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SYNTHESIS OF 4-(3'-[^{125}I]IODOANILINO)-6,7-DIALKOXYQUINAZOLINES: RADIOLABELED EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS

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SUMMARY

The preparation of two radioiodinated analogs of the epidermal growth factor receptor tyrosine kinase (EGFrTK) inhibitor PD153035 (4-(3'-bromoanilino)-6,7-dimethoxyquinazoline) are reported herein. The two analogs, 4-(3'-[^{125}I]iodoanilino)-6,7-dimethoxyquinazoline and 4-(3'-[^{125}I]iodoanilino)-6,7-diethoxyquinazoline, were synthesized via iododestannylation of the corresponding 4-(3'-trimethylstannylanilino)-6,7-dialkoxyquinazolines to form the desired I-125 labeled products in good yield, high radiochemical purity (>99%) and high specific activity.

KEY WORDS: epidermal growth factor receptor, iodine-125, PD153035, quinazoline, tyrosine kinase inhibitor.

INTRODUCTION

Protein tyrosine kinases (PTKs) regulate cell division, growth and differentiation. Activation of the PTKs is one of the first steps in the signal cascade that initiates these cellular processes. The epidermal growth factor receptor (EGFr) is a member of a family of PTK-linked receptors where the tyrosine kinase domain is an integral part of the receptor. The EGFr is a 170 kD transmembrane protein possessing an extracellular ligand binding domain and an intracellular tyrosine kinase domain. The binding of EGF to the ligand domain of two adjacent receptors promotes a

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conformational change that brings the two receptors together. The dimerization activates the tyrosine kinase towards phosphorylation of tyrosine residues on the adjacent receptor (interphosphorylation) as well as phosphorylation of other enzymes, thus propagating the signal throughout the cell (1-3).

The aberrant expression and activation of growth factor receptors in normal cells has been implicated in the promotion and proliferation of malignant growths (4). EGFr overexpression has been noted in a number of human neoplastic lesions (5) including lung cancer, endometrial carcinoma and breast cancer (6). Therapeutic response and patient survival has been negatively correlated with EGFr upregulation (7, 8). Small molecules capable of selective inhibition of the EGFr activation have been the target of intense research over the last several years in an effort to develop a therapeutic antitumor drug (9-11). Based on the concentration of receptors in the tumors, growth factor receptors have been sited as potential targets for imaging as well as for radiotherapeutic agents (12).

Several classes of compounds are being investigated as tyrosine kinase inhibitors (11). One class, 4-anilinoquinazolines, has been shown to be particularly potent and selective ATP site inhibitors (13). The most potent member of this class, 4-(3'-bromoanilino)-6,7-dimethoxyquinazoline (PD153035, 1), inhibits EGFr phosphorylation with a K_i of 5 pM and has demonstrated selectivity with only mM inhibition of other growth factor receptors (14).

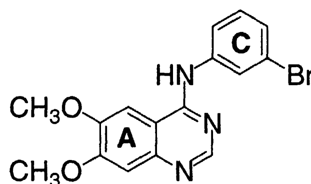

Figure 1. 4-(3'-bromoanilino)-6,7-dimethoxyquinazoline, PD153035, 1.

Several investigators have initiated programs to develop imaging agents based on the small molecule EGFr inhibitors. A number of radiolabeled analogs of PD153035 have been reported in prefatory communications. The compounds incorporate labeled substituents on the A or C rings of the anilino- or benzylamino- quinazoline (Figure 1). The C ring substituted analogs include 4-(3'-[^{125}I]iodoanilino)- (15), 4-(3'-[^{18}F]fluoro-5'-trifluoromethylanilino)- (16), 4-(3',4'-dichloro-6'-[^{18}F]fluoro-anilino)- (16), 4-(4'-[^{18}F]fluorobenzylamino)-dimethoxyquinazolines (17) and 4-(4'-[^{18}F]fluorobenzylamino)-diethoxyquinazoline (18). The 7-[^{18}F]fluoroethoxy- (19) and the 6- or 7-[^{11}C]methoxy- (19, 20) constitute the A ring labeled analogs. Preliminary in vitro studies with the 3'-[^{125}I]iodo analog demonstrated receptor mediated uptake in cells containing high EGFr titer (15). A more recent study of the ^{11}C-methoxy derivative demonstrated some uptake in human neuroblastoma xenographs in mice (21, 22). While neither of these studies were unequivocal, the evidence suggests that further studies towards the development of in vivo imaging agents for EGFr expression in tumors is warranted.

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As part of an ongoing effort to develop positron-emitting EGFr imaging agents in our laboratory, we sought to produce a labeled compound for use in radiometric binding studies. To this end we report herein the detailed synthesis of two iodine-125 labeled analogs of PD153035.

RESULTS AND DISCUSSION

The two iodinated analogs presented were chosen for labeling based on known structure activity relationships derived from the inhibition of EGFr tyrosine kinase activity by numerous analogs of PD153035 produced by Parke-Davis (23). The investigators found that replacing the bromine on PD153035 with iodine increased the IC_{50} value 35 times, albeit the iodo compound still retained subnanomolar inhibition of the EGFr tyrosine kinase (IC_{50} = 0.89 nM). Replacement of the 6 and 7 methoxy moieties with 6 and 7 ethoxy groups decreased the IC_{50} of PD153035 nearly 5 fold, 0.025 nM to 0.006 nM. Based on these data we prepared 3'-iodoanalino-6,7-diethoxyquinazoline and labeled it with ^{125}I in addition to the corresponding 6,7-dimethoxy analog.

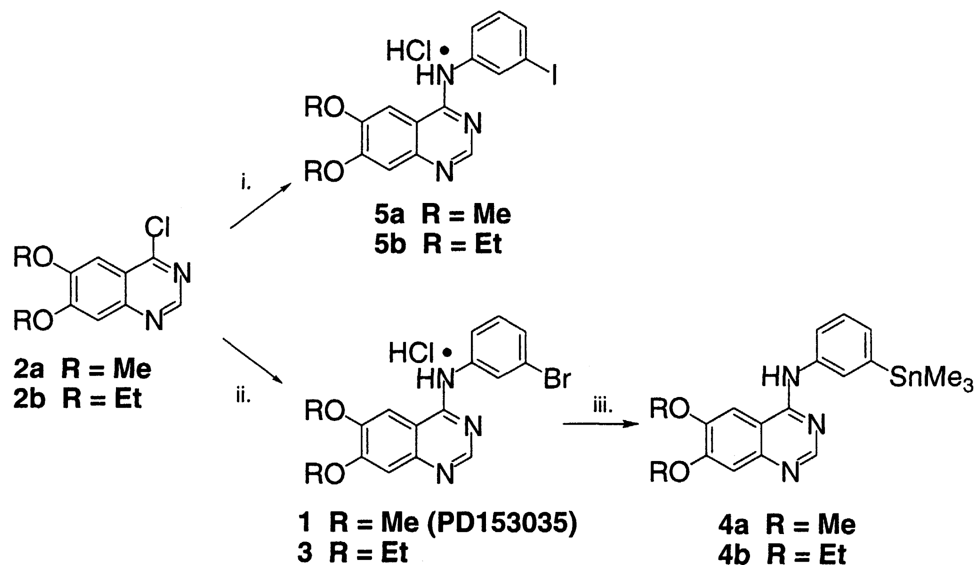

Figure 2. Synthetic routes for the iodoanilino- and trimethylstannylanilino-dialkoxyquinazolines. (i.) 3-iodoaniline, DMF, Δ; (ii.) 3-bromoaniline, DMF, Δ; (iii.) $(SnMe_3)_2$, $Pd(Ph_3)_4$, dioxane.

The synthetic route for the preparation of the analinoquinazolines is outlined in Figure 2. The common intermediates, 4-chloro-6,7-dimethoxy- **2a** and 4-chloro-6,7-diethoxyquinazoline **2b**, were used to prepare the nonradioactive iodine compounds and the trialkylstannyl precursors for labeling. The procedure outlined by Bridges *et al.* (23) was followed for the synthesis of **2a** starting from the

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commercially available dimethoxyanthranilic acid. The corresponding diethoxyanthranilic acid was not commercially available; however, it was produced in one step by the saponification of the available 2-amino-4,5-diethoxy-methyl benzoate (24). The synthesis of **2b** proceeded analogously to that of **2a**.

The bromo- and iodo-anilino analogs, **1**, **3**, **5a** and **5b**, were produced by heating the appropriate bromo- or iodo-aniline with the respective chloroquinazoline, **2a** or **2b**, in anhydrous DMF. This reaction proceeded very cleanly and gave high yields (84-91%) of the haloanilino compounds. This compares favorably to the reactions reported by Bridges *et al.* (23) where they used isopropanol as the solvent. The bromoanilino compounds, **1** and **3**, were converted into the corresponding trimethylstannyl derivatives by reacting with hexamethylditin in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in 55-60% yield.

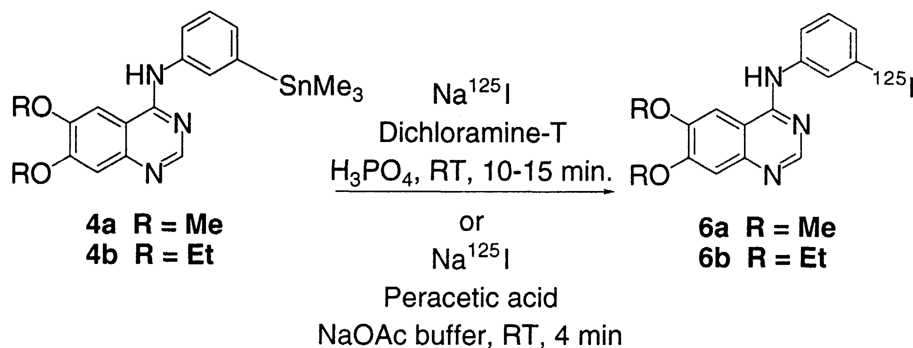

Figure 3. Radiosynthesis of 3'-[^{125}I]iodoanilino-quinazoline analogs of **6a** and **6b**.

The conversion of the stannylated compounds to the desired ^{125}I labeled quinazolines by two different methods is shown in Figure 3. The iododestannylation reaction proceeded rapidly, less than 15 minutes using dichloramine-T and less than 5 minutes using peracetic acid. The original radioidinations were carried out following an old Berkeley dichloramine-T procedure. Recently, we converted to the peracetic acid method. Purification by solid phase extraction (reversed-phase, C18) and HPLC gave either **6a** or **6b** in 40-65% radiochemical yield. The yields for the peracetic acid reactions were about 50% higher than the dichloramine-T reactions. The radiochemical purity of **6a** and **6b** was greater than 98% confirmed by normal phase TLC and coinjection with cold standard on reversed phase analytical HPLC (multiple solvent systems). Using either method, only one major radioactive product was identified on the HPLC; no other mono- or di-substituted species were formed in the reaction.

The specific activities of **6a** and **6b** ranged from 466-1900 Ci/mmol and the values were found to be independent of the method used to produce the labeled products. An HPLC chromatogram (Figure 4) of the crude **6a** dichloramine-T reaction mixture shows the separation between the radioiodinated material and the non-radioactive 3'-chloroanilinoquniazoline mass peak. The chloroanilinoquinazoline

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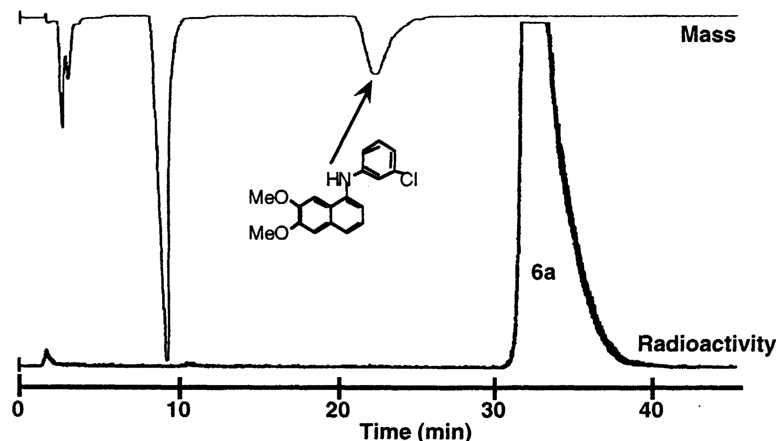

Figure 4. HPLC chromatogram of 6a produced by the dichloramine-T method. (conditions: analytical C18, 50:50 MeOH:H_2O, pH 7.4, flow 2 mL/min)

byproduct is not present in the peracetic acid produced radiotracer as expected. Comparing the two iodination methods, the peracetic acid reaction is more favorable for this chemistry.

EXPERIMENTAL

All chemicals were purchased from Aldrich Chemical Co. and were used without further purification. The 2-amino-4,5-diethoxy-methyl benzoate was purchased from Aldrich Specialty Chemicals. Chloroquinazolines 2a and 2b were prepared according to literature procedures (23,24). NMR spectra were obtained on a Bruker VBAMX400 400 MHz spectrometer. Elemental analyses were performed by the Microanalytical Laboratory at the College of Chemistry, University of California, Berkeley. Melting points were taken on a Mel-Temp™ apparatus and are reported uncorrected. Mass spectra were obtained on a Perkin Elmer SCIEX spectrometer at the SynPep Corporation, Dublin, CA, USA. Purification of the radioiodinated compounds was carried out by HPLC (column and conditions noted below in the synthesis section) with an in-line Linear™ UV-106 spectrophotometer to detect mass and a NaI detector and Ortec NIM components to measure the radioactivity.

4-(3'-bromoanilino)-6,7-dimethoxyquinazoline (1).

The preparation of 1 followed the method described below for 3. Yield 87%. ^{1}H NMR spectra were identical to those reported in the literature (23).

4-(3'-bromoanilino)-6,7-diethoxyquinazoline (3).

A clear, pale yellow anhydrous DMF solution (3 mL) of 4-chloro-6,7-diethoxyquinazoline 2b (0.1 g, 0.396 mmol) was combined with 3-bromoaniline

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(64.6 µL, 0.593 mmol) to form a clear, pale pink solution. Within 15 minutes of heating the reaction flask at 80° C under argon, precipitation of a white solid was observed. The heterogeneous solution was heated for an additional 45 minutes, then cooled to room temperature for 15 minutes. The solid was filtered and washed with ethyl acetate (20 mL) to give the hydrochloride salt of <u>**3**</u> as a bright white, pulpy solid. Yield 0.15 g (89%). m.p. 260° C. ^{1}H NMR ($CDCl_3$): δ 8.63 (*s*, 1H, Ar*H*), 7.88 (*s*, 1H, Ar*H*), 7.87 (*s*, 1H, Ar*H*), 7.59, (*d*, 1H, Ar*H*, J = 8.0 Hz), 7.38 (*d*, 1H, Ar*H*, J = 8.0 Hz), 7.31 (*t*, 1H, ArH, J = 8.0 Hz), 4.18 (*m*, 4H, OCH_2CH_3), 1.42 (*m*, 3H, OCH_2CH_3). APCI mass spec. 388.1, 390.1 [M+1]. Elemental analysis $C_{18}H_{19}BrClN_3O_2$ calcd. C 50.90, H 4.51, N 9.89; found C 49.32, H 4.66, N 9.44.

4-(3'-trimethylstannylanilino)-6,7-dimethoxyquinazoline (<u>4a</u>).

The preparation of <u>**4a**</u> starting from 40 mg (0.11 mmol) of the free base of <u>**1**</u> was carried out in a manner analogous to <u>**4b**</u>. Yield 30 mg (61%). ^{1}H NMR ($CDCl_3$): δ 8.64 (*s*, 1H, Ar*H*), 7.73 (*d*, 1H, Ar*H*, J = 8.0 Hz), 7.62 (*s*, 1H, Ar*H*), 7.40 (*t*, 1H, Ar*H*, J = 8.0 Hz), 7.28 (*d*, 1H, Ar*H*, J = 8.0 Hz), 7.26 (*s*, 1H, Ar*H*), 7.02 (*s*, 1H, Ar*H*), 4.02 (*s*, 6H, OCH_3), 0.30 (*s*, 9H, $Sn(CH_3)_3$). APCI mass spec. 446.1, 444.0, 442.1 [M+1]. Elemental analysis $C_{19}H_{23}N_3O_2Sn$ calcd. C 51.38, H 5.22, N 9.46; found C 51.59, H 5.47 N 9.12.

4-(3'-trimethylstannylanilino)-6,7-diethoxyquinazoline (<u>4b</u>).

The hydrochloride salt of <u>3</u> was first converted to the free base by partitioning the solid between ethyl acetate (3 mL) and 1*N* sodium hydroxide (2 mL). After thoroughly shaking the two layers, the ethyl acetate layer was separated and the aqueous base solution was extracted with additional ethyl acetate (2 x 3 mL). The ethyl acetate fractions were pooled, dried over magnesium sulfate, filtered, and solvent removed in vacuo to give an oil, then were recrystallized from diethyl ether to give white crystals (yield 60 mg, 66%). A toluene solution (5 mL) containing the free base <u>3</u> (75 mg, 0.493 mmol), hexamethylditin (48 µL, 0.592 mmol) and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (22.3 mg, 10 mol%) was heated at 105° C under argon for 16 hours, resulting in an intense, dark black solution. The palladium catalyst was removed by eluting through a short silica pad to give a clear yellow solution. The solution was concentrated in vacuo, then purified by radial chromatography (2 mm silica plate thickness; eluted first with hexanes, then gradually adjusted to 30% ethyl acetate/hexane, and finally to 100% ethyl acetate). Purity was confirmed by a single spot in TLC (silica, 75% ethyl acetate/hexane, R_f 0.55). Yield 50 mg (56%). ^{1}H NMR ($CDCl_3$): δ 8.62 (*s*, 1H, Ar*H*), 7.75 (*d*, 1H, Ar*H*, J = 8.0 Hz), 7.61 (*s*, 1H, Ar*H*), 7.39 (*t*, 1H, Ar*H*, J = 8.0 Hz), 7.27 (*d*, 1H, Ar*H*, J = 8.0 Hz), 7.23 (*s*, 1H, Ar*H*), 7.02 (*s*, 1H, Ar*H*), 4.22 (*m*, 4H, OCH_2CH_3), 1.55 (*m*, 6H, OCH_2CH_3), 0.30 (*s*, 9H, $Sn(CH_3)_3$). APCI mass spec. 474, 472.1, 470 [M+1]. Elemental Analysis $C_{21}H_{27}N_3O_2Sn$ calcd. C 53.42, H 5.76, N 8.90; found C 53.76, H 6.06, N 8.54.

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4-(3'-iodoanilino)-6,7-dimethoxyquinazoline (5a).

The preparation of **5a** followed the method described above for **3**. The chloroquinazoline **2a** (0.28 g, 1.22 mmol) was reacted with 1.5 equiv. of iodoaniline to yield 0.5 g (92%) of **5a**. m.p. 252-253° C. ^{1}H NMR (DMSO): δ 7.91 (*s*, 1H, Ar*H*), 7.31 (*s*, 1H, Ar*H*), 7.16 (*s*, 1H, Ar*H*), 6.80 (*d*, 1H, Ar*H*, J = 8.0 Hz), 6.70 (*d*, 1H, Ar*H*, J = 8.0 Hz), 6.36 (*s*, 1H, Ar*H*), 6.32 (*t*, 1H, Ar*H*, J = 8.0 Hz), 3.05 (*s*, 3H, OC*H*3), 3.03 (*s*, 3H, OC*H*3). APCI mass spec. 408.0 [M+1]. Elemental Analysis $C_{16}H_{15}ClIN_3O_2$ calcd. C 43.31, H 3.41, N 9.47; found C 43.66, H 3.45, N 9.51.

4-(3'-iodoanilino)-6,7-diethoxyquinazoline (5b).

The preparation of **5b** followed the method described above for **5a**. The chloroquinazoline **2b** (0.12 g, 0.46 mmol) was reacted with 1.5 equiv. of iodoaniline to yield 0.19 g (88%) of **5b**. m.p. 265-266° C. ^{1}H NMR (DMSO): δ 8.86 (*s*, 1H, Ar*H*), 8.20 (*s*, 1H, Ar*H*), 8.10 (*s*, 1H, Ar*H*), 7.75 (*d*, 1H, Ar*H*, J = 8.0 Hz), 7.67 (*d*, 1H, Ar*H*, J = 8.0 Hz), 7.30 (*s*, 1H, Ar*H*), 4.27 (*m*, 4H, OCH_2CH_3), 1.44 (*m*, 6H, OCH_2CH_3). APCI mass spec. 436.0 [M+1]. Elemental analysis $C_{18}H_{19}ClIN_3O_2$ calcd. C 45.83, H 4.06, N 8.91; found C 46.11, H 3.45, N 8.85.

4-(3'-[^{125}I]iodoanilino)-6,7-dimethoxyquinazoline (6a) or 4-(3'-[^{125}I]iodoanilinio)-6,7-diethoxyquinazoline (6b).

Dichloramine-T Method: A 4 mL vial equipped with a Teflon cap and a stir bar was charged with the 3'-trimethylstannylanilino-6,7-dialkoxyquinazoline precursor **4a** (~0.5 mg, 1.1 μmol) or **4b** (~0.5 mg, 1.1 μmol) in acetonitrile (200 μL). To the vial was added a solution of Na^{125}I (~1 mCi) followed by the addition of 85% phosphoric acid (50 μL) and dichloramine-T (20 μL of a 2 mg/mL solution in acetonitrile). After reacting at room temperature for 10-15 minutes, the mixture was quenched with 10% $Na_2S_2O_5$ (50 μL). The quenched solution was diluted with 5-10 mL of deionized H_2O, then eluted through an activated C18 Sep-Pak® trapping >95% of the measured activity. The cartridge was then eluted with 0.2 mL of methanol, then an additional 1.6 mL of methanol. The second elution fraction containing the bulk of the activity was slowly evaporated under a gentle stream of argon. The residue was dissolved in 2 mL of a buffered methanol/water solution (phosphoric acid/triethylamine) and chromatographed by HPLC (Waters μBondapak™ C18 column, 3.9 x 300 mm, 50% MeOH/water final pH 7.40, flow = 2 mL/min, retention time **6a**: 25-34.5 min or **6b**: 53-70 min.). The product was concentrated by trapping on an activated C18 Sep-Pak®. **6a** (0.5 mCi, 53% yield) or **6b** (0.45 mCi, 45% yield) was collected in 1 mL of methanol eluent.

Peracetic Acid Method: A 4 mL vial equipped with a Teflon cap and a stir bar was charged with the 3'-trimethylstannylanilino-6,7-dialkoxyquinazoline precursor **4a** (~0.5 mg, 1.1 μmol) or **4b** (~0.5 mg, 1.1 μmol) in acetonitrile (200 μL). To this vial was added sodium acetate buffer (0.6M, pH 4.5, 100 μL) and Na^{125}I followed by peracetic acid (30 μL, Aldrich). The reaction was stirred for 4 min. at room

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temperature and then quenched with 10% $Na_2S_2O_5$ (100 µL). The solution was made basic with saturated $NaHCO_3$ and transferred to a syringe. The reaction vial was rinsed with acetonitrile (100 µL) and added to the syringe along with 8 mL of water. The solution was passed through an activated C18 Sep-Pak® and the trapped radioiodinated product was eluted with 3 mL of MeOH and concentrated for HPLC purification (as noted above). The yield of **6a** and **6b** using this method was 60-65%.

Specific Activity Measurement: The purified labeled products, **6a** and **6b**, were concentrated and analyzed by reversed phase analytical HPLC (Phenomenex Bondclone™ 10 C18 column, 3.9 x 300 mm, 50-80% MeOH/water final pH 7.40, flow = 2 mL/min). The HPLC derived specific activity was calculated based on the activity injected and the mass/UV response measured relative to a standard curve.

CONCLUSION

We have successfully labeled two EGFr tyrosine kinase inhibitors with iodine-125 using two different synthetic methods. The peracetic acid method produced slightly higher yields of cleaner product in a one half to one third the time and is the preferred method for producing these compounds in the future. The compounds were produced in sufficiently high yield, high radiochemical purity and high specific activity. Both these compounds demonstrated receptor mediated affinity for the EGFr tyrosine kinase binding site in initial binding studies. One of these compounds may find utility in the radiometric binding assay we are developing for the measurement of the receptor binding affinity of novel EGFr inhibitors.

ACKNOWLEDGMENTS

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