Synthesis of Tetrahydrocarbazole Derivatives as Potent β_3-Adrenoceptor Agonists

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A series of 2-(3-chlorophenyl)-2-hydroxyethylamine derivatives containing a tetrahydrocarbazole linker were prepared and evaluated for their β_3-adrenoceptor agonistic activity. Several compounds showed potency comparable to CL-316243.

Key Words : β_3-Adrenoceptor, Tetrahydrocarbazole, Arylethanolamine, Antiobesty

Introduction

As a subclass of β-adrenoceptors,[1] β_3-adrenoceptor(β_3-AR)[2] is found on the cell surface of both white and brown adipocytes and mediates various metabolic processes such as lipolysis and thermogenesis.[3] Activation of human β_3-AR results in an increase of c-AMP level in adipocytes, leading to an elevation of metabolic rate. Therefore, discovery of a human β_3-AR agonist would be an attractive approach to the treatment of human disease states, such as obesity and type II diabetes.[4] Although many early β_3-AR agonists such as BRL 37344,[5] CL-316243,[6] AJ 9677,[7] and SR58611A[8] were tested in clinical trials, these β_3-AR agonists suffered a poor potency or substantial β_1-AR and β_2-AR mediated side effects in human. Recently a number of laboratories have been developing new classes of β_3-AR agonists, such as Solabegron[9] and N-5984,[10] having much higher potency and less side effects than the early β_3-AR agonists. However, those compounds still need improvement, and new β_3-AR agonists as viable antiobestic or antidiabetic agents with improved potency are pursued.

Most of β_3-AR agonists tested in clinical trials possess the 2-(3-chlorophenyl)-2-hydroxyethylamino group in the left-hand side and a carboxylic acid or its isostere in the right-hand side, which is considered to be critical for showing β_3-AR agonistic activity, and a variety of aromatic ring systems,[11] such as phenyl, pyridine,[12] indole, tetrahydronaphthalene, and benzodioxine, were used as a linker of β_3-AR agonists. With considering those, we decided to test a tetrahydrocarbazole moiety as a linker for a new potent β_3-AR agonist. In this paper we describe the synthesis and structure-activity study of a variety of 2-(tetrahydrocarbazol-3-ylamino)-1-(3-chlorophenyl)ethanol derivatives, leading to the discovery of a new and potent β_3-AR agonist.

Chemistry

The general synthetic route to tetrahydrocarbazole deriva-

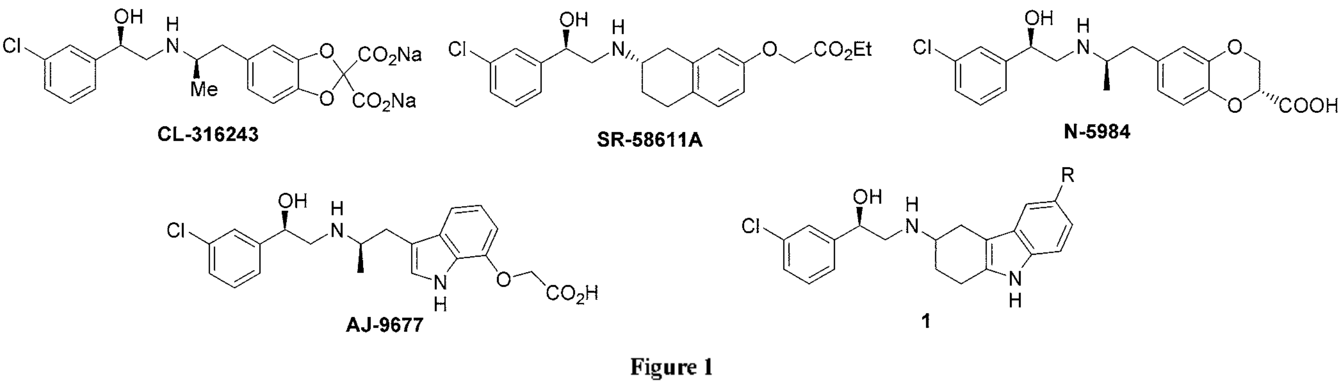
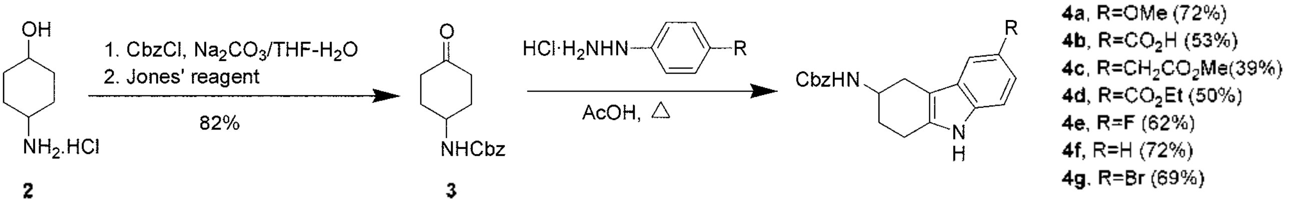


Figure 1



Scheme 1

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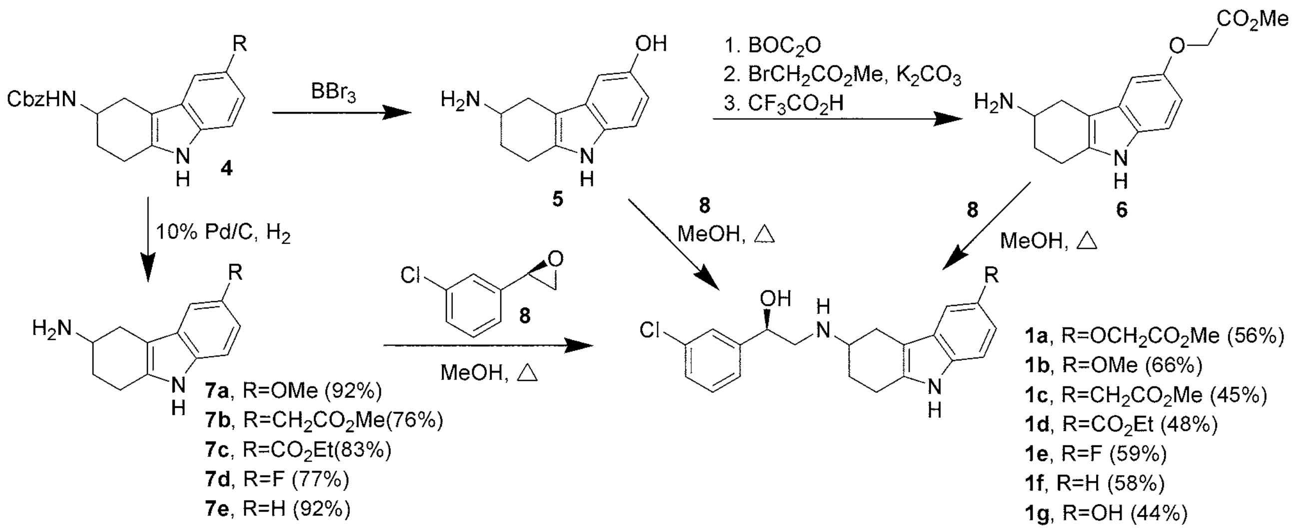
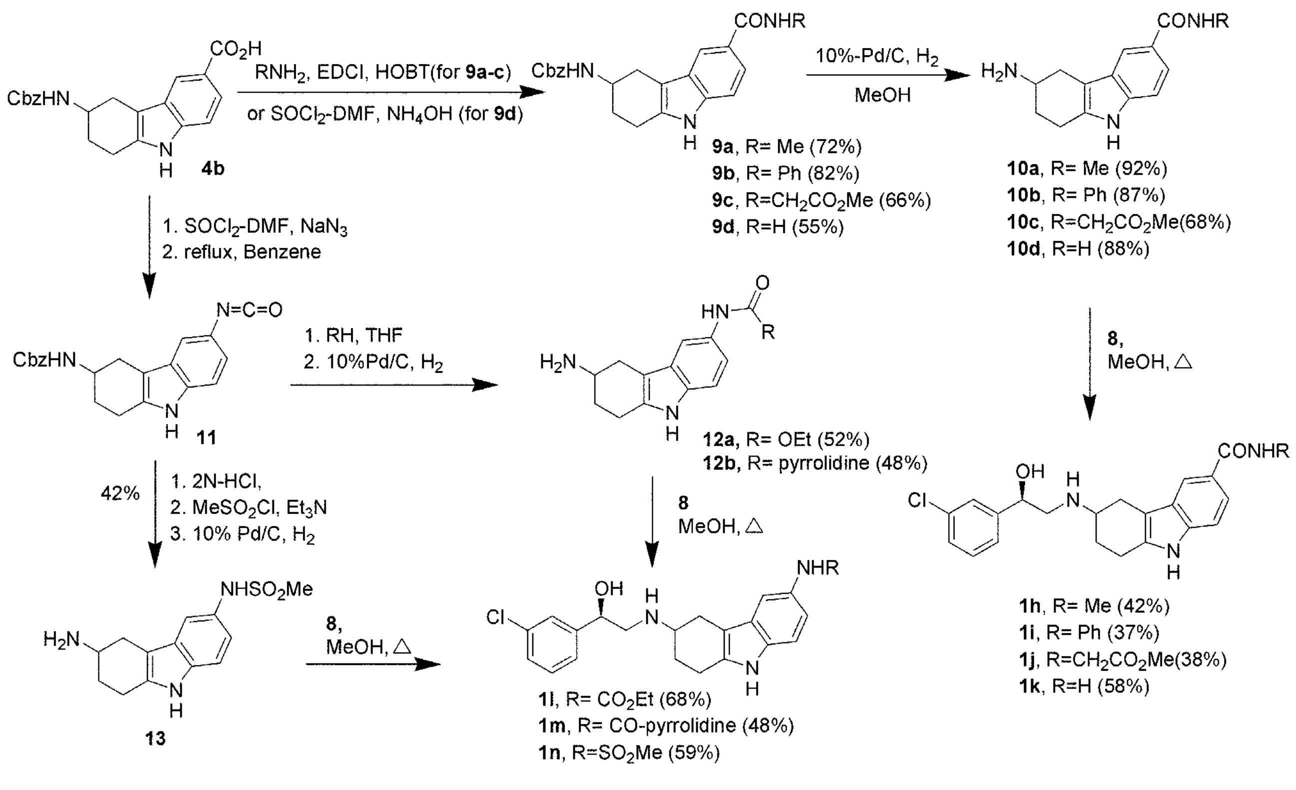


Scheme 2

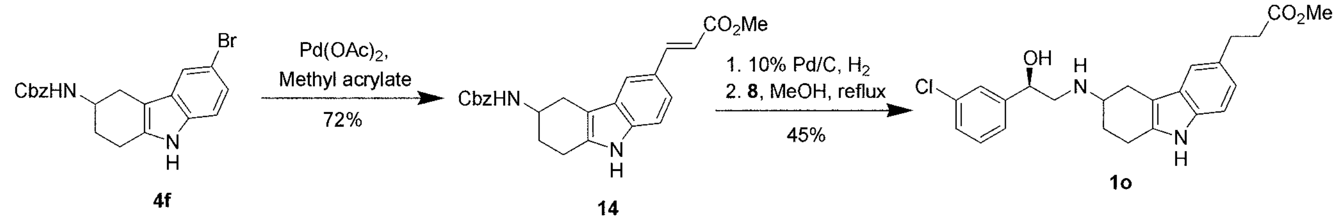


Scheme 3

tives is shown in Scheme 1. The 3-(benzyloxycarbonyl-amino)-1,2,3,4-tetrahydrocarbazole derivatives **4** were prepared by following similar methods described in literatures.[13]

The synthesis began with a commercially available 4-aminocyclohexanol **2**, which was treated with CbzCl and Na_2CO_3, followed by oxidation with Jones reagent to give the cyclohexanone **3**. Fisher cyclization of the cyclohexanone **3** with various aryl hydrazines in refluxing acetic acid gave the tetrahydrocarbazole derivatives **4a-g** (Scheme 1).

Synthesis of arylethanolamines **1a-g** was achieved as described in Scheme 2. Cleavage of the Cbz group and methyl ether using BBr_3 provided the corresponding 6-aminotetrahydrocarbazol-3-ol (**5**). Then, amino group was protected with Boc group followed by alkylation of phenol with methyl bromoacetate and subsequent deprotection of Boc amino group using CF_3CO_2H to furnish aminotetrahydrocarbazole **6**. A catalytic hydrogenolysis of **4a** and **4c-f** using Pd/C provided the aminocarbazole derivatives **7a-e**. For the synthesis of arylethanolamines **1a-g**, 3-aminotetrahydrocarbazole derivatives **5**, **6**, and **7a-e** were treated with an optically pure (*R*)-3-chlorostryrene oxide **8** in



Scheme 4

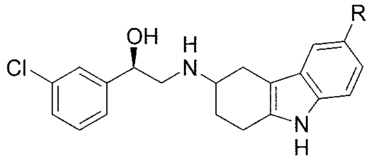
MeOH.

The arylethanolamines **1h-n** were prepared as outlined in Scheme 3. Coupling of the carboxylic acid **4b** with various amines using EDCI and HOBT to afford the amides **9a-c**, followed by a catalytic hydrogenolysis furnished amino-tetrahydrocarbazole **10a-c**. The carboxamide **9d** was readily synthesized by the activation of the carboxylic acid using $SOCl_2$-DMF followed by addition of ammonia/water.

For the synthesis of **12a-b** and **13**, the carboxylic acid **4b** was subjected to Curtis rearrangement condition using $SOCl_2$-DMF adduct as activating agent followed by heating in benzene to provide the isocyanate **11**. Nucleophilic addition of EtOH or pyrrolidine to isocyanate **11** by heating in THF and a subsequent hydrogenolysis afforded the aminotetrahydrocarbazoles **12a-b**. Hydrolysis of the isocyanate **11** in 2 *N*-HCl afforded the 6-aminotetrahydrocarbazole, which was treated with methansulfonyl chloride followed by catalytic hydrogenolysis to give the sulfonamide **13**. The arylethanolamines **1h-n** were prepared by following the same method as described in Scheme 2.

The arylethanolamine **1o** was prepared according to Scheme 4. Heck reaction of **4g** with methyl acrylate using $Pd(OAc)_2$ afforded the tetrahydrocarbazol acrylic ester **14**. Catalytic hydrogenation and hydrogenolysis followed by coupling with **8** afforded the arylethanolamine **1o**.

Table 1. *In vitro* Activity for Tetrahydrocarbazole Derivatives



Compd	R	IC_{50} (μM)	Ki (μM)
1a	OCH_2CO_2Me	1.20	0.64
1b	OMe	1.28	0.55
1c	CH_2CO_2Me	2.85	1.22
1d	F	0.79	0.34
1e	H	5.10	2.19
1f	OH	1.37	0.58
1g	CONHMe	2.58	1.10
1h	CONHPh	0.19	0.09
1i	$CONHCH_2CO_2Me$	0.40	0.17
1j	$CONH_2$	0.64	0.27
1k	CO_2Et	0.21	0.09
1l	$NHCO_2Et$	0.81	0.35
1m	NHCOpyrrolidine	24.93	10.69
1n	$NHSO_2Me$	2.12	0.91
1o	$CH_2CH_2CO_2Me$	6.68	2.86
CL-316243		1.17	0.62

Screening Results

The arylethanolamines were tested for their *in vitro* activity by using cell membrane expressing human β_3-AR (RB-HBETA3).[14] and the results are summarized in Table 1. CL-316243 was also included as a reference. Due to the difference of assay conditions, CL-316243 exhibited a relatively lower agonistic activity than that of previously reported data.[6]

As shown in Figure 1, the carboxylic acid or its ester functionalities in the right-hand side of β_3-AR agonist is important for maintaining β_3-AR agonist activity and desirable physical properties. As expected, introduction of the methoxycarbonylmethoxy group ($R=OCH_2CO_2Me$, **1a**) at C-6 position of tetrahydrcarbazole displayed comparable in vitro activity ($IC_{50}=1.2$ μM) to that of CL-316243 ($IC_{50}=1.17$ μM). A simple tetrahydrocarbazole **1e** without any substituent was about 5-fold less potent compared with **1a**. The compounds **1b**, **1d**, and **1f** with non-carboxylate functionalities were quite active, especially, the fluoro substituted compound **1f** was even more potent ($IC_{50}=0.79$ μM). Although the amide derivatives are known to be moderate isostere of carboxylic acid, we synthesized a variety of amide derivatives for evaluation. While the *N*-methylamide **1g** showed poor activity, the activities of the amide **1h**, **1i**, and **1k** were significantly increased. To our delight, phenyl amide **1h** was the most potent compound synthesized, which showed about 6-fold higher potency compared to that of CL-316243. In terms of tether length modifications, comparison of the activities of compounds **1c**, **1k**, and **1o** indicated that increasing length to methylene or ethylene led to diminished activity compared to that of the directly attached carboxylate **1k** ($IC_{50}=0.21$ μM). We also synthesized a series of tetrahydrocarbazolyl amine derivatives, such as carbamate (**1l**), urea (**1m**), and sulfonamide (**1n**), which all resulted in decreased activities.

In addition, all compounds were tested for their plasma glucose lowering activity in obese hyperglycemic *ob/ob* mice. Among them, 5 mg/kg/day of **1n** significantly reduced plasma glucose concentrations in 3 days from 231 mg/dl to 176 mg/dl, which was similar to that of CL-316243 (233 mg/dl to 152 mg/dl).[15]

Conclusions

The synthesis and SAR studies of substituted tetrahydrocarbazole derivatives have been discussed. The tetrahydrocarbazoles **1h** and **1k** showed about 5-fold potency *in vitro* β_3-AR activity compared with CL-316243. A further pharmacological evaluation of these compounds is in progress.

Experimental Sections

(4-Oxocyclohexyl)carbamic acid benzyl ester (3). To a suspension of 4-aminocyclohexanol hydrochloride (5 g, 32.97 mmol) and Na_2CO_3 (7g, 66 mmol) in THF-H_2O (4 : 1, 100 mL) was dropwise added benzyl chloroformate (5.2 mL, 36.27 mmol) in THF (5 mL) at 0 °C and the reaction mixture was stirred for 2 h at 0 °C. The mixture was diluted with EtOAc and the organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated to give a crude (4-hydroxycyclohexyl)carbamic acid benzyl ester (8.2 g), which was subjected to the next reaction without further purification.

To a solution of a crude (4-hydroxycyclohexyl)carbamic acid benzyl ester in acetone (100 mL) was added Jones' reagent (5.2 mL, 41.6 mmol) at 0 °C and the reaction mixture was stirred for 30 min, then quenched by addition of isopropyl alcohol (4 mL). After stirring for 5 min, the mixture was filtered, and washed with acetone. The filtrate was concentrated and partitioned between water and EtOAc. The organic layer was dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography (Hex: EtOAc = 3 : 1) to afford the cyclohexanone **3** (6.7g, 82%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37-7.30 (m, 5H), 5.04 (s, 2H), 3.84 (m, 1H), 2.40 (m, 2H), 2.27 (m, 2H), 1.99 (m, 2H), 1.68 (m, 2H).

(6-Methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)carbamic acid benzyl etster (4a). A solution of 4-methoxyphenyl hydrazine hydrochloride (1.94 g, 11.13 mmol), sodium acetate (1.25 g, 15.1 mmol), and cyclohexanone **6** (2.5 g, 10.12 mmol) in acetic acid (50 mL) was heated for 20 h at reflux. The solvent was removed *in vacuo* and the residue was partitioned between water and EtOAc. The organic layer was dried, concentrated, and purified by column chromatography (Hex : EtOAc = 4 : 1) to give the 6-methoxytetrahydrocarbazole **4a** (2.55 g, 72%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (brs, 1H), 7.53-7.25 (m, 7H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 8.0, 2.4 Hz, 1H), 5.12 (s, 2H), 4.94 (d, *J* = 7.6 Hz, 1H), 4.20 (m, 1H), 3.84 (s, 3H), 3.10 (dd, *J* = 15.6, 5.4 Hz, 1H), 2.80 (m, 2H), 2.63 (dd, *J* = 15.4, 6.8 Hz, 1H), 2.09 (m, 2H).

6-Benzyloxycarbonylamino-6,7,8,9-tetrahydro-5*H*-carbazole-3-carboxylic acid (4b). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.2 (brs, 1H), 9.72 (s, 1H), 8.58 (s, 1H), 7.63 (dd, *J* = 8.7, 1.2 Hz, 1H) 7.38-7.32 (m, 6H), 7.28 (d, *J* = 8.7 Hz, 1H), 5.05 (s, 2H), 3.84 (m, 1H), 2.97 (dd, *J* = 15.0, 5.1 Hz, 1H), 2.81 (m, 2H), 2.57 (dd, *J* = 15.0, 6.7 Hz, 1H), 2.05 (m, 1H), 1.80 (m, 1H).

(6-Benzyloxycarbonylamino-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl)acetic acid methyl ester (4c). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (brs, 1H), 7.35-7.30 (m, 6H), 7.21 (d, J =8.1 Hz, 1H), 7.04 (dd, *J* = 8.1, 1.6 Hz, 1H), 5.11 (s, 2H), 4.92 (m, 1H), 4.17 (m, 1H), 3.69 (s, 2H), 3.67 (s, 3H), 3.07 (dd, *J* = 15.4, 5.4 Hz, 1H), 2.79 (m, 2H), 2.59 (dd, *J* = 15.4, 6.7 Hz, 1H), 2.00 (m, 2H); MS (*m/e*), 392 (M^+, 11), 241 (100), 215 (17), 180 (41), 156 (37), 91 (53).

6-Benzyloxycarbonyl-6,7,8,9-tetrahydro-5*H*-carbazole-3-carboxylic acid ethyl ester (4d). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 1.6, 0.6 Hz, 1H), 8.07 (brs, 1H), 7.85 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.26 (dd, *J* = 8.5, 0.6 Hz, 1H), 7.35-7.33 (m, 5H), 5.11 (s, 2H), 4.94 (br d, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.17 (m, 1H), 3.13 (dd, *J* = 15.6, 5.4 Hz, 1H), 2.81 (m, 2H), 2.65 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.05 (m, 2H), 1.41 (t, *J* = 7.2 Hz, 3H); MS (*m/e*), 392 (M^+, 11), 347 (8), 241 (100), 215 (13), 168 (16), 91 (21).

(6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbzaol-3-yl)carbamic acid benzyl ester (4e). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 7.37-7.34 (m, 5H), 7.15 (dd, *J* = 8.7, 4.4 Hz, 1H), 7.04 (dd, *J* = 9.3, 2.4 Hz, 1H), 6.85 (m, 1H), 5.11 (s, 2H), 4.94 (m, 1H), 4.16 (m, 1H), 3.03 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.81-2.75 (m, 2H), 2.55 (dd, *J* = 15.4, 6.9 Hz, 1H), 2.00 (m, 2H); MS (*m/e*), 338 (M^+, 1), 186 (100), 161 (86), 91 (82).

(2,3,4,9-Tetrahydro-1*H*-carbazol-3-yl)carbamic acid benzyl ester (4f). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (brs, 1H), 7.44-7.27 (m, 5H), 7.19-7.06 (m, 2H), 5.11 (s, 2H), 4.92 (m, 1H), 4.20 (m, 1H), 3.09 (dd, *J* = 15.6, 5.4 Hz, 1H), 2.80 (m, 2H), 2.62 (dd, *J* = 15.6, 6.6 Hz, 1H), 2.19-1.85 (m, 2H); MS (*m/e*), 364 (M^+, 2), 256 (3), 213 (37), 168 (25), 91 (100).

(6-Bromo-2,3,4,9-tetrahydro-1*H*-carbzaol-3-yl)carbamic acid benzyl ester (4g). ^{1}H NMR (200 MHz, DMSO-d_6 + $CDCl_3$) δ 10.5 (brs, 1H), 7.45-7.06 (m, 8H), 6.38 (m, 1H), 5.09 (s, 2H), 4.02 (m, 1H), 3.00 (m, 1H), 2.84 (m, 2H), 2.58 (m, 1H), 2.10 (m, 1H), 1.95 (m, 1H); MS (*m/e*), 398 (M^+-1, 15), 247 (100), 221(22), 167 (60), 91 (61).

6-Amino-6,7,8,9-tetrahydro-5*H*-carbazol-3-ol (5). To a solution of (6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)carbamic acid benzyl ester (1.2 g, 3.42 mmol) in CH_2Cl_2 (30 mL) was added 1 M-BBr_3/CH_2Cl_2 (8.6 mL, 8.6 mmol) at 0 °C. The mixture was stirred for 6 h at room temperature, then quenched with addition of *sat*-$NaHCO_3$ solution at 0 °C. The mixture was basified with addition of 1 N-NaOH solution and extracted with EtOAc (3 × 20 mL), which was dried over Na_2SO_4, and concentrated to give the aminocarbazole **5** (0.36 g, 52%): ^{1}H NMR (200 MHz, CD_3OD) δ 7.04 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.24 (m, 1H), 3.15 (m, 1H), 2.90 (dd, *J* = 15.0, 5.4 Hz, 1H), 2.78 (m, 2H), 2.32 (*J* = 15.0, 8.4 Hz, 1H), 2.01 (m, 1H), 1.76 (m, 1H); MS (*m/e*), 202 (M^+, 44), 184 (10), 159 (100), 130 (6), 77 (5).

(6-Amino-6,7,8,9-tetrahydro-5*H*-carbazol-3-yloxy)acetic acid methyl ester (6). To a solution of **5** (0.28 g, 1.40 mmol) in THF-H_2O (4 : 1, 25 mL) was added Na_2CO_3 (0.44 g, 4.2 mmol) and $(BOC)_2O$ (0.63 g, 2.8 mmol) at 0°C and the mixture was stirred for 1h at 0°C. The solution was diluted with EtOAc and the organic layer was separated, washed with brine, dried, concentrated, and purified with column chromatography (Hex : EtOAc = 4 : 1) to give the BOC amino carbazole: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 (brs, 1H), 7.08 (d, J = 8.6 Hz, 1H), 7.79 (brs, 1H), 6.68 (dd, J = 8.4, 2.6 Hz, 1H), 5.63 (m, 1H), 4.76 (m, 1H), 2.93 (dd, J = 15.6, 5.0 Hz, 1H), 2.74 (m, 2H), 2.43 (J = 15.6, 7.0 Hz, 1H), 1.82 (m, 2H); MS (m/e), 302 (M^+, 100), 245 (29), 229 (38), 184 (78), 159 (94), 57 (46). To a solution of the BOC amino carbazole (0.23 g, 0.75 mmol) in acetone (10 mL) was added methyl bromoacetate (0.18 mL, 1.89 mmol), K_2CO_3 (0.42 g, 3.0 mmol), and a catalytic amount of KI, and the mixture was heated for 36 h at reflux. After cooling, the solvent was removed. The residue was partitioned between H_2O and EtOAc and the organic layer was separated, washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography (Hex : EtOAc = 10 : 1) to give the ester (0.24 g, 85%), which was then treated with CF_3COOH (2 mL) in CH_2Cl_2 (10 mL). The mixture was stirred for 13 h at room temperature and concentrated to give the amino carbazole **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (brs, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 2.3 Hz, 1H), 6.76 (dd, J = 8.4, 2.3 Hz, 1H), 4.66 (s, 2H), 3.81 (s, 3H), 3.28 (m, 1H), 2.99 (dd, J = 15.1, 5.3 Hz, 1H), 2.79 (m, 2H), 2.42 (J = 15.1, 8.4 Hz, 1H), 2.05 (m, 1H), 1.78 (m, 1H).

6-Methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-3-ylamine (7a). To a solution of the *N*-Cbz tetrahydrocarbazole **4a** (0.50 g, 1.43 mmol) and ammonium formate (0.37 g, 5.11 mmol) in EtOH (50 mL) was added 10%-Pd/C (125 mg), and the mixture was stirred for 24 h, then filtered through a pad of Celite, washed with ethanol. The filtrate was concentrated to give the amino tetrahydrocarbazole **7a** (0.29 g, 92%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (brs, 1H), 7.14 (d, J = 8.6 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 8.6, 2.4 Hz, 1H), 3.85 (s, 3H), 3.24 (m, 1H), 2.99 (dd, J = 15.3, 5.4 Hz, 1H), 2.79 (m, 2H), 2.42 (J = 15.3, 8.3 Hz, 1H), 2.02 (m, 1H), 1.78 (m, 1H); MS (m/e) 216 (M^+, 62), 199 (27), 173 (100), 158 (31).

(6-Amino-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl)acetic acid methyl ester (7b). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (brs, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 8.4, 2.4 Hz, 1H), 3.69 (s, 2H), 3.66 (s, 3H), 3.23 (m, 1H), 2.99 (dd, J = 15.4, 5.4 Hz, 1H), 2.79 (m, 2H), 2.42 (J = 15.4, 8.3 Hz, 1H), 2.02 (m, 1H), 1.78 (m, 1H).

6-Amino-6,7,8,9-tetrahydro-5*H*-carbazole-3-carboxylic acid ethyl ester (7c). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.85 (dd, J = 8.5, 1.6 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 4.39 (q, J = 7.4 Hz, 2H), 3.31 (m, 1H), 3.06 (dd, J = 15.2, 5.4 Hz, 1H), 2.82 (m, 2H), 2.49 (J = 15.2, 7.7 Hz, 1H), 2.05 (m, 1H), 1.81 (m, 1H), 1.41 (t, J = 7.4 Hz, 3H); MS (m/e), 258 (M^+, 37), 215 (100), 187 (35), 170 (19), 142 (13), 115 (11).

6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-ylamine (7d). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.17-7.04 (m, 2H), 6.84 (m, 1H), 3.32 (m, 1H), 2.96 (dd, J = 15.0, 5.0 Hz, 1H), 2.41 (m, 1H), 2.03 (m, 1H), 1.77 (m, 1H), 1.50 (s, 2H); MS (m/e), 204 (M^+, 48), 186 (19), 161 (100), 133 (15).

2,3,4,9-Tetrahydro-1*H*-carbazol-3-ylamine (7e). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.45 (dd, J = 7.0, 2.0 Hz, 1H), 7.25 (m, 1H), 7.19-7.01 (m, 2H), 3.31 (m, 1H), 3.04 (dd, J = 15.0, 5.2 Hz, 1H), 2.83 (m, 2H), 2.42 (dd, J = 15.0, 8.2 Hz, 1H), 2.05 (m, 1H), 1.85 (m, 1H); MS (m/e), 186 (M^+, 23), 168 (9), 143 (100), 115 (20).

(*R*)-{6-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-6,7,8,9-tetrahydro-5*H*-carbazol-3-yloxy}acetic acid methyl ester (1a). A solution of (*R*)-(+)-3-Chlorostyrene oxide (30 mg, 0.19 mmol) and the 6-aminotetrahydrocarbazole **6** (43 mg, 0.16 mmol) in MeOH (1 mL) was heated for 12 h. After cooling, the mixture was concentrated and the residue was purified with column chromatography (3% MeOH/CH_2Cl_2) to give the ethanolamine **1a** (38 mg, 56%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (brs, 1H), 7.25-7.23 (m, 4H), 7.12 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 2.3 Hz, 1H), 6.77 (dd, J = 8.4, 2.3 Hz, 1H), 4.71 (m, 1H), 4.66 (s, 2H), 3.81 (s, 3H), 3.28 (m, 1H), 3.15-3.10 (m, 2H), 2.99 (dd, J = 15.1, 5.3 Hz, 1H), 2.79 (m, 2H), 2.42 (d, J = 15.1, 8.4 Hz, 1H), 2.05 (m, 1H), 1.78 (m, 1H); HRMS (M^+) calcd for $C_{23}H_{25}ClN_2O_4$ 428.1503, found 428.1503.

(*R*)-1-(3-Chlorophenyl)-2-(6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-3-ylamino)ethanol (1b). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (brs, 1H), 7.25-7.22 (m, 4H), 7.15 (d, J = 8.5 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 8.6, 2.4 Hz, 1H), 4.71 (m, 1H), 3.85 (s, 3H), 3.24 (m, 1H), 3.16-3.12 (m, 2H), 2.99 (m, 1H), 2.79 (m, 2H), 2.42 (m, 1H), 2.02 (m, 1H), 1.79 (m, 1H).

(*R*)-{6-[2-Chlorophenyl]-2hydroxyethylamino}-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl}acetic acid methyl ester (1c). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (brs, 1H), 7.41-7.04 (m, 7H), 4.73 (m, 1H), 3.69 (s, 2H), 3.67 (s, 3H), 3.15-2.48 (m, 9H), 2.12 (m, 2H), 1.86 (m, 1H); MS (m/e), 412 (M^+, 13), 349 (11), 271 (65), 242 (47), 215 (57), 141 (100); HRMS (M^+) calcd for $C_{23}H_{25}ClN_2O_3$ 412.1554, found 412.1561.

(*R*)-6-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-6,7,8,9-tetrahydro-5*H*-carbazole-3-carboxylic acid ethyl ester (1d). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18 (brs, 2H), 7.84 (dd, J = 8.4, 1.4 Hz, 1H), 7.27 (s, 1H), 7.25-7.23 (m, 4H), 4.71 (m, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.15-3.11 (m, 3H), 3.09-2.52 (m, 6H), 2.15 (m, 1H), 1.86 (m, 1H), 1.41 (t, J = 7.2 Hz, 3H); MS (m/e), 412 (M^+, 6), 271 (65), 258 (18), 242 (19), 215 (100), 187 (33), 168 (31), 77 (41).

(*R*)-1-(3-Chlorophenyl)-2-(6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-ylamino)ethanol (1e). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82 (brs, 1H), 7.31-6.79 (m, 8H), 4.20 (m, 1H), 4.00 (m, 2H), 3.40 (m, 3H), 3.18-2.80 (m, 6H), 2.62 (m, 1H), 2.18 (m, 1H), 1.97 (m, 1H); MS (m/e), 354 (M^+, 29), 217 (13), 188 (22), 161 (100).

(*R*)-1-(3-Chlorophenyl)-2-(2,3,4,9-tetrahydro-1*H*-carbazol-3-ylamino)ethanol (1f). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (brs, 1H), 7.46-7.41 (m, 2H), 7.33-7.26 (m, 4H), 7.17-7.05 (m, 2H), 4.69 (m, 1H), 3.20-3.03 (m, 3H), 2.85-2.73 (m, 3H), 2.62-2.51 (m, 3H), 2.16 (m, 1H), 1.87 (m, 1H); MS (m/e), 342 (M^++2, 4), 340 (12), 199 (88), 170 (59), 143 (100).

(*R*)-6-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-6,7,8,9-tetrahydro-5*H*-carbazol-3-ol (1g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73 (brs, 1H), 7.41-7.03 (m, 4H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.70 (m, 1H), 3.24 (m, 1H), 3.15-3.12 (m, 2H), 2.90-2.78 (m, 2H), 2.32 (m, 1H), 2.01 (m, 1H), 1.76 (m, 1H).

(*R*)-({6-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-6,7,8,9-tetrahydro-5*H*-carbazole-3-carbonyl}amino)acetic acid ethyl ester (1j). A solution of the carboxylic acid **4** (0.36 g, 1 mmol), glycine ethyl ester hydrochloride (0.17 g, 1.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.28 g, 1.5 mmol), 1-hydroxybenzotriazole (0.16 g, 1.2 mmol), and triethylamine (0.78 mL, 2 mmol) in DMF (5 mL) was stirred at room temperature for 5 h. Ethyl acetate was added, and the mixture was washed with sat. $NaHCO_3$ solution, water, and brine. The organic solution was dried over $MgSO_4$, concentrated, and purified with column chromatography (Hex : EtOAc = 3 : 1) to give the amide **9c** (0.29 g, 66%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18 (brs, 1H), 8.09 (brs, 1H), 7.84 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.24 (d, *J* = 8.5, Hz, 1H), 7.34-7.33 (m, 5H), 5.12 (s, 2H), 4.93 (br d, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.16 (m, 1H), 3.12 (dd, *J* = 15.4, 5.4 Hz, 1H), 2.81 (m, 2H), 2.64 (dd, *J* = 15.4, 6.7 Hz, 1H), 1.95 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). The glycine amide **9c** was transformed to the arylethanolamine **1j** by following the procedure as described in the synthesis of **7a** and **1a**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.30 (brs, 1H), 7.89 (br s, 1H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.40 (m, 1H), 7.30-7.19 (m, 4H), 6.80 (br s, 1H), 4.74 (m, 1H), 4.25 (br s, 2H), 3.18-2.90 (m, 4H), 2.72 (m, 2H), 2.51 (m, 1H), 2.11 (m, 1H), 21.91 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H); HRMS (M^+) calcd for $C_{25}H_{28}ClN_3O_4$ 469.1768, found 469.1764.

(*R*)-6-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-6,7,8,9-tetrahydro-5*H*-carbazole-3-carboxylic acid phenylamide (1i). ^{1}H NMR (200 MHz, CD_3OD) δ 7.99 (brs, 1H), 7.61-7.56 (m, 3H), 7.36 (s, 1H), 7.28-7.19 (m, 6H), 7.03 (m, 1H), 4.72 (m, 1H), 3.57 (m, 1H), 3.46 (m, 1H), 3.08 (m, 3H), 2.91-2.77 (m, 5H), 2.50 (m, 1H), 2.11 (m, 1H), 1.80 (m, 1H); HRMS (M^+) calcd for $C_{27}H_{26}ClN_3O_2$ 459.1714, found 459.1711.

(*R*)-6-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-6,7,8,9-tetrahydro-5*H*-carbazole-3-carboxylic acid amide (1k). ^{1}H NMR (200 MHz, CD_3OD) δ 8.08 (d, *J* = 2.0 Hz, 1H), 1H), 7.71 (m, 1H), 7.52 (s, 1H), 7.42-7.33 (m, 4H), 4.85 (m, 1H), 3.38-2.93 (m, 10H), 2.64 (m, 1H), 2.28 (m, 1H), 2.08 (m, 1H), 1.96 (m, 1H); HRMS (M^+) calcd for $C_{21}H_{22}ClN_3O_2$ 383.1401, found 383.1400.

(*R*)-Pyrrolidine-1-carboxylic acid {6-[2-(3-chlorophenyl)-2-hydroxyethylamino]-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl}amide (1m). To a solution of DMF (0.32 mL, 4.1 mmol) in benzene (3 mL) was added thionyl chloride (0.32 mL, 4.4 mmol) at 0 °C and the solution was stirred for 10 min at room temperature. After cooling to −5 °C, the tetrahydrocarbazole carboxylic acid **4** (1.0 g, 2.75 mmol), pyridine (0.76 mL, 9.3 mmol), and sodium azide (0.61 g, 9.3 mmol) were added to the solution and the resulting suspension was stirred for 10 min, followed by additional stirring for 2 h at room temperature. The reaction mixture was poured into water, extracted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was dissolved in toluene (30 mL), heated for 10 min, and concentrated to give the isocyanate **11**, which was used for the next reaction without further purification. To a solution of isocyanate (0.2 g, 0.55 mmol) in THF (3 mL) was added pyrrolidine (0.23 mL, 2.77 mmol) and the mixture was heated for 12 h. After cooling, the mixture was partitioned between H_2O and EtOAc, and the organic layer was separated, washed with brine, dried, concentrated, and purified with column chromatography (Hex : EtOAc = 5 : 1) to give {6-[(pyrrolidine-1-carbonyl)-amino]-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl}carbamic acid benzyl ester **12b** (0.11 g, 46%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (brs, 1H), 7.40-7.35 (m, 6H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.00 (dd, *J* = 10.4, 1.6 Hz, 1H), 6.13 (s, 1H), 5.11 (s, 2H), 4.12 (m, 1H), 3.45 (m, 4H), 2.89 (dd, *J* = 15.6, 5.4 Hz, 1H), 2.68 (m, 2H), 2.38 (dd, *J* = 15.6, 7.2 Hz, 1H), 1.95 (m, 6H). The benzyl ester **12b** was transformed to the arylethanolamine **1m** by following the procedure as described in the synthesis of **7a** and **1a**: ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.31 (brs, 1H), 7.41-7.26 (m, 5H), 7.09 (m, 1H), 6.96 (m, 1H), 6.40 (s, 1H), 4.81 (m, 1H), 3.35 (m, 4H), 3.19 (m, 1H), 2.89-2.61 (m, 3H), 2.25 (dd, *J* = 15.4, 6.6 Hz, 1H), 1.92 (m, 1H), 1.79 (m, 4H), 1.67 (m, 1H).

(*R*)-N-{6-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl}methansulfonamide (1n). ^{1}H NMR (300 MHz, CD_3OD) δ 7.47 (brs, 1H), 7.35-7.28 (m, 4H), 7.22 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 1.1 Hz, 1H), 4.85 (m, 1H), 3.28 (m, 1H), 2.84 (s, 3H), 2.83-2.61 (m, 5H), 2.56 (m, 1H), 2.18 (m, 1H), 1.92 (m, 1H); HRMS (M^+) calcd for $C_{21}H_{24}ClN_3O_3S$ 433.1226, found 433.1225.

(*R*)-3-{6-[2-(3-Chlorophenyl)-2-hydroxyethylamino]-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl}propionic acid methyl ester (1o). A mixture of **4f** (0.21 g, 0.53 mmol), methyl acrylate (0.1 mL, 0.16 mmol), palladium acetate (20 mg), sodium acetate (93 mg, 1.1 mmol), and *N,N*-dimethylglycine (20 mg) in *N*-methylpyrrolidinone (5 mL) in pressure tube was heated for 12 h at 135 °C, and partitioned between saturated NH_4Cl and ethyl acetate. The organic layer was dried with $MgSO_4$, concentrated, and purified with column chromatography to give the tetrahydrocarbazole acrylate **14** (0.15 g, 72%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.15 (brs, 1H), 7.80 (d, *J* = 16.0 Hz, 1H), 7.55 (1, 1H), 7.37-7.21 (m, 7H), 6.39 (d, *J* = 16.0 Hz, 1H), 5.11 (s, 2H), 5.00 (brs, 1H), 4.14 (m, 1H), 3.80 (s, 3H), 3.09 (dd, *J* = 15.4, 5.2 Hz, 1H), 2.80 (m, 2H), 2.64 (dd, *J* = 15.4, 6.7 Hz, 1H), 2.04 (m, 2H); MS (*m/e*), 404 (M^+, 2), 296 (1), 252 (3), 91 (100). The acrylate **14** was transformd to the arylethanolamine **1o** by following the procedure as described in the synthesis of **7a** and **1a**. For the compound **1o**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.40 (s, 1H), 7.25-7.23 (m, 4H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.95 (dd, *J* = 8.2, 1.6 Hz, 1H), 4.73 (m, 1H), 3.66 (s, 3H), 3.15-2.49 (m, 13H), 2.10 (m, 1H), 1.85 (m, 1H); MS (*m/e*), 426 (M^+, 14), 285 (100), 256 (67), 229 (74), 156 (48); HRMS (M^+) calcd for $C_{24}H_{27}ClN_2O_3$

426.1710, found 426.1708.

Measurement of β_3-adrenoceptor binding affinity. To determine the binding affinity of **1a-o** on β_3-adrenoceptor, RB-HBETA$_3$ membrane was incubated with [^{125}I]-iodocyanopindolol (1.4 nM, 2000 Ci/mmol) and unlabeled ligand for 10 min at 37 °C. Propranolol (1 mM) was used to define non-specific binding. Incubation mixture was filtered over glass fiber (Wallac 140-521), washed and measured for radioactivity.

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