Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 1077–1080

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Heterocyclic Derivatives of 2-(3,5-Dimethylphenyl)tryptamine as GnRH Receptor Antagonists

Peter Lin,[a,*] Mamta Parikh,[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

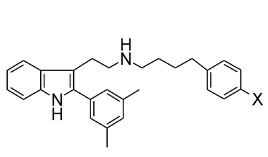
Abstract—A series of heterocyclic 2-(3,5-dimethylphenyl)tryptamine derivatives was prepared and evaluated on a rat gonadotropin releasing hormone receptor assay. The carbon tether length and heterocyclic ring attached to the amino group of 2-(3,5-dimethylphenyl)tryptamine were varied. Several of these derivatives were potent GnRH antagonists with the most potent compound having an IC_{50} of 16 nM.

The tryptamine-derived compound **1** (Fig. 1), has been previously disclosed[1,2] as a potent GnRH antagonist. However, the phenol compound (**1**) may be prone to conjugation and unwanted metabolic oxidation owing to the presence of the phenolic group. This possible metabolic liability prompted investigations to find suitable phenol surrogates. Our preceding paper[3] described one such study comprising tryptamine derivatives with side chains having a terminal *para*-substituted benzene ring (e.g., sulfonamide **2**). In this Letter we report our findings from a second study where the phenol ring is replaced by a variety of heterocycles.

Preparation of Compounds[4]

The compounds synthesized for this study were prepared by two general routes. The first method[3] involved a standard peptide amide bond formation between 2-(3,5-dimethylphenyl)tryptamine **4** and a carboxylic acid **3** (Scheme 1). The resulting secondary amides **5** were reduced with borane to give the corresponding amines **6**–**15** that are described in Table 1. The rat GnRH receptor binding data for compounds **6**–**15** are shown in Tables 3 and 4.

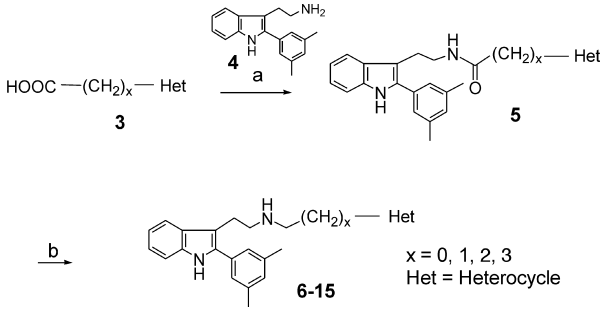
The second method, which was typically useful for the preparation of some four- and five-carbon tethered aromatic heterocyclic compounds, used a palladium(0) alkynylation reaction as the key step in the sequence. The preparation of a 2-pyridyl compound **20** is illustrative (Scheme 2). Reaction of 3-butyn-1-ol **16** and 2-bromopyridine **17** in a Castro–Stevens reaction gave acetylene **18**. The carbon–carbon triple bond in **18** was hydrogenated to give the saturated aliphatic chain primary alcohol. Swern oxidation of the alcohol afforded



1 X = OH
rat GnRH IC_{50} = 27 nM
human GnRH IC_{50} = 357 nM

2 X = $NHSO_2Me$
rat GnRH IC_{50} = 7 nM
human GnRH IC_{50} = 170 nM

Figure 1. Two Merck tryptamine-derived GnRH receptor antagonists.



Scheme 1. Reagents and conditions: (a) EDC, HOBt, CH_2Cl_2, rt; (b) BH_3·THF complex, THF, reflux, followed by $Me_2NCH_2CH_2OH$, reflux.

*Corresponding author. Tel.: +1-732-594-4646; fax: 1-732-594-5790; e-mail: peter_lin@merck.com
†Current address: Huffington Center for Aging, Baylor School of Medicine, One Baylor Plaza (M-320), Houston, TX 77030, USA.

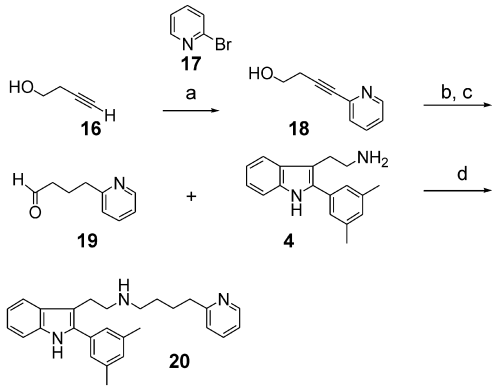
0960-894X/01/$ - see front matter
PII: S0960-894X(01)00133-0

aldehyde **19**. A reductive alkylation reaction between tryptamine[1] **4** and aldehyde **19** afforded the desired secondary amine product **20**, along with the tertiary amine sideproduct resulting from a second reductive amination. Other tryptamines (**21**–**26**, Table 2) were prepared using a similar protocol to that described in Scheme 2. The GnRH receptor binding data for compounds **21**–**26** are shown in Tables 3 and 4.

The α-methoxypyridine analogue **29** and α-pyridone **30** were synthesized as described in Scheme 3. 2,5-Dibromopyridine **27** was reacted with sodium methoxide in dimethylformamide (DMF) to give the 5-bromo-2-methoxy pyridine. The bromopyridine **28** was transformed into 2-methoxypyridine **29** using the reaction sequence described in Scheme 2. Reaction of methoxypyridine **29** with boron tribromide afforded the α-pyridone **30**.

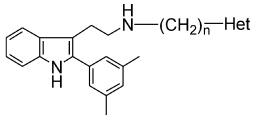
The three 2-aminopyridine derived analogues **33**–**35** were prepared from 2-amino-5-bromopyridine (**31**) according to Scheme 4. Acetylation in the presence of pyridine in THF gave the acetamide **32** from which the *N*-acetylated 2-aminopyridine **33** was obtained through a similar reaction sequence to that shown in Scheme 2. Hydrolysis of amide **33** gave the 2-aminopyridine **34**. The 2-pyridyl methanesulfonamide **35** was obtained from amine **34** by using a three-step reaction sequence comprising *t*-butoxycarbonyl protection (BOC-protection) of the secondary amine followed by methanesulfonamide formation and then BOC-deprotection.

The compounds listed in Tables 1 and 2 were evaluated in a rat GnRH receptor binding assay according to



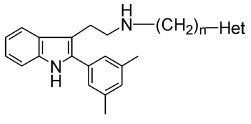
Scheme 2. Reagents and conditions: (a) $Pd(PPh_3)_4$, LiCl, CuCl, NEt_3, bromide **17**, 80 °C; (b) H_2, PtO_2, EtOH, rt; (c) oxalyl chloride, DMSO, NEt_3, CH_2Cl_2, −78 °C to rt; (d) $NaCNBH_3$, $MgSO_4$, anhyd MeOH, 0 °C.

Table 1. 2-Arylindole derivatives prepared from secondary amides by borane reduction



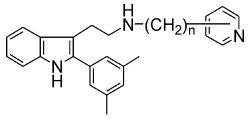
Compound	*n*	Heterocycle
6	1	2-Pyridyl
7	1	3-Pyridyl
8	1	4-Pyridyl
9	2	2-Pyridyl
10	2	3-Pyridyl
11	2	4-Pyridyl
12	3	3-Pyridyl
13	3	4-Pyridyl
14	4	4-Imidazolyl
15	4	7-(1,2,3,4-Tetrahydro)-1,8-napthyridyl

Table 2. 2-Arylindole derivatives prepared by reductive amination



Compd	*n*	Heterocycle
20	4	2-Pyridyl
21	4	3-Pyridyl
22	4	4-Pyridyl
23	5	3-Pyridyl
24	5	4-Pyridyl
25	4	5-Pyrimidinyl
26	4	3-Quinolinyl
29	4	5-(2-MeO)-Pyridyl
30	4	5-Pyrid-2-onyl
33	4	5-(2-AcNH)-Pyridyl
34	4	5-(2-Amino)pyridyl-
35	4	5-(2-MsNH)-Pyridyl

Table 3. Rat GnRH receptor binding IC_{50} values for the three pyridine isomers with different tether lengths



Isomer	Chain length				
	n = 1	*n* = 2	*n* = 3	*n* = 4	*n* = 5
2-pyridyl	**6**[a]	**9**		**20**	
	> 10 μM[b]	2 170 nM		450 nM	
3-pyridyl	**7**	**10**	**12**	**21**	**23**
	4 500 nM	200 nM	200 nM	40 nM	50 nM
4-pyridyl	**8**	**11**	**13**	**22**	**24**
	9 000 nM	160 nM	210 nM	16 nM	150 nM

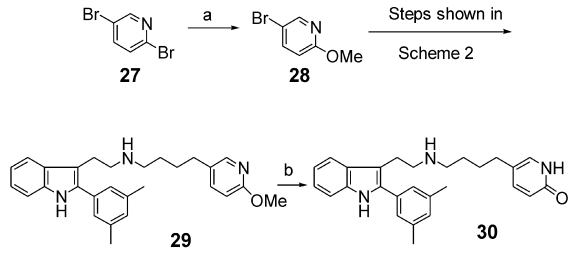
[a]The number in bold (e.g., **6**) refers to the compound number.
[b]Rat GnRH receptor binding assay IC_{50} values (nM or μM).

Table 4. Rat GnRH receptor binding IC_{50} values for different heterocyclic systems and a four-carbon tether

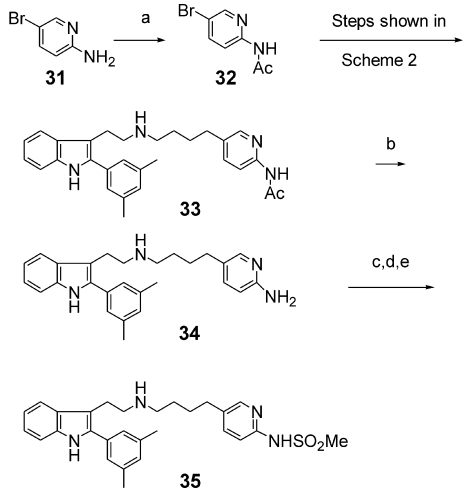
Compound	Rat GnRH receptor binding IC_{50} (nM)
14	450
15	1260
25	270
26	36
29	90
30	57
33	120
34	41
35	45

literature methods.[5,6] We looked first at different carbon tether length linking the pyridine ring and tryptamine nitrogen and surveyed which of the isomeric forms of pyridine was intrinsically more potent. The IC_{50} values obtained from the biological assay are presented in Table 3.

From this study, we found that one-carbon tether compounds (**6**, **7**, and **8**) were weakly active and 2-pyridyl derivatives (**6**, **9**, and **20**) were much less active than their 3- and 4-pyridyl counterparts (**7**, **10**, **21**, and **8**, **11**, **22**, respectively). For a 3-pyridyl system, moderate activity was achieved with tethers of two or three atoms length (**10** and **12**) while an approximately 5-fold increase in potency was seen when the tether was lengthened (**21**, $n=4$ and **23**, $n=5$). In the 4-pyridyl series, the receptor binding activity with tether lengths of $n=2$, 3 or 5 (**11**, $IC_{50}=160$ nM; **13**, $IC_{50}=210$ nM; and **24**, $IC_{50}=150$ nM) were essentially comparable. However, a sharp distinction was seen with a four-carbon tether. The most active analogue was the 4-pyridyl analogue attached with a four-carbon tether, **22**, ($IC_{50}=16$ nM) at the rat GnRH receptor. This IC_{50} value is similar to the affinity shown by the initial phenol lead compound **1** ($IC_{50}=27$ nM). Overall, tether lengths of approximately three to five carbons are well tolerated with a clear preference for a four-carbon linkage in the 4-pyridyl series. The ranking of the pyridine isomers with respect to potency is: 4-pyridyl≈3-pyridyl > 2-pyridyl.



Scheme 3. Reagents and conditions: (a) NaOMe, DMF, 100 °C; (b) BBr_3, CH_2Cl_2, −78 °C to rt.



Scheme 4. Reagents and conditions: (a) Ac_2O, pyridine, THF, rt; (b) NaOH, MeOH 45 °C; (c) $(BOC)_2O$, NEt_3, CH_2Cl_2, rt; (d) MsCl, NEt_3, CH_2Cl_2, 0 °C; (e) TFA, anisole, CH_2Cl_2, 0 °C to rt.

With the results of the preliminary study in hand, further examples of heterocyclic phenol mimetics of GnRH antagonist **1** were evaluated with the potency enhancing saturated four-carbon chain tether. Weak activity was observed in the 7-(1,2,3,4-tetrahydro)-1,8-napthyridyl analogue **15** ($IC_{50}=1260$ nM). The 5-pyrimidyl analogue **25** ($IC_{50}=270$ nM) and the 4-imidazolyl analogue **14** ($IC_{50}=450$ nM), had reduced potency. The 3-quinolyl analogue (**26**, $IC_{50}=36$ nM) had comparable potency to the 3-pyridyl analogue (**21**, $IC_{50}=40$ nM) implying that the extra aromatic ring apparently contributed little towards rat GnRH receptor binding.

We speculated that combination of either a hydroxyl[1] or a methanesulfonamide[3] group with a 3-pyridyl ring might have potency advantages. The pyridone **30** and the sulfonamide **35** were tested on the rat GnRH receptor binding assay. The two compounds, **30** and **35**, had respectable binding affinities to the rat GnRH receptor ($IC_{50}=57$ and 45 nM, respectively) that were comparable to phenol **1**. The desired additive effect of combining a pyridine ring system with a phenol or with a sulfonamide group that was anticipated was not observed. Intriguingly, two 3-pyridyl intermediates **29** ($IC_{50}=90$ nM) and **33** ($IC_{50}=120$ nM) were potent compounds and the basic 2-amino-3-pyridyl analogue **34** ($IC_{50}=41$ nM) had comparable potency to the phenol **1**. We speculate that under our assay conditions (pH≈7) weakly acidic groups[7] such as a phenol, a sulfonamide or a 2-aminopyridine group are partially protonated and can act as hydrogen bond donors interacting with the receptor binding pocket. We hypothesize that the pyridines[7] indirectly act as hydrogen bond donors through the potentiation of an associated water molecule.

Indeed, the phenol ring of indole antagonist **1** can be replaced by a heterocyclic ring. The rat GnRH antagonist compounds **6**–**12** and **20**–**24** helped to establish optimum tether lengths and position of the nitrogen in the pyridine ring is preferred. The 3- and 4-pyridyl substitutions were favored over the 2-pyridyl. A single atom tether length generally resulted in weaker receptor binding potency than longer tether lengths. Of these compounds, analogue **22**, which features a four-carbon tether and a 4-pyridine ring system, had a rat GnRH receptor binding $IC_{50}=16$ nM, which is between that of the phenol **1** and the methanesulfonamide **2**, previously reported.[1,3] The 'hybrid compounds' **30** and **34** did not have the anticipated increases in potency relative to the phenol **1** and sulfonamide **2**. Other heterocyclic ring systems may be substituted for the simple 3- and 4-pyridyl systems without loss of potency (viz. **26**, **29**, **33**, and **34**).

Acknowledgements

We are indebted to Ms. Amy Bernick and Dr. Lawrence Colwell for help with mass spectroscopic analysis of our compounds. Useful and perceptive discussions with Ralph Mosley, a member of the molecular modeling group, is also amicably acknowledged here. Our thanks to Robert Frankshun, Joseph Leone, Judy Pisano and

Mark Levorse who supplied us with synthetic intermediates used throughout the course of this study. Useful discussions with Drs. Robert DeVita, Jonathan Young and Feroze Ujjainwalla concerning the work described here are also gratefully acknowledged.

References and Notes

1. 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.
2. 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.
3. Lin, P.; Marino, D.; 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*, 1073.
4. 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.
5. 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
6. 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
7. 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. The values obtained are: 4-methylphenol (10.21 ± 0.13); *N*-(4-methylphenyl)methanesulfonamide (9.71 ± 0.5); 2-amino-4-methylpyridinium ion (7.38 ± 0.11); 4-methylpyridinium ion (5.94 ± 0.1); 4-methylanilinium ion (5.04 ± 0.1).