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Bioorganic & Medicinal Chemistry Letters 14 (2004) 5963–5966
Bioorganic & Medicinal Chemistry Letters

Tryptamine-based human β_3-adrenergic receptor agonists. Part 2: SAR of the methylene derivatives

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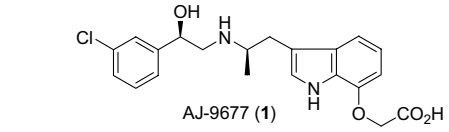
Received 27 August 2004; revised 14 September 2004; accepted 17 September 2004

Abstract—A series of tryptamine derivatives with modified sulfonamide were designed, synthesized, and evaluated for their ability to stimulate cAMP accumulation in CHO cells expressing the cloned human β_3-adrenergic receptor (AR). For this series of compounds, our objective was to symmetrize the α-position of the tryptamine moiety maintaining its activity and reducing the cost of production. Compound **11h**, having *m*-aminobenzene, exhibited excellent agonistic activity for β_3-AR with excellent subtype selectivity.

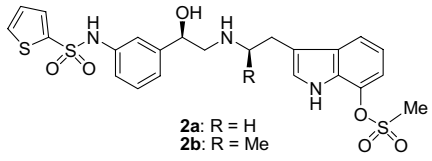
1. Introduction

In recent years, life-style related diseases such as noninsulin dependent diabetes mellitus (NIDDM) brought on by obesity has become a serious problem.[1] Elevating the metabolic rate by activating the human β_3-adrenergic receptor (AR) has attracted much attention as a novel approach in the treatment of NIDDM and obesity.[2] Therefore, the development of potent and selective β_3-AR agonists is an attractive goal for medicinal chemists.[3] In particular, subtype selectivity over both β_1- and β_2-ARs has been an important issue in developing β_3-AR agonists to avoid the adverse effects observed with early drug candidates.[4]

As previously reported, we succeeded in finding some novel tryptamine-based β_3-AR agonists such as compound **1** (AJ-9677)[5] and **2b**,[6] both which exhibited potent agonistic activity with excellent subtype selectivity. Compound **2b**, especially, showed considerable selectivity over the β_1- and β_2-ARs (EC_{50} ratio; 210- and 86-fold, respectively). However, these compounds have two chiral centers, which make the synthesis of the derivatives even more difficult, which would increase the cost of production. Therefore, we turned our attention to compound **2a** with just one chiral center as an analog of compound **2b**. Removal of the chiral methyl group in **2b** resulted in remarkable selectivity over the β_1- and β_2-ARs, but in a 10-fold decrease of the agonistic activity for β_3-AR compared to **2b** (Table 1). In this study, we provide evidence that the replacement of 2-thiophene moiety in **2a** with *m*-aminobenzene leads to a potent, highly selective, and cost desirable β_3-AR agonist.



AJ-9677 (**1**)



2a: R = H
2b: R = Me

2. Chemistry

The preparation of a series of tryptamine derivatives was performed using two methods (methods A or B in

Keywords: β_3-Adrenergic receptor; Agonist; Tryptamine.
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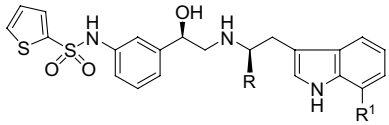
doi:10.1016/j.bmcl.2004.09.054

Table 1. Activity of tryptamine-based arylsulfonamides at the cloned human β-ARs (**1**)



Compd	R^1	R	EC_{50}, nM[a] (IA, %)[b]		
			β_3	β_1	β_2
2a	–OMs	H	1.7 (89)	(12)[c]	(23)[c]
2b	–OMs	Me	0.21 (97)	44 (36)	18 (50)
8a	–OBn	H	7.6 (81)	(10)[c]	(32)[c]
8b	–OMe	H	13 (87)	(6)[c]	(16)[c]
8c	–H	H	21 (73)	(2)[c]	(15)[c]
8d	–Me	H	25 (77)	(3)[c]	(9)[c]

[a] Agonistic activity was assessed by measuring cAMP accumulation in CHO cells expressing human β-ARs.

[b] Values in parentheses represent the intrinsic activity (IA) given as percentage of maximal stimulation with isoproterenol.

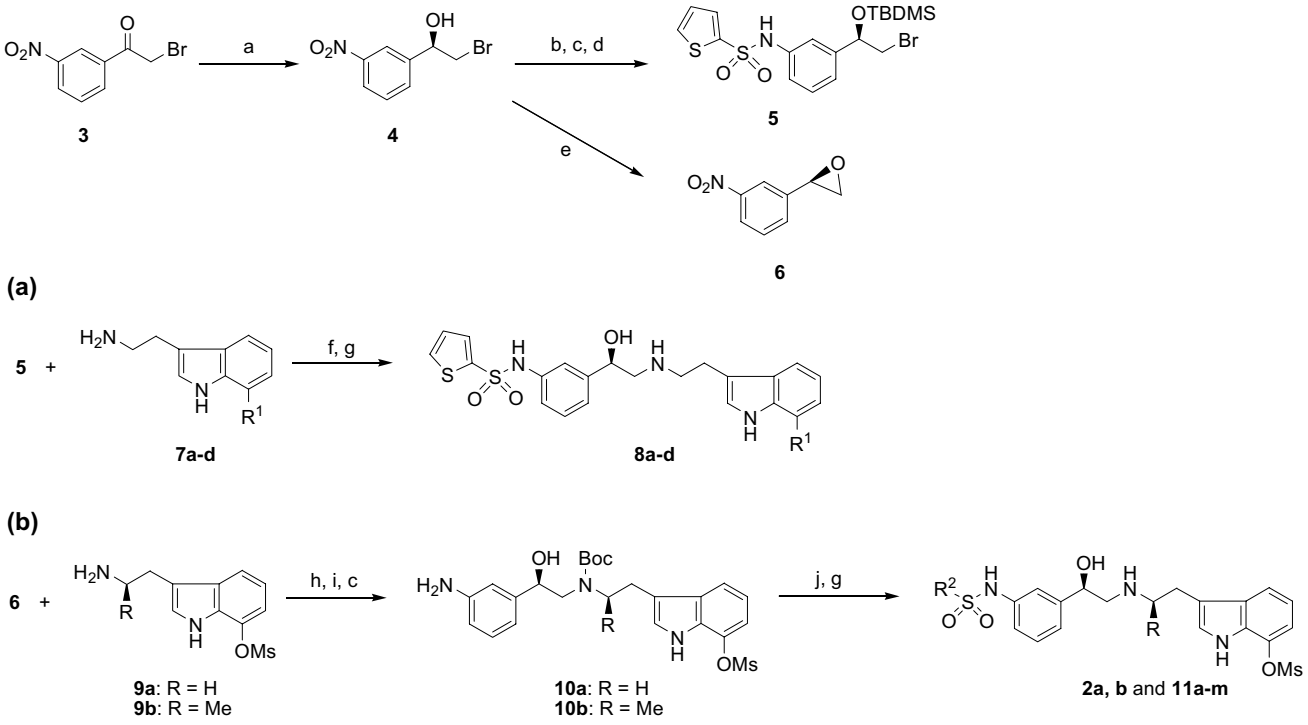
[c] EC_{50} was not determined. Values in parentheses represent % activity at 1000 nM.

Scheme 1).[7] The thiophenesulfonamide analogs **8a**–**d** were readily available from common intermediate **5** and commercial tryptamine derivatives **7a**–**d** as shown in Scheme 1A. Commercially available *m*-nitrophenacyl bromide **3** was reduced stereoselectively with a borane–THF complex in the presence of (*R*)-2-methyl-CBS-oxazaborolidine to give chiral alcohol **4**.[6] Protection of the chiral alcohol **4** with TBDMS, followed by reduction of the nitro group with Fe provided the corresponding aniline, which was treated with 2-thiophenesulfonyl chloride to afford common intermediate **5**. The resulting bromide **5** was treated with appropriately substituted tryptamines **7a**–**d** in the presence of diisopropylethylamine and KI, followed by deprotection of TBDMS afforded the desired compounds **8a**–**d**.

The 7-methanesulfonate derivatives **2a**,**b**, and **11a**–**m** were synthesized in five steps starting from common intermediate **6**, as shown in Scheme 1B. The alcohol **4** was treated with alkaline to provide epoxide **6**. The reaction of the resulting epoxide **6** with tryptamine derivatives **9a**,**b**[8] produced secondary amines, which were protected with Boc, and then reduced with Fe. The resulting anilines **10a**,**b** were treated with an appropriate sulfonyl chloride to afford sulfonamides. Finally, deprotection of the Boc group furnished the desired compounds **2a**,**b**, and **11a**–**m**.[9]

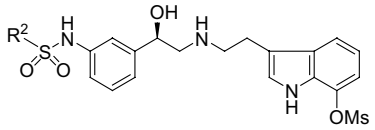
3. Biological evaluation

All compounds were tested in vitro for their ability to stimulate cAMP accumulation in CHO cells expressing the cloned human β_1-, β_2-, and β_3-ARs,[10] and the data are summarized in Tables 1–3. To identify compounds with improved agonistic activity for β_3-AR, we initially investigated the effect of the substituents R^1 at the 7-position of the indole ring on the β_3-agonistic activity (Table 1). 7-Benzyloxy derivative **8a** and 7-methoxy derivative **8b** showed moderate potency for β_3-AR (EC_{50} = 7.6 and 13 nM, respectively), but were still selective against β_1- and β_2-ARs. The fact that replacement



Scheme 1. Reagents: (a) (*R*)-2-methyl-CBS-oxazaborolidine, BH_3, THF; (b) TBDMSCl, iraidazole, DMF; (c) Fe, NH_4C1, EtOH, H_2O; (d) 2-thiophenesulfonyl chloride, pyridine, CH_2C1_2; (e) 2 N NaOH, THF; (f) *i*-Pr_2NEt, KI, MeCN; (g) 4 N HCl–AcOEt; (h) DMF; (i) $(Boc)_2O$, $CHC1_3$; (j) R^2–SO_2C1, pyridine, CH_2Cl_2.

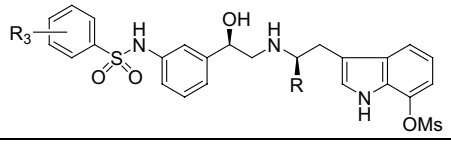
Table 2. Activity of tryptamine-based arylsulfonamides at the cloned human β-ARs (**2**)



Compd	R^2	EC_{50}, nM[a] (IA, %)[b]		
		β_3	β_1	β_2
11a	–Et	18 (85)	(3)[c]	(49)[c]
11b	$-CH_2CF_3$	48 (49)	(0)[c]	(24)[c]
11c	$-CH_2CH_2CH_2Cl$	20 (63)	(5)[c]	(37)[c]
11d	5-Bromothiophene	2.8 (82)	(6)[c]	(17)[c]
11e	4,5-Dichlorothiophene	6.7 (93)	(7)[c]	(18)[c]
11f	–Ph	2.0 (86)	(14)[c]	(15)[c]

[a] See footnote a in Table 1.
[b] See footnote b in Table 1.
[c] See footnote c in Table 1.

Table 3. Activity of tryptamine-based arylsulfonamides at the cloned human β-ARs (**3**)



Compd	R^3	R	EC_{50}, nM[a] (IA, %)[b]		
			β_3	β_1	β_2
11f	H	H	2.0 (91)	(13)[c]	(15)[c]
11g	2-NH_2	H	3.0 (80)	(7)[c]	(9)[c]
11h	3-NH_2	H	0.31 (105)	(3)[c]	(6)[c]
11i	4-NH_2	H	8.4 (85)	(5)[c]	(15)[c]
11j	3-OMe	H	0.94 (97)	(11)[c]	(10)[c]
11k	3-Cl	H	1.0 (96)	(11)[c]	(13)[c]
11l	3-F	H	2.4 (97)	(10)[c]	(8)[c]
11m	3-NH_2	Me	0.47 (92)	26 (51)	13 (42)

[a] See footnote a in Table 1.
[b] See footnote b in Table 1.
[c] See footnote c in Table 1.

of the methanesulfonate group in **2a** with hydrogen (**8c**) or a methyl group (**8d**) resulted in a considerable decrease in the β_3-agonistic activity (EC_{50} = 21 and 25 nM, respectively) suggests the oxygen at the 7-position of the indole ring was important for β_3-agonistic activity. These compounds also showed moderate intrinsic activity for β_3-AR (IA = 73% and 77%, respectively).

Effects of the substituents R^2 attached to the sulfonamide moiety on the left-hand side phenyl ring were then examined (Table 2). Replacement of the thiophene ring with an alkyl chain (compounds **11a**–**c**) resulted in a major decrease in the potency for β_3-AR, while maintaining the subtype selectivity. Trifluoroethyl derivative **11b** showed a substantial loss of intrinsic activity for β_3-AR (IA = 49%). However, extension of the alkyl chain resulted in a moderate increase in both EC_{50} and IA (**11b** vs **11c**). Halogen substituents at the thiophene ring in **2a** (compounds **11d**,**e**) slightly decreased the agonistic activity for β_3-AR (EC_{50} = 2.8 and 6.7 nM, respectively). It is interesting to note that benzenesulfonamide **11f** showed potent agonistic activity for

Table 4. Binding affinity of tryptamine-based arylsulfonamides at the cloned human β-ARs

Compd	Binding K_i, nM[a]		
	β_3	β_1	β_2
2a	33	230	223
2b	4.0	66	48
11h	2.6	89	70
11m	1.1	34	20

[a] Binding potency is reported as K_i, the binding inhibition constant, determined by inhibition of ^{125}I-iodocyanopindolol binding.

β_3-AR equal to the parent compound **2a** (EC_{50} = 2.0 nM), with high subtype selectivity. These results suggest that the aromatic function attached to the sulfonamide group was important for maintaining β_3-agonist activity.

Next, we examined the effect of substituents at the benzene ring in **11f** on the β_3-agonistic activity (Table 3). It was found that the activity of the *para*-amino analog **11i** was weaker by 4-fold (EC_{50} = 8.4 nM) relative to **11f**. The *ortho*-amino analog **11g** showed similar potency at β_3-AR (EC_{50} = 3.0 nM) as **11f**. However, the shift of the amino group to the *meta*-position (**11h**) dramatically improved agonistic activity for β_3-AR (EC_{50} = 0.31 nM) with considerable subtype selectivity. Furthermore, it was noteworthy that the agonistic activity of **11h** was almost equal to that of compound **11m** possessing the chiral methyl group. Encouraged by these results, we then prepared and tested some *meta*-substituted benzenesulfonamide derivatives with electron-donating or -withdrawing groups. As can be seen from Table 3, both analogs **11j** and **11k** containing either a methoxy group (electron-donating) or a chlorine atom (electron-withdrawing) showed excellent activity for β_3-AR. However, fluorine derivative **11l** was somewhat less active for β_3-AR than **11f**. All of these results suggest that the enhanced activity with *meta*-substitution is not caused by electronic effects, but rather result from steric effects and the hydrogen-bond donative property of the NH_2 group, which would be required for activating the receptor.

Compounds with low cAMP accumulation in β_1- and β_2-ARs may have antagonistic profiles, which may cause unwanted side effects. Thus, compounds **11h** and **11m** were subjected to β-ARs binding assays, and the results are shown in Table 4. In contrast to the parent compound **2a**, which showed weak binding affinity to the β_3-AR (K_i = 33 nM), *m*-aminobenzenesulfonamide derivative **11h** had a very strong binding constant (K_i = 2.6 nM). Furthermore, **11h** shows excellent selectivity over binding to the β_1- and β_2-ARs (34- and 27-fold, respectively). These results confirmed that **11h** had high selectivity for β_3-AR over β_1- and β_2-ARs. In vivo evaluation of these compounds for their ability to increase metabolic rate is in progress and will be reported in due course.

Acknowledgements

We would like to thank San Francisco Edit (www.sfedit.net) for their assistance in editing this manuscript.

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7. All final compounds were characterized using NMR, mass spectrometry, and HPLC.
8. (*R*)-α-Methyl-7-methanesulfonyloxytryptamine (R = Me, **9b**) was prepared as reported previously.[6] 7-Methanesulfonyloxytryptamine (R = H, **9a**) was synthesized from commercially available 7-benzyloxytryptamine using a procedure similar to the procedure for the preparation of **9b**.
9. Analogs **11g–i** and **11m** were prepared by treatment of the anilines **10a**,**b** with the corresponding nitrobenzenesulfonamide, followed by hydrogenation of the nitro group with Pd–C. Deprotection of the Boc group afforded the desired compounds.
10. In a previous report,[5] we used CHO cells expressing a high level of β_3-AR as a measurement of compound activity, that is, the receptor densities were 150,000 receptors/cell (β_3-AR), 12,000 receptors/cell (β_1-AR), and 30,000 receptors/cell (β_2-AR). To better evaluate the subtype selectivity, in this study, we used CHO cells expressing a low density of β_3-AR (13,000 receptors/cell), and high densities of β_1- and β_2-ARs (320,000 and 600,000 receptors/cell, respectively). The CHO cells expressing either human β_1-, β_2-, or β_3-AR were prepared as described by Kato, S.; Harada, H.; Taoka, I.; Kawashima, H. PCT Patent Application, WO 2000044721, 2000 and Kato, S.; Harada, H.; Hirokawa, Y.; Yoshida, N.; Kawashima, H. PCT Patent Application, WO 9616938, 1996.