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Synthesis of *N*-Pyridin-2-ylmethyl and *N*-Quinolin-2-ylmethyl Substituted Ethane-1,2-diamines

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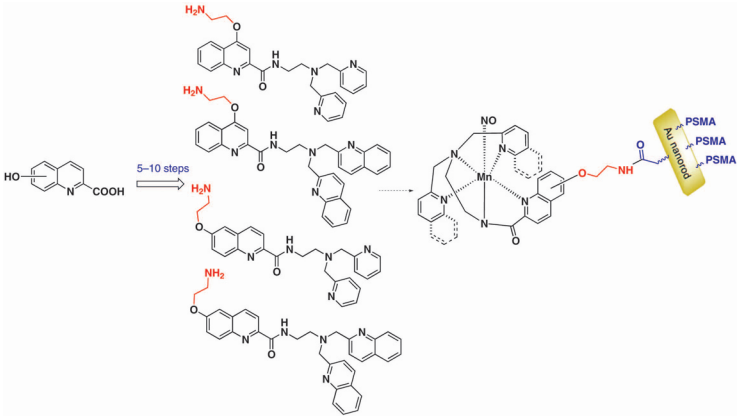

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Abstract Two *N*-(2-(bis(pyridin-2-ylmethyl)amino)ethyl)quinoline-2-carboxamides and two *N*-(2-(bis(quinolin-2-ylmethyl)amino)ethyl)quinoline-2-carboxamides have been synthesized. These structures contain five nitrogen atoms that can form coordinate bonds with metal ions such as Mn(II) and Fe(II). An additional coordinating bond can be formed between the metal ion and a neutral molecule of nitric oxide (NO). The resultant complexes are potentially useful agents for targeted delivery of NO to *in vivo* biological sites such as tumors, where the NO is released upon irradiation with long-wavelength light. Initial work involving the synthesis and characterization of these analogues is reported here.

Keywords ligands, nitric oxide, donor, pyridine-2-ylmethyl, quinolin-2-ylmethyl

Nitric oxide (NO) is an endogenously produced signaling molecule that is released into the endothelial cells by the action of nitric oxide synthases (NOSs). It plays important roles in a variety of physiological functions.[1–7] At low concentrations, NO plays its normal physiological roles as an anti-inflammatory, neurological signaling, and vasodilative agent. At high concentrations, NO is pro-inflammatory and pro-apoptotic.[8] Thus, agents that can enhance the NO concentrations at tumor sites could be used as anticancer therapeutics.[9–11] Recent studies have shown that NO can reverse prostate cancer resistance to chemotherapy and radiotherapy, increase tumor response to anticancer drugs, and promote cancer cell death.[12–17] NO can prohibit prostate cancer cells from entering interstitial tissue and inhibit cancer cell invasion and transmission.[18,19] Many NO delivery compounds, both organic and inorganic, have been explored as suitable NO donors.[20–22] NO has been mostly studied in the cardiovascular system and many organic nitrates, such as diazeniumdiolates, *S*-nitrosothiols, or hybrids of these, have been developed for application to various cardiovascular diseases.[21] These compounds are usually bioactivated *in vivo* by enzymes to release NO. The more recent discovery of the anticancer activities of NO has increased the interest in developing NO donors that can be delivered into the tumor tissue and release NO by light stimulus and used for photodynamic therapy (PDT) of cancer.[23,24] Metal nitrosyls have been demonstrated to release NO effectively upon illumination with low-frequency light.[25,26] One compound with the structure of *N*,*N*-bis(2-pyridylmethyl)amine-*N*-ethyl-2-pyridine-2-carboxamide ($PaPy_3H$) has been identified as an effective complexing agent for several metal ions, such as Mn(II), Mn(III), Fe(III), and Ru(III).[27–29] On replacing the pyridyl-2-carboxamide moiety in $PaPy_3H$ with a quinolyl-carboxamide structure, the resultant compound, *N*,*N*-bis(2-pyridylmethyl)amine-*N*-ethyl-2-quinoline-2-carboxamide ($PaPy_2QH$), has a significant redshift on forming the manganese nitrosyl complex due to additional conjugation (Figure 1). This complex can readily release NO upon illumination by near-infrared (NIR) light of low intensity (<5 mW, 780 nm).[29] A similar redshift was also observed for 1,2-bis(quinaldine-2-carboxamido)-4,5-dimethylbenzene (H_2Me_2bqb), in which a pyridine-2-carboxylic acid moiety was replaced with a quinolyl-2-carboxic acid group.[26,30]

In an effort to develop effective NO donors for the treatment of prostate cancer, we selected ($PaPy_2QH$) as the base structure and added moieties that can enable incorporation onto carboxylic group-containing gold-nanoparticles whose surfaces would be further modified with prostate-specific membrane antigens (PSMA-a10) for targeted delivery. Additionally, more conjugational moieties could be added to increase the redshift of the manganese nitrosyl complexes. These NO-Mn(II)-ligand-Au-PSMA nanoparticles could be delivered to the prostate tumor sites with high

specificity and thus minimize toxicity in other tissues. Herein, we report the synthesis and characterization of these compounds; their biological evaluation is ongoing and results will be reported elsewhere.

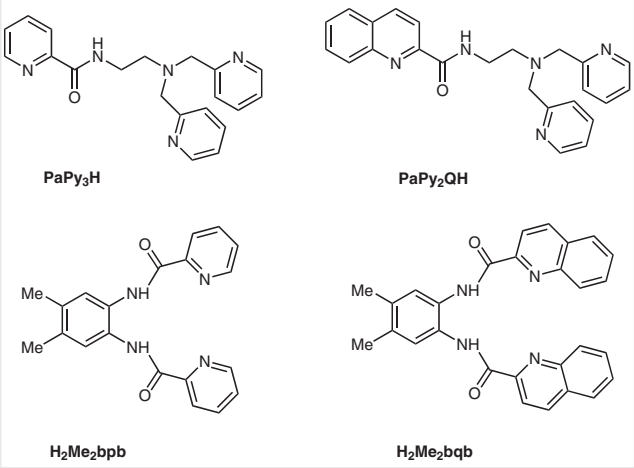


Figure 1 Representative structures of some metal ion nitrosyl ligands

$PaPy_2QH$ has been reported to be an effective manganese nitrosyl chelator and was used as the lead structure for our design studies. In order for the ligand to be attached to carboxyl groups on the surface of nanoparticles, an aminoethoxy group was selected, attached to the quinoline ring at either the 4- or 6-position due to the availability of the corresponding starting materials. In addition, a *N*,*N*-bis(2-quinolylmethyl)amino moiety was used to replace the *N*,*N*-bis(2-pyridylmethyl)amino group with the goal of inducing a redshift in the resultant compound UV absorption. We designed four $PaPy_3H$ derivatives (Figure 2). These analogues can form amide bonds with carboxyl groups and therefore can be incorporated onto gold-nanoparticles whose surfaces will be further modified with prostate-specific membrane antigens (PSMA-a10) after forming complexes with manganese(II) and NO (Scheme 1). According to the published results for $PaPy_2QH$, compounds **11**, **18**, **12**, and **19** formed complexes with Mn(II)-NO likely release NO by NIR light at or above 780 nm wavelength illumination.[29]

The chemistry used for the preparation of the 6-aminoethoxy substituted quinoline-2-carboxamide analogues is shown in Scheme 1. Both **11** and **12** were synthesized in 10 steps from the starting material 6-methoxyquinoline. N-Oxidation of the 6-methoxyquinoline with *m*-chloroperbenzoic acid (*m*CPBA) gave **2**, which was treated with trimethylsilyl cyanide to afford **3**, followed with hydrolysis with concentrated hydrochloride to give **4** in excellent yield, according to reported procedures.[31,32] Demethylation of **4** with boron tribromide resulted in a low yield and impurities. Treatment of **4** with either aluminum trichloride (refluxing in 1,2-dichloroethane) or sodium dodecane-1-thiolate (up to 140 °C) did not give any desired product.[33] Finally, HBr (48%) was used for this reaction and the demethylated product **5** was successfully obtained in good yield.[34] Analogue **5** was esterified in methanol to give methyl ester **6** and subsequently reacted with BOC-aminoethylbromide to afford intermediate **7**, which was then treated with excess ethylenediamine to form **8**. It should be noted that 20 mole equivalents of ethylenediamine are required for the conversion of **7** into **8** in order to avoid the formation of the double amidation product. It is also interesting to note that when *N*-(2-bromoethyl)phthalimide, instead of BOC-aminoethylbromide, was used to react with **6**, methyl 6-(phthalimidoethoxy)quinoline-2-carboxylate was obtained in excellent yield. However, when the 6-phthalimidoethoxy intermediate was used to react with ethylenediamine, a significant amount of impurity (more polar then

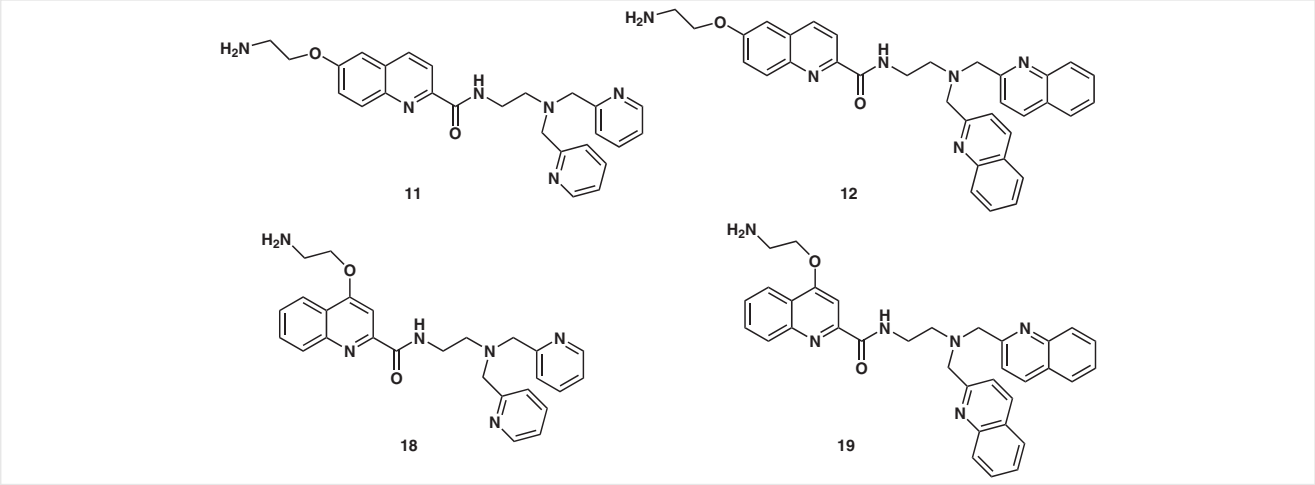
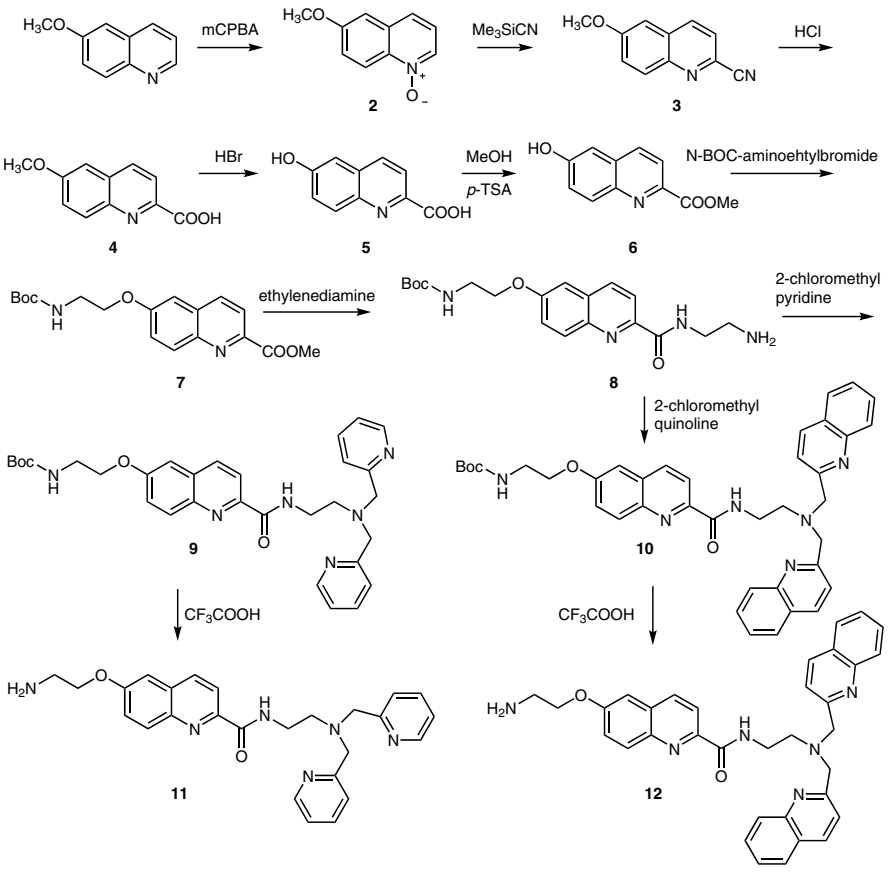


Figure 2 Structures of the newly designed manganese nitrosyl ligands with an aminoethoxy link that is to attach to a carboxylic group on the gold nanoparticles

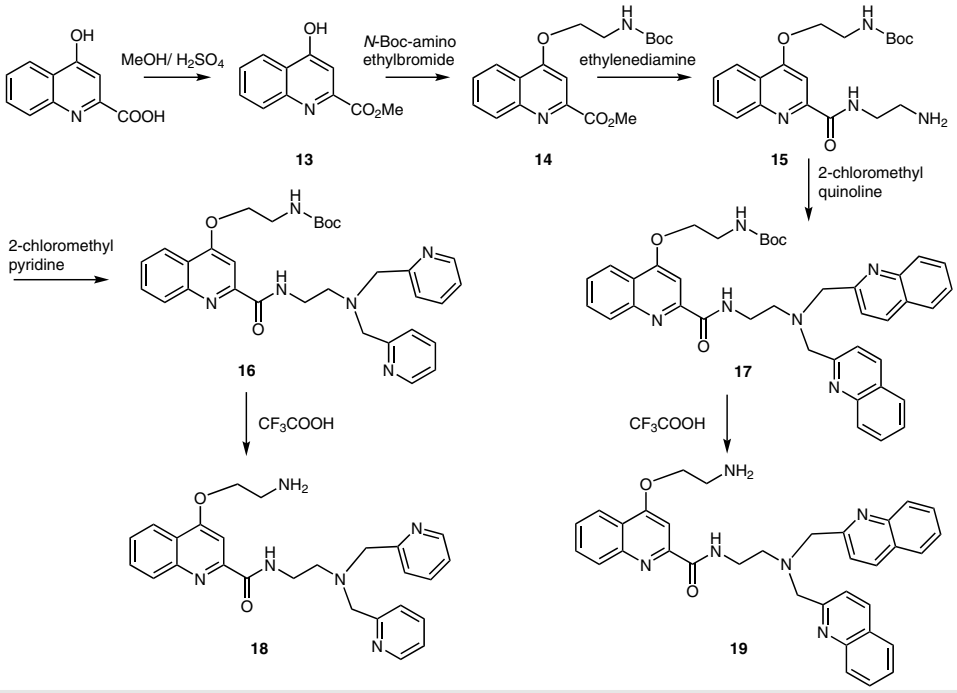
the expected product) was formed. This is likely due to the cleavage of the phthalimido moiety by ethylenediamine. Reaction of **8** with 2-chloromethylpyridine or 2-chloromethylquinoline gave intermediates **9** and **10**, respectively. A 10% excess of 2-chloromethylpyridine or 2-chloromethylquinoline for this reaction was desirable to get the best yields and to avoid the formation of quaternary ammonium by-product. Treatment of **9** and **10** with trifluoroacetic acid afforded the desired products **11** and **12**, respectively, in high yields.

The 4-aminoethoxy substituted analogues **18** and **19** were synthesized by using very similar chemistry, as shown in Scheme 2. Both were synthesized in five steps from the starting material 4-hydroxyquinaldic acid, by sequential esterification to give **13**, etherification with BOC-aminoethylbromide to give **14**, amidation with ethylenediamine to give **15**, and reaction either with 2-chloromethylpyridine to give **16** or with 2-chloromethylquinoline to give **17**. Finally, treatment of **16** and **17** with trifluoroacetic acid afforded the desired products **18** and **19**, respectively, in good overall yields.

The UV absorbance and fluorescence excitation and emission intensities of these analogues were measured. The spectroscopic wavelengths corresponding to the maximum intensities were recorded and the corresponding absorbance and fluorescence intensity measurements are shown in the Supporting Information (Table S1, Figures S1–6). Analogues **10**, **12**, **17**, and **19** showed the highest intensities in UV absorbance (Figures S1 and S2), likely due to the presence of two additional quinolinyl moieties compared to analogues **9**, **11**, **16**, and **18** that have two pyridinyl substituents. When the analogues were illuminated at their corresponding UV maximum absorbance wavelengths, most of them displayed high fluorescence intensities, with the exception of **16** and **17** (Figure S3 and S4). It is surprising that **18** and **19** displayed extremely high fluorescence intensities and had well over 1000 a.u. (arbitrary units) at both 0.1 µM (Figure S4) and 0.01 µM (data not shown) and still showed close to 200 a.u. even at 0.001 µM (data not shown). The analogues were further illuminated at the corresponding excitation wavelengths as shown in Table S1. Most compounds displayed high fluorescence emission intensities, with the exception of **16** and **17** (Figures S5 and S6). The same phenomenon was observed for **18** and **19**, which displayed ex-



Scheme 1 Synthesis of 6-aminoethoxy substituted analogues



Scheme 2 Synthesis of 4-aminoethoxy substituted analogues

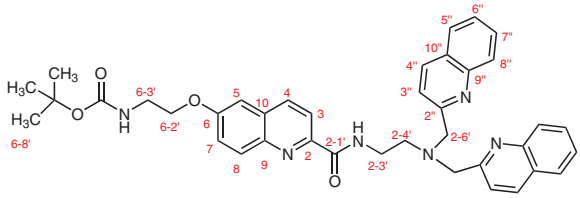
tremely high fluorescence intensities (Figure S6). The exact reasons for both the low and high fluorescence intensities for these analogues are not clear. Compounds **18** and **19** might be useful as fluorescent ligands for various imaging purposes and thus are worthy of further investigations.

The final products and the novel intermediates were characterized by both ^{1}H NMR and ^{13}C NMR spectroscopy. The assignments of resonances in the ^{1}H NMR spectra in the low-frequency region were relatively straightforward, but became difficult in the aromatic proton region with multiple aromatic moieties within the same molecule, such as in analogues **9**–**12** and **16**–**19**. On the other hand, their ^{13}C NMR spectra displayed well-defined patterns. Based on distortionless enhancement by polarization transfer (DEPT) spectroscopy, many of the C-13 resonance peaks could be assigned to their corresponding carbon atoms (Table 1). According to the DEPT ^{13}C NMR spectra, we could readily assign resonances at ~67–71 ppm to the 4- or 6-substituted (C4-2′ or C6-2′) -OCH_2- carbon atoms, ~53 ppm to the OCH_3 methyl ester carbon atom (analogues **7** and **14**), ~37–40 ppm to the -CH_2-NHBOC carbon atoms (C4-3′ or C6-3′), ~27.7–28.7 ppm to the three CH_3 (C4-8′ or C6-8′) of the BOC group, and ~60–61 ppm to the methylene carbon atom (C2-6′) of N(CH_2-pyr or -qui)$_2$, the latter due to its apparently high intensity. Resonances at ~53.1–53.6 ppm could be assigned to the -CH_2-N(heteroarylmethyl)$_2$ carbon atom (C2-4′), with the exception of **8** and **15**, which do not have bisheteroarylmethyl substituents, and ~40–41 ppm to the methylene carbon atom (C2-3′) of CO-NH-CH_2- structure, with the exception of analogue **18** (45.66 ppm due to deshielding effect of the two pyridine moieties). The exact assignments between C2-3′ and C4-3′ or between C2-3′ and C6-3′ were not obvious. Based on the significant downfield shifts of C2-4′ (as well as C2-6′), it is logical to assign the lower field signals to the C2-3′ due to the deshielding effect of three nearby aromatic substituents.

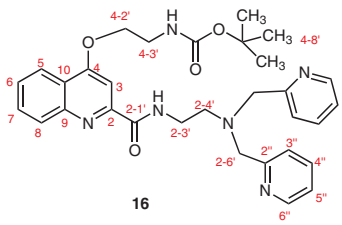
By comparing the ^{13}C spectrum of **11** to that of **9** and the spectrum of **12** to that of **10**, we can conveniently assign the resonances at ~164.3 ppm to the carbonyl carbon atom (C2-1′), ~158.3 ppm to C-2, ~148.2 ppm to C-6, ~142.4 ppm to C-9, and ~130.7 ppm to C-10 based on the presence (regular ^{13}C NMR) or absence (DEPT ^{13}C NMR) of the corresponding signals as well as the electron density of the substituted quinoline moiety. Due to the bispyridin-2-ylmethyl or bisquinolin-2-ylmethyl substitution, the signals of the corresponding pyridine or quinoline moieties displayed nearly double intensities and thus could be readily assigned to the corresponding carbon atoms. Thus, we assigned resonances at 159.76 ppm to C-2″, ~123.0 ppm to C-3″, ~136.7 ppm to C-4″, ~122.5 ppm to C-5″, ~149.2 ppm to C-6″ for the pyridine-2-methyl substituted analogues (**9** and **11**) based on the electron density of the substituted pyridine moiety. By the same reasoning, we could assign the C-13 signals for analogues **10** and **12**; that is, resonances at ~160.7 ppm to C-2″, ~121.5 ppm to C-3″, ~136.6 ppm to C-4″, ~126.6 ppm to C-5″, ~128.2 ppm to C-6″, ~129.0 ppm to C-7″, ~129.8 ppm to C-8″, ~147.4 ppm to C-9″, and ~127.4 ppm to C-10″. Finally, the remaining resonance signals for C-3, -4, -5, -7,

and -8 were not clearly defined due to the substituents' effect at the 2- and 6-positions (analogues **7**–**12**). Based on both the estimated electronic effect of substituents and the electron density of the quinoline moiety, we assigned resonances at ~124 ppm to C-3, ~136.5–136.8 ppm to C-4, ~106.6–106.9 ppm to C-5, ~119.3 ppm to C-7, and ~131 ppm to C-8. Similarly, the C-13 resonance signals for analogues **16**–**19** were assigned and are summarized in Table 1.

Table 1 Assignment of ^{13}C NMR Spectra of Compounds **7**–**12** and **14**–**19**[a]



10



16

	7	8	9	10	11	12	14	15	16	17	18	19
C-2					158.30	158.31					152.05	162.88
C-3	124.06	123.81	123.97	124.01	124.09	124.10	101.17	98.81	95.50	98.63	95.47	98.70
C-4	136.50	136.74	136.75	136.83	136.78	136.80					151.11	152.15
C-5	106.61	106.82	106.85	106.90	106.78	106.81	122.58	122.67	122.35	122.76	122.31	122.55
C-6					148.20	148.21	128.10	127.36	124.91	127.39	125.51	127.50
C-7	121.63	119.43	119.30	119.29	119.27	119.25	129.93	129.28	129.71	129.23	129.70	129.30
C-8	131.81	131.10	131.02	131.06	131.00	131.03	131.32	131.18	130.29	131.31	130.20	131.26
C-9					142.40	142.42					147.47	147.66
C-10					130.72	130.76					119.61	121.87
C6-2′	67.50	67.43	67.48	67.49	71.29	71.25						
C6-3′	39.79	40.82	37.20	37.21	37.20	37.22						
C6-8′	28.66	28.67	28.66	28.69								
C4-2′							68.61	68.17	61.51	68.47	59.19	71.86
C4-3′							39.60	39.61	37.06	37.34	37.06	37.34
C4-8′							28.68	28.69	27.71	28.69		
C2-1′					164.31	164.32					165.01	164.19
C2-3′	52.89	40.88	39.87	39.86	41.33	41.31	53.03	42.15	41.92	39.61	45.66	41.21
C2-4′		39.81	53.17	53.61	53.19	53.63		41.37	53.17	53.49	53.21	53.52
C2-6′			59.97	61.03	59.98	61.04			59.96	61.06	59.97	61.07
C-2″					159.76	160.69					159.77	160.68
C-3″			123.05	121.48	123.06	121.49			123.06	121.51	123.07	121.51
C-4″			136.75	136.62	136.78	136.63			136.80	136.64	136.81	136.64
C-5″			122.50	126.56	122.53	126.58			122.52	126.56	122.54	126.57
C-6″			149.19	128.17	149.20	128.18			149.19	128.15	149.20	128.17
C-7″				129.02		129.01				129.02		129.02
C-8″				129.83		129.84				129.83		129.84
C-9″						147.40						147.39
C-10″						127.39						127.38

[a] The atom labeling of the analogues is illustrated by analogues **10** and **16** with the 4- or 6-substituted quinoline-2-carbonyl as the parent structure, 2-, 4-, or 6-substituents being labeled by 2-n′, 4-n′ or 6-n′, respectively, and the secondary aromatic substituent (on the N) being labeled by C-n″.

In conclusion, we have synthesized four $PaPy_2QH$ derivatives in an attempt to develop ligands that could be used as metal ion nitrosyl complexes for application in prostate cancer treatment. In the first stage of this work, we characterized the final unchelated ligands as well as all the novel intermediates and conducted preliminary spectroscopic studies on the ligands. Most of these compounds displayed excellent fluorescence intensities, with the exception of **16** and **17**, which showed low fluorescence excitation and emission intensities. On the other hand, both **18** and **19** showed extremely high excitation and emission intensities, even at very low concentration, making them potentially useful as imaging agents in biological systems and therefore worthy of further investigation. Based on previous studies by several groups, the formation of manganese complexes may significantly enhance their spectroscopic intensity and cause a redshift of their maximum absorption. In the next stage, work will focus on the biological conjugation and *in vitro* and *in vivo* measurements.

All reactions were carried out in oven-dried glassware under a N_2 atmosphere, unless otherwise stated. All reagents or solvents purchased commercially were used directly without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) on silica gel F254 glass plates and visualized under UV light (254 and 365 nm). Temperatures were recorded using a regular thermometer without correction. Flash column chromatography was performed on silica gel (200–300 mesh). Melting points were measured using the capillary method without correction. ^{1}H NMR spectra were recorded with a Bruker Avance III 400 MHz NMR spectrometer at r.t. Chemical shifts were recorded as parts per million (ppm) downfield to tetramethylsilane (TMS). The following abbreviations are used for multiplicity of NMR signals and descriptions: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; dt, double triplet; dq, double quartet; br. broad; pyr, pyridine moiety; qui, quinoline moiety; N-sub pyr, N-substituted pyridine-2-methyl moiety; N-sub qui, N-substituted quinoline-2 methyl moiety. ^{13}C NMR or DEPT- ^{13}C-NMR) spectra were recorded with a Bruker Avance III 400 MHz NMR spectrometer (100 MHz).

6-Hydroxyquinoline-2-carboxylic Acid (5)

6-Hydroxyquinoline-2-carboxylic acid was prepared as described by Sarmiento et al.[31] To a 50 mL reaction bottle was added 6-methoxyquinoline (1.00 g, 6.28 mmol) and 1,2-dichloroethane (10 mL), the mixture stirred until it became a clear solution and then 85% 3-chlorobenzoperoxoic acid (7.53 mmol) in 1,2-dichloroethane (10 mL) was added dropwise. The mixture was stirred at 40 °C for 12 h and then transferred to a separatory funnel, washed with 10% Na_2SO_3, 10% K_2CO_3 and saturated brine, and dried over sodium sulfate. The solid was filtered off, solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography, eluting with EtOAc/MeOH (30:1) to give **2** as a white solid (0.91 g, 82.7% yield, 98.5% purity); mp 106–107 °C (lit.[35] 102–104 °C).

To a 50 mL reaction bottle was added **2** (0.25 g, 1.43 mmol), 1,2-dichloroethane (10 mL), trimethylsilyl cyanide (0.16 g, 1.57 mmol), and dimethylcarbamic chloride (0.15 g, 1.43 mmol). The solution was stirred at 60 °C for 3 h, cooled to r.t., poured into 10% aqueous sodium carbonate, extracted and washed with saturated brine, and dried over sodium sulfate. After filtering, the solvent was removed and the crude product was recrystallized from EtOAc to give **3** as a pale-yellow solid (0.22 g, 84.6% yield, 98.7% purity); mp 174–176 °C (lit.[36] 175–176 °C). ^{1}H NMR (DMSO-d_6): δ = 8.49–8.51 (d, 1 H), 8.02–8.04 (d, 1 H), 7.96–7.98 (d, 1 H), 7.55–7.58 (dd, 1 H), 7.51–7.52 (d, 1 H), 3.95 (s, 3 H).

A solution of **3** (1.50 g, 8.14 mmol) in concentrated hydrochloric acid (20 mL) was heated to reflux for 4 h. The mixture was cooled to r.t. and the yellow solid was filtered, washed with water, and recrystallized from EtOAc to give 6-methoxyquinoline-2 carboxylic acid **4** as a white solid (1.46 g, 88.5% yield, 97.3% purity); mp 183–185 °C; ESI-MS: m/z $[M + 1]^+$ calcd for $C_{11}H_9NO_3$: 203.20; found: 204.06.

A solution of **4** (1.00 g, 4.90 mmol) in 48% HBr (20 mL) was heated to reflux for 4 h. The mixture was cooled to r.t. and the solid was filtered and recrystallized from EtOH to give 6-hydroxyquinoline-2-carboxylic acid **5** as a white solid (0.70 g, 84.3% yield, 98.2% purity). ^{1}H NMR (DMSO-d_6): δ = 10.41 (s, 1 H), 8.29–8.31 (d, 1 H), 7.99–8.02 (m, 2 H), 7.41–7.44 (dd, 1 H), 7.22–7.23 (d, 1 H); ESI-MS: m/z $[M + 1]^+$ calcd. for $C_{10}H_7NO_3$: 189.17; found: 190.03.

6-Hydroxyquinoline-2-carboxylic Acid Methyl Ester (6)

A solution of **5** (5.00 g, 26.43 mmol) and *p*-toluenesulfonic acid monohydrate (0.10 g, 0.60 mmol) in MeOH (50 mL) was heated to reflux for 6 h. The mixture was concentrated in vacuo and the crude product was recrystallized from EtOAc to afford methyl 6-hydroxyquinoline-2-carboxylate **6** as a white solid (4.20 g, 76.3% yield, 98.8% purity); mp 196–197 °C. ^{1}H NMR (DMSO-d_6): δ = 10.46 (s, 1 H), 8.30–8.32 (d, 1 H), 7.99–8.03 (m, 2 H), 7.41–7.44 (dd, 1 H), 7.23–7.24 (d, 1 H), 3.93 (s, 3 H); ESI-MS: m/z $[M + 1]^+$ calcd. for $C_{11}H_9NO_3$: 203.20; found: 204.03; Anal. Calcd (%) for $C_{11}H_9NO_3$: C 65.02, H 4.46, N 6.89; found: C 64.88, H 4.37, N 6.74.

Methyl 6-{2-[(*tert*-Butoxycarbonyl)amino]ethoxy}quinoline-2-carboxylate (7)

N-Boc-aminoethylbromide was prepared according to a modified procedure reported by Chauhan et al.[37] A solution of di-*tert*-butyl dicarbonate (12.60 g, 57.73 mmol), triethylamine (10 mL) and EtOH (40 mL) was added dropwise to a solution of aminoethylbromide hydrochloride (10.00 g, 48.81 mmol) in EtOH (40 mL) at 0 °C under stirring. The mixture was stirred at r.t. overnight, then concentrated in vacuo, water (100 mL) was added, and the mixture extracted with EtOAc (2 × 100 mL). The combined extracts were washed with aq. ammonium, saturated brine, dried over sodium sulfate and filtered. The solvent was removed in vacuo to give *N*-Boc-aminoethylbromide as a colorless oil (10.5 g) that was used directly in the following reaction without further purification.

To a flask was added **6** (3.00 g, 14.76 mmol), DMF (25 mL), K_2CO_3 (8.30 g, 59.04 mmol), and N-Boc-aminoethylbromide (6.70 g, 29.52 mmol). The mixture was stirred at 80 °C for 5 h, then cooled to r.t. and poured into water, extracted with EtOAc (3 × 100 mL), washed with saturated brine, and dried over sodium sulfate. After filtering and removal of solvent, the crude product was purified by silica gel chromatography eluting with petroleum ether/EtOAc (1:3) to afford 6-{2-[(*tert*-butoxycarbonyl)amino]ethoxy}quinoline-2-carboxylic acid methyl ester **7** as a white solid (4.6 g, 86.8% yield, 98.5 % purity); mp113–114 °C. ^{1}H NMR (DMSO-d_6): δ = 8.40–8.42 (d, 1 H), 8.05–8.09 (m, 2 H), 7.48–7.50 (m, 2 H), 7.10–7.13 (t, 1 H), 4.13–4.16 (t, 2 H), 3.94 (s, 3 H), 3.39–3.42 (t, 2 H), 1.39 (s, 9 H). DEPT-^{13}C (DMSO-d_6): δ = 136.50, 131.81, 124.06, 121.63, 106.61, 67.50 (-O-*C*H$_2$-CH$_2$-NH-), 52.89 (O*C*H$_3$), 39.79 (-NH-CH$_2$-*C*H$_2$-O-), 28.66 (-C(*C*H$_3$)$_3$); ESI-MS: m/z $[M + 1]^+$ calcd for $C_{18}H_{22}N_2O_5$: 346.38; found: 347.16. Anal. Calcd (%) for $C_{18}H_{22}N_2O_5$: C 62.42, H 6.40, N 8.09; found: C 62.35, H 6.28, N 7.91.

6-(2-(*tert*-Butoxycarbonyl)aminoethoxy)-*N*-(2-aminoethyl)quinoline-2-carboxamide (8)

A solution of **7** (0.92 g, 2.66 mmol), ethylenediamine (3.20 g, 53.20 mmol), and MeOH (20 mL) was stirred at r.t. for 7 h. The mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (50 mL), washed with water (3 × 50 mL), dried over anhydrous sodium sulfate, filtered and solvent removed in vacuo. The crude product was purified by silica gel chromatography, eluting with chloroform/methanol (20:1) to give **8** as a pale-yellow solid (0.88 g, 88% yield, 97% purity); mp 120–121 °C. ^{1}H NMR (DMSO-d_6): δ = 8.87–8.90 (t, 1 H), 8.39–8.41 (d, 1 H), 8.10–8.12 (d, 1 H), 8.01–8.04 (m, 1 H), 7.48–7.50 (m, 2 H), 7.10–7.13 (t, 1 H), 4.12–4.15 (t, 2 H), 3.41–3.44 (m, 6 H), 2.80–2.83 (t, 2 H), 1.39 (s, 9 H). DEPT-^{13}C (DMSO-d_6): δ = 136.74, 131.10, 123.81, 119.13, 106.82, 67.43 (-O-CH_2-CH_2-NH-), 40.88 (-NH-CH_2-CH_2-NH_2), 40.82 (-NH-CH_2-CH_2-O-), 39.81 (-NH-CH_2-CH_2-NH_2), 28.67 (-C(CH_3)$_3$); ESI-MS: *m*/*z* [M + 2]$^+$ calcd for $C_{19}H_{26}N_4O_4$: 374.44; found: 376.20; Anal. Calcd (%) for $C_{19}H_{26}N_4O_4$: C 60.95, H 7.00, N 14.96; found: C 61.03, H 6.87, N 14.84.

6-[2-(*tert*-Butoxycarbonyl)aminoethoxy]-*N*-(2-{[di(pyridin-2-yl)methyl]amino}ethyl)quinoline-2-carboxamide (9)

A solution of **8** (0.61 g, 1.63 mmol), EtOH (10 mL), 10 M NaOH (0.65 mL, 6.52 mmol), and 2-chloromethylpyridine hydrochloride (0.59 g, 3.60 mmol) was stirred at 70 °C for 4 h. The mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (50 mL), washed with saturated brine, dried over anhydrous sodium sulfate and filtered. After removal of solvent, the crude product was purified by silica gel chromatography, eluting with chloroform/methanol (20:1) to afford **9** as a colorless semi-solid (0.77 g, 85% yield, 97.7% purity), ^{1}H NMR (DMSO-d_6): δ = 8.95–8.97 (t, 1 H), 8.47–8.48 (d, 2 H), 8.41–8.43 (d, 1 H), 8.07–8.09 (d, 1 H), 8.04–8.06 (d, 1 H), 7.50–7.60 (m, 6 H), 7.18–7.21 (m, 2 H), 7.10–7.13 (m, 1 H), 4.14–4.17 (t, 2 H), 3.85 (s, 4 H), 3.51–3.54 (m, 2 H), 3.40–3.43 (t, 2 H), 2.73–2.76 (t, 2 H), 1.39 (s, 9 H). DEPT-^{13}C (DMSO-d_6): δ = 149.19 (2Cs, N-sub pyr), 136.75 (2Cs of N-sub pyr + 1C of qui), 131.02 (1C, qui), 123.97 (1C, qui), 123.05 (2Cs, N-sub pyr), 122.50 (2Cs, N-sub pyr), 119.30 (1C, qui), 106.85 (1C, qui), 67.48 (-O-CH_2-CH_2-NH-), 59.97 (-N(CH_2–2-pyr)$_2$), 53.17 (-NH-CH_2-CH_2-N(CH_2–2-pyr)$_2$), 39.87 (-NH-CH_2-CH_2-N(CH_2–2-pyr)$_2$), 37.20 (-NH-CH_2-CH_2-O-), 28.66 (-C(CH_3)$_3$); ESI-MS: *m*/*z* [M + 2]$^+$ calcd for $C_{31}H_{36}N_6O_4$: 556.67; found: 558.28; Anal. Calcd (%) for $C_{31}H_{36}N_6O_4$: C 66.89, H 6.52, N 15.10; found: C 66.74, H 6.36, N 14.89.

6-[2-(*tert*-Butoxycarbonyl)aminoethoxy]-*N*-(2-{[di(quinolin-2-yl)methyl]amino}ethyl)quinoline-2-carboxamide (10)

A solution of **8** (4.50 g, 12.02 mmol) in EtOH (40 mL), 10 M NaOH (5 mL, 48.08 mmol), and 2-chloromethylquinoline hydrochloride (5.66 g, 26.44 mmol) was stirred at 70 °C for 5 h. The mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (100 mL), washed with brine, dried over anhydrous sodium sulfate and filtered. After removal of solvent, the crude product was recrystallized from EtOAc to afford **10** as a white solid (6.87 g, 87.0% yield, 98% purity); mp 145–146 °C. ^{1}H NMR (DMSO-d_6): δ = 8.92–8.94 (t, 1 H), 8.40–8.42 (d, 1 H), 8.11–8.13 (d, 2 H), 8.01–8.06 (m, 2 H), 7.95–7.97 (m, 2 H), 7.80–7.86 (m, 4 H), 7.67–7.70 (m, 2 H), 7.51–7.57 (m, 4 H), 7.11–7.13 (m, 1 H), 4.16–4.19 (t, 2 H), 4.06 (s, 4 H), 3.54–3.57 (t, 2 H), 3.40–3.44 (m, 2 H), 2.83–2.86 (t, 2 H), 1.39 (s, 9 H). DEPT-^{13}C (DMSO-d_6): δ = 136.83 (1C, qui), 136.62 (2Cs, N-sub qui), 131.06 (1C, qui), 129.83 (2Cs, N-sub qui), 129.02 (2Cs, N-sub qui), 128.17 (2Cs, N-sub qui), 126.56 (2Cs, N-sub qui), 124.01 (1C, qui), 121.18 (2Cs, N-sub qui), 119.29 (1C, qui), 106.90 (1C, qui), 67.49 (-O-CH_2-CH_2-NH-), 61.03 (-NH-CH_2-CH_2-N(CH_2–2-qui)$_2$), 53.61 (-NH-CH_2-CH_2-N(CH_2–2-qui)$_2$), 39.86 (-NH-CH_2-CH_2-N(CH_2–2-qui)$_2$), 37.21 (-NH-CH_2-CH_2-O-), 28.69 (-C(CH_3)$_3$); ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{39}H_{40}N_6O_4$: 656.79; found: 657.30. Anal. Calcd (%) for $C_{39}H_{40}N_6O_4$: C 71.32, H 6.14, N 12.80; found: C 70.07, H 5.92, N 12.73.

6-(2-Aminoethoxy)-*N*-(2-{[di(pyridin-2-yl)methyl]amino}ethyl)quinoline-2-carboxamide (11)

A solution of **9** (2.00 g, 3.60 mmol), dichloromethane (5 mL), and trifluoroacetic acid (6 mL, 34.28 mmol) was stirred at r.t. for 8 h. The mixture was concentrated in vacuo and the residue dissolved in dichloromethane (50 mL), washed with 2 M NaOH, saturated brine, dried over anhydrous sodium sulfate and filtered. After removal of solvent, the crude product was purified by silica gel chromatography, eluting with chloroform/methanol (20:1) to give **11** as a white solid (1.64 g, 92.0% yield, 98.2% purity); mp 65–66 °C. ^{1}H NMR (DMSO-d_6): δ = 8.96–8.98 (t, 1 H), 8.47–8.48 (d, 2 H), 8.41–8.43 (d, 1 H), 8.03–8.09 (m, 2 H), 7.55–7.60 (m, 5 H), 7.47–7.48 (d, 1 H), 7.18–7.21 (dd, 2 H), 4.10–4.12 (t, 2 H), 3.86 (s, 4 H), 3.50–3.55 (q, 2 H), 2.97–3.00 (t, 2 H), 2.74–2.77 (t, 2 H), 1.64 (b, 2 H). ^{13}C NMR (DMSO-d_6): δ = 164.31 (C=O), 159.76 (2Cs, N-sub pyr), 158.30 (1C, qui), 149.20 (2Cs, N-sub pyr), 148.20 (1C, qui), 142.40 (1C, qui), 136.78 (2Cs, N-sub pyr), 131.00 (1C, qui), 130.72 (1C, qui), 124.09 (1C, qui), 123.06 (2Cs, N-sub pyr), 122.53 (2Cs, N-sub pyr), 119.27 (1C, qui), 106.78 (1C, qui), 71.29 (-O-CH_2-CH_2-NH_2), 59.98 (-CH_2-N(CH_2-pyr)$_2$), 53.19 (-NH-CH_2-CH_2-N(CH_2-pyr)$_2$), 41.33 (-NH-CH_2-CH_2-N(CH_2-pyr)$_2$), 37.20 (-O-CH_2-CH_2-NH_2); ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{26}H_{28}N_6O_2$: 456.55; found: 457.22; Anal. Calcd (%) for $C_{26}H_{28}N_6O_2$: C 68.40, H 6.18, N 18.41; found: C 68.25, H 6.03, N 18.33.

6-(2-Aminoethoxy)-*N*-(2-((di(quinolin-2-yl)methyl)amino)ethyl)quinoline-2-carboxamide (12)

A solution of **10** (5.00 g, 7.61 mmol), dichloromethane (25 mL), and trifluoroacetic acid (12 mL, 68.56 mmol) was stirred at r.t. for 8 h. The mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (100 mL), washed with 2 M NaOH, saturated brine, dried over anhydrous sodium sulfate and filtered. After removal of solvent, the crude product was recrystallized from EtOAc to give **12** as a white solid (4.0 g, 95.0% yield, 98.0% purity); mp 155–156 °C. ^{1}H NMR ($CDCl_3$): δ = 8.86–8.88 (m, 1 H), 8.20–8.30 (m, 2 H), 8.01–8.04 (m, 3 H), 7.93–7.96 (m, 2 H), 7.83–7.86 (m, 2 H), 7.63–7.70 (m, 4 H), 7.45–7.53 (m, 3 H), 7.18–7.20 (m, 1 H), 4.18–4.21 (t, 2 H), 4.16 (s, 4 H), 3.70–3.71 (b, 2 H), 3.23–3.26 (m, 2 H), 3.00 (br, 2 H), 2.07 (br, 2 H). ^{13}C NMR (DMSO-d_6): δ = 164.32 (C=O), 160.69 (2Cs, N-sub qui), 158.31 (1C, qui), 148.21 (1C, qui), 147.40 (2Cs, N-sub qui), 142.42 (1C, qui), 136.80 (1C, qui), 136.63 (2Cs, N-sub qui), 131.03 (1C, qui), 130.76 (1C, qui), 129.84 (2Cs, N-sub qui), 129.01 (2Cs, N-sub qui), 128.18 (2Cs, N-sub qui), 127.39 (2Cs, N-sub qui), 126.58 (2Cs, N-sub qui), 124.10 (1C, qui), 121.49 (2Cs, N-sub qui), 119.25 (1C, qui), 106.81 (1C, qui), 71.25 (-O-CH_2-CH_2-NH_2), 61.04 (-CH_2-N(CH_2-qui)$_2$), 53.63 (-CH_2-N(CH_2-qui)$_2$), 41.31 (-NH-CH_2-CH_2-N(CH_2-qui)$_2$), 37.22 (-O-CH_2-CH_2-NH_2). ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{34}H_{32}N_6O_2$: 556.67; found: 557.24; Anal. Calcd (%) for $C_{34}H_{32}N_6O_2$ H_2O: C 71.06, H 5.96, N 14.62; found: C 69.92, H 5.83, N 14.53.

Methyl 4-Hydroxyquinoline-2-carboxylate (13)

A solution of 4-hydroxyquinoline-2-carboxylic acid (20.00 g, 96.54 mmol) and 2 drops of concentrated sulfuric acid in MeOH (50 mL) was heated at reflux for 12 h. The mixture was concentrated in vacuo, extracted with EtOAc, washed with saturated Na_2CO_3, saturated brine, dried over anhydrous sodium sulfate and filtered. The solvent was removed in vacuo and the crude product was recrystallized from EtOAc to afford **13** as a white solid (19.0 g, 93.0% yield, 98.1% purity); mp

221–222 °C. ^{1}H NMR (DMSO-d_6): δ = 8.11–8.13 (d, 1 H), 7.99–8.01 (d, 1 H), 7.74–7.78 (t, 1 H), 7.42–7.45 (t, 1 H), 6.76 (s, 1 H), 3.99 (s, 3 H); ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{11}H_9NO_3$: 203.20; found: 204.06.

Methyl 4-{2-[(*tert*-Butoxycarbonyl)amino]ethoxy}quinoline-2-carboxylate (14)

To a solution of **13** (10.00 g, 49.22 mmol) in DMF (50 mL) was added K_2CO_3 (27.00 g, 195.3 mmol) and *N*-Boc-aminoethylbromide (17.00 g, 75.86 mmol). The mixture was stirred at 80°C for 12 h and then cooled to r.t., poured into ice-water, extracted with EtOAc (3 × 100 mL), washed saturated brine and dried over anhydrous sodium sulfate. After filtration and removal of solvent, the crude product was recrystallized from EtOAc to afford **14** as a white solid (14.31 g, 84.0% yield, 98.9 % purity); mp 81–82 °C. ^{1}H NMR ($CDCl_3$): δ = 8.24–8.27 (m, 2 H), 7.77–7.81 (m, 1 H), 7.61–7.65 (m, 1 H), 7.58 (s, 1 H), 5.03 (br, 1 H), 4.35–4.38 (m, 2 H), 4.09 (s, 3 H), 3.74–3.76 (br, 2 H), 1.48 (s, 9 H). DEPT-^{13}C (DMSO-d_6): δ = 131.32, 129.93, 128.10, 122.58, 101.17, 68.61 (-O-CH_2-CH_2-NH-), 53.13 (OCH_3), 39.60 (-NH-CH_2-CH_2-O-), 28.68 (-C(CH_3)$_3$); ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{18}H_{22}N_2O_5$: 346.38; found: 347.17; Anal. Calcd (%) for $C_{18}H_{22}N_2O_5$: C 62.42, H 6.40, N 8.09; found: C 62.27, H 6.13, N 7.93.

4-[2-(*tert*-Butoxycarbonyl)aminoethoxy]-*N*-(2-aminoethyl)quinoline-2-carboxamide (15)

A solution of **14** (14.00 g, 40.42 mmol), ethylenediamine (48.60 g, 808.65 mmol), and MeOH (100 mL) was stirred at r.t. for 6 h. The mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (150 mL), washed with water (3 × 100 mL), saturated brine and dried over anhydrous sodium sulfate. After filtration and removal of solvent, the product was recrystallized from dichloromethane to give **15** as a white solid (14.60 g, 96.0% yield, 98.7% purity); mp 137–138 °C. ^{1}H NMR (DMSO-d_6): δ = 8.90–8.93 (t, 1 H), 8.30–8.32 (d, 1 H), 8.05–8.07 (d, 1 H), 7.82–7.86 (m, 1 H), 7.62–7.66 (m, 1 H), 7.55 (s, 1 H), 7.17–7.20 (t, 1 H), 4.29–4.32 (t, 2 H), 3.49–3.51 (m, 2 H), 3.36–3.41 (m, 2 H), 2.77–2.80 (t, 2 H), 1.39 (s, 9 H). DEPT-^{13}C (DMSO-d_6): δ = 131.18, 129.28, 127.36, 122.27, 98.81, 68.47 (-O-CH_2-CH_2-NH-), 42.15 (-NH-CH_2-CH_2-NH_2), 41.37 (-NH-CH_2-CH_2-NH_2), 39.61 (-NH-CH_2-CH_2-O-), 28.69 (-C(CH_3)$_3$); ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{19}H_{26}N_4O_4$: 375.44; found: 375.20; Anal. Calcd (%) for $C_{19}H_{26}N_4O_4$: C 60.95, H 7.00, N 14.96; found: C 60.72, H 6.86, N 14.74.

4-[2-(*tert*-Butoxycarbonyl)aminoethoxy]-*N*-(2-{[di(pyridin-2-yl)methyl]amino}ethyl)quinoline-2-carboxamide (16)

A solution of **15** (9.00 g, 24.04 mmol), water (40 mL), NaOH (3.80 g, 95.00 mmol), and 2-chloromethylpyridine hydrochloride (8.70 g, 53.04 mmol) was stirred at 70 °C for 6 h. The mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (100 mL), washed with saturated brine and dried over anhydrous sodium sulfate. After filtration and removal of the solvent, the crude product was purified by silica gel chromatography, eluting with chloroform/methanol (20:1) to afford **16** as a white solid (10.0 g, 74.7% yield, 98.3% purity); mp 131–133 °C. ^{1}H NMR ($CDCl_3$): δ = 8.95–8.98 (br, 1 H), 8.55–8.58 (m, 2 H), 8.28–8.30 (d, 1 H), 8.09–8.11 (d, 1 H), 7.78–7.82 (m, 1 H), 7.50–7.63 (m, 6 H), 7.09–7.12 (m, 2 H), 5.03 (br, 1 H), 4.35–4.38 (t, 2 H), 3.96 (s, 4 H), 3.74–3.75 (br, 2 H), 3.63–3.67 (m, 2 H), 2.88–2.91 (m, 2 H), 1.48 (s, 9 H). DEPT-^{13}C (DMSO-d_6): δ = 149.19 (2Cs, N-sub pyr), 136.80 (2Cs, N-sub pyr), 130.29 (1C, qui), 129.71 (1C, qui), 124.91 (1C, qui), 123.06 (2Cs, N-sub pyr), 122.52 (2Cs, N-sub pyr), 122.35 (1C, qui), 95.50 (1C, qui), 67.51 (-O-CH_2-CH_2-NH-), 59.96 (-N(CH_2-2-pyr)$_2$), 53.17 (-NH-CH_2-CH_2-N(CH_2-2-pyr)$_2$), 41.92 (-NH-CH_2-CH_2-N(CH_2-2-pyr)$_2$), 37.06 (-NH-CH_2-CH_2-O-), 27.71 (-C(CH_3)$_3$); ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{31}H_{36}N_6O_4$: 556.67; found: 557.30; Anal. Calcd (%) for $C_{31}H_{36}N_6O_4$: C 66.89, H 6.52, N 15.10; found: C 66.94, H 6.34, N 14.89.

4-[2-(*tert*-Butoxycarbonyl)aminoethoxy]-*N*-(2-{[di(quinolin-2-yl)methyl]amino}ethyl)quinoline-2-carboxamide (17)

A solution of **15** (5.33 g, 14.23 mmol), water (20 mL), NaOH (2.30 g, 57.50 mmol), and 2-chloromethylquinoline hydrochloride (6.70 g, 31.30 mmol) was stirred at 70 °C for 6 h. The mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (100 mL), washed with saturated brine and dried over anhydrous sodium sulfate. After the removal of the solid and the solvent, the crude material was purified by silica gel column and eluted with ethyl acetate/25% ammonium hydroxide (v/v = 200:1) to afford **17** as a white solid (7.1 g, 76.0% yield, 98.5% purity); mp 78–79 °C. ^{1}H NMR ($CDCl_3$): δ = 8.91 (br, 1 H), 8.31–8.33 (d, 1 H), 8.06–8.10 (m, 3 H), 7.94–7.96 (m, 2 H), 7.81–7.88 (m, 3 H), 7.63–7.69 (m, 6 H), 7.46–7.50 (m, 2 H), 5.05 (br, 1 H), 4.34–4.37 (t, 2 H), 4.16 (s, 4 H), 3.75–3.76 (br, 2 H), 3.68–3.70 (br, 2 H), 2.99–3.01 (t, 2 H), 1.49 (s, 9 H). DEPT-^{13}C (DMSO-d_6): δ = 136.64 (2Cs, N-sub qui), 131.31 (1C, qui), 129.83 (2Cs, N-sub qui), 129.23 (1C, qui), 129.02 (2Cs, N-sub qui), 128.15 (2Cs, N-sub qui), 127.39 (1C, qui), 126.56 (2Cs, N-sub qui), 122.76 (1C, qui), 121.51 (2Cs, N-sub qui), 98.63 (1C, qui), 68.47 (-O-CH_2-CH_2-NH-), 61.06 (-N(CH_2-2-qui)$_2$), 53.49 (-CH_2-N(CH_2-2-qui)$_2$), 39.61 (-CH_2-CH_2-N(CH_2-2-qui)$_2$), 37.34 (-NH-CH_2-CH_2-O-), 28.69 (-C(CH_3)$_3$); ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{39}H_{40}N_6O_4$: 656.79; found: 657.29; Anal. Calcd (%) for $C_{39}H_{40}N_6O_4$: C 71.32, H 6.14, N 12.80; found: C 71.27, H 5.96, N 12.67.

4-(2-Aminoethoxy)-*N*-(2-((di(pyridin-2-yl)methyl)amino)ethyl)quinoline-2-carboxamide (18)

A solution of **16** (10.00 g, 17.96 mmol), dichloromethane (50 mL), and trifluoroacetic acid (15 mL) was stirred at r.t. for 10 h. The mixture was concentrated in vacuo and the residue was added with dichloromethane (100 mL), washed with 2 N NaOH, saturated brine, and dried over anhydrous sodium sulfate. After removal of the solvent, the crude material was purified by silica gel column and eluted with ethyl acetate/25% ammonium hydroxide (v/v = 200:1) to give **18** as a white solid (7.4 g, 90.0% yield, 98.1 % purity); mp 155–156 °C. ^{1}H NMR ($CDCl_3$): δ = 8.92–8.93 (br, 1 H), 8.47–8.49 (m, 2 H), 8.29–8.31 (d, 1 H), 7.92–7.94 (d, 1 H), 7.73–7.77 (m, 1 H), 7.58–7.65 (m, 4 H), 7.51–7.55 (m, 1 H), 7.41–7.44 (m, 1 H), 7.19–7.22 (m, 2 H), 4.89–4.92 (m, 1 H), 3.85 (s, 4 H), 3.67–3.71 (m, 2 H), 3.48–3.52 (m, 2 H), 3.42–3.46 (m, 2 H), 2.71–2.74 (m, 2 H). ^{13}C NMR (DMSO-d_6): δ = 165.01 (C=O), 159.77 (2Cs, N-sub pyr), 152.05 (1C, qui), 151.11 (1C, qui), 149.20 (2Cs, N-sub pyr), 147.47 (1C, qui), 136.81 (2Cs, N-sub pyr), 130.20 (1C, qui), 129.70 (1C, qui), 125.51 (1C, qui), 123.07 (2Cs, N-sub pyr), 122.54 (2Cs, N-sub pyr), 122.31 (1C, qui), 119.61 (1C, qui), 95.47 (1C, qui), 59.97 (2Cs, -CH_2-N(CH_2-pyr)$_2$), 59.19 (-O-CH_2-CH_2-NH_2), 53.21 (-CH_2-N(CH_2-pyr)$_2$), 45.66 (CO-N-CH_2-CH_2-N), 37.06 (-CH_2-NH_2); ESI-MS: *m*/*z* [M + 2]$^+$ calcd for $C_{26}H_{28}N_6O_2$: 456.55 found: 458.21; Anal. Calcd (%) for $C_{26}H_{28}N_6O_2$ H_2O: C 65.80, H 6.37, N 17.71; found: C 65.64, H 6.29, N 17.82.

4-(2-Aminoethoxy)-*N*-(2-((di(quinolin-2-yl)methyl)amino)ethyl)quinoline-2-carboxamide (19)

A solution of **17** (1.00 g, 1.50 mmol), dichloromethane (5 mL), and trifluoroacetic acid (2 mL) was stirred at r.t. for 6 h. The mixture was concentrated in vacuo and the residue was added with dichloromethane (25 mL), washed with 2 N NaOH, saturated brine, and dried over anhydrous sodium sulfate. The crude material was purified by silica gel column and eluted with ethyl acetate/25% ammonium hydroxide

(v/v = 200:1) to give **19** as a white solid (0.73 g, 86.0% yield, 98.0% purity); mp148–149 °C. ^{1}H NMR ($CDCl_3$): δ = 8.94 (br, 1 H), 8.33–8.35 (m, 1 H), 8.07–8.12 (m, 3 H), 7.95–7.97 (m, 2 H), 7.82–7.7789 (m, 3 H), 7.65–7.70 (m, 6 H), 7.46–7.50 (m, 2 H), 4.33–4.36 (t, 2 H), 4.17 (s, 4 H), 3.68–3.72 (m, 2 H), 3.28–3.31 (t, 2 H), 2.99–3.02 (t, 2 H), 1.66 (br, 2 H). ^{13}C NMR (DMSO-d_6): δ = 164.19 (C=O), 162.88 (1C, qui), 160.68 (2Cs, N-sub qui), 152.15 (1C, qui), 147.66 (1C, qui), 147.39 (2Cs, N-sub qui), 136.64 (2Cs, N-sub qui), 131.26 (1C, qui), 129.84 (2Cs, N-sub qui), 129.30 (1C, qui), 129.02 (2Cs, N-sub qui), 128.17 (2Cs, N-sub qui), 127.50 (1C, qui), 127.38 (2Cs, N-sub qui), 126.57 (2Cs, N-sub qui), 122.55 (1C, qui), 121.87 (1C, qui), 121.51 (2Cs, N-sub qui), 98.70 (1C, qui), 71.86 (-O-**C**H_2-CH_2-NH_2), 61.07 (2Cs, -CH_2-N(**C**H_2-qui)$_2$), 53.52 (-**C**H_2-N(CH_2-qui)$_2$), 41.21 (N-**C**H_2-CH_2-N(CH_2-qui)$_2$), 37.34 (-**C**H_2-NH_2); ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{34}H_{32}N_6O_2$: 556.67; found: 557.25. Anal. Calcd (%) for $C_{34}H_{32}N_6O_2$ H_2O: C 71.06, H 5.96, N 14.62; found: C 70.89, H 6.02, N 14.57.

Spectroscopic Measurements

Solutions of the analogues were prepared in chloroform and diluted to a final concentration of 0.1 μM for all measurements. UV absorption spectra were recorded with a Meipuda UV-650 spectrophotometer (Shanghai, China). Fluorescence intensity spectra were measured with a Perkin–Elmer LS 55 fluorescence spectrometer.

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Supporting Information

Supporting information of ^{1}H NMR and ^{13}C NMR spectra as well as some UV and fluorescence measurement for this article is available online at https://doi.org/10.1055/s-0036-1590963.

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