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Novel Substituted 4-Aminomethylpiperidines as Potent and Selective Human β_3-Agonists. Part 1: Aryloxypropanolaminomethylpiperidines

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Abstract—The synthesis and SAR of a series of human β_3 adrenoreceptor agonists based on a template derived from a common pharmacophore coupled with 4-aminomethylpiperidine is described. Potent and selective agents were identified such as **26** that was in vitro active in CHO cells expressing human β_3-AR ($EC_{50} = 49$ nM, IA = 1.1), and in vivo active in a transgenic mouse model.

Stimulation of β_3 adrenoreceptors (AR), expressed on the cell surface of adipocytes in brown and white adipose tissue, is viewed as a potential treatment for obesity and non-insulin-dependent diabetes mellitus. Agonists of the β_3-AR activate an intracellular signaling process to initiate the lipolysis of triglycerides.[1] The resulting free fatty acids are processed by uncoupling protein (UCP) leading to thermogenesis.

The first generation of potent rat β_3-AR selective agonists was reported to show antiobesity and antihyperglycemic effects in animal models. One such clinical candidate[2] CL-316,243 was found to be 100- to 1000-fold less active at the human β_3-AR. Thus the rat β_3-AR did not effectively predict activity at the human β_3-AR.

An in vitro assay to more accurately predict activity at the human receptor has been developed employing the use of cloned chinese hamster ovary cells (CHO cells) expressing human β-AR's.[3] An increase in cAMP levels generated from stimulation of the human β_3-AR by an agonist is determined as a measure of lipolysis. Themogenesis is determined in an in vivo model using transgenic mice expressing the human β_3-AR.[4] An increase in themogenesis in these mice is compared to values determined in β_3-AR knockout mice (KO) expressing no β_3-AR. Compounds showing thermogenesis only in the mice with human β_3-AR are selective human β_3-AR agonists.

A program at Wyeth was established to develop a second generation of agonists selective to the human β_3-AR but devoid of agonism or antagonism at β_1-AR and β_2-AR. The template shown in Figure 1 was designed as a hybrid of a common pharmacophore[5] of β-AR binding ligands and 4-amino-methylpiperidine for the development of human β_3-AR agonists. The piperidinyl nitrogen provided a synthetically easy scaffold upon which to rapidly explore a variety of different substitutions without the introduction of a second chiral center.

Variations to the aryl moiety (Ar) and the R group were planned to find the optimal substituents to meet the program goals. Aryloxypropanolamines of Figure 1 are prepared by regiospecific ring opening of a chiral epoxide with a substituted aminomethylpiperidine in methanol at 60 °C overnight as shown in Scheme 1.

A variety of chiral epoxides were synthesized. The epoxide **1** of Scheme 2 was prepared by alkylation of (2*S*)-(+)-oxiranylmethyl-3-nitrobenzenesulfonate with 4-hydroxycarbazole[6] over potassium carbonate in 2-butanone.

A series of *t*-butyldiphenylsilyl (TBDPS) protected epoxides **2b**, **3b**, and **4b** was prepared by the reaction of

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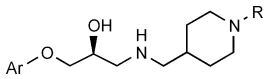
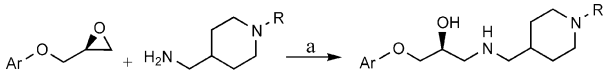
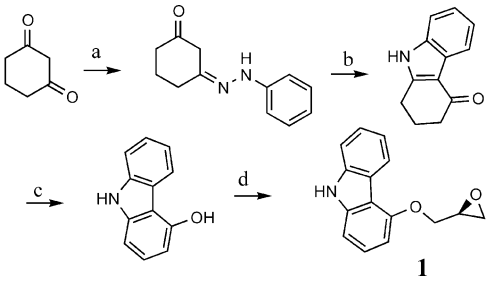


Figure 1. Aminomethylpiperidine template for development of β_3 aderenoreceptor agonism.



Scheme 1. (a) Methanol, 60 °C, 18 h, (25–55%).

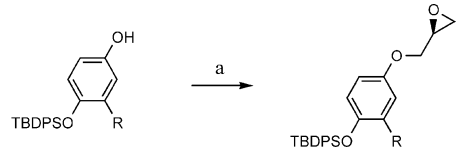


Scheme 2. (a) H_2O, $PhNHNH_2$ 91%;2 (b) trifluoroacetic acid (TFA), reflux, 65%; (c) 10% Pd/C mesityline, reflux, 46%; (d) (2*S*)-(+)-oxiranylmethyl-3-nitrobenzenesulfonate, K_2CO_3, 2-butanone, reflux,

mono-protected bis-phenolic precursors **2a**, **3a** and **4a** with *R*-(+)-glycidol under Mitsunobu[7] conditions as shown in Scheme 3.

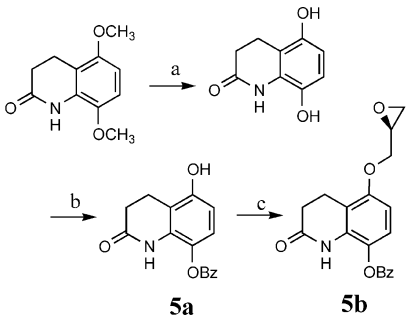
A similar approach was used in the preparation of **5b** from mono-benzyl protected **5a** as shown in Scheme 4.

Mitsunobu conditions were also used to form the chiral epoxides **6** and **7**. As outlined in Scheme 5 the epoxide is attached prior to the benzimidazole formation, a slight variation of literature conditions.[8] The 4-hydroxy-oxindole of Scheme 6 was prepared by literature conditions.[9]

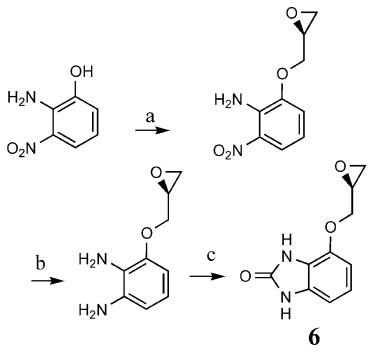


2a: R = H, **3a** R = F, **4a** R = $NHSO_2CH_3$ **2b**: R = H, **3b** R = F, **4b** R = $NHSO_2CH_3$

Scheme 3. (a) Ph_3P, diethylazodicarboxylate (DEAD), *R*-(+)-glycidol, (56–70%).



Scheme 4. (a) 40% HBr, 80%; (b) K_2CO_3, benzyl bromide, acetone, 27%; (c) (2*S*)-(+)-oxiranylmethyl-3-nitrobenzenesulfonate, K_2CO_3, 2-butanone, 82%.

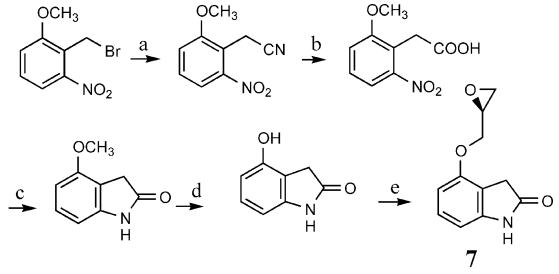


Scheme 5. (a) *R*-(+)-glycidol, Ph_3P, DEAD, 30%; (b) RaNi, H;2 (c) phosgene, DIEA, 69% for steps b and c.

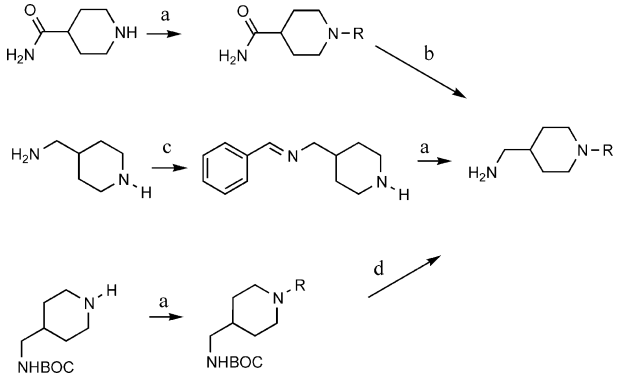
The R substitutions of Figure 1 were obtained via alkylation of one of three intermediates (amide, imide[10] or Boc) outlined in Scheme 7 with RX (R = aryl, alkyl, acyl, sulfonyl, X = halogen) in the presence diisopropylethyl amine (DIEA). When R = carbamoyl, compounds were prepared by reaction with an isocyanate.

A more specific series of analogues where R = 4-ureidobenzenesulfonyl was synthesized from two convergent routes. Starting from either the Boc protected piperidine **8** or aniline **9** depending upon the availability of precursors the target molecules **15** were prepared as outlined in Scheme 8.

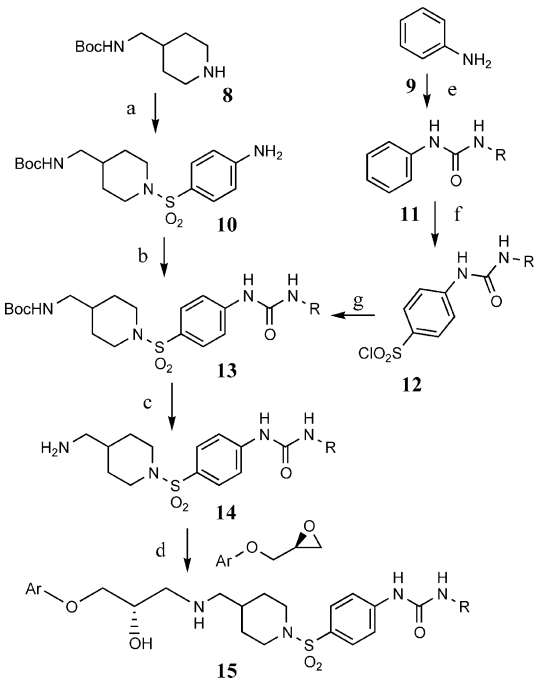
Specifically, sulfonylation of **8** gave the core intermediate structure **10**. The conversion of the anilino function of **10** into a ureido group was conveniently



Scheme 6. (a) NaCN, EtOH aq., 99%; (b) HCl, H_2SO_4, 97%; (c) H_2, 10% Pd/C, 97%; (d) 48% HBr, 73%; (e) *R*-(+)-glycidol, Ph_3P, DEAD, 53%.



Scheme 7. (a) RX, DIEA THF, (50–90%); (b) B_2H_6 or $LAH_,$ THF, 30–75%; (c) PhCHO, Dean-Stark trap, toluene;[10] (d) 2 N HCl, dioxane, 80–95%.



Scheme 8. (a) 4-aminobenzenesulfonyl chloride, DIEA, THF, 82%; (b) RNCO, dioxane (or triphosgene and RNH_2); (c) HCl dioxane (d) chiral epoxides **1**–**7**, MeOH, (TBAF to remove TBDPS if necessary); (e) RNCO, dioxane (or triphosgene and RNH_2); (f) chlorosulfonic acid, 70%; (g) 4-bocaminomethylpiperidine, DIEA, THF, 95%.

carried out either from reaction with triphosgene and a second amine or by treatment with a substituted isocyanate to give **13**. The same conditions were applied to the preparation of **11** from **9**. In the case of **11**, the sulfonyl chloride was installed by treatment with chlorosulfonic acid in a regiospecific fashion to give **12**. Thus the piperidine **8** was sulfonylated with **12** to give the common intermediate to both routes **13**. Deprotection of **13** to the free amine **14** followed by reaction with a chiral epoxide provided the target molecules **15**.

Full experimental details for the compounds in the schemes reported above and following tables are available in the published patent application.[12]

A series of analogues was prepared to develop a SAR of a variety of functional groups at the R position of Figure 1. The aryl group was held constant (Ar = 4-carbazolyl a moiety that is present in the beta blocker Carazolol, which also shows activity as an agonist at the human β_3-AR). The in vitro agonist activity at the human β-AR's, expressed as EC_{50}'s and the intrinsic activity versus isoproterenol, for the various R variations are shown in Table 1.

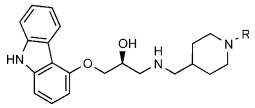
In general the compounds containing the carbazole moiety showed good selectivity for β_3-AR over the other β-AR's. The analogues **16**–**23** showed partial to complete agonism for the β_3-AR with EC_{50}'s in the submicromolar range. The most potent compound **21** (EC_{50} = 48 nM, IA = 0.62) was found to be significantly less active as an antagonist[11] relative to the beta blocker Carazolol: (1000-fold less at the β_1-AR and 25-fold less at β_2-AR). However, no compound containing the carbazole moiety showed any in vivo activity in the transgenic mouse model described earlier. As a result, further SAR development was focused on related analogues of **21**.

Substitutions to **15** were approached in a stepwise fashion with aryl functions other than the carbazole. The 4-hyroxyphenyl group, known to be active in related series, was chosen as a preferable aryl group from which to optimize the ureido function. A variety of ureas were prepared as outlined in Scheme 8. The results are tabulated in Table 2.

Compounds **25**–**32** were fully efficacious with a wide selectivity over the other β-AR's. Compound **26** was the most in vivo active compound with an increase in thermogenesis in the β_3 transgenic mice of $30 \pm 14\%$ at an ip dose of 10 mg/kg. The two of the more active uredio groups, octyl in **26** and 2,5-difluorobenzyl in **30**, were held constant and the variety of other aryl groups were evaluated. These results are tabulated in Table 3.

The most potent Ar replacement compound was **35** showing potent in vitro activity (EC_{50} = 1 nM, IA = 1.0) with greater than 300-fold selectivity over β_1-AR and

Table 1. In vitro agonist activity at human β-AR's for R variations[b]



Compd	R	β_3 EC_{50} nM[a] (IA)	β_1 EC_{50} nM[a] (IA)	β_2 EC_{50} nM
16	3,3,3-Trifluoropropyl	187 (0.99)	417 (0.13)	> 1000
17	Propyl	870 (0.56)	nt[d]	nt[d]
18	Isopropyl	290 (1.06)	nt[d]	nt[d]
19	Pentyl	319 (0.43)	nt[d]	nt[d]
20	Hexyl	665 (0.79)	> 1000	> 1000
21	4–Hexylureido–$C_6H_4SO_2$–	48 (0.62)	> 1000 (0.08)	> 1000
22	2-Naphthyl–SO_2–	380 (0.49)	nt[d]	nt[d]
23	3-(HOOC)–C_6H_4NHCO–	70 (0.29)	> 1000 (0.05)	> 1000
24	3-CF_3-2-pyridyl	ia[c]	nt[d]	nt[d]

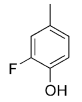
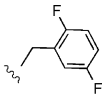
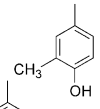
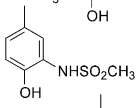
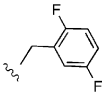
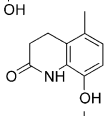
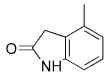
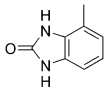
[a]β-AR agonist activities are expressed as EC_{50} values by a measurement of cAMP levels in CHO cells expressing human β-ARs.
[b]Intrinsic activity (IA) was determined as the maximal response of the compound divided by the maximal response of isoproterenol at 10 mM.
[c]ia = inactive.
[d]nt = not tested.

Table 2. In vitro agonist activity at human β-AR's for R variations of **15** when Ar = 4-HO-phenyl

Compd	R	β_3 EC_{50} nM (IA)	β_1 EC_{50} nM (IA)	β_2 (IA)
25	Hexyl	58 ± 10 (0.83)	10,900 (0.28)	0.2
26	Octyl	49 (1.1)	887 (0.16)	0.02
27	Phenyl	135 (0.83)	489 (0.38)	0
28	Cyclohexyl	60 (1.1)	1015 (0.29)	0
29	Isobutyl	126 (0.9)	nt	nt
30	2,5-DiF-benzyl	29 (0.82)	1010 (0.24)	0
31	3-(2-Thienyl)propyl–	20 (0.95)	2050 (0.62)	0
32	2-Pyridyl–	26 (0.92)	(0.18)	0.01

See footnotes for Table 1.

Table 3. In vitro agonist activity at human β-AR's for Ar and R variations of **15**

Compd	Ar	R	**β-3** EC_{50} nM (IA)	**β-1** EC_{50} nM (IA)	β−**2** EC_{50} nM (IA)
33			45 (0.83)	525 (0.19)	(0)
34		Octyl	306 (0.82)	nt	nt
35			1 (1.0)	353 (049)	454 (0.7)
36		Octyl	5 (0.91)	390 (0.63)	680 (0.26)
37		Octyl	55 (052)	nt	nt
38		Hexyl	10 (0.53)	nt	nt

See footnotes for Table 1.

over 400-fold selectivity over β_2-AR. Compound **35** was also in vivo active with an increase in thermogenesis of 18 + 2% at an ip dose of 10 mg/kg. Compound **35** however showed an increase in antagonistic activity at β_1-AR and β_2-AR when compared to **26**. (IC_{50} = 27 nM versus 6156 nM at β_1-AR and IC_{50} = 4 nM vs 268 nM at β_2-AR). The oxindole **37** and benzimidazole **38** analogues had low EC_{50}'s but the IA fell to around 50% of isoproterenol. Compounds **37** and **38** also demonstrated antagonism at β_1-AR and β_2-AR.

In conclusion, most analogues of the aryloxypropanol aminomethylpiperidines of Figure 1 were identified as in vitro potent and selective β_3-AR agonists. Compounds **26** and **35** also induced thermogenesis in the in vivo model and are potentially useful as antiobesity and antihyperglycemic agents in humans.

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5. (a) β_3-AR active compounds share a common pharmacophore as reported by Mejean A.; Guillaume, J.-L.; Strosberg, A. D. *Eur. J. Pharm.* **1995**, *291*, 359. (b) A subset of compounds based on this template has been published by Bovy, P. R.; Cecchi, R.; Venier, O. Int. Pat. Appl. WO 0144227, 2001. *Chem. Abstr.* **2001**, *135*, 46110, Cecchi, R. Int. Pat. Appl. WO0143744, 2001, *Chem. Abstr.* **2001**, *135*, 46105 and Cecchi, R.; Croci, T.; Guzzi, U.; Marsault, E. Int. Pat. Appl. WO 9965895 1999, *Chem Abstr.* **1999**, *132*, 35618.
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11. Selected compounds were evaluated as antagonists in a binding assay using CHO cells transfected with human β_1-AR or β_2-AR. IC_{50} values were determined by incubation of the test compound, at various concentrations, and the radioligand [^{125}I]iodocyanopindolol with these cells.
12. For full experimental details see. Steffan R. J.; Ashwell M. A.; Solvibile W. R.; Matelan, E. US21875300P, application submitted July 17, 2000.