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# Discovery of an Orally Bioavailable Alkyl Oxadiazole $\beta_3$ Adrenergic Receptor Agonist

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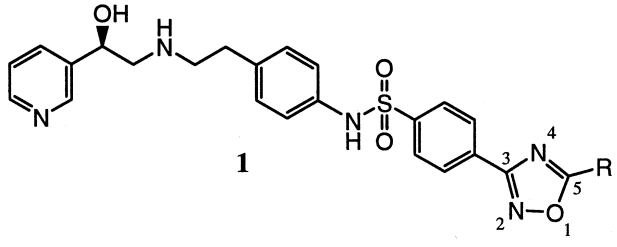
**Abstract**—5-*n*-Pentyl oxadiazole substituted benzenesulfonamide **8** is a potent and selective $\beta_3$ adrenergic receptor agonist ($\beta_3$ $EC_{50}=23$ nM, $\beta_1$ $IC_{50}=3000$ nM, $\beta_2$ $IC_{50}=3000$ nM). The compound has high oral bioavailability in dogs (62%) and rats (36%) and is among the most orally bioavailable $\beta_3$ adrenergic receptor agonists reported to date. 

## Introduction

β-Adrenoceptors are subclassified as $\beta_1$, $\beta_2$, and $\beta_3$. Increased heart rate is the primary consequence of $\beta_1$ adrenergic receptor ($\beta_1$ AR) stimulation, while bronchodilation and smooth muscle relaxation typically result from $\beta_2$ adrenergic receptor ($\beta_2$ AR) stimulation. Adipocyte lipolysis is mediated by atypical receptors, now called $\beta_3$ adrenergic receptors ($\beta_3$ AR), which are found on the cell surface of both white and brown adipocytes where their stimulation promotes both lipolysis and energy expenditure.[1] Thus, $\beta_3$ AR agonists may prove useful for the treatment of obesity.

Benzenesulfonamide derivatives were reported earlier as potent and selective agonists of the human $\beta_3$ adrenergic receptor ($\beta_3$ AR).[2] However, many of these compounds lack good oral bioavailability. In this paper we describe the synthesis and activity of 5-alkyl oxadiazole substituted benzenesulfonamides **1** with improved oral biovailability.[3]



**1**

## Chemical Synthesis

The 5-alkyl oxadiazoles **5**–**11** (Table 1), **12**–**16** (Table 2), and **17**–**20** (Table 3) were prepared as shown in Scheme 1.[4] The protected aniline **2**[2c] was coupled with 4-cyanobenzenesulfonyl chloride to provide the sulfonamide **3**. Treatment of sulfonamide **3** with hydroxylamine hydrochloride and potassium carbonate in ethanol at reflux temperature provided the corresponding amidoxime **4**. 5-Alkyl oxadiazoles **1** were obtained from the amidoxime **4** by acylation with the appropriate acid chloride in the presence of pyridine or with the appropriate acid in the presence of EDAC (ethyldimethylaminopropyl–carbodiimide hydrochloride), followed by thermal cyclization in pyridine or diglyme.[5] Removal of the *tert*-butylcarbamate protecting group was carried out by treatment with trifluoroacetic acid.

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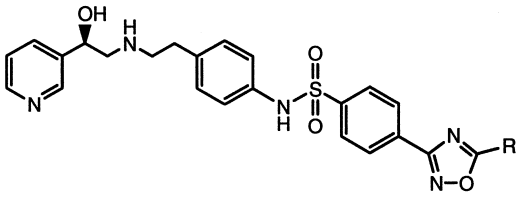
PII: S0960-894X(00)00267-5

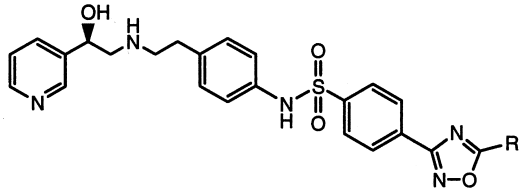
**Table 1.** SAR of 5-alkyl substituted oxadiazoles

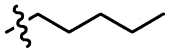
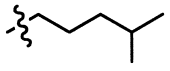
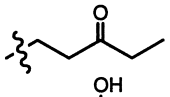
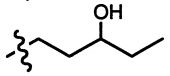
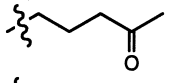
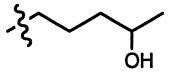


| Compound | R | $\beta_3$ (%act)[a] $EC_{50}$ (nM) | $\beta_1$ binding $IC_{50}$[b] (nM) | $\beta_2$ binding $IC_{50}$[b] (nM) |
|---|---|---|---|---|
| **5** | Me | >100 (15) | 10,000 | 10,000 |
| **6** | *n*-Pr | 87 (70) | 8500 | 8500 |
| **7** | *n*-Bu | 32 (86) | 55,000 | 6500 |
| **8** | *n*-Pen | 23 (53) | 5500 | 3000 |
| **9** | *n*-Hex | 35 (79) | 2000 | 1000 |
| **10** | *n*-Hep | 39 (86) | 2000 | 1415 |
| **11** | *n*-Oct | 54 (90) | 9000 | 2500 |

[a]Adenylyl cyclase activation given % of the 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-alkyl substituted oxadiazoles



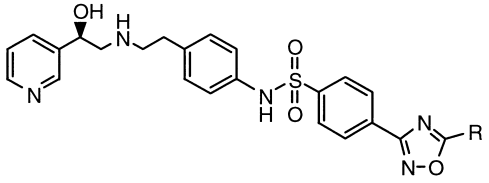
| Compound | R | $\beta_3$ (%act)[a] $EC_{50}$ (nM) | $\beta_1$ binding $IC_{50}$[b] (nM) | $\beta_2$ binding $IC_{50}$[b] (nM) |
|---|---|---|---|---|
| 8 |  | 23 (53) | 5500 | 3000 |
| 12 |  | 29 (58) | 26,000 | 995 |
| 13 |  | 66 (75) | 25,000 | 12,000 |
| 14 |  | 75 (53) | 56,000 | 24,000 |
| 15 |  | 130 (69) | 70,000 | 57,000 |
| 16 |  | >100 (20) | 10,000 | 44,000 |

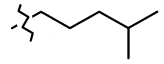
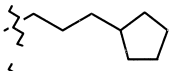
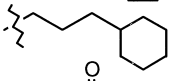
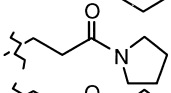
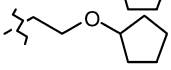
[a]Adenylyl cyclase activation given % of the maximal stimulation with isoproterenol.
[b]Receptor binding assay were carried out with membranes prepared from CHO cells expressing the cloned human receptor in the presence of $^{125}$I-iodocyanopindolol.

## Assay procedure

All compounds were screened for their ability to stimulate increases in cAMP in Chinese hamster ovary (CHO) cells expressing the cloned human $\beta_3$ AR.[6] The activity

**Table 3.** SAR of 5-alkyl substituted oxadiozoles



| Compound | R | $\beta_3$ (%act)[a] $EC_{50}$ (nM) | $\beta_1$ binding $IC_{50}$[b] (nM) | $\beta_2$ binding $IC_{50}$[b] (nM) |
|---|---|---|---|---|
| 12 |  | 29 (58) | 26,000 | 1000 |
| 17 |  | 15 (83) | 5500 | 962 |
| 18 |  | 19 (62) | 1970 | 660 |
| 19 |  | 120 (49) | 30,000 | 51,000 |
| 20 |  | 13 (70) | 8333 | 2667 |

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

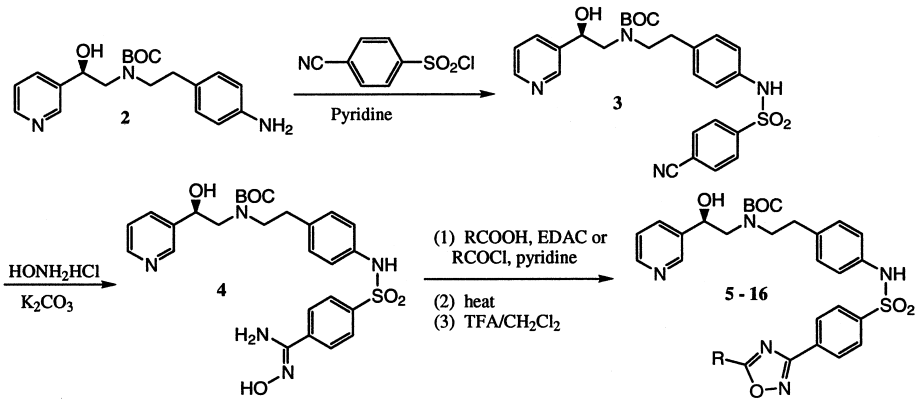
of an agonist at the $\beta_3$ AR is better described by its ability to stimulate adenylyl cyclase in a functional assay, since this method measures affinity for the high affinity, G-protein coupled state of the receptor. This assay accurately predicts the lipolytic potential of compounds in native adipocytes.[7] Binding affinities to these $\beta_1$ and $\beta_2$ ARs were also routinely measured, with efficacy at the $\beta_1$ and $\beta_2$ ARs determined for selected compounds. In vivo efficacy was evaluated by administering drugs to dogs or rhesus monkeys and measuring the level of glycerol release.

## Structure–activity relationships

As shown in Table 1, 5-alkyl oxadiazoles **5**–**11** are potent $\beta_3$ AR agonists with excellent selectivities over $\beta_1$ and $\beta_2$ AR binding activity (51- to 1700-fold and 28- to 200-fold, respectively). The $\beta_3$ AR activity increased as the length of the side chain increased from one to five carbons and decreased thereafter. 5-*n*-Pentyl-oxadiazole **8** was the most potent compound in this series of compounds and had 240-fold and 130-fold selectivities over $\beta_1$ and $\beta_2$AR binding, respectively. It was a weak partial agonist at both $\beta_1$ and $\beta_2$ ARs ($\beta_1$ AR $EC_{50}$ = 140,000 nM and $\beta_2$ AR $EC_{50}$ = 5000 nM, 16% activation relative to isoproterenol activation).

The 5-*n*-pentyl group of the oxadiazole **8** was modified as shown in Table 2. Methyl, carbonyl, and hydroxy groups were incorporated into different positions of the pentyl branch to form alkyls, ketones or alcohols **12–16.** None of them was more potent than the 5-*n*-pentyl oxadiazole **8**.

The 5-isohexyl oxadiazole **12** is a potent agonist. The cyclopentylpropyl **17** and cyclohexylpropyl **18** are slightly




**Scheme 1.**

more potent than the 5-*n*-pentyl oxadiazole **8**, but they are less selective, as shown in Table 3. Introduction of heteroatoms in the 5-alkyl side chains as in **19** and **20** resulted in compounds with less or similar potency.

5-*n*-Pentyl oxadiazole **8** was selected for pharmacokinetic studies in dog and rat (10 mg/kg po, 3 mg/kg iv). This compound has a half-life of 3.6 h and oral bioavailability of $62 \pm 18\%$ in the dog ($n = 2$). It has a half-life of 2.4 h and oral bioavailability of 36% in the rat. In the rhesus, 5-*n*-pentyl oxadiazole **8** produced a dose-dependent elevation of plasma glycerol ($ED_{50Gly} = 0.22$ mg/kg),[8] the maximum extent of which was comparable to that elicited by isoproterenol, indicating that **8** behaves as a full agonist for hyperglyceroemia. Under these conditions, no significant alteration in heart rate was evident at a dose level of 10 mg/kg.

In conclusion, we have discovered 5-alkyl substituted oxadiazoles as potent and selective $\beta_3$ agonists. 5-*n*-Pentyl substituted oxadiazole **8** has very good oral bioavailability in dogs and rats. In the following paper we discuss 5-benzyl and 5-phenoxymethylene substituted oxadiazoles with improved potency.

## Acknowledgements

We thank Mr. Paul Cunningham and Mr. Donald Hora, Jr. for assistance with the in vivo experiments, Ms. Amy Bernick for mass-spectral analyses, and Professor Grannemann (Wayne State University) for supplying the cloned human $\beta_3$ receptor.

## References and Notes

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8. For experimental details see ref 7.