JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2005; **48**: 855–871.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.960

Research Article

Synthesis and radioiodination of some 9-aminoacridine derivatives for potential use in radionuclide therapy

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Summary

Three derivatives of the DNA intercalating compound 9-aminoacridine, were prepared and radioiodinated for biological experiments. The compounds are the stannyl derivatives 3-{4-[3-(acridin-9-ylamino)-propoxy]-3-trimethylstannyl-phenyl}-propionic acid and acridin-9-yl-{3-[4-(2-amino-ethyl)-2-trimethylstannyl-phenoxy]-propyl}-amine which were synthesized from the corresponding iodo derivatives by palladium catalyzed reactions, and 4-[2-(acridin-9-ylamino)-ethyl]-phenol. The two stannylated compounds and the phenol were used as precursors for radioiodination and were labeled with ^{125}I using chloramine-T as an oxidant achieving high-to-excellent yields. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: 9-aminoacridine derivatives; radioiodination; chloramine-T; ^{125}I

Introduction

Acridine derivatives are among the most highly explored biologically active agents. Their biological stability and ability to bind efficiently to DNA are among the properties that could potentially make them useful anti-cancer agents.[1,2] It is believed that acridines bind to DNA by intercalation into the helix by extension of the backbone.[3,4] Intercalation of acridines was shown to increase by amino-group substitution at position 9.[5] Thus, several 9-aminoacridine derivatives have been synthesized and demonstrated to have high anti-tumor activity.[6–8]

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Contract/grant sponsor: Swedish Cancer Foundation
Contract/grant sponsor: INTAS; contract/grant number: 99-00806

Received 28 February 2005
Revised 24 April 2005
Accepted 25 April 2005

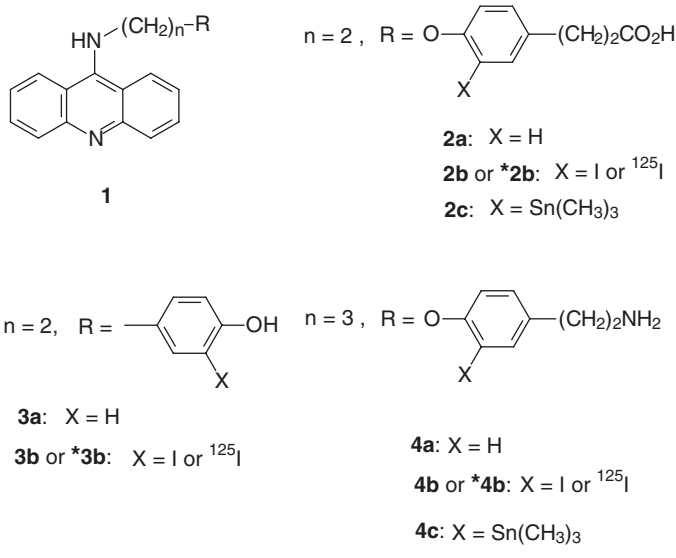


Figure 1. The 9-aminoacridine derivatives synthesized

The anti-tumor activity of the 9-aminoacridines is further enhanced by attachment of Auger electron-emitting radionuclides, such as ^{125}I. The short range of Auger electrons makes it possible to limit the biological effect of radiation on cells, where decay happens, sparing surrounding healthy tissues. On the other hand, since Auger electrons only travel a short distance, the compound containing the radionuclide has to be delivered to the nucleus of the tumor cell to effect total eradication of the cell.

The concept of 'two step targeting'[9–11] was introduced in our research group to ensure specific delivery of drugs to the cell nucleus. The first targeting step includes the specific delivery of DNA intercalating compounds to cancer cells and their internalization into the cytoplasm. Sterically stablized liposomes with polyethylene glycol are employed as drug transport vesicles at this step. In order to achieve higher specific delivery of the drug to the tumor cells, the liposomes are conjugated to targeting proteins or peptides such as epidermal growth factor (EGF), since their receptors are known to be overexpressed in some tumor cells compared to normal cells. In the second step, an Auger electron-emitting radionuclide, directed by its DNA intercalating part, enters into the nucleus and destroys the DNA of the tumor cell.

We have earlier reported the synthesis and radioiodination of the 9-aminoacridine derivatives *N*–[*ω*–(acridin-9-ylamino)-alkyl]-3-trimethylstannyl-benzamides where the alkyl group is propyl and octyl; and 2–(acridin-9-ylamino)-3-(4-hydroxy-phenyl)-propionic acid.[12]

This work describes the syntheses of a series of 9-aminoacridine derivatives labeled with ^{125}I, for potential use in targeted nuclide therapy. These

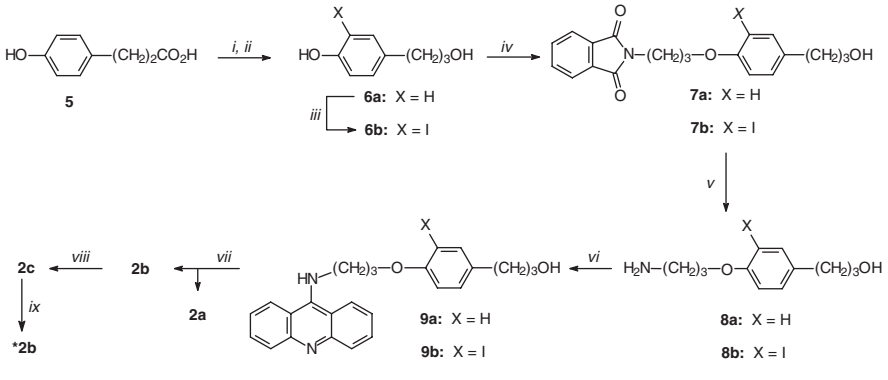
compounds are carboxylic acids (**2a**, **2b**, ***2b** and **2c**), phenols (**3a**, **3b** and ***3b**) and amines (**4a**, **4b**, ***4b** and **4c**) which are depicted in Figure 1.

Result and discussion

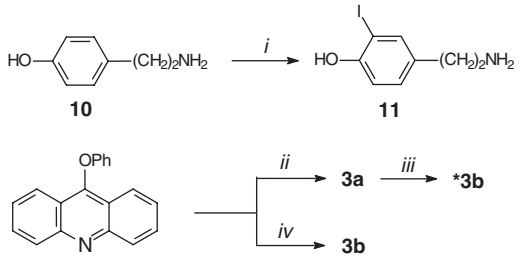
Synthesis

Carboxylic acid derivatives of acridine. The synthesis of the acridine derivatives **2a–c** is outlined in Scheme 1. Commercially available 3-(4-hydroxy-phenyl) propionic acid was converted to its corresponding ethyl ester by acid catalyzed esterification. The resulting ester was reduced using lithium aluminum hydride providing a high yield of the phenoxypropanol **6a**. Iodination of **6a** was carried out with molecular iodine and silversulfate at room temperature to yield the iodo derivative **6b** in good conversion. The phenoxy propanol **6a** and **6b** were reacted with *N*-(3-bromopropyl)phthalimide in the presence of K_2CO_3 to provide good-to-excellent yield of the protected amino compounds **7a** and **7b**, respectively. Excess of the *N*-(3-bromopropyl)phthalimide was required for complete consumption of the starting phenoxypropanols **6a** and **6b**. Removal of the phthalimide group was achieved by refluxing hydrazine monohydrate to afford the amines **8a** and **8b**.

The 9-phenoxyacridine was prepared from 9(10 H)-acridone via chloroacridine according to the method reported in the literature.[13,14] The reaction of amines **8a** and **8b** with 9-phenoxyacridine in molten phenol afforded the acridines **9a** and **9b**, respectively, within 30 min. Compounds **9a** and **9b** were subsequently oxidized to the corresponding carboxylic acids **2a** and **2b**, using Jones reagent. The iodo derivative **2b**, was converted to the corresponding



Scheme 1. (i) Ethanol, H_2SO_4, Δ; (ii) $LiAlH_4$, THF, Δ; (iii) I_2/Ag_2SO_4, CH_2Cl_2, RT; (iv) K_2CO_3, *N*-(3-bromopropyl)phthalimide, acetone, Δ, (v) $N_2H_4.H_2O$, methanol, Δ; (vi) 9-phenoxyacridine, molten phenol, 80°C; (vii) CrO_3, H_2SO_4, acetone, 0–10°C; (viii) Sn_2Me_6, $Pd(PPh_3)_4$, DMF; (ix) $Na^{125}I$, chloramine-T (CAT)



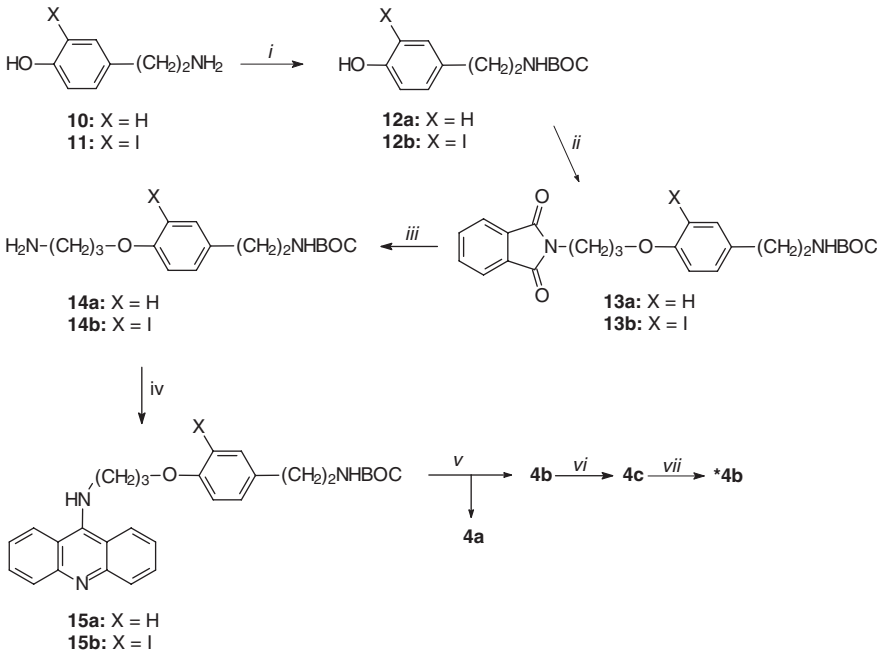
Scheme 2. (i) IPy_2BF_4, 10% TFA/CH_2Cl_2, RT; (ii) tyramine, phenol, 80°C; (iii) $Na^{125}I$, CAT; (iv) iodotyramine 11, phenol, 80°C

trimethylstannyl compound **2c** using a palladium(0) catalyzed cross-coupling reaction in good yield.

Phenolic derivatives of acridine. The synthesis of acridine derivatives **3a–b** is summarized in Scheme 2. Electrophilic monoiodination of commercially available tyramine **10** was performed using bis(pyridine)-iodonium tetrafluoroborate[15] in the presence of acid (10% TFA in CH_2Cl_2) giving a high yield of the known[16] *ortho*-iodo derivative **11**. The compound 4-[2-(acridin-9-yl-amino)-ethyl]-2-iodo-phenol (**3b)**, was prepared from 9-phenoxyacridine and iodotyramine **11** in molten phenol. The reaction resulted in total conversion after stirring for 1 h at 80°C. Compound **3a** was synthesized from the reaction of 9-phenoxyacridine with tyramine by means of a procedure similar to that used to prepare **3b**.

Amine derivatives of acridine. The synthesis of the acridine derivatives **4a–c** is depicted in Scheme 3. The tyramine derivatives **10** and **11** were protected with a BOC protecting group using di-*tert* butyl dicarbonate in basic media to give compound **12a** and **12b**, respectively, in quantitative yield. The compounds **12a** and **12b** were treated with K_2CO_3 and reacted with *N*-(3-bromopropyl)phthalimide to give the di-protected amines **13a** and **13b**, respectively. Selective deprotection[17] of the phthalimide part was carried out using hydrazine monohydrate to provide the BOC protected amines **14a** and **14b** in good yields.

The amines **14a** and **14b**, were reacted with 9-phenoxyacridine to afford the acridine derivatives **15a** and **15b**. The BOC protecting group was removed using dry HCl in ethylacetate to give the hydrochloride of compounds **4a** and **4b**. The iodide of compound **4b** was exchanged with trimethyltin using a palladium(II) catalyzed reaction to give the stannylated compound **4c** in good yield. This compound was used as a precursor for radioiodination and compound **4b** was used as a reference for the radioiodinated analog ***4b**. Compound **4a** was prepared in order to see whether direct radioiodination of the ring is possible. This, however, was unsuccessful.



Scheme 3. (i) $(BOC)_2O$, 10% Et_3N/MeOH, 54°C, aq. HCl; (ii) *N*-(3-bromopropyl)phthalimide, K_2CO_3, acetone, reflux; (iii) $N_2H_4.H_2O$, MeOH, reflux; (iv) 9-phenoxyacridine, phenol, 80°C; (v) dry HCl in EtOAc, RT; (vi) Sn_2Me_6, $(PPh_3)_2PdCl_2$, 1,4-dioxane, 85°C; (vii) chloramine-T, $Na^{125}I$

Table 1. Radioiodinated yield of acridine derivatives using CAT as oxidant, 5.0 µl aqueous ^{125}I-solution (3.7 GBq/ml) and 5 min reaction time

Entry	Substrate (mg/ml)	CAT (mg/ml)	Radioiodinated acridine derivatives	Yield (%)
1	**2c** (1)	1	***2b**	70 ± 0.5
2	**3a** (1)	8	***3b**	68 ± 0.5
3	**4c** (0.5)	1	***4b**	92 ± 0.3
4	**4c** (2)	8	***4b**	96 ± 0.4

Radiolabeling

Radioiodination of compounds **2c**, **3a** and **4c** with ^{125}I was performed using chloramine-T (CAT) as an oxidant. The various parameters, such as amount of substrate, amount of oxidant and reaction time were optimized for each reaction. The ^{125}I labeled compounds were obtained in good-to-excellent labeling yields in 5 min reaction time according to the radio-TLC analysis. The radiochemical yields of the three labeled compounds ***2b**, ***3b** and ***4b** are summarized in Table 1.

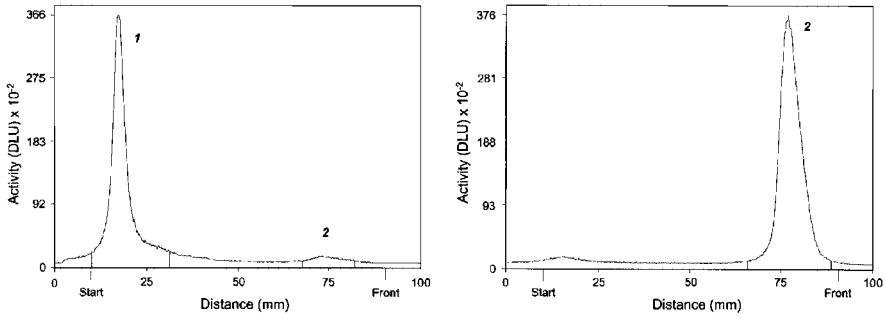


Figure 2. (a) Typical TLC-result for compound *4b using the general labeling procedure. Peak 1 corresponds to radiolabeled compound, *4b (R_f =0.1) and peak 2 corresponds to ^{125}I stabilized with carrier NaI (R_f =0.8) against oxidation. (b) Typical radio-TLC diagram of a blank experiment. Peak 2 corresponds to ^{125}I stabilized with carrier NaI (R_f =0.8) against oxidation

Figure 2(a) displays an illustrative radio-TLC diagram of [^{125}I]-iodide of compound **4c** using 20 µg of substrate in 40 µl of 1% acetic acid in methanol solution, 5 µl ^{125}I-solution (3.7 GBq/ml), and 10 µl Chloramine-T (CAT) solution (1 mg/ml in MeOH). The radio-TLC diagram shows a small peak of ^{125}I stabilized with carrier NaI (R_f = 0.8) and a major peak with $R_{f=}$0.1. This peak appeared only in reaction mixtures containing the substrate and was found to have the same R_f as the non-radioactive reference compound, **4b**; it thus, most likely represents the iodinated compound, ***4b**.

Blank experiments were performed using exactly the same conditions except that neat 1% acetic acid in methanol was used instead of the acridine derivatives. In all blank experiments, where no substrate or oxidant is added, only the peak with R_f = 0.8 (peak 2) was observed (see Figure 2(b)). This peak has the same retention factor as does NaI. The small peak at the start and at the end of the radio-TLC in the blank experiment are usually observed. The peak at the start is generally considered to be due to the presence of an oxidized form of [^{125}I]iodide.

Experimental

General

^{1}H and ^{13}C spectra were recorded in $CDCl_3$ (7.26 ppm ^{1}H, 77.0 ppm ^{13}C), CD_3OD (3.35 ppm ^{1}H, 49.0 ppm ^{13}C) or DMSO (2.49 ppm ^{1}H, 39.5 ppm ^{13}C) on a Varian Unity 400 spectrometer operating at 400 and 100.6 MHz, respectively. For column chromatography Merck silica gel 60 (230–400 mesh) was used. TLC was performed using Merck Silica 60 F_{254} gel. All solvents were dried according to standard methods unless otherwise stated. LC/MS was

conducted using AQA mass spectrometer with an electrospray positive ionization method in methanol solution. High resolution mass spectroscopy (HRMS) was conducted in Organisch Chemisches Institut der Universitaet Muenster, Germany. Melting points are uncorrected and were obtained using SMP3 Bibby Sterilin melting point apparatus. The notations 'benz' and 'acr' are used for benzene and acridine rings, respectively.

Materials for radiolabeling

Iodine-125, 370 MBq/99 µl as diluted solution in sodium hydroxide, was purchased from Amersham Biosciences, Amersham, UK. Methanol (HPLC grade) was used as supplied. High-quality ELGA water (resistance higher than 18 MΩ/cm^3) was used in preparing aqueous solutions. *N*-Chloro-*p*-toluene-sulfonamide sodium salt (chloramine-T, CAT) and sodium metabisulfite, $Na_2S_2O_5$ were both obtained from Sigma. Sodium iodide, NaI, pro analysis was used for preparation of solutions as delivered. The solutions of CAT (1.8 mg/ml solution in MeOH), $Na_2S_2O_5$ (2.16 mg/ml solution in H_2O) and NaI (10 mg/ml solution in H_2O) were always prepared fresh, 5 min before each experiment. The solutions of acridine derivatives were also prepared before each experiment.

Analytical techniques for radiolabeling

Silica gel 60 F_{254} thin layer chromatography plates (E. Merck, Darmstadt, Germany) were used for analysis. The reaction mixture (1–2 µl) was applied on a TLC plate, using a mixture of 20 ml (methanol): 40 µl (acetic acid) as eluent for compound ***4b**, and 100% MeOH for compound ***3b**, and 5:1, methanol:dichloromethane for ***2b**. The R_f values for the non-radiolabeled iodoacridine derivatives were used for comparison and were the same as those of their radiolabeled analog. The position of standard chromatography spots were determined visually either using UV light or the naked eyes. The distribution of radioactivity along the TLC strips (100 × 50 mm, elution path 80 mm) was measured using a Cyclone™ storage phosphor system (Packard Instruments Company Inc., Downers Grove, US) and analyzed using the OptiQuant™ image analysis software.

Synthesis

Preparation of 4-(3-hydroxy-propyl)-phenol[18] (**6a**). 3-(4-Hydroxy-phenyl)-propionic acid (20.0 g, 0.120 mol) was dissolved in 300 ml of absolute ethanol. H_2SO_4 (4.5 ml) was added and the solution was refluxed for 1 h 30 min. The reaction mixture was then cooled to room temperature. Water (30 ml) was added, and the ethanol was evaporated and the residue was extracted with dichloromethane. The combined extract was washed with brine, dried over

$MgSO_4$, filtered, evaporated and dried under reduced pressure to yield the 3-(4-hydroxy-phenyl)-propionic acid ethyl ester in 99%. This compound was used in the next reaction with out further purification.

To a suspension of $LiAlH_4$ (7.78 g, 0.205 mol) in dry THF (250 ml), a solution of 3-(4-hydroxy-phenyl)-propionic acid ethyl ester (21.50 g, 0.111 mol) in dry THF (150 ml) was added dropwise at room temperature. The mixture was stirred at 55°C for 12 h. The reaction was quenched by cautiously adding ethyl acetate, then water. The mixture was then acidified with conc. hydrochloric acid. The solvent was evaporated. The mixture was extracted with ethyl acetate. The combined organic layer was washed with water, saturated $NaHCO_3$ and finally with brine. Ethyl acetate was evaporated to give colorless oil which crystallized upon standing. The reaction afforded the pure compound **6a** (13.5 g, 80% yield) after column chromatography purification (3:1, ether pentane).

^{1}H NMR ($CDCl_3$): δ 7.1 (d, 2H, $J = 8.6$ Hz, benz), 6.78 (d, 2H, $J = 8.6$ Hz, benz), 3.72 (t, 2H, $J = 6.8$ Hz, $–CH_2OH$), 2.68 (t, 2H, $J = 7.8$ Hz, $PhCH_2–$), 1.9 (m, 2H, $CH_2\underline{CH_2}CH_2–$); ^{13}C NMR ($CDCl_3$): δ 153.7, 133.8, 129.46, 115.2, 62.3, 34.3, 31.1.

4-(3-Hydroxy-propyl)-2-iodo-phenol (**6b**). Ag_2SO_4 (2.50 g, 8.01 mmol) and I_2 (2.03 g, 8.01 mmol) were dissolved in dichloromethane. 4-(3-hydroxy-propyl)-phenol **6a** (1.23 g, 8.01 mmol) was then added. The reaction mixture was stirred at room temperature for 24 h. The yellow precipitate was filtered off. The filtrate was washed with sodiumthiosulfate ($Na_2S_2O_3$), water and then brine. The organic layer was dried over Mg_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (3:1, ether:pentane, $R_f = 0.34$) to afford compound **6b** (1.56 g, 70% yield) as a white solid. m.p. = 83.8−85.8°C. ^{1}H NMR ($CDCl_3$): δ 7.50 (s, 1H, benz), 7.06 (dd, 1H, $J = 8.3$, 2.0 Hz, benz), 6.90 (d, 1H, $J = 8.3$ Hz, benz), 3.66 (t, 2H, $J = 6.5$ Hz, $–CH_2–OH$), 2.62 (t, 2H, $J = 7.5$ Hz, benz–$CH_2–$), 1.83 (m, 2H, $J = 6.5$ Hz, $–CH_2–$); ^{13}C NMR ($CDCl_3$): δ 153.0, 137.8, 136.0, 130.2, 114.9, 85.6, 62.0, 34.2, 30.6.

2-{3-[4-(3-Hydroxy-propyl)-phenoxy]-propyl}-isoindole-1,3-dione (**7a**). 4-(3-Hydroxy-propyl)-phenol **6a** (1.00 g, 6.58 mmol) was dissolved in acetone. K_2CO_3 (0.91 g, 6.58 mmol) and *N*-(3-bromopropyl)phthalimide (3.50 g, 13.20 mmol) were added successively to the solution. The mixture was allowed to reflux for one day. The reaction was cooled to room temperature and after filtration the solvent was evaporated to give the crude product. Purification by column chromatography (4:1, CH_2Cl_2:acetone, $R_f = 0.62$) provided compound **7a** as a white solid, in quantitative yield.

m.p. = 100.5−106.5°. C^{1}H NMR ($CDCl_3$): δ 7.84 (m, 2H, phthalimide), 7.71 (m, 2H, phthalimide), 7.06 (d, 2H, $J = 8.3$ Hz, benz), 6.73 (d, 2H, $J = 8.3$ Hz, benz), 4.00 (t, 2H, $J = 6.5$ Hz, benzO–CH_2), 3.90 (t, 2H, $J = 7.2$ Hz, CH_2–OH), 3.65 (t, 2H, $J = 6.5$ Hz, CH_2–N), 2.62 (t, 2H, $J = 7.8$ Hz, benz–CH_2), 2.17 (qn, 2H, $J = 6.5$ Hz, benzO–CH_2–CH_2–), 1.85 (m, 2H, benz–CH_2–CH_2); ^{13}C NMR ($CDCl_3$): δ 168.4, 156.9, 139.1, 133.9, 132.1, 129.2, 123.2, 114.4, 65.7, 62.3, 35.5, 34.4, 31.1, 28.4.

2-{3-[4-(3-Hydroxy-propyl)-3-iodo-phenoxy]-propyl}-isoindole-1,3-dione (**7b**). The compound **7b** was obtained in 86% yield from iodo compound **6b** and two equivalent of *N*-(3-bromopropyl)phthalimide in a similar method as described for **7a**. HRMS (*m*/*z*): calculated for ($C_{20}H_{20}INO_4 + H^+$), ($C_{20}H_{20}INO_4 + Na$), 467.0594, 488.0335; found 467.0506, 488.0329, respectively. m.p. = 138.7−139.0°C. ^{1}H NMR ($CDCl_3$): δ 7.85-7.83 (m, 2H, phthalimide), 7.72-7.70 (m, 2H, phthalimide), 7.58 (s, 1H, benz), 7.08 (d, 1H, $J = 8.3$ Hz, benz), 6.70 (d, 1H, $J = 8.3$ Hz, benz), 4.05 (t, 2H, $J = 6.6$ Hz, benzO–CH_2–), 3.97 (t, 2H, $J = 6.9$ Hz, –CH_2–OH), 3.65 (t, 2H, $J = 6.6$ Hz, –CH_2–N–), 2.60 (t, 2H, $J = 7.7$ Hz, benz–CH_2–), 2.23 (qn, 2H, $J = 6.6$ Hz, benzO–CH_2−$\underline{CH_2}$−), 1.84 (m, 2H, benz–CH_2−$\underline{CH_2}$−); ^{13}C NMR ($CDCl_3$): δ 168.0, 156.0, 139.2, 136.2, 133.9, 129.3, 123.3, 112.0, 86.5, 67.1, 62.0, 35.6, 34.2, 30.6, 28.6.

3-[4-(Amino-propoxy)-phenyl]-propan-1-ol (**8a**). To a solution of 2-{3-[4-(3-hydroxy-propyl)-phenoxy]-propyl}-isoindole-1,3-dione **7a** (1.00 g, 2.95 mmol) in methanol was added hydrazine monohydrate (0.15 g, 2.95 mmol). The reaction mixture was allowed to reflux overnight. The solvent was evaporated and the crude product was purified by flash chromatography (3:2:0.04, CH_2Cl_2:MeOH:Et_3N, $R_f = 0.31$) to provide the amine **8a** (0.28 g, 46% yield) as a white solid.

^{1}H NMR ($CDCl_3$): δ 7.09 (d, 2H, $J = 8.4$ Hz, benz), 6.81 (d, 2H, $J = 8.4$ Hz, benz), 4.02 (t, 2H, $J = 6.8$ Hz, benzO–CH_2), 3.65 (t, 2H, $J = 7.0$ Hz, –CH_2–OH), 2.90 (t, 2H, $J = 6.8$ Hz, CH_2–N), 2.64 (t, 2H, $J = 7.6$ Hz, benz–CH_2–), 1.91 (qn, 2H, $J = 6.8$ Hz, benzO–CH_2−$\underline{CH_2}$−), 1.85 (m, 2H, benz–CH_2−$\underline{CH_2}$); ^{13}C NMR ($CDCl_3$): δ 157.1, 133.9, 129.2, 114.3, 65.8, 62.1, 39.3, 34.4, 33.0, 31.1.

3-[4-(3-Amino-propoxy)-2-iodo-phenyl]-propan-1-ol (**8b**). The compound **8b** was synthesized in 85% yield from **7b** by a similar procedure to that used for **8a**.

HRMS (*m*/*z*): calculated for ($C_{12}H_{18}INO_2 + H^+$), ($C_{12}H_{18}INO_2 + Na$), 336.0461, 358.0280; found 336.0451, 358.0269, respectively. ^{1}H NMR ($CDCl_3$): δ 1.81-1.86 (m, 2H, benz–CH_2−$\underline{CH_2}$−), 1.91-1.98 (m, 2H, benzO–

$CH_2-\underline{CH_2}-$), 2.60 (t, 2H, $J = 7.6$ Hz, benz–CH_2–), 2.98 (t, 2H, $J = 6.8$ Hz, –CH_2–N), 3.64 (t, 2H, $J = 7.0$ Hz, CH_2–OH), 4.07 (t, 2H, $J = 7.1$ Hz, benzO–CH_2–), 6.72 (d, 1H, $J = 8.2$ Hz, benz), 7.10 (d, 1H, $J = 8.2$ Hz, benz), 7.60 (s, 1H, benz); ^{13}C NMR ($CDCl_3$): δ 30.6, 32.6, 34.2, 39.4, 61.8, 67.4, 86.6, 111.9, 129.3, 136.2, 139.1, 155.7.

3-{4-[3-(Acridin-9-ylamino)-propoxy]-phenyl}-propan-1-ol (**9a**). 3-[4-(Amino-propoxy)-phenyl]-propan-1-ol **8a** (0.17 g, 0.83 mmol) in molten phenol was added to a solution of 9-phenoxyacridine (0.23 g, 0.83 mmol) in molten phenol. The mixture was stirred at ~80°C for 30 min. The mixture was then cooled to room temperature and subjected to flash chromatography (4:1:0.03, CH_2Cl_2:MeOH: Et_3N, $R_f = 0.51$) giving yellow powder of compound **9a** (0.22 g, 67% yield).

^{1}H NMR ($CDCl_3$): δ 1.86 (m, 2H, benz–$CH_2-\underline{CH_2}-$), 2.17 (qn, 2H, $J = 5.4$, 6.2Hz, benzO–$CH_2-\underline{CH_2}-$), 2.65 (t, 2H, $J = 7.1$ Hz, benz–CH_2), 3.67 (t, 2H, $J = 6.2$ Hz, CH_2–N), 4.02 (t, 2H, $J = 6.2$ Hz, CH_2–OH), 4.13 (t, 2H, $J = 5.4$ Hz, benzO–CH_2), 6.82 (d, 2H, $J = 8.3$ Hz, benz), 7.09 (d, 2H, $J = 8.3$ Hz, benz), 7.30 (t, 2H, $J = 8.6$ Hz, acr), 7.63 (t, 2H, $J = 8.6$ Hz, acr), 8.04 (d, 2H, $J = 8.6$ Hz, acr), 8.11 (d, 2H, $J = 8.6$ Hz, acr); ^{13}C NMR ($CDCl_3$): δ 30.52, 31.14, 34.43, 49.26, 61.64, 67.05, 114.23, 116.45, 122.77, 122.88, 128.96, 129.38, 129.83, 134.71, 149.08, 151.38, 156.43.

3-{4-[3-(Acridin-9-ylamino)-propoxy]-2-iodo-phenyl}-propan-1-ol (**9b**). This compound was prepared in 59% yield from **8b** using a method similar to that described for **9a**.

HRMS (*m*/*z*): calculated for ($C_{25}H_{25}IN_2O_2 + H^+$), 513.1039; found 513.1058. ^{1}H NMR ($CDCl_3$): δ 1.85 (m, 2H, $J = 6.3$ Hz, benz–CH_2–CH_2–), 2.27 (m, 2H, $J = 5.5$ Hz, 6.3 Hz, benzO–$CH_2-\underline{CH_2}-$), 2.62 (t, 2H, $J = 7.1$ Hz, benz–$\underline{CH_2}-$), 3.67 (t, 2H, $J = 6.3$ Hz, CH_2–N), 4.12 (t, 2H, $J = 6.3$ Hz, CH_2–OH), 4.17 (t, 2H, $J = 5.5$ Hz, benzO–CH_2–), 6.69 (d, 1H, $J = 8.1$ Hz, benz), 7.08 (m, 1H, $J = 8.1$ Hz, benz), 7.35 (m, 2H, $J = 7.9$ Hz, acr), 7.62 (s, 1H, benz), 7.66 (m, 2H, $J = 8.4$ Hz, acr), 8.06 (d, 2H, $J = 8.4$ Hz, acr), 8.18 (d, 2H, $J = 8.8$ Hz, acr); ^{13}C NMR ($CDCl_3$): δ 30.6, 30.8, 34.4, 48.7, 61.8, 67.8, 86.7, 112.5, 117.2, 123.1, 123.2, 129.4, 129.9, 136.9, 139.2, 151.4, 155.4.

3-{4-[3-(Acridin-9-ylamino)-propoxy]-phenyl}-propionic acid (**2a**). 3-{4-[3-(Acridin-9-ylamino)-propoxy]-phenyl}-propan-1-ol, **9a** (20 mg, 0.050 mmol) was dissolved in acetone (2 ml) and cooled to 0°C. CrO_3 (20.7 mg, 0.21 mmol) was dissolved in 3 M aqueous H_2SO_4 (0.5 ml) and added to the solution dropwise over a period of 15 min. The mixture was stirred at 0–10°C for 3 h. The reaction was quenched with water (2 ml). Column chromatography (4:1,

MeOH:CH_2Cl_2, $R_{f=}$0.41) afforded a yellow powder of compound **2a** (19 mg, 90% yield).

^{1}H NMR (CD_3OD): δ 2.41 (m, 2H, benzO–CH_2–$\underline{CH_2}$–), 2.54 (t, 2H, J = 7.2 Hz, benz–CH_2–), 2.79 (t, 2H, J = 7.4 Hz, –CH_2–CO_2H), 4.11 (t, 2H, J = 5.4 Hz, –CH_2–N), 4.37 (t, 2H, J = 6.4 Hz, benzO–CH_2–), 6.67 (d, 2H, J = 8.2 Hz, benz), 7.00 (d, 2H, J = 8.2 Hz, benz), 7.51 (t, 2H, J = 8.3 Hz, acr), 7.75 (d, 2H, J = 8.3 Hz, acr), 7.91 (t, 2H, J = 8.3 Hz, acr), 8.47 (d, 2H, J = 8.3 Hz, acr); ^{13}C NMR (CD_3OD): δ 30.3, 31.0, 36.8, 52.0, 62.2, 66.6, 73.5, 115.3, 119.6, 124.9, 130.3, 134.4, 136.4, 158.3, 159.6, 175.0.

3-{4-[3-(Acridin-9-ylamino)-propoxy]-2-iodo-phenyl}-propionic acid (**2b**). This compound was, a yellow powder, prepared in 92% from compound **9b** by using a similar procedure as was used for compound **2a**.

m.p. = 142.0−144.0°C. ^{1}H NMR (CD_3OD): δ 2.43 (m, 2H, benzO–CH_2–$\underline{CH_2}$–), 2.50 (t, 2H, J = 7.4 Hz, benz–CH_2–), 2.71 (t, 2H, J = 7.4 Hz, –CH_2–CO_2H–), 4.12 (t, 2H, J = 5.3 Hz, –CH_2–N), 4.35 (t, 2H, J = 6.5 Hz, benzO–CH_2–), 6.71 (d, 1H, J = 8.0 Hz, benz), 7.01 (d, 1H, J = 8.0 Hz, benz), 7.43–7.45 (m, 3H, acr and benz), 7.70 (d, 2H, J = 8.2 Hz, acr), 7.82 (t, 2H, J = 8.2 Hz, acr), 8.42 (d, 2H, J = 8.2 Hz, acr); ^{13}C NMR (CD_3OD): δ 30.2, 30.4, 36.4, 52.1, 67.5, 86.9, 113.4, 119.6, 125.1, 130.5, 136.3, 136.6, 140.0, 156.8, 174.7.

3-{4-[3-(Acridin-9-ylamino)-propoxy]-3-trimethylstannyl-phenyl}-propionic acid (**2c**). Compound **2a** (57.0 mg, 0.12 mmol) was dissolved in dry DMF and argon was bubbled through the solution for 15 min. Hexamethylditin (0.142 g, 0.48 mmol) and tetrakis triphenyl phosphine palladium(0) (27.7 mg, 0.024 mmol) were added successively. The reaction mixture was then stirred at 90°C for 3 h under an argon atmosphere. The black precipitate was filtered off and the solvent was evaporated. The crude product was then subjected to flash chromatography, 7:1 CH_2Cl_2:MeOH with a few drops of triethylamine as a mobile phase. The reaction provided a yellow powder of compound **2c** (50 mg, 74% yield).

^{1}H NMR ($CDCl_3$): δ 0.24 (s, tin satellites, 9H, $Sn(CH_3)_3$), 2.59-2.63 (m, 4 H, benzO–CH_2–CH_2), 2.90 (t, 2H, J = 7.4 Hz, –CH_2–CO_2–), 4.27-4.34 (m, 4 H, –CH_2N– and benzO–CH_2–), 6.84 (d, 1H, J = 8.3 Hz, benz), 7.06–7.12 (m, 3H, benz and acr), 7.19 (s, 1H, benz), 7.40 (t, 2H, J = 8.6 Hz, acr), 7.89 (d, 2H, J = 8.6 Hz, acr), 8.15 (d, 2H, J = 8.6 Hz, acr); ^{13}C NMR (CD_3OD): δ −8.87, 30.2, 30.4, 36.4, 52.1, 67.5, 86.9, 113.4, 119.6, 125.1, 130.5, 136.2, 136.6, 140.0, 156.8, 174.7.

4-(2-Amino-ethyl)-2-iodo-phenol (**11**)[16]. Tyramine (0.100 g, 0.73 mmol) was dissolved in 10% triflouroacetic acid in dichloromethane. Solid IPy_2BF_4 (0.41 g, 1.09 mmol) was added and the reaction was stirred at room

temperature for 1 h. The solvent was evaporated under reduced pressure. The residue was dissolved in methanol, sodium bicarbonate was added and the mixture was stirred for 1 h. The salt was filtered off and the solvent was evaporated. The crude product was then purified by column chromatography (1:9, methanol:CH_2Cl_2) to afford compound **11** (0.183 g, 95% yield) as a white solid.

^{1}H NMR (CD_3OD): δ 7.61 (d, 1H, $J = 2.4$ Hz, benz), 7.09 (dd, 1H, $J = 7.7$, 2.4 Hz, benz), 6.80 (d, 1H, $J = 7.7$ Hz, benz), 3.10 (t, 2H, $J = 7.4$ Hz, NCH_2–), 2.82 (t, 2H, $J = 7.4$ Hz, –CH_2–); ^{13}C NMR (CD_3OD): δ 157.3, 140.4, 130.9, 130.6, 116.1, 85.0, 42.0, 33.1.

4-[2-(Acridin-9-ylamino)-ethyl]-phenol (**3a**). A mixture of 9-phenoxyacridine (70.00 mg, 0.26 mmol) and tyramine (35.4 mg, 0.26 mmol) was dissolved in molten phenol. The solution was stirred at ~80°C for 1 h. The mixture was flashed on a silica gel with 100% ethylacetate in order to remove the phenol. The compound was then recovered by eluting with 4:1, CH_2Cl_2:MeOH. The reaction provided a yellow powder of compound **3a** (78 mg, 95% yield). HRMS (*m*/*z*): calculated for ($C_{21}H_{18}N_2O + H^+$), 315.1497; found 315.1465.

^{1}H NMR (in CD_3OD): δ 8.40 (d, 2H, $J = 9.3$ Hz, acr), 7.89 (t, 2H, $J = 9.3$ Hz, acr), 7.79 (d, 2H, $J = 9.3$ Hz, acr), 7.50 (t, 2H, $J = 9.3$ Hz, acr), 6.99 (d, 2H, $J = 8.1$ Hz, benz), 6.58 (d, 2H, $J = 8.1$ Hz, benz), 4.33 (t, 2H, $J = 6.0$ Hz, NCH_2–), 3.10 (t, 2H, $J = 6.0$ Hz, –CH_2–); ^{13}C NMR (CD_3OD): δ 159.5, 157.4, 142.1, 135.9, 130.9, 129.4, 126.3, 124.8, 120.5, 116.4, 114.3, 52.2, 36.1.

4-[2-(Acridin-9-ylamino)-ethyl]-2-iodo-phenol (**3b**). Synthesis was carried out using iodotyramine in the procedure similar to that used for **3a** to give 95% yield of **3b**. HRMS (*m*/*z*): calculated for ($C_{21}H_{17}IN_2O + H^+$), 441.0464; found 441.0519.

^{1}H NMR (CD_3OD): δ 8.37 (d, 2H, $J = 7.9$ Hz, acr), 7.90 (t, 2H, $J = 7.9$ Hz, acr), 7.76 (d, 2H, $J = 7.9$ Hz, acr), 7.52 (t, 2H, $J = 7.9$ Hz, acr), 7.32 (s, 1H, benz), 6.84 (dd, 1H, $J = 7.8$, 1.7 Hz, benz), 6.50 (d, 1H, $J = 7.8$ Hz, benz), 4.38 (t, 2H, $J = 6.9$ Hz, NCH_2–), 3.03 (t, 2H, $J = 6.9$ Hz, CH_2–); ^{13}C NMR (CD_3OD): δ 160.5, 156.9, 140.8, 136.4, 131.4, 131.0, 124.9, 119.7, 115.7, 84.5, 52.0, 35.7.

[2-(4-Hydroxy-phenyl)-ethyl]-carbamic acid tert-butyl ester (**12a**). Tyramine (0.10 g, 0.73 mmol) was added to a 10% solution of triethylamine in methanol (20 ml). Di-*tert* butyl dicarbonate (0.39 g, 1.46 mmol) was then added while stirring continuously. The reaction was stirred at 54°C for 30 min. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in ethylacetate.

Ice-cold aqueous HCl (pH ~ 3, 3 ml) was added. The solution was stirred at 0°C for 10 min, and extracted with ethylacetate (3 × 20 ml). The organic extracts were combined and dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (8:1, CH_2Cl_2:MeOH) to give the pure product **12a** (0.17 g, 98% yield) as a white solid.

^{1}H NMR ($CDCl_3$): δ 6.97 (d, 2H, $J = 8.0$ Hz, benz), 6.79 (d, 2H, $J = 8.0$ Hz, benz), 6.60 (bs, 1H, OH), 4.71 (bs, 1H, NH), 3.32 (m, 2H, CH_2N), 2.69 (t, 2H, $J = 7.0$ Hz, benz–CH_2), 1.46 (bs, 9H, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 156.3 (C═O), 154.9, 130.0, 129.7, 115.5, 79.6, 42.0, 35.1, 28.3.

[2-(4-Hydroxy-3-iodo-phenyl)-ethyl]-carbamic acid tert-butyl ester (**12b**). A yield of 72% of this compound was obtained using the same procedure as was used for compound **12a**.

HRMS (*m*/*z*): calculated for ($C_{13}H_{18}INO_3$ + Na), 386.0229; found 386.0228. m.p. = 128.4−128.9°C. ^{1}H NMR ($CDCl_3$): δ 7.48 (s, 1H, benz), 7.03 (d, 1H, $J = 8.2$ Hz, benz), 6.89 (d, 1H, $J = 8.2$ Hz, benz), 6.03 (bs, 1H, OH), 4.59 (bs, 1H, NH), 3.30 (m, 2H, CH_2–N), 2.68 (t, 2H, $J = 7.1$ Hz, CH_2); ^{13}C NMR ($CDCl_3$): δ 156.0, 153.8, 138.4, 132.8, 130.4, 115.0, 85.4, 79.5, 41.8, 34.8, 28.4.

(2-{4-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propoxy]-phenyl}-ethyl)-carbamic acid tert-butyl ester (**13a**). A mixture of BOC protected tyramine **12a** (0.10 g, 0.42 mmol), *N*-(3-bromopropyl)phthalimide (1.35 g, 5.04 mmol) and potassium carbonate (58.30 mg, 0.42 mmol) was dissolved in acetone. The reaction mixture was refluxed overnight under an inert atmosphere. The reaction was cooled to room temperature and the solvent was evaporated after filtration. The crude product was subject to flash chromatography using 2:1 pentane:ether until all excess bromophthalimide was eluted. The pure compound was then eluted from 100% ether. The reaction afforded (0.165 g, 93% yield) of compound **13a** as a white solid.

m.p. = 123.9−125.0°C. ^{1}H NMR ($CDCl_3$): δ 7.85 (m, 2H, phthalimide), 7.72 (m, 2H, phthalimide), 7.05 (d, 2H, $J = 8.3$ Hz, benz), 6.75 (d, 2H, $J = 8.3$ Hz, benz), 4.02 (t, 2H, $J = 6.0$ Hz, CH_2–O), 3.90 (t, 2H, $J = 6.0$ Hz, $\underline{CH_2}$−phthalimide), 3.30 (q, 2H, $J = 7.0$ Hz, CH_2–NH), 2.70 (t, 2H, $J = 7.0$ Hz, CH_2–benz), 2.18 (qn, 2H, $J = 6.0$ Hz, CH_2–$\underline{CH_2}$−CH_2), 1.40 (s, 9H, BOC); ^{13}C NMR ($CDCl_3$): δ 168.3, 157.3, 155.8, 134.2, 132.1, 131.0, 129.9, 123.5, 114.9, 79.2, 65.9, 41.9, 35.8, 29.9, 28.7, 28.6.

(2-{4-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propoxy]-3-iodo-phenyl}-ethyl)-carbamic acid tert-butyl ester (**13b**). This compound was prepared in 86% yield using a procedure similar to that described for **13a**.

^{1}H NMR ($CDCl_3$): δ 7.81 (dd, 2H, $J = 5.4$, 3.1 Hz, phthalimide), 7.69 (dd, 2H, $J = 5.4$, 3.1 Hz, phthalimide), 7.55 (s, 1H, benz), 7.07 (dd, 1H, $J = 8.5$,

2.0 Hz, benz), 6.70 (d, 1H, $J = 8.5$ Hz, benz), 4.58 (bs, 1H, NH), 4.04 (t, 2H, $J = 5.9$ Hz, CH_2–O), 3.95 (t, 2H, $J = 7.0$ Hz, $\underline{CH_2}$−phthalimide), 3.29 (q, 2H, $J = 7.0$ Hz, CH_2–NH), 2.67 (t, 2H, $J = 7.4$ Hz, CH_2–benz), 2.21 (m, 2H, $J = 5.9$ Hz, CH_2–$\underline{CH_2}$−CH_2), 1.40 (s, 9H, BOC); ^{13}C NMR ($CDCl_3$): δ 168.3, 155.9, 155.7, 139.5, 133.8, 133.3, 132.2, 129.6, 123.2, 112.0, 86.7, 67.0, 41.7, 35.5, 34.7, 28.5, 28.3.

{2-[4-(3-Amino-propoxy)-phenyl]-ethyl}-carbamic acid tert-butyl ester (**14a**). To compound **13a** (0.16 g, 0.38 mmol) dissolved in methanol (75 ml) was added hydrazine monohydrate (0.37 ml, 7.6 mmol). The reaction mixture was refluxed overnight. The reaction was cooled to room temperature and the solvent was evaporated. The residue was dissolved in 8:1, CH_2Cl_2:MeOH. The insoluble part was filtered off, and washed several times with the solvent. The solvent was evaporated and the residue was subject to flash chromatograpy with the solvent system 8:1, CH_2Cl_2: MeOH until all the phthalhydrazide was eluted. The compound was then recovered by eluting with 4:1:0.01 CH_2Cl_2:MeOH:Et_3N to give pure compound **14a** (100 mg, 90% yield) as a white solid.

m.p. =106.9−108.0°C. ^{1}H NMR ($CDCl_3$): δ 7.10 (d, 2H, $J = 8.7$ Hz, benz), 6.83 (d, 2H, $J = 8.7$ Hz, benz), 4.50 (bs, 1H, NHCO), 4.03 (t, 2H, $J = 5.8$ Hz, CH_2–O), 3.33 (m, 2H, CH_2NCO), 2.91 (t, 2H, $J = 6.8$ Hz, $\underline{CH_2}NH_2$), 2.74 (t, 2H, $J = 6.9$ Hz, benz–CH_2), 1.92 (m, 2H, CH_2–$\underline{CH_2}$−CH_2), 1.43 (bs, 9H, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 157.6, 155.9, 131.0, 129.7, 114.6, 79.0, 65.9, 41.9, 39.3, 35.3, 33.0, 28.4.

{2-[4-(3-Amino-propoxy)-3-iodo-phenyl]-ethyl}-carbamic acid tert-butyl ester (**14b**). Obtained in 87% yield from compound **13b** using a procedure similar to that used for compound **14a**.

m.p. = 153.1−155.7°C. ^{1}H NMR ($CDCl_3$): δ 7.54 (s, 1H, benz), 7.08 (d, 1H, $J = 9.1$ Hz, benz), 6.73 (d, 1H, $J = 9.1$ Hz, benz), 4.72 (bs, 1H, NHCO), 4.10 (t, 2H, $J = 5.8$ Hz, CH_2–O), 3.26 (m, 4 H, CH_2NCO, $\underline{CH_2}NH_2$), 2.65 (t, 2H, $J = 6.8$ Hz, benzCH_2), 2.26 (m, 2H, CH_2–$\underline{CH_2}$−CH_2), 1.39 (bs, 9H, $(CH_3)_3$); ^{13}C NMR (in $CDCl_3$), δ (ppm): 168.3, 156.2, 156.1, 139.7, 133.7, 130.0, 129.9, 114.8, 112.3, 86.9, 67.4, 42.0, 38.9, 35.0, 31.3, 28.6.

(2-{4-[3-(Acridin-9-ylamino)-propoxy]-phenyl}-ethyl)-carbamic acid tert-butyl ester (**15a**). A mixture of amine **14a** (50.00 mg, 0.17 mmol), 9-phenoxyacridine (46.1 mg, 0.17 mmol) and phenol was stirred at 80°C for 1 h. The mixture was cooled to room temperature and then subject to column chromatography. Phenol was first eluted with 100% ethylacetate and the product was then recovered by eluting with 3:1:0.01, CH_2Cl_2: MeOH:Et_3N. The reaction provided a quantitative yield of compound **15a** as a white solid.

m.p. = 112.0−114.0°C. ^{1}H NMR ($CDCl_3$): δ 8.13 (d, 2H, J = 8.6 Hz, acr), 7.99 (t, 2H, J = 8.6 Hz, acr), 7.60 (t, 2H, J = 7.8 Hz, acr), 7.30 (d, 2H, J = 7.8 Hz, acr), 7.10 (d, 2H, J = 8.7 Hz, benz), 6.83 (d, 2H, J = 8.7 Hz, benz), 4.70 (bs, 1H, NHCO), 4.16 (t, 2H, J = 5.6 Hz, acr–N–CH_2–), 4.07 (t, 2H, J = 6.5 Hz, CH_2–O), 3.34 (m, 2H, CH_2NCO), 2.73 (t, 2H, J = 7.9 Hz, benzCH_2–), 2.23 (m, 2H, CH_2–$\underline{CH_2}$−CH_2–), 1.44 (s, 9H, BOC); ^{13}C NMR ($CDCl_3$): δ 157.0, 155.9, 151.9, 131.7, 130.1, 129.8, 128.2, 123.1, 122.8, 116.2, 114.4, 79.0, 66.7, 48.8, 41.9, 35.3, 30.6, 28.4.

(2-{4-[3-(Acridin-9-ylamino)-propoxy]-3-iodo-phenyl}-ethyl)-carbamic acid tert-butyl ester (**15b**). A 91% yield of this compound was obtained using a procedure similar to that described for **15a**.

HRMS (m/z): calculated for ($C_{29}H_{32}IN_3O_3 + H^+$), 598.1567; found 598.1571. m.p. = 105.3−106.8°C. ^{1}H NMR ($CDCl_3$): δ 8.18 (d, 2H, J = 8.3 Hz, acr), 7.91 (t, 2H, J = 8.3 Hz, acr), 7.55 (s, 1H, benz), 7.52 (t, 2H, J = 8.0 Hz, acr), 7.23 (d, 2H, J = 7.0 Hz, acr), 7.02 (d, 1H, J = 8.2 Hz, benz), 6.63 (d, 1H, J = 8.2 Hz, benz), 4.85 (bs, 1H, NHCO), 4.13 (m, 4 H, acr–N–CH_2, –CH_2–O–), 3.3 (m, 2H, CH_2NCO–), 2.66 (t, 2H, J = 6.9 Hz, benzCH_2–), 2.23 (m, 2H, J = 5.7 Hz, –CH_2–$\underline{CH_2}$−CH_2–), 1.43 (s, 9H, BOC); ^{13}C NMR ($CDCl_3$): δ: 155.8, 152.9, 146.0, 140.2, 133.8, 131.7, 131.6, 130.1, 126.7, 124.6, 122.9, 122.1, 115.5, 113.0, 86.5, 67.2, 47.8, 42.0, 34.8, 30.4, 28.9.

Acridin-9-yl-{3-[4-(2-amino-ethyl)-phenoxy]-propyl}-amine (**4a**). To a solution of compound **15a** (0.14 g, 0.29 mmol) in methanol, 5 ml of 12.5 M dry HCl in ethylacetate was added. The resulting solution was stirred for 18 h. The completion of the reaction was confirmed by TLC (CH_2Cl_2:MeOH:HCOOH, 9:1:0.01). The reaction resulted in quantitative yield of **4a** as a yellow powder.

HRMS (m/z): calculated for ($C_{24}H_{25}N_3O + H^+$), 372.2076; found 372.2079. ^{1}H NMR (CD_3OD): δ 8.54 (d, 2H, J = 8.3 Hz, acr), 7.9 (t, 2H, J = 8.3 Hz, acr), 7.83 (d, 2H, J = 8.3 Hz, acr), 7.55 (t, 2H, J = 8.3 Hz, acr), 7.10 (d, 2H, J = 8.0 Hz, benz), 6.74 (d, 2H, J = 8.0 Hz, benz), 4.40 (t, 2H, J = 5.9 Hz, acrN–CH_2–), 4.15 (t, 2H, J = 4.8 Hz, benzO–CH_2–), 3.09 (t, 2H, J = 7.7 Hz, –$\underline{CH_2}$−NH_3), 2.87 (t, 2H, J = 7.7 Hz, benz–CH_2–), 2.45 (m, 2H, –CH_2–$\underline{CH_2}$−CH_2–); ^{13}C NMR ($CDCl_3$): δ 159.7, 152.0, 140.6, 136.4, 130.8, 130.2, 125.0, 119.6, 115.8, 113.0, 66.7, 47.9, 42.1, 33.6, 30.3.

Acridin-9-yl-{3-[4-(2-amino-ethyl)-2-iodo-phenoxy]-propyl}-amine (**4b**). Compound **4b** was prepared using the same method as for the amine **4a**.

HRMS (m/z): calculated for ($C_{24}H_{24}IN_3O + H^+$), 498.1042; found 498.1089. m.p. = 257.0−259.0°C. ^{1}H NMR (CD_3OD): δ 8.57 (d, 2H, J = 8.5 Hz, acr), 7.96 (t, 2H, J = 8.5 Hz, acr), 7.81 (d, 2H, J = 8.5 Hz, acr), 7.63 (d, 1H, J = 2.3 Hz, benz), 7.57 (t, 2H, J = 8.5 Hz, acr), 7.19 (dd, 1H,

$J = 8.7$, 2.3 Hz, benz), 6.88 (d, 1H, $J = 8.7$ Hz, benz), 4.50 (t, 2H, $J = 7.1$ Hz, acrN–CH_2–), 4.23 (t, 2H, $J = 5.9$ Hz, benzO–CH_2–), 3.1 (t, 2H, $J = 7.5$ Hz, –$\underline{CH_2}-NH_3$), 2.85 (t, 2H, $J = 8.2$ Hz, benz–CH_2–), 2.51 (m, 2H, –CH_2–$\underline{CH_2}-CH_2$–); ^{13}C NMR ($CDCl_3$): δ 158, 152.0, 140.6, 136.4, 132.6, 131.2, 125.1, 119.7, 115.0, 113.8, 87.3, 67.7, 48.2, 41.9, 33.1, 30.2.

Acridin-9-yl-{3-[4-(2-amino-ethyl)-2trimethylstannyl-phenoxy]-propyl}-amine (**4c**). The hydrogen chloride salt of compound **4b** was stirred with aqueous K_2CO_3 and extracted with CH_2Cl_2 to give the free amine. The organic phase was dried over magnesium sulfate. The solvent was evaporated and this free amine (20.0 mg, 0.04 mmol) was dissolved in dry 1,4-dioxane. The solution was bubbled with argon for 10 min in order to remove oxygen and carbon dioxide. Hexamethyldistannane (53.0 mg, 0.16 mmol) was added to the mixture and argon was bubbled through the reaction mixture for 4 min. Finally, bis-(triphenylphosphine)-palladium(II)-dichloride (9.20 mg, 0.01 mmol) was added and the reaction mixture was stirred at 85°C for 90 min. The reaction mixture was cooled to room temperature and the catalyst was filtered off through celite. After evaporation to dryness the crude mixture was applied to a flash chromatography column and eluted with mobile phase CH_2Cl_2:MeOH, 6:1 to give compound **4c** (18.2 mg, 85% yield) as a yellow powder.

^{1}H NMR ($CDCl_3$): δ 8.10 (m, 4 H, acr), 7.66 (t, 2H, $J = 7.6$ Hz, acr), 7.32 (m, 3H, acr + benz), 7.16 (d, 1H, $J = 8.6$ Hz, benz), 6.76 (d, 1H, $J = 8.6$ Hz, benz), 4.12 (t, 2H, $J = 7.1$ Hz, acrNCH_2–), 4.03 (t, 2H, $J = 5.9$ Hz, –CH_2O–), 2.93 (m, 2H, –$\underline{CH_2}-NH_3$), 2.70 (t, 2H, $J = 8.2$ Hz, benzCH_2–), 2.25(m, 2H, –CH_2–$\underline{CH_2}-CH_2$–), 0.23 (s + tin satellites, 9H, $J_{HSn} = 28$ Hz, $Sn(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 177.1, 168.0, 158, 152.0, 140.8, 136.4, 132.4, 130.0, 129.9, 124.8, 122.4, 121.0, 120.6, 114.9, 113.8, 84.3, 68.2, 48.2, 41.9, 33.1, 30.2, −8.9.

General ^{125}I-labeling procedure

The following stock solutions were prepared: Acridine derivatives (2 mg/ml) in methanol. *N*-chloro-*p*-toluenesulfonamide sodium salt (8 mg/ml) was dissolved in methanol prior to use.

In a typical labeling experiment 3.7 GBq/ml of [^{125}I]iodide was used. To 40 µl of 1% acetic acid methanol solution of acridine derivative, 5.0 µl aqueous ^{125}I-solution was added, followed by 10 µl CAT solution. The reaction mixture was vortexed for 5 min, quenched by the addition of 10 µl sodium metabisulfite solution, and 20 µl of NaI solution was added as carrier. Exact concentrations of solutions are given in Table 1. After mixing the reaction mixture, samples for radio-TLC analysis (1–2 µl) were collected. Blank experiments were run using exactly the same conditions, but neat 1% acetic acid methanol solution was used instead of the stock solution of acridine derivatives. All blank experiments were tested in both TLC systems.

Acknowledgements

This work was financially supported by the Swedish Cancer Foundation and by INTAS (Grant No. 99-00806).

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