Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 5245–5250
Bioorganic & Medicinal Chemistry Letters

# Discovery of potent and orally bioavailable heterocycle-based $\beta_3$-adrenergic receptor agonists, potential therapeutics for the treatment of obesity

Jennifer A. Lafontaine,[a,*] Robert F. Day,[a,†] Joe Dibrino,[a] John R. Hadcock,[a] Diane M. Hargrove,[a,‡] Michael Linhares,[b] Kelly A. Martin,[a] Tristan S. Maurer,[b] Nancy A. Nardone,[a] David A. Tess[b] and Paul DaSilva-Jardine[a]

[a]*Department of Cardiovascular and Metabolic Diseases, Pfizer Global Research and Development, Groton, CT 06340, USA*
[b]*Department of Pharmacokinetics, Dynamics and Metabolism, Pfizer Global Research and Development, Groton, CT 06340, USA*

Received 8 March 2007; revised 21 June 2007; accepted 27 June 2007
Available online 30 June 2007

**Abstract**—A novel series of heterocycle-based analogs were prepared and evaluated for their in vitro and in vivo biological activity as human $\beta_3$-adrenergic receptor (AR) agonists. Several analogs demonstrated potent agonist activity at the $\beta_3$-AR, functional selectivity against $\beta_1$- and $\beta_2$-ARs, and favorable pharmacokinetic profiles in vivo. Compound **17** increased oxygen consumption in rats, a measure of energy expenditure, with an $ED_{20\%}$ of 2 mg/kg.


The use of human $\beta_3$-adrenoreceptor ($\beta_3$-AR) agonists to increase metabolic rate has been widely studied as a potential approach for the treatment of obesity.[1] Since the identification of the $\beta_3$-AR some 25 years ago,[2] there have been numerous reports of arylethanolamine-based $\beta_3$-AR agonists, structurally related to the endogenous catecholamines adrenaline and noradrenaline (Fig. 1). Early work in the investigation of $\beta_3$-AR agonists revealed that the incorporation of acidic functionality can confer selectivity for the $\beta_3$ receptor over the $\beta_1$- and $\beta_2$-adrenoreceptors,[3] as in BRL-37344 (Fig. 1, **1**)[4] and CP-331679 (**2**).[5] This selectivity is essential to avoid unwanted effects on heart rate ($\beta_1$-mediated) and blood pressure ($\beta_2$-mediated), and as a result many of the $\beta_3$ agonists reported to date contain a carboxylic acid or an acid isostere.[6] Unfortunately, because these compounds are zwitterionic and often very polar, they are frequently reported to suffer from poor absorption and low oral bioavailability.[7]

Investigators at Merck have reported compounds in which the carboxylic acid moiety is replaced by a less acidic sulfonamide. Though many of these sulfonamides possess excellent in vitro potency and selectivity profiles, the potency is typically achieved at the expense of corresponding increases in molecular weight and lipophilicity.[8] Subsequently, sulfonamides, such as clinical candidate L-796568 (**3**, Fig. 2),[9] suffer from low oral bioavailability in preclinical species.[10] As part of our efforts to discover novel and selective $\beta_3$-AR agonists which also exhibit excellent pharmacokinetic properties, we explored compounds which replace the acidic moiety with neutral heterocycles, targeting compounds with lower molecular weights and moderate $c\log P$ values. We began our efforts by screening a number of heterocycles as potential replacements for the carboxylic acid, including imidazoles, triazoles, oxadiazoles, pyrazines, thiazoles, and oxazoles, among others. While most of the heterocycle replacements, as well as replacement with a phenyl ring, led to greatly diminished potencies at the $\beta_3$-AR, we found that thiazoles and oxazoles were well tolerated as carboxylic acid replacements.

The synthesis of the thiazole-containing analogs is described in Schemes 1 and 2. Starting from commercially available **4**, the phenyl ring was acetylated using a standard Friedel–Crafts procedure.[11] Bromination[12]

*Keywords*: $\beta_3$-Adrenergic receptor agonists; Obesity; Thermogenesis.
* Corresponding author at present address: Pfizer Global Research and Development, 10770 Science Center Drive, LaJolla, CA 92121, USA. Tel.: +1 858 526 4866; fax: +1 858 526 4469; e-mail: jennifer.lafontaine@pfizer.com
† Present address: Novartis Institutes for Biomedical Research, Inc., Cambridge, MA 02139, USA.
‡ Present address: Amylin Pharmaceuticals, LaJolla, CA 92121, USA.

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.06.072

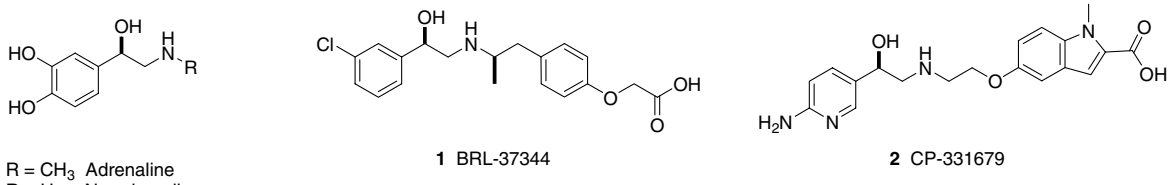



**Figure 1.** Adrenaline, noradrenaline, SmithKline Beecham's $\beta_3$-AR agonist BRL-37344, and Pfizer's CP-331679.

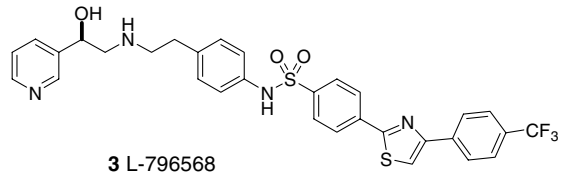


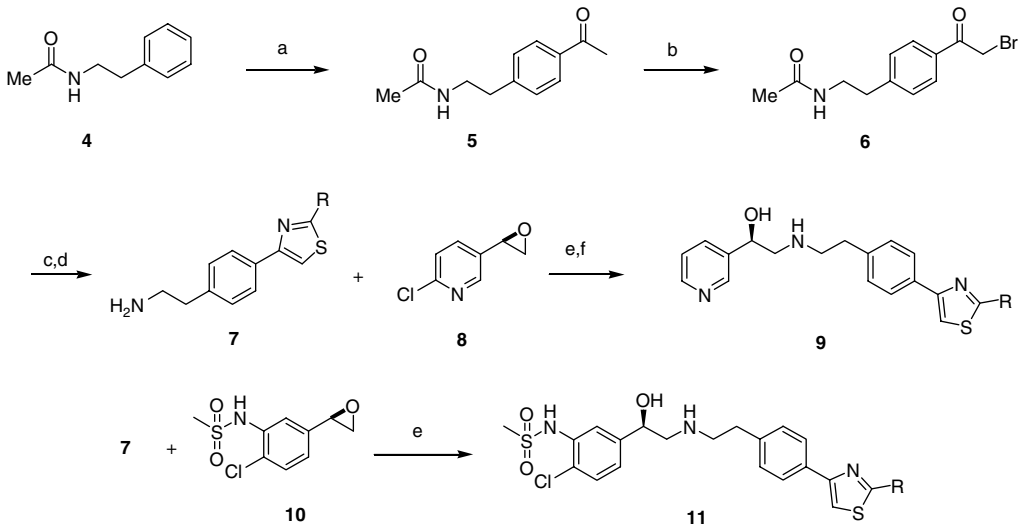

**Figure 2.** Merck's L-796568.

of the resulting ketone, followed by treatment with a thioamide at elevated temperature, afforded the thiazole **7**. Utilizing known pharmacophore replacements for the potentially metabolically labile catechol moiety of the endogenous hormones, we prepared analogs with 3-pyridyl and chlorosulfonamidephenyl-containing 'head groups.' Analogs **11** were constructed using the previously reported *N*-{2-chloro-5-[(2*R*)-oxiran-2-yl]phenyl}methanesulfonamide,[13] and the 3-pyridyl analogs were prepared from **7** in a two-step procedure using epoxide **8**.[14]

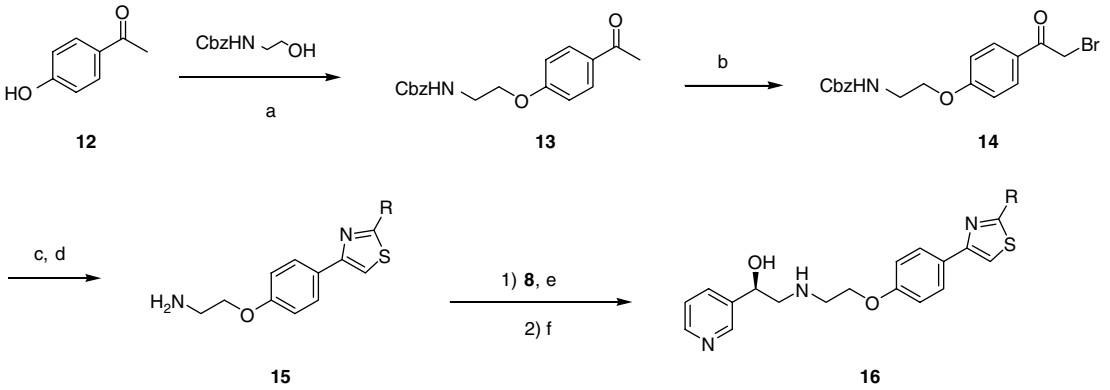
Table 1 describes thiazole-containing analogs of the structures **9** and **11**, many of which possess full agonist activity at the $\beta_3$-AR (relative to the full agonist isoproteronol). Though several of the analogs have good selectivity over $\beta_1$- and $\beta_2$-ARs, even the most potent of these analogs lack the low-nanomolar $\beta_3$-AR potency of compound **3**. Replacement of the 3-pyridyl head group with a 3-chlorophenyl moiety, which has been widely used in the $\beta_3$-AR agonist literature, gave compounds with only micromolar activity at the $\beta_3$-AR (data not shown). We therefore investigated other structural modifications to improve the $\beta_3$-AR potency of these analogs.

A survey of linkers between the amine and phenyl group (attached to the heterocycle) revealed that greatly improved potencies could be achieved by replacing the two carbon linker of **9** with an ethoxy linker, as in compound **16** (Scheme 2). The synthesis of these analogs began with a Mitsunobu[16] reaction on phenol **12** to introduce the ethanolamine linker. Bromination of the ketone, followed by cyclization to the thiazole and Cbz-deprotection under acidic conditions, gave amine **15**. Treatment of **15** with epoxide **8** and reduction of the pyridyl chloride gave analogs of structure **16**.

It was found that thiazoles bearing a range of small alkyl or heterocyclic groups gave improved in vitro efficacy and potency while retaining functional selectivity against $\beta_1$-AR and $\beta_2$-AR (Table 2). In this series, the pyridyl head group was found to be optimal, and **16a**, in which R = H, gave the best $\beta_3$-AR potency ($EC_{50}$ = 27 nM, see Table 2). Methyl analog **16b**, while less potent ($EC_{50}$ = 170 nm), had higher intrinsic agonist activity (106%) than **16a**. These analogs also possess optimal physiochemical properties, as they are characterized by excellent solubility,[17] low molecular weights, and moderate lipophilicity (for **16a**: solubility >10 mg/

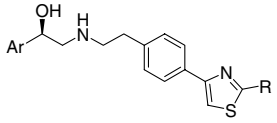


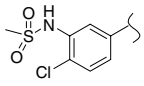
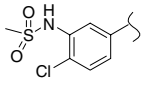
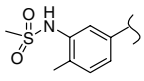

**Scheme 1.** Reagents and conditions: (a) $CH_3COCl$, $AlCl_3$, $CH_2Cl_2$, 0 °C to rt, 92%; (b) tetrabutylammonium tribromide, $CH_2Cl_2$/MeOH, (2:1), rt, 15 h, 83%; (c) $RCSNH_2$ (1 equiv), EtOH, 80 °C, 3 h, 90–100%; (d) concd HCl, 120 °C, 6–12 h, 85–91%; (e) EtOH, 80 °C, 76–88%; (f) ammonium formate, 10% Pd/C, MeOH, 16 h, rt, 77–90%.




**Scheme 2.** Reagents and conditions: (a) $PPh_3$, ADDP, toluene/THF, 0 °C to rt, 16 h, 84%; (b) tetrabutylammonium tribromide, $CH_2Cl_2$/MeOH (2:1), rt, 15 h, 90%; (c) $RCSNH_2$ (1 equiv), EtOH, 80 °C, 4 h, 58–74%; (d) anisole, methanesulfonic acid, $CH_2Cl_2$, 16 h, 80–89%; (e) EtOH, 90 °C, 16 h, 75–80%; (f) ammonium formate, 10% Pd/C, MeOH, 16 h, rt, 90–93%.

**Table 1.** β-Adrenergic activities for thiazoles **9** and **11**[15]




| | Ar | R | $\beta_3$-AR $EC_{50}$ μM (IA,%) | $\beta_1$-AR IA% @ 30 μM | $\beta_2$-AR IA% @ 30 μM |
|---|---|---|---|---|---|
| **3** | | | 0.003 (92) | 1 | 1 |
| **9a** | 3-Pyridyl | Me | 1.36 (55) | 6 | 7 |
| **9b** | 3-Pyridyl | Et | 2.25 (80) | 7 | 9 |
| **9c** | 3-Pyridyl | Ph | 2.74 (108) | 7 | 14 |
| **9d** | 3-Pyridyl | 3-Pyridyl | 1.19 (106) | 21 | 17 |
| **9e** | 3-Pyridyl | $CF_3$ | 4.49 (94) | 7 | 7 |
| **11a** |  | Me | 0.23 (121) | 8 | 32 |
| **11b** |  | Et | 0.13 (95) | 6 | 35 |
| **11c** |  | Ph | 0.49 (70) | 6 | 19 |

Agonist activities were assessed by measuring cAMP levels in Chinese hamster ovary cells expressing cloned human β-ARs. Intrinsic activities (IA) are expressed as a percentage of the maximal response of the full agonist isoproterenol. ND, not determined.

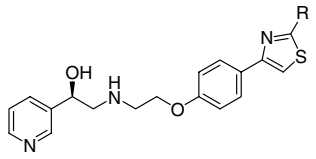
mL, MW = 341, and *c*log *P* = 1.71). Despite their selectivity in the functional assay, all of the compounds had $\beta_1$-AR binding affinities in the submicromolar range, which could potentially lead to heart rate lowering effects in vivo, though this outcome was not measured for these compounds.

In vivo pharmacokinetic studies carried out on **16a** showed the compound to have a good profile in rat, with a bioavailability of 53%, a moderate clearance (26 mL/$min^{-1}$ $kg^{-1}$), and volume of distribution (1.1 L/kg). Compound **16b** was characterized by a similar clearance (21 mL/$min^{-1}$ $kg^{-1}$) and volume (0.9 L/kg) in rat, but a lower oral bioavailability (25%). In dog, **16b** had an improved bioavailability (53%), a higher volume of distribution (5.0 L/kg), and moderate clearance (23 mL/$min^{-1}$ $kg^{-1}$).

Increases in resting oxygen consumption in rats have been widely used as a surrogate measure of energy expenditure produced by $\beta_3$-AR agonists.[18] Both **16a** and **16b**, when dosed orally, showed significant increases in resting oxygen consumption over a 2 h period (Table 3).[19] Compound **16b** gave a greater change in oxygen consumption than **16a**, perhaps because **16b** is more potent at the rat $\beta_3$-AR than **16a**.

As we continued our investigations of heterocyclic replacements for the acid moiety, we found that oxazoles could be employed to confer potent and selective $\beta_3$-AR agonism. In particular, we have found that oxazoles attached to the phenyl ring at the 4-position of the oxazole were potent $\beta_3$ agonists, as shown in Table 4, while the two isomeric oxazole analogs were at least 10-fold less potent.

**Table 2.** β-Adrenergic activities for series **16**[b]



**16**

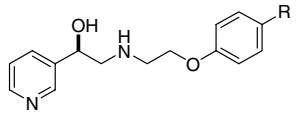
| | R | Functional activity[a] | | | Binding $K_i$[b] (μM) | | |
|---|---|---|---|---|---|---|---|
| | | $\beta_3$-AR $EC_{50}$ μM (IA, %) | $\beta_1$-AR IA,% at 30 μM | $\beta_2$-AR IA,% at 30 μM | $\beta_2$ ($K_{iH}$)[c] | $\beta_1$ | $\beta_1/\beta_3$ |
| **16a** | H | 0.027 (85) | 2 | 4 | 0.01 | 0.14 | 14.2 |
| **16b** | Methyl | 0.17 (106) | <5 | <5 | 0.12 | 0.10 | 0.80 |
| **16c** | $CF_3$ | 0.20 (150) | <6 | 9 | ND[d] | 0.10 | — |
| **16d** | Ethyl | 0.17 (106) | 7 | 19 | ND | 0.037 | — |
| **16e** | *c*-Pentyl | 0.29 (159) | 11 | 47 | ND | 0.13 | — |
| **16f** | Phenyl | 0.58 (53) | 14 | 18 | 0.50 | 0.15 | 0.15 |
| **16g** | 3-Pyridyl | 0.12 (121) | 10 | 21 | ND | 0.12 | — |
| **16h** | 4-Pyridyl | 0.065 (106) | 17 | 22 | ND | 0.097 | — |

[a] Agonist activities were assessed by measuring cAMP levels in Chinese hamster ovary cells expressing cloned human β-ARs. IA, intrinsic agonist efficacy, expressed as a percentage of isoproterenol maximum.
[b] Receptor binding assays were carried out with membranes from CHO cells expressing the cloned human receptor in the presence of $^{125}$I-iodocyanopindolol.
[c] $K_{iH}$, the inhibition constant for a drug representing the high affinity, agonist preferring binding site. Analysis of competition binding was best fit using a two-site binding analysis.
[d] ND, not determined.

**Table 3.** Increase in rat oxygen consumption

| | Δ $VO_2$ (0–120 min) | | Rat $\beta_3$-AR $EC_{50}$ μM (IA, %) |
|---|---|---|---|
| | 3 mg/kg po | 10 mg/kg po | |
| **16a** | 11% | ND | 0.026 (104) |
| **16b** | 20% | 32% | 0.013 (113) |

**Table 4.** Oxazole isomers



| | R | $\beta_3$-AR $EC_{50}$ μM (IA, %)[a] |
|---|---|---|
| **17** |  | **0.020 (94)** |
| **18** |  | 0.20 (98) |
| **19** |  | 0.52 (24) |

[a] Agonist activities were assessed by measuring cAMP levels in Chinese hamster ovary cells expressing cloned human β-ARs. IA, intrinsic agonist efficacy, expressed as a percentage of isoproterenol maximum.

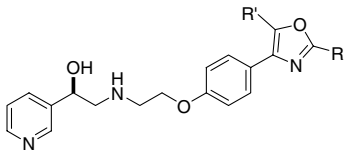
A survey of alkyl substitution on the oxazole ring (Table 5) showed that, as with the thiazoles, smaller substituents conferring minimal steric bulk afforded the best potencies. As shown in entries **26** and **27**, substitution on the 5-position of the oxazole led to a dramatic drop in $\beta_3$-AR activity. Similarly, alkyl substitution on the adjacent phenyl ring was not well tolerated, and modifications to the linker and pyridyl head group typically resulted in diminished activity or selectivity (data not shown). As in the thiazole series, the $-CH_2CH_2O-$ linker gave improved potencies over the ethano linker.

Of these analogs, the most potent and selective compound identified was compound **17**. In the functional cAMP assay, this compound is a full agonist at the $\beta_3$-AR ($EC_{50}$ = 20 nM), and in the binding assay, compound **17** has a $K_{iH}$ at $\beta_2$ of 10 nM. It exhibits weak binding affinity and exhibits antagonist properties at the $\beta_1$- and $\beta_2$-ARs with no intrinsic agonist activity (functional $K_b$'s: $\beta_1$ > 500 nM, $\beta_2$ > 1500 nM).[20]

The synthesis of compound **17** is shown in Scheme 3. Starting from bromoketone **28**,[21] treatment with a neat solution of formamide at elevated temperatures afforded oxazole **29** in moderate yield. Demethylation with methanesulfonic acid and methionine,[22] followed by alkylation with mesylate **31**[23], gave compound **32**. In this series it was found that the Mitsunobu reaction used to alkylate the phenol in the thiazole series was not high yielding, perhaps because compound **30** bears a less acidic phenol than Mitsunobu substrate **12**. Hydrogenation led to the liberated primary amine **33**, which was treated with epoxide **8**[14] to install the chiral ethanolamine of compound **34**. Finally, hydrogenation to remove the chlorine on the pyridyl ring provided the target compound **17** in good yield.

Studies on compound **17** have shown this analog to have an excellent PK profile in both rat and dog (see Table 6). Based on this promising profile, **17** was progressed into rat oxygen consumption studies, and was shown to increase oxygen consumption at all doses tested (0.3, 1, 3, and 10 mg/kg of crystalline HCl salt), ranging from

**Table 5.** A survey of oxazole substitution



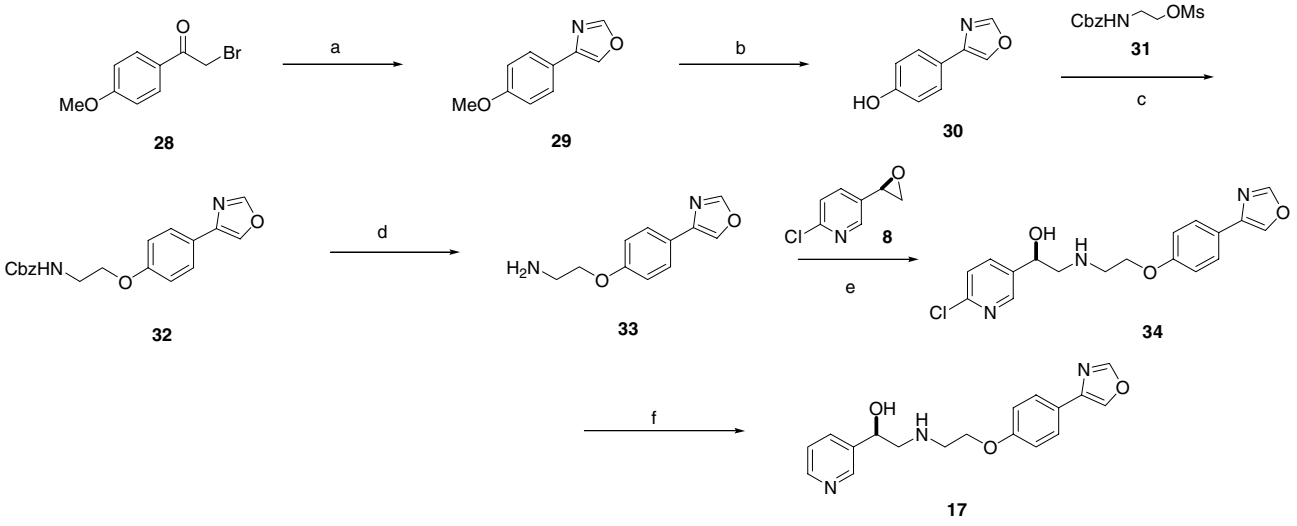
| | R | R′ | Functional activity[a] | | | Binding $K_i$[b] (μM) | | |
|---|---|---|---|---|---|---|---|---|
| | | | $\beta_3$-AR $EC_{50}$ μM (IA, %) | $\beta_1$-AR IA, % at 30 μM | $\beta_2$-AR IA, % at 30 μM | $\beta_2$ ($K_{iH}$)[c] | $\beta_1$ | $\beta_1/\beta_3$ |
| **17** | **H** | **H** | 0.020 (94) | 0 | 2 | 0.010 | 0.20 | 20 |
| **20** | Me | H | 0.037 (111) | 4 | 7 | 0.021 | 0.40 | 19 |
| **21** | Et | H | 0.057 (133) | 6 | 14 | 0.037 | 0.40 | 11 |
| **22** | *i*-Pr | H | 0.057 (135) | <10 | 26 | 0.049 | 0.36 | 7.4 |
| **23** | $CH_2OCH_3$ | H | 0.047 (110) | 8 | 13 | ND[d] | 0.21 | ND |
| **24** | $CH_2OBn$ | H | 0.22 (137) | 12 | 32 | ND | 0.05 | ND |
| **25** | $CH_2OH$ | H | 0.042 (94) | 5 | 4 | 0.03 | 0.27 | 8.6 |
| **26** | H | Me | 0.309 (80) | 2 | 0 | ND | 0.17 | ND |
| **27** | Me | Me | 0.606 (75) | 2 | 0 | ND | 1.55 | ND |

[a] Agonist activities were assessed by measuring cAMP levels in Chinese hamster ovary cells expressing cloned human β-ARs. IA, intrinsic agonist efficacy, expressed as a percentage of isoproterenol maximum.

[b] Receptor binding assays were carried out with membranes from CHO cells expressing the cloned human receptor in the presence of $^{125}$I-iodocyanopindolol.

[c] $K_{iH}$, the inhibition constant for a drug representing the high affinity, agonist preferring binding site. Analysis of competition binding was best fit using a two-site binding analysis.

[d] ND, not determined.




**Scheme 3.** Reagents and conditions: (a) formamide, 130 °C, 65%; (b) MsOH, DL-methionine, 75–85%; (c) $K_2CO_3$, DMSO, 70%; (d) 10% Pd/C, cyclohexadiene, 85%; (e) TMS acetamide, THF, reflux, 58%; (f) 10% Pd/C, ammonium formate, 85%.

**Table 6.** Compound **17** pharmacokinetic profile

| | Rat | Dog |
|---|---|---|
| *F* (%) | 66 | 59 |
| $t_{1/2}$ (h) (IV) | 1.4 | 5.1 |
| Cl (mL/min kg) | 13 | 6 |
| $V_{ss}$ (L/kg) | 0.89 | 2.8 |

**Table 7.** Increase in rat oxygen consumption for compound **17** (0–2 h)[19]

| Dose (mg/kg) | Increase in oxygen consumption (%) |
|---|---|
| 0.3 | 8 ± 2 |
| 1 | 11 ± 1 |
| 3 | 29 ± 4 |
| 10 | 42 ± 6 |

an 8% increase at the low dose to a 42% increase at 10 mg/kg (Table 7). The $ED_{20\%}$ was determined to be ~2 mg/kg (1.6 mg/kg of active), which compares favorably to data previously reported for $\beta_3$-AR agonists in rat oxygen consumption studies.[24] Despite the significant increases in oxygen consumption observed, only relatively small increases in heart rate were observed in rats (ca. 10% increase at the high dose of 10 mg/kg), a finding which corroborates the in vitro selectivity data for the compound.

In conclusion, we have identified a novel series of potent $\beta_3$-AR agonists which lack the acidic moiety present in most selective $\beta_3$ agonists, demonstrating that thiazoles and oxazoles are in this case viable pharmacophore replacements for carboxylic acids. The reported compounds were designed with moderate molecular weights and lipophilicities to have drug-like physiochemical properties, and several compounds show good pharmacokinetic profiles and in vivo efficacy in rats. Importantly, compound **17** has been shown to have minimal heart rate effects in preclinical animal studies. Based on their pharmacological and pharmacokinetic profiles, these $\beta_3$-AR agonists show promise as novel therapeutics for the treatment of obesity.

## Acknowledgment

The authors thank Dr. Robert Dow for helpful discussions throughout the course of this work.

## References and notes

1. For a review of the topic: Howe, R. *Drugs Fut.* **1993**, *18*, 529.
2. Tan, S.; Curtis-Prior, P. B. *Int. J. Obes.* **1982**, *7*, 409.
3. Sher, P. A.; Mathur, A.; Fisher, L. G.; Wu, G.; Skwish, S.; Michel, I. M.; Seiler, S. M.; Dickinson, E. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1583.
4. Arch, J. R. S.; Ainsworth, A. T.; Cawthorne, M. A.; Piercy, V.; Sennitt, M. V.; Thody, V. E.; Wilson, C.; Wilson, S. *Nature* **1984**, *309*, 163.
5. Dow, R. L. *Exp. Opin. Invest. Drugs* **1997**, *6*, 1811.
6. For reviews of $\beta_2$ agonists reported in the literature, see Ref. 5 Weber, A. E. *Ann. Rep. Med. Chem.* **1998**, *33*, 193.
7. As described for: CP-331679 in Ref. 5 and for CL-316243 in 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.
8. Mathvink, R. J.; Tolman, J. S.; Chitty, D.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Miller, R. R.; Stearns, R. A.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *J. Med. Chem.* **2000**, *43*, 3832, and references cited therein.
9. van Baak, M. A.; Hul, G. B. J.; Toubro, S.; Astrup, A.; Gottesdiener, K. M.; DeSmet, M.; Saris, W. H. M. *Clin. Pharmacol. Ther.* **2002**, *76*, 780.
10. Stearns, R. A.; Miller, R. R.; Tang, W.; Kwei, G. Y.; Tang, F. S.; Mathvink, R. J.; Naylor, E. M.; Chitty, D.; Colandrea, V. J.; Weber, A. E.; Colleti, A. E.; Strauss, J. R.; Keohane, C. A.; Feeney, W. P.; Iliff, S. A.; Chiu, S. L. *Drug Metab. Disp.* **2002**, *30*, 771.
11. Olah, G. A.. In *Friedel–Crafts and Related Reactions*; Wiley: New York, 1963; Vols. 1 and 2.
12. Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Fujisaki, S. . *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1159.
13. Lafontaine, J. A.; Morgan, B. P. PCT Int. Appl. WO 2003072572, 2003.
14. Dow, R. L.; Schneider, S. R. European Patent Application 1138685, 2001. (*R*)-Toluene-4-sulfonic acid 2-(6-chloropyridin-3-yl)-2-hydroxyethyl ester, described therein, was treated with 1 M NaOH in THF and water to afford epoxide **8** in 90% yield.
15. In all assays, each compound with an $EC_{50} < 100$ nM and IA > 50% was tested at least twice in functional assays. Similar potencies and intrinsic activities were observed in the assays.
16. Mitsunobu, O. *Synthesis* **1981**, 1.
17. Solubility measurements were made in pH 6.5 phosphate buffer.
18. Depocas, F.; Hart, J. S. *J. Appl. Physiol.* **1957**, *10*, 388.
19. Animals were removed from general housing in the morning (7–7:30 am) and were deprived of food and water for the length of the oxygen consumption measurements. Animals were weighed (310–350 g), marked, and placed into individual activity-monitored chambers ($17'' \times 17'' \times 5''$). The system was calibrated and the run started (8:00–8:30 am). Oxygen consumption measurements were made every 10 min for 3 h, and then the animals were dosed with the test compound or vehicle. Oxygen consumption measurements were continued for 2 h. Oxygen consumption values associated with periods of high ambulatory activity (>100 counts/10 min) were excluded from all calculations, as were the first five values of the run and the first value after dosing.
20. $K_b$ is the dissociation equilibrium constant for a competitive antagonist (the concentration which would occupy 50% of the receptors at equilibrium).
21. For the preparation of **28**, see: Ridge, D. N.; Hanifin, J. W.; Harten, L. A.; Johnson, B. D.; Menschik, J.; Nicolau, G.; Sloboda, A. E.; Watts, D. E. *J. Med. Chem.* **1979**, *22*, 1385.
22. For a representative procedure, see: Scott, R. W.; Neville, S. N.; Urbina, A.; Camp, D.; Stankovic, N. *Org. Process Res. Dev.* **2006**, *10*, 296.
23. Compound **31** was prepared in two steps from ethanolamine, which was first protected as the benzyl carbamate, and then converted to the mesylate, under standard conditions.
24. As in: Finley, D. R.; Bell, M. G.; Borel, A. G.; Bloomquist, W. E.; Cohen, M. L.; Heiman, M. L.; Kriauciunas, A.; Matthews, D. P.; Miles, T.; Neel, D. A.; Rito, C. J.; Sall, D. J.; Shuker, A. J.; Stephens, T. W.; Tinsley, F. C.; Winter, M. A.; Jesudason, C. D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5691.