Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 757–760

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

2,4-Thiazolidinediones as Potent and Selective Human β_3 Agonists

Baihua Hu,[a,*] John Ellingboe,[a] Iwan Gunawan,[a] Stella Han,[b] Elwood Largis,[b] Zenan Li,[a] Michael Malamas,[a] Ruth Mulvey,[b] Alexander Oliphant,[a] Fuk-Wah Sum,[a] Jeff Tillett[b] and Victoria Wong[a]

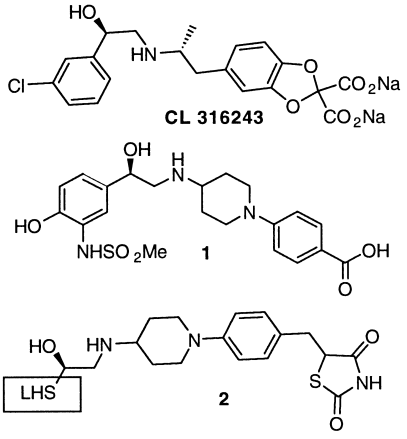
[a]*Chemical Sciences, Wyeth-Ayerst Research, Pearl River, NY 10965, USA*
[b]*Cardiovascular/Metabolic Diseases Research, Wyeth-Ayerst Research, Pearl River, NY 10965, USA*

Received 4 December 2000; accepted 12 January 2001

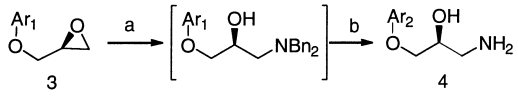
Abstract—Methylsulfonamide substituted 2,4-thiazolidinedione **22c** is a potent ($EC_{50} = 0.01\ \mu M$, IA = 1.19) and selective (more than 110-fold over β_1 and β_2 agonist activity) β_3 agonist. This compound has also been proven to be active and selective in an in vivo mode.

The β_3-adrenergic receptor (β_3-AR) has been shown to mediate various pharmacological and physiological effects such as lipolysis in white adipocyte tissue (WAT), thermogenesis in brown adipocyte tissue (BAT), and relaxation of urinary bladder detrusor tissue.[1] Consequently, several pharmaceutical firms, including ourselves, are engaged in developing potent and selective β_3-AR agonists for the treatment of obesity, type II diabetes, and frequent urination. CL316243,[2] discovered in our laboratories, has been shown to be an effective anti-obesity and anti-diabetic agent in rodents. However, human clinical trials with CL316243 have been disappointing due to structural differences between the human and the rodent β_3-AR. To discover potent human β_3-AR agonists we have established Chinese hamster ovary (CHO) cell line expressing the cloned human β_3-AR receptor that would more accurately predict the effects in humans. Using this human β_3-AR assay the 4-piperidino-benzoic acid derivative **1** was found to be a modestly potent human agonist ($EC_{50} = 0.22\ \mu M$, IA = 1.2).[2c] We decided to investigate whether incorporation of a carboxylic acid mimetic 2,4-thiazolidinedione would have a positive effect on β_3-AR agonist **1**. The synthesis and β_3-AR agonist activity of 2,4-thiazolidinedione **2** with several β-amino alcohols on the left-hand side (LHS) will be described in this communication.

The current β-amino alcohols for β_3-AR agonist LHS moieties belong to two general structural classes:[1]



aryloxypropanolamines and arylethanolamines. The aryloxypropanolamines that are not known in the literature were generally prepared from epoxides **3** by regioselective ring opening with dibenzylamine followed by debenzylation (Scheme 1). The required epoxides for **21a–c**, **e–f** (the substituents **a–f** for compounds **4**[3] and **21** are defined in Table 1) were prepared according to



Scheme 1. (a) Bn_2NH, MeOH; (b) HCO_2NH_4, Pd/C.

*Corresponding author. Fax: +1-845-732-5561; e-mail: hub@war.wyeth.com

0960-894X/01/$ - see front matter
PII: S0960-894X(01)00063-4

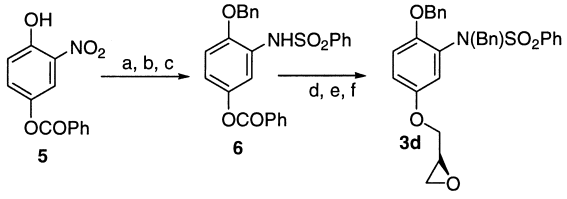
Table 1. Variation of LHS of 2,4-thiazolidinediones

Compound	Ar	β_3-AR[a] EC_{50} μM (IA)	β_2-AR[a] EC_{50} μM (IA)	β_1-AR[a] EC_{50} μM (IA)
CL316243		1.15 (0.63)	262 (0.43)	111 (0.21)
21a	Phenyl	0.04 (0.71)	(0.03)	2.02 (0.34)
21b	4-OH-Phenyl	0.012 (0.89)	(0.01)	2.86 (0.59)
21c	4-OH-3-$MeSO_2NH$-Phenyl	0.003 (1.1)	(0)	1.17 (0.99)
21d	4-OH-3-$PhSO_2NH$-Phenyl	0.38 (0.84)	NT[b]	NT
21e	5-Carbostyril	0.013 (1.2)	(0.05)	1.53 (1.17)
21f	4-(2-Benzimidazolone)	0.024 (1.1)	(0.03)	0.021 (0.41)
22a	3-Cl-Phenyl	0.17 (0.56)	NT	NT
22b	3-Pyridyl	0.9 (0.9)	NT	NT
22c	4-OH-3-$MeSO_2NH$-Phenyl	0.01 (1.19)	1.19 (0.67)	2.72 (0.82)
22d	4-Cl-3-$MeSO_2NH$-Phenyl	0.66 (0.59)	(0.02)	(0.03)
22e	3-$MeSO_2NH$-Phenyl	>10	NT	NT
22f	4-OH-3-$PhSO_2NH$-Phenyl	0.006 (0.93)	0.62 (0.5)	0.43 (0.46)

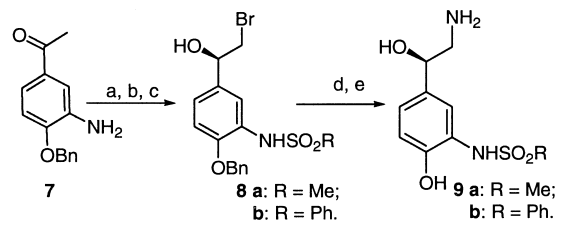
[a]β-ARs agonistic activities were assessed by measurement of cAMP accumulation levels in CHO cells expressing human β-ARs; the intrinsic activities (IA) were given as a fraction of the maximal stimulation with isoproterenol.
[b]NT = not tested.

literature procedures.[4] The corresponding 3-benzenesulfonamide epoxide **3d** for **21d** was synthesized as shown in Scheme 2. Benzylation of phenol **5**[5] with benzyl bromide followed by reduction of the nitro group and sulfonylation with benzenesulfonyl chloride gave **6**. The benzene-sulfonamide **6** was then benzylated again with benzyl chloride, and the benzoic ester was hydrolyzed. Alkylation of the resulting phenol with (2*S*)-glycidyl 3-nitro-benzene sulfonate gave the requisite **3d** (Scheme 2).

Several routes were used to prepare the arylethanolamines. The bromide **8b** was derived from aniline **7**[6] by sulfonamide formation, bromination and enantioselective reduction using Corey's (*R*)-2-meth-CBS-oxazaborolidine as the catalyst. Nucleophilic substitution of bromide **8** with sodium azide in DMSO[7] followed by debenzylation and azide reduction furnished the desired arylethanolamine **9** (Scheme 3). The azide **12** was



Scheme 2. (a) BnBr, K_2CO_3, DMF, 90%; (b) H_2, PtO_2, MeOH, 79%; (c) $PhSO_2Cl$, Et_3N, EtOAc, 61%; (d) BnCl, NaH, DMF, 70%; (e) NaOH, 82%; (f) (2*S*)-glycidyl 3-nitrobenzene sulfonate, K_2CO_3, DMF, 76%.

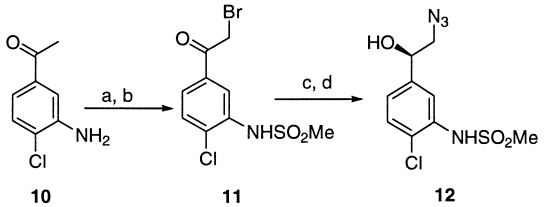


Scheme 3. (a) $PhSO_2Cl$, Py, CH_2Cl_2, 47%; (b) $CuBr_2$, $CHCl_3$, 53%; (c) (*R*)-2-methyl-CBS-oxazaborolidine, BH_3, THF, 61%; (d) NaN_3, DMSO; (e) H_2, Pd/C, MeOH, 71% for **9a** (steps d and e), 69% for **9b** (steps d and e).

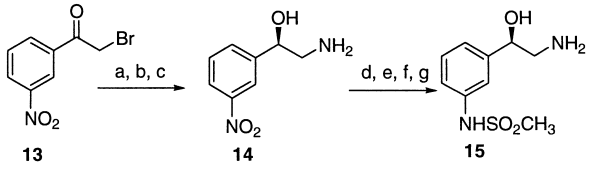
prepared from **10**[8] by a similar route as shown in Scheme 4. In this case, the azide instead of amine was used as a LHS moiety.

As indicated in Scheme 5, reduction of bromoketone **13** with Corey's CBS-borane followed by cyclization with NaOH gave the epoxide which underwent ring opening upon treatment with ammonia. The major product **14** was readily separated from the minor amount of the kinetically less favored isomer[9] by recrystallization. After protection of the amine moiety, reduction of the nitro group, sulfonylation of the resulting aniline followed by deprotection of the carbamate group provided **15**. The 3-pyridyl analogue **18** was prepared analogously to **14** from the bromoketone **16**[10] as shown in Scheme 6.

Thiazolidinediones **21a**–**f** or **22a**–**f** (the substituents **a**–**f** are defined in Table 1) were conveniently prepared as outlined in Scheme 7. A Knoevenagel condensation between aldehyde **19**[11] and 2,4-thiazolidinedione followed by catalytic hydrogenation and acidic hydrolysis



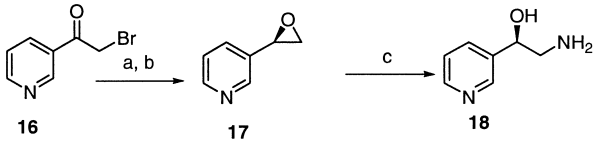
Scheme 4. (a) $PhSO_2Cl$, Py, CH_2Cl_2, 57%; (b) $CuBr_2$, $CHCl_3$, 96%; (c) (*R*)-2-methyl-CBS-oxazaborolidine, BH_3, THF; (d) NaN_3, DMSO; 64% over steps c and d.



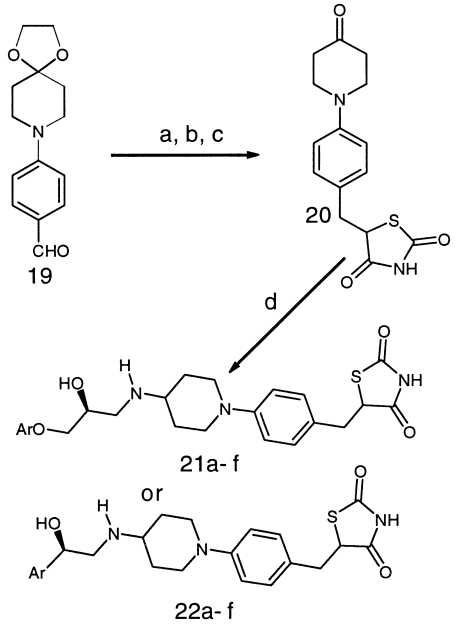
Scheme 5. (a) (*R*)-2-Methyl-CBS-oxazaborolidine, BH_3, THF, 90%; (b) NaOH, THF, 82%; (c) NH_3, MeOH, 70%; (d) $(Boc)_2O$, DMF, 78%; (e) Fe, NH_4Cl, $MeOH/H_2O$, 83%; (f) MsCl, Py, CH_2Cl_2, 49%; (g) TFA, CH_2Cl_2, 64%.

provided piperidones **20**. The desired final products (**21a–f** or **22a–f**)[12] were prepared by utilizing reductive amination of piperidones **20** with the appropriate aryloxypropanolamines, arylethanolamines or arylethanolazides.

We examined a variety of aryloxypropanolamines substituted 2,4-thiazolidinediones for their ability to stimulate an increase in cAMP in CHO cells expressing the cloned human β_3-AR receptor.[13] Phenoxy **21a** is a potent ($EC_{50} = 0.04\,\mu M$) agonist at the β_3 receptor, however, it is a partial agonist (defined as IA = 0.2–0.90) with 71% activation relative to (−)-isoproterenol and is only 50-fold selective over the β_1 agonist activity. The 4-hydroxylphenoxy **21b** is also a partial agonist, but it is more selective (238-fold) against the β_1 receptor. While the 3-methylsulfonamide phenoxy **21c** is a potent ($EC_{50} = 0.003\,\mu M$) full agonist (defined as IA >0.90) with IA value of 1.1, the bulky benzenesulfonamide phenoxy **21d** is 127-fold less potent. These results suggest that in the aryloxypropanolamine series the size of sulfonamide substituent (methylsulfonamide of **21c** vs benzenesulfonamide of **21d**) is important for β_3 agonist activity while the hydrogen bonding capacity (**21a–c**, 4-OH vs 4-H or 3-$MeSO_2NH$-4-OH) appears to be less important. Two heterocyclic derivatives were also examined, and the 5-carbostyril (8-hydroxy-3,4-dihydro-1*H*-quinolin-2-one) analogue **21e** is potent ($EC_{50} = 0.013\,\mu M$, IA = 1.2) and 117-fold selective over the β_1 agonist activity while the benzimidazolone analogue **21f** is also potent ($EC_{50} = 0.024\,\mu M$, IA = 1.1) but not selective over the β_1 receptor.



Scheme 6. (a) (*R*)-2-Methyl-CBS-oxazaborolidine, BH_3, THF, 34%; (b) NaOH, THF, 72%; (c) NH_3, MeOH, 72%.



Scheme 7. (a) 2,4-Thiazolidinedione, piperidine, EtOH, 99%; (b) H_2, Pd/C, MeOH; (c) HCl, 54% over steps b and c; (d) aryloxypropanolamines, arylethanolamines or arylethanolazides, $NaBH(OAc)_3$, DMF.

Next we examined various arylethanolamine substituted 2,4-thiazolidinediones. Introduction of a 3-chlorophenyl or 3-pyridyl (both are widely used as β_3 agonist LHS moieties[1]) group on **22** resulted in low potency compounds (**22a** and **22b**). To our delight, the 3-methylsulfonamide-4-hydroxy analogue **22c** is a potent agonist at the β_3 receptor ($EC_{50} = 0.01\,\mu M$, IA = 1.19) with more than 110-fold selectivity against both β_1- and β_2-ARs. Further modifications by replacement of 4-hydroxy with either 4-chloro or 4-hydrogen gave less potent compounds (**22d** and **22e**). In contrast to **21d**, replacement of the 3-methylsulfonamide (**22c**) with 3-benzenesulfonamide (**22f**) retained β_3 agonist activity ($EC_{50} = 0.006\,\mu M$, IA = 0.93) while selectivity over the β_1-AR is somewhat (~4-fold) decreased. These results suggest that, unlike the aryloxypropanolamine series, in the arylethanolamine series the hydrogen bonding capacity (4-OH vs 4-chloro or 4-H in **22c**, **22d**, and **22e**) is important for β_3 agonist activity while the size of the sulfonamide substituent (methylsulfonamide of **22c** vs benzenesulfonamide of **22f**) appears to be of little importance.

Selected compounds with a good agonist activity profile were examined in β_1 and β_2 binding assays, and aryloxypropanolamine derivatives **21e** and **21f** were found to bind tightly to β_1 and β_2 receptors with a binding constant K_i (determined by inhibition of ^{125}I-iodocyanopindolol)[14] in the range of 0.004–0.055 μM. These results suggest that the aryloxypropanolamines do in fact exhibit strong antagonist activity at the β_1 and β_2 receptors and therefore may cause unwanted side effects.[1] In contrast, the arylethanolamine **22c** has a K_i value of 3.28 μM for β_2 and 1.57 μM for β_1, confirming its selectivity over the β_1- and β_2-ARs.

The ability of β_3 agonist **22c** to treat or inhibit disorders related to obesity or type II diabetes was confirmed in an in vivo procedure[15] which compared thermogenesis in human β_3-AR transgenic mice (Tg mice) with β_3-AR knock out mice (KO mice). Administered 10 mg/kg (ip) to Tg mice and KO mice, **22c** is active (30±4% thermogensis) in Tg mice and inactive (−2±4% thermogensis) in KO mice.

In conclusion, LHS modifications on 2,4-thiazolidinediones have led to the identification of a potent and selective agonist **22c** with an EC_{50} of 0.01 μM, >110-fold selectivity over β_1- and β_2-AR agonist activity and active and selective in the in vivo procedure. It was subsequently found that slight modification on the 2,4-thiazolidinedione moiety (such as alkylation on the N-H, replacement of 2,4-thiazolidinedione with 1,2,4-oxadiazolidine-3,5-dione) led to more potent and selective compounds. The details of these modifications will be presented separately.

Acknowledgements

The authors acknowledge the members of the Wyeth-Ayerst Discovery Analytical Chemistry group for analytical and spectral determinations.

References and Notes

1. (a) For recent reviews on β_3-agonists see: Katsilambros, N. *Eur. J. Intern. Med.* **2000**, *11*, 65. (b) Weyer, C.; Gautier, J. F.; Danforth, E., Jr. *Diabetes Metab.* **1999**, *25*, 11. (c) Kordik, C. P.; Reitz, A. B. *J. Med. Chem.* **1999**, *42*, 181. (d) Weber, A. E. *Annu. Rep. Med. Chem.* **1998**, *33*, 193. (e) Dow, R. L. *Exp. Opin. Invest. Drugs* **1997**, *6*, 1811.

2. (a) Sum, F. W.; Gilbert, A.; Venkatesan, A. M.; Lim, K.; Wong, V.; O'Dell, M.; Francisco, G.; Chen, Z.; Grosu, G.; Baker, J.; Ellingboe, J.; Malamas, M.; Gunawan, I.; Primeau, J.; Largis, E.; Steiner, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1921. (b) Bloom, J. D.; Dutia, M. D.; Johnson, B. D.; Wissner, A.; Burns, M. G.; Largis, E. E.; Dolan, J. A.; Claus, T. H. *J. Med. Chem.* **1992**, *35*, 3081. (c) Hu, B. Unpublished results.

3. (a) For the synthesis of **4b** and **4f** see: Siegel, M. G.; Shuker, A. J.; Droste, C. A.; Hahn, P. J.; Jesudason, C. D.; Mcdonald, J. H., III; Matthews, D. P.; Rito, C. J.; Thorpe, A. *J. Mol. Div.* **1998**, *3*, 113. (b) Bell, M. G.; Crowell, T. A.; Matthews, D. P.; McDonald, J. H., III; Nee, D. A.; Shuker, A. J.; Winter, M. A. U.S. Patent 708,621, 1998; *Chem. Abstr.* **1998**, *129*, 148910.

4. Beeley, L. J.; Berge, J. M.; Chapman, H.; Dean, D. K.; Kelly, J.; Lowden, K.; Kotecha, N. R.; Morgan, H. K. A.; Rami, H. K.; Thompson, M.; Vong, A. K. K.; Ward, R. W. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 219 and references therein.

5. Svensson, M.; Helgee, B.; Bertil, K.; Andersson, G. *J. Mater. Chem.* **1998**, *8*, 353.

6. For the synthesis of **7** and **8a**, see: Washburn, W. N.; Girotra, R. N.; Sher, P. M.; Mikkilineni, A. B.; Poss, K. M.; Mathur, A.; Gavai, A.; Bisacchi, G. S. EP 659737, 1995; *Chem. Abstr.* **1995**, *124*, 8408

7. Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413.

8. Oelschlaeger, H.; Schreiber, O. *Liebigs Ann. Chem.* **1961**, *641*, 81.

9. Guy, A.; Ferroud, D. C.; Garreay, R.; Godefroy-Falguieres, A. *Synthesis* **1992**, 821.

10. Sarodnick, G.; Kempter, G. *Pharmazier* **1985**, *40*, 384.

11. Taylor, E. C.; Skotnicki, J. S. *Synthesis* **1981**, 606.

12. All final compounds and novel aryloxypropanolamines and arylethanolamines were characterized by ^{1}H NMR, mass spectrometry, and high-resolution mass spectrometry. All of the compounds that are being biologically evaluated are mixtures of diastereomers (the 2,4-thiazolidinedione adds a chiral center to the structure). For experimental details, see: Hu, B.; Sum, F.-W.; Malamas, M. PCT application, submitted, July, 2000.

13. The human β_3 receptor was cloned as described in Van, S. A.; Nahmias, C. K. S.; Briend-Sutren, M. M.; Strosberg, A. D.; Emorine, L. J. *Eur. J. Biochem.* **1993**, *213*, 1117. The human β_2 and β_1 receptors were cloned as described in Tate, K. M.; Briend-Sutren, M. M.; Emorine, L. J.; Delavier-Klutchko, C.; Marullo, S.; Strosberg, A. D. *Eur. J. Biochem.* **1993**, *196*, 357.

14. For radioligand binding procedure see: Zheng, W.; Nikulin, V. I.; Konkar, A. A.; Vansal, S. S.; Shams, G.; Feller, D. R.; Miller, D. D. *J. Med. Chem.* **1999**, *42*, 2287.

15. For measuring thermogenesis in human β_3-AR transgenic mice and β_3-AR knock out mice see: Susulic, V. S.; Frederich, R. C.; Lawitts, J.; Tozzo, E.; Khahn, B. B.; Harper, M.-E.; Himms-Hagen, J.; Flier, J. S.; Lowell, B. B. *J. Biol. Chem.* **1995**, *270*, 29483.