Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 1073–1076

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

2-(3,5-Dimethylphenyl)tryptamine Derivatives That Bind to the GnRH Receptor

Peter Lin,[a,*] Dominick Marino,[a] Jane-Ling Lo,[b] Yi Tien Yang,[b] Kang Cheng,[b] Roy G. Smith,[b] Michael H. Fisher,[a] Matthew J. Wyvratt[a] and Mark T. Goulet[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Biochemistry & Physiology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*

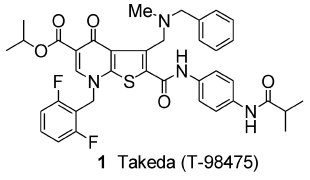
Received 11 December 2000; accepted 23 February 2001

Abstract—A series of 2-(3,5-dimethylphenyl)tryptamine derivatives was prepared and evaluated on a rat gonadotropin releasing hormone receptor assay. Some *para*-substituents on the 4-phenylbutyl side chain attached to the tryptamine nitrogen led to compounds with potent GnRH receptor binding. The study has helped define structural requirements for GnRH receptor binding for the 2-aryltryptamine GnRH antagonists. © 2001 Elsevier Science Ltd. All rights reserved.

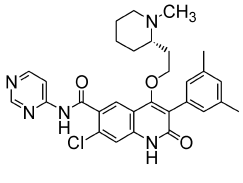
Since Schally's initial discovery[1,2] in 1971 of the decapeptide gonadotropin releasing hormone (GnRH), (synonymous with luteinizing hormone-releasing hormone—LHRH), much is now known as to how this peptide functions in mammalian biochemistry.[3–5] GnRH when released from the hypothalamus leads to stimulation of the GnRH receptor, a G-protein coupled receptor, located on gonadotrophes in the pituitary gland. The stimulated gonadotrophes, in turn release follicle stimulating hormone (FSH) and luteinizing hormone (LH), which interact with the tissues of the reproductive system. Several medical conditions[6] related to reproductive health that are likely to benefit from GnRH antagonist therapy are endometriosis, precocious puberty, and breast and prostate cancer.

In recent years effort has been directed toward finding drugs effective as GnRH antagonists. Several peptidyl[7,8] GnRH agonist and antagonist compounds are now known. GnRH peptidyl agonists have been approved for clinical use for some time and two peptide antagonists, Ganirelix (Antagon™) and Cetrorelix (Cetrotide®), are now currently available for clinical use in humans. More recently, attention has switched to finding nonpeptidyl GnRH antagonists. The advantages of using a nonpeptide GnRH antagonist drug are firstly, avoidance of the initial 'flare-up' condition that is often seen in patients receiving peptidyl GnRH agonist therapy and secondly, the potential with a small drug molecule for oral administration. In 1998, Takeda described peptidomimetic compounds that bind to the GnRH receptor that are based on thieno[2,3-*b*]pyridin-4-one[9] (e.g., **1**). Some quinolone-[10–14] (e.g., **2**) and 2-aryltryptamine-derived[15,16] (e.g., **3**) GnRH antagonist compounds have been reported by Merck authors in the past 18 months (Fig. 1).

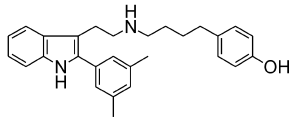
This Letter focuses on some phenol ring replacements of the Merck 2-arylindole GnRH antagonist **3**. Our investigations on phenol surrogates have helped increase our



1 Takeda (T-98475)



2 Merck



3 Merck

Figure 1. GnRH receptor antagonists recently reported by Takeda and by Merck.

*Corresponding author.Tel.: +1-732-594-4646; fax: +1-732-594-5790; e-mail: peter_lin@merck.com

PII: S0960-894X(01)00134-2

knowledge of the structure–activity relationships (SAR) for the 2-arylindole class of nonpeptide GnRH antagonists.

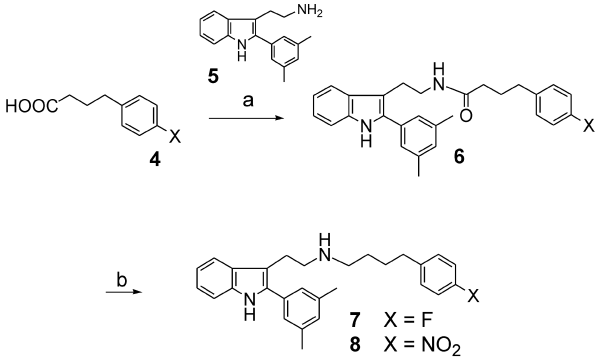
Preparation of Compounds[17]

In this study, side chains were attached to the tryptamine nitrogen of the 2-arylindole core **5** using the reaction sequence shown in Scheme 1. Thus, a 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) mediated amide bond formation between an appropriate *para*-substituted phenylbutyric acid **4** and the tryptamine **5** afforded amides **6**. These amides **6** were reduced with borane–tetrahydrofuran (BH_3·THF) complex to give the corresponding secondary amines **7** and **8**. Protection of tryptamine **8** as its *t*-butoxycarbonyl (BOC) derivative (Scheme 2) followed by catalytic hydrogenation using platinum(IV) oxide led smoothly to the aniline **9**. The latter served as a key intermediate for the synthesis of the amine derivatives depicted in Scheme 3.

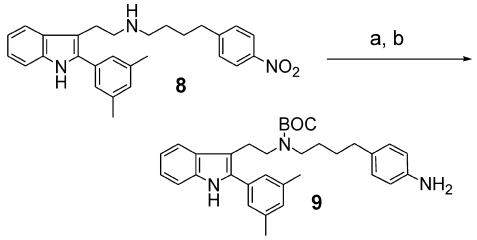
The parent aniline analogue **10** was obtained by treatment of aniline **9** with trifluoroacetic acid (TFA) in the presence of anisole. This TFA–anisole treatment for removing BOC-groups was used effectively to reveal the secondary amine nitrogen from other intermediates described below. Acetylation of the aniline **9** followed by TFA promoted deprotection gave the acetanilide **11**. The two urea compounds **12** and **13** were prepared by reacting aniline **9** with methyl isocyanate and ethyl isocyanate, respectively. The intermediary BOC-containing adducts were individually treated with the usual BOC-deprotection conditions to give the 2-aryltryptamine derivatives **12** and **13**. Also, the two corresponding methyl- and ethyl-sulfonylureas (**14** and **15**) were synthesized. Thus, the aniline **9** was reacted with two mono-alkylsulfamoyl chlorides in the presence of triethylamine. Removal of the BOC-group as described above gave the sulfonyl ureas **14** and **15**. Various sulfonamide derivatives (**16–19** R^3 = Me; Et; *i*-Pr and Ph, respectively, in Scheme 3) were obtained by reacting the aniline **9** with the appropriate sulfonyl chloride in the presence of triethylamine at 0 °C. The sulfonamide products were isolated and subsequent removal of the BOC group by the usual method led to the target compounds **16–19.**

The four-carbon tethered sulfonamide **25** was prepared as shown in Scheme 4. Protection of 3-butyn-1-ol, **20**, using *t*-butyldiphenylsilyl chloride (TBDPS-Cl) and imidazole gave the TBDPS-ether. A palladium(0) catalyzed reaction between this silyl ether with the *t*-butyl sulfonamide bromide **21** in triethylamine provided the acetylene **22**. Treatment of silyl ether **22** with tetrabutylammonium fluoride (TBAF) in THF followed by hydrogenation of the carbon–carbon triple bond using Adams' catalyst (PtO_2) gave the alcohol **23**. A chromium trioxide on Celite® oxidation of alcohol **23** to the aldehyde and a subsequent sodium chlorite oxidation afforded the acid **24**. The tryptamine **5** was reacted with acid **24** to give amide **25** as described above. The primary sulfonamide **26** was obtained from amide **25** after a BH_3·THF reduction and treatment with TFA and anisole.

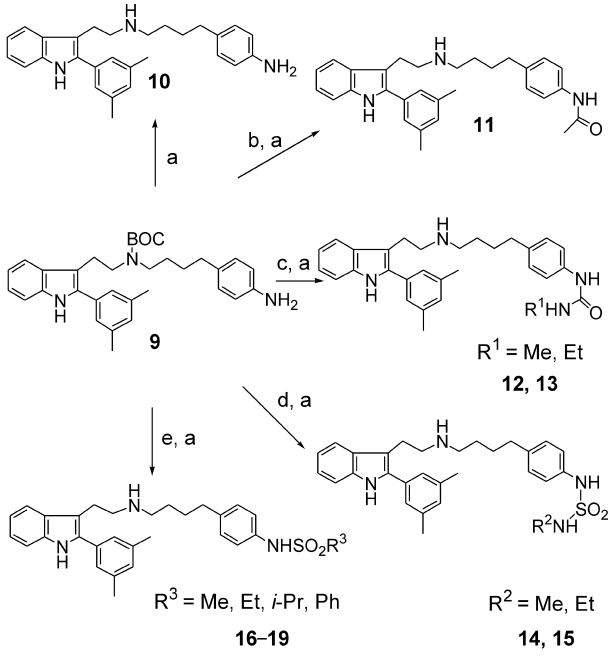
The various compounds listed in Table 1 containing phenol surrogates of compound **3** were evaluated. The compounds were all evaluated in a rat GnRH receptor binding assay and in two cases a human GnRH receptor



Scheme 1. Reagents and conditions: (a) EDC, HOBt, tryptamine **5**, CH_2Cl_2, rt; (b) BH_3·THF complex, THF, reflux.



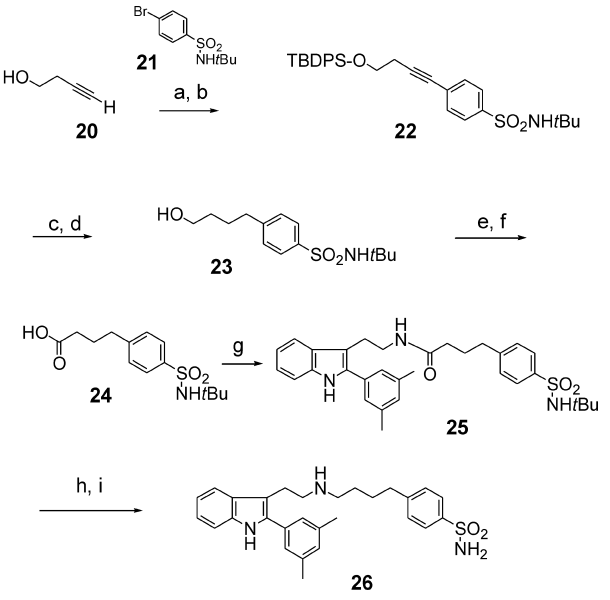
Scheme 2. Reagents and conditions: (a) $(BOC)_2O$, NEt_3, CH_2Cl_2, rt; (b) H_2 (1 atm), cat. PtO_2, EtOH, rt.



Scheme 3. Reagents and conditions: (a) TFA, anisole, dry CH_2Cl_2, rt; (b) CH_3COCl, pyridine, CH_2Cl_2, rt; (c) R^1NCO, NEt_3, CH_2Cl_2, rt; (d) R^2NHSO_2Cl, NEt_3, CH_2Cl_2, rt; (e) R^3SO_2Cl, NEt_3, CH_2Cl_2, 0 °C.

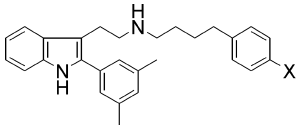
binding assay, according to the methods described previously.[10,12] The IC_{50} values obtained are also shown in Table 1.

The GnRH antagonist **3** is a phenol derivative. From some other work, conjugation and metabolism of phenol derivatives had been observed. Thus, this phenol of **3** may be a liability if it is retained in later designs of the 2-arylindole series of GnRH antagonists. The possibility of metabolism or conjugation of the phenol ring provided the impetus to study phenol ring surrogates.



Scheme 4. Reagents and conditions: (a) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, rt; (b) $Pd(PPh_3)_4$, LiCl, CuCl, NEt_3, bromide **21**, 80 °C; (c) TBAF, THF, rt; (d) H_2, cat. PtO_2, EtOH, rt; (e) CrO_3 on Celite®, CH_2Cl_2, rt; (f) $NaClO_2$, sulfamic acid, THF, H_2O, rt; (g) tryptamine **5**, EDC, HOBt, CH_2Cl_2, rt; (h) BH_3·THF complex, THF, reflux; (i) TFA, anisole, rt.

Table 1. GnRH binding IC_{50} values for the rat and human receptors



Compound	X	Rat GnRH receptor binding IC_{50}, nM	Human GnRH receptor binding IC_{50}, nM
3	-OH	27	357
7	-F	300	
8	$-NO_2$	500	
10	$-NH_2$	300	
11	-NHCOMe	200	
12	-NHCONHMe	48	
13	-NHCONHEt	28	
14	$-NHSO_2NHMe$	47	
15	$-NHSO_2NHEt$	40	
16	$-NHSO_2Me$	7	170
17	$-NHSO_2Et$	200	
18	$-NHSO_2iPr$	220	
19	$-NHSO_2Ph$	300	
26	$-SO_2NH_2$	36	

Our initial attempts at replacement of the phenolic hydroxyl **3** by a fluorine atom (**7**, $IC_{50} = 300$ nM) resulted in significant loss of receptor binding affinity to the rat GnRH receptor relative to the phenol **3** ($IC_{50} = 27$ nM). This observation probably implicated the need for a hydrogen bond donor group, as well as polarity for significant binding on the GnRH receptor. On that basis, poor receptor binding affinity was observed with a *para*-nitro phenyl group (**8**, $IC_{50} = 500$ nM). The simple aniline **10** ($IC_{50} = 300$ nM) and the acetanilide[18] **11** ($IC_{50} = 200$ nM) both of which are capable of acting as a hydrogen bond donor also showed poor receptor binding affinity to the rat GnRH receptor. Therefore, some derivatives of the aniline with $pK_a < 15$ were evaluated.[18] To our delight, the next series of analogues, the methylurea **12** ($IC_{50} = 48$ nM) and ethylurea **13** ($IC_{50} = 28$ nM) did achieve comparable receptor binding affinity to the phenol **3** as did the two sulfonyl ureas **14** ($IC_{50} = 47$ nM) and **15** ($IC_{50} = 40$ nM). Therefore, we were gratified to find that urea and sulfonylurea derivatives **12**–**15** did act as phenol surrogates of compound **3**.

The series of sulfonamides **16**–**19** was also of interest. The methanesulfonamide **16** ($IC_{50} = 7$ nM) was 4-fold more potent in binding than the phenol **3**. The methanesulfonamide **16** was also more potent ($IC_{50} = 170$ nM for **16** vs $IC_{50} = 357$ nM for **3**) at the human GnRH receptor. Other nonpeptide GnRH antagonists have also shown differences in their binding affinities toward the rat and human forms of the GnRH receptor.[9,13] We speculate that the 10-fold difference in binding between the rat and human GnRH receptor is due to receptor homology which is approximately 90% conserved.[19] Sterically more demanding ethyl-, isopropyl-, and benzene-sulfonamide groups were less potent and had IC_{50} values in the range 200–300 nM at the rat GnRH receptor. The 'reversed' primary sulfonamide **26** also showed potent binding affinity ($IC_{50} = 36$ nM) to the rat receptor, comparable to that of the phenol analogue **3**, but less potent than the methanesulfonamide **16**. Further studies were made in search of other phenol surrogates. One such study on heterocyclic ring replacements[20] of the phenol is described in the following Letter.

Based on the IC_{50} values presented in Table 1, some *para*-substituted benzene derivatives (e.g., compounds **12**–**17** and **26**) may indeed turn out to be valuable alternative structural motifs for substitution of the phenol ring of **3** that circumvent the metabolism problem associated with the phenol ring system. One such compound, methanesulfonamide **16**, appears to be a suitable, more potent replacement for the phenol containing GnRH antagonist **3**.

Acknowledgements

The authors are indebted to Dr. Eric E. Allen for helpful discussions relating to the preparation of the primary sulfonamide analogue **26** and to Ms. Amy Bernick and Dr. Lawrence Colwell for help with mass spectroscopic analysis of our compounds. Our gratitude to

Robert Frankshun, Joseph Leone and Mark Levorse who supplied us with synthetic intermediates used throughout the course of this study. Insightful discussions with Ralph Mosley of the molecular modeling group are graciously recognized. Helpful discussions with Drs. Robert DeVita, Feroze Ujjainwalla and Jonathan Young in the preparation of this manuscript are also gratefully acknowledged.

References and Notes

1. Schally, A. V.; Arimura, A.; Kastin, A. J.; Matsuo, H.; Baba, Y.; Reddin, T. W.; Nair, R. M. G.; Debeljuk, L.; White, W. F. *Science* **1971**, *173*, 1036.
2. Matsuo, H.; Baba, Y.; Nair, R. M. G.; Avimura, A.; Schally, A. V. *Biochem. Biophys. Res. Commun.* **1971**, *43*, 1334.
3. Kutscher, B.; Bernd, M.; Beckers, T.; Polymeropoulos, E. E.; Engel, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2148 and references cited therein.
4. Cui, J.; Smith, R. G.; Mount, G. R.; Lo, J.-L.; Yu, J.; Walsh, T. F.; Singh, S. B.; DeVita, R. J.; Goulet, M. T.; Schaeffer, J. M.; Cheng, K. *Mol. Endocrinol.* **2000**, *14*, 671.
5. Zhou, W.; Rodic, V.; Kitanovic, S.; Flanagan, C. A.; Chi, L.; Weinstein, H.; Maayani, S.; Millar, R. P.; Sealfon, S. C. *J. Biol. Chem.* **1995**, *270*, 18853.
6. Kardamakis, E.; Tzingounis, V. In *Biomed. Health Res.*; IOS: Amsterdam, 1999; Vol. 22 (Bioactive Peptides in Drug Discovery and Design: Medical Aspects), pp 275–285, and references cited therein.
7. Goulet, M. T. In *Annu. Rep. Med. Chem.* Bristol, J. A., Ed.; Academic: New York, 1995; Vol. 30, pp 169–178.
8. Behre, H. M.; Nordhoff, V.; Nieschlag, E. Ovul. Induct. Update '98, Proc. World Conf., 2nd, Meeting Date 1997. Filicori, M.; Flamigni, C., Ed.; Parthenon Publishing: Carnforth, UK, 1998; pp 107–113.
9. Cho, N.; Harada, M.; Imaeda, T.; Imada, T.; Matsumoto, H.; Hayase, Y.; Sasaki, S.; Furuya, S.; Suzuki, N.; Okuobo, S.; Ogi, K.; Endo, S.; Onda, H.; Fujino, M. *J. Med. Chem.* **1998**, *41*, 4190.
10. DeVita, R. J.; Hollings, D. D.; Goulet, M. T.; Wyvratt, M. J.; Fisher, M. H.; Lo, J.-L.; Yang, Y. T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2615.
11. DeVita, R. J.; Goulet, M. T.; Wyvratt, M. J.; Fisher, M. H.; Lo, J.-L.; Yang, Y. T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2621.
12. Walsh, T. F.; Toupence, R. B.; Young, J. R.; Huang, S. X.; Ujjainwalla, F.; DeVita, R. J.; Goulet, M. T.; Wyvratt, M. J., Jr.; Fisher, M. H.; Lo, J.-L.; Ren, N.; Yudkovitz, J. B.; Yang, Y. T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 443.
13. Young, J. R.; Huang, S. X.; Chen, I.; Walsh, T. F.; DeVita, R. J.; Goulet, M. T.; Wyvratt, M. J., Jr.; Fisher, M. H.; Lo, J.; Ren, N.; Yudkovitz, J. B.; Yang, Y. T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1723.
14. DeVita, R. J.; Walsh, T. F.; Young, J. R.; Jiang, J.; Ujjainwalla, F.; Toupence, R. B.; Parikh, M.; Huang, S. X.; Fair, J. A.; Goulet, M. T.; Wyvratt, M. J.; Lo, J.-L.; Ren, N.; Yudkovitz, J. B.; Yang, Y. T.; Cheng, K.; Cui, J.; Mount, G.; Rohrer, S. P.; Schaeffer, J. M.; Rhodes, L.; Drisko, J. E.; McGowan, E.; MacIntyre, D. E.; Vincent, S.; Carlin, J. R.; Cameron, J.; Smith, R. G. *J. Med. Chem.* **2001**, *44*, 917.
15. Chu, L.; Hutchins, J. E.; Weber, A. E.; Lo, J.-L.; Yang, Y. T.; Cheng, K.; Smith, R. G.; Fisher, M. H.; Wyvratt, M. J.; Goulet, M. T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 509.
16. Chu, L.; Lo, J.-L.; Yang, Y. T.; Cheng, K.; Smith, R. G.; Fisher, M. H.; Wyvratt, M. J.; Goulet, M. T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 515.
17. All of the final products and intermediates described in this paper have been fully characterized by thin-layer chromatography, MS and by ^{1}H NMR spectroscopy.
18. Note added in proof: Calculated pK_a values obtained from the ACD/pKa DB (version 4.50) computer program obtained from Advanced Chemistry Development Inc. are: 4-Me-C_6H_4-NHCOMe (15.13±0.7); 4-MeC_6H_4-NHCONHMe (14.24±0.46); 4-MeC_6H_4-SO_2NH_2 (10.20±0.10); 4-MeC_6H_4-OH (10.21±0.13); 4-MeC_6H_4-NHSO$_2$Me (9.71±0.50); 4-MeC$_6$H$_4$-NHSO$_2$NHMe (8.13±0.50); 4-MeC_6H_4-NH_3^+ (5.04±0.10).
19. Work relating to receptor sequences from the Biochemistry and Physiology department at Merck will be disclosed in due course.
20. For a related study concerned with heterocyclic rings as phenol surrogates see: Lin, P.; Parikh, M.; Lo, J.-L.; Yang, Y. T.; Cheng, K.; Smith, R. G.; Fisher, M. H.; Wyvratt, M. J.; Goulet, M. T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1077.