Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 2283–2286

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Tetrahydroisoquinoline Derivatives Containing a Benzenesulfonamide Moiety as Potent, Selective Human β_3 Adrenergic Receptor Agonists

Emma R. Parmee,* Linda L. Brockunier, Jiafang He, Suresh B. Singh, Mari R. Candelore, Margaret A. Cascieri, Liping Deng, Yong Liu, Laurie Tota, Matthew J. Wyvratt, Michael H. Fisher and Ann E. Weber

Departments of Medicinal Chemistry, Molecular Systems, and Biochemistry and Molecular Pharmacology, Merck Research Laboratories, Rahway, NJ 07065, USA

Received 21 June 2000; accepted 1 August 2000

Abstract—Tetrahydroisoquinoline derivatives containing a 4-(hexylureido)benzenesulfonamide were examined as human β_3 adrenergic receptor (AR) agonists. Notably, 4,4-biphenyl derivative **9** was a 6 nM full agonist of the β_3 AR. Naphthyloxy compound **18** (β_3 $EC_{50} = 78$ nM) did not activate the β_1 and β_2 ARs at 10 μM, and showed >1000-fold selectivity over binding to the β_1 and β_2 ARs.

In recent years, elevation of metabolic rate by activation of the human β_3 adrenergic receptor (AR) has attracted much attention as a potential approach toward the treatment of obesity.[1] Selectivity over both binding to and activation of β_1 and β_2 ARs has always been an important issue in developing β_3 AR agonists free of the side effects seen with early drug candidates.[2] Design of potent, selective human β_3 AR agonists has traditionally focused on compounds with an aryloxypropanolamine or arylethanolamine pharmacophore. These two groups are exemplified by phenoxypropanolamine **1** and pyridineethanolamine **2**, which have been recently reported from our laboratories (Fig. 1).[3,4] Both of these derivatives are very potent β_3 AR agonists (β_3 $EC_{50} = 0.43$ and 6.3 nM, respectively), which show excellent selectivity over binding to the β_1 and β_2 ARs (>440- and >1400-fold, respectively).

In a search for novel structural classes of β_3 AR agonists, we turned our attention to trimetoquinol **3** (TMQ), a human β AR agonist containing a tetrahydroisoquinoline core.[5] TMQ is a potent agonist of the human β_3 AR ($EC_{50} = 1.7$ nM, 92% activation), which exhibits only marginal selectivity over the β_1 and β_2 ARs (Table 1).[6] Other workers have investigated catechol bioisosteres in an effort to improve the selectivity of TMQ.[7] This led to the discovery of aminothiazole **4**, which in our assays was a weak partial agonist of the β_3 AR and did not activate the β_1 and β_2 ARs. It did not, however, show any selectivity for activation of the β_3 AR over binding to the β_1 and β_2 ARs (Table 1).

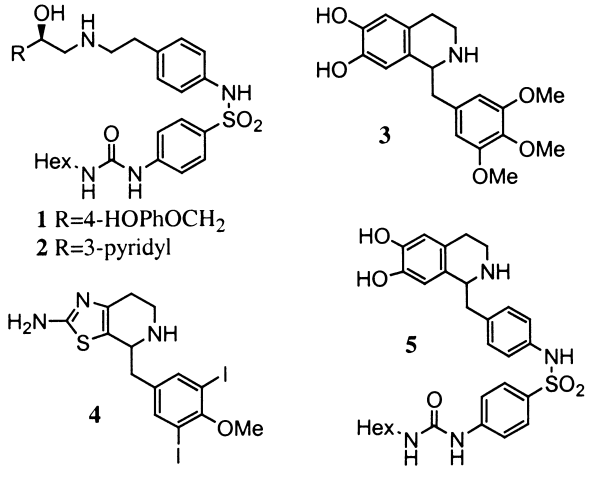


Figure 1.

The excellent in vitro profiles of analogues **1** and **2** are due in part to the presence of the benzenesulfonamide moiety,[3,4] and it was postulated that the selectivity of

*Corresponding author. Tel.: +1-732-594-6626; fax: +1-732-594-7877; e-mail: emma_parmee@merck.com

0960-894X/00/$ - see front matter
PII: S0960-894X(00)00459-5

TMQ might be enhanced by incorporation of the 4-(hexylureido)benzenesulfonamide into the potent tetrahydroisoquinoline backbone. Hence, amine **5** was prepared and tested at the human β ARs.[8,9] Despite a considerable drop in potency compared to TMQ, sulfonamide **5** retained all of its agonist efficacy at the β_3 AR with only minimal agonist activity at the β_1 and β_2 ARs. Selectivity over binding to the β_1 AR was also slightly improved (18- vs 4-fold).

Superimposition of low energy conformations of pyridineethanolamine **2** (pink) with tetrahydroisoquinoline **5** (green) revealed that when the β agonist pharmacophores are aligned, overlay of the benzenesulfonamide and hexyl urea moieties is not possible (Fig. 2).[10] In this paper we would like to describe our efforts to improve the potency and selectivity of benzyl derivative **5** by designing compounds in which all the hydrogen bonding regions of the molecule could be aligned with the corresponding groups in pyridineethanolamine **2**. Thus, the phenyl ring of the benzyl linker was replaced with either a biphenyl, naphthyl, or aryloxy unit (Schemes 1 and 2).

Biphenyl analogues **6**–**11** were prepared from bromides **13**–**15** by Suzuki coupling using either 3-aminophenyl boronic acid or the pinacol ester of 4-nitrophenyl boronic acid (Scheme 1).[11,12] In the latter case, the nitro group was then reduced with palladium hydroxide and hydrogen (which resulted in concomitant loss of the benzyl ethers) or Raney nickel and hydrazine. Reaction of the biphenyl anilines with 4-(hexylureido) benzenesulfonyl chloride[3] and deprotection yielded the desired compounds. Phenoxy derivative **12** was prepared directly from the nitro compound **16** in an analogous manner. The synthesis of both naphthalene compounds **17** and **18** originated from BOC protected 2-amino-6-hydroxynaphthalene **19** (Scheme 2).[13] Alkylation, saponification and treatment with oxalyl chloride gave acid chloride **20** (n = 1). Triflate formation, palladium coupling with TMS acetylene, and oxidative hydroboration yielded the acid precursor to **20** (n = 0). The acid chlorides were coupled with 3,4-dibenzyloxyphenethylamine hydrochloride, followed by sulfonamide formation to yield amides **21**. Cyclization and deprotection gave the desired compounds **17** and **18**.

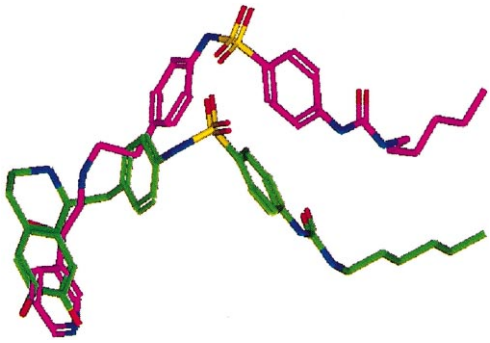


Figure 2. Superimposition of low energy conformations of pyridineethanolamine **2** (pink) and tetrahydroisoquinoline **5** (green).

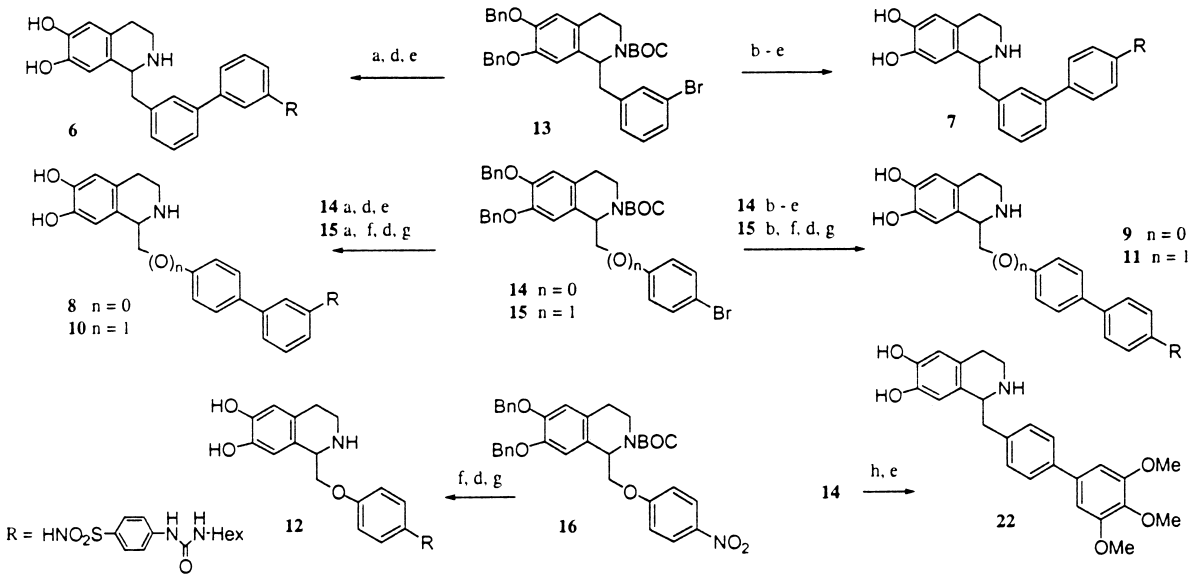
Compounds **6**–**12**, **17**, and **18** were tested at the cloned human β ARs and the results are shown in Table 1. Of the biphenyl derivatives **6**–**9**, the 4,4-substitution pattern was obviously preferred as compound **9** was >20-fold more potent than the other biphenyl derivatives (β_3 EC_{50} = 6 nM). Derivative **9** had an IC_{50} at the β_3 AR = 9.4 nM and hence showed >300-fold selectivity for both activation of and binding to the β_3 AR over binding to the β_1 and β_2 ARs. The compound exhibited only weak partial agonist activity at the β_1 and β_2 ARs (EC_{50} = 1800 and 340 nM, respectively). Additionally, several 4,4-biphenyl derivatives lacking the benzenesulfonamide were prepared and shown to be non-selective β AR agonists (β_3 EC_{50} = 8–230 nM, data not shown). The exception was 3,4,5-trimethoxy compound **22** (Scheme 1), which was prepared as a comparison to TMQ. The longer compound **22** was nearly 16-fold less potent than TMQ (β_3 EC_{50} = 27 nM), but showed improved selectivity over the β_1 and β_2 ARs.

Of the oxygen linked derivatives **10**–**12**, only the 4,4-biphenyl **11** showed any agonist activity at < 100 nM. It

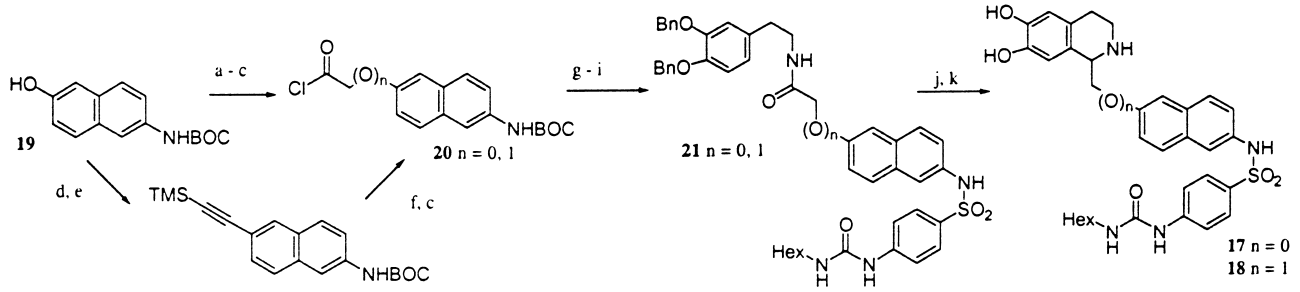
Table 1. Activity of tetrahydroisoquinoline derivatives **3**–**12**, **17**, **18** and **22**, at the cloned human β adrenergic receptors

Compound	β_3 EC_{50} nM (%act)[a]	β_1 EC_{50} nM (%act)[a]	β_1 binding IC_{50}[b] nM	β_2 EC_{50} nM (%act)[a]	β_2 binding IC_{50}[b] nM
3	1.7 (92)	14 (50)	6.1	3.5 (77)	6.1
4	800 (36)	(2 @ 10,000)	780	(1 @ 10,000)	56
5	66 (82)	(19 @ 10,000)	1200	(36 @ 10,000)	200
6	360 (62)	>10,000 (22)	530	2700 (36)	710
7	600 (64)	>1000 (12)	100,000	>1000 (33)	100,000
8	140 (100)	970 (69)	10,000	1300 (71)	32,000
9	6 (91)	1800 (44)	3000	340 (67)	3400
10	(10 @ 100)	nd[c]	6500	nd[c]	990
11	16 (72)	2400 (23)	2000	580 (29)	160
12	(4 @ 100)	nd[c]	1000	nd[c]	300
17	(7 @ 100)	nd[c]	1000	nd[c]	300
18	78 (72)	(3 @ 10,000)	80,000	(37 @ 10,000)	>100,000
22	27 (77)	6100 (45)	1800	1500 (85)	760

[a]Adenylyl cyclase activation given as % of the maximal stimulation with isoproterenol. Single point data are reported in parentheses as (% activation @ concentration 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.
[c]nd = Not determined.



Scheme 1. (a) 3-$NH_2PhB(OH)_2$·0.5 H_2SO_4, toluene, EtOH, 2 M Na_2CO_3, $Pd(PPh_3)_4$, 80 °C; (b) pinacol ester of 4-$NO_2PhB(OH)_2$, $Pd(dppf)Cl_2$, toluene, EtOH, 2 M Cs_2CO_3, 80 °C; (c) Raney Ni, NH_2NH_2, MeOH, 60 °C; (d) 4-(hexylureido)benzenesulfonyl chloride, py, CH_2Cl_2; (e) concd HCl, MeOH; (f) H_2, $Pd(OH)_2$, MeOH; (g) TFA, CH_2Cl_2; (h) 3,4,5-trimethoxyphenylboronic acid, $Pd(OAc)_2$, EtOH, $Ba(OH)_2$.



Scheme 2. (a) $BrCH_2CO_2Et$, Cs_2CO_3, DMF; (b) 5 N NaOH, MeOH; (c) $(COCl)_2$, CH_2Cl_2; (d) $PhNTf_2$, Et_3N, THF; (e) TMSCCH, Et_3N, $Pd(PPh)_2Cl_2$, DMF, 70 °C; (f) BH_3.THF, C_6H_{10}, THF then 2 N NaOH, H_2O_2, MeOH; (g) 3,4-dibenzyloxyphenethylamine hydrochloride, Et_3N, CH_2Cl_2; (h) TFA, CH_2Cl_2; (i) 4-(hexylureido)benzenesulfonyl chloride, py, CH_2Cl_2; (j) $POCl_3$, CH_3CN then $NaBH_4$, EtOH; (k) concd HCl, MeOH.

was a potent β_3 AR agonist (EC_{50} = 16 nM), however, the selectivity over binding to the β_2 AR was only 10-fold. A much greater degree of selectivity was seen with naphthyloxy derivative **18**. A moderately potent β_3 AR agonist (EC_{50} 78 nM, 72% activation), this derivative was >1000-fold selective for agonist activity at the β_3 AR over binding to the β_1 and β_2 ARs. Compound **18** exhibited only minimal agonist activity at the β_1 and β_2 ARs. Interestingly, naphthyl derivative **17**, lacking the oxygen linker, was devoid of agonist activity at the β_3 AR at <100 nM.

Low energy conformations of tetrahydroisoquinolines **9** and **18** were superimposed on pyridineethanolamine **2** in order to see if there was indeed superior alignment of the hydrogen bonding regions of the molecules (Figs. 3 and 4). As predicted the biphenyl derivative **9** showed improved overlap of the urea moiety, while the naphthyloxy compound **18** demonstrated excellent alignment of all parts of the molecule with pyridineethanolamine **2**.

In this paper we have described a novel series of β_3 AR agonists derived from trimetoquinol. In particular, the

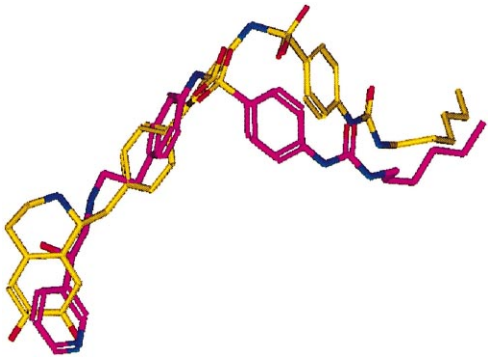


Figure 3. Superimposition of low energy conformations of pyridineethanolamine **2** (pink) and tetrahydroisoquinoline **9** (yellow).

4,4-biphenyl derivative **9** is a very potent compound (β_3 EC_{50} = 6 nM), which is a full agonist of the β_3 AR and exhibits good selectivity over binding to the β_1 and β_2 ARs. Also noteworthy is naphthyloxy derivative **18**, which shows excellent selectivity for the β_3 AR, with minimal binding to or activity at the β_1 and β_2 ARs. The improvements in selectivity for the β_3 AR seen in this

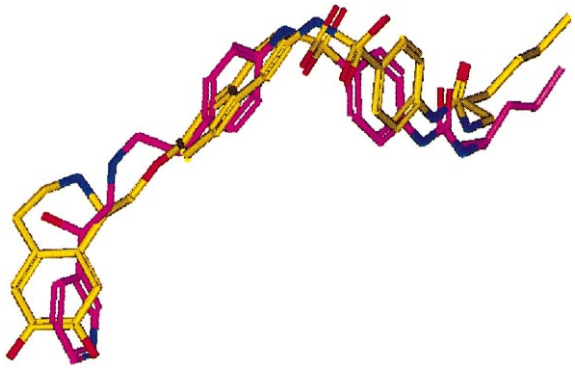


Figure 4. Superimposition of low energy conformations of pyridineethanolamine **2** (pink) and tetrahydroisoquinoline **18** (yellow).

class of compounds represent an important breakthrough in the design of structurally distinct human β_3 AR agonists as potential therapeutics for the treatment of obesity.

Acknowledgements

We thank Professor James G. Grannemann (Wayne State University) for supplying the cloned human β_3 AR and Ms. Amy Bernick for mass spectrometric analyses.

References and Notes

1. For recent reviews see: (a) Weyer, C.; Gautier, J. F.; Danforth, J. *Diab. Metab.* **1999**, *25,* 1. (b) Weber, A. E. *Annu. Rep. Med. Chem.* **1998**, *33*, 193. (c) Dow, R. L. *Exp. Opin. Invest. Drugs*, **1997**, *6*, 1811. (d) Lowell, B. B.; Flier, J. S. *Annu. Rev. Med.* **1997**, *48*, 307. (e) Arch, J. R. S.; Wilson, S. *Int. J. Obesity* **1996**, *20*, 191.

2. (a) Connacher, A. A.; Jung, R. T.; Mitchell, P. E. G. *Br. Med. J. Clin. Res. Ed.* **1988**, *296*, 1217. (b) Wheeldon, N. M.; McDevitt, D. G.; Lipworth, B. J. *Br. J. Clin. Pharmacol.* **1994**, *37*, 363.

3. Parmee, E. R.; Ok, H. O.; Candelore, M. R.; Tota, L.; Deng, L.; Strader, C. D.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1107.

4. Naylor, E. M.; Colandrea, V. J.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F., Jr.; 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.

5. Iwasawa, Y.; Kiyomot, A. *Jpn. J. Pharmacol.* **1967**, *18*, 85.

6. The human β_3 AR was obtained from Professor J. Grannemann (Wayne State Universtiy), Grannemann, J. G.; Lahners, K. N.; Rao, D. D. *Mol. Pharmacol.* **1992**, *42*, 964. The human β_1 and β_2 ARs were cloned as described in Frielle, T.; Collins, S.; Daniel, K. W.; Caron, M. G.; Lefkowitz, R. J.; Kobilka, B. K. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 7920 and Kobilka, B. K.; Dixon, R. A.; Frielle, T.; Dohlman, H. G.; Bolanoski, M. A.; Sigal, I. S.; Yan-Feng, T. L.; Francke, U.; Caron, M. G.; Lefkowitz, R. J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 46. The receptors were expressed in CHO cells at receptor densities of 46–88 fmol/mg (β_3 receptors) or 300–500 fmol/mg (β_1 and β_2 ARs). Agonist activity and binding affinity were assessed by measurement of cellular cAMP levels relative to isoproterenol and inhibition of ^{125}I-cyanopindolol binding, respectively.

7. (a) 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. (b) He, Y.; Nikulin, V. I.; Vansal, S. S.; Feller, D. R.; Miller, D. D. *J. Med. Chem.* **2000**, *43*, 591.

8. Prepared from the aniline described in Christoff, J. J.; Bradley, L.; Miller, D. D.; Lei, L.; Rodriguez, F.; Fraundorfer, P.; Romstedt, K.; Shams, G.; Feller, D. R. *J. Med. Chem.* **1997**, *40*, 85.

9. For experimental details, see Brockunier, L. L.; Parmee, E. R.; Weber, A. E. U. S. Patent 6 043 253, 2000. All compounds were purified by reverse-phase HPLC (eluent MeOH/H_2O/0.1% TFA) and characterized as their TFA salts by ^{1}H NMR, and mass spectrometry prior to submission for biological evaluation. The compounds prepared in this paper are racemic, however, it is known that all of the β AR activity resides in the (*S*) isomer of the tetrahydroisoquinoline series (see Fraundorfer, P. F.; Lezama, E. J.; Salazar-Bookman, M. M.; Fertel, R. H.; Miller, D. D.; Feller, D. R. *Chirality* **1994**, *6*, 76).

10. Twenty-six structurally diverse conformations of compounds **2**, **5**, **9**, and **18** were generated with the program Enumerate Torsions (ET) (Feuston, B. P.; Miller, M. D.; Culberson, J. C.; Nachbar, R. B.; Kearsley, S. K. *manuscript in preparation*), and each structure was energy minimized with MMFFS force field (Halgren, T. A.; *J. Comput. Chem.* **1999**, *20*, 720) and the Newton-Raphson method until the gradient converged (<0.001). Each of the 26 conformations for tetrahydroisoquinolines **5**, **9**, and **18** were then superimposed with the lowest energy conformation of pyridineethanolamine **2** with exhaustive enumeration of all possible superimposition's using the program SQ (Miller, M. D.; Sheridan, R. P.; Kearsley, S. K.; *J. Med. Chem.* **1999**, *42*, 1505). The highest scoring superimposition in each case was then further manually modeled to achieve best possible overlay with pyridineethanolamine **2**. The final model was then energy minimized to obtain a fully refined superimposed model that is consistent with the experimental data.

11. Compounds **13**–**16** were prepared from the appropriate phenyl or phenoxy acetic acid as described in ref 8.

12. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.

13. Prepared by BOC protection of 6-amino-2-naphthol, which was synthesized from 6-bromo-2-naphthol as described by Wisansky, W. A.; Ansbacher, S. In *Org. Synth.*, Collective Vol. 3; Horning, E. C., Ed.; Wiley: New York, 1955; p 307.