287.8-288.8
15	6ce		H	>99	86	286.5-288.5
16	6da		3-OH	>90	65	>300.0
17	6db		5-OH	>90	57	>300.0
18	6dc		3-*tert*-butyl	>95	46	262.0[c]
19	6dd		3,5-Di-*tert*-butyl	>99	56	286.0-287.5
20	6de		H	>95	81	270.5[c]

[a] Identified by the proportion of typical peak areas of ^{1}H NMR, assuming the half-unit Schiff-base ligand is the only major byproduct. HPLC cannot identify the exact percentage of this major impurity because of the large difference of their UV absorbances (254 or 214 nm). [b] One-step yield from diamino-2-qunioxalinol **4** to final product **6**. [c] At this temperature, these compounds were found to decompose.

purification after the substitution of the two fluorine atoms because the remaining unreacted ammonium hydroxide and water can be removed using high vacuum. This serves both to ease the process of parallel solution methods and reduce the costs of materials. After reduction by wet Pd on carbon, the target intermediates, diamino-2-quinoxalinols (**4**), are easily recrystallized from 95% ethanol. The purity and yield of each aim intermediate are very high (Table 1). The sulfur atom in intermediate **4d** (made from the methionine starting material) leads to a poisoning of the catalytic palladium on carbon, and the yield of this product is lower than others. For the sake of diversity of key intermediate diamino-2-quinoxalinols, we have selected four different kinds of methyl amino acids as the building blocks, including phenylalanine with an aromatic group, methionine containing a heteroatom (sulfur), and valine and leucine with simple alkyl groups at R_1. The available commercial salicylaldehyde derivatives are limited. Therefore, the aldehydes chosen included hydrophilic salicylaldehydes (dihydroxide, **5a** and **5b**) and hydrophobic salicylaldehyde (mono- and di-*tert*-butyl, **5c** and **5d**) to build our library (Scheme 2). These selections for our ligand library will also later provide a variety of compounds of varying solubility and coordination properties for the continuation of this product in metal coordination chemistry or applications.

Four different reactions were used to optimize the solution-phase parallel conditions (Figure 1). These were optimized from different times, temperatures, and solvents, as well as

balancing the ratios of diamino-2-quinoxalinols (**4)** to substituted salicylaldehyde derivatives (**5**). In some cases, microwave heating or sonication was applied for difficult reactions. According to previous preparations of Schiff base compounds in the literature,[29] we first selected methanol as the solvent with a ratio of 1:2.5 of diamino-2-quinoxalinol (**4)** to salicylaldehyde derivative (**5**), which was allowed to react at room temperature for 48 h. Under these conditions, the desired products were not obtained. When heated from room to reflux temperature, the major product is the half-unit ligand **6cdh** which has two possible structures and a small amount of the full unit targeted compound **6cd**; there are also small amounts of products **6ad** and with a high yield only of **6ae**. Regardless of which one of the potential isomeric products is **6cdh**, there is another amino group which needs to be reacted with the salicylaldehyde derivative, and hence, it is unnecessary for us to identify the exact structure. The increase of reaction time from 48 to 72 h did not result in additional full unit products nor did an increase of the reaction temperature benefit the reaction progress. Changing the solvent from methanol to higher-boiling point solvents (e.g., toluene, DMF, and benzene) allowed for increasing the refluxing temperature but did not produce the desired product. Initially, we resisted increasing the ratio of the salicylaldehyde derivative to the quinoxaline derivative without efficient scavenging resins to remove the excess aldehyde, and subsequently, both microwave and ultrasonic methods were tried without success.

Finally, when the ratio of salicylaldehyde derivative was increased from 1:2.5 to 1:5 (Figure 1), the yield of full unit target product went up from 20% to 31% for **6cd**. The yields of **6ad** and **6ae** did not change dramatically. When the ratio was increased to 1:7.5, the yields of target products increased to 52% for **6ad**, 44% for **6cd**, and 60% for **6ae**. Fortunately, the final products precipitate from the methanol solution. This is a very beneficial phenomenon for solution-phase parallel synthesis allowing the use of parallel filtration.[13] When the ratio was increased from 1:7.5 to 1:10, the yield of **6cd** and **6ae** increased to 57 and 77%, but the yields for **6ad** did not change significantly. Continuing to increase the ratio did lead to better result. The products were filtered directly resulting in yellow solids. These were washed with 95% ethanol and cold acetone 5 times each. It was determined that there was no final product in the filtered solution using TLC, and the yellow solids are very pure full unit ligand products. These were characterized by ^{1}H NMR, ^{13}C NMR, MS, and HRMS. The purity of **6ad**, **6cd**, and **6ae** identified by ^{1}H NMR is no less than 99%. For **6da**, at the ratio of 1:10 of **4d** to **5a**, we could not obtain any of the aim product **6da**, but when we increased the reaction concentration by reducing the volume of solvent of methanol, under a ratio of 1:10, we obtained a high yield of **6da** (65%).

The final conditions are a ratio of 1:10 of diamino-2-quinoxalinol to salicylaldehyde derivative at reflux temperature in a solution of methanol which is allowed to react for 48 h. When we synthesized this as a 4 × 5 library, we found that this procedure is very suitable for the solution-phase parallel synthesis of 2-quinoxalinol Schiff base ligands. The results are shown in Table 2. All of the twenty targeted products are synthesized by parallel methods, and their yield and purities are very high.

Conclusion

A 2-quinoxalinol salen (or Schiff-base) ligand library has been prepared by a simple and efficient solution-phase parallel method. It was found that these organic ligands are stable at high-temperature (<200 °C) and are not sensitive to oxygen, water, alkaline conditions, or most solvents. In the process, the synthetic method for the key intermediate quinoxaline has been further optimized and simplified from methods used in previous reports.

From the resulting yields under the optimized conditions, some trends are clear. With each quinoxaline, the yield of the product with aldehyde **5e** was significantly higher, most likely because of the limited steric hindrance, but the yields were quite good with aldehyde **5d**, which should be the most sterically hindered aldehyde. This is also the aldehyde with the best solubility. Products from this aldehyde are soluble in chlorinated solvents, whereas some of the compounds synthesized from aldehyde **5a** and **5b** are soluble only in DMSO. The most likely causes of the inhibition of product formation in reactions with aldehyde **5b** are hydrogen bonding or an unfavorable transition state. This is not, however, a straightforward elimination reaction. Further investigations are ongoing with computational analyses to identify and characterize the transition states in the final step of the Schiff base formation and the limits to the product formation in the ligand systems that result in decreased final yields. This will be the subject of a future report. Investigations to determine the bioactivity of the compounds, to investigate the solubilities of the ligands, to prepare metal complexes, and to determine the selectivity for a given metal or series of metals will also be included in later communications.

Experimental Section

All amino acid methyl esters, DFDNB, HCl (37%), and aldehydes were purchased from Acros. Ammonium hydroxide (5.0 N) and palladium on carbon (wet, 5%) were purchased from Aldrich. The starting materials were used as received. All organic solvents were from Fisher Scientific and were used directly for synthesis. HPLC analysis was performed on a Shimadzu apparatus equipped with a SPD-10A VP detector. The solutions for HPLC were eluted as 50:50 acetonitrile/H_2O with a buffer consisting of 0.05% TFA over 10 min at 1 mL/min and detection by UV at 254 nm. The column employed was a water C^{18} column (w33471F, 3.9 × 300 mm) from DIKMA. All melting points were recorded on a Mel-temp II melting point apparatus, and the values are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 250 spectrometer (operated at 250 and 62.5 MHz, respectively) or Bruker AV 400 spectrometer (operated at 400 and 100 MHz, respectively). Chemical shifts are reported as δ values (ppm). Some ^{1}H NMR data were collected using DMSO-d_6 and $CDCl_3$ to dissolve the samples because they were not completely soluble only in DMSO-d_6; however, if just $CDCl_3$ is used, the active protons do not appear in D_2O/water exchange experiments. The solvents used are indicted in the experimental details. The reaction

progress was monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Aluminum silica gel 60-F254 precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. The parallel synthesis was carried out on a Corning parallel synthesizer. Electrospray ionization mass spectrometry was performed on a Micromass QTOF mass spectrometer (Waters Corp, Milford MA). Direct probe samples were collected on a VG-70S mass spectrometer (Waters Corp., Milford MA). All UV data was collected using a Cary 50 UV−vis spectrophotometer with a xenon lamp and an equipment range from 200 to 1250 nm. IR spectroscopic data were collected using a SHIMSDZU Inc. IR, Prestige-21 Fourier transform infrared spectrophotometer and KBr solid samples. The samples for melting point, IR, and UV were purified by recrystallization or flash column chromatography of the final 2-quinoxalinol products.

General Procedure. One equivalent (10.0 mmol) of 1,5-difluoro-2,4-dinitrobenzene (DFDNB), 2.2 equiv (22 mmol) of diisopropylethylamine (DIPEA), and 1.0 equiv of methyl amino acid (10 mmol) were added to a stirring solution of 150 mL of THF. The reaction mixture was stirred continuously for 12 h at room temperature. After it was confirmed by TLC that the starting materials (DFDNB) had been consumed, 3 equiv (30 mmol) of ammonium hydroxide in water was added as a 5.0 N aqueous solution to the reaction mixture. The reaction solution is stirred at room temperature for an additional 5 h until the reaction was complete, and this was confirmed by TLC. The reaction solution was concentrated to dryness using a rotary evaporator resulting in a yellow oil or oily solid. The resultant yellow oil was dissolved in 100 mL of ethanol (95%) with stirring. To this, $HCOONH_4$, 20 equiv (0.2 mol), and 5% wet Pd−C (3.1 g, 7.0 g for containing sulfur, catalytic) were added under a protective N_2 atmosphere. The reaction mixture was heated to reflux temperature for 15−30 min. During this time, the reaction mixture changed from the initial yellow color to red and then to fluorescent yellow. After this time, the catalyst Pd−C and unreacted $HCOONH_4$ were filtered from the solution. The filtrate was put into freezer (0 °C) for 48−72 h until yellow crystals formed. If there no solids precipitated from the solution, sonication using an ultrasonic bath was used to help precipitate the diamino-2-quinoxalinol intermediate as a solid. Filtration of the solid from the reaction solution results in highly pure diamino-2-quinoxalinol intermediate. The synthetic yields from starting material of **4a**, **4b**, **4c**, and **4d** are 60, 59, 58, and 41%, respectively. After the samples were dried at high vacuum, HPLC, ^{1}H NMR, and ^{13}C NMR show that the purities of each of these are not less than 98%.

A solution of 10.0 equiv (1 mmol) of aldehyde derivatives in 6 mL of methanol was added to 1.0 equiv (0.1 mmol) of the diamino-2-quinoxalinol intermediate dissolved in 4 mL of methanol. The two are combined with stirring, and after the mixture was heated to reflux temperature for 1 h, it becomes deep yellow or dark. After continued heating at reflux temperature for 48 h, the product forms and precipitates as either dark yellow or red solids. The precipitate is filtered directly and washed with 95% ethanol and cold acetone 5 times each to obtain the 2-quinoxalinols Schiff base ligands as the final product. The yields of the final products range from 40 to 80% with purities of 90.0−99.0%. All of the final products were identified and characterized by ^{1}H NMR, ^{13}C NMR, MS, HRMS, UV−vis, and IR.

For synthesis of **6aa**, **6ca**, and **6db**, 1.0 equiv (0.1 mmol) of diamino-2-quinoxalinol intermediate was dissolved in 4 mL of methanol, and 10.0 equiv (1 mmol) of aldehyde derivative was dissolved in 2 mL ofmethanol. Under stirring, the solution becomes red after it is refluxed for 40 min; after it is kept refluxing for 48 h, there is a large amount of red precipitate. The precipitate filtered directly and washed with 95% ethanol and cold acetone 5 times each.

4a. ^{1}H NMR (400 MHz DMSO-d_6): δ 3.99 (s, 2H), 4.66 (bs, 2H), 5.47 (bs, 2H), 6.37 (s, 1H), 6.80 (s, 1H), 7.16−7.31 (m, 5H), 11.86 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.1, 152.2, 140.5, 139.4, 133.0, 129.4, 128.6, 126.4, 125.8, 111.0, 96.8, 38.8. Formula: $C_{15}H_{14}N_4O$. MS (M + H): 267.0. HRMS: found (267.1256), calcd (267.1246). IR: 3172.9 (bs), 3381.2 (bs), 3182.6 (bs), 3005.2, 1645.3, 1510.3, 1402.3, 1278.8 cm^{-1}. UV: 402.9 nm (bs).

4b. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.13 (d, J = 6.8, 6H), 3.33 (sept, 1H), 4.66 (bs, 2H), 5.36 (bs, 2H), 6.33 (s, 1H), 6.78 (s, 1H), 11.73 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.7, 154.7, 140.1, 132.8, 125.9, 125.5, 111.3, 96.9, 29.7, 21.0. Formula: $C_{11}H_{14}N_4O$. MS (M + H): 219.0. HRMS: found (219.1248), calcd (219.1246). IR: 3381.2 (bs), 3365.1 (bs), 2962.7, 2929.9, 1656.9, 1512.2, 1406.1, 1273.0 cm^{-1}. UV: 394.0 nm (bs).

4c. ^{1}H NMR (250 MHz DMSO-d_6): δ 0.90 (d, J = 6.7, 6H), 2.15 (m, 1H), 2.50 (d, 2H), 4.62 (bs, 2H), 5.39 (bs, 2H), 6.35 (s, 1H), 6.79(s, 1H), 11.98 (bs, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 155.4, 153.2, 140.1, 132.8, 126.0, 125.8, 111.2, 96.9, 41.7, 26.9, 23.0. Formula: $C_{12}H_{16}N_4O$. MS (M + H): 233.0. HRMS: found (233.1410), calcd (233.1402). IR: 3352.3 (bs), 3277.1 (bs), 2949.2, 2868.2, 2818.0, 1653.0, 1512.2, 1419.6, 1402.3, 1271.1 cm^{-1}. UV: 410.6 nm (bs), 299.1 (wbs).

4d. ^{1}H NMR (400 MHz DMSO-d_6): δ 2.09 (s, 3H), 2.83 (t, 2H), 2.95 (t, 2H), 5.19 (bs, 2H), 5.65 (bs, 2H), 6.39 (s, 1H), 6.82 (s, 1H), 11.99 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.2, 151.8, 140.4, 132.9, 126.2, 125.8, 111.1, 96.9, 32.9, 31.1, 15.1. Formula: $C_{11}H_{14}N_4OS$. MS (M + H): 251.0. HRMS: found (251.0966), calcd (251.0963). IR: 3321.4 (bs), 3219.2 (bs), 2920.2, 2879.7, 1643.4, 1510.3, 1402.3, 1273.0 cm^{-1}. UV: 391.0 nm (bs).

6aa. ^{1}H NMR (400 MHz DMSO-d_6): δ 4.14 (s, 2H), 6.77−7.34 (m, 12H), 7.87 (s, 1H), 8.83 (s, 1H), 9.04 (s, 1H), 9.22 (bs, 1H, D_2O exchangeable), 9.41 (bs, 1H, D_2O exchangeable), 12.18 (bs, 1H, D_2O exchangeable), 12.53 (bs, 1H, D_2O exchangeable), 12.99 (bs, 1H, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.6, 164.8, 160.7, 154.9, 150.0, 149.7, 146.2, 146.1, 145.7, 138.2, 137.9, 132.1, 129.7, 128.8, 126.9, 123.4, 122.9, 120.3, 120.2, 119.8, 119.6, 118.4, 106.0, 40.0. Formula: $C_{29}H_{22}N_4O_5$. MS: 507.0. HRMS: found (507.1666), calcd (507.1668). IR: 3392.8 (bs), 3005.2, 1656.8, 1616.3, 1467.8, 1271.1, 1234.4 cm^{-1}. UV: 383.0 nm (bs).

6ab. ^{1}H NMR (400 MHz DMSO-d_6): δ 4.14 (s, 2H), 6.74−7.35 (m, 12H), 7.87 (s, 1H), 8.74 (s, 1H), 8.97 (s, 1H),

9.08 (bs, 1H, D_2O exchangeable), 9.12 (bs, 1H, D_2O exchangeable), 11.43 (bs, 1H, D_2O exchangeable), 12.31 (bs, 1H, D_2O exchangeable), 12.50 (bs, 1H, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 163.8, 160.6, 155.0, 153.8, 153.5, 150.2, 150.0, 146.5, 138.0, 137.9, 132.1, 131.1, 129.7, 128.9, 126.9, 122.4, 121.7, 120.2, 119.9, 118.1, 117.9, 117.7, 117.5, 116.5, 105.9, 40.0. Formula: $C_{29}H_{22}N_4O_5$. MS (M + H): 507.0. HRMS: found (507.1667), calcd (507.1668). IR: 3387.0 (bs), 3005.0, 1662.6, 1616.4, 1573.9, 1487.1, 1282.7, 1153.4. UV: 378.0 nm (bs).

6ac. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.31 (s, 9H), 1.34 (s, 9H), 4.15 (s, 2H), 6.77−7.44 (m, 12H), 7.62 (s, 1H), 8.58 (s, 1H), 8.70 (s, 1H), 12.26 (bs, 1H), 13.42 (bs, 1H), 13.60 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 163.7, 160.6, 160.4, 155.1, 144.6, 138.4, 137.7, 137.4, 137.0, 133.9, 131.9, 131.7, 130.7, 129.3, 128.2, 126.4, 126.1, 119.2, 118.9, 118.7, 118.2, 117.9, 105.5, 34.7, 29.2. Formula: $C_{37}H_{38}N_4O_3$. MS (M + H): 587.0. HRMS: found (587.3028), calcd (587.3022). IR: 3437.2 (bs), 3417.9 (bs), 2953.0, 2912.5, 1672.3, 1606.7, 1500.6, 1431.2, 1394.5, 1197.8, 1143.8 cm^{-1}. UV: 285.7 (bs), 387.9 nm (bs).

6ad. ^{1}H NMR (250 MHz DMSO-d_6 and $CDCl_3$): δ 1.23 (s, 18H), 1.32 (s, 9H), 1.34 (s, 9H), 4.14 (s, 2H), 7.01 (s, 1H), 7.12−7.41 (m, 9H), 7.59 (s, 1H), 8.58 (s,1H), 8.68 (s, 1H), 12.22 (bs, 1H), 13.25 (bs, 1H), 13.36 (bs, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6 and $CDCl_3$): δ 165.9, 164.3, 160.2, 158.6, 158.3, 155.3, 144.9, 140.6, 140.5, 138.9, 137.2, 137.1, 136.9, 131.7, 131.5, 129.5, 128.7, 128.4, 128.2, 127.2, 127.0, 126.5, 118.4, 118.1, 118.1, 105.6, 35.1, 34.1, 31.5, 29.4. Formula: $C_{45}H_{54}N_4O_3$. MS (M + H): 699.0. HRMS: found (699.4276), calcd (699.4274). IR: 3435.2 (bs), 3415.9 (bs), 2956.9, 2910.6, 2873.9, 1656.9, 1612.5, 1529.6, 1477.5, 1442.8, 1261.5, 1168.9 cm^{-1}. UV: 299.1 (bs), 390.9 nm (bs).

6ae. ^{1}H NMR (400 MHz DMSO-d_6): δ 4.17 (s, 2H), 6.95−7.03 (m, 2H), 7.11 (s, 1H), 7.25−7.49 (m, 7H), 7.66 (d, 1H), 7.79 (d, 1H), 7.94 (s, 1H), 8.90 (s, 1H), 9.13 (s, 1H), 12.28 (bs, 1H), 12.57 (bs, 1H), 13.13 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 164.0, 160.9, 160.8, 160.6, 155.0, 146.0, 138.1,137.9, 134.5, 133.8, 133.1, 132.3, 132.2, 131.2, 129.8, 128.9, 126.9, 120.2, 120.0, 119.9, 119.6, 118.1, 117.2, 117.1, 105.8, 40.0. Formula: $C_{29}H_{22}N_4O_3$. MS (M + H): 475.0. HRMS: found (475.1762), calcd (475.1770). IR: 3448.7 (bs), 3427.5 (bs), 3055.2, 3030.2, 1654.9, 1610.6, 1570.1, 1481.3, 1276.9, 1197.8 cm^{-1}. UV: 305.6 (wbs), 335.9 (wbs), 390.5 nm (bs).

6ba. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.26 (d, J = 6.8 Hz, 6H), 3.50 (sept, 1H), 6.80 (t, 1H), 6.84 (t, 1H), 6.94 (d,1H), 6.99 (d, 1H), 7.01 (s, 1H), 7.14 (d, 1H), 7.22 (d, 1H), 7.92 (s, 1H), 8.87 (s, 1H), 9.11 (s, 1H), 9.24 (bs, 1H), 9.43 (bs, 1H), 12.24 (bs, 1H), 12.48 (bs, 1H), 13.06 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 165.6, 164.8, 154.6, 150.0, 149.7, 146.2, 146.1, 145.4, 138.1, 131.8, 131.1, 123.5, 122.9, 120.3, 120.2, 120.0, 119.6, 119.2, 118.3, 106.0, 30.4, 20.6. Formula: $C_{25}H_{22}N_4O_5$. MS (M + H): 459.0. HRMS: found (459.1675), calcd (459.1668). IR: 3421.7 (bs), 3059.1, 2966.5, 2926.0, 1656.9, 1616.4, 1556.6, 1465.9, 1373.3, 1273.0, 1230.6 cm^{-1}. UV: 306.5 (bs), 389.6 nm (bs).

6bb. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.23 (d, J = 6.8 Hz, 6H), 3.48 (sept, 1H), 6.74−7.12 (m, 7H), 7.88 (s, 1H), 8.74 (s, 1H), 9.01 (s,1H), 9.08 (bs, 1H, D_2O exchangeable), 9.13 (bs, 1H, D_2O exchangeable), 11.46 (bs, 1H, D_2O exchangeable), 12.36 (bs, 1H, D_2O exchangeable), 12.42 (bs, 1H, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.9, 164.3, 163.8, 154.6, 153.8, 153.5, 150.2, 150.0, 146.2, 138.2, 131.8, 130.9, 122.3, 121.7, 120.2, 120.0, 118.0, 117.9, 117.6, 116.5, 105.8, 30.4, 20.6. Formula: $C_{25}H_{22}N_4O_5$. MS (M + H): 458.0. HRMS: found (459.1665), calcd (459.1668). IR: 3400.5 (bs), 2962.7, 2926.0, 1656.9, 1627.9, 1579.7, 1490.8, 1400.0, 1273.0, 1219.0 cm^{-1}. UV: 299.1 (bs), 387.0 nm (bs).

6bc. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.27 (d, J = 6.8 Hz, 6H), 1.37 (s, 9H), 1.42 (s, 9H), 3.52 (sept, 1H), 6.93 (t, 1H), 6.95 (t, 1H), 7.20 (s, 1H), 7.38 (d, 1H), 7.44 (d, 1H), 7.54−7.58 (t, 2H), 8.00 (s, 1H), 8.94 (s, 1H), 9.19 (s,1H), 12.51 (bs, 1H), 13.73 (bs, 1H), 14.04 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 166.3, 165.5, 160.5, 160.4, 154.6, 144.5, 137.9, 137.6, 137.1, 137.0, 132.2, 132.0, 131.4, 131.3, 130.8, 119.7, 119.4, 119.1, 118.9, 118.3, 105.9, 34.9, 30.4, 29.7, 20.6. Formula: $C_{33}H_{38}N_4O_3$. MS (M + H): 539.0. HRMS: found (539.3024), calcd (539.3022). IR: 3429.4 (bs), 2956.9, 2872.0, 1660.7, 1606.7, 1467.8, 1431.2, 1388.8, 1270.0, 1199.7 cm^{-1}. UV: 302.2 (bs), 386.2 nm (bs)

6bd. ^{1}H NMR (400 MHz DMSO-d_6 and $CDCl_3$): δ 1.20 (s, 9H), 1.21 (s, 9H), 1.21 (d, J = 6.8 Hz, 6H), 1.29 (s, 9H), 1.32 (s, 9H), 3.52 (sept, 1H), 6.99 (s, 1H), 7.17 (s, 2H), 7.34 (s, 1H), 7.37 (s, 1H), 7.62 (s, 1H), 8.59 (s, 1H), 8.72 (s, 1H), 12.12 (bs, 1H), 13.28 (bs, 1H), 13.39 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6 and $CDCl_3$): 165.9, 165.7, 164.1, 158.5, 158.3, 155.1, 144.5, 140.5, 140.4, 138.8, 137.1, 136.9, 131.5, 131.2, 128.6, 128.1, 127.1, 126.8, 118.3, 118.1, 118.0, 105.4, 35.0, 34.1, 31.4, 30.3, 29.3, 20.1. Formula: $C_{41}H_{54}N_4O_3$. MS (M + H): 651.0. HRMS: found (651.4274), calcd (651.4268). IR: 3423.7 (bs), 2958.8, 2910.6, 2870.1, 1653.0, 1614.4, 1581.6, 1469.8, 1437.0, 1390.7, 1363.7, 1253.7, 1203.6 cm^{-1}. UV: 299.6 (bs), 387.9 nm (bs).

6be. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.23 (d, J = 6.8 Hz, 6H), 3.47 (sept, 1H), 6.91−7.00 (m, 4H), 7.08 (s, 1H), 7.39 (t, 1H), 7.44 (t, 1H), 7.66 (d, 1H), 7.76 (d, 1H), 7.93 (s, 1H), 8.87 (s, 1H), 9.15 (s, 1H), 12.28 (bs, 1H), 12.46 (bs, 1H), 13.14 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.1, 164.6, 163.9, 160.9, 160.6, 154.6, 145.7, 137.9, 134.4, 133.8, 133.1, 132.4, 132.0, 131.1, 120.2, 119.8, 119.5, 118.1, 117.2, 117.1, 105.7, 30.4, 20.6. Formula: $C_{25}H_{22}N_4O_3$. MS (M + H): 427.0. HRMS: found (427.1764), calcd (427.1770). IR: 3441.0 (bs), 2964.6, 2924.1, 1658.8, 1616.4, 1570.1, 1479.4, 1452.0[1], 1278.8, 1203.6 cm^{-1}. UV: 335.9 (bs), 387.9 nm (bs).

6ca. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.23 (d, J = 6.6 Hz, 6H), 2.27 (m, 1H), 2.71 (d, J = 7.0, 2H), 6.80 (t, 1H), 6.83 (t, 1H), 6.95 (d, 1H), 7.00 (d, 1H), 7.09 (s, 1H), 7.14 (t, 2H), 7.22 (t, 2H), 7.92 (s, 1H), 8.87 (s, 1H), 9.08 (s, 1H), 9.24 (bs, 1H, D_2O exchangeable), 9.42 (bs, 1H, D_2O exchangeable), 12.25 (bs, 1H, D_2O exchangeable), 12.47 (bs, 1H, D_2O exchangeable), 13.04 (bs, 1H, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.6, 164.7,161.7, 155.2, 150.0, 149.7, 146.2, 146.1, 145.4, 138.1, 131.9, 131.2, 123.4, 122.9, 120.3, 120.2, 120.0, 119.6, 119.2, 118.3, 106.0, 42.1, 26.6, 23.1. Formula: $C_{26}H_{24}N_4O_5$. MS (M + H): 473.0.

HRMS: found (473.1818), calcd (473.1825). IR: 3419.8 (bs), 2949.2, 2866.2, 1656.9, 1618.3, 1579.7, 1465.9, 1373.3, 1271.1, 1232.5. UV: 301.3 (bs), 381.0 nm (bs).

6cb. ^{1}H NMR (400 MHz DMSO-d_6): δ 0.98 (d, $J = 6.6$ Hz, 6H), 2.27 (m, 1H), 2.71 (d, $J = 7.0$, 2H), 6.77−6.91 (m, 4H), 7.06 (s, 2H), 7.14 (s, 1H), 7.92 (s, 1H), 8.77 (s, 1H), 9.01 (s, 1H), 9.12 (bs, 1H), 9.15 (bs, 1H), 11.49 (bs, 1H,), 12.36 (bs, 1H), 12.45 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.4, 163.7, 161.5, 155.2, 153.8, 153.5, 150.2, 150.0, 146.2, 138.2, 131.9, 131.1, 120.2, 119.9, 117.9, 117.6, 117.5, 116.5, 105.8, 42.1, 26.7, 23.1. Formula: $C_{26}H_{24}N_4O_5$. MS (M + H): 473.0. HRMS: found (473.1832), calcd (473.1825). IR: 3427.5 (bs), 3412.1 (bs), 2956.9, 2924.1, 1658.8, 1618.3, 1577.8, 1483.3, 1379.1, 1286.5, 1213.2. UV: 303.9 (bs), 395.7 nm (bs).

6cc. ^{1}H NMR (400 MHz DMSO-d_6): δ 0.99 (d, $J = 6.6$ Hz, 6H), 13.7 (s, 9H), 1.42 (s, 9H), 2.29 (m, 1H), 2.72 (d, $J = 7.0$, 2H), 6.93 (t, 1H), 6.95 (t, 1H), 7.20 (s, 1H), 7.38 (d, 1H), 7.44 (d, 1H), 7.53−7.58 (m, 2H), 8.01 (s, 1H), 8.93 (s, 1H), 9.16 (s, 1H), 12.51 (bs, 1H), 13.73 (bs, 1H), 14.03 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 165.5, 161.9, 160.5, 160.4, 155.2, 144.5, 137.9, 137.2, 137.0, 132.2, 132.0, 131.9, 131.4, 130.8, 119.7, 119.4, 119.1, 118.9, 118.2, 105.9, 42.1, 34.9, 29.7, 26.6, 23.1. Formula: $C_{34}H_{40}N_4O_3$. MS (M + H): 553.0. HRMS: found (553.3177), calcd (553.3178). IR: 3423.7 (bs), 2955.0, 2918.3, 2870.1, 1662.6, 1604.8, 1573.9, 1496.8, 1469.8, 1431.2, 1396.5, 1273.0, 1199.7 cm^{-1}. UV: 299.6 (bs), 382.7 nm (bs).

6cd. ^{1}H NMR (250 MHz DMSO-d_6 and $CDCl_3$): δ 0.82 (d, $J = 6.6$ Hz, 6H), 1.10 (s, 9H), 1.11 (s, 9H), 1.19 (s, 9H), 1.22 (s, 9H), 2.13 (m, 1H), 2.57 (d, $J = 7.1$, 2H), 6.88 (s, 1H), 7.04−7.06 (dd, 2H), 7.21 (d, 2H), 7.23 (d, 2H), 7.47 (s, 1H), 8.47 (s, 1H), 8.58 (s, 1H), 12.08 (bs, 1H), 13.15 (bs, 1H), 13.25 (bs, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6 and $CDCl_3$): δ 166.6, 164.1, 161.4, 158.4, 158.1, 155.6, 144.4, 140.4, 138.7, 136.9, 136.8, 131.3, 128.5, 128.0, 127.0, 126.8, 118.2, 118.0, 117.8, 105.4, 42.0, 34.9, 34.0, 31.3, 29.3, 26.5, 22.6. Formula: $C_{42}H_{56}N_4O_3$. MS (M + H): 665.0. HRMS: found (665.4431), calcd (665.4430). IR: 3423.7 (bs), 2956.9, 2920.1, 2880.1, 1656.9, 1616.4, 1583.6, 1469.8, 1437.0, 1386.8, 1367.5, 1255.7, 1207.4 cm^{-1}. UV: 301.3 (bs), 389.6 nm (bs).

6ce. ^{1}H NMR (250 MHz DMSO-d_6): δ 0.98 (d, $J = 6.5$ Hz, 6H), 2.27 (m, 1H), 2.70 (d, $J = 6.9$, 2H), 6.94−7.11 (m, 4H), 7.38 (s, 1H), 7.41−7.46 (m, 2H), 7.68 (d, 1H), 7.79 (d, 1H), 7.96 (s, 1H), 8.89 (s, 1H), 9.14 (s, 1H), 12.34 (bs, 2H), 13.14 (bs, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 164.6, 163.9, 161.7, 160.9, 160.6, 155.2, 145.6, 138.0, 134.4, 133.8, 133.1, 132.4, 132.0, 131.2, 120.2, 120.0, 119.8, 119.5, 118.0, 117.2, 105.8, 42.1, 26.6, 23.1. Formula: $C_{26}H_{24}N_4O_3$. MS (M + H): 441.0. HRMS: found (441.1922), calcd (441.1926). IR: 3441.0 (bs), 3425.6 (bs), 2955.0, 2922.2, 2864.3, 1658.8, 1616.4, 1572.0, 1485.2, 1384.9, 1278.8, 1203.6 cm^{-1}. UV: 383.6 nm (bs).

6da. ^{1}H NMR (400 MHz DMSO-d_6): δ 2.14 (s, 3H), 2.95 (t, 2H), 3.13 (t, 2H), 6.81 (t, 1H), 6.84 (t, 1H), 6.95 (d, 1H), 7.00 (d, 1H), 7.11 (s, 1H), 7.15 (d, 1H), 7.23 (d, 1H), 7.92 (s, 1H), 8.88 (s, 1H), 9.08 (s, 1H), 9.25 (bs, 1H, D_2O exchangeable), 9.43 (bs, 1H, D_2O exchangeable), 12.23 (bs, 1H, D_2O exchangeable), 12.53 (bs, 1H, D_2O exchangeable), 13.02 (bs, 1H, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.7, 164.8, 160.6, 155.0, 149.9, 149.7, 146.2, 146.1, 145.6, 138.2, 132.0, 131.1,123.4, 122.9, 120.3, 120.2, 120.0, 119.6, 119.2, 118.3, 106.1, 33.2, 30.5, 15.0. Formula: $C_{25}H_{22}N_4O_5S$. MS (M + H): 491.0. HRMS: found (491.1389), calcd (491.1389). IR: 3415.9 (bs), 2920.2, 2852.7, 1656.9, 1616.4, 1467.8, 1373.3, 1271.1, 1230.6 cm^{-1}. UV: 307.4 (bs), 390.5 nm (bs).

6db. ^{1}H NMR (400 MHz DMSO-d_6): δ 2.14 (s, 3H), 2.94 (t, 2H), 3.12 (t, 2H), 6.77−6.93 (m, 4H), 7.06 (s, 2H), 7.14 (s, 1H), 7.92 (s, 1H), 8.78 (s, 1H), 8.80 (s, 1H), 9.12 (bs, 1H), 9.16 (bs, 1H), 11.48 (bs, 1H), 12.34 (bs, 1H), 12.49 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.4, 163.8, 153.8, 153.5, 150.2, 150.0, 132.0, 121.7, 120.2, 119.9, 118.1, 117.9, 117.7, 116.5, 105.9, 33.1, 30.1, 15.2. Formula: $C_{25}H_{22}N_4O_5S$. MS (M + H): 491.0. HRMS: found (491.1384), calcd (491.1389). IR: 3439.1 (bs), 2972.3, 2924.1, 1654.9, 1624.1, 1575.8, 1477.5, 1388.8, 1282.7, 1220.9 cm^{-1}. UV: 302.2 (wbs), 391.4 nm (bs)

6dc. ^{1}H NMR (250 MHz DMSO-d_6): δ 1.36 (s, 9H), 1.40 (s, 9H), 2.14 (s, 3H), 2.94 (t, 2H), 3.11 (t, 2H), 6.93−6.98 (m, 2H), 7.20 (s, 1H), 7.39 (d, 1H), 7.41 (d, 1H), 7.54 (t, 2H), 8.00 (s, 1H), 8.93 (s, 1H), 9.14 (s, 1H), 12.56 (bs, 1H), 13.72 (bs, 1H), 14.01 (bs, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 166.9, 165.2, 160.6, 160.4, 154.9, 144.6, 138.1, 137.2, 137.0, 132.1, 131.8, 131.3, 130.6, 119.6, 119.3, 118.9, 118.7, 118.2, 105.9, 34.9, 33.2, 30.5, 29.6, 15.3. Formula: $C_{33}H_{38}N_4O_3S$. MS (M + H): 571.0. HRMS: found (571.2738), calcd (571.2743). IR: 3433.3 (bs), 3417.9 (bs), 2953.0, 2920.2, 2872.0, 1666.5, 1654.9, 1606.7, 1489.1, 1427.3, 1388.8, 1311.6, 1267.2 cm^{-1}. UV: 305.6 (bs), 389.6 nm (bs).

6dd. ^{1}H NMR (400 MHz DMSO-d_6 and $CDCl_3$): δ 1.20 (s, 9H), 1.21 (s, 9H), 1.29 (s, 9H), 1.32 (s, 9H), 2.15 (s, 3H), 2.90 (t, 2H), 3.12 (t, 2H), 6.97 (s, 1H), 7.14 (s, 2H), 7.31 (d, 1H), 7.34 (d, 1H), 7.56 (s, 1H), 8.55 (s, 1H), 8.65 (s, 1H), 12.20 (bs, 1H), 13.21 (bs, 1H), 13.32 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6 and $CDCl_3$): δ 165.8, 164.3, 159.8, 158.6, 158.3, 155.4, 144.9, 140.5, 140.4, 139.0, 137.1, 137.0, 131.4, 131.3, 128.7, 128.2, 127.1, 126.9, 118.3, 118.1, 118.0, 105.6, 35.0, 34.1, 33.1, 31.4, 30.6, 29.3, 15.5. Formula: $C_{41}H_{54}N_4O_3S$. MS (M + H): 683.0. HRMS: found (683.4005), calcd (683.3995). IR: 3441.0 (bs), 3425.6 (bs), 2956.9, 2914.4, 2870.1, 1656.9, 1616.4, 1583.6, 1469.8, 1433.1, 1386.8, 1269.2, 1259.5 cm^{-1}. UV: 302.2 (bs), 391.4 nm (bs).

6de. ^{1}H NMR (400 MHz DMSO-d_6): δ 2.14 (s, 3H), 2.95 (t, 2H), 3.13 (t, 2H), 6.95−7.04 (m, 4H), 7.12 (s, 1H), 7.42 (t, 1H), 7.47 (t, 1H), 7.70 (d, 1H), 7.79 (d, 1H), 7.96 (s, 1H), 8.91 (s, 1H), 9.14 (s, 1H), 12.30 (bs, 1H), 12.54 (bs, 1H), 13.12 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.7, 164.0, 160.9, 160.6, 155.0, 145.8, 138.1, 134.5, 133.8, 133.1, 120.2, 120.0, 119.9, 118.1, 117.2, 117.1, 105.8, 33.2, 30.5, 15.2. Formula: $C_{25}H_{22}N_4O_3S$. MS (M + H): 459.0. HRMS: found (459.1489), calcd (459.1491). IR: 3441.0 (bs), 3423.6 (bs), 2916.4, 2841.2, 2796.8, 1660.7, 1614.4, 1570.1, 1479.4, 1398.4, 1276.9, 1201.6. UV: 335.9 (bs), 387.0 nm (bs).

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