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Regioselective Synthesis of Asymmetrically Substituted 2-Quinoxalinol Salen Ligands

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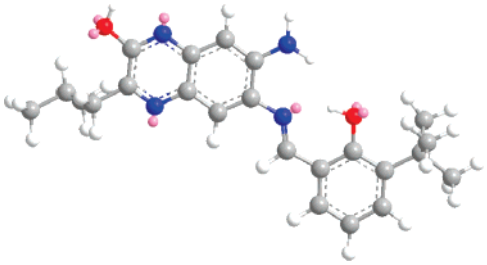

Diamino-2-quinoxalinols are reacted with salicylaldehyde derivatives to produce 2-quinoxalinol imines regioselectively as one isomer in good yield. Regioselectivity has been determined through the use of isotopic ^{15}N labeling experiments. The 2-quinoxalinol imines may then be reacted without further purification with additional salicylaldehyde derivatives to yield asymmetrically substituted 2-quinoxalinol salens.

Introduction

Salens and their metal complexes have found numerous applications in organic chemistry. Most notably, they have been found to be of great utility in the development of chiral catalysts, and have been used to increase the stereoselectivity of products in a variety of reactions including ring-opening of epoxides,[1] asymmetric epoxidation (AE),[2] hydrolytic kinetic resolution (HKR),[3] hetero-Diels−Alder reactions,[4] Pictet−Spengler reactions,[5] and hydrocyanation reactions.[6] Salen complexes with ruthenium, copper(I), and manganese(II) have also been of interest for their bioactivity. These metal complexes have been investigated as protein kinase inhibitors, as antitumor agents, as cytoprotective agents, and in catalytic scavengers of hydrogen peroxide.[7]

Previously, we have synthesized a library of symmetrical 2-quinoxalinol salens.[8] To incorporate these into chiral catalysts, the introduction of asymmetric substitution is necessary. Here, we have used the incorporation of the 2-quinoxalinol to the salen backbone to enable the facile synthesis of asymmetrically substituted salen-based ligands. In addition, the chemistry of 2-quinoxalinols has been applied in medicinal chemistry,[8,9] in dyes and pigments,[10] and in agricultural chemistry.[11]

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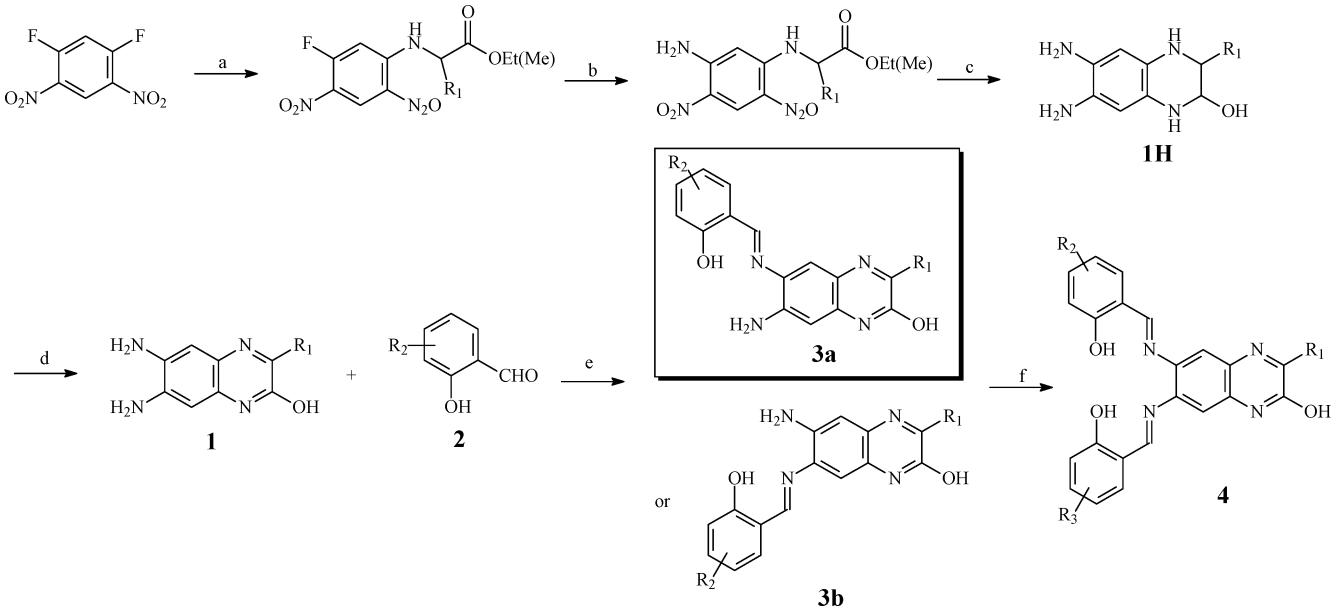
SCHEME 1. Reaction Route to 2-Quinoxalinol Imines 3a and Asymmetrically Substituted Salen 4[a]



[a] Key: (a) THF amino acid, 1 equiv, DIEPA; (b) $NH_3 \cdot H_2O$, THF; (c) Pd−C, $HCOONH_4$, 95% EtOH, N_2; (d) air or O_2; (e) MeOH, 80 °C; (f) MeOH, salicylaldehyde **2′**, 80 °C.

Given that compounds containing imine functional groups have broad applications in organic chemistry, the key intermediates, the 2-quinoxalinol imines, are also potentially very useful structures. One application of interest is in the preparation of amino acids via a Strecker reaction.[12] Catalyzed by chiral catalysts, nucleophilic addition to imines is also used for the preparation of compounds possessing secondary amine groups with high stereoselectivity.[13] Imines can also play a crucial role as catalyst supports in new coordination ligands.[14] In medicinal chemistry, imines have been found to have antitumor and antibacterial bioactivity[15] and to serve as protein synthesis inhibitors.[16] In recent reports, imine coordination ligands supporting copper metal complexes have been demonstrated to trap toxic gases.[17] In addition, imines are useful as protecting groups for amines.[18]

Other researchers have focused their efforts on the preparation of asymmetrical analogues of Jacobsen catalysts and the preparation of solid-phase catalysts with ring-opening metathesis polymerization (ROMP).[2c,3d,19] Asymmetrically substituted 2-quinoxalinol salens and their metal complexes not only have chiral character, but provide the additional advantage of additional points of substitution with three diversity sites, thereby providing additional means for altering the properties of the catalyst. Furthermore, this may allow them to be more easily prepared for use in solid-phase catalysts.

The synthesis of 2-quinoxalinol imines is challenging, because they are often unstable, particularly when using bulky imines.[20] The synthesis of the key intermediate, the 2-quinoxalinol imine (**3a**), from diamino-2-quinoxalinol (**1**) is a unique challenge, because of the difficulty in obtaining one isomer as the final product. If the reaction can be controlled such that only one amine is reacted with an aldehyde, this would provide a method to develop asymmetrically substituted 2-quinoxalinol salens. In the process of our research toward the synthesis of the symmetrical 2-quinoxalinol salen ligand library,[8] we isolated a side product determined to be the half unit salen ligand, that is, a single product, a 2-quinoxalinol imine (**3**). The use of this side product as a starting material for asymmetrically substituted ligands provides a means to overcome the difficulty of synthesis in producing regioselective or bulky 2-quinoxalinol imine

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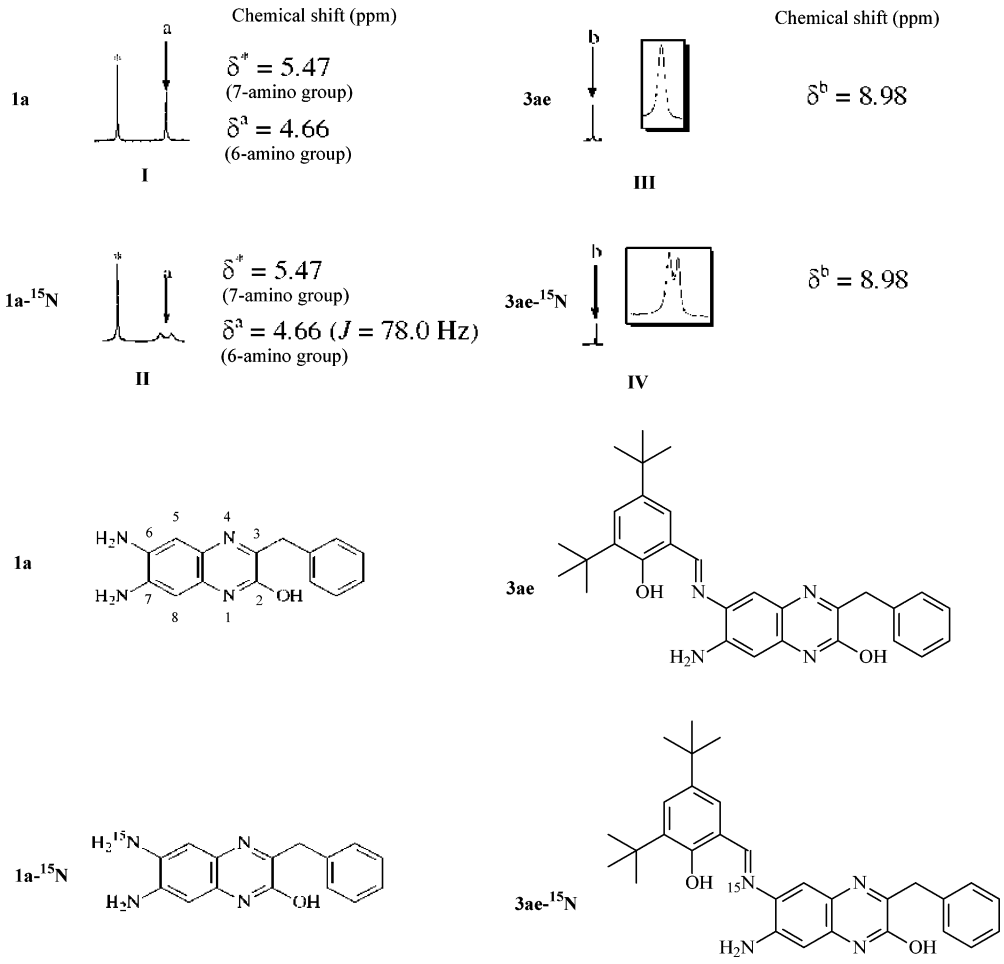


FIGURE 1. ^{1}H NMR results of intermediate (**1a**) and 2-quinoxalinol imines (**3ae**). Note: For intermediate **1a**, the ^{1}H NMR of the hydrogen of two amino groups has been shown. For 2-quinoxalinol imine (**3ae**), just the hydrogen on the carbon of the imine group has been shown.

compounds. In addition, these 2-quinoxalinol imines are stable in atmospheric conditions.

From our reaction route (Scheme 1), a second challenge was in the identification of the exact structure of the 2-quinoxalinol imines, because two isomers (**3a** or **3b**) are possible. Here, we have identified the exact structure of these 2-quinoxalinol imines using isotope ^{15}N labeled compounds and NMR technology, and we have determined the reaction to be regioselective. Using this information, we were able to prepare several 2-quinoxalinol imine intermediates for use as synthetic building blocks in the preparation of asymmetrically substituted salen-based ligands.

Results and Discussion

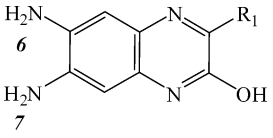
The general synthetic route for the formation of the 2-quinoxalinol salen ligands has been reported previously.[8] As part of this earlier work, we identified that the diamino-2-quinoxalinol (**1**) to salicylaldehyde derivatives (**2**) ratio of the starting materials used is crucial to the optimization of the reaction. When the ratio is 1:1.2, a 2-quinoxalinol imine is the major product with high regioselectivity. If the ratio of reactants is increased, the yield of symmetric 2-quinoxalinol salens increases. As the ratio of reactants reaches 1:10, the yield of the symmetric 2-quinoxolinol salen is much higher.[8]

The identification of 2-quinoxalinol imine intermediates in the reaction is important to determine the utility of these compounds in asymmetric syntheses, because two configurations (**3a** or **3b**) are possible. To identify the exact structure, we differentiated the two amino groups of the diamino-2-quinoxalinol intermediate (**1**) by replacing ammonium hydroxide with ^{15}N-labeled ammonium hydroxide during the secondary substitution of the 1, 5-difluoro-2,4-dinitrobenzene (DFDNB). Because of the heteronuclear coupling of ^{15}N, ^{1}H NMR can be used to demonstrate a difference between the two amino groups of intermediate **1**. Thus, in the 2-quinoxalinol imine intermediate, the position of the imine formation (whether on the ^{15}N or ^{14}N of intermediate **1**) can be identified. The simplified ^{1}H NMR spectra with intermediate **1a**, 2-quinoxalinol imine (**3ae**), and the ^{15}N-labeled intermediate **1a**, 2-quinoxalinol imine (**3ae**), are shown in Figure 1.

In Figure 1, for intermediate **1a**, the "a" labeled peaks corresponding to the two protons of the ^{14}N and ^{15}N amino groups are different in spectra I and II. In spectra I, it is a broad single peak, while in spectra II, with ^{15}N heteronulear coupling, the protons are split (J = 78.0 Hz). For the ^{15}N-labeling 2-quinoxalinol imines (**3ae-^{15}N**), the peaks marked "b" correspondng to the proton on the carbon of the imine group are split by ^{15}N (J = 3.0 Hz) (spectra IV), whereas it is still a single peak in spectra III. At the same time, in the spectra III and IV, the peak (δ=4.66 ppm) disappear. Therefore, it is obvious to conclude that the final structure of 2-quinoxalinol imines is **3ae**.

The reason as to why the 6-amino group has a higher reactivity than the 7-amino group can be explained based on

TABLE 1. Calculation Results of Intermediate 1



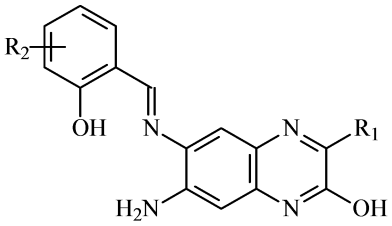
Intermediate	R_1	Charge of 6-nitrogen (δ_6)	Charge of 7-nitrogen (δ_7)	$\geq\delta_{6-7}$
1a		-0.857	-0.831	0.026
1b		-0.856	-0.831	0.025
1c		-0.861	-0.839	0.022
1d		-0.848	-0.817	0.039
1e	H	-0.852	-0.823	0.029

either a kinetic or a thermodynamic argument. In the kinetic explanation, the 2-quinoxalinol ring is an aromatic system, and the 2-hydroxyl group is an electron-donor group that increases the electron density of the carbon contacting the 6-amino group, thus making the 6-amino group more reactive than the 7-amino group (an α-nucleophile effect). This effect is evident in the ^{1}H NMR of intermediate **1** (Figure 1). There is a substantial difference between the chemical shift of hydrogen on 6- and 7-amino groups ($\Delta\delta = 0.81$ ppm, as identified in the labeling study). The two amino groups are in the same benzene ring, the upfield hydrogen of the 6-amino group must have more electron density, and, therefore, the 6-amino group is more reactive than the 7-amino group downfield.

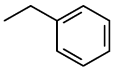
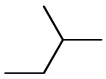
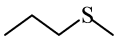
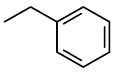
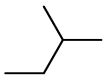
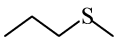
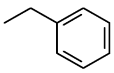
This can be confirmed by computational results. The density functional theory method B3LYP/6-31G(d) was used to characterize intermediate **1** and 2-quinoxalinol imines (**3a**) and ground states under vacuum with Gaussian 03.[21] Calculations with B3LYP/6-31G(d) were used for geometry optimizations and the calculation of vibrational frequencies, which confirmed all stationary points as minima and provided thermodynamic corrections. The effect of methanol was approximated by subsequent single-point calculations, using the conductor-like polarizable continuum model (CPCM).[22] The default Gaussian 03 dielectric constant of 32.63 was used for methanol. Partial charges for the intermediate (**1**) and 2-quinoxalinol imines (**3a**) were obtained by using CHELPG method.[23] The calculation results show that the 6-nitrogen in each case has more negative charge than the 7-nitrogen (Table 1). Therefore, the 6-amino group of 2-qunioxalinol should be more reactive than the 7-amino group.

Finally, for a justification based on thermodynamics, the minimized energy of three pair of 2-quinoxalinol imines isomers (**3ad** and **3bd**, **3af** and **3bf**, and **3ai** and **3bi**) has been calculated with the same method (vida supra) in the model of gas and methanol. The minimized energies of **3ad**, **3af**, and **3ai** are

TABLE 2. Formation of 2-Quinoxalinol Imines (3ax)



3a

Product	R_1	R_2	Yield (%)
3aa		3-*tert*-butyl	93.8[a]
3ab		3-*tert*-butyl	70.2[a]
3ac		3-*tert*-butyl	71.5[a]
3ad		3-*tert*-butyl	65.5[a]
3ae		3,5-Di-*tert*-butyl	76.7[a]
3af		3,5-Di-*tert*-butyl	66.0[a]
3ag		3,5-Di-*tert*-butyl	89.2[a]
3ah		3,5-Di-*tert*-butyl	80.0[a]
3ai		3-OH	68.5[a]
3aj	H	3-*tert*-butyl	-[b]
3ak	H	3,5-Di-*tert*-butyl	-[b]

[a] This is a one-step yield purified by column separation. [b] The major byproducts are **3aj-1** and **3ak-1**.

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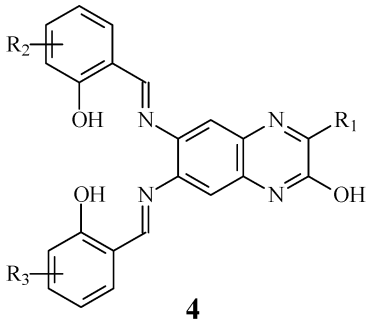
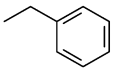
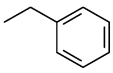
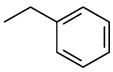
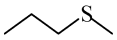
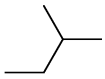
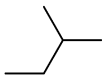
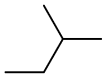
TABLE 3. Formation of Asymmetrically Substituted 2-Quinoxalinol Salen Ligands (4)



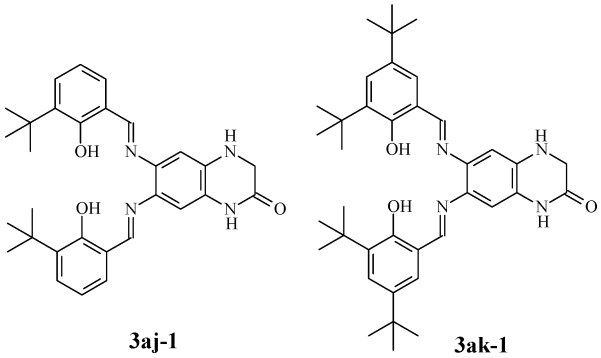
4

Product	R_1	R_2	R_3	Yield (%)[a]
4a		3-*tert*-butyl	3,5-Di-*tert*-butyl	49.1
4b		3-*tert*-butyl	H	60.5
4c		3,5-Di-*tert*-butyl	3-*tert*-butyl	41.0
4d		3-*tert*-butyl	3,5-Di-*tert*-butyl	54.2
4e		3-*tert*-butyl	H	63.0
4f		3,5-Di-*tert*-butyl	3-*tert*-butyl	44.7
4g		3-*tert*-butyl	3,5-Di-*tert*-butyl	50.0
4h		3-*tert*-butyl	H	68.5
4i		3,5-Di-*tert*-butyl	3-*tert*-butyl	38.5
4j		3-*tert*-butyl	3,5-Di-*tert*-butyl	50.5
4k		3-*tert*-butyl	H	66.4
4l		3,5-Di-*tert*-butyl	3-*tert*-butyl	43.7

[a] The yield is a two-step yield, that is, the yield from starting material **1** to final product **4.**

0.869, 0.931, and 0.954 kcal/mol lower in the gas model and 0.800, 0.889, and 1.061 kcal/mol lower in the MeOH model than their respective isomers (**3bd**, **3bf**, and **3bi**). Therefore, from the thermodynamic view, **3ad**, **3af**, and **3ai** are more stable than their isomers.

The synthetic method for the preparation of 2-quinoxalinol imines (**3a**) begins with the addition of 1.0 equiv of the intermediate (**1**) dissolved in 4 mL of methanol to a solution of 1.2 equiv of substituted salicylaldehyde (**2**) in 6 mL of methanol. The two are combined with stirring, and after heating at refluxing temperature for 1 h, the reaction mixture becomes deep yellow or red. Stirring at refluxing temperature was continued for 14 h, and monitored by TLC. Once it is observed that the reaction mixture no longer contains starting material (**1**), the reaction is stopped by allowing the mixture to cool to room temperature. Pure 2-quinoxalinol imines (**3a**) are obtained by flash column chromatography, using hexane:ethyl acetate (3:1) as eluent. According to this method, eight different 2-quinoxalinol imines (**3aa**−**ah**) were prepared (Table 2). The yield of final products ranges from 65% to 94%. When R_1 is a hydrogen atom, this diamino-2-quinoxalinol (**1e**) is not stable and was found to decompose on exposure to air. Because of this, it was directly used for the following reaction with 1.2 equiv of salicylaldehyde under nitrogen gas protection without purification after the reduction reaction. In fact, it is the undehydrogenating diamino-2-quinoxalinol **1H** that directly reacts with salicylaldehyde derivatives. The major byproducts are **3aj-1** (11.0%) and **3ak-1** (10.0%). The expected products **3aj** and **3ak**



3aj-1 **3ak-1**

may not be obtained. For sample **3ai**, a modified procedure was used. After heating to reflux temperature for 4 h, a red precipitate (**3ai**) forms. The red solid was filtered off and washed with 95% ethanol followed by acetone resulting in the pure final 2-quinoxalinol imine (**3ai**). Unlike the previous reactions, prolonging the reaction time did not increase the yield of product (**3ai**). Other salicylaldehyde derivatives with different functional groups in the 3 position were tried, but the expected final 2-quinoxalinol imines (e.g., **3a**) were not obtained. In contrast, in some cases, low yields of the symmetric 2-quinoxalinol salens were obtained. Presumably due to steric hindrance, we found that primarily when the 3 position has a bulky group such as the *tert*-butyl group, the 2-quinoxalinol imines (**3a**) were formed as the major products. The **3ai** is a special case, but when another intermediate (**1**) with a different group R_1 reacted with 2,3-dihydroxysalicylaldehyde, the expected products are not formed. These results demonstrate that the 2-quinoxalinol aromatic system and 3 position bulky group of salicylaldehyde are necessary to the regioselective effect. All of the final products were identified and characterized by ^{1}H NMR, ^{13}C NMR, MS, HR-MS, and IR. It is worth mentioning that in all cases mentioned above, the R_1 groups are electron-donor groups or the neutral H. In the case of reactions with an electron-withdrawing group on R_1, such as with a trifluoromethyl group, the resultant diamino-2-quinoxalinol is very unstable, and its 2-quinoxalinol imine was not obtained.

On the basis of these experiments, nine 2-quinoxalinol imines (**3aa**−**ai**) and twelve asymmetrically substituted 2-quinoxalinol salens (**4a**−***l***) were obtained (Table 3). The procedure for the synthesis of these asymmetrically substituted 2-quinoxalinol salens is unique and can be done in one pot. According to the general procedure of synthesis of 2-quinoxalinol imines **3a**, when the imines are formed without additional purification, a second substituted salicylaldehyde **2′** was directly added into the methanol reaction solution. The reaction mixture was allowed to heat to reflux temperature for another 14 h, and in the end, a precipitate forms. The end product can be filtered and washed with 95% ethanol and acetone 5 times each. The precipitates were directly identified by NMR and MS. The purities of the precipitates are very high. All of synthesized salens (**4a**−***l***) are of low solubility in water, hexane, methanol, or ethanol. When R_3 is H, these ligands are very soluble in DMSO or DMF, but not in DCM or $CHCl_3$, whereas other salens are, in contrast, soluble in DCM or $CHCl_3$, but of low solubility in DMSO.

Combinations of different R_1, R_2, and R_3 groups were tested. Altering the R_1 group does not appear to affect the reactivity of the 6,7-amino group. When intermediate **3a** is reacted with the first salicylaldehyde **2** containing the R_2 group 3-*tert*-butyl, R_3 of the second salicylaldehyde **2′** added could be H or 3,5-di-*tert*-butyl and the yields of these asymmetrically substituted 2-qunioxalinol salens (**4a**, **4b**, **4d**, **4e**, **4g**, **4h**, **4j**, and **4k**) are 50.0−70.0%, whereas when R_3 is a hydroxyl group, there is no expected product; however, when R_2 is 3,5-di-*tert*-butyl, there is only one combination that has a good yield of the asymmetrically substituted 2-qunioxalinol salens, that is, R_3 = 3-*tert*-butyl, and the yield is a bit lower (∼45%). The reason why these combinations can form and other combinations cannot form asymmetrically substituted 2-qunioxalinol salens is not entirely clear yet, but presumably it is due to steric hindrance in the transition state. This will be the subject of further investigations.

Conclusion

We have identified the exact structure of 2-quinoxalinol imines using isotope ^{15}N labeled compounds. Based on this, we have successfully developed a series of new compounds, the 2-quinoxalinol imines, and we have used these to generate a series of asymmetrically substituted 2-quinoxalinol salens. With the imine functional group in these compounds, we will continue with the development of artificial amino acids and labeled peptides, as well as secondary amine products for screening for bioactivity. With the asymmetrical 2-quinoxalinol salen ligands in hand, we will prepare metal complexes to identify their chiral character and develop complexes as potential new chiral catalysts. We also hope to be able to use the method used to prepare the asymmetrically substituted ligands in the preparation of ligands that can be mounted on solid phase supports. Finally, we will prepare new metal complexes and characterize their solid-state structures using X-ray diffraction for comparison with symmetrical salens.

Experimental Section

All amino acid methyl esters, DFDNB (1, 5-difluoro-2,4-dinitrobenzene), HCl (37%), ammonium hydroxide (5.0 N), and palladium on carbon (wet, 5%) were purchased and used as received. ^{15}N-Labeled ammonium hydroxide was purchased from Cambridge Isotope laboratories, Inc. All melting points were recorded, and the values were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 250 MHz NMR spectrometer (operated at 250 and 62.5 MHz, respectively) or 400 MHz spectrometer (operated at 400 and 100 MHz, respectively). Which instrument was used and when is indicated in the data provided. Chemical shifts are reported as δ values (ppm). NMR data were collected by using DMSO-d_6. D_2O/water exchange experiments were run in some experiments. The solvents used are indicted in the experimental details. Reaction progress was monitored by thin-layer chromatography (TLC), using 0.25 mm silica gel precoated plates with visualization by irradiation with a UV lamp. HRMS data were collected with electrospray ionization mass spectrometry or direct probe ionization. IR spectroscopic data were collected with use of KBr solid samples. Samples for melting point, IR, and NMR were purified by flash column chromatography. Calculations were run with Gaussian 03.

General Procedure: 3aa−ai. The synthesis of 2-quinoxalinol imine (**3a**) begins with the addition of 1.0 equiv of the intermediate 2-quinoxalinol (**1**) dissolved in 4 mL of methanol to a solution of 1.2 equiv of substituted salicylaldehyde derivatives (**2**) in 6 mL of methanol. The two are combined with stirring for 14 h, monitored by TLC. Once starting material (**1**) can no longer be seen by TLC, the reaction is considered complete. Pure 2-quinoxalinol imines (**3a**) are obtained by purification, using flash column chromatography with a solution of hexane:ethyl acetate (3:1) as eluent. For sample **3ai**, a modified procedure was used. The product begins to form as a red solid (**3ai**) after heating at refluxing temperature for 4 h. The red solid was filtered off and washed with 95% ethanol followed by acetone to obtain pure final 2-quinoxalinol imines (**3ai**).

4a−i. This procedure is the same as that for preparing the 2-quinoxalinol imine; however, when the starting material (**1**) can no longer be observed with TLC, a second salicylaldehyde derivative **2′** can be added directly to the reaction mixture. The mixture was then allowed to heat at refluxing temperature for an additional 14 h resulting in a large quantity of precipitates. These precipitates were isolated by filtering, and then washed with 95% ethanol and acetone 5 times each. The pure products were identified and characterized by NMR, IR, MS, and HRMS.

Experimental Data: 3aa: ^{1}H NMR (400 MHz DMSO-d_6) δ 1.44 (s, 9H), 4.04 (s, 2H), 5.84 (br s, 2H), 6.59 (s, 1H), 6.80 (s, 1H), 6.59−7.74 (m, 9H), 8.98 (s, 1H), 12.15 (br s, 1H), 13.58 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.4, 164.0, 159.8, 155.5, 154.2 145.6, 138.8, 136.8, 133.4, 132.3, 132.2, 132.0, 131.8, 130.4, 129.5, 129.2, 128.7, 126.6, 125.0, 120.0, 119.0, 117.1, 97.7, 40.0, 35.0, 30.0. Formula: $C_{26}H_{26}N_4O_2$. MS (M + H): 426.0. HRMS: found 426.2051, calcd 426.2056. IR: 3470.0 (br s), 3375.4 (br s), 3182.6, 2956.9, 2927.9 cm^{-1}, 2870.1, 1728.2, 1656.9, 1624.1, 1271.1 cm^{-1}. Melting point: 196.0−199.0 °C.

3ab: ^{1}H NMR (400 MHz DMSO-d_6) δ 1.20 (d, J = 6.8, 6H), 1.44 (s, 9H), 3.61 (sept, 1H), 5.77 (br s, 2H), 6.60 (s, 1H), 6.94 (t, 1H), 7.38 (d, 1H), 7.53 (d, 1H), 7.55 (s, 1H), 9.03 (s, 1H), 12.07 (br s, 1H), 13.64 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.8, 163.8, 159.8, 159.6, 155.1, 145.3, 136.8, 133.1, 132.1, 131.8, 130.4, 124.8, 120.1, 119.0, 117.7, 97.8, 35.0, 29.9, 20.8, 14.6. Formula: $C_{22}H_{26}N_4O_2$. MS (M + H): 378.0. HRMS: found 378.2052, calcd 378.2056. IR: 3442.9 (br s), 3402.4 (br s), 2958.8, 2872.0, 1710.9, 1651.1, 1626.0, 1502.6, 1234.4 cm^{-1}. Melting point: 250.0−253.0 °C (color changed).

3ac: ^{1}H NMR (250 MHz DMSO-d_6): δ 0.93 (d, J = 6.6, 6H), 1.43 (s, 9H), 2.19 (m, 1H), 2.58 (d, 2H), 5.77 (br s, 2H), 6.59 (s, 1H), 6.93 (t, 1H), 7.37(d, 1H), 7.52 (d, 1H), 7.55 (s, 1H), 8.99 (s, 1H), 12.06 (br s, 1H), 13.62 (br s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 163.8, 159.8, 155.8, 155.2, 145.3, 136.8, 133.2, 132.1, 131.7, 130.4, 125.0, 120.3, 119.0, 117.6, 97.8, 41.7, 34.9, 29.7, 26.8, 23.1. Formula: $C_{23}H_{28}N_4O_2$. MS (M + H): 392.0. HRMS: found 392.2206, calcd 392.2212. IR: 3392.8 (br s), 2954.9, 2924.1, 2866.2, 1710.0, 1626.0, 1600.9, 1371.4, 1232.5 cm^{-1}. Melting point: >300.0 °C.

3ad: ^{1}H NMR (250 MHz DMSO-d_6): δ 1.43 (s, 9H), 2.09 (s, 3H), 2.86 (t, 2H), 2.97 (t, 2H), 5.82 (br s, 2H), 6.59 (s, 1H), 6.93 (t, 1H), 7.37 (d, 1H) 7.51 (d, 1H), 7.53 (s, 1H), 12.11 (br s, 1H), 13.59 (br s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 163.9, 159.8, 155.5, 153.9, 145.5, 136.8, 133.3, 132.3, 131.8, 130.4, 125.0, 120.0, 119.0, 117.6, 97.8, 34.9, 32.8, 30.9, 29.7, 15.2. Formula: $C_{22}H_{26}N_4O_2S$. MS (M + H): 410.0. HRMS: found 410.1767, calcd 410.1776. IR: 3469.9 (br s), 3334.9 (br s), 2920.2, 2954.9, 2918.3, 2875.9, 1710.8, 1662.6, 1626.0, 1429.3, 1234.4 cm^{-1}. Melting point: 225.0−227.0 °C.

3ae: ^{1}H NMR (400 MHz DMSO-d_6): δ 1.31 (s, 9H), 1.44 (s, 9H), 4.05 (s, 2H), 5.81 (br s, 2H, D_2O exchangeable), 6.58 (s, 1H), 7.20−7.55 (m, 8H), 8.99 (s, 1H), 12.15 (br s, 1H, D_2O exchangeable), 13.32 (br s, 1H, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.2, 162.4, 160.5, 159.5, 145.7, 142.7, 141.4, 137.7, 137.5, 134.1, 133.0, 132.8, 131.8, 131.0, 130.6, 123.4, 121.8, 102.9, 40.0, 39.8, 38.9, 36.2, 34.2. Formula: $C_{30}H_{34}N_4O_2$. MS: 482.0. HRMS: found 482.2681, calcd 482.2682. IR: 3491.2 (br s), 3375.4, 2955.08, 2870.18, 2821.98, 1718.68, 1653.0, 1626.0, 1502.6, 1238.0 cm^{-1}. Melting point: 248.0−250.0 °C. **3ae-^{15}N:** ^{1}H NMR (400 MHz DMSO-d_6): δ 1.31 (s, 9H), 1.44 (s, 9H), 4.04 (s, 2H), 5.81 (br s, 2H, D_2O exchangeable), 6.58 (s, 1H), 7.21−7.55 (m, 8H), 8.98 (d, 1H), 12.14 (br s, 1H, D_2O exchangeable), 13.32 (br s, 1H, D_2O exchangeable).

3af: ^{1}H NMR (400 MHz DMSO-d_6): δ 1.18 (d, 6H), 1.26 (s, 9H), 1.28 (s, 9H), 4.00 (sept, 1H), 5.67 (br s, 2H), 6.59 (s, 1H), 7.40 (s, 1H), 7.54 (s, 1H), 7.58 (s, 1H), 9.04 (s, 1H), 12.06 (br s, 1H), 13.36 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 159.6, 157.5, 155.1, 145.2, 140.7, 136.0, 133.0, 132.3, 128.2, 127.4, 124.8, 119.4, 117.6, 97.7, 35.1, 34.4, 31.8, 29.8, 20.8, 14.6. Formula: $C_{26}H_{34}N_4O_2$. MS (M + H): 434. HRMS: found 434.2675, calcd 434.2682. IR: 3489.2 (br s), 3387.0, 2958.88, 2910.68, 2870.18, 2819.98, 1739.88, 1651.1, 1620.2, 1502.6, 1240.1 cm^{-1}. Melting point: 275.0−276.0 °C (color changed).

3ag: ^{1}H NMR (400 MHz DMSO-d_6): δ 0.94 (d, 6H), 1.32 (s, 9H), 1.44 (s, 9H), 2.20 (m, 1H), 2.59 (d, 2H), 5.76 (br s, 2H), 6.59 (s, 1H), 7.40 (s, 1H), 7.54 (s, 1H), 7.57 (s, 1H), 9.01 (s, 1H), 12.06 (br s, 1H), 13.36 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.4, 157.5, 155.8, 155.0, 145.3, 140.7, 136.0, 133.0, 132.4, 128.2, 127.5, 125.0, 119.4, 117.6, 97.7, 41.7, 35.1, 34.4, 31.8, 29.8, 26.7, 23.1. Formula: $C_{27}H_{36}N_4O_2$. MS (M + H): 448.0. HRMS: found 448.2839, calcd 448.2838. IR: 3489.2 (br s), 3400.5 (br s), 2955.0, 2866.2, 2818.0, 1653.0, 1626.0, 1500.6, 1234.4 cm^{-1}. Melting point: >300.0 °C.

3ah: ^{1}H NMR (250 MHz DMSO-d_6): δ 1.31 (s, 9H), 1.44 (s, 9H), 2.11 (s, 2H), 2.83 (t, 2H), 2.96 (t, 2H), 5.80 (br s, 2H), 6.59 (s, 1H), 7.40 (s, 1H), 7.56 (s, 1H), 7.70 (s, 1H), 8.99 (s, 1H), 12.12 (br s, 1H), 13.33 (br s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 164.5, 157.5, 155.5, 153.8, 145.4, 140.7, 136.1, 133.2, 132.5, 128.2, 127.5, 125.0, 119.4, 117.6, 97.6, 35.1, 34.4, 32.8, 31.8, 30.8, 29.8, 15.2. Formula: $C_{26}H_{34}N_4O_2S$. MS (M + H): 467. HRMS: found 467.2475, calcd 467.2480. IR: 3473.8 (br s), 3333.0 (br s), 2956.8, 2912.5, 2870.1, 1711.08, 1662.6, 1626.0, 1500.6, 1234.5 cm^{-1}. Melting point: 239.5−240.5 °C.

3ai: ^{1}H NMR (400 MHz DMSO-d_6): δ 4.04 (s, 2H), 5.87 (br s, 2H, D_2O exchangeable), 6.57 (s, 1H), 6.78−7.34 (m, 8H), 7.49 (s, 1H), 8.94 (s, 1H), 9.26 (br s, 1H, D_2O exchangeable), 12.13 (br s, 1H, D_2O exchangeable), 12.47 (br s, 1H, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.6, 155.5, 154.0, 149.0, 146.0, 145.8, 138.8, 133.4, 132.8, 129.5, 128.7, 126.6, 124.9, 122.9, 120.8, 119.3, 119.2, 117.4, 97.5, 39.0. Formula: $C_{22}H_{18}N_4O_3$. MS (M + H): 387.0. HRMS: found 387.1452, calcd 387.1457. IR: 3489.2 (br s), 3429.4 (br s), 3394.7 (br s), 2941.4, 2877.8, 2818.0, 1656.8,

1626.0, 1500.6, 1465.9, 1275.0, 1236.4 cm^{-1}. Melting point: 260.0−261.0 °C.

3aj-1: ^1H NMR (400 MHz $CDCl_3$ and DMSO-d_6): δ 1.40 (s, 9H), 1.41(s, 9H), 3.87 (s, 2H), 4.04 (t, 1H), 6.37−7.50 (m, 8H), 8.78 (s, 1H), 8.84 (s, 1H), 10.49 (br s, 1H), 14.09 (br s, 1H), 14.16 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 166.0, 163.8, 161.2, 160.3, 160.0, 137.9, 137.0, 136.9, 135.7, 132.6, 131.6, 131.2, 130.0, 126.7, 119.7, 118.8, 105.5, 103.7, 60.2, 34.9, 29.7. Formula: $C_{30}H_{34}N_4O_3$. MS (M): 498.3. HRMS: found 498.2628, calcd 498.2631. IR: 3386.9 (br s), 2955.8, 2877.8, 2818.0, 1680.2, 1609.6, 1519.4, 1430.6, 1303.4, 1143.5 cm^{-1}. Melting point: 255.0−256.0 °C (color changed).

3ak-1: ^1H NMR (400 MHz $CDCl_3$ and DMSO-d_6): δ 1.35 (s, 18H), 1.47 (s, 18H), 4.10 (s, 2H), 4.11 (t, 3H), 6.60 (s, 1H), 6.79 (s, 1H), 7.20−7.47 (m, 4H), 8.63 (s, 1H), 8.67 (s, 1H), 9.38 (br s, 1H), 13.55 (br s, 1H), 13.64 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 169.7, 163.2, 146.4, 145.3, 141.7, 133.1, 132.0, 123.1, 39.8, 38.9, 36.3, 34.2. Formula: $C_{38}H_{50}N_4O_3$. MS (M): 610.4. HRMS: found 610.3883, calcd 610.3891. IR: 3489.2 (br s), 3379.4 (br s), 3232.1 (br s), 2957.0, 2871.0, 2869.0, 1709.1, 1686.0, 1614.6, 1515.0, 1297.5, 1250.5 cm^{-1}. Melting point: 250.0−251.0 °C (color changed).

4a: ^1H NMR (400 MHz DMSO-d_6): δ 1.31 (s, 9H), 1.36 (s, 9H), 1.42 (s, 9H), 4.18 (s, 2H), 6.90−7.56 (m, 11H), 7.97 (s, 1H), 8.94 (s, 1H), 9.13 (s, 1H), 13.49 (br s, 1H, D_2O exchangeable), 14.01 (br s, 1H, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 164.9, 160.4, 158.4, 145.0, 140.7, 138.2, 137.8, 137.2, 136.7, 131.7, 130.6, 129.6, 128.6, 128.1, 126.7, 119.6, 118.6, 118.3, 35.1, 34.9, 34.3, 31.7, 29.7, 29.6, 25.7. Formula: $C_{41}H_{46}N_4O_3$. MS (M^+): 642.0. HRMS: found 642.3559, calcd 642.3570. IR: 3437.2 (br s), 3423.7 (br s), 2955.4, 2910.6, 2870.1, 1658.8, 1610.6, 1577.8, 1431.2.9, 1392.6.0, 1195.9, 1168.9 cm^{-1}. Melting point: 251.0−253.0 °C.

4b: ^1H NMR (400 MHz DMSO-d_6): δ 1.38 (s, 9H), 4.17 (s, 2H), 6.88−7.88 (m, 13H), 7.96 (s, 1H), 8.90 (s, 1H), 9.11 (s, 1H), 12.12 (br s, 2H), 14.46 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.7, 164.2, 160.8, 160.5, 155.0, 146.2, 137.9, 137.3, 137.1, 134.4, 132.2, 132.0, 131.7, 131.1, 130.6, 129.7, 128.9, 126.9, 120.5, 119.7, 119.6, 118.7, 118.0, 117.0, 105.7. Formula: $C_{33}H_{30}N_4O_3$. MS (M^+): 387.0. HRMS: found 530.2320, calcd 530.2318. IR: 3425.6 (br s), 3147.8 (br s), 3394.7 (br s), 2920.2, 2864.3, 2785.2, 1660.7, 1608.6, 1483.3, 1384.9, 1201.7, 1147.7 cm^{-1}. Melting point: 239.0−241.0 °C.

4c: ^1H NMR (400 MHz $CDCl_3$ and DMSO-d_6): δ 1.30 (s, 9H), 1.37 (s, 9H), 1.40 (s, 9H) 4.17 (s, 2H), 6.89−7.89 (m, 11H), 7.91 (s, 1H), 8.86 (s, 1H), 9.07 (s, 1H), 12.53 (br s, 1H), 13.65 (br s, 1H), 13.68 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 166.8, 166.7, 165.7, 160.7, 160.6, 160.4, 158.1, 154.9, 151.7, 144.6, 140.5, 138.4, 137.7, 137.2, 137.0, 136.3, 132.1, 131.8, 131.5, 131.2, 129.6, 128.7, 128.1, 127.9, 126.7, 119.6, 119.3, 118.9, 118.3, 105.9, 35.0, 34.9, 34.3, 31.9, 31.7, 29.6. Formula: $C_{41}H_{46}N_4O_3$. MS (M^+): 642.0. HRMS: found 642.3583, calcd 642.3570. IR: 3373.5 (br s), 2956.9, 2924.1, 2866.2, 1654.9, 1602.9, 1275.0, 1488.8, 1203.9, 1174.7 cm^{-1}. Melting point: 260.0−262.0 °C.

4d: ^1H NMR (400 MHz $CDCl_3$ and DMSO-d_6): δ 1.17 (s, 9H), 1.25 (s, 9H), 1.29 (s, 9H), 2.04 (s, 3H), 2.87 (t, 2H), 3.08 (t, 2H), 6.70−7.54 (m, 7H), 8.52 (s, 1H), 8.61 (s, 1H), 12.13 (br s, 1H), 13.15 (br s, 1H), 13.50 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 165.8, 165.5, 164.2, 160.7, 159.9, 159.8, 158.5, 158.2, 155.3, 144.9, 144.6, 140.5, 140.4, 138.9, 138.6, 137.7, 137.0, 136.9, 131.5, 131.4, 131.2, 130.8, 128.7, 128.1, 127.0, 126.8, 118.8, 118.2, 105.6, 35.0, 34.8, 34.1, 33.1, 30.6, 29.3, 29.2, 15.4. Formula: $C_{37}H_{46}N_4O_3S$. MS (M^+): 626.0. HRMS: found 626.3279, calcd 626.3291. IR: 3421.7 (br s), 2953.0 (br s), 2914.4 (br s), 2862.4, 1656.9, 1610.6, 1577.8, 1431.2, 1313.5, 1267.2 cm^{-1}. Melting point: 244.0−245.0 °C (color changed).

4e: ^1H NMR (400 MHz DMSO-d_6): δ 1.38 (s, 9H), 2.15 (s, 3H), 2.94 (t, 2H), 3.13 (t, 2H), 6.89−7.99 (m, 9H), 8.92 (s, 1H), 9.13 (s, 1H), 11.99 (br s, 1H), 12.49 (br s, 1H), 14.47 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 164.1, 160.8, 160.5, 154.8, 146.0, 137.3, 137.1, 134.4, 132.1, 132.0, 131.7, 131.0, 130.6, 120.5, 119.7, 119.6, 118.7, 118.0, 117.0, 105.7, 34.9, 33.2, 30.5, 29.6, 15.2. Formula: $C_{29}H_{30}N_4O_3S$. MS (M^+): 514.0. HRMS: found 514.2039, calcd 514.2039. IR: 3419.8 (br s), 2914.4, 2864.3, 2787.1, 1658.8, 1608.6, 1483.3, 1392.6, 1207.4, 1143.8 cm^{-1}. Melting point: 229.0−230.0 °C (color changed).

4f: ^1H NMR (400 MHz $CDCl_3$ and DMSO-d_6): δ 0.92 (s, 9H), 1.01 (s, 9H), 1.04 (s, 9H), 1.80 (s, 3H), 2.62 (t, 2H), 2.82 (t, 2H), 6.46−7.31 (m, 7H), 8.28 (s, 1H), 8.40 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 170.4, 170.3, 169.1, 168.6, 165.5, 165.3, 164.9, 163.0, 149.4, 149.3, 145.3, 143.7, 143.4, 142.5, 141.7, 138.9, 136.9, 136.4, 136.2, 135.9, 135.5, 135.3, 133.0, 131.8, 123.9, 123.7, 123.1, 122.7, 39.6, 39.0, 38.0, 37.9, 36.2, 35.4, 34.1, 34.0, 20.2. Formula: $C_{37}H_{46}N_4O_3S$. MS (M^+): 626.0. HRMS: found 626.3277, calcd 626.3291. IR: 3466.1 (br s), 3329.1 (br s), 2955.0, 2899.0, 2873.9, 1662.6, 1618.3, 1492.9.6, 1427.3, 1236.4, 1205.5, 1172.7 cm^{-1}. Melting point: 240.0−241.0 °C (color changed).

4g: ^1H NMR (400 MHz $CDCl_3$ and DMSO-d_6): δ 0.92 (d, 6H), 1.22 (s, 9H), 1.30 (s, 9H), 1.32 (s, 9H), 2.24 (m, 1H), 2.69 (d, 2H), 6.74−7.58 (m, 7H), 8.58 (s, 1H), 8.66 (s, 1H). 13.23 (br s, 1H), 13.41(br s, 1H), 13.56 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 165.0, 164.0, 163.0, 160.5, 158.6, 155.7, 144.7, 144.5, 140.5, 138.6, 137.7, 137.6, 137.1, 131.4, 131.1, 130.9, 130.7, 130.5, 128.7, 127.1, 119.1, 118.9, 118.3, 118.1, 117.8, 105.6, 42.1, 35.0, 34.8, 34.1, 31.4, 29.4, 29.3, 26.7, 22.7. Formula: $C_{38}H_{48}N_4O_3$. MS (M^+): 608.0. HRMS: found 608.3730, calcd 608.3726. IR: 3421.7 (br s), 2955.0 (br s), 2910.6 (br s), 2872.0, 1662.6, 1606.7, 1492.9, 1425.4, 1317.4, 1276.9, 1134.1, 1089.8 cm^{-1}. Melting point: 260.0−261.0 °C (color changed).

4h: ^1H NMR (250 MHz DMSO-d_6): δ 0.98 (d, 6H), 1.37 (s, 9H), 2.27 (m, 1H), 2.70 (d, 2H), 6.86−7.98 (m, 9H), 8.90 (s, 1H), 9.12 (s, 1H). 12.36 (br s, 1H), 14.01(br s, 1H), 14.48 (br s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 164.5, 164.1, 161.9, 161.6, 160.8, 160.5, 155.2, 145.8, 144.5, 137.9, 137.2, 137.1, 137.0, 134.3, 132.2, 132.0, 131.6, 131.4, 131.1, 130.7, 130.6, 120.5, 119.7, 119.6, 119.4, 119.1, 118.9, 118.6, 118.1, 117.9, 117.0, 105.8, 42.1, 34.9, 29.7, 26.6, 23.1. Formula: $C_{20}H_{32}N_4O_3$. MS (M^+): 496.0. HRMS: found 496.2472, calcd 496.2474. IR: 3435.2 (br s), 3423.7 (br s), 2953.0, 2916.4, 2868.2, 1656.9, 1610.6, 1473.6, 1431.2, 1392.6, 1276.8, 1193.9, 1143.8 cm^{-1}. Melting point: 271.0−273.0 °C (color changed).

4i: ^1H NMR (400 MHz $CDCl_3$ and DMSO-d_6): δ 0.91 (d, 6H), 1.22 (s, 9H), 1.28 (s, 9H), 1.32 (s, 9H), 2.23 (m, 1H), 2.69 (d, 2H), 6.73−7.58 (m, 7H), 8.58 (s, 1H), 8.66 (s, 1H). 13.22 (br s, 1H), 13.41(br s, 1H), 13.56 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 165.9, 165.2, 163.7, 161.8, 161.6, 160.7, 158.6, 155.7, 144.7, 144.4, 140.5, 138.6, 137.7, 137.6, 137.1, 131.4, 131.1, 131.0, 130.9, 130.7, 130.5, 128.7, 127.1, 119.1, 118.9, 118.3, 118.1, 117.7, 105.5, 42.1, 35.0, 34.8, 34.7, 31.4, 29.3, 29.2, 26.8, 22.7. Formula: $C_{38}H_{48}N_4O_3$. MS (M^+): 608.0. HRMS: found 608.3721, calcd 608.3726. IR: 3500.0 (br s), 2955.0 (br s), 2912.5 (br s), 2872.0, 1662.6, 1604.8, 1492.9, 1431.2, 1356.6, 1207.4, 1138.0 cm^{-1}. Melting point: 264.0−266.0 °C.

4j: ^1H NMR (400 MHz $CDCl_3$ and DMSO-d_6): δ 1.21 (d, 6H), 1.30 (s, 9H), 1.33 (s, 9H), 1.34 (s, 9H), 3.49 (m, 1H), 6.74−7.61 (m, 7H), 8.57 (s, 1H), 8.68 (s, 1H). 12.05 (br s, 1H), 13.22 (br s, 1H), 13.58 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 165.4, 163.5, 160.7, 160.5, 158.6, 158.1, 155.1, 144.7, 144.4, 140.5, 138.5, 137.8, 137.6, 137.1, 131.5, 131.3, 131.0, 130.9, 130.7, 130.4, 128.7, 127.1, 119.1, 118.9, 118.3, 118.2, 118.1, 117.9, 105.4, 35.0, 34.8, 34.1, 31.4, 30.3, 29.4, 29.3, 20.2. Formula: $C_{37}H_{46}N_4O_3$. MS (M^+): 594.0. HRMS: found 594.3566, calcd 594.3570. IR: 3415.9 (br s), 3138.2 (br s), 2955.0, 2872.0, 2792.9, 1664.6, 1606.7, 1489.1, 1479.4, 1211.3, 1184.3 cm^{-1}. Melting point: 269.0−271.0 °C.

4k: ^1H NMR (400 MHz $CDCl_3$ and DMSO-d_6): δ 1.27 (d, 6H), 1.38 (s, 9H), 3.51 (m, 1H), 6.89−7.99 (m, 9H), 8.91 (s, 1H), 9.16 (s, 1H). 12.06 (br s, 1H), 12.43 (br s, 1H), 14.52 (br s, 1H). ^{13}C

NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 164.6, 164.1, 161.0, 160.9, 160.6, 160.5, 154.6, 145.9, 137.2, 137.1, 134.4, 133.1, 132.0, 131.7, 131.0, 130.6, 120.6, 120.1, 119.7, 119.6, 119.5, 118.7, 118.1, 117.9, 117.2, 117.0, 105.6, 34.9, 30.4, 29.6, 20.6. Formula: $C_{29}H_{30}N_4O_3$. MS (M^+): 482.0. HRMS: found 482.2313, calcd 482.2318. IR: 3448.7 (br s), 3145.9 (br s), 2958.8, 2870.1, 2794.9, 1658.8, 1610.6, 1481.3, 1384.9, 1207.4, 1147.7 cm^{-1}. Melting point: 265.0−267.0 °C.

4*l*: ^1H NMR (400 MHz $CDCl_3$ and DMSO-d_6): δ 1.19−1.30 (m, 33H), 3.47 (m, 1H), 6.72−7.59 (m, 7H), 8.57 (s, 1H), 8.67 (s, 1H). 12.02 (br s, 1H), 13.35 (br s, 1H), 13.43 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 166.0, 165.4, 164.2, 160.7, 158.3, 155.0, 144.3, 140.4, 138.8, 137.7, 136.9, 131.5, 131.1, 131.0, 130.8, 128.1, 126.9, 118.9, 118.3, 118.2, 117.9, 105.5, 34.9, 34.7, 34.1, 31.3, 30.3, 29.3, 29.2, 20.1. Formula: $C_{37}H_{46}N_4O_3$. MS (M^+): 594.0. HRMS: found 594.3572, calcd 594.3570. IR: 3417.9 (br s), 3142.0 (br s), 2956.9, 2877.8, 2868.2, 1656.9, 1606.7, 1469.8, 1433.1, 1209.4, 1172.7 cm^{-1}. Melting point: 258.0−260.0 °C.

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Supporting Information Available: Full experimental and characterization data for all new compounds as reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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