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SAR Studies of Novel 5-Substituted 2-Arylindoles as Nonpeptidyl GnRH Receptor Antagonists

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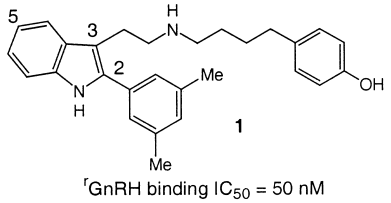
Abstract—The discovery of the potency-enhancing effect of 5-substitutions on the novel 2-arylindoles as nonpeptidyl GnRH receptor antagonists led to the identification of several analogues with high affinities on the GnRH receptor. The syntheses and SARs of these 5-substituted-2-arylindole analogues are reported.

In our previous letter,[1] we discussed a novel class of gonadotropin releasing hormone (GnRH) receptor antagonists, the 2-arylindoles, and the initial structure–activity studies, which concluded with a simplified linker between the phenol moiety and center amine, and with the optimized substituent, 3,5-dimethylphenyl, on the 2-position of the indole (**1**). In this letter, we describe the discovery of potency-enhancing 5-substitutions on the indole core. The subsequent investigation of SARs led to the identification of several analogues with high binding affinities on the rat GnRH receptor.



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[r]GnRH binding IC_{50} = 50 nM

5-Methoxytryptamine (**2**) was protected under the same conditions described in our previous reports (Scheme 1).[1,2] Bromination of phthalimide **3** with pyridine hydrobromide perbromide afforded the desired 2-bromo compound **4** as the major product. Due to the electron-donating nature of the 5-methoxy group, a small degree of 2,6-dibromination was also observed in this normally selective bromination reaction. The 2-bromo compound **4** was coupled with 3,5-dimethylphenylboronic acid (**5**) via a modified Suzuki reaction[2] to provide compound **6**, which was subsequently subjected to a series of previously reported transformations[1] to afford the final target **9** in good yield.

The 5-benzyloxy analogue (**10**) was prepared following the same sequence outlined in Scheme 1, starting with 5-benzyloxytryptamine (**11**).

The commercially available 5-benzyloxytryptamine (**11**) was also used as the building block for a variety of 5-substituted analogues (Schemes 2 and 3). The phthalimide **12**, prepared according to the synthetic scheme outlined in Scheme 1, was fully deprotected with palladium catalyzed hydrogenolysis followed by aqueous hydrazine to provide tryptamine **13**, which was subsequently coupled with acid **14** to afford amide **15**. Amide **15** was reduced with BH_3·THF and protected to give the advanced intermediate **16**. The phenolic compound **16** was reacted with triphosgene,[3,4] followed by trapping with various amines to afford carbamate compound **17**, which was then fully deprotected in one reaction with $Pd(OH)_2$ catalyzed hydrogenolysis to give the final target **18**. Care should be taken in the reaction of phenolic compound **16** to avoid excess triphosgene and reaction time so as to minimize reaction at the indole nitrogen.

When the amine (HNRR′) used in step h of Scheme 3 was piperazine, a large excess (~100 equiv) was used to

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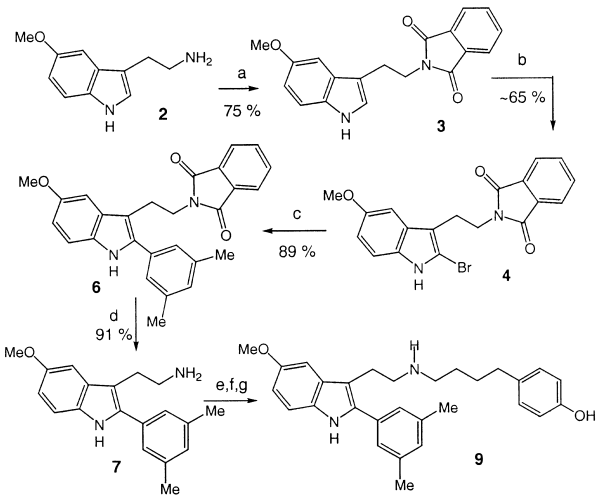
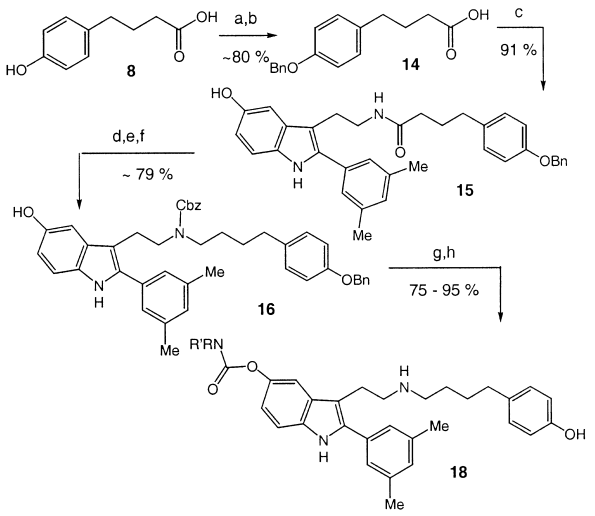
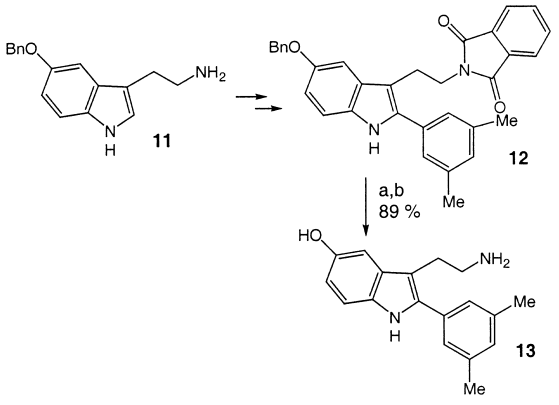


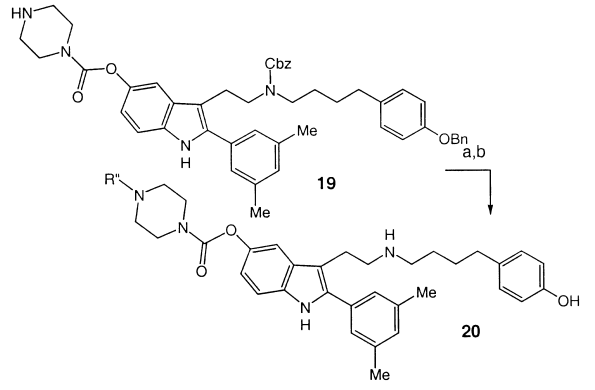
Scheme 1. Reagents and conditions: (a) *N*-carbethoxyphthalimide, THF, reflux; (b) pyridine hydrobromide perbromide, THF/$CHCl_3$; (c) 3,5-dimethylphenylboronic acid (**5**), Na_2CO_3, LiCl, $Pd(PPh_3)_4$, toluene/EtOH (1:1), reflux, 1.25 h; (d) hydrazine in H_2O, THF/EtOH, overnight; (e) 4-(4-hydroxyphenyl)butyric acid (**8**),[1] HOBT, EDAC, DMF/CH_2Cl_2; (f) BH_3·THF, THF, reflux, 3 h; (g) *N*,*N*-dimethylethanolamine, MeOH/THF, reflux, 3 h.



Scheme 3. Reagents and conditions: (a) BnBr, NaH, DMF; (b) NaOH, MeOH/H_2O; (c) **13**, HOBT, EDAC, CH_2Cl_2; (d) BH_3·THF, reflux; (e) *N*,*N*-dimethylethanolamine, MeOH/THF, reflux; (f) CbzCl, Hünig's base, CH_2Cl_2, −78 °C; (g) triphosgene, pyridine, CH_2Cl_2, 0 °C, 30 min; (h) HNRR′; (i) $Pd(OH)_2$, H_2, AcOH, MeOH, THF.



Scheme 2. Reagents and conditions: (a) 10% Pd on carbon, H_2 (1 atm), EtOAc, 2 days; (b) hydrazine in H_2O, THF/EtOH, overnight.



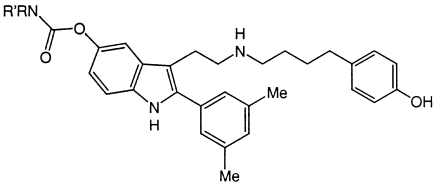
Scheme 4. Reagents and conditions: (a) R″X, Et_3N, CH_2Cl_2; (b) $Pd(OH)_2$, H_2, AcOH, MeOH/THF.

avoid over reaction on the remote nitrogen of the piperazinyl group. This remote nitrogen would later serve as an excellent handle for functionalizations to provide a wide range of analogues **20** (Scheme 4).

The observation that the 5-methoxy analogue **9** ($IC_{50} = 40$ nM)[5] was slightly more active than our previous lead compound **1** ($IC_{50} = 50$ nM), together with the fact that the substantially sized benzyloxy group in analogue **10** ($IC_{50} = 100$ nM) did not render the compound much less active than **1**, which lacked any 5-substitution, prompted us to further investigate various 5-substituents on the indole. Table 1 lists selected analogues and their binding affinities on the rat GnRH receptor.

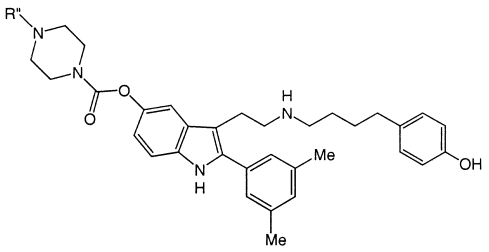
Although many different carbamates (**21**–**26**) had similar activities, none of them was particularly outstanding. However, upon further investigation, we discovered that functionalized piperazinyl compounds, especially

Table 1.



NRR′	Analogue	IC_{50} (nM)
MeHN–	**21**	30
Me_2N	**22**	30
EtHN	**23**	16
PrHN–	**24**	30
	**25**	32
	**26**	20
	**27**	100

Table 2.



R″	Analogue	IC_{50} (nM)
Me—	**28**	25
	**29**	30
	**30**	15
	**31**	30
	**32**	27
	**33**	32
MeO_2S–	**34**	6
EtO_2S–	**35**	4
$^{i}PrO_2S$–	**36**	7
PrO_2S	**37**	12

sulfonylated ones (**34**–**37**), exhibited potent binding activities (Table 2). In particular, the ethyl sulfonyl analogue **35** was shown to be 13-fold more active than our previous lead compound **1**.

The initial structure–activity relationship studies on the 5-position of the indole core of the novel 2-arylindoles as nonpeptidyl GnRH receptor antagonists led to the discovery of sulfonylated piperazinyl carbamate groups as potency-enhancing pharmacophores. The most potent compound in this series, analogue **35**, exhibited a 13-fold increase in rat GnRH binding activity relative to compound **1**, which lacked any 5-substitution. Further progress in this area will be reported in the near future.

Acknowledgements

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References and Notes

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5. Crude membranes prepared from rat pituitary glands were the GnRH receptor source and [^{125}I]buserelin (a peptidyl GnRH analogue) was used as the radio-labeled ligand. The competitive binding was conducted in a Tris–HCl based buffer at 4 °C for 90 min. The activities are presented as the IC_{50} for the inhibition of [^{125}I]buserelin binding to the receptors. A similar assay is described in ref 6 using a different radioligand.
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