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Substituted Oxazole Benzenesulfonamides as Potent Human β_3 Adrenergic Receptor Agonists

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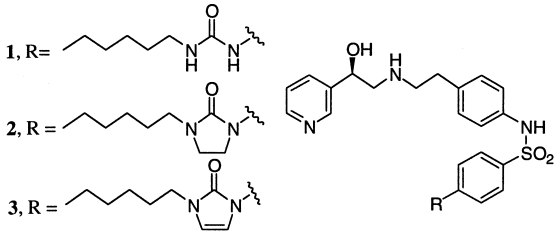
Abstract—As a part of our investigation into the development of orally bioavailable β_3 adrenergic receptor agonists, we have identified a series of substituted oxazole derivatives that are potent β_3 agonists with excellent selectivity against other β receptors. Several of these compounds showed excellent oral bioavailability in dogs. One example, cyclopentylethyloxazole **5f** is a potent β_3 agonist ($EC_{50} = 14$ nM, 84% activation) with 340-fold and 160-fold selectivity over β_1 and β_2 receptors, respectively, and has 38% oral bioavailability in dogs.

Introduction

Obesity results from an imbalance between energy obtained from ingestion of food and its expenditure by the body. The excess energy is stored in the form of body fat. Obesity can be treated by means of restricting food intake, decreasing internal fat absorption and/or increasing energy expenditure. The identification of a third β adrenergic receptor subtype (β_3 AR) led to the investigation of β_3 AR agonists as potential agents for the treatment of various metabolic diseases. Especially, the discovery that lipolysis and thermogenesis in brown adipose tissue are regulated by the β_3 AR led us to study β_3 AR agonists as anti-obesity agents.[1,2] Recently, we have reported[3,4] a series of 3-pyridylethanolamines as potent and selective human β_3 AR agonists with very little β_1 and β_2 adrenergic receptor activity, that are capable of increasing lipolysis and energy expenditure in animals. For example, urea **1**, imidazolidone **2**, and imidazolone **3** derivatives are very potent human β_3 agonists ($EC_{50} = 6.3$, 18 and 14 nM, respectively) however, all three compounds possess poor oral bioavailability in dogs (%F = < 1, 5.7 and 12, respectively, following oral administration in 0.05 M citric acid/0.05 M hydrochloric acid solution) due in part to extensive metabolism. With this in mind, we investigated the replacement of the urea moiety on the aryl sulfonamides by oxazoles.



Chemistry

Most of the β_3 AR agonists disclosed in this report were prepared by a convergent route comprising coupling of the aniline moiety **4**[5] with various sulfonyl chlorides followed by removal of the Boc protecting group (Scheme 1).

For the 2-substituted-5-aryl-oxazole derivatives **5**, the requisite sulfonyl chlorides were prepared by either direct chlorosulfonylation with chlorosulfonic acid (Method A) or in a two-step sequence[6] utilizing oxidative chlorination of a sulfinic acid lithium salt obtained from aryl bromides using *n*-butyl lithium and sulfur dioxide (Method B) as illustrated in Scheme 2.

Synthesis of the required 2-substituted-5-aryl oxazoles is shown in Scheme 3. The 2-alkyl substituted oxazoles **8** were synthesized as follows. Freshly prepared aryl-

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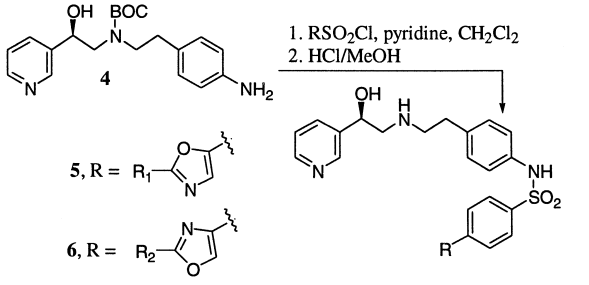
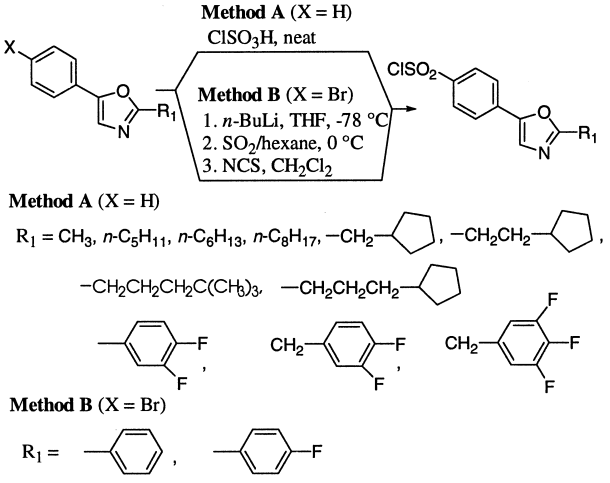
azidomethyl ketone **7** was reacted with LDA and then with an acid chloride or anhydride to give an O-acyl vinyl azide product. Subsequent cyclization into the 2-alkyl-5-aryl oxazoles **8** was effected with triethyl phosphite. The 2,5-diaryl-oxazoles **9** were obtained using a different route. EDAC coupling of 2-amino acetophenone hydrochloride with benzoic acid or 4-fluorobenzoic acid followed by cyclization/dehydration with phosphorus oxychloride gave the 2,5-diaryl oxazoles.

For most of the 2-substituted-4-aryl-oxazole derivatives **6a–k**, the sulfonyl chlorides were prepared according to Method A in Scheme 2. Synthesis of the required 2-substituted-4-aryl-oxazoles is illustrated in Scheme 4. Cyclization of 2-bromoacetophenone with the appropriate amide gave the 2-methyl- and 2-substituted aryl-4-phenyl oxazoles **10**. For 2-cyclopentyethyl and 2-aralkyl substituted 4-aryl oxazoles **12**, bromination of 2-methyl-4-phenyl oxazole (**11**, compound **10** with $R = CH_3$) with excess NBS[7] yielded 2-bromomethyl-5-bromo-4-phenyl oxazole (**12**). Subsequent cuprate displacement on the bromomethyl group and removal of the bromine at the 5-position of oxazole by catalytic hydrogenation furnished the appropriate oxazoles.

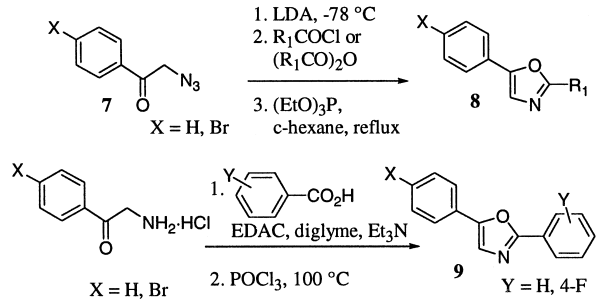
The preparation of 2-aryloxymethyl oxazole derivatives **6h–j** is shown in Scheme 5. The BOC protected 4-aminophenethyl amine was reacted with sulfonyl chloride **14**, prepared by Method A in Scheme 2 with compound **12** to give the adduct **15**. The phenoxy group was introduced onto sulfonamide **15** by a displacement reaction at the methylbromide. Subsequent acid treatment led to the phenethyl amine right-hand side **16**. The final compounds **6h–j** were prepared by reaction with epoxide **17**[5] and hydrogenation.



Scheme 1.



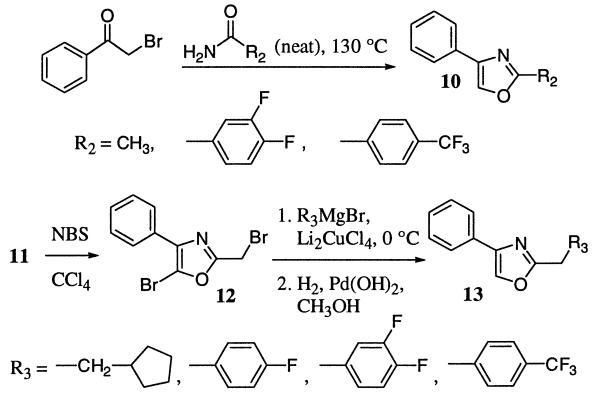
Scheme 2.



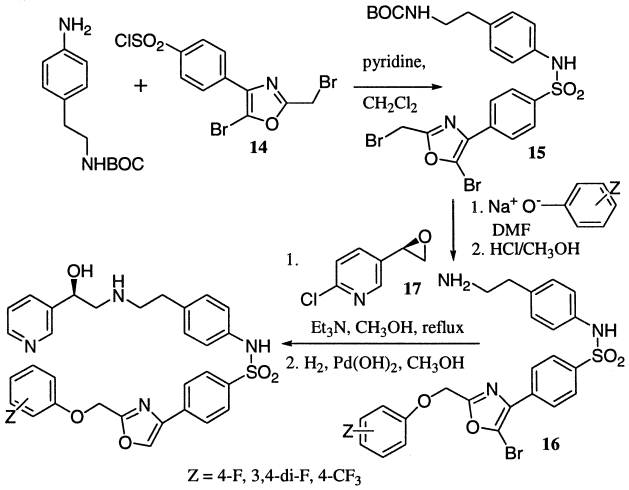
Scheme 3.

Results

All of the oxazole sulfonamide based compounds[8] described above were tested in vitro for their ability to stimulate increases in cAMP in CHO cells expressing the cloned human β_3 receptor. Because of low intrinsic activity at β_1 and β_2 receptors, binding affinities for β_1 and β_2 were measured using membranes prepared from



Scheme 4.

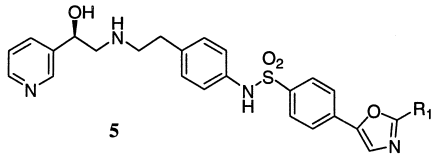


Scheme 5.

CHO cells expressing the cloned human β_1 and β_2 adrenergic receptors.[9] The results are shown in Tables 1 and 2.

Among *n*-alkyl chains in the 2-position of the 5-aryl-oxazoles (entries **5a**–**d**), increasing the alkyl chain length enhances the potency toward β_3-AR. However, the most potent of these, the *n*-octyl analogue **5d** suffers from low selectivity against β_1 and β_2 receptors. With this in mind, we examined the effect of the cycloalkyl analogues **5e**–**g**. All three derivatives are partial agonists of the human β_3 AR (63–85% activation relative to the full agonist isoproterenol) and show good β_3-selectivity over β_1 and β_2 ARs. Noteworthy is the bulky neo-pentyl derivative **5h**. It behaves as a full agonist, albeit with low efficacy (230 nM) and low selectivity. Substituted aryl **5i**–**k** and benzyl derivatives **5l** and **m** were also evaluated. These compounds in general are potent and selective β_3 agonists thus implying that a phenyl or benzyl group can serve as a lipophilic side-chain in place of the aliphatic side-chains. Introduction of fluorine in the phenyl ring resulted in an enhancement of potency and selectivity; the 3,4-difluorobenzyl derivative, **5l**, is a potent β_3 AR agonist (11 nM) and shows 680-fold and 420-fold binding selectivity over β_1 and β_2 ARs, respectively.

Table 1. Comparison of β_3 AR agonist activity and β_1 and β_2 binding affinity of compounds **5a**–**m**

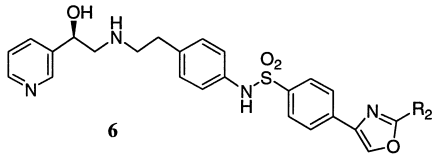


5

Compound	R_1	β_3 EC_{50} (% act)[a]	β_1 Binding IC_{50} (nM)[b]	β_2 Binding IC_{50} (nM)[b]
5a	Methyl	>100 (21)	7000	3000
5b	*n*-Pentyl	26 (70)	200	4000
5c	*n*-Hexyl	34 (78)	6000	1200
5d	*n*-Octyl	12 (77)	350	270
5e	*c*-Pentylmethyl	19 (68)	8000	2500
5f	*c*-Pentylethyl	14 (84)	4800	1800
5g	*c*-Pentylpropyl	5.3 (63)	1000	320
5h	4,4-Dimethylpentyl	230 (100)	2000	1000
5i	Phenyl	39 (88)	3000	3500
5j	4-*F*-Phenyl	37 (96)	6500	21,000
5k	3,4-di-*F*-Phenyl	35 (88)	31,000	3000
5l	3,4-di-*F*-Benzyl	11 (85)	7500	4700
5m	3,4,5-tri-*F*-Benzyl	9.2 (80)	2000	940

[a]Adenylyl cyclase activation is given as percent of the maximal stimulation with isoproterenol; EC_{50} values are reported in nM.
[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. Comparison of β_3 AR agonist activity and β_1 and β_2 binding affinity of compounds **6a**–**j**



6

Compound	R_1	β_3 EC_{50} (% act)[a]	β_1 Binding IC_{50} (nM)[b]	β_2 Binding IC_{50} (nM)[b]
6a	Methyl	76 (60)	37,000	30,000
6b	*c*-Pentylethyl	15 (65)	2000	3700
6c	4-CF_3-Phenyl	22 (84)	2100	1400
6d	3,4-di-F-Phenyl	35 (80)	1900	2200
6e	4-*F*-Benzyl	5.2 (93)	4700	3300
6f	3,4-di-*F*-Benzyl	4 (83)	2400	630
6g	4-CF_3-Benzyl	4.3 (76)	1200	310
6h	4-*F*-Phenoxymethyl	19 (95)	6500	9000
6i	3,4-di-*F*-Phenoxymethyl	2.3 (85)	6500	3500
6j	4-CF_3-Phenoxymethyl	210 (88)	42,000	20,000

[a]Adenylyl cyclase activation is given as percent of the maximal stimulation with isoproterenol; EC_{50} values are reported in nM.
[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.

The data for compounds containing 2-substituted-4-aryl-oxazoles are shown in Table 2 and follows a similar trend as that observed for the 2-substituted-5-aryl-oxazole series. Cyclopentylethyl derivative **6b** (β_3 $EC_{50} = 15$ nM) is equipotent to the corresponding 5-aryl-oxazole **6f** (β_3 $EC_{50} = 18$ nM). The phenyl (**6c** and **d**) and benzyl (**6e**–**g**) moieties are well tolerated and the efficacy was enhanced by introduction of electron withdrawing groups such as fluorine or trifluoromethyl. By replacing the benzyl moiety with a 3,4-difluorophenoxymethyl, derivative **6i** shows decreased β_1 and β_2 affinity but increased potency at the β_3 receptor.

Pharmacokinetic properties of some selected compounds **5f**, **5k**–**l** and **6c** were determined in dogs and the PK parameters are presented in Table 3. The oral bioavailabilties of these compounds are all greater than 30%, which was a significant improvement relative to imidazolidinone and imidazolone derivatives **2** and **3**. In addition, these oxazole derivatives have long half-lives (from 3.9 h to upwards of 13.2 h). The efficacy of the cyclopentylethyl oxazole **5f** was also examined in a rising dose infusion study in anesthetized rhesus monkeys.[2] The compound **5f** evokes hyper-glycerolemia ($ED_{50} = 0.09$ mg/Kg) with a maximum response equivalent to that of the full agonist isoproterenol. No significant change in heart rate was observed with compound **5f**.

In summary, we identified a new series of human β_3 AR agonists that contain oxazoles that are an effective replacement for the urea moiety found in compounds **1**–**3**. In general, these oxazole derivatives have good potency,

Table 3. Pharmacokinetics of compounds **5f**, **5k**–**l** and **6c** (3 mg/Kg iv and 10 mg/Kg po) in dogs

Compound	AUC iv[a] μg min/mL	AUC po[b] μg min/mL	$t\frac{1}{2}$ h	F (%)
5f	190.1±1.9	242.9±14.3	5.0	38.3
5k	95±11	122.1±2.9	7.4	38.6
5l	388±4.9	523.5±26	3.9	40.5
6c	201.3±22	217.9±18.4	13.2	32.5

[a]Fasted dogs ($n = 2$) were dosed intravenously at 3 mg/kg; plasma drug levels were determined by LC/MS/MS.
[b]Dogs ($n = 2$) were dosed orally at 10 mg/kg; plasma drug levels were determined by LC/MS/MS.

selectivity and significantly improved oral bioavailabilities. In particular, 2-cyclopentylethyl oxazole derivative **5f** is a potent β_3 AR agonist ($EC_{50} = 14$ nM, 84% activation) with >100-fold binding selectivity over β_1 and β_2 adrenergic receptors. This compound has excellent oral bioavailability in dogs (38%) with a half-life of 5 h and evoked hyperglycerolemia when administered orally to dogs at 10 mg/kg. In addition, intravenous administration of **5f** to anesthetized monkeys also induces hyperglycerolemia ($ED_{50} = 0.09$ mg/kg) with a maximum response equivalent to that of the full agonist isoproterenol, with no significant change in heart rate being observed.

Acknowledgements

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