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Efficient syntheses of isotopically labeled PD0198961, a novel synthetic coagulation factor Xa inhibitor

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PD0198961 was investigated as a potent and selective inhibitor of coagulation factor Xa for the treatment of thrombotic disorders. Radioactive and stable isotope-labeled PD0198961 were synthesized for absorption, distribution, metabolism and elimination studies of the compound in animals and for use as mass spectral internal standards in support of bioanalytical assays, respectively. [^{14}C]PD0198961 was prepared from [^{14}C]CuCN in four radiosynthetic steps in an overall yield of 48% with a radiochemical purity of >99%. The cyanation reaction of an aromatic bromide with inorganic [^{14}C]cyanide as a key radiolabeling step was investigated. The deuterium-labeling was accomplished in a different reaction sequence from the ^{14}C labeling. This convergent process introduced stable isotope labeling via *cis*-2,6-dimethyl[$^{2}H_5$]piperidine, which was synthesized by catalytic hydrogenation of 2,6-dimethylpyridine with deuterium gas.

Keywords: PD0198961; factor Xa; carbon-14 labeling; stable-isotope labeling; cyanation; amidine formation

Introduction

Factor Xa (FXa) has materialized as a key enzyme for the intervention of the blood coagulation cascade and for the development of new antithrombotic agents.[1] FXa is the lone enzyme responsible for the production of thrombin and therefore is an attractive target for the control of thrombus formation.[2] PD0198961 is a novel, potent (Ki = 0.83 nM) and selective FXa inhibitor used for the treatment of thrombotic disorders. A radiolabeled analog of PD0198961 was required to profile and measure the absorption, distribution, metabolism and elimination of the compound in animals. Stable-isotope labeled PD0198961 was also required for use as an internal standard for bioanalytical assay of phase I human clinical sample quantitative biotransformation studies. This paper focuses on efficient syntheses of both ^{14}C-labeled and ^{2}H-labeled analogs of PD0198961 (Figure 1).

Results and discussion

Unlabeled PD0198961 was originally synthesized in ten steps as shown in Scheme 1.[3] The step (**5–6**) for installing the aryl nitrile functionality was considered to introduce the ^{14}C radiolabel. However, the sequence of the original synthesis was not suitable to prepare radioactive labeled compounds. The major problems were that more than 50% of radioactivity would be lost as an *O*-akylation by-product in the *N*-alyklation step and a lot of undesired over-reduced byproducts were formed in the last hydrogenation reaction with Pd/C. To solve these problems, a new approach to the synthesis of isotope labeled PD0198961 has been explored (Scheme 2).

Therefore, our new approach was to prepare the aryl bromide precursor **12** and then introduce ^{14}C labeled cyano group in the later step. The available intermediate **5** was first treated with 1,5-dibromopentane in the presence of NaH to provide two isomers (*N*-alkylation and *O*-alkylation products). The desired *N*-alkylated compound **11** was isolated by flash column chromatography in 41% yield. Displacement of the alkyl bromide **11** with varying equivalents of 2,6-dimethylpiperidine was studied. The excess of 2,6-dimethylpiperidine as a reagent and a solvent was used previously in the original discovery synthesis (Scheme 1); however, it was not necessary to achieve high yields. It was found that 3 equiv. of 2,6-dimethylpiperidine in DMF was enough to obtain a good yield.

Cyanation of the aryl bromide **12** was a key radiolabeling step. The reaction was investigated in various reagents, solvents and molar ratios. The results were shown in Table 1. Using reaction conditions with KCN as a cyanation reagent and $Pd(PPh_3)_4$ as a catalyst (entry 1), which were similar to the

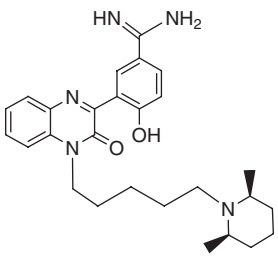

Figure 1. PD0198961.

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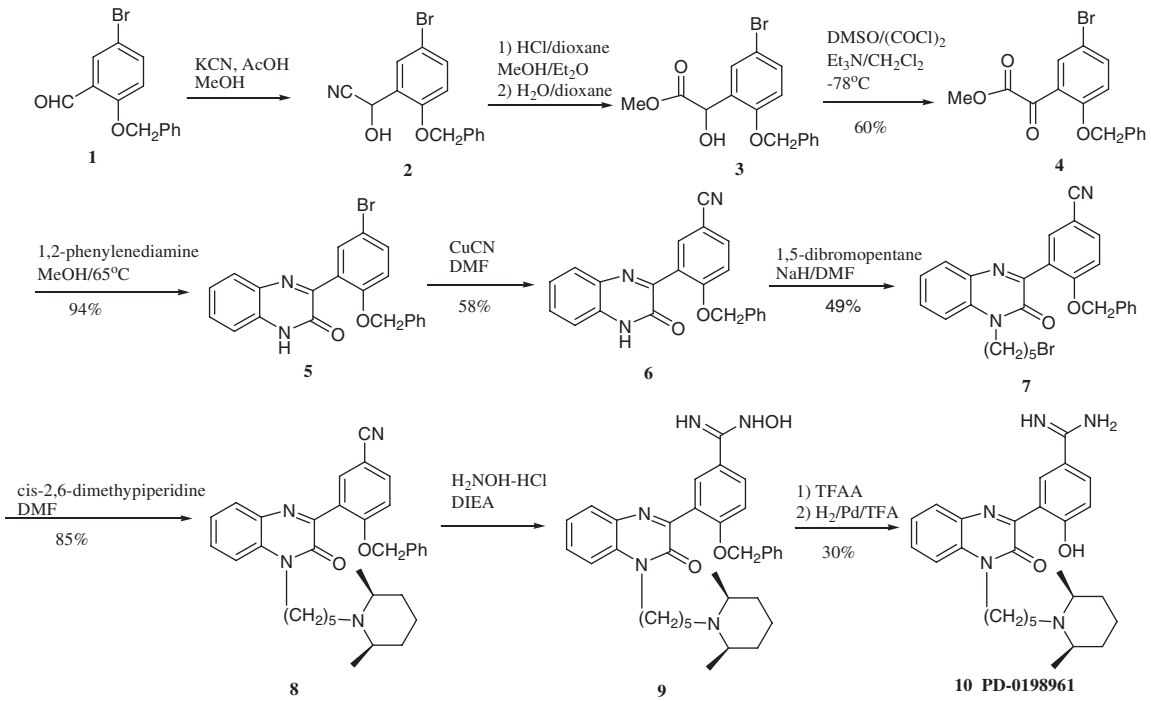
reported procedure,[4] a poor yield (10%) was observed. Application of CuCN in DMF gave a 40% isolated yield of the cyanide **13** within 24 h at 175°C. Increasing the molar ratio of CuCN to the compound **12** from 1.1 to 1.5 improved the yield to 55% (entry 3), while increasing the temperature of the cyanation reaction with CuCN from 175 to 210°C caused significant decomposition (entry 4). Interestingly, addition of pyridine to the cyanation reaction with CuCN improved the yield from 40 to 70% (entry 5). It was found that a higher reaction temperature resulted in the more decomposition. Therefore, by reducing the temperature to 160°C and increasing the reaction time to 48 h, we were able to obtain better isolated yields (entry 6,7).

Previously, PD0198961 was obtained by the treatment of cyanide **13** with hydroxylamine[5] followed by a catalytic hydrogenation. The uncontrolled over-reduction reaction caused poor yields and difficult separations. Therefore, the indirect transformations of cyanide to amidine were investigated. A classic method, i.e. alcoholysis of cyanide **13** in the presence of HCl gas followed by amination with NH_3 gas, worked just fine for our case, and provided the desired amidine **15** in an isolated yield of 61%. An alternative, one step transformation with methylchloroaluminum amide ($MeAlClNH_2$)[6] was tried without success. The catalytic hydrogenation to remove the protecting group was not applied due to the previous unsatisfactory results. Since compound **15** was fairly stable under acid conditions, the debenzylation of amidine **15** by concentrated HCl in MeOH provided the desired product in an excellent yield (98%) with a radiochemical purity of >99% and a specific activity of 54 mCi/mmol.

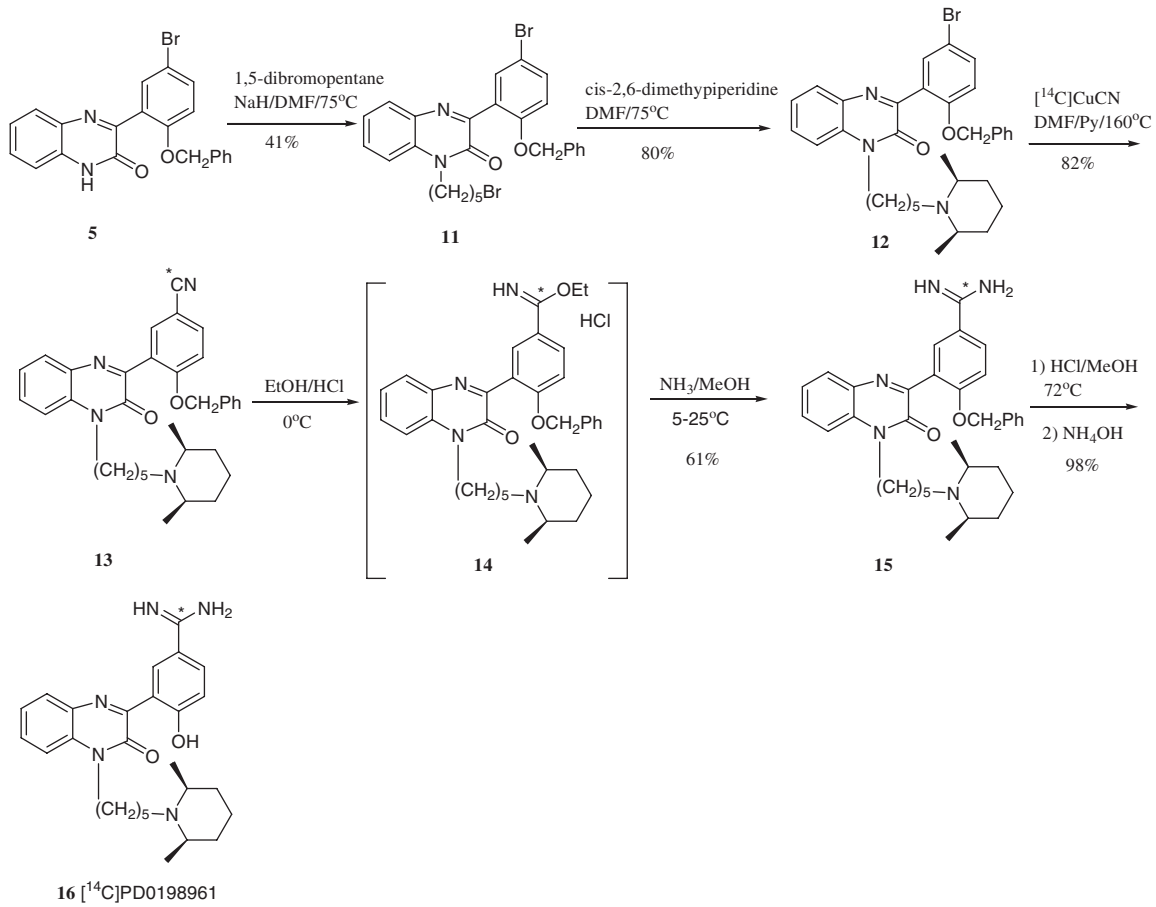
The synthesis of deuterated PD0198961 (M+5) was carried out by following the original reaction sequence (Scheme 3), which enabled us to incorporate the stable isotope labeled intermediate **18** into the target in the later steps. The hydrogenation reaction of 2,6-dimethylpyridine with D_2/PtO_2 in acetic acid[7] and deuterated acetic acid was studied. In acetic acid, the reaction provided a lot of unlabelled 2,6-dimethylpiperidine (D_0) besides deuterium labelled compounds (D_1–D_5). While in deuterated acetic acid, the desired product (M+5) was a major isotopomer (91% isotopic purity). A small amount of (M+4) and (M+6) was found, but no (M+0) was detected. These results indicated that the exchange occurred between deuterium from D_2 gas and hydrogen from acetic acid.

According to our previous study, use of an excess of 2,6-dimethylpiperidine as a reagent and solvent was not necessary to achieve high yield in next step. Therefore, about 3 equiv. of [D_5]2,6-dimethylpiperidine in DMF was used in the *N*-alkylation reaction to produce the desired compound **19** in an isolated yield of 86%. It was observed that the deuteriums in 2,6-positions of [D_5]2,6-dmethylpiperidine could be exchanged with protons from reagents (HCl) and solvents (H_2O) under heating conditions. To avoid losing deuteriums, deuterated solvents and reagents were used for the amidine formation and debenzylation reactions. The nitrile **19** was converted to the amidine **21** by using Pinner conditions in the presence of deuterated hydrochloric acid and ethanol followed by amination with NH_3 gas. Finally, the phenolic benzyl ether was removed by hydrolysis of the ether **21** in deuterated HCl and MeOH to afford the desired [D_5]PD0198961 in 39% overall yield.

In summary, ^{14}C labeled PD0198961 was synthesized in four radiosynthetic steps starting from [^{14}C]CuCN. The overall radiochemical yield was 48% with a radiochemical purity >99% and a specific activity 54.0 mCi/mmol. The study on the cyanation reaction of the aromatic bromide with inorganic [^{14}C]cyanide showed that the presence of pyridine in the CuCN cyanation reaction improved the yield from 40 to 87%. The deuterium-labeling was accomplished by PtO_2-catalyzed hydrogenation of

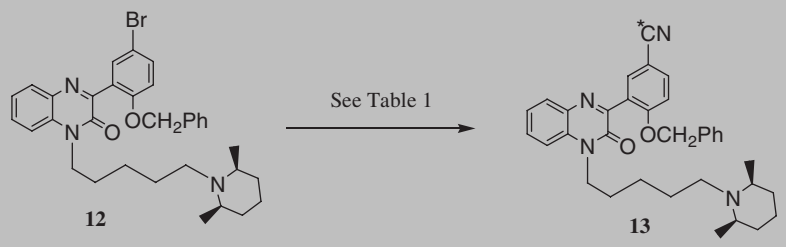


Scheme 1. Original synthesis of unlabeled PD0198961.



Scheme 2. Synthesis of [^{14}C] PD0198961.

Table 1. The cyanation of bromide **13**

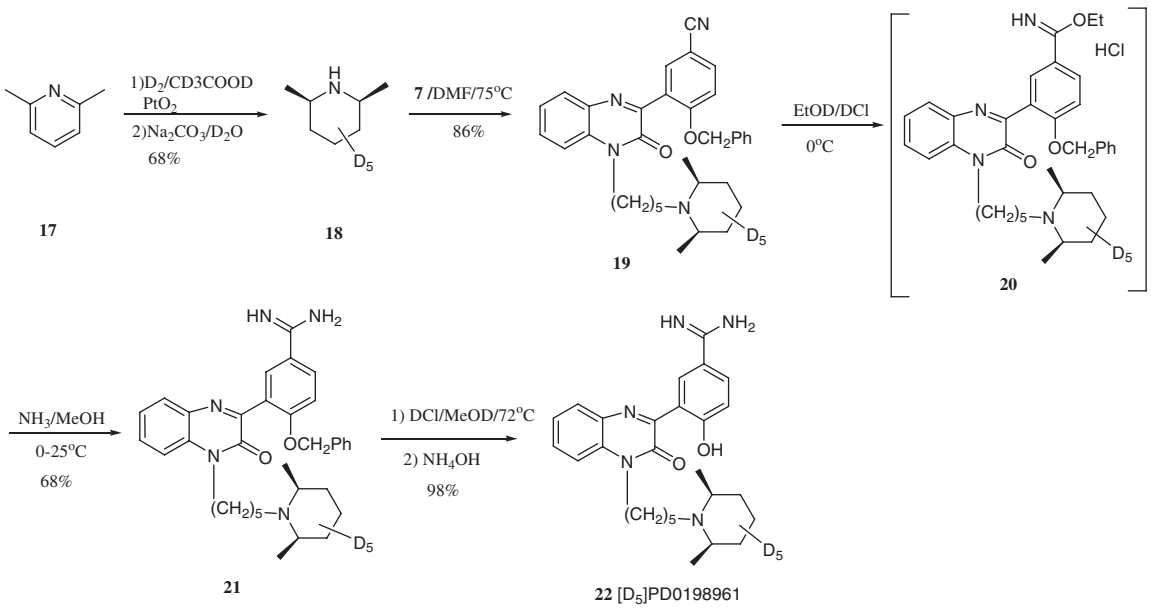


Entry	Condition	Molar ratio of **12**/MCN	Yield (%)
1	KCN/Pd(PPh$_3$)$_4$ 18-crown-6/THF-EtOH/85°C/24 h	1:1.2	10
2	CuCN/DMF/175°C/24 h	1:1.1	40
3	CuCN/DMF/175°/24 h	1:1.5	55
4	CuCN/NMP/210°/24 h	1:1.1	20
5	CuCN/DMF/Py/175°C/24 h	1:1.1	70
6	CuCN/DMF/Py/160°C/48 h	1:1.1	87
7	[^{14}C]CuCN/DMF/Py/160°C/48 h	1:1.1	82

2,6-dimethylpyridine to *cis*-2,6-dimethyl[$^2H_5$]piperidine, which was subsequently incorporated into the target molecule with excellent chemical purity (99.6%) and high isotopic enrichment (91% D_5).

Experimental

All reactions were carried out under an atmosphere of nitrogen unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded



Scheme 3. Synthesis of [D_5]PD0198961.

on a Varian Gemini 200 or 400 MHz instrument. Chemical purity of all labeled compounds was determined by HPLC and GC-MS or LC-MS. Purifications were done by flash column chromatography on Biotage Flash 40 system. [^{14}C]KCN (250 mCi, 54 mCi/mmol) was purchased from American Radiolabeled Chemicals, Inc. The intermediates 5 and 7 were provided by Chemical R&D, Ann Arbor Lab, Pfizer Inc. All prepared stable-isotope labeled compounds contained less than 0.01% of unlabeled material based on LC-MS analysis; otherwise as indicated.

3-(2-(Benzyloxy)-5-bromophenyl)-1-(5-bromopentyl)quinoxalin-2(1H)-one (**11**): To a solution of aryl bromide **5** (8.16 g, 20.0 mmol) in DMF (120 ml) was added NaH (60%, 2.40 g, 60.0 mmol) at 0°C. The resulting suspension was stirred at room temperature for 45 min. To the reaction mixture was then added 1,5-dibromopentane (16.0 ml, 117.7 mmol) at room temperature. The mixture was stirred at room temperature for 18 h, and then poured into water (300 ml). The aqueous layer was extracted with EtOAc (35 ml × 3). The combined organic layers were washed with brine (25 ml × 2) and dried over $MgSO_4$. The solvent was evaporated to give a colorless oil, which was applied to flash silica gel chromatography (6/1 hexane/EtOAc). The titled compound **11** was obtained as colorless oil (4.55 g, 41%). ^{1}H NMR ($CDCl_3$) 7.93 (dd, 1H), 7.62–7.49 (m, 2H), 7.39–7.26 (m, 8H), 6.92 (d, 1H), 5.10 (s, 2H), 4.26 (t, 2H), 3.39 (t, 2H), 1.95–1.57 (M, 6H); ^{13}C NMR ($CDCl_3$) 156.89, 156.185, 154.18, 137.15, 133.96, 133.63, 133.35, 133.29, 131.27, 131.15, 129.34, 128.86, 128.27, 127.67, 124.04, 115.17, 114.00, 113.85, 71.46, 42.65, 33.82, 32.69, 26.85, 25.99; MS (CI) *m/z* 554, 556; The *O*-alylation by-product was also isolated as a colorless oil (0.556 g, 50%). ^{13}C NMR 156.50, 156.39, 140.97, 139.04, 136.98, 133.81, 133.72, 133.60, 130.43, 129.50, 129.18, 128.93, 128.23, 127.355, 127.08, 126.94, 114.78, 113.73, 70.94, 66.82, 34.15, 32.73, 28.23, 25.20; MS (CI) *m/z* 554, 556

3-(2-(Benzyloxy)-5-bromophenyl)-1-(5-(cis-2,6-dimethylpiperidin-1-yl)pentyl)quinoxalin-2(1H)-one (**12**): To a solution of dibromide **11** (3.136 g, 5.65 mmol) in DMF (15 ml) was added *cis*-2,6-dimethylpiperidine (22.8 ml, 16.95 mmol). The solution was stirred at 75°C for 18 h, and then cooled to room temperature and poured into water (200 ml). The aqueous layer was extracted with EtOAc (50 ml × 3). The combined organic layers were washed with brine (50 ml × 10), and dried over $MgSO_4$. The solvent was evaporated to give an oily residue, which was applied to flash chromatography. The pure titled compound **12** was obtained as a colorless oil (2.68 g, 81%). ^{1}H NMR ($CDCl_3$) 7.90 (d, 1H), 7.60–7.43 (m, 2H), 7.44–7.21 (m, 8H), 6.88 (d, 2H), 5.07 (s, 2H), 4.23 (t, 2H), 2.77 (t, 2h), 2.35–2.48 (m, 2H), 1.80–1.21(m, 12H), 1.10 (d, 6H), 1.0–1.20 (m, 2H). ^{13}C NMR ($CDCl_3$) 156.89, 156.133, 154.16, 137.14, 133.89, 133.61, 133.35, 131.18, 131.10, 129.38, 128.83, 128.22, 127.65, 123.94, 115.16, 114.09, 113.78, 71.44, 56.06, 53.16, 48.48, 42.97, 35.39, 34.02, 27.73, 25.56, 25.12, 23.45, 23.07, 21.71; MS (CI) *m/z* 587, 589.

4-(Benzyloxy)-3-(4-(5-cis-2,6-dimethylpiperidin-1-yl)pentyl)-3-oxo-3,4-dihydroquinoxalin-2-yl-[^{14}C]benzonitrile (**13**): To a mixture of [^{14}C]CuCN (93.6 mCi, 1.73 mmol, 54 mCi/mmol) in pyridine (0.4 ml) and DMF (15 ml) was added the aryl bromide **12** (0.97 g, 1.65 mmol). The reaction mixture was stirred at room temperature for 20 min, and then at 160°C for 48 h. The precipitates were filtered off. The filtrate was poured into water (80 ml), and extracted with EtOAc (25 ml × 4). The combined organic layers were washed with 10% NH_4OH (15 ml × 2), water (15 ml × 2) and brine (15 ml × 2), and dried over $MgSO_4$. The concentration of the organic layer provided brown oily residue, which was applied to flash chromatography (20/1/0.1 CH_3Cl/MeOH/NH_4OH). The title compound **13** was prepared as a yellowish oil (0.871 g, 82%, radiochemical purity 98.4%, 54 mCi/mmol, 87.8 mCi). ^{1}H NMR (DMSO-d6) 7.95 (dd, 1H), 7.93 (d, 1H), 7.86 (d, 1H), 7.6–7.7 (m, 2H), 7.2–7.4 (m, 7H); 5.22 (s, 2H), 4.23 (t, 2H), 0.9–2.5 (m, 22H); MS (CI) *m/z* 535, 557.

4-(Benzyloxy)-3-(4-(5-((2R,6S)-2,6-dimethylpiperidin-1-yl)pentyl)-3-oxo-3,4-dihydroquinoxalin-2-yl)[^{14}C]benzamidine (**15**): Dry HCl gas was introduced to a reaction mixture of compound **13** (0.81 g, 81.5 mCi, 1.51 mmol) in dry EtOH (25 ml) at 0°C for 3.5 h. The reaction mixture was warmed up slowly to room temperature. The solvent was removed under reduced pressure to give ethyl imidate ether **14**. The crude compound **14** was dissolved in dry MeOH (16 ml). Dry NH_3 gas was introduced to the reaction

solution at 5°C for 3.5 h. The mixture was stirred at room temperature for 15 h. The concentration of the mixture gave crude yellow oil, which was applied to flash column chromatography. The title compound **15** was obtained as a white solid (0.509 g, 49.8 mCi, 61%). ^{1}HNMR (DMSO-d6) 8.65 (bs, 4H), 7.50 (dd, 1H), 7.90 (d, 1H), 7.85 (d, 1H), 7.66 (d, 2H), 7.42–7.24 (m, 7H), 5.23 (s, 2H), 4.24 (t, 2H), 2.65–2.43 (m, 2H), 2.31–2.1.5 (m, 2H); ^{13}C NMR (DMSO-d6) 163.33, 156.30, 154.41, 137.84, 134.29, 134.19, 133.01, 132.72, 131.51, 131.55, 129.86, 129.45, 129.37, 128.65, 125.61, 121.56, 116.19, 114.76, 72.26, 60.26, 60.58, 43.33, 33.69, 28.18, 24.95, 23.74, 18.89, 18.80; MS (CI) *m/z* 551, 553.

3-(4-(5-(Cis-2, 6-dimethyl|piperidin-1-yl)pentyl)-3-oxo-3, 4 - dihydroquinoxalin-2-yl)-4-hydroxy[1-^{14}C]benzamidine (**16, [^{14}C]PF0198961**): A mixture of compound **15** (0.213 g, 20.8 mCi, 0.385 mmol) in MeOH (6 ml) and concentrated HCl solution (3.5 ml) was stirred at 72°C for 24 h. The solvent was evaporated under reduced pressure to give the crude product **16** as a yellow oil, which was applied to flash column chromatography (alumina, $CH_3CN/H_2O/NH_4OH = 100/5/1$). The title compound [^{14}C]PD0198961 was obtained as a yellow solid (0.176 g, 20.5 mCi, 98%). ^{1}HNMR (CD_3OD) 9.31 (d, 1H), 7.96 (d, 1H), 7.85 (dd, 1H), 7.81–7.74 (m, 2H), 7.55–7.51 (m, 2H), 7.20, (d, 1H), 4.51 (t, 2H), 3.1–3.4 (m, 2H), 2.0–1.3 (m, 20H); ^{13}C NMR (CD_3OD) 163.30, 156.28, 154.40, 137.81, 134.26, 134.17, 133.0, 132.70, 131.48, 131.52, 129.84, 129.44, 129.36, 128.64, 125.62, 60.25, 60.59, 43.33, 33.68, 28.16, 24.93, 23.73, 18.85, 18.79; MS (CI) *m/z* 462, 464. Radiochemical purity: 99.1%; chemical purity: 99.6%; HPLC conditions: column: Hypersil BDS C18, 5 um, 4.6 × 250 mm; mobile phase: *A* = 0.1% THF in H_2O, *B* = 0.1% THF in CH3CN, initial to 5 min, *A*:*B* = 75:25, 5–10 min, *A*:*B* = gradient to 50:50, hold *A*:*B* = 50:50 to 30 min; flow rate: 1.0 ml/min; UV detection: 225 nm; retention time: 11.3 min. Specific activity: 54 mCi/mmol.

2,6-Cis-[D_5]dimethylpiperidine (**18**): A mixture of 2,6-dimethylpyridine (10 g, 93.5 mmol) in CD_3COOD (20 ml) was hydrogenated with D_2 gas under 50 psi in the presence of PtO_2 (1 g). The catalyst was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 ml). To this solution was added Na_2CO_3 (15 g). The suspension was stirred at room temperature for 2 h and filtered to give a colorless liquid. The distillation of the crude material gave the titled compound **18** as a colorless oil (7.4 g, 68%). ^{1}H NMR ($CDCl_3$) 1.6–1.4 (m, 2H), 1.3–1.1 (m, 1H), 0.98 (s, 6H); MS (CI) *m/z* 117, 118 (90%), 119

4-(Benzyloxy)-3-(4-(5-cis-2,6-[D5]dimethylpiperidin-1-yl)pentyl)-3-oxo-3,4-dihydroquinoxalin-2-yl-benzonitrile (**19**): A mixture of bromide **7** (0.812 g, 1.62 mmol) and compound **18** (0.60 g, 5 mmol) in DMF (2.0 ml) was stirred at 70°C for 24 h. The reaction mixture was poured into D_2O (15 ml), and extracted with EtOAc (20 ml × 3). The combined organic layers were washed with brine (6 ml × 2), and dried over $MgSO_4$. The solution was evaporated to give the crude product **19** as a yellow oil, which was applied to flash column chromatography (silica, CH_3Cl/MeOH/NH_4OH: 20/1/0.1). The title compound **19** was obtained as a colorless oil (0.751 g, 86%). ^{1}H NMR ($CDCl_3$) 7.93 (dd, 1H), 7.76 (dd, 1H), 7.67–7.57 (m, 1H), 7.42–7.26 (m, 8H), 7.06 (d, 1H), 5.17 (s, 2H), 4.26 (t, 2H), 2.73 (t, 2H), 1.80–1.70 (m, 3H), 1.56–1.15 (m, 6H), 1.08(s, 6H). ^{13}C NMR ($CDCl_3$) 160.91, 155.35, 154.05, 136.25, 135.65, 134.89, 133.60, 133.42, 131.45, 131.31, 128.99, 128.68, 128.56, 127.65, 124.15, 119.22, 114.19, 113.62, 105.04, 71.38, 48.46, 43.08, 35.50 (m), 27.76, 25.60, 23.65, 21.77, 21.63; MS (CI) *m/z* 539.

4-(Benzyloxy)-3-(4-(5-cis-2,6-dimethyl[D_5]piperidin-1-yl)pentyl)-3-oxo-3,4-dihydroquinoxalin-2-yl-benzonitrile (**21**): The same procedure as for the preparation of compound **15** was followed. From compound **19** (0.733 g) the title compound **21** was obtained as a white solid (0.514 g, 68%). ^{1}H NMR (CD_3OD) 8.0–7.87 (m, 3H), 7.72–7.60 (m, 2H), 7.48–7.25 (m, 7H), 5.25 (s, 2H), 4.34 (t, 2H), 2.80 (t, 2H), 1.78–1.65 (m, 2H), 1.58–1.29 (m, 7H), 1.12 (s, 6H); ^{13}C NMR (CD_3OD) 167.58, 163.30, 156.49, 155.75, 137.81, 134.71, 134.22, 132.95, 132.67, 131.50, 129.83, 129.41, 129.32, 128.71, 125.56, 121.70, 116.11, 114.67, 72.28, 57.37, 43.72, 34.68 (m), 28.56, 25.84, 23.02, 20.77, 20.61; MS (CI) *m/z* 556.

3-(4-(5-(Cis-2,6-dimethyl[D_5]piperidin-1-yl)pentyl)-3-oxo-3,4-dihydroquinoxalin-2-yl)-4-hydroxybenzamidine (**22, [D_5]PF0198961**): The same procedure as for the preparation of compound **16** was followed. From compound **21** (0.501 g) the title compound **22** was obtained as a bright yellow solid (0.41 g, 98%). ^{1}H NMR (CD_3OD) 11.95 (bs), 10.65 (bs), 9.30 (s, 1H), 9.17 (s, 1H), 8.27–7.15 (m, 5H), 4.27 (m, 2H), 3.91 (m, 4H), 3.09 (m, 3H), 1.85–1.42 (m, 6H), 1.02 (s, 6H); ^{13}C NMR (CD_3OD) 167.55, 163.28, 156.45, 155.73, 137.80, 134. 69, 134.20, 132.90, 132.68, 131.48, 129.80, 129.42, 129.31, 128.68, 125.54, 57.35, 43.70, 34.67 (m), 28.55, 25.83, 23.00, 20.77, 20.59; MS (CI) *m/z* 466 (91% isotopic purity); chemical purity (CP) 99.60%, HPLC conditions: column: Hypersil BDS C18, 5 um, 4.6 × 250 mm; mobile phase: *A* = 0.1% THF in H_2O, *B* = 0.1% THF in CH_3CN, initial to 5 min, *A*:*B* = 75:25, 5–10 min, *A*:*B* = gradient to 50:50, hold *A*:*B* 50:50 to 30 min; flow rate: 1.0 ml/min; UV detection: 225 nm; retention time: 11.3 min.

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