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Synthesis of the Serotonin Ligands, RS-56532-^{14}C and RS-66331-^{14}C From a Common Labelled Intermediate

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SUMMARY

Two approaches towards the synthesis of 3-chloro-4-amino-1,8-naphthalic anhydride-[^{14}C], which served as the common intermediate in the preparation of the two title compounds, are described. Although nucleophilic incorporation of the label via KCN was superior to an electrophilic sequence using CO_2, the latter approach was adopted since the nitrile could not be hydrolyzed to the desired acid. The specific activities of RS-56532-^{14}C and RS-66331-^{14}C were 56.8 mCi/mmol and 53.7 mCi/mmol, respectively.

Key Words: 5-HT, serotonin, C-14, RS-56532, RS-66331

INTRODUCTION

It has been recognized for some time that agonists and antagonists of 5-HT (5-hydroxytryptamine, serotonin) are responsible for a wide variety of biological effects (1). The mode of action of such compounds is based on the specificity of binding to any one of the many 5-HT receptor subtypes. RS-56532 and RS-66331 were shown to be potent 5-HT ligands (8a,8b). As such, they were considered to be promising therapeutic agents with potential for treatment of anxiety associated with withdrawal from drugs of abuse. The C-14 analogs of these compounds were required for the usual array of metabolism studies associated with the development of potential new drug entities. Since both compounds shared a common

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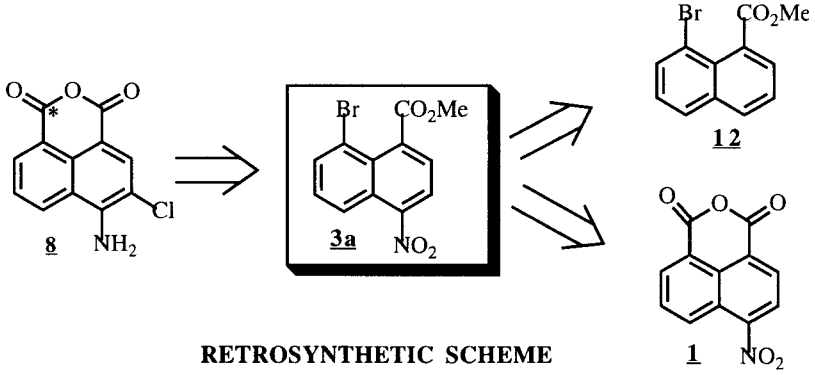
aromatic nucleus, i.e., 3-chloro-4-amino-1,8-naphthalic anhydride (**8**), we focused on the synthesis of that material as the key labelled intermediate. The two approaches investigated for the synthesis of (**8**) and its use to prepare RS-56532-^{14}C (**10**) and RS-66331-^{14}C (**11**) are described in detail.

RESULTS AND DISCUSSION

The portion of the target molecules (**10**) and (**11**) most amenable to labelling was one of the two carbonyl carbons. Such an approach would have the advantage of providing a labelled intermediate which was common to both compounds. Our initial efforts were, therefore, directed towards the penultimate intermediate 3-chloro-4-amino-1,8-naphthalic anhydride-[^{14}C] (**8**). The retrosynthetic scheme shown below indicates that (**8**) could be accessed via the bromo-nitro ester (**3a**), which in turn may be prepared from either of the commercially available substrates, 1-carbomethoxy-8-bromonaphthalene (**12**) or 4-nitro-1,8-naphthalic anhydride (**1**).

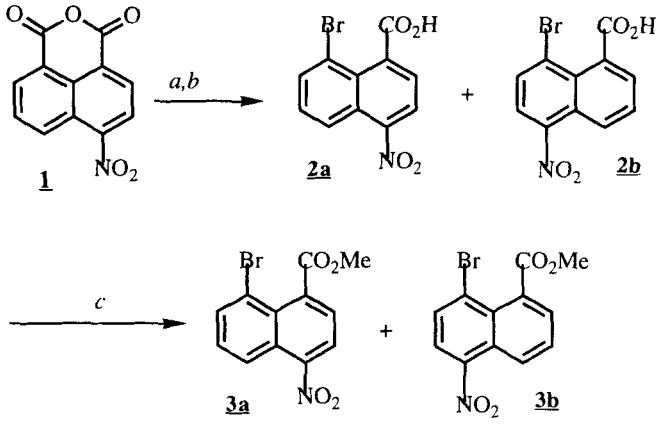


RETROSYNTHETIC SCHEME

Two approaches to (**3a**) were undertaken simultaneously. Thus, nitration of (**12**) with fuming nitric acid in acetic acid resulted in almost instant formation of a dinitro product. This reaction could not be controlled to give the desired mononitro product even when only one equivalent of nitric acid was added and the reaction was kept at 0°. However, treatment of (**12**) with 70% nitric acid in acetic acid at 65° followed by esterification with diazomethane afforded an inseparable mixture of 4-nitro and 5-nitro products in about 40% yield. Separation was not required since both isomers would convert to same 1,8-anhydride after carbonation and hydrolysis.

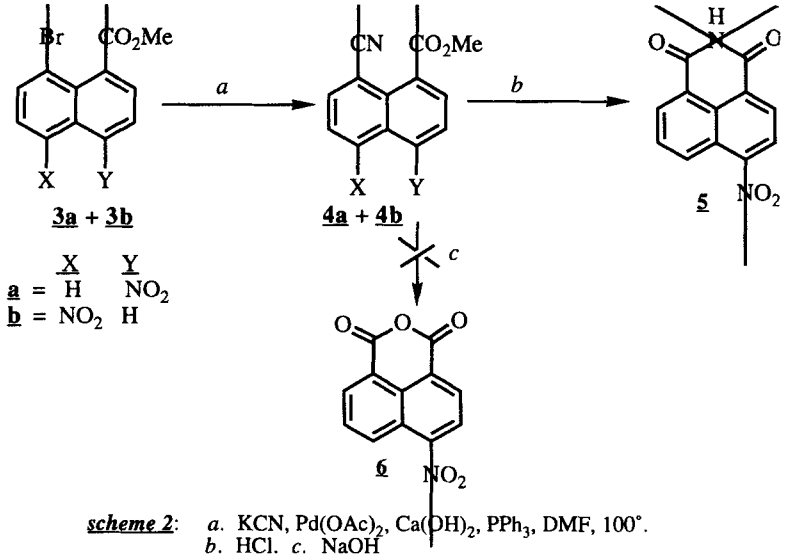
A superior approach (***scheme 1***) to (**3a**) involved heating a solution of (**1**) with mercuric oxide in acetic acid at reflux to give the aryl monomercury salt which was converted directly to (**2a,b**) by treatment with bromine and sodium bromide at 0° (2). Esterification with diazomethane afforded

a 66% yield of an inseparable mixture of 4-nitro and 5-nitro-8-bromonaphthalic acid methyl esters, (**3a**) and (**3b**), in a ratio of 9:1 as determined by NMR. Again, it was not necessary to purify the mixture of positional isomers.

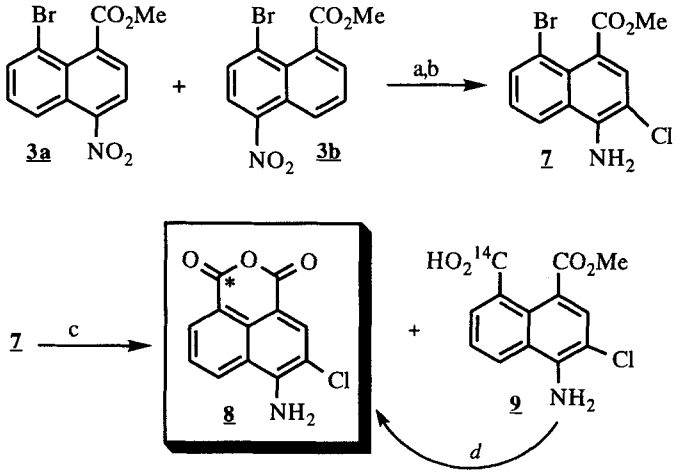


scheme 1: *a*. HgO, aq HOAc, reflux, 50h. *b*. Br_2, NaBr, HOAc, 0-90°, 1.25h
c. CH_2N_2, THF, ether

We investigated two ways of introducing a carbon label into (**3a**). The nucleophilic approach is depicted in ***scheme 2***. In a trial experiment, (**3a,b**) was treated with KCN in the presence of CuCN in N-methylpyrrolidinone (3) to furnish a 15% yield of cyano esters (**4a,b**). However, Pd^0 mediated cyanation afforded a 85% yield of the desired nitrile (4). Attempts to hydrolyze (**4a,b**) under a variety of basic conditions gave unidentifiable products. Acid hydrolysis gave the imide (**5**) which could not be converted anhydride (**6**). Moreover, although reduction ($NaBH_4/CuSO_4$) (5) of the nitro group of (**4a,b**) gave the corresponding amine (**12**) in good yield, subsequent hydrolysis under a variety of conditions, again afforded only unidentifiable mixtures. Unable to capitalize on the high yield obtained in the Pd^0 mediated cyanation of (**3a,b**), we turned our attention to the use of $^{14}CO_2$ in an electrophilic process as shown in ***scheme 3***. Selective reduction (6) of the nitro group in (**3a,b**) was accomplished using $SnCl_2 \cdot 2H_2O$ in ethyl acetate. This was an essential first step since it is known that nitro groups can be incompatible with lithium-halogen exchange reactions (7). Chlorination of the crude amine reaction mixture with dichlorodimethylhydantoin (halane), followed by flash chromatography, afforded the desired carbonation substrate (**7**) in 70% yield. The nmr spectrum of this material showed no evidence of the isomer expected from **3b**. Initial lithiation/carbonation experiments using t-BuLi/CO_2 resulted primarily in debromination to 3-chloro-4-amino-1-naphthoic acid methyl ester. None of the desired carbonation product was obtained. However, when (**7**) was pretreated with NaH, followed by n-BuLi at -78°,

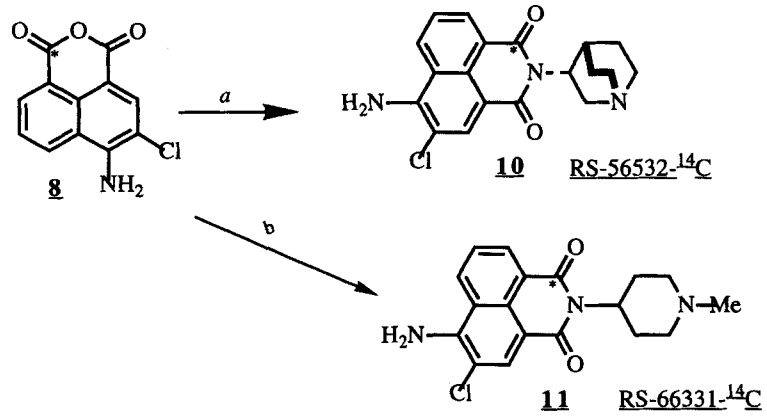


scheme 2: *a*. KCN, $Pd(OAc)_2$, $Ca(OH)_2$, PPh_3, DMF, 100°. *b*. HCl. *c*. NaOH



scheme 3: *a*. $SnCl_2.2H_2O$, EtOAc, 70°, 1 h; b. halane, -35° to-40°, 1.5 h. *c*. NaH (5 eq), THF, 0°; *n*-BuLi, -78°, 1 h; $Ba^{14}CO_3$, H_2SO_4, -198° to rt, 19 h. *d*. Silica gel, acetone, rt.

addition of a 20 fold excess of CO_2 and stirring for 6 h furnished the desired anhydride, (**8**), in 38% yield. In the subsequent labelling trial reactions, using a 2.5 fold excess of $^{14}CO_2$ and increasing the reaction time from 6h to 19h resulted in a 94% chemical yield (38% radiochemical yield) of a mixture of carbonation products (**8**) and (**9**). Stirring an acetone solution of this mixture over silica gel for two days resulted in complete conversion of the half acid (**9**) to the desired anhydride (**8**). Finally, reaction of (**8**) with (S)-3-aminoquinuclidine gave RS-56532-^{14}C (**10**) in 53% yield at a specific



scheme 4: *a.* (S) 3-aminoquinuclidine, MeOH. *b.* 4-amino-N-methylpiperidine

activity of 56.8 mCi/mmol. Treatment of the same intermediate with N-methyl-4-aminopiperidine afforded RS-66331-^{14}C (**11**) in 64% yield. ***Scheme 4*** (above) shows the latter two reactions.

In summary, both nucleophilic and electrophilic methods were developed to introduce C-14 into highly functionalized naphthalene precursors (**3a,b**) and (**7**). The resulting labelled anhydride (**8**) served as a common intermediate for the synthesis of two important 5-HT ligands at high specific activity.

EXPERIMENTAL

$Ba^{14}CO_3$ was purchased from Nordion International. Unlabelled reagents were purchased from Aldrich Chemical Co. and were used without purification. Solvents were HPLC grade. Radiochromatography was performed on a Bioscan 200 Scanner. Radioassays were obtained using a Packard 4000 liquid scintillation counter. UV spectra were obtained using a Hitachi UV-265 spectrophotometer. NMR spectra were recorded using a Varian EM 390 spectrometer. IR were recorded using a Nicolet 5PC FT-IR spectrometer. MS spectra were obtained on a Finning-MAT 8230 spectrometer.

4-Nitro-8-bromo-1-naphthalenecarboxylic acid (2a)
4-Nitro-1,8-naphthalic anhydride (**1**) (10 g, 41 mmol) was suspended in 163 mL of 0.78 M aq NaOH and was warmed to 90°. HgO (8.91 g, 41 mmol) was dissolved in 30 mL of AcOH/H_2O (1:4 v/v) and was added to the anhydride dropwise over 20 min. The mixture was made distinctly acidic by adding 15 mL of glacial acetic acid and was heated at reflux for 50 h. The reaction was cooled in an ice bath. The resulting precipitate was filtered, washed sequentially with H_2O, EtOH, Et_2O, and dried, to afford 14.5 g of crude mono-mercurated compound. This crude product was suspended in 150 ml of glacial acetic acid, cooled to 0 °C, and Br_2 (5.8 g

dissolved in 40 mL of concentrated aq NaBr) was added dropwise over 1 h. The mixture was warmed to 90° for 15 min, cooled, then poured into cold H_2O. The resulting precipitate was filtered, washed with H_2O, and dried to give 8 g of product (66% over two steps) as an inseparable mixture of 4-nitro and 5-nitro-8-bromonaphthalene-1-carboxylic acids.

TLC: silica gel (10% MeOH/acetone) R_f 0.15.
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.29 (d, 1 H, J = 7.9), 8.25 (d, 1 H, J = 8.6), 8.17 (d, 1 h, J = 6.9), 7.85 (d, 1 H, J = 7.9), 7.72 (t, 1 H, J = 7.9).
IR (KBr) 3856-3431, 3088, 1707, 1618, 1560, 1525, 1454, 1352, 1264, 1194, 1163, 1024, 860, 808, 765 cm^{-1}.
UV (MeOH) λ_{max} 340 (ε = 161), λ_{max} 220 (ε = 1270).
MS (EI) m/z (rel. inten.) 295 (M+, 8), 216 (100),186 (15),170 (25),125 (10).

1-Carbomethoxy-4-nitro-8-bromonaphthalene (3a)
To a solution of the mixture of bromo acids (0.5 g, prepared above) in THF (10 mL) at room temperature was added excess cold CH_2N_2 in Et_2O. The mixture was stirred for 20 min, and the excess CH_2N_2 was destroyed by addition of glacial acetic acid. Chromatography on silica gel with 10% Et_2O/hexane afforded 0.51 g of product. Proton NMR showed a 9:1 mixture of 4-nitro and 5-nitro isomers.

MP 122-126 °C.
TLC: silica gel (20% acetone/hexane) R_f 0.33.
^{1}H NMR (300 MHz, $CDCl_3$) for 4-nitro isomer δ 8.35 (dd, 1 H, J = 1, 6.8), 8.07 (d, 1 H, J = 7.7), 8.0 (dd, 1 H, J = 1.7, 8), 7.56 (dd, 1 H, J = 1, 7.7), 4.02 (s, 3 H), 5-nitro isomer δ 8.53 (dd, 1 H, J = 1.3, 8.4), 7.98 (s, 2 H), 7.65 (m, 2 H), 4.0 (s, 3 H).
IR (KBr) 1724, 1523, 1502, 1450, 1431, 1400, 1350, 1334, 1313, 1267, 1205, 1184, 1161, 1124, 997, 837, 810, 798, 765, 713 cm^{-1}.
UV (MeOH) λ_{max} 344 (ε = 317), λ_{max} 253 (ε = 567), λ_{max} 229 (ε = 899).
MS (EI) m/z (rel. inten.) 309 (M+, 10), 280 (10), 230 (100), 184 (25), 125 (12).

1-Carbomethoxy-3-chloro-4-amino-8-bromonaphthalene (7)
To a solution of 4-nitro and 5-nitro-1-carbomethoxy-8-bromonaphthalene (0.5 g, 1.62 mmol) in EtOAc (10 mL, 0.16 M) was added $SnCl_2.2H_2O$ (1.83 g, 8.09 mmol). The mixture was warmed to 70° for 1 h, cooled to room temperature, then poured into aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried and concentrated to give 480 mg of the amine product. The product was taken on to the next step without further purification.

TLC: silica gel (40% acetone/hexane) R_f 0.2.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8 (d,1 H, J = 7.4), 7.73, (d, 1 H, J = 8.7), 7.23 (t, 1 H, J = 7), 6.65 (d, 1 H, J = 7.7), 3.9 (s, 3 H).

To a solution of the above crude reaction product in CH_2Cl_2 (6.9 mL, 0.25 M) at -35° to -40° was added halane (0.356 g, 1.81 mmol) over 1.5 h. The mixture was stirred for an additional 1.5 h, poured into aqueous $NaHSO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried, and concentrated. Chromatography on silica gel (30% Et_2O/hexane) afforded 380 mg of pure (7) (70% over two steps).

TLC: silica gel (50% Et_2O/hexane) R_f 0.32.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, 1 H, *J* = 8.4, 1.1), 7.75 (dd, 1 H, *J* = 8.4, 1.1), 7.60 (s, 1 H), 7.30 (t, 1 H, *J* = 8.4), 3.94 (s, 3 H).
IR (KBr) 3422, 3339, 1705, 1630, 1412, 1354, 1321, 1277, 1253, 1203, 1178, 1074, 1020, 792, 750, 684, 630 cm^{-1}.
UV (MeOH) λ_{max} 344 (ε = 317), λ_{max} 229 (ε = 899), λ_{max} 253 (ε = 566).
MS (EI) m/z (rel. inten.) 315 (M+, 40), 282 (20), 234 (100), 219 (70).

3-Chloro-4-aminonaphthalic anhydride-^{14}C (8)
1-Carbomethoxy-3-chloro-4-amino-8-bromonaphthalene (7) (0.275 g, 0.88 mmol) and NaH (0.22 g, 4.4 mmol, prewashed with dry hexanes) were placed under vacuum in separate round bottom flasks connected to a vacuum line. THF was distilled from $LiAlH_4$ into each flask (7 mL in flask containing (7), 30 mL in flask containing NaH) which had been precooled to -78°. Then the vacuum in the flask containing (7) was released with nitrogen and the solution was transferred by means of a canula into the flask containing the NaH; an immediate yellow solution appeared. After 20 min, the yellow solution was cooled to -78° and *n*-BuLi (0.55 mL, 0.88 mmol, 1.6 M in hexanes) was injected. The reaction mixture was stirred for 1.3 h (red solution). The reaction flask was cooled to -196° with liquid N_2, and $Ba^{14}CO_3$ (125.4 mCi, 57 mCi/mmol, 0.437 g, 2.2 mmol), contained in an evacuated side-arm septum flask connected to the vacuum line, was acidified with concentrated H_2SO_4 (7 mL). The $^{14}CO_2$, thus generated, was vacuum transferred onto the lithiation reaction. The reaction flask was warmed to -78°. The reaction was stirred vigorously for 19 h and allowed to warm to ambient temperature during that time.

The excess $^{14}CO_2$ was transferred into a waste collection flask under reduced pressure. The reaction mixture was quenched with satd. $NaHCO_3$ (10 mL) and extracted with EtOAc to remove the neutral components (0.47 mCi). The aqueous solution was acidified with concentrated HCl to pH 3. A yellow solution formed which turned darker as the mixture was stirred at room temperature. After stirring the mixture for 2 d, the yellow precipitate which had formed was filtered. The mother liquor was still yellow, but after extraction with EtOAc the yellow color disappeared. The precipitate was dissolved in 2:1 acetone/EtOAc, combined with the organic extracts and dried over anhydrous $MgSO_4$. Silica gel TLC (30% acetone/hexane) of the crude product showed a mixture of anhydride (8) and half acid/ester (9). Radioassay of the crude mixture was 46.5 mCi. A silica gel column was packed in hexanes. The crude mixture was loaded

onto the column with acetone. The column was eluted with 100% hexanes then 50% acetone/hexane. Fractions which contained a mixture of half acid/ester (**9**) and anhydride (**8**) were combined. When this solution was allowed to stand over silica gel for two days, (**9**) converted completely over to the desired anhydride (**8**).

TLC: silica gel (40% acetone/hexane R_f 0.46 (anhydride).
Total activity 45.7 mCi (36.4% radiochemical yield based on $Ba^{14}CO_3$, 91.4% chemical yield).
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.82 (d, 1 H, *J* = 8), 8.45 (d, 1 H, *J* = 7), 8.23 (s, 1 H), 7.83 (s, 2 H), 7.76 (t, 1 H, *J* = 8).
IR (KBr) 3856, 3676, 3360, 2926, 1763, 1731, 1631, 1581, 1516, 1466, 1400, 1358, 1311, 1273, 1228, 1199, 1143, 1024, 993, 773 cm-1.
UV (MeOH) λ_{max} 416 (ε = 318), λ_{max} 272 (ε = 764).
MS (EI) m/z (rel. Inten.) 247 (M+, 45), 203, (100), 175 (50), 140 (30), 113 (25).

(S)-6-Amino-2-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2,3-dihydro-1,3-dioxo-1H-benz[de]isoquinolin hydrochloride, RS-56532-^{14}C (10)

To a solution of 3-chloro-4-amino-1,8-naphthalic anhydride-^{14}C (**8**) (14.3 mCi, 0.251 mmol) in MeOH (20 mL) was added (S)-3-aminoquinuclidine (32 mg, 0.251 mmol). The resulting mixture was heated at reflux for 3 h then cooled to 60° (bath temperature) for 14 h and again at reflux for 8 h. Although this process was repeated for 2 days starting material was still present. Therefore, more (S)-3-aminoquinuclidine (93 mg) was added and the mixture was refluxed 7 h then cooled to 60° (bath temperature) for 4 d. At this point, TLC analysis showed mostly product. The reaction mixture was concentrated, the excess (S)-3-aminoquinuclidine was sublimed from the product and the residue was purified by column chromatography (silica gel) using 60% EtOAc/MeOH to collect the unreacted starting material. The polarity of the solvent was adjusted to 60% EtOAc/MeOH with 1 mL NH_4OH to collect RS-56532-^{14}C. The product was concentrated, redissolved in EtOH, and concentrated again. This process was repeated three times to ensure removal of NH_4OH used in chromatography. The residue was dissolved in EtOH and acidified with 1.75 mL of 0.12 M HCl in EtOH. The mixture was stirred for 20 min, concentrated *in vacuo* to remove excess HCl, and redissolved in EtOH. The radiochemical purity was >98% using the methods described below.

TLC: silica gel (6.5:3.4:0.1 EtOAc/MeOH/NH_4OH);
RP-C_{18} (60% CH_3CN/ 0.03 M TEAP pH3).
HPLC: Biotage column 4.6 x 250, 20% CH_3CN/0.03 M TEAP pH3, 1 mL/min, monitored at 220 nm.
Total activity: 7.62 mCi (53% yield).
Specific activity: 56.8 mCi/mmol (by UV, EtOH, λ_{max} 259 nm, ε=19,523).

(S)-6-Amino-5-chloro-2-(1-methylpiperiolin-4-yl)-2,3-dihydro-1H-benz[de]isoquinolin-1,3-dione hydrochloride, RS 66331-^{14}C (11)

To a solution of **8** (7.62 mCi, 57 mCi/mmol) in 10 mL of EtOH was added methyl-4-aminopiperidine in 10 mL of EtOH. The resulting mixture was refluxed and monitored by TLC (silica gel, 40% acetone/hexane). After 1.5 d, the mixture was cooled , concentrated and applied to a silica gel column. Elution with 20% (2%NH_4OH/MeOH)/80% EtOAc afforded (**11**) which was still impure. A second chromatography was done using a solvent mixture of 50% (2% NH_4OH/MeOH) / 50% CH_2Cl_2. The pure fractions were combined, concentrated and redissolved in EtOH. The mixture was then acidified with 1.5 mL of 0.12 M aqueous HCl in EtOH. The mixture was stirred for 10 min, concentrated *in vacuo*, and the residue was redissolved in EtOH. This process was repeated three times to remove excess HCl. The radiochemical purity was >98% using the methods described below.

TLC: silica gel: 50%EtOH:50% EtOAC with 2 drops of NH_4OH, R_f = 0.48
RPC_{18}: 50% CH_3CN/50% pH 3 TEAP buffer, R_f = 0.25
HPLC: Beckmann ultrasphere C_8, 4.6 x 250, 18% CH_3CN/82% pH 3 TEAP buffer, 1 mL/min, 220 nm.
Total Activity: 4.9 mCi (64.3%).
Specific Activity: 53.72 mCi/mmol (UV, EtOH, λ = 259, ε = 21567.9).

1-Carbomethoxy-4-nitro-8-cyanonaphthalene (4)

A mixture of 1-carbomethoxy-8-bromo-nitro-naphthalenes (**3a,3b**) (1.59 g, 4.86 mmol), $Pd(OAc)_2$ (0.16 g, 0.7 mmol), $Ca(OH)_2$ (0.05 g, 0.73 mmol), PPh_3 (0.383 g, 1.46 mmol) and KCN (0.316 g, 4.86 mmol) in DMF (23 mL) was warmed to 100 °C for 5 h. The reaction was cooled and concentrated. Chromatography on silica gel (20% acetone/hexane) afforded 1.03 g of product as a mixture of 4-nitro and 5-nitro isomers (85%).

MP 155-158 °C.
TLC (20% acetone/hexane) R_f 0.16.
^{1}H NMR (300 MHz, $CDCl_3$) 4-nitro isomer δ 8.69 (dd, 1 H, *J* = 1,9), 8.21 (d, 1 H, *J* = 8), 8.18 (dd, 1 H, *J* = 1,7), 7.90 (d, 1 H, *J* = 8), 7.84 (dd, 1 H, *J* = 1.5, 7.4), 4.11 (s, 3 H), 5-nitro isomer δ 8.48 (dd, 1 H, *J* = 1.1, 8.7), 8.13 (s, 2 H), 7.98 (dd, 1H, *J* = 1.1, 7.4), 7.8 (m, 2 H), 4.09 (s, 3 H).
IR (KBr) 2229, 1739, 1528, 1430, 1359, 1346, 1326, 1278, 1247, 1208, 1199, 1189, 1105, 853, 818, 811, 773, 767, 730 cm^{-1}.
UV (MeOH) λ_{max} 310 (ε = 249), λ_{max} 226 (ε = 1442).
MS (EI) m/z (rel. inten.) 256 (M+, 100), 239 (10), 226 (35), 225 (90), 209 (20), 198 (30), 179 (45), 151 (60).

1-Carbomethoxy-4-amino-8-cyanonaphthalene (12)

To a solution of $CuSO_4$ (3 mg, 0.019 mmol) in 0.1 mL of H_2O was added a solution of 1-carbomethoxy-4-nitro-8-cyanonaphthalene (**4**) (0.05 g, 0.195 mmol) in EtOH (2 mL, 0.1 M) at 0°. $NaBH_4$ (37 mg, 0.98 mmol) was

added in portions over 5 min; gas evolution was apparent. The mixture was warmed to room temperature, stirred for 10 min, and quenched with water. The reaction was filtered over silica gel, dried over anhydrous $MgSO_4$, and concentrated. Chromatography on silica gel (70% Et_2O/hexane) afforded 30 mg of product as a single isomer (68%).

TLC (40% acetone/hexane) R_f 0.52.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, 1 H, *J* = 8.6), 7.97 (d, 1 H, *J* = 7.4), 7.77 (d, 1 H, *J* = 7.9), 4.75 (t, 1 H, *J* = 8.6), 6.78 (d, 1 H, *J* = 8.1), 4.01 (s, 3 H).
MS (EI) m/z (rel. Inten.) 226 (M^+, 50), 195 (100), 140 (35).

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