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Synthesis and SAR of Benzyl and Phenoxymethylene Oxadiazole Benzenesulfonamides as Selective β_3 Adrenergic Receptor Agonist Antiobesity Agents†

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Abstract—Benzyl and phenoxymethylene substituted oxadiazoles are potent and orally bioavailable β_3 adrenergic receptor (AR) agonists. The 4-trifluormethoxy substituted 5-benzyl oxadiazole **5f** has an EC_{50} of 8 nM in the β_3 AR agonist assay with 100-fold selectivity over β_1 and β_2 AR binding inhibition activity. Its oral bioavailability in dogs is $30 \pm 4\%$, with a half-life of 3.8 ± 0.4 h. In the anesthetized rhesus, **5f** evoked a dose-dependent glycerolemia ($ED_{50Gly} = 0.15$ mg/kg). Under these conditions a heart rate increase of 15% was observed at a dose level of 10 mg/kg.

Introduction

The 5-alkyl oxadiazole substituted benzenesulfonamide β_3 adrenergic receptor (β_3 AR) agonists reported in the previous paper[1] were further improved in potency while maintaining oral bioavailability by replacing the alkyl substituent with benzyl and phenoxymethylene groups. Rapid analogue synthesis was applied to prepare most of the compounds described in this investigation.

Chemical Synthesis

The 5-substituted oxadiazoles shown in Tables 1 and 2 were prepared as shown in Scheme 1.[2] Aniline derivative **1** linked to an HMPA (hydroxymethyl phenoxy acetic acid) resin (Novabiochem) was treated with 4-cyanobenzenesulfonyl chloride **2** and pyridine in anhydrous dichloromethane at 0 °C to provide sulfonamide **3**. Treatment of sulfonamide **3** with hydroxylamine hydrochloride and potassium carbonate in ethanol at reflux temperature provided the corresponding amidoxime **4**. The oxadiazoles **5–6** were obtained from **4** by acylation with the appropriate acid halide or anhydride in the presence of base or with an acid and a peptide coupling reagent such as ethyldimethylaminopropylcarbodiimide (EDC),[3] followed by heating in pyridine or diglyme to effect cyclization for 2–16 h at 110 °C. The later cyclization step could be accelerated if carried out in a microwave oven.[4] Cleavage from the resin was achieved with trifluoroacetic acid in dichloromethane.[5]

Synthesis of 3-oxadiazolyl and 5-oxadiazolylbenzenesulfonamides was also accomplished in solution without introducing resin in the reaction sequence. For the synthesis of 3-oxadiazolylbenzenesulfonamides **9** shown in Table 3, the aniline intermediate **7** was reacted with 4-chlorosulfonylbenzoic acid at room temperature overnight (Scheme 2). The reaction mixture was concentrated and the reddish residue was taken up into diglyme, followed by addition of an amidoxime and coupling agent EDC. The reaction was stirred at room temperature overnight, and then heated to 100 °C for 4 h in the same pot. The

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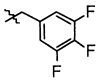
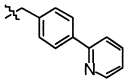
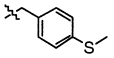
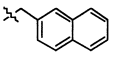
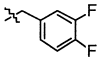
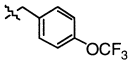
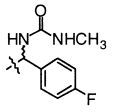
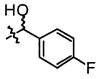
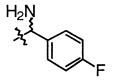
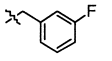
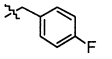
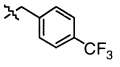
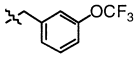
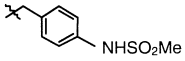
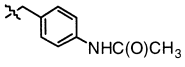
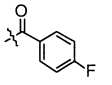
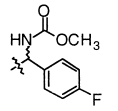
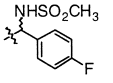
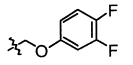
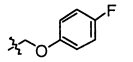
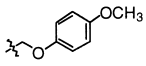
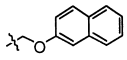
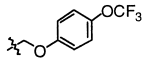
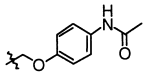
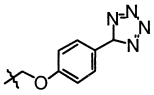
Table 1. SAR of 5-benzyl substituted oxadiazoles

Compound	R	β_3 (% act)[a] EC_{50} (nM)	β_1 IC_{50}[b] (nM)	β_2 IC_{50}[b] (nM)
5a		2 (87)	3000	720
5b		2 (71)	2100	4500
5c		3 (74)	16,000	9500
5d		5 (73)	550	1500
5e		6 (61)	2300	980
5f		8 (90)	1290	7600
5g		3 (67)	4500	1500
5h		8 (56)	65,000	2500
5i		8 (60)	4000	2000
5j		12 (93)	5000	695
5k		12 (74)	3000	1660
5l		15 (100)	2000	2000
5m		29 (86)	2000	5500
5n		79 (82)	2000	3000
5o		190 (98)	3000	5000
5p		10 (87)	2430	15,000
5q		10 (80)	2600	5400
5r		11 (81)	7000	2500

[a]Adenylyl cyclase activation given % of maximal stimulation with isoproterenol.
[b]Receptor binding assays were carried out with membranes prepared from CHO cells expressing the cloned human receptor in the presence of ^{125}I-iodocyanopindolol.

Table 2. SAR of 5-phenoxymethyene substituted oxadiazoles

Compound	R	β_3 (% act)[a] EC_{50} (nM)	β_1 IC_{50}[b] (nM)	β_2 IC_{50}[b] (nM)
6a		4 (85)	3660	1430
6b		4 (82)	715	490
6c		6 (71)	8000	2500
6d		6 (86)	2000	5000
6e		7 (76)	2500	90,000
6f		8 (82)	1000	5000
6g		31 (88)	2000	9500
6h		64 (79)	9000	8000

[a]Adenylyl cyclase activation given % of maximal stimulation with isoproterenol.
[b]Receptor binding assays were carried out with membranes prepared from CHO cells expressing the cloned human receptor in the presence of ^{125}I-iodocyanopindolol.

Table 3. β_3, β_1, and β_2 AR activity of 3-substituted oxadiazoles

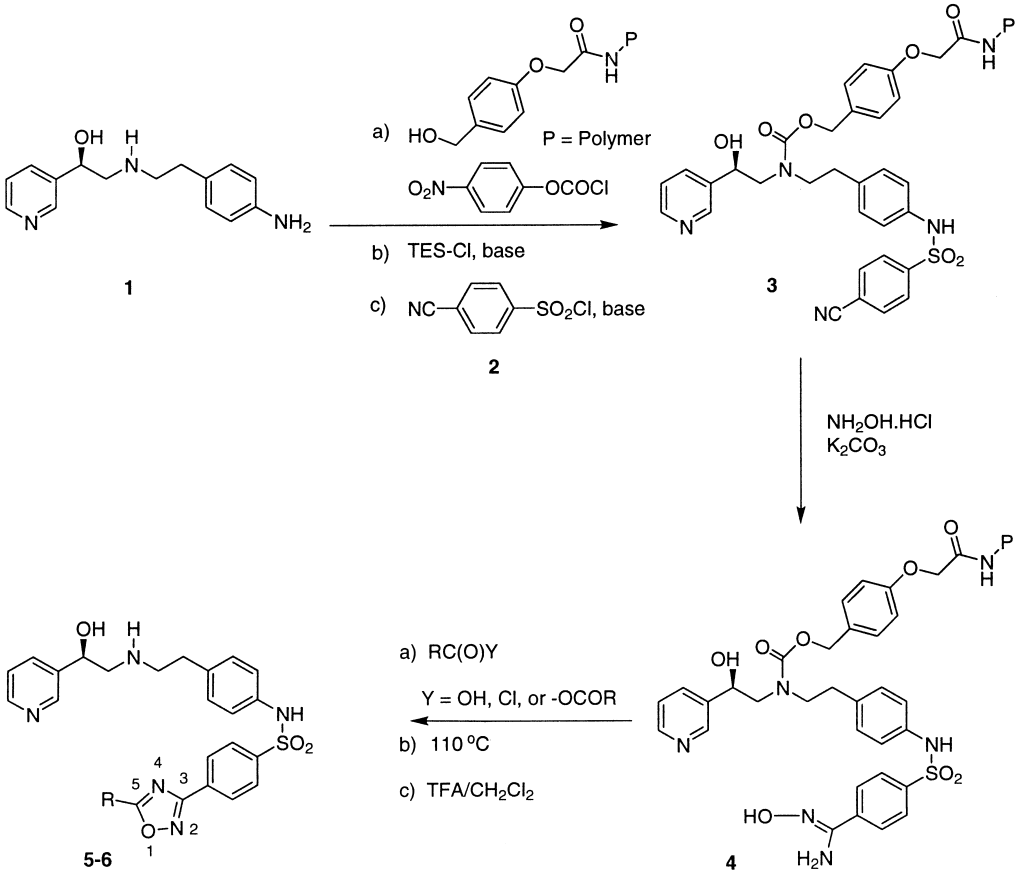
Compd	R	β_3(% act)[a] EC_{50} (nM)	β_1 IC_{50}[b] (nM)	β_2 IC_{50}[b] (nM)
9a	4-Fluorobenzyl	18 (61)	8000	4000
9b	3,4,-Diflurobenzl	12 (75)	5000	2500
9c	4-Fluorophenoxymethyl	8 (81)	4000	7500
9d	3,4-Difluorophenoxymethyl	12 (80)	3500	3500

[a]Adenylyl cyclase activation given % of maximal stimulation with isoproterenol.

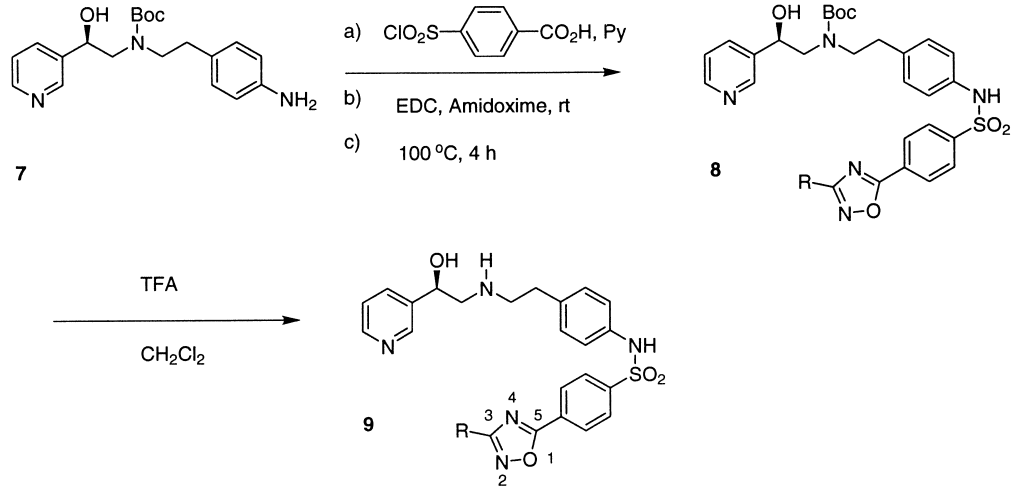
desired product **8** was isolated by silica gel flash chromatography in reasonable yields (30–50%). Removal of the tBoc protecting group was carried out in a solution of trifluoroacetic acid and dichloromethane (1:1) at room temperature for 1 h, and the product **9** was purified by silica gel chromatography.[5]

Structure–activity relationships

Benzyl substituents. As shown in Table 1, 5-benzyl substituted oxadiazoles are potent and selective β_3 AR agonists. The trifluoro **5a**, difluoro **5e**, and trifluoromethoxy benzyl **5f** have EC_{50}s of 2, 6, and 8 nM, respectively. However, the β_1 and β_2 activities are 160–1500 times less potent when compared to β_3 activities. Polar substituents such as sulfonamide **5n** and acetamide **5o** lower the β_3 activity. Functionalization of the benzylic carbon with hydroxy **5h**, carbamoyl **5q**, or amino **5i** groups did not depress the in vitro β_3 activity.



Scheme 1.



Scheme 2.

Phenoxymethylene substituents. As shown in Table 2, analogous to the 5-benzyl groups discussed above, phenoxymethylene substituents also enhance the β_3 activity. The difluoro **6a** and the trifluormethoxy **6f** have an EC_{50} of 4 and 8 nM, respectively, with 100-fold selectivity over β1 and β2 receptor binding inhibition activity.

3-Substituted oxadiazoles. The reversal of the oxadiazole ring hardly changes the spatial orientation of the substituent. As shown in Table 3, fluorinated 3-benzyl and fluorinated 3-phenoxymethyl substituents are potent inhibitors of the β_3 AR (**9a–d**). Oxadiazoles **9c–d** showed not only potent agonist β_3 AR activities, but also very good selectivity over the β_1 and β_2 adrenergic receptors.

In vivo profile of potent oxadiazoles. The 5-difluorobenzyloxadiazole **5e** (β_3 EC_{50} 6 nM) has an oral bioavailability of 54 ± 20% in dogs with a half-life of 3.4 ± 0.2 h. The oral bioavailability of 5-trifluoromethoxy benzyl **5f** (β_3 EC_{50} 8 nM) in dogs is 30 ± 4%, with half-life of 3.8 ± 0.4 h. In the anesthetized rhesus, **5f** evoked a dose-dependent

glycerolemia ($ED_{50Gly} = 0.15$ mg/kg). Under these conditions a heart rate increase of 15% was evident at a dose level of 10 mg/kg. This is consistent with the weak inhibition of **5f** against β_1 (IC_{50} 1290 nM) and β_2 (IC_{50} 7600 nM) adrenergic receptors.

Summary

Benzyl and phenoxymethylene substituted oxadiazoles are potent, selective and orally bioavailable β_3 AR agonists. The 4-trifluoromethoxy substituted benzyl oxadiazole **5f** has an EC_{50} of 8 nM in the β_3 AR agonist assay with 100-fold selectivity over β_1 and β_2 AR binding inhibition activity. In dogs, its oral bioavailability is $30 \pm 4\%$, with a half-life of 3.8 ± 0.4 h. In the anesthetized rhesus, **5f** evoked a dose-dependent glycerolemia ($ED_{50Gly} = 0.15$ mg/kg). Under these conditions a heart rate increase of 15% was observed at a dose level of 10 mg/kg. These compounds have good oral bioavailability and active in vivo. As such, they could be used as tools to evaluate the role of β_3 receptor agonists in obesity and diabetes.

Acknowledgements

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References and Notes

1. Feng, D. D.; Biftu, T.; Liang, G.-B.; Kuo, H.; Qian, X.; Naylor, E. M.; Colandrea, V. J.; Candelore, M. R.; Cascieri, M. A.; Colwell., L. F. Jr.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Stearns, R. A.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1427.
2. For experimental detail see Biftu, T.; Feng, D.; Fisher, M. H.; Kuo, K.; Liang, G.-B.; Weber, A. E. Patent Application WO 09746556 A1, 1997; *Chem. Abstr.* **1998**, 128, 75405f.
3. Liang, G.-B.; Feng, D. D. *Tetrahedron Lett.* **1996**, *37*, 6627.
4. Boualem, O.; Moeini, L.; Benoit, M.; Villemin, D.; Garrigues, B. *Synth. Comm.* **1995**, 1451.
5. All new compounds were characterized by NMR and mass spectrometry.