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New Oxadiazolidinedione Derivatives as Potent and Selective Human β_3 Agonists

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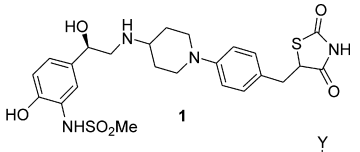
Abstract—As part of our investigation into the development of potent and selective human β_3 agonists, a series of thiazolidinedione analogues was prepared and evaluated for their biological activity on the human β_3-adrenergic receptor. The oxadiazolidinedione derivative **17** was found to be the most potent and selective compound in this study, with an EC_{50} value of 0.02 μM at the β_3 receptor, 259-fold selectivity over the β_1 receptor, and 745-fold selectivity over the β_2 receptor.

Potent and selective β_3-adrenergic receptor (β_3-AR) agonists are potential drugs for the treatment of obesity, type II diabetes, frequent urination, and related diseases.[1] Any β_1-AR or β_2-AR-agonism would likely cause increased heart rate or muscle tremor, respectively; both are unacceptable side effects in a drug. In a previous paper, 2,4-thiazolidinedione derivative **1** was reported as a potent and selective human β_3-AR agonist,[2] with an EC_{50} value of 0.01 μM, >110-fold selectivity over both the β_1- and β_2-ARs, and active and selective in in vivo procedures. The previous structure–activity relationship study on the left-hand side of general structure **2** revealed that the combination of 4-hydroxy and 3-methylsulfonamide on the phenyl ring was necessary for the thiazolidinedione based β_3 agonist's activity and selectivity. Herein we report further modification on **2** by introducing a variety of thiazolidinedione replacements, leading to the discovery of oxadiazolidinedione derivative **17** as a potent and selective human β_3 agonist.



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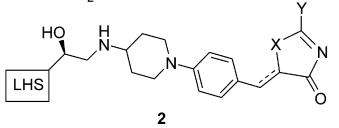

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The thiazolidinedione analogues described in this paper were readily prepared by utilizing reductive amination of piperidones with left-hand side amines[2] according to the synthetic Schemes 1–3. The thiazolidineones, hydantoins, and pseudothiohydantoins (**8**, **10**, and **13**) were prepared according to Scheme 1. A Knoevenagel condensation between aldehyde **3**[3] and 2,4-thiazolidinedione (**4a**), pseudothiohydantoin (**4b**) or hydantoin (**4c**) followed by acidic hydrolysis provided piperidones **6**. Reductive aminations between piperidones **6** and amine **7** gave the olefines (**8**). Compound **5** was converted to **9** by a hydrogen transfer reaction (5% sodium mercury amalgam) followed by an acidic ketal hydrolysis. Reductive amination of **9** with **7**, as described above, gave the reduced analogue **10**. Alkylation of thiazolidinedione **9a**[2] (the substituents **a**–**c** for compounds **4**, **5**, **6**, and **9** are defined to be the same as those defined for compound **8**) with *t*-butyl bromoacetate followed by reductive amination with **12** and acid hydrolysis produced **13**.

Oxadiazolidinedione **17** was prepared as outlined in Scheme 2. Reductive amination of **3** with hydroxylamine produced **14**, which upon treatment with N-TMS isocyanate and ketal hydrolysis afforded hydroxyurea **15**. The oxadiazolidinedione ring was formed by reacting the *N*-hydroxyurea **15** with methyl chloroformate and sodium hydride.[4] The final product **17** was obtained by reductive amination of **16** with **12** using essentially the same conditions as previously described in Scheme 1.

Synthesis of thiazolidinones (**20**, **22**, and **23**) was achieved as illustrated in Scheme 3. The thiazolidinone

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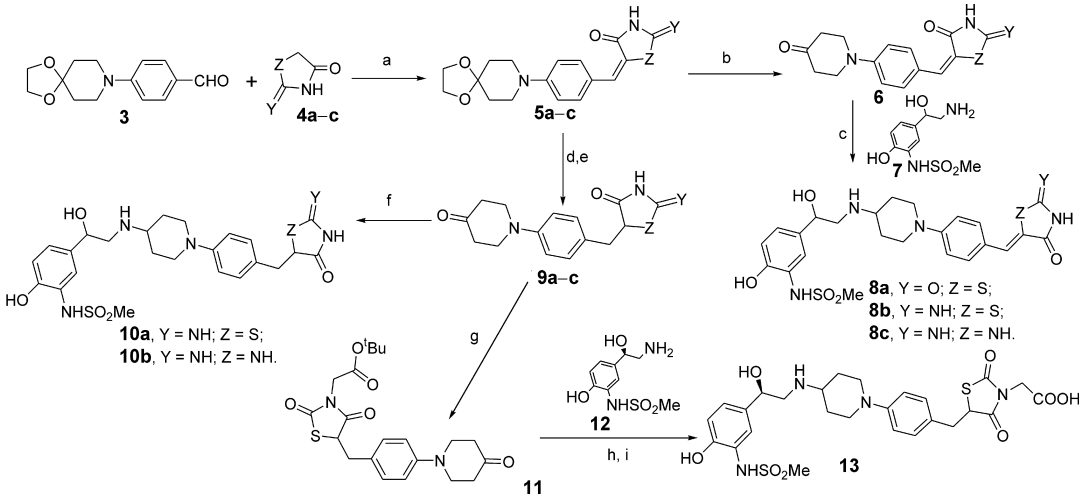
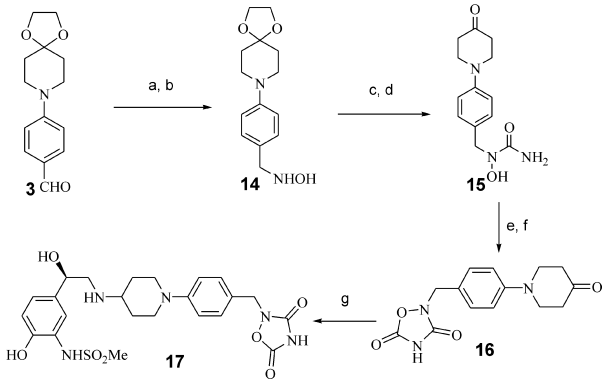


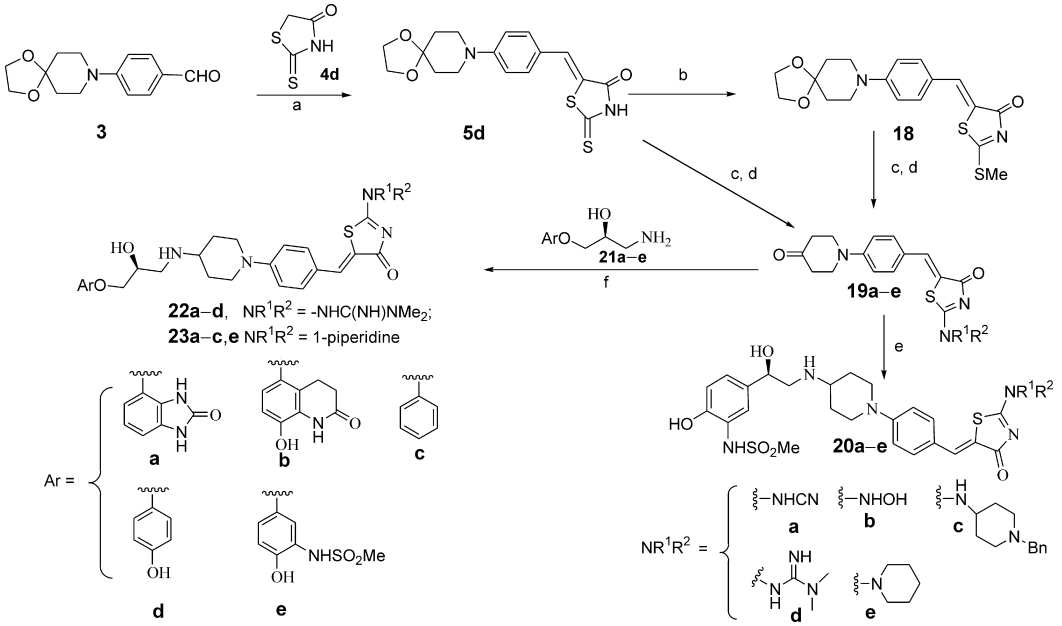
Scheme 1. (a) Piperidine, EtOH; (b) concd HCl; (c) $NaBH(OAc)_3$, DMF; (d) 5% Na/Hg, THF/H_2O; (e) concd HCl; (f) **7**, $NaBH(OAc)_3$, DMF; (g) $BrCH_2CO_2{}^tBu$; NaH, DMF, 76%; (h) **12**, $NaBH(OAc)_3$, DMF, 68%; (i) TFA, CH_2Cl_2, 58%.



Scheme 2. (a) NH_2OH HCl salt, NaOAc, 90%; (b) $NaCNBH_3$, MeOH, 78%; (c) Me_3SiNCO, THF/dioxane (1:1), 73%; (d) concd HCl, 98%; (e) $ClCO_2Me$, NaH, THF; (f) NaH, DMF, 85% over e and f; (g) **12**, $NaBH(OAc)_3$, DMF, 71%.

19b (the substituents for compounds **19a–e** are defined to be the same as those defined for compound **20**) was obtained by condensation of rhodanine **5d** with hydroxylamine in refluxing ethanol and ketal hydrolysis. Alternatively, alkylation of rhodanine **5d** with iodomethane provided the methylmercapto compound **18**. Reaction of compound **18** with various amines such as piperidine, 4-amino-1-benzylpiperidine, *N*,*N*-dimethylguanidine or cyanamide followed by ketal hydrolysis gave the desired intermediates **19a** and **19c–e**. Conversion of **19** to the final olefinic thiazolidinones (**20**, **22**, and **23**) was accomplished according to Scheme 1. In all cases of the Knoevenagel condensation, only the *Z* isomer was obtained for the olefinic product.[5]

The thiazolidinedione derivatives and related compounds were tested for their in vitro activity in stimulating an increase in cAMP levels in Chinese hamster



Scheme 3. (a) NaOAc, AcOH, 66%; (b) MeI, *N*,*N*-diisopropylethylamine, EtOH, 99%; (c) NHR^1R^2, EtOH; (d) concd HCl; (e) **12**, $NaBH(OAc)_3$, DMF; (f) $NaBH(OAc)_3$, DMF.

ovary (CHO) cells expressing the human β_3-, β_2-, and β_1-ARs[6] and the results are summarized in Tables 1 and 2. The olefinic thiazolidinedione **8a** was found to be as potent (β_3 $EC_{50} = 0.006\,\mu M$, IA = 1.03)[7] and selective (96-fold vs β_2 and 492-fold vs β_1) as **1**. The corresponding olefinic pseudothiohydantoin **8b** and hydantion **8c**, although having comparable agonist activity, were less selective against the β_2 (61- and 18-fold, respectively) and β_1 (113- and 38-fold, respectively) receptors. The reduced alkyl analogues **10a** and **10b** showed reduced β_3 potency ($EC_{50} = 0.09$ and $0.23\,\mu M$, respectively). Replacement of thiazolidinedione with oxadiazolidinedione (**17**) gave good potency ($EC_{50} = 0.02\,\mu M$, IA = 1.0) at the β_3 receptor and increased selectivity against the β_1 (259-fold) and β_2 receptors (745-fold).

Results from our earlier chemical series demonstrated that introduction of a carboxylic acid group on the right-hand side of 2-(1-phenyl-piperidin-4-ylamino)-ethanol β_3 agonists would enhance selectivity while maintaining the β_3 agonist activity.[8] Introducing a carboxylic acid group to **1** did enhance the β_2 selectivity. However, the activity of **13** was decreased 3-fold relative to **1**.

A variety of thiazolidinones with different substitution on the thiazolidinone ring were tested, some of which are shown in Tables 1 and 2. Thiazolidinones with a cyanamide (**20a**), hydroxylamine (**20b**) or 4-amino-1-benzylpiperidine (**20c**) substituent were generally very potent at the β_3 receptor (with EC_{50}'s of single digits nM and maximal activation 83–122% of that evoked by isoproterenol), however, they were not very selective against both the β_2 and β_1 receptors. Further modification of the substitution on the right-hand side of thiazolidinones led to guanidine **20d** and piperidine **20e**, which were found to be potent at the β_3 receptor (with EC_{50}'s of 0.003 and $0.009\,\mu M$, respectively) and moderately selective (73- to 423-fold) against the β_2 and β_1 receptors. In view of the potent activity and modest selectivity of **20d** and **20e**, two more series of thiazolidinones with phenoxypropanolamines[2] on the left-hand side were synthesized. In contrast to phenethanolamines **20a**–**e**, all of the tested phenoxypropanolamines (**22** and **23**) had no measurable β_2 agonist activity. For both the guanidine and piperidine series, many potent β_3-agonists were identified, including compounds with a carbostyril (**22b** and **23b**), benzimidazolone (**22a** and **23a**), or 4-OH-3-methylsulfonamide phenyl (**23e**) substituent. However, only benzimidazolones (**22a** and **23a**) displayed a good β_3 agonist selectivity profile. The guanidines with a phenoxy (**22c**) or 4-hydroxyphenoxy (**22d**) substituent had low potency at the β_3 receptors with EC_{50}'s of 0.94 and $0.4\,\mu M$, respectively.

Selected compounds with good agonist activity/selectivity profiles were examined in β_1 and β_2-AR binding assays (Table 3).[9] Benzimidazolone **22a** exhibited strong antagonist activity against both β_1 and β_2 receptors with binding constants (K_i) of $0.0038\,\mu M$ for β_2 and $0.0072\,\mu M$ for β_1. In contrast, compounds **13** and **17** exhibited low binding affinity ($K_i > 2\,\mu M$) for both β_2 and β_1 receptors, suggesting good selectivity for the β_3 receptor.

The ability of β_3 agonist **17** to treat or inhibit disorders related to obesity or type II diabetes was confirmed in an in vivo procedure,[10] which measured thermogenesis in human β_3 AR-transgenic mice (Tg mice). Administered 10 mg/kg (ip) to Tg mice, **17** produced a significant effect ($30 \pm 8\%$) in thermogenesis.

There have been a number of reports that the thiazolidinediones are high-affinity peroxisome proliferator-activated receptor (PPARγ) agonists, and there is a significant positive relationship between the in vitro

Table 1. Comparison of β_3-AR agonist activity and selectivity of thiazolidinediones and related analogues[7]

Compd	β_3-AR[a] EC_{50} (μM)(IA)	$S_{3/2}$[b] (IA)	$S_{3/1}$[b] (IA)
CL316243	1.15(0.63)	227(0.43)	97(0.21)
1	0.01(1.19)	119(0.67)	272(0.82)
8a	0.006(1.03)	96(0.83)	492(0.87)
8b	0.009(1.0)	61(0.40)	113(0.80)
8c	0.034(0.94)	18(0.38)	38(0.82)
10a	0.086(1.2)	27(0.19)	38(0.76)
10b	0.23(1.0)	nd[c]	nd
17	0.02(1.0)	259(0.59)	745(0.29)
13	0.034(1.1)	>290(0.0)	86(0.56)
20a	0.001(1.0)	48(0.54)	290(0.86)
20b	0.008(0.83)	28(0.86)	54(0.71)
20c	0.009(1.22)	10(0.58)	133(0.69)
20d	0.003(0.86)	110(0.47)	423(0.82)
20e	0.009(1.06)	97(0.62)	73(0.90)

[a]β-AR agonistic activities were assessed by measurement of cAMP accumulation levels in CHO cells expressing human β-ARs; the intrinsic activities (IA) were given as a fraction of the maximal stimulation with isoproterenol.
[b]Agonist selectivity for β_3 over β_n is defined by $S_{3/n} = \beta_n\ EC_{50}/\beta_3\ EC_{50}$.
[c]nd = not determined.

Table 2. Comparison of β_3-AR agonist activity and selectivity of thiazolidineones

Compd	β_3-AR[a] EC_{50} (μM)(IA)	β_2-AR[a] (IA)	β_1-AR $S_{3/1}$[b] (IA)
22a	0.01(0.94)	(0)	(0.09)
22b	0.002(1.0)	(0)	6(0.65)
22c	0.94(0.79)	nd[c]	nd
22d	0.40(0.93)	nd	nd
23a	0.009(0.95)	(0.25)	(0.25)
23b	0.006(1.1)	(0)	1.7(0.79)
23c	0.075(0.96)	(0)	221(0.47)
23e	0.001(1.0)	(0)	9(0.76)

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

Table 3. β_1-AR and β_2-AR binding inhibition constants (K_i)

Compd	β_1-AR Binding[a] (K_i, μM)	β_2-AR Binding[a] (K_i, μM)
13	9.10	2.10
17	9.49	74.0
22a	0.0038	0.0072

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

activity at the PPARγ receptor and the in vivo antihyperglycemic activity in genetically diabetic mice.[11] Although our compounds possess thiazolidinedione substituents, they showed essentially no activity (data not shown) at the PPARγ receptor.

In conclusion, the synthesis and structure–activity relationship of thiazolidinedione based β_3 agonists have been discussed. Replacement of the 2,4-thiazolidinedione group with an oxadiazolidinedione has led to the identification of a potent and selective agonist (**17**) with an EC_{50} of 0.02 μM, 259-fold selectivity over β_2 and 745-fold selectivity over β_1. It has also been showed to be thermogenic in human β_3-AR transgenic mice.

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