Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 2963–2967

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Novel Substituted 4-Aminomethylpiperidines as Potent and Selective Human β_3-Agonists. Part 2: Arylethanolaminomethylpiperidines

Robert J. Steffan,[a,*] Mark A. Ashwell,[a] William R. Solvibile,[a] Edward Matelan,[a] Elwood Largis,[b] Stella Han,[b] Jeffery Tillet[b] and Ruth Mulvey[b]

[a]*Chemical Sciences, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, USA*
[b]*Cardiovascular/Metabolic Diseases, Wyeth Research, 500 Arcola Rd, Collegeville, PA 19426, USA*

Received 13 March 2002; accepted 1 July 2002

Abstract—The synthesis and SAR of a series of β_3 adrenoreceptor agonists based on a novel template derived from 4-aminomethylpiperidine coupled with a common pharmacophore, arylethylamine, is described. This combination led to the identification of human β_3 adrenoreceptor agonists with in vivo activity 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[1] of the β_3-AR activate an intracellular signaling process in which initiates lipolysis of triglycerides. The resulting free fatty acids are processed by uncoupling protein (UCP) leading to thermogenesis.

Early efforts by our group in the β_3-AR agonist program at Wyeth identified selective agonists to human β_3-AR which were based on a hybrid template of chiral aryloxypropanolamines, common to β-AR antagonists, and 4-aminomethylpiperidines.[2] These compounds were found to be potent in vitro compounds to CHO cells transfected with the human β_3 adrenoreceptor. They were also selective over the other β-AR's but showed low bioavailability and metabolic cleavage of the aryl ether bond when incubated with human microsomes in the presence of NADH.

With the desire to prepare more metabolically stable analogues and improve bioavailability, our recent synthetic efforts have focused on modifying the aryloxypropanolaminomethylpiperidine template to the arylethanolaminomethylpiperidine template as shown in Figure 1. The metabolically unstable arylmethoxy linkage of the aryloxyaminomethylpiperidines was replaced by a direct bond.

Variations to the aryl moiety and the R-group were prepared to find the optimal substitutents for β_3-AR agonism while at the same time maintain the good selectivity over the other β AR's seen in the earlier aryloxypropanolaminomethylpiperidines.[1] The arylethanolaminomethylpiperidines of Figure 1 were prepared by reductive amination of a chiral arylethanolamine with a 4-formylpiperidine optimally substituted at the 1 position (Scheme 1).

The arylethanolamines were prepared as outlined in Schemes 2–4. The 4-hydroxy-3-methansulfonamidophenyl analogue **4** was prepared starting from the optimally substituted acetophenone **1**. Chlorination with benzyltrimethylammonium tetrachloroiodate[3] gave almost exclusively the monochlororinated intermediate **2**. Selective reduction with borane in the presence of (*R*)-2-methyl-CBS-oxazaborolidine[4] in THF gave the chiral alcohol **3.** The chlorine was then converted to the azide by treatment with sodium azide and sodium iodide in DMF. Hydrogenation of the azide provided the chiral phenethanolamine **4**.

The achiral indole **8** was prepared using literature conditions[5] from **5**, obtained by Friedel–Crafts reaction of

*Corresponding author. Fax: +1-484-865-9398; e-mail: steffar@wyeth.com

0960-894X/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0960-894X(02)00608-X

1-acetylindoline with chloroacetylchloride. The diacyl-*N*-benzyl compound **6** was deprotected with soduim hydroxide to give the intermediate **7**. Sequential oxidation with manganese dioxide followed by hydrogenation over palladium on carbon provided the arylethanolamine **8**.

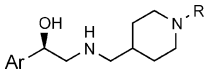
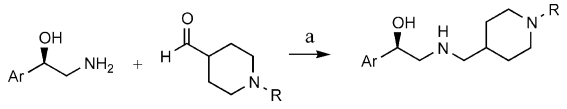
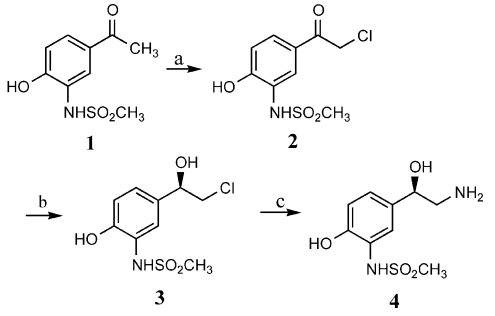


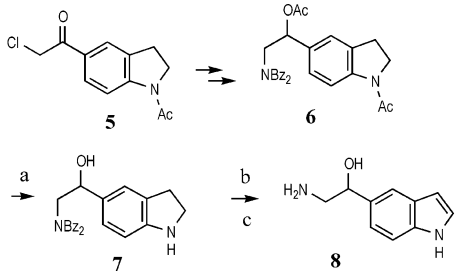
Figure 1. Aminomethylpiperidine template for development of β_3 aderenoreceptor agonism.



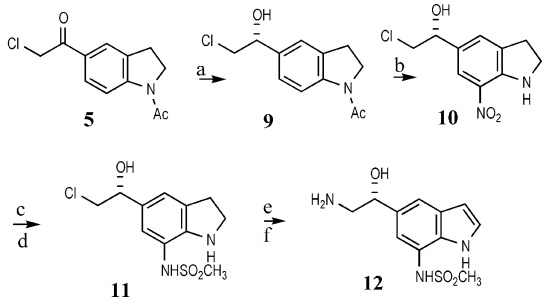
Scheme 1. (a) MeOH, HOAc, $NaCNBH_3$, (10–60%).



Scheme 2. (a) $C_6H_5CH_2N(CH_3)_3,^+ ICl_4^-$, 63%; (b) *(R+)*-2-methyl-CBS-oxazolborolidin, borane, 95%, 99% ee; (c) NaN_3, NaI, H_2, Pd/C, 96%.



Scheme 3. (a) NaOH, 90%; (b) MnO_2, THF, 95%; (c) H_2, 10% Pd/C, ethanol, 25%.

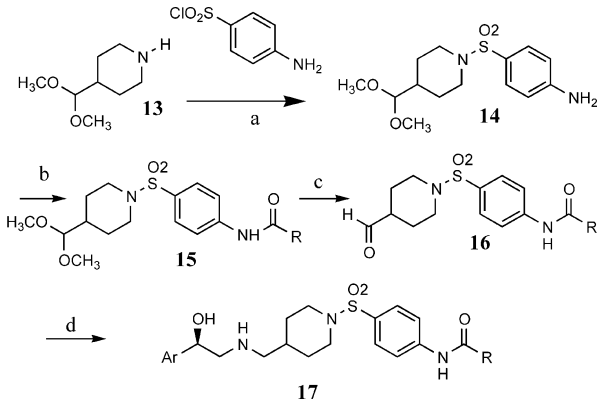


Scheme 4. (a) (*R*)-2-methyl-CBS-oxazoborolidine, borane, 33%, 92% ee; (b) $NaNO_3$, TFA, 40%; (c) H_2, Pd/C, 88%; (d) CH_3SO_2Cl, DIEA; (e) NaN_3, NaI, H_2, Pd/C; (f) MnO_2, 24% for steps d, e, and f.

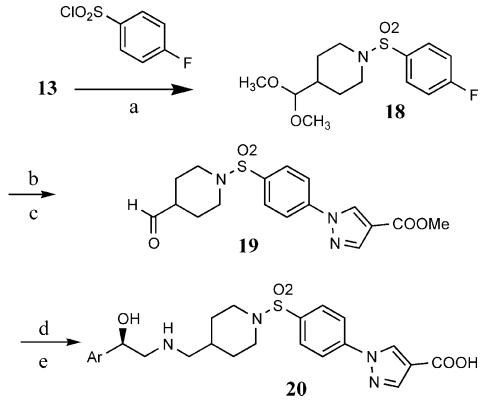
The synthesis of the intermediate **12**, a related analogue of **4**, is outlined in Scheme 4. Selective reduction of **5** with borane in the presence of (*R*)-2-methyl-CBS-oxazaborolidine[4] in THF gave the chiral alcohol **9**. Selective nitration of **9** to give **10** was accomplished by reaction with sodium nitrate in trifluoroacetic acid.[6] Reduction of the nitro group followed by sulfonylation with methansulfonyl chloride gave **11**. The chloro of **11** was converted to the azide with sodium azide and reduced by hydrogenation to provide the intermediate arylethanolamine **12**.

A variety of benzenesulfonamides substituted with a ureido function was prepared starting from the acetal of 4-formylpiperidine **13** as outlined in Scheme 5. Following sulfonylation, the intermediate **14** could be functionalized to the urea by reaction with triphosgene and a second amine or by treatment with a substituted isocyanate to give **15.** Deprotection was accomplished by either treatment with TFA of formic acid. The resulting formylpiperidine **16** was coupled with the intermediate arylethanol amines by reductive amination to give compounds represented by the template **17**.

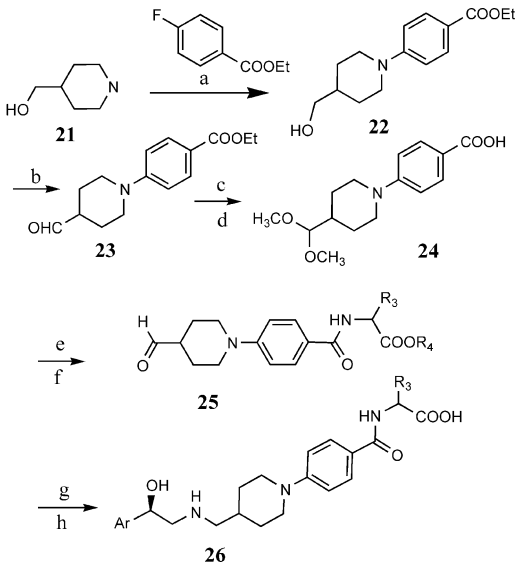
In place of ureido substituents, benzene sulfonamides substituted in the 4 posistion with heterocyles such as indoles or pryazoles were prepared from the 4-F analogue



Scheme 5. (a) THF, DIEA, 90%; (b) triphosgene, RNH_2 or RR^1NH, dioxane; (c) TFA (or HCOOH); (d) HOAc, $NaCNBH_3$, 25–50% for steps b and c.



Scheme 6. (a) THF, DIEA, 95%; (b) KH, ethyl pyrrole-4-carboxylate, DMF 118 °C; 18 h, 20%; (c) TFA (or HCOOH), 24%; (d) HOAc, $NaCNBH_3$,, MeOH, 30%; (e) NaOH aq, reflux, 65%.



Scheme 7. (a) K_2CO_3, CH_3CN reflux, 50%; (b) IBX, DMSO, 50 °C, 87%; (c) trimethylorthoformate, MeOH; (d) NaOH, 62% for steps b and c; (e) DIEA, amino acid, THFC; (f) TFA, (25–28%) for steps e and f; (g) HOAc, $NaCNBH_3$, MeOH; (h) deprotection of R_4.

19 as outlined in Scheme 6. The acetal of 4-formylpiperidine was sulfonylated with 4-fluorobenzenesulfonyl chloride to provide the intermediate **18**. The fluorine can be smoothly substituted by the potassium salt of the nitrogen heterocycle in DMF at 118 °C to provide the intermediate 4-hetero analogues like **19**.

Also prepared were indole-4-carboxylic acid and indole-2-acetic acid by the route in Scheme 6.

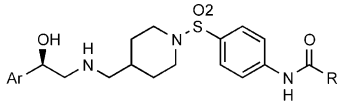
In another series of compounds, the sulfonamide moiety was replaced by a direct bond. Optimal substitution was accomplished using the 4-COOH template **24** as shown in Scheme 7. The intermediate **24** was obtained by first reaction of 4-hydroxymethylpiperidine with ethyl 4-fluorobenzoate at reflux in acetonitrile over potassium carbonate to provide upon oxidation with IBX[7] the aldehyde **23**. Following acetal formation, the acid moiety of **24** was funtionalized to a variety of such as the amides shown in template **26**.

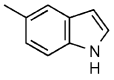
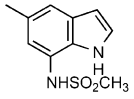
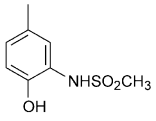
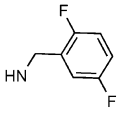
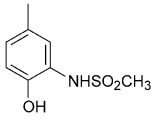
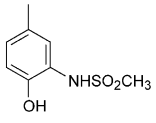
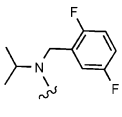
Full experimental details for the compounds in the schemes reported above and following tables are available in the published patent application.[8]

A series of analogues was prepared to develop an SAR of a variety of functional groups at the R and Ar positions of Figure 1. The first series of compounds focused on ureido substitutions previously identified in the aryloxypropanolaminomethylpiperidine series as an optimal substituion pattern. Aryl variations were minimal (Table 1).

When Ar was 4-hydroxy-3-methanesulfonylphenyl (**17 c–e**), all the compounds were were full agonists of the β_3-AR (IA's from 0.93 to 1.0) with good potency (EC_{50}'s from 5 to 27 nM). The compounds however showed little separation of activity from β_2-AR.

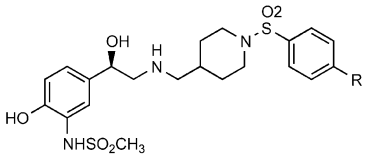
Table 1. In vitro agonist activity at human β-AR's for Ar and R variations of template **17**

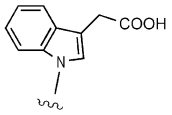
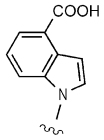
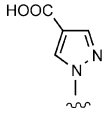


Compd	Ar	R	**β-3** EC_{50} nM (IA)	**β-1** EC_{50} nM (IA)	**β-2** EC_{50} nM (IA)
17a		NHoctyl	ia[a]	nt[b]	nt
17b		NHoctyl	ia	nt	nt
17c			5 (0.93)	3160 (049)	30 (0.73)
17d		Octyl	6 (1.0)	730 (0.56)	30 (0.7)
17e			27 (093)	6300 (1.21)	12 (0.89)

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

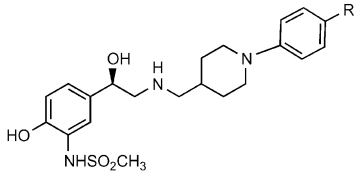
Table 2. In vitro agonist activity at human β-AR's for R variations



Compd	R	β_3 EC_{50} nM (IA)	β_1 EC_{50} nM (IA)	β_2 EC_{50}nM (IA)
27		11 (0.96)	30 (0.86)	30 (0.81)
28		9 (1.0)	50 (1.0)	60 (0.76)
29		43 (0.93)	1000 (0.16)	10 (0.34)
30	NH(C=O)Phe	31 (1.2)	520 (0.6)	20 (0.77)

See footnote for Table 1.

Table 3. In vitro agonist activity at human β-AR's for R variations of template



Compd	R	β_3 EC_{50} nM (IA)	β_1 EC_{50} nM (IA)	β_2 (IA)
31	–(C=O)Asp	6 (0.95)	580 (0.64)	5 (0.34)
32	–(C=O)Phe	31 (1.2)	520 (0.60)	20,000 (0.77)
33	–(C=O)Leu	10 (1.0)	1860 (0.68)	1000 (0.38)

See footnotes for Table 1.

The next series of analogues included benzenesulfonamides substituted with heterocycles and amino acids combined with the optimal aryl group where Ar = 4-hydroxy-3-methansulfonylphenyl. These analogues demonstrate some separation of activity between β_3-AR and β_2-AR as shown in Table 2.

Compounds retained reasonable potency and agonistic effects at the β_3-AR. A reasonable separation of activity was also noted in compound **29** for both β_1-AR and β_2-AR.

The best separation of activity was noted in the series of amino acid compounds where the sulfonamide was replaced with a direct bond. The results are tabulated in Table 3.

The compounds prepared were also evaluated in vivo using transgenic mice containing the human β_3-AR and β_3-AR knockout mice.[9] Compound **17d** showed an increase in themogenesis of $10 \pm 5\%$.

In conclusion, development of SAR around the arylethanolaminomethylpiperidine template of Figure 1 provided several in vitro potent compounds. Compounds that contained the 4-hydroxy-3-methanesulfonylphenyl moiety were most active with EC_{50}'s in the 5–45 nM range with full agonism to the β3-AR. Most of these analogues had significant β_2-AR agonism except compounds **29** and the direct bond analogues **31**–**33**. All of the analogues prepared had weak antagonistic activity[10] at β_1-AR and β_2-AR when compared to traditional beta blockers such as propanolol. The K_i's ranged from 240 nM for **27** and 6600 nM for the in vivo active **17d** at β_1-AR and 180 nM for **27** to 140 nM for **17d** at β_2-AR. The potent and selective agonists prepared have a potential use as antiobesity and antihyperglycemic agents in humans.

References and Notes

1. (a) Dow, R. L. *Exp. Opin. Invest. Drugs* **1997**, *6*, 1811. (b) Strosberg, A. D. *Annu. Rev. Pharmacol. Toxic.* **1997**, *37*, 421.
2. Steffan, R. J.; Ashwell, M. A.; Solvibile, W. R.; Matelan, E.; Largis, E.; Han, S.; Tillet, J.; Mulvey, R. *Bioor. Med. Chem. Lett.* **2002**, *12*, 2957.
3. Kajigaeshi, S.; Kakinami, T.; Ikeda, H.; Okamoto, T. *Chem. Express* **1988**, *3*, 659.
4. Corey, E. J.; Li, W.; Nagamitsu, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
5. Asselin, A. A.; Humber, L. G.; Crosilla, D.; Oshiro, G.; Wojdan, A.; Grimes, D.; Heaslip, R. J.; Rimele, T. J.; Shaw, C. C. *J. Med. Chem.* **1986**, *29*, 1009.

6. Spitzer, U. A.; Stewart, R. J. *Org. Chem.* **1974**, *39*, 3936.
7. o-Iodobenzoic acid (IBX) in DMSO Frigerio, M.; Santagostino, M *Tetrahedron Lett.* **1994**, *43*, 8019.
8. For full experimental details see: Steffan, R. J.; Ashwell M. A.; Solvibile, W. R.; Matelan, E; US21875300P, application submitted July 17, 2000.
9. Susulic, V. S.; Frederich, R. C.; Lawitts, J.; Tozzo, E.; Kahn, B. B.; Harper, M.-E.; Himms-Hagen, J.; Flier, J. S.; Lowell, B. B. *J. Biol. Chem.* **1995**, *270*, 29483.
10. 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}'s and K_i values were determined by incubation of the test compound, at various concentrations, and the radioligand [^{125}I]iodocyanopindolol with these cells.