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Synthesis and evaluation of [^{123}I]-indomethacin derivatives as COX-2 targeted imaging agents

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A novel series of iodinated indomethacin derivatives was synthesized, and evaluated as selective inhibitors of COX-2. Two candidate compounds *N*-(*p*-iodobenzyl)-2-(1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetamide (3) and 1-(*p*-iodobenzyl)-5-methoxy-2-methyl-3-indoleacetic acid (9) possessed optimum properties suitable for potential *in vivo* imaging. Arylstannane precursors for radioiododestannylation were synthesized in 70–85% yield from the iodo compounds by reaction with hexabutylditin and *tetrakis*(triphenylphosphine)palladium(0) in refluxing dioxane. Radioiododestannylation was conducted by reaction with carrier-added Na[^{123}I] in the presence of Chloramine-T in an EtOAc/H_2O binary system under acidic conditions (pH 3.5), allowing direct isolation of the labeled products by separation of the organic phase. Radioiodinated products [^{123}I]3 and [^{123}I]9 were recovered in a decay-corrected radiochemical yield of 86–87% and radiochemical purity of 98–99%.

Keywords: Iodine-123; indomethacin; iododestannylation; two-phase reaction; COX-2

Introduction

There are two cyclooxygenase (COX) genes in humans, which are responsible for the conversion of polyunsaturated fatty acids to prostaglandins.[1] COX-1 is constitutively expressed and, for the most part, appears to play a role in tissue homeostasis, whereas COX-2 is induced in response to a broad range of physiological and pathophysiological stimuli.[2–5] COX-2 mRNA and protein are detectable in a significant percentage of inflammatory and premalignant lesions,[6–8] and an even higher percentage of malignant tumors (e.g. colon adenocarcinoma, esophageal adenocarcinoma).[9,10] Studies have shown that the expression of COX-2 is an early event in tumorigenesis and that it plays a role in tumor progression.[11] Thus, COX-2 is a potential target for imaging a variety of cancers using radiolabeled COX-2 inhibitors, and some approaches toward this goal have been reported.[12]

^{18}F- and ^{123}I-labeled COX-2 inhibitors based on the diarylheterocycle class of inhibitors have been synthesized and selective uptake has been reported in COX-2-expressing cells.[13–16] Such selective uptake has not been rigorously demonstrated *in vivo* although promising preliminary data have been reported with an ^{123}I-labeled celecoxib derivative.[16] Other classes of COX-2 inhibitors may be more effective scaffolds for the development of targeted radiological imaging agents based on their potency, selectivity or pharmacokinetic properties. Our laboratory and others have reported that conversion of the nonselective COX inhibitor, indomethacin, into amide derivatives or replacement of the *p*-chlorobenzoyl moiety on the indole nitrogen with a *p*-bromobenzyl group yields inhibitors that display a high degree of COX-2-selectivity.[17,18] As a prelude to the evaluation of these classes of inhibitors for single photon emission computerized tomography imaging, we synthesized a series of iodo derivatives and evaluated their COX-2 inhibitory properties against purified proteins and in intact cell assays. The incorporation of iodine into both types of indomethacin derivatives yielded compounds that were active against purified COX-2 but many of them did not inhibit the enzyme in intact cells. The most promising compounds identified in cell-based assays were used as targets for stannylation-based introduction of ^{123}I. The chemistry reported herein includes an efficient two-phase method for ^{123}I incorporation that

A complete description of the experimental methods and compound charcterization is available online at http://www.interscience.wiley.com

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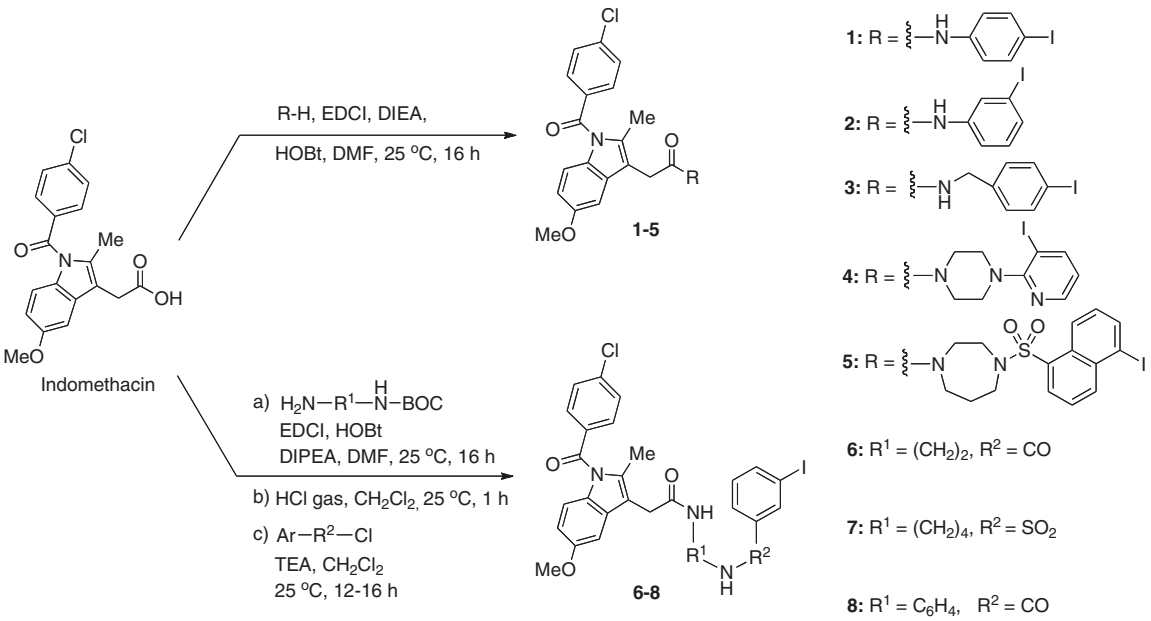
generates labeled compounds in high yield and purity without the need for further chromatographic purification.

Results

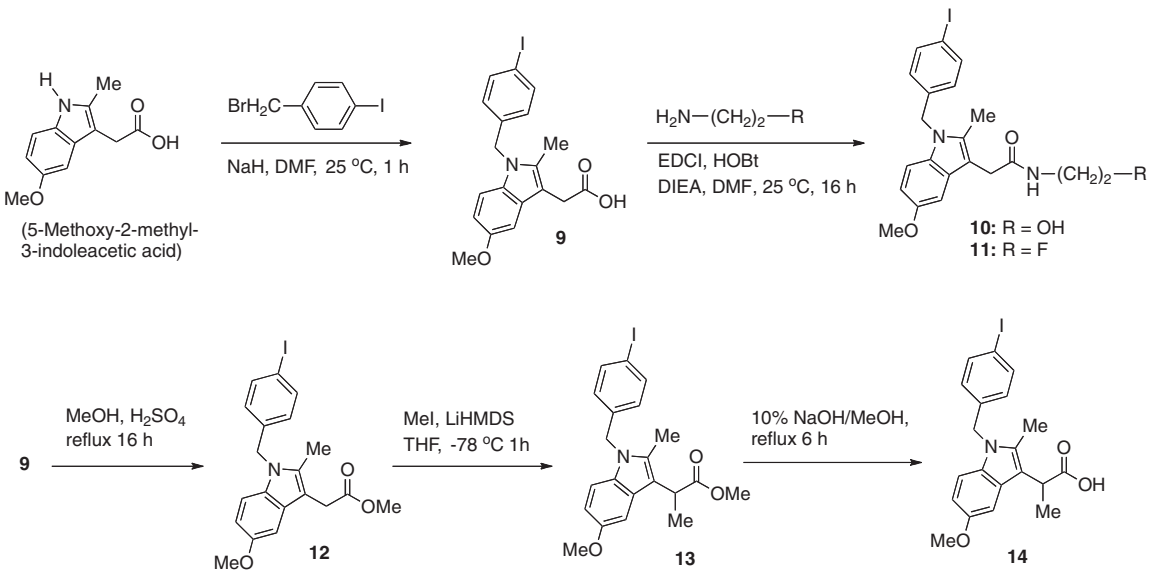
Chemistry and pharmacology

A series of indole amide derivatives was synthesized by coupling indomethacin with different amines (Scheme 1). For example, *N*-(*p*-iodobenzyl)-2-(1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetamide (**3**) was synthesized by a reaction of indomethacin with 4-iodobenzylamine using ethyl-1-[3-(dimethylamino)propyl]-3-ethylcarbodiamide (EDCI), 1-hydroxybenzotriazole hydrate (HOBt), *N,N*-diisopropylethylamine (DIEA), *N,N*-dimethylformamide (DMF) in 77% yield. A second series of iodinated indomethacin derivatives was generated based on *p*-halobenzyl substitution on the indole nitrogen; the *p*-bromobenzyl analog has been reported to be a selective COX-2 inhibitor.[18] We synthesized 1-(*p*-iodobenzyl)-5-methoxy-2-methyl-3-indoleacetic acid (**9**) by direct alkylation of 5-methoxy-2-methyl-3-indoleacetic acid with *p*-iodobenzylbromide in the presence of NaH in 67% yield (Scheme 2).

Each of the compounds was tested for its potency and selectivity for inhibition of recombinant human COX-2 and purified sheep COX-1 as previously described.[17] (Table 1). Compounds also were evaluated for their ability to inhibit COX-2 in intact cells using the mouse macrophage cell line RAW264.7. Although all of the indole amide compounds (**1–8**) were potent and selective inhibitors of purified recombinant COX-2, only **3** inhibited COX-2 in intact cells. In contrast to

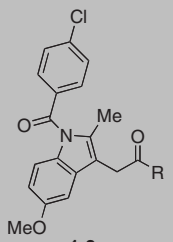


Scheme 1. Synthesis of iodinated compounds **1–8.**

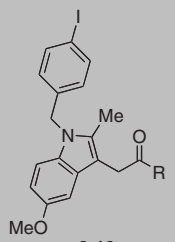


Scheme 2. Synthesis of iodinated compounds **9–14**.

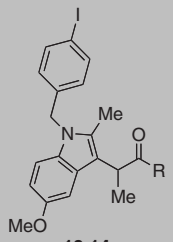
Table 1. COX-1 and COX-2 enzyme inhibition assay data against purified COX enzymes or LPS-activated RAW264.7 macrophages.



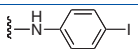
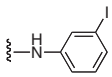
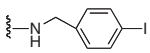
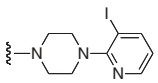
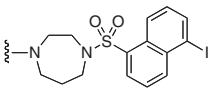
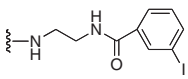
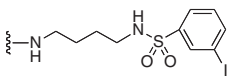
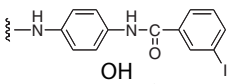
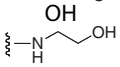
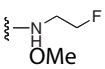
1-8



9-12



13-14

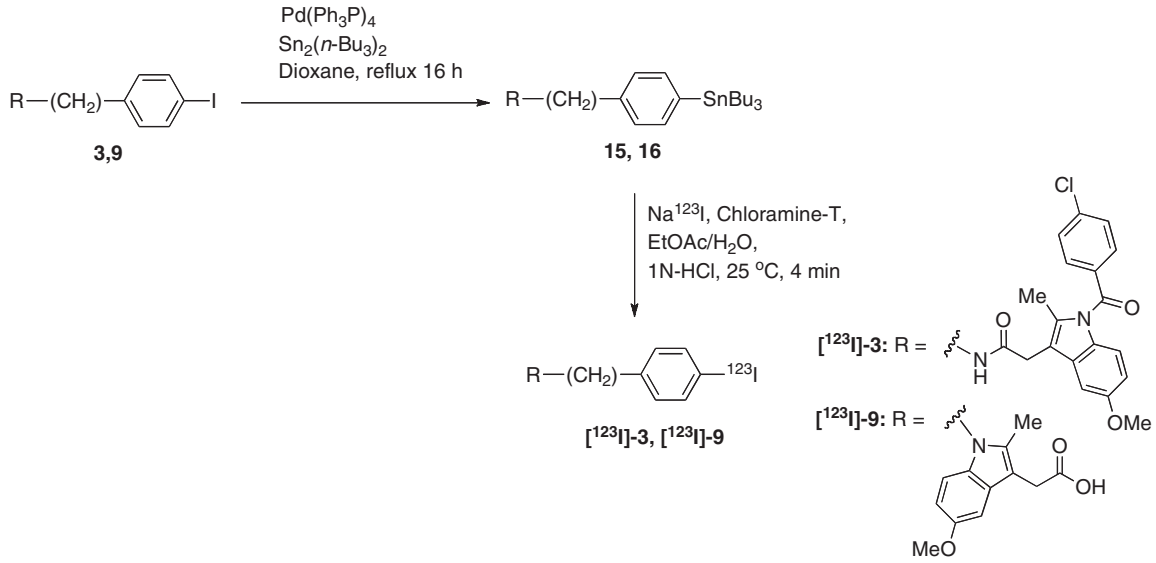
Compound No.	R	IC_{50} (μM)[a]		IC_{50} (μM) intact cells[b]
		COX-1	COX-2	
1		>66	0.12	≫1
2		>66	0.06	≫1
3		>66	0.12	1
4		>66	0.45	>1
5		>66	0.28	>1
6		>66	0.21	>1
7		>66	0.10	>1
8		>66	0.17	>1
9	OH	>66	0.40	0.08
10		>66	>66	n.d.
11		>66	>66	n.d.
12	OMe	>66	>66	n.d.
13	OMe	>66	>66	n.d.
14	OH	>66	1.71	1.49

[a]Ovine COX-1 (44 nM) or human COX-2 (66 nM) was preincubated with inhibitors at 25°C for 17 min show at 37°C for 3 min followed by the addition of [1–^{14}C]arachidonic acid (50 μM) at 37°C for 30 s. All assays were conducted in duplicate. IC_{50} values were determined by incubating several concentrations of inhibitors dissolved in dimethylsulfoxide (DMSO).
[b]Cells (6.2×10^6 cells/T25 flask) were activated with lipopolysaccharide (200 ng/mL) and β-interferon (10 U/mL) in serum-free DMEM for 7 h and then treated with inhibitor (0–2 μM) for 30 min at 37°C. Exogenous arachidonate metabolism was determined by adding [1–^{14}C]arachidonic acid (20 μM) for 15 min at 37°C. IC_{50} values are the average of two independent determinations. Cell line assay results were not determined (n.d.) with compounds that did not inhibit purified COX-2.

amides and esters of indomethacin, amides and esters of the *p*-iodobenzyl analog did not inhibit COX-2. We attempted to increase the potency by introducing a methyl group α to the carboxyl group. This substitution is present in many COX inhibitors, such as naproxen and flurbiprofen but had not been tested in the *N*-benzyl series of indomethacin analogs. Unfortunately, compound **14** was somewhat less potent than the unsubstituted compound **9**. Compound **13,** which is a methyl ester of compound **14**, also did not inhibit purified protein.

Radiochemistry

Compounds **3** and **9** showed the most promising properties as potential imaging agents and were chosen to label with ^{123}I. Aryltributylstannanes **15** and **16** were generated from the iodo



Scheme 3. Radiochemical synthesis of [^{123}I]**3** and [^{123}-I]**9**.

compounds by reaction with hexabutylditin and *tetrakis*(triphenylphosphine)palladium(0) in refluxing 1,4-dioxane. Radioiodination of the tributylstannyl derivatives was conducted in an EtOAc/H_2O binary-phase system by reaction with carrier-added [Na^{123}I] in the presence of Chloramine-T and aqueous 1 M HCl. Separation of the organic layer and evaporation afforded radiolabeled compounds [^{123}I]**3** or [^{123}I]**9** in a decay-corrected radiochemical yield of 86–87% and a radiochemical purity of 98–99%. A radio-TLC analysis of [^{123}I]-**9** is shown in Figure 2(a) and a radio-TLC analysis of Na^{123}I in Figure 2(b). HPLC analysis of the product showed the only radioactive peak to co-elute with standard iodo compound. The final specific activity of the radiolabeled products was 491 Ci/mmol (Scheme 3).

In vivo uptake and retention of compound 9 by COX-2 expressing tumors

The utility of compounds such as **3** and **9** for COX-2 targeted imaging depends on their stability *in vivo*. As a preliminary attempt to evaluate their *in vivo* stability, we assayed the uptake of compound **9** into a COX-2 expressing tumor. Female nude mice with 1483 human head and neck squamous cell carcinoma xenograft tumors (0.6 ± 0.1 cm^3) on the left flank were injected retroorbitally at a dose of 2 mg/kg compound **9** formulated with DMSO (16%)/EtOH (33%)/propylene glycol (17%)/warm sterile saline 34% (37°C). At 3 h post injection, the mice ($n = 3$) were anesthetized. Blood samples were quickly taken by cardiac puncture into a 1.5 mL heparinized tube on ice, followed by removal of the liver and tumor. The collected tissues were rinsed briefly in ice-cold PBS, blotted dry, weighed and snap-frozen in liquid nitrogen. The blood samples were centrifuged at 4°C at 6000 rpm for 5 min, and the plasma was transferred to clean tubes and frozen at −80°C. The tissue was homogenized in 100 mM Tris buffer, pH 7.0, and then an aliquot of the homogenate was mixed with 1.2 × volume of acetonitrile and kept at −20°C until phases formed. The acetonitrile was removed and the samples were dried, reconstituted and analyzed by reversed phase HPLC-UV using a Phenomenex 10 × 0.2 cm C18 or a Phenomenex 7.5 × 0.2 cm Synergi Hydro-RP column held at 40°C. The samples were quantified against a standard curve prepared from tissue homogenates of undosed control animals. The statistical comparisons of the experimental results were performed by Student's *t*-test at a significance level of 0.01 and 0.001. Intact compound **9** was identified in the COX-2 expressing nude mouse tumor (3 nmol/g tissue). This result suggests that compound **9** remains intact in the biological environment for a long enough period of time (3 h) to be taken up by the tumor.

Enzyme–inhibitor binding kinetics

Compounds like celecoxib and indomethacin are potent COX-2 inhibitors because they are slow, tight-binding inhibitors. They establish a rapid equilibrium with a loosely bound enzyme–inhibitor complex then slowly convert to a much more tightly bound complex. Their rate of dissociation from the tightly bound complex is very low (Equation (1)). Compounds **3** and **9** also are slow, tight-binding inhibitors. Figure 1(a) shows the time and concentration dependent inhibition of hCOX-2 by compound **9**. The inhibition of hCOX-2 proceeded rapidly and the inhibition plateau for compound **9** at high concentrations approached 0% activity remaining; this indicates a very slow rate of reversal of inhibition. Figure 1(b) displays a plot of the single exponential rate constants for inhibition as a function of concentration, which allows the determination of the equilibrium constant for initial association ($K_I = k_{-1}/k_1$). Compound **9** had a K_I value similar in nature to indomethacin ($K_I = 11.5 \pm 1.5$ versus 13.2 ± 2.3 μM), indicating a similar affinity for the enzyme with the two compounds. The association rate (k_2) of compound **9** with hCOX-2 was identical to indomethacin ($k_2 = 0.061$ s^{-1}) and the dissociation rate (k_{-2}) of compound **9** was very slow ($k_{-2} = 0.0022$ s^{-1}). Thus, once associated with COX-2, compound **9** (and compound **3**, not shown) remains very tightly associated.

$$E + I \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [EI] \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} EI^* \qquad (1)$$

Discussion

Two of the iodine-containing amide derivatives of indomethacin demonstrated selective COX-2 inhibitory activity (**3** and **9**), which is consistent with the model that was proposed for

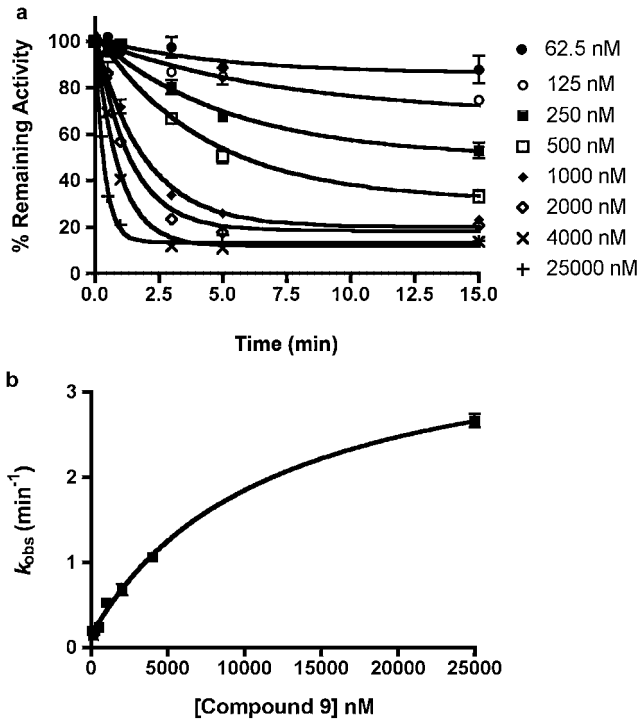


Figure 1. Kinetics of the time-dependent inhibition of hCOX-2 by compound **9**. Assays were performed as described in Experimental Procedures for time-dependent COX inhibition assays. Representative data are expressed as percent activity of the uninhibited control with nonlinear regression curves. The purified enzymes were pre-incubated with inhibitor at 37°C for various times (0, 0.5, 1, 3, 5, 10, 15, 30, 45, 60 and 120 min) prior to the addition of substrate (50 μM). (a) Data in this panel are shown to 15 min on the *x*-axis to illustrate the kinetics observed at shorter pre-incubation times. (b) Data in this panel represents the secondary plot of k_{obs} versus inhibitor concentration used to generate values for K_I, k_2 and k_{-2} using the following equation: $k_{obs} = ((k_2 * [I])/(K_I + [I])) + k_{-2}$.

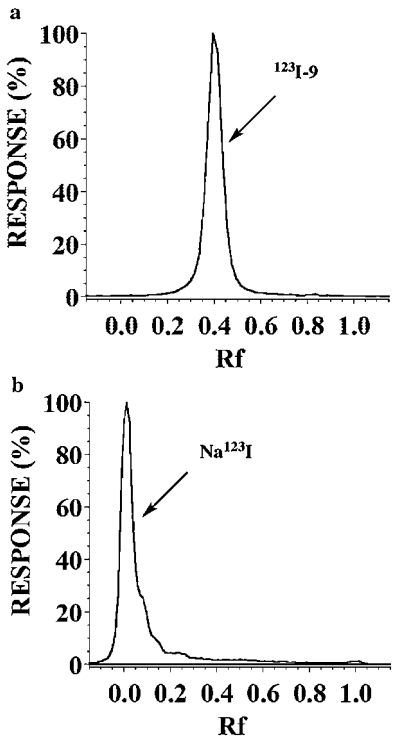


Figure 2. (a) Radio-TLC of [^{123}I]**9** reaction mixture organic phase on silica gel 60 using *n*-hexane: ethyl acetate (3:1 v/v). (b) Radio-TLC of Na^{123}I.

binding of similar amides of indomethacin to the COX-2 enzyme.[17] A striking observation from this study is that substitution of the *p*-chlorobenzoyl group of indomethacin with a *p*-iodobenzyl group generates compound **9**, which is a potent and selective COX-2 inhibitor. The molecular basis of this efficacy is yet to be determined. A four-fold decrease in potency was documented with the α–methylated product **14**. Although all of the indomethacin amides were potent COX-2 inhibitors against purified proteins, only compounds **3** and **9** inhibited COX-2 in activated macrophages so attention focused on these two compounds. Both compounds were slow, tight-binding inhibitors that associate tightly with COX-2. In addition, compound **9** exhibited sufficient metabolic stability to enable it to accumulate in a COX-2 expressing tumor *in vivo*.

Radiolabeling of the compounds via iododestannylation of the corresponding tributylstannyl precursor proceeded smoothly in the two-phase reaction mixture, which allowed isolation of radiochemically pure products by simple separation of the organic phase. Tonnesen *et al*. reported a number of two-phase reaction systems, which proved unsatisfactory due to slow and incomplete incorporation of the radionuclide.[19]

In conclusion, we report the identification of iodinated indomethacin derivatives that are selective inhibitors of purified and cellular COX-2 in a slow, tight-binding manner. We also report a two-phase radioiodination (^{123}I) protocol that is rapid, efficient and allows direct isolation of highly purified material without chromatography.

Experimental section

Silica gel column chromatography was performed using Sorbent silica gel standard grade, porosity 60 Å, particle size 32–63 μm (230 × 450 mesh), surface area 500–600 m^2/g, bulk density 0.4 g/mL, pH range 6.5–7.5, purchased from Sorbent Technologies (Atlanta, GA). All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification. ^{1}H NMR was taken on a Bruker AV-I console operating at 400.13 MHz. Experimental conditions included 2048 × 512 data matrix, 13 ppm sweep width, recycle delay of 1.5 s and 4 scans per increment. Mass spectrometric analyses were performed on a ThermoElectron TSQ 7000 triple quadrupole instrument in positive or negative ion mode using electrospray ionization. Radio TLC was carried out on polyester-backed silica gel 60 plates, eluted with *n*-hexane:ethyl acetate (3:1 v/v) and analyzed on a Bioscan® AR-2000 (Bioscan, Inc., Washington, DC). The purity and radiochemical purity of the final products were determined by HPLC on a Nucleosil C18 column (4.6 × 250 mm) using a gradient of 50–90% CH_3CN/H_2O) with UV detection at 290 nm.

Chemistry

*N-(p-Iodobenzyl)-2-(1-(p-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetamide (**3**)*

General procedure: To a stirred solution of indomethacin (3.57 g, 10 mmol) in DMF was added *p*-iodobenzylamine (2.33 g, 10 mmol), HOBt (2.02 g, 15 mmol), DIPEA (3.88 g, 30 mmol), EDCI (2.10 g, 11 mmol) at 25°C. The resultant mixture was stirred for 16 h at 25°C. Removal of solvent *in vacuo* afforded a residue, to which 100 mL water was added and extracted with EtOAc

(3 × 75 mL). The organic layer was collected, washed with water and evaporated *in vacuo*. The crude product was purified using silica gel column chromatography (35:7:1, $CHCl_3$:MeOH:NH_4OH) to give **3** as yellow solid (4.41 g, 77%) m.p. 200.5°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.20 (s, 3H, CH_3), 3.55 (s, 2H, CH_2CO), 3.71 (s, 3H, OCH_3), 4.20 (d, J = 6 Hz, 2H, CH_2Ar), 6.70 (dd, J = 9.0, 2.2 Hz, 1H, indolyl H-6), 6.95 (d, J = 9.0 Hz, 1H, indolyl H-7), 7.06 (d, J = 8.4 Hz, 2H, *p*-iodobenzyl H-2, H-6), 7.08 (d, J = 2.4 Hz, 1H, indolyl H-4), 7.58–7.66 (m, 4H, *p*-chlorobenzoyl H-3, H-5 and *p*-iodobenzyl H-3, H-5), 7.70 (d, J = 8.7 Hz, 2H, *p*-chlorobenzoyl H-2, H-6), 8.47–8.52 (m, 1H, $NHCOCH_2$). Mass (ESI) *m/z* $[M+H]^+$ calcd 573.04; found 573.13.

*1-(p-Iodobenzyl)-5-methoxy-2-methyl-3-indoleacetic acid (**9**)*

To a cold (0°C) stirred slurry of NaH (300 mg, 12.5 mmol) in DMF (50 mL) was added 5-methoxy-2-methyl-3-indoleacetic acid (1.1 g, 5 mmol). After stirring for 1 h at 0°C, *p*-iodobenzyl bromide (1.8 g, 6 mmol) was added and stirred 1 h at room temperature. The reaction mixture was then poured into a crushed ice/water mixture (100 g) and acidified with 10% aqueous HCl (pH 4). The resultant solid was filtered, washed (with cold water) and dried under vacuum. The crude product was purified using silica gel column chromatography (35:7:1, $CHCl_3$:MeOH:NH_4OH) to give **9** as a yellow solid (1.4 g, 67%) m.p. 237.4°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.23 (s, 3H, CH_3), 3.57 (s, 2H, CH_2CO), 3.72 (s, 3H, OCH_3), 5.29 [s, 2H, CH_2 (benzyl)], 6.66 (dd, J = 9.2, 2.4 Hz, 1H, indolyl H-6), 6.74 (d, J = 8.6 Hz, 2H, 4-iodobenzyl H-2, H-6), 6.97 (d, J = 2.4 Hz, 1H, indolyl H-4), 7.20 (d, J = 9.2 Hz, 1H, indolyl H-7), 7.62 (d, J = 8.6 Hz, 2H, 4-iodobenzyl H-3, H-5), Mass (ESI) *m/z* $[M+H]^+$ calcd 434.03; found 434.18.

Tin-chemistry

*N-(p-Tributylstannylbenzyl)-2-{1-(p-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl} acetamide (**15**)*

General procedure: To a stirred solution of *N*-{4-iodobenzyl}-2-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-ylacetamide (**3**) (1.5 g, 2.6 mmol) in 1,4 dioxane (30 mL) was added *tetrakis*(triphenylphosphine)palladium(0) (150 mg, 0.13 mmol) followed by hexabutylditin (1 mL). The reaction mixture was refluxed for 7 h. After cooling to room temperature, the solvent was removed *in vacuo* and product was purified using silica gel column chromatography (5:3, *n*-Hexane: EtOAc) to give the title compound (**15**) as a yellow solid (1.6 g, 70%) m.p. 109.7°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.81–0.85 {(m, 9H, H-1 ($3XCH_3$)}, 0.99–1.1 {(m, 6H, H-4 ($3XCH_2$)}, 1.24–1.32 { m, 6H, H-2 ($3XCH_2$)}, 1.44–1.50 {m, 6H, H-3 ($3XCH_2$)}, 2.24 (s, 3H, CH_3), 3.55 (s, 2H, CH_2CO), 3.71 (s, 3H, OCH_3), 4.20 (d, J = 6 Hz, 2H, CH_2Ar), 6.70 (dd, J = 9.0, 2.2 Hz, 1H, indolyl H-6), 6.74 (d, J = 8.6 Hz, 2H, *p*-tributylstannylbenzyl H-2, H-6), 6.95 (d, J = 9.0 Hz, 1H, indolyl H-7), 7.08 (d, J = 2.4 Hz, 1H, indolyl H-4), 7.40 (d, J = 8.6 Hz, 2H, *p*-tributylstannylbenzyl H-3, H-5), 7.58–7.66 (m, 4H, *p*-chlorobenzoyl H-3, H-5), 7.70 (d, J = 8.7 Hz, 2H, *p*-chlorobenzoyl H-2, H-6), 8.47–8.52 (m, 1H, $NHCOCH_2$). Mass (ESI) *m/z* $[M+H]^+$ calcd 737.25; found 737.29.

*1-(p-Tributylstannylbenzyl)-5-methoxy-2-methyl-3-indoleacetic acid (**16**)*

Using the same procedure as for **15** provided **16** as a yellow gummy mass (85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.80–0.84 {(m, 9H, H-1 ($3XCH_3$)}, 0.98–1.0 {(m, 6H, H-4 ($3XCH_2$)}, 1.23–1.31 {m, 6H, H-2 ($3XCH_2$)}, 1.43–1.49 {m, 6H, H-3 ($3XCH_2$)}, 2.23 [s, 3H, CH_3], 3.57 (s, 2H, CH_2CO), 3.72 (s, 3H, OCH_3), 5.26 [s, 2H, CH_2 (benzyl)], 6.67 (dd, J = 9.2, 2.4 Hz, 1H, indolyl H-6), 6.75 (d, J = 8.6 Hz, 2H, *p*-tributylstannylbenzyl H-2, H-6), 6.98 (d, J = 2.4 Hz, 1H, indolyl H-4), 7.20 (d, J = 9.2 Hz, 1H, indolyl H-7), 7.42 (d, J = 8.6 Hz, 2H, *p*-tributylstannylbenzyl H-3, H-5), Mass (ESI) *m/z* $[M+H]^+$ calcd for 600.24; found 600.21.

Radiochemistry

*N-(p-[^{123}I]iodobenzyl)-2-(1-(p-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetamide ([^{123}I]**3**)*

To a stirred solution of compound **15** (2.63 mg in 1 mL EtOAc) was added Na[^{123}I] (10 mCi in 500 μL 0.01N-NaOH), NaI (0.3 mg in 500 μL H_2O), chloramine-T trihydrate (0.8 mg in 500 μL in H_2O) and aqueous 1N-HCl (300 μL). After stirring the reaction mixture for 4 min at room temperature, water (1 mL) followed by EtOAc (1 mL) was added. The organic layer was collected, washed with water, and evaporated using argon or air-flow to give [^{123}I]**3** (8.6 mCi, radiochemical yield 86% and radiochemical purity 99%).

*1-(p-[^{123}I]iodobenzyl)-5-methoxy-2-methyl-3-indoleacetic acid ([^{123}I]-**9**)*

To a stirred solution of **16** (20 μg) in EtOAc (500 μL) was added Na[^{123}I] (17.2 mCi in 100 μL 0.01N-NaOH), NaI (4.5 μg in 100 μL H_2O), chloramine-T tri hydrate (7.7 μg in 100 μL in H_2O) and aqueous 1N-HCl (300 μL). After vortexing the reaction mixture for 4 min at room temperature, water (1 mL) followed by EtOAc (1 mL) was added. The organic layer was collected, washed with water, and evaporated using argon or air-flow to afford [^{123}I]**9** (14.9 mCi, radiochemical yield 87% and radiochemical purity 98%).

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Supporting Information Available: A complete description of the experimental methods and compound characterization. This material is available online at http://www3.interscience.wiley.com.

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