SYNTHESIS OF DOUBLE CARBON-14 LABELED CI-937[1] AND CI-942, POTENTIAL NEW ANTICANCER DRUGS

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SUMMARY

CI-937 and CI-942, compounds which show potent anticancer activity, were synthesized with double labeled high specific activity carbon-14. The key intermediate in the synthesis, 3,6-dichloro-[dicarbonyl-$^{14}C_2$]phthalic anhydride was made by treating 2-bromo-1,4-dichlorobenzene with n-butyllithium and $^{14}CO_2$ to give 2,5-dichloro[carboxy-^{14}C]benzoic acid, which was converted to its diethylamide. Ortho-directed lithiation followed by a second carboxylation produced the ortho acid-amide. Hydrolysis and dehydration generated the anhydride. Friedel-Crafts acylation of the anhydride with 1,4-benzenediol gave 1,4-dichloro-5,8-dihydroxy[9,10-$^{14}C_2$]-9,10-anthracenedione. Protection and hydrazination gave a chloroanthrapyrazole intermediate which was converted into [$^{14}C_2$]CI-937 or [$^{14}C_2$]CI-942 in two steps. The specific activities of the final compounds were 196 μCi/mg and 182 μCi/mg respectively.

Keywords: 3,6-dichloro[dicarbonyl-$^{14}C_2$]phthalic anhydride, 1,4-dichloro-5,8-dihydroxy[9,10-$^{14}C_2$]-9,10-anthracenedione, [$^{14}C_2$]CI-937, [$^{14}C_2$]CI-942, anticancer

INTRODUCTION

CI-937 (7,10-dihydroxy-2-[2-[(2-hydroxyethyl)amino]ethyl]-5-[[2-(methylamino)ethyl]amino]anthra[1,9-cd]pyrazol-6(2H)-one) (1) and CI-942 (5-[(3-Aminopropyl)amino]-7,10-dihydroxy-2-[2-[(2-hydroxyethyl)amino]ethyl]anthra-[1,9-cd]pyrazol-6(2H)-one (2), members of a series of 5-[(aminoalkyl)amino]-substituted anthra[1,9-cd]pyrazol-6(2H)-ones, exhibit potent broad spectrum activity against a panel of murine solid tumors.[2,3,4] Fry et al. have shown that these compounds are DNA intercalating agents and induce far less superoxide desmutase sensitive oxygen consumption than doxorubicin in the rat liver microsomal system, a property that may be indicative of a lesser cardiotoxicity.[5,6] On the basis of these properties, the ease of formulation, and possible lack of cross-resistance with doxorubicin,[2] these compounds are under further development as potential anticancer drugs.

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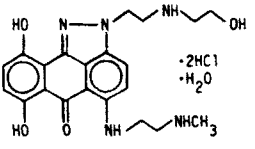
It was necessary to synthesize radioactive labeled material for pharmacokinetic and metabolic studies. Due to the potency of these compounds it was desirable to provide a high specific activity labeled material. To ensure a metabolically stable label, we chose to incorporate carbon-14 into the anthrapyrazole ring system. The desired specific activity was achieved by incorporation of two carbon-14 atoms per molecule.



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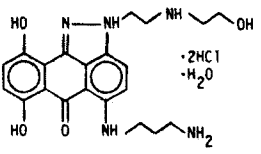

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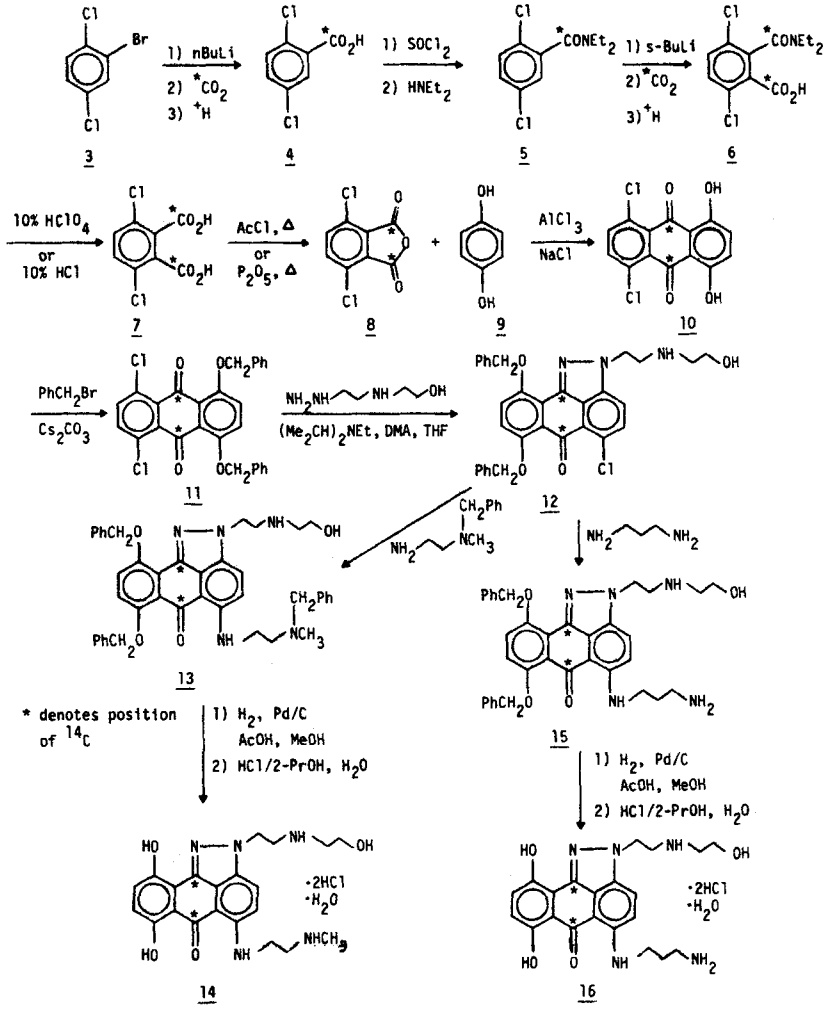
RESULTS AND DISCUSSION

CI-937 and CI-942 were first synthesized by Showalter et al.[7,8,9] The starting material for their synthesis was 1,4-dichloro-5,8-dihydroxy-9,10-anthracenedione. In order to adopt their synthesis it was thus desirable to develop an efficient synthesis of this compound double carbon-14 labeled. One approach to the synthesis of 1,4-dichloro-5,8-dihydroxy-9,10-anthracenedione was the Friedel-Crafts reaction between 1,3-isobenzofurandione (phthalic anhydride) and p-chlorophenol[10] followed by chlorination with Cl_2 in oleum.[11] Alternatively, if a suitable synthesis of 3,6-dichlorophthalic anhydride could be developed from a dichloroarene precursor, then the above chlorination reaction could be avoided. It was found that with careful control of the reaction conditions it was possible to use the latter approach.

The synthesis of 4,7-dichloro-[1,3-$^{14}C_2$]-1,3-isobenzofurandione (3,6-dichloro[dicarbonyl-$^{14}C_2$]phthalic anhydride) was accomplished by two successive carboxylation steps. It has been shown that n-butyllithium reacts selectively with the bromine in 1-bromo-4-chloro-2-fluorobenzene at -90° to -100°C.[12] Treatment of 2-bromo-1,4-dichlorobenzene (3) with n-butyllithium at -78°C followed by $^{14}CO_2$ produced 2,5-dichloro-[carboxy-^{14}C]benzoic acid (4) in a 90% yield. A reaction temperature of -78°C was sufficiently cold to produce a stable anion without the complication of benzyne formation.

To introduce the second carbon-14 on the molecule our strategy was to

direct an ortho lithiation at the 6 position of a derivative of 4. Reviews in the area suggested that an amide or an oxazoline derivative of 4 would be appropriate.[13-15] Beak and Brown[16] showed that the N,N-diethylcarboxamide was effective at ortho-directed lithiation with an m-Cl substituent. Thus



acid 4 was converted to 2,5-dichloro-N,N-diethyl[carbonyl-^{14}C]benzamide (5) through the acid chloride followed by treatment with N,N-diethylamine in a 98% yield. The ortho-directed lithiation was accomplished using s-butyllithium and N,N,N',N'-tetramethyl-1,2-ethanediamine in ethyl ether at -78° to -75°C. After carboxylation, 3,6-dichloro-2-[(diethylamino)[^{14}C]carbonyl][carboxy-^{14}C]benzoic

acid (6) was produced in a 72% yield. A reaction temperature of -78° to -75°C appeared to be optimal as in the first carboxylation. When the reaction was run at -90° to -100°C, only starting material was recovered. At temperatures warmer than -75°C side products formed. We also found that slightly higher yields were obtained in diethyl ether than tetrahydrofuran.

3,6-Dichloro[dicarbonyl-$^{14}C_2$]phthalic anhydride (8) was made by hydrolysis of 6 with perchloric acid followed by treatment of the phthalic acid 7 with acetyl chloride (Method A)[17] to give an 81% yield after sublimation. Since we experienced difficulty in isolating 7 in an anhydrous manner required for reaction with acetyl chloride, an alternative and improved method was subsequently developed. The amide 6 was hydrolyzed in dilute hydrochloric acid. After removal of the water in vacuum, the resulting mixture was sublimed in the presence of phosphorus pentoxide to give a 94% yield (two steps) of 8 (Method B).

The synthesis of 1,4-dichloro-5,8-dihydroxy-9,10-anthracenedione by the reaction of dichlorophthalic anhydride and 1,4-benzenediol (9) in an aluminum chloride-sodium chloride melt was previously reported.[18,19] Hence, anhydride 8 was treated with 9 in a mixture of aluminum chloride and sodium chloride at 180° to 220°C to produce 10 in a 93% yield after chromatography.

The remainder of the synthesis essentially followed that reported for the unlabeled compounds. The dihydroxy compound 10 was protected as the bis(phenylmethyl) ether 11 using (bromomethyl)benzene/cesium carbonate in a 91% yield. The use of cesium carbonate in place of the reported potassium carbonate reduced the reaction time from 48 h to 6.5 h. Compound 11 was treated with 2-[(2-hydrazinoethyl)amino]ethanol, N-ethyl-N-(1-methylethyl)-1-methylethanamine and potassium fluoride in a mixture of dimethylacetamide and tetrahydrofuran to give a 58% yield of 12.

Intermediate 12 was the divergence point in the synthesis of [$^{14}C_2$]CI-937 and [$^{14}C_2$]CI-942. In the original synthesis of CI-937, the side chain secondary amine on 12 was protected with a benzyl group. However, we discovered that 12 gave sufficient yields of 13 without a protection-deprotection step. Thus 12 was heated with N-methyl-N-(phenylmethyl)-1,2-

ethanediamine to give a 61% yield of 13 after recrystallization. The benzyl groups were removed by hydrogenolysis producing [$^{14}C_2$]CI-937 (14) in an 87% yield. The specific activity of 14 was 196 μCi/mg. The exact amount of HCl and H_2O was not determined, but under these same conditions the unlabeled material generally was isolated as the dihydrochloride monohydrate.

Compound 12 was heated with 1,3-propanediamine to produce a 53% yield of 15 after chromatography. Deprotection with the same conditions as before gave a 68% yield of [$^{14}C_2$]CI-942 (16). The specific activity of 16 was 182 μCi/mg.

This synthesis illustrates a number of useful reactions for the generation of double carbon-14 labeled compounds which could be of general use. The ortho-directed lithiation under carefully selected reaction conditions was shown to be very useful for incorporation of $^{14}CO_2$ into an aromatic system with other reactive functionality. The double labeled synthesis of dichlorophthalic anhydride can be applied to the synthesis of a wide variety of substituted phthalic anhydrides as well as phthalides. Compound 10 is a useful intermediate for the labeling of substituted anthracene systems and will be very useful in the labeling of other tetracyclic antitumor and antibiotic drugs.

EXPERIMENTAL

Barium [^{14}C]carbonate was purchased from American Radiolabeled Chemicals, and Pathfinder Laboratories, both of St. Louis, Missouri. 2-Bromo-1,4-dichlorobenzene was purchased from Fairfield Chemical Co., Inc., Blythewood, South Carolina. 2-[(2-Hydrazinoethyl)amino]ethanol and N-methyl-N-(phenylmethyl)-1,2-ethanediamine were supplied by the Preparations Laboratory, Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan. ^{1}H NMR spectra were determined on a Varian XL-200 (200 MHz) spectrometer. Chemical shifts were reported in δ units downfield from tetramethylsilane. Infrared spectra were run on a Perkin-Elmer 1430 spectrophotometer as liquid films or KBr pellets. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Liquid scintillation counting was performed with a Packard Tri-Carb 4530 liquid scintillation

counter using Mallinckrodt Handifluor or Beckman Ready-solve MP liquid scintillation cocktail. Thin layer chromatography (TLC) was done with E. Merck silica gel (0.25 mm) or Whatman reverse phase LKC-18F (0.20 mm) plates. TLC plates were analyzed for radiochemical purity (RCP) using Berthold LB-2832 automatic TLC-linear analyzer. High performance liquid chromatography (HPLC) was performed using a Spectra Physics 8700 or Kratos Spectroflow 400 solvent delivery system, Kratos 773 UV detector, United Technologies Packard Tri-Carb RAM 7500 or Trace radioactive flow detector, and Hewlett-Packard 3390A integrator. All compounds had identical R_f or T_R to that of authentic unlabeled standards.

2,5-Dichloro[carboxy-^{14}C]benzoic acid (4). To a solution of 2-bromo-1,4-dichlorobenzene (2.22 g, 9.00 mmol) in diethyl ether (30 mL) at -78°C was added n-BuLi (5.6 mL, 1.6 M in hexane) over 40 min and the mixture was stirred for 30 min. The anion was treated with $^{14}CO_2$ [from $Ba^{14}CO_3$ (500 mCi, 8.98 mmol, 56.0 mCi/mmol) treated with H_2SO_4] at -78°C for 90 min. The mixture was warmed to room temperature and quenched with water (10 mL) and 5% Na_2CO_3 (2 mL). The layers were separated and the ether layer was washed with 5% Na_2CO_3. The combined aqueous solution was acidified (conc. HCl), extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated in vacuum to give 1.545 g (90% yield) of 4: TLC, R_f = 0.31, RCP > 99%, silica gel, $PhCH_3$:AcOH (19:1); IR (KBr) 3090, 1630, 1605, 1290, 1235, 1105, 1050, 825 cm^{-1}.

2,5-Dichloro-N,N-diethyl[carbonyl-^{14}C]benzamide (5). A mixture of acid 4, thionyl chloride (8 mL) and dimethylformamide (five drops) was heated at 55°C for 16 h. The solution was concentrated in vacuum, then coevaporated with toluene. The residue was diluted with toluene (10 mL) and diethylamine (2.5 mL) then stirred at room temperature for 90 min. The toluene was evaporated in vacuum, and the residue was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was washed sequentially with 5% Na_2CO_3, 1 M HCl, and brine, dried ($MgSO_4$), and passed through a plug of silica gel. Concentration in vacuum left 1.995 g (98% yield) of 5 as a yellow oil: TLC R_f = 0.65, RCP > 98%, silica gel, CH_2Cl_2:MeOH (19:1); IR (liquid film) 2965, 2930, 1565, 1455, 1420, 1275, 1095 cm^{-1}.

3,6-Dichloro-2-[(diethylamino)[^{14}C]carbonyl][carboxy-^{14}C]benzoic acid (6). A solution of 5 (1.995 g, 7.94 mmol) and N,N,N',N'-tetramethyl-1,2-ethanediamine (1.22 mL, 8.1 mmol) in diethyl ether (45 mL) was cooled under nitrogen to an internal temperature of -70° to -75°C. s-Butyllithium (5.7 mL, 7.98 mmol, 1.4 M in cyclohexane) was added to the solution over 30 min keeping the temperature below -70°C, then stirred for 30 min. The anionic mixture was frozen (liq. N_2) and $^{14}CO_2$ [from $Ba^{14}CO_3$ (445 mCi, 7.94 mmol, 56 mCi/mmol) treated with conc. H_2SO_4] was transferred to the reaction flask. The mixture was warmed to -78°C and maintained there for 2 h then allowed to warm to room temperature over 16 h. The reaction mixture was diluted with water, the layers were separated, and the ether layer was washed with dilute NaOH. The combined aqueous layer was acidified with conc. HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried ($MgSO_4$), and evaporated to give 1.673 g (73% yield) of 6 as a white solid: TLC, R_f = 0.20, RCP > 92%, silica gel, EtOAc:AcOH (19:1); IR (KBr) 3400, 2975, 1657, 1535, 1450, 1210, 1135, 820 cm^{-1}.

3,6-Dichloro[dicarbonyl-$^{14}C_2$]phthalic anhydride (8) Method A. A mixture of 10% perchloric acid (30 mL) and 6 (1.088 g, 3.75 mmol) was heated at reflux for 3 h slowly forming a colorless solution. The volume of water was reduced in vacuum and the resulting suspension was extracted with diethyl ether. Extreme care must be exercised to remove the water from the ether layer. The dried diacid 7 was treated with acetyl chloride (10 mL) and heated to 50°C for 3 h. The solution was concentrated in vacuum. $PhCH_3$ was added to the residue and evaporated to leave a black solid. Sublimation for 50 h at 140°C gave a yellow solid which was resublimed at 110°C to leave 659 mg (81% yield) of 8 as a white solid.

3,6-Dichloro[dicarbonyl-$^{14}C_2$]phthalic anhydride (8) Method B. A mixture of 6 (1.672 g, 5.77 mmol) and 10% HCl (v/v, 25 mL) was refluxed for 2 h. The resulting colorless solution was evaporated in vacuum to give a quantitative yield of a mixture of 7 and diethylamine hydrochloride. This was placed with phosphorus pentoxide (1.065 g) in a sublimation apparatus and heated to 115°C for 10 min. A vacuum was applied and the product was collected by sublimation

over 5 h giving 1.1793 g (94% yield) of 8 as a white solid: mp 189-191°C; IR (KBr) 3090, 1690, 1455, 1200, 895, 830, 605 cm^{-1}.

1,4-Dichloro-5,8-dihydroxy[9,10-$^{14}C_2$]-9,10-anthracenedione (10). A mixture of aluminum chloride (6 g) and sodium chloride (1.3 g) was heated to 180°C under N_2. To this melt was added an intimate mixture of 8 (1.173 g, 5.43 mmol), 1,2-benzenediol (9) (616 mg, 5.6 mmol), and aluminum chloride (2 g). The temperature was raised to 220°C for 90 min. The hot purple mixture was poured into a mixture of ice/conc. HCl and stirred for 2 h. The solids were filtered, rinsed with water, and air dried overnight to afford 1.569 g (93% yield) of 10 as a red solid: TLC, R_f = 0.79, RCP > 94%; silica gel, CH_2Cl_2:MeOH (19:1).

1,4-Dichloro-5,8-bis(phenylmethoxy)[9,10-$^{14}C_2$]-9,10-anthracenedione(11). A mixture of (bromomethyl)benzene (0.6 mL, 5.04 mmol), cesium carbonate (1.64 g, 5.04 mmol), 10 (518 mg, 1.68 mmol), and acetone (15 mL) was refluxed for 6.5 h. The mixture was cooled, filtered, and the solids were rinsed with acetone and CH_2Cl_2. The filtrate was evaporated in vacuum to a yellow solid, which was triturated in hexane to give 745.3 mg (91% yield) of 11: TLC, R_f = 0.52, RCP > 97%; silica gel, $PhCH_3$:EtOH (19:1); IR (KBr) 1610, 1570, 1450, 1275, 1200, 1130, 1025, 765 cm^{-1}.

5-Chloro-2-[2-[(2-hydroxyethyl)amino]ethyl]-7,10-bis(phenylmethoxy)-[6,10b-$^{14}C_2$]anthra[1,9-cd]pyrazol-6(2H)-one (12). A mixture of 11 (745 mg, 1.52 mmol), 2-[(2-hydrazinoethyl)amino]ethanol (565 mg, 4.7 mmol), potassium fluoride (1.62 mg, 2.8 mmol), and N-ethyl-N-(1-methylethyl)-1-methyl-ethanamine (0.5 mL) in dry dimethylacetamide (3.0 mL) and tetrahydrofuran (2.5 mL) was heated at 80° to 90°C under N_2 for 5.5 h and then at room temperature for 12 h. The THF was removed with a rotary evaporator and the DMA by vacuum distillation. The oily residue was triturated with MeOH to crystallize 492 mg of 12 (58% yield) as an orange solid: TLC, R_f = 0.16, RCP = 71%, silica gel, $CHCl_3$:MeOH (19:1). The material was used crude or further purified by column chromatography on silica gel (treated with ethylene-diaminetetraacetic acid) eluted with CH_2Cl_2:MeOH:Et_3N (70:20:1).

2-[2-[(2-Hydroxyethyl)amino]ethyl]-5-[[2-[methyl(phenylmethyl)amino-ethyl]amino]-7,10-bis(phenylmethoxy)[6,10b-$^{14}C_2$]anthra[1,9-cd]pyrazol-6(2H)-one (13). A mixture of 12 (301 mg, 0.54 mmol) and N-methyl-N-(phenylmethyl)-1,2-ethanediamine (3.1 g, 19 mmol) was heated under N_2 at 130°C for 3 h. The solution was cooled to 60°C and diluted with 2-propanol (4 mL). After cooling to room temperature, the solids were filtered and washed with 2-propanol (2 mL) and hexane (3 x 10 mL) to give crude 13 as a rust colored solid. The material was triturated with n-propanol, filtered, and washed with 95% EtOH to give 223 mg (61% yield) of 12 as an orange solid: TLC, R_f = 0.19, RCP > 97%, silica gel, $CHCl_3$:MeOH (4:1); IR (KBr) 3420, 3060, 2930, 2850, 1695, 1550, 1450, 1260, 1190, 1030, 735 cm^{-1}.

7,10-Dihydroxy-2-[2-[(2-hydroxyethyl)amino]ethyl]-5-[[2-(methylamino)-ethyl]amino][6,10b-$^{14}C_2$]anthra[1,9-cd]pyrazol-6(2H)-one, dihydrochloride [$^{14}C_2$]CI-937 (14). A mixture of 13 (222 mg, 0.33 mmol), 20% Pd/C (20 mg), MeOH (3.5 mL), and AcOH (0.7 mL) was stirred under H_2 (1 atm) for 2.5 h. The reaction mixture was filtered through Celite, and the filter pad was rinsed with MeOH. Concentration of the filtrate gave a dark red solid which was dissolved in MeOH (3 mL), and treated with 3 M HCl in 2-propanol (0.5 mL). The resulting solid was collected and washed with MeOH and diethyl ether, then further purified by trituration sequentially in CH_2Cl_2, 2-propanol, and diethyl ether. The orange-red solid was dried in vacuum at 65°C to give 143 mg (87% yield) of 14: mp 271-277°C (dec.); specific activity 196 μCi/mg; TLC: RCP > 99%, a) R_f = 0.09, silica gel, EtOAc:Pyridine:AcOH:H_2O (5:2:2:1); b) R_f = 0.63, C18 (treated w/EDTA), MeOH:sat. NH_4Cl:H_2O (2:1:1); c) R_f = 0.33, silica gel, $CHCl_3$:MeOH:NH_4OH (70:25:5); HPLC T_R = 4.0 min, RCP > 98%, Rainin C18, 3 μ, 4.6 mm ID x 10 cm, CH_3CN:0.25 M NaOAc pH=4:0.1 M tetrasodium EDTA:0.02 M n-Bu_4NHSO_4 (8:20:2:70), flow rate 0.5 mL/min., UV @ 240 nm; IR (KBr) 3350, 2940, 2760, 1590, 1460, 1265, 1200, 810 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) 13.9 (s, 1H); 9.27 (m, 4H); 8.43 (d, 1H); 7.67 (d, 1H); 7.53 (d, 1H); 7.16 (d, 1H); 5.52 (t, 1H); 5.19 (m, 2H); 4.13 (m, 2H); 3.84 (m, 4H); 3.35 (m, 4H); 2.83 (s, 3H).

2-[2-[(2-Hydroxyethyl)amino]ethyl]-5-[(3-aminopropyl)amino]-7,10-bis-(phenylmethoxy)[6,10b-$^{14}C_2$]anthra[1,9-cd]pyrazol-6(2H)-one (15). A mixture of 1,3-propanediamine (5 mL, 60 mmol) and 12 (739 mg, 1.33 mmol) was heated under N_2 at 130°C for 90 min. The solution was cooled slightly and diluted with water (5 mL). After cooling to room temperature, the red solid was collected by filtration, and washed sequentially with water, n-propanol, and diethyl ether. This crude solid was purified by passing through a continuous eluting silica gel column using an azeotrope of $CHCl_3$ and MeOH as the eluting solvent to afford 414 mg (53% yield) of 15 as an orange solid: TLC, R_f = 0.40, RCP > 97%, silica gel, $CHCl_3$:MeOH:Et_3N (4:1:0.1).

5-[(3-Aminopropyl)amino]-7,10-dihydroxy-2-[2-[(2-hydroxyethyl)amino] ethyl][6,10b-$^{14}C_2$]anthra[1,9-cd]pyrazol-6(2H)-one dihydrochloride, [$^{14}C_2$]CI-942 (16). A mixture of 15 (414 mg, 0.70 mmol) and 20% Pd/C (20 mg) in MeOH (6 mL) and AcOH (1.5 mL) was stirred for 3 h under H_2 (1 atm). The red solution was filtered through Celite, and evaporated in vacuum. TLC showed the reaction was incomplete and thus the reaction was repeated as above for 3 h. The concentrated solids were dissolved in MeOH (5 mL) and treated with 3 M HCl in 2-propanol (0.5 mL). The precipitated red solid was filtered and washed with 2-propanol and diethyl ether. The material was recrystallized three times from EtOH-water, then triturated sequentially with CH_2Cl_2, 2-propanol, MeOH, and diethyl ether. The purified product was dried in vacuum at 65°C, then equilibrated with moist air to leave 237 mg (68% yield) of 16: mp >295°C (dec.); specific activity 182 μCi/mg; TLC: RCP > 95%, a) R_f = 0.39, silica gel (treated w/EDTA) $CHCl_3$:MeOH:conc. NH_4OH (70:25:5); b) R_f = 0.09, silica gel (treated w/EDTA), DMF:EtOH:conc. NH_4OH (70:25:5); c) R_f = 0.41, C18, MeOH:sat. NH_4Cl:water (4:1:1); HPLC: T_R = 5.8 min, RCP > 98%, Alltech C18, 10 μ, 4.6 mm ID x 25 cm, MeOH:0.05 M ammonium formate, pH=3 with HCOOH (40:60), flow rate 1.5 mL/min, UV @ 240 nm; IR (KBr) 3370, 2940, 1590, 1550, 1470, 1395, 1270, 1200, 1155, 810 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) 16.64 (s, 1H); 8.95 (m, 2H); 8.19 (d, 2H); 8.10 (s, 1H); 7.33 (t, 2H); 6.87 (d, 1H); 5.28 (s, 1H); 4.97 (m, 2H); 3.57 (m, 7H); 3.07 (m, 2H); 2.93 (t, 2H); 1.99 (m, 2H).

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