Preparation of Diastereomeric β-Aryloxymethylaminoalcohols Containing Nicotinic Acid Moiety and Their Binding Affinity to β_3-Adrenoreceptors

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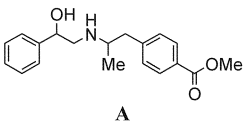
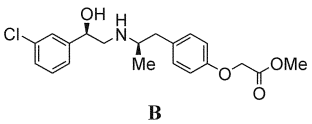
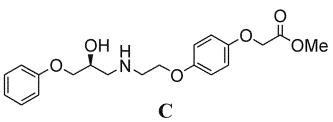
The identification of the third β-adrenergic *receptor* subtype (β_3AR) led to the *investigation* of β_3-adrenoreceptor agonists as potential agents for the treatment of various metabolic diseases.[1] Stimulation of β_3-adrenoreceptors on the surface of adipocytes evoked lipolysis and upregulation of the uncoupling protein (UCP1), which led to a net increase in energy utilization.[2,3] Thus, β_3-adrenoreceptor agonists may prove useful for the treatment of obesity.[3] In addition, the agonists have also demonstrated a direct improvement on glucose tolerance for treatment of Type II (non-insulin dependent) diabetes. Recently, many pharmaceutical companies have developed β_3-adrenoreceptor agonists, which have shown highly selective binding affinity to β_3-adrenoreceptors (**A**-**D**).[4] The literature reports have shown that the single diastereomer of β_3-adrenoreceptor agonists are often more potent or have less side effects compared to their racemates.[5] Of the numberous methods for the preparation of chiral aryl substituted β-aminoalcohols, the most direct method is alkylation of the corresponding chiral amine with arylethylene oxide.[6] However, direct alkylation in polar, protic solvents generally gave the desired products in low yields with significant amounts of regioisomer and multiply alkylated side products.[7]



A
BRL 26,830



B
BRL 3,5135



C
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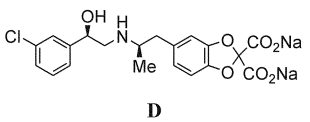


D
CL-316,243

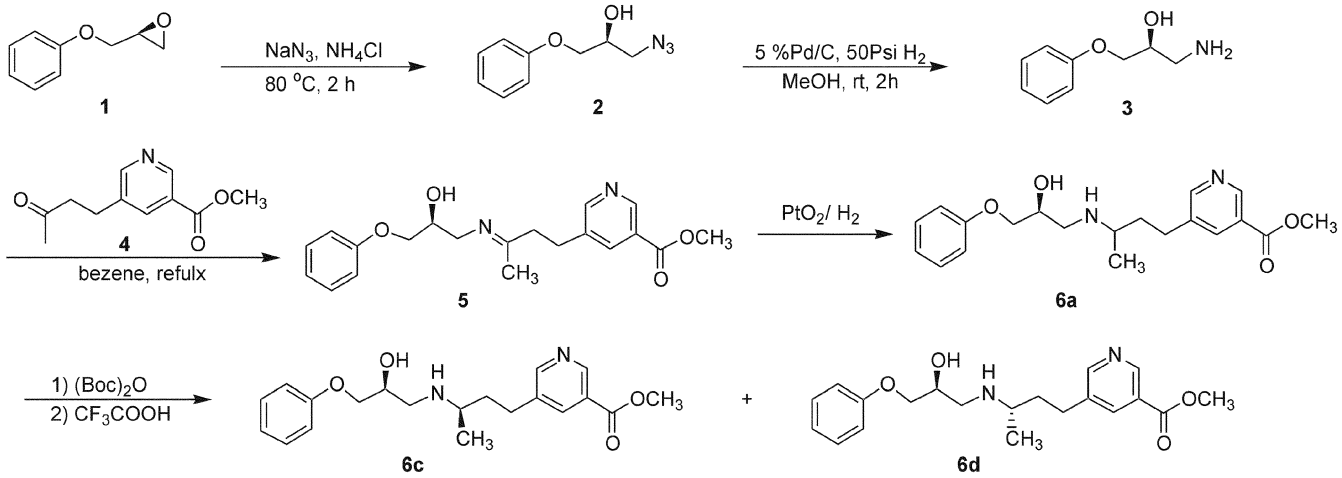
Currently, heteroarylethanolamines have also been reported to show significant β_3 agonist activity and minimal cross-reactivity at the β_1 and β_2 receptors.[8] The β-aminoalcohol could contain various heterocycles such as oxazole,[9] pyridine,[10] and indole.[11] In an effort to discover new lead compounds for β_3-adrenoreceptor agonist, we were posed with the problem of finding efficient and direct route to prepare optically pure diastereomeric β-arylaminoalcohols. We describe herein simple diastereomeric preparation of heterocyclic β-arylaminoalcohols containing nicotinic acid moiety and their binding affinity to β_3-adrenoreceptors.

Chemistry

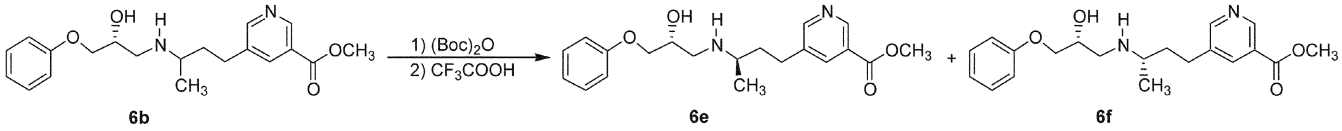
The synthetic procedures for the preparation of diastereomeric β-aminoalcohols are detailed in Scheme 1. The (*S*)-1-azido-3-phenoxypropane-2-ol (**2**) was obtained by the ring opening reaction of (*S*)-2-phenoxymethyloxirane (**1**) with NaN_3 in CH_3CN at 80 °C. The hydrogenation of 1-azido-3-phenoxypropane-2-ol (**2**) using Pd/C provided 1-amino-3-phenoxypropan-2-ol (**3**) in a quantitative yield. The 5-(3-oxobutyl)-nicotinic acid methyl ester (**4**) were prepared by palladium-catalyzed coupling reaction of 5-bromonicotinic acid methyl ester with 3-buten-2-ol in a 70-% yield.[12] The imino compound **5** was obtained by condensation of aminoalcohol **3** and ketone **4** by azeotrophic reflux in benzene. The diasteroisomeric mixture of **6a** was prepared by hydrogenation of imine **5** with PtO_2 catalyst under 60 psi hydrogen pressure in solvent. The Boc protected **6c** and **6d** were separated by MPLC with Merck Lobar RP-18 column and $CH_3CN : H_2O = 1 : 1$ as eluant. The compound **6c** and **6d** were obtained by deprotection of Boc group and neutralization. Another set of diastereomeric compounds **6e** and **6f** were also prepared by the same procedure with Scheme 1 except for (*R*)-2-phenoxymethyl-oxirane as a chiral substrate (Scheme 2). The stereochemistry of **6c**-**6f** were determined by comparison of literature spectra after ring formation to oxazolodinone with 1,1-carbonyldiimidazole.[13]

Screening Results

To determine the affinity of these β-aminoalcohols as β_3-adrenoreceptor agonists, the receptor binding assay was performed by using cell membrane expressing human β_3 adrenoreceptors (RB-HBETA$_3$).[14] The data are summarized in Table 1. Unexpectedly, the heterocyclic aminoalcohols containing nicotinic ester have shown similar binding affinities except for (*R*,*S*)-isomer **6e** which showed a quarter of the affinity compared to the other isomers.



Scheme 1



Scheme 2

Table 1. Comparison of the β_3AR Affinity of Diastereomeric β-Aminoalcohols

Entry	Compound	Configuration	IC_{50} (μM)	Ki (μM)
1	**6c**	*S,S*	1.28	0.67
2	**6d**	*S,R*	1.15	0.61
3	**6e**	*R,S*	4.57	2.41
4	6f	*R,R*	1.10	0.58
5	**BRL-35135**	*S,S*	3.62	1.91
6	**CL-316243**	*S,S*	1.17	0.62

Conclusions

The four diastereomers of heterocyclic β-aminoalcohols were easily prepared by separation of their Boc derivatives as the key step. The introduction of nicotinic acid moiety to β-aminoalcohols resulted in potent β_3-adrenergic receptor binding affinity. The nicotinic acid moiety could be a potential heterocyclic substrate for the development of β_3-adrenoreceptor agonists.

Experimental Sections

All chemicals were purchased and used without any further purifications The ^{1}H NMR spectra were obtained on a Varian Gemini 200 MHz or Bruker 300 MHz NMR Spectrometer. The GC-MS spectral were obtained on a Shimazu QP 1000 mass spectrometer. Melting points were deterimined on MU-TEM apparatus and were uncorrected. BRL-35135 and CL-316243 were prepared literature procedures[4b] and used as reference compounds.

(*S*)-2-Phenoxymethyloxirane (1)[15]. NaH (60% dispersion in mineral oil, 0.72 g, 18 mmol) was added to a solution of phenol (1.23 g, 13 mmol) in dry DMF (10 mL) and the resulting suspension was stirred for approximately 30 minutes until a clear solution was obtained. A solution of (*S*)-(+)-glycidyl 3-nitrobenzenesulfonate (3.1 g, 12 mmol) in dry DMF (7 mL) was slowly added to phenoxide solution. The mixture was stirred for 6 hours at 20 °C and poured into saturated aqueous NH_4Cl solution (50 mL). The product was extracted with ethyl ether (3×20 mL). The ethyl ether layer was dried over anhydrous $MgSO_4$ and concentrated. The (*S*)-2-phenoxymethyl oxirane was obtained 86 % yields by silica gel column chromatography.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.24 (m, 2H), 6.98-6.89 (m, 3H), 4.19 (dd, J = 10.9, 3.2 Hz, 1H), 3.93 (dd, J = 11.3, 5.6 Hz, 1H), 3.33 (m, 1H), 2.87 (t, J = 4.9 Hz, 1H), 2.73 (dd, J = 4.9, 2.6 Hz, 1H); Mass m/e (%) 150 (M^+, 26), 119 (10), 107 (35), 94 (100), 77 (50), 65 (40).

(*S*)-1-Azido-3-phenoxypropane-2-ol (2). The mixture of 0.6g (5 mmol) of (*S*)-2-phenoxymethyloxirane (**1**), 1.52 g (25 mmol) of NaN_3, and H_2O-acetonitrile (1 : 8, 9 mL) in 25 mL flask was stirred at 80 °C for 4 hours. The mixture was poured into 20 mL of cold water. The product was extracted with ethyl ether (2×20 mL). The organic layer was washed saturated NH_4Cl solution (20 mL) and water. The ethyl ether layer was dried over anhydrous $MgSO_4$ and concentrated. The (*S*)-1-azido-3-phenoxypropane-2-ol was obtained 97% yields by silica gel column chromatography.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.24 (m, 2H), 7.00-6.88 (m, 3H), 4.16 (m, 1H), 3.93 (d, J = 5.6 Hz, 1H), 3.50 (m, 1H), 2.71 (brs, 1H); Mass m/e (%) 167 (M^+, 3), 149 (4), 123 (23), 94 (100), 77 (25).

(*S*)-1-Amino-3-phenoxypropan-2-ol (3). The mixture of

(*S*)-1-azidophenoxypropane-2-ol (1.71 g, 8.9 mmol) and 5% Pd/C (0.2 g) and methanol (15 mL) in pressure bottle was hydrogenated under 60 psi of hydrogen for 4 h at room temperature. The resulting solution was filtered and concentrated. The was obtained 88% yields by silica gel column chromatography. mp 104-106 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.26 (m, 2H), 6.98-6.90 (m, 3H), 4.01-3.91 (m, 3H), 2.98 (dd, *J* = 12.8, 3.7 Hz, 1H), 2.86 (dd, *J* = 12.8, 6.4 Hz, 1H); Mass m/e (%) 193 (9, M^+), 119 (34), 107 (21), 94 (100), 77 (65), 65 (26).

5-(3-Oxobutyl)nicotinic acid methyl ester (4). To a 10-mL vial containing a magnetic stirring bar was added the following reagents; $Pd(OAc)_2$ (0.025 mmol), KOAc (1.0 mmol), LiCl (0.5 mmol), 3-buten-2-ol (1.0 mmol), methyl 5-bromonicotinate (0.5 mmol) and DMF (5 mL). The vial was sealed with a septum. The mixture was stirred at the 110 °C for 4 hours. The resulting mixture was diluted with ethyl acetate (20 mL) and washed with saturated aqueous NH_4Cl (2×20 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$ and concentrated. The product was obtained 70% yields by flash column chromatography. mp: 53-54 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.96 (d, 1H, *J* = 2.0 Hz), 8.66 (t, 1H, *J* = 2.4 Hz), 8.05 (d, 1H, *J* = 2.0 Hz), 3.87 (s, 3H), 2.89 (t, 2H, *J* = 7.4 Hz), 2.76 (t, 2H, *J* = 7.2 Hz), 2.09 (s, 3H); Mass m/e (%) 207 (13, M^+), 164 (75), 150 (14), 132 (32), 104 (24), 77 (14), 43 (100).

5-[3-(2-Hydroxy-3-phenoxypropylamino)butyl]nicotinic acid methyl ester (6a). A mixture of (*S*)-1-amino-3-phenoxypropan-2-ol (**3**) (1.0 mmol), 5-(3-oxobutyl)nicotinic acid methyl ester (**4**) (1.0 mmol), molecular sieve (2 g) and benzene (20 mL) in 50 mL flask was heated under azeotropic reflux for 20 hours. The resulting solution was filtered and concentrated. The 5-[2-(2-hydroxy-3-phenoxypropylimino)propyl]nicotinic acid methyl esters (**5**) was obtained 80% yields as oil. The crude imine (**5**) and PtO_2 (50 mg) were added to methanol (15 mL) in pressure bottle. The mixture was hydrogenated under 70 psi hydrogen for 4 h at room temperature. The resulting solution was filtered and concentrated. The aminoalcohol (**6a**) was obtained 63% yields by silica gel column chromatography. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.02 (d, 1H, *J* = 2.0 Hz), 8.60 (t, 1H, *J* = 2.0 Hz), 8.11 (d, 1H, *J* = 2.4 Hz), 7.24 (t, 2H, *J* = 8.0 Hz), 6.89-6.87 (m, 3H), 4.15-3.91 (m, 3H), 3.88 (s, 3H), 3.63 m, 2H), 2.89-2.70 (m, 5H), 1.86-1.67 (m, 2H), 1.19-1.16 (m, 3H); Mass m/e (%) 359 (100, M^{+1}), 332 (12), 181 (6), 149 (12), 111(13), 96 (14), 68 (13), 55 (12), 44 (37).

Separation of Boc protected 6c and 6d. 5-[3-(2-Hydroxy-3-phenoxypropylamino)butyl]nicotinic acid methyl ester (**6a**, mmol) and $(Boc)_2O$ were dissolved in 20 mL of CH_2Cl_2. The reaction mixture was stirred about 12 h at room temperature. The Boc protected **6a** was obtained quantitatively by concentration. The Boc protected diastereomers of **6c** and **6d** were separated by MPLC with Merck Lobar RP-18 column (440×37 mm, #10626) and $CH_3CN : H_2O$ = 1 : 1 eluent (UV-254 nM and 10 mL/min). The diastereoselectivity of **6c** and **6d** (44 : 56) was determined by HPLC with Waters Spherisor S 10 ODS2 (250×4.6 mm, #PS832515) and $CH_3CN : H_2O$ = 1 : 1 eluent (UV-254 nM and 1.0 mL/min). Boc-protected **6c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.05 (d, *J* = 2.0 Hz, 1H), 8.60 (d, 1H, *J* = 2.2 Hz), 8.10 (t, *J* = 2.0 Hz, 1H), 7.30-7.22 (m, 2H), 6.90-6.85 (m, 3H), 4.90 (brs, 1H), 4.13-4.02 (m, 4H), 3.91 (s, 3H), 3.42 (brs, 2H), 2.67 (t, *J* = 7.9 Hz, 2H), 1.94 (m, 1H), 1.77 (m, 2H), 1.47 (s, 9H), 1.21 (d, 3H, *J* = 6.4 Hz). Boc-protected **6d**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.06 (d, *J* =1.8 Hz, 1H), 8.58 (d, 1H, *J* = 1.8 Hz), 8.10 (t, *J* = 1.8 Hz, 1H), 7.26 (t, 2H, *J* = 6.8 Hz), 6.90 (m, 3H), 4.90 (brs, 1H), 4.20-3.91 (m, 4H), 3.91 (s, 3H), 3.42 (brs, 2H), 2.67 (t, *J* = 7.9 Hz, 2H), 1.94 (m, 1H), 1.77 (m, 2H), 1.47 (s, 9H), 1.21 (d, 3H, *J* = 6.4 Hz).

(*S,S*)-5-[3-(2-Hydroxy-3-phenoxypropylamino)butyl]-nicotinic acid methyl ester (6c). The Boc-protected **6c** (1 mmol) was dissolved in CH_2Cl_2 (10 mL). The trifluoroacetic acid (5 eqiuv) was added to the solution. The reaction mixture was stirred for 12 h at room temperature and neutralized with saturated Na_2CO_3 solution. The organic layer was separated and concentrated. The compound **6c** was obtained 85% yields as oil by silica gel column chromatography. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.96 (d, *J* =1.8 Hz, 1H), 8.53 (d, 1H, *J* = 1.8 Hz), 8.04 (t, *J* = 1.8 Hz, 1H), 7.26 (t, 2H, *J* = 6.8 Hz), 6.85 (m, 3H), 4.01-3.89 (m, 3H), 3.86 (s, 3H), 2.85-2.62 (m, 7H), 1.67 (m, 2H), 1.47 (s, 9H), 1.08 (d, *J* = 6.3 Hz, 3H); Mass (*m/e*) 358 (8, M^+), 221 (100), 194 (27).

(*S,R*)-5-[3-(2-Hydroxy-3-phenoxypropylamino)butyl]-nicotinic acid methyl ester (6d). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.97 (d, *J* = 2.0 Hz, 1H), 8.54 (d, 1H, *J* = 2.0 Hz), 8.04 (t, *J* = 2.2 Hz, 1H), 7.24-7.16 (m, 2H), 6.91-6.80 (m, 3H), 4.03-3.83 (m 3H), 3.87 (s, 3H), 2.97-2.60 (m, 7H), 1.68 (m, 2H), 1.08 (d, *J* = 6.3 Hz, 3H); Mass (*m/e*) 358 (5.6, M^+), 221 (100), 194 (29).

(*R,S*)-5-[3-(2-Hydroxy-3-phenoxypropylamino)butyl]-nicotinic acid methyl ester (6e). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.97 (d, *J* =2.0 Hz, 1H), 8.54 (d, 1H, *J* = 2.0 Hz), 8.04 (t, *J* = 2.2 Hz, 1H), 7.24-7.16 (m, 2H), 6.91-6.80 (m, 3H), 4.03-3.83 (m, 3H), 3.87 (s, 3H), 2.97-2.60 (m, 7H), 1.68 (m, 2H), 1.08 (d, *J* = 6.3 Hz, 3H); Mass (m/e) 359 (70, M^{+1}), 221 (100), 194 (30.1).

(*R,R*)-5-[3-(2-Hydroxy-3-phenoxypropylamino)butyl]-nicotinic acid methyl ester (6f). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.96 (d, *J* =1.8 Hz, 1H), 8.53 (d, 1H, *J* = 1.8 Hz), 8.04 (t, *J* = 1.8 Hz, 1H), 7.26 (t, 2H, *J* = 6.8 Hz), 6.85 (m, 3H), 4.01-3.89 (m, 3H), 3.86 (s, 3H), 2.85-2.62 (m, 7H), 1.67 (m, 2H), 1.47 (s, 9H), 1.08 (d, *J* = 6.3 Hz, 3H); MS (*m/e*), 359 (68.0, M^{+1}), 221 (100), 194 (25.3).

Measurement of β-adrenoceptor binding affinity. To determine the binding affinity of **6c-6f** on β_3-adrenorecetor, RB-HBETA3 membrane was incubated with [^{125}I]-iodocyanopindolol (1.4 nM, 2200 Ci/mmol) and unlabeled ligand for 10 min at 37 °C. Propranolol (1mM) 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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