Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 1971–1973

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Potent, Selective 3-Pyridylethanolamine β_3 Adrenergic Receptor Agonists Possessing a Thiazole Benzenesulfonamide Pharmacophore

Robert J. Mathvink,* J. Samuel Tolman, Dawn Chitty, Mari R. Candelore, Margaret A. Cascieri, Lawrence F. Colwell, Jr., Liping Deng, William P. Feeney, Michael J. Forrest, Gary J. Hom, D. Euan MacIntyre, Laurie Tota, Matthew J. Wyvratt, Michael H. Fisher and Ann E. Weber

Departments of Medicinal Chemistry, Biochemistry and Physiology, Pharmacology, and Comparative Medicine, Merck Research Laboratories, Rahway, NJ 07065, USA

Received 21 April 2000; accepted 28 June 2000

Abstract—A series of thiazole benzenesulfonamide-substituted 3-pyridylethanolamines was prepared and evaluated for their human β_3 adrenergic receptor agonist activity. Incorporation of aryl and heteroaryl substitution in the 4-position of the thiazole ring resulted in a number of highly potent and selective β_3 agonists. Results of preliminary in vivo evaluation of several of these compounds is described. © 2000 Elsevier Science Ltd. All rights reserved.

Obesity is becoming an increasing health concern in the United States and other industrialized countries, and considerable efforts in the last several years have been focused on the identification of viable therapeutic approaches to treating this condition.[1] Increasing metabolic rate through activation of β_3 adrenergic receptors (β_3 ARs) on the surface of adipocytes is one such approach.[2–5] Recent reports from our labs have described the in vitro activity and pharmacokinetic properties of pyridylethanolamine β_3 agonists **1**[6] and **2**[7] (Fig. 1). We recently described the discovery of a class of pyridylethanolamine β_3 AR agonists **3** possessing a substituted indoline-5-sulfonamide pharmacophore,[8] the most potent (EC_{50} 0.93 nm) and selective of which was the 4-octylthiazole analogue **3a** (Fig. 2).

Further SAR studies revealed that the presence of the indoline ring was not necessary for β_3 agonist activity: the 4-octyl-2-aminothiazole analogue **4a** displayed comparable in vitro potency and selectivity to that of its indoline counterpart. Herein we report that further modification of **4a** by removal of the amino linkage results in a new series of thiazole sulfonamides **5** with comparable or better β_3 agonist properties.

*Corresponding author. Tel.: +1-732-594-1504; fax: 1-732-594-5790; e-mail: robert_mathvink@merck.com

Chemistry

The synthetic route used to prepare the thiazole sulfonamides **5** is outlined in Scheme 1. Coupling of aniline **6**[9] with 4-cyanobenzenesulfonyl chloride, followed by treatment with hydrogen sulfide and triethylamine, afforded the intermediate thioamide **7**. Condensation of **7** with the requisite α-chloroketones, followed by TFA removal of the BOC protecting group, afforded the thiazole sulfonamides **5**.

Additionally, two compounds in the homologous series **8** were prepared by a similar route (Scheme 2). Thus, chlorosulfonation of phenyl thioacetamide afforded the *para*-substituted sulfonyl chloride, which was coupled with **6**, condensed with the requisite α-chloroketones, and deprotected to afford the homologs **8a** and **8f**. The structures of the thiazole 4-substituents incorporated into the final products **5** and **8** are shown in Figure 3.

Pharmacology

Compounds **5a–u**, **8a** and **8f** were tested in vitro for their ability to stimulate increases in cAMP in Chinese hamster ovary (CHO) cells expressing the cloned human β_3 receptor. The activity of an agonist at the β_3 AR is

0960-894X/00/$ - see front matter
PII: S0960-894X(00)00390-5

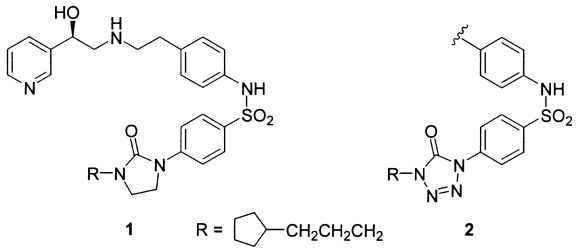


Figure 1.

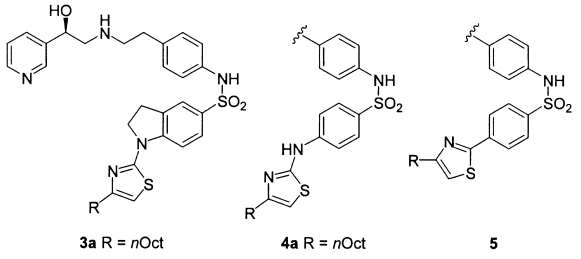
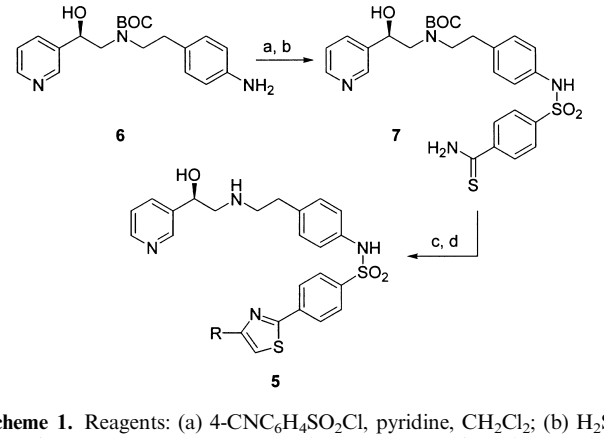
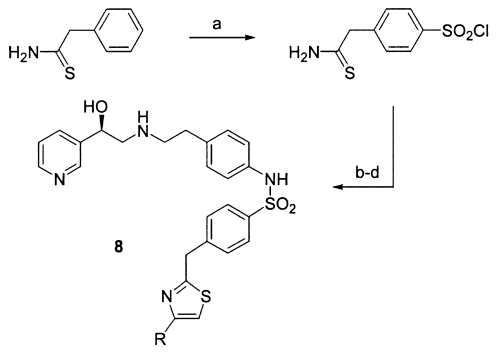


Figure 2.



Scheme 1. Reagents: (a) 4-$CNC_6H_4SO_2Cl$, pyridine, CH_2Cl_2; (b) H_2S, Et_3N, benzene, 22 °C; (c) $RCOCH_2Cl$, EtOH, 80 °C; (d) TFA, CH_2Cl_2.



Scheme 2. Reagents: (a) $ClSO_3H$, 80 °C, 4 h; (b) **6**, pyridine, CH_2Cl_2, 22 °C; (c) $RCOCH_2Cl$, EtOH, 80 °C; (d) TFA, CH_2Cl_2.

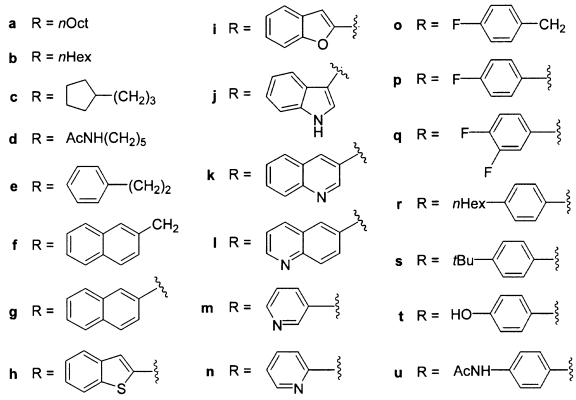


Figure 3. Thiazole 4-substituents for compounds **5** and **8**.

best described by its ability to stimulate adenylyl cyclase in a functional assay, since this method measures the affinity of a compound for the high-affinity, G-protein coupled state of the receptor. As a result, this assay accurately predicts the lipolytic potential of compounds in native adipocytes.[10] However, because the compounds under study generally have very low efficacy at β_1 and β_2 receptors, the activities of these compounds for the β_1 and β_2 ARs are better described by their binding affinities for these receptors. Thus, binding affinities to membranes prepared from CHO cells expressing the cloned human β_1 and β_2 ARs were determined, and permit an assessment of the selectivity of such compounds for the human β_3 receptor. The results are shown in Table 1.

In contrast to the SAR observed in the indoline series,[8] the thiazole sulfonamides **5a**–**c** possessing hydrophobic, long-chain alkyl groups exhibited relatively modest potency in the β_3 receptor assay. Introduction of a polar amide functionality (**5d**) or an aryl group (**5e**) into the distal end of the alkyl chain resulted in no improvement in β_3 agonist activity; however, situating a larger naphthyl group closer to the thiazole ring (**5f**–**g**) improved the β_3 agonist activity significantly. Replacement of the naphthyl substituent with various bicyclic heterocycles (**5h**–**l**) resulted in little or no loss in β_3 potency, while significantly increasing the selectivity over β_1 and β_2 binding. While substitution with a pyridyl group (**5m**–**n**) resulted in slightly less potent analogues, introduction of a substituted benzyl (**5o**) or phenyl ring (**5p**–**s**) resulted in increased potency. Interestingly, the most potent analogue in the series was **5r**, which possesses the combination of an aryl group directly attached to the thiazole ring and a hydrophobic alkyl group on the aryl ring. In contrast, analogues (**5t**–**u**) having polar functionality on the aromatic substituent were significantly less potent and selective. The homologs **8a** and **8f** were nearly equipotent with their counterparts **5a** and **5f** in vitro, although somewhat less selective.

Selected compounds were examined in vivo for their ability to elicit hyperglycerolemia.[11] Administered orally (10 mg/kg) to Beagle dogs, the most potent thiazoles in the series **5g** and **5r** produced little or no increase in serum glycerol levels. The octyl-substituted analogue **5a**, when administered intra venously (3 mg/kg) to Beagle dogs, resulted in a 2- to 6-fold increase in serum glycerol levels. Oral dosing with **5a** (10 mg/kg) also evoked hyper-glycerolemia, and the oral bioavailability of **5a** in dogs was determined to be 9%, which is comparable to that of its indoline analogue **3a** (13%), but modest relative to other pyridylethanolamine β_3 agonists such

Table 1. Comparison of β_3 AR agonist activity and β_1 and β_2 binding affinity of thiazole sulfonamides **5a–u** and **8a,f**

Compound	β_3 Agonist activity EC_{50}, nm (% act)[a]	β_1 Binding affinity IC_{50}, nm[b]	β_2 Binding affinity IC_{50}, nm[b]
5a	10 (84)	3700	3000
5b	51 (69)	40,000	620
5c	26 (95)	7000	3000
5d	50 (82)	50,000	16,000
5e	33 (70)	9000	910
5f	5.0 (75)	3300	2300
5g	2.0 (100)	13,000	6300
5h	5.8 (94)	100,000	93,000
5i	9.1 (91)	90,000	49,000
5j	4.9 (100)	30,000	50,000
5k	7.3 (79)	19,000	47,000
5l	2.7 (97)	6000	8000
5m	40 (69)	7000	3000
5n	22 (100)	6500	4000
5o	6.2 (57)	3000	2500
5p	9.5 (81)	1500	1900
5q	7.1 (92)	1700	1700
5r	1.2 (84)	52,000	90,000
5s	2.4 (100)	1600	2000
5t	45 (58)	1100	5700
5u	45 (82)	960	2100
8a	9.8 (79)	850	1000
8f	12 (83)	2500	2000

[a]Adenylyl cyclase activation given as % of the maximum 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.

as **1** (%F = 17)[6] and **2** (%F = 27).[7] However, aryl-substituted analogue **5q** also caused significant increases in serum glycerol levels upon oral and iv dosing, and its oral bioavailability in dogs (dosed 10 mg/kg po, 3 mg/kg iv) was found to be 36%. Moreover, **5q** exhibited a plasma half-life of 7.5 h, which is significantly longer than that observed for tetrazolone **2** ($t_{1/2}$ = 3.6 h).

Because of its attractive pharmacokinetic properties in dogs, **5q** was further evaluated in vitro for human β_3 binding affinity and functional efficacies at the human β_1 and β_2 receptors. At 10 μM, **5q** stimulates adenylyl cyclase stimulate increases in cAMP in Chinese hamster ovary (CHO) cells expressing the cloned human β_1 and β_2 receptors to the extent of 20 and 12%, respectively, of the maximum stimulation with isoproterenol. The EC_{50}'s for β_1 and β_2 activity were 2600 and 1800 nm, respectively, and the human β_3 IC_{50} for **5q** was determined to be 20 nm. Thus, **5q** shows 85-fold selectivity in binding affinity for the human β_3 AR, and greater than 350- and 250-fold functional selectivity over the β_1 and β_2 ARs, respectively.

In summary, we have identified a new class of potent and selective pyridylethanolamine β_3 agonists. Although their in vivo activities vary considerably depending on the thiazole 4-substituent, the improved pharmacokinetic profile of thiazole **5q** suggests that similar aryl-substituted thiazole sulfonamides may possess the necessary combination of biological potency and pharmacokinetic properties for an oral therapeutic agent. Work in this area is ongoing and will be communicated in due course.

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, Mr. Joe Leone for preparation of intermediate **6**, and Professor James G. Granneman (Wayne State University) for supplying the cloned human β3 receptor.

References and Notes

1. Kordik, C. P.; Reitz, A. B. *J. Med. Chem.* **1999**, *42*, 181.
2. Weber, A. E. *Annu. Rep. Med. Chem.* **1998**, *33*, 193.
3. Lowell, B. B.; Flier, J. S. *Annu. Rev. Med.* **1997**, *48*, 307.
4. Dow, R. L. *Exp. Opin. Invest. Drugs* **1997**, *6*, 1811.
5. Arch, J. R. S.; Wilson, S. *Int. J. Obes.* **1996**, *20*, 191.
6. Naylor, E. M.; Parmee, E. R.; Colandrea, V. J.; Perkins, L.; Brockunier, L.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Strader, C. D.; Tota, L.; Wang, P.-R.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 755.
7. Shih, T. L.; Candelore, M. R.; Cascieri, M. A.; Chiu, S.-H. L.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Miller, R. R.; Stearns, R. A.; Strader, C. D.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1251.
8. Mathvink, R. J.; Barritta, A. M.; Candelore, M. R.; Cascieri, M. A.; Deng, L.; Tota, L.; Strader, C. D.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1869.
9. Naylor, E. M.; Colandrea, V. J.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Strader, C. D.; Tota, L.; Wang, P.-R.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3087.
10. Fisher, M. H.; Amend, A. M.; Bach, T. J.; Barker, J. M.; Brady, E. J.; Candelore, M. R.; Carroll, D.; Cascieri, M. A.; Chiu, S.-H. L.; Deng, L.; Forrest, M. J.; Hegarty-Friscino, B.; Guan, X.-M.; Hom, G. J.; Hutchins, J. E.; Kelly, L. J.; Mathvink, R. J.; Metzger, J. M.; Miller, R. R.; Ok, H. O.; Parmee, E. R.; Saperstein, R.; Strader, C. D.; Stearns, R. A.; Thompson, G. M.; Tota, L.; Vicario, P. P.; Weber, A. E.; Woods, J. W.; Wyvratt, M. J.; Zafian, P. T.; MacIntyre, D. E. *J. Clin. Invest.* **1998**, *101*, 2387.
11. Compounds were dosed orally at 10 mg/kg as a solution of test compound dissolved in 0.5% methylcellulose/0.02% sodium laurel sulfate containing 2 equiv of HCl, and intravenously at 3 mg/kg in a vehicle consisting of polyethylene glycol 400 (PEG400), ethanol and normal saline (60:20:20 v/v/v). Blood samples were collected prior to dosing and at 5 (iv only), 15, and 30 min and 1, 2, 6, 8, and 24 h post dosing, for determination of plasma glycerol concentrations using a Sigma Triglyceride (GPO-TRINDER) assay kit. Those compounds that elicited elevated glycerol levels were analyzed for plasma drug concentrations by LC/MS/MS.