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Cyclic Amine Sulfonamides as Linkers in the Design and Synthesis of Novel Human β_3 Adrenergic Receptor Agonists

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Abstract—Piperidine, pyrrolidine, and azetidine sulfonamides were examined as linkers in designing novel human β_3 adrenergic receptor (β_3-AR) agonists. The azetidine derivative **37**, and piperidine derivatives **7**, **8**, and **13** were found to be potent β_3-AR agonists and have good selectivity against β_1- and β_2-AR.

Selective beta-3 adrenergic receptor (β_3-AR) agonists have been shown in rodent models to be effective agents for treating obesity and type II diabetes.[1] The selectivity of such agents minimizes the adverse side effects, namely, increased heart rate and muscle tremor, associated with β_1-AR and β_2-AR agonistic activities respectively. These promising results have prompted intensive research to discover β_3-AR agonists for therapeutic use in humans.[2] Despite the immense efforts of the last two decades, no β_3-AR agonists have been successfully developed to date. Several early drug candidates, identified based on the rodent β_3-AR, failed in human clinical trials.[1a] The advent of cloning of the human β_3-AR in 1989,[3] which was found to have different pharmacology from the rodent receptor,[4] spurred renewed interest to develop selective human β_3-AR agonists as anti-obesity and anti-diabetes agents. Some of these investigations have produced β_3-AR agonists that show promise in primate as well as human studies.[2a,2b,5] The potential use of β_3-AR agonists for treating urinary incontinence has also been reported recently.[6] In our continuing research to develop β_3-AR agonists for therapeutic use, we have discovered potent and selective human β_3-AR agonists containing cyclic amine sulfonamides as linkers. The design and synthesis, as well as some preliminary structure–activity relationship of these compounds will be described in this communication.

Most β_3-AR agonists reported in the literature possess the general structure **1** (Fig. 1), in which an aryloxy-propanolamine (R_1 = aryloxymethyl) or arylethanol-amine (R_1 = aryl) pharmacophore is attached to a substituted aryl group through an ethylene chain. In search of novel linkers to replace the ethylene chain, we investigated the cyclic amine sulfonamide derivatives **2**, **3**, and **4** as shown in Figure 1. The three sulfonamide linkers were designed to provide varying degree of spacing and conformational constraint, as well as additional hydrogen bonding capability in these molecules that we were interested in exploring.

Piperidine sulfonamide derivatives **2** were prepared by a convergent synthesis outlined in Scheme 1. 4-Piperidone hydrate was sulfonylated with an arylsulfonyl chloride[7] to give the sulfonamide **5** which underwent reductive amination with amines **6** to yield final products, **7**–**20**.[8] The requisite aryloxypropanol-amines **6a**–**c**, and arylethanolamine **6d** (Fig. 2) were prepared according to procedures reported in the literature.[9] Two examples of pyrrolidine sulfonamide **3** were synthesized as illustrated in Scheme 2. Racemic 3-pyrrolidinol was sulfonylated with 4-butoxybenzene-sulfonyl chloride to give compound **21**, which was converted to the benzylamine derivative **23** through amination of the mesylate **22**. Alkylation of the common intermediate **23** with the iodo compound **24**[9d] or the epoxide **25**,[9b] followed by hydrogenolysis, gave the corresponding products **26** and **27**.[8]

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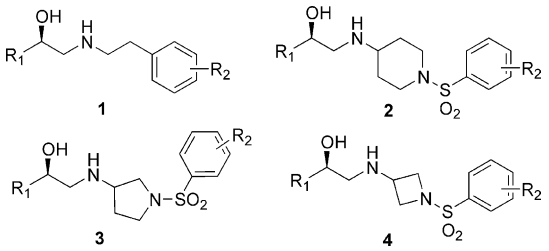
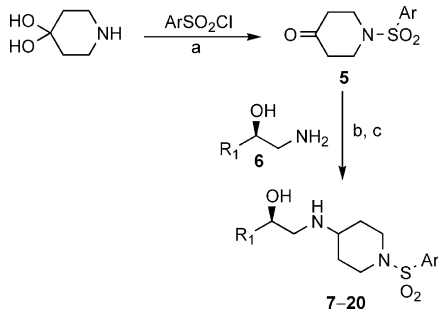


Figure 1.



Scheme 1. (a) Et_3N, CH_2Cl_2; (b) **6**, $CH(OMe)_3$, MeOH; (c) $NaBH(OAc)_3$, 1,2-dichloroethane.

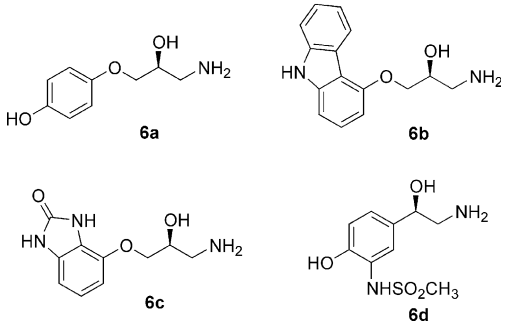
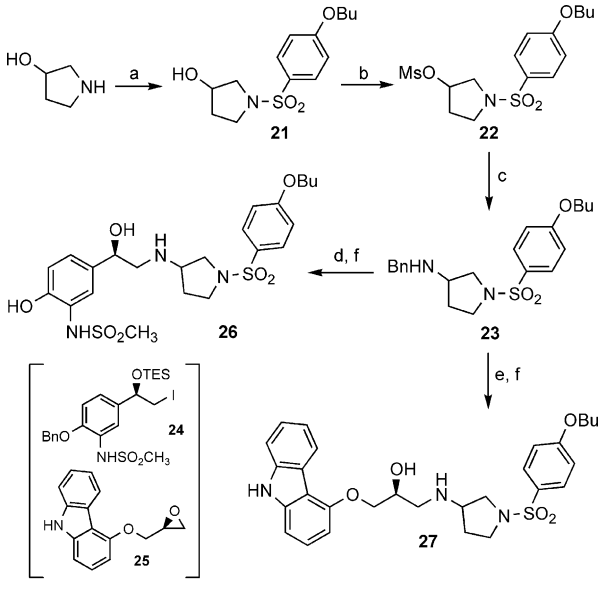


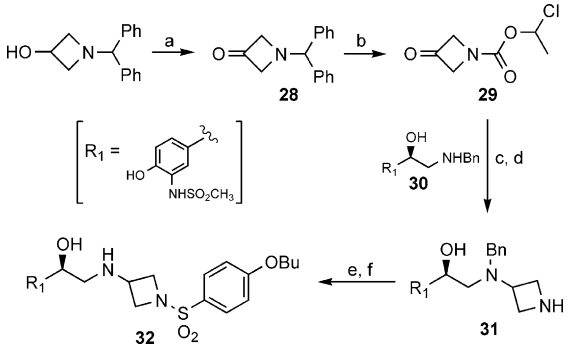
Figure 2.



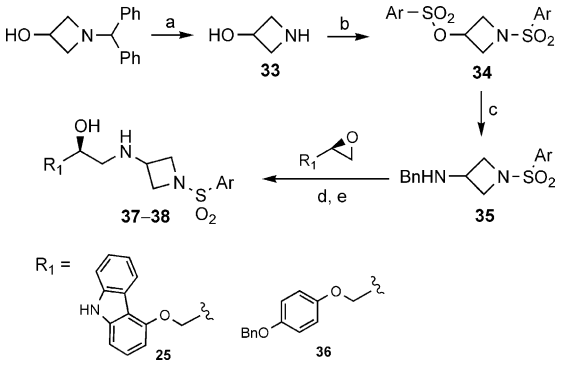
Scheme 2. (a) Et_3N, CH_2Cl_2; (b) CH_3SO_2Cl, Et_3N, CH_2Cl_2; (c) $BnNH_2$, THF, reflux; (d) **24**, *i*-Pr_2NEt, DMPU, 100 °C; (e) **25**, MeOH, reflux; (f) 10% Pd/C, ammonium formate, MeOH, reflux.

An azetidine sulfonamide incorporating the arylethanolamine **6d** was prepared according to Scheme 3. Commercially available 1-(diphenylmethyl)-3-hydroxyazetidine was oxidized to the azetidinone **28** under modified Swern oxidation conditions.[10] Removal of the diphenylmethyl group and protection of the amino function of **28** were accomplished in one step by treatment with 1-chloromethyl chloroformate,[11] yielding intermediate **29**. Reductive amination with arylethanolamine **30**, followed by methanolysis gave azetidine **31**, which was sufonylated with 4-butoxysulfonyl chloride, and then hydrogenolyzed to give product **32**.[8] An alternative synthetic route (Scheme 4) was employed to prepare azetidine sulfonamides containing the aryloxypropanol-amines **6a** and **6b**. Azetidinol **33**, obtained by hydrogenolysis of 1-(diphenylmethyl)-3-hydroxyazetidine, was sulfonylated with the appropriate arylsulfonyl chloride to give **34**. Displacement of the sulfonate group with benzylamine led to intermediate **35**. Ring opening reaction with epoxides **25**, and **36**,[9] and subsequent removal of the benzyl group yielded products **37–38**, respectively.[8]

The β_3-AR agonistic activity of all the cyclic amine sulfonamide final products described in this report were measured using Chinese hamster ovary (CHO) cells expressing the cloned human β_3-AR.[12] Selectivity against cloned human β_1- and β_2-ARs[13] was also determined for selected compounds. Results of these studies are summarized in Tables 1 and 2.



Scheme 3. (a) Phenyl dichlorophosphate, DMSO, Et_3N, CH_2Cl_2; (b) 1-chloroethyl chloroformate, CH_2Cl_2; (c) **30**, $NaBH(OAc)_3$, 1,2-dichloroethane; (d) MeOH, reflux; (e) 4-butoxysulfonyl chloride, Et_3N, CH_2Cl_2; (f) 10% Pd/C, ammonium formate, MeOH, reflux.



Scheme 4. (a) 10% Pd/C, ammonium formate, MeOH, reflux; (b) $ArSO_2Cl$, Et_3N, CH_2Cl_2; (c) $BnNH_2$, THF, reflux; (d) epoxide, MeOH, reflux; (e) 10% Pd/C, ammonium formate, MeOH, reflux.

Table 1. β-AR activities of piperidine sulfonamide derivatives

Compd	$R_1CH(OH)CH_2NH_2$	Ar	β_3-AR[a] EC_{50} μM (IA)[b]	β_1-AR[a] EC_{50} μM (IA)	β_2-AR[a] EC_{50} μM (IA)
7	**6a**	4-Methoxyphenyl	0.055 (0.74)	10.3 (0.46)	>100 (0.09)
8	**6b**	4-Methoxyphenyl	0.060 (0.88)	>100 (0.11)	>100 (0.03)
9	**6c**	4-Methoxyphenyl	0.12 (0.72)	>100 (0.32)	>100 (0.03)
10	**6a**	4-Butoxyphenyl	>2	NT	NT
11	**6b**	4-Butoxyphenyl	0.85 (0.74)	>100 (0.04)	>100 (0.07)
12	**6b**	4-*t*-Amylphenyl	0.92 (1.0)	NT	NT
13	**6b**	3,4-Dimethoxyphenyl	0.02 (1.2)	>100 (0.14)	>100 (0.02)
14	**6c**	3,4-Dimethoxyphenyl	0.09 (0.87)	>100 (0.33)	>100 (0.01)
15	**6a**	4-(Hexylureido)phenyl	>2	NT	NT
16	**6c**	4-(Hexylureido)phenyl	0.036 (0.74)	NT	NT
17	**6d**	4-(Hexylureido)phenyl	0.005 (0.82)	0.012 (0.66)	0.92 (0.26)
18	**6c**	2-Dibenzofuran	0.07 (0.64)	NT	NT
19	**6d**	2-Dibenzofuran	0.12 (0.88)	NT	NT
20	**6c**	4-Benzo-(2,1,3)-thiadiazole	0.85 (0.75)	NT	NT

[a]Agonistic activities were assessed by measuring cAMP levels in CHO cells expressing cloned human β-ARs; NT, not tested.
[b]Intrinsic activities (IA) were measured as fractions of the maximal response attained by isoproterenol.

Table 2. β-AR activities of pyrrolidine and azetidine sulfonamide derivatives

Compd	$R_1CH(OH)CH_2NH_2$	Ar	β_3-AR EC_{50} μM (IA)	β_1-AR EC_{50} μM (IA)	β_2-AR EC_{50} μM (IA)
26	**6d**	4-Butoxyphenyl	0.36 (0.79)	NT	NT
27	**6b**	4-Butoxyphenyl	>2	NT	NT
32	**6d**	4-Butoxyphenyl	1.1 (0.78)	NT	NT
37	**6a**	4-Butoxyphenyl	0.03 (0.82)	1.6 (0.49)	0.92 (0.39)
38	**6b**	4-Butoxyphenyl	>2	NT	NT

Within the piperidine series of compounds, the structure–activity relationship varies with each of the four aryloxypropanolamine and arylethanolamine (**6a**–**6d**) investigated. For analogues containing **6a** (**7**, **10**, and **15**), the smaller 4-methoxy group in **7** is superior to both 4-butoxy and 4-hexylureido groups in conferring β_3-AR activity. A similar trend also prevails for the **6b** derivatives (**8** and **13** are >15-fold more active than **11** and **12**), albeit to a lesser extent. The 4-hexylureidophenyl derivatives, **16** and **17**, incorporating amines **6c** and **6d**, respectively, have good β_3-AR activities comparing to the methoxy substituted compounds **9** and **14**. However, as indicated by compound **17**, the selectivity against β_1-AR is only marginal. The analogues with tricyclic and bicyclic aryl groups (**18**, **19**, and **20**) show moderate β_3-AR activities. In general, methoxy-substituted phenylsulfonamides in the piperidine series are beneficial for β_3-AR activity and selectivity as exemplified by compounds **7**, **8**, and **13**.

Comparing the piperidine (**11**), pyrrolidine (**27**), and azetidine (**38**) derivatives containing the aryloxy-propanolamine **6b**, the piperidine analogue shows better β_3-AR activity and good selectivity. Interestingly, for analogues containing **6a**, the azetidine **37** is superior to the piperidine **10**, and for analogues containing the arylethanolamine **6d**, the pyrrolidine **26** shows slightly better β_3-AR activity.

In conclusion, we have demonstrated that cyclic amine sulfonamides, such as piperidine sulfonamide, are useful linkers in designing human β_3-AR agonists. Compounds **7**, **8**, **13**, and **37** were found to have potent β_3-AR activity, as well as high selectivity against β_1-AR and β_2-AR. We have also developed efficient synthetic routes for the preparation of these cyclic amine sulfonamide derivatives, which will facilitate future investigations.

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References and Notes

1. (a) Weyer, C.; Gautier, J. F.; Danforth, E. *Diabetes Metabolism* **1999**, *25*, 11. (b) Pietri-Rouxel, F.; Strosberg, A. D. *Fundam. Clin. Pharmacol.* **1995**, *9*, 211.
2. Recent reviews: (a) Arch, J. R. S. *Eur. J. Pharmacol.* **2002**, *440*, 99. (b) de Souza, C. J.; Burkey, B. F. *Curr. Pharm. Design* **2001**, *7*, 1433. (c) Kordik, C. P.; Reitz, A. B. *J. Med. Chem.* **1999**, *42*, 181. (d) Webber, A. E. *Ann. Rep. Med. Chem.* **1998**, *33*, 194. (e) Dow, R. L. *Exp. Opin. Invest. Drugs* **1997**, *6*, 1811.
3. Emorine, L. J.; Marullo, S.; Briend-Sutren, M.-M.; Patay, G.; Tate, K.; Delavier-Klutchko, C.; Strosberg, A. D. *Science* **1989**, *245*, 1118.
4. Liggett, S. B. *Mol. Pharmacol.* **1992**, *42*, 634.
5. Van Baak, M. A.; Hul, G. B. J.; Toubro, S.; Astrup, A.; Gottesdiener, K. M.; DeSmet, M.; Saris, W. H. M. *Clin. Pharmacol. Ther.* **2002**, *71*, 272.
6. (a) Yamanishi, T.; Chapple, C. R.; Yasuda, K.; Yoshida, K.; Chess-Williams, R. *Brit. J. Pharmacol.* **2002**, *135*, 129. (b) Yamaguchi, O. *Urology* **2002**, *59*, 25. (c) Tanaka, N.; Tamai, T.; Mukaiyama, H.; Hirabayashi, A.; Muranaka, H.; Ishikawa, T.; Akahane, S.; Akahane, M. *Bioorg. Med. Chem.* **2001**, *9*, 3265. (d) Morita, T.; Iizuka, H.; Iwata, T.; Kondo,

S. J. *Smooth Muscle Res*. **2000**, *36*, 21. (e) Longhurst, P. A.; Levendusky, M. *Brit. J. Pharmacol*. **1999**, *127*, 1744.
7. 4-Hexylureidobenzenesulfonyl chloride was prepared according to: Chivers, G. E.; Cremlyn, R. J.; Guy, R.; Honeyman, R.; Reynolds, P. *Aust. J. Chem*. **1975**, *28*, 413 All other sulfonyl chlorides used are from commercial sources.
8. All final products were characterized by IR, ^{1}H NMR, low- and high-resolution mass spectrometry. Except the pyrrolidine derivatives, all compounds described are single isomers. For experimental details, see: Sum, F.-W.; Hu, B. PCT Int. Appl., WO 0206221.
9. (a) For the synthesis of **6a–6d**: Siegel, M. G.; Shuker, A. J.; Droste, C. A.; Hahn, P. J.; Jesudason, C. D.; Mcdonald, J. H., III; Matthews, D. P.; Rito, C. J.; Thorpe, A. *J. Mol. Div*. **1998**, *3*, 113. (b) Berridge, M. S.; Cassidy, E. H.; Terris, A. H.; Vesselle, J.-M. *Nucl. Med. Biol*. **1992**, *19*, 563. (c) Bell, M. G.; Crowell, T. A.; Matthews, D. P.; Mcdonald, J. H., III; Nee, D. A.; Shuker, A. J.; Winter, M. A. UA Patent 5,786,356. (d) Hu, B.; Ellingboe, J.; Gunawan, I.; Han, S.; Largis, E.; Li, Z.; Malamas, M.; Mulvey, R.; Oliphant, A.; Sum, F.-W.; Tillett, J.; Wong, V. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 757.
10. Liu, H. J.; Nyangulu, J. M. *Tetrahedron Lett*. **1988**, *29*, 3167.
11. Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem*. **1984**, *49*, 2081.
12. Van, S. A.; Nahmias, D. K. S.; Briend-Sutren, M. M.; Strosberg, A. D.; Emorine, L. J. *Eur. J. Biochem*. **1993**, *213*, 1117.
13. Tate, K. M.; Briend-Sutren, M. M.; Emorine, L. J.; Delavier-Klutchko, C.; Marullo, S.; Strosberg, A. D. *Eur. J. Biochem*. **1993**, *196*, 357.