# Design and Synthesis of Quipazine Based Re-Complexes for the Development of Potential SPECT Imaging Agents with $^{99m}$Tc for 5-HT Transporter

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6-Nitroquipazine has higher binding affinity for SERT than other selective serotonin reuptake inhibitors. We have prepared 6-nitroquipazine based rhenium complexes which would lead to the development of potential SPECT imaging agents with $^{99m}$Tc for 5-HT transporter.

**Key Words :** Serotonin, Radiotracer, SPECT, Technetium, Rhenium

## Introduction

Serotonin transporter (SERT), responsible for the reuptake of serotonin (5-HT), plays a key role in the regulation of synaptic serotonin levels.[1] Although not fully understood yet, 5-HT is thought to be implicated in many mental disorders including depression, anxiety, schizophrenia, eating disorders and obsessive compulsive disorder.[2] Serotonin transporter sites are the primary targets for common antidepressant drugs such as fluoxetine, sertraline, and paroxetine. *In vivo* imaging of SERT in living human beings have been pursued either by PET (positron emission tomography) or by SPECT (single photon emission computed tomography) in order to understand the neurological mechanisms underlying those psychiatric disorders.[3]

Except for a few successful cases, for example, [$^{11}$C](+)-McN5652[4] for PET and [$^{123}$I]IDAM[5] for SPECT, the development of such radiotracers has met with only limited success mostly due to their low signal to noise ratios and poor selectivity.[6] For a routine clinical use, SPECT imaging is preferred to PET technique for its operational convenience and practicality. Both $^{123}$I and $^{99m}$Tc are the common radionuclides suitable for SPECT imaging. Attachment of $^{123}$I to a target substrate is normally made through the displacement reaction of $^{123}$I with trialkyltin group on the aryl moiety of the target molecule. Introduction of $^{99m}$Tc is rather difficult, in synthetic point of view, since it requires a multidentate ligand, connected covalently to the substrate for stable Tc-complexes.[7] Furthermore, the connection of such chelating groups to a substrate inevitably causes the increase of molecular weight and possible conformational changes, which may lead to the reduction of its binding affinity in several orders. The advantages of $^{123}$I are, however, overshadowed by its lesser accessibility, requiring a cyclotron for its generation. It is thus much desirable to develop radiotracers based on more readily available $^{99m}$Tc, despite the aforementioned drawbacks.

In this present work, we wish to report synthesis of several 6-nitroquipazine ligands as well as Re- and Tc-complexes as novel potential radiotracers for the imaging of SERT. We chose 6-nitroquipazine for its high binding affinity with SERT.[8] In fact, Mathis *et al.* reported syntheses of 5-[$^{123}$I]-6-nitro quipazine and 5-[$^{76}$Br]-6-nitroquipazine derivatives for SPECT and PET imagings.[9] Rhenium is a congener of technetium in group VIIa of the periodic table that is commonly used as a model for synthetic viability and spectroscopic characterizations.

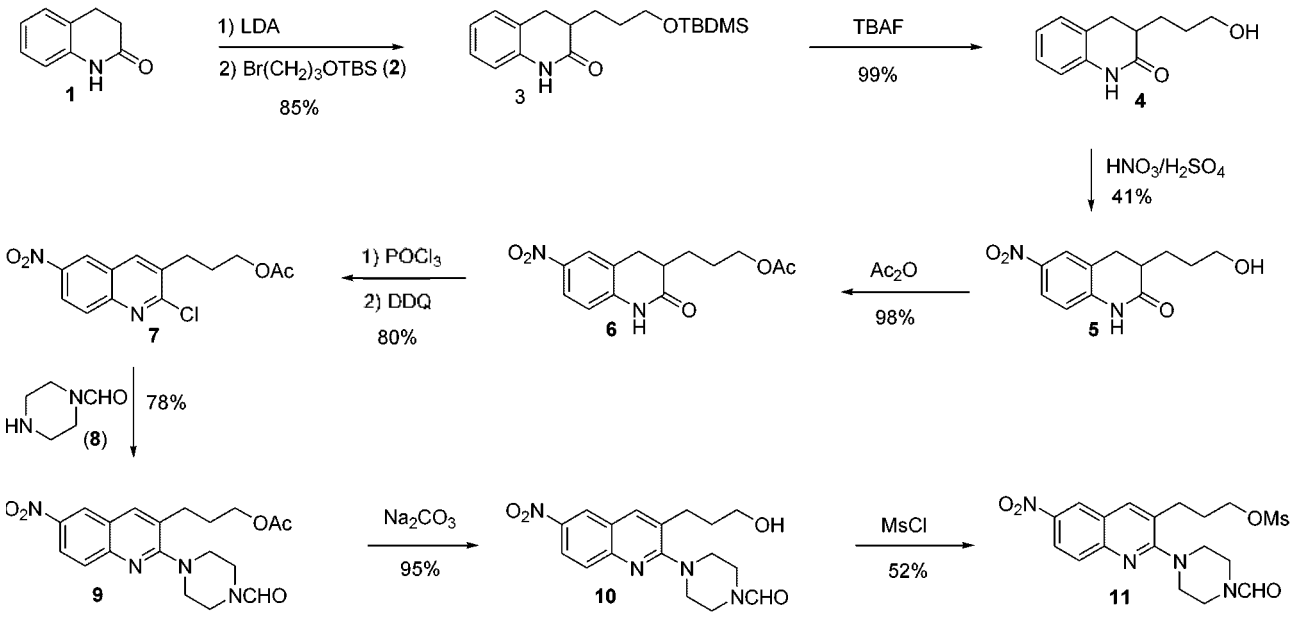
## Results and Discussion

Adopting the better synthetic procedures developed by one of us,[10] we prepared the key 6-nitroquipazine derivative **10** with hydroxypropyl handle, starting from 3,4-dihydro-2(1*H*)-quinolinone **1**. Deprotonation with 2.0 equiv of LDA at C3 position, followed by quenching with 3-bromopropanol TMS-ether (**2**) provided the silyl ether **3** in 85% yield. Desilylated alcohol was nitrated to give the dihydroquinolinone **5** in overall yield of 40%. The acetylated product **6** was treated with phosphorus oxychloride and DDQ to give the 2-chloroquipazine 7 in 80% isolated yield. Displacement reaction with 1-piperazinecarboxaldehyde (**8**) provided **9**, which was deacetylated to the alcohol **10**. The resulting alcohol was reacted with MsCl in $CH_2Cl_2$ to furnish the mesylate **11** in 52% yield (Scheme 1).

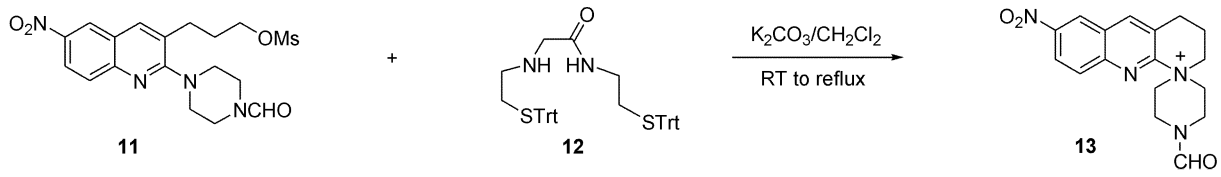
The mesylate **11**, however, did not undergo substitution reaction with the tetradentate ligand **12**. Instead, it underwent intramolecular displacement reaction, leading to the formation of the cyclic ammonium species **13** as shown in Scheme 2, which might be the reason for the low yield in the mesylation step.

Change of the mesylate group on **11** to the bromide or tosylate gave no improvements. Use of the OH group as a nucleophile would be a reasonable alternative. The alcohol **10** was treated with bromoacetyl bromide, before the coupling with **12** to provide the 6-nitroquipazine derivative **14** bearing the ligand for the chelation of Tc or Re.

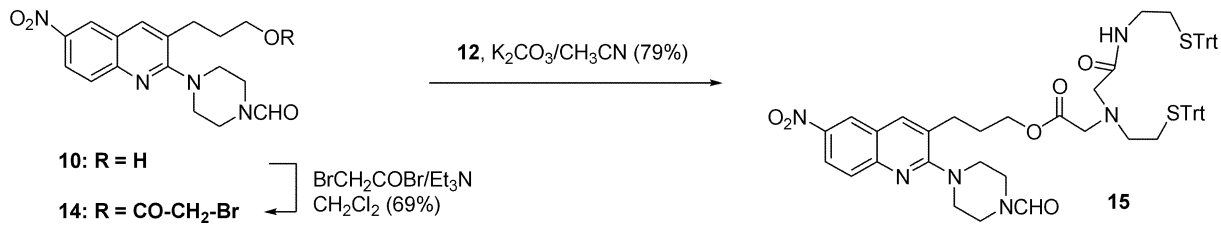
The ligand **15** was subjected to $^{99m}$Tc loading conditions to produce the $^{99m}$Tc-complex **16**, which was isolated in pure form by reversed phase HPLC. However, we noticed partial decomposition of the starting ligand and the product $^{99m}$Tc-



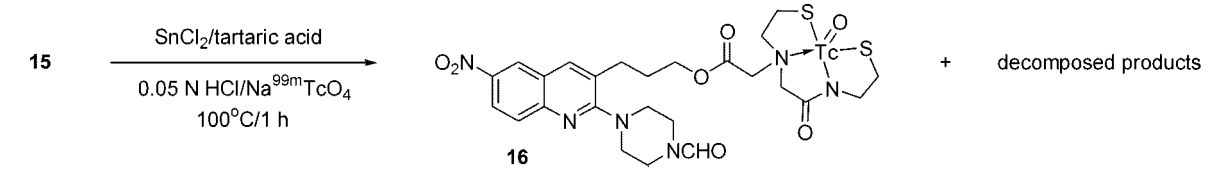

**Scheme 1.** Preparation of the piperazine substituted 6-nitroquipazine derivative.




**Scheme 2.** Result of the attempted displacement reaction of the mesylate **11** with **12**.




**Scheme 3.** Preparation of the 6-nitroquipazine-$N_2S_2$ ligand system **15**.



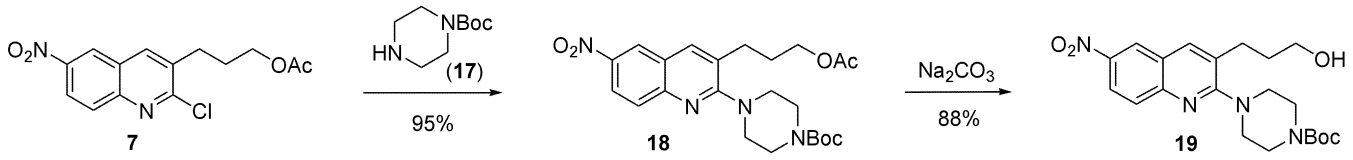

**Scheme 4.** Incorporation of $^{99m}$Tc onto the ligand **15**.

complex at the ester linkage during the incorporation of technetium (Scheme 4).

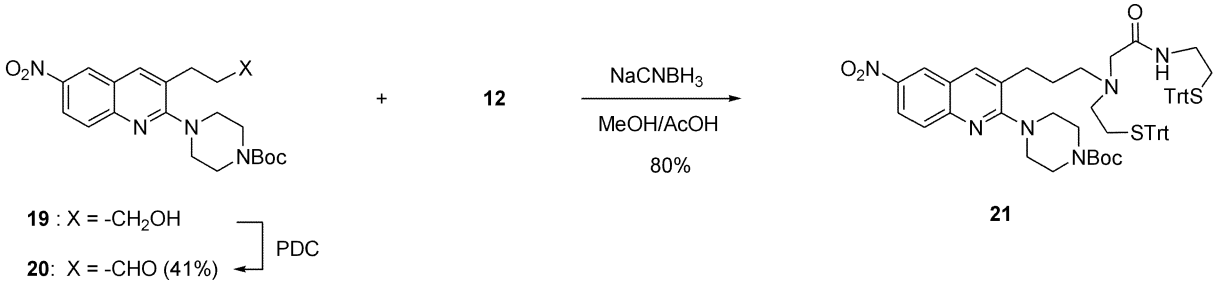
Due to the instability of the ester linkage, we decided to connect the $N_2S_2$ tetradentate ligand directly with the 6-nitroquipazine group *via* a reductive amination pathway. At this point, we changed the protecting group of the piperazine from formyl to the more stable Boc-group. With the same steps used for the alcohol **10**, we prepared the alcohol **19** bearing Boc protecting group in a comparable overall yield (Scheme 5).

Oxidation of the alcohol **19** did not proceed as smoothly as we expected, but still provided sufficient amount of the aldehyde **20** with PDC in 41% yield. Reductive amination of the aldehyde **20** was successfully carried out to give rise to the corresponding precursor **21** in 80% yield (Scheme 6).

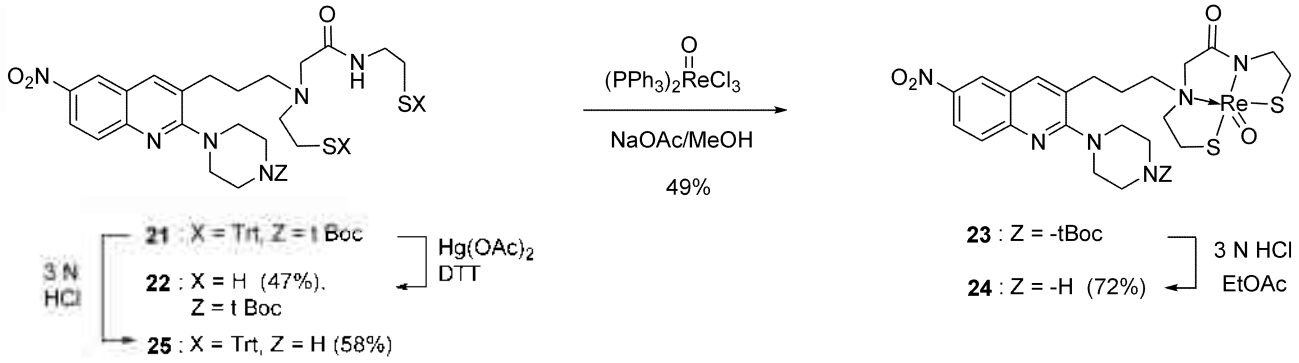
Removal of the trityl groups with $Hg^{+2}$ provided **22** in




**Scheme 5.** Preparation of the Boc-protected 6-nitroquipazine derivative.




**Scheme 6.** Oxidation and reductive amination of the alcohol **19**.




**Scheme 7.** Deprotection and formation of the Re-complex **23**, **24** and **25**.

moderate yield, which was subsequently treated with trichlorooxobis(triphenylphosphine)rhenium[11] to furnish the desired Re-complex **23** in 49% yield. We also prepared the Boc-deprotected Re-complex **24**, upon treatment of the complex **23** with 3 N HCl in EtOAc. The Boc-deprotected $^{99m}$Tc-complex, however, cannot be prepared with the same sequence used for the Re-complex **24**, for its short half-life ($t_{1/2}$ – 6 h). Thus, the Boc group on **21** was removed with 3 N HCl to the ligand system **25**, prior to Tc loading step (Scheme 7).

In summary, we have prepared two 6-nitroquipazine based Re-complexes for *in vitro* binding study against SERT and spectroscopic characterizations plus one $^{99m}$Tc-complex for *in vivo* SPECT imaging of SERT. Syntheses of $^{99m}$Tc-version of **23** and **24** as well as their *in vitro* and *in vivo* study are under progress and will be reported near future.

## Experimental Section

**General methods.** All $^1$H NMR spectra were recorded on a 400 MHz Varian NMR spectrometer operating at 400 MHz for $^1$H. Flash column chromatography was performed with Kieselgel 60 Art 9385 (230-400 mesh). All solvents used were purified according to standard procedures.

**3-[2-(4-Formylpiperazin-1-yl)-6-nitroquinoline-3-yl]propyl α-Bromoacetate (14).** To a solution of **10** (20 mg, 0.058 mmol) in 1.5 mL of anhydrous $CH_2Cl_2$ was dropwise added $Et_3N$ (8.9 μL, 0.064 mmol) at -20 °C. To the mixture was added bromoacetyl bromide (5.6 μL, 0.064 mmol) dropwise at -20 °C. After 15 min at -20 °C, the reaction mixture was warm to rt and stirred for 9 h, which was then quenched by the addition of water. The mixture was extracted with 10 mL of $CH_2Cl_2$ three times. The combined organic layer was dried over $Na_2SO_4$ and concentrated. The product was isolated by flash column chromatography with EtOAc/hexanes (2 : 1) to give **14** (18.7 mg) as a yellow solid in 69% yield: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* – 2.8 Hz, 1H), 8.34 (dd, *J* – 9.2, 2.4 Hz, 1H), 8.13 (s, 1H), 8.00 (s, 1H), 7.89 (d, *J* – 9.2 Hz, 1H), 4.26 (t, *J* – 6.0 Hz, 2H), 3.81 (s, 2H), 3.78-3.76 (m, 2H), 3.62-3.60 (m, 2H), 3.46-3.43 (m, 2H), 3.36-3.33 (m, 2H), 2.91 (t, *J* – 7.6 Hz, 2H), 2.20-2.13 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.0, 162.4, 160.8, 148.3, 144.0, 138.2, 135.0, 130.0, 128.7, 124.2, 123.4, 122.6, 65.3, 50.5, 50.0, 45.5, 40.0, 25.6; FT-IR ($CHCl_3$) 2924.5, 2854.4, 1738.0, 1670.8 cm$^{-1}$; HRMS (FAB) m/z $(M+1)^+$ calcd for $C_{19}H_{22}BrN_4O_5$ 465.0774, found 465.0785.

**3-[2-(4-Formylpiperazin-1-yl)-6-nitroquinoline-3-yl]propyl *N*-(2-tritylsulfanyl-ethyl)-[(2-tritylsufanylethylcabamoyl)-methyl]-α-aminoacetate (15)**. To a solution of **14** (18.7 mg, 0.04 mmol) in 1.5 mL of $CH_3CN$ was added **12** (55.9 mg, 0.08 mmol) and $K_2CO_3$ (8.5 mg, 0.08 mmol) at rt. After 24 h, the reaction mixture was quenched with water and extracted with 10 mL of $CH_2Cl_2$ three times. The organic layer was dried over $Na_2SO_4$ and concentrated. The product **15** (16 mg, 37%) was obtained by flash column chromatography with EtOAc/$CH_2Cl_2$ (2 : 1) as a yellow solid in 37% yield: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.56 (d, $J$ = 2.4 Hz, 1H), 8.32 (dd, $J$ = 9.2, 2.8 Hz, 1H), 8.09 (s, 1H), 7.91 (s, 1H), 7.87 (d, $J$ = 9.2 Hz, 1H), 7.50 (t, $J$ = 5.6 Hz, 1H), 7.37 7.12 (m, 30 H), 4.10 (t, $J$ = 6.4 Hz, 2H), 3.73 (dd, $J$ = 5.2, 4.8 Hz, 2H), 3.54 (dd, $J$ = 7.2, 4.4 Hz, 2H), 3.40 (dd, $J$ = 5.2, 3.2 Hz, 2H), 3.31 (dd, $J$ = 4.8, 4.4 Hz, 2H), 3.23 (s, 2H), 3.07 (s, 2H), 3.04 (dd, $J$ = 12.4, 6.4 Hz, 2H), 2.79 (dd, $J$ = 8.4, 7.6 Hz, 2H), 2.58 (t, $J$ = 6.8 Hz, 2H), 2.36 (t, $J$ = 6.4 Hz, 2H), 2.27 (t, $J$ = 6.4 Hz, 2H), 2.09-2.02 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.0, 170.8, 163.0, 161.3, 148.9, 145.16, 145.07, 144.5, 138.7, 130.5, 130.04, 130.00, 129.3, 128.45, 128.41, 127.27, 127.19, 124.8, 124.1, 123.2; 67.5, 67.4, 64.7, 58.8, 55.6, 54.5, 51.1, 50.5, 46.1, 40.6, 38.8, 32.8, 31.1, 29.4, 28.8, FT-IR ($CHCl_3$) 3343.4, 3057.9, 3008.5, 2960.0, 2925.6, 2855.5, 1738.9, 1673.1, 1617.2 cm$^{-1}$; HRMS (FAB) m/z (M+Na)$^+$ calcd for $C_{63}H_{62}N_6NaO_6S_2$ 1085.4070, found 1085.4063.

**The 6-nitroquipazine based $^{99m}$Tc-complex 16**. To a mixture of the ligand **15** (23 μg), $SnCl_2$ (125 μg) and 1 mg of tartaric acid in 0.05 N HCl (10 mL) was added sodium pertechnetate (370-740 MBq) at rt. Upon sonication for 1 min in water bath, the reaction mixture was heated to 100 °C for 1 h, before cooled to rt. The product mixture was analysed and purified by reversed phase HPLC using gradient system of $H_2O$ and acetonitrile with flow rate of 1 mL/min. The peak with retention time of 16 min showed correct UV profile and radioactivity.

**3-(3-Acetoxypropyl)-6-nitro-2-(4-*N*-Boc-piperazin-1-yl)-quinoline (18)**. The mixture of **7** (217 mg, 0.69 mmol) and Boc protected piperazine (**17**, 194 mg, 1.04 mmol) in 4 mL of anhydrous DMF was stirred for 36 h at 100 °C and then cooled to rt, poured into 50 mL of ice-crushed water. The resulting precipitate was filtered, washed with 50 mL of water and dried under suction for 10 min. The solid was dissolved in 50 mL of $CH_2Cl_2$, dried over $Mg_2SO_4$, concentrated and purified by column chromatography with EtOAc/hexanes (1 : 3) to give **18** (236 mg) as a yellow solid in 74% yield: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.59 (d, $J$ = 2.8 Hz, 1H), 8.31 (dd, $J$ = 9.2, 2.4 Hz, 1H), 7.96 (s, 1H), 7.85 (d, $J$ = 9.2 Hz, 1H), 4.14 (t, $J$ = 6.4 Hz, 2H), 3.65-3.62 (m, 4H), 3.37-3.34 (m, 4H), 2.86 (dd, $J$ = 8.0, 7.6 Hz, 2H), 2.13-2.04 (m, 2H), 2.06 (s, 3H), 1.50 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.4, 163.4, 155.3, 149.1, 144.3, 138.7, 131.0, 129.2, 124.7, 124.1, 123.1, 80.7, 77.3, 64.4, 50.6, 29.5, 29.2, 29.1, 21.7, 21.1; FT-IR ($CHCl_3$) 3013.8, 2926.7, 1738.8, 1696.3, 1236.7 cm$^{-1}$; HRMS (FAB) m/z (M+1)$^+$ calcd for $C_{23}H_{31}N_4O_6$ 459.2244, found 459.2245.

**3-(3-Hydroxypropyl)-6-nitro-2-(4-*N*-Boc-piperazin-1-yl)-quinoline (19)**. The mixture of **18** (236 mg, 0.51 mmol) and $K_2CO_3$ (162 mg, 1.53 mmol) in 5 mL of MeOH and 5 mL of $CH_2Cl_2$ was stirred for 15 h at rt. The reaction was quenched by adding 60 mL of water and the resulting solution was extracted with 20 mL of $CH_2Cl_2$ three times. The organic layer was dried over $Na_2SO_4$ and concentrated. The alcohol **19** (180 mg) was obtained by column chromatography with EtOAc/hexanes (2 : 1) as a yellow solid in 84% yield: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (d, $J$ = 2.4 Hz, 1H), 8.32 (dd, $J$ = 9.2, 2.4 Hz, 1H), 7.98 (s, 1H), 7.87 (d, $J$ = 9.2 Hz, 1H), 3.65-3.63 (m, 6H), 3.36-3.34 (m, 4H), 2.91 (t, $J$ = 7.6 Hz, 2H), 2.02-1.95 (m, 2H), 1.92 (bt, 1H), 1.49 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.6, 155.3, 149.0, 144.3, 138.9, 131.7, 129.2, 124.9, 124.0, 122.9, 80.7, 77.4, 62.2, 50.7, 33.6, 30.4, 29.2, 28.4; FT-IR ($CHCl_3$) 3440.7, 2925.8, 2856.8, 1694.2 cm$^{-1}$; HRMS (FAB) m/z (M+1)$^+$ calcd for $C_{21}H_{29}N_4O_5$ 417.2138, found 417.2145.

**3-(3-Oxapropyl)-6-nitro-2-(4-*N*-Boc-piperazin-1-yl)quinoline (20)**. The mixture of **19** (180 mg, 0.43 mmol) and pyridinium dichromate (485 mg, 1.29 mmol) in 7 mL of $CH_2Cl_2$ was stirred for 24 h at rt. The reaction mixture was then filtered through a pad of Celite with $CH_2Cl_2$ and concentrated. The product **20** (84 mg) was obtained by flash column chromatography with EtOAc/hexanes (1 : 2) as a yellow solid in 47% yield: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.86 (s, 1H), 8.58 (d, $J$ = 2.8 Hz, 1H), 8.31 (dd, $J$ = 9.2, 2.4 Hz, 1H), 7.92 (s, 1H), 7.86 (d, $J$ = 9.2 Hz, 1H), 3.64-3.62 (m, 4H), 3.36-3.34 (m, 4H), 3.13 (t, $J$ = 7.6 Hz, 1H), 2.95 (t, $J$ = 7.6 Hz, 2H), 1.50 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.6, 163.3, 155.3, 149.2, 144.5, 138.8, 130.3, 129.3, 124.7, 124.1, 123.3, 80.7, 77.3, 50.7, 44.1, 29.2, 24.9; FT-IR ($CHCl_3$) 2975.7, 2927.6, 2853.3, 1695.8, 1616.2 cm$^{-1}$; HRMS (FAB) m/z (M+1) calcd for $C_{21}H_{27}N_4O_5$ 415.1981, found 415.1965.

**3-(3-*N*-(2-Tritylsulfanylethyl)-*N*-[(2-tritylsufanylethyl-cabamoyl)methyl]amino-propyl)-6-nitro-2-(4-*N*-Boc-piperazin-1-yl)quinoline (21)**. To a solution of **20** (84 mg, 0.20 mmol) in 4 mL of MeOH/acetic acid (99 : 1) was added **12** (209 mg, 0.30 mmol) and sodium cyanoborohydride (19 mg, 0.30 mmol) at rt. After stirring for 5 h at rt, reaction mixture was quenched by adding 10 mL of water. The resulting solution was extracted with 15 mL of $CH_2Cl_2$ three times. The organic layer was dried over $Na_2SO_4$ and concentrated. The product **21** (153 mg) was obtained by flash column chromatography with EtOAc/hexanes (1 : 2) as a yellow solid in 71% yield: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.39 (d, $J$ = 2.4 Hz, 1H), 8.31 (dd, $J$ = 9.2, 2.8 Hz, 1H), 7.83 (d, $J$ = 9.2 Hz, 1H), 7.79 (s, 1H), 7.51 (t, $J$ = 6.0 Hz, 1H), 7.38-7.09 (m, 30 H), 3.57-3.56 (m, 4H), 3.29-3.26 (m, 4H), 3.04 (dd, $J$ = 12.4, 6.0 Hz, 2H), 2.90 (s, 2H), 2.71 (t, $J$ = 7.6 Hz, 2H), 2.45-2.35 (m, 6H), 2.28 (t, $J$ = 6.0 Hz, 2H), 1.86-1.78 (m, 2H), 1.49 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.3, 163.4, 155.3, 149.0, 145.2, 145.1, 144.3, 138.5, 131.2, 130.1, 130.0, 129.1, 128.5, 128.4, 127.4, 127.3, 127.1, 124.7, 124.2, 123.1, 80.1, 67.6, 67.5, 59.1, 55.4, 54.7, 50.5, 38.8, 33.0, 31.0, 30.1, 29.3, 28.2; FT-IR ($CHCl_3$) 3348.3, 3058.4, 2973.6, 2928.4, 2856.2, 1682.7 cm$^{-1}$; HRMS (FAB) m/z (M+Na)$^+$ calcd for $C_{65}H_{68}NaN_6O_5S_2$ 1099.4590, found

1099.4562.

**3-(3-*N*-(2-Mercaptoethyl)-*N*-[(2-mercaptoethylcabamoyl)methyl]aminopropyl)-6-nitro-2-(4-*N*-Boc-piperazin-1-yl)quinoline (22)**. To a stirred solution of **21** (153 mg, 0.14 mmol) in a 1 : 1 mixture of EtOAc and EtOH (7 mL) was added a solution of mercury (II) acetate (115 mg, 0.36 mmol) in EtOH (3 mL). The reaction mixture was stirred for 20 min at 80 °C and then cooled to rt. The reaction mixture was treated with dithiothreitol (65 mg, 0.42 mmol), stirred for an additional 10 min, before passed through a pad of Celite with EtOAc. The filtrate solution was concentrated and purified by column chromatography with MeOH/$CH_2Cl_2$ (1 : 100) to furnish **22** (46 mg) as a yellow solid in 56% yield: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.59 (d, $J$ = 2.4, 1H), 8.31 (dd, $J$ = 8.8, 2.4 Hz, 1H), 7.97 (s, 1H), 7.86 (d, $J$ = 8.8 Hz, 1H), 7.77 (t, $J$ = 6.0 Hz, 1H), 3.63-3.61 (m, 4H), 3.47 (dd, $J$ = 12.4, 6.0 Hz, 2H), 3.36-3.34 (m, 4H), 3.14 (s, 2H), 2.81 (t, $J$ = 7.2 Hz, 2H), 2.75-2.57 (m, 10H), 1.99-1.91 (m, 2H), 1.49 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.5, 163.4, 155.3, 149.1, 144.4, 138.4, 131.0, 129.2, 124.7, 124.1, 123.1, 80.8, 59.3, 58.4, 55.2, 50.6, 42.6, 30.5, 30.1, 29.2, 28.0, 25.5, 23.7; FT-IR ($CHCl_3$) 3343.2, 2974.0, 2929.4, 2856.0, 1681.8 cm$^{-1}$; HRMS (FAB) m/z (M+Na) calcd for $C_{23}H_{40}NaN_6O_5S_2$ 615.2399, found 615.2396.

**Re-complex 23**. To a stirred solution of **22** (46.7 mg, 0.079 mmol) in MeOH (13 mL) were added 1 M NaOAc in MeOH (1.2 mL, 1.185 mmol) and trichlorooxo-bis(triphenylphosphine)rhenium (79 mg, 0.095 mmol) at rt. The reaction mixture was heated to 80 °C and stirred for 2 h. The cooled reaction mixture was diluted with EtOAc (30 mL), washed with water, dried over $Na_2SO_4$ and concentrated. The Re-complex **23** (42.5 mg) was obtained by flash column chromatography with MeOH/$CH_2Cl_2$ (1 : 60) as yellow solids in 68% yield: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.62 (d, $J$ = 2.4 Hz, 1H), 8.34 (dd, $J$ = 9.2, 2.4 Hz, 1H), 8.02 (s, 1H), 7.90 (d, $J$ = 9.2 Hz, 1H), 4.60 (d, $J$ = 16.8 Hz, 1H), 4.55 (d, $J$ = 6.4, 5.2 Hz, 1H), 4.10 (d, $J$ = 16.8 Hz, 1H), 4.10-4.06 (m, overlapped, 1H), 3.96 (ddd, $J$ = 17.6, 14.8, 8.4 Hz, 1H), 3.63-3.57 (m, 4H), 3.34-3.31 (m, 4H), 3.33-3.31 (m, 4H), 3.28-3.23 (m, 2H), 3.21-3.13 (m, 2H), 2.91-2.84 (m, 3H), 2.33-2.22 (m, 2H), 1.70-1.62 (m, 2H), 1.50 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 187.2, 163.3, 155.3, 149.3, 144.6, 138.8, 129.7, 129.6, 124.7, 124.1, 123.6, 80.9, 67.5, 65.4, 63.7, 60.6, 50.9, 48.8, 39.8, 30.5, 29.6, 29.3, 25.3; FT-IR ($CHCl_3$) 2928.0, 2856.7, 1681.2, 1651.2, 965.8 cm$^{-1}$; HRMS (FAB) m/z (M+Na)$^+$ calcd for $C_{27}H_{37}NaN_6O_6ReS_2$ 815.1671, found 815.1703.

**Re-complex 24**. To a solution of **23** (32 mg, 0.040 mmol) in 3 mL of EtOAc was added 3 N HCl (1.5 mL) at rt. After stirring for 24 h at rt, the reaction mixture was diluted with EtOAc (10 mL), washed with 1 M $NaHCO_3$ (2 × 10 mL) and water (10 mL). The organic layer was dried over $Na_2SO_4$, concentrated and purified by column chromatography with MeOH/$CH_2Cl_2$ (1 : 10) to furnish **24** (20 mg) as a yellow solid in 72% yield: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.99 (s, 1H), 7.90 (d, $J$ = 9.2 Hz, 1H), 4.61 (d, $J$ = 16.0 Hz, 1H), 4.56 (d, $J$ = 6.4, 5.2 Hz, 1H), 4.11 (d, $J$ = 16.0 Hz, 1H), 4.10-4.06 (m, overlapped, 1H), 4.01-3.94 (m, 1H), 3.65-3.58 (m, 1H), 3.36-3.33 (m, 4H), 3.30-3.14 (m, 4H), 3.10-3.08 (m, 4H), 2.94-2.84 (m, 3H), 2.34-2.24 (m, 2H), 1.70-1.62 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 187.2, 163.6, 149.5, 144.5, 138.8, 129.7, 129.5, 124.6, 124.1, 123.5, 67.5, 65.3, 63.8, 60.0, 52.2, 48.8, 46.8, 39.8, 29.9, 25.2; FT-IR ($CHCl_3$) 2924.8, 2855.7, 1651.1, 964.9 cm$^{-1}$; HRMS (FAB) m/z (M+1)$^+$ calcd for $C_{22}H_{30}N_6O_4ReS_2$ 693.1327, found 693.1325.

**3-(3-*N*-(2-Tritylsulfanylethyl)-*N*-[(2-tritylsufanylethylcabamoyl)methyl]amino-propyl)-6-nitro-2-(piperazin-1-yl)quinoline (25)**. To a solution of **21** (16 mg, 0.015 mmol) in 1.5 mL of EtOAc wad added 3 N HCl (1 mL) at room temperature. After stirring for 24 h at rt, the reaction mixture was diluted with EtOAc (10 mL). The organic portion was washed with 1 N $NaHCO_3$ (2 × 10 mL) and water (10 mL). The organic layer was dried over $Na_2SO_4$ and concentrated. The product **25** (8.5 mg) was obtained by flash column chromatography with MeOH/$CH_2Cl_2$ (1 : 30) as a yellow solid in 58% yield: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.36 (d, $J$ = 2.4 Hz, 1H), 8.28 (dd, $J$ = 9.2, 2.4 Hz, 1H), 7.84 (d, $J$ = 9.2 Hz, 1H), 7.76 (s, 1H), 7.52 (t, $J$ = 6.0 Hz, 1H), 7.35-7.07 (m, 30H), 3.31-3.28 (m, 4H), 3.04 (dd, $J$ = 12.0, 6.4 Hz, 2H), 3.00-2.96 (m, 4H), 2.91 (s, 2H), 2.72-2.68 (m, 2H), 2.45-2.35 (m, 6H), 2.28 (t, $J$ = 6.0 Hz, 2H), 1.84-1.76 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.4, 163.7, 149.2, 145.2, 145.1, 144.0, 138.3, 131.3, 130.1, 130.0, 129.0, 128.5, 128.4, 127.4, 127.3, 124.5, 124.2, 123.0, 67.6, 67.5, 59.1, 55.3, 54.8, 51.9, 46.8, 38.8, 33.0, 31.0, 30.4, 28.1; FT-IR ($CHCl_3$) 2917.4, 2853.3, 1671.1, 1615.2 cm$^{-1}$; HRMS (FAB) m/z (M+1) calcd for $C_{60}H_{61}N_6O_5S_2$ 977.4247, found 977.4244.

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