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Development of Radioligands for the Imaging of Cardiac β -Adrenoceptors Using SPECT. Part I: Asymmetric Synthesis and Structural Characterization of Five New Iodine-Containing β -Adrenoceptor Antagonist Derivatives

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ABSTRACT. The asymmetric synthesis of a series of iodinated β -adrenoceptor ligands is described. One ligand, (S)-(-)-[1-(2-iodophenoxy)]-3'-(*tert*-butylamino)-2'-propanol (CYBL3), is based on the β -adrenoceptor antagonist penbutolol. The other ligands are N-iodovinyl and N-iodoaryl analogues of the β -adrenoceptor antagonist CGP12177. These have been synthesized from 2-amino-3-nitrophenol. Furthermore, radioiodinated [¹²³I]CYBL3 and [¹²³I](2'S,2"E)-[4-(3'-(1",1"-dimethyl-3"-iodo-2" propenylamino)-2'-hydroxypropoxy)]-benzimidazol-2-one have been prepared by radiolabelling the corresponding trialkyltin precursors using [¹²³I]-NaI in the presence of hydrogen peroxide. Copyright © 1997 Elsevier Science Inc. NUCL MED BIOL 24;1:1–7, 1997.

KEY WORDS. CGP12177, Penbutolol, β -Adrenoceptor, SPECT

INTRODUCTION

Single photon emission tomography (SPECT) and positron emission tomography (PET) both offer the possibility to measure receptor density noninvasively. With respect to the imaging of β -adrenergic receptors, until now only a few radioligands have been synthesized with either ¹¹C or ¹⁸F for PET. The β -adrenoceptor antagonist S-CGP12177 (4(3-*t*-butylamino-2-hydroxypropoxy)-benzimidazol-2-one (1–3) has been labelled successfully with ¹¹C, but the specific activity of this radioligand was rather low (400 to 1300 mCi/ μ mol) (2–4). More recently, the β -adrenoceptor antagonist carazolol has been labelled successfully with ¹⁸F and/or ¹¹C (5–8). Using this tracer, the β -adrenergic receptor population could be clearly visualized in the human heart.

One of the major advantages of SPECT over PET is that the isotopes used in SPECT, such as ¹²³I, have a significant longer half-life than do the isotopes used in PET (hours vs. minutes), thus allowing a substantial longer acquisition time in SPECT. Several investigators (9, 10) have studied the possible use of [¹²³I]iodocyanopindolol as a radioligand; however, this compound also displayed considerable affinity for serotonergic receptors. CGP12177 is a potent hydrophilic β -adrenoceptor antagonist. Therefore, we recently synthesized two iodinated analogues of CGP12177 (11) as a

radioligand for the imaging of β -adrenoceptors using SPECT. These two analogues were iodinated at the phenyl part of the molecule. Although one of the two analogues showed reasonable affinity for the β -adrenoceptor, a high nonspecific binding *in vivo* was observed.

In the present study, both the synthesis and the characterization of a few new analogues of S-CGP12177 are described where the iodine is positioned in the alkylamino group of the molecule. In addition, the synthesis of an iodine-containing compound with a high stereochemical resemblance to the nonselective, high-affinity β -adrenoceptor antagonist penbutolol is described. In Fig. 1 the structural formulas of S-CGP12177, penbutolol, and the newly synthesized compounds are shown. This paper deals with the synthesis and chemical characterization, whereas an accompanying paper describes the pharmacological characterization with respect to cardiac and pulmonary β -adrenoceptor, both *in vitro* and *in vivo*.

METHODS

All chemicals used were of the purest grades commercially available. α,α' -Azobisisobutyronitrile (AIBN) was obtained from E. Merck (Darmstadt, Germany). 1,1-Dimethylpropargylamine was purchased from Acros Chimica NV. Phosgene solution (20% in toluene) was purchased from Fluka Chemie AG. All solvents used were of *pro analysi* grade and were obtained from E. Merck (Darmstadt, Germany) or Aldrich.

The ¹H nuclear magnetic resonance (NMR) spectra were obtained using a Bruker AM-400 spectrometer at 400.13 MHz. The ¹³C NMR spectra were run using the same apparatus at 100.62 MHz

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FIG. 1. Structural formulas of the parent compounds S-CGP12177, penbutolol, CYBL3, CYBL4E, CYBL4A, CYBL5E, and CYBL6.

with proton-noise decoupling. All δ values are given in ppm downfield from tetramethylsilane. Melting points were measured on a Jenaval melting point microscope and are given as uncorrected data. Optical rotations were measured on a Jasco DIP-370 Digital Polarimeter. Ion spray mass spectroscopy was performed on a PE SCIEX API 300 MS/MS system. Thin-layer chromatography (TLC) was performed with Merck 60 F₂₅₄ silica gel plates, and compounds were visualized under UV light ($\lambda = 254$ nm) and with I₂ vapors. Flash chromatography was performed with Acros Chimica silica gel (35–70 μ m; pore diameter 6 nm). The enantiomeric purity of the final products was determined by separation of the enantiomers on a Chiralcel OD HPLC-column (Daicel, 25 cm $\times$ 0.46 cm i.d.) with i-PrOH/hexane mixtures, with a flow of rate of 0.75 mL/min. High-performance liquid chromatography (HPLC) was performed on a reverse-phase column (C-18, Radpak 4 μ m, Nova Pak 10 cm $\times$ 5 mm i.d.) using a Waters HPLC system consisting of a Model 600 pump operated with a Model 600E system controller and a Model 490E programmable wavelength detector set at 230 nm.

Synthesis of CYBL3 (Fig. 2)

(S)-2-PHENYL-3-*TERT*-BUTYL-5-(2'-*I*-IODOPHENOXY)METHYLOXAZOLIDINE (2). An amount of 240 mg (6 mmol) sodium hydride (60% dispersion in oil) was washed with pentane and suspended in 5 mL DMF in a 50-mL flask. The flask was chilled and 1.10 g (5 mmol) 2-iodophenol was added portionwise. The mixture was allowed to warm to room temperature and then stirred for 20 min. After the gas

evolution ceased, a solution of the tosylate of (S)-(-)-2-phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine (1) (12) (2.14 g; 5.5 mmol) in 5 mL DMF was added. The mixture was stirred for 8 h at 80°C. Then it was cooled, diluted with EtOAc, and washed with water. The organic phase was dried on MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc: hexane 30:70) to yield a syrup of 1.3 g of compound 2 as a mixture of diastereomers (ratio 1:2) (64%).

Minor diastereomer: $R_f = 0.44$ (TLC in EtOAc:hexane = 1:2). ¹H NMR (CDCl₃): δ 7.74 (dd, $J = 1.55$ Hz and $J = 7.8$ Hz, 1H), 7.56 (dd, $J = 1.60$ Hz and 7.7 Hz, 2H), 7.35–7.22 (m, 4H), 6.75–6.65 (m, 2H), 5.72 (s, 1H), 4.45–4.38 (m, 1H), 4.09 (dd, $J = 7.6$ Hz and $J = 12.2$ Hz, 1H), 3.75 (dd, $J = 7.5$ Hz and $J = 9.0$ Hz, 1H), 3.54 (dd, $J = 6.8$ Hz and $J = 11.6$ Hz, 1H), 3.06 (dd, $J = 6.8$ Hz and $J = 11.7$ Hz, 1H), 1.14 (s, 9H).

Major diastereomer: $R_f = 0.33$ (TLC in EtOAc:hexane = 1:2). ¹H NMR (CDCl₃): δ 7.79 (dd, $J = 1.5$ Hz and $J = 7.8$ Hz, 1H), 7.63 (dd, $J = 1.60$ Hz and 7.6 Hz, 2H), 7.40–7.27 (m, 4H), 6.84 (dd, $J = 1.21$ Hz and $J = 8.2$ Hz, 1H), 6.72 (dt, $J = 1.2$ Hz and $J = 7.6$ Hz, 1H), 5.62 (s, 1H), 4.45–4.38 (m, 1H), 4.19 (dd, $J = 4.10$ Hz and $J = 9.7$ Hz, 1H), 4.12 (dd, $J = 5.4$ Hz and $J = 9.6$ Hz, 1H), 3.38 (dd, $J = 5.9$ Hz and $J = 8.9$ Hz, 1H), 3.20 (t, $J = 9.0$ Hz, 1H), 1.09 (s, 9H). ¹³C NMR (CDCl₃): δ 157.3, 143.3, 139.3, 129.5, 128.1, 127.5, 122.8, 112.3, 91.7, 86.6, 73.6, 69.4, 53.2, 49.8, 28.2, 27.5.

(S)-(-)-[1-(2-*I*-IODOPHENOXY)]-3'-(-*TERT*-BUTYLAMINO)-2'-PROPANOL (CYBL3). (700 mg) Acetal 2 was stirred in 20 mL 1 N HCl at 70°C for 30 min. The mixture was cooled to room temperature and extracted with 2 $\times$ 20 mL diethylether to remove the benzaldehyde. The resulting aqueous layer was cooled in ice and basified with NaOH. Subsequent extraction with 2 $\times$ 25 mL CHCl₃, drying of the extract on NaSO₄, filtration and concentration of the filtrate *in vacuo* gave 560 mg (99.9%) CYBL3. Enantiomeric excess (ee) of 94.5% (retention times for the R- and S-enantiomer were 8.3 and 10.5 min, respectively, with i-PrOH/hexane = 1:9). $[\alpha]_D^{25} = -14.4^\circ$, $c = 0.5$, methanol). ¹H NMR (CDCl₃): δ 7.76 (d, $J = 7.8$ Hz, 1H), 7.30 (d, $J = 7.8$ Hz, 1H), 6.85 (d, $J = 8.2$ Hz, 1H), 6.75 (t, $J = 7.7$ Hz, 1H), 4.05 (d, $J = 4.9$ Hz, 2H), 4.00 (m, 1H), 2.92 (dd, $J = 4.5$ Hz and $J = 11.9$ Hz, 1H), 2.83 (dd, $J = 6.4$ Hz and $J = 11.9$ Hz, 1H), 1.13 (s, 9H). ¹³C NMR (CDCl₃): δ 157.1, 139.3, 129.5, 122.9, 112.3, 91.5, 71.8, 68.3, 50.3, 44.5, 29.2. Mass spectroscopy (Ion spray): m/z 350 (M+H)⁺.

(S)-([1-(2-*TRIMETHYLSTANNYL*PHENOXY)]-3'-(-*TERT*-BUTYLAMINO)-2'-PROPANOL (PRECURSOR OF [¹²³I]CYBL3) (3). To a solution of 740 mg (2.2 mmol) Me₃SnSnMe₃ in 0.7 mL toluene in an argon atmo-

FIG. 2. Reaction scheme for the synthesis of CYBL3 and the precursor of [¹²³I]CYBL3.

sphere were subsequently added 60 mg CYBL3 (0.18 mmol), 10 mg (8.7 μ mol) $\text{Pd}(\text{PPh}_3)_4$, and 50 μL triethylamine, respectively. This mixture was stirred for 3 h at 60°C. After cooling and concentration *in vacuo* the residue was subjected to chromatography on a silica column with EtOAc containing 2% Et_3N to give 20 mg **3** (42%). The δ values of ^1H NMR (CDCl_3): δ 7.49 (dd, J = 1.72 Hz and 7.0 Hz, 1H), 7.32 (dt, J = 1.75 Hz and 7.4 Hz, 1H), 6.99 (t, J = 7.2 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 4.03 (m, 1H), 4.0–3.85 (m, 2H), 2.90 (dd, J = 3.5 Hz and J = 11.9 Hz, 1H), 2.70 (dd, J = 7.8 Hz and J = 11.9 Hz, 1H), 1.12 (s, 3 $\times$ 3H), 0.28 (s (with satellite peaks at J = 26.8 and 28.0 Hz, 9H).

Synthesis of CYBL4E (Fig. 3)

(S)-(+)-[1-(2-AMINO-3-NITROPHENOXY)]-2',3'-EPOXYPROPANE (**4**).

An amount of 13.2 g (33 mmol) sodium hydride (60% dispersion in oil) was washed with pentane and suspended in 15 mL DMF in a 100-mL flask in an argon atmosphere. The flask was cooled in ice and 4.62 g (30 mmol) 2-amino-3-nitrophenol was slowly added over a 10-min period. The mixture was then warmed to room temperature. After stirring for 20 min, 8.4 g (32.5 mmol) *S*-glycidyl *m*-nitrobenzenesulfonate was added, and the reaction was allowed to continue for 2 h. The reaction mixture was then diluted with 100 mL EtOAc and washed with 50 mL of water. The organic phase was dried on Na_2SO_4 , filtrated, and concentrated to yield 6.3 g (**4**) as orange crystals. Melting point 103–105°C vs. 99°C as reported by Aigbirhio *et al.* (13) $[\alpha]_D = 11.8^\circ$ (c = 1.0, acetone). ^1H NMR (CDCl_3 : CD_3OD = 95:5) δ : 7.58 (d, J = 8.9 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.47 (t, J = 7.8 Hz, 1H), 4.33 (dd, J = 2.4 Hz and J = 11.4 Hz, 1H), 3.84 (dd, J = 6.4 Hz and J = 11.4 Hz, 1H), 3.20 (m, 1H), 2.81 (m, 1H), 2.68 (dd, J = 2.6 Hz and J = 4.8 Hz, 1H).

(S)-[1-(2-AMINO-3-NITROPHENOXY)]-3'-(PROPARGYLAMINO)-2'-PROPANOL (**5a**). To a solution of 110 mg (2.0 mmol) propargyl-

amine in 4 mL EtOH was added 105 mg (0.5 mmol) (**4**). The mixture was heated for 5 h at 50°C. Then the mixture was cooled to room temperature and concentrated. Flash chromatography with EtOAc yielded 96 mg **5a** (72%). R_f = 0.10 (TLC in EtOAc). ^1H NMR (CDCl_3): δ 7.76 (d, J = 8.9 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.59 (dd, J = 7.7 Hz and J = 8.9 Hz, 1H), 6.50 (br. s, 2H), 4.15–4.05 (m, 3H), 3.49 (d, J = 2.4 Hz, 2H), 3.05 (dd, J = 3.6 Hz and J = 12.3 Hz, 1H), 2.82 (dd, J = 7.8 Hz and J = 12.3 Hz, 1H), 2.27 (t, J = 2.4 Hz, 1H), and 7 mg [1-(2-amino-3-nitrophenoxy)]-2'-(propargylamino)-propan-3'-ol **10a** (5%). R_f = 0.30 (TLC in EtOAc). ^1H NMR (CDCl_3): δ 4.20–4.0 (m, 3H), 3.65 (dd, J = 2.4 Hz and J = 14 Hz, 1H), 3.52 (dd, J = 2.4 Hz, 1H), 2.90 (dd, J = 3.6 Hz and J = 12.3 Hz, 1H), 2.80 (dd, J = 7.8 Hz and J = 12.3 Hz, 1H), 2.28 (t, J = 2.4 Hz, 1H).

(S)-[4-(3'-PROPARGYLAMINO-2'-HYDROXYPROPOXY)]-BENZ-IMIDAZOL-2-ONE (**7a**). To a solution of 640 mg (2.4 mmol) aryl nitro derivative **5a** in 10 mL EtOH was added 2.9 g (12.9 mmol) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, and this mixture was stirred for 24 h at 80°C. Then it was concentrated *in vacuo* and dissolved in 15 mL 2 N HCl. The flask was cooled in ice, and 3 mL 1.93 M COCl_2 in toluene was added under vigorous stirring conditions. The mixture was stirred overnight and subsequently concentrated *in vacuo*. The residue was dissolved in MeOH, cooled in ice, and the mixture was made basic by adding 7 N NH_3 in MeOH. Chromatographic purification on silica with EtOAc:MeOH (9:1) gave 360 mg **7a** (57% over two steps). ^1H NMR (CDCl_3 : CD_3OD = 95:5) δ 6.97 (t, J = 8.1 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 4.20–4.10 (m, 3H), 3.52 (m, 2H), 2.92 (d, J = 5.90 Hz, 2H), 2.33 (t, J = 2.43 Hz, 1H).

(2'S,2"E)-[4-(3'-(3"-TRIBUTYLSTANNYL-2"-PROPENYL)AMINO-2'-HYDROXYPROPOXY)]-BENZIMIDAZOL-2-ONE (**9a**). To a solution of 26 mg of the ethynyl derivative **7a** in 1.5 mL toluene was added 240 μL Bu_3SnH (0.8 mmol) and 5 mg AIBN. The reaction was stirred

FIG. 3. Reaction scheme of the synthesis of CYBL4E, CYBL4A, and CYBL5E and the precursors of the ^{123}I -labelled compounds.

in an argon atmosphere for 6 h at 80°C. Then the mixture was cooled, concentrated *in vacuo*, and the residue was purified by chromatography on silica with EtOAc:MeOH:Et₃N (95:4:1) as the eluents to give 25 mg **9a** (45%). ¹H NMR (CDCl₃): δ 6.90 (t, J = 8.0 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.56 (d, J = 8.2 Hz, 1H), 6.14 (d, J = 19.0 Hz (with satellite peaks J = 36.3 Hz and J = 35.1 Hz, 1H), 6.05 (dt, J = 19.0 Hz and J = 4.8 Hz, 1H), 4.25 (m, 1H), 4.14 (m, 1H), 4.07 (dd, J = 5.6 Hz and J = 9.1 Hz, 1H), 3.39 (d, J = 4.8 Hz, 1H), 2.95 (dd, J = 9.0 Hz and 11.7 Hz, 1H), 2.84 (dd, J = 3.5 Hz and J = 11.7 Hz, 1H), 1.55–1.40 (m, 6H), 1.35–1.25 (m, 6H), 0.95–0.80 (m, 15H).

(2'-S,2'E)-[4-(3'-(3"-IODO-2"-PROPENYL)AMINO-2'-HYDROXYPROPOXY)]-BENZIMIDAZOL-2-ONE (CYBL4E). To a solution 25 mg of **9a** in 1 mL CHCl₃ was added dropwise a solution of 0.1 M I₂ in CHCl₃. After 2 h 0.5 mL 1 M KF and 0.5 mL 1 M NaHSO₃ were added, and the resulting mixture was stirred vigorously. The layers were separated, the aqueous layer was diluted with MeOH, and a white precipitate filtrated. The filtrate was concentrated and purified on silica with EtOAc:MeOH (9:1) to give 11 mg **CYBL4E** (63%). Ee of 94.4% (retention times for the R- and S-enantiomer were 21.3 and 25.9 min, respectively, with i-PrOH/hexane = 2:8), ¹H NMR (CDCl₃:CD₃OD = 95:5) δ: 6.98 (t, J = 8.1 Hz, 1H), 6.90 (d, J = 14.6 Hz, 1H, vinylic proton), 6.73 (d, J = 8.1 Hz, 1H), 6.71 (dt, J = 14.6 Hz and J = 7.3 Hz, 1H, vinylic proton), 6.62 (d, J = 7.9 Hz, 1H), 4.45 (m, 1H), 4.15 (m, 2H), 3.75 (m, 2H), 3.35 (m, 2H).

Synthesis of CYBL4A (Fig. 3)

The first four steps of the synthesis are similar to the first four steps of the synthesis of **CYBL4E** (Fig. 3).

(S)-[4-(3'-(2"-TRIBUTYLSTANNYL-2"-PROPENYL)AMINO-2'-HYDROXYPROPOXY)]-BENZIMIDAZOL-2-ONE (**8a**). To a mixture of 95 mg (0.36 mmol) ethnyl derivative **7a** and 200 μL (0.74 mmol) Bu₃SnH in 10 mL toluene was added 20 mg (17 μmol) Pd(PPh₃). The mixture was stirred at room temperature in an argon atmosphere. After 5 h the mixture was filtered and the filtrate was concentrated *in vacuo*. Flash chromatography with EtOAc (containing 2% Et₃N) yielded 17 mg **8a** (9%) and 40 mg of a mixed fraction containing **8a** and the regioisomer **9a**. ¹H NMR (CDCl₃:CD₃OD = 95:5) δ: 6.95 (t, J = 8.1 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 5.85 (d, J = 2.1 Hz (with satellite peaks at 64 Hz), 1H, vinylic proton), 5.25 (d, J = 2.1 Hz (with satellite peaks at 28 Hz), 1H, vinylic proton), 4.2–4.0 (m, 2H), 4.05–3.95 (m, 1H), 3.5–3.4 (m, 2H), 2.8 (m, 2H), 1.6–1.4 (m, 6H), 1.4–1.25 (m, 6H), 1.0–0.8 (m, 15H).

(S)-[4-(3'-(2"-IODO-2"-PROPENYL)AMINO-2'-HYDROXYPROPOXY)]-BENZIMIDAZOL-2-ONE (CYBL4A). To a solution of 15 g (27 μmol) **8a** in 1 mL CHCl₃:MeOH (9:1) was added dropwise a solution of 0.27 mL 0.1 M I₂ in CHCl₃. After 2 h, 0.5 mL 1 M KF and 0.5 mL 1 M NaHSO₃ were added, and the resulting mixture was stirred vigorously. Two separate layers emerged. The aqueous layer was diluted with MeOH. The white precipitate formed was removed by filtration. The filtrate was concentrated and purified by chromatography on silica with EtOAc:MeOH (9:1) to give 9 mg **CYBL4A** (85%). ¹H NMR (CDCl₃:CD₃OD = 9:1): δ 6.95 (t, J = 7.9 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.31 (s, 1H, vinylic proton), 5.93 (s, 1H, vinylic proton) 4.15–4.0 (m, 3H), 3.45 (m, 2H), 2.75 (m, 2H).

Synthesis of CYBL5E (Fig. 3)

(S)-[1-(2-AMINO-3-NITROPHENOXY)]-3'-(1",1"-DIMETHYLPROPARGYLAMINO)-2'-PROPANOL (**5b**). A solution of 210

mg (1 mmol) **4** and 0.5 mL (4 mmol) 1,1-dimethylpropargylamine in 3 mL EtOH was stirred 18 h at 45°C. Subsequently, the mixture was concentrated and purified chromatographically on silica with EtOAc:hexane (8:2) to yield 260 mg **5b** (87%). ¹H NMR (CDCl₃): δ 7.72 (dd, J = 1.1 and 8.1 Hz, 1H), 6.90 (dd, J = 0.8 and 7.7 Hz, 1H), 6.57 (dd, J = 7.7 and 8.8 Hz, 1H), 4.15–4.05 (m, 2H), 4.0 (dd, J = 6.7 and 9.4 Hz, 1H) 3.70 (br. s, 2H), 2.91 (m, 2H), 2.38 (s, 1H), 1.43 and 1.40 (2 × s, 2 × 3H).

(S)-[4-(3'-(1",1"-DIMETHYLPROPARGYLAMINO)-2'-HYDROXYPROPOXY)]-BENZIMIDAZOL-2-ONE (**7b**). To a solution of 260 mg (0.87 mmol) aryl nitro derivative **5b** in 10 mL EtOH was added 1.35 g (5.9 mmol) SnCl₂ · 2H₂O, and this mixture was stirred for 4 h at 80°C. It was then concentrated *in vacuo* and dissolved in 20 mL 2 N HCl. The flask was cooled in ice, and 2 mL 1.93 M COCl₂ in toluene was added to the vigorously stirred solution. The resulting mixture was stirred overnight, and subsequently concentrated *in vacuo*. The residue was dissolved in MeOH, cooled in ice, and the mixture was made basic by adding 7 N NH₃ in MeOH. Elution on silica with EtOAc:MeOH (9:1) yielded 252 mg **7b**. Ee of 99% (retention times for the R- and S-enantiomer were 10.4 and 13.9 min, respectively, with i-PrOH/hexane = 2:8), ¹H NMR (CDCl₃:CD₃OD = 67:33): δ 7.0 (t, J = 8.1 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 4.50–4.40 (m, 1H), 4.18 (m, 2H), 3.48 (dd, J = 3.6 Hz and 12.3 Hz, 1H), 3.37 (dd, J = 9.3 Hz and 12.3 Hz, 1H), 2.98 (s, 1H) 1.77 (s, 2 × 3H).

(2'S,2"E)-[4-(3'-(1",1"-DIMETHYL-3"-TRIBUTYLSTANNYL-2"-PROPENYLAMINO)-2'-HYDROXYPROPOXY)]-BENZIMIDAZOL-2-ONE (**9b**). To a mixture of 90 mg (0.3 mmol) of the ethynyl derivative **7b** in 2 mL toluene were added 0.5 mL (1.6 mmol) Bu₃SnH and 5 mg AIBN. The reaction was stirred in an argon atmosphere for 5 h at 75°C. Then the mixture was cooled, concentrated *in vacuo*, and chromatographed on silica with EtOAc:MeOH:Et₃N (95:4:1) to give 103 mg **9b** (59%). ¹H NMR (CDCl₃): δ 6.95 (t, J = 8.1 Hz, 1H), 6.72 (dd, J = 0.59 Hz and 7.7 Hz, 1H), 6.59 (dd, J = J = 0.59 Hz and 8.4 Hz, 1H), 5.98 (d, J = 19.5 Hz (with satellite peaks J = 36.2 Hz and J = 34.6 Hz and 16.7 Hz and 15.3 Hz), 1H), 5.86 (d, J = 19.5 Hz (with satellite peaks J = 34.0 Hz and J = 32.4 Hz and 14.4 Hz and 13.9 Hz), 1H), 4.12–4.03 (m, 2H), 3.93 (dd, J = 8.1 Hz and 10.1 Hz, 1H), 2.61 (d, J = 6.06 Hz, 2H), 1.60–1.40 (m, 6H), 1.35–1.28 (m, 6H), 1.21 (m, 2 × 3H), 1.0–0.8 (m, 15H).

(2'S,2"E)-[4-(3'-(1",1"-DIMETHYL-3"-IODO-2" PROPENYLAMINO)-2'-HYDROXYPROPOXY)]-BENZIMIDAZOL-2-ONE (CYBL5E). To a solution of 35 mg (0.06 mmol) **9b** in 2 mL CHCl₃ was added dropwise a solution of 0.1 M I₂ in CHCl₃. After 2 h, the mixture was diluted with 10 mL CHCl₃, and 0.5 mL 1 M KF and 0.5 mL 1 M NaHSO₃ were added. The resulting mixture was stirred vigorously. The layers were separated, and the organic phase was concentrated to a residue that was purified by chromatography on silica with EtOAc:MeOH (9:1) to give 22 mg **CYBL5E** (87%). ¹H NMR (CDCl₃:CD₃OD = 9:1): δ 6.97 (dd, J = 8.1 Hz and J = 8.2 Hz, 1H), 6.73 (dd, J = 0.6 Hz and J = 8.1 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 6.59 (d, J = 14.8 Hz, 1H), 6.39 (d, J = 14.8 Hz, 1H), 4.2 (m, 1H), 4.1 (dd, J = 3.9 Hz and J = 5.6 Hz, 1H), 4.03 (dd, J = 6.2 Hz and J = 9.5 Hz, 1H), 2.87 (dd, J = 3.5 Hz and J = 11.9 Hz, 1H), 2.79 (dd, J = 8.7 Hz and J = 11.9 Hz, 1H), 1.36 (s, 6H). MS(ionspray): m/z 418 (M+H)⁺.

Synthesis of CYBL6 (Fig. 4)

4-IODOBENZYLAMINE. An amount of 600 mg (2 mmol) 4-iodobenzyl bromide (**14**) was stirred in 10 mL 7 M NH₃ in methanol for 5 days at room temperature. The mixture was thereafter concen-

trated, and to the residue a solvent mixture of 60 mL CHCl_3 and water (2:1) was added. Subsequently, Na_2CO_3 was added, followed by vigorous shaking. The organic layer was dried on Na_2SO_4 and concentrated, to yield 400 mg 4-iodobenzylamine (85%). $^1\text{H NMR}$ (CDCl_3): δ 7.64 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 3.81 (s, 2H). $^{13}\text{C NMR}$ (CDCl_3): δ 142.7, 137.4, 129.8, 91.8, 45.8.

(S)-[1-(2-AMINO-3-NITROPHENOXY)]-3'-(PARA-IODOBENZYL-AMINO)-2'-PROPANOL (5c). To a solution of 400 mg (1.1 mmol) 4-iodobenzylamine in 4 mL EtOH was added 230 mg (1.1 mmol) **4**. The reaction mixture was heated for 5 h at 50°C . The mixture was then cooled to room temperature and concentrated. Flash chromatography (EtOAc; EtOAc:methanol = 9:1) gave 215 mg **5c** (40%). $^1\text{H NMR}$ (CDCl_3): δ 7.75 (dd, J = 1.1 Hz and J = 8.9 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 7.8 Hz, 1H), 6.58 (dd, J = 7.8 Hz and J = 8.9 Hz, 1H), 6.45 (br. s, 2H), 4.08 (m, 2H), 4.03 (m, 2H), 3.79 (q_{AB} , J = 13.5 Hz, 2H), 2.89 (dd, J = 3.6 Hz and J = 12.2 Hz, 1H), 2.76 (dd, J = 7.8 Hz and J = 12.2 Hz, 1H).

(S)-[4-(3'-(PARA-IODOBENZYLAMINO)-2'-HYDROXYPROPOXY)]-BENZIMIDAZOL-2-ONE (CYBL6). To a solution of 165 mg (0.3 mmol) aryl nitro derivative **5c** in 10 mL EtOH was added 600 mg (2.7 mmol) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, and this mixture was stirred for 5 h at 80°C . Then it was concentrated *in vacuo* and dissolved in 20 mL 2 N HCl. The flask was cooled in ice, and 2 mL of 1.93 M COCl_2 in toluene was added to the vigorously stirred solution. The resulting mixture was stirred overnight, which resulted in crystallization. Filtration and recrystallisation in isopropanol/ether gave 138 mg **CYBL6** (95%) as grey crystals. Ee of 91.4% (retention times for the R- and S-enantiomer were 10.8 and 13.5 min, respectively, with i-PrOH/hexane = 1:9). $[\alpha]_{\text{D}} = -4.5^\circ$ (c = 0.42, methanol). $^1\text{H NMR}$ (CDCl_3 : CD_3OD = 9:1): δ 7.66 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 6.96 (t, J = 8.1 Hz, 1H), 6.72 (d, J = 7.9 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 4.15–4.08 (m, 2H), 3.96 (dd, J = 6.6 Hz and J = 9.2 Hz, 1H), 3.78 (q_{AB} , J = 13.5 Hz, 2H), 2.7 (m, 2H). MS(ionspray): m/z 440 ($\text{M}+\text{H}$) $^+$.

Radiolabelling

SYNTHESIS OF [^{123}I]CYBL3. To a solution of 100 μg **3** in 150 μL ethanol and 200 μL of a slightly acidic buffer was added [^{123}I]NaI (specific activity 5000 Ci/mmol). To this mixture was added 40 μL HOAc and 40 μL 30% H_2O_2 . After stirring the mixture at room temperature for 10 min, the reaction was terminated by the addition

of 150 μL 300 mg/mL NaHSO_3 solution. Then the mixture was loaded on a C-18 cartridge (Bond Elute, 1 mL) and washed with water. The [^{123}I]CYBL3 was eluted from the cartridge with 2 mL EtOH/HCl (20:1, v/v). The eluate was evaporated and the residue was dissolved in EtOH and purified on a C-18 reverse-phase HPLC. Elution with ethanol/acetate buffer (pH = 9) (50:50, v:v) yielded [^{123}I]CYBL3, which was loaded on a second C18 cartridge, washed with 1 mL water, and eluted with 2 mL EtOH/HCl (20:1 v:v). Finally, the eluate was evaporated and the residue dissolved in 200 μL EtOH, to which was added 4 mL of an isotonic acetate buffer (pH = 4.7). The resulting solution was filtered on a 0.22- μm membrane (Millex GV, 13 mm). Identity and purity were further analyzed by TLC (free iodine R_f = 0.75 and [^{123}I]CYBL3 R_f = 0.35 with EtOH:EtOAc:HOAc = 9:9:2 v:v:v) and HPLC (*vide supra*). The radioactive product [^{123}I]CYBL3 exhibited identical mobilities on TLC and HPLC with those of the nonradioactive product. Radiochemical purity was >95%. The specific activity of [^{123}I]CYBL3 obtained, verified by combined radioactivity measurement and UV-absorbance detection with HPLC, amounted to 5000 Ci/mmol.

SYNTHESIS OF [^{123}I]CYBL5E. The radioactive [^{123}I]CYBL5E was obtained from its tributyl tin precursor **9b** using the method described for the synthesis of [^{123}I]CYBL3. The identity and purity was analyzed with TLC ([^{123}I]CYBL5E R_f = 0.45 with EtOH:EtOAc:HOAc = 9:9:2 v:v:v) and HPLC (*vide supra*). The radioactive product [^{123}I]CYBL5E exhibited identical mobilities on TLC and HPLC with those of the nonradioactive product. Radiochemical purity was >95%. The specific activity of [^{123}I]CYBL5E obtained amounted to 5000 Ci/mmol.

RESULTS AND DISCUSSION

Synthesis of CYBL3

A serious problem in the design of new radioiodinated receptor binding ligands is the fact that introduction of the iodine in compounds may affect the affinity for the receptor when compared to the noniodinated parent compound. Penbutolol bearing a large, lipophilic cyclopentyl group in the *ortho*-position of the alkoxy substituent has a high affinity to the β -adrenoceptor. In order to construct a compound that has a high stereochemical resemblance and a comparable lipophilicity, it was decided to synthesize CYBL3 (*vide Fig. 2*).

CYBL3 is readily obtainable by reaction of the anion of 2-iodophenol with the tosylate of (S)-(-)-2-phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine (**1**) (12, 15), followed by hydrolysis of the benzaldehyde protective group. Reaction of CYBL3 with hexamethylditin in the presence of tetrakis(triphenylphosphine)palladium resulted in the formation of the corresponding trimethylstannyl derivative (**3**) (16), which is an excellent precursor for [^{123}I]CYBL3. The radioiodination of **3** was accomplished by an oxidative radioiododestannylation reaction using [^{123}I]NaI in the presence of hydrogen peroxide. The radiolabelled compound [^{123}I]CYBL3 was readily separated from the starting material by HPLC purification.

Synthesis of CYBL4A, -4E, -5, and -6

Several β -adrenoceptor ligands that have been labelled previously for imaging purposes were not successful due to their high lipophilicity (17, 18). Because CGP12177 combines a high affinity for the β -adrenoceptor with a low lipophilicity, it is attractive to examine its analogues. It is known that modifications of the *N*-alkyl functionality are possible, while the affinity for the receptor is re-

FIG. 4. Reaction scheme for the synthesis of CYBL6 and its intermediates.

tained. Although the introduction of an iodine atom combined with a linker moiety results in a decrease of hydrophilicity, the resultant compounds are still rather hydrophilic. Therefore, we designed a series of *N*-iodoalkyl analogues of CGP12177. These compounds CYBL4A, CYBL4E, CYBL5, and CYBL6 were synthesized from 2-amino-3-nitrophenol. The reactions schemes are given Fig. 3 and 4. First the *S*-epoxide **4** is formed by reaction of sodium 2-amino-3-nitrophenoxide with *S*-glycidyl *m*-nitrobenzenesulfonate (19). In a recent study it was established that this method results in a product of high enantiomeric purity (13). The propanolamine side chain is formed by reaction of the appropriate amine with the epoxide in ethanol at a temperature of 50°C. In the reactions with propargylamine and *para*-iodobenzylamine, the formation of the desired propanolamines (**5a** and **5c**) is accompanied by a small amount of their regioisomers (**10a** and **10c**) (20) (Fig. 5). These regioisomers were easily separated by column chromatography. The structures of the regioisomers were assigned with ¹H NMR on the basis of their different ABX-spin-systems (21). The reaction of 1,1-dimethylpropargylamine was found to be regioselective. Apparently, the attack at the less accessible side of the epoxide is prevented by the steric bulk of the two methyl groups.

In previous syntheses of CGP12177 the benzimidazolone ring system was constructed by reduction of the nitro group to an amine with hydrogen in the presence of a metal catalyst followed by reaction with phosgene (13, 22). This method is not suited for the reduction of **5a** and **5b** because of the simultaneous reduction of the alkyne function to an alkene (23, 24). The reduction of **5c** to the diamino compound **6c** is expected to proceed with an accompanying deiodination side reaction (25, 26). Therefore, we studied an alternative reduction method. It was found that heating the compounds **5a,b**, and **c** with SnCl₂ in ethanol resulted in a selective reduction of the nitro function (27), whereas the alkyne and the iodobenzyl functionalities are maintained. The thus obtained diamino compounds (**6a,b**, and **c**) were found to be unstable and therefore directly reacted with phosgene to form the desired benzimidazolone.

The alkynylamino compounds **7a** and **7b** were hydrostannylated with Bu₃SnH. In principle, three regioisomers may be formed in this reaction. However, it is possible to obtain predominantly a chosen regioisomer by a proper choice of reaction conditions. Thus, heating an ethynylamino compound in the presence of the radical initiator AIBN in an aprotic solvent as toluene results in the selective formation of the *E*-isomer. When the hydrostannylation is performed in toluene in the presence of a palladium(0) catalyst at room temperature the α -isomer is obtained, albeit this is accompanied by the formation of a considerable amount of the *E*-isomer (28, 29). It was found that only the propargyl derivative **7a** could be transformed to the α -tributylstannyl isomer. Several attempts to perform the palladium-catalyzed hydrostannylation with the dimethylpropargylamine **7b** resulted in decomposition. In the present study no attempts to the formation of the *Z*-tributylstannyl isomer have

been made. The tributylstannylallyl intermediates **8a**, **9a**, and **9b** were converted with retention of configuration to the corresponding (iodoallyl)amino compounds CYBL4A, CYBL4E, and CYBL5E via the reaction with iodine in chloroform.

In the present study, the synthesis of a number of new iodinated ligands is described. Based on penbutolol we designed CYBL3. Replacement of the cyclopentyl group of penbutolol for an iodine atom resulted in CYBL3, which is one of the simplest members of the class of phenoxypropanolamines possessing the essential elements for binding to the β -adrenoceptor and an iodine atom.

Finally, the new *N*-iodoalkyl analogues of CGP12177 can be subdivided in iodovinyl compounds (Fig. 2) and an iodoaryl derivative (CYBL6). The radiolabelled forms of these compounds are readily available by oxidative iododestannylation, which resulted in compounds with a high specific activity.

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FIG. 5. Reaction of the production of the regioisomers **10a** and **10c** from **5a** and **5c**.

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