Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 213–216

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

N-(Sulfonamido)alkyl[tetrahydro-1*H*-benzo[*e*]indol-2-yl]amines: Potent Antagonists of Human Neuropeptide Y Y5 Receptor

James J. McNally,[a] Mark A. Youngman,[a] Timothy W. Lovenberg,[b] Diane H. Nepomuceno,[b] Sandy J. Wilson[b] and Scott L. Dax[a,*]

[a]*Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Welsh and McKean Roads, Spring House, PA 19477, USA*

[b]*Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, 3210 Merryfield Row, San Diego, CA 92121, USA*

Received 4 October 1999; accepted 16 November 1999

Abstract—[3a,4,5,9b-Tetrahydro-1*H*-benzo[*e*]indol-2-yl]amines were prepared via reductive amination and concomitant cyclization of α-cyanomethyl-β-aminotetralins. *N*-acylation with Ω-sulfonamido-carboxylic acids and subsequent reduction afforded a series of *N*-(sulfonamido)alkyl[tetrahydro-1*H*-benzo[*e*]indol-2-yl]amines, which bound to the human neuropeptide Y Y5 receptor with nanomolar affinity.

Neuropeptide Y (NPY), a 36 amino acid protein found abundantly in the central and peripheral nervous systems, is a powerful stimulant of feeding.[1–4] Five different NPY receptor subtypes (Y1, Y2, Y4(PP), Y5, and Y6) that bind NPY and related peptides (peptide YY (PPY), pancreatic polypeptide (PP) and truncated NPY analogues)[5–14] are recognized today as members of the superfamily of G-protein coupled receptors. Activation of the Y1 and Y5 receptor subtypes appears to be responsible for centrally-mediated NPY-induced feeding responses.[13,15–17] Compounds that antagonize the Y5 receptor can be effective in reducing food intake in animal models of feeding.[18] Consequently, a host of small molecule Y5 antagonists have been developed in attempts to provide a novel therapy for the treatment of obesity and other human eating disorders.[19] We wish to report here that tetrahydro-1*H*-benzo[*e*]indol-2-ylamines, when substituted with appropriate (sulfonamido)alkyl groups, afford compounds that bind with nanomolar affinity to the human Y5 receptor. To our knowledge, the 3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indol-2-ylamine tricycle is a novel ring system whose structure we confirm via X-ray crystallographic analysis.

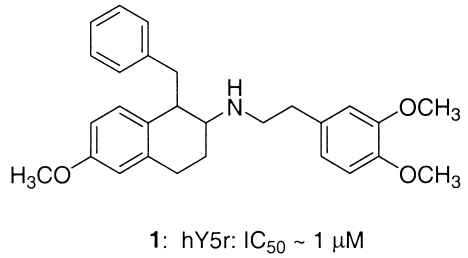
Screening of our in-house chemical library identified a novel *N*-phenethyl-α-benzyl-β-aminotetralin **1** (Fig. 1) as having low micromolar binding affinity for the human Y5 receptor. Unfortunately, *N*-aralkylated α-benzyl-β-aminotetralins homologues were, in general, similarly hampered by poor aqueous solubility, high lipophilicity and modest binding affinity. We therefore decided to introduce functional groups into the tetralin ring substituent in an attempt to improve the physical characteristics of the series and to provide a synthetic handle upon which other structural modifications would be accessible.

β-Tetralones were obtained from phenylacetic acids via cyclization upon reaction with ethylene gas and aluminum trichloride using the method of Sims.[20] Treatment of β-tetralone **2** with pyrrolidine afforded the corresponding enamine **3** which smoothly underwent alkylation with bromoacetonitrile. The resultant iminium salt **4** was subjected to acid hydrolysis to provide α-cyanomethyl-β-tetralone **5**. Reductive amination (ammonium acetate, sodium cyanoborohydride in methanol with heating) induced cyclization to the tricycle and subsequent treatment with acid allowed for isolation of *cis*-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indol-2-ylamines **6** as stable hydrochloride salts (Scheme 1). Interestingly, α-cyanomethyl-β-aminotetralin, a putative intermediate from reductive amination, could not be isolated from the reaction mixture.

With the tetrahydro-1*H*-benzo[*e*]indol-2-ylamine tricycle in-hand, we chose to carry out *N*-acylations and alkylations in an attempt to enhance Y5 receptor binding

*Corresponding author. Tel.: +1-215-628-5211; fax: +1-215-628-4985; e-mail: sdax@prius.jnj.com

0960-894X/00/$ - see front matter
PII: S0960-894X(99)00676-9



1: hY5r: IC_{50} ~ 1 μM

Figure 1.

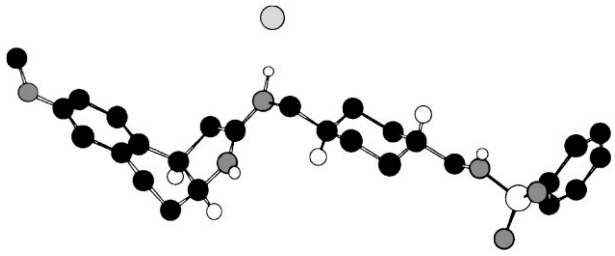
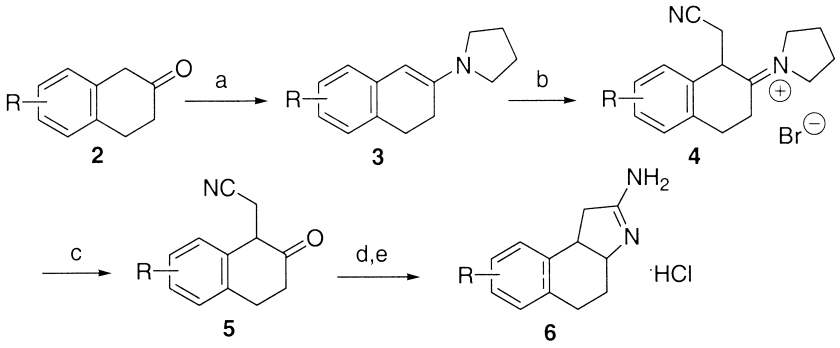


Figure 2. X-ray crystal structure of **8c**.

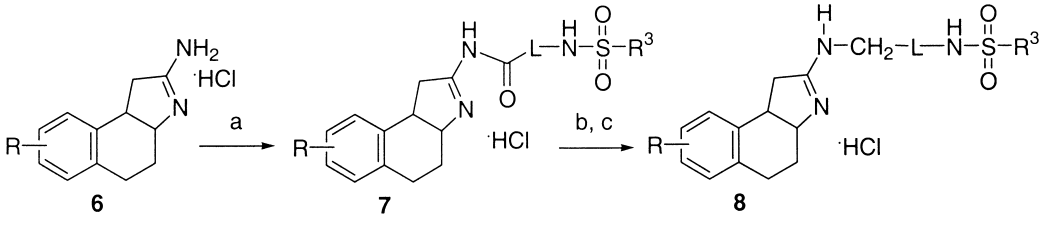
affinity. Thus cyclic amidines **6** were condensed with a series of Ω-sulfonamido-carboxylic acids derived from tranexamic acid and lysine. Standard peptide coupling protocols (HBTU/DMF) cleanly afforded the desired amide adducts **7** in high yield.[21] Subsequent reduction (lithium aluminum hydride), followed by treatment with acid provided the corresponding amines **8** as acid addition salts[22] (Scheme 2).

The structures of the final products were confirmed by spectroscopic data and X-ray diffraction analysis of a crystalline congener (**8c**).[23] The crystal structure (Fig. 2) reveals the *cis*-junction of the amidine ring, alkylation of the exocyclic nitrogen atom and that the endocyclic C–N bond is shorter (1.25 Å) than the exocyclic C–N bond (1.34 Å). This ring system, the [3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indol-2-yl]amine tricycle, is novel, as are the *N*-alkylated and acylated derivatives we disclose here.

The *N*-(sulfonamido)alkyl-[3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indol-2-yl]amines **8** and the corresponding amide precursors **7** were evaluated for binding affinity to the human neuropeptide Y Y5 receptor using a stably-transfected HEK293 cell line and measuring competitive inhibition of binding of ^{125}I-PYY (Table 1). In general, the arylsulfonamido group was needed for measurable binding affinity; amine precursors **6** were inactive and simple *N*-acetylation (**7a**) failed to significantly enhance binding. As with other sulfonamide-derived Y5 antagonists,[18,19] the *trans*-cyclohexylmethyl scaffold (L group) gives an optimum spacing between the sulfonamido group and the basic amine site, as evident by potent binding affinity (**7b–7f** and **8b–8f**). However, the aminopentyl scaffold, derived from lysine, affords water-soluble compounds with only slightly diminished affinity (**7g**). A cursory examination of substituents on the tetrahydro-benzo[*e*]indol-2-ylamine tricycle and the benzenesulfonamide terminus indicated that aryl substituents at these sites have little impact on binding affinity, although the C-7 hydroxy substituent on the tetrahydro-benzo[*e*]indole does enhance activity considerably. A combination of these preferred structural features gave **8d**, which is among the most potent

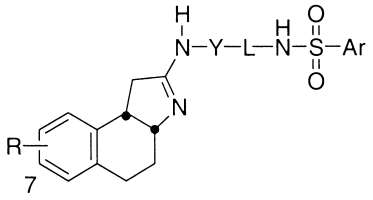


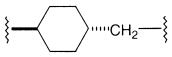
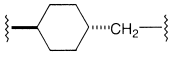
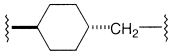
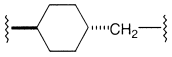
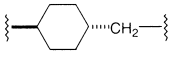
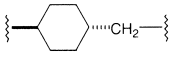
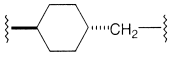
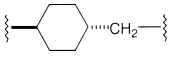
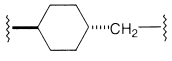
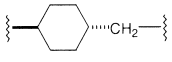
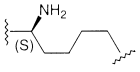
Scheme 1. Reagents: (a) pyrrolidine (1.3 equiv)/PhH reflux (-H_2O); (b) $NCCH_2Br$ (1.3 equiv)/CH_3CN; (c) HOAc, H_2O, CH_2Cl_2/MeOH; (d) $Na(BH_3)CN$ (5 equiv), NH_4Oac (15 equiv)/MeOH; (e) HCl.



Scheme 2. Reagents: (a) HOOC–L–$\overset{H}{N}$–SO_2-R^3, HBTU (1.05 equiv), DIEA (3.3 equiv)/DMF; (b) LAH (5.0 equiv)/THF; (c) HCl.

Table 1. Y5 Receptor binding affinity[a] of *N*-substituted [3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indol-2-ylamines[b]



Entry	R	Y	L	Ar	Y5 IC_{50} (nM)
7a	7-OMe	C=O	CH_3	—	>1000
7b	(H)	C=O		Ph	60
8b	(H)	-CH_2-		Ph	39
7c	7-OMe	C=O		Ph	91
8c	7-OMe	-CH_2-		Ph	57
7d	7-OH	C=O		Ph	9
8d	7-OH	-CH_2-		Ph	1
7e	7-Cl	C=O		Ph	111
8e	7-Cl	-CH_2-		Ph	54
7f	7-OMe	C=O		(2-F)Ph	121
8f	7-OMe	-CH_2-		(2-F)Ph	35
7g	7-F	C=O		(2-F)Ph	202

[a]HEK293 cells were stably transfected with the human NPY5 cDNA. Membranes from cell pellets were prepared in 20 mM HEPES, 10 mM NaCl, 0.22 mM KH_2PO_4, 1.3 mM $CaCl_2$, 0.8 mM $MgSO_4$ at pH 7.4. Membranes were incubated with compounds and ^{125}I-PYY (80 pM) for 45 minutes at room temperature. After centrifugation and washing, the remaining membrane radioactivity was measured (counts) using a gamma counter (Packard Cobra II). The total binding was determined in the absence of compounds and non-specific binding was determined in the presence of 300 nM NPY. Non-specific binding (counts) was subtracted from the radioactivity (counts) remaining on membranes after incubation with test compound and this value was divided by the total specific binding (counts) to determine percent (%) specific bound. % Specific binding was plotted versus log compound concentration using the program Prism (Graphpad Software, San Diego, CA). IC_{50} values were determined as the concentration of compound that inhibited 50% of the total specific binding; data in Table 1 are average values from at least two experiments.

[b]Compounds are racemates except for **7g**, which is a set of diastereomers.

Y5 receptor ligands reported to date (IC_{50} = 1 nM). Compounds **7b**, **8c**, **7d** and **8d** were shown to be antagonists since they did not stimulate binding of labeled GTPγS in a Bowes melanoma cell line transfected with the human Y5 receptor, but in the presence of PYY, were able to inhibit incorporation of ^{35}S label.

Summary

N-(Sulfonamido)alkyl-[3a,4,5,9b-tetrahydro-1*H*-benzo-[*e*]indol-2-yl]amines are potent antagonists of the human neuropeptide Y Y5 receptor. These compounds embody a novel heterocyclic core that is prepared via cyanomethylation of β-tetralones followed by reductive amination and concomitant cyclization. Subsequent acylation occurs on the exocyclic nitrogen atom and can be used to install a pendant arylsulfonamide group. Amide reduction affords *N*-(sulfonamido)alkylated tetrahydro-1*H*-benzo[*e*]indol-2-yl]amines which exhibit nanomolar binding affinity for the Y5 receptor.

Acknowledgements

We thank A. Reitz, V. Day,[23] P. McDonnell, D. Gauthier and C. Kordik for their help.

References and Notes

1. Clark, J. T.; Kalra, P. S.; Crowley, W. R.; Kalra, S. P. *Endocrinology* **1984**, *115*, 427.
2. Levine, A. S.; Morley, J. E. *Peptides* **1984**, *5*, 1025.
3. Stanley, B. G.; Leibowitz, S. F. *Life Sci.* **1984**, *35*, 2635.
4. Stanley, B. G.; Leibowitz, S. F. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 3940.
5. Wahlestedt, C.; Grundemar, L.; Häkanson, R.; Heilig, M.; Shen, G. H.; Zukowska-Grojec, Z.; Reis, D. J. *Ann. NY Acad. Sci.* **1990**, *611*, 7.
6. Larhammar, D.; Blomqvist, A. G.; Yee, F.; Jazin, E.; Yoo, H.; Wahlestedt, C. *J. Biol. Chem.* **1992**, *267*, 10935.
7. Wahlestedt, C.; Yanaihara, N.; Häkanson, R. *Regul. Pept.* **1986**, *13*, 307.
8. Fuhlendorff, J. U.; Gether, U.; Aakerlund, L.; Langeland-Johansen, N.; Thoegersen, H.; Melberg, S. G.; Olsen, U. B.; Thastrup, O.; Schwartz, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 182.
9. Grundemar, L.; Wahlestedt, C.; Reis, D. J. *J. Pharmacol. Exp. Ther.* **1991**, *258*, 633.
10. Laburthe, M.; Chenut, B.; Rouyer-Fessard, C.; Tatemoto, K.; Couvineau, A.; Servin, A.; Amiranoff, B. *Endocrinology* **1986**, *118*, 1910.
11. Castan, I.; Valet, P.; Vosin, T.; Quiteau, N.; Laburthe, M.; Lafontan, M. *Endocrinology* **1992**, *131*, 1970.
12. Gerald, C. P. G.; Weinshank, R. L.; Walker, M. W.; Branchek, T. WO 97/46250. Synaptic Pharmaceutical Corporation, USA, 1997.
13. Gerald, C.; Walker, M. W.; Criscione, L.; Gustafson, E. L.; Batzl-Hartmann, C.; Smith, K. E.; Vaysse, P.; Durkin, M. M.; Laz, T. M.; Linemeyer, D. L.; Schaffhauser, A. O.; Whitebread, S.; Hofbauer, K. G.; Taber, R. I.; Branchek, T. A.; Weinshank, R. L. *Nature* **1996**, *382*, 168.
14. Weinberg, D. H.; Sirinathsinghji, D. J. S.; Tan, C. P.; Shiao, L.-L.; Morin, N.; Rigby, M. R.; Heavens, R. H.; Rapoport,

D. R.; Bayne, M. L.; Cascieri, M. A.; Strader, C. D.; Linemeyer, D. L.; MacNeil, D. J. *J. Biol. Chemistry* **1996**, *271*, 16435.
15. Inui, A. *Trends Pharmacol. Sci.* **1999**, *20*, 43.
16. Stanley, B. G.; Magdalin, W.; Seirafi, A.; Nguyen, M. M.; Leibowitz, S. F. *Peptides* **1992**, *13*, 581.
17. Kirby, D. A.; Koerber, S. C.; May, J. M.; Hagaman, C.; Cullen, M. J.; Pelleymounter, M. A.; Rivier, J. E. *J. Med. Chem.* **1995**, *38*, 4579.
18. Criscione, L.; Rigollier, P.; Batzl-Hartmann, C.; Rueger, H.; Stricker-Krongrad, A.; Wyss, P.; Brunner, L.; Whitebread, S.; Yamaguchi, Y.; Gerald, C.; Heurich, R. O.; Walker, M. W.; Chiesi, M.; Schilling, W.; Hofbauer, K. G.; Levens, N. *J. Clin. Invest.* **1998**, *102*, 2136.
19. Ling, A. L. *Exp. Opin. Ther. Patents* **1999**, *9*, 375.
20. Sims, J. J.; Cadogan, M.; Selman, L. H. *Tetrahedron Lett.* **1971**, *14*, 951.
21. *cis*-3a,4,5,9b-Tetrahydro-7-methoxy-*N*-[*trans*-4-[(phenylsulfonyl)amino]methyl]cyclohexyl]carbonyl]-1*H*-benz[*e*]indol-2-ylamine (**7c**). A solution of *trans*-4-[(benzenesulfonamido)-methyl]cyclohexane carboxylic acid (1.16 g, 4.15 mmol), *O*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (1.58 g, 4.15 mmol) and *N,N*-diisopropylethylamine (2.41 mL, 13.8 mmol) in *N,N*-dimethylformamide (15 mL) was stirred at ambient temperature for 15 min. 3a,4,5,9b-Tetrahydro-7-methoxy-1*H*-benz[*e*]indol-2-ylamine hydrochloride (1.0 g, 3.96 mmol) was added, and the resultant solution was heated to 45 °C for 1.5 h. The solution was poured into ice water and the precipitate collected by filtration, washed with water and air dried. This solid was triturated with diethyl ether to give *cis*-3a,4,5,9b-tetrahydro-7-methoxy-*N*-[*trans*-4-[(phenylsulfonyl)amino]methyl]cyclohexyl]carbonyl]-1*H*-benz[*e*]indol-2-amine **7c** as a colorless solid (1.87 g, 95%). NMR (DMSO-d_6): δ 0.69–0.89 (m, 2H), 1.10–1.34 (m, 3H), 1.63–1.88 (m, 5H), 2.10–2.27 (m, 1H), 3.24–3.50 (m, 3H), 3.70 (s, 3H), 4.04–4.13 (m, 1H), 6.63 (d, 1H), 6.74 (d of d, 1H), 7.05 (d, 1H), 7.54–7.67 (m, 4H) and 7.74–7.83 (m, 2H); MS 496 $(M+H)^+$.
22. *cis*-3a,4,5,9b-Tetrahydro-7-methoxy-*N*-[*trans*-4-[(phenylsulfonyl)amino]methyl]cyclohexyl] methyl]-1*H*-benz[*e*]indol-2-ylamine (**8c**). Amide **7c** (1.6 g, 3.22 mmol) was added in portions, with stirring, to a solution of lithium aluminum hydride (16.1 mmol) in tetrahydrofuran (36 mL) at ambient temperature. The resultant solution was heated at reflux for 45 min. The solution was cooled on an ice bath and a solution of water (0.65 mL) in tetrahydrofuran (5 mL) was carefully added, followed by the addition of 10% aqueous sodium hydroxide (0.65 mL) and water (2.1 mL). The resultant suspension was stirred at ambient temperature for 30 min and dried over sodium sulfate. The insoluble material was removed by filtration and washed with tetrahydrofuran. The solvent was evaporated in vacuo, the residue was dissolved in a minimum amount of isopropanol and treated with a concentrated solution of hydrogen chloride in isopropanol. The solvents were evaporated in vacuo to give the desired amine hydrochloride salt **8c** as a pale pink solid (1.38 g; ~75% HPLC purity). A 300 mg portion of this material was purified by preparative HPLC (C_{18} reverse-phase column (4×45 cm) eluting with a gradient of water:acetonitrile:trifluoroacetic acid (90:10:0.1 to 10:90:0.1) (v/v)) to give material which was treated with ethanolic hydrogen chloride to give pure *cis*-3a,4,5,9b-tetrahydro-7-methoxy-*N*-[[*trans*-4-[[(phenylsulfonyl)amino]methyl]cyclohexyl]methyl]-1*H*-benz[*e*]indol-2-yl amine hydrochloride **8c** as a colorless solid (0.15 g). NMR (DMSO-d_6): δ 0.70–0.94 (m, 4H), 1.20–1.50 (m, 2H), 1.62–1.77 (m, 4H), 1.80–1.94 (m, 2H), 2.55–2.73 (m, 5H), 3.03–3.16 (m, 2H), 3.31–3.46 (m, 1H), 3.63–3.73 (m, 1H), 3.71 (s, 3H), 4.24–4.32 (m, 1H), 6.70 (d, 1H), 6.79 (d of d, 1H), 7.14 (d, 1H), 7.55–7.67 (m, 4H), 7.74–7.82 (m, 2H), 9.66 (br t, 1H) and 10.09 (br s, 1H); MS 482 $(M+H)^+$.
23. Cambridge Crystallographic Data Centre deposition number CCDC 135130; submitted by V. Day, Crystalytics Company, PO Box 82286, Lincoln, NE 68501, USA.